Probabilistic Models of Infectious Disease Dynamics

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Introduction

The aim of these Notes is to present the essentials of the basic probabilistic models of the propagation of epidemics. These are very serious issues concerning public health. During the 14th century, the black plague killed between 30% and 50% of Europe's population. In 1720 a plague epidemic decimated almost half of the population of Marseille and one fourth of the population of Provence. The Spanish flu in 1918–1919 killed between 30 et 100 million humans. It resulted from a particularly virulent $H1N1$ strain. It has been probably the most severe pandemic in human history so far. Even with the progress of medicine and vaccination, several illnesses have not been eradicated (e.g. malaria), and new ones have appeared (HIV, SARS, Ebola), some of them propagating faster than in the past, due to more rapid and massive transportation. In addition, we should not forget the hospital–acquired infections (even in the cleanest hospitals of the rich part of the world), and the serious problem of antibiotic resistance of bacteria. As a matter of fact, the fight against epidemics is not a problem of the past for humanity. It is a problem of the present and the future, in particular in Africa.

A little more than one hundred years ago, Sir Ronald Ross, a british medical doctor who contributed to the understanding of malaria (together

with among others the Italian Giovanni Battista Grassi and the French Laveran, Ross and Laveran won a Nobel prize) wrote : *"As a matter of fact all epidemiology, concerned as it is with variation of disease from time to time and from place to place, must be considered mathematically (...) and the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand"*. As a matter of fact, Ross deduced from mathematical arguments conclusions concerning malaria, which his colleagues physicians had difficulties to accept.

The main aim of these Notes is to describe some aspects of mathematical epidemiology, with an emphasis on probabilistic models. Learning this topics is also a good way to learn mathematics and mathematical modeling. Historically, deterministic models have received most attention. But as we shall see, probabilistic modeling is essential. We shall also discuss some of the associated statistical procedures.

These notes are very much inspired by the recent monograph by Diekmann, Heesterbeek and Britton [1]. Section 17.5 is taken from [3].

1 Epidemics in a closed population

We are going to assume here, and in a great part of these Notes, that the studied epidemic concerns a population of fixed size N. This is justified whenever, and it is often the case, the epidemic under study has a life time which rather short, compared with the time scale of the fluctuations of the population size. Some results will be established for large N (we shall study the limit of the model as $N \to \infty$), others for arbitrary N.

We consider the situation where 1 or a smll number of infected individuals are introduced in a population of susceptibles. We discuss the following questions :

- Under which circumstances might a major epidemic start, and what is the probability that such an event occur ?
- In case a major epidemic develops, at which speed does it progress ?
- Which fraction of the total population will be eventually hit by the epidemic ?
- How long will the epidemic last ?

In order to answer those questions, we first need, in order to formulate a mathematical model of the epidemic,

- to describe the process of contacts which propagates the illness;
- to describe how the population mixes (who meets whom ?), and which fraction of the contacts of an infected individual will be with "susceptible" individuals;
- to precise the probability that such a contact yields the transmission of the illness.

Let us first explain that our models will *compartmental models*, which means that the population under consideration will be divided into compartments, each individual belonging to one and only one of those compartments. The number of compartments depends upon the choice of a particular model and of course upon the type of illness under study. The main compartments are :

S like susceptible, it is the subset of those individuals which might contract the illness at the occasion of an encounter with an infectious individual;

E like exposed, it is the subset of those individuals who are suffering from the illness, but they are in the incubation phase, they are not contagious;

I like infectious, it is the subset of those individuals who are suffering from the illness, and are contagious;

R like removed, it is the subset of those individuals who have suffered from the illness, and have recovered; they have acquired immunity concerning the illness, they are not susceptible to contract it again. One might include dead individuals in the compartment R.

The propagation of the illness is the result of an encounter between an individual from compartment I and an individual from compartment S. What is the meaning of *encounter* ? It depends upon the illness. In case of HIV, it means a sexual intercourse (or a contact of bloods, for example through an exchange of syringe). In the case of malaria, it means a bite of a human by a mosquito, where one of the two is susceptible (of type S), the other one being infectious (of type I). In case of the flu, SARS, contact can just

mean shaking hands, or an infectious individual sneezing in the face of a susceptible (same for the whooping cough).

Let us suppose that each individual of type I meets other individuals at rate c (meaning that this individual meets in average c individuals per unit time). In other words, encounters of that individual with other individuals of the population happen according to a rate c Poisson process (see section 2 below). The next question is : whom does that infectious individual meet ? We shall assume in almost all of these Notes that the population is fully mixed, which means that the individual who is met is chosen uniformly among all individuals of the population except himself. Other more realistic situations will be discussed in other courses of this school. Our assumption allows to simplify the model, and obtain first interesting results, as we shall see.

2 Interlude 1. The Poisson Process

This rather simple process will be central in what follows. Let $\lambda > 0$ be given. A rate λ Poisson (counting) process is defined as

$$P_t = \sup\{k \geq 1,\ T_k \leq t\},$$

where $0 = T_0 < T_1 < T_2 < \cdots < T_k < \cdots < \infty$, the r.v.'s $\{T_k - T_{k-1},\ k \geq 1\}$ being independent and identically distributed, each following the law $\mathrm{Exp}(\lambda)$. We have

Proposition 1. *For all $n \geq 1$, $0 < t_1 < t_2 < \cdots < t_n$, the r.v.'s $P_{t_1}, P_{t_2} - P_{t_1}, \ldots, P_{t_n} - P_{t_{n-1}}$ are independent, and for all $1 \leq k \leq n$, $P_{t_k} - P_{t_{k-1}} \sim Poi[\lambda(t_k - t_{k-1})]$.*

Proof Let us first prove that for all $t, s > 0$,

$$\mathbb{P}(P_{t+s} - P_t = 0 | P_t = k, T_1, T_2, \ldots, T_k) = \exp(-\lambda s).$$

Indeed

$$\begin{aligned}
&\mathbb{P}(P_{t+s} - P_t = 0 | P_t = k, T_1, T_2, \ldots, T_k) \\
&\quad = \mathbb{P}(T_{k+1} > t + s | P_t = k, T_k) \\
&\quad = \mathbb{P}(T_{k+1} - T_k > t + s - T_k | T_{k+1} - T_k > t - T_k > 0) \\
&\quad = \mathbb{P}(T_{k+1} - T_k > s) \\
&\quad = \exp(-\lambda s).
\end{aligned}$$

Let now $n \geq 1$. For $1 \leq i \leq n$, we define $X_{n,i} = \mathbf{1}_{\{P_{t+is/n} - P_{t+(i-1)s/n} \geq 1\}}$, and finally $S_n = X_{n,1} + X_{n,2} + \cdots + X_{n,n}$. It follows from the first part of the proof that conditionally upon $\sigma\{P_r,\ 0 \leq r \leq t\}$, the r.v.'s $X_{n,1}, X_{n,2}, \ldots, X_{n,n}$ are i.i.d., each Bernoulli with parameter $1 - e^{-\lambda s/n}$. Then conditionally upon $\sigma\{P_r,\ 0 \leq r \leq t\}$, S_n is binomial with parameters $(n, 1 - e^{-\lambda s/n})$. But $S_n \to P_{t+s} - P_t$ a.s. as $n \to \infty$, while its conditional law given $\sigma\{P_r,\ 0 \leq r \leq t\}$ converges towards the Poisson distribution with parameter λs, according to the following Lemma. The Proposition follows. □

We have used the following well–known result. Recall the notation $B(n, p)$ for the binomial law with parameters n and p, where $n \geq 1$ and $0 < p < 1$.

Lemma 2. *For all $n \geq 1$, let U_n be a $B(n, p_n)$ random variable. If $np_n \to \lambda$ as $n \to \infty$, with $\lambda > 0$, then U_n converges in law towards $Poi(\lambda)$.*

A Poisson process will be called standard if its rate is 1. If P is a standard Poisson process, then $\{P(\lambda t),\ t \geq 0\}$ is a rate λ Poisson process.

We will also use the following

Exercise 1. *Let $\{P_t,\ t \geq 0\}$ be a rate λ Poisson process, and $\{T_k,\ k \geq 1\}$ the random points of this Poisson process, such that for all $t > 0$, $P_t = \sup\{k \geq 1,\ T_k \leq t\}$. Let $0 < p < 1$. Suppose that each T_k is selected with probability p, not selected with probability $1 - p$, independently of the others. Let P'_t denote the number of selected points on the interval $[0, t]$. Then $\{P'_t,\ t \geq 0\}$ is a rate λp Poisson process.*

3 Start of an epidemic

During the initial phase of an epidemic, there are very few infectious individuals, so that we can pretend that any encountered individual is susceptible.

We now need to precise the probability that an infectious individual infects an encountered susceptible. Consider an individual who has been infected at the initial time $t = 0$. He is in state E when $0 \leq t \leq T_1$, in state I when $T_1 \leq t < T_2$, and in state R when $t \geq T_2$. He will infect a susceptible encountered at time t with probability

$$\begin{cases} 0, & \text{if } t < T_1; \\ p, & \text{si } T_1 \leq t < T_2; \\ 0, & \text{si } t \geq T_2. \end{cases}$$

We state the

Definition 3. *Thee "basic reproduction number" is the quantity R_0 defined as the mean number of susceptibles whom an infectious individual infects, during the initial phase of the epidemic.*

Note that "during the initial phase of the epidemic" is an essential precision. This means "while all encountered individuals are susceptibles". With the above notations, if we let $\Delta T = T_2 - T_1$, then

$$R_0 = cp\mathbb{E}[\Delta T].$$

4 Interlude 2. Branching processes

We describe here the basic results concerning discrete time branching processes, also called Bienaymé–Galton–Watson processes.

Consider an ancestor (at generation 0) who has X_0 children, such that

$$\mathbb{P}(X_0 = k) = q_k,\ k \geq 0 \quad \text{et} \ \sum_{k\geq 0} q_k = 1.$$

Define $m = \mathbb{E}[X_0] = \sum_{k\geq 1} k\ q_k$.

Each child of the ancestor belongs to generation 1. The i–th of those children has himself $X_{1,i}$ children, where the r.v.'s $\{X_{k,i},\ k \geq 0, i \geq 1\}$ are i.i.d., all having the same law as X_0. If we define Z_n as the number of individuals in generation n, we have

$$Z_{n+1} = \sum_{i=1}^{Z_n} X_{n,i}.$$

Let g denote the generating function of the r.v. X_0, i.e.

$$g(s) = \sum_{k=0}^{\infty} q_k s^k = \mathbb{E}[s^{X_0}],\ 0 \leq s \leq 1.$$

We have $g(0) = q_0$, $g(1) = 1$, $g'(1) = m$, $g'(s) > 0$, $g''(s) > 0$, for all $0 \leq s \leq 1$ (we assume that $q_0 > 0$ and $q_0 + q_1 < 1$). Let us compute the

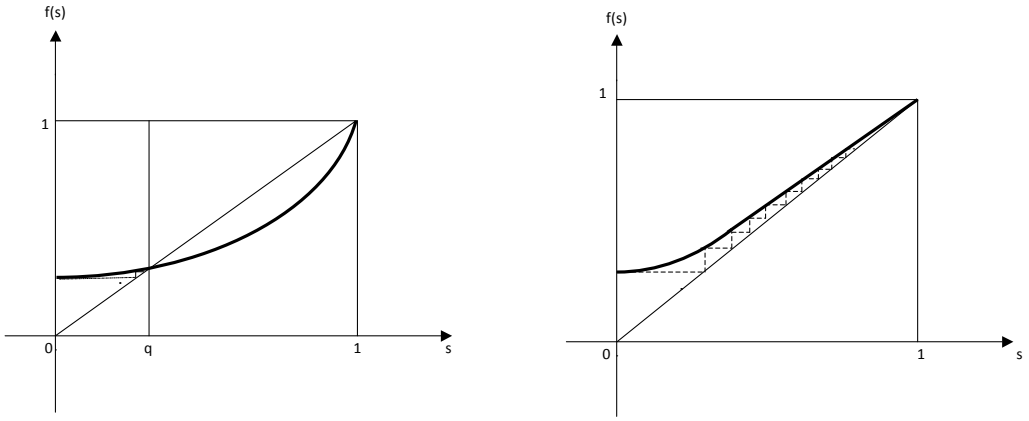

Figure 1: Graphs of g in case $m > 1$ (left) and in case $m \leq 1$ (right).

generating function of Z_n : $g_n(s) = \mathbb{E}[s^{Z_n}]$.

$$\begin{aligned} g_n(s) &= \mathbb{E}\left[s^{\sum_{i=1}^{Z_{n-1}} X_{n-1,i}}\right] \\ &= \mathbb{E}\left[\mathbb{E}\left[s^{\sum_{i=1}^{Z_{n-1}} X_{n-1,i}}\middle| Z_{n-1}\right]\right] \\ &= \mathbb{E}\left[g(s)^{Z_{n-1}}\right] \\ &= g_{n-1} \circ g(s). \end{aligned}$$

If we iterate this argument, we obtain

$$g_n(s) = g \circ \cdots \circ g(s),$$

and also

$$\begin{aligned} \mathbb{P}(Z_n = 0) &= g^{\circ n}(0) \\ &= g\left[g^{\circ(n-1)}(0)\right]. \end{aligned}$$

Hence if $z_n = \mathbb{P}(Z_n = 0)$, $z_n = g(z_{n-1})$, and $z_1 = q_0$. We have $z_n \uparrow z_\infty$, where $z_\infty = \mathbb{P}(Z_n = 0$ from some n on). The proof of the following Proposition is essentially clear from Figure 1.

Proposition 4. *If $m \leq 1$, then $\mathbb{P}(Z_n = 0) \to 1$ as $n \to \infty$, and $z_\infty = 1$.*

If $m > 1$, $\mathbb{P}(Z_n = 0) \to z_\infty$ as $n \to \infty$, where z_∞ is the smallest solution of the equation $z = g(z)$.

In the second case, with probability $1 - z_\infty$, the branching process does not go extinct. Let us show that $W_n = m^{-n}\, Z_n$ is a martingale.

$$\begin{aligned}\mathbb{E}(W_{n+1}|Z_n) &= m^{-n}\mathbb{E}\left(m^{-1}\sum_1^{Z_n} X_{n,i}|Z_n\right)\\ &= m^{-n} Z_n\\ &= W_n.\end{aligned}$$

One can show that $W_n \to W$ a.s. as $n \to \infty$, and moreover

$$\{W > 0\} = \{\text{the branching process does not go extinct}\}.$$

5 The start of the epidemic

The start of the epidemic behaves as a BGW process, with $m = R_0$, since as long as we can pretend that any encountered individual is susceptible, the various processes of transmission of the illness are independent. What is the relation between z_∞ and R_0 ? Conditionally upon ΔT, the number of contacts of an infectious individual at the start of the epidemic is k with probability

$$e^{-c\Delta T}\frac{(c\Delta T)^k}{k!},$$

each of those contacts resulting in an infection with probability p. We then deduce from Proposition 1 and Exercise 1 that, conditionally upon ΔT, the number of susceptibles infected by one infectious individual at the start of the epidemic is k with probability

$$\exp\left(-cp\Delta T\right)\frac{(cp\Delta T)^k}{k!}.$$

We now compute z_∞ in two cases.

5.1 ΔT constant

Assume that this constant value is independent of the considered individual. Then g is the generating function of the Poisson distribution with parameter

$R_0 = cp\Delta T$.

$$\begin{aligned} g(s) &= \sum_{k=0}^{\infty} e^{-R_0} \frac{(R_0 s)^k}{k!} \\ &= e^{R_0(s-1)}. \end{aligned}$$

Hence z_∞ is the smallest solution of equation $z = e^{R_0(z-1)}$.

5.2 $\Delta T \sim \mathbf{Exp}(\alpha)$.

In this case, the generating function g is given as

$$\begin{aligned} g(s) &= \alpha \int_0^{\infty} e^{cph(s-1)} e^{\alpha h} dh \\ &= \frac{\alpha}{\alpha - cp(s-1)}. \end{aligned}$$

It is the generating function of a geometric distribution, in other words

$$\mathbb{P}(X_0 = k) = \left(\frac{cp}{cp+\alpha}\right)^k \frac{\alpha}{cp+\alpha}.$$

Here $R_0 = cp/\alpha$, z_∞ is the smallest solution of the equation

$$z = \frac{1}{1 - R_0(z-1)}.$$

Consequently

$$z_\infty = \frac{1}{R_0}.$$

We see in particular that the relation between z_∞ and R_0 depends very much upon the details of the model.

5.3 Remark on the speed of propagation of the epidemic

That speed does not depend only upon ΔT, but upon the pair (T_1, T_2). If we compare the demography of a country where each women has three children between the age of 20 and the age of 25, with that of another country where

each women has three children between the age of 35 and the age of 40, it is rather clear that the speed at which those two populations evolve are different.

The two quantities cp and ΔT being kept constant, we can choose two pairs (T_1^*, T_2^*) and (T_1^{**}, T_2^{**}) such that $R_0^* > R_0^{**}$ and $V^* < V^{**}$. We shall discuss this issue again later.

6 The final size of the epidemic in case of no major outbreak

Let $X_1, X_2, \ldots$ be i.i.d. $\mathbb{N}$–valued r.v.'s, all having the same law as X_0. Let Z denote the final size of the epidemic (i.e. the total number of individuals which are infected at some stage of the epidemic, including the initially infected individual).

Proposition 5. *For all $k \geq 1$,*

$$\mathbb{P}(Z = k) = \frac{1}{k}\mathbb{P}(X_1 + X_2 + \cdots + X_k = k - 1).$$

Proof Consider the process of depth–first search of the genealogical tree of the infected individuals. The tree is explored from the root. Suppose we have visited k vertices. The next visit will be to the leftmost still unexplored son of this individual, if any; otherwise to the leftmost unexplored son of the nearest ancestor of the last visited individual. X_1 is the number of sons of the root. X_k is the number of sons of the k-th visited individual. This exploration of the tree ends at step k if and only if $X_1 \geq 1$, $X_1 + X_2 \geq 2$, $X_1 + X_2 + X_3 \geq 3$, ... $X_1 + X_2 + \cdots X_{k-1} \geq k - 1$, and $X_1 + X_2 + \cdots + X_k = k - 1$. Let us rewrite those conditions. Define

$$\begin{aligned} Y_i &= X_i - 1,\ i \geq 1, \\ S_k &= Y_1 + Y_2 + \cdots + Y_k. \end{aligned}$$

A trajectory $\{Y_i,\ 1 \leq i \leq k\}$ explores a tree of size k iff the following conditions are satisfied

$$(C_k) \quad S_0 = 0, S_1 \geq 0, S_2 \geq 0, \ldots, S_{k-1} \geq 0, S_k = -1.$$

The statement of the Proposition is equivalent to

$$\mathbb{P}(Z=k)=\frac{1}{k}\mathbb{P}(Y_1+Y_2+\cdots+Y_k=-1).$$

Denote by V_k the set of sequences of k integers ≥ -1 which satisfy conditions (C_k), and U_k the set of sequences of k integers ≥ -1 which satisfy the unique condition $S_k=-1$. We will use circular permutations operating on the Y_i's. For $1\leq i,\ell\leq k$, let

$$(i+\ell)_k=\begin{cases} i+\ell, & \text{if } i+\ell\leq k;\\ i+\ell-k, & \text{if } i+\ell>k.\end{cases}$$

For each $1\leq \ell\leq k$, let $Z_i^\ell=Y_{(i+\ell)_k}$, $S_j^\ell=\sum_{i=1}^j Z_i^\ell$ for $1\leq i\leq k$. Clearly $S_k^\ell=-1$ for all ℓ as soon as (C_k) is satisfied. On the other hand $S^k\equiv S$ is the only trajectory which satisfies conditions (C_k). The other S^ℓ hit the value -1 before rank k. The Z^ℓ's are sequences of integers ≥ -1 of length k, whose sum equals -1. Finally to each element of V_k we have associated k distinct elements of U_k, all having the same probability.

Reciprocally, to one element of $U_k\backslash V_k$, choosing $\ell=\underset{1\leq i\leq k}{\operatorname{argmin}} S_i$ and using the above transformation, we deduce that $S^\ell\in V_k$.

Finally, to each trajectory of V_k, we associate k trajectories of U_k, who all have the same probability, and which are such that the inverse transformation gives back the same trajectory of V_k. The result is proved. □

Note that we have clearly

$$\sum_{k\geq 1}\mathbb{P}(Z=k)\begin{cases}=1, & \text{if } \mathbb{E}R_0\leq 1;\\ <1, & \text{if } \mathbb{E}R_0>1,\end{cases}$$

which is not so obvious from the Proposition.

Example 6. *Suppose that the joint law of the X_i's is $Poi(\mu)$, with $0<\mu<1$. Then $X_1+\cdots+X_k\sim Poi(k\mu)$, and consequently*

$$\begin{aligned}\mathbb{P}(Z=k)&=\frac{1}{k}\mathbb{P}(X_1+\cdots+X_k=k-1)\\ &=e^{-\mu k}\frac{(\mu k)^{k-1}}{k!}.\end{aligned}$$

This law of Z is called the Borel distribution with parameter μ. Note that

$$\begin{aligned}\mathbb{E}Z &= 1 + \mu + \mu^2 + \cdots \\ &= \frac{1}{1-\mu}.\end{aligned}$$

Example 7. *Consider now the case where $X_i \sim \mathcal{G}(p)$, where we mean here the geometric distribution where the value 0 is taken with probability p. The law of $X_i + 1$ is the geometric distribution with parameter p whose support is $\mathbb{N}$, in other words $\mathbb{P}(X_i + 1 > k) = (1-p)^k$. $k + X_1 + \cdots + X_k$ follows the negative binomial distribution with parameters (k, p). Hence*

$$\begin{aligned}\mathbb{P}(Z = k) &= \frac{1}{k}\mathbb{P}(k + X_1 + \cdots + X_k = 2k - 1) \\ &= \frac{1}{k}\binom{2k-2}{k-1} p^k (1-p)^{k-1} \\ &= \frac{(2k-2)!}{k!(k-1)!} p^k (1-p)^{k-1}.\end{aligned}$$

In case $p > 1/2$, $\mathbb{E}Z = (2p-1)^{-1}p$.

7 The case of a major outbreak

7.1 Approximation of the initial phase of the epidemic by a branching process

In case of a major outbreak, i.e. the epidemic hits a fraction of the total population, how long can we approximate the epidemic by a branching process ?

Suppose that the epidemic starts with a unique initial infected individual. The probability that the first k contacts are with susceptibles is

$$1\left(1 - \frac{1}{N}\right)\left(1 - \frac{2}{N}\right) \times \cdots \times \left(1 - \frac{k-1}{N}\right),$$

which tends to 1 as $N \to \infty$, for any fixed k. Suppose now that $k = k_N$

depends upon N. Then

$$\begin{aligned} 1\left(1-\frac{1}{N}\right)\left(1-\frac{2}{N}\right)\times\cdots\times\left(1-\frac{k_N-1}{N}\right) & \\ &= 1-\sum_{j=1}^{k_N-1}\frac{j}{N}+k_N^2\ O\left(\frac{1}{N^2}\right) \\ &= 1-\frac{k_N(k_N-1)}{N}+k_N^2\ O\left(\frac{1}{N^2}\right) \\ &\to 1, \end{aligned}$$

if $k_N = \circ(\sqrt{N})$. Note the number of generations needed by a BGW process to reach the value $\sqrt{N}$ is of the order of $\log(N)$. Indeed since $m^{-n}Z_n \to W$, we expect that, in case of non extinction, for n large enough, Z_n is of the order of $m^n W$. But if $m^n W = \sqrt{N}$, this implies that

$$\begin{aligned} n\log(m)+\log(W) &= \frac{1}{2}\log(N), \\ n &= \frac{\log N}{2\log m}-\frac{\log W}{\log m}. \end{aligned}$$

This argument is of course not rigorous, since the fact that $m^{-n}Z_n \to W$ does not imply that Z_n is close to $m^n W$. In fact one can show that $(Z_n)^{-1/2}[Z_n - m^n W]$ converges towards a centered Gaussian r.v. with variance $(m^2-m)^{-1}\sigma^2$, if σ^2 is the variance of the reproduction law (provided that variance is finite). One can also prove a law of iterated logarithm, which goes in the same direction. Those results justify the above (rather vague) statement.

7.2 Total size of the epidemic

Conditionally upon ΔT, the probability that a given susceptible escapes infection by a given infectious individual is $\exp(-cp\Delta T/N)$. Hence the probability that a given susceptible escapes infection by a given infectious individual is

$$\mathbb{E}\left[e^{-cp\Delta T/N}\right].$$

The probability that a given susceptible escapes infection by a set of k infectious individuals is

$$\mathbb{E}\left[e^{-cp(\Delta T_1+\cdots+\Delta T_k)/N}\right].$$

If k is of the order of N, then from the Law of Large Numbers, for N large,

$$\frac{\Delta T_1 + \cdots + \Delta T_k}{N} \sim \frac{k}{N} \mathbb{E}(\Delta T).$$

Hence the probability that a given susceptible escapes infection by a fraction $\frac{k}{N}$ of infectious individuals is

$$e^{-cp\frac{k}{N}\mathbb{E}[\Delta T]} = e^{-\frac{k}{N}R_0}.$$

Let Y denote the total number of individuals who are infected in the course of the epidemic. $\frac{Y}{N}$ is the fraction of the population hit by the illness. As we shall see below, the law of large numbers tells us that Y/N is approximatively constant if N is large. The fraction of the population which escapes the illness is $\sigma = 1 - Y/N$. Since each individual is hit by the the illness with the same probability, we have that

$$\begin{aligned} \sigma &= \mathbb{P}(\text{escaping infection}) \\ &= \exp(-R_0 Y/N), \end{aligned}$$

hence

$$\sigma = e^{-R_0(1-\sigma)}.$$

Note that $\sigma = S(\infty)/N = s(\infty)$, and we have already encountered this equation.

8 The Sellke construction

We number the individuals from 0 to N :

$$0\ 1\ 2\ 3\ \ldots\ N.$$

0 denotes the initially infected individual, and the individuals numbered from 1 to N are all susceptible at time 0.

Let

$Q_1, Q_2, \ldots, Q_N$ be i.i.d. r.v.'s, with the law Exp(1);

$(T_{1,0}, \Delta T_0), (T_{1,1}, \Delta T_1), \ldots, (T_{1,N}, \Delta T_N)$ i.i.d. r.v.'s, with the law $\mathbb{P}_L \otimes \mathbb{P}_I$, where $\mathbb{P}_L$ is the law of the latency period and $\mathbb{P}_I$ that of the infectious period.

Individual 0 has the latency period $T_{1,0}$ and the infectious period ΔT_0. We denote below

$$L(t) \text{ the number of individuals in state } E \text{ at time } t;$$
$$I(t) \text{ the number of individuals in state } I \text{ at time } t.$$

We define the cumulated force of infection experienced by an individual, between times 0 and t as

$$\Lambda_C(t) = \frac{cp}{N} \int_0^t I(s)ds.$$

For $i = 1, \ldots, N$, individual i is infected at the time when $\Lambda_C(t)$ achieves the value Q_i (which might be considered as the "level of resistance to infection of individual i"). The j–th infected susceptible has the latency period $T_{1,j}$ and the infectious period ΔT_j. The epidemic stops when there is no more individual in either latent of infectious state. Then $\Lambda_C(t)$ does not grow any more, $\Lambda_C(t) = \Lambda_C(\infty)$. The individuals such that $Q_i > \Lambda_C(\infty)$ escape infection.

We put the Q_i's in increasing order : $Q_{(1)} < Q_{(2)} < \cdots < Q_{(N)}$. It is the order in which individuals are infected in Sellke's model. Note that Sellke's model respects the durations of latency and infection. In order to show that Sellke's construction gives a process which has the same law as the process defined above, it remains to verify that the rates at which infections happen are the correct ones.

In the initial model, we assume that each infectious meets other individuals at rate c. Since each individual has the same probability of being the one who is met, the probability that a given individual is that one is $1/N$. Hence the rate at which a given individual is met by an infectious one is c/N. Each encounter between a susceptible and an infectious individual achieves an infection with probability p. Hence the rate at which a given individual is infected by a given infectious individual is cp/N. The rate at which an infectious individual infects susceptibles is then $cpS(t)/N$. Finally the epidemic propagates at rate $cpS(t)I(t)/N$.

Let us go back to Sellke's construction. At time t, $S(t)$ susceptibles have not yet been infected. Each of those corresponds to a $Q_i > \Lambda_C(t)$. At time t, the slope of the curve which represents the function $t \mapsto \Lambda_C(t)$ is $cpI(t)/N$.

If $Q_i > \Lambda_C(t) = x$, then

$$\begin{aligned}\mathbb{P}(Q_i > x + y | Q_i > x) &= e^{-y}, \text{ hence} \\ \mathbb{P}(Q_i > \Lambda_C(t+s) | Q_i > \Lambda_C(t)) &= \exp\left(-\frac{cp}{N}\int_t^{t+s} I(r)dr\right) \\ &= \exp\left(-\frac{cp}{N} I(t)s\right),\end{aligned}$$

if I is constant on the interval $[t, t+s]$.

Consequently, conditionally upon $Q_i > \Lambda_C(t)$,

$$Q_i - \Lambda_C(t) \sim \text{Exp}\left(\frac{cp}{N} I(t)\right).$$

The same is true for those $S(t)$ Q_i which are $> \Lambda_C(t)$. Then the first Q_i to come is the minimum of those, hence the waiting time after $\Lambda_C(t)$ for the next infection follows the law $\text{Exp}\big(\frac{cp}{N} I(t)S(t)\big)$, if no removal of an infectious individual happens in the mean time, which would modify $I(t)$.

Then in Sellke's construction, at time t the next infection comes at rate

$$\frac{cp}{N} I(t)S(t),$$

as in the above described model.

9 Interlude 3. Generalization of the Poisson process

A rate λ Poisson process ($\lambda > 0$) is a counting process $\{Q_t,\ t \geq 0\}$ such that $Q_t - \lambda t$ is a martingale. Let $\{P(t),\ t \geq 0\}$ be a standard Poisson process (i.e. with rate 1). Then $P(\lambda t) - \lambda t$ is martingale, and it is not hard to show that $\{P(\lambda t),\ t \geq 0\}$ is a rate λ Poisson process. Let now $\{\lambda(t),\ t \geq 0\}$ be a measurable and locally integrable $\mathbb{R}_+$–valued function. Then the process $\{Q_t := P\left(\int_0^t \lambda(s)ds\right),\ t \geq 0\}$ is called a rate $\lambda(t)$ Poisson process. Clearly $Q_t - \int_0^t \lambda(s)ds$ is a martingale.

Let now $\{\lambda(t),\ t \geq 0\}$ be an $\mathbb{R}_+$–valued stochastic process, which at each time t depends only upon the past of Q below. Then the counting process

$$Q_t := P\left(\int_0^t \lambda(s)ds\right),\ t \geq 0$$

has again the property that

$$Q_t - \int_0^t \lambda(s)ds \text{ is a martingale.}$$

It is sometimes called "a doubly stochastic Poisson process" or a Cox process. Of course the increments of Q_t are not Poisson distributed. In particular, the process which counts the new infections, which we have described in the preceding section, takes the form

$$P\left(\frac{cp}{N}\int_0^t I(r)S(r)dr\right).$$

10 LLN and CLT for the final size of the epidemic

Define, for $0 \leq w \leq N+1$, with the notation $[w]$ = integer part of w,

$$\mathcal{J}(w) = \frac{cp}{N}\sum_{i=0}^{[w]-1} \Delta T_{(i)}.$$

Note that $i = 0$ is the index of the initially infected individual, $\Delta T_{(i)}$ is the latency period of individual whose resistance level is $Q_{(i)}$.

$\mathcal{J}(w)$ is the infection pressure produced by the first $[w]$ infected individuals (including number 0). For any integer k, $\mathcal{J}$ is of course constant on the interval $[k, k+1)$. Define for $v > 0$,

$$\mathcal{Q}(v) = \sum_{i=1}^{N} \mathbf{1}_{\{Q_i \leq v\}}.$$

The total number of infected individuals in the epidemic is

$$\begin{aligned} Y &= \min\left\{k \geq 0;\ Q_{(k+1)} > \frac{pc}{N}\sum_{i=0}^{k}\Delta T_i\right\} \\ &= \min\left\{k \geq 0;\ Q_{(k+1)} > \mathcal{J}(k+1)\right\} \\ &= \min\left\{w \geq 0;\ \mathcal{Q}(\mathcal{J}(w+1)) = w\right\}. \end{aligned} \tag{1}$$

Suppose indeed that $Y = i$. Then according to (1),

$$\begin{aligned} \mathcal{J}(j) > Q_{(j)}, \quad \text{hence } \mathcal{Q}(\mathcal{J}(j)) \geq j, \quad \forall j \leq i, \\ \text{and } \mathcal{J}(i+1) < Q_{(i+1)} \quad \text{hence } \mathcal{Q}(\mathcal{J}(i+1)) < i+1. \end{aligned}$$

In other words $Y = i$ iff i is the smallest integer such that

$$\mathcal{Q}(\mathcal{J}(i+1)) < i+1, \quad \text{hence } = i.$$

10.1 Law of Large Numbers

Let us index $\mathcal{J}$ and $\mathcal{Q}$ by N, the population size, so that they become $\mathcal{J}_N$ and $\mathcal{Q}_N$. We now define

$$\begin{aligned} \overline{\mathcal{J}}_N(w) &= \mathcal{J}_N(Nw) \\ \overline{\mathcal{Q}}_N(v) &= \frac{\mathcal{Q}_N(v)}{N}. \end{aligned}$$

As $N \to \infty$,

$$\begin{aligned} \overline{\mathcal{J}}_N(w) &\to cp\mathbb{E}(\Delta T)w = R_0 w, \quad \text{and} \\ \overline{\mathcal{Q}}_N(v) &\to 1 - e^{-v} \quad \text{a.s.} \end{aligned}$$

Hence

$$\overline{\mathcal{Q}}_N \circ \overline{J}_N(w) \to 1 - e^{-R_0 w}.$$

We have

$$\begin{aligned} \frac{Y_N}{N} &= \min\left\{ \frac{w}{N} \geq 0; \ \mathcal{Q}_N(\mathcal{J}_N(w+1)) = w \right\} \\ &= \min\left\{ s \geq 0; \ \frac{1}{N}\mathcal{Q}_N\left(\mathcal{J}_N\left(N\left(s + \frac{1}{N}\right)\right)\right) = s \right\} \\ &= \min\left\{ s \geq 0; \ \overline{\mathcal{Q}}_N\left(\overline{\mathcal{J}}_N\left(s + \frac{1}{N}\right)\right) = s \right\}. \end{aligned}$$

Then Y_N/N converges a.s. towards the smallest positive solution of equation

$$1 - e^{-R_0 x} = x.$$

- If $R_0 \leq 1$, the unique solution of this equation is $x = 0$.
- If $R_0 > 1$, there is another solution $x > 0$.

This solution $0 < x < 1$ is the size (measured as the proportion of the total population) of a "significant " epidemic, if it goes off, which happens with probability $1 - z_\infty$.

10.2 Central Limit Theorem

From the classical CLT, as $N \to \infty$,

$$\begin{aligned}\sqrt{N}(\overline{\mathcal{J}}_N(w) - R_0 w) &= \frac{pc\sqrt{w}}{\sqrt{Nw}} \sum_{i=1}^{[Nw]} [\Delta T_i - \mathbb{E}(\Delta T_i)] \\ &\Rightarrow A(w),\end{aligned}$$

where $A(w) \sim \mathcal{N}(0, p^2c^2\mathrm{Var}(\Delta T)w)$. One can in fact show that, as processes

$$\{\sqrt{N}(\overline{\mathcal{J}}_N(w) - R_0 w),\ 0 \le w \le 1\} \Rightarrow \{A(w),\ 0 \le w \le 1\},$$

where $\{A(w),\ 0 \le w \le 1\}$ is a Brownian motion (i.e. a centered Gaussian process with independent increments and continuous trajectories) such that $\mathrm{Var}(A(w)) = r^2 R_0^2 w$, where $r^2 = (\mathbb{E}\Delta T)^{-2}\mathrm{Var}(\Delta T)$. It is easy to show that for all $k \ge 1$, all $0 < w_1 < \cdots < w_k \le 1$, if we define $A_N(w) := \sqrt{N}(\overline{\mathcal{J}}_N(w) - R_0 w)$,

$$(A_N(w_1), \ldots, A_N(w_k)) \Rightarrow (A(w_1), \ldots, A(w_k)).$$

One can show convergence in a stronger sense, but describing that would force us to introduce more complicated mathematical notions.

Consider now $\overline{\mathcal{Q}}_N$. Again from the usual CLT,

$$\begin{aligned}B_N(v) &= \sqrt{N}(\overline{\mathcal{Q}}_N(v) - [1 - e^{-v}]) \\ &= \frac{1}{\sqrt{N}} \sum_{i=1}^{N} \left[\mathbf{1}_{\{Q_i \le v\}} - (1 - e^{-v})\right] \\ &\Rightarrow B(v),\end{aligned}$$

where $B(v) \sim \mathcal{N}(0, e^{-v}(1 - e^{-v}))$. We have again a functional convergence, according to the Kolmogorov–Smirnov theorem, towards a time changed Brownian bridge. In simpler words, $\{B(v),\ v \ge 0\}$ is a centered Gaussian process with continuous trajectories whose covariance is specified by the identity $\mathbb{E}[B(u)B(v)] = e^{-u\vee v} - e^{-(u+v)}$.

Recall that the above Law of Large Numbers has been obtained by taking the limit in the equation

$$\overline{\mathcal{Q}}_N\left(\overline{\mathcal{J}}_N\left(s + N^{-1}\right)\right) = s.$$

Making use of the two above CLTs, we get

$$\begin{aligned} s &= 1 - e^{-\overline{\mathcal{J}}_N\left(s+N^{-1}\right)} + N^{-1/2} B_N(\overline{\mathcal{J}}_N(s+N^{-1})) \\ &= 1 - \exp\left(-R_0(s+N^{-1}) + N^{-1/2} A_N(s+N^{-1})\right) \\ &\quad + N^{-1/2} B_N\left(R_0(s+N^{-1}) + N^{-1/2} A_N(s+N^{-1})\right). \end{aligned}$$

Let $s = s^* + s_N N^{-1/2} + \circ(N^{-1/2})$, where s^* satisfies $e^{-R_0 s^*} = 1 - s^*$. We obtain

$$\begin{aligned} s^* + s_N N^{-1/2} + \circ(N^{-1/2}) &= 1 - \exp\left(-R_0 s^* - R_0 s_N N^{-1/2} - A_N(s^*) N^{-1/2} + \circ(N^{-1/2}\right) \\ &\quad + N^{-1/2} B_N(R_0 s^*) + \circ(N^{-1/2}) \\ &= 1 - e^{-R_0 s^*} + N^{-1/2} e^{-R_0 s^*} \left(R_0 s_N + A_N(s^*)\right) \\ &\quad + N^{-1/2} B_N(R_0 s^*) + \circ(N^{-1/2}). \end{aligned}$$

We simplify this relation by making use of the equation which specifies s^*. Multiplying the remaining terms by $N^{1/2}$, we deduce

$$[1 - (1-s^*)R_0] s_N = B_N(R_0 s^*) + (1-s^*) A_N(s^*).$$

Hence $s_N \Rightarrow \Xi$, where

$$\Xi \sim \mathcal{N}\left(0, \frac{s^*(1-s^*)}{(1-(1-s^*)R_0)^2}\left(1 + r^2(1-s^*)R_0^2\right)\right).$$

Finally Y_N follows asymptotically the distribution

$$\mathcal{N}\left(Ns^*, N\frac{s^*(1-s^*)}{(1-(1-s^*)R_0)^2}\left(1 + r^2(1-s*)R_0^2\right)\right).$$

11 Partially vaccinated population

Suppose that a fraction v of the total population is vaccinated (with a vaccine with 100% efficiency).

The the initial population of susceptibles is $N(1-v)$, instead of N, since Nv individuals have been vaccinated and are immune.

The basic reproduction number is modified. The mean number of individuals whom an infectious individual infects during the initial phase of the epidemic is no longer $R_0 = cp\mathbb{E}[\Delta T]$, but rather

$$R_v = (1-v)R_0 = (1-v)cp\mathbb{E}[\Delta T].$$

If $R_v \leq 1$, there is no chance of a major outbreak. This inequality is equivalent to

$$v \geq 1 - \frac{1}{R_0}.$$

The right hand side of this inequality is the critical vaccination coverage.

Exercise 2. *Suppose that the vaccine does not produce a 100% immunity, but that the probability that the encounter of an infectious and a vaccinated individual results in an infection with probability $p_v < p$, where p is the probability that a susceptible be infected after an encounter with an infectious. Compute the corresponding basic reproduction number $R_{v'}$.*

12 Duration of a major epidemic

Denote by T_N the duration of a major epidemic. T_N takes the form

$$T_N = c_1 \log N + c_2 + c_3 \log N + X,$$

where the term $c_1 \log N$ is the duration of the initial phase, c_2 is the duration of the intermediate phase, which is essentially independent of the size N of the population, $c_3 \log N$ is the duration of the final phase (similar to the initial phase), and X is a random term, which takes into account mainly the random aspects of the initial and final phases.

13 Law of Large Numbers

Suppose there is no latency period ($T_1 = 0$ a.s.) and that $\Delta T \sim \text{Exp}(\alpha)$. Consider a SIR model with constant population size equal to N. Let $S(t)$ denote the number of susceptibles at time t, $I(t)$ the number of infectious, $R(t)$ the number of "removed" (i.e. "healed and immune"). We could add a transition from R to S, and possibly suppress the compartment R. This would produce the models $SIRS$ and SIS.

In our model, two types of events happen :

1. infection of a susceptible (such an event decreases $S(t)$ by one, and increases $I(t)$ by one); those events happen at rate

$$\frac{\beta}{N} S(t) I(t), \quad \text{where } \beta = cp;$$

2. recovery of an infectious (such an event decreases $I(t)$ by one, and increases $R(t)$ by one); those events happen at rate

$$\alpha I(t).$$

Hence the following equations, with $P_1(t)$ and $P_2(t)$ two standard mutually independent Poisson processes :

$$\begin{aligned}
S(t) &= S(0) - P_1\left(\frac{\beta}{N}\int_0^t S(s)I(s)ds\right), \\
I(t) &= I(0) + P_1\left(\frac{\beta}{N}\int_0^t S(s)I(s)ds\right) - P_2\left(\alpha\int_0^t I(s)ds\right), \\
R(t) &= R(0) + P_2\left(\alpha\int_0^t I(s)ds\right).
\end{aligned}$$

Of course $S(t) + I(t) + R(t) = S(0) + I(0) + R(0) = N$. We can clearly forget the third equation. Let us define $s_N(t) = S(t)/N$, $i_N(t) = I(t)/N$.Te equations for the proportions of susceptibles and infectious are written

$$\begin{aligned}
s_N(t) &= s_N(0) - \frac{1}{N}P_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right), \\
i_N(t) &= i_N(0) + \frac{1}{N}P_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right) - \frac{1}{N}P_2\left(\alpha N\int_0^t i_N(r)dr\right).
\end{aligned}$$

Define the two martingales $M_1(t) = P_1(t) - t$, $M_2(t) = P_2(t) - t$. We have

$$\begin{aligned}
s_N(t) &= s_N(0) - \beta\int_0^t s_N(r)i_N(r)dr - \frac{1}{N}M_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right), \\
i_N(t) &= i_N(0) + \beta\int_0^t s_N(r)i_N(r)dr - \alpha\int_0^t i_N(r)dr + \frac{1}{N}M_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right) \\
&\quad - \frac{1}{N}M_2\left(\alpha N\int_0^t i_N(r)dr\right).
\end{aligned}$$

Consider the process

$$\mathcal{M}_N(t) := \frac{1}{N}M_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right).$$

Let $\mathcal{F}_t = \sigma\{s_N(r), i_N(r),\ 0 \le r \le t\}$.

Lemma 8. *$\{\mathcal{M}_N(t),\ t \geq 0\}$ is a $\mathcal{F}_t$–martingale which satisfies*

$$\mathbb{E}\left[\mathcal{M}_N(t)\right] = 0, \quad \mathbb{E}\left[|\mathcal{M}_N(t)|^2\right] = \frac{\beta}{N}\mathbb{E}\int_0^t s_N(r) i_N(r) dr.$$

Proof The martingale property follows from the fact that for all $0 < r < t$

$$\begin{aligned} &\mathbb{E}\left[P_1\left(\beta N \int_0^t s_N(u) i_N(u) du\right) - P_1\left(\beta N \int_0^r s_N(u) i_N(u) du\right) \middle| \mathcal{F}_r \right] \\ &\quad = \beta N \mathbb{E}\left[\int_r^t s_N(u) i_N(u) du \middle| \mathcal{F}_r \right]. \end{aligned} \tag{1}$$

We now establish that identity.

For $n \geq 1$, $0 \leq u \leq t$, let

$$[u]_n = \begin{cases} u & , \text{si } u \leq r; \\ r + \frac{k}{n}(t-r), & \text{si } r + \frac{k}{n}(t-r) \leq u < r + \frac{k+1}{n}(t-r). \end{cases}$$

Let $\mathcal{F}_{t'} = \sigma\{s_N(u), i_N(u),\ 0 \leq u \leq t'\}$, and

$$\begin{aligned} A_n(t') &= \beta N \int_0^{t'} s_N([u]_n) i_N([u]_n) du, \\ B_n(t') &= \alpha N \int_0^{t'} i_N([u]_n) du. \end{aligned}$$

For $a < b$, we denote $P_i((a,b]) = P_i(b) - P_i(a)$, and $u_k = r + \frac{k}{n}(t-r)$. Note that

$$\begin{aligned} &\mathbb{E}\left[P_1(A_n(t)) - P_1(A_n(r)) \middle| \mathcal{F}_r\right] = \mathbb{E}\left[\sum_{k=1}^n P_1((A_n(u_{k-1}), A_n(u_k)]) \middle| \mathcal{F}_r\right] \\ &= \mathbb{E}\left[\sum_{k=1}^n \mathbb{E}\left(P_1((A_n(u_{k-1}), A_n(u_{k-1}) + s_N(u_{k-1})\frac{t-r}{n}]) \middle| \mathcal{F}^n_{u_{k-1}} \right) \middle| \mathcal{F}_r \right] \\ &= \mathbb{E}\left[\sum_{k=1}^n \{ s_N(u_{k-1})\frac{t-r}{n} \} \middle| \mathcal{F}_r\right] \\ &= \mathbb{E}\left[A_n(t) - A_n(r) \middle| \mathcal{F}_r\right]. \end{aligned}$$

It remains to let $n \to \infty$ in order to deduce (1).

The martingale property implies that $\mathbb{E}\mathcal{M}_N(t) = 0$. Let us compute the expectation of the square. For $n \geq 1$ fixed, $0 \leq i \leq n$, let $t_i = it/n$. We have

$$\mathbb{E}\left[\mathcal{M}_N(t)^2\right] = \mathbb{E}\sum_{i=0}^{n-1} \left|\mathcal{M}_N(t_{i+1}) - \mathcal{M}_N(t_i)\right|^2.$$

As $n \to \infty$,

$$\sum_{i=0}^{n-1} \left|\mathcal{M}_N(t_{i+1}) - \mathcal{M}_N(t_i)\right|^2 \to \sum_{0<r\leq t} \left|\Delta\mathcal{M}_N(r)\right|^2 \quad \text{a.s.},$$

where the above sum is taken over all jump times of $\mathcal{M}_N(r)$, and $\Delta\mathcal{M}_N(r)$ denotes the jump of the process $\mathcal{M}_N$ at time r. It is not too hard to deduce from a uniform integrability argument that

$$\mathbb{E}\left[\mathcal{M}_N(t)^2\right] = \mathbb{E}\sum_{0<r\leq t} \left|\Delta\mathcal{M}_N(r)\right|^2.$$

Indeed, as soon as $t_{i+1} - t_i \leq 1$, since $0 \leq s_N(r), i_N(r) \leq 1$,

$$\begin{aligned}
\left|\mathcal{M}_N(t_{i+1}) - \mathcal{M}_N(t_i)\right|^2 &\leq \frac{2}{N^2}\left|P_N(t_{i+1}) - P_N(t_i)\right|^2 + \beta^2\left(\int_{t_i}^{t_{i+1}} s_N(r)i_N(r)dr\right)^2 \\
&\leq \frac{2}{N^2}\left|P_N(t_{i+1}) - P_N(t_i)\right|^2 + \beta^2(t_{i+1} - t_i) \\
\sum_{i=0}^{n-1} \left|\mathcal{M}_N(t_{i+1}) - \mathcal{M}_N(t_i)\right|^2 &\leq \frac{2}{N^2}\left|P_N(t)\right|^2 + \beta^2 T.
\end{aligned}$$

But

$$\sum_{0<r\leq t} \left|\Delta\mathcal{M}_N(r)\right|^2 = \frac{1}{N^2}P_1\left(\beta N\int_0^t s_N(r)i_N(r)dr\right).$$

The last formula of the statement follows from the martingale property of $\mathcal{M}_N(r)$. □

Let

$$\mathcal{N}_N(t) = \frac{1}{N}M_2\left(\alpha N\int_0^t i_N(r)dr\right).$$

We show as in the above Lemma that $\mathcal{N}_N(t)$ is a zero mean martingale, and such that

$$\mathbb{E}\left[\mathcal{N}_N(t)^2\right] = \frac{\alpha}{N}\mathbb{E}\int_0^t i_N(r)dr.$$

We deduce in particular from the above results that

Corollary 9. *As $N \to \infty$, for all $T > 0$,*

$$\sup_{0 \le t \le T} \{|\mathcal{M}_N(t)| + |\mathcal{N}_N(t)|\} \to 0$$

in probability.

We have in fact the a.s. convergence to 0 of the same quantities !

Proposition 10. *As $N \to \infty$, for all $T > 0$,*

$$\sup_{0 \le t \le T} \{|\mathcal{M}_N(t)| + |\mathcal{N}_N(t)|\} \to 0 \quad a.s.$$

PROOF We consider the term $\mathcal{M}_N$. Since the proportions $s_N(t)$ et $i_N(t)$ take values in the interval $[0, 1]$,

$$\sup_{0 \le t \le T} |\mathcal{M}_N(t)| \le \frac{1}{N} \sup_{0 \le r \le \beta N T} |M_1(r)|.$$

The Law of Large Numbers for Poisson processes (see below) tells us that for all $t > 0$,

$$\frac{P_1(Nt)}{N} \to t \quad \text{a.s. as } N \to \infty.$$

Note that we have pointwise convergence of a sequence of increasing functions towards a continuous (and of course increasing) function. Consequently from the second Dini Theorem, this convergence is uniform on any compact interval, hence for all $T > 0$,

$$\frac{1}{N} \sup_{0 \le r \le \beta N T} |M_1(r)| \to 0 \quad \text{a.s.}$$

□

We now prove the Law of Large Numbers for Poisson processes

Proposition 11. *Let $\{P(t),\ t \ge 0\}$ be a rate λ Poisson process. Then*

$$t^{-1} P(t) \to \lambda \quad a.s. \ as \ t \to \infty.$$

PROOF Consider first for $n \ge 1$

$$\begin{aligned} n^{-1} P(n) &= n^{-1} \sum_{i=1}^{n} [P(i) - P(i-1)] \\ &\to \lambda \quad \text{a.s. as } n \to \infty \end{aligned}$$

from the standard Law of Large Numbers, since the r.v.'s $P(i) - P(i-1)$, $1 \leq i \leq n$ are i.i.d., Poisson with parameter λ. Now

$$t^{-1}P(t) = \frac{[t]}{t}[t]^{-1}P([t]) + t^{-1}\{P(t) - P([t])\}$$
$$\left|t^{-1}P(t) - \lambda\right| \leq \left|\frac{[t]}{t}[t]^{-1}P([t]) - \lambda\right| + t^{-1}\{P([t]+1) - P([t])\}.$$

But

$$t^{-1}\{P([t]+1) - P([t])\} = t^{-1}P([t]+1) - t^{-1}P([t])$$

is the difference of two sequences which converge towards the same limit, hence it converges to 0 a.s. □

We can now prove

Theorem **12. Law of Large Numbers** *If* $(s_N(0), i_N(0)) \to (s_0, i_0)$ *as* $N \to \infty$, *then*

$$\sup_{0 \leq t \leq T} \{|s_n(t) - s(t)| + |i_N(t) - i(t)]\} \to 0$$

a.s., where $(s(t), i(t)),\ t \geq 0\}$ *is the unique solution of the ODE*

$$\begin{cases} \dfrac{ds}{dt}(t) = -\beta s(t)i(t),\ t > 0, \\ \dfrac{di}{dt}(t) = \beta s(t)i(t) - \alpha i(t),\ t > 0, \\ s(0) = s_0,\ i(0) = i_0. \end{cases}$$

Proof Define $X(t) = \begin{pmatrix} s(t) \\ i(t) \end{pmatrix}$, $X_N(t) = \begin{pmatrix} s_N(t) \\ i_N(t) \end{pmatrix}$, $\overline{X}_N(t) = X(t) - X_N(t)$, $Y_N(t) = \begin{pmatrix} \mathcal{M}_N(t) \\ \mathcal{N}_N(t) - \mathcal{M}_N(t) \end{pmatrix}$, and finally $F\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} -\beta xy \\ \beta xy - \alpha y \end{pmatrix}$. For $0 \leq x, y, x', y' \leq 1$,

$$\left\| F\begin{pmatrix} x \\ y \end{pmatrix} - F\begin{pmatrix} x' \\ y' \end{pmatrix} \right\| \leq C(\alpha, \beta) \left\| \begin{pmatrix} x \\ y \end{pmatrix} - \begin{pmatrix} x' \\ y' \end{pmatrix} \right\|.$$

We have

$$\overline{X}_N(t) = \overline{X}_N(0) + \int_0^t [F(X(r)) - F(X_N(r))]dr + Y_N(t).$$

From Proposition 10, for all $T > 0$, $\sup_{0\leq t\leq T} \|Y_N(t)\| \to 0$ a.s. as $N \to \infty$. Let $\varepsilon_N(t) = \sup_{0\leq r\leq t} \|Y_N(r)\|$. We have

$$\|\overline{X}_N(t)\| \leq \|\overline{X}_N(0)\| + C(\alpha,\beta)\int_0^t \|\overline{X}_N(r)\|dr + \varepsilon_N(t).$$

It then follows from Gronwall's Lemma (see below) that

$$\sup_{0\leq r\leq t} \|\overline{X}_N(r)\| \leq \left(\|\overline{X}_N(0)\| + \varepsilon_N(t)\right) \exp\left(C(\alpha,\beta)t\right).$$

The result then follows from the assumption $\|\overline{X}_N(0)\| \to 0$, plus the fact that que $\varepsilon_N(t) \to 0$ a.s. as $N \to \infty$. □

Of course we can write ODEs for other epidemiological models : SEIR, SEIRS, SIRS, SIS, SIV, Malaria, etc...

Caution ! This "Law of Large Numbers" approximation is only valid when $s, i > 0$, i.e. when significant fractions of the population are infectious and are susceptible. The ODE is of course of no help to compute the probability that the introduction of a unique infectious results in a major epidemic. However, as we shall see now, we can recover from the ODE the same Basic Reproduction Number R_0 and the dichotomy $R_0 \leq 1$, $R_0 > 1$.

Note that at the beginning of the epidemic $s(t) \sim 1$, and in this case the equation for $i(t)$ becomes

$$\frac{di}{dt}(t) \simeq (\beta - \alpha)i(t).$$

If $\beta \leq \alpha$, the solution of the ODE does not increase, when starting from a small value. This means that there won't be any major epidemic, if we start from a small number of initial infected individuals. On the contrary, if $\beta > \alpha$, as soon as $i(t)$ achieves a positive value, it increases. The equilibrium $i = 0$ is unstable. Of course the ODE gives us no indication whatsoever as to what is the probability that, starting from a small number of infected individuals, the epidemic reaches a stage where a significant proportion of the population is hit.

Note that $\beta \leq \alpha$ is equivalent to $\beta/\alpha \leq 1$. In the model considered in this section, $\alpha^{-1} = \mathbb{E}\Delta T$, and $\beta = cp$. Hence $\frac{\beta}{\alpha} = R_0$! The essential parameter can be read of from the ODE.

The vast majority of the literature on mathematical models in epidemiology considers ODEs of the type of equations which we have just obtained. The probabilistic point of view is more recent.

Lemma 13. Gronwall *Let $a, b \geq 0$ and $\varphi : [0, T] \to \mathbb{R}$ be such that for all $0 \leq t \leq T$,*

$$\varphi(t) \leq a + b \int_0^t \varphi(r)dr.$$

Then $\varphi(t) \leq ae^{bt}$.

Proof We deduce from the asumption that

$$e^{-bt}\varphi(t) - be^{-bt} \int_0^t \varphi(r)dr \leq ae^{-bt},$$

or in other words

$$\frac{d}{dt}\left(e^{-bt} \int_0^t \varphi(r)dr\right) \leq ae^{-bt}.$$

Integrating this inequality, we deduce

$$e^{-bt} \int_0^t \varphi(r)dr \leq a\frac{1 - e^{-bt}}{b}.$$

Multiplying by be^{bt} and exploiting again the assumption yields the result. □

Exercise 3. *Let us consider Ross' model of malaria (see also exercise 10 below), which we rewrite in a stochastic form. Denote by $H(t)$ the number of humans who are infected by malaria, and by $V(t)$ the number of mosquitos who are infected by malaria at time t. Let N_H denote the total number of humans, and by N_V the total number of mosquitos, which are supposed to be constant in time. The humans (resp. the mosquitos) which are not infected are all supposed to be susceptibles. Let $m = N_V/N_H$, a the mean number of stings of humans by one mosquito par time unit, p_1 the probability that the sting of a susceptible human by an infected mosquito infects the human, and by p_2 the probability that a susceptible mosquito gets infected while stinging an infected human. We assume that the infected humans (resp. mosquitos) heal at rate γ (resp. at rate μ).*

1. *What is the mean number of stings that a human suffers per time unit ?*

2. *Given 4 mutually independent standard Poisson processes $P_1(t)$, $P_2(t)$, $P_3(t)$ et $P_4(t)$, justify the following as a stochastic model of the propa-*

gation of malaria.

$$H(t) = H(0) + P_1\left(ap_1\int_0^t V(s)\frac{N_H - H(s)}{N_H}ds\right) - P_2\left(\gamma\int_0^t H(s)ds\right)$$
$$V(t) = V(0) + P_3\left(amp_2\int_0^t H(s)\frac{N_V - V(s)}{N_V}ds\right) - P_4\left(\mu\int_0^t V(s)ds\right).$$

3. *Define now (with $N_H = N$, $N_V = mN$)*

$$h_N(t) = \frac{H(t)}{N_H}, \quad v_N(t) = \frac{V(t)}{N_V}.$$

Write the equation for the pair $(h_N(t), v_N(t))$. Show that as $N \to \infty$, with m constant, $(h_N(t), v_N(t)) \to (h(t), v(t))$, solution of Ross' ODE :

$$\frac{dh}{dt}(t) = ap_1 mv(t)(1 - h(t)) - \gamma h(t)$$
$$\frac{dv}{dt}(t) = ap_2 h(t)(1 - v(t)) - \mu v(t).$$

14 Interlude 4 : Martingales

14.1 Discrete time martingales

$(\Omega, \mathcal{F}, \mathbb{P})$ being our standing probability space, let be given an increasing sequence $\{\mathcal{F}_n,\ n \geq 1\}$ of sub–σ–algebras of $\mathcal{F}$.

Definition 14. *A sequence $\{X_n,\ n \geq 0\}$ of r.v.'s is a called a martingale if*

1. *For all $n \geq 0$, X_n is $\mathcal{F}_n$–measurable and integrable,*
2. *For all $n \geq 0$, $\mathbb{E}(X_{n+1}|\mathcal{F}_n) = X_n$ a. s.*

A sub–martingale is a sequence which satisfies the first condition and $\mathbb{E}(X_{n+1}|\mathcal{F}_n) \geq X_n$. A super–martingale is a sequence which satisfies the first condition and $\mathbb{E}(X_{n+1}|\mathcal{F}_n) \leq X_n$.

It follows readily from Jensen's inequality for conditional expectations the

Proposition 15. *If $\{X_n,\ n \geq 0\}$ is a martingale, $\varphi : \mathbb{R} \to \mathbb{R}$ a convex function such that $\varphi(X_n)$ is integrable for all $n \geq 0$, then $\{\varphi(X_n),\ n \geq 0\}$ is a sub–martingale.*

We shall need the notion of stopping time

Definition 16. *A stopping time τ is an $\mathbb{N} \cup \{+\infty\}$–valued r.v. which satisfies $\{\tau = n\} \in \mathcal{F}_n$, for all $n \geq 0$.*

We have Doob's optional sampling theorem :

Theorem **17.** *If $\{X_n,\ n \geq 0\}$ is a martingale (resp. a sub–martingale), and τ_1, τ_2 two stopping times s.t. $\tau_1 \leq \tau_2 \leq N$ a. s., then X_{τ_i} is $\mathcal{F}_{\tau_i}$ measurable and integrable, $i = 1, 2$ and moreover*

$$\begin{aligned} &\mathbb{E}(X_{\tau_2}|\mathcal{F}_{\tau_1}) = X_{\tau_1} \\ (\textit{resp.}\quad &\mathbb{E}(X_{\tau_2}|\mathcal{F}_{\tau_1}) \geq X_{\tau_1}). \end{aligned}$$

Proof For all $A \in \mathcal{B}$, $n \geq 0$,

$$\{X_{\tau_i} \in A\} \cap \{\tau_i = n\} = \{X_n \in A\} \cap \{\tau_i = n\} \in \mathcal{F}_n,$$

and moreover

$$|X_{\tau_i}| \leq \sum_{k=1}^{N} |X_k|,$$

which establishes the first part of the statement.

Let $A \in \mathcal{F}_{\tau_1}$. Then

$$A \cap \{\tau_1 < k \leq \tau_2\} = A \cap \{\tau_1 \leq k-1\} \cap \{\tau_2 \leq k-1\}^c \in \mathcal{F}_{k-1}.$$

Indeed, we have

$$\begin{aligned} A \cap \{\tau_1 \leq k-1\} &= \cup_{j=1}^{k-1} A \cap \{\tau_1 = j\} \ \in \mathcal{F}_{k-1} \\ \text{and also } \ \{\tau_2 \leq k-1\}^c &\in \mathcal{F}_{k-1}. \end{aligned}$$

Let $\Delta_k = X_k - X_{k-1}$. We have

$$\begin{aligned} \int_A (X_{\tau_2} - X_{\tau_1}) d\mathbb{P} &= \int_A \sum_{k=1}^{n} \mathbf{1}_{\{\tau_1 < k \leq \tau_2\}} \Delta_k d\mathbb{P} \\ &= \sum_{k=1}^{n} \int_{A \cap \{\tau_1 < k \leq \tau_2\}} \Delta_k d\mathbb{P} \\ &= 0 \end{aligned}$$

or else ≥ 0, depending upon whether $\{X_n,\ n \geq 0\}$ is a martingale or a sub–martingale. □

We have a first Doob's inequality

Proposition 18. *If $X_1, \ldots, X_n$ is a sub–martingale, then for all $\alpha > 0$,*

$$\mathbb{P}(\max_{1 \leq i \leq n} X_i \geq \alpha) \leq \frac{1}{\alpha}\mathbb{E}(X_n^+).$$

Proof Define the stopping time $\tau = \inf\{0 \leq k \leq n,\ X_k \geq \alpha\}$ and let $M_k = \max_{1 \leq i \leq k} X_i$. We have

$$\{M_n \geq \alpha\} \cap \{\tau \leq k\} = \{M_k \geq \alpha\} \in \mathcal{F}_k.$$

Hence $\{M_n \geq \alpha\} \in \mathcal{F}_\tau$. From the optional sampling Theorem,

$$\begin{aligned}
\alpha\mathbb{P}(M_n \geq \alpha) &\leq \int_{\{M_n \geq \alpha\}} X_\tau d\mathbb{P} \\
&\leq \int_{\{M_n \geq \alpha\}} X_n d\mathbb{P} \\
&\leq \int_{\{M_n \geq \alpha\}} X_n^+ d\mathbb{P} \\
&\leq \mathbb{E}(X_n^+).
\end{aligned}$$

□

We have finally a second Doob's inequality

Proposition 19. *If $M_1, \ldots, M_n$ is a martingale, then*

$$\mathbb{E}\left[\sup_{0 \leq k \leq n} |M_k|^2\right] \leq 4\mathbb{E}\left[|M_n|^2\right].$$

Proof Let $X_k = |M_k|$. From Proposition 15, $X_1, \ldots, X_n$ is a sub–martingale. It follows from the proof of Proposition 18 that, with the notation $X_k^* = \sup_{0 \leq k \leq n} X_k$,

$$\mathbb{P}(X_n^* > \lambda) \leq \frac{1}{\lambda}\mathbb{E}\left(X_n \mathbf{1}_{X_n^* > \lambda}\right).$$

Consequently

$$\begin{aligned}\int_0^\infty \lambda \mathbb{P}(X_n^* > \lambda) d\lambda &\leq \int_0^\infty \mathbb{E}\left(X_n \mathbf{1}_{X_n^* > \lambda}\right) d\lambda \\ \mathbb{E}\left(\int_0^{X_n^*} \lambda d\lambda\right) &\leq \mathbb{E}\left(X_n \int_0^{X_n^*} d\lambda\right) \\ \frac{1}{2}\mathbb{E}\left[|X_n^*|^2\right] &\leq \mathbb{E}(X_n X_n^*) \\ &\leq \sqrt{E(|X_n|^2)}\sqrt{E(|X_n^*|^2)},\end{aligned}$$

from which the result follows. □

14.2 Continuous time martingales

We are now given an increasing collection $\{\mathcal{F}_t,\ t \geq 0\}$ of sub–σ–algebras.

Definition 20. *A process $\{X_t,\ t \geq 0\}$ of r.v.'s is a called a martingale if*

1. *for all $t \geq 0$, X_t is $\mathcal{F}_t$–measurable and integrable;*
2. *for all $0 \leq s < t$, $\mathbb{E}(X_t|\mathcal{F}_s) = X_s$ a. s.*

A sub–martingale is a sequence which satisfies the first condition and $\mathbb{E}(X_t|\mathcal{F}_s) \geq X_s$. A super–martingale is a sequence which satisfies the first condition and $\mathbb{E}(X_t|\mathcal{F}_s) \leq X_s$.

Suppose $\{M_t,\ t \geq 0\}$ is a right–continuous martingale. For any $n \geq 1$, $0 = t_0 < t_1 < \cdots < t_n$, $(M_{t_0}, M_{t_1}, \ldots, M_{t_n})$ is a discrete time martingale, to which Proposition 19 applies. Since

$$\sup_{0 \leq s \leq t} |M_s| = \sup_{\text{Partitions of } [0,t]} \sup_{1 \leq k \leq n} |M_{t_k}|,$$

Consequently Proposition 19 implies readily

Proposition 21. *If $\{M_t,\ t \geq 0\}$ is a right–continuous martingale,*

$$\mathbb{E}\left[\sup_{0 \leq s \leq t} |M_s|^2\right] \leq 4\mathbb{E}\left[|M_t|^2\right].$$

15 Central Limit Theorem

We write (s_N, i_N) in the form

$$s_N(t) = s(t) + \frac{1}{\sqrt{N}} U_N(t),$$
$$i_N(t) = i(t) + \frac{1}{\sqrt{N}} V_N(t),$$

and we look for the limiting law of the process $(U_N(t), V_N(t))$ as $N \to \infty$. It is plain that

$$\begin{aligned}
s(t) + \frac{U_N(t)}{\sqrt{N}} &= s(0) - \beta \int_0^t s(r)i(r)dr - \frac{\beta}{\sqrt{N}} \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}} \right) dr \\
&\quad - \frac{1}{N} M_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) dr \right), \\
i(t) + \frac{V_N(t)}{\sqrt{N}} &= i(0) + \beta \int_0^t s(r)i(r)dr + \frac{\beta}{\sqrt{N}} \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}} \right) dr \\
&\quad - \alpha \int_0^t i(r)dr - \frac{\alpha}{\sqrt{N}} \int_0^t V_N(r)dr \\
&\quad + \frac{1}{N} M_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) \right) \\
&\quad - \frac{1}{N} M_2 \left(\alpha N \int_0^t \left(i(r) + \frac{V_N(r)}{\sqrt{N}} \right) dr \right).
\end{aligned}$$

We use the ODE satisfied by $(s(t), i(t))$ in order to suppress the terms of order 1 in the above, and multiply the remaining terms by $\sqrt{N}$, from which

we deduce

$$
\begin{aligned}
U_N(t) &= -\beta \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}} \right) dr \\
&\quad - \frac{1}{\sqrt{N}} M_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) dr \right), \\
V_N(t) &= \beta \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}} \right) dr - \alpha \int_0^t V_N(r) dr \\
&\quad + \frac{1}{\sqrt{N}} M_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) \right) \\
&\quad - \frac{1}{\sqrt{N}} M_2 \left(\alpha N \int_0^t \left(i(r) + \frac{V_N(r)}{\sqrt{N}} \right) dr \right).
\end{aligned}
$$

Let

$$
\begin{aligned}
\mathcal{M}_1^N(t) &= \frac{1}{\sqrt{N}} M_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) \right), \\
\mathcal{M}_2^N(t) &= \frac{1}{\sqrt{N}} M_2 \left(\alpha N \int_0^t \left(i(r) + \frac{V_N(r)}{\sqrt{N}} \right) dr \right).
\end{aligned}
$$

Let $[\mathcal{M}_1]_t = \sum_{0 \le s \le t} |\Delta \mathcal{M}_1(s)|^2$, and efine analoguously $[\mathcal{M}_2]_t$. We have

$$
\begin{aligned}
[\mathcal{M}_1^N]_t &= \frac{1}{N} P_1 \left(\beta N \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) dr \right), \\
[\mathcal{M}_2^N]_t &= \frac{1}{N} P_2 \left(\alpha N \int_0^t \left(i(r) + \frac{V_N(r)}{\sqrt{N}} \right) dr \right).
\end{aligned}
$$

If we define

$$
\begin{aligned}
\langle \mathcal{M}_1^N \rangle_t &= \beta \int_0^t \left(s(r)i(r) + \frac{s(r)V_N(r) + i(r)U_N(r)}{\sqrt{N}} + \frac{U_N(r)V_N(r)}{N} \right) dr, \\
\langle \mathcal{M}_2^N \rangle_t &= \alpha \int_0^t \left(i(r) + \frac{V_N(r)}{\sqrt{N}} \right) dr,
\end{aligned}
$$

then with the notation

$$
\mathcal{F}_s^N = \sigma\{ s_N(r), i_N(r),\ 0 \le r \le t \},
$$

then we deduce by an analogous computation to that done in Lemma 8, for $0 \leq r < t$,

$$\mathbb{E}\left[|\mathcal{M}_1^N(t) - \mathcal{M}_1^N(r)|^2 \Big| \mathcal{F}_r^N\right]$$
$$= \beta \mathbb{E}\left[\int_r^t \left(s(u)i(u) + \frac{s(u)V_N(u) + i(u)U_N(u)}{\sqrt{N}} + \frac{U_N(u)V_N(u)}{N}\right) du \Big| \mathcal{F}_r^N\right],$$
$$\mathbb{E}\left[|\mathcal{M}_1^N(t) - \mathcal{M}_1^N(r)|^2 \Big| \mathcal{F}_r^N\right]$$
$$= \alpha \mathbb{E}\left[\int_r^t \left(i(u) + \frac{V_N(u)}{\sqrt{N}}\right) du \Big| \mathcal{F}_r^N\right].$$

A priori estimate It follows from Lemma 8 that

$$\mathcal{M}_1^N(t) = -U_N(t) - \beta \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}}\right) dr,$$
$$\mathcal{M}_2^N(t) = \mathcal{M}_1^N(t) - V_N(t) + \beta \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + \frac{U_N(r)V_N(r)}{\sqrt{N}}\right) dr$$
$$- \alpha \int_0^t V_N(r) dr.$$

Moreover from the definitions of $U_N(t)$ and $V_N(t)$,

$$|U_N(t)| \leq 2\sqrt{N}, \quad |V_N(t)| \leq 2\sqrt{N}.$$

Hence we deduce from the formulas for $\langle \mathcal{M}_1^N \rangle_t$ and $\langle \mathcal{M}_2^N \rangle_t$

$$\mathbb{E}[(\mathcal{M}_1^N(t))^2] \leq 9\beta t,$$
$$\mathbb{E}[(\mathcal{M}_2^N(t))^2] \leq 3\alpha t,$$
$$\mathbb{E}(|\mathcal{M}_1^N(t)|) \leq 3\sqrt{\beta t},$$
$$\mathbb{E}(|\mathcal{M}_2^N(t)|) \leq \sqrt{3\alpha t}$$

But

$$|U_N(t)| \leq \beta \int_0^t (|V_N(r)| + 3|U_N(r)|)\, dr + |\mathcal{M}_1^N(t)|,$$
$$|V_N(t)| \leq \alpha \int_0^t |V_N(r)| dr + \beta \int_0^t (|V_N(r)| + 3|U_N(r)|)\, dr + |\mathcal{M}_1^N(t)| + |\mathcal{M}_2^N(t)|.$$

Summing up those two inequalities, and taking advantage of Gronwall's Lemma and of the above estimates of the two martingales, we deduce that for all $T > 0$, there exist two constants $C_1(\alpha, \beta, T)$ and $C_2(\alpha, \beta, T)$ (for the second estimate we take the square before taking the expectation) such that

$$\begin{aligned} &\sup_{N\geq 1,\ 0\leq t\leq T} \mathbb{E}\left(|U_N(t)| + |V_N(t)|\right) \leq C_1(\alpha, \beta, T), \\ &\sup_{N\geq 1,\ 0\leq t\leq T} \mathbb{E}\left(|U_N(t)|^2 + |V_N(t)|^2\right) \leq C_2(\alpha, \beta, T). \end{aligned} \tag{1}$$

Lemma 22. *For all $T > 0$,*

$$\sup_{N\geq 1} \mathbb{E}\left(\sup_{0\leq t\leq T} \left[|U_N(t)|^2 + |V_N(t)|^2\right]\right) < \infty.$$

Proof

$$\sup_{0\leq r\leq t} |U_N(r)|^2 \leq 18\beta^2 t \int_0^t \left(|V_N(r)|^2 + 5|U_N(r)|^2\right) dr + 2 \sup_{0\leq r\leq t} |\mathcal{M}_1(r)|^2.$$

It follows from Doob's inequality that

$$\begin{aligned} \mathbb{E}\left(\sup_{0\leq r\leq t} |\mathcal{M}_1(r)|^2\right) &\leq 4\mathbb{E}\langle \mathcal{M}_1\rangle_t \\ &\leq 4 \times 9\beta t. \end{aligned}$$

Hence the first part of the result follows from the last two inequalities combined with (1). The second part of the result follows analogously. □

Convergence in law The proof of convergence follows from the Lemma

Lemma 23. *Let $\{P(t),\ t \geq 0\}$ be a standard Poisson process. Let $M(t) = P(t) - t$. Then for any sequence $\{t_N,\ N \geq 1\}$ of real numbers such that $N^{-1/2} t_N \to 0$ as $N \to \infty$,*

$$\left\{ \frac{M(Nt + \sqrt{N} t_N)}{\sqrt{N}},\ t \geq 0 \right\} \Rightarrow \{B(t),\ t \geq 0\},$$

where $B(t)$ is a standard Brownian motion.

PROOF We shall only prove convergence of the finite dimensional distributions. It is in fact sufficient to prove that for any $t > 0$ fixed,

$$\frac{M(Nt + \sqrt{N}t_N)}{\sqrt{N}} \Rightarrow B(t),$$

since on the left we have a process with asymptotically stationary and independent increments, and the limit has those properties.

For each $t \geq 0$, the convergence $N^{-1/2}M(Nt) \Rightarrow B(t)$ follow from the usual Central Limit Theorem. Indeed

$$\frac{M(Nt)}{\sqrt{[Nt]}} = \frac{1}{\sqrt{[Nt]}} \sum_{i=1}^{[Nt]} [M(i) - M(i-1)] + \frac{M(Nt) - M([Nt])}{\sqrt{[Nt]}},$$

the r.v.'s $M(i) - M(i-1)$ are i.i.d. centered with variance 1, and the last term above converges in probability to 0 as $N \to \infty$, hence

$$\begin{aligned} \frac{M(Nt)}{\sqrt{[Nt]}} &\to \mathcal{N}(0,1), \\ \frac{M(Nt)}{\sqrt{N}} &= \frac{\sqrt{[Nt]}}{\sqrt{N}} \times \frac{M(Nt)}{\sqrt{[Nt]}} \\ &\Rightarrow B(t), \end{aligned}$$

where $B(t)$ follows the law $\mathcal{N}(0,t)$. Now

$$\frac{M(Nt + \sqrt{N}t_N)}{\sqrt{N}} = \frac{M(Nt)}{\sqrt{N}} + \frac{M(Nt + \sqrt{N}t_N) - M(Nt)}{\sqrt{N}},$$

and it remains to prove that

$$\frac{M(Nt + \sqrt{N}t_N) - M(Nt)}{\sqrt{N}} \to 0$$

in probability, as $n \to \infty$. But

$$\begin{aligned} \mathbb{P}\left(\left| \frac{M(Nt + \sqrt{N}t_N) - M(Nt)}{\sqrt{N}} \right| > \varepsilon \right) &\leq \frac{1}{N\varepsilon^2} \mathrm{Var}\left(M(Nt + \sqrt{N}t_N) - M(Nt) \right) \\ &= \frac{\sqrt{N}\, t_N}{N\varepsilon^2} \\ &\to 0, \end{aligned}$$

provided $N^{-1/2}t_N \to 0$ as $N \to \infty$. $\square$

It remains to show :

Proposition 24. *Lemma 23 remains true with t_N random, provided $N^{-1/2}\mathbb{E}[|t_N|] \to 0$ as $N \to \infty$.*

Proof We need to show that

$$\frac{M(Nt+\sqrt{N}t_N) - M(Nt)}{\sqrt{N}} \to 0$$

in probability, as $N \to \infty$.

$$\begin{aligned}\mathbb{P}\left(\frac{|t_N|}{\sqrt{N}} > \eta\right) &\leq \frac{1}{\eta}\frac{\mathbb{E}|t_N|}{\sqrt{N}} \\ &\to 0,\end{aligned}$$

as $N \to \infty$. Let $\varepsilon > 0$ be fixed. We have

$$\begin{aligned}&\left\{\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right\} \\ &\subset \left\{\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right\} \cap \left\{0 \leq t_N \leq \eta\sqrt{N}\right\} \\ &\quad \bigcup \left\{\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right\} \cap \left\{-\eta\sqrt{N} \leq t_N \leq 0\right\} \bigcup \left\{\frac{|t_N|}{\sqrt{N}} > \eta\right\}.\end{aligned}$$

The probability of the first event on the right can be estimated as follows, using Doob's inequality

$$\begin{aligned}\mathbb{P}\left(\sup_{0\leq s\leq N\eta} \frac{|M(Nt+s) - M(Nt)|}{\sqrt{N}} > \varepsilon\right) &\leq \frac{4}{N\varepsilon^2}\mathbb{E}\left(|M(N(t+\eta)) - M(Nt)|^2\right) \\ &\leq \frac{4\eta}{\varepsilon^2}.\end{aligned}$$

Estimating analogously the probability of the second event, and that of the third one by Chebychef's inequality, we get

$$\mathbb{P}\left(\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right) \leq \frac{8\eta}{\varepsilon^2} + \frac{\mathbb{E}|t_N|}{\eta\sqrt{N}}.$$

Let $\eta = \varepsilon^3/16$, from which we deduce

$$\mathbb{P}\left(\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right) \leq \frac{\varepsilon}{2} + \frac{16\mathbb{E}|t_N|}{\varepsilon^3\sqrt{N}}.$$

Then if N is large enough such that $\frac{\mathbb{E}|t_N|}{\sqrt{N}} \leq \varepsilon^4/32$,

$$\mathbb{P}\left(\frac{|M(Nt+\sqrt{N}t_N) - M(Nt)|}{\sqrt{N}} > \varepsilon\right) \leq \varepsilon.$$

The Proposition follows since this result holds for any $\varepsilon > 0$. □

We use this Proposition first with $M = M_1$, t being replaced by $\beta \int_0^t s(r)i(r)dr$ and

$$t_N = \beta \int_0^t \left(s(r)V_N(r) + i(r)U_N(r) + N^{-1/2}U_N(r)V_N(r)\right) dr$$

which satisfies $\mathbb{E}|t_N| \leq C$, then with $M = M_2$, t being replaced by $\alpha \int_0^t i(r)dr$ and $t_N = \alpha \int_0^t V_N(r)dr$, which again satisfies $\mathbb{E}|t_N| \leq C$. In order to get the joint law of both limits, we exploit the fact that the product $M_1(t)M_2(t)$ is a martingale.

Moreover one can rather easily show that the sequence $\{(U_N(t), V_N(t)),\ t \geq 0\}$ is tight as a process whose trajectories belong to $C([0,+\infty); \mathbb{R}^2)$. Hence along a subsequence

$$\{(U_N(t), V_N(t)),\ t \geq 0\} \Rightarrow \{(U(t), V(t)),\ t \geq 0\},$$

where the limit satisfies

$$U(t) = -\beta \int_0^t [s(r)V(r) + i(r)U(r)]\, dr + \sqrt{\beta} \int_0^t \sqrt{s(r)i(r)} dB_1(r),$$

$$V(t) = \beta \int_0^t [s(r)V(r) + i(r)U(r)]\, dr - \alpha \int_0^t V(r)dr - \sqrt{\beta} \int_0^t \sqrt{s(r)i(r)} dB_1(r)$$
$$+ \sqrt{\alpha} \int_0^t \sqrt{i(r)} dB_2(r).$$

The process $\{(U(t), V(t)),\ t \geq 0\}$ is a Gaussian process of the Ornstein–Uhlenbeck type.

The law of the limit is uniquely determined. Hence the whole sequence converges.

Exercise 4. *Let us go back to Exercise 3. We now define $X_N(t)$ and $Y_N(t)$ by letting $h_N(t) = h(t) + \frac{X_N(t)}{\sqrt{N}}$, $v_N(t) = v(t) + \frac{Y_N(t)}{\sqrt{N}}$. Write the equation satisfied by the Ornstein–Uhlenbeck process $(X(t), Y(t)) = \lim_{N\to\infty}(X_N(t), Y_N(t))$.*

16 Time needed by an epidemic to go extinct, and the critical population size

Let us go bak to the general stochastic model, with a demographic effect.

Individuals are born at the constant rate μN, each individual lives a time $\mathrm{Exp}(\mu)$. An individual contacts another individual of the population at rate $\gamma = cp$, and this contact results in an infection if one of the two individuals is infectious, and the other one is susceptible. We assume homogeneous mixing : any infectious infects any given susceptible at rate γ/N. The durations of the infection periods are i.i.d., with the common law $\mathrm{Exp}(\alpha)$.

Hence $S(t)$ is a birth and death process, with births at rate $N\mu$ and deaths at rate $S(t)\mu$. The death rate is the same for susceptible and infectious individuals.

The epidemic starts with a unique infected individual which is introduced in a population of susceptibles. Its stops when there is no more infected individual. The time when this happens is called the extinction time of the epidemic. Note that we have made two simplifying assumptions in our model

1. the rate of births is not exactly proportional to the size of the population, but to its equilibrium value N;

2. the rate of contacts of an infectious with a given individual is γ/N, and not γ divided by the exact population size.

Those simplifications allow us in particular to reduce our model to a 2–dimensional model.

Concerning the increase of the death rate due to the epidemic, it can be included in the rate α (a death caused by the infection is considered as a removed).

In our model, the pair $(S(t), I(t))$ is a continuous time Markov process.

Its rates matrix Q satisfies

$$Q_{(n,m),(n',m')} = \begin{cases} \mu N, & \text{si } (n',m') = (n+1,m); \\ \mu n, & \text{si } (n',m') = (n-1,m); \\ \frac{\gamma}{N} nm, & \text{si } (n',m') = (n-1,m+1); \\ (\alpha+\mu)m, & \text{si } (n',m') = (n,m-1); \\ 0, & \text{si } (n',m') \notin \{(n,m),(n+1,m),(n-1,m),(n-1,m+1),(n,m-1)\}. \end{cases}$$

Let

$$(\overline{S}(t), \overline{I}(t)) = \left(\frac{S(t)}{N}, \frac{I(t)}{N} \right).$$

The mean infection time of an individual is $(\alpha+\mu)^{-1}$. During that period, and during the initial phase of the epidemic, an infectious infects at rate γ. Then

$$R_0 = \frac{\gamma}{\alpha+\mu}.$$

Example 25. Realistic values of the parameters. *We may assume that $\mu^{-1} = 75$ years (mean life time of an individual). Hence $\mu = 1/75$.*

The mean duration of infection depends upon the illness, say it is one week, hence $1/\alpha = 1/52$, $\alpha = 52$.

For most childhood diseases, a typical value of R_0 is 10. In other words

$$\gamma = R_0(\mu+\alpha) \sim 500.$$

Note that in that case, $\mu + \alpha \sim \alpha$, hence $R_0 \sim \gamma/\alpha$.

Assume that $R_0 > 1$, and we are interested in the duration of a major epidemic. As $N \to \infty$, $(\overline{S}(t), \overline{I}(t)) \to (s(t), i(t))$, solution of the ODE

$$\begin{cases} s'(t) = \mu(1-s(t)) - \gamma s(t) i(t), \\ i'(t) = \gamma s(t) i(t) - (\mu+\alpha) i(t). \end{cases}$$

This ODE has two equilibria : the disease free equilibrium $(1,0)$ and the endemic equilibrium $(\hat{s}, \hat{i})$, with $\hat{s} = R_0^{-1}$, $\hat{i} = (\mu+\alpha)^{-1}\mu(1-R_0^{-1}) = \varepsilon(1-R_0^{-1})$, where $\varepsilon = (\mu+\alpha)^{-1}\mu \sim \mu/\alpha$.

If $R_0 > 1$, the disease free equilibrium is unstable, while the endemic equilibrium is stable.

Example 26. *With the above data, we have $\hat{s} = 0,1$, $\hat{i} = 0,00024$.*

More generally, if $R_0 >> 1$ and $\varepsilon << 1$, $\hat{\imath}$ is small. The ODE gives us a clue about the time needed to reach a value close to the equilibrium. When the equilibrium is reached, the small value of $\hat{\imath}$ makes it easy for the random fluctuations to lead the epidemic to extinction.

1st case : when i is close to $\hat{\imath}$, the random fluctuations lead rather quickly to extinction;

2d case : there is no quick extinction, and a second epidemic starts (which hits much less individuals than the first one, since $\hat{s} << s(0)$).

etc.

The law of the extinction time is multimodal, with a first peak near the time taken to reach $\hat{\imath}$, and a series of much smaller peaks.

Once $\hat{\imath}$ has been reached, we are in the situation of a quasi–stationary distribution. The extinction time follows an exponential distribution, by the same argument as above. Denote by $\{q_{S,I},\ S \geq 0, I \geq 1\}$ this quasi–stationary distribution. The parameter of this exponential distribution equals $(\alpha+\mu)\sum_S q_{S,1}$, hence

$$\mathbb{E}(T_Q) = \frac{1}{(\alpha+\mu)\sum_S q_{S,1}} = \frac{1}{\mu}\frac{\varepsilon}{\sum_S q_{S,1}}.$$

How can one compute $\sum_S q_{S,1}$? For this purpose we will approximate the quasi–stationary distribution by a Gaussian law which we now specify.

Let us go back to our model. If $(\overline{S}(t), \overline{I}(t)) = \left(\frac{S(t)}{N}, \frac{I(t)}{N}\right)$,

$$\overline{S}(t) = \overline{S}(0) + \frac{1}{N}P_1(\mu N t) - \frac{1}{N}P_2\left(\mu N \int_0^t \overline{S}(r)dr\right) - \frac{1}{N}P_3\left(\gamma N \int_0^t \overline{S}(r)\overline{I}(r)dr\right)$$

$$\overline{I}(t) = \overline{I}(0) + \frac{1}{N}P_3\left(\gamma N \int_0^t \overline{S}(tr)\overline{I}(r)dr\right) - \frac{1}{N}P_4\left((\alpha+\mu)N \int_0^t \overline{I}(r)dr\right).$$

Hence

$$\overline{S}(t) = \overline{S}(0) + \mu t - \mu \int_0^t \overline{S}(r)dr - \gamma \int_0^t \overline{S}(r)\overline{I}(r)dr + \frac{1}{N}M_1(\mu N t) - \frac{1}{N}M_2\left(\mu N \int_0^t \overline{S}(r)dr\right) - \frac{1}{N}M_3\left(\gamma N \int_0^t \overline{S}(r)\overline{I}(r)dr\right)$$

$$\overline{I}(t) = \overline{I}(0) + \gamma \int_0^t \overline{S}(r)\overline{I}(r)dr - (\alpha+\mu)\int_0^t \overline{I}(r)dr + \frac{1}{N}M_3\left(\gamma N \int_0^t \overline{S}(r)\overline{I}(r)dr\right) - \frac{1}{N}M_4\left((\alpha+\mu)N\int_0^t \overline{I}(r)dr\right).$$

The law of large numbers tells us that in the limit $N \to \infty$

$$s'(t) = \mu(1-s(t)) - \gamma s(t)i(t)$$
$$i'(t) = \gamma s(t)i(t) - (\alpha+\mu)i(t).$$

Define

$$\begin{pmatrix} U_t \\ V_t \end{pmatrix} = \lim_{N\to\infty} \sqrt{N}\begin{pmatrix} \overline{S}(t) - s(t) \\ \overline{I}(t) - i(t) \end{pmatrix}.$$

The process $\begin{pmatrix} U_t \\ V_t \end{pmatrix}$ satisfies

$$d\begin{pmatrix} U_t \\ V_t \end{pmatrix} = \begin{pmatrix} -\mu - \gamma i(t) & -\gamma s(t) \\ \gamma i(t) & \gamma s(t) - (\alpha+\mu) \end{pmatrix}\begin{pmatrix} U_t \\ V_t \end{pmatrix} dt + dM_t,$$

where M_t is a Gaussian martingale (in fact a Brownian motion) such that

$$\mathbb{E}(M_t M_t') = \begin{pmatrix} \mu\int_0^t (1+s(r))dr + \gamma\int_0^t s(r)i(r)dr & -\gamma\int_0^t s(r)i(r)dr \\ -\gamma\int_0^t s(r)i(r)dr & (\alpha+\mu)\int_0^t i(r)dr + \gamma\int_0^t s(r)i(r)dr \end{pmatrix}.$$

Since we consider our processes for large time, we can replace $s(r)$ et $i(r)$ by $\hat{s}$ and $\hat{\imath}$. The above system becomes

$$d\begin{pmatrix} U_t \\ V_t \end{pmatrix} = \begin{pmatrix} -\mu R_0 & -(\alpha+\mu) \\ \mu(R_0-1) & 0 \end{pmatrix}\begin{pmatrix} U_t \\ V_t \end{pmatrix} dt + dM_t,$$

$$\begin{aligned} \mathbb{E}(M_t M_t') &= t\begin{pmatrix} 2\mu & -\mu\left(1-\frac{1}{R_0}\right) \\ -\mu\left(1-\frac{1}{R_0}\right) & 2\mu\left(1-\frac{1}{R_0}\right) \end{pmatrix} \\ &= t\Lambda. \end{aligned}$$

Let

$$A = \begin{pmatrix} -\mu R_0 & -(\alpha+\mu) \\ \mu(R_0-1) & 0 \end{pmatrix}, \ \mathcal{V} = \frac{1}{R_0^2} \begin{pmatrix} \frac{1}{\varepsilon} + R_0 & -R_0 \\ -R_0 & R_0 - 1 + \varepsilon R_0^2 \end{pmatrix}.$$

One can show that

$$\begin{pmatrix} U_t \\ V_t \end{pmatrix} \overset{\text{en loi}}{\longrightarrow} \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathcal{V} \right).$$

This result follows from the identities :

$$\begin{aligned} \frac{d}{dt} \mathbb{E} \begin{pmatrix} U_t \\ V_t \end{pmatrix} &= A \mathbb{E} \begin{pmatrix} U_t \\ V_t \end{pmatrix} = 0, \\ \frac{d}{dt} \text{Cov} \begin{pmatrix} U_t \\ V_t \end{pmatrix} &= A \text{Cov} \begin{pmatrix} U_t \\ V_t \end{pmatrix} + \text{Cov} \begin{pmatrix} U_t \\ V_t \end{pmatrix} A' + \Lambda. \end{aligned}$$

Hence $\mathcal{V}$ is such that $A\mathcal{V} + \mathcal{V}A' = \Lambda$. I is asymptotically Gaussian, with mean $\mu_I = N\hat{\imath}$, and variance $\sigma_I^2 = N\frac{R_0 - 1 + \varepsilon R_0^2}{R_0^2}$. We want to estimte

$$q_{\cdot,1} = \sum_S q_{S,1} = \lim_{t\to\infty} \mathbb{P}(I(t) = 1 | I(t) > 0),$$

which we approximate by

$$\frac{\frac{1}{\sigma_I}\varphi\left(\frac{1-\mu_I}{\sigma_I}\right)}{\Phi\left(\frac{\mu_I - 0{,}5}{\sigma_I}\right)},$$

where φ (resp. Φ) denotes the density (resp. the distribution function) of the law $\mathcal{N}(0,1)$. Note that we have approximated $\mathbb{P}(I(t) > 0)$ by $\mathbb{P}(I(t) > 0,5) = 1 - \Phi(\sigma^{-1}(0,5 - \mu_I)) = \Phi(\sigma_I^{-1}(\mu_I - 0,5))$. The above ratio is approximated by

$$\frac{\frac{1}{\sigma_I}\varphi\left(\frac{\mu_I}{\sigma_I}\right)}{\Phi\left(\frac{\mu_I}{\sigma_I}\right)}.$$

Note that

$$\frac{\mu_I}{\sigma_I} = \frac{\sqrt{N}\varepsilon(R_0 - 1)}{\sqrt{R_0 - 1 + \varepsilon R_0^2}} \simeq \sqrt{N\varepsilon^2(R_0 - 1)}.$$

Hence

$$\begin{aligned}\mathbb{E}(T_Q) &\simeq \frac{1}{\mu}\frac{\varepsilon}{q_{\cdot,1}}\\ &\simeq \frac{1}{\mu}\frac{\varepsilon\Phi(\sqrt{N\varepsilon^2(R_0-1)})}{\frac{R_0}{\sqrt{2\pi N(R_0-1)}}\exp(-N\varepsilon^2(R_0-1)/2)}\\ &\simeq \frac{\sqrt{2\pi}}{\mu}\frac{\sqrt{N\varepsilon^2(R_0-1)}}{R_0}e^{N\varepsilon^2(R_0-1)/2}\Phi(\sqrt{N\varepsilon^2(R_0-1)})\\ &\sim \exp\left(\frac{N\varepsilon^2(R_0-1)}{2}\right).\end{aligned}$$

The last line gives the order of magnitude of the quantity of interest.

In case of vaccination of the proportion v of the population, we must replace N by $N(1-v)$ an R_0 by $R_0(1-v)$.

Critical population size If $N\varepsilon^2$ is "small", there will be no major epidemic.

If $N\varepsilon^2$ is "large", a major epidemic might happen.

Note that before vaccination, measles was endemic in Great Britain, while the epidemic would go extinct after each outbreak in Iceland.

Notice that if $Z \sim \mathcal{N}(0,1)$, $\mathbb{P}(|Z| \geq 3) \simeq 0,23\%$. But

$$\frac{\mu_I}{\sigma_I} \simeq \sqrt{N\varepsilon^2(R_0-1)}.$$

One may decide that the critical value N_c is such that (the factor 3 below is arbitrary)

$$\sqrt{N_c\varepsilon^2(R_0-1)} = 3$$

$$N_c = \frac{9}{\varepsilon^2(R_0-1)}.$$

If we take into account vaccination, we get

$$N_c = \frac{9}{(1-v)\varepsilon^2(R_0(1-v)-1)}.$$

Example 27. *In case of measles,* $R_0 = 15$, $\varepsilon = 1/3750$, $N_c = 9,04 \times 10^6$.

Example 28. *Measles with a vaccination rate* $v = 0,9$. *Then* $R_0 - 1 = 14$ *should be replaced by* $(1-v)(R_0(1-v)-1) = 0,05$. *Hence we must multiply the above value of* N_c *by the factor* $14/0,05$. *The result is* 2531×10^6.

17 Computation of R_0

17.1 The Perron–Frobenius theorem

The proof of the following classical result can be found e.g. in [4], see the proof of Theorem 2.7 there.

Theorem **29.** *Let A be a square matrix, which is positive and irreducible. The spectral radius of A is a simple eigenvalue of A, whose associated eigenvector has all its coordinates positive.*

If moreover A is aperiodic, then any other eigenvalue has a modulus which is strictly smaller than the spectral radius.

A positive : $A_{i,j} \geq 0$ for all i, j.

A irreducible : for all $i \neq j$, there exists $n \geq 1$ such that $(A^n)_{i,j} > 0$.

A aperiodic : there exists $n \geq 1$ such that $(A^n)_{i,j} > 0$ for all i, j.

The spectral radius of A is defined as the $\lim_{n\to\infty} \|A^n\|^{1/n}$ (it is also the largest modulus of all eigenvalues).

17.2 Computation of R_0 in case of malaria

Female mosquitos strive for a fixed number of blood meals per unit time. Hence the mean number of stings which a human suffers by unit time (from female mosquitos) is proportional to the ratio of the two densities $D_{\text{mosquitos}}/D_{\text{humans}}$.

Consider an infected mosquito. Suppose that her mean infection period is T_m, during which she stings humans at rate c. Each of those stings results in the transmission of malaria with probability p_m. The mean number of individuals which a mosquito infects is then cp_mT_m.

Consider an infected human. Suppose that his mean infection time is T_h, during which he is stung at rate k, each sting resulting in the infection of the mosquito (if susceptible) with probability p_h. The mean number of mosquitos infected by such a human is then kp_hT_h.

Consequently

$$R_0 = c^2 T_m T_h p_m p_h \frac{D_{\text{mosquitos}}}{D_{\text{humans}}}.$$

17.3 Computation of R_0 in case of a sexually transmitted illness

Suppose that the mean number of women infected by one man is 100, and the mean number of men infected by a women is 10. Hence the transmission matrix

$$K = \begin{pmatrix} 0 & 100 \\ 10 & 0 \end{pmatrix}.$$

In two "generations", the mean number of individuals of the same species infected by a given individual is 1 000. Hence $R_0 = \sqrt{1000}$ = spectral radius of K = largest eigenvalue.

17.4 Computation of R_0 in case of a general compartmental model

Consider the ODE of the model, which we linearize in the neighborhood of $I(t) = 0$, since R_0 is the potential of infection of one infected individual, introduced in a fully susceptible population.

Let x be the vector which describes the sizes of the infected sub–populations.

$$\dot{x} = (T + \Sigma)x,$$

where T is the matrix which describes the transmission of the illness by contact; Σ is the matrix which describes the transitions from one state to another, without contact.

Example 30. *Suppose there are two latent states E_1 and E_2, which change to infected resp. at rates ν_1 and ν_2, and those infected individuals produce by contact E_1–type individuals at rate $p\beta$, E_2–type individuals at rate $(1-p)\beta$. In addition, each individual dies at rate μ, and the infected individuals heal at rate α. In other words*

$$\begin{aligned} \dot{E}_1 &= p\beta I - (\nu_1 + \mu)E_1, \\ \dot{E}_2 &= (1-p)\beta I - (\nu_2 + \mu)E_2, \\ \dot{I} &= \nu_1 E_1 + \nu_2 E_2 - (\alpha + \mu)I. \end{aligned}$$

Here

$$T = \begin{pmatrix} 0 & 0 & p\beta \\ 0 & 0 & (1-p)\beta \\ 0 & 0 & 0 \end{pmatrix}, \ \Sigma = \begin{pmatrix} -(\nu_1 + \mu) & 0 & 0 \\ 0 & -(\nu_2 + \mu) & 0 \\ \nu_1 & \nu_2 & -(\alpha + \mu) \end{pmatrix}.$$

Digression about the matrix Σ Consider a jump Markov process, with the four 4 states (E_1, E_2, T, R), where

$$\begin{aligned} E_1 &= \text{ latent sate 1} \\ E_2 &= \text{ latent sate 2} \\ I &= \text{ infectious} \\ R &= \text{ removed or dead.} \end{aligned}$$

The rates matrix of this process is given by

$$Q = \begin{pmatrix} -(\nu_1+\mu) & 0 & \nu_1 & \mu \\ 0 & -(\nu_2+\mu) & \nu_2 & \mu \\ 0 & 0 & -(\alpha+\mu) & \alpha+\mu \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The state R is absorbing. Let

$$\Sigma = Q^t = \begin{pmatrix} -(\nu_1+\mu) & 0 & 0 & 0 \\ 0 & -(\nu_2+\mu) & 0 & 0 \\ \nu_1 & \nu_2 & -(\alpha+\mu) & 0 \\ \mu & \mu & \alpha+\mu & 0 \end{pmatrix}.$$

Note that $(e^{t\Sigma})_{ij} = (e^{tQ})_{ji}$ is the probability to be in state i at time t, starting from state j at time 0.

In fact, if we limit ourselves to $1 \leq i, j \leq 3$, this quantity equals also

$$(e^{t\Sigma})_{ij}, \quad \text{with } \Sigma = \begin{pmatrix} -(\nu_1+\mu) & 0 & 0 \\ 0 & -(\nu_2+\mu) & 0 \\ \nu_1 & \nu_2 & -(\alpha+\mu) \end{pmatrix}.$$

Now for all $1 \leq i, j \leq 3$, $(e^{t\Sigma})_{ij} \to 0$ as $t \to \infty$. We have

$$\int_0^\infty (e^{t\Sigma})_{ij} dt = \text{ mean sojourn time in state } i, \text{ starting from state } j \text{ at time 0.}$$

But since $e^{\infty\Sigma} = 0$,

$$\int_0^\infty \Sigma e^{t\Sigma} dt = -I,$$

and

$$\int_0^\infty e^{t\Sigma} dt = -\Sigma^{-1}$$

which is a matrix with positive coefficients. Note that

$$\begin{aligned}
T_{ij} &= \text{ rate at which a } j \text{ produces an } i,\\
(-\Sigma^{-1})_{jk} &= \text{ mean sojourn time of an initial } k \text{ in state } j \text{ since}\\
\left(\int_0^\infty e^{t\Sigma}dt\right)_{jk} &= \mathbb{E}\left(\int_0^\infty \mathbf{1}_{\{X(t)=j\}}dt\Big|X(0)=k\right),\\
(T(-\Sigma^{-1}))_{ik} &= \text{ mean number of } i\text{'s that an initial } k \text{ induces during his life time.}
\end{aligned}$$

Hence

$$R_0 \text{ is the spectral radius of the matrix } K = -T\Sigma^{-1}.$$

Back to the above example

$$-\Sigma^{-1} = \begin{pmatrix} \frac{1}{\nu_1+\mu} & 0 & 0\\ 0 & \frac{1}{\nu_2+\mu} & 0\\ \frac{\nu_1}{(\nu_1+\mu)(\alpha+\mu)} & \frac{\nu_2}{(\nu_2+\mu)(\alpha+\mu)} & \frac{1}{\alpha+\mu}\end{pmatrix},$$

$$K = \begin{pmatrix} \frac{p\beta\nu_1}{(\nu_1+\mu)(\alpha+\mu)} & \frac{p\beta\nu_2}{(\nu_2+\mu)(\alpha+\mu)} & \frac{p\beta}{\alpha+\mu}\\ \frac{(1-p)\beta\nu_1}{(\nu_1+\mu)(\alpha+\mu)} & \frac{(1-p)\beta\nu_2}{(\nu_2+\mu)(\alpha+\mu)} & \frac{(1-p)\beta}{\alpha+\mu}\\ 0 & 0 & 0\end{pmatrix}.$$

Exercise 5. *The two matrices K and K' below give the same R_0*

$$K' = \begin{pmatrix} \frac{p\beta\nu_1}{(\nu_1+\mu)(\alpha+\mu)} & \frac{p\beta\nu_2}{(\nu_2+\mu)(\alpha+\mu)}\\ \frac{(1-p)\beta\nu_1}{(\nu_1+\mu)(\alpha+\mu)} & \frac{(1-p)\beta\nu_2}{(\nu_2+\mu)(\alpha+\mu)}\end{pmatrix},$$

namely

$$R_0 = \left(\frac{p\nu_1}{\nu_1+\mu} + \frac{(1-p)\nu_2}{\nu_2+\mu}\right)\frac{\beta}{\alpha+\mu} = TrK'.$$

There is a good reason to restrict oneself to the two states E_1 and E_2, which are the states of the "start of infection".

On the other hand, if we consider the unique states I, and compute the mean number of I's which a unique I induces, we recover the same R_0, without matrix or eigenvalue !

Exercise 6. *Recover the above K_{ij} by the interpretation "mean number of i's produced by a j".*

Exercise 7. COMPUTATION OF R_0 IN A MODEL OF INFECTION OF CELLS BY VIRUSES

We consider the following model, where C denotes the number of target cells, C^* the number of infected cells, V the number of viruses. We assume that this triplet satisfies the ODE

$$\begin{aligned}\frac{dC}{dt} &= \lambda - kCV - \delta C\\ \frac{dC^*}{dt} &= kCV - (\mu+\delta)C^*\\ \frac{dV}{dt} &= pC^* - kCV - cV.\end{aligned}$$

We consider the ODE reduced to the two last equations, which we want to put in the form

$$\frac{d}{dt}\begin{pmatrix}C^*\\ V\end{pmatrix} = [T+\Sigma]\begin{pmatrix}C^*\\ V\end{pmatrix},$$

where T and $-\Sigma^{-1}$ are positive matrices, such that R_0 is the spectral radius of the matrix $-T\Sigma^{-1}$. We consider the three following choices for the matrices T and Σ:

$$T_1 = \begin{pmatrix}0 & 0\\ p & 0\end{pmatrix},\ \Sigma_1 = \begin{pmatrix}-(\mu+\delta) & kC\\ 0 & -(kC+c)\end{pmatrix};$$

$$T_2 = \begin{pmatrix}0 & kC\\ p & 0\end{pmatrix},\ \Sigma_2 = \begin{pmatrix}-(\mu+\delta) & 0\\ 0 & -(kC+c)\end{pmatrix};$$

$$T_3 = \begin{pmatrix}0 & kC\\ 0 & 0\end{pmatrix},\ \Sigma_3 = \begin{pmatrix}-(\mu+\delta) & 0\\ p & -(kC+c)\end{pmatrix}.$$

1. *Justify the three decompositions, from the point of view of the biological interpretation (the transition from 1. to 2., a virus enters a target cell, is it a state transition of the virus, or a reproduction event ?).*

2. *Compute R_0 in the three cases.*

3. *Compare the three results. What do they have in common ? Can you explain the differences and the identities ?*

Exercise 8. *Flowers are cultivated in a field. Slips are withdrawn from these flowers at rate δ. Those slips are planted in a greenhouse.*

Flowers which mature in the greenhouse are replanted in the field at rate ρ. We admit that the system is at its equilibrium, with population sizes N_1 in the field, and N_2 in the greenhouse.

Mushrooms start to proliferate among the flowers, with the following transmission mechanism. Each infected flower in the field (resp. in the greenhouse) infects each non infected flower in the field (resp. in the greenhouse) at rate α (resp. β). Moreover, each time a slip is removed from the field, it is infected with probability p.

The infected flowers of the field (resp. of the greenhouse) die at rate μ (resp. γ). Since we are interested in the beginning of the infection, we neglect the fact that the sizes of the populations will not remain constant.

1. *We denote by $C_1(t)$ (resp. $C_2(t)$) the size of the field (resp. greenhouse) population of flowers hit by the mushroom. Justify the following model for the evolution of $(C_1(t), C_2(t))$:*

$$\frac{dC_1}{dt}(t) = \alpha(N_1 - C_1(t))C_1(t) - \mu C_1(t) + \rho C_2(t)$$
$$\frac{dC_2}{dt}(t) = p\delta C_1(t) + \beta(N_2 - C_2(t))C_2(t) - (\gamma + \rho)C_2(t).$$

2. *Linearise the above ODE in the neighborhood of $(C_1, C_2) = (0, 0)$. Write the linearized system in the form*

$$\frac{d}{dt}\begin{pmatrix} C_1 \\ C_2 \end{pmatrix} = [T + \Sigma]\begin{pmatrix} C_1 \\ C_2 \end{pmatrix}.$$

3. *Compute the matrix $K = T(-\Sigma^{-1})$ and its spectral radius (do not try to simplified the formula).*

4. *Compute R_0 for this model.*

Example 31. The virus of bovine diarrhea

Assume "horizontal" transmission at rate β_1, "vertical" transmission at rate β_2. Those horizontally infected go through state E before going to state I.

A cow which was pregnant during less than 150 days before being infected, and which heals (and then is in state Z) before delivering, gives birth to a veal in state P. Those transmit infection, reproduce, at rates different from the others.

Let γ denote the healing rate, p_1 the probability of ending in state Z, $1/\alpha$ the mean time during which an infected fetus is weared, p_2 the probability that an infected fetus survives, ν the transition rate from state E to state I, μ the natural death rate, a and b the reduction of the reproduction rate and the increase of the death rate of infected individuals. The model reads

$$\begin{aligned}
\dot{E} &= (\beta_1 I + \beta_2 P)S - (\nu+\mu)E \\
\dot{I} &= \nu E - (\gamma+\mu)I \\
\dot{Z} &= p_1\gamma I - (\alpha+\mu)Z \\
\dot{P} &= p_2\alpha Z + (\mu-a)P - (\mu+b)P
\end{aligned}$$

We have

$$\begin{aligned}
k_{12} &= \frac{\beta_2}{\mu+b} = \text{ mean number of } E\text{'s produced by a } P \\
k_{22} &= \frac{\mu-a}{\mu+b} \\
k_{11} &= \frac{\nu}{\mu+\nu}\times\frac{\beta_1}{\gamma+\mu} \\
k_{21} &= \text{ mean number of } P\text{'s produced by an } E \ \leq 1.
\end{aligned}$$

$$K = \begin{pmatrix} \frac{\nu}{\mu+\nu}\times\frac{\beta_1}{\mu+\gamma} & \frac{\beta_2}{\mu+b} \\ \frac{\nu}{\mu+\nu}\times\frac{\gamma p_1}{\mu+\gamma}\times\frac{\alpha p_2}{\alpha+\mu} & \frac{\mu-a}{\mu+b} \end{pmatrix}$$

Exercise 9. *1. Suppose in the above example that $\beta_1 = 0$. Show that in this case*

$$\begin{aligned}
R_0 &= \frac{1}{2}B + \frac{1}{2}\sqrt{B^2+4A}, \qquad \text{with} \\
B &= \frac{\mu-a}{\mu+b},\ A = \frac{\nu}{\mu+\nu}\frac{\gamma p_1}{\mu+\gamma}\frac{\alpha p_2}{\alpha+\mu}\frac{\beta_2}{\mu+b}.
\end{aligned}$$

2. Show that $A+B \neq R_0$, but $R_0 > 1 \Leftrightarrow A+B > 1$.

Exercise 10. COMPUTATION OF R_0 IN ROSS' MALARIA MODEL *We consider the following ODE which was proposed by Ross as a model of the transmission of malaria.*

$$(*)\begin{cases} \dfrac{dx}{dt} = mab_1 y(1-x) - \gamma x \\ \dfrac{dy}{dt} = b_2 a(1-y)x - \mu y, \end{cases}$$

where x (resp. y) is the proportion of infected individuals among humans (resp. among female anopheles – those mosquitos which are susceptible of transmitting malaria – below we shall write mosquito instead of female anopheles). We assume that the size H of the human population is constant, as well as that V of mosquitos. The parameter $m = V/H$ is the so–called "density of mosquitos" (one says also "vectors", since the mosquitos are the vectors of malaria). a is the mean number of stings done by a mosquito per time unit. b_1 is the probability that a sting of a susceptible human by an infected mosquito transmits the parasite, b_2 the probability that a susceptible mosquito gets infected while stinging an infected human. Mosquitos die at rate μ, infected humans heal at rate γ.

1. *Compute the mean number of susceptible humans which a given infected mosquito (call it z) infects during her life, and the mean number of infections which she generates, assuming that all humans are susceptible.*

2. *Assuming that almost all mosquitos are susceptible, what is the mean number of mosquitos which the humans infected by the mosquito z will infect, before healing ?*

3. *Write the linearized (in the neighborhood of $(x, y) = (0, 0)$) version of equation $(*)$*

4. *Write the linearized equation in the form*

$$\frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} = [T + \Sigma]\begin{pmatrix} x \\ y \end{pmatrix}.$$

5. *Compute the inverse matrix Σ^{-1}.*

6. *Compute R_0. Compare with the result of question 2. Discuss the notion of "generation" in the case of malaria.*

17.5 Computation of R_0 in case of an epidemic on a graph

We consider an epidemic on a *configuration graph*. A graph $\mathcal{G}$ is a pair $(\mathcal{V}, \mathcal{E})$, where $\mathcal{V}$ is the set of vertices, and $\mathcal{E}$ the set of edges. An edge $e \in \mathcal{E}$ is a pair (v, w) of vertices, i.e. $v, w \in \mathcal{V}$. Our graphs will be non oriented, which

means that $(v,w) \in \mathcal{E}$ iff $(w,v) \in \mathcal{E}$. Given a vertex $v \in \mathcal{V}$, we say that another vertex w is a neighbor of v if $(v,w) \in \mathcal{E}$. The individuals in the population constitute the vertices of the graph, and the edges represent the social relations between individuals

An epidemic on a graph is characterized by the fact that an infected individual might infect his neighbors on the graph, and only them.

We consider the case of an epidemic on a *configuration graph*. Such a graph is constructed as follows. To each vertex is associated a degree, which is an integer. The degrees of various individuals are i.i.d., with the common law $(p_k,\ k \geq 1)$. The degree of a vertex is the number of edges which connect this vertex to other vertices of the graph. At each vertex are attached a number of half edges equal to its degree. We construct the graph by connecting each half–edge randomly to another half–edge.

We assume that each infected individual remains infectious during a time which is exponential with parameter ρ. During his infection period, each half–edge attached to the corresponding vertex transmits infection at rate λ. This implies that, conditionally upon the fact that the infected individual is located on a vertex with degree k, and that his infection time is y, the number of susceptibles which this individual infects follows the $B(k-1, 1-e^{-\lambda y})$ distribution. Hence the mean number of such infected, conditionally upon k and y, is $(k-1)(1-e^{-\lambda y})$. The infection time is exponential with parameter ρ. What is the law of the degree k ?

The first infected individual infects an individual with degree k with probability $(\sum_{\ell \geq 1} \ell p_\ell)^{-1} k p_k$. Hence if ξ is an integer–valued r.v. with the law $(p_k,\ k \geq 1)$,

$$\begin{aligned} R_0 &= \frac{\sum_{k\geq 1}(k-1)kp_k}{\sum_{k\geq 1} kp_k}\ \rho \int_0^\infty (1-e^{-\lambda y})e^{-\rho y}dy \\ &= \frac{\mathbb{E}[\xi(\xi-1)]}{\mathbb{E}[\xi]}\left(1-\frac{\rho}{\lambda+\rho}\right) \\ &= \frac{g''(1)}{g'(1)}\frac{\lambda}{\lambda+\rho}, \end{aligned}$$

if g denotes the generating function of the r.v. ξ.

Let us now compute the probability of extinction of the branching process which approximates the start of the epidemic. This is a fixed point of the generating function of the number of individuals which a typical infectious individual infects during the start of the epidemic, in other words the solution

of the equation

$$z = \frac{\rho}{g'(1)} \sum_{k\geq 1} \int_0^\infty \left(z + e^{-\lambda y}(1-z)\right)^{k-1} k\, p_k\, e^{-\rho y} dy$$
$$= \frac{\rho}{g'(1)} \int_0^\infty g'\left(z + e^{-\lambda y}(1-z)\right) e^{-\rho y} dy.$$

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