FACULTY OF MATHEMATICS, PHYSICS AND INFORMATICS
COMENIUS UNIVERSITY
BRATISLAVA

THE MATHEMATICS OF INFECTIOUS DISEASES

MASTER'S THESIS

Bratislava 2007 Lenka Bubniaková

THE MATHEMATICS OF INFECTIOUS DISEASES

MASTER'S THESIS

Lenka Bubniaková

COMENIUS UNIVERSITY

FACULTY OF MATHEMATICS, PHYSICS AND INFORMATICS

DEPARTMENT OF MATHEMATICAL ANALYSIS AND NUMERICAL MATHEMATICS

mathematics

Director of Studies: Doc.RNDr.Jaroslav Jaroš,Csc.

BRATISLAVA 2007

Abstract

BUBNIAKOVÁ, Lenka: The Mathematics of Infectious Diseases [Master's Thesis]. Comenius University in Bratislava. Faculty of Mathematics, Physics and Informatics; Department of mathematical analysis and numerical mathematics. Director od Studies: Doc. RNDr. Jaroslav Jaroš CSc., Bratislava: FMFI UK, 2007.

This study aims at providing an understanding of deterministic modeling applied to the population dynamics of infectious diseases. In the first chapters, it includes historical backround, motivations and the terminology needed to understand the problems and the models themselves. Later it deals with SI, SIR and SEIR models and their modifications, which were made for these models in order to fit the data more precisely. At last, it deals with SIR and SEIR model with non-linear incidence rates and the stability of its solutions.

key words: mathematical epidemiology, (deterministic) SI/SIR/SEIR models

Abstract

BUBNIAKOVÁ, Lenka: Matematika infekčných chorôb [diplomová práca]. Univerzita Komenského v Bratislave. Fakulta matematiky, fyziky a informatiky; Katedra matematickej analýzy a numerickej matematiky. Vedúci diplomovej práce: Doc. RNDr. Jaroslav Jaroš CSc., Bratislava: FMFI UK, 2007.

Cieľom tejto práce je vnesenie svetla do deterministického modelovania, aplikovaného v populačnej dynamike infekčných chorôb. V prvých kapitolách práca zahŕňa historický úvod, motivácie a terminológiu, ktorá je potrebná na porozumenie problematike a modelom samotným. Neskôr sa v práci rozoberajú SI, SIR a SEIR modely aj s ich modifikáciami, ktoré vznikli kvôli vernejšiemu modelovaniu reality. Nakoniec sa v práci opisujú SIR a SEIR modely s nelineárnymi incidenčnými pomermi a stabilita ich riešení.

kľúčové slová: matematická epidemiológia, (deterministické) SI/SIR/SEIR modely

Contents

List of Figures

Chapter 1

Introduction

"I simply wish that, in a matter which so closely
concerns the wellbeing of the human race, no decision
shall be made without all the knowledge which
a little analysis and calculation can provide."
Daniel Bernoulli 1760

Infectious diseases have ever been a great concern of human kind since the very beginning of our history. At present, we still have to deal with plagues and diseases. Millions of people die annually from measles, malaria, tuberculosis, AIDS, ... and billions of others are infected. There was a belief in 1960s that infectious diseases would be soon eliminated with the improvement in sanitation, antibiotics, vaccinations, medical science and medical care. However, they are still the major causes of mortality in the developing countries. Moreover, infectious disease agents adapt and evolve, therefore we can observe new infectious diseases emerging and some already existing diseases re-emerged, sometimes after hundreds of years and/or even mutated. At present we know bacteria which are able to swim in pure bleach or survive in a dose of penicillin.

Together with the threat of biological weapons, whose research is lately concerned about microorganisms and lethal infectious diseases, we have great motivation to understand the spread and control of infectious diseases and their transmission characteristics. Mathematical epidemiology contributed to the understanding of the behavior of infectious diseases, its impacts and possible future predictions about its spreading. Mathematical models are used in comparing, planning, implementing, evaluating and optimizing various detection, prevention, therapy and control programs.

Epidemiology is the study of health and disease in human population. It is

the study of the distribution and determinants of health-related events in specified populations, and the application of this study to control health problems.

When talking about an *infectious disease*, we talk about a communicable disease. It is an illness which arises through transmission of an infectious agent (or its toxic products) from an infected individual to a host. The transmission can be either direct or indirect:

Direct Transmission - transfer of an infectious agent from the infected individual directly to the host (touching, biting, sexual intercourse, ...)
Indirect Transmission - transfer of an infectious agent by contaminated inanimate objects (aerosolized agents suspended in air for a long period of time, environment contamination, water/food contamination, ...)

The disease causing agent can be either micro parasitic or macro parasitic. The former follows the human → human transfer concept (gonorrhea, tuberculosis), while the latter follows the human → carrier → human concept (malaria - mosquito, black plague - rats). The *carrier* is an individual who harbors the infectious agent but does not show any symptoms of clinical illness. It is a potential source of infection because the carrier can transmit the agent.
The main disease causing microorganisms are:

viruses (influenza, measles, rubella, chicken pox, ...),
bacteria (meningitis, gonorrhea, tuberculosis, ...),
parasites (fleas, ticks, ...)
fungi (skin mould)
protozoa
helminths (worms)
prions.

The prions were discovered just recently and there is strong evidence that they are the cause for spongiform encephalopathy (BSE or "mad cow disease"). Actually, most of the diseases that cause epidemics are quite new: Lyme disease (1975), Legionarre's disease (1976), toxic - shock syndrome (1978), hepatitis C (1989), hepatitis E (1990), hantavirus (1993). Acquired immunodeficiency syndrome (AIDS) with its agent human immunodeficiency virus (HIV) is the most spread disease for which we still cannot find an effective treatment. We recognized the virus in 1982. People die in millions due to this virus each year and millions of others are infected.

We differ in epidemic, endemic and pandemic:
endemic - habitual presence (usual occurrence) of a disease within a given geographical area;
a disease always present
epidemic - occurrence of an infectious disease clearly in excess of normal expectancy;
sudden outbreak of a disease
pandemic - worldwide epidemic affecting exceptionally high proportion of the global population

Some factors associated with the increased risk of human disease are shown in the table:

Host Characteristics	Agent	Environmental Factors
Age	Biologic (Bacteria, Viruses)	Temperature
Sex	Chemical (Poison, Smoke)	Altitude
Race	Physical (Trauma, Radiation)	Crowding
Occupation	Nutritional (Lack, Excess)	Housing
Marital Status		Neighborhood
Genetics		Water, Food
Previous Diseases		Air Pollution
Immune Status		Sanity

It is becoming very easy for new diseases to spread as the viruses adapt to the medicine and vaccination and change their structure. Another factor which supports the spread of epidemics is the modern transportation which enables millions of people to cross international boarders and transfer exotic diseases. Population explosion and missing sanitation and/or medical care in underdeveloped countries is the main cause of great epidemics which kill millions of people. Also, with the rising standard in our medical service, we often loose our natural immunity. It is so due to the sterile environment we live in or due to vitamins we take in the form of pills, instead of getting them from the natural sources. Our body does not have any need to create antibodies for certain diseases because we get them in the form of vitamin pills or vaccination. There are many other factors which can affect the disease spreading and its speed. The mathematical models I describe in this paper provide great insight into disease spreading, ways how to control it and give reasoned estimates and/or predictions.

Chapter 2

Historical Background

The first major epidemic which we can find in the records of historians and scholars is the Plague of Athens (430 - 428 BC). The most precise description is provided by the first scientific historian - Thucydides (460 - 400 BC) - including the symptoms, disease progression and numbers of deaths. Hippocrate's (459 - 337 BC) work, "On the Epidemics", tells us about the factors which were affecting the disease spreading and ways of the spreading at that time.

Epidemics, which were killing in millions, occurred in 14th century when 25 million people died in Europe due to Bubonic Plague (Black Death, 1347 - 1350). The Black Death virus stayed within the population after the end of the epidemic outbreak and reappeared in Britain (Plague of London) in 1665. Its name, Black Death, comes from its symptoms: the black color of the tell-tale lumps that foretold its presence in a victim's body and death for the inevitable result. The plague germs were carried by fleas which lived as parasites on rats. The islands were never totally free of the plague (the plague stayed within the population on the endemic level), but it was like an unpleasant possibility that people just learned how to live with it while they got on with their business. This time it was different, the virus mutated. The plague killed more than 100 000 people in the town of London during the next epidemic strike. Another disastruous epidemic attacked Aztecs' population in 16th century - Smallpox plague killed 35 million. A recent influenza pandemic occurred after the First World War and killed 20 million of the world's population (1919). At present, we still have great outbreaks of epidemics: 1905-1906 the Bombay plague, 2003 SARS in Singapore (Severe Acute Respiratory Syndrome). We have also threats of epidemics as the viruses mutate very quickly (eg. the virus of Creutzfeldt Jacob's disease mutated and "mad cow disease" appeared; the avian influenza virus changed in a way that it passed on to humans).

Although the epidemiology itself has long history, mathematical study of dis-

eases and their spreading is at most just over three hundred years old. It all started in 1662 when John Graunt published his "Natural and Political Observations made upon the Bills of Mortality". In this book, he discussed various demographic problems of seventeenth century Britain. He made observations on the death records and calculated risks of death concerning certain disease. Graunt's analysis of the various causes of death provided the first systematic method for estimating the comparative risks of dying from the plague as against other diseases. This is the first approach to the theory of competing risks which is now used in modern epidemiology.

A century later, Daniel Bernoulli showed more theoretical approach to the effects of a disease. In 1760 he published the first epidemiological model. His aim was to demonstrate that inoculation with live virus obtained directly from a patient with a mild case of smallpox would reduce the death rate and increase the population of France. D'Alembert developed in 1761 an alternative method for dealing with competing risks of death, which is applicable to non-infectious diseases as well as to infectious diseases.

In middle 1800's Louis Pasteur confirmed experimentally the germ theory of the disease and he created the first vaccine for rabies. At the same time, Robert Koch became famous for the discovery of the anthrax bacillus (1877), the tuberculosis bacillus (1882) and the cholera vibrio (1883) and for his development of Koch's postulates. Diseases were no more punishment of gods or some kind of witchcraft. The science could explain "why" and mathematics could explain "how". Pragmatic approaches were limited and there was appropriate theory to explain the mechanism by which epidemics spread. The idea of passing on a bacterial disease through contact between an infected and healthy individual became familiar.

Modern mathematical biology begins with Hamer. He in 1906 first applied the Simple Mass Action Principle [1] for a deterministic epidemic model in discrete time. Ross's Simple Epidemic Model was published in 1911 and Generalised Epidemic Model produced by Kermack and McKendrick in 1927. These models have

[1]The Law of Mass Action has applicability in many areas of science. In chemistry, it is also called Fundamental Law of Chemical Kinetics (the study of rates of chemical reactions), formulated in 1864 - 1879 by the Norwegian scientists Cato M. Guldberg (1836 - 1902) and Peter Waage (1833 - 1900). The law states that for a homogeneous system, the rate of any simple chemical reaction is proportional to the probability that the reacting molecules will be found together in a small volume. Applied to population processes, if the individuals in population mix homogeneously, the rate of interaction between two different cohorts of the population is proportional to the product of the numbers in each of the cohorts concerned. If several processes occur simultaneously, then the effects on the numbers in any given cohort from these processes are assumed to be additive. Therefore in case of epidemic modeling, the law is applied to rates of transition of individuals between two interacting categories of the population (e.g. susceptibles who become infectives after an adequate contact).

deterministic character and are still widely used although new models were created taking into consideration various factors like migration, vaccination and its gradual loss, chemotherapy, quarantine, passive immunity, genetic heterogeneity, non-uniformly distribution of population, etc. For some diseases there exist specific models which describe their behavior. In 1969 important generalisations were made for epidemic models by Severo, and also by Anderson and May. They did not expect homogeneous mixing of population. Following these results, in 1987 Liu showed important results concerning non-linear incidence rates in their equations (incidence - number of new cases per unit time). Great number of models have been formulated, mathematically analyzed and applied to infectious diseases. Special models have been created for diseases like smallpox, malaria, AIDS, SARS, measles, rubella, cholera, whooping cough, diphteria, gonorrhea, syphilis, herpes, etc.

Chapter 3

Stochastic versus Deterministic Models

Two types of models are useful in the study of the infectious diseases at the population scale: these are stochastic and deterministic models.

Stochastic models rely on chance variation in risks of exposure, disease, and other factors. They provide much more insight into an individual-level modeling, taking into consideration small population size where every individual plays an important role in the model. Hence, they are used when known heterogeneities are important as in small or isolated populations. Stochastic models have several advantages. More specifically, they allow close watching of each individual in the population on a chance basis. They, however, can be laborious to set up and need many simulations to yield useful predictions. These models can become mathematically very complex and do not contribute to an explanation of the dynamics.

Deterministic models, also known as compartmental models, attempt to describe and explain what happens on the average at the population scale. They fit well large populations. These models categorize individuals into different subgroups (compartments). The SEIR model, for example, includes four compartments represented by the Susceptibles, Exposed, Infectious and Recovered. Between those compartments we have transition rates which tell us how the size of one compartment changes with respect to the other (see Figure 4.1). The best known transition rate is the force of infection or the attack rate which measures the rate at which susceptibles become infected (labeled β in the Figure 4.1).

Most of the models describing infectious disease behavior, which have been used until now, are deterministic because they require less data, are relatively easy to set up, and because the computer softwares are widely available and user-friendly. The dynamics of the SEIR model (and therefore SIR, SIS, SI and other models as well) are now well understood so that deterministic models are commonly used to explore whether a particular control strategy will be effective. Furthermore, many other more complex models exist that can incorporate stochastic elements.

Chapter 4

Models and Notation

Epidemic modeling has three main aims. The first is to understand the spreading mechanism of the disease. For this, the essential part is a mathematical structure (equations give us threshold values and other constants which we use to describe the behavior of the disease). The second aim is to predict the future course of the epidemic (e.g. see subsection 6.1.1 - The Threshold Theorem of Epidemiology). The third is to understand how we may control the spread of the epidemic (education, immunization, isolation, ...). In order to make a reliable model and predictions, to develop methods of control, we must be sure that our model describes the epidemic closely, it contains all its specific features. So it is important to validate models by checking whether they fit the observed data.

In deterministic models, population size of the compartments are assumed to be functions of discrete time $t = 0, 1, 2, \ldots$ or differentiable functions of continuous time $t \geq 0$. This enables us to derive sets of difference or differential equations governing the process. The evolution of this process is deterministic in the sense that no randomness is allowed.

In order to make a model for a disease in a population we divide the population in few classes and we study the change of their numbers in time. The choice of which compartments to use in the model depends on the characteristics of a particular disease and the purpose of the model. Compartments with labels such as M, S, E, I, and R are used for the epidemiological classes. (see Figure 3.1)

If a pregnant woman is infected, her antibodies are transfered across placenta, so the new born infant has temporary passive immunity to that infection. The class M contains these infants with the *passive immunity*. When the infant looses his passive immunity, it enters the class of *susceptibles* S, together with the infants who did not get the maternal immunity. This is the class of people who can get infected. So when there is an adequate contact of an infective individual (from

class I) with a susceptible individual (from class S) and this individual gets infected, then this susceptible enters the class of *exposed* individuals E. These are the people in latent period who are infected but not yet infectious. When they become infectious (they are able to communicate the disease), then they enter class I - *infectious*. And finally, they enter the class R - *recovered*. These are people with permanent immunity - which is acquired. Acronyms for epidemiology models are based on the flow patterns between these compartments: SI, SIS, SIR, SIRS, MSEIR, MSEIRS, SEIR, SEIRS, SEI, SEIS.

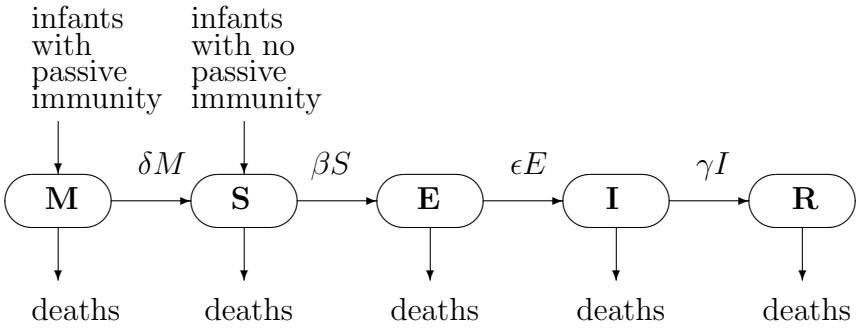
The threshold for many epidemiology models is the *basic reproduction number* R_0. It reflects the average number of infected people, when one infected individual is introduced into a host population where everyone is susceptible. It is a threshold quantity which determines whether the epidemic will occur or not. So if the number of infected individuals is higher than this value, then the epidemic spreads across the population. Realistic infectious disease models also took into consideration time t and age a as independent variables because the risks from an infection may be related to age, vaccination programs and time when the vaccination is taken by the individual, etc.

The infection rate of susceptibles individuals through contacts with infectious individuals is called *horizontal incidence* (S $\rightarrow$ I). If
S(t) denotes the number of susceptibles at time t,
I(t) denotes the number of infectives at time t,
N denotes the population size,
then we can write: $s(t) = \frac{S(t)}{N}$ and $i(t) = \frac{I(t)}{N}$ (fractions of respective populations)

If β is the average number of contacts (sufficient for transmission) of a person per unit time, then $\frac{\beta I}{N} = \beta i$ is average number of contacts with infectives per unit time of one susceptible. $\frac{\beta I}{N} S = \beta N i s$ is the number of new cases per unit time (because $S = Ns$). In this case the horizontal incidence is called *standard incidence*. The Simple Mass Action Principle $\eta IS = \eta(Ni)(Ns)$, with η as a mass action coefficient, is a standard for horizontal incidence. Comparing, we get $\eta N = \beta$. So *contact rate* β increases linearly with population size. Therefore we can write: $\frac{\eta N^v SI}{N}$ is the standard incidence if $v = 0$ and it is a mass action incidence if $v = 1$. As experiments show, standard incidence is more realistic than the simple mass action incidence [1] . Vertical incidence is sometimes considered. It is the incidence where an infant is born with an disease from its mother (infection rate of infants by their mothers).

[1]HETHCOTE,H.W.. The Mathematics of Infectious Diseases. Iowa: Siam Review, Vol.42, No.4, 2000, pp.603

Figure 4.1: MSEIR model



Lets introduce the threshold quantities. The *basic reproduction number* R_0 is the average number of secondary infections produced by one infected individual put into completely susceptible host society. That individual is there for the entire infectious period. The *contact number* σ is defined as average number of contacts of a typical infective during the infectious period. The contact have to be sufficient to transmit the disease. And another threshold quantity is the *replacement number* R - average number of secondary infections produced by a typical infective during the entire period of infectiousness. All the three threshold quantities are the same at the beginning of the epidemic. R_0 is defined only at the beginning of the epidemic but R and σ are defined at any times. For most models R_0 and σ are the same but there are diseases where it is not true. After an epidemic R_0 is always more than R. The susceptible fraction is then less than 1, what means that not all adequate contacts result in a new infective. Therefore R is always less than σ in all the models (while $R_0 = \sigma$ holds just for some models).

$$R_0 \geq \sigma \geq R$$

Now suppose that the numbers in model compartments change as in Figure 4.1 . These correspond to exponentially distributed waiting times in the compartments [2]. Let show it on the exposed class. By calculation we get $E(t) = e^{-\epsilon t}$ is the fraction which is still in exposed class, t units after entering this class and with $1/\epsilon$ as the mean waiting time called *mean latent period*. Similarly $1/\delta$ is *the mean period of passive immunity* and $1/\gamma$ is *the mean infectious period*.

[2]HETHCOTE, H.W.. The Mathematics of Infectious Diseases. Iowa: Siam Review, Vol.42, No.4, 2000, pp.603

M (m)	Passive immune infants (fraction of M)
S (s)	Susceptible (fraction of S)
E (e)	Exposed (fraction of E)
I (i)	Infectious (fraction of I)
R (r)	Recovered with acquired immunity (fraction of R)
β	Contact rate
$1/\delta$	Average period of passive immunity
$1/\epsilon$	Average latent period
$1/\gamma$	Average infectious period
R_0	Basic reproduction number
σ	Contact number
R	Replacement number

Chapter 5

SI Model

The SI Model is the simplest one among the epidemic models. That is why it is also called the *Simple Model*. We divide the population just in the susceptible compartment S(t) and the infectious compartment I(t). We do assume the disease to be highly infectious but not serious, which means that the infectives remain in contact with susceptibles for all time $t \geq 0$. We also assume that the infectives continue to spread the disease till the end of the epidemic, the population size to be constant (S(t) + I(t) = N) and homogeneous mixing of population. Infection rate is proportional to the number of infectives, i.e.

$$\beta = r\lambda I$$

We have a pair of ordinary differential equations for this model:

$$\frac{dS(t)}{dt} = -r\lambda I(t)S(t) \tag{5.1}$$

$$\frac{dI(t)}{dt} = r\lambda I(t)S(t) \tag{5.2}$$

where

$$N = S(t) + I(t)$$

$$S(t) = N - I(t)$$

and therefore we get

$$\frac{dI}{dt} = r\lambda I(t)\Big[N - I(t)\Big], \tag{5.3}$$

what is known as the *logistic growth equation*.

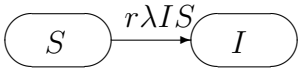


Figure 5.1: SI model

That is a separable non-linear ordinary differential equation so we calculate:

$$\frac{1}{I(t)(N-I(t))}\frac{dI}{dt} = r\lambda$$

$$\int_0^t \frac{1}{I(t)(N-I(t))}\frac{dI}{dt}\mathrm{d}t = \int_0^t r\lambda \mathrm{d}t$$

$$\int_{I(0)}^{I(t)} \frac{1}{u(N-u)}\mathrm{d}u = \int_0^t r\lambda \mathrm{d}t$$

$$\frac{1}{N}\int_{I(0)}^{I(t)} \left[\frac{1}{u} + \frac{1}{N-u}\right]\mathrm{d}u = \int_0^t r\lambda \mathrm{d}t$$

$$[ln(u) - ln(N-u)]_{u=I(0)}^{I(t)} = r\lambda N t$$

$$[ln(t) - ln(N-t)] - [lnI(0) - ln(N-I(0))] = r\lambda N t$$

$$ln\frac{I(t)}{N-I(t)}\frac{N-I(0)}{I(0)} = r\lambda N t$$

$$e^{r\lambda N t} = \frac{I(t)(N-I(0))}{I(0)(N-I(t))} = \frac{NI(t) - I(t)I(0)}{NI(0) - I(t)I(0)}$$

$$e^{r\lambda N t}[NI(0) - I(t)I(0)] = NI(t) - I(t)I(0)$$

$$Ne^{r\lambda N t}I(0) - e^{r\lambda N t}I(t)I(0) = NI(t) - I(t)I(0)$$

$$I(t)[I(0) - N - I(0)e^{r\lambda N t}] = Ne^{r\lambda N t}I(0)$$

$$I(t) = \frac{Ne^{r\lambda N t}I(0)}{I(0) - N - I(0)e^{r\lambda N t}}$$

$$I(t) = \frac{I(0)N}{I(0) + (N-I(0))e^{-r\lambda N t}} \tag{5.4}$$

As we can see I approaches N asymptotically with $t \to \infty$.
Therefore finally every susceptible joins the infectious compartment in this model,

everybody becomes infected what is, in fact, the "end" of the epidemic in mathematical sense. But both $S(t) \geq 0$ and $I(t) \geq 0$ for all positive finite values of t, so we may ask when there is the end of the epidemic in practical terms. We could define this as $T_1 \equiv inf\{t : I(t) > N - 1\}$, i.e. when the number of infectives is within 1 of its final value. As $I(t)$ has positive derivative for finite t, we determine T_1 from $I(T_1) = N - 1$. From (5.4) we then get:

$$\frac{I(0)N}{I(0) + (N - I(0))e^{-r\lambda NT_1}} = N - 1$$

$$I(0) = (N-1)I(0) + (N-1)N - I(0)e^{-r\lambda NT_1}$$

$$\ln \frac{I(0)N - (N-1)I(0)}{(N-1)(N-I(0))} = -r\lambda NT_1$$

$$\ln \frac{I(0)N - I(0)N - I(0)}{(N-1)(N-I(0))} = -r\lambda NT_1$$

$$T_1 = \frac{1}{r\lambda N} \ln \frac{(N-1)(N-I(0))}{I(0)} \tag{5.5}$$

We can get view of the progress of the disease by plotting the rate of occurrence of new infectives $dI(t)/dt$ into a graph (see Figure 5.2).

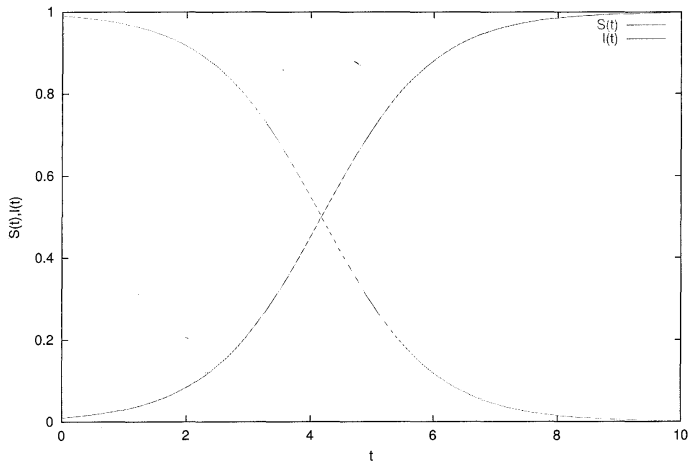


Figure 5.2: Simple epidemic

5.1 Model Refinement

The SI model is the simplest model for the modeling of an infectious disease behavior. However, the data obtained from the statistics and surveys do not always fit in this model. If we plot observed data on the graph (the dependency of the number of infctives on time) we can see that the logistic model fits the observed data well near the beginning and end of the epidemic, but not so well in between. We can improve the model by extending the equation (5.3) in this form:

$$\frac{dI}{dt} = kI\left[1 - \left[\frac{I}{N}\right]^p\right] \tag{5.6}$$

where p and k are constants. We try to find constant p when creating a model from the statistics and observed data. Substitute $u = (I/N)^p$. Then $I = (uN^p)^{1/p} = u^{1/p}N$ and

$$du = \frac{pI^{p-1}}{N^p}dI$$

$$du = \frac{p[u^{1/p}N]^{p-1}}{N^p}dI$$

$$du = \frac{pu^{(p-1)/p}N^{p-1}}{N^p}dI$$

$$du = pu^{(p-1)/p}N^{-1}dI$$

So we write (5.6) as

$$\frac{1}{pu^{(p-1)/p}N^{-1}}du = ku^{1/p}N[1-u]dt$$

$$\frac{1}{u^{(p-1)/p}u^{1/p}[1-u]}du = kNpN^{-1}dt$$

$$\frac{1}{u[1-u]}du = kpdt$$

In similar way as previous equation, we calculate this one:

$$\int_{u(0)}^{u(t)} \frac{1}{u} + \frac{1}{1-u}du = \int_0^t kpdt$$

$$[\ln u - \ln(1-u)]_{u(0)}^{u(t)} = pkt$$

$$\int_0^t \frac{1}{u} + \frac{1}{1-u}du = pkt$$

$$\ln u(t) - \ln[1-u(t)] - \ln u(0) + \ln[1-u(0)] = pkt$$

$$\ln\left[\frac{u(t)\ln[1-u(t)]}{u(o)[1-u(t)]}\right] = pkt$$

$$e^{pkt} = \frac{u(t)[1-u(0)]}{u(0)[1-u(t)]}$$

$$e^{pkt} = \frac{u(t)-u(0)u(t)}{u(0)-u(t)u(0)}$$

$$e^{pkt}[u(0)-u(0)u(t)] = u(t)-u(t)u(0)$$

$$u(t) = \left[\frac{I(t)}{N}\right]^p = \frac{e^{pkt}u(0)}{1+u(0)[e^{pkt}-1]}$$

$$I(t) = \frac{N}{\left[\frac{1}{u(0)e^{pkt}} + \left[1-\frac{1}{e^{pkt}}\right]\right]^{1/p}}$$

$$I(t) = \frac{N}{[1+Ke^{-pkt}]^{1/p}}$$

If $I(0) = I_0$ we get:

$$I(t) = \frac{N}{[1+[(N/I_0)^p - 1]e^{-pkt}]^{1/p}} \tag{5.7}$$

where p and k are constants.

Looking at Figures (5.3) and (5.4) we can compare the extension to which the Simple Model and the Modified Model respectively follow the reality.

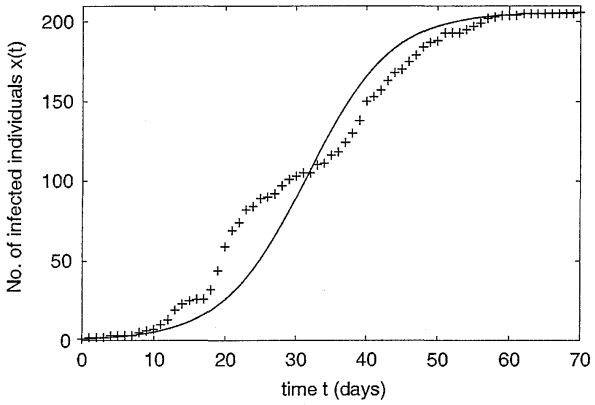


Figure 5.3: Outbreak data (+) and Simple Model solution (-)

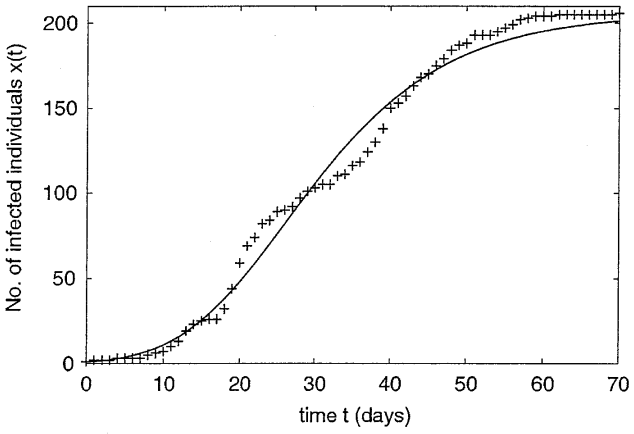


Figure 5.4: Outbreak data (+) and Modified Model solution (-)

5.2 Model Modifications

5.2.1 Fisher's Equation

In this model we take into consideration the number of individuals in the compartments in a certain time and place. We speak about *population densities* of susceptibles and infectives. Our assumptions remain the same, meaning a constant population size $N = S(x,t) + I(x,t)$, no recovery or latent period, homogeneous mixing of population and we add one more assumption: individuals disperse by a diffusion process with a diffusion constant D. In this case we have the partial differential equations:

$$\frac{\partial S}{\partial t} = -r\lambda I(x,t)S(x,t) + D\frac{\partial^2 S}{\partial x^2}$$

$$\frac{\partial I}{\partial t} = r\lambda I(x,t)S(x,t) + D\frac{\partial^2 I}{\partial x^2}.$$

Because we know that $S(x,t) = N - I(x,t)$ we can use it to get

$$\frac{\partial I}{\partial t} = r\lambda I(x,t)[N - I(x,t)] + D\frac{\partial^2 I}{\partial x^2}.$$

This is so called Fisher's Equation, introduced by Fisher in 1937 for the spread of a gene in a population.

We look for the traveling wave solution. Let $I(x,t) = \bar{I}(z)$ where $z = x - ct$, then we calculate

$$\frac{\partial I(x,t)}{\partial t} = \frac{\partial \bar{I}(x,t)}{\partial z}\frac{\partial z}{\partial t} = \frac{\partial \bar{I}}{\partial z}(-c)$$

$$\frac{\partial^2 I}{\partial x^2} = \frac{\partial}{\partial x}\left[\frac{\partial \bar{I}}{\partial z}\underbrace{\frac{\partial z}{\partial x}}_{=1}\right] = \frac{\partial}{\partial x}\left[\frac{\partial \bar{I}}{\partial z}\right] = \frac{\partial}{\partial z}\frac{\partial z}{\partial x}\frac{\partial \bar{I}}{\partial z} = \frac{\partial^2 \bar{I}}{\partial z^2}.$$

Hence, the system transforms into the following

$$-c\frac{\partial \bar{I}}{\partial z} = r\lambda \bar{I}(z)[N - \bar{I}(z)] + D\frac{\partial^2 \bar{I}}{\partial z^2}.$$

Let put this equal to zero to find the steady-states

$$0 = D\frac{\partial^2 \bar{I}}{\partial z^2} + c\frac{\partial \bar{I}}{\partial z} - r\lambda \bar{I}^2(z) + r\lambda \bar{I}(z)N.$$

So we have two equilibria:

- $\bar{I} = 0$
- $\bar{I} = N$.

By linearising about $\bar{I}$ we get

$$D\frac{\partial^2 \bar{I}}{\partial z^2} + c\frac{\partial \bar{I}}{\partial z} + r\lambda N\bar{I}(z) = 0.$$

Suppose the solution is of the form $\bar{I}(z) = e^{\alpha z}$ and then we get the characteristic equation

$$D\alpha^2 + c\alpha + r\lambda N = 0$$

and so

$$\alpha = \frac{-c \pm \sqrt{c^2 - 4Dr\lambda N}}{2D}.$$

- If $c^2 - 4Dr\lambda N < 0$ then α is complex and $\bar{I}(z) = Ae^{\alpha z} = Ae^{\alpha(u+iv)} = e^{zu}[A_1 \cos zv + A_2 \sin zv]$. That means for some z, $\bar{I}(z) < 0$. But we want a non-oscillatory solution so we are looking for the other case.
- $c^2 - 4Dr\lambda N \geq 0$, which implies $|c| \geq c_{min} = 2\sqrt{Dr\lambda N}$.

For many initial conditions, solutions of this problem tend to the traveling wave with minimum wave speed.

5.2.2 The New Model

This model is analogous to the Fisher's Equation Model, but we also take into consideration migration of the population from one place to the other. The population density is constant, $S(x,t)+I(x,t)=N$, we have homogeneous mixing of population, no recovery or latent period, no birth or death. The individuals leave the place at rate D and the proportion of individuals leaving place y and going to x is $k(x,y)$. The system is then composed of two integro-differential equations:

$$\frac{\partial S}{\partial t} = -r\lambda I(x,t)S(x,t) - DS(x,t) + D\int_\Omega k(x,y)S(y,t)dy$$
$$\frac{\partial I}{\partial t} = r\lambda I(x,t)S(x,t) - DI(x,t) + D\int_\Omega k(x,y)I(y,t)dy.$$

We follow the steps in the previous model and we get the traveling wave solution: $S(x,t) = N - I(x,t)$ and therefore

$$\frac{\partial I}{\partial t} = r\lambda I(x,t)[N - I(x,t)] - dI(x,t) + D\int_\Omega k(x,y)I(y,t)dy$$

assuming $k(x,y) = k(x-y)$, $\Omega = R$ and $I(x,t) = \bar{I}(z)$ with $z = x - ct$ we have

$$-c\frac{\partial \bar{I}}{\partial z} = r\lambda \bar{I}(z)[N - \bar{I}(z)] - D\bar{I}(z) + D\int_R k(z-y)\bar{I}(y)dy.$$

We have the same equilibria as in the previous model: $\bar{I}(z) = 0$ and $\bar{I}(z) = N$, and we linearise around zero to get linear integro-differential equation:

$$-c\frac{\partial \bar{I}}{\partial z} = r\lambda N\bar{I}(z) - D\bar{I}(z) + D\int_R k(z-y)\bar{I}(y)dy.$$

Again, assuming that the solution is of the form $e^{\theta z}$, we get the characteristic equation

$$c\theta = r\lambda N - D + D\int_R k(u)e^{\theta u}du.$$

Also in this model we want a non-oscillatory solution, so we get:

$$c_{min} = D\left(\int_R k(u)e^{\theta u}du\right)'$$
$$r\lambda N = D\left[1 - \int_R k(u)e^{\theta u}du + \theta\left(\int_R k(u)e^{\theta u}du\right)'\right].$$

For many initial conditions, solutions of this problem tend to the traveling wave with minimum wave speed.

Chapter 6

SIR Models

In fact, there are two SIR models [1] formulated. They describe either an epidemic (that is a rapid outbreak of an infectious disease) or they describe an endemic (a disease present in the population for a long period of time where the class of susceptibles is being nourished by new income from births or recovered individuals who lost their temporal immunity). These two models are the foundations for the modern mathematical epidemiology and are still widely used in practice.

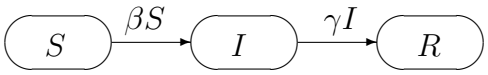


Figure 6.1: SIR model

[1] The SIR model is sometimes known as The Compartmental Model, Generalised Model or Kermack-McKendrick's Model after two mathematicians who formulated it first in 1927.

6.1 The General Epidemic Model

We assume that the population size is large and constant (except for death from the disease) and behaves as a "perfect" gas of particles in the sense that we assume homogeneous mixing for continuous time $t \geq 0$. Any person who has completely recovered from the disease acquired permanent immunity and the disease has a negligibly short incubation period (so an individual who contracts the disease becomes infective immediately afterwards). That enables us to divide the population into three compartments (see Figure 6.1): S(t) - susceptibles, I(t) - infectives, R(t) - recovered. Infection rate is proportional to the number of infectives, i.e.

$$\beta = r\lambda I$$

We have a system of equations:

$$\frac{dS(t)}{dt} = -r\lambda S(t)I(t) \tag{6.1}$$

$$\frac{dI(t)}{dt} = r\lambda I(t)S(t) - \gamma I(t) \tag{6.2}$$

$$\frac{dR(t)}{dt} = \gamma I(t) \tag{6.3}$$

$$\begin{cases} S(0) = S_0 > 0 \\ I(0) = I_0 > 0 \\ R(0) = R_0 = 0 \end{cases} \tag{6.4}$$

We can see that $\frac{d}{dt}[S(t) + I(t) + R(t)] = 0$, therefore it is true that the population size is constant:

$$S(t) + I(t) + R(t) = N. \tag{6.5}$$

We have the non-linear system of equations (6.1) - (6.4), so we calculate:

$$\frac{dI}{dS} = \frac{\gamma - r\lambda S}{r\lambda S} = \frac{\gamma}{r\lambda S} - 1 \tag{6.6}$$

$$dI = \left[\frac{\gamma}{r\lambda S} - 1\right] dS$$

$$\int_0^t 1 dI = \int_0^t \left[\frac{\gamma}{r\lambda S} - 1\right] dS$$

$$\left[\,|\,\right]_{t=0}^{t} = \left[\frac{\gamma}{r\lambda} lnS - S\right]_{t=0}^{t}$$

$$I(t) - I_0 = \frac{\gamma}{r\lambda} lnS(t) - \frac{\gamma}{r\lambda} lnS_0 - S(t) - S_0$$

$$S(t) + I(t) - \frac{\gamma}{r\lambda} lnS(t) = S_0 + I_0 - \frac{\gamma}{r\lambda} lnS_0 = const \tag{6.7}$$

what is a *conserved quantity*. So finally we have:

$$I(t) = S_0 + I_0 - S(t) + \rho ln \frac{S(t)}{S_0} \tag{6.8}$$

where $\rho \equiv \frac{\gamma}{\beta} \equiv \frac{\gamma}{r\lambda}$. Parameter ρ is called *relative removal rate*.

In the next subsection we are going to take a closer look at this system with its obits and we will get some results, which will enable us to see the course of the epidemic and make some predictions about its behaviour.

6.1.1 Threshold Theorem of Epidemiology

Lets observe the properties of this system of equations and the information it provides. Summing up (6.1) and (6.2) we get:

$$\frac{d}{dt}[S(t) + I(t)] = -\gamma I(t) < 0. \tag{6.9}$$

Therefore we have

$$S(t) + I(t) < N$$

what implies that the solution to the system is global in time.
From the relation (6.5) we have that $R(t) = N - S(t) - I(t)$. This enables us to consider just the system (6.1) - (6.2) because it is a closed system of differential equations. Now we are going to look at the orbits of this system.

$$\frac{dI}{dS} = \frac{\beta SI - \gamma I}{-\beta I} = -1 + \frac{\rho}{S}. \tag{6.10}$$

By integration we get

$$I(S) = I_0 + S_0 - S + \rho ln\frac{S}{S_0} \tag{6.11}$$

what is analogical to (6.8). The quantity $-1 + \frac{\rho}{S}$ is positive for $S < \rho$ and negative for $S > \rho$. Hence, I(S) is an increasing function of S for $S < \rho$ and decreasing function of S for $S > \rho$. From (6.10) we also see that $I(0) = -\infty$ and $I(S_0) = I(0) > 0$. Consequently, there exists a unique point S_∞, $0 < S_\infty < S_0$, such that $I(S_\infty) = 0$ and $I(S) > 0$ for $S_\infty < S \leq S_0$. The point $(S_\infty, 0)$ is an equilibrium point of (6.1)-(6.2) since both $\frac{dS}{dt}$ and $\frac{dI}{dt}$ vanish when $I = 0$. Therefore the orbits for $t_0 \leq t < \infty$ have the form described in the phase plane for this system (see Figure 6.2). When we look at this phase plain, we can observe the course of the epidemic as t runs from t_o to ∞. Point $(S(t), I(t))$ runs along the curve (6.11) and it moves in the direction of decreasing S, since S(t) decreases monotonically with time:
from (6.1) we observe

$$\frac{d}{dt}S(t) < 0$$

so that $S(t)$ is a decreasing function and

$$\lim_{t\to\infty} S(t) = S_\infty. \tag{6.12}$$

We can also obtain S_0 as the unique root of (6.3) for $t \to \infty$:

$$I_0 + S_0 - S_\infty + \rho ln\frac{S_\infty}{S_0} = 0. \tag{6.13}$$

S_∞ denotes the number of susceptibles who were never infected. But we can calculate the number of susceptibles at any time t from (6.1) and (6.3):

$$\frac{dS}{dR} = -\frac{1}{\rho}S(t)$$

$$\frac{1}{S}dS = -\frac{1}{\rho}dR$$

$$[lnS]_0^t = [-\frac{1}{\rho}R]_0^t$$

$$lnS(t) - lnS_0 = -\frac{1}{\rho}R(t) + \frac{1}{\rho}R_0$$

$$lnS(t) = lnS_0 + \frac{[R_0 - R(t)]}{\rho}$$

$$S(t) = e^{lnS_0 + \frac{[R_0 - R(t)]}{\rho}}$$

$$S(t) = S_0 e^{-\frac{[R(t) - R_0]}{\rho}} \geq S_0 e^{-\frac{N}{\rho}} > 0 \tag{6.14}$$

We see that this will be always a positive value, hence there always remains some susceptibles who are never infected.

To sum it up, if a small group of infectives is inserted into a group of susceptibles S_0 and $S_0 < \rho$, then the disease will die out rapidly. On the other hand, if $S_0 > \rho$, then $I(t)$ increases as $S(t)$ decreases to ρ, where it achieves its maximum value. $I(t)$ starts to decrease when $S(t)$ falls bellow this *threshold value* ρ. We may draw the following conclusions:

Theorem 1. *Let $(S(t), I(t))$ be a solution of (6.1)-(6.4) in $T = \{(S, I) : S \geq 0, I \geq 0, S + I \leq N\}$. If $S_0 < \rho$ then $I(t)$ decreases to 0 as $t \to \infty$. If $S_0 > \rho$ then $I(t)$ first increases up to a maximum value $I_{max} = I_0 + S_0 - \rho - ln\frac{\sigma}{S-0}$ and then decreases to 0 as $t \to \infty$. Also, $S(t)$ is a decreasing function and the limiting value S_∞ is the unique root of the equation $I_0 + S_0 - S_\infty + ln\frac{S_\infty}{S_0} = 0$*

It remains to demonstrate I_{max}. This is very interesting value, especially when we are interested in how harshly will the epidemic strike the population. We have $\frac{dI}{dt} = \beta SI - \gamma I = (\beta S - \gamma)I$. For the maximum holds $I' = 0$ and therefore $\beta S - \gamma = 0 \Rightarrow \beta S = \gamma \Rightarrow S = \frac{\gamma}{\beta} = \rho$. And so we get:

$$I_{max} = -\rho + \rho ln\rho + N - \rho lnS_0. \qquad \square$$

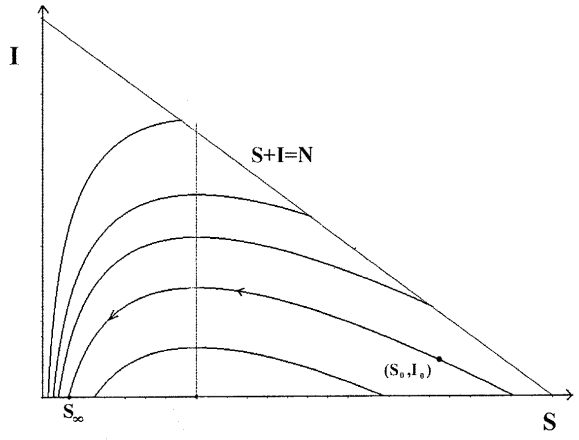


Figure 6.2: SI phase plane for the system (6.1)-(6.4)

Let's introduce *the basic reproductive number* for this model. We want to know how many secondary infectives appear in the population (composed only of susceptibles) after we introduce one infective into this population.

$$\frac{dI}{dt} = r\lambda SI - \gamma I = (r\lambda S - \gamma)I \approx (r\lambda N - \gamma)I$$

because we suppose $S_0 \approx N$. Now

$$R_0 := \frac{r\lambda N}{\gamma} = \frac{N}{\rho} \tag{6.15}$$

where $1/\gamma$ is the average infectious period. It is a decreasing function for $R_0 < 1$, therefore population of infectives dies out; but if $R_0 > 1$ it is an increasing function and the epidemics spreads. Or in other words, epidemic spreads if $N > \rho$ resp. $S_0 > \rho$ i.e. the initial number of susceptibles must exceed a threshold value ρ, otherwise the epidemic will die out.

Theorem 2. *Kermack - McKendrick. A general epidemic evolves according to the differential equations (6.1)-(6.3) from initial values* $(S_0, I_0, 0)$*, where* $S_0 + I_0 = N$.
(i) (Survival and Total Size). When infection ultimately ceases spreading, a positive number S_∞ *of susceptibles remains uninfected, and the total number*R_∞ *of individuals ultimately infected and removed equals to* $S_0 + I_0 - S_\infty$*. It is the unique root of the equation*

$$N - R_\infty = S_0 + I_0 - R_\infty = S_0 e^{-\frac{R_\infty}{\rho}}, \tag{6.16}$$

where $I_0 < R_\infty < S_0 + I_0$, $\rho = \gamma/\beta$ being the relative removal rate.
(ii) (Threshold Theorem). A major outbreak occurs if and only if $\frac{dI}{dt}(0) > 0$; this happens only if initial number of susceptibles $S_0 > \rho$.
(iii) (Second Threshold Theorem) If S_0 exceeds ρ by a small quantity ν, and if the initial number of infectives I_0 is small relative to ν, then the final number of susceptibles left in the population is approximately $\rho - \nu$, and $R_\infty \approx 2\nu$. In other words, the level of susceptibles is reduced to a point as far below the threshold as it originally was above it.

Proof:

(i) I have already come to these conclusions in the previous pages, so I am going to say just a brief summing up. From the equations (6.1) and (6.3) we have the following

$$\frac{1}{S}\frac{dS}{dt} = -\frac{\beta}{\gamma}\frac{dR}{dt} = -\frac{1}{\rho}\frac{dR}{dt},$$

from which we get

$$S(t) = S_0 e^{\frac{R_0 - R(t)}{\rho}}$$

Hence

$$S(t) = S_0 e^{-\frac{R(t)}{\rho}}, \tag{6.17}$$

as we assume R_0 to be equal to zero. As it is already shown in (6.13) and (6.14), for $t \to \infty$ we get

$$S_\infty = S_0 e^{-\frac{R_\infty}{\rho}} > 0.$$

$N - R_\infty = S_0 + I_0 - R_\infty = N - R_\infty = I_\infty + S_\infty$ where $I_\infty = 0$. Therefore $N - R_\infty = S_0 e^{-\frac{R_\infty}{\rho}}$.

(ii) In other words, we have to introduce an infective individual in the population full of susceptibles, if if we want to observe spreading of the infection. And this individual has to communicate the disease to the susceptibles, who again produce secondary cases and so on. If $\frac{dI}{dt} = 0$ ($\frac{dI}{dt} < 0$), it means that the infection has come to its peak (it is dying out). As I showed before (see section about the basic reproductive number R_0 and relation (6.15)) the infection will spread only if the initial number of susceptibles exceeds the relative removal rate ρ.

(iii) It remains to demonstrate this last part of the theorem. Using relations (6.3) and (6.17) together with the constraint on the population size yields

$$\frac{dR}{dt} = \gamma(N - R(t) - S_0 e^{-\frac{R(t)}{\rho}}).$$

This equation does not have an explicit solution for R in terms of t. But we can expand $e^{-\frac{R(t)}{\rho}}$ according to the formula $e^{-x} = 1 - x + \frac{1}{2}x^2 + O(x^3)$ and neglect the last term. We get

$$\frac{dR}{dt} \approx \gamma\left[N - S_0 + R\left(\frac{S_0}{\rho} - 1\right) - \frac{R^2 S_0}{2\rho^2}\right]$$

We express the right-hand side as following:

$$\frac{dR}{dt} \approx \frac{\rho^2\gamma}{2S_0}\left[(N - S_0)\frac{2S_0}{\rho^2} + \left(\frac{S_0}{\rho} - 1\right)^2 - \left(\frac{S_0}{\rho^2}\left[R - \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right)\right]\right)^2\right].$$

Setting

$$\alpha = \left[\frac{2S_0}{\rho^2}(N - S_0) + \left(\frac{S_0}{\rho} - 1\right)^2\right]^{\frac{1}{2}} \tag{6.18}$$

We get

$$\frac{dR}{dt} \approx \frac{\rho^2\gamma}{2S_0}\left[\alpha^2 - \left(\frac{S_0}{\rho^2}\left[R - \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right)\right]\right)^2\right]. \tag{6.19}$$

And we substitute

$$\alpha \tanh v = \frac{S_0}{\rho^2}\left[R - \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right)\right]. \tag{6.20}$$

So we get:

$$\frac{dR}{dt} \approx \frac{\rho^2\gamma}{2S_0}(\alpha^2 - \alpha^2 \tanh^2 v) \tag{6.21}$$

From the relation for α in (6.20) we also have:

- $R = \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right) + \frac{\rho^2\gamma}{S_0}\tanh v \Rightarrow$

$$\frac{dR}{dt} = \frac{\rho^2\alpha}{S_0} sech^2 v \frac{dv}{dt}. \tag{6.22}$$

- at $t = 0 \Rightarrow R_0 = 0 \Rightarrow$

$$v_0 = \tanh^{-1}\left(-\frac{1}{\alpha}\left[\frac{S_0}{\rho} - 1\right]\right) \tag{6.23}$$

Hence, (6.21) and (6.22) gives:

$$\frac{dR}{dt} \approx \frac{\rho^2\gamma}{2S_0}(\alpha^2 - \alpha^2 \tanh^2 v) = \frac{\rho^2}{S_0}\alpha sech^2 v \frac{dv}{dt}$$

$$\frac{\rho^2\gamma\alpha^2}{S_0} \underbrace{(1 - \tanh^2 v)}_{sech^2 v} = \frac{\rho^2\alpha}{S_0} sech^2 v \frac{dv}{dt}$$

because we know: $1 - \tanh^2 x = 1 - \frac{\sinh^2 x}{\cosh^2 x} = \frac{\cosh^2 x - \sinh^2 x}{\cosh^2 x} = \frac{1}{\cosh^2 x} = sech^2 x$. Hence,

$$\frac{dv}{dt} \approx \frac{1}{2}\gamma\alpha,$$

so

$$v \approx \frac{1}{2}\gamma\alpha t + v_0 \tag{6.24}$$

and we get the solution for $R(t)$ by solving the differential equation

$$\frac{dR}{dt} = \frac{\rho^2\alpha}{S_0} sech^2 v \frac{dv}{dt}$$

$$\int_0^t dR = \int_0^t \frac{\alpha\rho^2}{S_0} sech^2 v dv = \frac{\rho^2\alpha}{S_0}\int_0^t sech^2 v dv$$

$$R(t) = \frac{\alpha\rho^2}{S_0}[\tanh v]_0^t = \frac{\alpha\rho^2}{S_0}[\tanh v - \tanh v_0]$$

where we use the formula (6.24) to get

$$R(t) = \frac{\alpha\rho^2}{S_0}[\tanh(\frac{1}{2}\alpha\gamma t + v_0) - \frac{\alpha\rho^2}{S_0}[\tanh v_0]]$$

$$R(t) = \frac{\alpha\rho^2}{S_0}\left[\tanh\frac{1}{2}\alpha\gamma t + v_0\right] + \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right)$$

$$R(t) = \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right) + \frac{\alpha\rho^2}{S_0}\left[\tanh\frac{\alpha\gamma t}{2} + v_0\right]$$

and finally using (6.23) we obtain:

$$R(t) = \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1\right) + \frac{\alpha\rho^2}{S_0}\tanh(\frac{1}{2}\gamma\alpha t - \varphi) \tag{6.25}$$

$$\varphi = \tanh^{-1}\left[\frac{1}{\alpha}\left(\frac{S_0}{\rho} - 1\right)\right] \tag{6.26}$$

(6.25)-(6.26) defines a symmetric bell shaped curve (see Figure 6.4). It is so called *epidemic curve* of the disease . Epidemiologists are highly interested in this curve because we use it to compare the results predicted by our model with the data from public health statistics. During the epidemic we cannot accurately ascertain the number of new infectives, because we can recognize only those infectives who seek medical aid. Therefore this curve tells us whether the model follows the reality and to what extension.

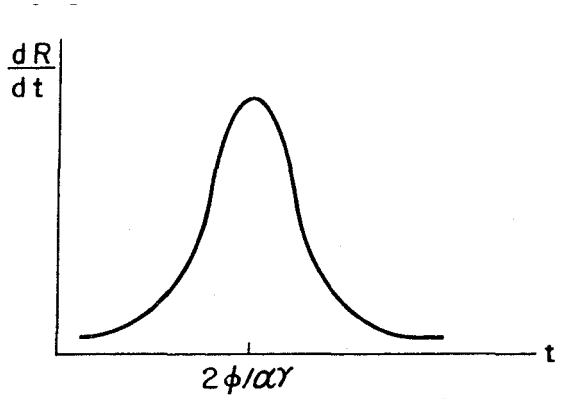


Figure 6.3: Epidemic curve

From the last equation we approximate $R_\infty = \lim_{t\to\infty} R(t)$, namely

$$R_\infty \approx \frac{\rho^2}{S_0}\left(\frac{S_0}{\rho} - 1 + \alpha\right).$$

Now, taking into consideration (6.18), when $2S_0(N - S_0) \ll (S_0 - \rho)^2$ and $S_0 > \rho$,

$$R_\infty = 2\rho\left(1 - \frac{\rho}{S_0}\right),$$

from which we get

$$R_\infty \approx 2\nu$$

if we take into consideration that $S_0 = \rho + \nu$ for some $\nu > 0$. Equivalently, $S_\infty \approx \rho + \nu - 2\nu = \rho - \nu$. □

The major significance of these statements was a mathematical proof, that in a major outbreak of a disease satisfying the simple model, not all of the susceptible population would get infected. According to our assumptions, we want susceptible population to be large, what would happen, for example, in a big city, in a closed community like a dormitory houses on universities, etc.

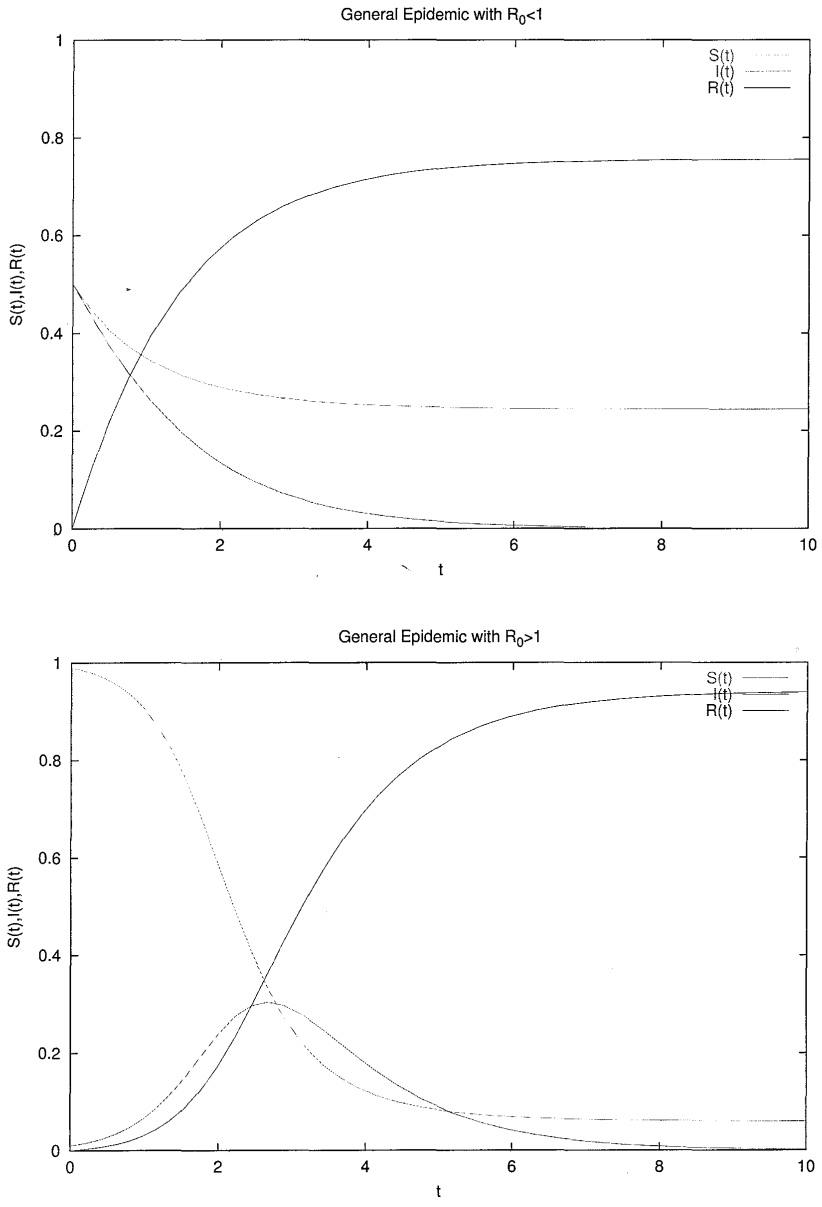


Figure 6.4: General Epidemic

6.1.2 Model Modification - Vaccination

The previous model does not consider any factor or element affecting the progress of the disease, like e.g. vaccination. If we assume that the susceptibles are vaccinated against the disease at a rate v, proportional to their number, then we have a modified system:

$$\frac{dS}{dt} = -r\lambda SI - vS$$

$$\frac{dI}{dt} = r\lambda SI - \gamma I.$$

We look at the orbits of this system:

$$\frac{dI}{dS} = \frac{r\lambda SI - \gamma I}{-r\lambda SI - vS} = \frac{\gamma I - r\lambda SI}{r\lambda SI - vS} = \frac{I(\gamma - r\lambda S)}{S(r\lambda I - v)}$$

$$\frac{r\lambda I + v}{I} dI = \frac{\gamma - r\lambda S}{S} dS$$

$$\left[r\lambda + \frac{v}{I}\right] dI = \left[\frac{\gamma}{S} - r\lambda\right] dS$$

$$[r\lambda I + v \log I]_0^1 = [\gamma \log S - r\lambda S]_{S(I_0)}^{S(I)}$$

So we get

$$r\lambda I(S) + v \log \frac{I(S)}{I_0} = \gamma \log \frac{S}{S_0} - r\lambda S + c$$

where c is a constant and it is equal to $r\lambda S_0 + r\lambda I_0$.
Taking into consideration the recovered class, we can show that $S(t)$ approaches to zero as t approaches to infinity for every solution of $(S(t), I(t))$ of this system:

$$\frac{dS}{dR} = \frac{-r\lambda SI - vS}{\gamma I} = \frac{S(-r\lambda I - v)}{\gamma I}$$

$$\frac{1}{S} dS = -fracr\lambda I + v\gamma I dR$$

$$\log \frac{S}{S_0} = -\frac{r\lambda I - v}{\gamma I}(R(t) - R_0)$$

$$S(t) = S_0 e^{-\frac{r\lambda I + v}{\gamma I}(R(t) - R_0)},$$

what tends to zero when we go to infinity with time.

The vaccinations can be of different kinds and the models may change from one disease to another. For comparison, lets assume that susceptibles are now vaccinated against the disease at a rate v proportional to the product of their numbers and the square of the members of $I(t)$:

$$\frac{dS}{dt} = -r\lambda SI - vSI^2$$

$$\frac{dI}{dt} = I(r\lambda S - \gamma).$$

so we look at the orbits again:

$$\frac{dI}{dS} = \frac{I(r\lambda S - \gamma)}{-r\lambda SI - vSI^2} = \frac{r\lambda S - \gamma}{-r\lambda S - vSI} = \frac{\gamma - r\lambda S}{S(r\lambda + vI)}$$

$$(vI + r\lambda I)dI = \frac{\gamma - r\lambda S}{S} dS$$

$$\left[\frac{vI^2}{2} + r\lambda I\right]_{I(S_0)}^{I(S)} = \left[\gamma \log S - r\lambda S\right]_{S_0}^{S}$$

$$\frac{vI^2 S}{2} + r\lambda I(S) - vI_0^2 - r\lambda I_0 = \gamma \log S - r\lambda S - \gamma \log S_0 + r\lambda S_0$$

$$\frac{vI^2(S)}{2} + r\lambda I(S) = \gamma \log S - r\lambda S + \underbrace{\gamma \log S_0 + r\lambda S_0 + vI_0^2 + r\lambda I_0}_{=const}.$$

Applying the same procedure we get, that at the end of the epidemic outbreak there will be some suscetibles left in the population:

$$\frac{dS}{dR} = \frac{-r\lambda SI - vSI^2}{\gamma I} = \frac{-r\lambda S - vSI}{\gamma} = \frac{S(-r\lambda - vI)}{\gamma}$$

$$\frac{1}{S} dS = \frac{-r\lambda - vI}{\gamma} dR$$

$$[\log S]_{S_0}^{S(t)} = \left[e^{\frac{-r\lambda - vI}{\gamma} R}\right]_{t_0}^{t}$$

$$S(t) = S_0 e^{\frac{-r\lambda - vI}{\gamma} \underbrace{[R(t) - R_0]}_{< N - vS_0}} \geq S_0 e^{-\frac{r\lambda - vI}{\gamma}[N - vS_0]} > 0.$$

We can also define an *intensity* i of the epidemic which is an important tool for

comparing the strikes. We define it as the proportion of the total number of susceptibles that finally contract the disease. We get:

$$i = \frac{I_0 + (S_0 - S_\infty)}{S_0}$$

where S_∞ is the root of the equation $S = S_0 e^{\frac{S - S_0 - I_0}{\rho}}$. We have already showed that $S(R) = S_0 e^{-\frac{R(t)}{\rho}}$ and we know that $R(\infty)$ is equal to the total population without the left susceptibles and infectives (this term is zero), so ve have $R_\infty = \underbrace{S_0 + I_0}_{N} - S - 0$. And we got that $S_\infty = S_0 e^{(S - S_0 - I_0)/\rho}$.

6.2 The General Endemic Model

Previous analysis showed that epidemic ceases to exist due to depletion of susceptibles below the threshold value $\rho = \frac{N}{R_0}$. Therefore, in case of an endemic presence, the susceptibles have to be kept over this value. There are two ways of achieving this: the first one is the case of non-immunizing diseases, the other is taking into consideration the vital dynamics of the system (births and deaths).

The former is so called SIS model with the system of equations:

$$\frac{dS}{dt} = -r\lambda SI + \gamma I$$

$$\frac{dI}{dt} = r\lambda SI - \gamma I$$

with initial conditions:

$$S(0) = S_0$$

$$I(0) = I_0.$$

The R-compartment is missing because an infective individual goes back to the class of susceptibles after recovery. It is so due to the fact, that this individual can not acquire immunity for the disease. This is one possibility to get an endemic model but it is not the SIR model, with which I deal in this chapter so I am going to concentrate on the other case.

The General Endemic Model is the SIR model with vital dynamics given by the system of equations:

$$\frac{dS}{dt} = \mu N - \mu S - \beta IS \tag{6.27}$$

$$\frac{dI}{dt} = \beta IS - \gamma I - \mu I \tag{6.28}$$

$$\frac{dR}{dt} = \gamma I - \mu R \tag{6.29}$$

$$S(0) = S_0 \geq 0, I(0) = I_0 \geq 0, R(0) = R_0 \geq 0. \tag{6.30}$$

Again, we assume that for the population size N holds the relation: $N = S(t) + I(t) + R(t)$. This model is almost the same as general epidemic model, except that it has an inflow of newborns into the susceptible compartment and we also assume

deaths (vital dynamics). μ denotes the per capita death rate (in case of μN birth rate) and therefore the life expectancy is μ^{-1}. But as we can see from the first two equations (6.27) and (6.28), this is a closed system (R is not on the right-hand side of those equations) and therefore we can again disregard R from our analysis.

Lets study the "infection free" state $(N, 0)$. We can observe, in (6.27) and (6.28), that the right-hand side of these differential equations for I has a factor I, and a factor $\beta S - \mu - \gamma$. Linearisation amounts to replacing S by N in the second factor, and leads to the following equation:

$$\frac{dI}{dt} = (\beta N - \mu - \alpha\gamma)I.$$

Hence, we have stability if $\beta N - \mu - \alpha\gamma < 0$ and instability if $\beta N - \mu - \alpha\gamma > 0$. Lets mark

$$R_0 = \frac{\beta N}{\gamma + \mu}.$$

We got the *basic reproductive ratio* for this model. So in other words, we have stability for $R_0 < 1$ and instability for $R_0 > 0$.
For $I \neq 0$, $\frac{dI}{dt} = 0$ recquires $\beta S - \mu - \gamma = 0 \Rightarrow \overline{S} = \frac{\mu+\gamma}{\beta}$. We can rewrite this in the following form: $\frac{\overline{S}}{N} = \frac{\mu+\gamma}{\beta N} = \frac{1}{R_0}$. The same observation also shows that $S = \frac{\mu+\gamma}{\beta} = \frac{N}{R_0}$ is an isocline, so along orbits the variable I takes its maxima and minima on this line. In particular, the steady-state has to lie on this line. It is not very surprising [2] , since in a steady state a case has to produce, on average, one secondary case and the expected number of secondary cases is R_0 multiplied by the reduction fraction $\overline{S}/N$. So in an endemic steady state $(S, I) = (\overline{S}, \overline{I})$ with $\overline{I} > 0$ necessarily

$$\frac{\overline{S}}{N} = \frac{1}{R_0}.$$

Note, that if we can estimate $\overline{S}/N$ (from blood samples taken at random), we can estimate $R_0 = N/\overline{S}$.

If we put $\frac{dS}{dt} = 0$ in (6.27) we find

$$\overline{I} = \frac{\mu N - \mu\overline{S}}{\beta\overline{S}} = \frac{\mu}{\beta}\left(\frac{\mu N}{\mu\overline{S}} - 1\right) = \frac{\mu}{\beta}(R_0 - 1).$$

[2] In subsection 6.1.1 the same argument applies to the minima of I at which S is increasing. In other words, $S = \frac{N}{R_0}$ is an isocline. (See Figure (6.2) of the orbits of the system (6.1) - (6.2) for comparison.)

So in endemic steady state

$$\overline{I} = \frac{\mu}{\beta}(R_0 - 1). \tag{6.31}$$

Equivalent to this is the formula

$$\frac{\overline{I}}{N} = \frac{(\gamma+\mu)^{-1}}{\mu^{-1}}\left(1 - \frac{\overline{S}}{N}\right).$$

This expresses the relative steady-state incidence in terms of the life expectancy μ^{-1}, the expected length of the infectious period $(\gamma+\mu)^{-1}$ and the steady-state fraction of susceptibles $\overline{S}/N$.
Summing up, the the system admits the following steady states:

- $\bar{S} = N \quad \bar{I} = 0 \quad \bar{R} = 0$
- $\bar{S} = \frac{N}{R_0} \quad \bar{I} = \frac{\mu N}{\gamma+\mu}\left(1 - R_0\right) \quad \bar{R} = \frac{\gamma N}{\gamma+\mu}\left(1 - \frac{1}{R_0}\right)$

and while the disease free equilibrium always exists, the endemic one stands only for $R_0 > 1$ (see Figure 6.5)

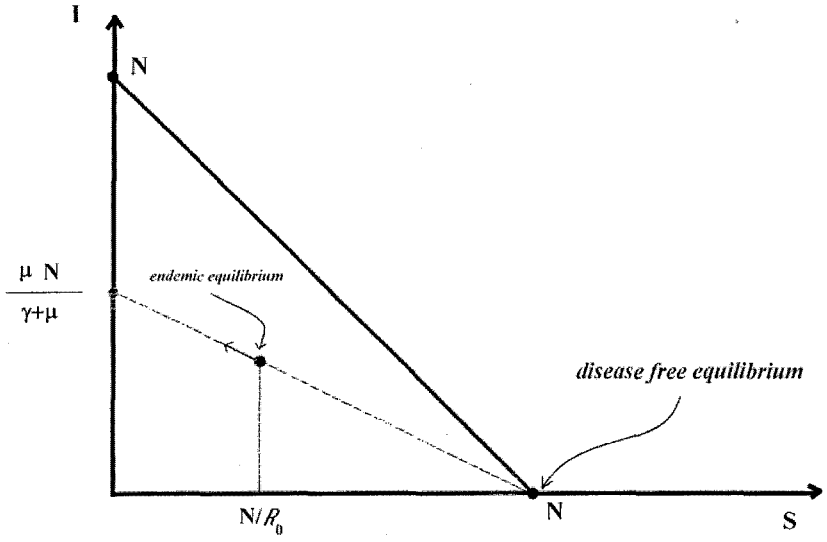


Figure 6.5: Steady states for an endemic

So we now know what the steady-state looks like, however this steady-state does not guarantee that the balance between constant inflow of new susceptibles and the removals from deaths and/or infection is exact at every instant. There has to be a balance but it may be over a longer period of time interval. So fluctuations around the steady-state are not necessarily damped. In order to find out what happens in this model, we linearise around the steady-state.

The linearised system has solutions which depend (by factor $e^{\lambda t}$) for some values of λ. When this value is real, it denotes the growth/decay rate. When it is a complex number, then $Re\{\lambda\}$ denotes the growth/decay rate and $Im\{\lambda\}$ denotes the frequency of the oscillations which accompany the growth/decay. The principle of the linear stability guarantees that, provided that $Re\{\lambda\}$ are non-zero $\forall\lambda$, the information about solutions of the linearised system is carried over to the solutions of the non-linear system (as long as these stay in a close neighborhood of the steady-state).

The linearised system is fully characterised by Jacobi matrix J and the λs are the eigenvalues of this matrix. They are found by solving the characteristic equation $det(\lambda I - J) = 0$, which is a polynomial of degree n, where n is the dimension of the system. For us $n = 2$, so the characteristic equation is of the form

$$\lambda^2 - T\lambda + D = 0. \tag{6.32}$$

Here, T is the trace of the matrix $J = (j_{i,j})_{1\leq i,j\leq 2}$ (i.e. the sum of the diagonal elements) and D is determinant of J. Then we get:

$$\lambda = \frac{T \pm \sqrt{T^2 - 4D}}{2}.$$

So we have that $T < 0$ and $D > 0$ is the condition for linearised stability (or so called decaying exponentials) and $T^2 < 4D$ is the condition for the oscillations appearing around the steady-state.

Lets look at our system (6.27) and (6.28), calculate the Jacobi matrix and evaluate its elements for $S = \overline{S}$ and $I = \overline{I}$:

$$\begin{array}{l}
\frac{\partial}{\partial S}(\mu N - \beta SI - \mu S) = -\beta I - \mu = -\beta\overline{I} - \mu \\
\frac{\partial}{\partial I}(\mu N - \beta SI - \mu S) = -\beta S = -\beta\overline{S} \\
\frac{\partial}{\partial S}((\beta S - \mu - \gamma)I) = \beta I = \beta\overline{I} \\
\frac{\partial}{\partial I}((\beta S - \mu - \gamma)I) = \beta S - \mu - \gamma = 0
\end{array}$$

so the corresponding Jacobi matrix is:

$$\begin{pmatrix} -\beta\overline{I} - \mu & -\beta\overline{S} \\ \beta\overline{I} & 0 \end{pmatrix}$$

We can easily see that the trace of the matrix is

$$T = -\beta\overline{I} - \mu < 0 \tag{6.33}$$

and that its determinant is

$$D = \beta^2\overline{SI} > 0 \tag{6.34}$$

and therefore the roots of the characteristic equation have negative real parts. According to the principle of linearised stability the endemic steady state is locally asymptotically stable.

In fact, the endemic steady state is globally asymptotically stable. We will prove it with the help of the Lyapunov function [3]

$$V(S, I) = S - \overline{S}lnS + I - \overline{I}lnI$$

Lets derivate it to get:

$$\begin{aligned}
\frac{dV}{dt} &= \frac{\partial V}{\partial S}\frac{dS}{dt} + \frac{\partial V}{\partial I}\frac{dI}{dt} \\
&= \left(1 - \frac{\overline{S}}{S}\right)(\mu N - \beta SI - \mu S) + \left(1 - \frac{\overline{I}}{I}\right)I(\beta S - \gamma - \mu) \\
&= (S - \overline{S})\left(\frac{\mu N}{S} - \beta I - \mu + \beta I - \beta\overline{I}\right) \\
&= (S - \overline{S})\left(\frac{\mu N}{S} - \frac{\mu N}{\overline{S}}\right) \\
&= -\frac{\mu N}{S\overline{S}}(S - \overline{S})^2 = -\frac{\mu R_0}{S}\left(S - \frac{N}{R_0}\right)^2
\end{aligned}$$

where $\overline{S} = \frac{\alpha+\mu}{\beta}$ and $\mu N - \beta\overline{SI} - \mu\overline{S} = 0$. Hence, we can see that $\frac{dV}{dt} < 0$ except on the line $S = \frac{N}{R_0}$, where it is equal to zero. At this line we have $\frac{dI}{dt} = 0$ and $\frac{dS}{dt} = \mu N - (\mu + \beta I)\frac{N}{R_0}$. So $\frac{dS}{dt} > 0$ for $I < \overline{I}$ and $\frac{dS}{dt} < 0$ for $I > \overline{I}$. Orbits cannot stay on the "line", unless we consider the steady-state. The LaSalle's Invariance Principle [4] allows us to conclude, that all orbits which stay bounded do converge to the steady state. On the other hand, the boundedness of the orbits is a direct consequence of our assumptions (a constant population birth rate,

[3] see Remark 3

[4] see Remark 4

while the per capita death rate is constant). Mathematically this is reflected in the invariance of the region $\{(S,I) : S \geq 0,\ I \geq 0,\ S+I \leq N\}$ (note that $\frac{d}{dt}(S+I) = \mu N - (\mu(S+I) - \gamma I \leq \mu N - \mu(S+I))$.

Remark 1. ω-limit of a point $\bar{x} : \omega(\bar{x}) = \{\bar{y} \in R^n : \bar{y}(t_k) \to \bar{y}$ for some sequence $t_k \to \infty\}$

Remark 2. α-limit of a point $\bar{x} : \alpha(\bar{x}) = \{\bar{y} \in R^n : \bar{y}(t_k) \to \bar{y}$ for some sequence $t_k \to -\infty\}$

Remark 3. (Lyapunov Second Theorem on Stability)
If $f = (f_1, f_2, ..., f_n) : R^n \to R^n$ is a continuous differentiable function, $f(0) = 0$ and there exists continuous differentiable function $V(x) : R \to R$, such that it is true:
(i) $V(x) \geq 0$ and $V(x) = 0 \Leftrightarrow x = 0$
(ii) $\exists$ continuous function $W(x) : R \to R$ such that $W(x) \geq 0\ \forall x \in R$ and $W(x) = 0 \Leftrightarrow x = 0$
(iii) $\dot{V}(x) = \sum_{j=1}^{n} \frac{\partial V(x)}{\partial x_j} f_j(x) \leq -cW(x)\ \forall x \in R$ where $c \geq 0$ is a constant
$\Rightarrow$ the system is said to be asymptotically stable in the sense of Lyapunov and the function $V(x)$ is called the Lyapunov function for this system.

Remark 4. (LaSalle's Invariance Principle)
Suppose there is a neighborhood D of 0 and a continuously differentiable (time-independent) positive definite function $V : D \to R$, whose orbital derivative $\dot{V}$ with the respect to the autonomous system $\dot{x} = f(x)$ is negative semidefinite. Let I be the union of all complete orbits contained in

$$\{x \in D : \dot{V}(x) = 0\}.$$

$\Rightarrow$ there is a neighborhood U of 0, such that $\forall x_0 \in U\ \omega(x_0) \subseteq I$.

In real life, life expectancy μ^{-1} is usually much bigger than the duration of the infectious period γ^{-1}. We are going to show that the model predicts damped oscillations around the steady state. We will also find their relaxation time and frequency [5].
Using (6.33) and (6.34) in the characteristic equation (6.32) we can rewrite it as:

$$\lambda^2 + (\beta\overline{I} + \mu)\lambda + \beta^2\overline{SI} = 0.$$

With relations $R_0 = \frac{\beta N}{\gamma+\mu}$ and (6.30), and dividing the equation by μ^2 we obtain:

$$\left(\frac{\lambda}{\mu}\right)^2 + (R_0 - 1 + 1)\frac{\lambda}{\mu} + (R_0 - 1)\frac{\beta}{\mu}\frac{N}{R_0} = \left(\frac{\lambda}{\mu}\right)^2 + R_0\frac{\lambda}{\mu} + \frac{\gamma+\mu}{\mu}(R_0 - 1) = 0.$$

[5] relaxation time - the time interval, in which the amplitude of the oscillations diminishes by a factor e^{-1}

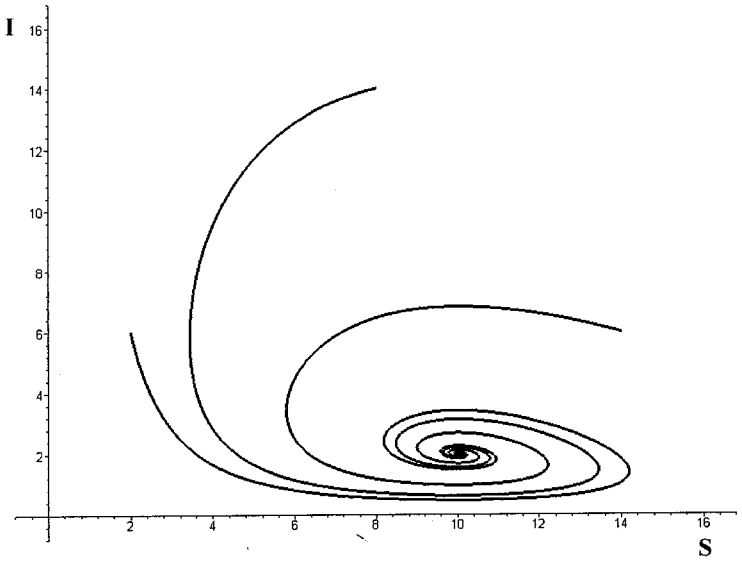


Figure 6.6: Part of the solution trajectory for endemic problem

When $\frac{1}{\mu} \gg \frac{1}{\gamma}$, we have $\frac{\gamma}{\mu} \gg 1$, and consequently we approximate the last term by $\frac{\gamma}{\mu}(R_0 - 1)$. The equation

$$y^2 + R_0 y + \frac{\gamma}{\mu}(R_0 - 1) = 0$$

has roots:

$$y = \frac{-R_0 \pm \sqrt{R_0^2 - 4\frac{\gamma}{\mu}(R_0 - 1)}}{2}.$$

If we use the assumption $\frac{\gamma}{\mu} \gg 1$ again, we see that the expression under the square root is negative ($R_0 > 1$ in endemic steady state) and that the roots are, in the first approximation,

$$\frac{\gamma}{\mu} = y = -\frac{R_0}{2} \pm i\sqrt{\frac{\gamma}{\mu}(R_0 - 1)}.$$

So we have:

- relaxation time $\frac{1}{|Re\{\lambda\}|}$ equals to $\frac{2}{\mu R_0}$
- frequency equals to $\sqrt{\gamma\mu(R_0 - 1)}$ with respect to the small parameter $\frac{\mu}{\gamma}$.

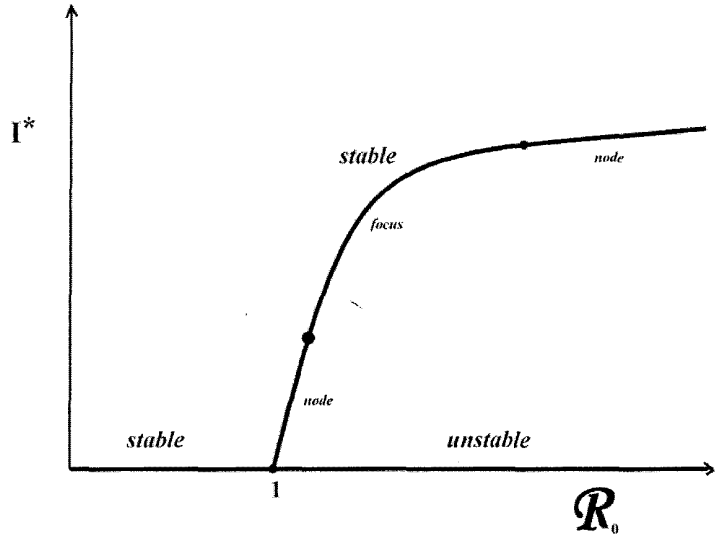


Figure 6.7: Bifurcation diagram for endemic model

For $\frac{\gamma}{\mu} \gg 1$ the relaxation time is of the order $\frac{1}{\mu}$ but the period $\frac{2\pi}{\sqrt{\mu\gamma(R_0-1)}}$ is of the order of $\frac{1}{\sqrt{\mu}}$, so the ratio between the two goes to infinity for $\mu \downarrow 0$. Therefore, we should see many oscillations before the steady state is reached.

6.2.1 Herd Immunity and Vaccination

After all those statements and conclusions, we know that the endemicity depends on the basic reproduction number R_0. This threshold value can tell us, whether the disease will invade in the population and spread out or not. If $R_0 > 1$, a single infective introduced in the completely susceptible population can establish the disease. If this infective has replaced himself with more than one infective at the end of his disease, then an epidemic outbreak is produced which drives the population to the globally attractive endemic state.

The outbreak does not have to occur necessarily. There can be certain number of immunes in the population and therefore the number of susceptibles can be too low. Although, this situation will not remain because the there is constant inflow of susceptible newborns who replace the immunes. So it seems, that if we can keep the level of immunes at certain level, then the probability of an epidemic outbreak is very low. This number of immunes can be kept at a constant level artificially by vaccination or also by natural infection. This is so called *herd immunity*. It protects directly the immune individuals from reinfection but also provides an indirect protection to susceptible population.

We may increase the level of immunes e.g. by *vaccination*. But this has to be done in a sufficiently high level in order to guarantee herd immunity. If we consider vaccination in the last model, we have to put in the system of equations another term depending on the vaccination, which transfers susceptibles into the recovered class. So the system (6.27)-(6.30) transforms into:

$$\frac{dS}{dt} = \mu N - \beta IS - \mu S - vS \tag{6.35}$$

$$\frac{dI}{dt} = \beta IS - (\gamma + \mu)I \tag{6.36}$$

$$\frac{dR}{dt} = (\gamma + v)I - \mu R \tag{6.37}$$

$$S(0) = S_0, \quad I(0) = I_0, \quad R(0) = R_0 \tag{6.38}$$

From this system we have the steady-states:

$$\bar{S} = \frac{\mu N}{\mu + v}, \quad \bar{I} = 0, \quad \bar{R} = \frac{vN}{\mu + v}$$

$$\bar{S} = \frac{N}{R_0}, \quad \bar{I} = \frac{\mu N}{\mu + \gamma}\left(1 - \frac{\mu + v}{\mu R_0}\right), \quad \bar{R} = \frac{(\gamma + v)N}{\gamma + \mu}\left(1 - \frac{\mu + v}{\mu R_0}\right).$$

So we can see, that we have plenty of immunes in the disease free state, and so the invasion condition for establishing the endemic state is

$$\frac{\mu R_0}{\mu + v} > 1.$$

Consequently, we must have vaccination rate satisfying

$$v > \mu(R_0 - 1).$$

The most important threshold value for the disease dynamics has the parameter R_0. Using formula (6.13) and approximating $I_0 = 0$ we get

$$R_0 = \frac{lnS_\infty - lnS_0}{S_\infty - S_0}.$$

Another way to express R_0 is to use the relation for endemic steady state:

$$R_0 = \frac{N}{\bar{S}}.$$

Now we can relate R_0 to the *average age of attack* A. It is the age of an individual when being infected. It is the time spent when being in the susceptible compartment before entering the infective compartment. And this is inverse of the force of the infection at the endemic equilibrium

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

Hence,

$$R_0 = 1 + \frac{1}{\mu A}.$$

6.3 Critical Community Size and Time - Scale Differences

[6]

One, studying the spreading of the epidemics and its mathematical models, asks questions concerning how long will it take for the epidemic to diminish. Is that going to be days, weeks, months or even years? I have asked myself this questions and I was given this question several times. It seems that there is an observation which suggests, that we can find N for which infection tends to maintain in the population, whereas for smaller N it would die out and reintroducing of the infectious agent would be necessary in order to the spread of the infection. The idea of the critical community size appeared. This section is included in this paper to give more insight and enlightment on the spreading of an infectious agent in time and it shows relation between the endemic-epidemic occurrance.

Within the stochastic models the agent will go extinct with certainty. So we cannot define the critical community size just on the basis of the extinction criterion alone, the expected time till extinction has to be taken into consideration as well. This will be an increasing function of the population size N.

We may chose an arbitrary constants $T > 0$ and $p \in (0, 1)$ and declare that the population size is above criticality if the probability of extinction before time T is less than p (p depends on the initial condition). The number of constants can be reduced to one by taking into consideration limits. Concentrating on the limit $N \to \infty$ we can only see that expected time to extinction tends to infinity, taking astronomical values of the order of e^{cN} for N large. Therefore, we have to consider more assumptions.

What we do, is that we consider approaching the infinity in a two-parameter plane, spanned by the N axis and the γ/μ axis (ratio of the two time scales). So we have concluded, that along the N axis the expected time till extinction goes to infinity. Along the γ/μ axis, for $\gamma/\mu \to \infty$, we find opposite behavior (instantaneous extinction after the first outbreak).

We are interested in so called "phase transition", i.e. the way of approaching infinity in this plane such that the expected time till extinction neither blows up nor diminishes to zero; instead, it stays bounded away from zero. We try to determine the paths in the plane which provide the transition: $\frac{\gamma}{\mu}\frac{1}{\sqrt{N}}$ should be bounded (see below).

We cannot really take the limit because we do not exactly know how is ex-

[6]For detailed information on calculations and analysis see Nåsell, I.. On the time to extinction in recurrent epidemics, J. Roy. Stat. Soc., B, 61 (1999), 309-330.

tinction time "bounded". So we have to make an arbitrary choice for a constant. Therefore we "define" $\frac{\gamma}{\mu}\frac{1}{\sqrt{N}} = C$ as the critical relationship, determine $\frac{\gamma}{\mu}$, choose $C = 1$ and compute N_{crit}.

We consider the system (6.27)-(6.28) and we put $\beta = \frac{\delta}{N}$ to show the dependence on the population size. As we have already seen, the steady state value for I is given by

$$\bar{I} = \frac{\mu(N-\bar{S})N}{\beta N\bar{S}} = \frac{\mu N}{\mu+\gamma}\left(1-\frac{\bar{S}}{N}\right) = \frac{\mu}{\mu+\gamma}N\left(1-\frac{1}{R_0}\right),$$

since $\bar{S} = \frac{\mu+\gamma}{\beta N} = \frac{N}{R_0}$.

For births processes, it is well known that demographic stochasticity leads to fluctuations of the order of $\sqrt{N}$, with N the population size [7]. Assume $R_0 = O(0)$ what means that changes in N do not substantially influence R_0. Also assume that $\frac{\mu}{\mu+\gamma} = O(\frac{1}{\sqrt{N}})$. These assumptions were made such that they imply $\bar{I} = O(\sqrt{N})$ (the average level of infected individuals in the population lies within the range of natural fluctuations). The agent will extinct, sooner or later. When $\mu \gg \gamma$ we have that $\frac{\mu}{\mu+\gamma} = \frac{\mu}{\gamma}$ and from our assumptions $\frac{\gamma}{\mu} = O(\sqrt{N})$. Since $R_0 = \frac{\beta N}{\mu+\gamma} = O(1)$, this requires also $\frac{\beta N}{\mu} = O(\sqrt{N})$.

So there is not a criticality directly in the community size, but rather a critical relationship between population size and the ratio of the two time scales involved (that of demography and that of transmission). When both $\frac{1}{\sqrt{N}}\frac{\gamma}{\mu}$ and $\frac{1}{\sqrt{N}}\frac{\beta N}{\mu}$ are really small, we expect a single outbreak of an epidemic and when they are large we expect an endemic situation; everything in between is considered to be critical. The approximate formula for expected extinction time under critical conditions according to Nåsell (1999) is

$$\bar{t}_{extinction} = \frac{(R_0-1)N}{2(\frac{\gamma}{\mu})^2}\frac{1}{\mu}.$$

Note that the right hand side is $O(\frac{1}{\mu})$ when $\frac{\gamma}{\mu}$ is $O(\sqrt{N})$, what is completely in line with the text above.

[7] See Nisbet and Gurney (1982), Goel and Richter-Dyn (1974), Taylor and Karlin (1984).

Chapter 7

SEIR Model

The SEIR model contains one more compartment, as it is apparent from its name. The new compartment is so called *exposed compartment E*. These are the people who are infected but the symptoms of the disease are not yet visible. They can not communicate the disease either. These people are in so called *latent period*. For some disease, it takes certain time for an infective agent to multiple inside the host up to the critical level so that the disease actually manifest itself in the body of the host. This is called an *incubation period*. We have the same assumptions as in the previous models, that is homogeneous mixing (mass action principle), constant population size and the rates of change from one compartment to the other follow the system bellow:

$$\frac{dS}{dt} = \mu N - \beta SI - \mu S \tag{7.1}$$

$$\frac{dE}{dt} = \beta SI - \mu E - \theta E \tag{7.2}$$

$$\frac{dI}{dt} = -\mu I + \theta E - \gamma I \tag{7.3}$$

$$\frac{dR}{dt} = -\mu R + \gamma I \tag{7.4}$$

The probability to survive the latency period and to enter the infectious period equals to $\frac{\theta}{\theta+\mu}$. Therefore the basic reproductive number in this case will be $R_0 = \frac{\theta}{\theta+\mu}\frac{\beta N}{\gamma+\mu}$.

Now look at the steady states. Putting $\frac{dI}{dt} = 0$ we get $\bar{E} = \frac{\gamma+\mu}{\theta}\bar{I}$, while $\frac{dE}{dt} = 0$ leads to $\beta\bar{S}I = (\mu+\theta)\bar{E}$. Combining these two relations, we obtain, after deviding out a factor $\bar{I}$ (we are determining the endemic steady state so we are not interested

in $\bar{I} = 0$), that $\beta\bar{S} = \frac{1}{\theta}(\mu + \theta)(\gamma + \mu)$ or, equivalently, $\bar{S} = \frac{N}{R_0}$. From $\frac{dS}{dt} = 0$ we get that $\bar{I} = \frac{\mu N - \mu\bar{S}}{\beta\bar{S}} = \frac{\mu}{\beta}(R_0 - 1)$.

Analogously to the derivation in the previous chapter we derive the Jacobi matrix and the the characteristic equation. The linearised system is now described by the 3×3 matrix

$$\begin{pmatrix} -(\beta\bar{I} + \mu) & 0 & -\beta\bar{S} \\ \beta\bar{I} & -(\mu + \theta) & \beta\bar{S} \\ 0 & \theta & -(\mu + \gamma) \end{pmatrix}$$

and the eigenvalues are the roots of the characteristic equation

$$\lambda^3 + (\mu R_0 + 2\mu + \gamma + \theta)\lambda^2 + \mu R_0(\gamma + \mu + \theta)\lambda + \mu(R_0 - 1)(\gamma + \mu)(\theta + \mu) = 0.$$

When γ and θ are relatively close to μ and μR_0 then we can approximate the roots of the characteristic equation by the roots of the equation

$$\lambda^3 + (\gamma + \theta)\lambda^2 + \mu R_0(\gamma + \theta)\lambda\mu(R_0 - 1)\gamma\theta = 0.$$

We can write this equation we as

$$\lambda^3 + (\gamma + \theta)\left(\lambda^2 + \mu R_0\lambda + \mu(R_0 - 1)\frac{\gamma\theta}{\gamma + \theta}\right).$$

It is concluded that this cubic equation has one root $\lambda \approx -(\gamma+\theta)$ (corresponding to perturbations that decay rapidly) and two other roots given approximately by the roots of the quadratic equation in the braces [1]. Hence, the period of the oscillations is given by $\pi\sqrt{\bar{a}\frac{\gamma+\theta}{\gamma\theta}}$, in other words $\frac{1}{\gamma}$n has to be replaced by $\frac{\gamma+\theta}{\gamma\theta} = \frac{1}{\gamma} + \frac{1}{\theta}$, which is still in the expected duration of the "infection", in the sense of the period between being infective and becoming immune.

[1] Anderson,R.M. and May,R.M.. Infectious Diseases of Humans: Dynamics and Control. Oxford: Oxford University Press, 1991, Appendix C, p.668

Chapter 8

SIR and SEIR Models with Non-bilinear Incidence Rates

We already know what are the important factors for the spreading of an epidemic. For an infective agent in order to spread across the susceptible population it is necessary to have, for example, an adequate contact with the susceptibles. Then it is for example the size of the population or the basic reproductive number. All those aspects we considered in the previous models. However, there is a lot more that can affect the spread of a disease, its speed and impact. As I showed in previous chapters, herd immunity and migration could be some factors. Then it can be the spatial non-uniformly distribution of population in such a way, that the rates of transmission of an infectious disease can be higher in some places than in the others. Another factor is genetic heterogeneity: individuals - carriers, who do not show any symptoms of the disease, or those individuals in the asymptomatic stage, who evade the sanitary vigilance, can complicate the control of the disease and increase the risk of infection in the population.

The possibility of an infective individual to communicate the disease to the susceptibles therefore may depend on the virulence of the microorganism (infective agent), the extend to which they are discharged, the degree of proximity (geographical location), school groupings, family size, social habits, etc. In homogeneous mixing of individuals are all those aspects averaged out, and all the epidemiological and demographic processes are treated as occurring at rates that depend only on the compartment densities. Inhomogeneities associated with age-specific differences in contact rates, geographical location, social and cultural habits, genetic heterogeneity within the host population ... all those may be important in particular applications.

Anderson & May [1] slightly modified homogeneous mixing assumptions. Then Severo [2] [3], instead of a direct product between S and I, considered that the probability of a new infection might be expressed as the product between S with power $1-b$ and I with power l. The powers l and b are called the *infection power* and *safety-in-numbers power*, respectively.

Let us consider the global properties of SIR and SEIR model with the incidence rate of the form $\beta I^p S^q$ for the particular case $p \leq 1$ (We can clearly see that putting $p = q = 1$ we get the general epidemic/endemic model). We have the following systems, where b denotes the birth rate, μ is the susceptible death rate, γ is the infective removal rate (including mortality rate) and θ is the rate with which the exposed population moves into the infective class; $\sigma \geq \theta$ includes also mortality of the exposed individuals. The R compartment is omitted due to the constant population size N.:

SIR

$$\frac{dS}{dt} = b - \beta I^p S^q - \mu S \tag{8.1}$$

$$\frac{dI}{dt} = \beta I^p S^q - \gamma I. \tag{8.2}$$

Under the assumption $0 < p < 1$ the system has two equilibria: infection free steady-state $(S_0, I_0) = (\frac{b}{\mu}, 0)$ and endemic steady-state $(\bar{S}, \bar{I})$ such that

$$\gamma \bar{I} = \beta \bar{I}^p \bar{S}^q, \quad \mu \bar{S} + \gamma \bar{I} = b, \quad \gamma \bar{I} = \theta \bar{E}. \tag{8.3}$$

SEIR

$$\frac{dS}{dt} = b - \beta I^p S^q - \mu s \tag{8.4}$$

$$\frac{dE}{dt} = \beta I^p S^q - \sigma E \tag{8.5}$$

$$\frac{dI}{dt} = \theta E - \gamma I. \tag{8.6}$$

Similarly, we have two equlibria: infection free steady-state $(S_0, E_0, I_0) = (\frac{b}{\mu}, 0, 0)$ and an endemic steady-state $(\bar{S}, \bar{E}, \bar{I})$ satisfying

$$\frac{\sigma}{\theta}\gamma\gamma\bar{I} = \beta \bar{I}^p \bar{S}^q, \mu\bar{S} + \frac{\sigma}{\theta}\gamma\bar{I} = b, \gamma\bar{I} = \theta\bar{E}. \tag{8.7}$$

[1] Anderson, R.M. and May,R.M.. Infectious Diseases of Humans: Dynamics and Control. Oxford: Oxford University Press, 1992.

[2] Severo, N.C.. Generalisations of some stochastic epidemic models: Math.Biosc., 4, 1969, 395-402.

[3] Severo, N.C.. The probabilities of some stochastic epidemic models: Biometrika, 56, 1969, 197-201.

In case that $p > 1$ then these systems have either one, two or no steady states.

Theorem 3. *If $p \leq 1$, then the endemic steady-states of the systems (7.5)-(7.6) and (7.8)-(7.10) are globally asymptotically stable. The stability does not depend on the value of the parameter q.*

Proof:
We assume $p, q \neq 1$ and construct the Lyapunov function [4] of the form

$$V(S,E,I) = AS\left(1+\frac{1}{q-1}\left(\frac{\bar{S}}{S}\right)^q\right)+BI\left(1+\frac{1}{p-1}\left(\frac{\bar{I}}{I}\right)^p\right)+C(E-\bar{E}lnE). \quad (8.8)$$

For SEIR system, $A = C = 1$, $B = \frac{\sigma}{\theta}$; for the SIR system $A = B = 1$ and $C = 0$. Function V is continuous for all $S, E, I > 0$ and it satisfies

$$\frac{\partial V}{\partial S} = A\left(1 - \left(\frac{\bar{S}}{S}\right)^q\right),$$

$$\frac{\partial V}{\partial E} = C\left(1 - \frac{\bar{E}}{E}\right),$$

$$\frac{\partial V}{\partial I} = B\left(1 - \left(\frac{\bar{I}}{I}\right)^p\right).$$

Hence, it is obvious that the endemic steady state is the only extremum and the global minimum of the function in the positive octant R^3_+. Therefore our function V is indeed a Lyapunov function.

Now we look closely at the SEIR system. Using relations
$b = \mu\bar{S} + B\gamma\bar{I}, \quad \beta\bar{I}^p\bar{S}^q = B\gamma\bar{I}, \quad \gamma\bar{I} = \theta\bar{E}, \quad B\theta = \sigma$
for the endemic steady state, Lyapunov function V satisfies

[4] This is a generalisation of the Lyapunov functions used for the SEIR and SIR models. Compare with the Lyapunov function constructed in section 6.2 for the General Endemic Model, p.36

$$\frac{dV}{dt} = b - \beta I^p S^q - \mu S - b\frac{\bar{S}^q}{S^q} + \beta I^p \bar{S}^q + \mu\frac{\bar{S}^q}{S^{q-1}} + \beta I^p S^q - \sigma E -$$
$$- \beta I^p S^q \frac{\bar{E}}{E} + \sigma\bar{E} + B\left[\theta E - \gamma I - \theta\frac{\bar{I}^p}{I^p}E + \gamma\frac{\bar{I}^p}{I^{p-1}}\right]$$
$$= B\gamma\bar{I}\left[2 - \frac{\bar{S}^q}{S^q} + \frac{I^p}{\bar{I}^p} - \frac{\bar{E}}{E}\frac{S^q I^p}{\bar{S}^q\bar{I}^p} - \frac{I}{\bar{I}} - \frac{E}{\bar{E}}\frac{\bar{I}^p}{I^p} + \left[\frac{I}{\bar{I}}\right]^{1-p}\right]$$
$$+ \mu\bar{S}\left[1 - \frac{S}{\bar{S}} - \frac{\bar{S}^q}{S^q} + \left[\frac{S}{\bar{S}}\right]^{1-q}\right]$$
$$= -B\gamma\bar{I}[v^{1-p} - 1][v^p - 1] + B\gamma\bar{I}\left[3 - \frac{1}{u^q} - w - \frac{u^q}{w}\right] + \mu\bar{S}[1-u]\left[1 - \frac{1}{u^q}\right],$$

where $u = \frac{S}{\bar{S}}$, $v = \frac{I}{\bar{I}}$ and $w = \frac{E\bar{I}^p}{\bar{E}I^p}$. If $p < 1$ then $h(v) = (v^p - 1)(v^{1-p} - 1) \geq 0$ for all $v > 0$ (the equality holds only if $u = w = 1$). What is more, $(1-u)\left(1 - \frac{1}{u^q}\right) \leq 0$ for all $u, q > 0$. Hence, the condition $p < 1$ means that $\frac{dV}{dt} \leq 0$ for all $S, E, I > 0$, where the equality hold only in the point of steady-state $(\bar{S}, \bar{E}, \bar{I})$. The Lyapunov asymptotic stability theorem tells us that this steady-state is globally asymptotically stable for the whole R^3_+.

If either $p - 1$ or $q = 1$, we have to replace the corresponding term in the relation for V in (7.12), $\frac{\bar{I}^p}{p-1}I^{1-p}$, or $\frac{\bar{S}^q}{q-1}S^{1-q}$ respectively, by the term $-\bar{I}\log I$, or $-\bar{S}\log S$. If $p = q = 1$ then we get the bilinear incidence rates and
$V(S, I) = A(S - \bar{S}\log S) + B(I - \bar{I}\log I) + C(E - \bar{E}\log E)$.

The case of the SIR model is analogous. It is also clear that this result does not depend on the value of parameter q. □

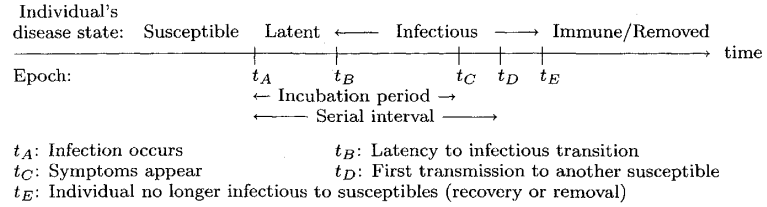


Figure 8.1: Diagramatic representation of disease progress in an individual

In Figure 7.1 note that t_D is considered to lie in the interval (t_B, t_E), so $t_D > t_C$ (as shown) and $t_D < t_C$ are both possible.

Chapter 9

Conclusion

Mathematical model is a lie that helps us to discover the truth.

Theoretical developments have presented more than just mathematical exercises. Theory and fact are intertwined, mutually nourishing each other. One of the most important development in biology within the last quarter-century has been the integration of mathematical and theoretical reasoning into it. And it is a great example of applications of mathematics into real life. Biology can tell us, when was the peak of the epidemic, how many individuals got infected, etc ... It can tell us the numbers, but can it foretell? Can the biologists tell us something about the threshold value basic reproduction ratio or whether the epidemic will spread or die out if we introduce an infectious agent into the susceptible population? These questions can be answered by the mathematicians, however we need the know-how of the biologists and their "numbers" too. We need each other to provide a complex view of the situation and to model the reality. I found the mathematical epidemiology to be one of the most applicable areas for a mathematical thoughts and reasoning. It is straightforward, easily understandable and shows results.

Originally, it was intended that the focus of this paper would be broader with some more models of specific diseases and with studying those already described in it (and their modifications) in much greater detail. After a while, I realized that for this purpose it would take dozens of publications. But I considered necessary to introduce the simple models as well as the general ones and the motivation for their creation. Those models suit the data well and/or are easily modified. The mathematics itself is not very demending (as long as we have seen in this paper) although in some specific models and the newest articles we find models dealing with the chaos theory and/or with systems composing of many (and different) in-

teracting populations. In 1965, D.G.Kendall [1] wrote (referring to A.G.McKendrick and R.Ross who shaped the epidemic theory in the form we study and see it today):

"Mathematicians may be blamed for subsequently carrying the game to far,
but its highly respectable medical origin should not be overlooked."

I certainly disagree with the opinion that we are carrying the game to far, as long as we model the reality. Of coarse, no model can be perfect in the sense that it cannot take into consideration all the disease and population characteristics. That is why we call them models, we neglect facts which we consider less important nad/or less affecting the course of the disease. This is the reason for the first line in this chapter: Mathematical model is a lie that helps us to discover the truth.

In my opinion, mathematics is an essential part of the scientific view on the problem of the disease spreading and gives great insight into the mechanisms of this spreading and also of its control. We shoud certainly continue to search for those new insights into the mechanisms of population dynamics of infectious diseases, especially those of high priority in the world today. Infectious agents have already had decisive influences on the history of mankind and the future asks for predictions and rational control decisions. Mathematical models with the tools for the analysis are capable of doing this. According to the father of modern epidemic theory, Sir Ronald Ross, who wrote [2]:

"As a matter of fact all epidemiology, concerned as it is with variation of disease from time to time or from place to place, *must* be considered mathematically (...), if it is to be considered scientifically at all. (...) And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand."

[1] Kendal,D.G.. Mathematical models of the spread of infection: Mathematics and Computer Science in Biology and Medicine. HMSO London, 1965, pp. 213-225.

[2] ROSS, R.R.. The Prevention of Malaria. London: Churchill, 2nd edition, 1911.

Chapter 10

Reference

1. ANDERSON, R.M. and MAY, R.M.. Infectious Diseases of Humans - Dynamics and Control. Oxford, New York: Oxford University Press, 1991.

2. ANDERSON, R.M. and MAY, R.M.. Directly transmitted infectious diseases: control by vaccination. Science, 215:10531060, 1982.

3. ANG, K.Ch.. A Simple Model for a SARS Epidemic. Teaching Mathematics and its Applications, vol.23, No.4, 2004

4. BAILEY, N.T.J.. The Mathematical Theory of Infectious Diseases. London: Griffin, second edition, 1975.

5. BLOWER, S.. An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it. Reviews

6. DALEY,D.J. and GANI, J.. Epidemic Modeling - An Introduction. Cambridge: Cmabridge University Press, 2005

7. DIEKMANN, O. and HEESTERBEEK, J.A.P.. Mathematical Epidemiology of Infectious Diseases - Model Building, Analysis and Interpretation. New York: John Wiley and Sons, LTD, 2000.

8. HETHCOTE, H.W.. The Mathematics of Infectious Diseases. Siam Review, Vol.42, No.4, 2000

9. HETHCOTE, H.W.. Three basic epidemiological models. Heidelberg: Springer-Verlag, 1994, Lect. Notes in Biomathematics, Vol.100.

10. IANNELLI, M.. The Mathematical Modeling of Epidemics. Bolzano: Lec.1 Essential Epidemics, 2005

11. KOROBEINIKOV, A. and MAINI, P.K.. A Lyapunov Function and Global Properties for SIR and SEIR Epidemiological Models with Nonlinear Incidence Rates. Mathematical Biosciences and Engeneering, vol.1, No.1, 2004

12. MURRAY, J.D.. Mathematical Biology: I. An Introduction. New York: Springer, 2001 Third Edition.

13. NASELL, I.. On the time to extinction in reccurent epidemics. J. Roy. Stat. Soc., B, 61 (1999), 309-330.

14. ROSS, R.R.. The Prevention of Malaria. London: Churchill, 2nd edition, 1911.

15. SEVERO, N.C.. Generalisations of some stochastic epidemic models. Math. Biosc., 4 (1969)

16. SEVERO, N.C.. The probabilities of some stochastic epidemic models. Biometrika, 56 (1969)
in Medical Virology 2004; 14: 275288.

17. YANG, H.M.. Population Dynamics and the Epidemiological Model Proposed by Severo. Matematica Aplicada e Computacional, No.2, 2002.