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Ingegneria dell'Informazione

Dynamic models for the analysis of epidemic spreads

Modelli dinamici per l'analisi di diffusioni epidemiche

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Chapter 1

Introduction

1.1 Historical aside on epidemics

The history of epidemics is an ever fascinating area; from past to nowadays a lot of people have been interested in diseases development and their influence upon human kind because of the difficulty of foreseeing possible conseguences of the spread of dangerous diseases. The study of epidemic, recently, has come up with a huge number and variety of models and explanations for the spread and cause of epidemic outbreaks, and, in this work, we will see and try to analyze some of them.

The Black Death, in the 14th century, is just the most famous epidemic historically and we will briefly talk about it some pages forward in (Section 5.2). Moving across the Ataltic Ocean, the first major epidemic in the U.S.A. was the *Yellow Fever* epidemic in Philadelphia in 1793 in which about 5'000 people died out of a population of around 50'000, although estimates suggest that about 20'000 fled the city [6]. Another episode of epidemic is described by Thucydides, the *Plague of Athens* (430-428 BC) wich has exercised classical scholars for very long time; one of the interesting aspects of this disease is that there is no mention of person-to-person contagion wich now we accept so freely; this can give an idea of how much our comprehension of these aspects have greatly improved from time ago, also thanking to the study of mathematical models.

Only since the end of *World War II*, public health strategy has focused on the elimination and control of organism wich causes disease. The advent of new antibiotics changed the whole ethos of disease control. Another past scientists conviction was that microbes were biologically stationary targets and hence would not mutate in resistance to drugs and other biological influences. This wrong belief started to change after the emergence of microbes that could swim in a pool of bleach, grow on a bar of swoap, and ignore doses of penicillin larger than those effective in the 1950's.

Another aspect in the current spread of diseases is with the modern era

of transportation, allowing more than a million people a day to cross international borders; the threat of a major outbreak of exotic diseases is very real. Modelling and historians can play an increasingly significant role also in this side. Models can be extremely useful in giving reasoned estimates for the level of vaccination for the control of directly transmitted infectious diseases and their use in immunology and virology is also growing very quickly.

There are four main disease-causing microrganisms: viruses, bacteria, parasites and fungi. In this work we will see some models for the population dynamics of disease agents, this does not mean the inclusion of all possible effects, but rather the incorporation in the model mechanism, in a simple way as possible, of what appear to be the major components.

The classical theorical papers on epidemic models by Kermack and McKendrick (1927, 1932, 1933) have had a major influence in the development of mathematical models and are still relevant in a surprising number of epidemic simulations, as we will see soon in the later chapters.

1.2 Mathematical modeling of infectious diseases

A disease is infectious if the causive agent, whether a virus, bacterium, protozoa, or toxin, etc., can be passed from one host to another through modes of transmission such as direct physical contacts, arial droplets, water or food, disease vectors, mother to newborns, etc, [12].

The objective of a mathematical model of an infectious disease is to simulate the transmission process of the disease, which can be described generally as follows: when infectious individuals are introduced into a group of susceptibles, the disease is passed to other individuals through its modes of transmission, and the disease spreads in the group. If the number of infected individuals explodes in a short period of time, an epidemic occurs. Infected individuals recover from infection, either through treatment or due to action of the immune system, and gain varios degree of acquired immunity against the infection. When the pool of susceptible individuals is depleted, new infections will stop, and the epidemic slows down and stops. If fresh susceptibles are added to the group, either from birth or migration, or if the reinfection is easy, then epidemic may last very long, and the infection may persist in the group over a long period of time. In this case, the disease is said to be endemic in the group. If the disease spreads to a large geographic area, far beyond the location of initial occurrence, we say that a pandemic occurs.

Why is mathematical modeling of infectious diseases useful? Part of the reason is that traditional methods using experimental and statistical approaches may not be adequate for various aspetcs:

- Infectious diseases often affect a large population of individuals over a large geographic area. Experiments conducted in laboratories are

often inadequate simply because of the huge difference in scales.

- For infectious diseases of humans, large scale experiments may be impossible or unethical.
- Existing data sets about the disease may not be complete or accurate for the statistical analysis to be reliable.

By comparing the model outcomes with existing knowledge or data of the disease, we can use the model to test various hypotheses about the disease. There are often many issues associate with mathematical modeling:

- Due to our limited knowledge about infectious disease, realistic assumptions about its transmission process are not always possible.
- Model validation using disease data may be difficult or almost impossible.
- Mathematical analysis of the model may be limited by the existing mathematical theory.

There is always a trade-off in mathematical modeling between more realistic models and our ability to analyze mathematically the model and obtain useful informations. There are three general approaches to model infectious diseases:

- Statistical models, constructed to deal with a specific set of data.
- Deterministic models, use differential and difference equations of various forms. These are good for making predictions, but also are not expect to be valid if the population size can become very small.
- Stochastic models, populations are treated as stochastic processes. This decision is suitable for small groups, but mathematical analysis is difficult.

In this work we only discuss deterministic models, but take in mind that the probability that the last few infected individuals will infect another person is not deterministic and so in these cases this type of models is not accurate and, as seen above, we would have to use a stochastic model.

Chapter 2

Modeling of epidemics

2.1 Kermack-McKendrick simple model

Almost since the beginning of recorded history there have been epidemics. An epidemic may be described as a sudden outbreak of a disease that infects a substantial portion of the population in a region before it disappears. One of the question that first attrached the attention of scientists interested in the study of the spread of communicable diseases was why diseases would suddenly develop in a community and then disappear just as suddenly without infecting the entire community. If a small group of infected is introduced into a large population, a basic problem is to describe the spread of the infection within the population as a function of time. And this is what this work briefly tries to explain.

W.O. Kermack and A.G. McKendrick [11] formulated a model with the population divided into compartments, namely a susceptible class S, who can catch the disease; an infective class I, who have the disease and can transmitt it; and a removed class R, those who have either had the disease, or are recovered, immune or isolated until recovered. The progress of individuals in this system is schematically represented by (Figure 2.1):

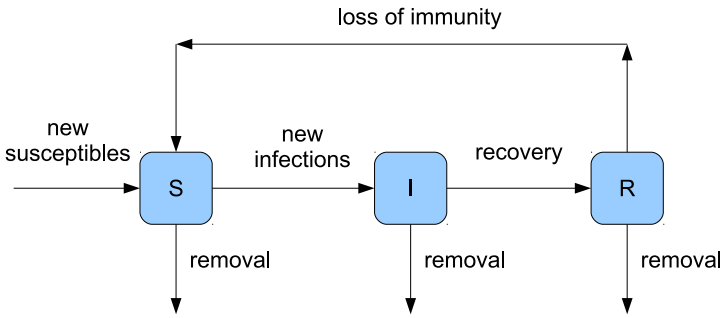


Fig. 2.1: Transfer diagram for SIR model.

Before introducing the equations of this model, we have to make some assumptions about the transmission process of the infection and incubation period:

- The mode of transmission is horizontal, through direct contact between hosts.
- The mixing of individual hosts is homogeneous and thus the *Law of Mass Action* holds: the number of contacts between hosts from different compartments depends only on the number of hosts in each compartment.
- Rates of transfer from a compartment are proportional to the population size of the compartment.
- The incubation period is short enough to be negligible, so individuals become infectious upon infection.
- There is no loss of immunity and no possibility of reinfection.
- No input of new susceptibles and no removal from any compartments.
- The total host population remains a constant.

With these assumptions, we illustrate the transmission progress in a transfer diagram

$$S \Longrightarrow I \Longrightarrow R$$

and the differential equations that describe this model are:

$$\frac{dS}{dt} = -\lambda IS \tag{2.1}$$

$$\frac{dI}{dt} = \lambda IS - \gamma I \tag{2.2}$$

$$\frac{dR}{dt} = \gamma I, \tag{2.3}$$

with initial conditions

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

Where $\lambda > 0$ is the infection rate and $\gamma > 0$ the removal rate of infectives. We are of course interested only in nonnegative solutions for *S, I, R*. This is a basic model but, even so, we can make some highly relevant general comments about epidemics and adequately describe some specific epidemics with such a model.

Some of these observations are listed above:

- Let
$$N(t) = S(t) + I(t) + R(t)$$
denote the total host population; then, by adding (2.1)-(2.3), we have
$$\frac{dN}{dt} = 0$$
and thus $N(t) = N_0 = S_0 + I_0$ is a constant.

- From (2.1) we have
$$\frac{dS}{dt} \leq 0.$$
Therefore,
$$S(t)$$
is always decreasing, in particular $S(t) \leq S_0$.

- Rewrite equation (2.2) as
$$\frac{dI}{dt} = (\lambda S - \gamma)I. \tag{2.4}$$
We start defining $\rho = \frac{\gamma}{\lambda}$, that is sometimes called the *realtive removal rate*,then, we have the following two cases:
  - If $S_0 < \rho$, then $\frac{dI}{dt}\Big|_{t=0} < 0$. Since $S(t) \leq S_0 < \rho$, we know $I'(t) < 0$ for all $t \geq 0$, thus $I(t)$ strictly decreases. As a result, no epidemics can occur in this case.
  - If $S_0 > \rho$, then $S(t) > \rho$ for $t \in [0, \overline{t})$ for some $\overline{t} > 0$. This implies $I'(t) > 0$ and thus $I(t)$ strictly increases for $t \in [0, \overline{t})$. As a result, an epidemic happens.

This demostrates the well-known *threshold pehenomenon*: there is a threshold value S_0 that population size must exceed for an epidemic to occur. Later, in (Chapter 3), we will deeper discuss this aspect.

An important parameter is

$$R_0 = \frac{S_0}{\rho}$$

where R_0 is the *basic reproduction rate* of the infection, that is the number of secondary infections produced by one primary infection in a whole susceptible population. Here $\frac{1}{\gamma}$ is the average infectious period. If more than one secondary infection is produced from one primary infection, that is, $R_0 > 1$, clearly an epidemic ensues.

Clearly one way to reduce the reproduction rate is to reduce the number of suceptibles, S_0. Vaccination is the more common method of doing this and it has been successful in eradicating smallpox. Vaccination not only provides protection for the individual, it also provides it for the community at large since it keeps the effective reproduction rate below the level which would allow an epidemic to start. This is the so-called "herd immunity" . The point is that once the threshold herd immunity level of R_0 has been reached and memory of former diseases fades, there is the possibility that people will not have their children vaccinated but have a free ride instead, namely, the unvaccinated have effectively the same immunity. However, the important thing to keep in mind is that an epidemic can start and rise very quickly if the reproduction rate increases beyond the critical value for an epidemic.

We can derive some useful analytical results from this simple model. From (2.1) and (2.2)

$$(2.5) \quad \frac{dI}{dS} = -\frac{(\lambda S - \gamma)I}{\lambda S I} = -1 + \frac{\rho}{S}, \quad \rho = \frac{\gamma}{\lambda}, \quad (I \neq 0).$$

The singularities all lie on the $I = 0$ axis. We can obtain from (2.4) the phase plane trajectories as

$$(2.6) \quad I + S - \rho ln(S) = constant = I_0 + S_0 - \rho ln(S_0).$$

If an epidemic exists we would like to know how much severe it will be, though what portion of the population size will catch the disease. From (2.4) the maximum I, I_{max}, occurs at $S = \rho$ where $\frac{dI}{dt} = 0$. From (2.6), with $S = \rho$,

$$(2.7) \quad I_{max} = \rho ln\rho - \rho + I_0 + S_0 - \rho ln S_0 = N - \rho + \rho ln\frac{\rho}{S_0}.$$

It may not necessarily be a severe epidemic as is in the case of I_0 close to I_{max}.

Since the axis $I = 0$ is a line of singularities, on all trajectories $I \to 0$ as $t \to \infty$. From (2.1) and (2.3),

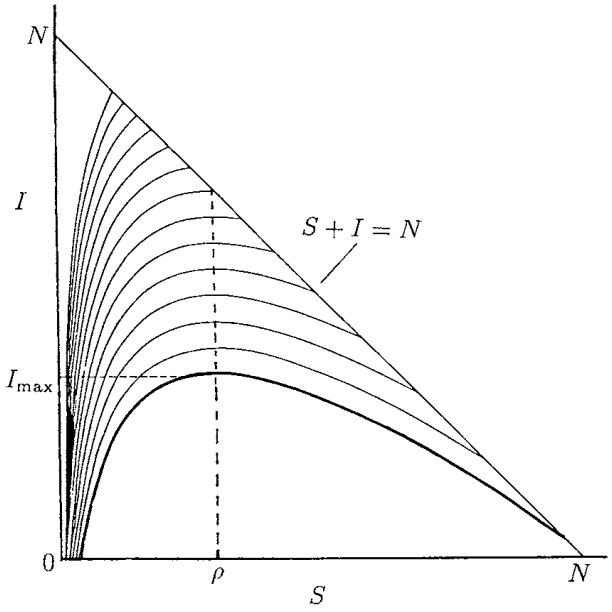


Fig. 2.2: Phase trajectories in the susceptibles (S) - infectives (I)

$$\begin{aligned} (2.8)\quad & \tfrac{dS}{dR} = -\tfrac{S}{\rho} \\ & \Rightarrow S = S_0 e^{-\frac{R}{\rho}} \geq S_0 e^{-\frac{N}{\rho}} > 0 \\ & \Rightarrow 0 < S(\infty) \leq N. \end{aligned}$$

Infact from (Figure 2.2), $0 < S(\infty) < \rho$. We then get the total number of susceptibles who catch the disease in the course of the epidemic as

$$I_{total} = I_0 + S_0 - S(\infty).$$

An important implication of this analysis is that the disease dies out from a lack of infectives and *not* from a lack of susceptibles.

The threshold result for an epidemic is directly related to the relative removal rate, ρ : if $S_0 > \rho$ an epidemic ensues, whereas it does not if $S_0 < \rho$. For a given disease, the relative removal rate varies with the community and hence determines whether an epidemic may occur in one community and not in another one. For example, if the density of susceptibles is high and the removal rate, γ, of infectives is low then an epidemic is likely to occur.

2.2 Real epidemics and simulations comparison

Real epidemics

Now we will see two examples of real past epidemics and then compare their set of data to Matlab® simulations that describe the Kermack-McKendrick model.

Bombay Plague Epidemic, 1905-1906

This plague epidemic lasted for almost a year. The number of removed persons per week, that is $\frac{dR}{dt}$, was approximately equal to the number of deaths per week. The epidemic was not severe (relatively to population size) because it did not affect a large part of the population.

Influenza Epidemic in an English Boarding School, 1978

This is a case of flu epidemic in a school with 763 boys. It seems that one infected boy initiated the epidemic, that is one of the requirements of the model we analyzed in the last section. The epidemic was severe because it interested almost all the boys of the school, [6].

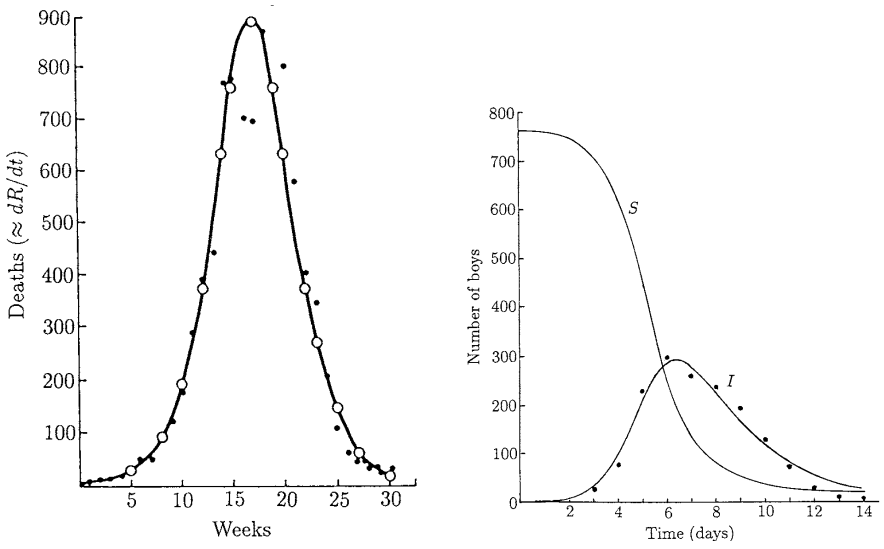


Fig. 2.3: (a) Bombay plague epidemic. Comparison between data (•) and theory (○), (b) Influenza epidemic data (•) for a boys' boarding school.

Matlab® simulations and comments

Using Matlab® we can implement a program that can solve Kermack-McKendrick differential equations and plot some graphs about trends of susceptibles, infectives and recovereds.

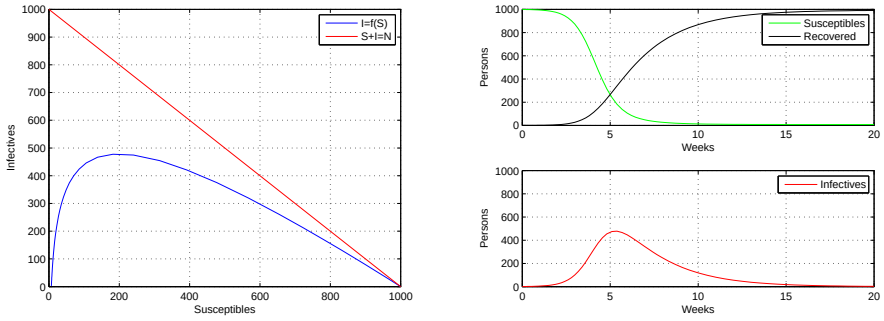
Here the code of the program for this simple model:

```
function [t,S,I,R] =ke_mck()
%Solve SIR equation in Matlab

% to have an epidemy, gamma/lambda must be < S0
lambda=0.002; % infection rate
gamma=0.4; % removal rate

%initial conditions
N=1000; % population size
I0=1; % infectives
S0=N-I0; % susceptibles
tmax=20;
S=S0;
I=I0;
R=N-S-I; % removed, for death or for recovery
tt=[0 tmax];

% The main iteration
[tt,x]=ode45(@diff_SIR,tt,[S I R],[],[lambda gamma]);
S=x(:,1);
I=x(:,2);
R=x(:,3);

% plots the graphs of S,I,R
subplot(2,1,1);
plot(tt,S,'g',tt,R,'k');
grid on;
xlabel('Weeks');
ylabel('Persons');
legend('Susceptibles','Recovered');
axis([0 tmax 0 N]);

subplot(2,1,2);
plot(tt,I,'r');
grid on;
xlabel('Weeks');
ylabel('Persons');
legend('Infectives');
axis([0 tmax 0 N]);

%plots the phase plane trajectories of S - I
figure;
plot(S,I);
grid on;
axis([0 N 0 N]);
hold on;
n=[0 N];
y=I0+S0-n;
plot(n,y,'r');
xlabel('Susceptibles');
ylabel('Infectives');
legend('I=f(S)','S+I=N');
axis([0 N 0 N]);
```

```
% Calculates the differential rates used in the integration
function dx=diff_SIR(tt,x,parameter)
lambda=parameter(1);
gamma=parameter(2);
S=x(1);
I=x(2);
R=x(3);
dx=zeros(3,1);
dx(1)=-lambda*S*I; % first equation
dx(2)=lambda*S*I-gamma*I; % second equation
dx(3)=gamma*I; % third equation
```

In which has been used the function *ode45* for the resolution of the differential system and we have started the simulation from initial conditions where population size was of $1'000$ people in which was introduced a first infected host. Of course we can change these values and parameters, λ and γ, ones to get different trends and situations.

The graphs we get out from this simulation are:



(a) (b)

Fig. 2.4: Graphs plotted by Matlab® program: (a) Phase plane trajectory, (b) S-I-R trends.

From (Figure 2.4) we can notice similarities to (Figure 2.3) and so it is simple to demonstrate that even if the Kermack-McKendrick is a very simple model to describe an epidemic, it is quite good in particular cases that follows the assumptions we made in the beginning of (Chapter 2).

2.3 Demography and routes of transmission

Demography

If a disease is not of short duration, then (2.1), the equation for the susceptibles, should include birth and death terms. Mortality due to natural

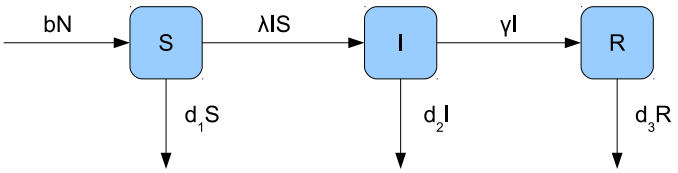


Fig. 2.5: Transfer diagram for SIR model with demographical factors.

causes should also be included in equation (2.2), for the infectives, and in (2.3), for the removed class.

To add demographical factors into the Kermack-McKendrick model, we need to make some assumptions on the birth, death, and growth rates of the host population; the simplest of wich is the proportional assumption that the birth or death rate are proportional to the population size. A model that incorporates these assumptions is depicted in (Figure 2.5) with the corresponding system of differential equations.

$$\frac{dS}{dt} = bN(t) - S(t)(\lambda I(t) + d_1) \tag{2.9}$$

$$\frac{dI}{dt} = \lambda I(t)S(t) - (\gamma + d_2)I(t) \tag{2.10}$$

$$\frac{dR}{dt} = \gamma I(t) - d_3 R(t) \tag{2.11}$$

$$N(t) = S(t) + I(t) + R(t). \tag{2.12}$$

Here b is the natural birth rate constant, d_1, d_2 and d_3 are death rate constants for compartments S, I, and R, respectively. Rate d_2 may include both natural and disease-caused death. If we add (2.9)-(2.11), we obtain

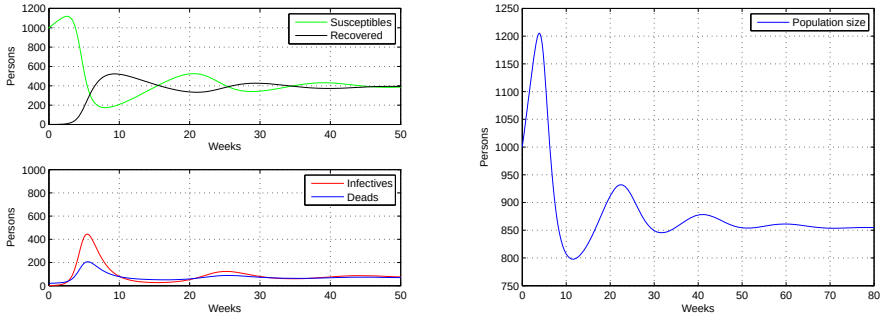
$$\frac{dN}{dt} = bN(t) - d_1 S(t) - d_2 I(t) - d_3 R(t).$$

So this implies that $N(t)$ will vary in time. In the particular case that $d_1 = d_2 = d_3$, we have

$$\frac{dN}{dt} = (b - d)N(t)$$

and thus

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



(a) (b)

Fig. 2.6: (a)Susceptibles and recovereds, infectives and deads trends ,(b) Population size trend.

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

Using the Matlab® program of the past section modified properly to fit this new model that include also demography, we can implement and simulate this new system of differential equations.

If we compare (Figure 2.6) with (Figure 2.4), differences made by the implementation of demography in the model are very noticeable. First of all we see that population size initially increases due to the number of susceptible newborns, that is bigger than the number of deads; but when the epidemic ensues the situation changes rapidly and the population size begin to fluctuate. After a while the situation stabilizes at a particular population size and susceptibles, infectives value. This is clearly an example of endemic because there still are some infectives in the population at the end of the epidemic.

A general consideration we can make, is that from now, all other generalized models using also demography, will be more fluctuating and instable than the first simple Kermack-McKendrick model; we accept this because better describes the real behaviour of an epidemic outbreak and the following recovering stage.

Routes of transmission

In the SIR model, the infection is assumed to be through direct contact of an infectious and a susceptible host. This is often called *horizontal transmission*. Other modes of transmissions exist for many diseases. One of them is *vertical transmission* in which the pathogens are passed to a newborn or newly born directly from an infected mother. Example of diseases that can be transmitted vertically include HIV/AIDS, "Chargas" disease,

and Hepatitis B. To model vertical transmission, we assume that a fraction p of the newborns from infected population becomes infected at birth, and the remaining fraction $(1-p)$ is susceptible. The following diagram, (Figure 2.7), illustrates a case with both horizontal and vertical transmissions.

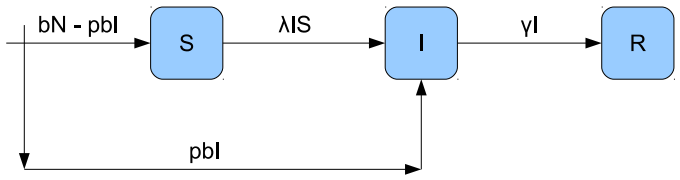


Fig. 2.7: Transfer diagram for SIR model with both horizontal and vertical transmission.

Here, $b \cdot N$ is the total number of newborns with natural birth rate b, $p \cdot b \cdot I$ is the number of newborns who are infected at birth, $(b \cdot N - p \cdot b \cdot I)$ is the number of healthy but susceptible newborns.

2.4 Asymptomatic population and disease latency

Disease latency

Another generalization of the SIR model we are going to study, includes also an hypothetical disease latency and incubation period. Many diseases have a latent or incubation period, that means: when a susceptible has become infected, namely some pathogens are introduced in the host organism, he is not yet infectious, that is when a person could be considered contagious. Measles, for example, has an 8 to 13 day latent period, or AIDS has an incubation time from a few months to years. Infact, when the pathogens accumulate in a sufficiently large number and when they have reached the targeted organs, they begin to cause sufficient damage to the host body so that the host becomes symptomatic, and the host is capable to transmit the pathogens to other hosts. The period from the time of the infection to the time of showing symptoms is called *incubation period*. Instead the period from the time of infection to the time of being infectious is called *latent period*.

To include these aspects to a mathematical model, the simplest way is to divide the infected compartment into two compartments: a latent compartment E and an infectious compartment I, and assume the transfer from E to I satisfies the proportional rate assumption, namely, give by κE, with rate constant κ. We have a new transfer diagram in (Figure 2.8) that describes this new model also known as SEIR model.

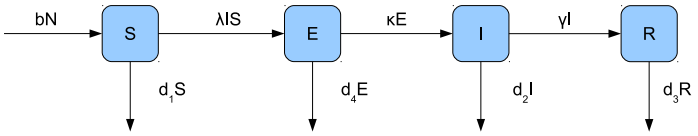


Fig. 2.8: Transfer diagram for SEIR model.

Asymptomatic population

Some diseases have also an asymptomatic stage in which there is some infectivity rather than there are no experienced symptoms. This may be modeled by assuming infectivity reduced by a factor ϵ_A during an exposed stage. The analogue transfer diagram of (Figure 2.8) so becomes like (Figure 2.9) and leads to a system of differential equations:

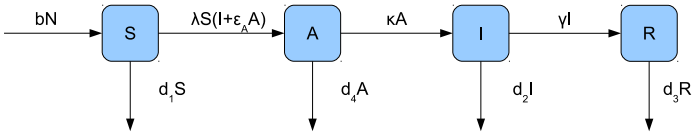


Fig. 2.9: Transfer diagram for SIR model with disease latency and asymptomatic stage, namely SAIR model.

$$\frac{dS}{dt} = bN(t) - S(t)(\lambda I(t) + \lambda \epsilon_A A(t) + d_1) \tag{2.13}$$

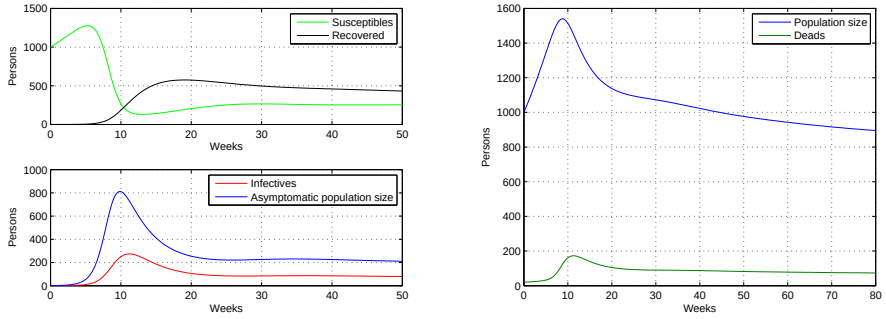
$$\frac{dI}{dt} = \kappa A(t) - (\gamma + d_2)I(t) \tag{2.14}$$

$$\frac{dR}{dt} = \gamma I(t) - d_3 R(t) \tag{2.15}$$

$$\frac{dA}{dt} = S(t)(\lambda I(t) + \lambda \epsilon_A A(t)) - (\kappa + d_4)A(t). \tag{2.16}$$

Where we have used $A(t)$, for asymptomatic, in place of $E(t)$ as one of the compartments. In the system we can see the proportionality of the reducing infectivity factor to the asymptomatic population size, that, as the other compartments, has a her own death rate d_4.

Using the Matlab® program properly modified to fit this new model, we can implement these new equations that considers also disease latency and asymptomatic population. Next page we can see the graphs plotted by the simulation.



(a) (b)

Fig. 2.10: (a)Susceptibles and recovereds, infectives and asymptomatics trends ,(b) Population size and deads trends.

Analyzing (Figure 2.10), we can see that there are a lot of asymptomatics, but indeed only a minor part of them are really infectives; this is not strange, infact we can explain this looking at (2.13)-(2.16). It's obvious that only a fraction κ of the asymptomatic population becomes infective, while the remaining part is stuck in the A compartment because they were not really asymptomatic but simple susceptibles.

2.5 Public health: isolation and quarantine

An actual epidemic differs considerably from the idealized models, as was shown by the SARS epidemic of 2002-2003. Some noticeable differences are:

- Diagnosed infectives may be hospitalized, both for treatment and to isolate them from the rest of the population.
- Contact tracing of diagnosed infectives may identify people at risk of becoming infectives, who may be quarantined (instructed to remain at home and to avoid contacts) and monitored, so that they may be isolated immediately if and when they become infectives.
- Isolation may be imperfect; in-hospital transmission of infection was a major problem in the SARS epidemic.

All these generalizations have been considered in studies of the SARS epidemic of 2002-2003. While these ideas were suggested in SARS modelling, though they are anyway relevant to any epidemic. When no vaccine is available, isolation and quarantine are the main measures available for attempting to manage an outbreak of a new disease. We assume that an epidemic has started, but that the number of infectives is small and almost

all members of the population are still susceptibles, and we formulate a model to describe the course of an epidemic when management measures are begun under the following assumptions:

- Asymptomatic members may be infectives with infectivity reduced by a factor ϵ_A, $0 \leq \epsilon_A < 1$.
- Asymptomatic members who are not isolated become infectives at rate κ_1.
- We introduce a class Q of quarantined members and a class J of isolated members.
- Asymptomatic members are quarantined at a rate $\mu_1 A$ (in practice, a quarantine will also be applied to many susceptibles, but we ignore this in the model). The effect of this assumption is that some susceptibles make fewer contacts than the model assumes. Quarantine is not perfect, but reduces the contact rate by a factor ϵ_Q.
- There may be transmission of the disease by isolated members, with an infectivity factor of ϵ_J.
- Infectives are diagnosed and isolated at a rate $\mu_2 I$. In addition, quarantined members are monitored and isolated immediately when they develop symptoms, at a rate $\kappa_2 Q$.
- Infectives leave the infective class at rate $\gamma_1 I$ and isolated members leave the isolated class at rate $\gamma_2 J$.
- Every compartment has a death rate $d_1, d_2, d_3, d_4, d_5, d_6$ respectively for S, I, R, A, Q, J.

These assumptions lead to the SAQIJR model, that may describe in a quite good way the outbreak of an epidemic with public health management measures:

$$\frac{dS}{dt} = bN(t) - S(t)(\lambda I(t) + \lambda\epsilon_A\epsilon_Q Q(t) + \lambda\epsilon_A A(t) + \lambda\epsilon_J J(t) + d_1) \tag{2.17}$$

$$\frac{dI}{dt} = \kappa_1 A(t) - (\gamma_1 + \mu_2 + d_2)I(t) \tag{2.18}$$

$$\frac{dR}{dt} = \gamma_1 I(t) + \gamma_2 J(t) - d_3 R(t) \tag{2.19}$$

$$\frac{dA}{dt} = S(t)(\lambda I(t) + \lambda\epsilon_A A(t) + \lambda\epsilon_A\epsilon_Q Q(t) + \lambda\epsilon_J J(t)) - (\kappa_1 + \mu_1 + d_4)A(t) \tag{2.20}$$

$$\frac{dQ}{dt} = \mu_1 A(t) - (\kappa_2 + d_5)Q(t) \tag{2.21}$$

$$\frac{dJ}{dt} = \kappa_2 Q(t) + \mu_2 I(t) - (\gamma_2 + d_6)J(t). \tag{2.22}$$

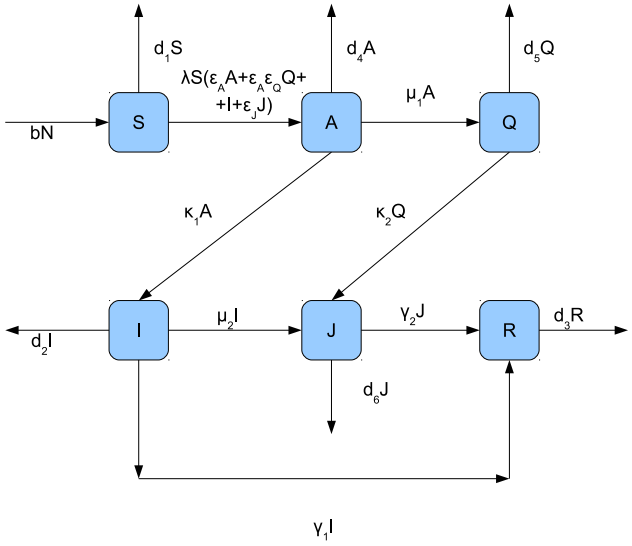


Fig. 2.11: Transfer diagram for SAQIJR model.

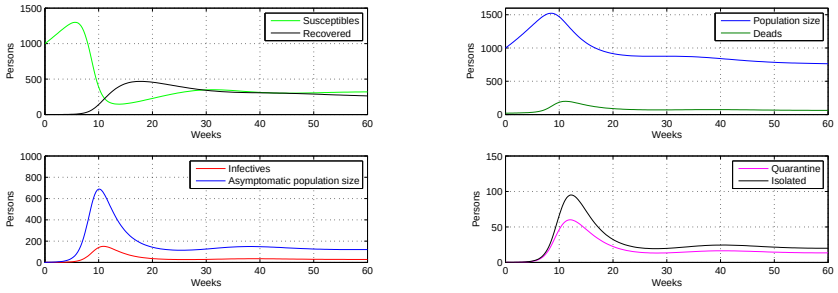
The model, before management measures are begun, is (2.13)-(2.16), the special case, with

$$\mu_1 = \mu_2 = \kappa_2 = \gamma_2 = d_5 = d_6 = 0, \quad \kappa_1 = \kappa, \quad \gamma_1 = \gamma,$$

of (2.17)-(2.22).

This model is equivalent to the SARS model of [1] except for the lack of an extension to a general contact rate in place of standard incidence.

Using the Matlab® program properly modified with these new assumptions, we can implement this new model that considers also improvements made by public health. Here the graph plotted by the simulation:



(a) (b)

Fig. 2.12: (a)Susceptibles and recovereds, infectives and asymptomatics trends ,(b) Population size and deads, isolateds and quarantineds trends.

So we can understand, as we hoped, that the number of deads and of the infectives has decreased from the last simulation we did, (Figure 2.10), thus improvements made by public health management measures are essentials. Another way to fight against the outbreak of an epidemic is vaccination, but we will see this particular case in the next section.

2.6 Vaccination and acquired immunity

Vaccination

If a vaccine is available for a disease that threatens an epidemic outbreak, a vaccinated class, that is protected at least partially against infection, should be included in a model. While this is probably not relevant for an outbreak of a new disease, it would be an important aspect for modeling for example an influenza outbreaks or a bioterrorist outbreak of smallpox. By immunizing a large portion of the susceptible host population before or at the beginning of the disease outbreak, we can reduce the initial number S_0 of susceptibles to a level that is below the threshold $\frac{\gamma}{\lambda}$ and so no epidemic will occur.

To model this new situation, we add the assumption that in a unit of time a fraction φ of the susceptible class is vaccinated. The vaccination may reduce but not completely eliminate susceptibility to infection. We model this by including a factor σ, $0 \leq \sigma \leq 1$, in the infection rate of vaccinated members, with $\sigma = 0$ meaning that the vaccine is perfectly effective and $\sigma = 1$ meaning that the vaccine has no effect. We assume also that the vaccination loses effect at a proportional rate θ. We describe the new model by including a vaccinated class V , with a trasfer diagram (Figure 2.13) and a system of differential equations:

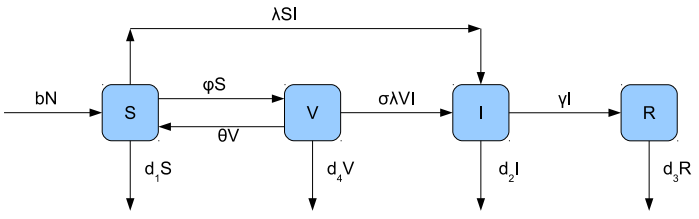


Fig. 2.13: Transfer diagram for a vaccination model.

$$\frac{dS}{dt} = bN(t) + \theta V(t) - S(t)(\lambda I(t) + \varphi + d_1) \tag{2.23}$$

$$\frac{dI}{dt} = I(t)(\lambda S(t) + \lambda\sigma V(t) - \gamma - d_2) \tag{2.24}$$

$$\frac{dR}{dt} = \gamma I(t) - d_3 R(t) \tag{2.25}$$

$$\frac{dV}{dt} = \varphi S(t) - V(t)(\lambda\sigma I(t) + \theta + d_4). \tag{2.26}$$

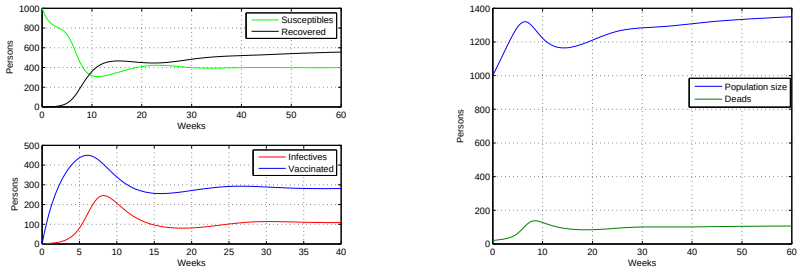
There are essentially two different scenarios:

- The first is an outbreak of a new disease for which a vaccine (supposedly developed originally for some other diseases) is available. Then the population would not have been vaccinated before the beginning of the disease outbreak and we would take $S_0 = N_0$ where N_0 is the whole opulation, and $V_0 = 0$.
- The second scenario is the outbreak of a disease against which the population has been prevaccinated; in this case we would assume that the population size has reached the disease-free equilibrium of (2.23)-(2.26); namely,

$$S = \frac{\theta}{\theta+\varphi} N_0, \qquad V = \frac{\varphi}{\theta+\varphi} N_0.$$

And these two different initial conditions determine variations on the reproduction number, that we will analyze in the *Threshold analysis* chapter, (Chapter 3).

Using the Matlab® program properly modified for this particular case, we can implement this SVIR model with vaccination compartment. Here the graph plotted by the simulation:



(a) (b)

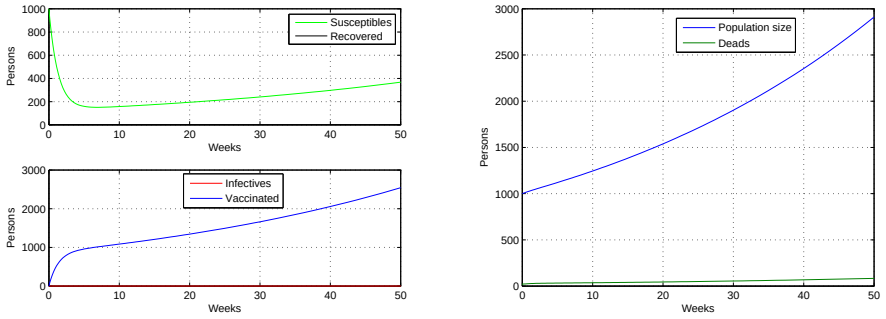
Fig. 2.14: (a)Susceptibles and recovereds, infectives and vaccinateds trends ,(b) Population size and deads trends.

Now, modifying φ, θ and σ values, we can simulate the ideal situation, that means the below assumptions are respected, and see how does the model respond.

The assumptions of idealization are:

- Most of population is vaccinated ($\varphi \to 1$).
- The efficacy of the vaccine is very high ($\theta \to 0$).
- The probability of vaccinated class members to catch the disease is very low ($\sigma \to 0$).

And so the graphs plotted by the simulation result like (Figure 2.15) instead of (Figure 2.14).



(a) (b)

Fig. 2.15: Same as (2.14) but with an ideal vaccine.

Where we can clearly see that no epidemic occurs due to the susceptible population size never reaches the threshold value and, even if initially there is an infective person, an epidemic can not start. This can give an idea of the importnace of developing good vaccines because, as seen, it could be essential to avoid the spread of dangerous diseases. The result of including also a vaccinated class in the model, in the end, permit to resize the dimensions of an epidemic or, in the better cases, it escludes entirely the possibility that an epidemic can start.

Acquired immunity

When an infected host recovers from an infection, it usually maintains a certain degree of immunity against reinfection from the same stain of pathogens. If the infection has caused an immune response, antibodies produced by the host usually remain in the body for a period of time and guard the body from the same antigens.

Without exposure to reinfection, immunity again a specific infection will wane and eventually disappear. Certain diseases such as measles are known to cause a permanent immunity in humans so that no reinfection occurs once recovered. In terms of compartment models, loss of immunity results in a transfer of recovered individuals to the susceptible compartment, as depicted in the following (Figure 2.16), in which we assume the constant rate δ is proportional to the number of recovered individuals.

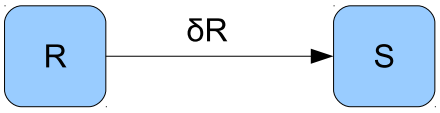


Fig. 2.16: Transfer diagram with loss of immunity.

In this chapter we have seen a lot of generalizations of the first simple Kermack-McKendrick model and, as shown, they can be simply applied to real epidemics and help studying their outbreaks and ways to fight against their spread. An important part of this work is made by the *threshold value*, and just for this we will speak about it in the next chapter.

Chapter 3

Threshold phenomenon and reproduction rate

The threshold phenomenon often described in the past chapter is a main point of the study of epidemics because it determines if there will be or not an epidemic outbreak and, if so, how much severe it will be. Once we know these things, we understand that modyfing that value, we can have different scenarios, better or worse, and so may be possible to control epidemics or create a situation where it is difficult that an epidemic will develop.

The *basic reproduction number* R_0, also called the basic reproductive number or the basic reproductive ratio, is the single most important parameter in epidemic modeling. It measures the average number of the secondary infections caused by a single infective in an entirely susceptible population during its whole infectious period,[5]. In the context of Kermack-McKendrick model, R_0 can be expressed as

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

wich can be interpreted as (Figure 3.1).

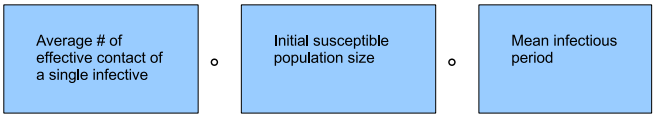


Fig. 3.1: Interpretation of R_0.

Using R_0, the threshold phenomenon previously described can be expressed as follows:

- If $R_0 < 1$, then epidemics will not occur;
- If $R_0 > 1$, an epidemic will outbreak.

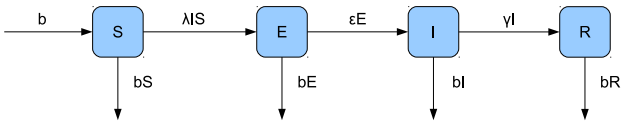


Fig. 3.2: SEIR model with constant demography rates.

We will see that a threshold value in this form occurs in many epidemic models. In particular, considering the SEIR model, like (Figure 3.2), the basic reproduction number is given by

$$R_0 = \lambda \cdot \frac{\epsilon}{\epsilon+b} \cdot \frac{1}{\gamma+b}, \tag{3.1}$$

wich can be interpreted as (Figure 3.3).

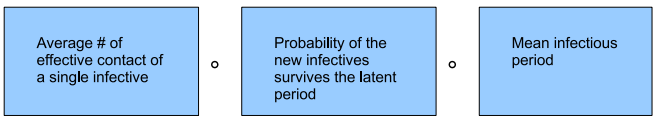


Fig. 3.3: Interpretation of (3.1).

Note that the mean infectious period $\frac{1}{\gamma+b}$ is understood as the mean period an individual remains infective and alive. We also note that the initial susceptible population does not appear in R_0. The reason for this is that, in this model, the total population $N(t) = S(t) + E(t) + I(t) + R(t)$ remains a constant, [4].

Speaking about the SAQIJR model, (Figure 3.3), we define the *control reproduction number* R_c to be the number of secondary infections caused by a single infective in a population consisting essentially only of susceptibles with the control measures in place. It is analogous to the basic reproduction number, but instead of describing the beginning of the disease outbreak, it describes the beginning of the recognition of the epidemic. We assume that this occurs soon enough so that the total population size is still approximately N_0, the initial population size. The basic reproduction number is the value of the control reproduction number before management measures are implemented.

In addition, there is a *time-dependent effective reproduction number* R^*, or also running reproduction number, that continues to track the number of secondary infections caused by a single infective as the epidemic continues with management measures (quarantine of asymptomatics and isolation of symptomatics) in place. It is not diffcult to show that if the inflow into the population from travellers and new births is small (for example, if the epidemiological time scale is much faster than the demographic time scale), our model implies that R^* will become and remain less than unity, so that

the epidemic will always die out. Even if $R_c > 1$, the epidemic will abate eventually when the effective reproduction number becomes less than unity. However, it should be remembered that if the epidemic takes so long to die out that there are enough new births and immigrants to keep $R^* > 1$, there will be an endemic equilibrium, meaning that the disease will establish itself and remain in the population.

We may calculate R_c in the same way as we have calculated R_0 but using the full model with quarantined and isolated classes. Though the running reproduction number R^* is the control reproduction number with N_0 replaced by $N(t)$ to reflect the change in total population size and multiplied by $\frac{S}{N}$ to reflect the fact that the fraction of contacts by an infected member, wich are with a scusceptible and thus can produce a new infection, is $\frac{S}{N}$.

When models get more complicated, R_0 may be harder to derive directly from the transfer diagram. Other methods for deriving R_0 exists and most of them are based on the stability analysis of the disease-free equilibrium.

Chapter 4

Modeling of veneral diseases

4.1 Introduction

The incidence of sexually transmitted diseases (STDs), such as gonorrhea, chlamydia, syphilis and, of course, AIDS, is a major health problem in both developed and developing countries. In the U.S.A., for example, as reported by the *Centers for Disease Control*, in 1996 there were over 300'000 cases of gonorrhea reported and over 11'000 cases of syphilis and nearly 500'000 cases of chlamydia.

STDs have certain characteristics which are different from other infections. One difference is that they are mainly restricted to the sexually active community, so the assumption of uniform mixing in the whole population is not really justified. Another one is that often the carrier is asymptomatic (that is, the carrier shows no symptoms) until quite late in the development of the infection. A third crucial difference is that STDs induce little or no acquired immunity following an infection.

The vertical transmission of STDs from mother to newborn children is another of the threats and tragedies of many STDs. Another problem is the appearance of new strains: in connection with AIDS, HIV-1 is the common virus but a relatively new one, HIV-2 has now been found.

In this chapter we present some simple classical epidemic models which incorporates some of the basic elements in both heterosexual and homosexual spread of venereal diseases.

For the model here, a general one for STDs, we assume there is uniformly promiscuous behaviour in the population we are considering. As a simplification, we consider only heterosexual encounters. The population consists of two interacting classes, males and females, and infection is passed from a member of one class to one of the other class. It is a *criss-cross* type of disease in which each class is the disease host for the other.

Since the incubation period for venereal diseases is usually quite short,

in gonorrhea, for example, it is 3 to 7 days, when compared to the infectious period. We divide the promiscuous male population into susceptibles, S, infectives, I , and a removed class, R; we denote the similar female groups by S^*, I^* and R^*. If we do not include any transition from the removed class to the susceptible group, the infection dynamics are schematically represented in (Figure 4.1).

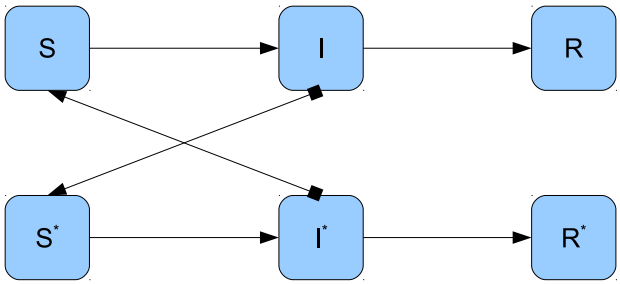


Fig. 4.1: General tranfer diagram for STDs, where I^* infects S and I infects S^*.

In the next section we will talk in particular about the HIV virus, how to modelize its development among a homosexual population and how to contrast it using a drug combination therapy.

4.2 HIV: background, basic epidemic model and drug therapy

Background

The major horror of the AIDS (autoimmune deficiency syndrome) epidemic is in Africa where around 70% of the total AIDS deaths in the world have occurred and half of all newborn babies in Africa are HIV positive.

AIDS, unlike its early image as a homosexual disease, is now very much a heterosexual disease. In an *United Nations AIDS* (UNAIDS) report for World AIDS Day, it says that of the 22.3 million adults in sub-Saharan Africa with HIV, 55% of them are women.

The lack of knowledge about HIV creates enormous difficulties in designing effective control programs, not to mention those for health care facilities. Education programs about how AIDS can spread are the minimum requirement to limit its development. Those that have been pursued, have had some success but even their use and new ones have often been blocked by the religious establishments. There are an estimated 16'000 new cases a day and that around 27 million people are HIV-positive but do not know it.

AIDS is arguably the major epidemic of the 20th century and perhaps of all time. Its progression has exceeded the gloomy view expressed in [3] and now in the 21st century can only give pessimists cause for optimism.

The human immunodeficiency virus, HIV, leads to acquired immune deficiency syndrome, AIDS. HIV is a retrovirus and like most of the viruses in this family of viruses, the Retroviridae, only replicates in dividing cells.

Infection by the virus HIV-1, the most common variety, has many highly complex characteristics, most of which are still not understood. The fact that the disease progression can last more than 10 years from the first day of infection is just one of them.

Since the mid 1980's, numerous models, deterministic and stochastic, have been developed to describe the immune system and its interaction with HIV. It is a highly controversial area. Stochastic models aim to account for the early events in the disease when there are few infected cells and a small number of viruses. But most models have been deterministic; deterministic models, which attempt to reflect the dynamic changes in mean cell numbers, are more applicable to later stages of the process when the population is large.

(Figure 4.2) shows a typical course of HIV infection. Immediately after infection the amount of virus detected in the blood, V, increases rapidly. After a few weeks to months the symptoms disappear and the virus concentration falls to a lower level. An immune response to the virus occurs and antibodies against the virus can be detected in the blood. A test, now highly refined, to detect these antibodies determines if a person has been exposed to HIV. If the antibodies are detected, a person is said to be HIV-positive or seropositive.

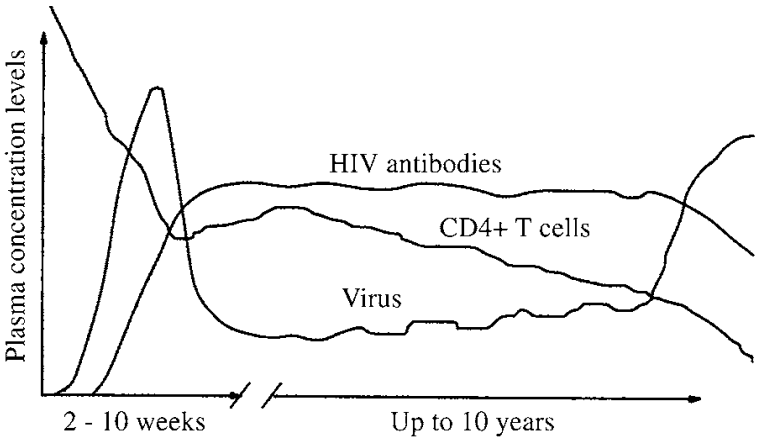


Fig. 4.2: Schematic time course of a typical HIV infection.

In 1994, David Ho (Aaron Diamond AIDS Research Center) ran an experiment which examined the response of 20 patients infected with HIV to a protease inhibitor. The results were dramatic. (Figure 4.3) shows the amount of virus measured in blood plasma that fell rapidly once the drug

was given.

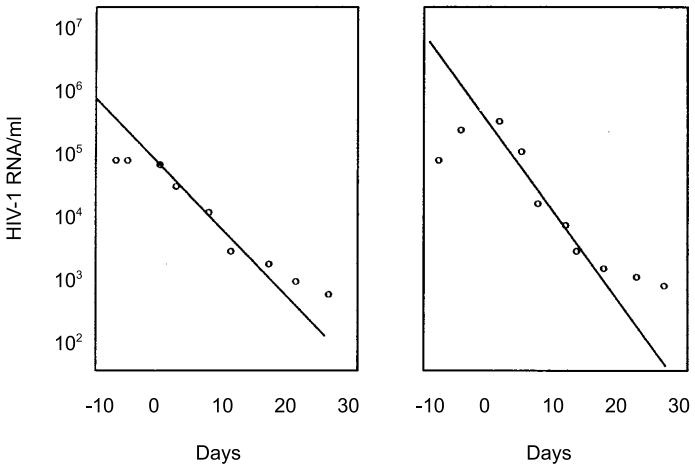


Fig. 4.3: HIV-1 rapid declines with protease inhibitor treatment started at t = 0.

Basic epidemic model

Here we are interested in the development of an AIDS epidemic in a homosexual population. Let us assume there is a constant immigration rate B of susceptible males into a population of size $N(t)$. Let $X(t), Y(t), A(t)$ and $Z(t)$ denote respectively the number of susceptibles, infectious males, AIDS patients and HIV-positive men who are noninfectious. We assume susceptibles die naturally at a rate μ; if there were no AIDS, the steady state population would then be $N^* = \frac{B}{\mu}$. We assume AIDS patients to die at a rate d: $\frac{1}{d}$, the average life expectancy of an AIDS patient, is of the order of months to years, more often the latter. (Figure 4.4) is a flow diagram that describes our model.

As in previous models, we consider uniform mixing. A reasonable first model system, based on the flow diagram in (Figure 4.4), is then

$$(4.1) \quad \frac{dX}{dt} = B - \mu X(t) - \lambda c X(t), \qquad \lambda = \frac{\beta Y(t)}{N(t)}$$

$$(4.2) \quad \frac{dY}{dt} = \lambda c X(t) - (\upsilon + \mu) Y(t)$$

$$(4.3) \quad \frac{dA}{dt} = p\upsilon Y(t) - (d + \mu) A(t)$$

$$(4.4) \quad \frac{dZ}{dt} = (1 - p)\upsilon Y(t) - \mu Z(t)$$

$$(4.5) \quad N(t) = X(t) + Y(t) + A(t) + Z(t).$$

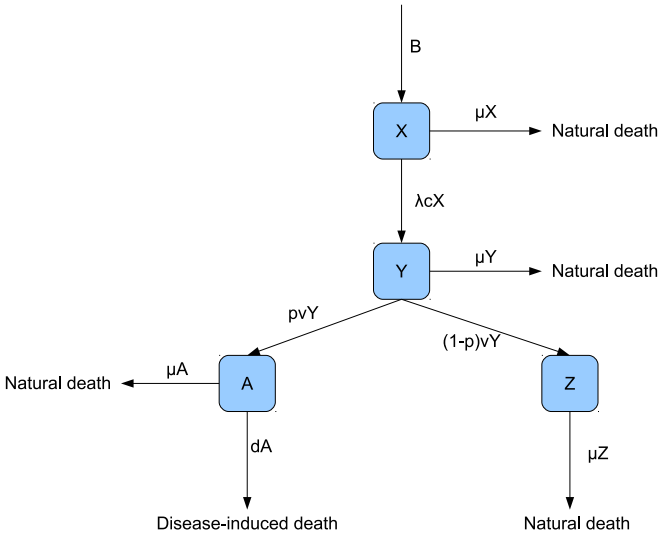


Fig. 4.4: Transfer diagram of the disease as modeled by the system (4.1)-(4.5).

Here B is the recruitment rate of susceptibles, μ is the natural (non-AIDS-related) death rate, λ is the probability of acquiring infection from a randomly chosen partner ($\lambda = \frac{\beta Y(t)}{N(t)}$, where β is the transmission probability), c is the number of sexual partners, d is the AIDS-related death rate, p is the proportion of HIV-positives who are infectious and υ is the rate of conversion from infection to AIDS, here taken to be constant. $\frac{1}{\upsilon}$, equal to D, is then the average incubation time of the disease.

Note that in this model the total population $N(t)$ is not constant, as was the case in the epidemic model in (Section 2.1). If we add equations (4.1)-(4.4) we get

$$\frac{dN}{dt} = B - \mu N(t) - dA(t). \tag{4.6}$$

An epidemic ensues if the basic reproductive rate $R_0 > 1$: that is, the number of secondary infections which arise from a primary infection is greater than 1. In (4.5) if, at $t = 0$, an infected individual is introduced into an otherwise infection-free population of susceptibles, we have initially $X \approx N$ and so near $t = 0$,

$$\frac{dY}{dt} \approx (\beta c - \upsilon - \mu)Y(t) \approx \upsilon(R_0 - 1)Y(t).$$

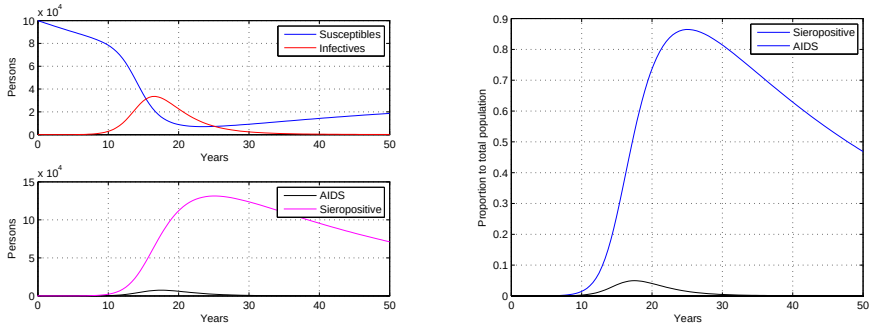
since the average incubation time, $\frac{1}{\upsilon}$, from infection to development of the disease, is very much shorter than the average life expectancy, $\frac{1}{\mu}$, of a

susceptible; that is, $\upsilon \gg \mu$. Thus the approximate threshold condition for an epidemic to start is, from the last equation,

$$R_0 \approx \frac{\beta c}{\upsilon} > 1.$$

Here the basic reproductive rate R_0 is given in terms of the number of sexual partners c, the transmission probability β and the average incubation time of the disease $\frac{1}{\upsilon}$.

Numerical simulations of the model by the system of equations (4.1)-(4.4) give a clear picture of the epidemic development after the introduction of HIV virus into a susceptible homosexual population. (Figure 4.5) shows one such simulation obtained by a Matlab® program based on the model we wrote and started from an intial population of 10'000 homosexuals: the model predicts that HIV incidence reaches a maximum around 15 to 18 years after the introduction of the virus into the population.



(a) (b)

Fig. 4.5: (a) Susceptibles, Infectives, AIDS and Seropositive trends,(b) Seropositive and AIDS trends in proportion to total population size.

The model here is for a homosexual population. Now that the epidemic is very much heterosexual other models are required. The approach described here is a reasonable starting point. The models we now discuss take a very different approach to HIV infection, infact we deal with the actual viral population and not human population.

Drug combination therapy

Protease inhibitors are drugs which target the protease enzymes in the cell and cause newly produced viruses to be noninfectious. There is no

single drug (nor even a combination of them) which completely kills the HIV infection because of the ability of the virus to mutate into a drug resistant form. It takes time, however, for a new form to evolve. The idea behind combination drug treatment is: when the infection is treated with two quite different antiviral drugs, the time the virus takes much longer for a mutiple-drug resistant strain to emerge than if the virus had to contend with only one toxic drug.

We consider each drug to be less then perfect, which thus allows for viral mutation to a resistant form if administered independently. Let n_p be a measure of the effectiveness of a protease inhibitor or combination of protease inhibitors in blocking production of infectious viruses, so this will affect the viral dynamics directly and the T-cells indirectly. Other commonly used drugs are reverse transcriptase inhibitors, of which AZT is perhaps the best known. After the development of the protease inhibitors, a combination, or cocktail, therapy which included multiple drugs was prescribed. For instance, patients would take a combination of three drugs made of up of a protease inhibitor and two reverse transcriptase inhibitors. This combination was dramatic initially in reducing the number of viral peptides detectable in the patient and it was thought that this might be the cure for the AIDS virus. Unfortunately, with a virus as complex as the HIV, it was only a matter of time before the emergency of resistant viruses ensued.

We develop a four-species model which includes an equation for uninfected T-cells, T , productively infected T-cells, T^* (not all infected T-cells produce the virus), infectious viruses, V_I and noninfectious viruses, V_{NI}. The model consists of the following equations which we motivate below.

$$\frac{dT}{dt} = s + pT(t)(1 - \frac{T(t)}{T_{max}}) - d_T T(t) - kV_I(t)T(t) \tag{4.7}$$

$$\frac{dT^*}{dt} = (1 - n_{rt})kV_I(t)T(t) - \delta T^*(t) \tag{4.8}$$

$$\frac{dV_I}{dt} = (1 - n_p)N(t)\delta T^*(t) - cV_I \tag{4.9}$$

$$\frac{dV_{NI}}{dt} = n_p N \delta T^* - cV_{NI}. \tag{4.10}$$

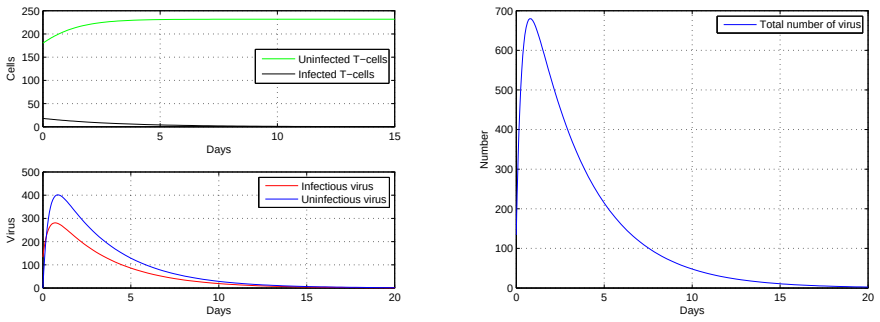
In the T-cell equation we consider the cells to be destroyed proportionally to the number of infected viruses and cells with clearance parameter k. With the reverse transcriptase (RT) drug like AZT, the RT-inhibitor acts on the source term for productively infected T-cells with $0 \leq n_{rt} \leq 1$ the measure of its efficacy; if $n_{rt} = 1$ it is completely effective and prevents all production of infected T-cells while if $n_{rt} = 0$ it implies no RT-inhibitor is given. In the T^* equation the effect of the RT-inhibitor is to reduce the production of the infected cells. These cells also have natural death with a rate parameter, δ. The protease inhibitor acts on the source of the virus and so appears in the

V_I equation with n_p a measure of its efficacy. The specific appearance in the equations for the effects of the drugs is due to the cellular mechanisms of each drug and the stage at which they aim to target during infection. When a drug is completely effective we set $n_p = 1$ or $n_{rt} = 1$. In the infected virus V_I equation there is a factor N which is the bursting parameter for the viral production after lysis.

The infected viruses are considered to die naturally at a rate c. Finally the non-infectious viruses are produced with a rate dependent on the protease drug and we assume they die off at the same rate as the infected ones. This model lets us explore the effect of the drugs on the HIV by varying, in particular, the parameters n_{rt} and n_p. For example, if $n_p = 0$ we are using only the reverse transcriptase, or RT-inhibitors. We now analyse this system in several ways and compare the results with the patient data.

Implementing this model in a Matlab® program like in the paragraph before, we can have an idea how viruses reacts to the drug therapy, for example see (Figure 4.6) that is a simulation in wich initial conditions are:

$$T \sim 180\ cells/mm^3, \quad T^* \sim 2\%\ T - cells,$$
$$V_I \sim 134 \cdot 10^3\ virions/ml, \quad V_{NI} = 0\ virions/ml.$$



(a) (b)

Fig. 4.6: (a) Infected, uninfected T-cells and viruses trends ,(b) total number of viruses trend .

So, in the end, we have seen in wich way the HIV virus develops and affects a population of homosexual persons, and in wich way initially this problem seemed to be solved by the combination drug therapy. Unfortunately as we said this therapy is no longer effective because of the ability of the HIV-1 virus to resist drugs and so another way to heal AIDS affected patients has to be found.

4.3 Gonorrhea and other STDs

Back to some argoments we mentioned in (Section 4.1), gonorrhea is a criss-cross type of disease and its development could be described by (Figure 4.1), in particular the contraction of gonorrhea does not confer immunity and so an individual removed for treatment becomes susceptible again after recovery. In this case a better dynamics flow diagram for gonorrhea is shown in (Figure 4.7).

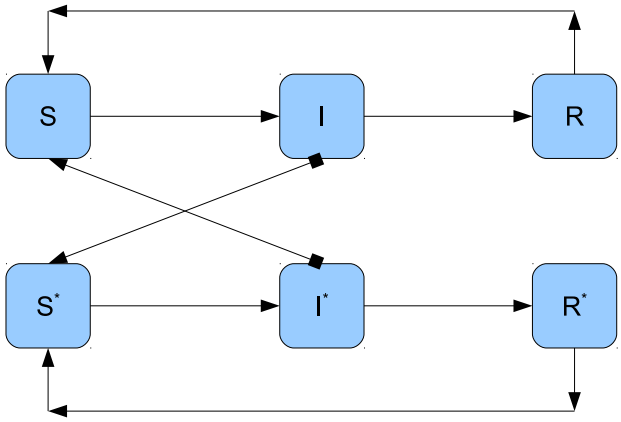


Fig. 4.7: Transfer diagram for a criss-cross disease with no immunity.

An even simpler version involving only susceptible and infective compartments is described in (Figure 4.8).

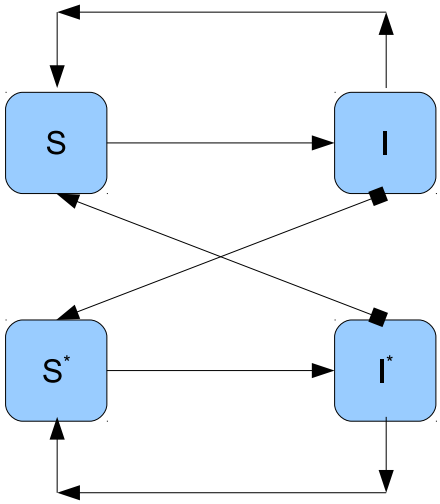


Fig. 4.8: Transfer diagram for the simpler model we analyze for gonorrhea.

It is a criss-cross SI model. We take the total number of males and females to be constant and equal to N and N^* respectively. Then, for (Figure 4.8),

$$S(t) + I(t) = N, \quad S^*(t) + I^*(t) = N^*. \tag{4.11}$$

As before we now take the rate of decrease of male susceptibles to be proportional to the male susceptibles and to the infectious female population with a similar form for the female rate. We assume that once infectives have recovered they rejoin the susceptible class. A model for (Figure 4.8) is then (4.11) together with

$$\frac{dS}{dt} = -rS(t)I^*(t) + aI(t) \tag{4.12}$$

$$\frac{dI}{dt} = rS(t)I^*(t) - aI(t) \tag{4.13}$$

$$\frac{dS^*}{dt} = -r^*S^*(t)I(t) + a^*I^*(t) \tag{4.14}$$

$$\frac{dI^*}{dt} = r^*S^*(t)I(t) - a^*I^*(t). \tag{4.15}$$

where r, a, r^* and a^* are positive parameters. We are interested in the progress of the disease given initial conditions

$$S(0) = S_0, \quad I(0) = I_0, \quad S^*(0) = S_0^*, \quad I^*(0) = I_0^*.$$

Although (4.12)-(4.15) is a 4th-order system, with (4.11) we reduce it to a 2nd-order system in either S and S^* or I and I^*. In the latter case we get

$$\frac{dI}{dt} = rI^*(t)(N - I(t)) - aI(t) \tag{4.16}$$

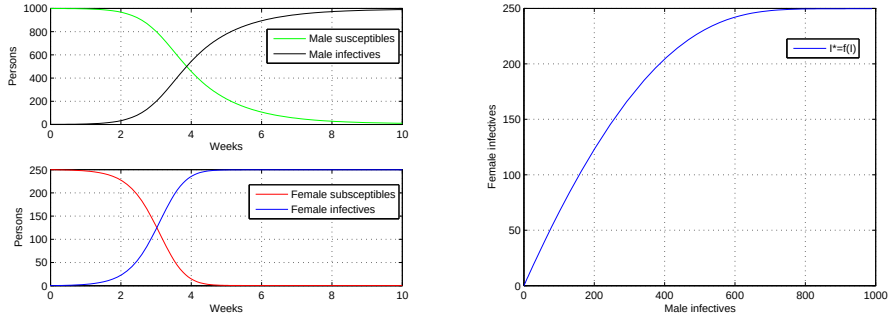
$$\frac{dI^*}{dt} = r^*I(t)(N^* - I^*(t)) - a^*I^*(t), \tag{4.17}$$

which can be analysed in the (I, I^*) phase plane in the standard way (as in Chapter 2). The equilibrium points, that is, the steady states of (4.16)-(4.17), are $I(t) = 0 = I^*(t)$ and

$$I_s = \frac{NN^* - \rho\rho^*}{\rho + N^*}, \quad I_s^* = \frac{NN^* - \rho\rho^*}{\rho^* + N}, \quad \rho = \frac{a}{r}, \quad \rho^* = \frac{a^*}{r^*}.$$

Thus nonzero positive steady state levels of the infective populations exist only if $\frac{NN^*}{\rho\rho^*} > 1$: this is the threshold condition, somewhat analogous to that found in (Chapter 3).

Also this model could be simulated with a Matlab® program and here in (Figure 4.9) we have the graphs plotted.



(a) (b)

Fig. 4.9: (a) Male and female susceptibles and infectives respectively ,(b) Phase trajectory in the male infectives (I) - female infectives (I^*).

Although the SI model in this section is a particularly simple one, it is not too unrealistic. In the case of gonorrheal infections, however, it neglects many relevant factors. For example, as already mentioned a large proportion of females, although infected and infectious, show no obvious symptoms; that is, they form an asymptomatic group. There are, infact, various population subgroups. For example, we could reasonably have susceptible, symptomatic, treated infective and untreated infective groups.

Chapter 5

Outlines of geographic spread

5.1 Spatial models

The geographic spread of epidemics is less well understood and much less studied than the temporal development and control of diseases and epidemics. The usefulness of realistic models for the geotemporal development of epidemics like infectious disease, drug abuse fads or rumours or misinformation, is clear. The key question is how to include and quantify spatial effects. In this section we describe a diffusion model for the geographic spread of a general epidemic which we then apply to a well-known historical epidemic, namely, the ever fascinating mediaeval Black Death of 1347-1350.

We consider here a simpler version of the epidemic model discussed in detail in (Chapter 2). We assume the population consists of only two populations, infectives $I(x,t)$ and susceptibles $S(x,t)$ which interact. Now, however, I and S are functions of the space variable x as well as the time t, like in [7]. We model the spatial dispersion of I and S by simple diffusion and initially consider the infectives and susceptibles to have the same diffusion coefficient D. As before we consider the transition from susceptibles to infectives to be proportional to $r \cdot S \cdot I$, where r is a constant parameter. This form means that $r \cdot S$ is the number of susceptibles who catch the disease from each infective. The parameter r is a measure of the transmission efficiency of the disease from infectives to susceptibles. We assume that the infectives have a disease-induced mortality rate $a \cdot I$; $\frac{1}{a}$ is the life expectancy of an infective. With these assumptions the basic model mechanism for the development and spatial spread of the disease is then

$$\frac{\partial S}{\partial t} = -rI(x,t)S(x,t) + D\nabla^2 S(x,t) \tag{5.1}$$

$$\frac{\partial I}{\partial t} = rI(x,t)S(x,t) - aI(x,t) + D\nabla^2 I(x,t). \tag{5.2}$$

where a, r and D are positive constants. The problem we are now interested in, consists of introducing a number of infectives into a uniform population with initial homogeneous susceptible density S_0 and determining the geotemporal spread of the disease.

Here we consider only the one-dimensional problem. We nondimensionalise the system by writing

$$I^* = \frac{I}{S_0}, \quad S^* = \frac{S}{S_0}, \quad x^* = \left(\frac{rS_0}{D}\right)^{\frac{1}{2}} x,$$

$$t^* = rS_0 t, \quad \lambda = \frac{a}{rS_0},$$

and so the model becomes:

$$\frac{\partial S}{\partial t} = -IS + \frac{\partial^2 S}{\partial x^2} \tag{5.1}$$

$$\frac{\partial I}{\partial t} = IS - \lambda I + \frac{\partial^2 I}{\partial x^2}. \tag{5.2}$$

The three parameters r, a and D in the dimensional model (5.1)-(5.2) have been reduced to only one dimensionless grouping, λ. The basic reproduction rate (see Chapter 3) of the infection is $\frac{1}{\lambda}$; it has several equivalent meanings. For example, is the number of secondary infections produced by one primary infective in a susceptible population. It is also a measure of the two relevant timescales, namely, that associated with the contagious time of the disease, $\frac{1}{rS_0}$, and the life expectancy, $\frac{1}{a}$, of an infective.

The specific problem we investigate here is the spatial spread of an epidemic wave of infectiousness into a uniform population of susceptibles. We want to determine the conditions for the existence of such a travelling wave and, when it exists, its speed of propagation.

We look for travelling wave solutions in the usual way (see Chapter 2) by setting

$$I(x,t) = I(z), \quad S(x,t) = S(z), \quad z = x - ct.$$

where c is the wavespeed, which we have to determine. This represents a wave of constant shape travelling in the positive x-direction.

If $\lambda > 1$ no wave solution exists so this is the necessary threshold condition for the propagation of an epidemic wave. In dimensional terms the threshold condition is (5.3).

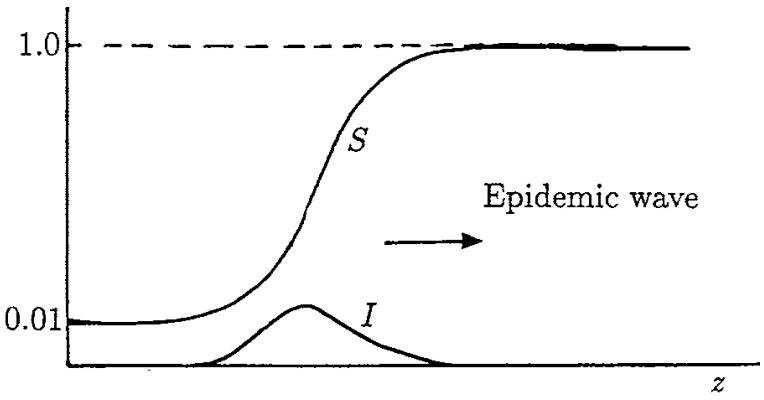


Fig. 5.1: Travelling epidemic wave of constant shape, calculated from the partial differential equations system (5.1)-(5.2).

$$(5.3) \quad \lambda = \frac{a}{rS_0} < 1.$$

This is the same threshold condition found in (Chapter 2) for an epidemic to exist in the spatially homogeneous situation.

The threshold result (5.3) has some important implications. For example, we see that there is a minimum critical population density $S_c = \frac{a}{r}$ for an epidemic wave to occur. On the other hand for a given population S_0 and mortality rate a, there is a critical transmission coefficient $r_c = \frac{a}{S_0}$ which, if not exceeded, prevents the spread of the infection. With a given transmission coefficient and susceptible population we also get a threshold mortality rate, $a_c = rS_0$, which, if exceeded, prevents an epidemic. So, the more rapidly fatal the disease is, the less chance there is of an epidemic wave moving through a population. All of these have implications for control strategies. The susceptible population can be reduced through vaccination or culling. For a given mortality and population density S_0, if we can, by isolation, medical intervention and so on, reduce the transmission factor r of the disease, it may be possible to violate condition (5.3) and hence again prevent the spread of the epidemic. Finally with $\lambda < 1$ as the threshold criterion, we note that a sudden influx of susceptible population can raise S_0 above S_c and hence initiate an epidemic.

5.2 The Black Death: 1347-1350

The fascination with the Black Death, the catastrophic plague pandemic that swept through Europe in the mid-14th century, has not abated with the passage of time. The Black Death, principally bubonic plague, was caused by an organism (Bacillus pestis) and was transmitted by fleas, mainly from black rats, to man. It was generally fatal.

The plague was introduced to Italy in December 1347, brought there by ship from the East where it had been raging for years. During the next few years it spread up through Europe at approximately 200-400 miles a year.

About a quarter to a third of the population died and approximately 80% of those who contracted the disease died within 2-3 days. (Figure 5.2) shows the geotemporal spread of the wavefront of the disease.

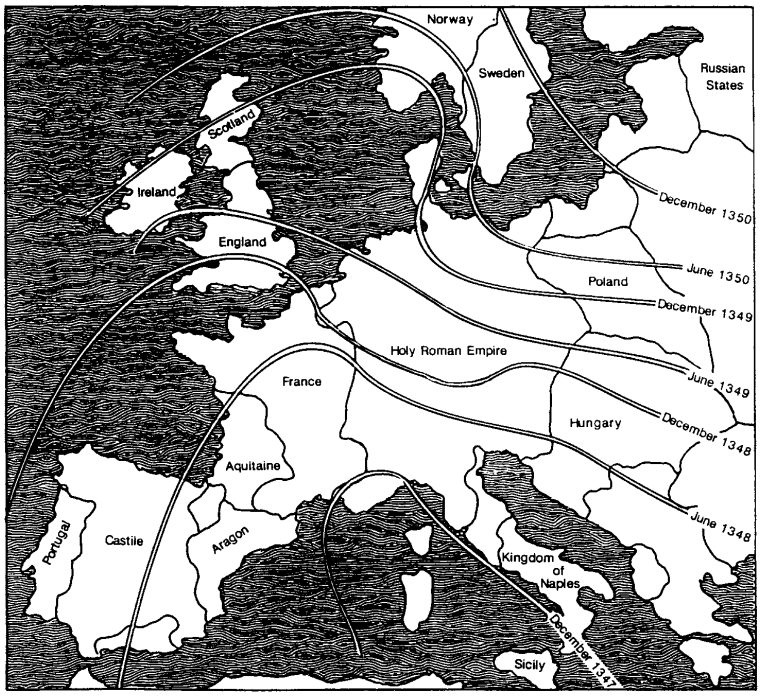


Fig. 5.2: Chronological spread of the Black Death in Europe from 1347 to 1350.

After the Black Death had passed, around 1350, a second major outbreak of plague appeared in Germany in 1356. From then on periodic outbreaks seemed to occur every few years although none of them were in the same class as regards severity as the Black Death epidemic of 1347.

The disease, of which there are three kinds, bubonic, pneumonic and septicemic, is caused by a bacillus carried primarily by fleas which are in turn carried by rats, mice and a host of other animals. Septicemic plague involves the bacilli multiplying extremely rapidly in the victim' s blood and is almost invariably fatal (even now), whether treated or not; the victim usually dies very quickly and often suddenly. Septicemic plague often develops from the pneumonic form which is extremely contagious.

There is a widely held belief that plague more or less ceased to be a problem after the Great Plague of London. This is far from the case. The last plague pandemic started in Yunnan in China about 1850 and only finished officially, according to the *World Health Organisation*, in 1959: more than 13 million deaths have been attributed to it, and it affected most parts of the world. The reported cases (and through ignorance or political expediency the figures must clearly be considered lower bounds) since 1959 makes it clear that plague epidemics are still with us.

The disease is carried by a large number of native wild animals. Rats

are by no means the sole carrier: it has been found in nearly 30 different mammals including, for example, squirrels, chipmunks, coyotes, prairie dogs, mice, voles, domestic pets and bats. The present complacency about the relatively small annual number of plague deaths is hardly justified.

To return now to our modelling, let us apply our simple epidemic model to the spread of the Black Death. We first have to estimate the relevant parameters, not a simple task with the paucity of hard facts about the social conditions of the time. There were about 85'000'000 people in Europe in 1347 which gives a population density $S_0 \approx 50/mile^2$. It is particularly difficult to estimate the transmission coefficient r and the diffusion coefficient D. Let us suppose that the spread of news is governed by diffusion with a diffusion coefficient D; this gives a value of $D \approx 104 miles^2/year$. To transmit the disease, the fleas have to jump from rats to humans and humans have to be close enough to infect other humans; this is reflected in the value of r . These give $\lambda = \frac{a}{rS_0} \approx 0.75$. With the wavespeed given by (Figure 5.1) in terms of the model parameters.

Of course, such a model is extremely simple and does not take into account a number of factors, such as the nonuniformity in population density, the stochastic element and so on. Nevertheless it does indicate certain global features of the geographic spread of an epidemic. Plague is a zoonosis (a disease which spreads from animals to humans) and in many areas where it is prevalent rats are clearly implicated. So a more complicated model crucially incorporates the rat, as well as human, populations and includes stochasticity. This could show that the disease can reside in rat subpopulations thereby letting the disease persist for many years.

5.3 Rabies: brief history and spatial spread among foxes

Brief history

Rabies is arguably the most horrifying disease; the patient undergoes the most frightening nightmarish experiences before dying in prolonged and terrifying agony. In spite of the fact that an effective rabies vaccination is now available, even totally reliable if given soon after being in contact with a rabid animal, the horror of rabies is almost as rampant today as it ever was. If a person reaches the actual rabid stage, that is, displays the clinical symptoms, there is no cure, nor has there ever been a reliably recorded case of a cure.

Some myths about rabies also mention vampires, and they were widely believed in transmitting this disease, during the last quarter of the 17th century. They were thought to be reanimated corpses which rose from their graves, seeking nourishment by sucking the blood of sleeping persons. Ra-

bies is also zoononis, like plague, that is, a disease that can be transmitted from vertebrates to humans, and in the rabid stage can cause unpredictable violent and aggressive behaviour.

Let us now consider some of the symptoms of human rabies. Most humans develop the "furious" form of the disease, rather than the paralytic form, and insomnia, uncontrolled agitation, hydrophobia (the former name for the disease), muscular spasms, fear of seeing themselves in a mirror and other extremely ghastly and bizarre manifestations.

Rabies can be transmitted person-to-person in a variety of ways such as animal (or human) bites, genital mucosae and so on. Numerous theories have been put forward for the legend from simple superstition to schizophrenia. During times of epidemics bodies were sometimes buried in shallow graves and dug up by dogs and wolves, thus giving rise to the idea that vampires rose from their graves.

In England in the 19th century there were several outbreaks (the numbers were in fact very small) which wreaked havoc and spawned some hilarious laws and views. Rabies is still a very serious disease that exists with varying degrees of severity in practically all countries of the world except for Britain, Ireland, Sweden, Australia, New Zealand and a few others. Vaccination has been a major control strategy for rabies in parts of Europe. With such widespread global movement of people and animals it is inevitable that rabies will continue to be introduced into countries hitherto free of the disease. Britain' s paranoia about rabies has not been helped with the Channel Tunnel and the fact that bats can carry the disease. The vampire bat is an important reservoir for rabies in, for example, Mexico and Latin America where it has been the origin of rabies outbreaks in cattle. In Asia, Latin America and Africa it is mainly enzootic dog rabies that is the serious problem. Most humans contract the disease through direct bite or scratch from a rabid animal although aerosol transmission in caves with infected bats is also possible. Although rabies is rare in the U.S., when it occurs, it is almost always from a bite from an infected bat.

Human-to-human transmission can also occur.

Spatial spread among foxes

Rabies, as mentioned in the last paragraph, is widespread throughout the world and epidemics are quite common. During the past few hundred years, Europe has been repeatedly subjected to rabies epidemics. Rabies, a viral infection of the central nervous system, is transmitted by direct contact, and the dog is the principal transmitter of the disease to man.

(Figure 5.3) shows the advance of the rabies epidemic in France obtained from data from the *French Centre National d' Etudes sur la Rage* every two years between 1969 and 1977 on the northeastern part of the country. A

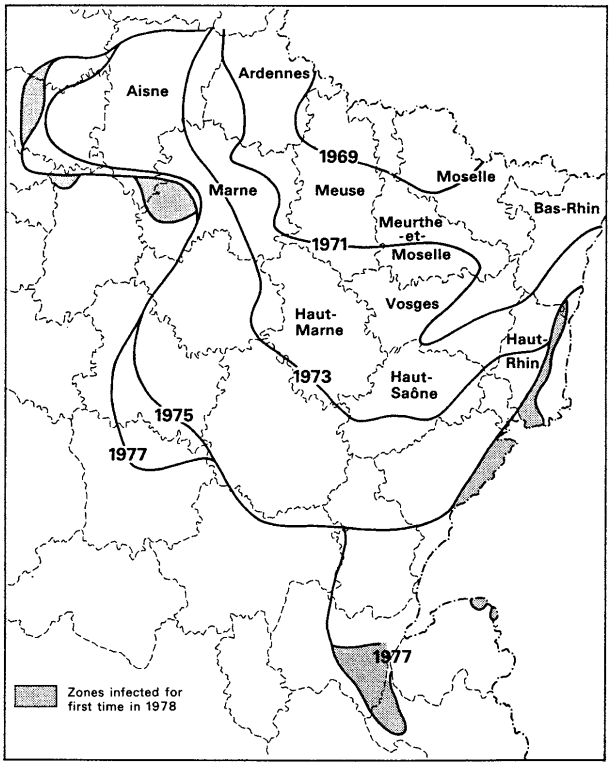


Fig. 5.3: Spatial advance of the rabies epizootic in France from 1969 to 1977.

rabies epidemic was also moving a few years ago rapidly up the east coast of America: the main vector there was the racoon.

The spatial spread of epidemics is usually a very complex process, and rabies is no exception. Although many animals are involved, a basic, and reasonable, assumption is that the ecology of foxes, the principal vectors, determines the dynamics of the spread of rabies. We further assume that the spatial spread of the epizootic is due primarily to the random erratic migration of rabid foxes.

We can use a model similar to the one presented in the (Section 5.1) and obtain the travelling wave of this epidemic in (Figure 5.4):

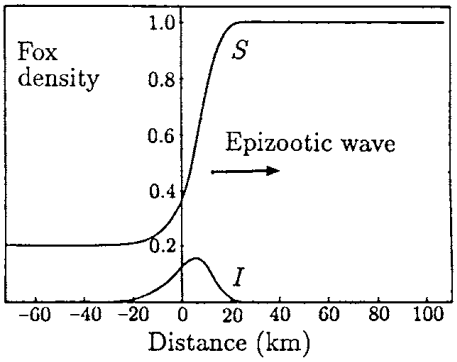


Fig. 5.4: Epidemic wavefront solution for the susceptible (S) and infected (I) fox population.

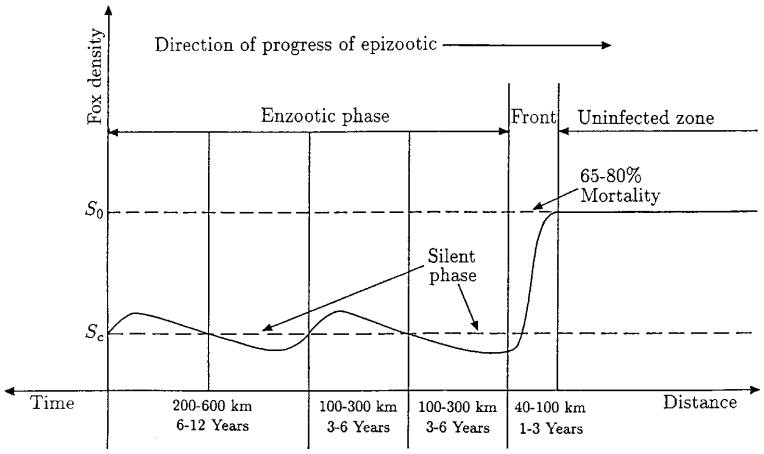


Fig. 5.5: Fluctuations in the susceptible fox population density as a function of the passage of the rabies epizootic obtained from data from *Centre National d' Etudes sur la Rage*, 1977.

Let us now compare the qualitative form of the susceptible fox population in the epidemic of (Figure 5.4) with that obtained from data of continental Europe as illustrated in (Figure 5.5). There is a clear schematic difference in the behaviour behind the front in the two figures. Clearly after the passage of the wavefront the susceptible population will start to increase again since the foxes find themselves in an environment which admits a larger carrying capacity. In other words, the timescale of the model we used, is considerably shorter than that associated with the oscillations in (Figure 5.5).

Let us now return to the observation in (Section 5.2) about the subsequent outbreaks of plague which followed the initial Black Death epidemic. If we modify the susceptible equation in the model (5.1)-(5.2) to take into account the recovery of the population we again get subsequent periodic outbreaks of the disease following the initial epidemic similar to those shown in (Figure 5.5). This is just a bit too facile an explanation since it was the interaction of populations which governed the Black Death, people, fleas, rats and so on. In spite of the simplicity of the model discussed here the results qualitatively capture some of the major phenomena observed. As with so many of the models we have discussed, even such a simple approach can elicit relevant questions.

Chapter 6

Conclusion

We have established that general epidemic models behave in the same way asymptotically, in the sense that there is a basic reproduction number which determines whether there will be an epidemic or an epidemic wave and that an epidemic will pass through a population leaving some members untouched. We conjecture that this would remain true for more complicated models with more compartments and more stages, including models with heterogeneity of mixing. Of course, our first Kermack-McKendrick model assumes that the course of the epidemic is rapid enough that demographic effects may be ignored. If this is not true, then it would be possible for a disease to become endemic, as seen in (Section 2.3) and later sections.

The underlying assumptions in all the models we have described are that the size of the compartments is big enough that deterministic models are appropriate, and that the mixing of members is homogeneous. While these assumptions are probably reasonable once an epidemic is well underway, events at the beginning of an epidemic may be quite different. To model events with a small number of infectives in a population of susceptibles, we should use a branching process stochastic model because of its peculiarities, it can describe the beginning of an epidemic better than deterministic models we have seen.

Another thing we have to consider is that our models treated an epidemic in a single location, ignoring travel of individuals who may be infective between locations. Modern transportation has permitted the rapid transfer of infectious diseases over great distances, and an aspect of epidemic management that has become important is the screening of travellers who may be infective. Epidemic models which include some movement into and out of populations are a natural extension of the models considered in this work.

However we have seen in wich way teorically we can limit or even prevent the outbreak of an epidemic, and this will always be an important topic for the future of human kind because every day new viruses are discovered and the probability that one of these could be dangerous enough to cause a

severe and deadly epidemic is not trascurable. So, studying the dynamcs of infectious diseases is very useful to real world because we can understand how the spread of a disease works and react properly to save thousands or million of life all around the world.

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