An Introduction to Mathematical Epidemiology

Michael Y. Li

Department of Mathematical and Statistical Sciences
University of Alberta
Edmonton, Alberta
T6G 2G1 Canada
mli@math.ualberta.ca

Contents

Chapter 1

Important Concepts in Mathematical Epidemiology

1.1 Mathematical modeling of infectious diseases: issues and approaches

A disease is *infectious* if the causative agent, whether a virus, bacterium, protozoa, or toxin, etc., can be passed from one host to another through modes of transmission such as direct physical contacts, arial droplets, water or food, disease vectors, mother to newborns, etc.

A mathematical model of an infectious disease is a description in mathematical language of the disease *transmission process*: when infectious individuals are introduced into a group of susceptibles, the disease is passed to other individuals through its modes of transmission, and the disease spreads in the group. If the number of infected individuals explodes in a short period of time, a *disease outbreak* occurs. Infected individuals recover from infection, either through treatment or due to action of the immune system, and gain various degree of acquired immunity against the infection. When the pool of susceptible individuals is depleted or due to strict disease control measures, number of new infections will decline and may diminish within a short time. This is typically called an *epidemic*. For instance, the SARS outbreak in 2003 was an epidemic. If fresh susceptibles are added to the group, either from birth or migration, or if the reinfection is easy, then epidemic may last very long, and the infection may persist in the group over a long period of time. In this case, the disease is said to be *endemic* in the group. For instance, old diseases such as measles, Tuberculosis and malaria are endemic in many regions of the world. If the disease spreads to a large geographic area, far beyond the location of initial occurrence, we say a *pandemic* occurs. The 1918 Spanish flu that spread to all continents and killed over 50 million people is a classic case of global pandemics. The 2009 H1N1 influenza outbreak in Mexico had spread to all over the world within a few months and was declared a pandemic by the WHO.

Facing an imminent epidemic, the public health authorities will be looking for answers to the following important questions:

1. How severe will the epidemic be? The severity can be measured in two different ways:
   - Total number of infected people who may require medical care;
   - Maximum number of infected people at any given time;
2. How long will it last? What will be its time course?
3. How effective will quarantine or vaccination be?

4. How much of vaccine or anti-viral drugs should be stockpiled?

5. What are effective measures to contain, control, and eliminate an endemic disease?

Partial answers may be obtained from a variety sources and means. Mathematical modeling can be an important tool that can assist public health authorities to make the correct decisions.

This brings us to the obvious question: why is mathematical modeling of infectious diseases useful? Part of the reason is that traditional methods using experimental and statistical approaches may not be adequate for various reasons:

1. Infectious diseases often affect a large population of individuals over a large geographic area. Experiments conducted in laboratories are often inadequate simply because of the huge difference in scales.

2. For infectious diseases of humans, large scale experiments may be impossible or unethical.

3. Existing data sets about the disease may not be complete or accurate for statistical analysis to be reliable.

4. Since repeated experiments of disease infection in a population is not possible, disease data often represents a small sample, a single experiment, with huge amount of information. It is a challenge for statistics theory which is built on large samples.

Mathematical modeling can provide understanding of underlying mechanisms for the disease spread, help to pinpoint key factors in the disease transmission process, suggest effective control and preventive measures, and provide estimate for the severity and potential scale of the epidemic. It is possible to estimate the model parameters and validate a mathematical model using existing disease data. Put it simply, mathematical modeling should become part of the toolbox for public health research.

The next question we would like to know is how to does a mathematical model work? Generally speaking, the modeling process involves the following six stages:

(1) Make assumptions about the disease transmission process.

(2) Set up mathematical models for the transmission process based on these assumptions.

(3) Perform mathematical analysis on the model to understand the dynamical behaviours of the models. This is typically done by applying the existing mathematical theories in conjunction with numerical simulations.

(4) Interpret the mathematical findings within the modeling context. These interpretations form our understanding of the disease transmission process entailed by the set of assumptions made in Step (1).

(5) Estimate model parameters and validate the model using disease data.

(6) Improve the model by modifying earlier assumptions, and produce more accurate understanding of the disease process.

From this we can see that a mathematical model is always an approximation of the real disease process. It is a mathematical formulation of our hypotheses about the disease transmission process. This brings about another important role a mathematical model can play: by comparing the model outcomes with existing knowledge or data of the disease, one can use the model to test various hypotheses about the disease. Very often, this approach has the advantage of saving enormous amount of time and resources, when compared to traditional experimental approaches.

One should caution that a mathematical model is not magical bullet either. There are often many difficulties associate with mathematical modeling. The following is a list of important issues involved in the mathematical modeling process:

1. Due to our limited knowledge about an infectious disease, realistic assumptions about its transmission process is not always possible. Various degree of simplification needs to be made. Very often, our assumptions are simply hypotheses. When making interpretations of mathematical finding from the model, one always needs to keep these limitations in mind.

2. Model validation using disease data is important because it provides a test on our modeling hypotheses. This may not always possible or may be difficult to do depending on the availability and the quality of data.

3. Mathematical analysis of the model may be limited by the existing mathematical theory.

There is always a trade-off in mathematical modeling between more realistic models, usually more complicated, and our ability to analyze the model mathematically and obtain useful information from the model for interpretation. Advancement in

mathematical theory and methodology often allows us to successfully use more realistic models.

There are three general approaches to mathematical modeling of infectious diseases.

(1) Statistical models. These models are very data oriented and are constructed to deal with a specific set of data.

(2) Deterministic models. These are typically models using differential and difference equations of various forms. The key assumption is that the size of susceptible and infectious population are definite functions of time. The models describe the dynamical inter-relations among the rates of change and population sizes.

- Advantage: Mathematical theories for this type of models are more mature. They are good for making predictions.
- Drawbacks: these models are not expected to be valid if the population sizes can become very small when random perturbations become more important.

(3) Stochastic models. In this type of models, populations are treated as stochastic processes. Models describe dynamic interrelations of their probability distributions.

- Advantages: Stochastic models are suitable to deal with small groups such as individuals and households.
- Drawbacks: Mathematical analysis of stochastic models is difficult due to lack of a general mathematical theory.

The lecture notes attempt to give an introduction to deterministic models and their mathematical analysis.

1.2 Deterministic epidemic models: compartmental approach

In this section, we explain how to set up a mathematical model for the transmission process of an infectious disease using a compartmental approach. We first partition the host population into mutually exclusive groups – compartments, according to the

natural history of the disease. For a simple infectious disease, possible compartments may be:

$$S: \text{ susceptible hosts}, \quad I: \text{ infectious hosts}, \quad R: \text{ recovered hosts}.$$

Then, we illustrate the transmission process schematically in a transfer diagram, also called a carton:

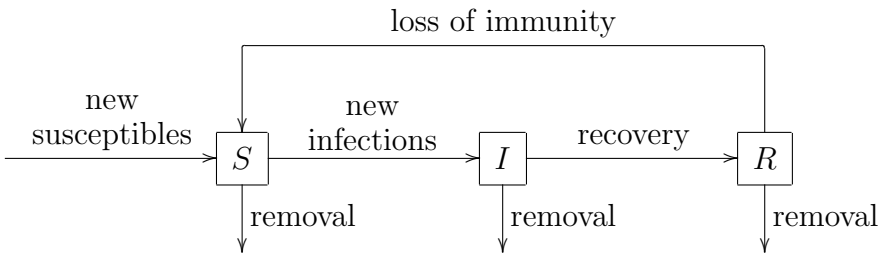


Figure 1.1: Transfer diagram for a SIR compartment model

The goal of modeling is to track the number of individual hosts in each of the three compartments at any given time t, and we denote these numbers by $S(t), I(t)$, and $R(t)$ accordingly. To set up the compartmental model, we consider a small time interval $[t, t + \Delta t]$ and the net change in the number of individuals in each compartment. We arrived at the following equations

$$\begin{aligned}
\Delta S(t) &= \boxed{\text{new susceptibles}} + \boxed{\text{transfer from } R} - \boxed{\text{new infections}} - \boxed{\text{removal from } S} \\
\Delta I(t) &= \boxed{\text{new infections}} - \boxed{\text{transfer into } R} - \boxed{\text{removal from } I} \\
\Delta R(t) &= \boxed{\text{transfer from } I} - \boxed{\text{transfer into } R} - \boxed{\text{removal from } R}
\end{aligned} \tag{1.1}$$

If we divide both sides of these equations by Δt and let $\Delta t \to 0^+$, then the left hand sides will give derivatives $S'(t), I'(t)$, and $R'(t)$, since

$$\frac{\Delta S(t)}{\Delta t} = \frac{S(t + \Delta t) - S(t)}{\Delta t} \to S'(t), \quad \text{as } \Delta t \to 0^+,$$

and similar relations hold for $I'(t)$ and $R'(t)$. The terms on the right hand side will become instantaneous rates of incidence, transfer and removal, etc. We thus have

the following equations

$$\begin{aligned} S'(t) &= \boxed{\text{influx of new susceptibles}} + \boxed{\text{transfer rate from } R} - \boxed{\text{incidence rate}} \\ &\quad - \boxed{\text{removal rate from } S} \\ I'(t) &= \boxed{\text{incidence rate}} - \boxed{\text{transfer rate into } R} - \boxed{\text{removal rate from } I} \\ R'(t) &= \boxed{\text{transfer rate from } I} - \boxed{\text{transfer rate into } R} - \boxed{\text{removal rate from } R}. \end{aligned} \tag{1.2}$$

If we can write all the terms on the right hand side as functions of $S(t), I(t)$, and $R(t)$, we will obtain a system of differential equations, which will be our model. It is important to note that the exact way these terms depend on $S(t), I(t)$, and $R(t)$ is entirely dependent of our hypotheses on the processes of disease transmission and population transfer among compartments. Therefore, different hypotheses will give rise to different forms of the model, and hence may lead to very different model outcomes. If data is available to verify our model outcomes, then the model can be used to test the validity of our hypotheses about the disease transmission process. In the next section, we will see how basic hypotheses can be made to derive some of the classic epidemic models.

1.3 An example: Kermack-McKendrick model

To demonstrate how various rates in equation (1.2) may depend on $S(t), I(t)$, and $R(t)$, we make the following hypotheses about the transmission process of an infectious disease and its host population.

1. The mode of transmission is horizontal through direct contact between hosts.

2. The mixing of individual hosts is homogeneous and thus the *Law of Mass Action* holds: the number of contacts between hosts from different compartments depends only on the number of hosts in each compartment. In particular, the *incidence rate* - number of new infections per unit time, can be expressed as $\lambda I(t)S(t)$, where λ is called the *transmission coefficient*.

3. Rates of transfer from a compartment is proportional to the population size of the compartment. For instance, the rate of transfer from I to R, the *recover rate*, can be written as $\gamma I(t)$, for some rate constant γ.

4. Infected individuals becomes infectious upon infection and there is no latent period.

5. There is no loss of immunity and possibility of reinfection. This implies that the transfer rate from R back to S is zero.

6. There is no input of new susceptibles and no removal from any compartments. The influx of new susceptibles is zero, and so are the removal rates from all compartments.

7. The total host population remains a constant. This is a direct result of our assumption 6. But we state it here explicitly to emphasize the fact. The dynamics of epidemic models can be more complicated if the total population varies with time.

Very restrictive may they appear, these assumptions are quite plausible for certain disease spread within student population on a campus, where mixing in mainly through going to classes, cafeteria and other public places. Based on these assumptions, the transfer diagram in Figure 1.1 becomes

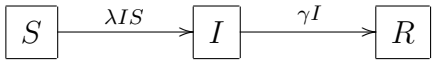


Figure 1.2: Transfer diagram for a simple SIR model

Substituting all terms in (1.2) by our mathematical descriptions, we obtain the following system of differential equations:

$$\frac{dS}{dt} = -\lambda IS \tag{1.3}$$

$$\frac{dI}{dt} = \lambda IS - \gamma I \tag{1.4}$$

$$\frac{dR}{dt} = \gamma I, \tag{1.5}$$

with initial conditions

$$S(0) = S_0 > 0, \quad I(0) = I_0 > 0, \quad R(0) = 0.$$

In the model, functions $S(t), I(t)$ and $R(t)$ are *variables*. Since they denote number of people, they are expected to take nonnegative values. Constants λ and γ are model *parameters*, and they are assumed to be nonnegative since they denote rate constants. If the values of model parameters λ and γ are known, then for each set of

initial conditions S_0 and I_0, model (1.3)-(1.5) has a unique solution $(S(t), I(t), R(t))$ that produces prediction for the time course of the epidemic for $t > 0$. Here $t = 0$ marks the beginning time of the epidemic.

Even when the values of parameters are not known, some simple observations about the solutions to system (1.3) - (1.5) can be made that hold for all or a large set of possible parameter values.

1. Let $N(t) = S(t) + I(t) + R(t)$ denote the total host population. Then, by adding (1.3) - (1.5), we have
$$\frac{dN}{dt} = 0$$
and thus the total population $N(t) = N_0 = S_0 + I_0$ remains a constant.

2. From equation (1.3) we obtain
$$\frac{dS}{dt} \leq 0.$$
Therefore, $S(t)$ is always decreasing. In particular, $S(t) \leq S_0$.

3. Rewrite equation (1.4) as
$$\frac{dI}{dt} = (\lambda S - \gamma)I.$$
Then, we have following two cases:

   (a) If $S_0 < \frac{\gamma}{\lambda}$, then $\left.\frac{dI}{dt}\right|_{t=0} < 0$. Since $S(t) \leq S_0 < \frac{\gamma}{\lambda}$, we know $I'(t) < 0$ for all $t \geq 0$, and thus $I(t)$ strictly decreases. As a result, no epidemics can occur in this case.

   (b) If $S_0 > \frac{\gamma}{\lambda}$, then $S(t) > \frac{\gamma}{\lambda}$ for $t \in [0, \bar{t})$ for some $\bar{t} > 0$. This implies $I'(t) > 0$ and thus $I(t)$ strictly increases for $t \in [0, \bar{t})$. As a result, an epidemic happens.

   This demonstrates the well-known *threshold phenomenon*: there is a threshold value S_0 must exceeds for an epidemic to occur.

   We see that it is possible to derive properties of solutions without knowing specific values of model parameters. Our analysis can identify parameters regions for distinct model outcomes. This is the power and often the objective of mathematical analysis. We will revisit this model in great detail in the next chapter.

1.4 Important concepts in compartmental modeling

1.4.1 Transfer rates

For the simple Kermack-McKendrick model considered in the previous section, we assumed that the recover rate, or the rate of transfer from compartment I to R, is given by γI. This is equivalent to assuming the following:
(**H**) the fraction of infectious population that recovers per unit time is a constant γ.

Proportional transfer rates as assumed in (H) are often used for transfers between compartments in simple compartmental models. However, one needs to understand that this is only one of many assumptions one can make about population transfers. In fact, our assumption that recovery rate is in proportion to the size of infectives is by no means universal. In the following, we will develop a better mathematical understanding of the proportional transfer rate, and consider other possible alternatives.

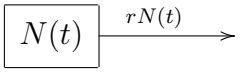


Figure 1.3: A compartment C

Consider a general compartment of total population size $N(t)$, and individuals leave the compartment at a rate $rN(t)$ $(r > 0)$. Then the size $N(t)$ satisfies

$$\frac{dN(t)}{dt} = rN(t), \qquad r > 0,$$

and thus $N(t) = N_0 e^{-rt}$, or

$$\frac{N(t)}{N_0} = e^{-rt} \tag{1.6}$$

Therefore, e^{-rt} gives the fraction of the population that remains in the compartment C. In probability terms, e^{-rt} is the probability of an individual who enters C at time $t = 0$ and remains in C at time $t > 0$. Since we are interested in the population transfer out of C, we consider

$$F(t) = \begin{cases} 1 - e^{-rt}, & t \geq 0, \\ 0, & t < 0, \end{cases} \tag{1.7}$$

which gives the fraction of population that have left C during the time period $[0, t)$, or the probability of an individual who has left C during $[0, t)$. Here we see that $F(t)$ has the characteristics of a probability distribution. In fact, let X denote the random variable of the residence time in C, the time period from entrance to exit, of an individual. Then we see that

$$F(t) = \text{Prob}\,[\,X \leq t\,]. \tag{1.8}$$

In another word, $F(t)$ is the *probability distribution function* of individual exit time from C and it satisfies the following properties:

(a) $F(t) \geq 0$

(b) $F(t) \to 0$, as $t \to -\infty$

(c) $F(t) \to 1$, as $t \to +\infty$.

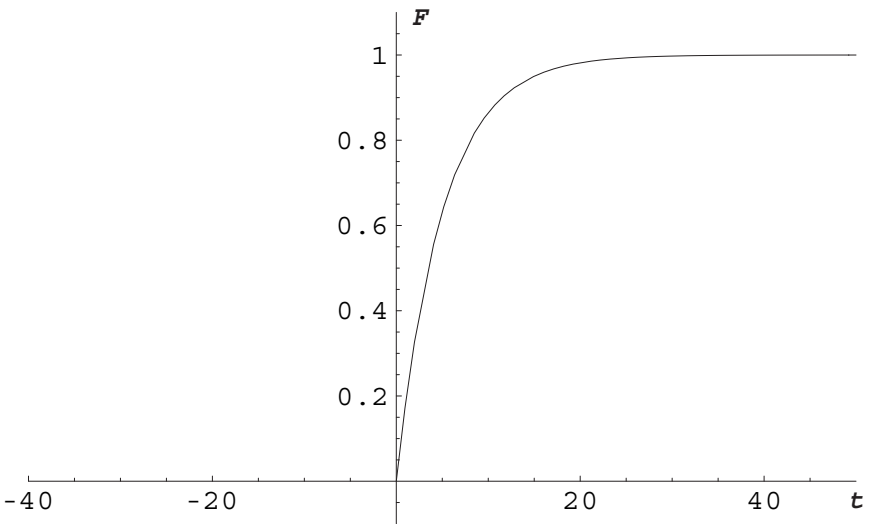


Figure 1.4: A probability distribution.

Now we see that the assumption of proportional exit rate is the same as the following

($\mathbf{H}'$) the time for an individual to exit compartment C has an exponential distribution.

We can also describe the random variable X in terms of probability density function $f(t) = \frac{d}{dt}F(t)$, namely

$$f(t) = \begin{cases} re^{-rt}, & t \geq 0, \\ 0, & t < 0, \end{cases} \tag{1.9}$$

which has the following properties

(a) $f(t) \geq 0$

(b) $\int_{-\infty}^{\infty} f(t)dt = 1$

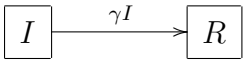
(c) $F(t) = \text{Prob}\,[\,X \leq t\,] = \int_{-\infty}^{t} f(s)ds$.

The expected value, also called the *mean value*, of X is

$$E[X] = \int_{-\infty}^{\infty} tf(t)dt = \frac{1}{r}. \tag{1.10}$$

Therefore, the mean exit time, under the proportional exit rate assumption, is $\frac{1}{r}$.

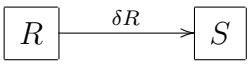
In term of transfers from compartment I to R, the period from the time an individual becomes infectious to the time of recovery is called the *infectious period*. The following transfer diagram



is equivalent to assuming that the infectious period of individuals has an exponential distribution

$$F(t) = \begin{cases} 1 - e^{-\gamma t}, & t \geq 0, \\ 0, & t < 0, \end{cases}$$

and $\frac{1}{\gamma}$ is the mean infectious period. Similarly, the transfer diagram



assumes that the immune periods of individuals has an exponential distribution

$$F_1(t) = \begin{cases} 1 - e^{-\delta t}, & t \geq 0, \\ 0, & t < 0, \end{cases}$$

and the mean immune period is $\frac{1}{\delta}$.

The question now becomes that how would we set up the model equations if individual infectious periods has a general probability distribution $P(t) = 1 - F(t)$? We will revisit the SIR model (1.3)-(1.5) with this general assumption. We can see that the change in assumption on the infectious period does not impact the S equation (1.3). We need to derive equations for $I(t)$ and $R(t)$. Let the residence time X has the probability distribution function $F(t) = \text{Prob}[X < t]$ as defined in (1.8). We consider the associated *survival function*

$$G(t) = 1 - F(t) = \text{Prob}[X > t].$$

For any given time $\tau > 0$, $G(t-\tau)$ is the percentage of individuals who are infected at time τ and are still infective at time t. Therefore, the number of individuals who are infected at time τ and remain infective at time t is given by

$$\lambda I(\tau)S(\tau)G(t-\tau).$$

Therefore, at time t, the accumulative number of individuals in the I compartment since $\tau = 0$ is

$$I(t) = I_0(t) + \int_0^t \lambda I(\tau)S(\tau)G(t-\tau)\,d\tau, \tag{1.11}$$

where $I_0(t)$ is the accumulative number of individuals who are infected at $\tau = 0$ and remain infective at time $t > 0$. Similarly, the R equation is given by

$$R(t) = R_0(t) + \int_0^t \lambda I(\tau)S(\tau)(1 - G(t-\tau))\,d\tau. \tag{1.12}$$

We see that the new SIR model (1.3), (1.11) and (1.12) with generally distributed infectious periods is a differential-integral system.

In the special case when $F(t) = 1 - e^{-\gamma t}$ is an exponential distribution, we have $G(t) = e^{-\gamma t}$, and from (1.11)

$$I(t) = I_0(t) + \int_0^t \lambda I(\tau)S(\tau)e^{-\gamma(t-\tau)}\,d\tau,$$

and $I_0(t) = I(0)e^{-\gamma t}$ by (1.6). Therefore,

$$\begin{aligned} I'(t) &= I_0'(t) + \lambda I(t)S(t) - \gamma \int_0^t \lambda I(\tau)S(\tau)e^{-\gamma\tau}\,d\tau \\ &= I_0'(t) + \lambda I(t)S(t) - \gamma(I(t) - I_0(t)). \end{aligned}$$

Since $I_0'(t) = -\gamma I_0(t)$, we obtain the original equation (1.3)

$$I'(t) = \lambda I(t)S(t) - \gamma I(t).$$

Similarly, we have from (1.12),

$$R'(t) = \gamma I(t).$$

This reaffirms our claim that the SIR model in the form of ODE (1.3)-(1.3) assumes exponentially distributed infectious period.

Let us take another special case when infectious periods have the following survival function

$$G(t) = \begin{cases} 1 & \text{if } -\infty < t < \omega, \\ 0 & \text{otherwise.} \end{cases}$$

Correspondingly, $F(t) = 1 - G(t)$ is the Heaviside function at $t = \omega$ for some constant $\omega > 0$. Then, the equation for $I(t)$ becomes

$$I(t) = I_0(t) + \int_{t-\omega}^{t} \lambda I(\tau)S(\tau)\, d\tau,$$

and thus, for $t > \omega$,

$$I'(t) = I_0'(t) + \lambda I(t)S(t) - \lambda I(t-\omega)S(t-\omega).$$

Since $I_0(t) = 0$ for $t > \omega$, we arrive at a differential equation with a time delay ω,

$$I'(t) = \lambda I(t)S(t) - \lambda I(t-\omega)S(t-\omega). \tag{1.13}$$

Similarly, for $t > \omega$,

$$R(t) = R_0(t) + \int_{0}^{t-\omega} \lambda I(\tau)S(\tau)\, d\tau,$$

and

$$R'(t) = \lambda I(t-\omega)S(t-\omega). \tag{1.14}$$

Here we have used the fact the $R_0(t) = 1$ for $t > \omega$. We see here that the delayed differential equation model (1.3),(1.13) and (1.14) is the result of assuming the infectious periods has a Heaviside distribution function, or Dirac delta density function at $t = \omega$.

1.4.2 Modeling disease incidence

Disease *incidence* is the rate at which new infections occur, namely, fraction of newly infected population (reported and non-reported) per unit time. This should be distinguished from disease *prevalence*, which measures the fraction of infected population at time t.

1. Simple incidence forms

The incidence term in the Kermack-McKendrick model in Section 1.3 is given by βIS, which is often called simple mass-action incidence, or bilinear incidence. It is based on the Law of Mass Action, first derived for chemical kinetics in 1864 by Waage and Guldberg, the rate of chemical reaction is proportional to the density (or amount) of the reactants.

$$\begin{aligned} A \;+\; B \;&\Longleftrightarrow\; A\,B \\ \text{rate} \;&=\; k\,[A]\,[B] \end{aligned}$$

The underlying assumptions of the Law of Mass Action are

(1) homogeneous mixing so that contact rate only depends on the density of reactants;

(2) conservation of total mass;

(3) low reactant density.

We see that, for contacts among humans, these assumptions are at best crude approximations. Modifications of any of these assumptions will lead to different incidence forms.

2. The effects of saturation

If a host population is saturated with infectious individuals, the rate of new infections will only be determined by the number of susceptibles S, and homogeneous mixing is no longer valid. To describe incidence rate in this situation, we can learn from standard theory of enzyme kinetics. The reaction rate v_0 has a nonlinear dependence on the concentration $[A]$ of the substrate A given by the Michaelis-Menton equation

$$v_0 = \frac{v_{\max}[A]}{K + [A]} \tag{1.15}$$

In this equation, $v_{\max}$ is the maximum reaction rate, and K is the Michaelis-Menton constant.

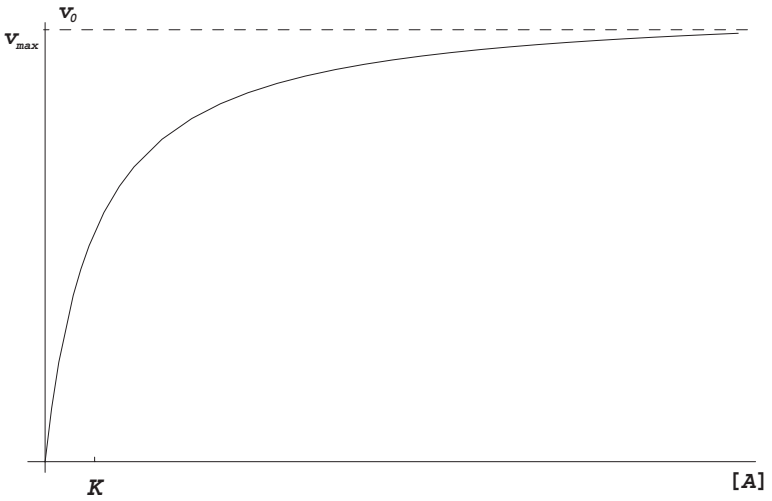


Figure 1.5: Michaelis-Menton reaction curve

We see from the graph of Michaelis-Menton reaction that when substrate concentration $[A]$ is getting large, reaction rate v_0 saturates at the constant $V_{\max}$.

The function

$$f(x) = \frac{ax}{K + x} \tag{1.16}$$

is often called Monod function, or Hollings's type II function in ecology literature. The saturation effect on the disease incidence can be modeled using the Monod function to give

$$\frac{\beta IS}{K + I}, \tag{1.17}$$

so that when the population of I is large, the incidence rate is approximately λS. Other incidence forms can be

$$\frac{\beta I^m S}{K + I^m}, \quad m > 0. \tag{1.18}$$

Similarly, saturation of susceptibles may be modeled by

$$\frac{\beta I S^n}{K + S^n}, \quad n > 0. \tag{1.19}$$

3. Varying total population size

Another way to derive disease incidence is the following. Let $S(t), I(t), R(t)$, and $N(t) = S(t) + I(t) + R(t)$ denote the sizes of susceptible, infectious, recovered, and total population, respectively. Let λ be the average per capita contact number among individuals per unit time, and p the probability that a contact will produce an infection. Then the incidence is given by

$$p\lambda \cdot \frac{S(t)}{N(t)} \cdot I(t)$$

which can be decoded as

average # of effective contact produced by each infective	$\cdot$	probability of a contact is made with a susceptible	$\cdot$	total number of infectious individuals

If we combine the probability p with the contact number λ, so that λ is the per capita effective contact number, then the incidence is given by

$$\frac{\lambda}{N} IS. \tag{1.20}$$

When the total population size N is a constant, then incidence in (1.20) is the same as the simple mass-action incidence. However, when $N(t)$ varies with t, things become more complicated. We consider two simple cases.

Case 1. Contact number λ is independent of the total population size. In this case, the incidence is given by

$$\frac{\lambda I(t) S(t)}{N(t)}, \tag{1.21}$$

where λ is a constant. This form is called the proportionate incidence or standard incidence.

Case 2. Contact number is proportional to the total population size, namely

$$\lambda(N) = \beta N$$

for a constant β. Then the incidence is again of the simple mass-action form

$$\beta I(t) S(t). \tag{1.22}$$

Many research articles have been devoted to suitability of these different incidence forms [].

Instead of justifying suitability of these two different incidence forms, we examine the different assumptions behind them. We have seen that the difference lies in the assumption on how contact rate varies with the total population size. It is reasonable to assume that the contact rate is in proportion to the total population density. Therefore, the difference between incidence forms (1.21) and (1.22) lies in the assumption on how total population density changes as the total population size varies.

Assumption 1: population density is independent of population size. This is likely the case in a rural population, since as population size increases, rural towns tends to expand to maintain a constant population density.

Assumption 2: population density is in proportion to population size. This is likely the case for a big urban population where the city is confined in space; an increase in population size will proportionally increase the population density.

In this sense, proportionate incidence (1.21) maybe more suitable for a population in a rural setting, whereas the bilinear incidence is suitable for a big urban population.

1.4.3 Demography: birth, death, and population growth

To add demographical factors into the Kermack-McKendrick models (1.3)-(1.5), we need to make various assumptions on the birth, death, and growth of the host population, the simplest of which is the proportional rate assumption that the birth or death rate is proportional to the population size. A model that incorporates these assumptions is depicted in the diagram in Figure 1.6 with the corresponding system of differential equations (1.23)

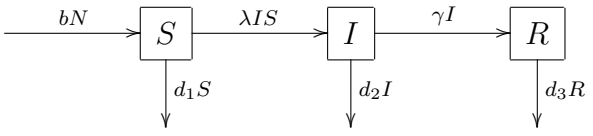


Figure 1.6: Transfer diagram for a SIR model with birth and death

$$\begin{aligned} S'(t) &= bN(t) - \beta I(t)S(t) - d_1 S(t) \\ I'(t) &= \beta I(t)S(t) - (\gamma + d_2)I(t) \\ R'(t) &= \gamma I(t) - d_3 R(t) \\ N(t) &= S(t) + I(t) + R(t) \end{aligned} \tag{1.23}$$

Here b is the natural birth rate constant, d_1, d_2, and d_3 are death rate constants for compartments S, I, and R, respectively. Rate constant d_2 may include both natural and disease-caused death. If we add the first three equations in (1.23), we obtain

$$N'(t) = bN(t) - d_1 S(t) - d_2 I(t) - d_3 R(t).$$

In general, this implies that $N(t)$ will vary in time. In the special case when $d_1 = d_2 = d_3 = d$, we have

$$N'(t) = (b - d)N(t)$$

and thus

$$N(t) = N_0 e^{(b-d)t}.$$

If $b > d$, $N(t) \to \infty$ exponentially as $t \to \infty$; if $b < d$, $N(t) \to 0$ exponentially as $t \to \infty$; if $b = d$, $N(t) \equiv N_0$, a constant.

Exponential growth and decay of the total population is often modified by the logistic growth,

$$N'(t) = (b - d)N(t) - \frac{N(t)^2}{K}, \tag{1.24}$$

where b, d are natural birth and death rates, respectively, and $(b - d)K$ is the carrying capacity for the population. The logistic growth can be incorporated into the Kermack-McKendrick model as follows

$$\begin{aligned} S'(t) &= bN(t) - \frac{N(t)^2}{K} - \beta I(t)S(t) - dS(t) \\ I'(t) &= \beta I(t)S(t) - (\gamma + d)I(t) \\ R'(t) &= \gamma I(t) - dR(t). \end{aligned} \tag{1.25}$$

More discussions on epidemic models with density dependent demographics, we refer the reader to [7].

1.4.4 Disease latency: latent and incubation periods

Disease infection begins with the transmission of the pathogen from one host to another. After the pathogens invades the host body, they need to be able to evade

Figure 1.7: Graphical illustration of incubation and latent periods

or overcome the host immune response, and be able to multiply or replicate. When the pathogens accumulate sufficiently large numbers and when they have reached the targeted organs, they begin to cause sufficient damage to the host body so that the host becomes symptomatic, and the host is capable to transmit the pathogens to other hosts. The period from time of infection to time of showing symptoms is called the *incubation period*. The period from time of infection to time of being infectious is called the *latent period*. See the illustration in Figure 1.7 for relations between these two periods. During the latent period, a host may or may not show symptoms, but the host is not capable of transmitting pathogens to other hosts.

To incorporate latency in a mathematical model, we need to make some basic assumptions about the latency of the disease. The simplest way this is done is to divide the infected compartment into two compartments: a latent compartment E and a infectious compartment I, and assume the transfer from E to I satisfies the proportional rate assumption, namely, given by ϵE, with rate constant ϵ. From our discussions in Section 1.4.1, we know that this is equivalent to assuming that individual latency has an exponential distribution, and $1/\epsilon$ is the mean latent period. We have a new transfer diagram in Figure 1.8, which leads to a system of differential equations (1.26).

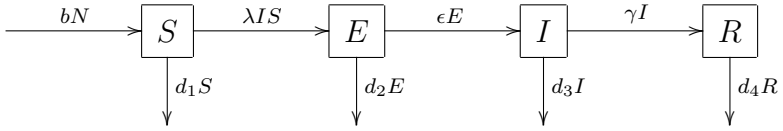


Figure 1.8: Transfer diagram for a SEIR model

$$\begin{aligned} S'(t) &= bN(t) - \beta I(t)S(t) - d_1 S(t) \\ E'(t) &= \beta I(t)S(t) - (\epsilon + d_2)E(t) \\ I'(t) &= \epsilon E(t) - (\gamma + d_3)I(t) \\ R'(t) &= \gamma I(t) - d_4 R(t) \\ N(t) &= S(t) + E(t) + I(t) + R(t). \end{aligned} \tag{1.26}$$

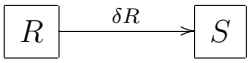
This is a SEIR model. Variations of the model can be derived when different incidence

and demographic terms are used.

1.4.5 Acquired immunity

When an infected host recovers from an infection, it usually maintains certain degree of immunity against reinfection from the same stain of pathogens. If the infection has caused a humoral immune response, antibodies produced by the host usually remain in the body for a period of time and guard the body from the same antigens. Memory T lymphocytes of the immune system has the ability to remember the antigens they are specifically created for, and they live long after the infection for the purpose to mount a much quicker immune response when the same pathogenic antigen is recognized. Mild immune responses can also be induced by inoculation or immunization so that the body is stocked with the right kind of antibodies or memory T cells to fight the infection.

Without exposure to reinfection, immunity again a specific infection will wane and eventually disappear. Certain diseases such as measles are known to cause a permanent immunity in humans so that no reinfection occurs once recovered. In terms of compartment models, loss of immunity results in a transfer of recovered individuals to the susceptible compartment, as depicted in the following figure, in which we assume the rate is proportional to the number of recovered individuals.



Other assumptions on the rate of transfer can be made according to our discussions in Section 1.4.1.

1.4.6 Route of transmission: horizontal and vertical

In the Kermack-McKendrick model, the infection is assumed to be through direct contact of an infectious and a susceptible host. This is often called *horizontal transmission*. Other modes of transmissions exist for many diseases. One of them is *vertical transmission* in which the pathogens are passed to a newborn or newly born directly from an infected mother. Example of diseases that can be transmitted vertically include HIV/AIDS, Chargas' disease, and Hepatitis B. To model vertical transmission, we assume that a fraction p of the newborns from infected population becomes infected at birth, and the remaining fraction $(1-p)$ are susceptible. The following diagram illustrates a case with both horizontal and vertical transmissions.

Here, bN is the total newborns with natural birth rate b, pbI is the number of newborns who are infected at birth, $bN-pbI$ is the number of healthy but susceptible

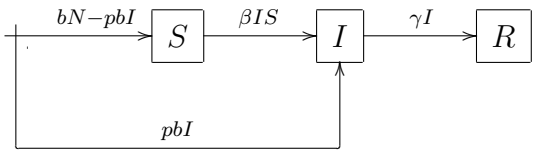


Figure 1.9: Transfer diagram for a SIR model with vertical transmission

newborns. The resulting model is described by the following system of differential equations.

$$\begin{aligned} S'(t) &= bN(t) - pbI(t) - \beta I(t)S(t) \\ I'(t) &= pbI(t) + \beta I(t)S(t) - \gamma I(t) \\ R'(t) &= \gamma I(t). \end{aligned} \tag{1.27}$$

A good reference for mathematical modeling of vertically transmitted diseases is the book by Busenberg and Cooke [3].

1.4.7 Heterogeneity: age, spatial, social, infectivity, multiple hosts, and disease vectors

The Kermack-McKendrick model considers a single homogeneous host population. In reality, host populations are far from being homogeneous. Many characteristics of the host population contribute to heterogeneity: vulnerability to a particular disease and its case fatality generally varies greatly among different age groups; certain social groups may have much higher incidence of sexually transmitted diseases than the general population; different ethnical groups may have different susceptibility to certain diseases. An important environmental factor for the great inhomogeneity of disease transmission is the spatial spread; an infectious disease typically starts from an outbreak in a location and spread elsewhere. For vector-borne diseases and diseases that involve several hosts, there exists the inhomogeneity between the disease vector, intermediate host and the host. These factors need to be incorporated into a mathematical model to realistically represent the disease transmission process. In this section, we will discuss how to incorporate age structures into our basic model. Addition of other factors will be discussed in later chapters.

Let $S(a,t), I(a,t)$, and $R(a,t)$ be the number of individuals who are susceptible, infectious, and recovered at age a and time t, respectively. Here a, t are considered as independent variables. The rate of change of the population in each compart-

ment should account for changes due to time, as we have seen in Section 1.2, and changes due to age, which are described as partial derivatives with respect to a: $\frac{\partial S(a,t)}{\partial a}$, $\frac{\partial I(a,t)}{\partial a}$, and $\frac{\partial R(a,t)}{\partial a}$, respectively. The Kermack-McKendrick model with age structure becomes a system of partial differential equations

$$\begin{aligned}
\frac{\partial S(a,t)}{\partial t} + \frac{\partial S(a,t)}{\partial a} &= -\int_0^\infty \beta(a,b)I(b,t)db\, S(a,t) \\
\frac{\partial I(a,t)}{\partial t} + \frac{\partial I(a,t)}{\partial a} &= \int_0^\infty \beta(a,b)I(b,t)db\, S(a,t) - \gamma(a)I(a,t) \\
\frac{\partial S(a,t)}{\partial t} + \frac{\partial S(a,t)}{\partial a} &= \gamma(a)I(a,t).
\end{aligned} \tag{1.28}$$

Birth terms will appear as boundary conditions at $a = 0$:

$$\begin{aligned}
S(0,t) &= \int_{a_0}^\infty [b(a)N(t,a) - p(a)b(a)I(t,a)\,]da, & S(a,0) &= \psi(a), \\
I(0,t) &= \int_{a_0}^\infty p(a)b(a)I(t,a)\,da, & I(a,0) &= \phi(a), \\
R(0,t) &= 0, & R(0,a) &= \xi(a).
\end{aligned} \tag{1.29}$$

Here, parameter $b(a)$ denotes the birth rate for populations at age a, and $p(a)$ is the fraction of infective newborns from populations at age a. The term $p(a)b(a)I(t,a)$ in the boundary conditions is due to vertical transmission, and $(\psi(a), \phi(a), \xi(a))$ denotes the initial age distribution. The age dependent force of infection is given by

$$\lambda(a,t) = \int_0^\infty \beta(a,b)I(b,t)db,$$

where $\beta(a,b)$ is the transmission coefficients from the subpopulation at age b to the subpopulation at age a.

For discussions and analysis of age structured epidemic models, see [11, 12, 22].

1.4.8 Disease control and prevention measures: immunization and quarantine

Apart from medical treatment, two most effective and commonly used preventive and control measures for infectious diseases are immunization and quarantine.

An effective vaccine can protect an otherwise susceptible host against possible infection. By immunizing a large portion of the susceptible host population before

or at the beginning of a disease outbreak, we can reduce the initial number S_0 of susceptibles to a level that is below the threshold $\frac{\gamma}{\beta}$, and by our threshold result in Section 1.3, a full-blown epidemic can be prevented. From a compartmental modeling viewpoint, vaccination moves susceptibles directly to the recovered compartment without going through the I compartment. If we assume that a fraction p of all susceptibles are vaccinated, then we arrive at the the transfer diagram in Figure 1.10 and a system of differential equations

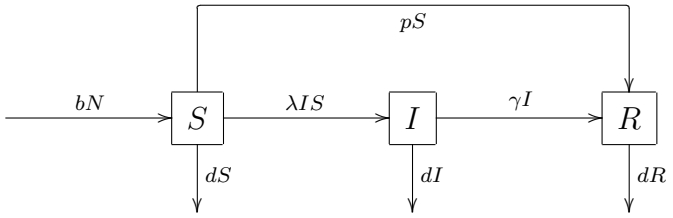


Figure 1.10: Transfer diagram for a SIR compartment model with vaccination

$$\begin{aligned} S' &= bN - \lambda IS - dS - pS \\ I' &= \lambda IS - (d+\gamma)I \\ R' &= pS + \gamma I - dR \\ N &= S + I + R \end{aligned} \tag{1.30}$$

One of the issues with vaccination is that a vaccine can be "leaky", namely, the immune protection on hosts can wane in time and hosts can gradually become susceptible again. To model a leaky vaccine, a new compartment V of vaccinated hosts can be added, and we obtain the transfer diagram in Figure 1.11

Here δ is the rate constant for vaccine waning. A set of differential equations can be readily written down based on the transfer diagram.

Quarantine is a measure that isolate infectious individuals and hence prevent them from the infecting others. This can slow down and even stop the transmission process. We introduce a new compartment Q for the quarantined individuals, and assume that quarantine is carried out in such a way that a fraction p of infectious individuals will be isolated. A simple transfer diagram is depicted in Figure 1.12.

Here δ is the rate constant for the recovery of quarantined individuals.

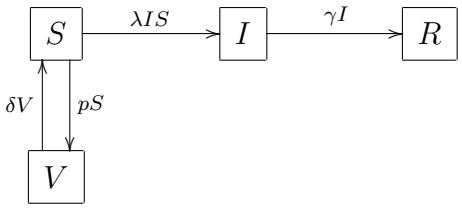


Figure 1.11: A vaccination model with a leaky vaccine

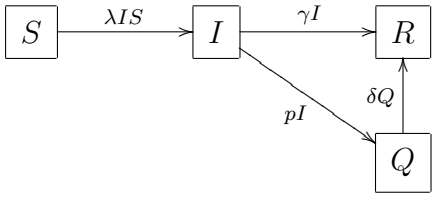


Figure 1.12: A SIR model with quarantine

1.4.9 The basic reproduction number $\mathcal{R}_0$

The basic reproduction number $\mathcal{R}_0$, also called the basic reproductive number or the basic reproductive ratio, is the single most important parameter in epidemic modeling. It measures the average number of the secondary infections caused by a single infective in an entirely susceptible population during its whole infectious period.

In the context of Kermack-Mckendrick model, $\mathcal{R}_0$ can be expressed as

$$\lambda \cdot S_0 \cdot \gamma$$

which can be interpreted as

average # of effective contact of a single infective	$\cdot$	initial susceptible population	$\cdot$	mean infectious period

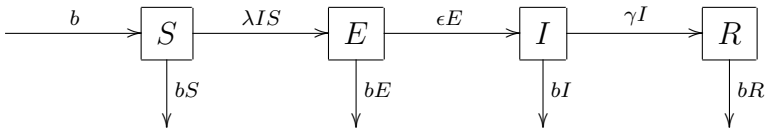
Using $\mathcal{R}_0$, the threshold phenomenon described in Section 1.3 can be expressed as follows:

If $\mathcal{R}_0 < 1$, then epidemics will not occur;

If $\mathcal{R}_0 > 1$, an epidemic will occur.

We will see that threshold in this form occurs in many epidemic models.

For a transfer diagram the basic reproduction number is given by



$$\mathcal{R}_0 = \lambda \cdot \frac{\epsilon}{\epsilon + b} \cdot \frac{1}{\gamma + b},$$

which can be interpreted as

average # of effective contact of a single infective	$\cdot$	probability of the new infective survives the latent period	$\cdot$	mean infectious period

Note here that the mean infectious period $\frac{1}{\gamma+b}$ is understood as the mean period an individual remains infective and alive. We also note that the initial susceptible population does not appear in $\mathcal{R}_0$. The reason for this is that, in this model, the total population $N = S + E + I + R$ remains a constant and is scaled to 1.

When models get more complicated, $\mathcal{R}_0$ may be harder to derive directly from the transfer diagram. Other methods for deriving $\mathcal{R}_0$ exists. Most of them is based on the stability analysis of the disease-free equilibrium. In later chapters, we will illustrate various ways to derive and interpret $\mathcal{R}_0$.

For more detailed description and discussions on the basic reproduction number for epidemic models, we refer the reader to [1, 2, 5, 6, 9, 18, 20]. A practical approach to the computation of $\mathcal{R}_0$ for complex epidemic models is given in [19].

Chapter 2

Mathematical Analysis of Epidemic Models: Five Classic Examples

2.1 Kermack-McKendrick model

In this section we carry out detailed mathematical analysis and derive various important properties of solutions to the Kermack-McKendrick model

$$\begin{aligned} \frac{dS}{dt} &= -\beta IS \\ \frac{dI}{dt} &= \beta IS - \gamma I \\ \frac{dR}{dt} &= \gamma I, \end{aligned} \tag{2.1}$$

with initial conditions $S(0) = S_0 > 0, I(0) = I_0 > 0, R(0) = R_0 \geq 0$.

2.1.1 Simple properties of solutions

Property 1. Model (2.1) is well posed.

By well-posedness we mean that nonnegative initial conditions lead to nonnegative solutions, namely, $S_0 \geq 0, I_0 \geq 0, R_0 \geq 0$ imply $S(t) \geq 0, I(t) \geq 0, R(t) \geq 0$ for $t \geq 0$. Another way to describe this is that the positive cone of $\mathbb{R}^3$

$$\mathbb{R}^3_+ = \{\, (S, I, R) \in \mathbb{R}^3 \mid S \geq 0, I \geq 0, R \geq 0 \,\} \tag{2.2}$$

is positively invariant with respect to (2.1).

The positive invariance of $\mathbb{R}^3_+$ can be verified by examining the direction of the vector field $(-\beta IS, \beta IS - \gamma I, \gamma I)$ of (2.1) on each coordinate plane. We want to show the vector field is either tangent to the coordinate or pointing to the interior of $\mathbb{R}^3_+$.

On the SR-plane: $I = 0$ on this plane, and

$$\frac{dI}{dt}\Big|_{I=0} = 0.$$

This shows that the vector field on the SR-plane is tangent to the SR-plane. This also implies that the SR-plane itself is invariant – solutions starting on the SR-plane remain on the plane. Biologically, this means that if there is no infection at the beginning, there remains no infection.

On the IR-plane: $S = 0$ on this plane, and

$$\frac{dS}{dt}\Big|_{S=0} = 0.$$

Therefore, the IR-plane is also invariant. No solutions in the interior of $\mathbb{R}^3_+$ can escape through the IR-plane or the SR-plane.
On the SI-plane: $R = 0$ on this plane, and

$$\frac{dR}{dt}\Big|_{R=0} = \gamma I \geq 0.$$

Therefore, the vector field on the SI-plane point to the interior of $\mathbb{R}^3_+$. No solutions can escape the interior through the SI-plane. We thus have shown that all solutions starting in $\mathbb{R}^3_+$ remain in $\mathbb{R}^3_+$ for $t > 0$.
Property 2. Total population is constant.

Let $N(t) = S(t) + I(t) + R(t),\ N_0 = S_0 + I_0 + R_0$. Adding all three equations in (2.1) we obtain

$$N'(t) = 0 \quad \text{for all } t \geq 0$$

which implies $N(t) = N_0$ for all $t \geq 0$.
Property 3. Solutions to (2.1) exist for $t \in (-\infty, +\infty)$.

From Properties 1 and 2 we know that solutions $(S(t), I(t), R(t))$ are bounded in its maximal interval of existence. Fundamental theory of ODE tells us that solutions can be extended for all time.
Property 4. Limits $S(\infty) = \lim_{t\to\infty} S(t)$, $I(\infty) = \lim_{t\to\infty} I(t)$, $R(\infty) = \lim_{t\to\infty} R(t)$ exist.

From (2.1) we know

$$S'(t) = -\beta I(t)S(t) \leq 0.$$

Therefore, $S(t)$ is decreasing and bounded below by 0, and thus $S(\infty) \geq 0$ exists. Similarly

$$R'(t) = \gamma I(t) \geq 0$$

implies that $R(t)$ increases and bounded above by N_0. Therefore, $R(\infty) \geq 0$ exists. From

$$I(t) = N_0 - S(t) - R(t)$$

we know that $I(\infty) = N_0 - S(\infty) - R(\infty) \geq 0$ exists.
Property 5. $S_0 > 0, I_0 > 0$ imply $0 < S(\infty) < S_0$ and $I(\infty) = 0$.

With loss of generality we may assume that $S_0 > 0, I_0 > 0, R_0 = 0$, since otherwise, we may choose $\overline{N}_0 = N_0 - R_0$. Then $S(t) > 0, I(t) > 0, R(t) > 0$ for $t > 0$. Dividing equations for S and R, we have

$$\frac{dS}{dR} = -\frac{\beta}{\gamma} S.$$

Solving this equation for S we obtain

$$S(R) = S_0 e^{-\frac{\beta}{\gamma}R} \geq S_0 e^{-\frac{\beta}{\gamma}N_0} > 0. \tag{2.3}$$

Therefore, $0 < S(\infty) < S_0$.

From the S equation and the fact that $S(\infty), I(\infty)$ exist we know

$$\lim_{t\to\infty} S'(t) = -\beta I(\infty)\, S(\infty) \quad \text{exists.}$$

Furthermore $\lim_{t\to\infty} S'(t) = 0$. Otherwise if $\lim_{t\to\infty} S'(t) = \alpha < 0$, then $S'(t) < \alpha/2$ for $t \geq T$, and thus

$$S(t) < S_0 + \frac{\alpha}{2}t < 0 \quad \text{for } t > -\frac{2S_0}{\alpha}.$$

This contradicts $S(t) > 0$ for all $t > 0$. Therefore $S(\infty)I(\infty) = 0$ and $S(\infty) > 0$, which implies $I(\infty) = 0$.

We can draw the following two important conclusions based on these properties.

(1) The disease eventually dies out. The model describes an epidemic disease.

(2) There is always a fraction $S(\infty)/S_0$ of susceptibles that escape infection. The epidemic does not stop because of exhaustion of susceptibles.

2.1.2 Phase portrait in the SI-plane: epidemic curves

For a better understanding of solutions, we will try to view them in the SI-plane. Consider only the S, I equations

$$\begin{aligned} \frac{dS}{dt} &= -\beta IS \\ \frac{dI}{dt} &= \beta IS - \gamma I \end{aligned} \tag{2.4}$$

in the first quadrant of the SI-plane. Dividing the two equations we obtain

$$\frac{dI}{dS} = -1 + \frac{\gamma}{\beta S} = -1 + \frac{\rho}{S}, \tag{2.5}$$

where $\rho = \gamma/\beta$ is the threshold number for S_0. Integrating (2.5) we obtain

$$I = -S + \rho \log S + C. \tag{2.6}$$

Here C is an constant to be determined from S_0, I_0. This implies that trajectories $(S(t), I(t))$ of system (2.4) are given by the family of curves defined by (2.6). These curves are depicted in Figure 2.1.

We can observe several characteristics of the phase curves.

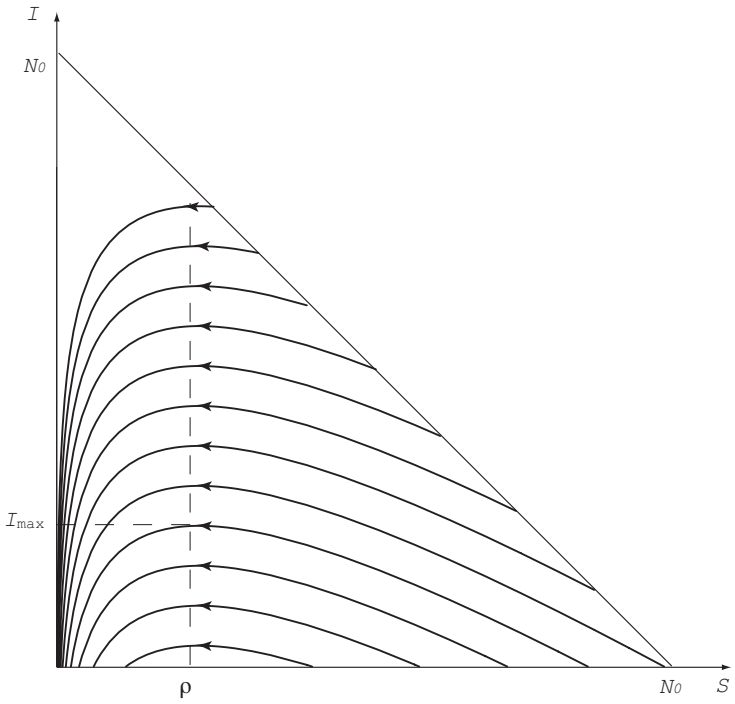


Figure 2.1: Family of epidemic curves

(1) The maximum value of I, $I_{\max}$, is achieved when $S = \rho$ – the threshold value. This fact is also clear from the equation of I, since $I' = 0$ if and only if when $S = \rho$, and $S = \rho$ is a critical point for I.

(2) If $S < \rho$, then $I(t)$ decreases monotonically and no epidemic occurs.

(3) If $S_0 > \rho$, then $I(t)$ initially increases monotonically until $S = \rho$, and then as $S(t)$ decreases past ρ, $I(t)$ will decrease to 0.

Clearly, cases (2) and (3) confirm the threshold phenomenon we have observed in Section 1.3

2.1.3 Final size formula and severity of epidemics

Rewrite (2.6) as

$$\phi(S, I) = S + I - \rho \log S = c. \tag{2.7}$$

Assume that $I_0 \approx 0$. From

$$\phi(S_0, 0) = \phi(S_\infty, 0),$$

we obtain

$$S_0 - S_\infty = \rho(\log S_0 - \log S_\infty), \tag{2.8}$$

and

$$\rho = \frac{S_0 - S_\infty}{\log S_0 - \log S_\infty}. \tag{2.9}$$

Note that S_∞ gives the number of susceptible individuals who escape the epidemics, and can be used as an indicator of the severity of the epidemics. Equation (2.8) is often called the *final size equation*. If the basic reproduction number $\mathcal{R}_0 = \frac{S_0}{\rho} = \frac{\beta}{\gamma} S_0$ is known for a disease, then equation (2.8) can be used to estimate the final size S_∞. On the other hand, after an epidemic, the final size S_∞ is known, and equation (2.9) can be used to estimate the basic reproductions number $\mathcal{R}_0$, which will leads to an estimate of the transmission rate β.

The severity of an epidemic can also be measured in terms of the accumulated number of infected individuals, also called the size of an epidemic

$$\text{size of epidemic} = S_0 - S_\infty. \tag{2.10}$$

If we know that $R(0) = 0$ and $I(0) \approx 0$, then we have

$$S_0 - S_\infty = R_\infty. \tag{2.11}$$

This relation is clear from biological interpretation. It can also be derived mathematically. Dividing equations of S and R in (2.1) we have

$$-\rho \frac{dS}{S} = dR.$$

Integrating both sides and using the final size formula (2.8) we obtain

$$\rho(\log S_0 - \log S_\infty) = R_\infty = S_0 - S_\infty.$$

A third way to measure the severity of an epidemic is the maximum number of the infected, $I_{\max}$, which can be used to prepare sufficient hospital capacity. From relation (2.6) we obtain

$$c = I_0 + S_0 - \rho \log S_0 = N_0 - \rho \log S_0,$$

and thus

$$I = -S + \rho \log S + N_0 - \rho \log S_0. \tag{2.12}$$

Since $\frac{dI}{dS} = 0 \iff S = \rho$, we can derive

$$I_{\max} = I(\rho) = -\rho + \rho \log \rho + N_0 - \rho \log S_0. \tag{2.13}$$

Once the basic reproduction number $\mathcal{R}_0 = \frac{S_0}{\rho}$ is estimated, $I_{\max}$ can be estimated from this relation.

2.1.4 Kermack-McKendrick Threshold Theorem

To arrive a their now famous threshold theorem, Kermack and McKendrick obtained approximate solutions of (2.1). Using $S + I + R = N_0$, the R equation in (2.1) can be rewritten as

$$\frac{dR}{dt} = \gamma(N_0 - R - S).$$

Using relation (2.3), $S(R) = S_0 e^{-R/\rho}$, we obtain

$$\frac{dR}{dt} = \gamma(N_0 - R - S_0 e^{-\frac{R}{\rho}}). \tag{2.14}$$

To solve (2.14), we expand $e^{-R/\rho}$ at $R = 0$ up to the second order and obtain

$$\frac{dR}{dt} = \gamma\Big[N_0 - S_0 + \Big(\frac{S_0}{\rho} - 1\Big)R - \frac{S_0}{2\rho^2}R^2\Big]. \tag{2.15}$$

Solving this equation we obtain

$$R(t) = \frac{\rho^2}{S_0}\Big[\frac{S_0}{\rho} - 1 + \alpha \tanh(\frac{1}{2}\alpha\gamma t - \phi)\Big], \tag{2.16}$$

where

$$\begin{aligned} \alpha &= \Big[\Big(\frac{S_0}{\rho} - 1\Big)^2 + \frac{2S_0 I_0}{\rho^2}\Big]^{\frac{1}{2}}, \\ \phi &= \tanh^{-1}\frac{1}{\alpha}\Big(\frac{S_0}{\rho} - 1\Big). \end{aligned} \tag{2.17}$$

Therefore

$$\frac{dR}{dt} = \frac{\gamma\alpha^2\rho^2}{2S_0}\mathrm{sech}^2\Big(\frac{1}{2}\alpha\gamma t - \phi\Big). \tag{2.18}$$

If $I_0 \approx 0$ and $S_0 > \rho$, then we have from (2.17), $\alpha = \frac{S_0}{\rho} - 1$, and from (2.16)

$$R(t) = \frac{\rho^2}{S_0}\Big(\frac{S_0}{\rho} - 1\Big)\Big[1 + \tanh\Big(\frac{\gamma}{2}(\frac{S_0}{\rho} - 1)t + \phi\Big)\Big]. \tag{2.19}$$

Letting $t \to \infty$ we obtain an approximate value for the size $R_\infty = S_0 - S_\infty$ of the epidemic

$$R_\infty = 2\rho\Big(1 - \frac{\rho}{S_0}\Big). \tag{2.20}$$

If we write $S_0 = \rho + \nu$ for $\nu > 0$, then

$$\begin{aligned} R_\infty &= 2\rho\Big(1 - \frac{\rho}{\rho+\nu}\Big) = 2\rho\frac{\nu}{\rho+\nu} \\ &= 2\nu\frac{\rho}{\rho+\nu} \approx 2\nu. \end{aligned}$$

Namely, the size of the epidemic is roughly 2ν. Therefore,

$$S_\infty = S_0 - R_\infty = \rho + \nu - 2\nu = \rho - \nu.$$

This relation leads to the following threshold theorem of Kermack-McKendrick.

Theorem 2.1.1 (Threshold Theorem) (1) *An epidemic occurs if and only if S_0 exceeds the threshold ρ.*

(2) *If $S_0 = \rho + \nu$, then after the epidemic, the susceptibles is reduced by an amount of approximately 2ν, namely, $S_\infty \approx \rho - \nu$.*

If all cases in an epidemic terminate in death, then R can be considered as the removed class, and $\frac{dR}{dt}$ will be the rate for disease death. This can be fitted to the weekly death register data. Kermack and McKendrick used relation (2.18) to fit the data from Bubonic plague in Bombay in 1905-06. As shown in Figure 2.2, it is an exceptionally good fit.

Figure 2.2: Bubonic plague in Bombay in 1905-06

Exact solutions to (2.1) were obtained by Kendall in 1956. In present days, numerical solutions can be easily obtained using computer software and are used to fit the data.

Exercise Solve equation (2.14).

2.2 A model for disease with no immunity

Consider an infectious disease that confers no immunity. Ignoring demographics and latency, we have the following transfer diagram

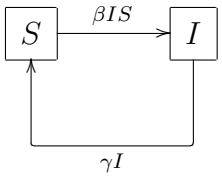


Figure 2.3: Transfer diagram for a SIS model

Infected individuals return to the susceptible compartment upon recovery. This type of models are called SIS models. The equations are

$$\begin{aligned} S'(t) &= -\beta IS + \gamma I \\ I'(t) &= \beta IS - \gamma I \end{aligned} \tag{2.21}$$

Initial conditions are $S(0) = S_0, I(0) = I_0$. As we have seen in previous sections, $N = S + I = N_0 = S_0 + I_0$. We will see that, in this model, there will be two possible outcomes for an initial outbreak: it either terminates or becomes endemic. To see this, we replace $S = N_0 - I$ in the second equation and obtain

$$I' = \beta I(N_0 - I) - \gamma I = (\beta N_0 - \gamma - \beta I)I,$$

or

$$I' = (\beta N_0 - \gamma)I\Big(1 - \frac{I}{N_0 - \frac{\gamma}{\beta}}\Big). \tag{2.22}$$

Let

$$f(I) = (\beta N_0 - \gamma)I\Big(1 - \frac{I}{N_0 - \frac{\gamma}{\beta}}\Big). \tag{2.23}$$

Then the differential equation (2.22) can be written as

$$I' = f(I). \tag{2.24}$$

We will show that properties of solutions to (2.24) can be largely determined from the graph of $f(I)$, which is depicted in Figure 2.4, using a procedure called the *phase-line analysis*. The basic ideas of the phase-line analysis is as follows: since solutions

of an ODE in the form of (2.24) can only move along a straight line and solutions can self intersect, we know each solution $I(t)$ is either monotonically increasing ($I'(t) > 0$) or monotonically decreasing ($I'(t) < 0$). From (2.24) we also know that the sign of $I'(t)$ can be determined by the graph of f: in an interval on the I-axis where $f(I) > 0$, solutions are increasing and moving to the right; in an interval where $f(I) < 0$, solutions are decreasing and moving to the left. These situations are depicted in Figure 2.4 in which the arrows on the I-axis denote the direction solutions are moving. Equilibria of (2.24) are solution that do not depend on t, and hence are points where $f(I) = 0$ or where the graph of f intersects the I-axis. If the arrows on either side of an equilibrium I^* are moving towards I^*, then solutions near I^* are convergent to I^*, and thus I^* is asymptotically stable. On the other hand, if the arrows are moving away from I^*, then I^* is a unstable equilibrium.

If we apply the phase-line analysis to (2.24) with $f(I)$ given in (2.23), we see that the graph of f has two possible configurations, depending on the sign of $\beta N_0 - \gamma$, see Figure 2.4 (a) and (b). Based on Figure 2.4, we arrive at the following result.

Proposition 2.2.1 (1) *If* $\frac{\beta N_0}{\gamma} < 1$, *then, for any* $0 < I_0 < N_0$, $I(t) \to 0$ *monotonically as* $t \to \infty$.

(2) *If* $\frac{\beta N_0}{\gamma} > 1$, *then, for any* $0 < I_0 < N_0$, $I(t) \to N_0 - \frac{\gamma}{\beta}$ *monotonically as* $t \to \infty$.

(Proof is left as an exercise)

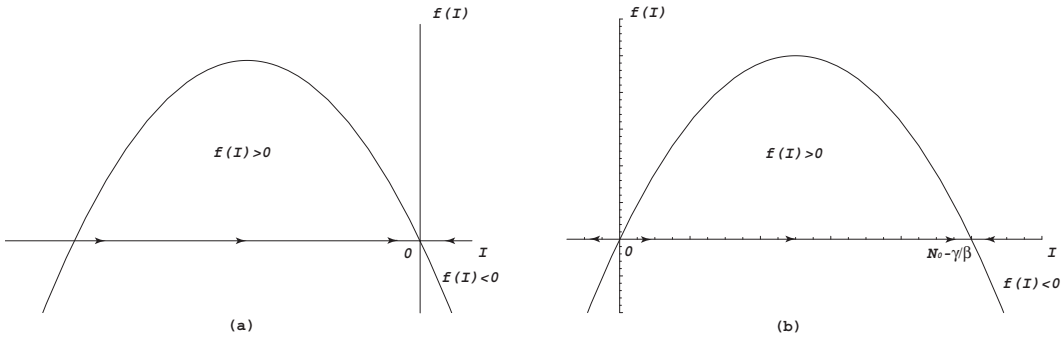


Figure 2.4: Graphical demonstration of phase-line analysis.

Recall that $\mathcal{R}_0 = \frac{\beta N_0}{\gamma}$ denotes the basic reproduction number. Proposition 2.2.1 can be reinterpreted as follows for solutions $(S(t), I(t))$ of (2.21).

(1) If $\mathcal{R}_0 < 1$, then $(S(t), I(t)) \to (N_0, 0)$ as $t \to \infty$.

(2) If $\mathcal{R}_0 > 1$, then $(S(t), I(t)) \to (\frac{\gamma}{\beta}, N_0 - \frac{\gamma}{\beta})$.

The two equilibria $P_0 = (N_0, 0)$ and $P^* = (\frac{\gamma}{\beta}, N_0 - \frac{\gamma}{\beta})$ are called the *disease-free equilibrium* and the *endemic equilibrium*, respectively. Summarize the preceding discussion, we arrive at a threshold theorem. Let

$$\Gamma = \{(S, I) \in \mathbb{R}^2_+ \mid S + I = N_0\}$$

be the feasible region.

Theorem 2.2.2 (1) *For each $N_0 > 0$, there are two possible equilibria in the feasible region Γ: the disease-free equilibrium $P_0(N_0, 0)$ and the endemic equilibrium $P^* = (\frac{\gamma}{\beta}, N_0 - \frac{\gamma}{\beta})$.*

(2) *If $\mathcal{R}_0 < 1$, then all solutions in Γ converge to P_0.*

(3) *If $\mathcal{R}_0 > 1$, then all solutions with $I_0 > 0$ converges to P^*.*

Biological interpretations:

1. The basic reproduction number $\mathcal{R}_0$ serves as a threshold parameter that determines the outcome of a initial outbreak.

2. For the same value of $\mathcal{R}_0$, the outcomes are the same for all initial conditions.

3. When $\mathcal{R}_0 < 1$, the disease dies out from the population. From the monotonicity of $S(t)$ and $I(t)$, we know that no epidemic will develop.

4. Because $(\frac{\gamma}{\beta}, N_0 - \frac{\gamma}{\beta})$ is an equilibrium, $S(t)$ stays only on one side of $\frac{\gamma}{\beta}$, and thus $I'(t) = I(t)(\beta S(t) - \gamma)$ does not change sign. As a consequence, $I(t)$ is monotone. See Figure 2.5

Exercise. Consider an ODE in $\mathbb{R}^n$,

$$x' = f(x)$$

and assume that f is a C^1 function. Suppose a solution $x(t) \to \overline{x}$ as $t \to \infty$. Show $\overline{x}$ is an equilibrium, i.e., $f(\overline{x}) = 0$.

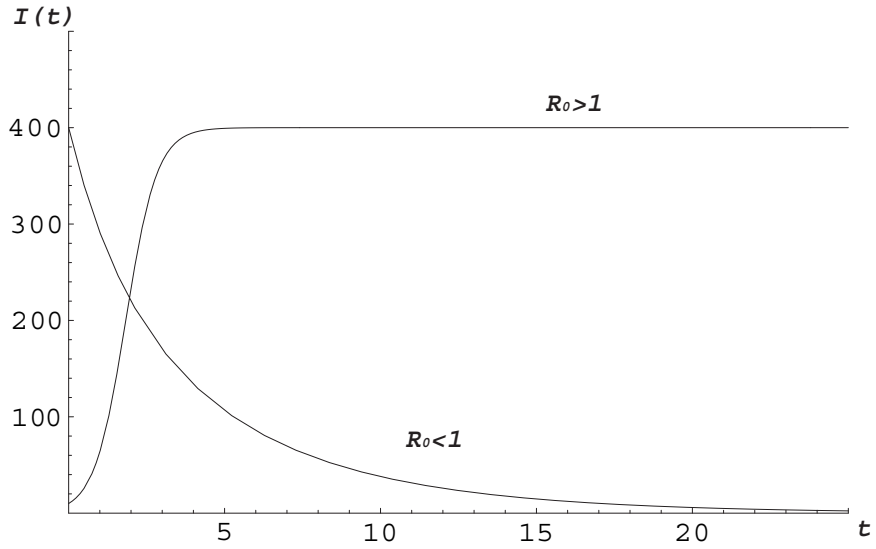


Figure 2.5: Time plots of $I(t)$.

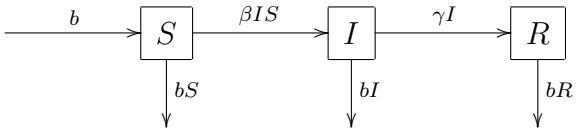


Figure 2.6: Transfer diagram for a Kermack-McKendrick model with demography

2.3 A model with demography

Consider the following Kermack-McKendrick model with demography.

Here, the birth and death processes are assumed to have the same rate constant b, and the disease is not fatal, so the total population is kept as a constant, which is scaled to be 1. The differential equations are

$$\begin{aligned} S' &= b - \beta IS - bS \\ I' &= \beta IS - \gamma I - bI \\ R' &= \gamma I - bR. \end{aligned} \tag{2.25}$$

The feasible region for (2.25) is

$$G = \{(S, I, R) \in \mathbb{R}^3_+ \mid S + I + R = 1\}.$$

We would like to know if the threshold theorem in the previous section still holds for this model, with the basic reproduction number $\mathcal{R}_0 = \frac{\beta}{\gamma+b}$. Because of the conservation law $S + I + R = 1$, we will be able to reduce the number of equations by 1. System (2.25) is in fact a 2-dimensional system. To simplify our analysis, we can ignore the R equation since the first two equations in (2.25) do not contain R. Once behaviours of $(S(t), I(t))$ are known, those of $R(t)$ can be readily obtained from $R = 1 - S - I$. For this reason, we can consider the following equivalent system

$$\begin{aligned} S' &= b - \beta IS - bS \\ I' &= \beta IS - \gamma I - bI \end{aligned} \tag{2.26}$$

in a 2-dimensional feasible region

$$\Gamma = \{(S, I) \in \mathbb{R}^2_+ \mid 0 \le S + I \le 1\}.$$

2.3.1 Disease-free and endemic equilibria

Based on our experience in Section 2.3, long-time outcomes of the disease are manifested in the form of equilibria, or solutions that do not change in time. To find equilibria of (2.26), we set $S' = I' = 0$ and obtain

$$\begin{aligned} b - \beta IS - bS &= 0 \\ \beta IS - \gamma I - bI &= 0. \end{aligned} \tag{2.27}$$

Solving these equations, we obtain two possible equilibria: $P_0 = (1, 0)$, the disease-free equilibrium, and $P^* = (S^*, I^*)$, the endemic equilibrium, where

$$S^* = \frac{b+\gamma}{\beta}, \quad I^* = \frac{b[\beta - (b+\gamma)]}{\beta(b+\gamma)}.$$

Note that P^* falls outside of the feasible region Γ if $\mathcal{R}_0 = \frac{\beta}{b+\gamma} < 1$, and coincides with P_0 when $R_0 = 1$. We have the following conclusion.

Proposition 2.3.1 *System* (2.26) *has two possible equilibria.*

(1) *If* $\mathcal{R}_0 \le 1$, *then* $P_0 = (1, 0)$ *is the only equilibrium in* Γ.

(2) *If* $\mathcal{R}_0 > 1$, *then both* P_0 *and the endemic equilibrium* P^* *exist in* Γ.

2.3.2 Local stability analysis of equilibria

Local stability of P_0 and P^* determine the disease outcomes when initial conditions are close to the equilibrium. A standard method of investigating local stability is by the method of linearization, as explained in Section 3.2 of Chapter 3.
1. Stability of P_0. The Jacobian matrix of (2.26) at P_0 is

$$J(P_0) = \begin{bmatrix} -b & -\beta \\ 0 & \beta - (b+\gamma) \end{bmatrix},$$

which has two eigenvalues $\lambda_1 = -b, \lambda_2 = \beta - (b+\gamma)$. Therefore, P_0 is locally asymptotically stable if $\lambda_2 < 0$, or if $\mathcal{R}_0 < 1$, and P_0 is a saddle (unstable) if $\mathcal{R}_0 > 1$. When $\mathcal{R}_0 = 1$, $\lambda_2 = 0$. P_0 is no longer a hyperbolic equilibrium in this case, and the method of linearization is not applicable. The stability of P_0 when $\mathcal{R}_0 = 1$ will be dealt with using the method of Lyapunov function in Section 3.3.
2. Stability of P^*. The Jacobian matrix at $P^* = (S^*, I^*)$ is

$$J(P^*) = \begin{bmatrix} -\beta I^* - b & -\beta S^* \\ \beta I^* & 0 \end{bmatrix}.$$

Finding eigenvalues of this matrix is more involved than that of $J(P_0)$. We will use the Routh-Hurwitz conditions in Section 3.2 to determine the stability. Straightforward calculation leads to

$$\operatorname{tr}(J(P^*)) = -\beta I^* - b = -\frac{b}{S^*} < 0, \tag{2.28}$$

$$\det(J(P^*)) = \beta I^* S^* > 0, \quad \text{if } \mathcal{R}_0 > 1. \tag{2.29}$$

Therefore, by the Routh-Hurwitz criteria, we know that P^* is locally asymptotically stable if $\mathcal{R}_0 > 1$, or as long as it exists in Γ.

2.3.3 Bifurcation digram

We see in Sections 2.3.1 and 2.3.2 that the number of equilibria in Γ, together with their local stability, is determined by the values of R_0. Such a dependence can be depicted in a bifurcation diagram, as shown in Figure 2.7

We make the following observations about the bifurcation diagram.

1. For $0 < \mathcal{R}_0 < 1$, there is only one equilibrium, P_0, and it is asymptotically stable, as marked by a solid line.

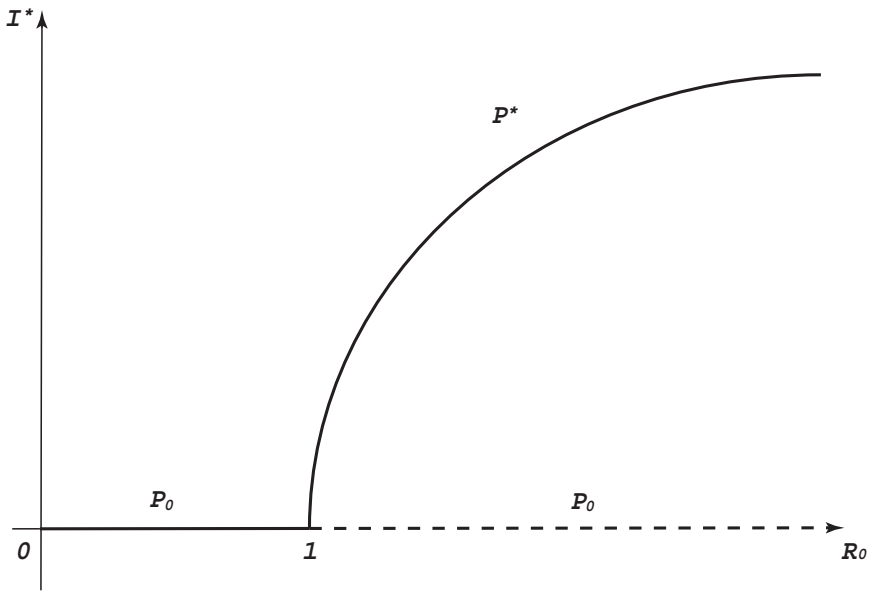


Figure 2.7: Bifurcation diagram for a Kermack-McKendrick model with demography

2. $\mathcal{R}_0 = 1$ is a bifurcation value; as $\mathcal{R}_0$ increases across 1, P_0 continues to exist and a new equilibrium P^* occurs. Furthermore, P_0 loses its stability when $\mathcal{R}_0 > 1$ and P^* gains stability as it gains its existence. P_0 is marked with a dashed line and P^* with a solid line.

The type of bifurcation shown in Figure 2.7 is called a *transcritical* bifurcation, a very common bifurcation that occurs in many epidemic models.

2.3.4 Establishing the global stability of P_0: the method of Lyapunov-LaSalle

As we have seen in Section 2.2, when $\mathcal{R}_0 < 1$, all solutions converge to the disease-free equilibrium P_0. We show that the same result holds for model (2.26). In this case, we say that P_0 is *globally stable* in the feasible region Γ. The method we use to show the global stability is the method of Lyapunov-LaSalle. Consider a Lyapunov function

$$L(S, I) = I.$$

Then its derivative along a solution $(S(t), I(t))$ is

$$\begin{aligned} \frac{dL}{dt} &= \frac{dI}{dt} = I(\beta S - \gamma - b) \leq I(\beta - \gamma - b) \\ &\leq 0, \quad \text{if } \mathcal{R}_0 \leq 1. \end{aligned} \tag{2.30}$$

Therefore, LaSalle's Invariance Principle ([]) implies that all limit points of solutions to (2.26) belong to the largest invariance set in

$$K = \{(S, I) \in \Gamma \mid \frac{dL}{dt} = 0\}.$$

From (2.30) we know that $\frac{dL}{dt} = 0$ if and only if either (1) $I = 0$ or (2) $\mathcal{R}_0 = 1$ and $S = \frac{\gamma+b}{\beta}$. In case (2), we necessarily have $S = \frac{\gamma+b}{\beta}, I = I^*$. In case (1), any solution of (2.26) staying in the set where $I = 0$ will satisfy $S' = b - bS$, and thus $S(t) \to 1$ as $t \to \infty$. In both cases, the only compact invariant set in the set K is the singleton $\{P_0\}$. This implies that all solutions in Γ converge to P_0. We can also show that the existence of the Lyapunov function L and the global convergence imply local stability of P_0. Therefore, we have shown that P_0 is globally stable in Γ when $\mathcal{R}_0 \leq 1$.

2.3.5 Establishing the global stability of P^*: phase-plane analysis

We now show that, if $\mathcal{R}_0 > 1$, all solutions with $I_0 > 0$ will converge to the endemic equilibrium P^*. For this goal, we will use the Poincaré-Bendixson theory in the following steps. Assume that $\mathcal{R}_0 > 1$.

Step 1 Show that system (2.26) has no nonconstant periodic solutions using the Bendixson-Dulac criteria (Theorem 3.6.5, Section3.6).

Step 2 By the Poincaré-Bendixson Theorem (Theorem 3.6.2, Section3.6) and the fact that P^* is the only equilibrium in the interior $\overset{\circ}{\Gamma}$ of Γ, all solutions with $I_0 > 0$ must have P^* as an omega limit point, and thus can get arbitrarily close to P^*.

Step 3 Since P^* is locally asymptotically stable, any solution that gets sufficiently close to P^* must converge to P^*. Therefore, all solutions with $I_0 > 0$ converge to P^*, and P^* is globally stable in $\overset{\circ}{\Gamma}$.

It only remains to show that (2.26) has no nonconstant solutions. Write (2.26) as

$$\begin{aligned} S' &= P(S,I) \\ I' &= Q(S,I). \end{aligned} \tag{2.31}$$

Let $\alpha(S,I) = \frac{1}{I}$ be a Dulac multiplier. Then

$$\begin{aligned} \frac{\partial}{\partial S}(\alpha P) + \frac{\partial}{\partial I}(\alpha Q) &= \frac{\partial}{\partial S}\Big(\frac{b}{I} - \beta S - \frac{bS}{I}\Big) + \frac{\partial}{\partial I}(\beta S - b - \gamma) \\ &= -\beta - \frac{b}{I} < 0, \quad \text{in } \overset{\circ}{\Gamma}. \end{aligned}$$

Therefore, the Bendixson-Dulac condition holds in $\overset{\circ}{\Gamma}$ and no nonconstant periodic solutions exist in $\overset{\circ}{\Gamma}$.

Summarizing the analysis in previous sections, we obtain the following threshold theorem.

Theorem 2.3.2 (1) *If $\mathcal{R}_0 \le 1$, the disease-free equilibrium is the only equilibrium in the feasible region Γ, and it is globally stable in Γ.*

(2) *If $\mathcal{R}_0 > 1$, then P_0 is unstable, and the endemic equilibrium P^* is globally stable in the interior $\overset{\circ}{\Gamma}$.*

Behaviours of solutions can be shown graphically in the SI-space, where each solution $(S(t), I(t)$ can be regarded as a parametric curve, called an *orbit*, starting from its initial point $(S(0), I(0))$. When the limiting behaviours of all orbits are shown, we obtain the *phase portrait* of system (2.25). The phase portraits of system (2.25) in both cases (a) and (b) established in Theorem 2.3.2 are depicted in Figure 2.8. The type of analysis employed in the section to establish the phase portraits is called the *phase-plane analysis*.

Exercise. Use the phase-plane analysis to prove a threshold theorem for the SIRS model depicted in the transfer diagram in Figure 2.9.

2.4 A SIR model with varying total population: homogeneous systems

Consider an SIR model whose transfer diagram is depicted in Figure 2.10. In the

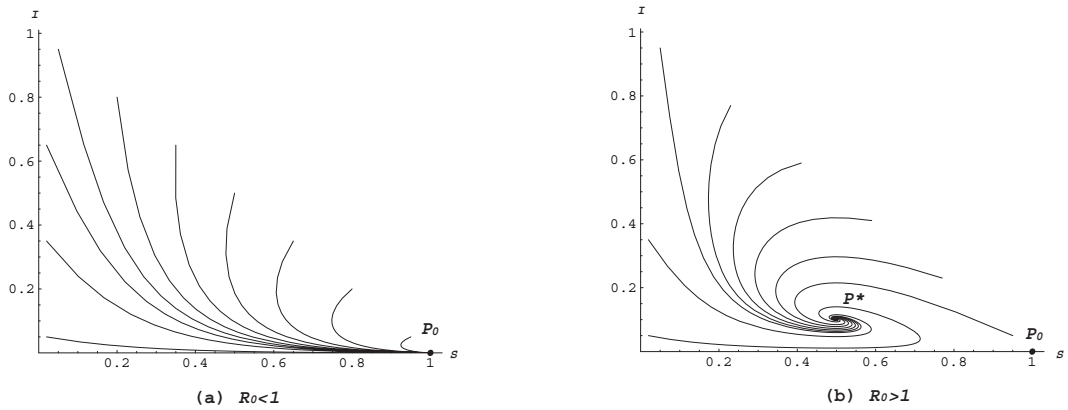


Figure 2.8: Phase portraits of an SIR model

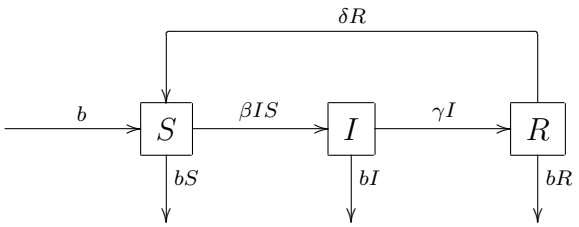


Figure 2.9: Transfer diagram for a SIRS model

model, $N = S + I + R$ denotes the total population. We assume that the birth process is in the form of bN, and the incidence is the standard incidence $\frac{\lambda IS}{N}$. The modeling equations are

$$\begin{aligned} S' &= bN - \frac{\lambda IS}{N} - dS \\ I' &= \frac{\lambda IS}{N} - \gamma I - dI \\ R' &= \gamma I - dR. \end{aligned} \tag{2.32}$$

The total population N satisfies

$$N' = (b - d)N \tag{2.33}$$

If $b \neq d$, then $N(t)$ varies with time t. Thus (2.32), unlike (2.25), can not directly reduced to a 2-dimensional system. However, (2.32) is a homogeneous system of

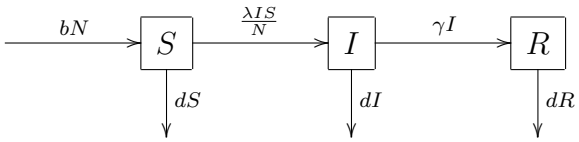


Figure 2.10: Transfer diagram for an SIR model

degree 1. This property allows us to transform it into a system that is reducible to 2 dimensions, and can be analyzed using the phase-plane analysis in Section 2.3. We first establish a general framework for homogeneous systems.

In general, a system in $\mathbb{R}^n$

$$x' = f(x), \quad x \in \mathbb{R}^n \tag{2.34}$$

is said to be *homogeneous of degree* 1 if $f(x)$ satisfies

$$f(\lambda x) = \lambda\, f(x), \quad \lambda > 0,\ x \in \mathbb{R}^n. \tag{2.35}$$

Examples of functions that satisfy (2.35) include

$$f(x) = Ax, \quad \text{where } A \text{ is an } n \times n \text{ matrix} \tag{2.36}$$

$$f(x_1, x_2) = \frac{x_1 x_2}{x_1 + x_2}, \quad (x_1, x_2) \in \mathbb{R}^2. \tag{2.37}$$

Proposition 2.4.1 (Euler Identity) *Suppose that $f(x)$ is homogeneous of degree 1, namely, $f(x)$ satisfies (2.35). Then*

$$\sum_{i=1}^{n} \frac{\partial f(x)}{\partial x_i}\, x_i = f(x). \tag{2.38}$$

Proof. Differentiating (2.35) with respect to λ we obtain

$$\sum_{i=1}^{n} \frac{\partial f(\lambda x)}{\partial x_i}\, x_i = f(x).$$

Setting $\lambda = 1$ we obtain the Euler Identity.

Suppose that (2.34) represents a biological model for which the positive cone $\mathbb{R}^n_+$ is positively invariant. Then the homogeneity of f allows us to introduce a set of new variables

$$y_i = \frac{x_i}{N}, \quad i = 1, 2, \cdots, n,$$

where $N = x_1 + x_2 + \cdots + x_n \neq 0$, and $x_i \geq 0$. Then $y = (y_1, \cdots, y_n) \in \mathbb{R}^n_+ \setminus \{0\}$ satisfies

$$\begin{aligned} y' &= \frac{x'}{N} - \frac{x}{N^2} N' = \frac{1}{N} f(x) - \frac{x}{N^2} \sum_{i=1}^n f_i(x) \\ &= f\Big(\frac{x}{N}\Big) - \frac{x}{N} \sum_{i=1}^n f_i\Big(\frac{x}{N}\Big) \quad \text{(by (2.35))} \\ &= f(y) - y \sum_{i=1}^n f_i(y). \end{aligned}$$

Namely,

$$y' = f(y) - y \sum_{i=1}^n f_i(y), \tag{2.39}$$

and

$$\sum_{i=1}^n y_i = 1. \tag{2.40}$$

System (2.39) is the projection of (2.34) onto the hyperplane (simplex) $\sum_{i=1}^n y_i = 1$, so it is of dimension $n - 1$.

Back to our model (2.32). It is straightforward to verify that

$$f(S, I, R) = \Big(bN - \frac{\lambda IS}{N} - dS, \frac{\lambda IS}{N} - (d + \gamma)I, \gamma I - dR\Big)$$

with $N = S + I + R$ is homogeneous of degree 1. Let

$$s = \frac{S}{N}, \quad i = \frac{I}{N}, \quad r = \frac{R}{N}. \tag{2.41}$$

Then, we can write a system for the fractional variables (s, i, r) following (2.39), or derive the system by direct differentiation. For instance,

$$\begin{aligned} s' &= \frac{S'}{N} - \frac{S}{N^2} N' = \frac{1}{N}\Big(bN - \frac{\lambda IS}{N} - dS\Big) - \frac{S}{N^2}(b - d)N \\ &= b - \lambda is - ds - s(b - d) = b - \lambda is - bs. \end{aligned}$$

Equations for i and r can be derived similarly. Therefore, we obtain

$$\begin{aligned} s' &= b - \lambda is - bs \\ i' &= \lambda is - (b+\gamma)i \\ r' &= \gamma i - br \end{aligned} \tag{2.42}$$

with

$$s + i + r = 1. \tag{2.43}$$

Note that system (2.42) has the same form as system (2.25). We can apply the same phase-plane analysis as in Section 2.3 to arrive at the following result. Let

$$\mathcal{R}_0 = \frac{\lambda}{(b+\gamma)}$$

and

$$\Gamma = \{(s,i,r) \in \mathbb{R}^3_+ \mid s + i + r = 1\}.$$

Theorem 2.4.2 *The global dynamics are completely determined by the basic reproduction number $\mathcal{R}_0$. More specifically*

(1) *If $\mathcal{R}_0 \leq 1$, the disease-free equilibrium $P_0 = (1,0,0)$ is the only equilibrium in the feasible region Γ, and it is globally stable in Γ.*

(2) *If $\mathcal{R}_0 < 1$, then P_0 is unstable, and the endemic equilibrium*

$$P^* = \Big(\frac{b+\gamma}{\lambda}, \frac{b[\lambda-(b+\gamma)]}{\lambda(b+\gamma)}, \frac{\gamma[\lambda-(b+\gamma)]}{\lambda(b+\gamma)}\Big)$$

is globally stable in the interior $\overset{\circ}{\Gamma}$.

With the dynamics of (2.42) completely understood, we can turn to the original system (2.32). First, we note that at any equilibrium of (2.32), we necessarily have $N'(t) = 0$. If $b \neq d$, this implies $N = 0$, and thus $S = I = R = 0$, which is biologically irrelevant. Therefore, system (2.32) has no biologically relevant equilibria! How do solutions to (2.32) behave? In general, they either exponentially go to zero, or exponentially go to infinity, as we see below.

Case I. $b = d$. In this case, $N'(t) = 0$ and thus $N(t)$ is a constant, which can be scaled to 1, and thus (2.32) reduces to (2.25) or (2.42).

Case II. $b < d$. In this case, $N(t) \to 0$ exponentially as $t \to \infty$. Therefore, $S(t), I(t)$ and $R(t)$) converges to 0 exponentially as $t \to \infty$ since $0 \leq S(t), I(t), R(t) \leq N(t)$.

Case III. $b > d$. In this case, $N(t) \to \infty$ exponentially as $t \to \infty$. We consider two subcases.

(IIIa) If $\mathcal{R}_0 < 1$, then, as $t \to \infty$, $\frac{S(t)}{N(t)} = s(t) \to 1$, and thus $S(t) \to \infty$. From the I equation in (2.32) we obtain

$$I'(t) = [\lambda - (d+\gamma)]I + (\frac{S}{N} - 1)I.$$

Since $\frac{S}{N} - 1 \to 0$ exponentially, the behaviour of $I(t)$ is determined by the principal part

$$I'(t) = [\lambda - (d+\gamma)]I.$$

Therefore

(1) $I(t) \to 0$ exponentially if $R_1 = \frac{\lambda}{d+\gamma} < 1$;

(2) $I(t) \to \infty$ exponentially if $R_1 > 1$ (but $\frac{I(t)}{N(t)} \to 0$ exponentially).

In case (1), $I(t) \to 0$ exponentially, and thus $R(t)$ is determined by the principal part of the R equation

$$R' = -dR.$$

This implies that $R(t) \to 0$ if $R_1 < 1$. In case (2), there exists $a, \epsilon, T > 0$ such that $I(t) \geq ae^{\epsilon t}$ for $t \geq T$. From the R equation in (2.32)

$$R' = \gamma I - dR$$

we obtain, for $t > T$,

$$\begin{aligned} R(t) &= R(0)e^{-dt} + \gamma e^{-dt} \int_0^t I(\tau) e^{d\tau}\, d\tau \\ &\geq a\gamma e^{dt} \int_T^t e^{(\epsilon+d)\tau}\, d\tau = \frac{a\gamma}{d+\epsilon}\Big(e^{\epsilon t} - e^{-d(t-T)+\epsilon T}\Big) \\ &\to \infty, \quad \text{as } t \to \infty. \end{aligned}$$

Therefore, $S(t), I(t), R(t) \to \infty$ as $t \to \infty$ if $R_1 > 1$.

(IIIb) If $\mathcal{R}_0 > 1$, then, as $t \to \infty$,

$$\frac{S(t)}{N(t)} = s(t) \to \frac{b+\gamma}{\lambda} > 0, \quad \frac{I(t)}{N(t)} = i(t) \to i^* > 0, \quad \frac{R(t)}{N(t)} = r(t) \to r^* > 0.$$

Therefore, $S(t) \to \infty$, $I(t) \to \infty$ and $R(t) \to \infty$ as $t \to \infty$.

We see that, for model (2.32), outcomes of the disease is better described in terms of fractional variables, rather than the population sizes. In particular, we have the following conclusion.

(1) If $\mathcal{R}_0 = \frac{\lambda}{b+\gamma} \leq 1$, then the disease always dies out from the population in the sense that the fraction of infectious population (usually called the *disease prevalence*) goes to zero as $t \to \infty$.

(2) If $\mathcal{R}_0 > 1$, then any initial outbreak will lead to an endemic disease in the sense that the infectious fraction approaches a positive constant as $t \to \infty$.

Exercises.

- A function $x \mapsto f(x) \in \mathbb{R}^n$ defined for $x \in \mathbb{R}^n$ is homogeneous of degree $\delta > 0$ if f satisfies
$$f(\lambda x) = \lambda^\delta f(x), \quad \lambda > 0,\ x \in \mathbb{R}^n. \tag{2.44}$$
Give several examples of functions that are homogeneous of degree δ, and derive the Euler Identity in this case.

- Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be homogeneous of degree $\delta > 0$. Let $\phi : \mathbb{R}^n \to \mathbb{R}$ be a scalar-valued function that is homogeneous of degree 1. Assume that ϕ is positive definite, namely
$$\phi(x) \geq 0 \quad \text{and } \phi(x) = 0 \text{ if and only if } x = 0. \tag{2.45}$$
Let $x(t) \neq 0$ be a solution of the differential equation $x' = f(x)$, and
$$y(t) = \frac{x(t)}{\phi(x(t))}.$$
Derive the differential equation satisfied by $y(t)$, which will be the projected equation of $x' = f(x)$ onto the sphere
$$\phi(x) = 1.$$

- Using the same method in this section to analyze the models described in Figures 2.11 and 2.12.

2.5 Ross-MacDonald model for Malaria: a monotone system

Malaria is caused by parasites of the species Plasmodium. The parasites are transmitted to people through the bites of infected female mosquitoes when they are taking a

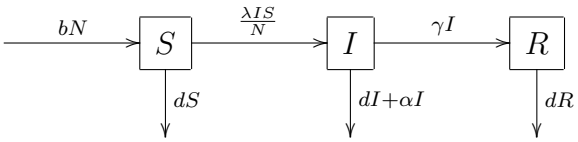


Figure 2.11: Transfer diagram for a SIR model with disease-caused death

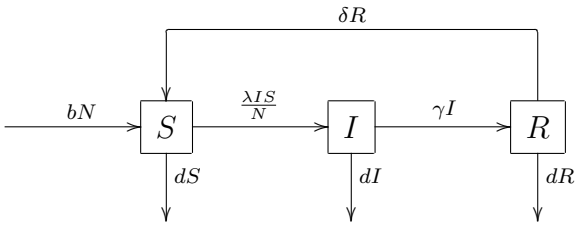


Figure 2.12: Transfer diagram for a SIRS model

blood-meal. The parasites go through long and complicated life cycles while living in humans and mosquitoes, each of which is critical for their survival and transmission. Since its transmission critically depends on the disease *vector* mosquitoes, Malaria is a typical example of *vector-borne* diseases. The transmission of the malaria parasites between human and mosquitoes is through mosquito bites: when a healthy mosquitos bites an infected human, she takes in the parasites with the blood and becomes infected; when an infected mosquito bites a healthy human, a small amount of saliva is injected into the human body from the saliva gland of the mosquito which Malaria parasites have invaded, and the parasites enters the human body. In the human body, the parasites first migrates into the liver where they mature and release their young into the blood steam; they will be picked up by mosquitoes taking a blood meal, and the infection cycle continues.

2.5.1 Modeling Malaria transmission

The earliest work of mathematical modeling of Malaria transmission dynamics was done in the early 1900 by R. Ross [], who was awarded the Nobel Prize for Medicine for his medical research on Malaria. Ross models were later further developed by G.

MacDonald []. To formulate the Ross-MacDonald model for Malaria transmission, we consider a human and a mosquito populations, and assume, for simplicity, that both populations have a constant size H and V, respectively. Let S_h and I_h denote the susceptible and infectious humans, S_v and I_v the susceptible and infectious female mosquitoes. Here, we only consider female mosquitoes because only female mosquitoes take blood-meals to produce eggs. Important parameters used in the model is listed in the following table:

a : biting rate (number of humans bitten per mosquito in a unit time)
b_1 : probability of human infection occurring from an infectious bite
b_2 : probability of mosquito infection occurring from an infectious bite
μ_h : human birth and death rates
μ_v : mosquitoes birth and death rates
γ_h : human recovery rate
γ_v : mosquito recovery rate

The transmission process of Malaria between the human and mosquito populations is depicted in Figure 2.13

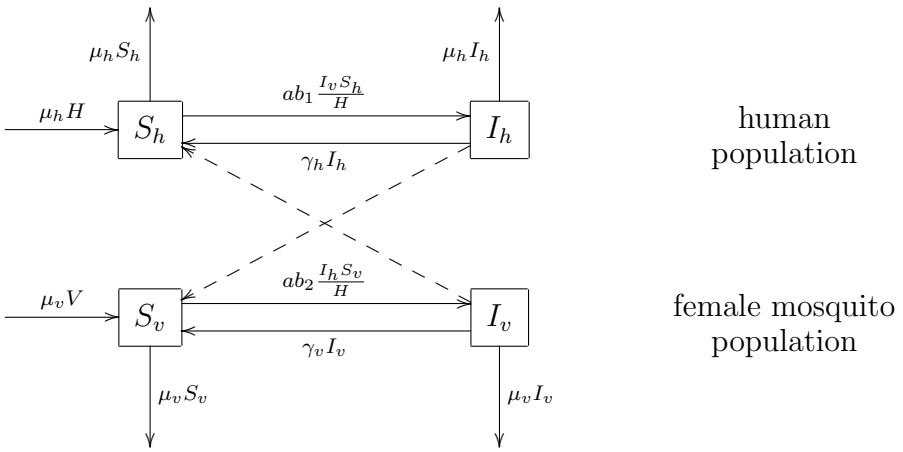


Figure 2.13: Transfer diagram for Ross-MacDonald model. Solid arrows indicate transfer. Dashed arrows indicate cross infection

Here, the Malaria incidence in the human population is calculated as follows

$$a \cdot b_1 \cdot \frac{S_h}{H} \cdot I_v,$$

which can be interpreted as the average number of infectious bite per unit time (a) times the probability of an infectious bit will produce a human infection (b_1), times the probability of the bite is on an susceptible human $\frac{S_h}{H}$, and then times the number of infectious female mosquitoes.

To derive the Malaria incidence in the mosquito population, let $\tilde{a}$ denote the mosquito biting frequency, namely, the average number of mosquitos that bit a human within a unit time. Then a and $\tilde{a}$ are related in the relation

$$a\,V \;=\; \tilde{a}\,H \tag{2.46}$$

Using parameter $\tilde{a}$, the incidence in the mosquito population is given by

$$\tilde{a} \cdot b_2 \cdot \frac{S_v}{V} \cdot I_h.$$

Replace $\tilde{a}$ by the biting rate a using relation (2.46), we obtain the malaria incidence in the mosquito population

$$a \cdot b_2 \cdot \frac{I_h}{H} S_v.$$

Using the transfer diagram, we can derive the following differential equations

$$\begin{aligned}
S_h' &= \mu_h H - a b_1 \frac{S_h I_v}{H} - \mu_h S_h + \gamma_h I_h \\
I_h' &= a b_1 \frac{S_h I_v}{H} - \mu_h I_h - \gamma_h I_h \\
S_v' &= \mu_v V - a b_2 \frac{S_v I_h}{H} - \mu_v S_v + \gamma_v I_v \\
I_v' &= a b_2 \frac{S_v I_h}{H} - \mu_v I_v - \gamma_v I_v.
\end{aligned} \tag{2.47}$$

Based on our analysis in the previous section, we see that model (2.47) is a homogeneous system of degree 1. Using fractional variables

$$s_h = \frac{S_h}{H},\ i_h = \frac{I_h}{H},\ s_v = \frac{S_v}{V},\ i_v = \frac{I_v}{V},\ m = \frac{V}{H},$$

we can derive the following system

$$\begin{aligned} s_h' &= \mu_h - ab_1 m s_h i_v - \mu_h s_h + \gamma_h i_h \\ i_h' &= ab_1 m s_h i_v - \mu_h i_h - \gamma_h i_h \\ s_v' &= \mu_v - ab_2 s_v i_h - \mu_v s_v + \gamma_v i_v \\ i_v' &= ab_2 s_v i_h - \mu_v i_v - \gamma_v i_v. \end{aligned} \tag{2.48}$$

Since $s_h + i_h = 1$ and $s_v + i_v = 1$, we may choose to keep only two of the four variables, say i_h and i_v, which give the prevalence in the human and mosquito populations, respectively. Let $x = i_h$ and $y = i_v$, then $s_h = 1 - x$ and $s_v = 1 - y$. Substituting into (2.48) we obtain the following equivalent system

$$\begin{aligned} x' &= amb_1 y(1 - x) - \gamma_1 x \\ y' &= ab_2 x(1 - y) - \gamma_2 y. \end{aligned} \tag{2.49}$$

Here, we have set new parameters $\gamma_1 = \mu_h + \gamma_h$ and $\gamma_2 = \mu_v + \gamma_v$. We will consider system (2.49) in the following bounded region

$$\Gamma = \{(x, y) \in \mathbb{R}^2_+ \mid 0 \le x \le 1,\, 0 \le y \le 1\}. \tag{2.50}$$

By examining the direction of the vector field on the boundary of Γ we can verify that Γ is positively invariant with respect to system (2.49).

2.5.2 Equilibria and the basic reproduction number

System (2.49) has two possible equilibria: the disease-free equilibrium $P_0 = (0, 0)$, which corresponds to infectious individuals are absent in both human and mosquito populations, and an endemic equilibrium $P^* = (x^*, y^*)$, where x^*, y^* are given by

$$x^* = \frac{a^2 mb_1 b_2 - \gamma_1 \gamma_2}{ab_2(amb_1 + \gamma_1)}, \quad y^* = \frac{a^2 mb_1 b_2 - \gamma_1 \gamma_2}{amb_1(ab_2 + \gamma_2)}.$$

We note that $x^*, y^* > 0$ if and only if the following condition holds

$$\mathcal{R}_0 = \frac{a^2 mb_1 b_2}{\gamma_1 \gamma_2} > 1. \tag{2.51}$$

The $\mathcal{R}_0$ in the above expression is the basic reproduction number for the Malaria transmission. Heuristically, it can be interpreted as follows. A primary human case has a recovery rate γ_1, and the average infectious period is $\frac{1}{\gamma_1}$. During this time,

the average number of mosquito bites from the susceptible fraction of mosquitoes is $\frac{a}{\gamma_1}$, which gives a total $\frac{ab_2}{\gamma_1}$ infected mosquitoes. Each of these mosquitoes will survive for an average time $\frac{1}{\gamma_2}$ and makes a total of $\frac{a}{\gamma_2}$ bites, which will lead to a total of $\frac{amb_1}{\gamma_2}$ secondary human infections. Therefore, the average total of secondary human infections from a single primary human case is $\frac{ab_2}{\gamma_1}\frac{amb_1}{\gamma_2}$, which gives the basic reproduction number in (2.51).

Local stability analysis can be carried out at each of the two equilibrium, using techniques in Section 2.3.2. We arrive at the following result.

Theorem 2.5.1 *Let $\mathcal{R}_0$ be defined in* (2.51)*.*

(1) *If $\mathcal{R}_0 \leq 1$, then system* (2.49) *has only the disease-free equilibrium $P_0 = (0, 0)$, and it is globally asymptotically stable in Γ.*

(2) *If $\mathcal{R}_0 > 1$, then P_0 is unstable, and a unique endemic equilibrium $P^* = (x^*, y^*)$ exists and is globally asymptotically stable in the interior of Γ.*

2.5.3 Monotonicity and the global dynamics

The global stability of the disease-free equilibrium P_0 when $\mathcal{R}_0 \leq 1$, and of the endemic equilibrium P^* when $\mathcal{R}_0 > 1$ can be done similarly as in Section 2.3, using a Lyapunov function or the Poincaré-Bendixson theory. In this section, we will show that system (2.49) is a monotone system, which allows us to use the machinery developed for monotone systems (Chapter 3) and establish the global stability.

We first show that system (2.49) is a monotone system, by the definition in Chapter 3. The Jacobian matrix of (2.49) is

$$J(x, y) = \begin{bmatrix} -\gamma_1 - amb_1 y & amb_1(1-x) \\ ab_2(1-y) & -\gamma_2 - ab_2 x \end{bmatrix}.$$

We see that the off-diagonal terms are both positive. System (2.49) is therefore a cooperative system and is irreducible, and its solutions preserve the order defined by the positive quadrant.

Next, we verify that system (2.49) is strictly sublinear. Let $0 < \lambda < 1$ and

$$F(x, y) = (P(x, y), Q(x, y)) = (amb_1 y(1-x) - \gamma_1 x, ab_2 x(1-y) - \gamma_2 y)$$

be the vector field of system (2.49). Then

$$\begin{aligned} P(\lambda x, \lambda y) &= amb_1 \lambda y(1 - \lambda x) - \gamma_1 \lambda x \\ &= \lambda[amb_1 y(1 - \lambda x) - \gamma_1 x] \\ &> \lambda[amb_1 y(1-x) - \gamma_1 x] = \lambda P(x, y). \end{aligned}$$

Similarly, we can verify that $Q(\lambda x, \lambda y) > \lambda Q(x, y)$, for $(x, y) \in \Gamma$ and $x > 0, y > 0$. This implies that $F(x, y)$ is strictly sublinear. We can thus apply Theorem 3.7.5 to prove the global stability of P_0 when $\mathcal{R}_0 \leq 1$, and that of P^* when $\mathcal{R}_0 > 1$.

2.5.4 Exercises

Gonorrhea is a sexually transmitted disease (STD). Gonorrhea is caused by bacteria *Neisseria gonorrhoeae*, and is spread between people through sexual contacts. Persons who have had gonorrhea and received treatment can get re-infected. The Center for Disease Control and Prevention (CDC) estimates that more than 700,000 persons in the U.S. get new gonorrheal infections each year. A mathematical model for gonorrhea transmission dynamics was formulated and analyzed in Lajmanovich and Yorke (1976). The model include cross-infections among arbitrary number of groups.

1. Since gonorrhea infection yields little immune protection against reinfection, the transmission dynamics fit an SIS model. Explain the assumptions made in the following transfer diagram and use the diagram to derive a single population model for gonorrhea transmission.

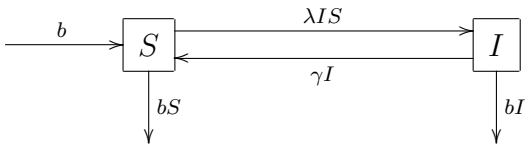


Figure 2.14: Transfer diagram for a single population gonorrhea model.

(a) Show that the total population $N = S + I$ remains a constant.

(b) Derive the system for the fractional variables $s = \frac{S}{N}$ and $i = \frac{I}{N}$.

(c) Discuss the feasible region of the system and its equilibria.

(d) Derive the basic reproduction number $\mathcal{R}_0$ for the system from its biological definition, and show that the $\mathcal{R}_0$ you have derived is a threshold parameter: if $\mathcal{R}_0 \leq 1$, the system has the only disease-free equilibrium, and if $\mathcal{R}_0 > 1$, the system has a unique endemic equilibrium.

(e) Using the relation $s + i = 1$ to reduce the system of two equations to a single equation for the variable i, and use the phase-line analysis to discuss the local and global stability of each equilibrium. Verify that if $\mathcal{R}_0 < 1$ then the disease-free equilibrium is globally asymptotically stable; if $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable, and the endemic equilibrium is globally asymptotically stable.

2. Sexual contacts within a population is not homogeneous; some people have more sexual partners than others. One way to model heterogeneous mixing is to divide the population into groups and allow a greater degree for within group contacts than intergroup contacts. Explain the assumptions that are made in the following transfer diagram for a two-group gonorrhea model, and use the transfer diagram to derive the model equations.

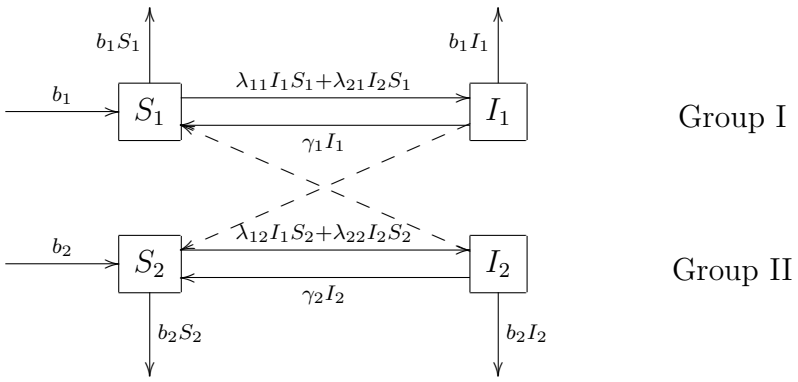


Figure 2.15: Transfer diagram for a two-group gonorrhea model. Solid arrows indicate transfer. Dashed arrows indicate cross infection

(a) Repeat the discussions (a) – (d) in the previous exercise for the new model you have derived.

(b) Using the relations $s_1 + i_1 = 1$ and $s_2 + i_2 = 1$ for fractional variables $s_k = S_k/N_k$ and $i_k = I_k/N_k$, $k = 1, 2$, to reduce the four-dimensional system to a two-dimensional system for the prevalence variables i_1 and i_2.

(c) Carry out local stability analysis for each equilibrium using linearization. Verify that the value of $\mathcal{R}_0$ determines the stability of equilibria: if $\mathcal{R}_0 < 1$ then the disease-free equilibrium is locally asymptotically stable; if $\mathcal{R}_0 > 1$, then the disease-free equilibrium is unstable, and the endemic equilibrium is locally asymptotically stable.

(d) Prove that the disease-free equilibrium is globally stable in the feasible region when $\mathcal{R}_0 \leq 1$, using the method of Lyapunov functions and the LaSalle Invariance Principle.

(e) Prove that the endemic equilibrium is globally asymptotically stable in the interior of the feasible region when $\mathcal{R}_0 > 1$, using the Poincaré-Bendixson Theorem and the Bendixson-Dulac criteria.

(f) Prove the global stability of the endemic equilibrium (when $\mathcal{R}_0 > 1$) by constructing a global Lyapunov function.

(g) Show that the reduced system for i_1 and i_2 is a monotone system and is sublinear. Prove the global stability of the disease-free equilibrium (when $\mathcal{R}_0 \leq 1$) and of the endemic equilibrium (when $\mathcal{R}_0 > 1$) using the properties of monotone systems.

3. Draw a transfer diagram for an n-group gonorrhea model, where $n > 0$ is an arbitrary integer. Derive a system of differential equations based on your transfer diagram. Derive a system for the fractional variables, and then reduce the system to a system for the n prevalence variables. Try to repeat the discussions in previous exercises on the equilibria and local stability. Can you derive the basic reproduction number $\mathcal{R}_0$? Can you show that, if $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium? How would you go about proving the global stability of the disease-free equilibrium and the endemic equilibrium? Which of the methods in previous exercises is applicable?

Chapter 3

Basic Mathematical Tools and Techniques

3.1 Stability of equilibrium solutions

Consider an open set D in the phase space $\mathbb{R}^n$, and a function $f \in C^1(D \to \mathbb{R}^n)$, called a *vector field*. A system of differential equations can be defined as Consider an ODE in $\mathbb{R}^n$

$$x' = f(x). \tag{3.1}$$

A *solution* to (3.1) in an interval $\mathcal{I} \subset \mathbb{R}$ is a differentiable function $\varphi : \mathcal{I} \to \mathbb{R}^n$ such that

$$\varphi'(t) = f(\varphi(t)).$$

When the vector field $f(x)$ is smooth (C^1), the fundamental theory of differential equations ensures that, for each initial point $x_0 \in D$, a unique solution $x(t, x_0)$ exists in an interval $\mathcal{I} = (-\alpha, \alpha)$ such that $x(0, x_0) = x_0$. We say such a solution starts from the initial point x_0. A solution can be extended to its maximal interval of existence. If a solution $x(t, x_0)$ remains in a compact subset of D during its maximal interval of existence, then it exists for all $t \in \mathbb{R}$. The orbit of a solution $x(t, x_0)$ is the set

$$\gamma(x_0) = \{x(t, x_0) \ : \ t \in \mathbb{R}\}.$$

A solution $x(t)$ is called an *equilibrium*, or steady-state, if it is a constant for all t, namely, $x(t) = \overline{x}$ for $t \in \mathbb{R}$. In this case, $\overline{x}$ satisfies $f(\overline{x}) = 0$ since $x'(t) \equiv 0$. A *periodic solution* $x(t)$ of period $T > 0$ satisfies $x(t + T) = x(t)$ for all $t \in \mathbb{R}$, and its orbit $\gamma = \{x(t) \ : \ 0 \le t < T\}$ is a simple closed smooth curve. For this reason, a periodic orbit is also called a closed orbit. For equilibria and periodic solutions, we are interested in their *stability* properties. Intuitively, an equilibrium $\overline{x}$ is stable if any solution starting close to $\overline{x}$ remains close to $\overline{x}$. Mathematically, we have the following definitions.

Definition. An equilibrium $\overline{x}$ of system (3.1) is

(1) *stable*, if for each ϵ-neighbourhood $N(\overline{x}, \epsilon)$ of $\overline{x}$, there exists a δ-neighbourhood $N(\overline{x}, \delta)$ of $\overline{x}$ such that $x_0 \in N(\overline{x}, \delta)$ implies $x(t, x_0) \in N(\overline{x}, \epsilon)$ for all $t \ge 0$;

(2) *asymptotically stable*, if $\overline{x}$ is stable and, there exists b-neighbourhood $N(\overline{x}, b)$ such that $x_0 \in N(\overline{x}, b)$ implies $x(t, x_0) \to \overline{x}$ as $t \to \infty$.

In the above definition, an asymptotically stable equilibrium $\overline{x}$ is said to attract points in a neighbourhood $N(\overline{x}, b)$. The set of points that are attracted by $\overline{x}$ is an open set and is called the *basin of attraction* of $\overline{x}$.

3.2 Stability analysis by linearization

A standard method of stability analysis is by *linearization*. Let $\overline{x} = 0$ be an equilibrium, namely, $f(0) = 0$, and thus $f(x)$ can be written in Taylor expansion as

$$f(x) = A\,x + F(x), \tag{3.2}$$

where the matrix

$$A = \frac{\partial f}{\partial x}(0)$$

is the Jacobian matrix of f at 0, and

$$F(x) = f(x) - Ax.$$

Therefore $F(0) = 0$ and $\frac{\partial F}{\partial x}(0) = 0$. In the expansion (3.2), Ax is the linearization of f at 0 and $F(x)$ is the higher order term. The linearized system of (3.1) at the equilibrium 0 is

$$y' = Ay. \tag{3.3}$$

We have the following standard result on stability.

Theorem 3.2.1 *Let A and F be given in* (3.2)*. If $y = 0$ is asymptotically stable for the linearized system* (3.3)*, then the equilibrium $\overline{x}$ is asymptotically stable for the nonlinear system* (3.1)

By Theorem 3.2.1, it is sufficient to investigate the asymptotic stability of an equilibrium for the linearized system. Regarding the latter, we have the following result.

Theorem 3.2.2 *The solution $y = 0$ is asymptotically stable for the linear system* (3.3) *if all eigenvalues of A have negative real parts.*

To verify an $n \times n$ matrix has n eigenvalues with negative real parts can be a challenging task when n is large, especially if entries of A contain non-numerical parameters. A algorithm by Routh-Hurwitz can be used to derive a set of necessary and sufficient conditions, typically called the Routh-Hurwitz conditions. For $n = 2, 3$, the Routh-Hurwitz conditions are as follows.

(1) All eigenvalues of a 2×2 matrix A have negative real parts if and only if

$$\mathrm{tr}(A) < 0 \quad \text{and} \quad \det(A) > 0. \tag{3.4}$$

(2) All eigenvalues of a 3×3 matrix A have negative real parts if and only if

$$\mathrm{tr}(A) < 0, \quad \det(A) < 0, \text{and} \quad \mathrm{tr}(A)\,a_2 - \det(A) < 0 \tag{3.5}$$

where a_2 denotes the sum of 2×2 principal minors of A.

3.3 Stability analysis using Lyapunov functions

Let $U \subset \mathbb{R}^n$ a neighbourhood of 0 and $V \in C^1(U \to \mathbb{R})$ be a real-valued function. The gradient vector of $V(x)$ is

$$\text{grad } V(x) = \left(\frac{\partial V}{\partial x_1}, \cdots, \frac{\partial V}{\partial x_n} \right).$$

Let $f(x)$ be the vector field of system (3.1). The derivative of V in the direction of f is defined as

$$\overset{*}{V}(x) = \text{grad } V(x) \cdot f(x).$$

$\overset{*}{V}(x)$ is also called Lyapunov derivative with respect to system (3.1). The function $V(x)$ is called a *Lyapunov function* of system (3.1) at an equilibrium $x = 0$ if $\overset{*}{V}(x) \leq 0$ for $x \in U$. Let $x(t)$ be a solution of system (3.1) that stays in U, then

$$\frac{d}{dt} V(x(t)) = \text{grad } V(x(t)) \cdot x'(t) = \text{grad } V(x(t)) \cdot f(x(t)) = \overset{*}{V}(x(t)) \leq 0.$$

Therefore, $V(x(t))$ decreases along a solution of system (3.1) in a neighbourhood of $x = 0$. The following theorems give a direct method of establishing stability using a Lyapunov function.

Theorem 3.3.1 *Suppose that a function $V(x)$ exists such that*

(1) $V(x) \geq 0$ *for* $x \in U$ *and* $V(x) = 0$ *if and only if* $x = 0$;

(2) $\overset{*}{V}(x) \leq 0$ *for* $x \in U$.

Then the equilibrium $x = 0$ of system (3.1) is locally stable.

Theorem 3.3.2 *Suppose that a function $V(x)$ exists such that*

(1) $V(x) \geq 0$ *for* $x \in U$ *and* $V(x) = 0$ *if and only if* $x = 0$;

(2) $\overset{*}{V}(x) \leq 0$ *for* $x \in U$ *and* $\overset{*}{V}(x) = 0$ *if and only if* $x = 0$.

Then the equilibrium $x = 0$ of system (3.1) is locally asymptotically stable.

A function V satisfying assumption (1) in the above theorems is called *positive definite* at $x = 0$. Similarly, the Lyapunov derivative $\overset{*}{V}(x)$ in the assumption (2) of Theorem 3.3.2 is negative definite at $x = 0$. If an equilibrium $\overline{x} \neq 0$, we may consider a change of variables $\tilde{x} = x - \overline{x}$ so that system (3.1) becomes

$$\tilde{x}' = F(\tilde{x}),$$

where $F(\tilde{x}) = f(\tilde{x} + \overline{x})$. Then $F(0) = f(\overline{x}) = 0$ and we have shifted the equilibrium $\overline{x}$ to 0, and Theorems 3.3.1, 3.3.2 will be applicable. The following result is an instability result.

Theorem 3.3.3 *Suppose that a function $V(x)$ exists such that*

(1) *$V(0) = 0$ and there exists sequence $x_n \to 0$ such that $V(x_n) < 0$ for all n;*

(2) *$\overset{*}{V}(x) \leq 0$ for $x \in U$ and $\overset{*}{V}(x) = 0$ if and only if $x = 0$.*

Then the equilibrium $x = 0$ of system (3.1) is unstable.

Let $G \subset \mathbb{R}^n$ be an open set. A function $V(x)$ is said to be a Lyapunov function with respect to G if

$$\overset{*}{V}(x) \leq 0, \quad \text{for } x \in G.$$

Let K be the largest invariant subset in the set $\{x \in G : \overset{*}{V}(x) = 0\}$. Since $V(x(t))$ decreases along a solution $x(t, x_0)$ of system (3.1), the omega-limit set of the solution,

$$\omega(x_0) = \{x \in G : \text{there exists } t_n \to \infty \text{ such that } x(t_n, x_0) \to x_1 \text{ as } n \to \infty\},$$

is contained in the set where $\overset{*}{V}(x) = 0$. Since omega-limit sets are invariant, we know $\omega(x_0)$ must be contained in the largest invariant subset K. We thus have the following LaSalle's Invariance Principle.

Theorem 3.3.4 *If a solution $x(t, x_0)$ stays entirely in G for $t \geq 0$. Then its omega-limit set $\omega(x_0) \cap U \subset K$.*

Corollary 3.3.5 *If E contains a single point $\overline{x}$, then $\overline{x}$ is an equilibrium and solutions that stay entirely in G for $t \geq 0$ converge to $\overline{x}$ as $t \to \infty$.*

If we also know that $\overline{x}$ is locally stable, and that all solutions starting in G remain in G (in this case, G is said to be positively invariant), then Corollary 3.3.5 implies that $\overline{x}$ is *globally* asymptotically stable in the region G.

3.4 Stability of periodic solutions: the Floquet theory

Let $x = p(t)$ be a nonconstant periodic solution of period T of system (3.1), and

$$\gamma = \{p(t) \ : \ 0 \le t < T\}$$

be its orbit. Stability analysis of a periodic orbit is more involved than that of an equilibrium. First of all, we make an observation that the notion of Lyapunov stability as we give for equilibria in Section3.1 is not appropriate for periodic solutions. The phase portrait of a nonlinear pendulum equation

$$x''(t) + \sin x(t) = 0 \tag{3.6}$$

consists of a family of periodic orbits as concentric circles centered at the origin, see Figure 3.1. Each of these orbits should be considered "stable." However, each periodic orbit has a different period. Therefore, for two periodic solutions $p(t), q(t)$ whose orbits are close to each other, $|p(t)-q(t)|$ will not necessarily be small for all t, and thus unstable according to the definition in Section 3.1. This situation motivates the following notion of orbital stability, in the sense that the distance between two orbits remain close while $|p(t) - q(t)|$ may not be.

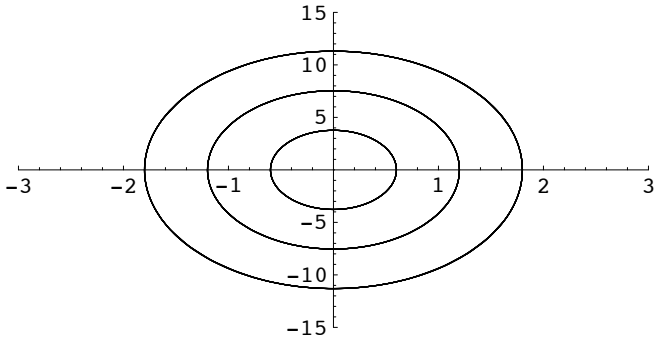


Figure 3.1: A family of nested periodic orbits of the pendulum equation; these orbits all have the same periods if the pendulum equation is linear, while they have different periods if the pendulum equation is nonlinear as in equation (3.6).

Definition. A periodic solution $x = P(t)$ is said to be

(1) *orbitally stable* if for all $\epsilon > 0$, there exists $\delta > 0$ such that $|x_0 - p(0)| < \delta$ implies $d(x(t, x_0), \gamma) < \epsilon$, where $d(x, \gamma) = \min_{y\in\gamma} |x - y|$ is the distance from x to γ.

(2) *orbitally asymptotically stable* if (a) it is orbitally stable and (b) there exists $\delta_1 > 0$ such that $|x_0 - p(0)| < \delta_1$ implies $d(x(t, x_0), \gamma) \to 0$ as $t \to \infty$. In this case, the periodic orbit is called a *limit cycle*.

By these definitions, the periodic orbits in Figure 3.1 are orbitally stable but not orbitally asymptotically stable.

To analyze the stability of a periodic solution $x = p(t)$, we also use the method of linearization and consider the linearized system of (3.1) along $x = p(t)$,

$$y'(t) = \frac{\partial f}{\partial x}(p(t))\, y(t) \tag{3.7}$$

We note that system (3.7) is a linear system with periodic coefficients. Structures of the solution space of this type of systems is described in the Floquet theory.

Theorem 3.4.1 (Floquet Theory)

(1) *A fundamental matrix of system* (3.7) *can be written in the form*

$$Y(t) = P(t)e^{Lt}, \tag{3.8}$$

where $P(t)$ *is a* $n \times n$ *matrix-valued function, periodic in* t *with period* T, $P(0) = I_{n\times n}$, *and* L *is a* $n \times n$ *constant matrix.*

(2) *Eigenvalues of* L *are called Floquet exponents, and eigenvalues of* $Y(T) = e^{LT}$ *are called Floquet multipliers.*

(3) *System* (3.7) *has a noncontant periodic solution of period* T *if and only if a Floquet multiplier is equal to* 1, *or equivalently, a Floquet exponent is equal to* 0.

We can verify by direct differentiation that $y(t) = p'(t)$ is a nonconstant periodic solution to system (3.7). Therefore, by Theorem 3.4.1-(3), one of its Floquet multipliers is 1, and we can write all Floquet multipliers of $x = p(t)$ as

$$1,\ \lambda_1,\ \cdots,\ \lambda_{n-1}. \tag{3.9}$$

A fundamental result in nonlinear differential equations states that $x = p(t)$ is asymptotically stable if the remaining $n - 1$ Floquet multipliers, $\lambda_1, \cdots, \lambda_{n-1}$, all have modulus less than 1.

Theorem 3.4.2 *The periodic solution $x = p(t)$ is orbitally asymptotically stable if the Floquet multipliers $\lambda_1, \cdots, \lambda_{n-1}$ in (3.9) have modulus less than 1.*

While Theorem 3.4.2 is a fundamental stability result, we point out that estimation of Floquet multipliers is not a easy task. A method due to Poincaré for two-dimensional systems will be given in Section 3.6. A more recent method for higher dimensional systems was developed in Muldowney [14].

3.5 Global dynamics of 1-dimensional systems: phase-line analysis

Consider a scalar differential equation

$$x' = f(x) \tag{3.10}$$

where $f \in C^1(\mathbb{R} \to \mathbb{R})$ is a real-valued function. Stability analysis of this class of equations can be done using a graphical method called the *phase-line analysis*. Suppose the graph of f is as shown in Figure3.2. Then, each intersection of the graph with the x-axis is a zero of $f(x)$, and thus is an equilibrium of equation (3.10). If between two consecutive zeros of f, the graph is above the x-axis, and thus $f(x) > 0$. For a solution $x(t, x_0)$ with x_0 in this interval, $x'(t) = f(x(t)) > 0$. Then $x(t)$ is monotonically increasing and converges to the equilibrium on the right as $t \to \infty$. Similarly, if the graph of f is below the x-axis, then $x(t, x_0)$ converges to the equilibrium on the left as $t \to \infty$. Also observe that, if the derivative $f'(\overline{x}) < 0$ at an equilibrium $\overline{x}$, then the slope of the tangent line to the graph at $\overline{x}$ is negative, and solution near $\overline{x}$ will converge to $\overline{x}$, and hence $\overline{x}$ is stable. On the other hand, if $f'(\overline{x}) > 0$, then $\overline{x}$ is unstable since solutions near $\overline{x}$ move away from $\overline{x}$ in this case. We thus have the following useful results.

Proposition 3.5.1

(1) *An equilibrium $\overline{x}$ of equation (3.10) satisfies $f(\overline{x}) = 0$.*

(2) *If $f(x) > 0$ for $x \in (a, b)$, then solutions starting in (a, b) monotonically increase; If $f(x) < 0$ for $x \in (a, b)$, then solutions starting in (a, b) monotonically decrease.*

(3) *If $f'(\overline{x}) < 0$ then the equilibrium $\overline{x}$ is stable; if $f'(\overline{x}) > 0$ then $\overline{x}$ is unstable.*

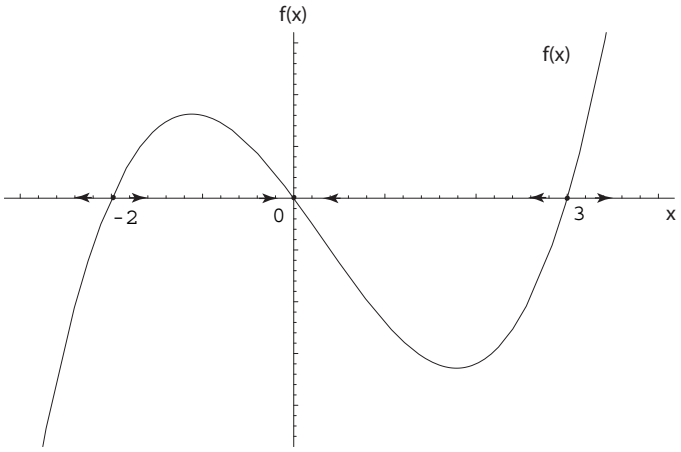


Figure 3.2: Phase-line analysis

As an example, let us consider the logistic equation for population growth

$$N'(t) = rN(t)\Big[1 - \frac{N(t)}{K}\Big], \tag{3.11}$$

where $r > 0$ is the intrinsic growth rate and K is the carrying capacity. Let

$$f(N) = rN(t)\Big[1 - \frac{N(t)}{K}\Big].$$

Then the graph of $f(N)$ has intersect the N-axis at the two equilibria $N = 0$ and $N = K$. Assume that $r > 0$. Then the graph is above the N-axis between 0 and K, and below the N-axis in the rest parts, see Figure 3.3.
By Proposition 3.5.1, we know that, if $r > 0$, the equilibrium $N = 0$ is unstable and $x = K$ is stable. Furthermore, solutions $N(t, N_0)$ with $0 < N_0 < K$ monotonically increase and converge to $N = K$ as $t \to \infty$, and solutions $N(t, N_0)$ with $N_0 > K$ monotonically decreases and converge to $N = K$ as $t \to \infty$. This allows us to produce the time plots for solutions $N(t, N_0)$ for different N_0, see Figure 3.4.

3.6 Global dynamics of 2-dimensional systems: phase-plane analysis

We consider a 2-dimensional system of differential equations

$$x' = f(x), \tag{3.12}$$

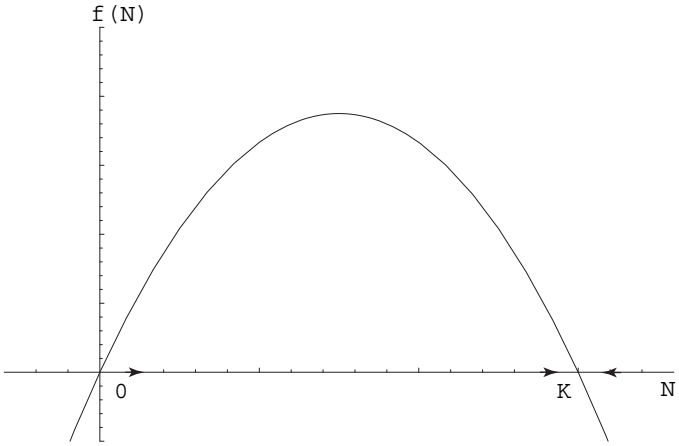


Figure 3.3: Phase-line analysis for the logistic equation when $r > 0$. The equilibrium $N = 0$ is unstable and the equilibrium at the carrying capacity $N = K$ is stable.

where $f \in C^1(\mathbb{R}^2 \to \mathbb{R}^2)$. We assume that all solutions to system (3.12) exist for all time $t \geq 0$ and investigate their asymptotic behaviours as $t \to \infty$. The followings are some important concepts.

Definition. Let $x(t, x_0)$ be a solution to system (3.12).

- The positive semi-orbit of $x(t, x_0)$ is $\gamma^+(x_0) = \{x(t, x_0) \mid t \geq 0\}$.
- The negative semi-orbit of $x(t, x_0)$ is $\gamma^-(x_0) = \{x(t, x_0) \mid t \leq 0\}$.
- The orbit of $x(t, x_0)$ is $\gamma(x_0) = \{x(t, x_0) \mid t \in \mathbb{R}\} = \gamma^+(x_0) \cup \gamma^-(x_0)$.

Definition. Limit sets.

- The ω-limit set of $x(t, x_0)$ is

$$\omega(x_0) = \{x \mid \text{there exists } t_n \to \infty \text{ such that } x(t_n, x_0) \to x.\} \tag{3.13}$$

- The α-limit set of $x(t, x_0)$ is

$$\alpha(x_0) = \{x \mid \text{there exists } t_n \to -\infty \text{ such that } x(t_n, x_0) \to x.\} \tag{3.14}$$

Definition. A subset $K \subset \mathbb{R}^2$ is

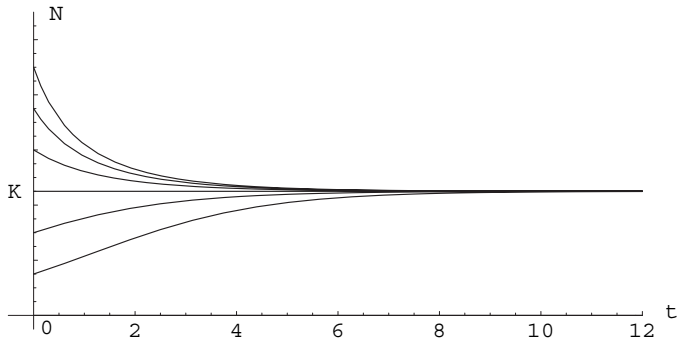


Figure 3.4: Time plots of solutions to the logistic equation when $r > 0$. The equilibrium $N = 0$ is unstable since nearby solutions move away from it, while the equilibrium $N = K$ is asymptotically stable since all nearby solutions converge to it as $t \to \infty$.

- positively invariant, if $x_0 \in K \implies x(t, x_0) \in K$, $t \geq 0$;
- negatively invariant, if $x_0 \in K \implies x(t, x_0) \in K$, $t \leq 0$;
- invariant, if it is both positively and negatively invariant, namely, $x_0 \in K \implies x(t, x_0) \in K$, $t \in \mathbb{R}$.

Theorem 3.6.1 *Properties of limit sets.*

(1) *A limit set is closed;*

(2) *If $\gamma^+(x_0)$ (or $\gamma^-(x_0)$) is pre-compact, then $\omega(x_0)$ (or $\alpha(x_0)$) is nonempty, compact, and connected;*

(3) *Limit sets are invariant.*

To investigate asymptotic behaviours of a solution $x(t, x_0)$, we try to characterize its limit sets. Example of limit sets include a single equilibrium, a periodic orbit, a homoclinic orbit or a heteroclinic cycle. A limit set in higher dimensional systems can also be very complicated such as the well-know Lorenz attractor in $\mathbb{R}^3$, which is close related to chaotic dynamics. The qualitative theory of differential equations try to classify all limit sets in a given system. In this respect, some of the best theories were developed for 2-dimensional systems, largely due to the work of Poincaré and Bendixson. These results are collectively called the Poincaré-Bendixson theory.

Theorem 3.6.2 (The Poincaré-Bendixson Theorem) *Let $D \subset \mathbb{R}^2$ be open and $f \in C^1(D \to \mathbb{R}^2)$. Assume*

(1) *$\gamma^+(x_0) \subset K \subset\subset D$ and K is compact;*

(2) *$\omega(x_0)$ contains no equilibria.*

Then $\omega(x_0)$ is a periodic orbit.

The Poincaré-Bendixson Theorem is often used to prove the existence of periodic orbits.

Corollary 3.6.3 *Assume that*

(1) *$K \subset D$ is compact;*

(2) *K contains no equilibria;*

(3) *K contains a semiorbit.*

Then K contains a nonconstant periodic orbit.

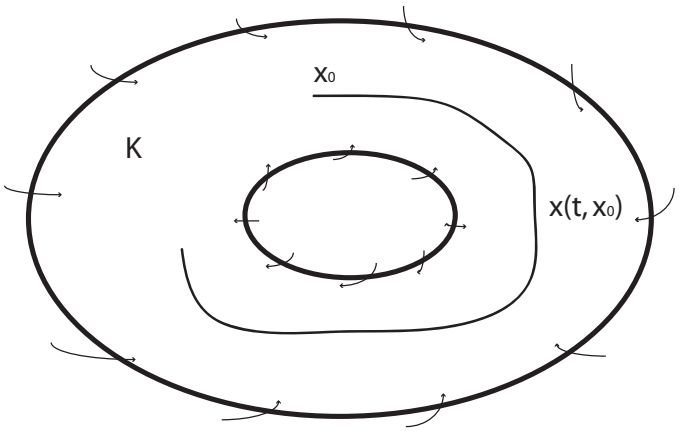


Figure 3.5: A bounded orbit $x(t, x_0)$ in an positively invariant annulus K that has no equilibria. The omega limit set of $x(t, x_0)$ is a periodic orbit.

We note that the Poincaré-Bendixson Theorem as stated here does not provide any information on $\omega(x_0)$ if $\omega(x_0)$ contains equilibria. In the case that when all equilibria of the system are hyperbolic (therefore isolated), if $\omega(x_0)$ is not a single equilibrium, then it consists of finite number of equilibria, together with their connecting orbits. See P. Hartman's ODE book [8] for related results. In the case when equilibria can be non-hyperbolic, limit sets can contain infinitely many equilibria.

Excercise. Construct a planar system such that

(1) the unit circle consists entirely of equilibria;

(2) the omega limit set of each non-equilibrium positive semi-orbit is the unit circle.

Theorem 3.6.4 (Poincaré's Stability Condition) *Assume that $n = 2$. A T-periodic solution $p(t)$ of system (3.12) is orbitally asymptotically stable if*

$$\int_0^T \operatorname{div} f(p(t))\, dt \,<\, 0. \tag{3.15}$$

Proof. Let $\lambda_1 = 1, \lambda_2$ be the two Floquet multipliers of $x = p(t)$, as discussed in Section 3.5. Let $Y(t)$ be the fundamental matrix of the linearized system with respect to $x = p(t)$. Then λ_1, λ_2 are eigenvalues of $Y(T)$. By the Liouville's formula,

$$\lambda_2 = \lambda_1\, \lambda_2 = \det Y(T) = e^{\int_0^T \operatorname{tr} \frac{\partial f}{\partial x}(p(t))dt} = e^{\int_0^T \operatorname{div} f(p(t))dt}.$$

Therefore, Poincaré's condition implies $0 < \lambda_2 < 1$, and hence the orbital asymptotic stability of $p(t)$, by Theorem 3.4.2.

Exercise. Suppose that system (3.12) has only one equilibrium. Show that the system has a unique periodic orbit if, for each periodic orbit γ, the condition

$$\oint_\gamma \operatorname{div} f < 0$$

holds.

Theorem 3.6.5 (Bendixson's Negative Criterion) *Let $D \subset \mathbb{R}^2$ be a simply connected region. If*

$$\operatorname{div} f(x) \,<\, 0, \quad (\textit{or} > 0) \quad x \in D, \tag{3.16}$$

then no periodic orbits can lie entirely in D.

Proof. Let $x = (u, v)$ and $f(x) = (P(u, v), Q(u, v))$. Suppose a periodic orbit

$$\gamma = \{(u(t), v(t)) \ : \ 0 \leq t < T\} \subset D.$$

Let G be the region enclosed in the interior of γ. Under the right orientation of γ, Green's Theorem implies

$$\begin{aligned} 0 > \iint_G \Big(\frac{\partial P}{\partial u} + \frac{\partial Q}{\partial v}\Big)\, dudv \ &= \ \oint_\gamma (Pdv - Qdu) = \int_0^T (Pv' - Qu')dt \\ &= \int_0^T (PQ - PQ)dt = 0, \end{aligned}$$

and the contradiction establishes the theorem.

Remarks.

(a) Bendixson's condition requires that $\operatorname{div}(f)$ does not change sign in D.

(b) From the proof, we can see that Bendixson's condition rules out periodic orbits, homoclinic orbits, and heteroclinic cycles.

Exercise. Construct an example to show that the Bendixson's criterion as stated in Theorem 3.6.5 is no longer true in $\mathbb{R}^n$ for $n > 2$, namely, negative divergence condition may not be able to rule out periodic orbits in dimensions higher than 2.

However, suitable conditions (other than the divergence condition) can be derived in higher dimensions that rule out periodic orbits. We refer interested readers to the work of Li and Muldowney [13].

Exercise. Show that if the Bendixson's condition holds in an annular region $D \in \mathbb{R}^2$, then D can contain at most one periodic orbit. Can you generalize this result?

Corollary 3.6.6 (Dulac's Criteria) *Assume that $D \subset \mathbb{R}^2$ is simply connected. If there is a scalar-valued function $\alpha(x)$ such that*

$$\operatorname{div}(\alpha f)(x) < 0 \quad (or > 0) \quad x \in D,$$

then D contains no periodic orbits.

Proof. Follow the same proof of Theorem 3.6.5, apply the Green's Theorem to $(\alpha P, \alpha Q)$.

3.7 Metzler matrices and monotone systems

Let M be a $n \times n$ real matrix. We say that M is a Metzler matrix if all off-diagonal entries are nonnegative. Metzler matrices were introduced in the economics literature after Metzler, whose work provided the essential development of the theory. The importance of Metzler matrices is well recognized in other fields including biology and engineering. Development of Metzler matrices also coincide with that of M-matrices. A matrix M is a M-matrix if and only if $-M$ is Metzler.

For two real matrices $A = (a_{ij})$ and $B = (b_{ij})$, we say that

(a) $A \leq B$ if and only if $a_{ij} \leq b_{ij}$ for all $1 \leq i, j \leq n$.

(b) $A < B$ if and only if $A \leq B$ and $A \neq B$.

(c) $A \ll B$ if and only if $a_{ij} < b_{ij}$ for all $1 \leq i, j \leq n$.

A matrix A is said to be *nonnegative* if $A \geq 0$, and *positive* if $A > 0$. Such orders can also be defined for vectors in $\mathbb{R}^n$, and we can define nonnegative vectors and positive vectors in a similar manner.

Let $\lambda_1, \cdots \lambda_n$ be the eigenvalues of A, the *spectral radius* of A is defined as

$$\rho(A) = \max\{|\lambda_i| \ : \ i = 1, \cdots, n\}, \tag{3.17}$$

namely, the largest modulus of eigenvalues of A. The *stability modulus* of A is defined as

$$s(A) = \max\{\mathrm{Re}(\lambda_i) \ : \ i = 1, \cdots, n\}, \tag{3.18}$$

namely, the greatest real part of eigenvalues of A. If $s(A) < 0$, we say that A is *stable*. In another words, a matrix is stable if all its eigenvalues have negative real parts.

A *permutation matrix* is a binary matrix that has exactly one entry equal to 1 in each row and each column and 0 elsewhere. A permutation matrix P represents a specific permutation of n elements and, when used to multiply another matrix A, can produce the permutation in the rows or columns of A. A nonnegative matrix A is *reducible* if, for some permutation matrix P,

$$PAP^T = \begin{bmatrix} A_1 & 0 \\ A_2 & A_3 \end{bmatrix},$$

and A_1, A_3 are square matrices. Otherwise, A is *irreducible*. Irreducibility of A can be checked using the directed graph associated with A. The *directed graph* $G(A)$

associated with $A = (a_{ij})$ has vertices $\{1, 2, \cdots, n\}$ with a directed arc (i, j) from i to j iff $e_{ij} \neq 0$. It is *strongly connected* if any two distinct vertices are joined by an oriented path. Matrix A is irreducible if and only if $G(A)$ is strongly connected.

The following Perron-Frobenious theorem is well known.

Theorem 3.7.1 (Perron-Frobenious Theorem) *Let $A \geq 0$ be an $n \times n$ real matrix.*

(1) *The spectral radius $\rho(A)$ is an eigenvalue of A with respect to a nonnegative eigenvector.*

(2) *If A is also irreducible, then $\rho(A)$ is a simple eigenvalue, and the associated eigenvector is positive.*

For Metzler matrices, we have the following version of Perron-Frobenious theorem

Theorem 3.7.2 (Perron-Frobenious Theorem for Metzler Matrices) *Let A be an $n \times n$ Metzler matrix. Then the stability modulus $\sigma(A)$ is an eigenvalue of A with respect to a nonnegative eigenvector.*

The following are some of useful properties of Metzler matrices.

Theorem 3.7.3 *Let A be an $n \times n$ Metzler matrix. Then the following statements are equivalent.*

(1) *A is stable.*

(2) *A is nonsingular and $-A^{-1} \geq 0$.*

(3) *For each $b \gg 0$, there exists $x \gg 0$ such that $Ax + b = 0$.*

(4) *There exists $x > 0$ such that $Ax \ll 0$.*

(5) *There exists $x \gg 0$ such that $Ax \ll 0$.*

Metzler matrices are related to the concept of monotone dynamical systems. A mapping $f : \mathbb{R}^n \to \mathbb{R}^n$ is said to be *monotone* if, for $x, y \in \mathbb{R}^n$,

$$x \leq y \quad \Longrightarrow \quad f(x) \leq f(y).$$

It is *strongly* monotone if, for $x, y \in \mathbb{R}^n$,

$$x < y \quad \Longrightarrow \quad f(x) \ll f(y).$$

Let $D \in \mathbb{R}^n$ be a convex subset. Let $F : D \to \mathbb{R}^n$ be a C^1 vector field. Consider a system of differential equations in $\mathbb{R}^n$

$$x' = F(x). \tag{3.19}$$

Let $x(t, x_0)$ be the unique solution to system (3.19) such that $x(0, x_0) = x_0$. The *flow* φ_t generated by system (3.19) is defined as $\varphi_t(x_0) = x(t, x_0)$. System (3.19) is said to be monotone or strongly monotone if its flow φ_t is monotone or strongly monotone, respectively.

Theorem 3.7.4 *Let F be a C^1 vector field in $\mathbb{R}^n$ defined on a convex subset $D \subset \mathbb{R}^n$. Then system* (3.19) *is monotone if and only if, for each $x \in D$, the Jacobian matrix $DF(x)$ is Metzler. Furthermore, if $DF(x)$ is also irreducible, then* (3.19) *is strongly monotone.*

A mapping $T : \mathbb{R}^n \to \mathbb{R}^n$ is said to be *sublinear* if

$$0 < \lambda < 1,\ x > 0 \quad \Longrightarrow \quad T(\lambda x) \geq \lambda T(x),$$

strictly sublinear if

$$0 < \lambda < 1,\ x \gg 0 \quad \Longrightarrow \quad T(\lambda x) > \lambda T(x),$$

and *strongly sublinear* if

$$0 < \lambda < 1,\ x \gg 0 \quad \Longrightarrow \quad T(\lambda x) \gg \lambda T(x).$$

The following stability result is useful.

Theorem 3.7.5 *Let $F : \mathbb{R}^n \to \mathbb{R}^n$ be a C^1 vector field. Assume*

(a) *The nonnegative orthant $\mathbb{R}^n_+$ is positively invariant with respect to system* (3.19).

(b) *System* (3.19) *is strongly monotone.*

(c) *$F(x)$ is strictly sublinear.*

(d) *Solutions to system* (3.19) *are bounded for $t \geq 0$.*

Then

(1) *If* $F(0) = 0$, *then either all solutions in* $\mathbb{R}^n_+$ *tend to the equilibrium* 0, *or there exists an equilibrium* $p \gg 0$ *that is globally asymptotically stable in the region* $\mathbb{R}^n_+ \setminus \{0\}$.

(2) *If* $F(0) > 0$, *then there exists equilibrium* $p \gg 0$ *that is globally asymptotically stable in* $\mathbb{R}^n_+$.

Note: Section 3.7 is adapted from lecture notes of Professor Gauthier Sallet of Université Paul Verlaine, France.

Chapter 4

Parameter Estimation and Nonlinear Least Squares Methods

In this chapter, we deal with he problem of parameter estimation. We have seen from Chapter 2 that the outcomes of an epidemic model critically depend on the values of model parameters. While analytical analysis of models can be very useful for understanding of qualitative outcomes, accurate estimation of parameter values is essential for reliable quantitative predictions. Certain parameters such as birth rates, natural death rates and recovery rates can be estimated from population and epidemiological data. For instance, if the mean life expectancy at birth of the population under study is 70 years, then its natural death rate can be approximated as $d = 1/70 \approx 0.0143$, if the time unit is year. Similarly, if the mean infectious period of the disease is 6 months and the time unit is year, then the recovery rate is $\gamma = 1/0.5 = 2$. The time unit is important in such a conversion. If the time unit is month in these examples, then the natural death rate is $d = 1/(70 \times 12) \approx 0.00119$, and the recovery rate is $d = 1/6 \approx 0.1667$.

Certain parameters are not so easily estimated directly from data. Most notably is the transmission coefficient β in the incidence term βIS. If reliable yearly incidence or prevalence data for the disease is available, then we can obtain an estimation of β by best fitting the model outcome to the given data. For simple models, this may be done by manually adjusting values of β to get the satisfactory fit. For more complicated models, or for estimation multiple parameter values, a systematic approach for the fitting is desirable. This is often achieved through the *nonlinear least square method*. We will first introduce the classical method of linear least squares for curve fitting, and then examine a nonlinear version of the curve fitting problem. With a basic understanding of these simple problems, we will discuss nonlinear least square problems associated with parameter estimation of epidemic models.

4.1 Curve fitting and linear least-square problem

Curve-fitting problems. Given data points (x_1, y_1), $\cdots$, (x_n, y_n), we consider the following curve-fitting problems.

(1) Find a straight line $y = ax + b$ that "best fits" all the data points.

(2) Find a m-th order polynomial

$$y = a_m x^m + a_{m-1} x^{m-1} + \cdots + a_1 x + a_0$$

that "best fits" all data points.

(3) Find a curve of form

$$y = a_0 f_0(x) + a_1 f_1(x) + \cdots + a_m f_m(x)$$

that "best fits" all data points. Here $f_0(x), f_1(x), \cdots, f_m(x)$ are given functions.

We see that Problem (1) is a special case of Problem (2), and Problem (2) is a special case of Problem (3) with $f_i(x) = x^i$, $i = 0, 1, \cdots, m$. For simplicity of presentation, we will use Problem (1) as an example. Problems (2) and (3) can be dealt with the same way.

Least-square fitting. Suppose that $y = a_1 x + a_0$ is a line of the best fitting, also called a *line of regression*. We need to clarify the meaning of best fitting. When $n > 2$, there is little hope for a line to pass through more than two data points, namely for all the following equations to hold simultaneously:

$$\begin{aligned} y_1 &= a_1 x_1 + a_0 \\ y_2 &= a_1 x_2 + a_0 \\ &\cdots \\ y_n &= a_1 x_n + a_0. \end{aligned}$$

We look for a best fitting line that minimizes the total error

$$d(a_0, a_1) = [y_1 - (a_1 x_1 + a_0)]^2 + \cdots + [y_n - (a_1 x_n + a_0)]^2. \tag{4.1}$$

From Table 4.1, we see that $d(a_0, a_1)$ measures the total error between data y_i and prediction $a_1 x_i + a_0$ for $i = 1, \cdots n$. This problem is also a standard minimization problem: we look for a pair $(\hat{a}_0, \hat{a}_1)$ such that the function $d(a_0, a_1)$ reaches a minimum. The choice of the euclidean norm for the measure of error gives rise to the term "least square". It ensures that $d(a_0, a_1)$ is a differentiable function. It also allows the utilization of euclidean dot product and orthogonal projection.

A mathematical formulation of the least-square problem. Let

$$b = \begin{bmatrix} y_1 \\ \vdots \\ y_n \end{bmatrix}, \quad A = \begin{bmatrix} 1 & x_1 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix}, \quad x = \begin{bmatrix} a_0 \\ a_1 \end{bmatrix}.$$

Then a least square solution $(\hat{x}) = (\hat{a}_0, \hat{a}_1)^T$ satisfies

$$\|b - A\hat{x}\| \leq \|b - Ax\| \tag{4.2}$$

	data	prediction	error
x_1	y_1	$a_1x_1 + a_0$	$y_1 - (a_1x_1 + d_0)$
x_2	y_2	$a_1x_2 + a_0$	$y_2 - (a_1x_2 + d_0)$
$\cdots$	$\cdots$	$\cdots$	$\cdots$
x_n	y_n	$a_1x_n + a_0$	$y_n - (a_1x_n + d_0)$

Table 4.1: Data, prediction and errors

for all $x \in \mathbb{R}^2$. Here $\|\cdot\|$ denotes the euclidean norm and the superscript T denotes the transposition matrices.

More generally, we allow $A_{m\times n}$ be a $m \times n$ matrix, and $b \in \mathbb{R}^m$. Then a least square solution $\hat{x} \in \mathbb{R}^n$ is a *least-square solution* of $Ax = b$ satisfies

$$\|b - A\hat{x}\| \leq \|b - Ax\| \tag{4.3}$$

for all $x \in \mathbb{R}^n$.

A least-square solution $\hat{x}$ can be found based on geometrical observations. First we note that the set

$$\text{col}(A) = \{Ax \ : \ x \in \mathbb{R}^n\}$$

is the column space $\text{col}(A)$ of matrix A. Therefore, minimizing $d = \|b - Ax\|$ is equivalent to finding the distance from vector b to the subspace $\text{col}(A)$. From geometry, we know that such distance is achieved at the orthogonal projection of b onto the subspace $\text{col}(A)$,

$$\hat{b} = \text{Proj}_{\text{col}(A)}b.$$

Therefore, the least-square solution necessarily satisfies

$$A\hat{x} = \hat{b}. \tag{4.4}$$

It would be desirable to find a solution $\hat{x}$ of (4.4) without having to find the projection $\hat{b}$. Again, from geometry, we observe that $b - \hat{b}$ is orthogonal to the subspace $\text{col}(A)$, and thus $(b - A\hat{x}) \perp \text{col}(A)$. In terms of the dot product, we have

$$(b - A\hat{x}) \cdot \text{all columns of } A = 0.$$

Written in matrix form, this relation becomes

$$A^T(b - A\hat{x}) = 0.$$

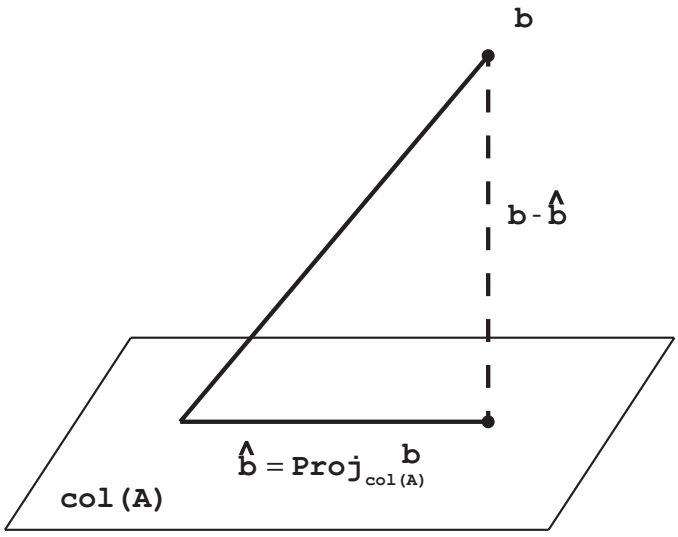


Figure 4.1: A geometric illustration of the least-square solution $\hat{x}$.

Based on these observations, we know that a least-square solution $\hat{x}$ necessarily satisfies the following *normal system*

$$A^T A\hat{x} = A^T b. \tag{4.5}$$

This gives the following theorem.

Theorem 4.1.1 *A least-square solution $\hat{x}$ satisfies the normal system* (4.5).

A least-square solution $\hat{x}$ may not be unique. However, when solutions to system (4.4) or (4.5) are unique, the least-square solution must be unique. The following uniqueness result is standard from linear algebra.

Theorem 4.1.2 *The following statements are equivalent.*

(1) *The least-square solution is unique for each $b \in \mathbb{R}^m$.*

(2) *The columns of A are linearly independent (A has full rank).*

(3) *Matrix $A^T A$ is invertible, and $\hat{x} = (A^T A)^{-1} A^T b$.*

Example 1. Find the line $y = a_0 + a_1 x$ that best fits data points $(2,1)$, $(5,2)$, $(7,3)$ and $(8,3)$.

Solution. In this case,

$$A = \begin{bmatrix} 1 & 2 \\ 1 & 5 \\ 1 & 7 \\ 1 & 8 \end{bmatrix}, \quad b = \begin{bmatrix} 1 \\ 2 \\ 3 \\ 3 \end{bmatrix}, \quad x = \begin{bmatrix} a_0 \\ a_1 \end{bmatrix}.$$

The normal system $A^T Ax = A^T b$ becomes

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ 2 & 5 & 7 & 8 \end{bmatrix} \begin{bmatrix} 1 & 2 \\ 1 & 5 \\ 1 & 7 \\ 1 & 8 \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 2 & 5 & 7 & 8 \end{bmatrix} \begin{bmatrix} 1 \\ 2 \\ 3 \\ 3 \end{bmatrix},$$

namely,

$$\begin{bmatrix} 4 & 22 \\ 22 & 142 \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \end{bmatrix} = \begin{bmatrix} 9 \\ 57 \end{bmatrix}.$$

Therefore

$$\begin{bmatrix} a_0 \\ a_1 \end{bmatrix} = \begin{bmatrix} 4 & 22 \\ 22 & 142 \end{bmatrix}^{-1} \begin{bmatrix} 9 \\ 57 \end{bmatrix} = \frac{1}{84} \begin{bmatrix} 142 & -22 \\ -22 & 4 \end{bmatrix} \begin{bmatrix} 9 \\ 57 \end{bmatrix} = \begin{bmatrix} \frac{2}{7} \\ \frac{5}{14} \end{bmatrix}.$$

This gives $a_0 = \frac{2}{7}$, $a_1 = \frac{5}{14}$, and the least square line

$$y = \frac{2}{7} + \frac{5}{14} x.$$

Example 2. Find a quadratic curve that best fit the data points

$$(2,1),\ (-1,5),\ (6,2),\ (4,-1).$$

Solution. A quadratic curve has the form

$$y = a_2 x^2 + a_1 x + a_0.$$

We want to find coefficients $(\hat{a}_0, \hat{a}_1, \hat{a}_2)$ such that

$$\begin{aligned} d = {} & [(\hat{a}_0 + 2\hat{a}_1 + 4\hat{a}_2) - 1]^2 + [(\hat{a}_0 + (-1)\hat{a}_1 + \hat{a}_2) - 5]^2 \\ & + [(\hat{a}_0 + 6\hat{a}_1 + 36\hat{a}_2) - 2]^2 + [(\hat{a}_0 + 4\hat{a}_1 + 16\hat{a}_2) - (-1)]^2 \end{aligned}$$

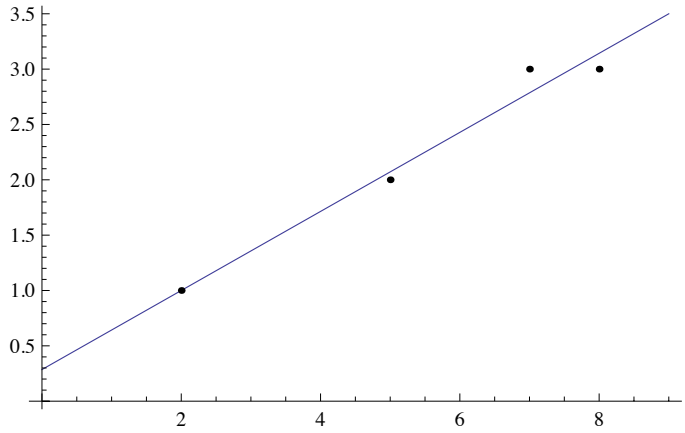


Figure 4.2: The least-square line for Example 1.

is the smallest among all choices of (a_0, a_1, a_2). Let

$$A = \begin{bmatrix} 1 & x_1 & x_1^2 \\ 1 & x_2 & x_2^2 \\ 1 & x_3 & x_3^2 \\ 1 & x_4 & x_4^2 \end{bmatrix} = \begin{bmatrix} 1 & 2 & 4 \\ 1 & -1 & 1 \\ 1 & 6 & 36 \\ 1 & 4 & 16 \end{bmatrix}, \quad b = \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \end{bmatrix} = \begin{bmatrix} 1 \\ 5 \\ 2 \\ -1 \end{bmatrix}, \quad x = \begin{bmatrix} a_0 \\ a_1 \\ a_2 \end{bmatrix}.$$

Then, the normal system $A^T Ax = A^T b$ becomes

$$\begin{bmatrix} 1 & 1 & 1 & 1 \\ 2 & -1 & 6 & 4 \\ 4 & 1 & 36 & 16 \end{bmatrix} \begin{bmatrix} 1 & 2 & 4 \\ 1 & -1 & 1 \\ 1 & 6 & 36 \\ 1 & 4 & 16 \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \\ a_2 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 2 & -1 & 6 & 4 \\ 4 & 1 & 36 & 16 \end{bmatrix} \begin{bmatrix} 1 \\ 5 \\ 2 \\ -1 \end{bmatrix},$$

namely,

$$\begin{bmatrix} 4 & 11 & 57 \\ 11 & 57 & 287 \\ 57 & 287 & 1569 \end{bmatrix} \begin{bmatrix} a_0 \\ a_1 \\ a_2 \end{bmatrix} = \begin{bmatrix} 7 \\ 5 \\ 65 \end{bmatrix}.$$

The system has a uniques solution

$$\hat{a}_0 = \frac{4871}{1639} \approx 2.9719, \quad \hat{a}_1 = -\frac{12515}{6556} \approx -1.909, \quad \hat{a}_2 = \frac{1853}{6556} \approx 0.2826,$$

and the unique least-square quadratic curve for the given data points is

$$y = 0.2826x^2 - 1.909x + 2.9719.$$

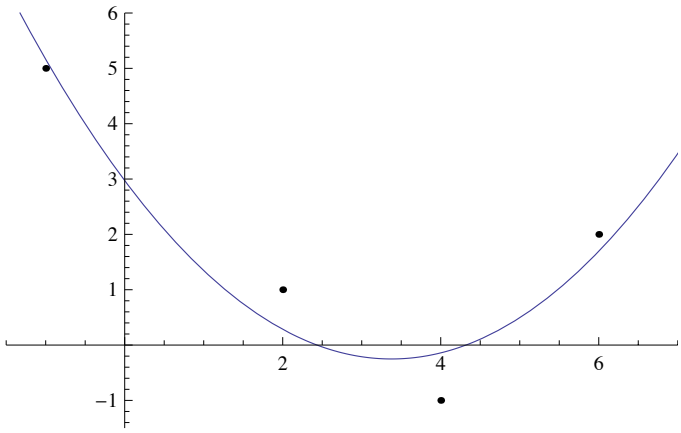


Figure 4.3: The least-square parabola for Example 2.

We see from these two examples that linear least-square problems we deal with in this section covers best fit using linear functions (lines) as well as nonlinear functions (parabolas). The common feature of the linear least square problems is that a best-fit function is in the form of linear combinations of basis functions, and finding the best-fit function is to find the best choice of coefficients (or parameters). In certain cases when the best-fit function has nonlinear dependence on parameters, the method for linear least-square problem can be applied after a suitable transformation.

Example 3. Find the least-square function of form

$$x(t) = a_0 e^{a_1 t}, \quad t > 0,\ a_0 > 0$$

for the data points

$$(t_1, x_1),\ (t_2, x_2),\ \cdots, (t_n, x_n), \quad x_1,\ x_2, \cdots, x_n > 0.$$

Solution. Let

$$y(t) = \ln x = \ln a_0 + a_1 t,$$

and

$$b_0 = \ln a_0, \quad b_1 = \ln a_1, \quad y_1 = \ln x_1, \quad \cdots, \quad y_n = \ln x_n.$$

Then, we can first solve the following linear least-square problem:

Find the least-square curve among

$$y(t) = b_0 + b_1 t, \quad t > 0$$

for data points $(t_1, y_1),\ \cdots,\ (t_n, y_n)$.

This problem can be solved using the linear least-square method as in Example 1 to produce a least-square solution $(\hat{b}_0, \hat{b}_1)$. The best fit curve to the original problem is then given by

$$x(t) = \hat{a}_0 e^{\hat{a}_1 t},$$

where $\hat{a}_0 = e^{\hat{b}_0}$, $\hat{a}_1 = \hat{b}_1$.

4.2 Nonlinear least-square problem

Let $\beta = (\beta_1, \cdots, \beta_m)$ be a multidimensional parameter. Consider a family of curves $y - f(x, \beta)$ that depend on parameter β.

Nonlinear Least-Square Fitting: Given data points

$$(x_1, y_1),\ (x_2, y_2),\ \cdots,\ (x_n, y_n),$$

find a parameter value $\hat{\beta}$ such that the curve $y = f(x, \hat{\beta})$ minimizes

$$S(\beta) = \sum_{i=1}^{n} (y_i - f(x_i, \beta))^2 \tag{4.6}$$

The reader should think about why the method of linear least-square problem discussed in the previous section will not work for this problem. We will treat $S(\beta)$ as a smooth function of β and employ multi-variable calculus to find its minimum. In fact, a minimum of $S(\beta)$ in $\mathbb{R}^m$ must be achieved at a critical point, namely, where

$$\frac{\partial S}{\partial \beta_j} = 0, \quad j = 1, \cdots, m. \tag{4.7}$$

Using the chain rule for differentiation, we rewrite system (4.19) as

$$\sum_{i=1}^{n} [y_i - f(x_i, \beta)] \Big(- \frac{\partial f}{\partial \beta_j}(x_i, \beta) \Big) = 0, \quad j = 1, \cdots, m. \tag{4.8}$$

This system may still be nonlinear in β through nonlinear dependence in $f(x_i, \beta)$. Numerical schemes are used to find an approximate solution.

Starting from an initial guess $\beta^{(0)}$ of β, and let $\beta^{(k)}$ increase by a step size $\Delta\beta$, which may vary with each step. Define:

$$\beta^{(k+1)} = \beta^{(k)} + \Delta\beta^{(k+1)}, \quad k = 0, 1, 2, \cdots.$$

We approximate $f(x_i, \beta)$ by its Taylor polynomial at $\beta^{(k)}$

$$f(x_i, \beta) \approx f(x_i, \beta^{(k)}) + \sum_{s=1}^{n} \frac{\partial f(x_i, \beta^{(k)})}{\partial \beta_s} (\beta_s - \beta_s^{(k)}).$$

Let

$$J = \Big(\frac{\partial f(x_i, \beta^{(k)})}{\partial \beta_j} \Big) = (J_{ij})$$

be the Jacobian matrix at $\beta^{(k)}$. Then equation (4.20) can be approximated by

$$\sum_{i=1}^{n} \Big[y_i - f(x_i, \beta^{(k)}) - \sum_{s=1}^{m} J_{is} (\beta_s - \beta_s^{(k)}) \Big] [-J_{ij}] = 0, \quad j = 1, \cdots, m. \tag{4.9}$$

Let

$$\Delta y_i = y_i - f(x_i, \beta^{(k)}),$$
$$\Delta \beta_j^{(k+1)} = \beta_j^{(k+1)} - \beta_j^{(k)}.$$

Then equation (4.21) can be rewritten as

$$\sum_{i=1}^{n} \sum_{s=1}^{m} J_{is} J_{ij} \Delta \beta_s^{(k)} = \sum_{i=1}^{n} J_{ij} \Delta y_i. \tag{4.10}$$

In matrix form this can be written as

$$J^T J \Delta \beta = J^T \Delta y, \tag{4.11}$$

System (4.23) is called the *normal equation*.

The following iteration scheme for this nonlinear least-square method is called the Gauss-Newton Method:

(1) Choose an initial value $\beta^{(0)}$.

(2) Solve the normal equation (4.23) for $\Delta \beta^{(1)}$.

(3) Update β by $\beta^{(1)} = \beta^{(0)} + \Delta \beta^{(1)}$.

(4) Repeat the iteration until convergence is achieved (when difference $\beta^{(k+1)} - \beta^{(k)}$ is below margin of error.)

There are many other methods for nonlinear least-square problems that aim at improving efficiency and rate of convergence.

If $f(x,\beta)$ is a linear function of β, say

$$f(x,\beta) = \alpha(x)\cdot\beta,$$

where $\alpha(x) = (\alpha_1(x),\cdots,\alpha_m(x))$ and $\cdot$ denote the dot product in $\mathbb{R}^m$, then we would expect that the Gauss-Newton method will lead to the linear least-square method. Indeed,

$$f(x_i,\beta) = \alpha(x_i)\cdot\beta = \sum_{j=1}^{m}\alpha_j(x_i)\beta_i, \quad i = 1,\cdot,n,$$

and

$$S(\beta) = \sum_{i=1}^{n}(y_i - \alpha(x_i)\cdot\beta)^2.$$

Therefore,

$$\begin{aligned}\frac{\partial S}{\partial\beta_j} &= \sum_{i=1}^{n}(y_i - \alpha(x_i)\cdot\beta)(-\alpha_j(x_i)) \\ &= -\sum_{i=1}^{n}\alpha_j(x_i)(y_i - \alpha(x_i)\cdot\beta), \quad j = 1,\cdots,m.\end{aligned} \tag{4.12}$$

Let $A = (\alpha_j(x_i))$. Then equation (4.24) can be written in matrix form as

$$A^T y - A^T A\,\beta = 0,$$

which gives the normal equation

$$A^T A\,\beta = A^T y$$

of the linear least-square problem.

Example 4. Given data

$$(1,4.6),\ (2,8.82),\ (3,16),\ (4,31.3),\ (5,58.5),$$

Find the best-fit curve $x = a_0 e^{a_1 t}$.

Solution 1. Using transformation

$$y = \ln x,\ b_0 = \ln a_0,\ b_1 = a_1,$$

we obtain

$$y = b_0 + b_1 t$$

and new data set

$$(1, 1.526),\ (2, 2.177),\ (3, 2.773),\ (4, 3.444),\ (5, 4.069).$$

We will apply the linear least-square method. Let

$$A = \begin{bmatrix} 1 & 1 \\ 1 & 2 \\ 1 & 3 \\ 1 & 4 \\ 1 & 5 \end{bmatrix},\ b = \begin{bmatrix} 1.526 \\ 2.177 \\ 2.773 \\ 3.444 \\ 4.069 \end{bmatrix},\ y = \begin{bmatrix} b_0 \\ b_1 \end{bmatrix}.$$

The normal equation $A^T Ay = A^T b$ becomes

$$\begin{bmatrix} 5 & 15 \\ 15 & 55 \end{bmatrix} \begin{bmatrix} b_0 \\ b_0 \end{bmatrix} = \begin{bmatrix} 13.989 \\ 48.32 \end{bmatrix}.$$

Solving this system we obtain

$$\begin{bmatrix} b_0 \\ b_0 \end{bmatrix} = \begin{bmatrix} 5 & 15 \\ 15 & 55 \end{bmatrix}^{-1} \begin{bmatrix} 13.989 \\ 48.32 \end{bmatrix} = \begin{bmatrix} 0.892 \\ 0.635 \end{bmatrix}.$$

This gives

$$a_0 = e^{0.892} = 2.44,\ a_1 = b_1 = 0.635,$$

and the least-square curve is

$$x = 2.44e^{0.635t}.$$

Solution 2. We will use Gauss-Newton method to solve the nonlinear least-square problem directly. Consider the nonlinear function

$$f(t, a) = a_0 e^{a_1 t}, \quad a = (a_0, a_1).$$

The Jacobian matrix is

$$J = \begin{bmatrix} e^{a_1} & a_0 e^{a_1} \\ e^{2a_1} & 2a_0 e^{2a_1} \\ e^{3a_1} & 3a_0 e^{3a_1} \\ e^{4a_1} & 4a_0 e^{4a_1} \\ e^{5a_1} & 5a_0 e^{5a_1} \end{bmatrix}$$

and the normal equation $J^TJ\Delta a = J^T\Delta y$ becomes

$$\begin{bmatrix} e^{2a_1}+e^{4a_1}+e^{6a_1}+e^{8a_1}+e^{10a_1} & a_0(e^{2a_1}+2e^{4a_1}+3e^{6a_1}+4e^{8a_1}+5e^{10a_1}) \\ a_0(e^{2a_1}+2e^{4a_1}+3e^{6a_1}+4e^{8a_1}+5e^{10a_1}) & a_0^2(e^{2a_1}+4e^{4a_1}+9e^{6a_1}+16e^{8a_1}+25e^{10a_1}) \end{bmatrix}.$$

$$\begin{bmatrix} \Delta a_1 \\ \Delta a_2 \end{bmatrix} = \begin{bmatrix} e^{a_1} & e^{2a_1} & e^{3a_1} & e^{4a_1} & e^{5a_1} \\ a_0e^{3a_1} & 2a_0e^{2a_1} & 3a_0e^{3a_1} & 4a_0e^{4a_1} & 5a_0e^{5a_1} \end{bmatrix} \begin{bmatrix} \Delta y_1 \\ \Delta y_2 \\ \Delta y_3 \\ \Delta y_4 \\ \Delta y_5 \end{bmatrix}.$$

Here

$$\begin{bmatrix} \Delta a_1 \\ \Delta a_2 \end{bmatrix} = \begin{bmatrix} a_0^{(k+1)} - a_0^{(k)} \\ a_1^{(k+1)} - a_1^{(k)} \end{bmatrix},$$

and

$$\Delta y_i = y_i - a_0^{(k)} e^{a_1^{(k)}}, \quad 1 \le i \le 5.$$

Choosing an initial vector

$$\begin{bmatrix} a_0^{(0)} \\ a_1^{(0)} \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}$$

and using the iteration scheme

$$\begin{bmatrix} a_0^{(k+1)} \\ a_1^{(k+1)} \end{bmatrix} = \begin{bmatrix} a_0^{(k)} \\ a_1^{(k)} \end{bmatrix} + (J^TJ)^{-1}J^T \begin{bmatrix} y_1 - a_0^{(k)}e^{a_0^{(k)}} \\ y_2 - a_0^{(k)}e^{a_0^{(k)}} \\ y_3 - a_0^{(k)}e^{a_0^{(k)}} \\ y_4 - a_0^{(k)}e^{a_0^{(k)}} \\ y_5 - a_0^{(k)}e^{a_0^{(k)}} \end{bmatrix}$$

we obtain

$$\begin{bmatrix} a_0^{(1)} \\ a_1^{(1)} \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix} + \begin{bmatrix} 25472.8 & 123383 \\ 133383 & 602214 \end{bmatrix}^{-1} \begin{bmatrix} 2.718 & 7.389 & 20.086 & 54.598 & 148.413 \\ 2.718 & 14.778 & 60.257 & 218.393 & 742.066 \end{bmatrix} \begin{bmatrix} 1.882 \\ 1.431 \\ -4.086 \\ -23.298 \\ -89.913 \end{bmatrix}$$

$$= \begin{bmatrix} 1.386 \\ 0.801 \end{bmatrix}$$

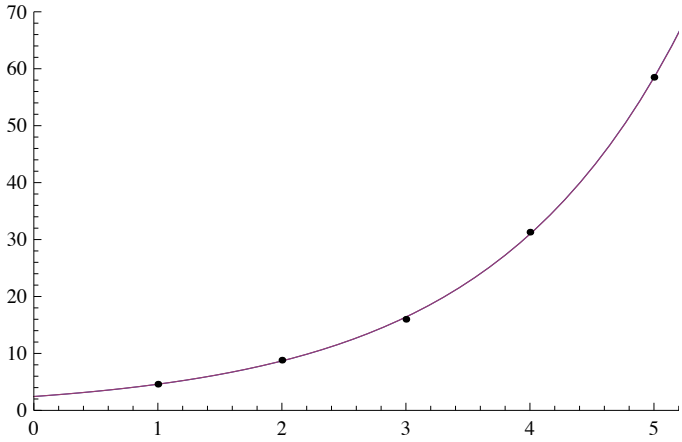


Figure 4.4: The least-square curve for Example 4.

Iterating again we obtain

$$\begin{bmatrix} a_0^{(2)} \\ a_1^{(2)} \end{bmatrix} = \begin{bmatrix} 1.386 \\ 0.801 \end{bmatrix} + \begin{bmatrix} 3777.53 & 24873.7 \\ 24873.7 & 166018 \end{bmatrix}^{-1} \begin{bmatrix} 2.228 & 4.965 & 11.064 & 24.653 & 54.934 \\ 3.089 & 13.768 & 46.017 & 136.716 & 380.802 \end{bmatrix} \begin{bmatrix} 1.511 \\ 1.936 \\ 0.661 \\ -2.879 \\ -17.66 \end{bmatrix}$$

$$= \begin{bmatrix} 2.104 \\ 0.651 \end{bmatrix}.$$

The subsequent iterations can be calculated as

$$\begin{bmatrix} a_0^{(3)} \\ a_1^{(3)} \end{bmatrix} = \begin{bmatrix} 2.428 \\ 0.635 \end{bmatrix}, \quad \begin{bmatrix} a_0^{(4)} \\ a_1^{(4)} \end{bmatrix} = \begin{bmatrix} 2.431 \\ 0.636 \end{bmatrix}, \quad \begin{bmatrix} a_0^{(5)} \\ a_1^{(5)} \end{bmatrix} = \begin{bmatrix} 2.431 \\ 0.636 \end{bmatrix}, \quad \cdots.$$

We see that if the margin of error is three decimal points, then we have achieved the required accuracy at the 4th iteration and obtain

$$a_0 = 2.431, \quad a_1 = 0.636$$

Comparing with the answer in Solution 1, we see that they agree up to the first decimal point. The resulting curves are shown in Figure 4.5. The two curves are virtually indistinguishable.

4.3 Parameter estimation for epidemic models

Suppose that our epidemic model is described by a system of differential equations

$$\begin{aligned} x' &= f(x,\beta), \quad x \in \mathbb{R}^d,\ t \in [0,T], \\ x(0) &= x_0. \end{aligned} \tag{4.13}$$

Here $\beta \in \mathbb{R}^m$ is a m-dimensional parameter, and $[0,T]$ is the time interval in which we investigate the epidemics. Since the disease data, whether epidemiological or demographical, is given at discrete times $t_1, t_2, \cdots, t_p \in [0,T]$ in the form

$$(t_1,x_1),\ (t_2,x_2),\ \cdots,\ (t_p,x_p), \quad x_i \in \mathbb{R}^d, \tag{4.14}$$

it is natural that we represent a solution $x(t,\beta)$ by its values at these discrete points

$$x(t,\beta) \approx (x(t_1,\beta), x(t_2,\beta), \cdots, x(t_p,\beta)).$$

In this notation, the dependence of the solution on initial condition x_0 is understood and suppressed. In fact, in the following discussion, we will keep x_0 fixed and discuss fitting the parameter β. We use a vector to denote the data points

$$x = (x_1, x_2, \cdots, x_p).$$

Then the euclidean distance between our solution and the data can be measured by

$$S(\beta) = d(x(t,\beta),x)^2 = \sum_{i=1}^{p} |x(t_i,\beta) - x_i|^2 \tag{4.15}$$

When multiple data sets are available to fit the same model, say

$$(t_1,x_1^k),\ (t_2,x_2^k),\ \cdots,\ (t_p,x_p^k), \quad x_i^k \in \mathbb{R}^d, \tag{4.16}$$

for $k = 1, 2, \cdots, n,$ we denote

$$x^k = (x_1^k, x_2^k, \cdots, x_p^k).$$

The distance between a solution and the data is measured by

$$S(\beta) = \sum_{k=1}^{n} d(x(t,\beta),x^k)^2 = \sum_{k=1}^{n}\sum_{i=1}^{p} |x(t_i,\beta) - x_i^k|^2 \tag{4.17}$$

In least-square fitting, we look for a value $\hat{\beta}$ of model parameter β such that $S(\beta)$ is a minimum. Such as problem is clearly a nonlinear least-square problem, since the dependence of a solution $x(t, \beta)$ on the parameter β is through a highly nonlinear system of differential equations.

We note that the least-square parameter fitting using $S(\beta)$ in (4.17) may not be the most general or practical. Very often the disease data is given in terms of disease incidence or prevalence, while concurrent data for susceptibles, exposed and latent, or recovered may not be available. As a consequence, parameters need to fitted to data available only to part of the variables.

We can apply the Gauss-Newton method to the least-square parameter fitting problem. The differential equations can be discretized to give a difference equation for the solution. The normal equation for the difference equation can be derived and then solved by Gauss-Newton iteration. When the number of equations in (4.23) is large, this amounts to excessive human effort for code writing. An alternative to this approach is to take advantage of the powerful direct search routines of software packages such as Matlab. We will explain this approach in the following. An example using a simple SIR model is provided, together with the Matlab codes.

In the example, for a simple SIR model, data points for the I and N variables are given, three different Matlab functions are used to find the least-square fit for the influx of susceptible λ and the transmission coefficient β. One Matlab function is *lsqcurvefit* that takes the model, the initial guess for the the unknown parameters, the time points and data points, and then solve the nonlinear least-square problem directly. The second Matlab function we use is the well-known *fminsearch*. We first define $S(\beta)$ as the sum of squares of the errors. With an initial guess of the unknown parameters, the model can be numerically solved to produce a value for $S(\beta)$. fminsearch take both $S(\beta)$ and the initial guess of the parameter value

Let $\beta = (\beta_1, \cdots, \beta_m)$ be a multidimensional parameter. Consider a family of curves $y - f(x, \beta)$ that depend on parameter β.

Nonlinear Least-Square Fitting: Given data points

$$(x_1, y_1),\ (x_2, y_2),\ \cdots,\ (x_n, y_n),$$

find a parameter value $\hat{\beta}$ such that the curve $y = f(x, \hat{\beta})$ minimizes

$$S(\beta) = \sum_{i=1}^{n} (y_i - f(x_i, \beta))^2 \tag{4.18}$$

The reader should think about why the method of linear least-square problem discussed in the previous section will not work for this problem. We will treat $S(\beta)$

as a smooth function of β and employ multi-variable calculus to find its minimum. In fact, a minimum of $S(\beta)$ in $\mathbb{R}^m$ must be achieved at a critical point, namely, where

$$\frac{\partial S}{\partial \beta_j} = 0, \quad j = 1, \cdots, m. \tag{4.19}$$

Using the chain rule for differentiation, we rewrite system (4.19) as

$$\sum_{i=1}^{n} [y_i - f(x_i, \beta)] \Big(- \frac{\partial f}{\partial \beta_j}(x_i, \beta) \Big) = 0, \quad j = 1, \cdots, m. \tag{4.20}$$

This system may still be nonlinear in β through nonlinear dependence in $f(x_i, \beta)$. Numerical schemes are used to find an approximate solution.

Starting from an initial guess $\beta^{(0)}$ of β, and let $\beta^{(k)}$ increase by a step size $\Delta\beta$, which may vary with each step. Define:

$$\beta^{(k+1)} = \beta^{(k)} + \Delta\beta^{(k+1)}, \quad k = 0, 1, 2, \cdots.$$

We approximate $f(x_i, \beta)$ by its Taylor polynomial at $\beta^{(k)}$

$$f(x_i, \beta) \approx f(x_i, \beta^{(k)}) + \sum_{s=1}^{n} \frac{\partial f(x_i, \beta^{(k)})}{\partial \beta_s} (\beta_s - \beta_s^{(k)}).$$

Let

$$J = \Big(\frac{\partial f(x_i, \beta^{(k)})}{\partial \beta_j} \Big) = (J_{ij})$$

be the Jacobian matrix at $\beta^{(k)}$. Then equation (4.20) can be approximated by

$$\sum_{i=1}^{n} \Big[y_i - f(x_i, \beta^{(k)}) - \sum_{s=1}^{m} J_{is} (\beta_s - \beta_s^{(k)}) \Big] [-J_{ij}] = 0, \quad j = 1, \cdots, m. \tag{4.21}$$

Let

$$\Delta y_i = y_i - f(x_i, \beta^{(k)}),$$
$$\Delta \beta_j^{(k+1)} = \beta_j^{(k+1)} - \beta_j^{(k)}.$$

Then equation (4.21) can be rewritten as

$$\sum_{i=1}^{n} \sum_{s=1}^{m} J_{is} J_{ij} \Delta \beta_s^{(k)} = \sum_{i=1}^{n} J_{ij} \Delta y_i. \tag{4.22}$$

In matrix form this can be written as

$$J^T J\Delta\beta = J^T \Delta y, \tag{4.23}$$

System (4.23) is called the *normal equation*.

The following iteration scheme for this nonlinear least-square method is called the Gauss-Newton Method:

(1) Choose an initial value $\beta^{(0)}$.

(2) Solve the normal equation (4.23) for $\Delta\beta^{(1)}$.

(3) Update β by $\beta^{(1)} = \beta^{(0)} + \Delta\beta^{(1)}$.

(4) Repeat the iteration until convergence is achieved (when difference $\beta^{(k+1)} - \beta^{(k)}$ is below margin of error.)

There are many other methods for nonlinear least-square problems that aim at improving efficiency and rate of convergence.

If $f(x, \beta)$ is a linear function of β, say

$$f(x, \beta) = \alpha(x) \cdot \beta,$$

where $\alpha(x) = (\alpha_1(x), \cdots, \alpha_m(x))$ and $\cdot$ denote the dot product in $\mathbb{R}^m$, then we would expect that the Gauss-Newton method will lead to the linear least-square method. Indeed,

$$f(x_i, \beta) = \alpha(x_i) \cdot \beta = \sum_{j=1}^{m} \alpha_j(x_i)\beta_i, \quad i = 1, \cdot, n,$$

and

$$S(\beta) = \sum_{i=1}^{n} (y_i - \alpha(x_i) \cdot \beta)^2.$$

Therefore,

$$\begin{aligned} \frac{\partial S}{\partial \beta_j} &= \sum_{i=1}^{n} (y_i - \alpha(x_i) \cdot \beta)(-\alpha_j(x_i)) \\ &= -\sum_{i=1}^{n} \alpha_j(x_i)(y_i - \alpha(x_i) \cdot \beta), \quad j = 1, \cdots, m. \end{aligned} \tag{4.24}$$

Let $A = (\alpha_j(x_i))$. Then equation (4.24) can be written in matrix form as

$$A^T y - A^T A\,\beta = 0,$$

which gives the normal equation

$$A^T A\,\beta = A^T y$$

of the linear least-square problem.

Example 4. Given data

$$(1, 4.6),\ (2, 8.82),\ (3, 16),\ (4, 31.3),\ (5, 58.5),$$

Find the best-fit curve $x = a_0 e^{a_1 t}$.

Solution 1. Using transformation

$$y = \ln x,\ b_0 = \ln a_0,\ b_1 = a_1,$$

we obtain

$$y = b_0 + b_1 t$$

and new data set

$$(1, 1.526),\ (2, 2.177),\ (3, 2.773),\ (4, 3.444),\ (5, 4.069).$$

We will apply the linear least-square method. Let

$$A = \begin{bmatrix} 1 & 1 \\ 1 & 2 \\ 1 & 3 \\ 1 & 4 \\ 1 & 5 \end{bmatrix},\ b = \begin{bmatrix} 1.526 \\ 2.177 \\ 2.773 \\ 3.444 \\ 4.069 \end{bmatrix},\ y = \begin{bmatrix} b_0 \\ b_1 \end{bmatrix}.$$

The normal equation $A^T A y = A^T b$ becomes

$$\begin{bmatrix} 5 & 15 \\ 15 & 55 \end{bmatrix} \begin{bmatrix} b_0 \\ b_0 \end{bmatrix} = \begin{bmatrix} 13.989 \\ 48.32 \end{bmatrix}.$$

Solving this system we obtain

$$\begin{bmatrix} b_0 \\ b_0 \end{bmatrix} = \begin{bmatrix} 5 & 15 \\ 15 & 55 \end{bmatrix}^{-1} \begin{bmatrix} 13.989 \\ 48.32 \end{bmatrix} = \begin{bmatrix} 0.892 \\ 0.635 \end{bmatrix}.$$

This gives

$$a_0 = e^{0.892} = 2.44,\ a_1 = b_1 = 0.635,$$

and the least-square curve is

$$x = 2.44e^{0.635t}.$$

Solution 2. We will use Gauss-Newton method to solve the nonlinear least-square problem directly. Consider the nonlinear function

$$f(t, a) = a_0 e^{a_1 t}, \quad a = (a_0, a_1).$$

The Jacobian matrix is

$$J = \begin{bmatrix} e^{a_1} & a_0 e^{a_1} \\ e^{2a_1} & 2a_0 e^{2a_1} \\ e^{3a_1} & 3a_0 e^{3a_1} \\ e^{4a_1} & 4a_0 e^{4a_1} \\ e^{5a_1} & 5a_0 e^{5a_1} \end{bmatrix}$$

and the normal equation $J^T J \Delta a = J^T \Delta y$ becomes

$$\begin{bmatrix} e^{2a_1} + e^{4a_1} + e^{6a_1} + e^{8a_1} + e^{10a_1} & a_0(e^{2a_1} + 2e^{4a_1} + 3e^{6a_1} + 4e^{8a_1} + 5e^{10a_1}) \\ a_0(e^{2a_1} + 2e^{4a_1} + 3e^{6a_1} + 4e^{8a_1} + 5e^{10a_1}) & a_0^2(e^{2a_1} + 4e^{4a_1} + 9e^{6a_1} + 16e^{8a_1} + 25e^{10a_1}) \end{bmatrix}.$$

$$\begin{bmatrix} \Delta a_1 \\ \Delta a_2 \end{bmatrix} = \begin{bmatrix} e^{a_1} & e^{2a_1} & e^{3a_1} & e^{4a_1} & e^{5a_1} \\ a_0 e^{3a_1} & 2a_0 e^{2a_1} & 3a_0 e^{3a_1} & 4a_0 e^{4a_1} & 5a_0 e^{5a_1} \end{bmatrix} \begin{bmatrix} \Delta y_1 \\ \Delta y_2 \\ \Delta y_3 \\ \Delta y_4 \\ \Delta y_5 \end{bmatrix}.$$

Here

$$\begin{bmatrix} \Delta a_1 \\ \Delta a_2 \end{bmatrix} = \begin{bmatrix} a_0^{(k+1)} - a_0^{(k)} \\ a_1^{(k+1)} - a_1^{(k)} \end{bmatrix},$$

and

$$\Delta y_i = y_i - a_0^{(k)} e^{a_1^{(k)}}, \quad 1 \le i \le 5.$$

Choosing an initial vector

$$\begin{bmatrix} a_0^{(0)} \\ a_1^{(0)} \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix}$$

and using the iteration scheme

$$\begin{bmatrix} a_0^{(k+1)} \\ a_1^{(k+1)} \end{bmatrix} = \begin{bmatrix} a_0^{(k)} \\ a_1^{(k)} \end{bmatrix} + (J^T J)^{-1} J^T \begin{bmatrix} y_1 - a_0^{(k)} e^{a_0^{(k)}} \\ y_2 - a_0^{(k)} e^{a_0^{(k)}} \\ y_3 - a_0^{(k)} e^{a_0^{(k)}} \\ y_4 - a_0^{(k)} e^{a_0^{(k)}} \\ y_5 - a_0^{(k)} e^{a_0^{(k)}} \end{bmatrix}$$

we obtain

$$\begin{bmatrix} a_0^{(1)} \\ a_1^{(1)} \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \end{bmatrix} + \begin{bmatrix} 25472.8 & 123383 \\ 133383 & 602214 \end{bmatrix}^{-1} \begin{bmatrix} 2.718 & 7.389 & 20.086 & 54.598 & 148.413 \\ 2.718 & 14.778 & 60.257 & 218.393 & 742.066 \end{bmatrix} \begin{bmatrix} 1.882 \\ 1.431 \\ -4.086 \\ -23.298 \\ -89.913 \end{bmatrix}$$

$$= \begin{bmatrix} 1.386 \\ 0.801 \end{bmatrix}$$

Iterating again we obtain

$$\begin{bmatrix} a_0^{(2)} \\ a_1^{(2)} \end{bmatrix} = \begin{bmatrix} 1.386 \\ 0.801 \end{bmatrix} + \begin{bmatrix} 3777.53 & 24873.7 \\ 24873.7 & 166018 \end{bmatrix}^{-1} \begin{bmatrix} 2.228 & 4.965 & 11.064 & 24.653 & 54.934 \\ 3.089 & 13.768 & 46.017 & 136.716 & 380.802 \end{bmatrix} \begin{bmatrix} 1.511 \\ 1.936 \\ 0.661 \\ -2.879 \\ -17.66 \end{bmatrix}$$

$$= \begin{bmatrix} 2.104 \\ 0.651 \end{bmatrix}.$$

The subsequent iterations can be calculated as

$$\begin{bmatrix} a_0^{(3)} \\ a_1^{(3)} \end{bmatrix} = \begin{bmatrix} 2.428 \\ 0.635 \end{bmatrix}, \quad \begin{bmatrix} a_0^{(4)} \\ a_1^{(4)} \end{bmatrix} = \begin{bmatrix} 2.431 \\ 0.636 \end{bmatrix}, \quad \begin{bmatrix} a_0^{(5)} \\ a_1^{(5)} \end{bmatrix} = \begin{bmatrix} 2.431 \\ 0.636 \end{bmatrix}, \quad \cdots .$$

We see that if the margin of error is three decimal points, then we have achieved the required accuracy at the 4th iteration and obtain

$$a_0 = 2.431, \quad a_1 = 0.636$$

Comparing with the answer in Solution 1, we see that they agree up to the first decimal point. The resulting curves are shown in Figure 4.5. The two curves are virtually indistinguishable.

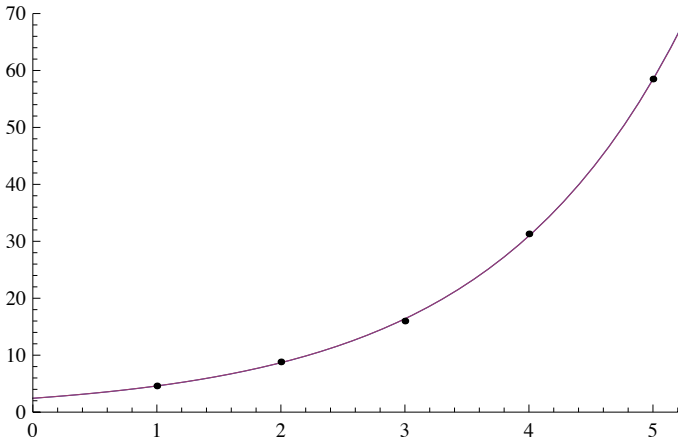


Figure 4.5: The least-square curve for Example 4.

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