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Time to extinction in branching processes and its role in population experiments and epidemiological modelling

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С голямо удоволствие искам да изразя чувството си на благодарност към всички, които са ме насърчавали през изминалите години.

Първите ми думи на благодарност са за моя учител проф. дмн Николай Янев за всички безценни съвети, разговори, дискусии, градивна критика и подкрепа през целия ми професионален път на развитие.

Безкрайно съм благодарна на всички колеги от секция „Вероятности и статистика“ на Института по математика и информатика на БАН, където премина по–голямата част от научната ми кариера, за креативната атмосфера на висок професионализъм, за което трябва да призная оставам задължена.

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ПРЕДГОВОР

Хабилитационният труд се състои от две части, обединени от теоретичните изследвания на свойствата на разпределението на времето за израждане на класическия разклоняващ се процес (РП) на Биенеме–Галтон–Уотсън, както и на процесите в непрекъснато време – на Белман–Харис и Севастянов. Първата част е мотивирана и посветена на приложение на теорията на РП при моделиране на популационни експерименти и се състои от четири глави, следващи съответно съдържанието на публикации с номера [15], [16], [11], [12] от списъка на публикациите, представени за участие в конкурса. Втората част е свързана с изследване и моделиране на процеси в епидемиологията и също се състои от четири глави, чието съдържание съответства на публикациите с номера [4], [5] и [7], [8], [9], [10],[1] от списъка на публикациите, представени за участие в конкурса.

Резултатите, обобщени в този хабилитационен труд са докладвани на Националния семинар по Стохастиика с р-л професор дмн Николай М. Янев, както и на редица международни научни конференции и семинари като традиционната Международна конференция по теория на вероятностите и математическа статистика, провеждана у нас през 2008, 2010, 2012, както и на специализираните работни семинари в Бадахос, Испания – 2009, 2012 и други (вж. Авторската справка).

Накрая бих искала да поясня избора на английски език за написването на този труд. Макар и да съзнавам напълно, че за нуждите на един престижен български университет, какъвто е Софийският университет, написването на български език би бил един несъмнен плюс за този труд, смятам че по отношение на възможностите за популяризирането и разпространението му – английският език дава несъмнено повече такива и би стимулирал младите учени към усъвършенстване на този език. Английският език все повече се утвърждава като международен език в областта на математиката. Това в крайна сметка би направило младите български учени по–равностойни конкуренти спрямо останалите учени в света.

Contents

General Introduction

Survey of the state-of-the-art in the field and motivation

Branching processes theory originates from the study of human populations and their destiny. However the main object is not to study neither biological populations such as animals, bacteria or cells, nor physical populations such as splitting particles in a neutron transport. Contemporary branching processes theory can be used to answer questions about any idealized population where in general the members generate new sets of members.

The probabilistic theory of branching models started in the second half of 19^{th} century, with the objective to give answer to the problem of extinction of family lines of the European aristocracy, according to forerunners Bienaymé (1845) and Galton and Watson (1874). Their outstanding study actually formed part of the development of the Theory of Probability and Mathematical Statistics according to numerous monographs published on this theory and its applications. Among others we would like to point out those of Harris (1989), Sevast'yanov (1971), Athreya and Ney (1972), Jagers (1975), Asmussen and Hering (1983), Harris (1989), Guttorp (1991), Kimmel and Axelrod (2002), Haccou, Jagers and Vatutin (2005), Ahsanullah and Yanev (2008) or González et al. (2010), the book (in Bulgarian) for students with classical (and some modern) models of branching processes published recently by Slavtchova-Bojkova and N. Yanev (2007) and the extensive review paper by Mitov and Yanev (2009) dedicated to the results of the Bulgarian branching school founded by Professor Nickolay Yanev.

I. J. Bienaymé introduced in 1845 the first model of branching processes, and years later, in 1874, independently of him, Galton and Watson published their first work on such kind of processes, although the terminology "Branching Process" was introduced by A.N. Kolmogorov and Dmitriev (1947). The branching model, commonly called the Bienaymé–Galton–Watson process, has been widely studied and applied to describe the behaviour of systems whose components (cells, particles, individuals in general) reproduce, transform, and die, in fields as diverse as Biology, Epidemiology, Genetics, Medicine, Nuclear Physics, Demography, Financial Mathematics, Algorithms, etc. (see, for example, Yanev and Yakovlev (1989, 2006, 2007), Pakes (2003), Devroye (1998), G. Alsmeyer,

C. Gutiérrez, and R. Martínez (2011), Farrington and Grant (1999) or Epps (2009)).

The main purpose of this habilitation thesis is to present some new ideas, results and applications of the branching processes theory motivated by modeling purposes of population experiments and epidemiology. The presented results are based on the following publications: Bruss and Slavtchova–Bojkova (1999), Slavtchova–Bojkova (2000, 2007), Martinez and Slavtchova–Bojkova (2005), Gonzáles, Martínez and Slavtchova–Bojkova (2009, 2010a, 2010b, 2010c), Ball, Gonzáles, Martínez and Slavtchova–Bojkova (2014), Mitova–Bobcheva, Slavtchova–Bojkova, Kojouharova, Kurchatova (2011) and Angelov, Slavtchova–Bojkova (2012). The work is organized as follows: the first part is concerned with the main idea of application of the branching stochastic models with immigration for modeling population, re-population and wastewater experiments. The problem originates from estimating the waiting time to the successful experiment in a series of population and re-population experiments with different species, which have disappeared for some reason. It is worth mention here that by "waiting time to a successful experiment" we understand the time before the beginning of that newly introduced population which survives in this environment. The research is developed exploring Bienaymé–Galton–Watson (Chapter 1) and Bellman-Harris branching processes (Chapter 2) and finally is generalized for Sevast'ynov's age-dependent processes (Chapter 3). Of course the last model of Sevast'ynov's processes is generalizing the previous ones, but the methodology in the three cases is different and that is why we are following the natural way of the developed research and would like to notice here that possible extensions are those for multitype processes and more general branching models, as well. To estimate the probability density functions of the life–cycle and the waiting time to the successful experiment, a programme code, which allows input of a mortality density and a special form of reproduction law was developed. In Chapter 4 a comparison between simulation and numerical methods for estimating the distribution of the time to extinction of Bellman-Harris BP and the total waiting time, are presented.

The study of stochastic monotonicity and continuity properties of the extinction time of Bellman-Harris branching processes depending on their reproduction laws is presented in the second part. Moreover, their

applications are shown in an epidemiological context, obtaining an optimal criterium to establish the proportion of susceptible individuals in a given population, which has to be vaccinated in order to eliminate an infectious disease. First the spread of infection is modeled by a Bellman-Harris branching process and a simulation-based method to determine the optimal vaccination policies is provided (Chapter 6).

Next we are dealing with a Sevast'yanov's age-dependent branching process, describing outbreaks of an infectious disease with incubation period. The main goal is again to define the optimal proportion of susceptible individuals that has to be vaccinated in order to eliminate the disease, but for a more adequate model. To this end we study the stochastic monotonicity and continuity properties of the time to extinction of an infection, depending on the proportion of the immune individuals into the population. From these results, we suggest a vaccination policy based on the mean of the infection survival time. Finally, we provide a simulation-based method to determine the optimal vaccination level and as an illustration we analyze the data from outbreaks of avian influenza spreading in Vietnam at the end of 2006 (see Chapter 7).

The basic epidemiological problems concerned with the monitoring and forecasting of the epidemics propagation in a given population and with the estimation of the so called basic reproduction number, i. e. the mean number of infected individuals by one infectious are presented in Chapter 7. Bayesian approach for predicting outbreaks, implemented in the statistical software R (see Höhle (2005)) applied on surveillance data of mumps collected in Bulgaria for the period 2000–2008 is presented in Section 8.2. A detailed description of the method could be seen in Höhle (2005). The official data is kindly provided by the National Center of Infectious and Parasitic diseases at the Ministry of Health, Bulgaria. It has been collected on a weekly base and presents the epidemic picture by regions in the country for 2000–2008 year.

Usually we do not have complete information about the spread of the disease – do not know the number of infected by each infectious individual. The combination of branching models and Bayesian methods allows us to estimate the basic reproduction number using real data on reported cases, collected by institutions for control of public health. In Chapter 9 the Bayesian estimation approach is considered for the same data set of mumps propagation in Bulgaria. It is assumed that the offspring dis-

tribution of the branching process belongs to the family of generalized power series distributions, which is quite a broad class of discrete distributions, including binomial, Poisson and geometric ones. It turns out that for this wide class of distributions, we are able to obtain exactly the distribution of the total progeny of the Biemeymé–Galton–Watson branching processes, which we need for estimation of the offspring mean. We find both point and interval estimates of the offspring mean, applying a Bayesian approach by simulating the posterior distribution using Metropolis–Hastings algorithm. The algorithm is implemented in the language and environment for statistical computing `R`, version 2.11.1 (see `R` development Core Team).

Chapter 10 is concerned with Crump—Mode—Jagers branching processes, describing spread of an epidemic depending on the vaccinated proportion of the population. Births in the branching process are aborted independently with a time–dependent probability given by the fraction of the population vaccinated. Stochastic monotonicity and continuity results for a wide class of functions (e.g., extinction time and total number of births over all time) defined on such a branching process are proved using coupling arguments, leading to optimal vaccination schemes to control corresponding functions (e.g., duration and final size) of epidemic outbreaks.

Finally, I would like to make one technical remark about the references. To ease the reading, each part is finishing with separate list of references consisting of the corresponding bibliographies included in the concrete part. These are Chapter 5 and Chapter 11, respectively.

Part I

BP in population experiments

Chapter 1

Time to extinction in Galton–Watson BP

1.1 Introduction

How long does it take to populate an environment (forest, river,lake, ...) with a new species, or to re-populate an environment with previously existing species which have disappeared? There is always a positive probability of extinction so that, even with a supercritical reproduction, there may be several failures before the re-population experiment becomes successful. Secondly, what conclusions can one draw from an early disappearance of the newly introduced population? For example, does it imply that the average reproduction mean (fecundity) is very low in the new environment? Similarly, what may the total (estimated) progeny of populations which failed to develop in the long run tell us about the chances of a success of the next trial. These are questions which may interest biologists and environmentalists. In general, they are hard to answer, however.

One of the major reasons for this difficulty is that the circumstances under which re-population experiments are done, are not always the same. First of all, the environment may change, as for instance dry summers may have reduced water levels in rivers and lakes, or other populations interacting with the goal population may have decreased or increased. Secondly, the goal population itself may change. So, for instance, fishery–bred pyke may first have to learn to catch prey, and birds

may have to learn to catch flies. Sometimes re-population experiments may be abandoned too early. There was an interesting article in The Wall Street Journal Europe, (summer 1996) about re–population experiments with trout. First trials were reportedly unsuccessful until fisheries started training the trout to feed also on worms and insects before they were released. The problem may have been that the trout recognized only the pellet food they were used to in the fisheries as food and starved in open waters, as the article indicated.

We could not find a reference on the problem of inference from expected waiting times and expected progeny on fertility rates, but we found several papers which are related. The problem of the total progeny was treated by several authors (see e.g. Jagers (1975), p. 39, Harris (1989), p. 32) but the interest focussed on questions of rates of growth, and this conditioned on survival.We should also mention Karlin and Tavaré (1982) who studied the asymptotic behavior of the probabilities of hitting the absorbing states,the times needed to hit these states, and the conditional distributions of the number of particles (for models allowing catastrophes). Bhattacharjee(1987) and Shaked and Shantikumar (1987) investigated the distribution of the extinction moment for subcritical and critical BGW processes. The goal of the article of Bruss and Slavtchova–Bojkova (1999) is to provide answers for the simple case, where all newly introduced populations are supposed to behave like i.i.d. Bienaymé–Galton–Watson (BGW) branching processes. (For the review of the results in branching processes theory see Vatutin and Zubkov (1993)). This setting implies ideal independence assumptions, so that we can get explicit answers through generating functions. This is very "generous" simplification of real world problems of this kind,but in this way one obtains explicit answers. Particular attention is paid to the fallacy of believing that if one has, for each trial, the choice between several variants of a certain population it would be a good strategy to discard those which seemingly disappeared most quickly.

In what follows in this chapter we first introduce the model (Section 1.2). It is a version of BGW process with immigration in the state zero. We distinguish between deterministic immigration (of one individual, say) and random immigration in order to differentiate between complete (initial) control of the experiment and incomplete control.

The next Section 1.3 contains the main results and proofs. In Theo-

rem A.1 we compute the life-time distribution of a cycle, its conditional distribution (given extinction) and the total length of unsuccessful life-cycles. Theorem A.2 gives the corresponding answers for random immigration. In the remainder of this section we study the total progeny of the process. The probability generating function (p.g.f.) of the conditional total progeny given the finiteness of the first life cycle is obtained in Theorem A.3. In Theorem A.4 we compute and give an approximation of the expected total progeny for deterministic immigration.Then we compute also the variance of the progeny. In the subsequent section these results are given for the random immigration.

Finally, Section 1.5 shows an example of "extinction bias" which may mislead decision makers in population experiments.

1.2 Model

We shall consider the following population process (Z_n), starting at time zero with random number ν of particles (individuals), i.e. $Z_0 = \nu$. Each particle lives unit time and produces at the end of its life a random number ξ of particles independently of the existing ones. The probability generating function (p.g.f.) of offspring is denoted by

$$f(s) = \sum_{k=0}^{\infty} p_k s^k, \quad |s| \leq 1, \quad p_k = P(\xi = k).$$

Z_n counts the number of particles existing (alive) at time n. Let ξ_i^k be independent identically distributed (i.i.d.) copies of ξ denoting the number of children of the ith particle in the kth generation. We define $\tilde{Z}_n = \xi_1^n + \cdots + \xi_{Z_{n-1}}^n$, i.e. $\tilde{Z}_n$ is the classical BGW process. When the population becomes extinct we suppose to have a random number ν of immigrants from an outside source, so that the immigration time is considered to be the starting time of a new process. (The first process starts from immigration of ν particles (individuals) at time 0.) We denote the p.g.f. of ν by

$$h(s) = \sum_{k=1}^{\infty} u_k s^k, \quad |s| \leq 1, \quad u_k = P(\nu = k).$$

Such processes were first studied (in the critical case) by Foster (1971) and Pakes (1971, 1974).

On the other hand, the process we consider is best described as a φ–branching process (Sevastyanov and Zubkov (1974), Yanev (1975)). Yanev's model allows for φ to be random, so that our process is a φ-process defined by

$$\varphi(n) = \begin{cases} \nu, & n = 0, \\ n, & n \geq 1, \end{cases}$$

where ν has the p.g.f. $h(s)$. (There are further generalizations of φ-process, but our work does not extend to these. For example, the process $(Z_t^A)_{t\geq 0}$ studied by Bruss (1978, Theorem 3) can be interpreted as such a φ–branching process where the φ's can depend on each other and on the whole process before extinction, but in general only sufficient conditions for extinction are possible in this case.)

For a branching process with immigration (Z_n) we shall call life periods (cycles) the intervals $(n_0, n_0 + \tau)$ of maximum lenght on which $\inf_{n_0 \leq n \leq n_0+\tau} Z_n > 0$. Thus (Z_n) may have several life-periods, the last one always being infinite, provided the process is supercritical. If the process is subcritical it will have a.s. infinitely many life periods, of course.

We shall be interested in the last instant M of immigration, i.e. in the "birth time" of that process which will finally survive forever. Specifically we shall derive the distribution of the first life period T, the conditional distribution of T and the conditional expectation of T, both conditioned on the event $\{T < \infty\}$. Finally we derive the expectation of the waiting time M to the beginning of the first process which will survive forever, and show how higher moments can be derived.

It is well–known from the theory of branching processes (see e.g. Athreya and Ney, 1972) that the probability of extinction q of BGW process is the smallest non–negative root of the equation $f(s) = s$, and $q = 1 \iff m = f'(1) \leq 1$. The parameter m is called the reproduction mean, and the supercritical, critical and subcritical case corresponds to $m > 1$, $m = 1$ and $m < 1$, respectively.

So, if $Z_0 = 1$ we have $P\{M = 0\} = P\{\text{first process does not die out}\} = 1 - q$.

1.3 Main results

Waiting times for deterministic immigration of one particle

We first consider the special case $h(s) = s$, where $u_1 = 1$ (deterministic immigration of one particle). Let $T_1, T_2, \ldots$ be the life periods of those consecutive processes dying out before the surviving process is initiated. They are i.i.d. copies of the random variable (r.v.) T, say.

Let us denote $v_k = P\{T \leq k\}$.

Theorem A.1 *The life–period T and the last instant M of immigration of the process (Z_n) have the following properties:*

(i) $P(T \leq k|T < \infty) = \dfrac{1}{q} f_{k-1}(p_0)$ *for* $k = 1, 2, \ldots$, *where q is the probability of extinction of the classical Bienaymé–Galton–Watson process;*

(ii) $E(T|T < \infty) = 1 + \dfrac{1}{q} \displaystyle\sum_{k=0}^{\infty} [q - f_k(p_0)]$;

(iii) $E(M) = \dfrac{q}{(1-q)} \left\{ 1 + \dfrac{1}{q} \displaystyle\sum_{k=0}^{\infty} [q - f_k(p_0)] \right\}$.

Proof. Recall that $v_k = f_k(0)$ for $k = 1, 2, \ldots$, where $f_0(s) = s$, $f_{k+1}(s) = f(f_k(s))$, and $v_0 = 0$.

(i) follows immediately using that

$$\begin{aligned} P(T \leq k|T < \infty) &= \frac{P(T \leq k; T < \infty)}{P(T < \infty)} \\ &= \frac{P(T \leq k)}{q} = \frac{v_k}{q} = \frac{f_{k-1}(p_0)}{q}. \end{aligned} \tag{A.1}$$

To prove (ii) we will use (A.1) (i) and $T \geq 1$ (by definition). Since the conditional expectation $E(T|T < \infty)$ is finite by definition we can write it in the form

$$E(T|T < \infty) = \sum_{k=1}^{\infty} P(T \geq k|T < \infty) = \sum_{k=0}^{\infty} P(T > k|T < \infty),$$

since all terms are non–negative, so that

$$\begin{aligned} E(T|T<\infty) &= \sum_{k=0}^{\infty}(1-P(T\le k|T<\infty)) \\ &= 1+\frac{1}{q}\sum_{k=0}^{\infty}[q-f_k(p_0)]. \end{aligned} \tag{A.2}$$

Finally, to see (iii) note that the expectation of the total waiting time M can be written as

$$\begin{aligned} E(M) &= qE(T_1|T_1<\infty)+q^2E(T_2|T_2<\infty)+\cdots \\ &= E(T|T<\infty)q\sum_{k=0}^{\infty}q^k=\frac{q}{(1-q)}E(T|T<\infty), \end{aligned} \tag{A.3}$$

where T_1, T_2, ... are i.i.d. copies of T. Here the first equality holds since q^k is the probability that at least k cycles die out. Thus (iii) is proved. □

We also mention here that for subcritical and critical BGW processes the distribution of the extinction moment τ is such that $P(\tau=n|\tau\ge n)=r(n)$ decreases monotonically. This has been proved by Bhattacharjee (1987) and Shaked and Shantikumar (1987).

Waiting times for random immigration

The next theorem provides the generalization of the previous one when $Z_0=\nu_1$, and all consecutive cycles are supposed to start with a random number of individuals, where the distribution of ν_i is defined by p.g.f. $h(s)$. In this case T_1^*, T_2^*, ... are the life cycles of those processes dying out before the surviving process is initiated. They are i.i.d. copies of the r.v. T^*, say, since the immigration variables ν_1, ν_2, ... are i.i.d. and since $f(s)$ is the same for all cycles.

Theorem A.2 *Let M^* be the last instant of immigration of the process (Z_n), starting with $Z_0=\nu$, and let T^* be as above. Then*

(i) $E(T^*|T^*<\infty)=1+\sum_{k=0}^{\infty}\left(1-\frac{h(f_{k-1}(p_0))}{h(q)}\right)$;

(ii) $E(M^*) = \dfrac{h(q)}{(1-h(q))}\left\{1+\sum_{k=0}^{\infty}\left(1-\dfrac{h(f_{k-1}(p_0))}{h(q)}\right)\right\}$.

Proof. Using again the finiteness of the conditional expectation of T^*, and $T^* \geq 1$, we obtain

$$\begin{aligned} E(T^*|T^*<\infty) &= \sum_{k=1}^{\infty} P(T^* \geq k|T^*<\infty) = \sum_{k=0}^{\infty} P(T^* > k|T^*<\infty) \\ &= \sum_{k=0}^{\infty}(1-P(T^* \leq k|T^*<\infty)). \end{aligned} \tag{A.4}$$

Conditioning on the number of immigrants ν_1 we use that $h(q) = P(T^*<\infty)$, where q is, as before, the smallest solution of $f(s)=s$ on $[0,1]$. Therefore

$$P(T^* \leq k|T^*<\infty) = \frac{P(T^* \leq k)}{h(q)}.$$

Also,

$$\begin{aligned} P(T^* \leq k) &= \sum_{j=1}^{\infty} P(T^* \leq k|\nu=j)u_j \\ &= \sum_{j=1}^{\infty}(P(T \leq k))^j u_j = h(v_k). \end{aligned} \tag{A.5}$$

From (A.4) and (A.5) we obtain then

$$\begin{aligned} E(T^*|T^*<\infty) &= \sum_{k=0}^{\infty}(1-\frac{h(v_k)}{h(q)}) \\ &= 1+\sum_{k=0}^{\infty}(1-\frac{h(f_{k-1}(p_0))}{h(q)}). \end{aligned} \tag{A.6}$$

Similarly to the proof of Theorem A.1 (iii), statement (ii) follows by the same arguments, but now conditioning on the event $T^*<\infty$. In this

case $P(Z_n \to 0 | Z_0 = \nu_1) = h(q)$. Using (A.4) implies then statement (ii). □

We will need the expectation of the number of cycles N to wait until the last cycle. We have

$$\begin{aligned} E(N) &= 1(1-h(q)) + 2h(q)(1-h(q)) + 3h(q)^2(1-h(q)) + \cdots \\ &= (1-h(q)) \left. \frac{d(\sum_{k=1}^{\infty} x^k)}{dx} \right|_{x=h(q)} = \frac{1}{(1-h(q))}. \end{aligned} \tag{A.7}$$

1.4 The total progeny of a cycle

Of particular interest will be the conditional total progeny of the population (Z_n) conditioned on the event $\{T \leq n\}$. Again we will first start with the case $h(s) = s$.

Deterministic immigration of one particle

We denote the conditional p.g.f. by $g_n(s) = E(s^{Z_0+Z_1+\ldots+Z_n} | T \leq n)$. The index n stands thus for the maximum life cycle length and not for the n-th iteration.

Theorem A.3 *For the conditional p.g.f. $g_n(s)$ we have the following recurrence relation*

$$g_n(s) = \frac{s}{v_n} f(v_{n-1} g_{n-1}(s)). \tag{A.8}$$

Remark A.1 *This is related with the recurrence relations for the p.g.f. of the unconditional total progeny (see e.g. Jagers (1975), p. 39), but conditioning produces quite a different form.*

Proof. Conditioning on the number of particles at the first generation we obtain

$$\begin{aligned} g_n(s) &= E(E(s^{\sum_{k=0}^{n} Z_k} | T \leq n, Z_1)) \\ &= s \sum_{j=0}^{\infty} E(s^{\sum_{k=0}^{n} Z_k} | T \leq n, Z_1 = j) P(Z_1 = j | T \leq n). \end{aligned} \tag{A.9}$$

By Bayes' formula we obtain

$$P(Z_1 = j|T \le n) = \frac{P(T \le n|Z_1 = j)P(Z_1 = j)}{P(T \le n)} = \frac{v_{n-1}^j p_j}{v_n}. \tag{A.10}$$

Further, given that the first ancestor has j descendants, the event $\{T \le n\}$ is realized if and only if all j i.i.d. copies of the BGW process die out before time n, i.e. have a life cycle of length less or equal to $n-1$.

Therefore it follows from (A.10) that

$$g_n(s) = s\sum_{j=0}^{\infty}(g_{n-1}(s))^j \frac{(v_{n-1})^j p_j}{v_n} = \frac{s}{v_n} f(v_{n-1}g_{n-1}(s)),$$

which completes the proof. □

The next step in our analysis will be the computation and approximation of the expected total progeny conditioned on the finiteness of the first life cycle.

Theorem A.4 *The expected total progeny Y conditioned on the event $\{T \le n\}$ is given recursively by $y_1 = E(Y|T \le 1) = 1$,*

$$y_n = E(Y|T \le n) = 1 + f'(v_n)y_{n-1}(1)\frac{v_{n-1}}{v_n}, \quad n = 2, 3, \ldots. \tag{A.11}$$

If $m \ne 1$ then

$$\lim_{n\to\infty} y_n = \frac{1}{1 - f'(q)}. \tag{A.12}$$

Proof. Note that $y_n = g_n'(1)$. First we will prove two auxiliary lemmas.

Lemma A.1 *Let the sequence $\{X_n\}$ be defined by*

$$X_1 = 1; \quad X_{n+1} = 1 + a_n X_n W_n, \quad n = 1, 2, \ldots, \tag{A.13}$$

where $a_n \uparrow a$, $0 \le a < 1$, and $W_n \uparrow 1$ as $n \to \infty$. Then

$$\lim_{n\to\infty} X_n = \frac{1}{1 - a}. \tag{A.14}$$

Proof. We prove by induction that $\{X_n\}$ is increasing. Indeed $X_2 = 1+a_1X_1W_1 \geq 1 = X_1$. Suppose now that $X_n \geq X_{n-1}$. Then by induction hypothesis

$$X_{n+1} = 1 + a_nX_nW_n \geq 1 + a_nX_{n-1}W_n \geq 1 + a_{n-1}X_{n-1}W_{n-1} = X_n,$$

since $W_n \geq W_{n-1}$ and $a_n > a_{n-1}$. Therefore $\{X_n\}$ is increasing.

To see that $\{X_n\}$ is bounded by $\dfrac{1}{1-a}$ note that $X_{n+1} \leq 1 + a_nX_n \leq 1 + aX_n$, since $W_n \leq 1$ and $\{a_n\}$ is increasing to a.

Now, $X_1 = 1 \leq \dfrac{1}{1-a}$, $X_2 = 1 + a_1X_1 = 1 + a_1 \leq 1 + a \leq \dfrac{1}{1-a}$. Suppose that $X_n \leq \dfrac{1}{1-a}$. Then by induction hypothesis

$$X_{n+1} \leq 1 + a_nX_n \leq 1 + \frac{a_n}{1-a} \leq \frac{1}{1-a}.$$

It follows that $X_n \leq \dfrac{1}{1-a}$ for all n, so that $\{X_n\}$ converges. Since, its limit, l say, is unique it follows from (A.13) and $\{a_n\} \uparrow a$, $\{W_n\} \uparrow 1$ that l must satisfy $l = 1 + al$. This completes the proof. □

We now prove

Lemma A.2 $W_n = \dfrac{v_{n-1}}{v_n} \uparrow 1$.

Proof. It is clear that $v_n \uparrow q$, so that $W_n \longrightarrow 1$ as $n \to \infty$.

We still have to show that (W_n) is increasing, i. e. $v_n^2 \geq v_{n-1}v_{n+1}$.

Since $v_n = f_n(0)$, this means

$$f_n^2(0) \geq f_{n-1}(0)f_{n+1}(0). \tag{A.15}$$

We first prove, that

$$\frac{f_{n+1}(0) - f_n(0)}{f_n(0) - f_{n-1}(0)} \leq 1, \quad n = 1, 2, \ldots$$

Indeed, recall that q is the smallest solution of the equation $f(s) = s$ on $[0, 1]$.

Suppose first that $q < 1$.

Since $f(1) = 1$ and $f(q) = q$ we have $(f(1) - f(q))/(1 - q) = 1$. The mean value theorem of differential calculus implies that $f'(x) = 1$ for some $x \in [q, 1]$. Since $f'(s)$ is increasing on $[0, 1]$ it follows that $f'(s) \leq 1$ for $s \in [0, q]$. Again from the mean value theorem we have then

$$\forall x, y \in [0, q], \quad x \neq y : \frac{f(y) - f(x)}{y - x} \leq 1.$$

Consequently, the last inequality must hold for $x = f_n(0)$ and $y = f(x)$. This confirms the above statement for $q < 1$.

Now, if $q = 1$, then we know that $f'(1) = m \leq 1$ (critical or subcritical case). Therefore $f'(1) \leq 1$ for all $s \in [0, 1]$ and the same reasoning holds.

Thus $f_{n+1}(0) - f_n(0) \leq f_n(0) - f_{n-1}(0)$ holds for all $n = 1, 2, \ldots$.

Denoting $f_n(0) - f_{n-1}(0) = \Delta_n$ we have $\Delta_n \geq \Delta_{n+1}$ and

$$f_{n+1}(0) = f_n(0) + \Delta_{n+1}, \quad f_{n-1}(0) = f_n(0) - \Delta_n.$$

Then (A.15) holds if

$$f_n(0)^2 \geq (f_n(0) - \Delta_n)(f_n(0) + \Delta_{n+1}),$$

which is straightforward. Thus $W_n \uparrow 1$. □

Now (A.11) follows by differentiating (A.9) at $s = 1$, i. e.

$$g_n'(1) = \frac{1}{v_n} f(v_{n-1} g_{n-1}(1)) + \frac{1}{v_n} f'(v_{n-1} g_{n-1}(1)) g_{n-1}'(1) v_{n-1},$$

which becomes after simplification

$$g_n'(1) = 1 + f'(v_{n-1}) g_{n-1}'(1) \frac{v_{n-1}}{v_n}.$$

Since $y_n = g_n'(1)$ we have (A.11).

To see (A.12) recall Lemma A.2 and put $a_n = f'(v_n)$, $X_n = g_n'(1)$ and $a = f'(q)$ in Lemma A.1. Also, since v_n is increasing and $f'(s)$ is an increasing function of s we have that $f'(v_n) = a_n$ is increasing in n and $\lim_{n \to \infty} f'(v_n) = f'(q)$ since f' is continuous and $v_n \uparrow q$. This completes the proof. □

The variance of the conditional total progeny

We now compute the variance of the total progeny. The second derivative of (A.8) at $s = 1$ yields

$$\begin{aligned} g_n''(1) &= g_{n-1}''(1) f'(v_{n-1}) \frac{v_{n-1}}{v_n} \\ &+ v_{n-1} g_{n-1}'(1) \{2f'(v_{n-1}) + \frac{v_{n-1}}{v_n} f''(v_{n-1}) g_{n-1}'(1)\}. \end{aligned} \tag{A.16}$$

By similar monotonicity arguments as before it is easy to check that

$$\lim_{n\to\infty} g_{n-1}''(1) = \frac{q}{(1-f'(q))^2}(2f'(q) + \frac{f''(q)}{1-f'(q)}). \tag{A.17}$$

Therefore

$$\begin{aligned} \mathrm{Var}(Y|T \le n) &= g_{n-1}''(1) + g_n'(1) - (g_n'(1))^2 = \frac{v_{n-1}}{v_n} \Big\{ g_{n-1}''(1) f'(v_{n-1}) \\ &+ 2v_n g_{n-1}'(1) f'(v_{n-1}) + v_{n-1} (g_{n-1}'(1))^2 f''(v_{n-1}) \\ &- g_{n-1}'(1) f'(v_{n-1}) + (g_{n-1}'(1))^2 (f'(v_{n-1})^2) \frac{v_{n-1}}{v_n} \Big\}. \end{aligned} \tag{A.18}$$

It is straightforward from (A.18) that all terms are monotonically increasing in n and bounded above, so that $\lim_{n\to\infty} \mathrm{Var}(Y|T \le n)$ must exist. Since it is unique we have

$$\begin{aligned} \lim_{n\to\infty} \mathrm{Var}(Y|T \le n) = \frac{1}{(1-f'(q))^3} \{ &2qf'(q)(1-f'(q))(2f'(q)-1) \\ &+ qf''(q) - f'(q)[1-f'(q)]\}. \end{aligned}$$

Random immigration

Now for general $h(s) = \sum_{k=1}^{\infty} u_k s^k$, let Y^* be the total progeny for a cycle initiated by ν_1 immigrants ($Z_0 = \nu_1$).

Then denoting the length of the first life cycle by T^* we have

$$\begin{aligned} E(Y^*|T^* \le n) &= E(E(Y_n^1 + \cdots + Y_n^{\nu_1}|T^* \le n; \nu_1)) \\ &= \sum_{k=1}^{\infty} E(Y^*|T^* \le n, \nu_1 = k) P(\nu_1 = k|T^* \le n) \\ &= \sum_{k=1}^{\infty} E\left(\sum_{j=1}^{k} Y_n^j | T_1 \le n, \ldots, T_k \le n\right) P(\nu_1 = k|T^* \le n), \end{aligned} \tag{A.19}$$

where Y_n^j denotes the total progeny of the initial j-th particle up to time n. Here T_1, T_2, ..., T_k are i.i.d. copies of the life cycle T of a BGW process starting with one particle at time zero. It is important to note that Y_n^j is independent of all T_l with $1 \le j \ne l \le k$. Therefore

$$E(Y_n^1 + \cdots + Y_n^k | T_1 \le n, \ldots, T_{\nu_1} \le n; \nu_1 = k) = kE(Y_n^1 | T_1 \le n). \tag{A.20}$$

By Bayes' formula we obtain

$$P(\nu_1 = k|T^* \le n) = \frac{P(T^* \le n|\nu_1 = k)P(\nu_1 = k)}{P(T^* \le n)} = \frac{(v_n)^k u_k}{h(v_n)}. \tag{A.21}$$

Then using (A.20) and (A.21) we have

$$\begin{aligned} E(Y^*|T^* \le n) &= \sum_{k=1}^{\infty} k g_n'(1) \frac{(v_n)^k u_k}{h(v_n)} \\ &= \frac{g_n'(1) v_n}{h(v_n)} \left. \frac{d(\sum_{k=1}^{\infty} x^k u_k)}{dx} \right|_{x=v_n} \\ &= \frac{g_n'(1) v_n h'(v_n)}{h(v_n)}. \end{aligned}$$

Therefore, using $(v_n) \uparrow q$, $g_n'(1) \uparrow (1 - f'(q))^{-1}$ and the continuity of h and h',

$$\lim_{n\to\infty} E(Y^*|T^* \leq n) = \frac{qh'(q)}{(1 - f'(q))h(q)}.$$

Similarly we could to proceed to compute $\mathrm{Var}(Y^*|T^* \leq n)$ and higher moments.

1.5 Application

Inference from total progeny or early extinction

In population experiments it is usually easier to see that a new introduction has been successful than to know whether, and if so, when extinction has occurred. In many cases statistical data are only provided by interest groups, such as by members of angling associations, hunters, hobby photographers, etc. If, for example, fishermen don't catch the new species or simply do not see them any more they imply after a couple of years that extinction has occurred.

However, one must be careful to draw hasty conclusions after failed experiments. To be specific, suppose three types of trout (rainbow trout, brown trout and sea trout, say) were introduced in similar waters and that each of these seems to have disappeared after some time, but that the brown trout were reported in highest numbers or over the largest number of years. Is it then most promising to bet on brown trout for a new experiment? The frequency of reports must be thought of as being positively correlated with the total progeny and the latter with the reproduction mean of that species. However a statistical inference of this kind would be false, as we see in the following example.

Let $f_p(s) = p + 0.4s + (0.6 - p)s^2$ be the p.g.f. of the reproduction law of a BGW process parameterized by $p = P(Z_1 = 0|Z_0 = 1)$. The case $p = 0.3$ corresponds to the critical case $m = 1$, ($0 < p < 0.3$ supercritical, $0.3 < p \leq 0.6$ subcritical). Clearly, $q = q(p)$ is the smallest solution of $q = p + 0.4q + (0.6 - p)s^2$ in $[0, 1]$, and $m = m(p) = 1.6 - 2p$. As a function of p these are defined on $[0, 0.6]$.

We have chosen the class $\{f_p\}$ such that, as a function of p, the mean has a constant slope and that this expected value is symmetric

with respect to $p = 0.3$. One can also easily verify that the Breny–Seneta condition (see Breny (1962) and Seneta (1967)) is satisfied and that indeed $E(Y|T < \infty) \longrightarrow \infty$ as $p \to 0.3$.

Extinction entails a very strong bias. If a decision maker decides to try again with that species (brown trout) which seems to have been best adapted so far he may discard those species with a much higher fertility rate m. The point is that he has to take that decision after extinction. It is simply very improbable that a process with a "comfortable" mean $m > 1$ would die out late. The higher the mean of a population the more probable it becomes that this population would, after extinction, be excluded from further experiments. One may call this "extinction bias" to parallel the notion of "survival bias" known in many forms in statistical inference, though the probabilistic argument is not directly comparable.

We conclude that the problem is more serious than it looks first. Independent control studies to assess prior probability of extinction are likely to be environment-bias. On the other hand, it is not always possible to reduce the prior probability of extinction by releasing a large number of animals.

Chapter 2

Time to extinction in continuous–time BP

2.1 Introduction

The goal of this chapter is to explain some puzzling phenomena and answer questions of interest for biotechnologists and environmentalists. First, how long does take the final establishment of bacterial cultures in wastewater laboratory experiments? As there is always a positive probability of extinction, it is possible to have several unsuccessful trials before the bacterial cultures start to grow irreversibly. Secondly, what conclusions can one draw from an early extinction of a bacterial culture in different types of wastewater? Does it imply that the offspring mean in these environments is low? Similarly, our study might help decision makers to take a choice based on comparative laboratory results in one and the same environment cultivated with different bacterial strains. In general, such questions related to real world problems of industrial wastewater treatment are hard to answer. One of the major reasons for this difficulty is that the circumstances under which the experiments are made in natural and artificial basins, like lagoons, ponds and lakes, are not always the same.

We present an age-dependent branching model with immigration and theoretically analyze how one can extract exact information about some important characteristics of this model, as the mean reproduction and

total progeny. On the other hand, using that model, we treat the problem of inference from expected waiting times and expected progeny on the fertility rates.

Let us shortly remind again that in the discrete-time case, the problem concerning the total progeny was investigated by several authors (Jagers, 1975, p. 39; Harris, 1989, p. 32), however, their main interest is focussed on questions of rates of growth, and this conditioned on survival. Karlin and Tavaré (1982) studied the asymptotic behavior of the probabilities of hitting the absorbing states, the times needed to hit these states, and the conditional distributions of the number of particles (for models allowing catastrophes). Bhattacharjee (1987) and Shaked and Shantikumar (1987) investigated the distribution of the extinction moment for subcritical and critical Bienaymé–Galton–Watson processes.

In the work of Jacobson (1985) was carried out a numerical investigation of the rate of convergence of the extinction probability for a discrete-time age-dependent branching process, in case when the lifetime has a distribution function close to gamma distribution. Jacobson established a quick convergence for the processes that differ essentially from the critical ones. Otherwise (for critical processes) the convergence is slow.

The problem of inference from expected waiting times and expected progeny on fertility rates, was first treated by Bruss and Slavtchova–Bojkova (1999). In their article the simple case, in which all newly introduced populations are supposed to behave like independent identically distributed (i.i.d.) Bienaymé–Galton–Watson branching processes was studied. Here, we consider the next very natural step, i.e. the continuous–time age–dependent branching processs. Such processes in general are not Markovian. However, the results remain valid in this case, and, we are aware that this is still a simplification of a real life problem but an explicit solution can be given in terms of generating functions.

For the above mentioned theoretical results we show a computation procedure and computer runs based on binary and Poisson reproductive rule. Since Powell (1955) found that the lifespan of bacteria follows a gamma distribution, and reproduction at death is characteristic of bacteria-like organisms, a discretized gamma density was used for all runs.

We discuss an example of "extinction bias" which may mislead decision makers in cultivation experiments.

2.2 Model Formulation

We will first outline an age–dependent branching process with immigration in the state zero. Consider a population process starting at time 0 with a single progenitor of age 0 whose life–length τ has distribution $G(t) = P(\tau \leq t)$, $G(0^+) = 0$. With probability p_k, $k \geq 0$ it produces at the end of its life k similar individuals (of age 0, with the same life–length τ and reproduction distribution $\{p_k\}$, $\sum_{k=0}^{\infty} p_k = 1$). The probability generating function (p.g.f.) of the number of ξ offsprings is denoted by

$$f(s) = \sum_{k=0}^{\infty} p_k s^k, \quad |s| \leq 1, \quad p_k = P(\xi = k).$$

Provided that there is at least one offspring, the death–and–reproduction process is repeated, and continues as long as individuals exist.

Let $\tilde{Z}(t)$ be the number of individuals existing at time t, or the state of the process $(\tilde{Z}(t))_{t\geq 0}$ at time t. Note that a line becomes extinct once $\tilde{Z}(t) = 0$ for some t (and for all t thereafter), and that the above process is "age–dependent" (i.e. the probability that an individual living at time t dies in the interval $(t, t + dt)$ is, in general, a nonconstant function of t). The process $(\tilde{Z}(t))$ is the so–called Bellman–Harris branching process (see, for example, Athreya and Ney, 1972, pp. 137–144). Every time the process $(\tilde{Z}(t))$ hits the state zero we suppose to have an immigration of one particle from an outside source. With $(Z(t))_{t\geq 0}$ we shall denote the process with immigration in the state zero.

The discrete version of such type of processes was first studied (in the critical case) by Foster (1971) and Pakes (1971, 1975).

Life cycles

For a branching process with immigration $(Z(t))_{t\geq 0}$ we call life periods (cycles) the intervals $(t_0, t_0 + T)$ of maximal length on which

$\inf_{t_0 \le t \le t_0+T} Z(t) > 0$. Thus $(Z(t))$ may have several life–periods, the last one always being infinite, provided the process is supercritical. If the process is subcritical it will have a.s. infinitely many life periods.

Total waiting time

We are interested in the last instant M of immigration, i. e. in the "birth time" of that process which will finally survive forever. Specifically, we shall derive the conditional distribution of the length T of the first life period and the conditional expectation of T, both conditioned on the event $\{T < \infty\}$. We shall also study the expectation of the total waiting time M to the beginning of the first process which will survive forever. Finally, we shall analyze the total progeny of a cycle and shall obtain its conditional expectation and variance, both conditioned on $\{T < \infty\}$.

Criticality and extinction

It is well–known from the theory of branching processes (see e.g. Athreya and Ney, 1972, p. 139–144) that the probability q of eventual extinction of Bellman–Harris process $(\tilde{Z}(t))$ is the smallest non–negative root of the equation $f(s) = s$, and $q = 1 \iff m = f'(1) \le 1$. The parameter m is called the reproduction mean, and the supercritical, critical and subcritical cases correspond to the relations $m > 1$, $m = 1$ and $m < 1$, respectively.

So, if $Z(0) = 1$ we have $P\{M = 0\} = P\{$ the initial particle does not die out without any offspring$\} = 1 - q$.

2.3 Results

Waiting times and life–cycles to successful experiment

Let $T_1, T_2, \ldots$ be the lengths of the life periods of those consecutive processes dying out before the surviving process is initiated (i.i.d. copies of the r.v. T).

Let $v(t) = P(T \le t)$.

The following result shows the computation of the conditional distribution of the length of a life–cycle, its conditional expectation (given extinction) and the expectation of the total length of unsuccessful life–cycles.

Theorem B.1 *The length T of the life–period and the last instant M of immigration of the process $(Z(t))$ have the following properties:*

$$P(T \leq t | T < \infty) = \frac{v(t)}{q}, \tag{B.1}$$

$t > 0$, $v(0) = P(Z(0) = 0) = 0$, where q is the extinction probability of of the Bellman–Harris process $(\tilde{Z}(t))$;

$$E(T | T < \infty) = \frac{1}{q} \int_0^\infty (q - v(t)) dt; \tag{B.2}$$

$$E(M) = \frac{q}{(1-q)} E(T | T < \infty). \tag{B.3}$$

The proof of the Theorem is given in the Appendix.

The total progeny of a cycle

Our particular interest will be focused to the total progeny $N(t)$ of a cycle conditioned on the event $\{T \leq t\}$. So, let $g_t(s) = E(s^{N(t)} | T \leq t)$.

Theorem B.2 *The probability generating function $g_t(s)$ of the conditional total progeny given the finiteness of the first life cycle satisfies the recurrence relation*

$$g_t(s) = \frac{s}{v(t)} \int_0^t f(v(t-y) g_{t-y}(s)) dG(y). \tag{B.4}$$

The expected total progeny $N(t)$ of a cycle conditioned on the event $\{T \leq t\}$ has the following properties:

$$\begin{aligned} m(t) = E(N(t)|T \leq t) &= \frac{1}{v(t)} \int_0^t m(t-y)v(t-y)f'(v(t-y))dG(y) \\ &+ \frac{1}{v(t)} \int_0^t f(v(t-y))dG(y). \end{aligned} \tag{B.5}$$

In the case $m \neq 1$ (i.e. non–critical cases) for the estimated total progeny of a cycle it is hold

$$E(N_\infty|T < \infty) = \frac{1}{1 - f'(q)}. \tag{B.6}$$

For the variance of the estimated total progeny of a cycle is as follows

$$\mathrm{Var}(N_\infty|T < \infty) = \frac{1}{(1 - f'(q))^3}\{qf''(q) + f'(q) - f'(q)^2\}. \tag{B.7}$$

2.4 Computer results

Apparently, as it is illustrated by the computer runs for the critical case, the distribution of the life–cycle conditioned on ultimate extinction has a very long tail. The most significant result shown in the graphs is that for super- and subcritical branching models the conditional distributions of the lifetime given extinction coincide. The reason is explained in the next paragraph and an appropriate example is represented.

DISCUSSION

Inference from estimated total progeny or early extinction

One must be careful not to draw hasty conclusions after failed experiments. To be specific, suppose that three different types of bacterial culture (α, β, γ, say) were introduced in similar wastewater and that each of these seems to have disappeared after some time, but that the α–type strains were reported in highest numbers or over the largest period of time. Is it then most promising to bet on α–type bacterial culture for a new experiment? The frequency of reports must be thought of as being positively correlated with the total progeny and the later with the reproduction mean of that bacterial culture. However such a conclusion would be erroneous, as we see in the following example. It is the number of times the process becomes extinct before it grows irreversibly, that will help to decide if the process is sub- or supercritical.

Example

Let $f_p(s) = p + 0.35s + (0.65 - p)s^2$ be the p.g.f. of the reproduction law of a Bellman–Harris process parameterized by $p = P\{\text{the initial progenitor dies without any offspring}\}$. The case $p = 0.325$ corresponds to the critical case $m = 1$, ($0 < p < 0.325$ supercritical, $0.325 < p \leq 0.65$ subcritical). Clearly, $q = q(p)$ is the smallest solution of $q = p + 0.35q + (0.65-p)q^2$ in $[0, 1]$ or $q = \min\left\{1, \dfrac{p}{(0.65 - p)}\right\}$, and $m = m(p) = f_p'(1) = 1.65 - 2p$, which decreases as p increases, whereas

$$E(N_\infty | T < \infty) = \frac{1}{1 - f_p'(q(p))} = \frac{1}{2|p - 0.325|},$$

which in the supercritical case increases as p increases.

It is worth noting that within this family of p.g.f.'s, in the supercritical case $p < 0.325$ the effect of conditioning on ultimate extinction is that $f(qs)/q$ is another member of the family with p replaced by $0.65 - p$. That is why if the supercritical process does die out then it is impossible from the statistical point of view to distinguish it from the subcritical one.

CONCLUSION

Extinction entails a very strong bias. If a decision maker decides to try again with that strains (α–type) which seems to have been best adapted so far he may exclude those strains with a much higher fertility rate m. The point is that he has to take that decision after extinction. It is simply very improbable that a process with a "comfortable" mean $m > 1$ would die out late. The higher the mean of a population the more probable it becomes that this population would, after extinction, be excluded from further experiments.

We conclude that the problem is of a greater significance that it might appear at the first sight. Independent control studies to assess prior probability of extinction are likely to be environment-bias.

2.5 Appendix

Proof of Theorem B.1

Recall that from the classical theory of Bellman-Harris branching processes (Athreya and Ney, 1972, pp. 137–171) for the extinction probability by time t we have the following renewal equation: $v(t) = \int_0^t f(v(t-u))dG(u)$, $t > 0$, $v(0) = 0$.

To prove (B.2) we will use that the conditional expectation $E(T|T < \infty)$ is finite by definition and we can write it in the form

$$E(T|T<\infty) = \int_0^\infty (1 - P(T \le t|T<\infty))dt = \frac{1}{q}\int_0^\infty (q - v(t))dt.$$

Finally, to see (B.3) note that the expectation of the total waiting time M can be written as

$$\begin{aligned} E(M) &= qE(T_1|T_1<\infty) + q^2E(T_2|T_2<\infty) + \cdots \\ &= E(T|T<\infty)q\sum_{k=0}^{\infty} q^k = \frac{q}{(1-q)}E(T|T<\infty), \end{aligned}$$

where T_1, T_2, ... are i.i.d. copies of T. Here the first equality holds since q^k is the probability that at least k cycles die out. Thus (B.3) is proved. □

Proof of Theorem B.2

A decomposition of the conditional (on event $\{T \leq t\}$) sample space in accordance with the life-length τ and the number of offspring ξ of the initial particle suggests the relation:

$$\begin{aligned} g_t(s) &= \frac{E(s^{N(t)} I(T \leq t))}{P(T \leq t)} \\ &= \frac{1}{v(t)} \{E(E(s^{N(t)} I(T \leq t) | \tau \leq t, \xi)) \\ &+ E(E(s^{N(t)} I(T \leq t) | \tau > t, \xi))\}, \end{aligned}$$

where $I(.)$ denotes the indicator function.

It is clear that the second summand on the right side in (B.8) is zero.

Now for the first term we obtain

$$\begin{aligned} E(E(s^{N(t)} I(T \leq t) | \tau \leq t, \xi)) &= s \sum_{j=0}^{\infty} p_j \int_0^t [E s^{N(t-y)} v(t-y)]^j dP(\tau \leq y) \\ &= s \int_0^t \sum_{j=0}^{\infty} p_j g_{t-y}^j(s) v^j(t-y) dP(\tau \leq y) \\ &= s \int_0^t f(v(t-y) g_{t-y}(s)) dG(y). \end{aligned}$$

(B.8)

Then from (B.8) and (B.9) we obtain (B.4). □

(B.5) follows by differentiating (B.4) at $s = 1$, i. e.

$$\begin{aligned} g_t'(1) &= \frac{1}{v(t)} \int_0^t g_{t-y}'(1) f'(v(t-y) g_{t-y}(1)) v(t-y) dG(y) \\ &+ \frac{1}{v(t)} \int_0^t f(v(t-y)) g_{t-y}(1) dG(y), \end{aligned}$$

which becomes after simplification

$$g_t'(1) = \frac{1}{v(t)} \int_0^t g_{t-y}'(1) f'(v(t-y)) v(t-y) dG(y) + \frac{1}{v(t)} \int_0^t f(v(t-y)) dG(y).$$

Since $m(t) = g_t'(1)$ we have (B.5).

The convergence results (B.6) and (B.7) for conditioning on $\{T < \infty\}$ follow by observing that an age–dependent supercritical branching process conditioned on ultimate extinction behaves like a subcritical one with reproduction p.g.f. $f(qs)/q$. The techniques of embedded generation process (Athreya and Ney, 1972, p. 141) implies a direct verification of this fact. After that, as the result about total progeny in the subcritical case (Jagers, 1975, pp. 39-42) remains true for age–dependent branching processes, we obtain that there exists the conditional expectation $E(s^{N_\infty} | T < \infty) = g(s)$, where $g(s)$ is the unique solution of the equation:

$$g(s) = \frac{s f(q g(s))}{q}. \tag{B.9}$$

From (B.10) it is a matter of straightforward computations to verify that

$$E(N_\infty | T < \infty) = g'(1) = \frac{1}{1 - f'(q)}, \tag{B.10}$$

and

$$\begin{aligned} E(N_\infty (N_\infty - 1) | T < \infty) &= g''(1) \\ &= \frac{1}{(1 - f'(q))^2} \left[2 f'(q) + \frac{q f''(q)}{1 - f'(q)} \right]. \end{aligned} \tag{B.11}$$

Therefore from (B.12) and (B.13) it follows

$$\begin{aligned} Var(N_\infty|T<\infty) &= g''(1)+g'(1)-g'(1)^2 \\ &= \frac{1}{(1-g'(q))^3}\{qg''(q)+g'(q)-g'(q)^2\}. \end{aligned}$$

This completes the proof. □

Similarly we could proceed to compute the higher moments of N_∞.

Chapter 3

Time to extinction in Sevasty'anov BP

3.1 Introduction

Strongly motivated by the need of models to accurately design, study and predict the development of biological populations, concerning a variety of problems arising, for example in population and re-population experiments, wastewater treatment, evolution of resistance to antibiotics, etc., we focus our efforts to the age-dependent branching models with immigration as a suitable tool in doing such analysis. Specifically, one of the problems of applied ecology is what to do, when to do it, and how to assess and improve the actions taken, when particular species disappear. These are, for example population and re-population experiments with trout, birds, and other species (see Bruss and Slavtchova–Bojkova (1999)), or wastewater treatment experiments in (Slavtchova–Bojkova (2000)). In the context of this general concern we propose a technique, motivated by the above mentioned diversity of problems which can be modeled with Sevast'yanov's age-dependent branching processes allowing immigration. Another important motivation for this work is the challenge of natural incorporation of some biological characteristics into a model and their proper interpretation, when applied in biology, ecology, environmental studies, decision making, etc. In this work the stress is on the improvement of the approach applied in Bruss and Slavtchova–Bojkova (1999) and Slavtchova–Bojkova (2000) towards the incorpora-

tion of the dependence of the particle reproduction on the particle's age. Sevast'yanov's model describes better real life cases (see Sevast'yanov (1971)).

The problem of inference from expected waiting times and expected progeny on fertility rates was proposed for the first time in the context of population and re-population experiments with different types of species in Bruss and Slavtchova–Bojkova (1999). The classical Bienaymé–Galton–Watson branching process (BGWBP) with immigration in zero state was used as a model describing the population development and exact answers were obtained when all newly introduced populations behave like independent identically distributed (i.i.d.) BGWBP. In Slavtchova–Bojkova (2000) similar results were generalized for the distribution of the life-cycle, waiting time to a successful experiment and the estimated total progeny, all conditioned on ultimate extinction, using the so called age-dependent branching model or Bellman-Harris branching process (BHBP) with immigration in zero. In this case the process is called "age-dependent" in sense that the probability for an individual living at time t to die in the interval $(t, t+dt)$ is, in general, a non-constant function of t, but the reproduction is still one and the same random variable, which distribution does not depend on the particle's age. The motivation of paper by Slavtchova–Bojkova (2000) has arisen in the context of wastewater treatment by bacterial cultures. As it was found in Powel (1955) the lifespan of bacteria-like organisms follows a gamma distribution, and reproduction at death is characteristic of bacteria-like organisms, so age-dependent processes can be used as more adequate mathematical models for such real phenomena.

In the discrete-time case the theoretical and simulation results for the life-cycle distribution and the similar characteristics, which appear naturally in the context of bisexual BGWBP, were obtained in Gonzales, Molina and Del Puerto (2001). It should be emphasized that all sample paths of the resurrection model are positive.

We would like to point out that in the disctere–time case, the problem concerning the total progeny was investigated in Harris (1989), Jagers (1975). However, the main interest is focused on the questions of rates of growth, and this conditioned on survival. Some authors, see for example Karlin and Tavaré, studied the asymptotic behavior of the probabilities of hitting the absorbing states, the times needed to hit these states, and the

conditional distributions of the number of particles (for models allowing catastrophes).

On the other hand, however, it is important to pay consideration here to another aspect in the theory of Markov branching processes with instantaneous immigration (MBPII) or resurrection, considered in pertinent literature. In Pakes (1993) it is shown that a realistic model can be constructed, if the state-space is restricted to the natural numbers. The problem of constructing a version of the MBPII which allows instantaneous resurrection from zero have been tackled in Chen and Renshaw (1990). The authors promote their models as realistic descriptions of situations where populations are quickly restored from extinction, by reintroduction, or rapid migration, as in island biogeography.

The last advancements towards modeling of biological phenomena by branching processes have been published in the monograph Haccou, Jagers and Vatutin (2005) with lots of real world examples and problems.

The main goal of this study is to generalize the results for the life-cycle length and total waiting time for the Sevast'yanov's age–dependent branching model, where not only cell generation times differ between particles, but the offspring distribution may depend on the age of each particle. Such processes in general are non–Markovian. However, the analogous results remain true in that case, and, we are aware that this is still a simplification of a real world problem but an explicit solution (see paragraph 3.3) can be given in terms of Laplace–Stieltjes transforms and generating functions.

3.2 Model formulation

Consider a population branching process $(Z_t : t \geq 0)$ having as state–space the non–negative integers with zero as an absorbing state. Let $Z_0 = 1$, and $T = \inf\{t : Z_t = 0\} \leq \infty$. Next, let $\{(Z_t(n)) : n = 1, 2, \ldots\}$ be independent identically distributed (i.i.d.) copies of Z_t with $Z_0(n) = 1$. Let $T_0 = H_0 = 0$ and for all $n \geq 1$ let $T_n = \inf\{t : Z_t(n) = 0\}$ and $H_n = \sum_{0 \leq j \leq n} T_j, (n \geq 1)$. Note that $\{T_n\}$ are i.i.d. random variables. Thus H_n is the time of the n^{th} extinction event, provided it is finite, and the convention $H_0 = 0$ implies the entire process begins with an extinction at $t = 0^-$. Hence $N = \sup\{n : T_n = \infty\}$ is the number of the

index of the first infinite cycle. In addition, let us suppose that $(Z_t : t \geq 0)$ is Sevast'yanov's age–dependent branching process, starting at time 0 with a single progenitor of age 0, whose life–length τ has distribution $G(t) = P(\tau \leq t)$, $G(0^+) = 0$. With probability $h_t(k)$, $t > 0$, $k \geq 0$ it produces at the end of its life k similar individuals of age 0, with the same life–length distribution as that of τ and reproduction distribution $\{h_t(k)\}$, where $h_t(k) = P(\xi = k|\tau = t)$, $\sum_{k=0}^{\infty} h_t(k) = 1$, for every $t > 0$. Let us denote the p.g.f. of the number of offspring ξ generated at age t by

$$h(t; s) = \sum_{k=0}^{\infty} h_t(k)s^k, \quad |s| \leq 1.$$

Then, the process we are interested in is

$$\widetilde{Z}_t = Z_{t-H_{n-1}}(n) \quad \text{if} \quad H_{n-1} \leq t < H_n \quad (n = 1, \ldots, N).$$

Life cycles

For the branching process $(\widetilde{Z}_t)_{t\geq 0}$ we shall call life cycles the intervals (H_{n-1}, H_n), $n = 1, 2, \ldots, N-1$. Thus $(\widetilde{Z}_t)$ may have several life cycles, the last one always being infinite, provided the process is super-critical. If the process is sub–critical it will have a.s. infinitely many life cycles.

Lifetime of the process $(\widetilde{Z}_t)_{t\geq 0}$ before escaping from extinction.

Lifetime of the process $(\widetilde{Z}_t)_{t\geq 0}$ before escaping from extinction will be defined as $L = H_{n-1}$, i.e. the "birth time" of the first infinite life cycle. We shall also study the expectation of the lifetime L. Finally, we shall analyze the total progeny during the lifetime of the process $(\widetilde{Z}_t)_{t\geq 0}$ and shall obtain its expectation and variance.

Criticality and extinction

Let $q = \lim_{t\to\infty} P_0(t)$, where $P_0(t) = P(Z_t = 0)$. It is known that q is the smallest root of the equation

$$\int_0^{\infty} h(t; s)dG(t) = s$$

(see e.g. Sevast'yanov (1972)).

Then the criticality parameter of the process Z_t turns out to be

$$m = \int_0^\infty m(t) dG(t),$$

where $m(t) = h'_s(t;1)$ and the extinction probability $q = 1$ iff $m \leq 1$. The parameter m is called the reproduction mean, and the super–critical, critical and sub–critical cases correspond to the relations $m > 1$, $m = 1$ and $m < 1$, respectively. So, if $Z_0 = 1$ we have $P\{L = 0\} = P\{\text{first process does not die out}\} = 1 - q$.

3.3 Main results

Suppose $q = P(T < \infty) < 1$, so that $\tau(\theta) = E(e^{-\theta T})$ satisfies $\tau(0) = q$. Thus $L = 0$ if the initial population is immortal, i.e. $T_1 = \infty$.

Let

$$F(t) = P(T \leq t) = \int_0^t h(u; F(t-u)) dG(u). \tag{C.1}$$

Proposition C.1 *The Laplace–Stieltjes transform $\lambda(\theta) := E(e^{-\theta L})$, satisfies:*

$$\lambda(\theta) := \frac{1-q}{1-\tau(\theta)}.$$

Proof. It follows by

$$\lambda(\theta) := E(e^{-\theta L}) = \sum_{n\geq 0} E(e^{-\theta H_n}; T_{n+1} = \infty) = (1-q) \sum_{n\geq 0} \tau^n(\theta) = \frac{1-q}{1-\tau(\theta)}.$$

□

The total progeny of a life cycle.

First, we are interested in the total progeny V of a life cycle and its expectation, in order to make some inferences on the fertility rates of the particles. So, let $g(t;s) = E(s^V; T \leq t)$.

Proposition C.2 *The expected total progeny V of a life cycle satisfies the following equation:*

$$\nu(t) := E(V; T \le t) = F(t) + \int_0^t \nu(t-y) h'_s(y; F(t-y)) dG(y), \tag{C.2}$$

where $F(t)$ is defined by (C.1).

In the case $m \neq 1$ (i.e. non–critical cases) the expected total progeny of a life cycle is:

$$E(V; T < \infty) = \frac{q}{1 - \int_0^\infty h'(t; q) dG(t)}. \tag{C.3}$$

Proof. It is obvious from the branching property that the p.g.f. $g(t; s)$ of the total progeny of a life cycle satisfies the recurrence relation

$$g(t; s) = s \int_0^t h(y; g(t-y; s)) dG(y). \tag{C.4}$$

Since $g(1; t) = F(t)$, after differentiating (C.4) we obtain (C.2).

From $q = F(\infty)$ and $\nu(t) \uparrow \nu := E(V; T < \infty)$, dominated convergence yields (C.3). □

The total progeny of the $(\widetilde{Z}_t)_{t\ge 0}$ before explosion.

Suppose that $\{Z_t(n)\}$ are supercritical Sevast'yanov's branching processes, in which case with probability one will appear a process that is going to explode. We are interested in the total progeny W of the process $\widetilde{Z}_t$, i.e. the number of all existing particles during the all finite cycles before explosion. Assume $p_0 > 0$ and let V_n denote the total progeny within $Z_t(n), n = 1, 2, \ldots$. Then

$$W = \sum_{n=1}^{\infty} [V_1 \mathbb{I}\{T_1 < \infty\} + \cdots + V_n \mathbb{I}\{T_n < \infty\}] \mathbb{I}\{T_{n+1} = \infty\}, \tag{C.5}$$

where the summands $V_i, i = 1, \ldots, n$ are i.i.d. and independent of $\{T_{n+1}\}$.

Let us denote $g(s) := E(s^{V_n}|Z_0(n) = 1) = E(s^{V_n}; T_n < \infty|Z_0(n) = 1)$, because $V_n = \infty$ if $\mathbb{I}\{T_n = \infty\} = 1$.

Moreover, $g(1) = P(T_n < \infty|Z_0(n) = 1) = q$, the extinction probability starting with one particle. Observing that $W = 0$ if $T_1 = \infty$, (C.5) yields

$$E(s^W) = (1-q) + \sum_{n\geq 1} g^n(s)(1-q) = \frac{1-q}{1-g(s)}. \tag{C.6}$$

Now, for a given p.g.f. $h(t;s)$ of a Sevast'yanov's branching process using the relation (C.3) we obtain that the expected total progeny within extinct cycles is

$$EW = \frac{q}{(1-q)(1-\int_0^\infty h'_s(t;q)dG(t))}.$$

After differentiating (C.5) once more at $s = 1$ it is a matter of straightforward computations to verify that

$$E[W(W-1)] = \frac{1}{1-q}\{\frac{2q}{(1-q)(1-\int_0^\infty h'_s(t;q)dG(t))} + \mu\},$$

where

$$\mu := \frac{\nu(2\int_0^\infty h'_s(t;q)dG(t) + \int_0^\infty h''_{ss}(t;q)dG(t))}{1-\int_0^\infty h'_s(t;q)dG(t)}.$$

□

3.4 Simulation results

In general, one of the best features of branching processes is that the exact theoretical results have a natural interpretation and can be directly used for numerical and simulation studies.

When using Bellman-Harris branching model allowing immigration, the computation procedure was implemented by recursive equations to compute the probability of extinction by certain epoch (see Slavtchova–Bojkova (2000)). It was illustrated how the duality between sub–critical and super–critical branching processes given extinction can make decision makers take the wrong decision.

However, as it does not look easy to derive analogous results for the Sevast'yanov's population models, we develop a code for a simulation system of different branching models with immigration, including BGWBP, BHBP and Sevast'yanov's ones. No programming is necessary and all input data can be entered in user–friendly dialog boxes and graphics and (numerical) results can be easily and quickly obtained. The results can be stored in the database table and may be analyzed easily. The code can be used for actual design, prediction and estimation of the parameters of different classes of branching processes, both in discrete and continuous time. The simulation system is a simple professional tool that might be used by biologists, engineers and decision makers for simulation of the processes which could appear to be suitable for modeling of some real

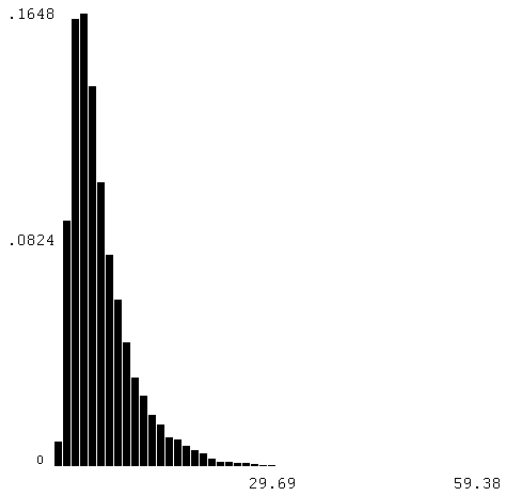

Figure 3.1: Histogram of probability densities of a life cycle $T|T < \infty$ with $\Gamma(6, 1)$ life-time of each particle and Poisson reproduction distribution, depending logarithmic from the particle's age.

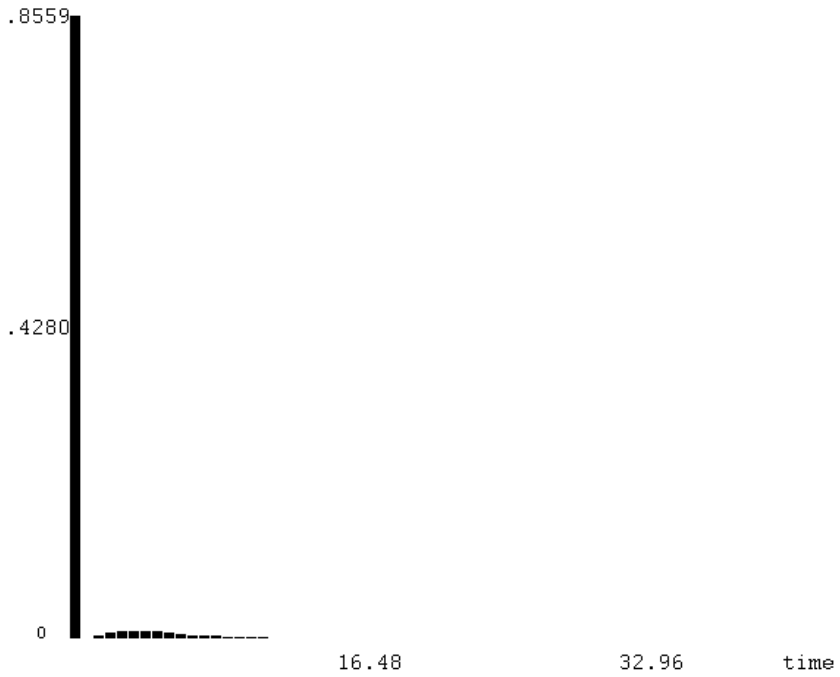

Figure 3.2: Histogram of probability densities of a total waiting time L with $\Gamma(6,1)$ life–time of each particle and Poisson reproduction distribution, depending logarithmic from the particle's age.

world problems related to population and re-population experiments. Moreover, the simulation software system allows input of a mortality density and a special form of the reproduction law with particle's age dependence. Up to now exponential, logarithmic and polynomial functions are proposed to model the age–dependency. We apply the Monte–Carlo method to approach the behaviour of the variables $T|T < \infty$ and L. For the variable $T|T < \infty$, we simulate the process $(Z_t : t \geq 0)$ whereas the process $(\widetilde{Z}_t : t \geq 0)$ is considered to study the variable L. All runs are with $\Gamma(6,1)$ life–time distribution of each particle and Poisson reproduction distribution, depending in logarithmic way from the particle's age.

As an example we have simulated 100 000 paths of each process. In Figure 3.1 and Figure 3.2 we show the estimate density functions for

the variables $T|T < \infty$ and L. From the simulation we estimate the probability of extinction of the process $(Z_t : t \geq 0)$ by 0.1447. Moreover, the sample mean for $T|T < \infty$ is 6.6650 and for L the sample mean is 1.1255.

3.5 Conclusions

In population experiments it is usually easier to see if a new introduction has been successful than to know whether, and when, extinction has occurred. In many cases statistical data are only provided by interest groups, hunters, photographers, etc. Independent control studies to assess the prior probability of extinction are likely to be environment-biased. On the other hand, it is not always possible to reduce the prior probability of extinction by releasing a large numbers of individuals. The point is that extinction involves a very strong bias. The discrete mass in the origin for the density function of L is the consequence of $P(L = 0) = 1 - q$. Indeed, the estimated extinction probability of the process $(Z_t : t \geq 0)$ equals to 0.1447.

To generalize the inference results on fertility rates and illustrate how the duality between sub–critical and super–critical branching processes given extinction can mislead decision–makers, the study of the behaviour of the extinction probability by given time when using Sevast'yanov's model, will be reserved for future research.

Chapter 4

Comparison between numerical and simulation methods for age–dependent BP with immigration

4.1 Introduction

In biological treatment of industrial wastewater by cells feeding on a substrate in a bio-reactor, bio-technologists and environmentalists ask about how long takes the final establishment of bacterial cultures in wasted water. This question is directly related to the study of the extinction time of cells feeding and of the number of trials necessary before the bacterial culture starts to grow irreversibly.

As a convenient tool to treat this problem, Slavtchova–Bojkova (2000, 2004) proposed the use of a special class of branching processes, namely age-dependent branching processes with immigration in the state zero. In these works, implicit equations for the distribution function (d.f.) of both, the life period of a bacterial culture and the total waiting time to the beginning of that population which will survive forever, were determined. However, these equations turned out to be very useful from a practical viewpoint, because the d.f. are not determined in a direct way. That is why, it is reasonable to try to estimate them by means of these equations using numerical method. The goal of the paper is to provide

and to compare two different approaches: one by means of a numerical method and another one by means of simulation.

In the next section we define the probability model and fix the notation. In Sections 4.3 and 4.4, the numerical procedure and Monte–Carlo method for simulation are provided and applied to particular cases, respectively. Finally, in Section 4.5 we compare the proposed methods.

4.2 Probability Model

We will first outline an age–dependent branching process $\{Z(t)\}_{t\geq 0}$. Consider a population process starting at time 0 with a single progenitor of age 0 whose life–length τ has distribution $G(t) = P(\tau \leq t)$, $G(0^+) = 0$. With probability p_k, $k \geq 0$, it produces at the end of its life k similar individuals (of age 0), with the same life-length distribution $G(t)$ and reproduction distribution $\{p_k\}_{k\geq 0}$ ($\sum_{k=0}^{\infty} p_k = 1$). The probability generating function (p.g.f.) of the number ξ of offspring, is denoted by

$$f(s) = \sum_{k=0}^{\infty} p_k s^k, \ |s| \leq 1, \ p_k = P(\xi = k).$$

Provided that there is at least one descendent, the death–and–reproduction process is repeated, and continues as long as individuals exist.

Let us denote by $Z(t)$ the number of individuals existing in the population at time t or the state of the age–dependent process $\{Z(t)\}_{t\geq 0}$ at time t. Note that a path becomes extinct once $Z(t) = 0$ for some t (and for all t thereafter), and that the above process is "age–dependent" in the sense that the probability an individual living at time t dies in the interval $(t, t+dt)$ is, in general, a non-constant function of t. The process $\{Z(t)\}_{t\geq 0}$ is the so–called Bellman–Harris branching process (see, for example, Athreya and Ney (1972), pp. 137–144). Now, let us introduce the process of interest $\{\widetilde{Z}(t)\}_{t\geq 0}$, i. e. every time the process $\{Z(t)\}_{t\geq 0}$ hits the state zero we suppose to have an immigration of one particle from an outside source. Then, $\{\widetilde{Z}(t)\}_{t\geq 0}$ is the process with immigration in the state zero introduced by Mitov and Yanev (1985). Let us notice that Foster (1971) and Pakes (1975) first studied the discrete-time version of these processes. However, their results concern mainly the asymptotic behaviour of the processes.

For a branching process with immigration $\{\widetilde{Z}(t)\}_{t\geq 0}$ we call life periods (cycles) the intervals $(t_0, t_0 + T_{t_0})$ of maximal length on which $\inf_{t_0\leq t<t_0+T_{t_0}} Z(t) > 0$. We denote $T := T_0$. The variable T is improper one with probability $1-q$, i.e. $P(T<\infty) = q$, where q is the probability of eventual extinction of the process $\{Z(t)\}_{t\geq 0}$. Thus $\{\widetilde{Z}(t)\}_{t\geq 0}$ may have several life periods, the last one always being infinite, provided the process is supercritical ($m := f'(1) > 1$). On the set $\{T<\infty\}$ (means that at least once a certain extinction is observed), Slavtchova–Bojkova (2000) obtained that

$$q(t) := P(T \leq t | T<\infty) = \frac{1}{q}\int_0^t f(v(t-u))dG(u) \tag{D.1}$$

for $t > 0$, where $v(t) := P(Z(t) = 0)$ and $v(0) = P(Z(0) = 0) = 0$. Moreover

$$E(T|T<\infty) = \frac{1}{q}\int_0^\infty (q - v(t))dt.$$

Notice that if $q = 1$, then $q(t) = v(t)$ for all $t \geq 0$. It is known that $v(t) = \int_0^t f(v(t-u))dG(u)$ (see Athreya and Ney (1972), pp. 138).

In the supercritical case, we denote by M the last instant of immigration, i. e. the "birth time" of that process which will finally survive forever. It is verified that $P(M=0) = 1-q$, $P(M<\infty) = 1$ and on the event $\{M>0\}$, i.e. at least one immigration is necessary or equivalent the first life cycle is finite ($T<\infty$), Slavtchova–Bojkova (2004) obtained that

$$P(M \leq t | T<\infty) = (1-q)(\delta_{t0} + \sum_{i=1}^{\infty} q^i v^{*i}(t)), \tag{D.2}$$

where $\delta_{t0} = 1$ if $t = 0$ or 0 if $t \neq 0$ and $v^{*(i+1)}(t) = \int_0^t v^{*i}(t-u)dv(u)$, with $v^{*0}(t) = 1$, $v^{*1}(t) = v(t)$. Moreover

$$E(M) = \frac{q}{1-q}E(T|T<\infty).$$

Although, the equations (D.1) and (D.2) show a mathematical relation of the variables T and M, it is not possible to obtain explicitly an

equation for each variable. In the next sections we provide two computational procedures, one numerical and another one by simulation, which concern the estimation of the conditional (given ultimate extinction) distribution of the life–length cycle T and of the conditional distribution of so called total waiting time M to the beginning of the successful experiment.

4.3 Numerical Method

In what follows we will describe the idea of the computational procedure and the two concrete examples we applied it to. Let l be the maximum number of offspring an individual can have, r be the greatest age an individual can live to, and $g(.)$ be the life–length density. There are two mutually exclusive ways a trajectory can become extinct by time t: the progenitor dies by time t with probability $1 - G(t)$ and leaves no offspring, or the progenitor dies at time $1 \leq s < t$ with probability $g(s)$, having had $1 \leq k \leq l$ offspring and each of the k offsprings' lines becomes extinct by time t. To compute the probability of extinction $v(t)$ by time t of the Bellman-Harris branching process $\{Z(t)\}_{t\geq 0}$ we will use the following recurrence equations

$$v(t) = p_0 G(t) + \sum_{s=1}^{t-1} \sum_{k=1}^{l} p_k v^k (t-s) g(s), \quad \text{if } t < r$$

and

$$v(t) = p_0 + \sum_{s=1}^{r} \sum_{k=1}^{l} p_k v^k (t-s) g(s), \quad \text{if } t \geq r,$$

obtained after time discretization of the renewal type integral equation satisfied by $v(t)$, i.e.

$$v(t) = \int_0^t f(v(t-u)) dG(u).$$

It is relevant to remark that as $q(t) = q^{-1}v(t)$, then approaching $v(t)$, $q(t)$ is also obtained.

To study the implications of the above method we compute the conditional distribution of a life cycle T of an age–dependent branching process with immigration and of the total waiting time M when adopting as a probability density function (p.d.f.) for cell generation times the $\Gamma(\alpha, \beta)$ form for this distribution with p.d.f., $h(x) = \dfrac{e^{-x\beta}\beta^{\alpha}x^{\alpha-1}}{\Gamma(\alpha)}$, for $x > 0$, and mean $\lambda = \dfrac{\alpha}{\beta}$, where $\alpha = 6$ and $\beta = 1$. We consider two cases for the offspring distribution. First we suppose the offspring distribution to belong to the family of p.g.f. $h_p(s) = p + 0.4s + (0.6 - p)s^2$, parameterized by $p = P\{\text{the initial progenitor dies without any offspring}\}$. The computational results for $p = 0.05$ (which corresponds to a supercritical case with $m = 1.5$ and $q = 0.09$) are presented in the Figure 4.1, where we show the conditional density function of the life–period T given that $T < \infty$ (left graphic), $q(t)$ (central graphic) and conditional density function of the total waiting time M given that $M > 0$ (right graphic). In addition, we obtained for the conditional expected value of T on the event of certain extinction, i.e. $E(T|T < \infty) = 11.92$ and for the unconditional $E(M) = 1.17$ in this case.

Secondly, we implemented the computation when the offspring distribution is geometrical one with $p = 2/5$ (which corresponds to a supercritical case with $m = 1.5$ and $q = 0.66$). The obtained results are shown on the Figure 4.2. To compare with the results obtained by simulation procedure, here we have $E(T|T < \infty) = 12.46$ and $E(M) = 24.2$.

4.4 Simulation Method

We apply the Monte-Carlo method to approach the behavior of the variables T and M, and estimate the density functions using a Gaussian kernel. For the variable T, we simulate the process $\{Z(t)\}_{t\geq 0}$ whereas the process $\{\widetilde{Z}(t)\}_{t\geq 0}$ is considered to study the variable M.

For the examples of the previous section, we have simulated 100000 paths of each one. In Figure 4.3 and Figure 4.4 we show the estimate density functions for the variables T (left graphic) and M (right graphic), and the estimate cumulative distribution function $q(t)$ (central graphic), both of them given that $T < \infty$, for example 1 and 2 respectively. From the simulation for example 1 we estimate the probability of extinction

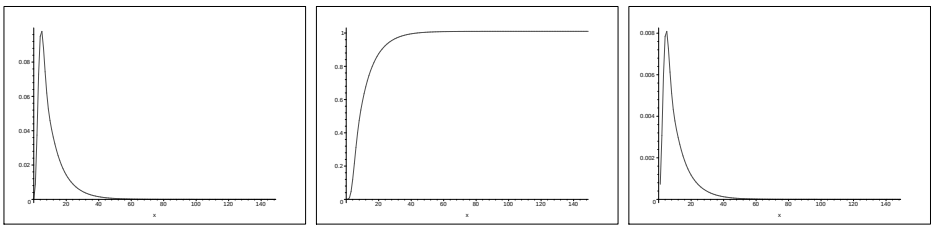

Figure 4.1

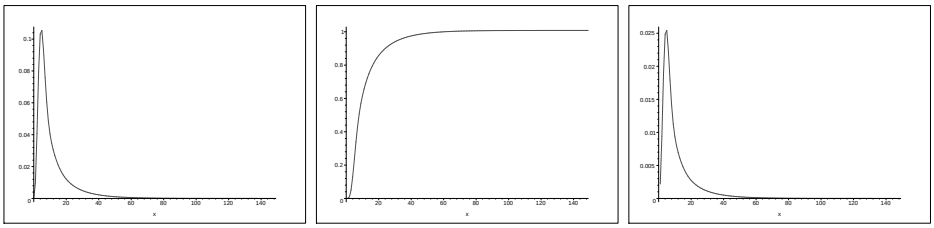

Figure 4.2

by 0.09154 with 95% confidence interval $(0.08971, 0.09329)$. Moreover, the sample mean for $T|T < \infty$ is 11.43823 with 95% confidence interval $(11.25729, 11.61917)$ and for M and $M|M > 0$ the sample mean are 1.0955 and 12.25531 with 95% confidence interval $(12.05606, 12.45457)$ and $(1.06745, 1.123552)$, respectively.

For example 2 we estimate the probability of extinction by 0.66349 with 95% confidence interval $(0.66056, 0.66642)$. The sample mean for $T|T < \infty$ is 11.93946 with 95% confidence interval $(11.85343, 12.02550)$ and for M and $M|M > 0$ the sample mean are 23.9818 and 35.89016 with 95% confidence interval $(23.77459, 24.18902)$ and $(35.62259, 36.15773)$, respectively.

4.5 Discussion

First, we would like to point out that both methods applied for the estimation of the distribution of the life-cycle T and of the total waiting time M lead to similar results. For the numerical procedure we only use Newton-Raphson method (see Jacobson, 1985) for the integral equation

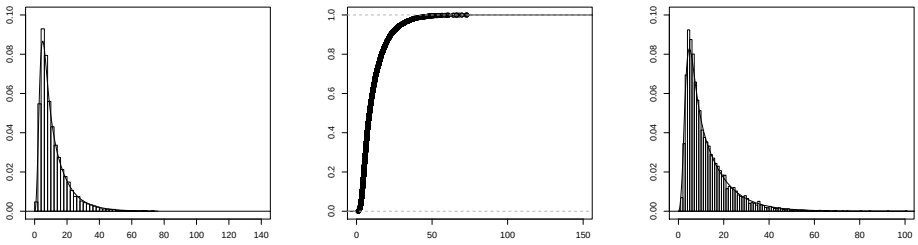

Figure 4.3

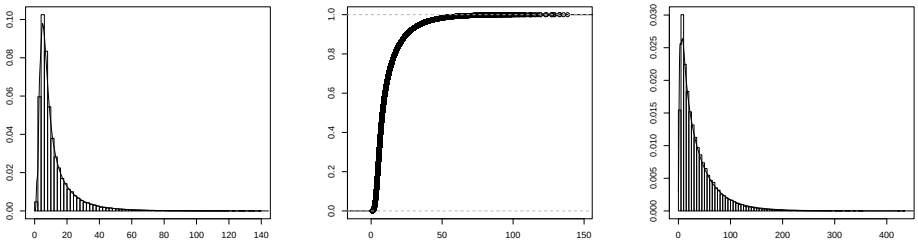

Figure 4.4

satisfied by the extinction probability and the theoretical results for the Bellman-Harris branching processes. As a disadvantage here we would point out that for an arbitrary probability offspring distribution, actually we have to use truncated distribution.

In addition, applying the above mentioned time-discrimination computation procedure we need to impose some restrictions: fix the maximal age an individual can live to and a maximal number of offspring an individual can have.

On the other side, using simulation method to have more accurate estimates we need more and more simulations. Another problem which we face is that we need to make a decision in advance when it is reasonable to stop in order to assure that the process "will survive forever". However, this method allow us to estimate the errors through confidence intervals.

Finally, we would like to point out, that as illustrated by the two examples, the variable M strongly depends on the magnitude of q, in spite of both examples have the same reproduction mean. On the other hand, the behavior of the variable T is very similar in both cases.

Chapter 5

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Part II

Branching models in epidemiology

Chapter 6

Continuous time branching model

6.1 Introduction

The Bellman–Harris branching process (BHBP) is a continuous–time model, which has been widely studied in the stochastic processes theory (see for example Chapter 4 in Ahtreya and Ney (1972) for details). Moreover, from a practical outlook, it has been used to describe the evolution of populations along time in different situations, as for example, to solve many problems related to cell populations (see for example Axelrod et al. (1993), Axelrod et al. (1997), Kimmel (1985), Kimmel et al. (1986), Yakovlev and Yanev (2006) and Yakovlev and Yanev (2007)).

It is well–known that a BHBP becomes extinct or explode to infinity depending on the mean value of its reproduction law. This property is inherited from its embedding Galton–Watson process (EGWP), leading us to the classification of subcritical, critical and supercritical cases. Then, the extinction happens almost surely (a.s.) in the subcritical and critical cases, and has a positive probability in the supercritical case (obviously under the corresponding conditions to avoid trivial cases).

However, the time necessary for the extinction of a BHBP can not be deduced from its EGWP. This time is a random variable which depends on the continuous-time structure of the BHBP on its own. Even though the study of the extinction time is very interesting from both theoretical

and practical view points, it has not been considered deeply enough (see for example Agresti (1974), Farrington and Grant (1999), Hainzmann (2009) and Pakes (1989)). Gonzáles, Martínez and Slavtchova–Bojkova (2010a) deal with this problem, investigating the dependence of the extinction time of a BHBP on its reproduction law. Moreover, they apply the obtained results in an epidemiological context. Actually, the problem of how to model the evolution of an infectious disease is very important and widely considered in the recent literature (see for example Becker and Britton (2004), Farrington et al. (2003), Isham (2005), Mode and Sleeman (2000) and Pakes (1989). However only in few papers (see for example Andersson and Britton (2000), Barbour (1975), Farrington and Grant (1999) and Nasell (2002)) the waiting time to extinction of the disease has been used as a main tool to determine a vaccination policy. Mainly because there are not enough results on this r.v. In the work Gonzáles, Martínez and Slavtchova–Bojkova (2010a) a new approach to this topic was proposed.

In this chapter we study consecutively some properties of the distribution function of the extinction time of a BHBP, mainly those related to stochastic monotonicity and continuity depending on its reproduction law. Then, we apply this study to investigate the behavior of the time elapsed by an infectious disease becomes extinct depending on the proportion of the immune individuals of the population. We consider diseases which follow a SIR (susceptible–infected–removed) scheme. It is well–known that branching processes fit adequately this scheme (see Andersson and Britton (2000) and Ball and Donnelley (1995)). So, first, we model the spread of infection by a BHBP. Then we study its extinction time distribution and we propose an optimal vaccination level to immunize individuals in the population, based on the quantiles of such distribution. To guarantee the applicability of these results, we propose a simulation-based method which allows us to calculate the optimal proportion of susceptible individuals to be vaccinated. We also provide an illustrative example. Finally, to ease the reading, the proofs are presented in paragraph 5.7.

6.2 Properties of the extinction time

In this paragraph we study some properties related to the extinction time of BHBPs. First we draw our attention on obtaining results concerning to a BHBP with fixed reproduction law, which is referenced in terms of its probability generating function. Then, we study the properties of the extinction time of BHBPs with different reproduction laws but with the same distribution of the life-length. Specifically, we establish stochastic monotonicity and continuity properties depending on the reproduction law.

To this aim, we denote by T_f the extinction time of a BHBP, $\{Z_t\}_{t\geq 0}$, initiated at time 0 with a single individual, with reproduction law given by its p.g.f. $f(\cdot)$ and life–length with distribution function (d.f.) $G(\cdot)$ such that $G(0^+) = 0$, i.e., there is null probability of instantaneous death. Mathematically, we have

$$T_f = \inf\{t \geq 0 : Z_t = 0\},$$

where Z_t denotes the number of individuals of the population at time t. Intuitively, T_f is the maximal time that the population survives when the probability generating function of the reproduction law is $f(\cdot)$.

Fixed the p.g.f. $f(\cdot)$, we denote by $v_f(\cdot)$ the d.f. of the extinction time T_f, i.e.

$$v_f(t) = P(T_f \leq t),\ t \in \mathbb{R}.$$

Since $G(0^+) = 0$, then $v_f(0) = 0$. Furthermore, using the methods given in Athreya and Ney (1972) (see p. 139, Theorem IV.2.1), it is easy to deduce that $v_f(\cdot)$ is the unique bounded function that satisfies the integral equation:

$$\text{(E.1)} \qquad v_f(t) = \begin{cases} 0, & t < 0, \\ \displaystyle\int_0^t f(v_f(t-s))dG(s), & t \geq 0. \end{cases}$$

Moreover, let q_f be the extinction probability of a BHBP started with one ancestor and with reproduction law given by its p.g.f. $f(\cdot)$. It is clear that $q_f = P(T_f < \infty)$ and it is also well-known that $q_f = 1$ iff $m_f \leq 1$, where m_f denotes the reproduction mean associated to $f(\cdot)$. So that,

for such a p.g.f. $f(\cdot)$ with $m_f > 1$, $v_f(\cdot)$ is the d.f. of a non-proper r.v. because $P(T_f < \infty) < 1$. In any case, it follows that

$$\widetilde{v}_f(t) = P(T_f \leq t | T_f < \infty) = \frac{v_f(t)}{q_f},\ t \geq 0, \tag{E.2}$$

and from (E.1) it is easy to obtain that $\widetilde{v}_f(\cdot)$ also satisfies the equation

$$\widetilde{v}_f(t) = \int_0^t g(\widetilde{v}_f(t-s))dG(s),\ t \geq 0,$$

where $g(s) = q_f^{-1} f(q_f s)$ is a p.g.f. such that $m_g < 1$, that is, $\widetilde{v}_f(t) = v_g(t)$, for all $t \in \mathbb{R}$. Therefore, without loss of generality, from now on, in many situations we can consider a p.g.f. $f(\cdot)$ such that the extinction time T_f is a proper r.v., i.e. $m_f \leq 1$.

The d.f. $v_f(\cdot)$ inherits some properties of the d.f. $G(\cdot)$ as follows. Both of them have support on the non-negative real numbers. Moreover, if the d.f. of the life-length $G(\cdot)$ is discrete, then the d.f. of the extinction time $v_f(\cdot)$ is also discrete. For the absolutely continuous case we obtain the analogous result.

Proposition E.1 *If $G(\cdot)$ is an absolutely continuous d.f., then $v_f(\cdot)$ is also an absolutely continuous d.f.*

The d.f. $v_f(\cdot)$ is determined implicitly from (E.1). However, it is useful to obtain procedures which allow us to know or at least to approximate the value of this function on each point t. To this end, we introduce the functional operator $H_f(\cdot)$, defined on any function $u(\cdot)$ from the non-negative real numbers $\mathbb{R}_+$ to the closed interval $[0, 1]$, as follows:

$$H_f(u)(t) = \int_0^t f(u(t-s))dG(s),\ t \geq 0.$$

Also, for all $n \geq 1$, we denote by $H_f^n(\cdot)$ the n-th composition of the operator $H_f(\cdot)$, that is, $H_f^{n+1}(u)(\cdot) = H_f(H_f^n(u))(\cdot)$, $n = 1, 2, \ldots$ and $H_f^1(u)(\cdot) = H_f(u)(\cdot)$. Using this notation, from (E.1) we obtain that $v_f(\cdot)$ is the unique bounded function satisfying the fixed-point equation $u(\cdot) = H_f(u)(\cdot)$. We also derive the following result:

Theorem E.1 *If $f(\cdot)$ is a p.g.f., then for each function $h : \mathbb{R}_+ \to [0,1]$, it is verified that*

$$v_f(t) = \lim_{n\to\infty} H_f^n(h)(t),\ t \geq 0. \tag{E.3}$$

This result, besides giving us a way to approximate the d.f. $v_f(\cdot)$ at each point, provides a useful tool to investigate the behaviour of the extinction times for BHBPs with different reproduction laws and the same life–length distribution. So, next we consider the behaviour of $v_f(\cdot)$ depending on $f(\cdot)$, when $G(\cdot)$ is fixed.

Theorem E.2 *Let $f(\cdot)$ and $g(\cdot)$ be p.g.f. If $f(s) \leq g(s)$ for all $0 \leq s \leq 1$, then $v_f(t) \leq v_g(t)$ for all $t \geq 0$.*

Remark E.1 *It is not hard to obtain that if the reproduction law given by $f(\cdot)$ is stochastically greater than that given by $g(\cdot)$, then $f(s) \leq g(s)$ for all $0 \leq s \leq 1$. But, in general, the viceversa is not true.*

From the previous theorem we deduce that the condition $f(s) \leq g(s)$ for all $0 \leq s \leq 1$ implies that the extinction time of the BHBP with p.g.f. $f(\cdot)$ is stochastically greater than that of the BHBP with p.g.f. $g(\cdot)$, i.e., the monotonicity property of the p.g.f.s is inherited by the d.f. of the extinction time.

Now, we show in the following result that minor changes in the p.g.f. $f(\cdot)$ generates minor changes in the extinction time.

Theorem E.3 *Let $f(\cdot)$ be a p.g.f. such that $m_f < 1$. For each $\varepsilon > 0$, there exists $\delta = \delta(\varepsilon, f) > 0$ such that if $g(\cdot)$ is a p.g.f. satisfying*

$$\sup_{0\leq s\leq 1} |f(s) - g(s)| \leq \delta,$$

then

$$\sup_{0\leq t<\infty} |v_f(t) - v_g(t)| \leq \varepsilon.$$

Remark E.2 1) *It is important to point out that given a p.g.f. it is possible to find another one so close to that as one wants. Actually, fixed $f(\cdot)$ and any $\delta > 0$, there exists a p.g.f. $g(\cdot)$ such that $\sup_{0\leq s\leq 1} |f(s) - g(s)| \leq \delta$. Indeed, since $f(\cdot)$ is a uniformly continuous function on the*

interval $[0,1]$*, then there exists* $0<\alpha<1$ *such that* $|f(s)-f(s^*)|\leq\delta$*, for all* s,s^* *with* $0\leq s,s^*\leq 1$ *and* $|s-s^*|\leq\alpha$*. For each* $0\leq s\leq 1$*, let* $g(s)=f(\alpha+(1-\alpha)s)$*. We will show in the next section that* $g(\cdot)$ *is a p.g.f. Since* $\alpha+(1-\alpha)s-s\leq\alpha$ *for all* $0\leq s\leq 1$*, then* $\sup_{0\leq s\leq 1}|f(s)-g(s)|\leq\delta$*.* 2) *In the previous theorem, specifically, we have proved a continuity property for the d.f.* $v_f(\cdot)$ *depending on* $f(\cdot)$*, when* $m_f<1$*. Taking into account (E.2), we can also deduce this continuity property when* $m_f>1$*. Indeed, let* $f(\cdot)$ *be a p.g.f. such that* $m_f>1$*. From the embedded generation process associated with the BHBP and the equation* $f(q_f)=q_f$*, it is not hard to obtain the continuity of* q_f *depending on* $f(\cdot)$*. Moreover, since* $v_f(t)=q_f v_g(t)$*, where recall* $g(s)=q_f^{-1}f(q_f s)$ *is a p.g.f. such that* $m_g<1$*, then from the previous theorem the continuity property can be proved.*

6.3 Application to epidemic modelling

Branching processes have been widely used to model epidemics and to describe the evolution of an infectious disease following a SIR scheme, at least in their early stages, (see, for example, Andersson and Britton (2000), Ball and Donnelley (1995), Haccou, Jagers and Vatutin (2005), Kimeml and Axelrod (2002), Mode and Sleeman (2000) and Pakes (2003)). In particular, infectious diseases with long incubation period and negligible contagious time, such as avian flu, measles, mumps, can be described by a BHBP.

To model the spread of an infectious disease by using BHBP, we consider the following scheme. Let us assume that three types of individuals may exist in the population: infected, healthy but susceptible to catch the infection (susceptible individuals), and healthy and immune to this disease. The disease is spreading when an infected individual is in contact with susceptible individuals. Notice that during the incubation period, the infected individual as yet neither shows any symptoms of the disease nor passes the disease to any susceptible individual. Moreover, when the infectious disease is observed in an individual, this individual is either isolated (for example in human or animal populations) or culled (for example in animal populations with very dangerous diseases), so that the individual ceases to be infective. Hence, just after the incubation period

and before to be isolated or culled, there is a very short contact period (in comparison with the incubation one) in which the individual may infects others. We denote by p_k the probability that one infected individual contacts k healthy individuals, $k \geq 0$, and by α ($0 \leq \alpha \leq 1$) the proportion of immune individuals of the population. We suppose that both infected and immune individuals are dispersed uniformly in the population. Furthermore, we assume that the population size is fixed and large enough in comparison with the number of infected individuals, so that α and the contact distribution law, $\{p_k\}_{k\geq 0}$, can be considered stable along time (see Isham (2005)). Notice that this is neither a restriction in critical and subcritical processes because of their almost sure extinction, nor in the early stages of supercritical processes.

Under these assumptions, the probability that an infected individual transmits the disease to k susceptible individuals when α is the proportion of immune individuals in the population, is given by

$$p_{\alpha,k} = \sum_{j=k}^{\infty} \binom{j}{k} \alpha^{j-k}(1-\alpha)^k p_j, \tag{E.4}$$

i.e. the infected individual has been in contact with j healthy individuals and among them there have been k susceptible individuals. We call $\{p_{\alpha,k}\}_{k\geq 0}$ the infection distribution law when the proportion of immune individuals of the population is α. Notice that if every individual is non-immune, $\alpha = 0$, then every individual will be infected whenever he/she contacts an infected one, i.e. $p_{0,k} = p_k$, for all $k \geq 0$. On the other hand, if all individuals are immune, $\alpha = 1$, then the infection does not spread, i.e. $p_{1,k} = 0$, for all $k > 0$. Following this spreading scheme along time, infected individuals pass on the disease to other susceptible individuals and so on. We model the number of infected individuals in a population with a proportion α of immune individuals by a BHBP, such that its offspring law is determined by the infection distribution law $\{p_{\alpha,k}\}_{k\geq 0}$ and the d.f. of the life-length of an infected individual is given by an arbitrary d.f. $G(\cdot)$ of a non-negative r.v. By life-length we mean the period (measured in real time) till either he/she infects susceptible individuals or the disease disappears in this individual, that is, the incubation period. Notice that we assume the life-length of an infected individual depends neither on the proportion of immune individuals in the population nor on the contact distribution law.

In order to immunize a proportion of susceptible individuals, we suppose that a vaccination policy is applied. Our objective is to determine what proportion, α, of these individuals might be vaccinated/immunized to guarantee the extinction of the disease, possibly in a given period of time. We call this proportion vaccination level. Specifically, we deal with the problem of determining the optimal vaccination level depending not only on the speed of the transmission of the disease, expressed in terms of infection distribution law $\{p_{\alpha,k}\}_{k\geq 0}$, but also on the time till the epidemic becomes extinct after the vaccination process finishes. To this end, we first study the behaviour of the extinction time of the epidemic depending on the vaccination level, applying the results of the previous sections. Then, from this study, we propose an optimal vaccination level, and finally we illustrate determining of this optimal vaccination level by means of a simulation method.

6.4 The extinction time of the epidemic

In what follows, our goal is to investigate the distribution of the extinction time of a BHBP depending on the vaccination level α. To this end, for each α such that $0 \leq \alpha \leq 1$, we denote by $f_\alpha(\cdot)$ the p.g.f. of $\{p_{\alpha,k}\}_{k\geq 0}$. From (E.4) it is easy to obtain that

$$f_\alpha(s) = f(\alpha + (1-\alpha)s),\ 0 \leq s \leq 1, \tag{E.5}$$

being $f(\cdot)$ the p.g.f. of $\{p_k\}_{k\geq 0}$. Moreover, we denote by T_α the extinction time of a BHBP initiated at time 0 with a single infected individual and with p.g.f. $f_\alpha(\cdot)$ and by $v_\alpha(\cdot)$ the d.f. of T_α. Intuitively, T_α is the maximal time that the infection survives into the population when the proportion of immune individuals is α.

Also we denote by m the mean of contacts of an infected individual and by m_α the mean of susceptible individuals, who are infected by a contagious individual, given that the proportion of immune individuals in the population is α. Then, from (E.4) it is easy to calculate that

$$m_\alpha = (1-\alpha)m. \tag{E.6}$$

Taking into account (E.6), $m_\alpha \leq 1$ is equivalent to $\max\{0, 1-m^{-1}\} \leq \alpha \leq 1$, which depends on the mean of contacts of an infected individual.

In order to simplify the notations, from now on we denote by $\alpha_{\inf} = \max\{0, 1 - m^{-1}\}$ the smallest proportion of immune individuals, so that the infectious disease becomes extinct a.s.
From the properties of $f(\cdot)$, (E.5) and Theorems E.2 and E.3, it is not hard to obtain that for each $t \geq 0$, the function $v_\alpha(t)$ is non-decreasing and continuous on α for $\alpha_{\inf} < \alpha \leq 1$, i.e. in continuous way the greater is the proportion of immune individuals, the more probable is that the infectious disease disappears faster.

Furthermore, some parameters of T_α inherit these properties of $v_\alpha(\cdot)$. Next we investigate the monotonicity and the continuity properties of the quantiles of the distribution of the infection extinction time, depending on the proportion of the immune individuals into the population.

For fixed α and p, with $\alpha_{\inf} \leq \alpha \leq 1$ and $0 < p < 1$, we denote by t_p^α the quantile of order p of the variable T_α. We have the following result.

Theorem E.4 *Let p be such that $0 < p < 1$.*

1. *If $\alpha_{\inf} \leq \alpha_1 < \alpha_2 \leq 1$, then $t_p^{\alpha_2} \leq t_p^{\alpha_1}$.*

2. *If α is such that $0 < m_\alpha < m_{\alpha_{\inf}}$, then $\lim_{\widetilde{\alpha} \to \alpha^+} t_p^{\widetilde{\alpha}} = t_p^\alpha$.*

Moreover,

a) If $v_\alpha(t_p^\alpha) = p$, then $t_p^\alpha \leq \lim_{\widetilde{\alpha} \to \alpha^-} t_p^{\widetilde{\alpha}} \leq t^*$, with $t^* = \sup\{t : v_\alpha(t) = p\}$.

b) If $v_\alpha(t_p^\alpha) > p$, then $\lim_{\widetilde{\alpha} \to \alpha^-} t_p^{\widetilde{\alpha}} = t_p^\alpha$.

c) If $v_\alpha(\cdot)$ is an increasing and absolutely continuous function, then $\lim_{\widetilde{\alpha} \to \alpha} t_p^{\widetilde{\alpha}} = t_p^\alpha$.

Remark E.3 *Notice that if $G(\cdot)$ is an increasing and absolutely continuous function defined on the non–negative real numbers, we deduce from Proposition E.1 that $v_\alpha(\cdot)$ is also of the same type and therefore, for $\alpha_{\inf} < \alpha \leq 1$, t_p^α is a continuous function depending on α.*

6.5 Determining vaccination policies

When an infectious disease is strongly detrimental for the population where it is spreading, such that it becomes an epidemic, then a vaccination policy should be applied to prevent the susceptible individuals and terminate the epidemic. Since it is impossible to immunize the whole population in most of the cases, only a proportion of susceptible individuals can be prevented by vaccination. How to determine this proportion is an important problem which depends on multiple factors. A significant factor for public authorities to assess the vaccination efficiency, is the time that the infectious disease should be allowed to survive after vaccination.

In what follows we propose an optimal proportion of susceptible individuals to be immunized. Without loss of generality, we suppose that before vaccination, every healthy individual who is in contact with an infected individual is not immune, i.e. the contact always produces the infection. Then, before the vaccination, with probability p_k an infected individual passes the disease on k susceptible individuals. Moreover, after the vaccination process, we suppose that every vaccinated individual is immune to the infectious disease. If at the end of the vaccination process we have a proportion α of susceptible individuals which has been vaccinated, then with probability $p_{\alpha,k}$ (see (E.4)) an infected individual transmits the disease to k susceptible individuals.

To guarantee the extinction of the disease a.s., α should be at least equal to α_{inf}. Intuitively, we have obtained that the increasing of the vaccination level leads to the decreasing (stochastically) of the extinction time of the infection. Obviously, the best is to vaccinate all the population, but it is not reasonable from practical standpoint in most of the cases. That is why, we propose a possible way of defining optimal proportion of vaccinated individuals, to guarantee that the infection terminates by given instant of time after the vaccination process ended. The vaccination policy is based on the quantiles of the extinction time T_α. For fixed p and t, with $0 < p < 1$ and $t > 0$, we look for vaccination policies which guarantee that the infectious disease becomes extinct, with probability greater than or equal to p, not later than time t after the vaccination process ended. Let us suppose that we have vaccinated a proportion α of susceptible individuals. If at the end of the vaccination

process there is a single infected individual of the population, since this infected individual might have already lived some time before, then the probability that the disease becomes extinct no later than time t after vaccination process is greater than or equal to $v_\alpha(t)$. In Appendix a mathematical justification of this fact is provided.

On the other hand, if there are z infected individuals at the end of the vaccination process, since each individual reproduces/infects independently from the others, then the probability that the disease becomes extinct no later than time t after vaccination process can be bounded by $(v_\alpha(t))^z$.

Consequently, any vaccination level α such that $v_\alpha(t) \geq p^{(z)}$ or equivalently $t^\alpha_{p^{(z)}} \leq t$, with $p^{(z)} = p^{1/z}$, could be used. Taking this fact into account, we propose as optimal vaccination policy that one, which corresponds to the smallest α of all of them, i.e.

$$\begin{aligned} \alpha_q = \alpha_q(p,t,z) &= \inf\{\alpha : \alpha_{\inf} \leq \alpha \leq 1, v_\alpha(t) \geq p^{(z)}\} \\ &= \inf\{\alpha : \alpha_{\inf} \leq \alpha \leq 1, t^\alpha_{p^{(z)}} \leq t\}. \end{aligned}$$

Applying the monotonicity and continuity properties of the functions $v_\alpha(t)$ and t^α_p (depending on α) we have that $v_{\alpha_q}(t) \geq p^{(z)}$ and $t^{\alpha_q}_{p^{(z)}} \leq t$ if $\alpha_q > \alpha_{\inf}$. Notice that since $(v_\alpha(t))^z$ is a lower bound of the probability of interest, then some α less than α_q could also be followed to this aim. Moreover, although t and p have been fixed arbitrarily, in order to find a solution of the problem, it is necessary that $t \geq t^1_{p^{(z)}}$ or equivalently $p^{(z)} \leq v_1(t)$.

6.6 A simulation–based method for determining vaccination policies

In the previous paragraphs we have proposed a vaccination policy defined by α_q. This vaccination policy depends on the d.f. of extinction time. Therefore, to calculate α_q, it is necessary to know $v_\alpha(\cdot)$, for α such that $\alpha_{\inf} \leq \alpha \leq 1$. Although $v_\alpha(\cdot)$ satisfies (E.1), in general it is not possible to obtain this function in a closed form. Recently, some numeric and simulation methods have been provided in order to approximate the function satisfying (E.1) and (E.3). In what follows we determine α_q approximating $v_\alpha(\cdot)$ by means of a simulation–based method when $\{p_k\}_{k\geq 0}$

and $G(\cdot)$ are considered known. When α is fixed, such that $\alpha_{\inf} \leq \alpha \leq 1$, we apply the Monte–Carlo method to estimate the empirical d.f. of extinction time when the proportion of immune individuals is α. Taking different α's sufficiently close, then we approach α_q from its definition. To simulate the spread of the disease when the proportion of immune individuals is α, it is enough to know $G(\cdot)$ and $\{p_k\}_{k\geq 0}$. Usually, the life-length distribution and the contact distribution law are estimated from the information that becomes available as the epidemic proceeds (see, for example, Johnson, Susarla and Van Ryzin (1979)).

Next we illustrate the simulation-based method by means of the following example. Let the life-length of an infected individual follow gamma distribution $\Gamma(2,1)$. Also let the contact distribution law follow Poisson distribution with parameter m. These types of distributions have been related to such kind of problems (see for example Farrington and Grant (1999), Farrington et al. (2003) and Mode and Sleeman (2000)). From (E.5) we have

$$f_\alpha(s) = f(\alpha + (1-\alpha)s) = e^{-m(1-\alpha-(1-\alpha)s)} = e^{-m_\alpha(1-s)},\ 0 \leq s \leq 1,$$

which means that infection distribution law also follows Poisson distribution with parameter $m_\alpha = (1-\alpha)m$, which is the expectation of susceptible individuals catching the disease from infected individuals. Notice that, for fixed m, α is determined one-to-one by m_α. Therefore, instead of calculating α_q, we determine $m_q = (1-\alpha_q)m$. From the definition of α_q, we obtain

$$m_q = m_q(t,p,z) = \sup\{m_p : 0 \leq m_p \leq 1, u_{m_p}(t) \geq p^{(z)}\},$$

where $u_{m_p}(\cdot)$ is the d.f. of the extinction time when infection distribution law follows Poisson distribution with parameter m_p. Notice that $v_\alpha(\cdot) = u_{m_\alpha}(\cdot)$ and that m_q is independent on the magnitude of m.

Therefore, to approximate m_q we only need to obtain the empirical distribution $u_{m_p}(\cdot)$ for $0 \leq m_p \leq 1$, using the Monte–Carlo method. To this end, for each fixed m_p, 10.000 processes have been simulated and their extinction time have been calculated. In left graphic of Figure 6.1 the behaviour of empirical d.f. $u_{m_p}(\cdot)$ for several m_p's is shown. Notice that increasing m_p the extinction time also increases (stochastically).

As an example, to compute m_q we take $p = 0.9$, $t = 15$ and $z = 3$. Then we have $p^{(z)} = 0.965$. The behaviour of the estimated value of

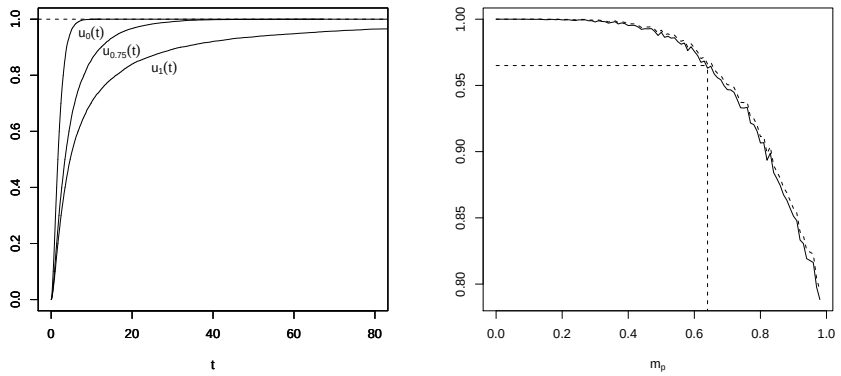

Figure 6.1: Left graphic: Behaviour of the empirical distribution functions of $u_{m_p}(\cdot)$ depending on m_p. Right graphic: Behaviour of estimated value of $u_{m_p}(15)$, jointly with an upper confidence bound at level 95%, depending on m_p (doted line).

$u_{m_p}(15)$, jointly with an upper confidence bound at level 95%, depending on m_p, is given in the right graphic of Figure 6.1. It is illustrated that, given $p^{(z)} = 0.965$, an approximation of $m_q(15, 0.9, 3)$ is 0.64.

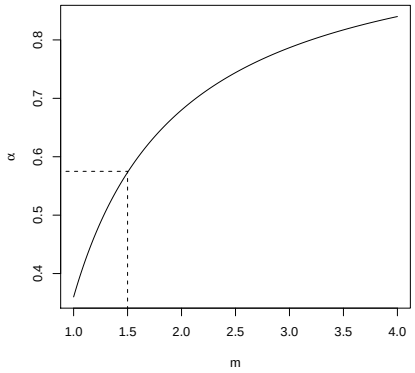

Figure 6.2: Proportion of individuals to be vaccinated depending on m and taking into account $m_q(15, 0.9, 3) = 0.64$.

Finally, in Figure 6.2 we illustrate the proportion of individuals to be vaccinated depending on m and taking into account $m_q(15, 0.9, 3)$. Notice that, if the mean m of contacts per individual is close to 1.5, then we need to vaccinate about 57% of the population in order to guarantee that the infectious disease becomes extinct with probability greater than or equal to 0.9 not latter than time 15 after vaccination period ended.

Remark E.4 *For the computer simulation, we used the language and environment for statistical computing and graphics* **R** *("GNU S") (see R Development Core Team (2009)).*

6.7 Proofs

In this paragraph we provide the proofs of the results stated in the previous ones.

Proof of Proposition E.1

For all $t \geq 0$, we have

$$\begin{aligned} v_f(t) &= \int_0^t f(v_f(t-s))dG(s) \\ &= f(0)G(t) + (1-f(0))\int_0^t F_f(t-s)dG(s), \end{aligned} \tag{E.7}$$

with $F_f(y) = (1-f(0))^{-1}(f(v_f(y)) - f(0))$ for $y \geq 0$. Since $f(\cdot)$ is a p.g.f. and $v_f(\cdot)$ is a d.f., then $F_f(\cdot)$ is also a d.f. on non-negative real numbers, and therefore

$$\int_0^t F_f(t-s)dG(s) = \int_0^\infty F_f(t-s)dG(s) = (F_f * G)(t),$$

is the convolution of $F_f(\cdot)$ and $G(\cdot)$. If $G(\cdot)$ is an absolutely continuous d.f., then it is well–known that $F_f * G(\cdot)$ is also an absolutely continuous d.f. (see Billingsley (1986), p. 272). Therefore, since $v_f(\cdot)$ is a convex linear combination of two absolutely continuous d.f., then it is also an absolutely continuous d.f. □

Proof of Theorem E.1

Let $h(\cdot)$ be a function from $\mathbb{R}_+$ to the closed interval $[0,1]$. In order to obtain the result it is enough to prove the following four statements:

S1. For all $t \geq 0$, $\widetilde{G}(t) \leq H_f(h)(t) \leq G(t)$, with $\widetilde{G}(t) = f(0)G(t)$.

S2. $H_f(\cdot)$ is a non-decreasing operator, i.e. if $h_i : \mathbb{R}_+ \to [0,1]$, with $i \in \{1,2\}$, are two functions such that $h_1(t) \leq h_2(t)$ for all $t \geq 0$, then $H_f(h_1)(t) \leq H_f(h_2)(t)$ for all $t \geq 0$.

S3. For all $t \geq 0$, there exist $u_1(t) = \lim_{n\to\infty} H_f^n(\widetilde{G})(t)$ and $u_2(t) = \lim_{n\to\infty} H_f^n(G)(t)$.

S4. $u_1(\cdot)$ and $u_2(\cdot)$ are solutions of the fixed point equation $u(\cdot) = H_f(u)(\cdot)$, and then $v_f(\cdot) = u_1(\cdot) = u_2(\cdot)$.

Indeed, from these statements it is easy to prove that for all $n \geq 1$ and $t \geq 0$

$$\begin{aligned} v_f(t) &= u_1(t) = \lim_{n\to\infty} H_f^n(\widetilde{G})(t) \leq \lim_{n\to\infty} H_f^{n+1}(h)(t) \\ &\leq \lim_{n\to\infty} H_f^n(G)(t) = u_2(t) = v_f(t). \end{aligned}$$

It remains to prove the statements *S1-S4*.

S1. Since $f(\cdot)$ is an increasing function such that $f(1) = 1$, we have

$$\widetilde{G}(t) = f(0)G(t) \leq \int_0^t f(h(t-s))dG(s) \leq G(t).$$

S2. Since $f(\cdot)$ is an increasing function and $h_1(t) \leq h_2(t)$ for all $t \geq 0$, then the statement is shown.

S3. By *S1*, *S2* and taking iterations we have, for each $t \geq 0$, that $\{H_f^n(\widetilde{G})(t)\}_{n\geq 1}$ is an upper bounded non-decreasing sequence and $\{H_f^n(G)(t)\}_{n\geq 1}$ is a lower bounded non–increasing sequence. So, the statement is deduced.

S4. Since $f(\cdot)$ is a continuous function, then by *S3* and applying the Dominated Convergence Theorem it follows for each fixed $t \geq 0$

$$\begin{aligned} u_1(t) &= \lim_{n\to\infty} H_f^{n+1}(\widetilde{G})(t) \\ &= \lim_{n\to\infty} \int_0^t f(H_f^n(\widetilde{G})(t-s))dG(s) \\ &= \int_0^t f\left(\lim_{n\to\infty} H_f^n(\widetilde{G})(t-s)\right) dG(s) \\ &= \int_0^t f(u_1(t-s))dG(s) = H_f(u_1)(t). \end{aligned}$$

Moreover, since $v_f(\cdot) = H_f(v_f)(\cdot)$ and $u_1(\cdot)$ is bounded, then $u_1(\cdot) = v_f(\cdot)$, because only one bounded function is a solution of (E.1) (see Athreya and Ney (1972), p. 139). In the same way we deduce the statement for the function $u_2(\cdot)$. □

Proof of Theorem E.2

Since $v_f(\cdot)$ is a distribution function and $f(s) \leq g(s)$ for all $0 \leq s \leq 1$, then for each $t \geq 0$

$$H_f(v_f)(t) \leq H_g(v_f)(t).$$

Taking this fact into account and (E.1), we have $v_f(t) \leq H_g(v_f)(t)$, for all $t \geq 0$. Moreover, by *S2* in proof of Theorem E.1 and taking again iterations, for all $n \geq 1$ and $t \geq 0$, we obtain

$$v_f(t) \leq H_g^n(v_f)(t),$$

and the proof is completed from Theorem E.1. □

Remark E.5 *We notice that the proof of Theorem E.1 and Theorem E.2 hold even when $m_f > 1$.*

Proof of Theorem E.3

We show by induction on n, for each $n \geq 1$, that for all $t \geq 0$

$$|H_f^n(G)(t) - H_g^n(G)(t)| \leq \varepsilon(1 - m_f^n). \tag{E.8}$$

Fixed $t \geq 0$ and $\delta = \varepsilon(1 - m_f)$, since $G(\cdot)$ is a d.f., for $n = 1$ we deduce that

$$|H_f(G)(t) - H_g(G)(t)| \leq \int_0^t |f(G(t-s)) - g(G(t-s))| dG(s) \leq \varepsilon(1 - m_f).$$

By induction hypothesis, (E.8) holds for n. Then for $n+1$ we have

$$\begin{aligned} |H_f^{n+1}(G)(t) - H_g^{n+1}(G)(t)| &\leq |H_f(H_f^n(G))(t) - H_f(H_g^n(G))(t)| \\ &+ |H_f(H_g^n(G))(t) - H_g(H_g^n(G))(t)|. \end{aligned}$$

By *S1* and *S2* of proof of Theorem E.1 and iterating, we deduce, for all $n \geq 1$, that $H_f^n(G)(t) \leq 1$ and $H_g^n(G)(t) \leq 1$. Taking these facts into account, we obtain

$$\begin{aligned} &|H_f(H_f^n(G))(t) - H_f(H_g^n(G))(t)| \leq \\ &\quad \leq \int_0^t |f(H_f^n(G)(t-s)) - f(H_g^n(G)(t-s))| dG(s) \\ &\quad \leq m_f \sup_{0 \leq s^* < \infty} |H_f^n(G)(s^*) - H_g^n(G)(s^*)| \\ &\quad \leq \varepsilon(1 - m_f^n) m_f, \end{aligned}$$

and

$$\begin{aligned} &|H_f(H_g^n(G))(t) - H_g(H_g^n(G))(t)| \leq \\ &\quad \leq \int_0^t |f(H_g^n(G)(t-s)) - g(H_g^n(G)(t-s))| dG(s) \\ &\quad \leq \varepsilon(1 - m_f). \end{aligned}$$

Therefore, we conclude that

$$|H_f^{n+1}(G)(t) - H_g^{n+1}(G)(t)| \leq \varepsilon(1 - m_f^n) m_f + \varepsilon(1 - m_f) = \varepsilon(1 - m_f^{n+1}).$$

Since $m_f < 1$, from (E.8) by applying Theorem E.1 we obtain

$$\sup_{0 \leq t < \infty} |v_f(t) - v_g(t)| \leq \varepsilon,$$

and therefore the proof is completed. □

Proof of Theorem E.4

Let p be such that $0 < p < 1$.

1. Let $\alpha_1,\ \alpha_2$ be such that $\alpha_{\inf} \leq \alpha_1 < \alpha_2 \leq 1$. Taking into account stochastic monotonicity property of the extinction time, we obtain

$$p \leq v_{\alpha_1}(t_p^{\alpha_1}) \leq v_{\alpha_2}(t_p^{\alpha_1}),$$

and therefore, by definition of $t_p^{\alpha_2}$, we deduce that $t_p^{\alpha_2} \leq t_p^{\alpha_1}$.

2. Let α be such that $0 < m_\alpha < m_{\alpha_{\inf}}$. From the previous part, we guarantee the existence of $\lim_{\widetilde{\alpha}\to\alpha^+} t_p^{\widetilde{\alpha}}$, which is equal to $\overline{t} = \sup\{t_p^{\widetilde{\alpha}} : \widetilde{\alpha} > \alpha\}$. Therefore $\overline{t} \leq t_p^{\alpha}$. On the other hand, from continuity property of the extinction time, we deduce that for each $\varepsilon > 0$ there exists $\eta = \eta(\varepsilon, \alpha) > 0$ such that

$$p - \varepsilon \leq v_{\widetilde{\alpha}}(t_p^{\widetilde{\alpha}}) - \varepsilon \leq v_\alpha(t_p^{\widetilde{\alpha}}) \leq v_\alpha(\overline{t}),$$

for all $\widetilde{\alpha}$ such that $0 < \widetilde{\alpha} - \alpha \leq \eta$. Then $p \leq v_\alpha(\overline{t})$ and so $t_p^{\alpha} = \overline{t}$.

(a) Applying the first part, we deduce that $\lim_{\widetilde{\alpha}\to\alpha^-} t_p^{\widetilde{\alpha}}$ exists, that it is equal to $\underline{t} = \inf\{t_p^{\widetilde{\alpha}} : \widetilde{\alpha} < \alpha\}$, and that $t_p^{\alpha} \leq \underline{t}$. Next, we prove that $\underline{t} \leq t^*$. We split the proof in two cases, $v_\alpha(t^*) > p$ and $v_\alpha(t^*) = p$. First we consider the case $v_\alpha(t^*) > p$. Let $\varepsilon = v_\alpha(t^*) - p$. From continuity property of the extinction time we deduce that there exists $\eta = \eta(\varepsilon, \alpha) > 0$ such that

$$v_\alpha(t^*) - v_{\widetilde{\alpha}}(t^*) \leq \varepsilon = v_\alpha(t^*) - p$$

for all $\widetilde{\alpha}$, $0 < \alpha - \widetilde{\alpha} \leq \eta$. Then $p \leq v_{\widetilde{\alpha}}(t^*)$ and therefore we have $t_p^{\widetilde{\alpha}} \leq t^*$ and consequently $\underline{t} \leq t^*$.

Finally, we consider the case $v_\alpha(t^*) = p$. By the definition of t^*, we have $p < v_\alpha(t)$ for all $t > t^*$. For each $t > t^*$, let $\varepsilon = v_\alpha(t) - p$. From continuity property of the extinction time, we deduce that there exists $\eta = \eta(\varepsilon, \alpha) > 0$ such that

$$v_\alpha(t) - v_{\widetilde{\alpha}}(t) \leq \varepsilon = v_\alpha(t) - p,$$

for all $\widetilde{\alpha}$, $0 < \alpha - \widetilde{\alpha} \leq \eta$. Then $p \leq v_{\widetilde{\alpha}}(t)$, $t_p^{\widetilde{\alpha}} \leq t$ and $\underline{t} \leq t$, and consequently $\underline{t} \leq t^*$.

(b) It is proved as the previous case when $v_\alpha(t^*) > p$, replacing t^* by t_p^{α}.

(c) From (a) we obtain that $\lim_{\widetilde{\alpha}\to\alpha^-} t_p^{\widetilde{\alpha}} = t_p^{\alpha}$, and the proof is completed. □

6.8 Appendix

We consider a BHBP initiated with one individual, with reproduction law $\{p_{k,\alpha}\}_{k\geq 0}$, where $0 \leq \alpha \leq 1$, with d.f. of the initial progenitor's life-length $G^*(\cdot)$ and with d.f. of the life–length $G(\cdot)$ for other individuals. We suppose that $G^*(t) \geq G(t)$ for all $t \geq 0$. In epidemiological context, this condition reflects the fact that the life-length distribution $G^*(\cdot)$ of the initial individual after vaccination, is always less than or equal to its total life-length, given by $G(\cdot)$.

We denote by $\widehat{T}_\alpha$ the extinction time of such a BHBP. Also, we denote by $\widehat{v}_\alpha(\cdot)$ the d.f. of the extinction time $\widehat{T}_\alpha$, i.e. $\widehat{v}_\alpha(t) = P(\widehat{T}_\alpha \leq t)$, for all $t \in \mathbb{R}$. Following a heuristic derivation as in Athreya and Ney (1972) (see p. 138) we obtain the integral equation

$$\widehat{v}_\alpha(t) = \int_0^t f_\alpha(v_\alpha(t-s))dG^*(s),\ t \geq 0. \tag{E.9}$$

From (E.7) and (E.9), for all $t \geq 0$ one obtains

$$v_\alpha(t) = f_\alpha(0)G(t) + (1 - f_\alpha(0))(F_\alpha * G)(t)$$

and

$$\widehat{v}_\alpha(t) = f_\alpha(0)G^*(t) + (1 - f_\alpha(0))(F_\alpha * G^*)(t),$$

where $F_\alpha * G^*(\cdot)$ means the convolution of $F_\alpha(\cdot)$ and $G^*(\cdot)$, with

$$F_\alpha(y) = (1 - f_\alpha(0))^{-1}(f_\alpha(v_\alpha(y)) - f_\alpha(0)),$$

for all $y \geq 0$. Since $G^*(t) \geq G(t)$ for all $t \geq 0$, then $(F_\alpha * G^*)(t) \geq (F_\alpha * G)(t)$ for all $t \geq 0$ and therefore $\widehat{v}_\alpha(t) \geq v_\alpha(t)$, for all $t \geq 0$.

Chapter 7

Sevastyanov's Branching model in epidemiological modelling

7.1 Introduction

When an infectious disease is strongly detrimental for the population where it is spreading, control measures should be applied to protect the susceptible individuals. Vaccination programme represents one of the most effective ways of controlling. However, immunizing the whole population is impossible in most of cases (because there exists a real impossibility or it is very expensive) and then only a proportion of susceptible individuals can be immunized by vaccination. In this last situation, infections can still occur and their spread depend on the vaccination level. How to determine this proportion is an important public health problem in its own right, which depends on multiple factors. A significant factor for public authorities to assess the vaccination efficiency is the time elapsed by the infectious disease in becoming extinct after vaccination, called time to extinction of the disease.

The aim of this section is to provide an approach to this problem modelling epidemic spread and controlling its time to extinction by means of branching processes. These processes have been applied widely to model epidemic spread (see for example the monographs Andersson and Britton (2000), Daley and Gani (1999), Mode and Sleeman (2000) or

Pakes (2003)).

In terms of epidemic spreading we draw our attention to the SIR (Susceptible–Infective–Removed) model. Measles, mumps or avian flu are examples of infectious diseases which follow this spreading scheme model. We notice that branching processes approach is appropriate for homogeneously mixing population, when the number of infected individuals is small in relation to the total population size (see Isham (2005)). For this reason, we shall assume this scenario. Clearly this happens during the early stages of an epidemic.

The study of the spread of infectious disease following the SIR model and depending on a vaccination/immunized level has been considered in De Serres, Gay and Farrington (2000), using branching processes in discrete time. However, these models are not appropriate to evaluate the time to extinction in real time, but only by generations. This is the reasons for suggesting here a more accurate approach to this problem. From now on, we propose to model the number of infectious individuals in the population depending on the vaccination level by means of Sevast'yanov's age-dependent branching processes (see Sevast'yanov (1971)). This model is a particular case of the general branching process (see Jagers (1975), also called Crump–Mode–Jagers (CMJ) branching process, which is the most adequate model to fit infectious diseases following SIR scheme (see Ball and Donnelley (1995)). The Sevast'yanov's branching process (SBP) is specially adequate to model the evolution of diseases with incubation period (and a negligible contact period) for which the virulence of the disease could be a function of this period. Therefore, using SBPs, our target is to determine the optimal proportion of susceptible individuals which might be immunized by vaccination to guarantee the extinction of the disease within a given period of time. An advance without proofs of this work has been published in Gonzáles, Martínez and Slavtchova–Bojkova (2009).

The chapter has been splitted in 8 subsections. First, we model the spread of the disease by way of SBPs which depend on the proportion of immune individuals in the population. For that reason in the subsequent section we consider the time to extinction of an infectious disease, depending on the proportion of immune individuals into the population. Then, we study the main monotonicity and continuity properties of the time to extinction. In the subsequent section, first we propose a policy

for defining the optimal vaccination/immunized level, based on the mean of the time to extinction distribution of the disease. Moreover, we provide a simulation based method to calculate the optimal proportion of susceptible individuals to be vaccinated. At the end of this chapter we analyze the data from avian influenza spreading in Vietnam at the end of 2006. In the following section we point out concluding remarks. Finally, the proofs are consigned to the end in the Section 6.9.

7.2 Model of epidemic spread

We assume that three types of individuals may exist in the population: infected, healthy but susceptible to catch the infection (susceptible individuals), and healthy and immune to this disease (immune individuals). The disease is spreading when an infected individual is in contact with a susceptible one and any contact between infectious and susceptible individuals implies new infective. The survival time of the disease in an infected individual will be treated as the "age" of this individual in the branching model. On the other hand, it is essential for the epidemic we are trying to model, that the survival time of the disease consists of two periods: an incubation or latency period and comparatively very short (negligible) contact period. During the incubation period the infectious individual does not yet pass the disease to any susceptible and the symptoms of the disease do not appear yet in this individual. Moreover, when the infectious disease is observed in an individual, this is either isolated (for example in the case of human populations) or culled (for example in the case of very contagious animal diseases like classical swine fever, foot–and–mouth disease or avian influenza), and then the individual stops being infective. For that reason we consider that the "offspring", meaning in epidemic setting the number of contacts, is produced in a very short period of time (called the contact period) and that it happens only once after the incubation period. One final but very essential remark is that the disease may have different levels of severity during its survival period. So, it would be a mistake to model a survival time of a disease and the number of contacts as mutually independent. All the above considerations lead us to conclude that SBP is adequate to fit the evolution of an infectious disease with these characteristics.

More specifically, for modelling the epidemic spread we denote by $p_k(u)$ the probability that one infected individual with survival time (incubation plus contact periods) $u > 0$ contacts k healthy individuals, $k \geq 0$, and by α $(0 \leq \alpha \leq 1)$ the proportion of immune individuals in the population. We assume that the population size is fixed and large enough so that α and the family of contact distribution laws, $\{p_k(u)\}_{k\geq 0}$, $u > 0$, can be considered stable along time. Then, it is not hard to obtain that the probability that an infected individual with survival time $u > 0$ transmits the disease to k susceptible individuals is given by

$$p_{\alpha,k}(u) = \sum_{j=k}^{\infty} \binom{j}{k} \alpha^{j-k}(1-\alpha)^k p_j(u), \tag{F.1}$$

i.e., the infected individual with survival time u has been in contact with $j(= k, k+1, \ldots)$ healthy individuals and among them there have been k susceptible individuals. We call the family $\{p_{\alpha,k}(u)\}_{k\geq 0}$, $u > 0$, the infection distribution laws when the proportion of immune individuals in the population is α. Notice that if every individual is non-immune, $\alpha = 0$, then every individual will be infected whenever contacts an infected one, i.e., $p_{0,k}(u) = p_k(u)$, for all $k \geq 0$, $u > 0$. On the other hand, if all individuals are immune, $\alpha = 1$, then the infection does not spread, i.e. $p_{1,k}(u) = 0$, for all $k \geq 0$, $u > 0$. Following this spreading scheme along time, infected individuals pass on the disease at the end of their survival time to other susceptible individuals and so on. We model the number of infected individuals when the proportion of immune individuals in the population is α by a SBP, such that its offspring law is determined by the family of infection distribution laws $\{p_{\alpha,k}(u)\}_{k\geq 0}$, $u > 0$, and the distribution function (d.f.) of the survival time of an infected individual is given by an arbitrary d.f. $G(\cdot)$ on the non-negative real numbers. Let us remind that by survival time we mean the period (measured in real time) consisting from the incubation period and contact period (very short–negligible in comparison to the incubation period). Notice that we assume the family of contact distribution laws depends on the survival time of each infected individual.

7.3 The time to extinction of the epidemic

The objective of this section is to investigate the distribution of the time to extinction of a SBP depending on the vaccination level α and when the family of contact distribution laws is $\{p_k(u)\}_{k\geq 0},\ u > 0$. To this end, for each α, $0 \leq \alpha \leq 1$, we denote by T_α the time to extinction of a SBP initiated at time 0 with a single infected individual, with family of infection distribution laws $\{p_{\alpha,k}(u)\}_{k\geq 0},\ u > 0$, and with d.f. of the survival time $G(\cdot)$. Intuitively, T_α is the maximal time that the infection survives into the population when the proportion of immune individuals is α. From now on, we denote by $v_\alpha(\cdot)$ the d.f. of the extinction time T_α, i.e. $v_\alpha(t) = P(T_\alpha \leq t)$ for all $t \in \mathbb{R}$. For each $u > 0$ we also denote by $f_\alpha(u, \cdot)$ the probability generating function (p.g.f.) of $\{p_{\alpha,k}(u)\}_{k\geq 0}$. Moreover, we suppose that $G(0^+) = 0$, i.e., there is null probability of instantaneous *death* and consequently $v_\alpha(0) = 0$. Then, from Sevast'yanov (1971) we deduce that $v_\alpha(\cdot)$ is the unique bounded function such that

$$v_\alpha(t) = \begin{cases} 0, & t < 0, \\ \displaystyle\int_0^t f_\alpha(u, v_\alpha(t-u))dG(u), & t \geq 0. \end{cases} \tag{F.2}$$

This expression plays an important role in our study, together with the following relation between α and the family of contact distribution laws. Let $m(u)$ be the mean of contacts of an infected individual with survival time u, and $m_\alpha(u)$ be the mean number of susceptible individuals which are infected by a contagious individual with survival time u, given that the proportion of immune individuals in the population is α. Let also $m = \int_0^\infty m(u)dG(u) < \infty$ and $m_\alpha = \int_0^\infty m_\alpha(u)dG(u) < \infty$, $0 \leq \alpha \leq 1$. Intuitively, m is the average number of contacted individuals by a contiguous individual during its survival time and m_α is the average number of infected individuals when the vaccination level is α. Then, from (F.1) it is easy to obtain that

$$m_\alpha = (1-\alpha)m. \tag{F.3}$$

Also, it is easy to prove that

$$f_\alpha(u, s) = f(u, \alpha + (1-\alpha)s),\ 0 \leq s \leq 1,\ u > 0, \tag{F.4}$$

with $f(u, \cdot)$ the p.g.f. of the contact distribution law $\{p_k(u)\}_{k\geq 0},\ u > 0$.

Moreover, let $q_\alpha = P(T_\alpha < \infty)$ be the extinction probability of a SBP with family of reproduction laws $\{p_{\alpha,k}(u)\}_{k\geq 0}$, $u > 0$. It is well known that $q_\alpha = 1$ iff $m_\alpha \leq 1$ (see Sevast'yanov (1971)). Notice that m_α is the critical threshold parameter of our model. So that, for such an α for which $m_\alpha > 1$, $v_\alpha(\cdot)$ is the d.f. of a non-proper random variable (r.v.) because $P(T_\alpha < \infty) < 1$.

From now on, we consider α such that the extinction time T_α is a finite r.v., i.e. $m_\alpha \leq 1$, which implies that the infectious disease becomes extinct almost surely (a.s.). Taking into account (F.3), $m_\alpha \leq 1$ is equivalent to $\max\{0, 1 - m^{-1}\} \leq \alpha \leq 1$, which depends on the mean of contacts of an infected individual. In order to simplify the notations, we denote by $\alpha_{inf} = \max\{0, 1-m^{-1}\}$ the smallest proportion of immune individuals, so that the infectious disease becomes extinct a.s. Notice that the corresponding mean $m_{\alpha_{inf}} = \min\{1, m\}$ is the greatest mean number of susceptible individuals catching the disease by an infected individual, so that it is guaranteed that the disease becomes extinct a.s. Moreover, $m_1 = 0$, i.e., the infectious disease does not spread to any susceptible individual and therefore the extinction time is given by the survival time of the initial infected individual, i.e., $v_1(t) = G(t)$ for all $t \geq 0$. It stands to reason that if there are non-immune individuals into the population, then it is probable that the infectious disease takes more time to become extinct. In the following result, we show this fact investigating the behaviour of $v_\alpha(\cdot)$ depending on the parameter α and when the family of contact distribution laws is fixed.

Theorem F.1 *If $0 \leq \alpha_1 < \alpha_2 \leq 1$, then $v_{\alpha_1}(t) \leq v_{\alpha_2}(t)$, for all $t \geq 0$.*

Intuitively, it is clear that the greater is the proportion of the immune individuals, more probable the infectious disease disappears faster. Consequently, for any α with $\alpha_{inf} \leq \alpha \leq 1$, the d.f. $v_\alpha(\cdot)$ is upper bounded by $v_1(\cdot) = G(\cdot)$ and lower bounded by $v_{\alpha_{inf}}(\cdot)$. Furthermore, all of them are lower bounded by $v_0(\cdot)$, which is not necessary to be a proper d.f.

Moreover, we obtain that minor change in the proportion of the immune individuals causes minor change in the extinction time.

Theorem F.2 *Let α be such that $m_\alpha < m_{\alpha_{inf}}$. Then for each $\varepsilon > 0$ there exists $\eta = \eta(\varepsilon, \alpha) > 0$ such that for all α^*, with $m_{\alpha^*} \leq 1$ and*

$|\alpha - \alpha^*| \leq \eta$, *it is satisfied*

$$\sup_{0 \leq t < \infty} |v_\alpha(t) - v_{\alpha^*}(t)| \leq \varepsilon.$$

More specifically, we have proved the continuity of the d.f. $v_\alpha(\cdot)$ depending on α, for $\alpha_{inf} < \alpha \leq 1$. Notice that α_{inf} has been excluded, which matches with $m_\alpha = \min\{1, m\}$. This is not necessary if $m < 1$. Moreover, the continuity is uniform along the time.

Furthermore, some parameters of T_α inherit these properties of $v_\alpha(\cdot)$. In what follows we establish the monotonicity and the continuity properties of the mean of the distribution of the infection extinction time, depending on α. Let's denote by μ_α the mean of time to extinction of infectious disease when the proportion of immune individuals is α. Since T_α is a non-negative r.v., then

$$\mu_\alpha = E[T_\alpha] = \int_0^\infty (1 - v_\alpha(t))dt. \tag{F.5}$$

Theorem F.3

1. *If* $\alpha_{inf} \leq \alpha_1 < \alpha_2 \leq 1$, *then* $\mu_{\alpha_2} \leq \mu_{\alpha_1}$.

2. *If* $\overline{\alpha}$ *is such that* $0 < m_{\overline{\alpha}} < m_{\alpha_{inf}}$ *and* $\sup\{\mu_\alpha : \overline{\alpha} < \alpha \leq 1\} < \infty$, *then* $\mu_{\overline{\alpha}}$ *is finite and* $\mu_{\overline{\alpha}} = \lim_{\widetilde{\alpha} \to \overline{\alpha}^+} \mu_{\widetilde{\alpha}}$. *Moreover, for all* α *with* $\overline{\alpha} < \alpha \leq 1$, *it follows that* $\lim_{\widetilde{\alpha} \to \alpha} \mu_{\widetilde{\alpha}} = \mu_\alpha$.

Remark F.1 *If the process starts with* z *infected individuals, then its time to extinction when the proportion of immune individuals in the population is* α, *will be* $T_{\alpha,z} = \max\{T_\alpha^{(1)}, \ldots, T_\alpha^{(z)}\}$, *where* $T_\alpha^{(i)}$ *are i.i.d. r.v. with the same distribution as* T_α. *So denoting by* $v_{\alpha,z}(\cdot)$ *the distribution function of* $T_{\alpha,z}$, *we have that* $v_{\alpha,z}(t) = (v_\alpha(t))^z$, $t \in \mathbb{R}$. *From this expression and considering the properties of the power functions, it is easy to establish for* $v_{\alpha,z}(\cdot)$ *the same properties of monotonicity and continuity as those of* $v_\alpha(\cdot)$. *Moreover, these properties can be extended to the mean value of* $T_{\alpha,z}$, *that we will denote by* $\mu_{\alpha,z}$.

7.4 Determining vaccination policies

In this section we propose a method of obtaining the optimal proportion of susceptible individuals to be immunized. To guarantee the extinction of the disease almost surely (a.s.), the proportion of immune individuals in the population after vaccination, α, should be at least equal to α_{inf}. But, we are going to propose a possible way of defining optimal proportion of individuals to be vaccinated (immunized), to guarantee not only that the infection terminates after the vaccination period but also that this happens within a given period of time. The procedure is based on the mean of the time to extinction.

Let us recall that we model the spread of the disease by a SBP as follows. Without loss of generality, we suppose that before vaccination, every healthy individual which is in contact with an infected individual is non-immune, i.e. the contact always produces the infection. At an arbitrary time t_0 after the infection occurred into the population, the vaccination process of susceptible individuals starts. We suppose that this vaccination process finishes at time t_1. Therefore $t_1 - t_0$ is the time that is taken for immunization, called the vaccination period. We suppose that this vaccination period is fixed a priori by public authorities and that it does not depend on the proportion to be vaccinated. We also suppose that every vaccinated individual is immune to the infectious disease at least after time t_1. Actually, we consider the vaccination period to include not only the vaccination process but also the time that each vaccinated individual takes to develop the immunological response, and that the efficacy of vaccination is complete. Given the binomial scheme, this latter assumption does not lack of generality.

7.5 Vaccination based on the mean value of the time to extinction

For fixed $\tau > 0$, we are interested in investigating vaccination policies, which guarantee that the average time to extinction of an infection after vaccination period, t_1, is less than or equal to $t_1 + \tau$. We determine these vaccination policies applying the results of the previous section as follows. Let us suppose that we have vaccinated a proportion α of

susceptible individuals. If at the end of the vaccination period there is a single infected individual into the population, then this infected individual might have already lived some time before time t_1. Therefore the probability that the disease becomes extinct no latter than time $t_1+\tau$ is greater than or equal to $v_\alpha(\tau)$.

However, the number of infected individuals at time t_1 is a random variable depending on α and on the number of infected individuals at the time t_0. We shall approximate it by its expected value. In general this is hard to calculate, but it is upper-bounded by the expected number of infected individuals at time t_1 providing the vaccination policy has not been applied. Indeed, if $Z(t_1)$ denotes the number of infected individuals at time t_1, assuming that there has been no vaccination and the individuals have already lived some time before t_1, then the probability that the disease becomes extinct no later than time $t_1+\tau$ is greater than or equal to $F(t_1, v_\alpha(\tau))$, where $F(t_1,\cdot)$ denotes the p.g.f. of $Z(t_1)$. By Jensen's inequality, $F(t_1, v_\alpha(\tau)) \leq (v_\alpha(\tau))^{E[Z(t_1)]}$. Therefore, if z is the greatest integer number smaller than or equal to the expected value $E[Z(t_1)]$, then the probability that the disease becomes extinct no latter than time $t_1+\tau$ can be bounded by $v_{\alpha,z}(\tau) = (v_\alpha(\tau))^z$. The expected value of $Z(t_1)$ can be determined by means of a renewal integral equation (see Sevast'yanov (1971)).

Then, any vaccination level α such that $\mu_{\alpha,z} \leq \tau$ could be followed. The optimal vaccination policy is that one which corresponds to the smallest α, that is,

$$\alpha_{\text{opt}} = \alpha_{\text{opt}}(\tau, z) = \inf\{\alpha : \alpha_{\text{inf}} \leq \alpha \leq 1, \mu_{\alpha,z} \leq \tau\}.$$

Taking into account the results of the previous section we have that $\mu_{\alpha_{\text{opt}},z} \leq \tau$ if $\alpha_{\text{opt}} > \alpha_{\text{inf}}$. Therefore, vaccinating a proportion α_{opt} of susceptible individuals, the infectious disease becomes extinct in average, no latter than time τ after vaccination period. Moreover, although τ has been chosen arbitrarily, in order to find a solution of the problem, it is necessary that $\tau \geq \mu_{1,z}$.

The vaccination policy α_{opt} depends on the d.f. of time to extinction. Therefore, to calculate α_{opt}, it is necessary to know $v_\alpha(\cdot)$, for α such that $\alpha_{\text{inf}} \leq \alpha \leq 1$. Although $v_\alpha(\cdot)$ satisfies the integral equation defined by (F.2), in general it is not possible to obtain this function in closed form. Recently, some numerical and simulation methods have been pro-

vided in order to approximate the solution of integral equations (see for example Brunner (1997) or Martinez and Slavtchova–Bojkova (2005)). We determine α_{opt} approximating $v_\alpha(\cdot)$ by means of a simulation–based method when $\{p_k(u)\}_{k\geq 0}$, $u > 0$, and $G(\cdot)$ are considered known. For each fixed α we apply the Monte–Carlo method to approximate the d.f. of time to extinction, $v_\alpha(\cdot)$. We approximated α_{opt} by simulating various sufficiently close α's. To simulate the spread of the disease when the proportion of immune individuals is α, it is enough to know $G(\cdot)$ and $\{p_k(u)\}_{k\geq 0}$, $u > 0$. Usually, the survival time distribution and the family of contact distribution laws are estimated from the information that becomes available as the epidemic proceeds (see, for example Guttorp (1991) and Johnson, Susarla and Ryzin (1979)).

7.6 Analyzing the control measures for avian influenza in Vietnam

It is well-known that highly pathogenic H5N1 avian influenza virus requires an incubation period after which it appears to be extremely virulent for a variety of domestic and wild bird species (see for example IDSA (2007)). The usual routes of bird-to bird transmission are airborne transmission if birds are in close proximity, or direct contact with contaminated respiratory secretions. Also, since the contact period is considered to be very short (negligible) in comparison with the incubation period, an SBP is appropriate to model the spread of H5N1 virus in birds.

According to the official reports given by the World Organization for Animal Health (see the web page `http://www.oie.int`), Vietnam has been the country with greatest number of outbreaks of avian influenza in domestic birds from the end of 2003. In 7^{th} December 2006 an outbreak started widespread itself in the southern part of the country and became extinct on 14^{th} January 2007 (see OIE (2007)). The left plot of Figure 7.1 shows the numbers of infected domestic birds detected each day along this period. The non–zero values are also given in Table 7.1. From 20^{th} December the number of cases decreases, probably because some control measures were taken (see OIE (2007)). We guess that these strategies should have started before 19^{th} December.

Table 7.1: Non-null values of infected domestic birds detected between 7^{th} December 2006 and 14^{th} January 2007.

Date	Cases	Date	Cases	Date	Cases	Date	Cases	Date	Cases
7 Dec	80	22 Dec	382	27 Dec	140	1 Jan	8	7 Jan	330
13 Dec	188	23 Dec	127	28 Dec	189	3 Jan	160	8 Jan	42
14 Dec	225	24 Dec	12	29 Dec	60	4 Jan	378	9 Jan	10
19 Dec	6073	25 Dec	262	30 Dec	18	5 Jan	240	12 Jan	880
20 Dec	40	26 Dec	1908	31 Dec	130	6 Jan	300	14 Jan	1621

Next, we analyze the spread of the H5N1 avian influenza virus in Vietnam from 19^{th} December until 14^{th} January by comparing it with the simulated times to extinction of SBP for different vaccination levels. First, in order to apply the above simulation–based method, we consider that $G(\cdot)$ is the d.f. of a gamma distribution and, for each $u > 0$, $\{p_k(u)\}_{k\geq 0}$ follows a Poisson distribution with parameter λu, being $\lambda > 0$. These types of distributions have been found to be appropriate for the survival time (including incubation and contact periods) and the number of contacts, respectively (see for example Daley and Gani (1999), Farrington and Grant (1999), Farrington, Kannan and Gay (2003) or Mode and Sleeman (2000)). Intuitively, λ represents the power of the virus. The average number of infected individuals is considered proportional to time, i.e. the longer the survival period (in our case almost equal to incubation period, because contact period is negligible), the more infected individuals there will be. Taking into account that the incubation period of H5N1 avian influenza virus is estimated at between 3 and 7 days (see IDSA (2007)) – this can be observed in our data at the beginning of the outbreak– we consider the gamma distribution with mean 5 and shape 16, to guarantee that the survival period in 90% of individuals is between 3 and 7 days. Therefore, we deduce that $m = 5\lambda$. Since the number of infected individuals at the first outbreak (on 7^{th} December) is 80, and after the incubation period (in 13^{th} and 14^{th} December) the total number of infected individuals was 413, we can estimate the rate m, using Lotka's estimator, as $\widehat{m} = 413/80$ (see Guttorp (1991)). We did not take more outbreaks into account in our consideration because, as was observed above, some control measures have been applied before 19^{th}

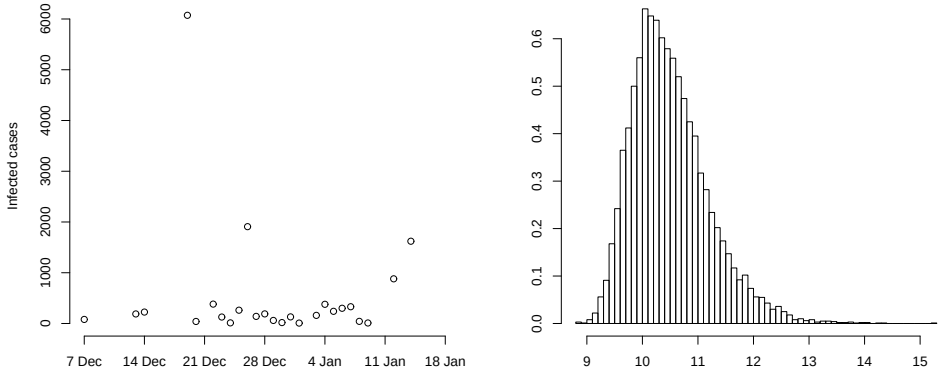

Figure 7.1: Left: Numbers of infected domestic birds detected between 7^{th} December 2006 and 14^{th} January 2007. Right: Histogram of simulated times to extinction for $\alpha = 1$.

December. Thus, in order to apply our method, we consider this date the end of vaccination period. We estimate the number of individuals incubating the virus at this date at $z = 413\widehat{m} \simeq 2132$. Finally, for each vaccination level, α, $0 \leq \alpha \leq 1$, we deduce from (F.4) that $\{p_{k,\alpha}(u)\}_{k\geq 0}$ also follows a Poisson distribution with parameter $u(1-\alpha)\lambda$, $u > 0$.

The right–hand plot of Figure 7.1 shows the histogram of 10,000 simulated times to extinction for $\alpha = 1$, i.e. when all susceptible individuals are immunized. Assuming that our model fits well, we deduce from the fact that the virus took close to 30 days to become extinct after the vaccination time, while the maximum of simulated extinction times is less than 30, that the control measures followed in Vietnam did not cover all the susceptible individuals. Consequently, the control measures in Vietnam correspond to a vaccination level $\alpha < 1$ in our setting. Let us now determine α_{opt} which corresponds to these control measures. From Theorem F.1 we deduce that the smaller is α the longer the time to extinction. This behaviour is shown in the left–hand panel of Figure 7.2 where the empirical d.f. of the time to extinction is plotted for $\alpha = 1, 0.95, 0.90$ and 0.85. Since the virus took close to 30 days to become extinct, then we deduce that the vaccination level must have been close to 1. Taking

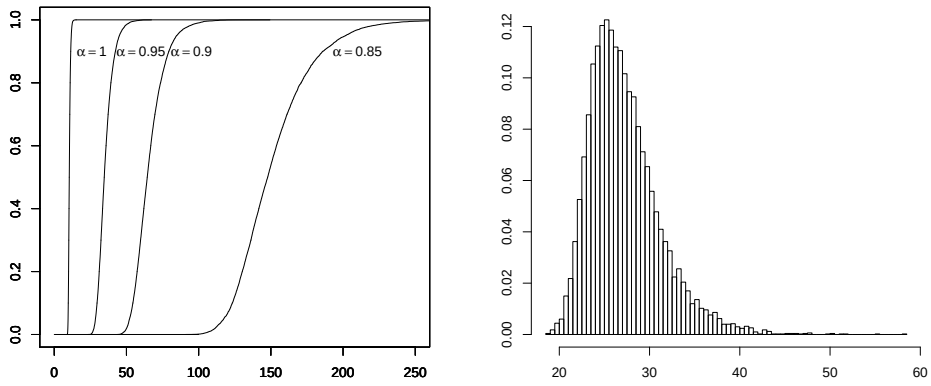

Figure 7.2: Left: Empirical d.f. of the time to extinction for $\alpha = 0.85, 0.90, 0.95$ and 1. Right: Histogram of simulated extinction times for $\alpha = 0.97$.

into account the vaccination policy based on the mean value of the time to extinction, we obtain by applying the simulation–based method, that $\alpha_{\text{opt}}(\tau = 30, z = 2132) = 0.97$. The right-hand panel of Figure 7.2 shows the histogram of 10,000 simulated times to extinction for $\alpha = 0.97$. In conclusion, the control strategies followed in Vietnam correspond, in our setting, to a vaccination level close to 1 ($\alpha_{\text{opt}} = 0.97$). Of course one must observe that such a high proportion is connected with the great risk of death not only in the birds but also in the human population in the case of of bird–to–human transmission.

Remark F.2 *For the computer simulation, we used the language and environment for statistical computing and graphics* **R** *("GNU S") (see R Development Core Team).*

7.7 Concluding remarks

We have presented a method for defining an optimal vaccination level of a population where a strongly detrimental disease has started to spread following a SIR scheme. We tackled this problem using a continuous–

time branching model, namely the Sevast'yanov age-dependent branching process, taking the age and reproduction of an individual are not to be independent. In epidemiological terms, this lack of independence takes into account that the number of contacts of an infected individual will depend on the survival time of an infection.

We are aware of the fact that the Sevast'yanov's branching model we have proposed here is a particular case of the general branching process. In particular, SBPs follow from general branching processes if reproduction is assumed to occur once at the end of the individual's life and the offspring depends on the age of the individual. They are therefore appropriate for modeling infectious diseases with an incubation period and negligibly short contact period. Using this SBP model, we were able to define an optimal vaccination level using the mean value of the time to extinction of the epidemics after vaccination took place.

We used a real set of data from the outbreaks of avian influenza virus that spread in South Vietnam at the end of 2006 to illustrate the application of the technique. Our analysis, assuming SBP fits the situation well, showed that the model would indeed be useful for controlling the spread of avian influenza virus.

Mathematically, we established monotonicity and continuity properties for the time to extinction of SBP.

Generalization of the results in the framework of the general branching processes seems to be an important direction for further investigations.

7.8 Proofs

In this section we provide the proofs of the results of the paper. For each α such that $0 \leq \alpha \leq 1$, we introduce the functional operator $H_\alpha(\cdot)$, defined on set of functions $h(\cdot)$ from non–negative real numbers, $\mathbb{R}_+$, to the interval [0,1], as follows

$$H_\alpha(h)(t) = \int_0^t f_\alpha(s, h(t-s))dG(s),\ t \geq 0.$$

Also, for all $n \geq 1$, we denote by $H_\alpha^n(\cdot)$ the n^{th} composition of the operator $H_\alpha(\cdot)$. With this notation, (F.2) can be rewritten as the fixed–point

equation $v_\alpha(t) = H_\alpha(v_\alpha)(t)$, $t \geq 0$. Moreover, $v_\alpha(\cdot)$ has the following property:

Proposition F.1 *Fixed α, $0 \leq \alpha \leq 1$, for every function $h(\cdot)$ from $\mathbb{R}_+$ to the interval $[0,1]$, it is satisfied*

$$v_\alpha(t) = \lim_{n\to\infty} H_\alpha^n(h)(t), \quad t \geq 0.$$

Proof.

Let α, $0 \leq \alpha \leq 1$, and $h\colon \mathbb{R}_+ \to [0,1]$. To proof the result it will be enough to establish the following statements:

A1. For each $t \geq 0$,
$$\widetilde{G}(t) \leq H_\alpha(h)(t) \leq G(t)$$
with $\widetilde{G}(t) = \int_0^t f_\alpha(s,0)dG(s)$.

A2. $H_\alpha(\cdot)$ is a non-decreasing functional operator, i.e., if $h_i\colon \mathbb{R}_+ \to [0,1]$, $i = 1,2$, are functions such that $h_1(t) \leq h_2(t)$, for all $t \geq 0$, then
$$H_\alpha(h_1)(t) \leq H_\alpha(h_2)(t), \quad \text{for all } t \geq 0.$$

A3. For each $t \geq 0$, there exist
$$u_1(t) = \lim_{n\to\infty} H_\alpha^n(\widetilde{G})(t) \quad \text{and} \quad u_2(t) = \lim_{n\to\infty} H_\alpha^n(G)(t).$$

A4. $u_1(\cdot)$ and $u_2(\cdot)$ are solutions of the fixed–point equation $h(\cdot) = H_\alpha(h)(\cdot)$, and then $v_\alpha(\cdot) = u_1(\cdot) = u_2(\cdot)$.

Indeed, from these four statements it can be established that, for $t \geq 0$,

$$\begin{aligned} v_\alpha(t) &= u_1(t) = \lim_{n\to\infty} H_\alpha^n(\widetilde{G})(t) \leq \lim_{n\to\infty} H_\alpha^{n+1}(h)(t) \\ &\leq \lim_{n\to\infty} H_\alpha^n(G)(t) = u_2(t) = v_\alpha(t). \end{aligned}$$

Let's prove *A1–A4*.

A1. It is clear considering that, for each $s \geq 0$ and $0 \leq t \leq 1$,

$$f_\alpha(s,0) \leq f_\alpha(s,t) \leq f_\alpha(s,1) = 1.$$

A2. This statement is due to the fact that for every $s \geq 0$, $f_\alpha(s,\cdot)$ is an increasing function.

A3. By *A1-A2*, for each $t \geq 0$

$$\widetilde{G}(t) \leq H_\alpha(\widetilde{G})(t) \leq H_\alpha(G)(t) \leq G(t).$$

So, by an iterative procedure, for $n \geq 1$ and each $t \geq 0$

$$H_\alpha^n(\widetilde{G})(t) \leq H_\alpha^{n+1}(\widetilde{G})(t) \leq H_\alpha^{n+1}(G)(t) \leq H_\alpha^n(G)(t).$$

Therefore, $\{H_\alpha^n(\widetilde{G})(t)\}_{n\geq 1}$ is a non–decreasing sequence upper bounded by 1, and then there exists $u_1(t) = \lim_{n\to\infty} H_\alpha^n(\widetilde{G})(t)$, $t \geq 0$. Moreover, $\{H_\alpha^n(G)(t)\}_{n\geq 1}$ is a non–increasing sequence lower bounded by 0, and then there exists $u_2(t) = \lim_{n\to\infty} H_\alpha^n(G)(t)$, $t \geq 0$.

A4. Let's prove this statement for $u_1(\cdot)$. In a similar way it can be proved for $u_2(\cdot)$.

Let $t \geq 0$, then using *A3*, the fact that $f_\alpha(s,\cdot)$ is increasing and continuous for each $s \geq 0$, and the dominated convergence theorem, it can be established that

$$\begin{aligned}
u_1(t) &= \lim_{n\to\infty} H_\alpha^{n+1}(\widetilde{G})(t) \\
&= \lim_{n\to\infty} \int_0^t f_\alpha(s, H_\alpha^n(\widetilde{G})(t-s))dG(s) \\
&= \int_0^t \lim_{n\to\infty} f_\alpha(s, H_\alpha^n(\widetilde{G})(t-s))dG(s) \\
&= \int_0^t f_\alpha(s, \lim_{n\to\infty} H_\alpha^n(\widetilde{G})(t-s))dG(s) \\
&= \int_0^t f_\alpha(s, u_1(t-s))dG(s) \\
&= H_\alpha(u_1)(t).
\end{aligned}$$

Since $u_1(\cdot)$ is a bounded function verifying the fixed–point equation $h(\cdot) = H_\alpha(h)(\cdot)$ and $v_\alpha(\cdot)$ is the unique bounded function verifying this equation, then $u_1(t) = v_\alpha(t)$, for every $t \geq 0$. This concludes the proof.□

Proof of Theorem F.1

Let α_1, α_2 be such that $0 \leq \alpha_1 < \alpha_2 \leq 1$. Then, as $v_{\alpha_1}(\cdot)$ is a distribution function,

$$\alpha_1 + (1-\alpha_1)v_{\alpha_1}(t-s) \leq \alpha_2 + (1-\alpha_2)v_{\alpha_1}(t-s)$$

for all $0 \leq s \leq t$. Therefore

$$\begin{aligned} f_{\alpha_1}(s, v_{\alpha_1}(t-s)) &= f(s, \alpha_1 + (1-\alpha_1)v_{\alpha_1}(t-s)) \\ &\leq f(s, \alpha_2 + (1-\alpha_2)v_{\alpha_1}(t-s)) = f_{\alpha_2}(s, v_{\alpha_1}(t-s)), \end{aligned}$$

and then $v_{\alpha_1}(t) = H_{\alpha_1}(v_{\alpha_1})(t) \leq H_{\alpha_2}(v_{\alpha_1})(t)$, for all $t \geq 0$.

Taking into account that the functional operators $H_\alpha(\cdot)$ are non-decreasing (see *S2* in the proof of Proposition F.1, it is clear that $v_{\alpha_1}(t) \leq H^n_{\alpha_2}(v_{\alpha_1}(t))$, for all $t \geq 0$ and $n \geq 1$. Then, applying Proposition F.1, for all $t \geq 0$,

$$v_{\alpha_1}(t) \leq \lim_{n\to\infty} H^n_{\alpha_2}(v_{\alpha_1}(t)) = v_{\alpha_2}(t),$$

concluding the proof. □

Proof of Theorem F.2

Let $\varepsilon > 0$ and let α be such that $m_\alpha < m_{\alpha_{inf}} = \min\{1, m\}$. Let also $\eta = \eta(\varepsilon, \alpha) = \varepsilon(1-m_\alpha)m^{-1}$. Given α^* such that $m_{\alpha^*} \leq 1$ and $|\alpha - \alpha^*| \leq \eta$, since for all t, $0 \leq t \leq 1$, $|\alpha + (1-\alpha)t - (\alpha^* + (1-\alpha^*)t)| \leq |\alpha - \alpha^*|$, from the mean value theorem and (F.4), it follows that for every $s > 0$ and $0 \leq t \leq 1$,

$$|f_\alpha(s,t) - f_{\alpha^*}(s,t)| \leq m(s)|\alpha - \alpha^*| \leq m(s)\eta. \tag{F.6}$$

Taking into account this fact, next we show by induction on n, for each $n \geq 1$, that

$$|H^n_\alpha(G)(t) - H^n_{\alpha^*}(G)(t)| \leq \varepsilon(1-m^n_\alpha),\ t \geq 0. \tag{F.7}$$

Fixed $t \geq 0$, for $n = 1$ we deduce from (F.6), that

$$\begin{aligned} |H_\alpha(G)(t) - H_{\alpha^*}(G)(t)| &\leq \int_0^t |f_\alpha(s, G(t-s)) - f_{\alpha^*}(s, G(t-s))| dG(s) \\ &\leq \varepsilon(1-m_\alpha) m^{-1} \int_0^\infty m(s) dG(s) \varepsilon(1-m_\alpha). \end{aligned}$$

By induction hypothesis, (F.7) holds for n. Then for $n+1$ we have that

$$\begin{aligned} |H_\alpha^{n+1}(G)(t) - H_{\alpha^*}^{n+1}(G)(t)| &\leq |H_\alpha(H_\alpha^n(G))(t) - H_\alpha(H_{\alpha^*}^n(G))(t)| \\ &\quad + |H_\alpha(H_{\alpha^*}^n(G))(t) - H_{\alpha^*}(H_{\alpha^*}^n(G))(t)|. \end{aligned}$$

Moreover, using again the mean value theorem,

$$\begin{aligned} &|H_\alpha(H_\alpha^n(G))(t) - H_\alpha(H_{\alpha^*}^n(G))(t)| \leq \\ &\leq \int_0^t |f_\alpha(s, H_\alpha^n(G)(t-s)) - f_\alpha(s, H_{\alpha^*}^n(G)(t-s))| dG(s) \\ &\leq \int_0^t m_\alpha(s) |H_\alpha^n(G)(t-s) - H_{\alpha^*}^n(G)(t-s)| dG(s) \\ &\leq m_\alpha \sup_{0 \leq s < \infty} |H_\alpha^n(G)(s) - H_{\alpha^*}^n(G)(s)| \\ &\leq \varepsilon(1-m_\alpha^n) m_\alpha, \end{aligned}$$

and, from (F.6),

$$\begin{aligned} &|H_\alpha(H_{\alpha^*}^n(G))(t) - H_{\alpha^*}(H_{\alpha^*}^n(G))(t)| \leq \\ &\leq \int_0^t |f_\alpha(s, H_{\alpha^*}^n(G)(t-s)) - f_{\alpha^*}(s, H_{\alpha^*}^n(G)(t-s))| dG(s) \\ &\leq \varepsilon(1-m_\alpha). \end{aligned}$$

Therefore, we conclude that

$$|H_\alpha^{n+1}(G)(t) - H_{\alpha^*}^{n+1}(G)(t)| \leq \varepsilon(1-m_\alpha^n) m_\alpha + \varepsilon(1-m_\alpha) = \varepsilon(1-m_\alpha^{n+1}).$$

Finally, using Proposition F.1 and the fact that $m_\alpha < 1$, from (F.7), we obtain that

$$\sup_{0\le t<\infty} |v_\alpha(t) - v_{\alpha^*}(t)| \le \varepsilon,$$

and then the proof is completed. □

Proof of Theorem F.3

1. Let α_1, α_2 be such that $\alpha_{\inf} \le \alpha_1 < \alpha_2 \le 1$. From Theorem F.1, we have that $v_{\alpha_1}(t) \le v_{\alpha_2}(t),\ t \ge 0$, and taking into account (F.5), it follows that $\mu_{\alpha_2} \le \mu_{\alpha_1}$.

2. Let $\overline{\alpha}$ be such that $0 < m_{\overline{\alpha}} < m_{\alpha_{\inf}}$ and $M = \sup\{\mu_\alpha : \overline{\alpha} < \alpha \le 1\} < \infty$. First we show that $\mu_{\overline{\alpha}}$ is finite. For fixed $\varepsilon > 0$ and $N > 0$. Applying Theorem F.2, there exists $\eta = \eta(\overline{\alpha}, \varepsilon, N)$ such that for all $\alpha > \overline{\alpha}$, with $\alpha - \overline{\alpha} \le \eta$, it follows that

$$v_\alpha(t) - v_{\overline{\alpha}}(t) \le N^{-1}\varepsilon,\ t \ge 0.$$

Therefore,

$$\int_0^N (1 - v_{\overline{\alpha}}(t))dt \le \int_0^N (N^{-1}\varepsilon + 1 - v_\alpha(t))dt \le \varepsilon + M,$$

and we deduce that $\mu_{\overline{\alpha}}$ is finite. Hence, there exists $n_0 = n_0(\varepsilon, \overline{\alpha}) > 0$ such that

$$\int_{n_0}^\infty (1 - v_{\overline{\alpha}}(t))dt \le 2^{-1}\varepsilon. \tag{F.8}$$

Let α be such that $\alpha \ge \overline{\alpha}$. Then, after applying Theorem F.2, we guarantee that there exists $\eta = \eta(\alpha, \varepsilon, n_0) > 0$ such that if $|\widetilde{\alpha} - \alpha| \le \eta$, then $|v_\alpha(t) - v_{\widetilde{\alpha}}(t)| \le (2n_0)^{-1}\varepsilon$ for all $t \ge 0$, and therefore

$$\int_0^{n_0} |v_\alpha(t) - v_{\widetilde{\alpha}}(t)|dt \le 2^{-1}\varepsilon.$$

Moreover, since (F.8) holds, from Theorem F.1, we have, for $\widetilde{\alpha} \ge \overline{\alpha}$, that

$$\int_{n_0}^\infty |v_{\widetilde{\alpha}}(t) - v_\alpha(t)|dt \le 2^{-1}\varepsilon,$$

and the proof is completed. □

7.9 Comparison of vaccination policies based on simulations

In the previous section we have proposed two vaccination policies. That gives rise to the natural question which one and when is reasonably to use? That is why, in what follows we compare the two approaches by way of simulation examples, modelling the spread of the disease by means of SBP with the distributions of the incubation period and of the number of contacts (remain, every contact produces infection when there are no immune individuals in the population) belonging to probability distributions, commonly used in epidemic modelling for such situations.

Namely, we consider as incubation period distribution (plus the negligible short contact period) a gamma distribution and for the contact distribution a Poisson distribution with parameter λu, being $\lambda, u > 0$. These types of distributions turned out to be appropriate for the incubation period and the number of contacts (or infected individuals generated by one infected individual), respectively (see for example Daley and Gani (1999), Farrington and Grant (1999), Farrington et al. (2003) or Mode and Sleeman (2000)). Intuitively, λ represents the power of the virus and u the length of the incubation period. Hence, the average number of infected individuals by one infected individual is considered proportional to its incubation period, i.e. the larger incubation period is, the larger will be the number of infected individuals. With respect to incubation distribution, we have chosen gamma distribution with mean 15 and shape 30, which guarantee that the survival period in more than 95% of individuals is between 10 and 21 days. Moreover, with respect to contact distribution we have selected $\lambda = 1/3$. A similar model was used to fit H5N1 Vietnam data (see OIE (2007) and Gonzáles et al. (2010b)). For the last selected parameters, we deduce that m, the average number of individuals which are infected by one infectious individual, is 5 (when there are no immune individuals in the population). Moreover, we deduce that $\alpha_{\text{inf}} = 0.8$. This means that to get the disease under control, i.e. to guarantee that it will disappear, we must vaccinate at least 80% of the susceptible individuals. But we want guarantee not only the extinction, but also that it happens in a given period of time.

To this aim, from now on, we consider that $z = 1$. Intuitively, this could mean that new outbreaks, after vaccination, starts with only one

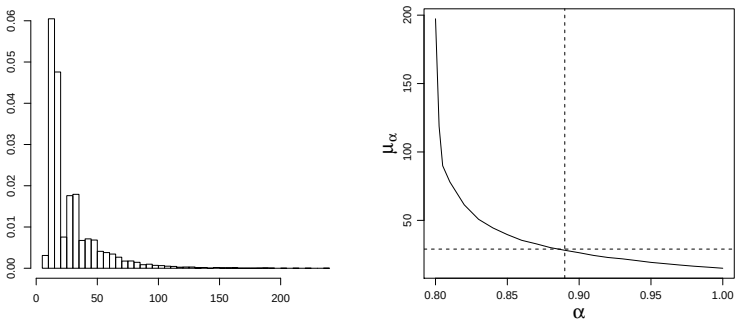

Figure 7.3: Left: Histogram of simulated extinction times for $\alpha = 0.89$. Right: Behaviour of $\mu_{\alpha,1}$ depending on α.

infectious individual. Therefore, in this case, to determine both vaccination policies, we obtain the empirical approximation to the distribution $v_\alpha(\cdot)$, for $0.8 \leq \alpha \leq 1$, using the Monte-Carlo method. To this end, for each α in a grid of step 0.01, 10 000 processes have been simulated and their duration have been obtained. As an example, in left graphic of Figure 7.3 we show the histogram of simulated times to extinction for $\alpha = 0.89$.

As an illustration of both vaccination policies we take $\tau = 30$, which is actually twice the mean incubation period. In right graphic of Figure 7.3, the behaviour of the mean time to extinction, $\mu_{\alpha,1}$, depending on α is shown. Then, we derive that the optimal vaccination policy based on the mean of the time to extinction is $\alpha_\mu(30, 1) = 0.89$. From the simulated extinction times for $\alpha = 0.89$ we estimate $v_{0.89}(30)$ by 0.682. This means that if 89% of the population is immunized, then the probability that the disease disappears in less than 30 days is 0.682. Comparing that to the optimal vaccination policy based on the quantiles, what we are telling is that $\alpha_q(0.682, 30, 1) = 0.89$. We notice that $p = 0.682$ is greater than 0.5, because of the skewness of the distribution of the time to extinction (see left graphic of Figure 7.3). Therefore, vaccinating 89% of susceptible individuals, it is guaranteed that at least 68.2% of new outbreaks take no more than 30 days to disappear. Finally, we notice that this probability is not very high. The larger that probability is, the larger will be the

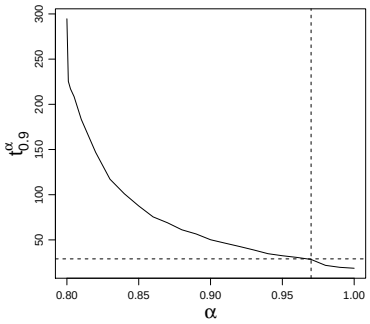

Figure 7.4: Behaviour of $t^{\alpha}_{0.9}$ depending on α.

optimal vaccination coverage based on the quantiles. Indeed, in Figure 7.4, the behaviour of $t^{\alpha}_{0.9}$, a value such that $v_{\alpha}(t^{\alpha}_{0.9}) = 0.9$, depending on α is shown. $t^{\alpha}_{0.9}$ is a such value which allows us to establish that 90% of outbreaks, when the proportion of immune individuals in the population is α, will last less than a time $t^{\alpha}_{0.9}$. From Figure 7.4, we derive that the optimal vaccination policy based on the quantiles of the time to extinction when $p = 0.9$ is $\alpha_q(0.9, 30, 1) = 0.97$, greater than 0.89. Therefore, if we want to guarantee with probability 0.9 that the disease disappears before 30 days, then we have to vaccinate 97% of the susceptible population.

From the previous study, we suggest that if the infectious disease is not extremely detrimental for the population and we want to control it in a reasonable time, then the policies based on the mean could be adequate, guaranteeing with probability higher than 0.5, the disease becomes extinct in the desired period of time and therefore it is under control. On the other hand, when the infectious disease is highly detrimental, we would like to eliminate it in the predefined time with high probability. In this case, vaccination policies based on the quantiles are preferrable, although this will imply an optimal vaccination rate greater than that based on the mean.

Discussion

In the review paper (see Slavtchova–Bojkova et al.(2010c)) we have surveyed two methods for defining an optimal vaccination rate of a population, where a detrimental disease starts to spread. We have tackled this problem using continuous–time branching models, in terms of which then, we have supposed that the age and reproduction of an individual are not necessarily independent. The latter in terms of epidemic takes into account that the number of contacts of an infected individual can depend on the incubation period of the infection. The novelty of our approach is in the use of models allowing us to work in continuous time, as it is in fact in most real world situations. The methods are rather different from the well-established discrete settings, widely used for modelling the early stages of epidemic spread. Concretely, we have used the Bellman–Harris and Sevast'yanov branching processes. These are particular cases of the general branching process which is the model that best fit an epidemic process as it was proved by Ball and Donnelly (1995). Nevertheless, this process is more complicated than both models we have considered, involving more unknown parameters, and our processes are appropriate enough at least to model infectious diseases with incubation period and negligible short contact period. In any case, generalizations of our results in the framework of the general branching processes seem to be an interesting direction for further investigations.

Chapter 8

Applications with mumps data of Bulgaria

8.1 Introduction

In an attempt to meet the threats of infectious diseases to society, public health authorities have created comprehensive mechanisms for the collection of disease data. As a consequence, the abundance of data has demanded the development of automated algorithms for the detection of abnormalities and aberrations. Typically, such an algorithm monitors a univariate time series of counts using a combination of heuristic methods and statistical modelling. Prominent examples of surveillance algorithms are the work by Stroup et al. (1989) and Farrington et al. (1996). A comprehensive survey of outbreak detection methods can be found in Farrington and Andrews (2003). The R-package surveillance was written with the aim of providing a test-bench for surveillance algorithms.

The purpose of the analysis in this work is to illustrate the basic functionality of the package with R-code examples. Section 7.2 contains a short description of how to use the surveillance algorithms and presents the results with description of the data set we used.

8.2 Bayesian approach for predicting outbreaks

Bayesian approach for predicting outbreaks, implemented in the statistical software R (see Höhle (2005)) is applied on surveillance data of mumps collected in Bulgaria for the period 2000–2008. A detailed description of the method is beyond the scope of this work and could be seen in Höhle (2005). The official data is kindly provided by the National Center of Infectious and Parasitic diseases at the Ministry of Health, Bulgaria. It has been collected on a weekly base and presents the epidemic picture by regions in the country for 2000–2008 year. The data clearly shows that there was epidemic outbreak in the country in 2007 and 2008 (see Kojouharova M. et al. (2007)). The distribution of infected cases by regions for this period is visualized in Figure 8.1.

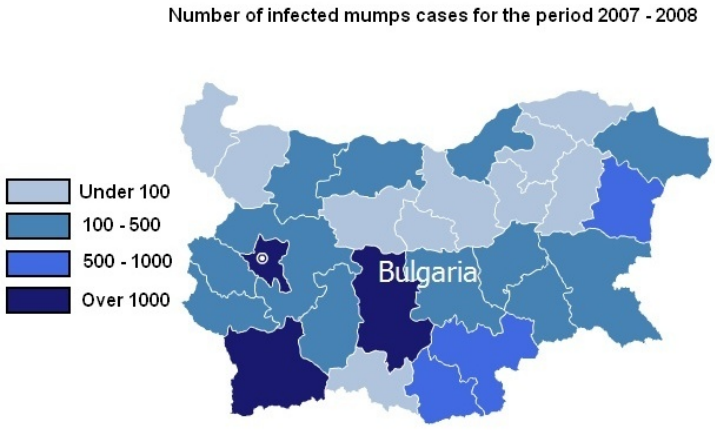

Figure 8.1: Number of infected mumps cases for the period 2007–2008

Using R-software we apply the following model on our data. Let us denote by $\{y_t;\ t = 1, \ldots, n\}$ the time series of counts representing the surveillance data. Due to the fact that such data is typically collected on a weekly basis it is also convenient to use the following notation $\{y_{i:j}\}$, where $j = \{1, \ldots, 52\}$ presents the number of weeks in the year and $i = \{-b, \ldots, -1, 0\}$ are the corresponding years. The years have been indexed in such a way that the last year for which we have data has index

0. Let $y_{0:t}$ be the number of cases of the current week (denoted week t in year 0), b the number of years to go back in time and w the number of years around t to include from those previous years. The zero year will be denoted by w_0. Hence the set of chosen weeks/years for which we want to trace the disease is:

$$R(w, w_0, b) = \left(\bigcup_{i=1}^{b} \bigcup_{j=-w}^{w} y_{-i:t+j} \right) \cup \left(\bigcup_{k=-w_0}^{-1} y_{0:t+k} \right).$$

Note that the number of cases of the current week is not a part of $R(w, w_0, b)$. The aim of the surveillance algorithm described above is to create a prediction $\hat{y_{t:0}}$ for the current week of the process. This prediction is then compared to the actual observed value $y_{0:t}$. If the observed value is much higher than the predicted one we get an alert, which warns us to investigate further the reasons for this. The red triangles on the graphs represent the alarms (Fig. 8.2).

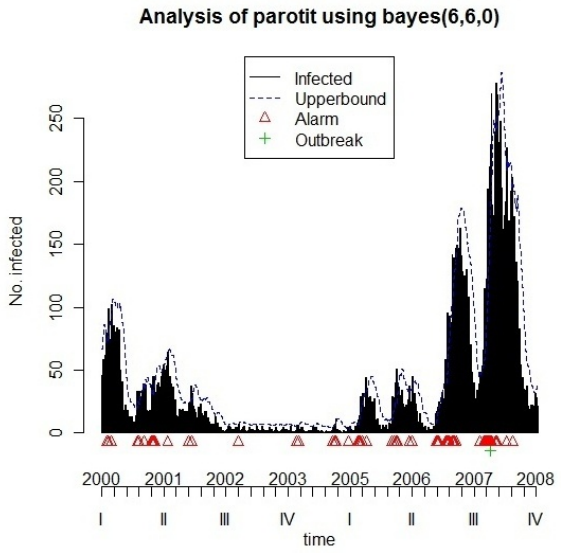

Figure 8.2: Bayesian approach for predicting outbreaks

We apply the $R(6, 6, 0)$ model for the data we have for the regions of Plovdiv and Sofia as the epidemic outbreak in these two regions was significant. The histograms at Figure 8.3 give us a clear idea of the spread

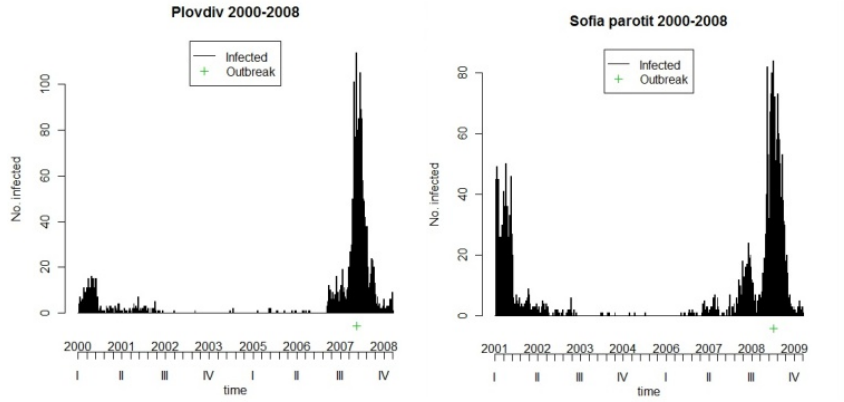

Figure 8.3: Analysis of Sofia and Plovdiv

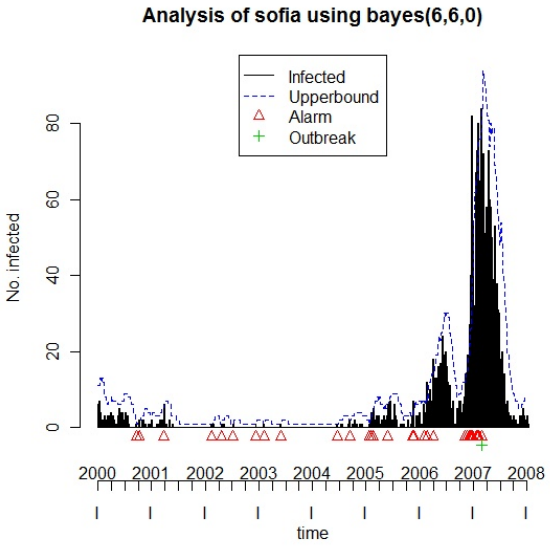

Figure 8.4: Analysis of Sofia using Bayes(6,6,0)

of infected mumps cases in these regions for the period 2000–2008. As we see, there were very few infected cases during 2001–2006. In 2007 and 2008, the number of infected cases significantly increased and grew into epidemic outbreak in the end of 2007 and in the beginning of 2008.

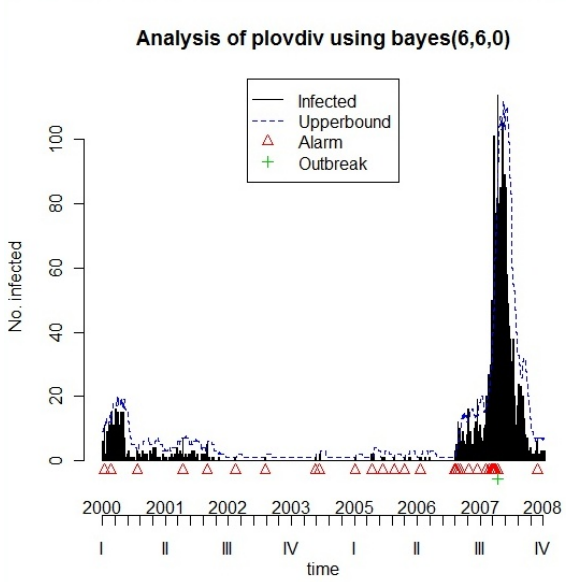

Figure 8.5: Analysis of Plovdiv using Bayes(6,6,0)

In order to apply the Bayesian model on our data we first need to format the data in such a way so that it can be used by the R DisProg class. Then we draw infection spread charts for the period 2000-2008. We choose week 7 of 2008 and week 50 of 2007 for outbreak peak for Sofia and Plovdiv correspondingly. We apply the Bayesian model that uses data for the last six weeks, i.e. $R(w, w_0, b) = R(6, 6, 0)$ on our data. The chart in figure 8.2 is produced by applying $R(6, 6, 0)$ on aggregated data of the country. Figures 8.4 and 8.5 represent the curve of the expected infected cases for the regions of Sofia and Plovdiv, respectively.

The results we get for Sofia and Plovdiv are quite close. This can be explained with the fact that in both regions there are enough outbreaks that occurred in a short time period. On the other hand, as these two outbreaks are the two biggest in the country, they describe the epidemic picture in Bulgaria very well. It's essential to clarify here that as the epidemic situation in the country quite differs from one region to another, it's always better to make predictions for the disease spread, based on the data collected for the separate regions. In this way we will get a more clear and precise idea as to which regions are threatened with epidemic.

It's also important to take into account the increasing mobility nowadays, that could lead to importing infected cases from one region into another.

Conclusion

The statistical methods we applied here provide a simple framework for analyzing surveillance data of infectious diseases. The quality of the collected data is of a particular importance for the adequate application of the statistical methods. It would lead to an added value to the results of the applied measures from the surveillance of infectious diseases, in general. The extra vaccinations as applied in the case of mumps in Bulgaria were inevitable and could be optimized as to gain a desired effect.

Chapter 9

Bayesian estimation of the offspring mean

9.1 Biological background and motivation

The fundamental epidemiological quantity determining whether an infectious disease will persist in a host population is the basic reproduction number, R_0 (see Anderson, May (1991) and Heesterbeek, Dietz (1996)). This is defined as the average number of secondary infections caused in a susceptible population by a typical infected. R_0 is a key factor in determining how fast an infection will spread in a population. If $R_0 > 1$, the infectious agent has the potential to persist indefinitely, whilst if $R_0 < 1$, the incidence of infection will decay to zero. The reason is clear: if a primary infection is unable to generate at least one replacement secondary infection, the numbers of infected in the population will inevitably decline through time.

This work presents a Bayesian approach of estimating R_0 for infectious diseases like mumps, measles and possibly others, that follows so-called SIR (susceptible $\rightarrow$ infective $\rightarrow$ removed) and SEIR (susceptible $\rightarrow$ exposed $\rightarrow$ infective $\rightarrow$ removed) scheme in epidemiological context, from the case data comprising of the number of infected on a weekly base. Our methods are stochastic and rely on the theory of branching processes. The last have been proven to suit well for the purpose of infectious disease surveillance, since they require data only on outbreak sizes. However, we are well aware of the fact that the methods rely

on an approximation to the epidemic process. We show that branching process models, applied to surveillance of mass vaccination programmes in conditions of elimination, might be of practical use for public health authorities.

Under the assumption that each infective infects a random number of individuals in accordance with some probability distribution and that this distribution does not change over time and is the same for all individuals, it is reasonable to model the number of infected by a branching process. We will use the simplest class of branching processes – Bienaymé–Galton–Watson processes. In fact, the assumption that the distribution of the number of infected individuals by one infectious does not change over time, is not always realistic, because increasing the number of infectious individuals reduces the number of susceptible to the disease. However, in populations with large number of susceptible – over 100, this assumption is not away from reality (see Farrington, Kanaan, Gay (2003)). Since these are discrete time processes, we count the number of infected by each infectious not in real time, but at the end of its infectious period (the period during which one infective could transmit the disease to others susceptible). Despite its idealization, such models are widely used in epidemiology, for example see Becker (1974), Heyde (1979), Farrington, Grant (1999), Yanev, Tsokos (1999), Farrington, et al. (2003). More complex branching process also have been applied for modeling of infectious diseases, see Marschner (1992), Ball, Donnelly (1995), Becker, Britton (2004), González, Martínez, Slavtchova-Bojkova (2009, 2010b) and Jacob (2010).

Usually we do not have complete information about the spread of the disease – do not know the number of infected by each infectious individual. Models of branching processes and application of Bayesian methods allow us to estimate the basic reproduction number R_0 using data on reported cases, collected by institutions for control of public health. A similar approach was proposed by Farrington, et al. (2003).

We will apply the inference to real data on the number of reported cases of mumps in Bulgaria during the period 2005–2008 provided by the National Center of Infectious and Parasitic Diseases. It will be assumed that the offspring distribution of the branching process belongs to the family of generalized power series distributions, which is quite a broad class of discrete distributions, including binomial, Poisson and geometric

ones. It turned out that for this wide class of distributions, we are able to obtain exactly the distribution of the total progeny of the BGWBP, which we need for estimation of offspring mean λ. We find both point and interval estimates of λ, applying a Bayesian approach by simulating the posterior distribution using Metropolis–Hastings algorithm. The algorithm is implemented in the language and environment for statistical computing `R`, version 2.11.1 (see `R` development Core Team).

Section 8.2 introduces the models of BGWBP and the total progeny, as well, in the context of the spread of infectious diseases. In Section 8.3 the Bayesian estimation approach is considered. Section 8.4 shows how these models are applied to the data on reported cases of mumps in Bulgaria.

9.2 Bienaymé–Galton–Watson BP

Branching processes model the dynamics of populations of individuals, generating a random number of individuals of the same or different type. In general, the individuals might be of different nature – elementary particles, cells, plants, animals, people and many others. A more detailed exposition of the theory of branching processes can be found, for example in Jagers (1975) or Slavtchova–Bojkova and Yanev (2007). In this section we will consider branching processes as a model of the spread of an infectious disease in a human population.

Bienaymé–Galton–Watson process – definition

We assume that each infectious individual infects a random number of susceptible individuals distributed as a random variable X. Let us start with s infected individuals. All infected individuals due to a contact with them are called first generation, and let us denote their number by Z_1. Infected individuals in contact with the first generation form the second generation, with Z_2 individuals, etc. This process can be depicted as a tree (a set of trees).

Let $X_i(n)$ are independent and identically distributed random variables (i.i.d. r.v.) with the same distribution as X. The distribution of X is called offspring distribution, the mean of X is denoted by $\lambda = EX$.

Formally, we define $\{Z_n, n = 0, 1, 2, \ldots\}$ as follows:

$$\begin{aligned} Z_0 &= s \\ Z_1 &= X_1(0) + \ldots + X_s(0) \end{aligned}$$

$$\begin{aligned} Z_2 &= X_1(1) + \ldots + X_{Z_1}(1) \\ &\vdots \\ Z_n &= X_1(n-1) + \ldots + X_{Z_{n-1}}(n-1) = \sum_{i=1}^{Z_{n-1}} X_i(n-1), \end{aligned}$$

where $X_i(n-1)$ is the number of infected by i-th individual of $(n-1)$-th generation. The sequence of r.v. $\{Z_n, n = 0, 1, 2, \ldots\}$ is called Bienaymé–Galton–Watson process.

The event $\{Z_n = 0, \text{ for some } n \geq 1 \mid Z_0 = 1\}$ is called extinction. Denote the probability of extinction $q = P\{Z_n = 0, \text{ for some } n \geq 1 \mid Z_0 = 1\}$. From the theory of branching processes it is known that for $\lambda \leq 1$, $q = 1$, and for $\lambda > 1$, $q < 1$.

If the process starts with s individuals, the probability of extinction is $\{Z_n = 0, n \geq 1 \mid Z_0 = s\} = q^s$.

Depending on whether the offspring mean λ is less than, equal to or greater than 1, process is called subcritical, critical and supercritical, respectively.

We'll assume that X has a generalized power series distribution, i.e.

$$P(X = k) = \frac{a_k \theta^k}{A(\theta)}, \quad k \in \mathcal{K}$$

where $a_k \geq 0$, $A(\theta) = \sum_k a_k \theta^k$, $\theta > 0$, $\mathcal{K} \subseteq \{0, 1, 2, \ldots\}$. The parameter θ is called canonical parameter. Distributions of this type are the binomial, Poisson, negative binomial (in particular – the geometric). The mean of X is

$$\lambda = EX = \frac{\theta A'(\theta)}{A(\theta)}.$$

In the case of Poisson distribution we have:

$$P(X = k) = \frac{e^{-\theta} \theta^k}{k!}, \qquad k = 0, 1, 2, \ldots$$

$$a_k = \frac{1}{k!}, \qquad A(\theta) = e^{\theta}, \qquad \lambda = EX = \theta;$$

And for the Geometric case:

$$P(X = k) = \theta^k(1-\theta), \qquad k = 0, 1, 2, \ldots$$

$$a_k = 1, \qquad A(\theta) = \frac{1}{1-\theta}, \qquad \lambda = EX = \frac{\theta}{1-\theta}.$$

9.3 Total progeny in a BGWBP

As we noticed, one of the reasons to use branching processes as models of infectious disease spread is the obvious fact, that the offspring mean λ is identified as a basic reproduction number R_0 in epidemiology. Our task is to estimate λ on the basis of data on the number of infected individuals. Most often we do not have data on the number of infected ones by each infectious, but of the total number of infected individuals for a given period of time. Therefore, our estimation of λ will be based on the total number of infected individuals by the end of the outbreak, called a total progeny in a branching processes' context.

Let us denote by Y the total progeny of BGWBP or the total number of infected individuals by the end of the outbreak. It is defined as follows

$$Y = \sum_{n=0}^{\infty} Z_n.$$

Then as a consequence, the distribution of Y has the form

$$P(Y = r) = \frac{s}{r} P(X_1 + X_2 + \ldots + X_r = r - s), \qquad r = s,\ s+1,\ s+2, \ldots$$

where $X_1, X_2, \ldots, X_r$ are i.i.d.r.v. with the same distribution as X (see Jagers (1975)). It is obvious that the distribution of Y is given by r-th convolution of X.

In what follows we'll show the method of obtaining total progeny distribution given the offspring one in particular cases of Poisson and geometric offspring distributions. Geometric and Poisson offspring distributions correspond respectively to the limiting branching process for a general stochastic epidemic and a Reed–Frost epidemic model (see Ball (1983)).

Poisson offspring

Let the offspring distribution be Poisson:

$$P(X = k) = \frac{e^{-\lambda}\,\lambda^k}{k!}, \qquad k = 0, 1, 2, \ldots$$

Using that the sum of r i.i.d. Poisson r.v. has Poisson distribution with parameter λr we directly express:

$$P(X_1 + X_2 + \ldots + X_r = k) = \frac{e^{-\lambda r}(\lambda r)^k}{k!}.$$

Thus the distribution of the total progeny is:

$$\begin{aligned} P(Y = r) &= \frac{s}{r}\, P(X_1 + X_2 + \ldots + X_r = r - s) \\ &= \frac{s}{r}\, \frac{e^{-\lambda r}(\lambda r)^{r-s}}{(r-s)!}, \qquad r = s,\ s+1,\ s+2, \ldots, \end{aligned}$$

i.e. Y has a Borel–Tanner distribution (see Haight, Breuer (1960)).

Geometric offspring

Let the offspring distribution be geometric:

$$P(X = k) = \theta^k(1 - \theta), \qquad k = 0, 1, 2, \ldots$$

Using the relation between λ and the canonical parameter θ in terms of generalized power series distributions, it is easy to see, that we have the following presentation:

$$P(X = k) = \frac{\lambda^k}{(1+\lambda)^{k+1}}, \qquad k = 0, 1, 2, \ldots$$

Now, having in mind that the sum of i.i.d. geometric random variables has a negative binomial distribution, it follows:

$$P(X_1 + \cdots + X_r = k) = \binom{r+k-1}{k} \frac{\lambda^k}{(1+\lambda)^k} \frac{1}{(1+\lambda)^r}.$$

In this case, the distribution of the total progeny will be as follows:

$$\begin{aligned} P(Y=r) &= \frac{s}{r}\,P(X_1+X_2+\cdots+X_r=r-s) \\ &= \frac{s}{r}\binom{r+r-s-1}{r-s}\frac{\lambda^{r-s}}{(1+\lambda)^{r-s}}\frac{1}{(1+\lambda)^r} \\ &= \frac{s}{r}\binom{2r-s-1}{r-s}\frac{\lambda^{r-s}}{(1+\lambda)^{2r-s}}, \qquad r=s,\ s+1,\ s+2,\ldots, \end{aligned}$$

i.e. Y has a distribution of Haight (see Haight (1961)).

9.4 Bayesian estimation of λ

In this section we will consider the basic ideas of Bayesian approach for parameter estimation, in particular, applied to the offspring mean of BGWBP. We will use the Metropolis–Hastings algorithm, with which some computational difficulties in Bayesian estimation could be avoided. More details on this topic can be found in Robert (2007), Robert and Casella (2004, 2010) and Hoff (2009).

Actually, we will estimate λ having data from a single outbreak, i.e. knowing that the total number of infected is y, and the initial number of infected is s. In this case the likelihood function for λ has the form:

$$L(y|\lambda) = P(Y=y; s, \lambda).$$

Following a Bayesian approach, we assume that the parameter λ is a random variable with prior distribution $\pi(\lambda)$. Then the posterior density is given by the Bayes' formula:

$$f(\lambda|y) = \frac{L(y|\lambda)\pi(\lambda)}{\int_0^\infty L(y|\lambda)\pi(\lambda)d\lambda}.$$

If we use squared error loss function, the Bayesian estimate of λ, will be the mean of the posterior distribution:

$$\widehat{\lambda} = E(\lambda|y).$$

Concerning the interval estimation of λ, let us recall that the interval $[a, b]$ is called $100(1-\alpha)\%$ highest posterior density interval (HPDI) for parameter λ, if the following conditions are satisfied:

(a1) $P(\lambda \in [a, b] \mid y) = 1 - \alpha$, for a fixed $\alpha \in (0, 1)$;

(a2) If $\lambda_1 \in [a, b]$ and $\lambda_2 \notin [a, b]$, then $f(\lambda_1|y) > f(\lambda_2|y)$.

In general, the explicit calculation of the posterior density $f(\lambda|y)$ is difficult. To avoid such difficulties, we use Metropolis–Hastings sampling based on random walk to evaluate the posterior distribution. This algorithm allows us to simulate any random variable, if we know its density up to a normalizing constant, in our case: $f(\lambda|y) = cL(y|\lambda)\pi(\lambda)$ and is not necessary to calculate $c = 1/\int_0^\infty L(y|\lambda)\pi(\lambda)d\lambda$.

After generating $\lambda_1, \lambda_2, \ldots, \lambda_N \sim f(\lambda|y)$ we will use their empirical distribution as an approximation of $f(\lambda|y)$. So the Bayesian estimate of λ will be:

$$\widehat{\lambda} = \frac{\lambda_1 + \lambda_2 + \cdots + \lambda_N}{N}.$$

As prior distributions for λ will be considered uniform $U[0, 2]$ and log-normal $LN(\mu = 0, \sigma = 1)$. Both have median 1, i.e., are neutral with respect to whether $\lambda < 1$ or $\lambda > 1$.

Considering two cases for offspring distribution – Poisson and geometric, the likelihood function $L(y|\lambda)$ will be the Borel–Tanner probability mass function and the Haight probability mass function, respectively.

9.5 Mumps in Bulgaria – estimation of reproduction number

In this section we will illustrate the described methods for estimation of offspring mean of BGWBP, using data on the number of reported cases of mumps in Bulgaria during the period 2005–2008.

Mumps

Mumps is a viral infectious disease of humans and spreads from person to person through the air. The period between mumps transmission and the beginning of mumps symptoms is called the incubation period for mumps. This period is between 14 and 24 days (median 18 days). The infectious period starts about 2 days before the onset of symptoms and usually, an individual with mumps symptoms is immediately isolated from the population. In view of the length of the incubation period, we consider that an outbreak in a region is a sequence of weeks with no more than three consecutive weeks without cases. That is, when we observe more than three weeks without cases we consider that the outbreak has become extinct, with the next outbreak starting in the first subsequent week in which there is at least one new case.

In 2007 in Bulgaria there was an outbreak of mumps. Over 60% of those infected at the beginning of the year are aged between 15 and 19 years, about 20% between 20 and 24 years. It is assumed that the outbreak was the result of poor immunization policy in the 80s. One third of patients aged between 15 and 19 years have never been vaccinated, about half was given only one dose of vaccine, which is found not effective. Over 90% of 20-24-years-old have not been vaccinated against mumps (see Kojouharova, Kurchatova, Marinova, Georgieva (2007)).

Data

The data, provided by the National Center of Infectious and Parasitic Diseases, consists of the number of reported cases of mumps in Bulgaria during the period 2005 to 2008, on weekly base for each of 28 regions of the country. We will treat 28 regions separately.

Estimates of the reproduction number

We consider each outbreak as a realization of a branching process. The data that is observed about the process are the total number y of infected and the initial s number of infectious. We will estimate the reproduction number for the outbreaks in Sofia-city and in the regions of Kyustendil and Lovech. For the offspring distribution we consider 2 distributions – Poisson and geometric and for each of them we use 2 prior distributions

– uniform and log-normal, so we get a total of 4 estimates for λ. For each of the options we generate 5000 random numbers with the corresponding posterior distribution and ignore the first 500. For calculating highest posterior density interval we use the function `HPDinterval` from `coda` package (see Plummer, Best, Cowles, Vines (2010)).

Sofia-city

In Sofia-city during the period from the 40th week of 2006 to the 52nd week of 2008 a total number of 2124 cases of mumps was reported and the initial number of infectious individuals was 2, i.e. $y = 2124; s = 2$. Point estimates for λ and HPD intervals (95% HPDI = 95 percent highest posterior density interval) are given in Table 9.1.

	Offspring distribution	*Prior distribution*	$\widehat{\lambda}$	95% HPDI
1	Poisson	Uniform	1.0011	$[0.9577, 1.0436]$
2	Poisson	Log-normal	0.9981	$[0.9540, 1.0412]$
3	Geometric	Uniform	1.0002	$[0.9459, 1.0646]$
4	Geometric	Log-normal	0.9996	$[0.9383, 1.0598]$

Table 9.1: Point and interval estimates of λ for Sofia-city.

One can see that the estimates $\widehat{\lambda}$ and HPD intervals are quite close for different assumptions about offspring and prior distributions.

The region of Kyustendil

In the region of Kyustendil during the period from the 4th week of 2007 to the 33rd week of 2008, there were a total number of 405 cases of mumps. The initial number of infectives was 2 ($y = 405; s = 2$). Estimates for λ and HPD intervals are given in Table 9.2.

Again we note that estimates $\widehat{\lambda}$ are quite close for different assumptions about offspring and prior distributions. HPD intervals for the geometric offspring distribution are wider than in the case of Poisson off-

	Offspring distribution	*Prior distribution*	$\widehat{\lambda}$	95% HPDI
1	Poisson	Uniform	0.9990	$[0.9055, 1.1019]$
2	Poisson	Log-normal	0.9942	$[0.9030, 1.1047]$
3	Geometric	Uniform	0.9972	$[0.8558, 1.1257]$
4	Geometric	Log-normal	0.9997	$[0.8659, 1.1330]$

Table 9.2: Point and interval estimates of λ for the region of Kyustendil.

spring distribution, i.e. posterior distribution of λ is more dispersed in the case of geometric offspring distribution.

The region of Lovech

In the region of Lovech during the period from 24th to 34th week of 2008 there was an outbreak with 29 infected, and 5 initial cases ($y = 29; s = 5$). Estimates for λ and HPD intervals are given in Table 9.3.

	Offspring distribution	*Prior distribution*	$\widehat{\lambda}$	95% HPDI
1	Poisson	Uniform	0.8606	$[0.5338, 1.2171]$
2	Poisson	Log-normal	0.8349	$[0.5224, 1.1422]$
3	Geometric	Uniform	0.9127	$[0.5018, 1.4115]$
4	Geometric	Log-normal	0.8735	$[0.4752, 1.3838]$

Table 9.3: Point and interval estimates of λ for the region of Lovech.

Here we noticed that in the case of geometric offspring distribution and uniform prior distribution (option 3) the estimate $\widehat{\lambda}$ is greater than the others. Again, HPD intervals for the geometric offspring distribution are wider than for the Poisson distribution.

Discussion

With different assumptions about the offspring distribution and prior distribution we get similar estimates of the reproduction number for Sofia-city and the region of Kyustendil – approximately 1. For the region of Lovech estimates slightly vary from distributions – between 0.83 and 0.91.

Estimates of R_0 in Sofia-city and the region of Kyustendil show that mumps is not eliminated in these areas, which can be attributed to poor vaccination for certain age groups in these regions. Estimates of R_0 in the region of Lovech are consistent with the small number of cases in the region. We are in debt to some accuracy aspects of the modeling approach and their comment is left depending on the case study.

In conclusion, we could summarize that Bayesian estimation using Metropolis–Hastings sampling works very efficiently in combination with BGWBP and might be of direct use to decision makers in public health sector.

Chapter 10

Crump–Mode–Jagers branching processes with application to vaccination

10.1 Introduction

Branching processes have been applied widely to model epidemic spread (see for example the monographs by Andersson and Britton (2000), Daley and Gani (1999) and Mode and Sleeman (2000), and the review by Pakes (2003)). The process describing the number of infectious individuals in an epidemic model may be well approximated by a branching process if the population is homogeneously mixing and the number of infectious individuals is small in relation to the total size of the susceptible population, since under these circumstances the probability that an infectious contact is with a previously infected individual is negligible (see, for example, Isham (2005)). Such an approximation dates back to the pioneering works of Bartlett (1955) and Kendall (1956),and can be made mathematically precise by showing convergence of the epidemic process to a limiting branching process as the number of susceptibles tends to infinity (see Ball (1983), Ball and Donnelly (1995) and Metz (1978)). The approximation may also be extended to epidemics in populations that are not homogeneously mixing, for example those containing small mixing units such as households and workplaces (see Pellis et al. (2012)).

Before proceeding we give outline descriptions of some common branch-

ing process models (see e.g. Jagers (1975)) for further details), which describe the evolution of a single–type population. In all of these models individuals have independent and identically distributed reproduction processes. In a Bienaymé–Galton–Watson branching process, each individual lives for one unit of time and then has a random number of children, distributed according to a random variable, ζ say. In a Bellman–Harris branching process (BHBP), each individual lives until a random age, distributed according to a random variable I say, and then has a random number of children, distributed according to ζ, where I and ζ are independent. The Sevast'yanov branching process (SBP) is defined similarly, except I and ζ may be dependent, so the number of children an individual has is correlated with that individual's lifetime. Finally, in a general branching process, also called a Crump–Mode–Jagers (CMJ) branching process, each individual lives until a random age, distributed according to I, and reproduces at ages according to a point process ξ. More precisely, if an individual, i say having reproduction variables (I_i, ξ_i), is born at time b_i and $0 \leq \tau_{i1} \leq \tau_{i2} \leq \ldots \leq I_i$ denote the points of ξ_i, then individual i has one child at each of times $b_i + \tau_{i1}, b_i + \tau_{i2}, \ldots$.

This chapter is primarily concerned with models for epidemics of diseases, such as measles, mumps and avian influenza, which follow the so–called SIR (Susceptible $\rightarrow$ Infective $\rightarrow$ Removed) scheme in a closed, homogeneously mixing population or some of its extensions. A key epidemiological parameter for such an epidemic model is the basic reproduction number R_0 (see Heesterbeek and Dietz (1996)), which in the present setting is given by the mean of the offspring distribution of the approximating branching process. In particular a major outbreak (i.e. one whose size is of the same order as the population size) occurs with non–zero probability if and only if $R_0 > 1$. Suppose that $R_0 > 1$ and a fraction c of the population is vaccinated with a perfect vaccine in advance of an epidemic. Then R_0 is reduced to $(1 - c)R_0$, since a proportion c of infectious contacts is with vaccinated individuals. It follows that a major outbreak is almost surely prevented if and only if $c \geq 1 - R_0^{-1}$. This well known result, which gives the critical vaccination coverage to prevent a major outbreak and goes back at least to 1964 (e.g. Smith (1964)), is widely used to inform public health authorities.

Observe that, if the population is large, both the total size and the duration of an outbreak may still be appreciable when R_0 is reduced to

its critical value of one. Indeed, in the limit as the population size tends to infinity, both of these quantities have infinite expectation under any plausible modelling assumptions. Thus González et al. (2010a), (2010b) studied properties of the time to extinction of an epidemic given that a fraction c of individuals is vaccinated, when the number of infectious individuals in the population is modelled by a continuous–time BHBP and a (more general) continuous–time SBP, respectively. In an earlier work, De Serres et al. (2000) used a discrete–time Bienaymé–Galton–Watson branching process to study the spread of an infectious disease under various control measures, specifically to estimate the effective (i.e. post-control) value of R_0 from observations on size and durations of small outbreaks.

The main objective in González et al. (2010a), (2010b) was to determine the optimal proportion of susceptible individuals which has to be vaccinated so that the mean (or given quantile of the) extinction time of the disease is less than some specified value. To that end, stochastic monotonicity and continuity properties of the distribution function and mean of the time that the infection survives, depending on the vaccination coverage rate were first determined.

As a consequence of the above result, many analyses of vaccination strategies in the epidemic modelling literature have focussed on reducing R_0 to its critical value of one. However, if the population is large, both the total size and the duration of an outbreak may still be appreciable. Indeed, in the limit as the population size tends to infinity, both of these quantities have infinite expectation under any plausible modelling assumptions. In practice, there may be a cost associated with an individual contracting the disease being modelled, in which case it is of interest to determine vaccination strategies which reduce the expected value of the total cost of an outbreak to an acceptable level. Alternatively, it may be desired to control the duration of an outbreak, for example if the presence of an outbreak means that restrictions are placed on the population within which it is spreading. The above remarks pertain to the common situation of controlling an epidemic that is in its increasing phase. A different situation arises with diseases, such as measles and mumps, which are controlled by mass vaccination but small outbreaks still occur among unvaccinated individuals. Supplementary vaccination may be used to reduce the size or duration of such outbreaks (as in the

illustrative example of mumps in Bulgaria. A similar phenomenon occurs with pathogens, such as monkeypox virus, which primarily affect animals but spill over into human populations giving stuttering chains of human–to–human transmission (Lloyd–Smith et al. (2009)). In at least some of the above scenarios it may be the case that a specific vaccination level cannot be achieved immediately but rather the fraction of the population that is vaccinated will be time–dependent. The aim of this paper is to develop a methodology based on branching processes for addressing the above issues in a unified fashion.

González et al. (2010a), (2010b) studied properties of the time to extinction of an epidemic given that a fraction c of individuals is vaccinated, when the number of infectious individuals in the population is modelled by a continuous–time BHBP and a (more general) continuous–time SBP, respectively. In an earlier work, De Serres et al. (2000) discrete–time Bienaymé–Galton–Watson branching process to study the spread of an infectious disease under various control measures, specifically to estimate the effective (i.e. post–control) value of R_0 from observations on size and durations of small outbreaks. The main objective in González et al. (2010a), (2010b) was to determine the optimal proportion of susceptible individuals which has to be vaccinated so that the mean (or given quantile of the) extinction time of the disease is less than some specified value. To that end, stochastic monotonicity and continuity properties of the distribution function and mean of the time that the infection survives, depending on the vaccination coverage rate were first determined.

In the present chapter we extend the results in González et al. (2010a), (2010b) in several directions that are both practically and theoretically important. First we assume that the spread of infection is modelled as a CMJ branching process. The CMJ branching process is appropriate for modelling the early stages of a very wide variety of SIR epidemics, and includes both BHBP and SBP as special cases. Secondly, we consider more general vaccination processes. In González et al. (2010a), (2010b) it was assumed that the fraction of the population that is vaccinated remained constant with time. We now allow this fraction to be an arbitrary but specified function of time, thus capturing for example the setting in which people are vaccinated as the disease spreads. Thirdly, we consider the control of more general functions of the epidemic process. González et al. (2010a), (2010b) focused on controlling the duration of the epi-

demic. The methods developed in this chapter are applicable to a wide class of functions of the epidemic process. In addition to the duration of an outbreak, this class includes, for example, the total number of people infected and the maximum number of infected people present during the epidemic.

The methodology developed here is very different from that of González et al. (2010a), (2010b). The key stochastic monotonicity and continuity results in these previous papers were obtained by analysis of integral equations governing properties of the time to extinction of the branching process. In the present chapter, a main tool is coupling and, in particular, a pruning method of constructing a realization of a vaccinated process from that of the corresponding unvaccinated process. This methodology turns out to be very powerful and applicable to a broad range of processes.

In the next Section 10.2, we describe a very general model for an SIR epidemic in a closed, homogeneously mixing community and explain why its early spread may be approximated by a CMJ branching process. We introduce a very general vaccination process and give the basic coupling construction for obtaining a realization of the vaccinated epidemic process from that of the unvaccinated process. The theoretical results are given in Section 10.3.

10.2 Model and coupling construction

Consider first the following model for the spread of an epidemic in a closed, homogeneously mixing population. Initially there are a infectives and N susceptibles. Infectious individuals have independent and identically distributed life histories $\mathcal{H} = (I, \xi)$, where I is the time elapsing between an individual's infection and his/her eventual removal or death and ξ is a point process of times, relative to an individual's infection, at which infectious contacts are made. Each contact is with an individual chosen independently and uniformly from the population. If a contact is with an individual who is susceptible then that individual becomes infected and itself makes contacts according to its life history. If a contact is with an individual who is not susceptible then nothing happens. The epidemic ceases as soon as there is no infective present in the population.

Note that, for simplicity, we assume that every infectious contact with a susceptible necessarily leads to that susceptible becoming infected. The model is easily extended to the situation when each contact with a susceptible is successful (i.e. leads to infection) independently with probability p by letting $\mathcal{H} = (I, \xi')$, where ξ' is a suitable thinning of ξ.

The above model is essentially that introduced by Ball and Donnelly (1995), who noted that it included as special cases a range of specific models that had hitherto received considerable attention in the literature. For example, SIR and SEIR (Susceptible $\to$ Exposed (i.e. latent $\to$ Infective $\to$ Removed) models come under the above framework. The only difference between the above model and that in Ball and Donnelly (1995) is that, in the latter, each contact is with an individual chosen independently and uniformly from the N initial susceptibles (rather than from the entire population of $N + a$ individuals). In the same paper, a coupling argument (which also holds for the present model) is used to prove strong convergence, as the number of initial susceptibles $N \to \infty$ (with the number of initial infectives a held fixed), of the process of infectives in the epidemic model to a CMJ branching process (see Jagers (1975), in which a typical individual lives until age I and reproduces at ages according to ξ. Thus for large N, the epidemic may be approximated by the CMJ branching process. The approximation assumes that every contact is with a susceptible individual. The proof in Ball and Donnelly (1995) maight be extended to epidemics other than SIR, e.g. SIS (Susceptible $\to$ Infective $\to$ Susceptible) and SIRS (Susceptible $\to$ Infective $\to$ Removed $\to$ Susceptible), by suitably generalizing the life history $\mathcal{H}$ to allow for removed individuals to become susceptible again (see e.g. Ball (1999) in the context of epidemics among a population partitioned into households). Indeed, for a very broad class of homogeneously mixing epidemic models, the early stages of an epidemic in a large population with few initial infectives may be approximated by a CMJ branching process.

This research is concerned with the use of vaccination schemes to control an epidemic, for example, in terms of its duration or of the total number of individuals infected. We are thus interested in the short–term behaviour of the epidemic, so we model the epidemic as a CMJ branching process, $Z = \{Z(t) : t \geq 0\}$, where $Z(t)$ denotes the number of infected individuals at time t. Thus $Z(0)$, which we assume to be fixed, represents the number of infected individuals at the beginning of the outbreak.

We model the vaccination process by a function $\alpha : [0, \infty) \to [0, 1]$, such that $\alpha(t)$ is the proportion of the population that are immune at time t ($t \geq 0$). Thus the probability that a contact at time t is with a susceptible (i.e. non–immune) individual is $1 - \alpha(t)$. If the vaccine is perfect, i.e. it confers immunity immediately with probability one, then $\alpha(t)$ is given by the proportion of the population that has been vaccinated by time t. If the vaccine is imperfect then that is implicitly included in the function α. For example, if the vaccine is all–or–nothing (i.e. it renders the vaccinee completely immune with probability ε, otherwise it has no effect), then $\alpha(t) = \varepsilon\tilde{\alpha}(t)$, where $\tilde{\alpha}(t)$ is the proportion of the population that has been vaccinated by time t. Note that if the immunity conferred by vaccination does not wane then α is nondecreasing in t. We denote by $Z_\alpha = \{Z_\alpha(t) : t \geq 0\}$ the vaccination version of Z, in which each birth in Z is aborted independently, with probability $\alpha(t)$ if the birth time is at time t.

Let $\mathcal{A}$ be the space of all functions $\alpha : [0, \infty) \to [0, 1]$. We construct coupled realizations of Z and Z_α ($\alpha \in \mathcal{A}$) on a common probability space $(\Omega, \mathcal{F}, P)$ as follows. Let $(\Omega_1, \mathcal{F}_1, P_1)$ be a probability space on which are defined independent life histories $\mathcal{H}_1, \mathcal{H}_2, \ldots$, each distributed as $\mathcal{H}$, which are pieced together in the obvious fashion to construct a realization of Z. More specifically, the life histories $\mathcal{H}_1, \mathcal{H}_2, \ldots, \mathcal{H}_a$ are assigned to the a initial infectives and, for $i = 1, 2, \ldots$, the ith individual born in Z is assigned the life history $\mathcal{H}_{a+i}$. Note that with this construction Z may be viewed as a tree, which is augmented with birth and death times of branches. Let $(\Omega_2, \mathcal{F}_2, P_2)$ be a probability space on which is defined a sequence $U_1, U_2, \ldots$ of independent random variables, each uniformly distributed on $(0, 1)$. Let $(\Omega, \mathcal{F}, P) = (\Omega_1 \times \Omega_2, \mathcal{F}_1 \times \mathcal{F}_2, P_1 \times P_2)$. Then, for $\alpha \in \mathcal{A}$, a realization of Z_α is constructed on $(\Omega, \mathcal{F}, P)$ as follows. For $i = 1, 2, \ldots$, let b_i denote the time of the ith birth in Z, if such a birth occurs. Then this birth is deleted in Z_α if and only if $U_i \leq \alpha(b_i)$. If a birth is deleted in Z_α, then none of the descendants of that individual in Z occurs in Z_α. Thus, if the jth birth in Z is such a descendant then U_j is redundant in the construction of Z_α. With the tree setting in mind, the process of deleting an individual and all of its descendants is called *pruning*.

Finally, we give some notation concerned with functions in $\mathcal{A}$, which will be used throughout the paper. For $\alpha, \alpha' \in \mathcal{A}$, write $\alpha \prec \alpha'$ if

$\alpha(t) \leq \alpha'(t)$ for all $t \in [0, \infty)$. Also, for any $c \in [0, 1]$ and any $t_0 \geq 0$, define the function $\alpha_c^{t_0} \in \mathcal{A}$ by

$$\alpha_c^{t_0}(t) = \begin{cases} 0 & \text{if } t < t_0, \\ c & \text{if } t \geq t_0. \end{cases}$$

Thus, for example, α_c^0 denotes the constant function equal to c and α_0^0 denotes the constant function equal to 0.

10.3 Monotonicity and continuity properties depending on vaccination α

Functions $f(Z_\alpha)$ monotone to pruning

Let $f(Z)$ be any non-negative function of Z taking values in the extended real line $\mathbb{R} \cup \{\infty\}$ and, for $\alpha \in \mathcal{A}$, let $\mu_\alpha^f = \mathrm{E}[f(Z_\alpha)]$. Again with the tree setting in mind, we say that f is monotonically decreasing with pruning, and write $f \in \mathcal{P}$, if $f(Z^P) \leq f(Z)$ almost surely whenever Z^P is obtained from Z by pruning. For an event, E say, let 1_E denote the indicator function of E. Examples of functions that are monotonically decreasing with pruning include:

(i) the extinction time $T = \inf\{t \geq 0 : Z(t) = 0\}$ and $1_{\{T>t\}}$, where $t \in [0, \infty)$ is fixed;

(ii) the maximum population size (number of infected individuals in the epidemic context) over all time, $M = \sup_{t \geq 0} Z(t)$ and $1_{\{M>x\}}$, where $x \in [0, \infty)$ is fixed;

(iii) $N(t)$, the total number of births (new infections in the epidemic context) in $(0, t]$, where $t \in [0, \infty)$ is fixed, and the total number of births over all time (outbreak total size in the epidemic context) $N(\infty) = \lim_{t \to \infty} N(t)$, together with the corresponding indicator functions $1_{\{N(t)>x\}}$ and $1_{\{N(\infty)>x\}}$, where $x \in [0, \infty)$ is fixed.

Throughout this chapter, we assume that Z is non–explosive, i.e. that $\mathrm{P}(N(t) < \infty) = 1$ for any $t \in (0, \infty)$. Conditions which guarantee this property may be found in Jagers (1975), Section 6.2.

Monotonicity and continuity of mean of $f(Z_\alpha)$

In what follows, we derive monotonicity and continuity properties of $\mathrm{E}[f(Z_\alpha)]$, when viewed as a function of the vaccination process α, for functions f that are monotonically decreasing with pruning.

Theorem H.1 *If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$ and $f \in \mathcal{P}$, then $\mu_\alpha^f \geq \mu_{\alpha'}^f$.*

Proof. The result follows immediately from the above construction of Z and Z_α, $\alpha \in \mathcal{A}$, on $(\Omega, \mathcal{F}, P)$, since f is monotonically decreasing with pruning and $Z_{\alpha'}$ may be obtained from Z_α by successive prunings.

We now give conditions under which μ_α^f is continuous in α. For $\alpha, \alpha' \in \mathcal{A}$, let $\|\alpha - \alpha'\| = \sup_{t\in[0,\infty)} |\alpha(t) - \alpha'(t)|$ and, for $t > 0$, let $\|\alpha - \alpha'\|_t = \sup_{s\in[0,t]} |\alpha(s) - \alpha'(s)|$. For $t > 0$, write $f \in \mathcal{P}_t$ if $f \in \mathcal{P}$ and $f(Z)$ depends on Z only through $\{Z(s) : 0 \leq s \leq t\}$. Let m be the offspring mean for Z. For $c \in [0, 1]$, let m_c denote the offspring mean of $Z_{\alpha_c^0}$, so $m_c = (1 - c)m$. Further, let $c_{\inf} = \max(0, 1 - m^{-1})$ and note that $m_{c_{\inf}} \leq 1$. For $t_0 \geq 0$ and $c \in [0, 1]$, let

$$\mathcal{A}(c, t_0) = \{\alpha \in \mathcal{A} : \alpha(t) \geq c \text{ for all } t \geq t_0\}.$$

□

Theorem H.2 *(a) Fix $t > 0$, let $f \in \mathcal{P}_t$ and suppose that there exists a non-negative real-valued function $\hat{f}$, with $\mathrm{E}[\hat{f}(Z)] < \infty$, such that, for P-almost all $\omega \in \Omega$,*

$$f(Z_\alpha(\omega)) \leq \hat{f}(Z(\omega)) \quad \textit{for all } \alpha \in \mathcal{A}. \tag{H.1}$$

Then, for each $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\|_t \leq \eta$,

$$|\mu_\alpha^f - \mu_{\alpha'}^f| \leq \varepsilon. \tag{H.2}$$

(b) Suppose that $m < \infty$. Let $f \in \mathcal{P}$ and $t_0 \geq 0$, and suppose that there exists a non-negative real-valued function $\hat{f}(Z_{\alpha_{c_{\inf}}^{t_0}})$, with $\mathrm{E}[\hat{f}(Z_{\alpha_{c_{\inf}}^{t_0}})] < \infty$, such that, for P-almost all $\omega \in \Omega$,

$$f(Z_\alpha(\omega)) \leq \hat{f}(Z_{\alpha_{c_{\inf}}^{t_0}}(\omega)) \quad \textit{for all } \alpha \in \mathcal{A}(c_{\inf}, t_0). \tag{H.3}$$

Then, for each $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that (H.2) holds for all $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ satisfying $\|\alpha - \alpha'\| \leq \eta$.

Proof.

(a) For $n = 1, 2, \ldots$ and $\alpha, \alpha' \in \mathcal{A}$, let

$$B_n(\alpha, \alpha') = \bigcap_{i=1}^{n} \{\omega \in \Omega : U_i(\omega) \notin (\min(\alpha(b_i), \alpha'(b_i)), \max(\alpha(b_i), \alpha'(b_i))]\},$$

and let $B_0(\alpha, \alpha') = \Omega$. Now $\mathrm{P}(N(t) < \infty) = 1$, since Z is non-explosive . Observe that if $\omega \in B_{N(t)}(\alpha, \alpha')$ then, by construction, $Z_\alpha(s, \omega) = Z_{\alpha'}(s, \omega)$ for all $s \in [0, t]$, whence $f(Z_\alpha(\omega)) = f(Z_{\alpha'}(\omega))$ since $f \in \mathcal{P}_t$. Now, for any $\alpha \in \mathcal{A}$,

$$\mu_\alpha^f = \mathrm{E}\left[f(Z_\alpha) 1_{B_{N(t)}(\alpha,\alpha')}\right] + \mathrm{E}\left[f(Z_\alpha) 1_{B^c_{N(t)}(\alpha,\alpha')}\right],$$

where $B^c_{N(t)}(\alpha, \alpha') = \Omega \setminus B_{N(t)}(\alpha, \alpha')$. Thus, for any $\alpha, \alpha' \in \mathcal{A}$,

$$\mu_\alpha^f - \mu_{\alpha'}^f = \mathrm{E}\left[f(Z_\alpha) 1_{B^c_{N(t)}(\alpha,\alpha')}\right] - \mathrm{E}\left[f(Z_{\alpha'}) 1_{B^c_{N(t)}(\alpha,\alpha')}\right],$$

whence, since f is non-negative,

$$|\mu_\alpha^f - \mu_{\alpha'}^f| \leq \mathrm{E}\left[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha,\alpha')}\right].$$

Now

$$\mathrm{E}\left[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha,\alpha')}\right] = \mathrm{E}\left[\hat{f}(Z) \mathrm{E}\left[1_{B^c_{N(t)}(\alpha,\alpha')} | Z\right]\right].$$

Further, (i) Z determines $N(t)$ and (ii) $(U_1, U_2, \ldots)$ is independent of Z, so, P-almost surely,

$$\begin{aligned}\mathrm{E}\left[1_{B^c_{N(t)}(\alpha,\alpha')} | Z\right] &= 1 - \prod_{i=1}^{N(t)} (1 - |\alpha(b_i) - \alpha'(b_i)|) \\ &\leq 1 - (1 - \delta)^{N(t)},\end{aligned}$$

where $\delta = \|\alpha - \alpha'\|_t$. Hence, P-almost surely,

$$\mathrm{E}\left[1_{B^c_{N(t)}(\alpha,\alpha')} | Z\right] \leq \mathrm{E}\left[1_{B^c_{N(t)}(\alpha_0^0,\alpha_\delta^0)} | Z\right],$$

whence, for $\alpha, \alpha' \in \mathcal{A}$,

$$\begin{aligned} |\mu^f_\alpha - \mu^f_{\alpha'}| &\leq \mathrm{E}\left[\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0, \alpha^0_\delta)}\right] \\ &= \hat{\mu}_t(\delta) \quad \text{say.} \end{aligned} \tag{H.4}$$

Now $\mathrm{P}(N(t) < \infty) = 1$, so P–almost surely,

$$\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0, \alpha^0_\delta)} \to 0 \quad \text{as } \delta \downarrow 0$$

(in fact $\hat{f}(Z) 1_{B^c_{N(t)}(\alpha^0_0, \alpha^0_\delta)} = 0$ for all $\delta \in [0, \delta^*)$, where $\delta^* = \min(U_1, U_2, \ldots, U_{N(t)})$), so by the dominated convergence theorem $\hat{\mu}_t(\delta) \to 0$ as $\delta \downarrow 0$. Thus, given $\varepsilon > 0$, there exists η such that $\hat{\mu}_t(\delta) \leq \varepsilon$ for all $\delta \in (0, \eta)$ and the theorem follows using (H.4).

(b) For $\alpha \in \mathcal{A}(c_{\inf}, t_0)$, the process Z_α can be viewed as a vaccinated version of the process $Z_{\alpha^{t_0}_{c_{\inf}}}$ with vaccination function $\tilde{\alpha}$ given by

$$\tilde{\alpha}(t) = \begin{cases} \alpha(t) & \text{if } t < t_0, \\ \frac{\alpha(t)}{1 - c_{\inf}} & \text{if } t \geq t_0. \end{cases}$$

Note that $Z_{\alpha^{t_0}_{c_{\inf}}}$ has offspring mean m until time t_0, and $m_{c_{\inf}} \leq 1$ after time t_0. Thus, since Z is non-explosive (so $\mathrm{P}(Z(t_0) < \infty) = 1$), the total number of births over all time in $Z_{\alpha^{t_0}_{c_{\inf}}}$ (i.e. $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$) is finite almost surely. Also, $\|\tilde{\alpha} - \tilde{\alpha}'\| \leq (1 - c_{\inf})^{-1} \|\alpha - \alpha'\|$. The proof then proceeds as in part (a), but with Z and $N(t)$ replaced by $Z_{\alpha^{t_0}_{c_{\inf}}}$ and $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$, respectively, and α, α' replaced by $\tilde{\alpha}, \tilde{\alpha}'$.

□

Remark H.1 *1. Suppose that $m \leq 1$. Then $c_{\inf} = 0$ and it follows that $Z_{\alpha^{t_0}_{c_{\inf}}} = Z$ and $\mathcal{A}(c_{\inf}, t_0) = \mathcal{A}$. Thus, for any $f \in \mathcal{P}$, Theorem H.2(b) implies that, for any $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that (H.2) holds for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\| \leq \eta$.*

2. Suppose that $m > 1$ and $f \in \mathcal{P}$. Then the argument used to prove Theorem H.2(b) breaks down since $\mathrm{P}(Z(\infty) < \infty) < 1$. Thus with our argument we can prove continuity in α of μ^f_α for $f \in \mathcal{P}_t$, for

any $t > 0$, but not for $f \in \mathcal{P}$. However, this is no restriction from a practical viewpoint since t in Theorem H.2(a), or t_0 in Theorem H.2(b), can be made arbitrarily large. For example, in any real life–setting there will be a maximum time frame over which it is of interest to evaluate the performance of a vaccination process and t or t_0 can be chosen accordingly.

Monotonicity and continuity of distribution function of $f(Z_\alpha)$

Using the previous results we establish in this subsection monotonicity and continuity properties of the distribution function of $f(Z_\alpha)$. For $f \in \mathcal{P}$ and $\alpha \in \mathcal{A}$, let

$$v_\alpha^f(x) = \mathrm{P}(f(Z_\alpha) \le x) = 1 - \mathrm{E}[1_{\{f(Z_\alpha) > x\}}], \quad x \ge 0,$$

be the distribution function of the random variable $f(Z_\alpha)$.

For $\alpha \in \mathcal{A}$ and $t \in [0, \infty]$, let $\phi_{N_\alpha(t)}(s) = \mathrm{E}[s^{N_\alpha(t)}]$ $(0 \le s \le 1)$ denote the probability generating function of $N_\alpha(t)$. Suppose that $P(N_\alpha(t) < \infty) = 1$. Then $\phi_{N_\alpha(t)}(1-) = 1$ and $\phi^{-1}_{N_\alpha(t)}(u)$ is well-defined for all $u \in [u_{\alpha,t}, 1]$, where $u_{\alpha,t} = \mathrm{P}(N_\alpha(t) = 0)$. Extend the domain of $\phi^{-1}_{N_\alpha(t)}$ by defining $\phi^{-1}_{N_\alpha(t)}(u) = 0$ for $u \in [0, u_{\alpha,t})$. Define the function $\delta_{\alpha,t} : [0,1] \to [0,1]$ by

$$\delta_{\alpha,t}(\varepsilon) = 1 - \phi^{-1}_{N_\alpha(t)}(1-\varepsilon), \quad 0 \le \varepsilon \le 1. \tag{H.5}$$

Note that $\delta_{\alpha,t}(\varepsilon) > 0$ if $\varepsilon > 0$ and $\lim_{\varepsilon \downarrow 0} \delta_{\alpha,t}(\varepsilon) = 0$.

Theorem H.3 *(a) Suppose that $f \in \mathcal{P}$ and $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$. Then*

$$v_\alpha^f(x) \le v_{\alpha'}^f(x) \quad \text{for all } 0 \le x \le \infty. \tag{H.6}$$

(b) Fix $t > 0$ and suppose that $f \in \mathcal{P}_t$. Then, for any $\varepsilon > 0$,

$$\sup_{0 \le x < \infty} |v_\alpha^f(x) - v_{\alpha'}^f(x)| \le \varepsilon \tag{H.7}$$

for all $\alpha, \alpha' \in \mathcal{A}$ satisfying $\|\alpha - \alpha'\|_t \le \delta_{\alpha_0^0,t}(\varepsilon)$.

(c) Suppose that $f \in \mathcal{P}$. *Then, for any* $\varepsilon > 0$, *(H.7) holds for all* $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ *satisfying* $\|\alpha - \alpha'\| \leq \delta_{\alpha^{t_0}_{c_{\inf}}, \infty}(\varepsilon)$.

Proof.

(a) Fix $x \in [0, \infty)$ and let $\tilde{f}_x$ be the function of Z given by $\tilde{f}_x(Z) = 1_{\{f(Z) > x\}}$. Then $\tilde{f}_x \in \mathcal{P}$ and (H.6) follows from Theorem H.1, since $v^f_\alpha(x) = 1 - \mathrm{E}[\tilde{f}_x(Z_\alpha)]$.

(b) For each $x \in [0, \infty)$,

$$|v^f_\alpha(x) - v^f_{\alpha'}(x)| = |\mathrm{E}[\tilde{f}_x(Z_\alpha)] - \mathrm{E}[\tilde{f}_x(Z_{\alpha'})]|$$

and $\tilde{f}_x(Z_\alpha(\omega)) \leq 1$ for all $\alpha \in \mathcal{A}$ and all $\omega \in \Omega$. Fix $t > 0$ and note that $\tilde{f}_x \in \mathcal{P}_t$, since $f \in \mathcal{P}_t$. It then follows from (H.4), taking $\hat{f}(Z) = 1$, that, for $x \in [0, \infty)$ and $\alpha, \alpha' \in \mathcal{A}$,

$$|v^f_\alpha(x) - v^f_{\alpha'}(x)| \leq \hat{\mu}_t(\|\alpha - \alpha'\|_t), \tag{H.8}$$

where, for $\delta \in [0, 1]$,

$$\hat{\mu}_t(\delta) = \mathrm{P}\left(B^c_{N(t)}(\alpha^0_0, \alpha^0_\delta)\right) = 1 - \mathrm{E}\left[(1-\delta)^{N(t)}\right] = 1 - \phi_{N(t)}(1-\delta).$$

Recall that $N(t) = N_{\alpha^0_0}(t)$ and note that $P(N_{\alpha^0_0}(t) < \infty) = 1$ since Z is non-explosive. Thus $\phi^{-1}_{N_{\alpha^0_0}(t)}(u)$ is well defined for all $u \in [0, 1]$ and the theorem follows since $1 - \phi_{N_{\alpha^0_0}(t)}(1 - \delta_{\alpha^0_0, t}(\varepsilon)) \leq \varepsilon$.

(c) The proof is similar to part (b) but with $N_{\alpha^0_0}(t)$ replaced by $N_{\alpha^{t_0}_{c_{\inf}}}(\infty)$.

□

Remark H.2 *1. Observe that the function* $\delta_{\alpha^0_0, t}$, *defined using (H.5), is independent of both* f *and* x, *so the uniform continuity of* $v^f_\alpha(x)$, *with respect to* α, *holds uniformly over all* $f \in \mathcal{P}$ *and all* $x \in [0, \infty)$.

2. Similar to Remark 1 after Theorem H.2, Theorem H.3(c) shows that if $m \leq 1$ *(so* $P(N(\infty) < \infty) = 1$*) and* $f \in \mathcal{P}$ *then, for any* $\varepsilon > 0$, *(H.7) holds for all* $\alpha, \alpha' \in \mathcal{A}$ *satisfying* $\|\alpha - \alpha'\| \leq \delta_{\alpha^0_0, \infty}(\varepsilon)$.

Monotonicity and continuity of quantiles of $f(Z_\alpha)$

In applications we wish to control the quantiles of $f(Z_\alpha)$, so we now derive related monotonicity and continuity properties. Fix $f \in \mathcal{P}$ and $\alpha \in \mathcal{A}$, and define, for $0 < p < 1$,

$$x^f_{\alpha,p} = \inf\{x : v^f_\alpha(x) \geq p\},$$

with the convention that $x^f_{\alpha,p} = \infty$ if $v^f_\alpha(x) < p$ for all $x \in [0, \infty)$. Thus $x^f_{\alpha,p}$ is the quantile of order p of the random variable $f(Z_\alpha)$. For $\alpha \in \mathcal{A}$, let $\mathcal{A}^+(\alpha) = \{\alpha' \in \mathcal{A} : \alpha \prec \alpha'\}$. For a sequence $\{\alpha_n\}$ and α in $\mathcal{A}$, we define $\lim_{n\to\infty} \alpha_n = \alpha$ to mean $\lim_{n\to\infty} \|\alpha_n - \alpha\| = 0$.

Theorem H.4 *Suppose that $f \in \mathcal{P}$ and $p \in (0, 1)$.*

(a) If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$, then $x^f_{\alpha',p} \leq x^f_{\alpha,p}$.

(b) Suppose further that $f \in \mathcal{P}_t$ for some $t > 0$ and $\alpha \in \mathcal{A}$ is such that $x^f_{\alpha,p} < \infty$. Let $\{\alpha_n\}$ be any sequence in $\mathcal{A}$ satisfying $\lim_{n\to\infty} \alpha_n = \alpha$. Then $\lim_{n\to\infty} x^f_{\alpha_n,p} = x^f_{\alpha,p}$ in each of the following cases:

(i) $\alpha_n \in \mathcal{A}^+(\alpha)$ for all n;

(ii) v^f_α is continuous and strictly increasing at $x^f_{\alpha,p}$.

Proof.

(a) By Theorem H.3(a), $\{x : v^f_\alpha(x) \geq p\} \subseteq \{x : v^f_{\alpha'}(x) \geq p\}$, which implies $x^f_{\alpha',p} \leq x^f_{\alpha,p}$.

(b) Choose $t > 0$ such that $f \in \mathcal{P}_t$. Let $x_{\sup} = \limsup_{n\to\infty} x^f_{\alpha_n,p}$ and $x_{\inf} = \liminf_{n\to\infty} x^f_{\alpha_n,p}$. Suppose that (i) holds. Then by part (a), $x_{\sup} \leq x^f_{\alpha,p}$. Fix $\varepsilon > 0$. Then, since $\lim_{n\to\infty} \alpha_n = \alpha$ and $\|\alpha_n - \alpha\|_t \leq \|\alpha_n - \alpha\|$, there exists n_0 such that $\|\alpha_n - \alpha\|_t \leq \delta_{\alpha^0_0,t}(\varepsilon)$ for all $n \geq n_0$, where $\delta_{\alpha^0_0,t}(\varepsilon)$ is defined at (H.5) – recall that $N(t) = N_{\alpha^0_0}(t)$. Now, $\alpha \prec \alpha_n$, hence, by Theorem H.3 (a) and (b), $v^f_{\alpha_n}(x) - v^f_\alpha(x) \leq \varepsilon$, for all $x \geq 0$ and for all $n \geq n_0$. In particular, setting $x = x^f_{\alpha_n,p}$ and noting that $v^f_{\alpha_n}(x^f_{\alpha_n,p}) \geq p$ since $v^f_{\alpha_n}$ is right–continuous, yields that $v^f_\alpha(x^f_{\alpha_n,p}) \geq p - \varepsilon$ for all $n \geq n_0$. Hence, $v^f_\alpha(x_{\inf}) \geq p - \varepsilon$, since v^f_α is increasing and right–continuous.

This holds for all $\varepsilon > 0$, so $v^f_\alpha(x_{\inf}) \geq p$, whence $x_{\inf} \geq x^f_{\alpha,p}$. Thus, $x_{\inf} = x_{\sup} = x^f_{\alpha,p}$, so $\lim_{n\to\infty} x^f_{\alpha_n,p} = x^f_{\alpha,p}$, as required.

Suppose that (ii) holds. First we assume that $\alpha_n \prec \alpha$ for all n. Then, by part (a), $x_{\inf} \geq x^f_{\alpha,p}$. Note that $v^f_\alpha(x^f_{\alpha,p}) = p$, since v^f_α is continuous at $x^f_{\alpha,p}$, and $v^f_\alpha(x) > p$ for all $x > x^f_{\alpha,p}$, since v^f_α is strictly increasing at $x^f_{\alpha,p}$. Fix $x > x^f_{\alpha,p}$ and let $\varepsilon = v^f_\alpha(x) - p$, so $\varepsilon > 0$. As before, there exists n_0 such that $\|\alpha_n - \alpha\|_t \leq \delta_{\alpha^0_0,t}(\varepsilon)$ for all $n \geq n_0$. It then follows from Theorem H.3 that

$$v^f_\alpha(x) - v^f_{\alpha_n}(x) \leq \varepsilon = v^f_\alpha(x) - p \quad \text{for all } n \geq n_0.$$

Thus $v^f_{\alpha_n}(x) \geq p$ for all $n \geq n_0$, whence $x^f_{\alpha_n,p} \leq x$ for all $n \geq n_0$, which implies that $x_{\sup} \leq x$. Since this holds for any $x > x^f_{\alpha,p}$, it follows that $x_{\sup} \leq x^f_{\alpha,p}$, which combined with $x_{\inf} \geq x^f_{\alpha,p}$ yields the required result.

Now, we consider an arbitrary sequence $\{\alpha_n\}$ that converges to α. For $q = 1, 2, \ldots$, define functions α^+_q and α^-_q by $\alpha^+_q(s) = \min\{\alpha(s) + \frac{1}{q}, 1\}$ and $\alpha^-_q(s) = \max\{\alpha(s) - \frac{1}{q}, 0\}$ $(s \geq 0)$. Then $\lim_{q\to\infty} \alpha^+_q = \lim_{q\to\infty} \alpha^-_q = \alpha$. Further, $\alpha^-_q \prec \alpha \prec \alpha^+_q$ for each $q = 1, 2, \ldots$. Hence, by part (i) and the above, $\lim_{q\to\infty} x^f_{\alpha^+_q,p} = \lim_{q\to\infty} x^f_{\alpha^-_q,p} = x^f_{\alpha,p}$. For any fixed $q \in \mathbb{N}$, $\alpha_n \prec \alpha^+_q$ for all sufficiently large n, so Theorem H.4(a) implies that $\liminf_{n\to\infty} x^f_{\alpha_n,p} \geq x^f_{\alpha^+_q,p}$. Letting $q \to \infty$ then yields that $x_{\inf} \geq x^f_{\alpha,p}$. A similar argument using the sequence $\{\alpha^-_q\}$ shows that $x_{\sup} \leq x^f_{\alpha,p}$, whence $\lim_{n\to\infty} x^f_{\alpha_n,p} = x^f_{\alpha,p}$, as required.

□

Remark H.3 *1. It is straightforward to extend Theorem H.4(b) to a family of vaccination processes with a continuous index set, for example $\{\alpha_s : s \in \mathcal{I}\}$, where $\mathcal{I}$ is a connected subset of $\mathbb{R}^d$ for some $d \in \mathbb{N}$. Theorem H.4(b) implies that, under appropriate conditions, $\lim_{s\to s^*} x^f_{\alpha_s,p} = x^f_{\alpha_{s^*},p}$. We use this extension when studying optimal vaccination policies in the next subsection.*

2. Invoking Remark 2 after Theorem H.3 shows that if $m \leq 1$ then Theorem H.4(b) holds with $\mathcal{P}_t$ replaced by $\mathcal{P}$.

Optimal vaccination policies based on mean and quantiles

From the above monotonicity and continuity properties of mean and quantiles, we propose next how to choose optimal αs, i.e. optimal vaccination policies in a sense that is made clear below, from a subset $\mathcal{A}^*$ of $\mathcal{A}$. Fix $f \in \mathcal{P}$, $b > 0$ and $0 < p < 1$, and let $\mathcal{A}_b^f = \{\alpha \in \mathcal{A}^* : \ \mu_\alpha^f \leq b\}$ and $\mathcal{A}_{p,b}^f = \{\alpha \in \mathcal{A}^* : \ x_{\alpha,p}^f \leq b\}$. Notice that if, for example, f is the time to extinction, then $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$ comprise those vaccination policies in $\mathcal{A}^*$ for which the mean and the quantile of order p, respectively, of the time to extinction is less than or equal to some bound b. Then it is of interest to search for optimal vaccination policies which satisfy these properties.

Then, if they exist, optimal vaccination policies based on the mean are

$$\operatorname*{argmax}_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f$$

and optimal vaccination policies based on the quantiles are

$$\operatorname*{argmax}_{\alpha \in \mathcal{A}_{p,b}^f} x_{\alpha,p}^f.$$

We notice that the sets $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$ can be empty. If they are not empty, optimal vaccination policies may not be unique when a total order is not defined on the sets $\mathcal{A}_b^f$ and $\mathcal{A}_{p,b}^f$. Otherwise, provided the conditions of Theorems H.1, H.2 and H.4 are satisfied, the monotonicity and continuity properties of mean and quantiles of $f(Z_\alpha)$ proved in those theorems imply that there exist unique $\alpha_{opt,b}^f \in \mathcal{A}_b^f$ and $\alpha_{opt,p,b}^f \in \mathcal{A}_{p,b}^f$ such that

$$\mu_{\alpha_{opt,b}^f}^f = \max_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f \quad \text{and} \quad x_{\alpha_{opt,p,b}^f,p}^f = \max_{\alpha \in \mathcal{A}_{p,b}^f} x_{\alpha,p}^f.$$

Intuitively, $\alpha_{opt,b}^f$ and $\alpha_{opt,p,b}^f$ are the smallest vaccination policies in $\mathcal{A}^*$ such that the mean and the pth quantile, respectively, of $f(Z_{\alpha_{opt,b}^f})$ and $f(Z_{\alpha_{opt,p,b}^f})$ are less than or equal to b. Before giving some simple examples of $\mathcal{A}^*$, we discuss briefly conditions that ensure the existence and uniqueness of optimal policies.

For fixed $f \in \mathcal{P}$, define the binary relation $\prec_f$ on $\mathcal{A}$ by $\alpha \prec_f \alpha'$ if and only if $\mu_\alpha^f \leq \mu_{\alpha'}^f$. Observe that, if $\alpha \prec \alpha'$ then, by Theorem H.1, $\alpha' \prec_f \alpha$ for any $f \in \mathcal{P}$. The relation $\prec_f$ is not an ordering, because $\alpha \prec_f \alpha'$ and $\alpha' \prec_f \alpha$ imply only that $\mu_\alpha^f = \mu_{\alpha'}^f$ (and not that $\alpha = \alpha'$). However, we can consider the equivalence relation $\sim_f$ on $\mathcal{A}$ defined by $\alpha \sim_f \alpha'$ if and only if $\mu_\alpha^f = \mu_{\alpha'}^f$. Then $\prec_f$ is a total ordering on the quotient set $\mathcal{A}/\sim_f$, i.e. the set of all possible equivalence classes, using the obvious definition of $\prec_f$ on $\mathcal{A}/\sim_f$.

Given a subset $\mathcal{A}^*$ of $\mathcal{A}$, a simple condition that ensures the existence of $\operatorname{argmax}_{\alpha \in \mathcal{A}_b^f} \mu_\alpha^f$ for any fixed $b > 0$ is that the set of real numbers $\{\mu_\alpha^f : \alpha \in \mathcal{A}^*\}$ is closed. More precisely, this ensures the existence of an equivalence class on which the maximum is attained. To obtain a unique maximum requires that $\prec_f$ is a total ordering on $\mathcal{A}^*$ (or at least on $\mathcal{A}_b^f$ for fixed b). Note that even if $\prec$ is a total ordering on $\mathcal{A}^*$, Theorem H.1 does not ensure that $\prec_f$ is a total ordering on $\mathcal{A}^*$. For the latter we require that $\mu_\alpha^f > \mu_{\alpha'}^f$ for all $\alpha, \alpha' \in \mathcal{A}^*$ satisfying $\alpha \prec \alpha'$ and $\alpha \neq \alpha'$. The coupling argument in Section 10.2 can be used to show that this holds for any practically useful f and it is assumed implicitly in the sequel. Similar arguments to the above pertain for optimal vaccination policies based on quantiles.

A simple example of $\mathcal{A}^*$ is the set of constant functions, i.e., $\mathcal{A}^* = \{\alpha_c^0 : \ 0 \leq c \leq 1\}$. On this set, the total order is defined by the order of the real numbers. Another example is the set $\mathcal{A}^* = \{\alpha_{M,t_v,p_0} : \ M \geq 0, 0 \leq p_0 \leq 1, 0 \leq t_v \leq p_0^{-1}\}$, where, for $s \geq 0$,

$$\alpha_{M,t_v,p_0}(s) = \begin{cases} 0, & \text{if } s \leq M \\ p_0(s - M), & \text{if } M < s \leq M + t_v \\ t_v p_0, & \text{if } M + t_v < s. \end{cases} \tag{H.9}$$

For fixed M, t_v and p_0, the function α_{M,t_v,p_0} describes the proportion of immune individuals in the population when the vaccination process starts at time M, takes t_v time units and the proportion of individuals vaccinated per unit time is p_0. We notice that a total order on $\mathcal{A}^*$ is not possible. However, in practice, M and p_0 are usually known before vaccination begins, and therefore, the functions can be parameterized through t_v alone. For fixed M and p_0, denote $\alpha_{t_v} = \alpha_{M,t_v,p_0}$ and $\mathcal{A}^* =$

$\{\alpha_{t_v} : c_{\inf} p_0^{-1} \leq t_v \leq p_0^{-1}\}$. Then $\prec_f$ is a total ordering on $\mathcal{A}^*$ and Theorem H.2(b) ensures that $\{\mu_\alpha^f : \alpha \in \mathcal{A}^*\}$ is closed, so, provided $\mathcal{A}_b^f$ is non–empty, the optimal vaccination policy exists and is unique. Moreover, it and the corresponding optimal policies based on the mean and quantiles are given by $\alpha_{t^f_{\mathrm{opt},\mu}}$ and $\alpha_{t^f_{\mathrm{opt},p}}$, with

$$t^f_{\mathrm{opt},\mu} = \inf\{t_v : \mu^f_{\alpha_{t_v}} \leq b\} \quad \text{and} \quad t^f_{\mathrm{opt},p} = \inf\{t_v : x^f_{\alpha_{t_v},p} \leq b\},$$

respectively.

Finally, we notice that, usually, μ_α^f and $x^f_{\alpha,p}$ cannot be derived in a closed form. Therefore, in order to obtain optimal vaccination policies, we need to approximate them. The coupling construction can be used to give a Monte–Carlo based estimation. Suppose, for simplicity of argument, that $m \leq 1$. Fix $n \geq 1$, for $i = 1, \ldots, n$, one can simulate a realization $Z^{(i)}$ of Z and $U_j^{(i)}$ of U_j, for $j = 1, 2, \ldots, N^{(i)}(\infty)$, where $N^{(i)}(\infty)$ is the total number of births in $Z^{(i)}$. For each $\alpha \in \mathcal{A}^*$, we obtain a realization $f(Z_\alpha^{(i)})$ of $f(Z_\alpha)$, for $i = 1, \ldots, n$. From these realizations we estimate μ_α^f and $x^f_{\alpha,p}$.

Time to extinction

We specialise the preceeding results to the case when evaluation of a vaccination strategy α is based on the associated distribution of the time to extinction of the virus in an outbreak. To this end, for $z \in \mathbb{N}$, we denote by $T_{\alpha,z}$ the time to extinction of the process Z_α when $Z(0) = z$, i.e.

$$T_{\alpha,z} = \inf\{t \geq 0 : Z_\alpha(t) = 0\}.$$

Thus, $T_{\alpha,z}$ is the maximal time that the infection survives in the population in an outbreak when the time-dependent proportion of immune individuals is given by α and the number of infected individuals at the beginning of the outbreak is z. Now individuals infect independently of each other, so we have that

$$T_{\alpha,z} = \max\{T_{\alpha,1}^{(1)}, T_{\alpha,1}^{(2)}, \ldots, T_{\alpha,1}^{(z)}\},$$

where $T_{\alpha,1}^{(i)}$ are independent random variables with the same distribution as $T_{\alpha,1}$. Hence

$$\mathrm{P}(T_{\alpha,z} \leq t) = (v_\alpha(t))^z,$$

where $v_\alpha(t) = \mathrm{P}(T_{\alpha,1} \leq t)$. Therefore, to analyze the behaviour of $T_{\alpha,z}$, for any z, it is sufficient to study $T_{\alpha,1}$ through v_α. From now on, we denote $T_{\alpha,1}$ by T_α.

We first use the results of Sections 10.3 to derive some continuity and monotonicity properties of the distribution function v_α. When every individual is immune, i.e. $\alpha(t) = 1$ for all $t > 0$, the infectious disease does not spread to any susceptible individual and then the extinction time is given by the survival time of the initial infected individual. It stands to reason that if there are non-immune individuals in the population, then it is probable that the infectious disease takes more time to become extinct. In the following result, which is an immediate application of Theorem H.3(a) with $f = T$, we show this fact investigating the behaviour of v_α depending on the function α.

Corollary H.1 *Suppose that* $\alpha, \alpha' \in \mathcal{A}$ *satisfy* $\alpha \prec \alpha'$. *Then* $v_\alpha(t) \leq v_{\alpha'}(t)$, *for all* $t \geq 0$.

Intuitively, it is clear that the greater the proportion of immune individuals, the more likely it is that the infectious disease disappears quickly. Consequently, for any $\alpha \in \mathcal{A}$, the distribution function v_α is bounded above by $v_{\alpha_1^0}$, the distribution function of the survival time of the initial infected individual, and bounded below by $v_{\alpha_0^0}$, which is not necessarily a proper distribution function. Moreover, we obtain that minor changes in the proportion of the immune individuals generate minor changes in the distribution of outbreak duration. The following result is an immediate application of Theorem H.3(b), (c) with $f = T$.

Corollary H.2 *(a) Fix* $t > 0$. *Then, for each* $\varepsilon > 0$,

$$\sup_{0 \leq u \leq t} |v_\alpha(u) - v_{\alpha'}(u)| \leq \varepsilon,$$

for all $\alpha, \alpha' \in \mathcal{A}$ *satisfying* $\|\alpha - \alpha'\|_t \leq \delta_{\alpha_0^0, t}(\varepsilon)$.

(b) Fix $t_0 \geq 0$. *Then, for each* $\varepsilon > 0$,

$$\sup_{0 \leq t < \infty} |v_\alpha(t) - v_{\alpha'}(t)| \leq \varepsilon,$$

for all $\alpha, \alpha' \in \mathcal{A}(c_{\inf}, t_0)$ *satisfying* $\|\alpha - \alpha'\| \leq \delta_{\alpha_{c_{\inf}}^{t_0}, \infty}(\varepsilon)$.

Finally, we consider the quantiles of T_α. For $\alpha \in \mathcal{A}$ and $0 < p < 1$, let $t_{\alpha,p} = \inf\{t : v_\alpha(t) \geq p\}$ be the quantile of order p of T_α.

Corollary H.3 *(a) If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$, then $t_{\alpha',p} \leq t_{\alpha,p}$ for every $0 < p < 1$.*

(b) Suppose that $\alpha \in \mathcal{A}$ and $0 < p < 1$ are such that $t_{\alpha,p} < \infty$ and v_α is continuous and strictly increasing at $t_{\alpha,p}$. Then $\lim_{n\to\infty} t_{\alpha_n,p} = t_{\alpha,p}$, for any sequence $\{\alpha_n\}$ in $\mathcal{A}$ satisfying $\lim_{n\to\infty} \alpha_n = \alpha$.

Proof.

(a) The result follows directly from Theorem H.4(a), on setting $f = T$.

(b) Let $t = t_{\alpha,p} + 1$ and $f = \min\{T, t\}$, so $f \in \mathcal{P}_t$. The conditions on $t_{\alpha,p}$ and v_α ensure that $t_{\alpha,p} = x^f_{\alpha,p}$ for all $\alpha \in \mathcal{A}$. The result then follows immediately from Theorem H.4(b).

□

Corollary H.3 can be extended to a family of vaccination processes with a continuous index set; cf. Remark 2 following Theorem H.4. In order to apply Corollary H.3, we need to determine conditions which guarantee that v_α is both continuous and strictly increasing.

Theorem H.5 *Suppose that the lifetime random variable I is continuous. Then, for any $\alpha \in \mathcal{A}$, v_α is a continuous distribution function.*

Proof.

Let $B_0 = 0$ and, for $n = 1, 2, \ldots$, let B_n denote the time of the nth birth in Z, with the convention that $B_n = \infty$ if $N(\infty) < n$. For $n = 0, 1, \ldots, N(\infty)$, let I_n and $D_n = B_n + I_n$ denote respectively the lifetime and time of death of the nth individual born in Z. Let $\mathcal{D} = \{D_0, D_1, \ldots, D_{N(\infty)}\}$ denote the random set of all death-times in Z. Observe that, for any $t > 0$ and any $\alpha \in \mathcal{A}$, $T_\alpha = t$ only if $t \in \mathcal{D}$. Thus it is sufficient to show that $\mathrm{P}(t \in \mathcal{D}) = 0$ for any $t > 0$.

Fix $t > 0$ and define $D_n = \infty$ for $n > N(\infty)$. Then, since $\mathrm{P}(N(t) < \infty) = 1$,

$$\mathrm{P}(t \in \mathcal{D}) = \mathrm{P}\left(\bigcup_{n=0}^{\infty} \{D_n = t\}\right) \leq \sum_{n=0}^{\infty} \mathrm{P}(D_n = t). \tag{H.10}$$

Further, for $n = 0, 1, \ldots,$

$$\begin{aligned}
\mathrm{P}(D_n = t) &= \mathrm{P}(N(t) \geq n)\mathrm{P}(D_n = t | N(t) \geq n) \\
&= \mathrm{P}(N(t) \geq n)\mathrm{E}_{B_n | N(t) \geq n}[\mathrm{P}(D_n = t | B_n, N(t) \geq n)] \\
&= \mathrm{P}(N(t) \geq n)\mathrm{E}_{B_n | N(t) \geq n}[\mathrm{P}(I_n = t - B_n | B_n, N(t) \geq n)] \\
&= \mathrm{P}(N(t) \geq n)\mathrm{E}_{B_n | N(t) \geq n}[\mathrm{P}(I_n = t - B_n)] \\
&= 0,
\end{aligned}$$

since I_n is independent of both B_n and $\{N(t) \geq n\}$, and I is continuous. It then follows from (H.10) that $\mathrm{P}(t \in \mathcal{D}) = 0$, which completes the proof. □

We notice that under weak conditions, the function v_α is strictly increasing. Indeed, let R be the number of points of ξ in $[0, I]$, so R is a random variable giving the number of offspring of a typical individual in the CMJ branching process Z. Suppose that $\mathrm{P}(R = 0) > 0$ and that $I|R = 0$ is an absolutely continuous random variable, having density $f_{I|R=0}$ satisfying $f_{I|R=0}(t) > 0$ for all $t \in (0, \infty)$. Then it is easily seen that, for any $\alpha \in \mathcal{A}$, v_α is strictly increasing on $(0, \infty)$, since, for any open interval (a, b) in $(0, \infty)$, the probability that the initial individual has no offspring and dies in (a, b) is strictly positive. It is straightforward to give conditions under which v_α is strictly increasing on $(0, \infty)$ when I has bounded support. For example, suppose that $\mathrm{P}(R = 0)$ and $\mathrm{P}(R = 1)$ are both strictly positive, and $I|R = 0$ and $B|R = 1$ are both absolutely continuous with densities that are strictly positive on $(0, t_I)$, for some $t_I > 0$. Here, B is the age that a typical individual has his/her first child. Then, given any interval $(a, b) \subset (0, \infty)$, there exists $n_0 \in \mathbb{N}$ such that with strictly positive probability (i) each of the first n_0 individuals in Z has precisely one child, (ii) the $(n_0 + 1)$th individual in Z has no children and (iii) $T \in (a, b)$. It then follows that $\mathrm{P}\left(T_\alpha \in (a, b)\right) > 0$, provided $\alpha(t) < 1$ for all $t > 0$. □

As an illustration of how to apply our theoretical results and to show their usefulness, we analyze a mumps data set from Bulgaria. In Bulgaria, an increasing number of new cases of individuals infected with mumps has been observed in recent years. This might be a result of a poor immunization of birth cohorts 1982–1992 (see Kojouharova et al. (2007)). In such a situation, it is necessary to provide supplementary doses of

mumps, measles and rubella (MMR) vaccine targeted at those cohorts in order to shorten the duration of the outbreaks.

Thus the objective in Ball et all. (2014) is to determine, using the observed data, optimal vaccination levels based on the time to extinction that guarantee, with a high probability, that the outbreak durations will be less than some suitable bound. As an example, we determine the percentage of the target cohort that must be vaccinated to guarantee that only primary and first-generation cases will be observed in at least 90% of outbreaks.

In order to apply our results, we model the spread of mumps by a CMJ branching process. This is reasonable since mumps is an infectious disease which follows the SEIR scheme, and in general, the early stages of outbreaks following this scheme can be approximated by a CMJ branching process. Although this is the general situation, a deeper discussion is needed in the case of mumps. This disease concerns predominantly young people in schools and universities, which means small separate populations and population–dependent propagation. Hence the approximation of mumps outbreaks in these populations by CMJ processes is valid only when outbreaks are very short, which is the case for the outbreaks studied.

The data we analyze (reported by the Bulgarian Ministry of Health) are the total number of new cases of infected individuals with mumps observed weekly in each province of Bulgaria from 2005 to 2008, whose birth cohorts were poorly immunized. Notice that we do not observe outbreak durations, so, first, we describe the procedure to derive the outbreak durations from these data. Then, taking into account the main features of mumps transmission, we select an appropriate general branching process to describe the evolution of infected individuals in an outbreak and estimate its main parameters from the data set. Finally, once the model is fitted, we propose optimal vaccination levels based on the quantiles of the outbreak duration. The detailed modelling methodology could be seen in the Ball et all. (2014).

General conclusion

In general, the results presented in this habilitation thesis are focussed to the application of the theory of branching processes, especially of the properties of the time to extinction in the fields of population experiments and epidemiology.

Following the structure of the included publications, one could find the main conclusions and directions for future research at the end of each chapter.

Part I is addressing the problem of inference from expected waiting times and expected progeny on fertility rates, treated in terms of Bienaymé–Galton–Watson, Bellman–Harris and Sevastyánov branching processes.

Part II supports the understanding that the mathematical and computer simulation models are the fundamental experimental tools in epidemiology. The only data usually available are from naturally occurring epidemics or from the natural incidence of endemic diseases. Unfortunately, even these data are not complete since many cases are not reported. Since repeatable experiments and accurate data are usually not available in epidemiology, mathematical and computer simulation models must be used to perform necessary theoretical experiments with different parameter values and different data sets.

Chapter 11

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Резюме

Настоящият хабилитационен труд е подготвен във връзка с участието ми в конкурс за професор по научно направление 4.5. Математика, научна специалност вероятности и статистика (разклоняващи се стохастични процеси), обявен в "Държавен вестник" бр. 13/ 14. 02. 2014 г. Целта на хабилитационния труд е да представи в синтезиран вид част от постиженията ми обединени в две тематични направления: Разклоняващи се процеси (РП) като модели на популационни експерименти и като модели в епидемиологията.

Изложението на хабилитационния труд е структурирано съгласно изискванията на Правилника за условията и реда за придобиване на научни степени и за заемане на академични длъжности във ФМИ на СУ "Св. Кл. Охридски", Глава 6 Допълнителни разпоредби, алинея 5: *"Хабилитационен труд" е научно съчинение, съдържащо съществени и оригинални резултати, обединени от обща тема. Трудът следва да съдържа обзор на предметната област, мотивация за изследването, изложение на резултатите и съответните изводи.*

В изложението, което следва ще направя кратка съпоставка на съдържанието по глави и съответните публикации, свързани с тях.

Част I отразява резултатите, получени в публикации с номера (по списъка на научните трудове, представени за участие в конкурса): [15–16], [11–12].

Новите резултати са съдържание на [11–12] и представляват естествено продължение на [15–16].

Обща характеристика: В тази част на базата на наблюдения върху броя на индивидите в интересуващата ни популация се прави статистически извод за това с какъв вид да продължат следващите експерименти. Тези резултати като цяло могат да се прилагат при редица проблеми, свързани с опазване на околната среда и запазване на биологичното разнообразие в природата. Като примери могат да бъдат посочени опити за зарибяване на езера, при които се оценява времето за осъществяване на такъв експеримент, както и причините за успешен или неуспешен експеримент и доколко последните са свързани със средата и/или само с репродуктивните качества на

конкретния вид. За да се види колко подвеждащ всъщност е този проблем, е посочен клас разпределения на потомството от един индивид, при който надкритичния и докритичния случаи на процесите не се различават от статистическа гледна точка, при условие, че се използват данните за общия брой частици (което най-често се случва в практиката) и е наблюдавано израждане на популацията. В [15–16] на посочените проблеми е даден отговор в случаите, когато за модел на популацията се предполагат процесите на Биенеме–Галтън–Уотсън (в дискретно време) [12] и Белман–Харис (с непрекъснато време) [13] с имиграция в нулата. В непрекъснатия случай при гама разпределено време на живот на индивидите числено са пресметнати точните разпределения при Поасоново и биномно разпределение на потомството. Уместно е да отбележим, че резултатите са качествено различни от подобни в това направление, т.к. процесите се изследват при условие за израждане.

В Глава 1 математическият модел, който се разглежда е класическият разклоняващ се процес на Биенеме–Галтон–Уотсън, модифициран с имиграция в състоянието нула. Изследвани са свойствата на времето за чакане, докато всички започнали израждащи се жизнени цикли на такъв процес не се появяват повече (т.е. това е общото време на чакане, докато популацията се стабилизира и след този интервал от време нататък нараства неограничено). След това е получен очаквания общ брой потомци за един цикъл и е показан метод (основан на апарата на пораждащите функции) за намиране на моментите от по–висок ред. С оглед на приложенията, основната цел е да се покаже, че статистическите изводи от наблюдаваните дължини на жизнените цикли или оценките за общия брой потомци в тях, относно степените на раждаемост на процеса, трябва да бъдат третирани с повишено внимание. Като пример се дискутират популационни експерименти с пъстърва.

В Глава 2 са изследвани свойствата на времето за чакане до оцеляването (завинаги/изобщо) на надкритичен, зависещ от възрастта на индивидите разклоняващ се процес, модифициран с имиграционна компонента. При условие за задължително (в смисъл, че то е факт - наблюдавано е) израждане на процеса, анализираме условното разпределение на дължината на един цикъл на живот и математическо-

то му очакване. След това са получени оценки на очаквания условен общ брой на потомците за един цикъл, както и неговите моменти от по-висок ред. Като цяло, моделът произхожда от проблема за оценка на времето на чакане до "успешен експеримент" при пречистване на промишлени отпадъчни води чрез бактериални културни системи. Представени са илюстративни примери чрез симулации на два репродуктивни закона с различно математическо очакване на репродуктивността.

Основната идея в Глава 3 е използване на разклоняващите се стохастични модели с имиграция за моделиране на популационни и повторни популационни експерименти и експерименти за пречистване на отпадъчни води произхожда от проблема за оценяване "времето на чакане" до успешен експеримент в серия от популационни и повторни популационни експерименти с различни биологически видове, които са изчезнали по някаква причина. Да напомним, че под "време на чакане до успешен експеримент" разбираме времето, преди началото на онази "нововъведена" популация, която оцелява в средата. Предишните изследвания, използуващи разклоняващи се процеси на Биенеме–Галтон–Уотсън и Белман–Харис, са обобщени в тази глава за зависещите от възрастта (age–dependent) процеси на Севастьянов. За да се оцени функцията на вероятностната плътност на един жизнен цикъл на последния тип процеси и времето на чакане до успешен експеримент, е разработен софтуер, който позволява въвеждане на вероятностната плътност на смъртност (респ. време на живот) на индивидите и специална форма на вероятностното разпределение на възпроизводството на всеки индивид.

Глава 4 има за цел да осигури и да сравни числен и симулационен методи за оценка на разпределението на някои величини, свързани с даден разклоняващ се модел, зависещ от възрастта на частиците, който допуска имиграция в състоянието нула. По–конкретно, анализираме поведението на следните величини: времето до израждане и времето на чакане до началото на онази популация, която ще оцелее. Тези величини са силно свързани с популационните и повторните популационни експерименти в биологията и пречистване на отпадъчни води. Навсякъде в статията илюстрираме предложените методи с подходящи примери.

Част II отразява резултатите, получени в публикации с номера (по списъка на научните трудове, представени за участие в конкурса): [1], [4–5], [7-10].

Обща характеристика: Всички резултати в тази част са нови и са посветени на приложение на разклоняващите се процеси при моделиране на процеси, възникващи при разпространението на заразни заболявания с инкубационен период – една естествена област за тяхното приложение, както и източник на своеобразни и нови проблеми за теорията. Основната идея, която може да се проследи е използването на разклоняващи се процеси *с непрекъснато време* за моделиране на реалните явления, които се следят от службите по надзор на инфекциозните заболявания. Това е отличителна черта на този подход от съществуващите досега, като трябва да отбележим, че като най–адекватен е общият модел РП, а именно т. нар. модел на Кръмп–Мод–Ягерс, за който е доказано, че може да служи като апроксимация (сходимостта е п.с.) на един епидемичен процес в цялото му многообразие. Този фундаментален резултат обаче е трудно приложим за реални явления поради трудностите при идентифицирането на модела. Последните изследвания в тази посока са съдържание на публикацията [1] и ще се спрем на тях в прегледа на съответната глава. От друга страна, методологията развита в тази част позволява да се включи още една съществена характеристика за ефективността на предприетите мерки, а именно времето, за което е желателно да затихне разпространението на наблюдавания епидемичен/инфекциозен взрив, в зависимост от ваксинационното покритие на населението. Последователно, в Глава 6, така изложените проблеми са решени в термините на РП на Белман–Харис (т.е. когато времето на живот на индивидите в популацията е непрекъснато, но все още имаме независимост на възпроизводството от продължителността на живот). Доказани са монотонност и непрекъснатост на разпределението на времето на живот на един такъв процес, свойства на базата на които след това се развиват ваксинационни стратигии и на базата на симулационни данни е илююстриран един възможен сценарий. След, което в Глава 7 е направено обобщение за РП на Севастьянов (т.е. когато възпроизводството на индивидите зависи от продължителността на живот) и експеримент с реални данни – за разпространението на птичи грип във Виетнам, 2006 г. В параграф

7.9 е направено сравнение на двете ваксинационни стратегии – базирани на математическото очакване и квантилите на разпределението на времето до елиминиране на епидемията и са посочени предимствата и недостатъците в единия и другия случай. В Глави 8 и 9 се изследва и моделира процеса на разпространение на епидемичен паротит в България чрез средствата на разклоняващите се процеси с цел, от една страна да се проследи и обясни наблюдаваното развитие на това заразно заболяване в страната, а от друга за да се направи прогноза за бъдещото му разпространение. По–кокретно, Глава 9 е посветена на изследване на основното репродуктивно число R_0 - фундаментална характеристика в епидемиологията, свързана с това колко бързо ще се разпространява едно заболяване в дадена популация. R_0 се дефинира като средния брой на новозаразените от един заразен индивид. Предложено е Бейсово оценяване на параметъра R_0, мотивирано от информацията, съдържаща се в събираните данни. На практика тези данни не предоставят информация за броя заразени от един заразен индивид, а за общия брой на новозаразените на седмична база. Тази публикация илюстрира едно естествено приложение на разклоняващите се процеси, поради точното идентифициране на разклоняващата се структура при разпространението на епидемии и директната интерпретация на R_0 като средния брой наследници на един индивид в контекста на теорията на разклоняващите се процеси.

Целта на Глава 8 е да представи приложимостта на Бейсовата методология за мониторинг и предвиждане на евентуални взривове по данни от надзора, събирани за ваксино–предотвратими болести, като заушка, морбили и вероятно и други. Тестваме възможностите на R–пакета “surveillance”, специално написан за мониторинг на данни от надзора за разпространение на епидемичния паротит, с данните за България, любезно предоставени от Националния Център по Заразни и Паразитни Болести в България.

В Глава 9 е разгледан еднотипов разклоняващ се процес на Биенеме–Галтон–Уотсън, с разпределение на потомството от класа на обощените разпределения от типа на степенен ред като модел на на разпространението на инфекциозно заболяване в популацията. Основната цел е да намерим основното репродуктивно число R_0, което представ-

лява средния брой наследници на един индивид, прилагайки Бейсов подход. Единствените данни, които са на разположение са първоначалния и общия брой на заразените лица. Използваме Метрополис–Хейстингс алгоритъм за симулиране на постериорното разпределение. Полезността на описания метод се показва за някои реални данни за броя на отчетените случаи на заушка (паротит) в България през периода 2005–2008.

Глава 10 съдържа последните резултати, свързани с продължение на изследванията, мотивирани от необходимостта от по–точни и по–адекватни модели за целите на епидемиологичното моделиране. Тя е частично свързана със статията [1] и включва теоретичните резултати, които представляват обобщение на предходните в цикъла статии [7–10], както в теоретично, така и в приложно отношение. На първо място РП на Кръмп–Мод–Ягерс са подходящи модели за ранните етапи на много широк клас епидемични процеси, известни като SIR (Susceptible – Infected – Removed), SIS (Susceptible – Infected – Susceptible) и SEIR (Susceptible – Infected – Removed – Susceptible) и включват като частни случаи РП на Биенеме–Галтон–Уотсън и Белман–Харис. На второ място за разлика от моделите обект на изследване в [7–10], ваксинационното покритие се мени във времето, което безспорно е по–реалистично, отколкото в предходните случаи, когато се предполага, че е константа. Допускането, че частта на ваксинираните може да бъде произволна, но известна като функция, меняща се по времето, позволява да обхванем случаите, когато хората се ваксинират, по време на разпространение на болестта. Освен това тази функция може да бъде свързана не само с ваксинация, а изобщо с произволен контрол върху разпространението на болестта, който води до намаляване или на броя на податливите, или на вероятността, че всеки контактен става инфектиран. На трето място разглеждаме по–общи функции на контрол на епидемичния процес. Докато в [7–10] се акцентира върху времето за затихване на епидемичния взрив, като критерий за контрол на епидемичното разпространение, последните резултати се отнасят за по–широк клас от функции като например, общия брой на заразените индивиди, максималния брой на заразените и продължителността на епидемичния взрив. По отношение на методите, чрез които са получени резултатите – те са качествено различни от тези в [7–10] и основно са свързани с т. нар.

coupling метод (метод на сдвояване) и особено с pruning метода (метод на орязването) за конструиране на реализациите на процеса след ваксинацията по тези преди нея. Последния метод е особено важен, т.к. той води до разработване на Монте–Карло алгоритми за определяне на оптималното ваксинационно покритие. И накрая бих искала да отбележа, че разработения метод може да бъде разширен така, че да включва алтернативни формулировки на ваксинационния процес. Например, можем да дефинираме ценова функция, свързана с всеки ваксинационен процес и да търсим ваксинационен процес при който се минимизира тази функция.

Като доказателство за влиянието на представените резултати върху развитието на изследванията в съответните области може да се види справката за забелязани цитирания на представените по–горе публикации.