Einführung in die Mathematische Epidemiologie

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7 A complex model for Schistosomiasis

7.1 Medical and biological information about schistosomiasis

Die nachfolgenden Daten müssen noch aktualisiert werden; sie entsprechen dem Wissensstand von 1999.

Schistosomiasis (bilharzia) is a severe tropical disease. It is endemic in most regions where it occurs, that is in parts of Asia, Africa and South America. Estimates of how many people are infected vary from 200 to 400 million (1997). It was described by the ancient Egyptians 3,000 years ago (they mentioned blood in the urine as a symptom) and Napoleon's troops suffered terribly from this disease during the Egyptian campaign. The worm (schistosome) which causes this disease was first discovered by the German doctor Theodor Bilharz (1825 - 1862), hence the German name "Bilharziose" for the disease. The whole cycle was first completely understood at the beginning of this century.

7.1.1 Description of the cycle

Schistosomiasis is caused by schistosomes. A schistosome is a special type of worm that belongs to the class of trematodes. There are various types such as Schistosomiasis haematobium (Africa, Arabic countries and India), S. mansoni (Africa, Arabian peninsula, Caribbean and South America), S. japonicum (Southeast Asia and East Asia), S. intercalatum (West Africa). The whole infection process includes a definitive host and an intermediate host. The definitive host is usually a human being in whom sexual reproduction takes place. But depending on the type of schistosomiasis it may be any mammal (S. japonicum). The intermediate hosts are snails of the types Bulinus, Biomphalaria and Oncomelania (depending on the type of schistosomiasis) who live in fresh water. The reproduction in the snails is asexual. The whole process consists of the following parts (as understood in 1999); see page 19 of chapter 2 ("Biological Introduction"):

Worm in blood vessel of man — Egg — Miracidium — Intermediate host (snails) — Larva stages in snails — Cercaria

Male and female schistosomes mate in the blood vessels of the large intestine or bladder of man and produce eggs. Schistosomes can live for several years (estimates range from 2 to 20 years). The eggs are deposited in the bladder (90 %) or the large intestine (10 %). They are released with urine or faeces. If the urine or faeces are released into a well-disposed environment, the eggs can develop. This "well-disposed environment" means that the eggs are required to fall into fresh water, if possible standing or otherwise with not too high a current, at a temperature of at least 20^o C. Mineral conditions should not be too extreme and the snails mentioned above must live in the same water. Then the eggs hatch and become miracidia. These miracidia must penetrate the snails in one or two days. Through diverse stages of asexual reproduction inside the snails finally after approximately 5 weeks so-called cercariae leave the snails and swim around in the water. If they find a man in the next 1 or 2 days they penetrate his skin in only a few minutes. After some 4 to 12 weeks (depending on the type of schistosomiasis) the now adult worms reach the blood vessels of the large intestine and the bladder. Then they mate again completing the cycle.

In schistosome mating the thicker male embraces the female (see again page 19 of chapter 2 ("Biological Introduction")). The whole body of the male looks "split". This is where the disease got its name from: Schistosome is $\sigma\chi i\zeta\epsilon\iota\nu\sigma\tilde{\omega}\mu\alpha$ in Greek, where "$\sigma\chi i\zeta\epsilon\iota\nu$" means "split" and "$\sigma\tilde{\omega}\mu\alpha$" means "body".

7.1.2 Effects, diagnosis, treatment and fighting of schistosomiasis

The **effects on infected humans** are as follows: dermatitis and vomiting at the beginning, cough, temperature, pain in the chest (from eggs that get stuck in the blood vessels of the lungs), diarrhoea, blood in the urine, higher susceptibility to other diseases, kidney disease, cancer and cysts (especially in the liver).

Schistosomiasis is **diagnosed** mainly by detecting eggs, either in the sediment of urine or bladder biopsy or in the stool or through rectal biopsy depending on the type of schistosomiasis.

Treatment is with Praziquantel or (depending on the type of schistosomiasis) Metrifonate or Oxamniquine.

Measures against the spread of the disease are:

1) Treatment as mentioned above to kill the schistosomes in humans and therefore prevent eggs maintaining the cycle.

2) Sanitary installations and sewage treatment so that the eggs in the urine and faeces do not reach the area where there are intermediate hosts (snails).

3) Killing of snails through chemical substances or by supporting their natural enemies.

4) Preventing people from being infected by the cercariae through diverse infrastructural investments.

These measures have been implemented in various parts of the world. Some remarks should perhaps be made. The first measure is expensive in relation to the amount of money available in developing countries. But for tourists from rich countries who get infected it is a standard method. The second measure is surely very expensive and for the next few years not a high priority. Additionally it would be very impracticable in East Asia because looking at S. japonicum almost every mammal can serve as definitive host and the disease would be perpetuated in any case. This is too a main drawback of the first measure in East Asia. As regards the third measure, whilst the massive use of chemical substances to kill the snails created massive damage to the environment, the second possibility (support of the natural enemies of the snails) seems to be a good method, although it has not been possible to make the epidemic disappear completely. The fourth measure is used successfully too and does not necessarily need foreign capital to be implemented. Examples are the construction of simple bridges or sheltered sites where washing can be done. On the other hand it should be mentioned that other investments into the infrastructure, especially for irrigation have had a very bad impact on this epidemic and led to tremendous increases in the prevalence of this disease, that is the proportion of infected people, for instance in the Sahel.

The development of an effective vaccine has not yet been successful but research is continuing.

7.1.3 Social consequences and other diseases

Besides the tremendous direct health-problems associated with this disease and the consequences for the socio-economic situation there is a sex-specific point that should be mentioned. Women are infected more often with this disease and the infection usually turns out to cause more problems in women. The reason for women getting infected more often is that quite often in Africa *they* do the washing and fetch water and so are exposed more intensively. If a woman is infected, the symptoms are much the same as if she were infected by sexually transmissible diseases. So quite often women are worried to tell anybody about their pain and do not go to a medical doctor until the disease becomes chronic.

It might now be convenient to give the reader a brief overview of the importance of this disease in comparison to **other diseases**. In religious writings such as the bible we get quite a lot of information about diseases that bothered people **in the past**. As we have noted, bilharzia was such a disease. Other diseases, such as the plague, which were very important in former times, are no threat to the richer countries today and smallpox is an example of a disease which has been completely eradicated since about 1978. So the reader must be aware of the fact that the numbers below are **current numbers** and the situation was (especially for bilharzia) quite different 10, 30, 100 or 1,000 years ago.

The following summary does not take into account the severity of the diseases. The order of this summary is according to how many people are infected at present. Some diseases are mentioned, such as toxoplasmosis, which usually stay sub-clinical. On the other hand, other diseases which are clearly a threat to many countries and kill worldwide even more than 1 million people a year might not be mentioned. A description of these diseases and the impact can be found on the www-sites of the World Health Organisation (see below). Additionally we would point out that several worm-diseases are usually aggregated while we mention them all separately.

Toxoplasmosis — Perhaps about one third of the world's population are infected by toxoplasmosis. This is a disease caused by a protozoan which lives

	in cats, soil, and numerous mammals. People get infected by eating contaminated meat or vegetables.
Ascariasis	About 800 million people are infected with a nematode that causes ascariasis. Infection results from consumption of contaminated salad, vegetables, or water.
Hookworm	The hookworm-disease is caused by a nematode. About 670 million people are infected. Infection is by penetration through the skin.
Trachoma	Trachoma is a bacterial infection. About 600 to 700 million people are estimated to be infected with this disease. The infection can be transmitted simply by hand, towels or flies.
Pinworm	About 550 million people are infected by the pinworm. Infection results from uptake of eggs by carrier contacts, bed linen, food or dust.
Trichuriasis	Another nematode causes trichuriasis. About 520 million people are infected with this disease. People get infected by consumption of contaminated salads and vegetables.
Malaria	Malaria is one of the worst diseases and is caused by protozoans. About 300 to 500 million people get infected every year, killing up to one million annually. Transmission is by a mosquito.
Hepatitis	Hepatitis is caused by a virus. More than 2 billion people alive today have been infected with hepatitis B and some 350 million are chronically infected. Some 100 million are chronically infected with the hepatitis C virus. Depending on the type of hepatitis the infection is transmitted by consumption of contaminated food or water (hepatitis A) or direct or even indirect blood-contact (hepatitis B).
Giardiasis	About 200 million people suffer from giardiasis caused by a protozoan. Infection is by person-to-person transfer, sexual contacts or consumption of contaminated water or food.
Lymphatic filariases	About 120 million suffer from lymphatic filariases. This disease is caused by nematodes and transmission is by mosquitoes.

Strongyloidiasis	About 75 million people suffer from strongyloidiasis. This disease is caused by a nematode and infection is feco-oral.
Hymenolepiasis nana	A tapeworm causes hymenolepiasis nana. About 75 million people have this disease. Infection takes place via direct contact with other infected people or through ingestion of contaminated food or drinks.
Taeniasis saginata	About 40 to 60 million people suffer from taeniasis saginata. An infection with this tapeworm results from ingestion of smoked or undercooked beef such as tartare.
HIV/AIDS	About 33.4 million people suffer from HIV/AIDS and more than 12 million people have already died of this disease (1998). Infection is mainly sexual. In 1995 more than 333 million new cases of **other sexually transmissible diseases (STDs)** occurred.

Further information about schistosomiasis can be found in Jordan and Webbe (1969, 1982), Stürchler (1988) and Basch (1991). Good articles (in German) about this disease can be found in the "Neue Zürcher Zeitung"; see Trüeb (1985) and Feldmeier (1995a, 1995b, 1997, 1998). Data on prevalence etc. of schistosomiasis is discussed in chapter 5 of the thesis of Christoph Luchsinger and compared with the simulated results using our models. Data on various diseases can be found at the following internet-sites:

1) "http://www.who.ch". This is the "World Health Organisation" in Geneva. The data above is from that site and Stürchler (1988).

2) "http://www.cdc.gov/cdc.html". This is the site of the "Center for Disease Control in Atlanta, USA".

7.2 Modelling schistosomiasis

7.2.1 Early models

We only give a very brief overview of earlier attempts to model this disease. For a more detailed discussion of the previous models we recommend the introduction to Kafetzaki's Ph.D. thesis (Kafetzaki (1993)) and Woolhouse (1991, 1992).

The first attempt to model the transmission of schistosomiasis was made by **Hairston** (1962, 1965). However, his model was not a dynamic model; he only looked at the equilibrium situation. It is not possible to make any predictions with his model.

The first dynamic model was developed by **George Macdonald**, at that time director of the Ross Institute of Tropical Hygiene in London, see Macdonald (1965). A slight simplification of his model was examined by Woolhouse (1992) and Barbour (1996) - Barbour was the PhD-Advisor of Christoph Luchsinger. In their version, they did not distinguish between male and female worms but only looked at female worms that had mated. The main idea behind these models was that each living female parasite in a man produces a constant flow of infection into the snail-population throughout her life. On the other hand, each infected snail produces a constant flow of infection in the other direction. In these models, the factor limiting the development of the infection is that a snail produces the same flow of infection no matter how often it is infected. Such an assumption is justified through data of Pesigan et al (1958). Some limiting factor must be incorporated into a model in order to prevent infinite growth. This model does not represent reality in an acceptable way for two main reasons:

1) In typical models of epidemic spread there is a certain combination of parameters, the **"Basic Reproduction Ratio"**, which is central in determining the behaviour of the model. It is commonly denoted by R_0. R_0 is usually defined to be the lifetime expected number of offspring of an adult parasite under ideal conditions. As can be easily imagined and as is usually the case, if $R_0 > 1$ an epidemic can develop and if $R_0 < 1$ it cannot develop. So eliminating the disease is equivalent in these terms to altering the relevant parameters so that R_0 becomes smaller than 1. This is a theoretical concept. In the models of Macdonald (1965), Woolhouse (1992) and Barbour (1996, pages 136 and 137), R_0 can apparently be estimated in the field merely by measuring the prevalence of infection in snails: In these models, if $\overline{y}$ denotes the equilibrium proportion of infected snails, the relationship between R_0 and $\overline{y}$ is

$$R_0 = \frac{1}{1-\overline{y}}.$$

The levels of prevalence of infection in snails found in practice are usually very low, of the order of 0.1-10%, roughly corresponding to values of R_0 between 1 and 1.1. A range so

narrow would be astonishing in view of the variability of the parameters involved in the definition of R_0 from place to place, and it is unlikely that R_0 should everywhere have a value that was just enough to sustain transmission, and no more, especially in view of the apparent resistance of transmission to attempts at control. So something must be wrong.

2) In Barbour (1978) a period of latent infection in the snails was included. Additionally a seasonal and spatial heterogeneity amongst the human population was studied. The conclusion was that without including a non-linear mechanism *in the definitive host* , the model cannot mirror real data appropriately. Therefore immunity (or crowding effects) in the human population must be included.

Other models (stochastic and deterministic) have other drawbacks such as:

3) The distribution of the number of parasites per human: Looking at the distribution of the data of Cheever (1968), the ratio "variance / mean" was 537, while in many models, due to the assumptions used in building these models, this ratio was 1 (Poisson distribution of parasites per human).

The reader has seen that there have been a variety of attempts to model this disease. Therefore we can ask ourselves: "which model should be chosen?" In Barbour (1996) this question is answered in the following way:

> A model is valuable insofar as it enables one to better understand the phenomenon. No model can be expected to mirror every aspect precisely, and it may well be the case that a variety of models are equally valid, in the sense that they give useful information about different aspects. The more precise the information desired, the more detailed the model has to be; however, the more detailed the model, the greater the danger that it becomes incomprehensible. A reasonable approach consists of both simple and detailed models, the detailed models for quantitative predictions, and the simple models for qualitative understanding and for checking the detailed model. None of the models should be made more detailed than is necessary for the purposes for which they are used.

7.2.2 Our models and notation

In the above title the word "our" stands for the following researchers: Prof. Dr. A.D. Barbour, Dr. Maria Kafetzaki, Dr. J.A.P. Heesterbeek and myself, Christoph Luchsinger.

In total eight models were developed: stochastic and deterministic, linear and non-linear, with and without mortality of humans; this explains why we have 8 models: $2 \times 2 \times 2 = 8$. The four stochastic and the four deterministic models are connected to each other in a one to one fashion. The 4 linear models are also connected to the 4 non-linear models one to one in the sense that each linear model serves as a good (and mathematically much easier to handle) approximation to the initial phase of the corresponding non-linear model. In what follows we first discuss the assumptions we are going to make. The assumptions are almost the same for all 8 models because the 8 models are closely related. In the thesis of Christoph Luchsinger 8 models were presented, giving the rates of change in the stochastic models and the systems of differential equations in the deterministic models. Here only two stochastic models, linear and non-linear are presented, both without mortality.

The assumptions we make for all models are as follows. We suppose that people make potentially infectious contacts according to a Poisson process of rate λ. These people act independently of one another and "mix infinitely fast", meaning that if such a contact occurs at any time t, the infectious person meets any other person with the same chance. If an infected person makes a potentially infectious contact with another individual who is already infected nothing happens, so there is no super infection, that is we assume concomitant immunity. But in the linear models we look at the initial phase of the epidemic and therefore assume that every contact is made with an uninfected individual. These assumptions are translated into mathematical language in the following way: in the non-linear models we have to alter the contact-rate λ to be λx_0 (where x_0 represents the *proportion* of uninfected people in the stochastic model) while in the linear model we can leave the contact-rate λ unchanged.

It might be necessary to point out a misunderstanding that might emerge. We have said that people act independently of one another in infecting other people and the infection process is therefore modelled with independent Poisson processes. But if somebody infects someone else, there are always two people involved. So one might think that the Poisson processes are not independent of each other. We therefore make clear that (in correspondance with the biological situation) there is always a person that infects, and a person that (at least potentially) gets infected. The infection process of every person is modelled

with a Poisson process and then we can choose these infection processes independently of each other.

In contrast to most other models, none of the eight models directly includes the intermediate host. We make the following assumptions. If person A having k worms has a potentially infectious contact with an uninfected person B, then an infection with j worms develops in person B with probability p_{kj}. Clearly we have $\sum_{j\geq 0} p_{kj} = 1$ for all k and we additionally assume that $p_{00} = 1$. We denote by F_k the distribution $\{p_{kj}, j \geq 0, j \in \mathbb{N}\}$. Since we assume that the worms act independently of one another, F_k is the $k-$th convolution of F_1. We denote the mean of F_1 by $\theta > 0$, that is $\theta := \sum_{j\geq 1} j p_{1j}$ and the variance by $\sigma^2 < \infty$, that is $\sigma^2 := \sum_{j\geq 0}(j-\theta)^2 p_{1j}$. The convolution F_k has mean $k\theta$ and variance $k\sigma^2$.

If a person gets infected he carries one or more worms in his body. We assume that these are all female worms or better: we do not distinguish at all amongst the sexes and assume therefore that a single worm can produce eggs. We assume that these worms act independently of one another in producing eggs and in their length of life (and therefore in the length of time they produce eggs). We model the length of life of a worm in the human body with an exponential distribution with parameter μ.

In the models with mortality of humans (not treated here) we model the length of life of each person with an exponential distribution with parameter κ. We assume that an infection does not increase mortality of humans and people die independently of each other. Clearly all worms die if their host dies, moreover, in the non-linear models we assume that as soon as a person dies he is replaced by an uninfected person (a child maybe).

Some remarks should be made about whether these assumptions are justified.

The assumptions of exponentially distributed lifetimes of worms in humans and of humans themselves are mainly a compromise to make the mathematics easier.

Then we implicitly make the assumption that the infection process is by group-infection and not trickle-infection: We assume that people get all their burden of infection at once (the j worms from above), and not one at a time. This is now a clear assumption which is not easy to prove in real life. The theoretical thoughts behind this theory are that eggs are deposited in large numbers in an area and so lots of snails are infected there. So,

when a person enters that area he risks being infected by several cercariae. In particular it is a matter of chance (or better bad luck) if someone gets infected at all and if so with how many worms. This theory has been developed in Barbour (1977).

An important assumption is concomitant immunity as a limiting factor in human beings. Concomitant immunity means that people get infected and then are immune to further infections until they have fully recovered. There are immunological theories which support this assumption, but the mechanism is not fully understood yet. Looking at real data, the situation seems very complex: In Pesigan et al. (1958) the prevalence of schistosomiasis japonicum was studied. Looking at the proportion of infected as a function of age we have an increase until the age of about 15 years and then a levelling off. This could be due to concomitant immunity as we model it. In fact, looking at simulated results in chapter 5.3 of the thesis of Christoph Luchsinger, we get very much the same picture through simulations as we have in real data. Looking at other types of schistosomiasis such as S. mansoni we have the following situation: If we look at the proportion of infected people as a function of their age (see Smithers and Terry (1969), Warren (1973), Kloetzel and da Silva (1967)) we see that the proportion of infected people increases dramatically until the age of about 15 and then decreases again until the age of 30 where it stabilises. People might argue that the contact-rate (λ) is much smaller in that age-group because older people do not have so much water-contact as young children. But as Klötzel and da Silva (1967) showed, looking at immigrants who come into an endemic region, that it is the time that a person spends in such a region that lets him develop an acquired immunity. Our particular model of concomitant immunity does not lead to the decline from ages 15 to 30 described above.

Researchers are uncertain about what is really going on. Mathematicians merely assume a theory and then look whether predicted data from simulations based on models fit real data well. If not, the assumptions are not justified; if yes, it *might well be* that there is something going on in reality which behaves as postulated in our models.

Only two models are going to be written out in terms of rates at which the state changes.

The first stochastic model was developed in Barbour and Kafetzaki (1993). Suppose that there are M individuals in our system. Let x be an infinite dimensional Markov process

$$x(\omega, t) : \Omega \times [0, \infty) \to \{[0, 1] \cap M^{-1}\mathbb{Z}\}^{\infty}.$$

We assume that $\sum_{j \geq 0} x_j(0) = 1$ and $x_j(0) \geq 0$, $j \geq 0$. In this model $x_j(t),\ j \geq 0$, denotes the *proportion* of individuals at time t, $t \geq 0$, who are infected with j worms. The rates at which x changes are as follows (time t suppressed):

$$\begin{aligned} &x \to x + M^{-1}(e_{j-1} - e_j) \text{ at rate } jM\mu x_j \ ;\ j \geq 1, \\ &x \to x + M^{-1}(e_k - e_0) \text{ at rate } \lambda M x_0 \sum_{l \geq 1} x_l p_{lk} \ ;\ k \geq 1, \end{aligned} \tag{7.1}$$

where e_i denotes the i-th co-ordinate vector in $\mathbb{R}^{\infty}$. We call this model SN; this stands for **S**tochastic **N**on-linear. At this point it is convenient to explain why we have *these* rates: there are jMx_j worms in individuals with j worms and they all die at a rate of μ. If such a worm dies, the proportion of individuals with j worms decreases by $1/M$ and the proportion of individuals with $(j-1)$ worms increases by $1/M$. This explains the first transition-rate. The second transition is an infection: there are $x_l M$ individuals with l worms who make contacts according to a Poisson process of rate λ. But only those contacts that take place with uninfected individuals are infective. So the rate must be decreased by multiplying by the proportion of uninfected people x_0. Then we must include the probability that such an infection leads to an infection with k worms, hence the probability p_{lk}. All other rates are explained in a similar way.

The next stochastic model was developed in Barbour (1994). Let X be an infinite dimensional Markov process

$$X(\omega, t) : \Omega \times [0, \infty) \to \{[0, \infty) \cap \mathbb{Z}\}^{\infty}.$$

We assume that $0 < \sum_{j \geq 1} X_j(0) = M < \infty$ and $X_j(0) \geq 0,\ j \geq 1$. In this model $X_j(t),\ j \geq 1$, denotes the *number* of individuals at time t, $t \geq 0$, that are infected with j

worms. The rates with which X changes are as follows (time t suppressed):

$$\begin{aligned} &X \to X + (e_{j-1} - e_j) \text{ at rate } j\mu X_j \ ; \ j \geq 2, \\ &X \to X - e_1 \text{ at rate } \mu X_1 \ ; \ (j = 1), \\ &X \to X + e_k \text{ at rate } \lambda \sum_{l \geq 1} X_l p_{lk} \ ; \ k \geq 1. \end{aligned} \tag{7.2}$$

We call this model SL; this stands for **S**tochastic **L**inear. The difference between models SN and SL is the following: in model SL the contact rate is λ and there is no limiting factor in the model. In model SN the contact rate is altered from λ to λx_0, because only those infectious contacts that are with an uninfected individual lead to a new infection.

Remark: To end this chapter we might add that our models could be considered for modelling the hookworm disease too. In this case the description is even closer to reality, because no intermediate host exists in the transmission of that disease.

7.3 Analysing our models

Let us define

$$R_0 := \frac{\lambda\theta}{\mu}$$

and

$$R_1 := \frac{\lambda e \log\theta}{\mu}.$$

These are quantities which emerge as being critical in determining the behaviour of the models without mortality, as, for instance, in Theorem 7.4 below. R_0 is what would usually be called the basic reproduction ratio, because it denotes the average number of offspring of a single parasite during his whole lifetime in the absence of density dependent constraints. This can be seen in the following way: A worm has an exponentially distributed lifetime with parameter μ which means that his expected lifetime is μ^{-1}. During such a life he makes contacts at a rate of λ per time unit and on average these contacts result in infections with θ worms. We will try to interpret R_1 at the end of this chapter.

By the expression **threshold behaviour** we *usually* denote general statements of the following type: If $R_0 > 1$ the epidemic develops in deterministic systems and if $R_0 < 1$ the epidemic dies out. In a stochastic environment statements are *usually* such that if $R_0 > 1$ the epidemic has a positive probability to develop and if $R_0 \leq 1$ the epidemic dies out almost surely.

The results can be summarised as follows: In the non-linear stochastic model (SN) the epidemic dies out almost surely, no matter what values the parameters take (Theorem 7.3). This behaviour is due to the finite number of individuals in the system. On the other hand, if we let the number of individuals tend to infinity in a way to be specified later, we found threshold results, depending on θ, which give us a better insight of the development of the epidemic (Theorem 7.4). In the linear stochastic model (SL) we have again threshold results depending on θ (Theorem 7.2). This result is analogous to Theorem 7.4 in the non-linear case. Besides that we could compute the exact value of the expectation of the number of parasites at any time in the linear stochastic model (equations (7.3)).

7.3.1 The stochastic linear model SL

In this section the model SL (stochastic, linear) is analysed. We first want to be sure that the process SL is 'regular', in the sense that it makes only finitely many transitions in any finite time interval [0,T], almost surely. This is shown in the following

Lemma 7.1 *The process X that evolves according to SL is regular.*

Proof of Lemma 7.1 If there are infinitely many transitions in a finite time interval [0,T], there must be infinitely many infections too in [0,T]. But this is impossible as can be seen by comparison with a pure birth process of rate λ - which is regular.

□

Next a result of Barbour (1994) is presented. In that paper the model SL (stochastic, linear) is analysed. Theorem 7.2 describes the threshold behaviour in the model SL and gives the expected number of parasites at time t:

Theorem 7.2 *Let us assume that* $0 < \sum_{j\geq 1} X_j(0) < \infty$. *Then the following result holds:*

Case 1): $\theta \leq e$. *Then* $\mathbb{P}[\lim_{t\to\infty} \sum_{j\geq 1} X_j(t) = 0] = 1$ *if and only if* $R_0 \leq 1$.

Case 2): $\theta > e$. *Then* $\mathbb{P}[\lim_{t\to\infty} \sum_{j\geq 1} X_j(t) = 0] = 1$ *if and only if* $R_1 \leq 1$.

In addition, the expected number of parasites in SL grows at an exponential rate $(\lambda\theta - \mu)$*:*

$$\mathbb{E}[\sum_{j\geq 1} jX_j(t)] = (\sum_{j\geq 1} jX_j(0))e^{(\lambda\theta-\mu)t}. \tag{7.3}$$

7.3.2 The stochastic non-linear model SN

This model was analysed in Barbour and Kafetzaki (1993)).

The first result shows that in the non-linear stochastic model without mortality of humans, the epidemic dies out with probability one no matter what values the parameters take.

Theorem 7.3 [Barbour and Kafetzaki (1993), Theorem 2.3] *In the model SN the infection dies out with probability one, that is*

$$\mathbb{P}[\lim_{t\to\infty} x(t) = e_0] = 1.$$

Remark As a consequence of Theorem 7.3 the process SN is in particular 'regular', in the sense that it makes only finitely many transitions in any finite time interval [0,T] almost surely.

Idea of the proof:

Looking at Theorem 7.3 we see that the epidemic *finally* dies out almost surely in SN no matter what values the parameters take. But the behaviour of SN in finite time (and with M large) is quite different depending on whether R_i, $i \in \{0, 1\}$, is greater or smaller than one. This is made more precise in

Theorem 7.4 *Fix $y \in \mathbb{N}_0^\infty$, such that $0 < Y := \sum_{j\geq 1} y_j < \infty$, and suppose that for each $M > Y$ we have $x_j(0) = y_j/M$ for all $j \geq 1$. Then in model SN we have the following threshold behaviour:*

Case 1): $\theta \leq e$. Then

$$\lim_{t\to\infty} \lim_{M\to\infty} \mathbb{P}\big[\sum_{j\geq 1} x_j(t) = 0\big] = 1 \text{ if and only if } R_0 \leq 1.$$

Case 2): $\theta > e$. Then

$$\lim_{t\to\infty} \lim_{M\to\infty} \mathbb{P}\big[\sum_{j\geq 1} x_j(t) = 0\big] = 1 \text{ if and only if } R_1 \leq 1.$$

Explanation The initial number of infected individuals stays constant and equal to Y; as M tends to ∞, only the initial number of uninfected individuals $Mx_0 = M - Y$ grows.

2) We let M tend to ∞ first (with t fixed). In the linear models the contact rate λ stays the same no matter how many individuals are infected. But in the non-linear model this contact rate is altered by multiplying it with the proportion of uninfected λx_0. As we increase M, we only increase the initial number of uninfected individuals. The initial proportion of uninfected tends to 1 as M tends to infinity. So we almost have a linear model (at least in the initial phase). So it is not too surprising, that we have analogous results to those in Theorem 7.2. Note that it is vital to let M converge to infinity first and then we let t converge to infinity. Otherwise these probabilities would be 0 in all cases because of Theorem 7.3.

Proof of Theorem 7.4 The idea of the proof is to show that for fixed M there exists a linear process X/M which is *in all components* larger than our original x, and such that,

the larger we choose M, the more x behaves like X/M. Then we use Theorem 7.2 (we do *not* use Theorem 7.4 to prove Theorem 7.2).

1. First we have to find that linear process X: For this we define a trivariate Markov process $(X^{(nl)}(t), X^{(r)}(t), R'(t))$. "$nl$" stands for non-linear, "r" stands for residual and the meaning of R' is explained later. In fact, each of the components in $(X^{(nl)}, X^{(r)})$ are themselves infinite dimensional: The first component is an infinite vector $(X_j^{(nl)}(t))_{j\geq 0}$ and the second component is an infinite vector $(X_k^{(r)}(t))_{k\geq 1}$. We assume that $X_j^{(nl)}(t) \in \mathbb{N}_0$ and $X_k^{(r)}(t) \in \mathbb{N}_0$ for all t, j, k. We choose the initial values to be such that $X_0^{(nl)}(0) = M - Y$, $X_j^{(nl)}(0) = y_j$ for $j \geq 1$ and $X_k^{(r)}(0) = 0$ for $k \geq 1$. Our aim is to construct $X^{(nl)}$ and $X^{(r)}$ such that $X_j := X_j^{(nl)} + X_j^{(r)}$ behaves like SL for $j \geq 1$. We define the univariate, random process $R'(t)$ to have values on the nonnegative integers and to have initial value $R'(0) = 0$. We let these processes develop according to the following rates:

$$\left(X^{(nl)}, X^{(r)}, R'\right) \to \left(X^{(nl)} + (e_{j-1} - e_j), X^{(r)}, R'\right)$$

at rate $j\mu X_j^{(nl)}$; $j \geq 1$, (death of a parasite in the non-linear process)

$$\left(X^{(nl)}, X^{(r)}, R'\right) \to \left(X^{(nl)} + (e_k - e_0), X^{(r)}, R'\right)$$

at rate $\lambda(X_0^{(nl)}/M) \sum_{l\geq 1} X_l^{(nl)} p_{lk}$; $k \geq 1$, (infection in the non-linear process)

$$\left(X^{(nl)}, X^{(r)}, R'\right) \to \left(X^{(nl)}, X^{(r)} + (e_{j-1} - e_j), R'\right)$$

at rate $j\mu X_j^{(r)}$; $j \geq 2$, (death of a parasite in the residual process)

$$\left(X^{(nl)}, X^{(r)}, R'\right) \to \left(X^{(nl)}, X^{(r)} - e_1, R'\right)$$

at rate $\mu X_1^{(r)}$, (death of a parasite in the residual process when $j = 1$). As can be seen, non of the above events change the state of R'.

Let us first motivate the rates to come. Define $R(u) := \sum_{j\geq 1} X_j^{(r)}(u)$, and $N(u) := \sum_{j\geq 1} X_j^{(nl)}(u)$. Then we define $\tau := \inf\{u : N(u) > a\}$ for a a (usually large) positive number to be chosen later. Our aim is to define a time-homogeneous Poisson process R' such that almost surely the following relation holds:

$$R'(u) \geq I[R(u) > 0]I[u < \tau]. \tag{7.4}$$

As we construct $X^{(r)}$ such that X develops according to SL, we already know that the total rate at which infections take place in $X^{(r)}$ (and so in R) must be

$$\lambda \sum_{k\geq 1} \big(\sum_{l\geq 1} X_l^{(r)}(u) p_{lk} + (1 - X_0^{(nl)}(u)/M) \sum_{l\geq 1} X_l^{(nl)}(u) p_{lk} \big).$$

But in (7.4), the right side is 0 at time 0 and as long as $u < \tau$ increases to 1 as soon as a first infection takes place in $X^{(r)}$. This happens at rate

$$\lambda (1 - X_0^{(nl)}(u)/M) \sum_{k\geq 1} \sum_{l\geq 1} X_l^{(nl)}(u) p_{lk}$$

as until then $R = 0$. Let us have a closer look at this rate, as long as $u < \tau$:

$$\begin{aligned} \lambda (1 - X_0^{(nl)}(u)/M) \sum_{k\geq 1} \sum_{l\geq 1} X_l^{(nl)}(u) p_{lk} &\leq \lambda (1 - X_0^{(nl)}(u)/M) \sum_{l\geq 1} X_l^{(nl)}(u) \\ &\leq \lambda \big(1 - \frac{M-a}{M}\big) a = \lambda a^2/M \end{aligned}$$

So we define a time-homogeneous Poisson process R' of rate $\lambda a^2/M$ coupled to the development of R in the following way:

Define

$$\begin{aligned} b(u) &:= a^2/M \\ &\quad - \sum_{k\geq 1} \big(\sum_{l\geq 1} X_l^{(r)}(u) p_{lk} + (1 - X_0^{(nl)}(u)/M) \sum_{l\geq 1} X_l^{(nl)}(u) p_{lk} \big). \end{aligned}$$

Note that we have just shown that $b(u) \geq 0$ until the first infection takes place in the residual process and as long as $u < \tau$. Then, if $b(u) \geq 0$ we have the following rates

$$\big(X^{(nl)}, X^{(r)}, R' \big) \to \big(X^{(nl)}, X^{(r)} + e_k, R' + 1 \big)$$

at rate

$$\lambda \sum_{l\geq 1} X_l^{(r)} p_{lk} + \lambda (1 - \frac{X_0^{(nl)}}{M}) \sum_{l\geq 1} X_l^{(nl)} p_{lk} \; ; \; k \geq 1,$$

this is an infection in the residual process. Additionally, we have the following changes

$$\big(X^{(nl)}, X^{(r)}, R' \big) \to \big(X^{(nl)}, X^{(r)}, R' + 1 \big)$$

at rate

$$\lambda a^2/M - \sum_{k\geq 1}\big(\lambda \sum_{l\geq 1} X_l^{(r)} p_{lk} + \lambda(1 - \frac{X_0^{(nl)}}{M}) \sum_{l\geq 1} X_l^{(nl)} p_{lk}\big).$$

Now if $b < 0$, we have the following rates

$$\big(X^{(nl)}, X^{(r)}, R'\big) \to \big(X^{(nl)}, X^{(r)} + e_k, R'\big)$$

at rate

$$\lambda \sum_{l\geq 1} X_l^{(r)} p_{lk} + \lambda(1 - \frac{X_0^{(nl)}}{M}) \sum_{l\geq 1} X_l^{(nl)} p_{lk}\ ;\ k \geq 1,$$

this is again an infection in the residual process. Additionally, we have the following changes

$$\big(X^{(nl)}, X^{(r)}, R'\big) \to \big(X^{(nl)}, X^{(r)}, R' + 1\big)$$

at rate $\lambda a^2/M$. With this construction (7.4) holds almost surely for the following reasons: we showed that $b \geq 0$ until the first infection, R' increases too at the first infection but does not decrease any more, additionally, note that we look at $I_{\{R>0\}}$ and not R in (7.4).

As only the first two components of this process are important in part 1 of the proof, we repeat for better understanding the last part of the rate at which the first two co-ordinates change, neglecting R':

$$\big(X^{(nl)}, X^{(r)}\big) \to \big(X^{(nl)}, X^{(r)} + e_k\big) \text{ at rate}$$

$$\lambda \sum_{l\geq 1} X_l^{(r)} p_{lk} + \lambda(1 - \frac{X_0^{(nl)}}{M}) \sum_{l\geq 1} X_l^{(nl)} p_{lk}\ ;\ k \geq 1.$$

R' is a time-homogeneous Poisson process of rate $\lambda a^2/M$. The reader can easily check that $X^{(nl)}/M$ behaves according to SN. Let us look at the sum $X_j := (X^{(nl)} + X^{(r)})_j$ for $j \geq 1$. The development of X is that of SL and it is independent of M, as the rates involving M cancel. M also appears in the initial values, but there it only appears in the initial number of uninfected individuals; since X does not include the zero co-ordinate, it is independent of M.

2. We now have to examine the limit

$$\lim_{M\to\infty} \mathbb{P}\big[\sum_{j\geq 1} x_j(t) = 0\big].$$

For all fixed M we introduce the notation $L(u) := \sum_{j\geq 1} X_j(u)$, where we still have $N(u) := \sum_{j\geq 1} X_j^{(nl)}(u)$ and $R(u) := \sum_{j\geq 1} X_j^{(r)}(u)$.
Now we fix t and define $L := L(t), N := N(t)$ and $R := R(t)$. Note that while the distributions of $N(u)$ and $R(u)$ depend on M, the distribution of $L(u)$ does not depend on M. We have

$$\mathbb{P}\big[\sum_{j\geq 1} x_j(t) = 0\big] = \mathbb{P}\big[\sum_{j\geq 1} X_j^{(nl)}(t) = 0\big] = \mathbb{P}\big[N = 0\big]. \tag{7.5}$$

As $L = N + R$ we have

$$\begin{aligned}\mathbb{P}\big[N = 0\big] &= \mathbb{P}\big[L - R = 0\big] \\ &= \mathbb{P}\big[L - R = 0 | R = 0\big]\mathbb{P}\big[R = 0\big] + \mathbb{P}\big[L - R = 0 | R > 0\big]\mathbb{P}\big[R > 0\big] \\ &= \mathbb{P}\big[L = 0\big] + \mathbb{P}\big[L - R = 0 | R > 0\big]\mathbb{P}\big[R > 0\big]. \end{aligned} \tag{7.6}$$

The last equality holds because if $L = 0$ then $R = 0$ too.

The next step is to show that $\mathbb{P}\big[R > 0\big]$ tends to 0 as M tends to infinity. Define a bivariate Markov process (X, B) such that X is the SL process and behaves as before. Additionally we add a univariate random variable $B \geq 0$. The initial values are $X_j(0) = y_j$ for $j \geq 1$ and $B(0) = 0$ and let us recall that $Y := \sum_{j\geq 1} y_j$. The vector (X, B) changes according to the following rates:

$$\begin{aligned}&\big(X, B\big) \to \big(X + (e_{j-1} - e_j), B\big) \text{ at rate } j\mu X_j \ ; \ j \geq 2, \\ &\big(X, B\big) \to \big(X - e_1, B + 1\big) \text{ at rate } \mu X_1 \ ; \ (j = 1), \\ &\big(X, B\big) \to \big(X + e_k, B\big) \text{ at rate } \lambda \sum_{l\geq 1} X_l p_{lk} \ ; k \geq 1, \\ &\big(X, B\big) \to \big(X, B + 1\big) \text{ at rate } \lambda B + \lambda \sum_{l\geq 1} X_l p_{l0}.\end{aligned}$$

As is easily seen, X is still our linear process constructed in step 1. B cancels almost surely every loss of an infected individual in the linear process X: an infected individual drops out of the system if a parasite dies in an individual with only one worm and additionally B cancels infections with zero parasites in the linear process X through adding that rate in the fourth line of our rates. Hence, if we define $\tilde{L} := L + B$, then $\tilde{L}$ is almost surely a

pure birth process of rate λ. If L increases, $\tilde{L}$ increases too, but $\tilde{L}$ does not decrease when L decreases; more, the growing part B of the sum $\tilde{L} = L + B$ contributes increasingly to the growth of $\tilde{L}$.

We can now argue as follows: For positive a, to be chosen later (the reader should think of a being much larger than Y), we have the following relations:

$$\mathbb{P}\big[N > a\big] \leq \mathbb{P}\big[\tilde{L} > a\big] \leq \frac{1}{a}\mathbb{E}\big[\tilde{L}\big] = \frac{1}{a}Ye^{\lambda t}.$$

If we choose a such that $a^{-1}Ye^{\lambda t} < \epsilon$, for an arbitrary $\epsilon > 0$, we can continue as follows: As $\tau := \inf\{u : N(u) > a\} \leq \infty$,

$$\begin{aligned}
\mathbb{P}\big[R > 0\big] &= \mathbb{P}\big[RI_{\{t<\tau\}} + RI_{\{t\geq\tau\}} > 0\big] \\
&\leq \mathbb{P}\big[RI_{\{t<\tau\}} > 0\big] + \mathbb{P}\big[RI_{\{t\geq\tau\}} > 0\big] \\
&\leq \mathbb{P}\big[RI_{\{t<\tau\}} > 0\big] + \mathbb{P}\big[I_{\{t\geq\tau\}} > 0\big] \\
&\leq \mathbb{P}\big[RI_{\{t<\tau\}} > 0\big] + \epsilon.
\end{aligned} \tag{7.7}$$

In the last inequality we used that N is dominated by $\tilde{L}$. We now have to show that $\mathbb{P}\big[RI_{\{t<\tau\}} > 0\big]$ tends to 0 as M tends to infinity. But by (7.4)

$$\mathbb{P}\big[RI_{\{t<\tau\}} > 0\big] = \mathbb{P}\big[I_{\{R>0\}}I_{\{t<\tau\}} > 0] \leq \mathbb{P}\big[R' > 0] = 1 - \exp(-t\lambda a^2/M),$$

as the probability of no event in that Poisson process until time t is $\exp(-t\lambda a^2/M)$. So, letting M tend to infinity, we have in (7.7), as $\epsilon > 0$ was chosen arbitrarily, that $\lim_{M\to\infty}\mathbb{P}[R > 0] = 0$. Hence, from (7.5) and (7.6) we have

$$\lim_{M\to\infty}\mathbb{P}\big[\sum_{j\geq 1} x_j(t) = 0\big] = \mathbb{P}\big[L(t) = 0\big].$$

3. We now have to examine the expression

$$\lim_{t\to\infty}\mathbb{P}\big[L(t) = 0\big]$$

to finish the proof.

The first directions ($\theta \leq e$ and $R_0 \leq 1$ or $\theta > e$ and $R_1 \leq 1$) follow immediately: We can use Theorem 7.2 because convergence to 0 a.s. implies convergence to 0 in probability (note that $\{L(t) = 0\} = \{L(t) > 1/2\}^c$).

The inverse directions ($\theta \leq e$ and $R_0 > 1$ or $\theta > e$ and $R_1 > 1$) need the following reasoning: Let us define the random process $I(t)$ in the following way:

$$I(t) := \begin{cases} 1 & \text{if } L(t) > 0 \\ 0 & \text{if } L(t) = 0. \end{cases}$$

As $I(t)(\omega)$ is a decreasing function in t for each ω, $\lim_{t\to\infty} I(t)$ exists a.s. and so we can define a.s. the limit-function I_∞ as follows:

$$I_\infty(\omega) := \lim_{t\to\infty} I(t)(\omega).$$

By Theorem 7.2 we have $\mathbb{P}\big[I_\infty = 0] =: q < 1$ under the above constraints. But as $I(t)$ is a decreasing function, we have $\mathbb{P}[I(t) = 0] \leq \mathbb{P}[I_\infty = 0] = q < 1$ completing the proof.

□

The remainder of chapter 2.2 comes from Barbour (1994): When $\theta > e$ and $R_1 < 1 < R_0$, the expected number of parasites $\mathbb{E}[\sum_{j\geq 1} jX_j(t)]$ increases with t, but, for $\beta = 1/\log\theta$, $\mathbb{E}[\sum_{j\geq 1} j^\beta X_j(t)]$ tends to zero (see proof of Theorem 7.2, Case 2, first direction in Barbour (1994)). This suggests that the expected number of parasites is in this case dominated by the possibility of having a few individuals with very large parasite burdens. Thus, to understand why $\lambda e \log\theta/\mu = 1$ emerges as a threshold, we consider what happens to individuals infected by large numbers of parasites. As time goes by, the number of parasites carried by such an individual decreases almost exactly exponentially at rate μ, and from time to time, at rate λ, he causes new infections, each of which starts with almost θ times as many parasites as he currently carries. Thus, on a *logarithmic* scale, his parasite burden decreases almost linearly towards zero at rate μ, and each of those he infects behaves in similar fashion, but with initial burden having a value almost $\log\theta$ greater than his current burden.

This motivates the following definition of a branching process Y with drift. $Y(t)$ describes the positions in $\mathbb{R}_+$ of a random number of particles. Each particle drifts steadily

at rate μ towards 0, and is annihilated upon reaching 0. Until this time, it gives birth to further particles according to a Poisson process of rate λ, independently of all other particles. If a particle is born to a parent at position x, it is initially placed at position $x+\log\theta$, and it thereafter behaves according to the same rules governing drift, annihilation and reproduction, independently of all other particles. We are interested in the distribution of $N_Y \leq \infty$, the total number of particles ever in existence. By scaling, we can equivalently take $\lambda' = 1$ and $\mu' = 1$, then setting $d := \lambda \log\theta/\mu$ for the translation at birth. Clearly, the larger the value of d, the larger the values to be expected of N_Y. Let $\mathbb{P}_s$ denote the distribution conditional on starting with a single particle at position s.

Theorem 7.5 [Barbour (1994), Theorem 3.1] *If $d \leq 1/e$, then we have $\mathbb{P}_s[N_Y < \infty] = 1$ for all s, and $\mathbb{E}_d[N_Y] \leq e$. If $d > 1/e$, $\mathbb{P}_s[N_Y < \infty] < 1$ for all s.*

Remark The change at the critical value of d is quite abrupt. When d takes the value $1/e$, not only is N_Y almost surely finite, but its mean is also finite (and equal to e under $\mathbb{P}_d$), although, for any $d > 1/e$, there is a positive probability that $N_Y = \infty$. Note that $d = 1/e$ represents $\lambda e \log\theta/\mu = 1$ in the notation of the original problem. This suggests the interpretation that, for $R_1 \leq 1$, the few individuals with large numbers of parasites are unable to support the growth of X, but that when $R_1 > 1$ they can.

7.4 Discussion

Interpretation of the R_i's

Models with mortality

Deterministic models

Are these results relevant in real life - are the assumptions so complicated?

7.5 References

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