SOFIA UNIVERSITY "ST. KLIMENT OHRIDSKI"

FACULTY OF MATHEMATICS AND INFORMATICS
DEPARTMENT OF PROBABILITY, OPERATION RESEARCH AND STATISTICS

DISSERTATION FOR DOCTOR OF SCIENCES DEGREE IN MATHEMATICS

BRANCHING PROCESSES MODELLING WITH APPLICATION IN EPIDEMIOLOGY AND CANCER RESEARCH

Maroussia Nikiforova Bojkova, Ph.D.

SOFIA, BULGARIA
2017

Contents

Preface

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) [15] and Galton and Watson [45]. 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 [60], Sevast'yanov [118] , Athreya and Ney [12], Jagers [67], Asmussen and Hering [10], Guttorp [50], Kimmel and Axelrod [74], Haccou, Jagers and Vatutin [52], Ahsanullah and Yanev [2] or González et al. [46], the book (in Bulgarian) for students with classical (and some modern) models of branching processes published recently by Slavtchova-Bojkova and N. Yanev [131] and the extensive review paper by Mitov and Yanev [94] dedicated to the results of the Bulgarian branching school founded by Professor Nickolay Yanev.

I. J. Bienaymé [15] 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 [79]. 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 [139], [140], [138], Pakes [108], Devroye [33], G. Alsmeyer, C. Gutiérrez, and R. Martínez [8], Farrington and Grant [40] or Epps [36]).

The main purpose of this dissertation thesis is to present several original and innovative results in the field of the branching processes theory and is applications motivated by modeling purposes of epidemiology and cancer disease. The presented results are obtained in the priod 1996–2016 and published in 13 journal articles – cited as [[6], [7], [19], [20], [47], [48], [49], [121], [122], [123], [125], [130], [132]] in the bibliography. Content is organized into three parts. Each part is divided in chapters. Each chapter is entitled as the eponymous article and for the convenience of the reader it begins with the necessary notations and preliminaries even they were already used before.

The Part I is concerned with the theoretical study of a class of non–decomposable branching processes, in discrete and continuous time, with two types of immigration - in the state zero and of a renewal type.

In Chapter 1 the age–dependent branching processes allowing two types of immigration , i.e. one in the state zero and another one according to the i.i.d. times of an independent ergodic renewal process, are studied. The multidimensional case is consid-

ered and asymptotic properties and limit theorems are established both in subcritical and supercritical cases. These results generalise both the results of the discrete theory and those for the one–dimensional continuous–time. model.

The purpose of Chapter 2 is to present a probabilistic proof under week conditions of the convergence in probability of the subcritical age–dependent branching processes allowing two different types of immigration, i.e. one type in the state zero and another one according to the i.i.d. times of an independent ergodic renewal process.

In Chapter 3 we prove a strong law of large numbers and a central limit theorem for the the Bellman–Harris process with immigration at zero and immigration of renewal type (BHPIOR) processes. Similar conclusions are obtained for their discrete–time counterparts (lifetime per individual equals one), called Galton–Watson processes with immigration at zero and immigration of renewal type (GWPIOR). Our approach is based on the theory of regenerative processes, renewal theory and occupation measures and is quite different from those in earlier related work using analytic tools.

Chapter 4 completes the study of the BHPIOR processes, generalizing the convergence in probability for p-type ($p > 1$) ones.

The study of stochastic monotonicity and continuity properties of the extinction time of Bellman–Harris and Sevastyanov's branching processes depending on their reproduction laws is presented in the Part II. 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 5).

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 6).

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 7 the Bayesian estimation approach is considered for the same data set of mumps propagation in Bulgaria. It is 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 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 [112] development Core Team).

The Chapter 8 is concerned with Crump-–Mode-–Jagers branching processes, describing spread of an epidemic depending on the proportion of the population that is vaccinated. 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. The theory is illustrated by applications to the control of the duration of mumps outbreaks in Bulgaria.

In Chapter 9 is considered the use of vaccination schemes to control an epidemic in terms of the total number of individuals infected. In particular, monotonicity and continuity properties of total progeny of Crump—Mode–Jagers branching processes are derived depending on vaccination level. Furthermore, optimal vaccination polices based on the mean and quantiles of the total number of infected individuals are proposed. Finally, how to apply the proposed methodology in real situations is shown through a simulated example motivated by an outbreak of influenza virus in humans, in Indonesia.

Part III contains results related to the cancer modelling by means of branching processes. The corresponding algorithms and numerical and simulation codes are developed to show the significance of the life–length distribution of cells for the risk of escaping the further development of cancer. In Chapter 10 special new class of branching processes with two types and in continuous time are introduced to model the dynamics of the number of different types of cells, which due to a small reproductive ratio are fated to become extinct. However, mutations occurring during the reproduction process may lead to the appearance of a new type of cells that may escape extinction. This is a typical real world situation with the emergence of scatters after local eradication of a certain type of cancer during the chemotherapy. Mathematically, we are deriving the numbers of mutations of the escape type and their moments. A cell of the "mutation" type, which leads possibly to the beginning of a lineage, that will allow indefinite survival is called "successful mutant". Using the results about the probability generating function of the single–type branching processes, an answer about the distribution of the waiting time to produce a "successful mutant" in continuous–time setting is obtained. In general, our results aim to prove the limits of expanding the methods used by Serra and Haccou [117] for different schemes leading to mutation.

A numerical method and related algorithm for solving the integral equations is developed in Chapter 11, in order to estimate the distribution of the waiting time to the escaping extinction mutant cell is born. Numerical studies demonstrate that the proposed approximation algorithm reveals the substantial difference of the results in discrete–time setting. In addition, to study the time needed for the mutant cell population to reach high levels a simulation algorithm for continuous two-type decomposable branching process is proposed. Two different computational approaches together with the theoretical studies might be applied to different kinds of cancer and their proper treatment. I would like to

express my deep gratitude to all my coauthors with whom I worked together over the years and who played a crucial role in my formation as a mathematician – at the first place to my supervisor Prof. Nikolay Yanev (Institute of Mathematics and Informatics at Bulgarian Academy of Sciences), Prof. Miguel Gonzalez and Prof. Rodrigo Martinez (University of Extremadura, Spain), Prof. Gerold Alsmeyer (Muenster University, Germany) Prof. Frank Ball (Nottingham University, United Kingdom).

I am also grateful to my colleagues from the Department of Probability, Operational Research and Statistics at the Faculty of Mathematics and Informatics of Sofia University, where I have been working for 13 years and to my colleagues from the Department of Operations Research, probability and statistics at the Institute of Mathematics and Informatics for their collaboration.

I am also grateful to my family for supporting and believing.

Part I

Non–decomposable BHBP with immigration

Chapter 1

Multi–type BHBP with two types of immigration

1.1 Introduction

The theory of multi-type Bellman-Harris branching processes (BHBP), together with its discrete counterpart, the Bienaymé-Galton-Watson processes, has been treated by many authors. Excellent surveys are contained in Mode [96], Athreya and Ney [12], Sevastyanov [118], etc. For the first time single–type branching processes with state–dependent immigration appeared in Foster's [43] and Pakes' papers [102], [105]. In these works a Bienaymé–Galton–Watson process allowing immigration whenever the number of particles is zero was investigated. Foster [43] studied the asymptotics of the probability of extinction and of the first two moments, and obtained the limit distribution of the processes under proper normalization in the critical case. Later the continuous–time Markov analog of this process was studied by Yamazato [143].

BHBPIO (i.e. BHBP with immigration only in the state zero) were introduced and investigated in the critical case by Mitov and Yanev [92], [93]. Their asymptotic results generalized those obtained by Foster [43] and Yamazato [143]. In the non–critical cases limit results for the above–mentioned processes were obtained by Slavtchova and Yanev [129]. Mitov [89], [88] extended the results for the multidimensional model in the critical case, while the non–critical cases were studied in an author's paper [120].

Weiner [136] placed the last model in a new setting by allowing in addition a renewal immigration component. For BHBPIOR (i.e. BHBPIO which admit in addition a renewal immigration component) he proved that in the critical case the rate of convergence in probability is $Ct^2/\log t$ as $t \to \infty$, where C is a certain constant. In contrast to this, Slavtchova–Bojkova and Yanev [128] obtained that the subcritical processes have a linear growth. In the supercritical case they generalized Athreya's result [11] for the BHBPIOR refining and making more precise the estimates of the growth of the processes on the set of non–extinction. Under the classical $X \log X$ condition a convergence in distribution was proved and the properties of the limit were investigated. It is the purpose of this chapter to carry on this investigation for the multidimensional model.

On the other hand, Kaplan and Pakes [70] studied the supercritical BHBP allowing in addition an immigration at the event times of an ergodic renewal process (BHBPRI).

It turns out that their approach could be applied to the multidimensional BHBPIOR to establish almost sure convergence (Theorem A.3). The reason is that the convergence depends only on the asymptotics of the underlying age-dependent processes, so we can apply similar approach to study the more general model with two types of state-dependent immigration.

However, Kaplan [71] obtained a sufficient condition for the existence of a proper limiting distribution of the subcritical multi–type BHBPRI and generalized many of the results of the discrete theory and those of the one-dimensional continuous time model. In comparison with his result the situation with BHBPIOR is rather different. In contrast to Kaplan's [71] and the author's [120] results, we here establish that the rate of convergence in probability of the subcritical processes is $\mathbf{D}t$, as $t \to \infty$, where $\mathbf{D}$ is a constant vector (Theorem A.1). It would be desirable to have a proof of this result under only a second moment hypothesis.

1.2 Definitions and notation

The prototype of the branching processes to be studied in this chapter is the model of the BHBPIOR defined by Weiner [136].

Let $p > 1$ be an integer constant. About p-dimensional vectors $\mathbf{x} = (x_1, x_2, \ldots, x_p)$, $\mathbf{y} = (y_1, y_2, \ldots, y_p)$, $\mathbf{1} = (1, 1, \ldots, 1)$, $\mathbf{0} = (0, 0, \ldots, 0)$ etc., we denote $\mathbf{xy} = \sum_{i=1}^{p} x_i y_i$, $\mathbf{x}^{\mathbf{y}} = (x_1^{y_1}, x_2^{y_2}, \ldots, x_p^{y_p})$ and $\mathbf{x} \geq \mathbf{y}$ or $\mathbf{x} > \mathbf{y}$ if $x_i \geq y_i$ or $x_i > y_i$ for $1 \leq i \leq p$ respectively.

Let $\{\mathbf{X}(t) = (X^{(1)}(t), \ldots, X^{(p)}(t))\}_{t \geq 0}$ be a p-dimensional population process, wherein the individuals reproduce according to a p-dimensional BHBPIO augmented by an independent immigration component $\{\nu_i\}_{i \geq 1}$ of the same processes at the event times $\{\tau_i\}_{i \geq 1}$ of a given renewal process.

$\mathbf{X}(t)$ counts the number of the particles of the various types alive at time t, $t > 0$, $\mathbf{X}(0) = \mathbf{0}$. The intervals $T_1 = \tau_1, T_2 = \tau_2 - \tau_1, \ldots$ between successive immigrations and the sizes of the immigrants are assumed to be independent identically distributed random variables (i.i.d.r.v.) with a common distribution function (d.f.) $G_0(t)$.

The $\{\nu_i\}_{i \geq 1}$ are i.i.d. with common probability generating function (p.g.f.) $f_0(s)$. The p-dimensional BHBPIO $\{\mathbf{Z}(t) = (Z^{(1)}(t), \ldots, Z^{(p)}(t))\}_{t \geq 0}$ is governed by a vector of the life-time distributions $\mathbf{G}(t) = (G^{(1)}(t), \ldots, G^{(p)}(t))$, a vector of the offspring p.g.f. $\mathbf{h}(\mathbf{s}) = (h^{(1)}(\mathbf{s}), \ldots, h^{(p)}(\mathbf{s}))$, a multidimensional p.g.f. $f(\mathbf{s})$ of the random vectors $\{\mathbf{Y}_i = (Y_i^{(1)}, \ldots, Y_i^{(p)})\}_{i \geq 1}$ of the immigrants in the state zero and the common d.f. $K(t)$ of the duration $\{X_i\}_{i \geq 1}$ of staying in the state zero, where $\mathbf{s} = (s_1, \ldots, s_p)$. It is assumed that $a = \int_0^\infty t dK(t) < \infty$.

Now we recall the definition of the p-dimensional BHBPIO given by Mitov [89]:

$$\mathbf{Z}(t) = \mathbf{Z}_{N(t)+1}(t - S_{N(t)} - X_{N(t)+1}) \mathbb{I}_{\{S_{N(t)} + X_{N(t)+1} < t\}}, \quad \mathbf{Z}(0) = \mathbf{0}, \tag{A.1}$$

where $\mathbf{Z}_i(t) = (Z_i^{(1)}(t), \ldots, Z_i^{(p)}(t))$, $t > 0$, $\mathbf{Z}_i(0) = \mathbf{Y}_i$, $i \geq 1$, is a p-dimensional BHBP starting with random vector of particles, with particle life d.f. $G^{(k)}(t)$, $G^{(k)}(0+) = 0$, and p.g.f. of the offsprings $h^{(k)}(\mathbf{s})$, $k = 1, \ldots, p$. As usual $N(t) = \max\{n \geq 0 : S_n \leq t\}$ is the number of renewal events for the renewal process $\{S_n\}_{n=0}^\infty$ with $S_0 = 0, S_n = \sum_{i=1}^{n} U_i, U_i =$

$X_i + \sigma_i$, where $\sigma_i = \inf\{\ t : \mathbf{Z}_i(t) = \mathbf{0}\}$.

Let us mention that the process defined by (A.1) could be interpreted as follows: starting from the zero state, the process stays at that state random time X_i with d.f. $K(t)$ and after that a random vector $\mathbf{Y}_i$ of immigrants of different types enters the population, according to the p.g.f. $f(\mathbf{s})$. The further evolution of the particles is independent and in accordance with a vector $\mathbf{G}(t)$ of the life-time distributions and a vector $\mathbf{h}(\mathbf{s})$ of the p.g.f. of the offsprings. Then the process hits zero after a random period σ_i, depending of the evolution of the inner BHBP $\mathbf{Z}_i(t)$. The following evolution of the process could be presented as the replication of such i.i.d. cycles.

Slavtchova–Bojkova and Yanev [129] analyzed the above model for the case $p = 1$ and the problem of determining necessary and sufficient conditions for the existence of a limiting distribution in the non–critical cases was investigated.

Using the Definition (A.1) the p- dimensional BHBPIOR $\mathbf{X}(t)$ admits the following representation:

$$\mathbf{X}(t) = \sum_{i=1}^{n(t)} \sum_{j=1}^{\nu_i} \mathbf{Z}_{ij}(t - \tau_i), \tag{A.2}$$

where $\{\mathbf{Z}_{ij}(t)\}_{t\geq 0, i,j\geq 1}$ is the set of i.i.d. stochastic processes defined on a common probability space, each having the same distribution as the multidimensional BHBPIO $\mathbf{Z}(t)$ and

$$n(t) = \max\{n : \tau_n \leq t\}. \tag{A.3}$$

Set:

$$\begin{array}{ll} m_{ij} = \frac{\partial h^{(i)}(\mathbf{1})}{\partial s_j}, & b_{ij}^k = \frac{\partial^2 h^{(k)}(\mathbf{1})}{\partial s_i \partial s_j}, \\ \beta_i = \frac{\partial f(\mathbf{1})}{\partial s_i}, & n_{ij} = \frac{\partial^2 f(\mathbf{1})}{\partial s_i \partial s_j}, \end{array}$$

$c_0' = f_0'(1)$, $c_0'' = f_0''(1)$, $L(t) = \mathbb{P}\{X_i + \sigma_i \leq t\}$, $\nu_0 = \int_0^\infty t dL(t)$, $\mu_0 = \int_0^\infty x dG_0(x)$, $\mu_i = \int_0^\infty x dG^{(i)}(x), i, j, k = 1, \ldots, p$, $\mathbf{M} = \{m_{ij}\}_{1\leq i,j\leq p}$, $H_{ij}(t) \equiv m_{ij} G^{(i)}(t)$, $\mathbf{H}(t) = \{H_{ij}\}_{1\leq i,j\leq p}$.

Let $H_{ij}^{(n)}(t)$ be the n-th fold convolution of $H_{ij}(t)$, where recursively, $H_{ij}^{(1)}(t) = H_{ij}(t)$, $H_{ij}^{(n)}(t) = \int_0^t \sum_{l=1}^p H_{il}^{(n-1)}(t-u) dH_{lj}(u)$, for $n \geq 1$ and $H_{ij}^{(0)}(t) = U(t)$, where $U(t) = 1$, $t \geq 0$, $U(t) = 0$, $t < 0$.

In order to avoid technical difficulties, we make the following assumptions.

Assumption I.

(i) $f_0(0) < 1, 0 < m_{ij} < \infty, 1 \leq i, j \leq p$;

(ii) $G_0(0^+) = 0, G^{(i)}(0^+) = 0, 1 \leq i \leq p$, $\nu_0 < \infty$, $\mu_i < \infty$, $\mu_0 < \infty$, $\beta_i < \infty$;

(iii) $\mathbf{h}(\mathbf{s})$ is not singular;

(iv) $\mathbf{M}$ is strictly positive;

(v) $G_0(t)$, $G^{(i)}(t)$, $1 \leq i \leq p$, $K(t)$ and $L(t)$ are non-lattice distributions.

Assumption II.

The "Malthusian" parameter α_0 exists for the p-dimensional BHBP $\{\hat{\mathbf{Z}}(t)\}$. Let $\hat{\mathbf{M}}(t)$ be the matrix whose (i,j) entry is $m_{ij}\int_0^\infty e^{-\alpha_0 t}dG^{(i)}(t)$. The Malthusian parameter is that number α_0 (unique if it exists) such that the maximal eigenvalue of $\hat{\mathbf{M}}(t)$ is one.

It follows from Assumption I that the matrix $\mathbf{M}$ has a maximal eigenvalue ρ which is positive, simple, and has associated positive left and right eigenvectors $\mathbf{u}$ and $\mathbf{v}$; $\mathbf{u}$ and $\mathbf{v}$ are normalized so that $(\mathbf{u},\mathbf{1}) = (\mathbf{v},\mathbf{u}) = 1$. As it is done in the classical theory, we will call the process $\{\mathbf{X}(t)\}_{t\geq 0}$ supercritical, critical or subcritical depending on whether $\rho > 1, = 1$ or < 1.

1.3 Integral equations

Let us denote $\Phi(t,\mathbf{s}) = \mathbb{E}\mathbf{s}^{\mathbf{Z}(t)}$, $\Phi(0,\mathbf{s}) = 1$, $\Phi_0(t,\mathbf{s}) = \mathbb{E}\mathbf{s}^{\mathbf{X}(t)}$, $\Phi_0(0,\mathbf{s}) = 1$, $\Phi_0(t,\tau,\mathbf{s}_1,\mathbf{s}_2) = \mathbb{E}\{\mathbf{s}_1^{\mathbf{X}(t)}\mathbf{s}_2^{\mathbf{X}(t+\tau)}\}$, $\tau \geq 0$, $\mathbf{F}(t,\mathbf{s}) = \mathbb{E}\mathbf{s}^{\hat{\mathbf{Z}}(t)} = (F_1(t,\mathbf{s}),\ldots,F_p(t,\mathbf{s}))$, $\mathbf{F}(0,\mathbf{s}) = \mathbf{s}$.

It is well-known (see e.g. Sevastyanov [118]), that the functions $F_k(t,\mathbf{s}) = \mathbb{E}\{\mathbf{s}^{\hat{\mathbf{Z}}_k(t)}|\hat{\mathbf{Z}}_k(0) = \mathbf{e}_k\}$, ($\mathbf{e}_k$ is p-dimensional vector which k-th component is one and the others are equal to zero), satisfy the following system of integral equations:

$$\begin{aligned} &F_k(t,\mathbf{s}) = \int_0^t h^{(k)}(\mathbf{F}(t-u,\mathbf{s}))dG^{(k)}(u) + s_k(1-G^{(k)}(t)),\\ &F_k(0,\mathbf{s}) = s_k, k = 1,\ldots,p. \end{aligned} \tag{A.4}$$

It is not difficult to show that the p.g.f. $\Phi_0(t,\mathbf{s})$ admits the representation

$$\Phi_0(t,\mathbf{s}) = \int_0^t \Phi_0(t-u,\mathbf{s})f_0(\Phi(t-u,\mathbf{s}))dG_0(u) + 1 - G_0(t), \tag{A.5}$$

where the p.g.f. $\Phi(t,\mathbf{s})$, satisfies the renewal equation (see Mitov [89])

$$\Phi(t,\mathbf{s}) = \int_0^t \Phi(t-u,\mathbf{s})dL(u) + 1 - K(t) - L(t) + \int_0^t f(\mathbf{F}(t-u,\mathbf{s}))dK(u). \tag{A.6}$$

The proof is quite similar to that for the single–type case and we omit it.

By the law of total probabilities it is not difficult to obtain the equation

$$\begin{aligned} \Phi_0(t,\tau,\mathbf{s}_1,\mathbf{s}_2) &= \int_0^t \Phi_0(t-u,\tau,\mathbf{s}_1,\mathbf{s}_2)f_0(\Phi(t-u,\tau,\mathbf{s}_1,\mathbf{s}_2))dG_0(u)\\ &+ \int_t^{t+\tau} \Phi_0(t+\tau-u,\mathbf{s}_2)f_0(\Phi(t+\tau-u,\mathbf{s}_2))dG_0(u)\\ &+ (1-G_0(t+\tau)), \end{aligned} \tag{A.7}$$

where $\Phi(t,\tau,\mathbf{s}_1,\mathbf{s}_2)=\mathbb{E}[\mathbf{s}_1^{\mathbf{Z}(t)}\mathbf{s}_2^{\mathbf{Z}(t+\tau)}|\mathbf{Z}(0)=\mathbf{0}]$. satisfies the following integral equation:

$$\begin{aligned}\Phi(t,\tau,\mathbf{s}_1,\mathbf{s}_2) &= \int_0^t \Phi(t-u,\tau,\mathbf{s}_1,\mathbf{s}_2)dL(u)+1-K(t+\tau)\\ &+\int_0^t[\mathfrak{F}(t+\tau-u,\mathbf{s}_2)-\mathfrak{F}(t+\tau-u,\mathbf{0})]dK(u)\\ &+\int_0^{t+\tau}\Phi(t+\tau-u,\mathbf{s}_2)dL(u)+\int_0^t\mathfrak{F}(t-u,\tau,\mathbf{s}_1,\mathbf{s}_2)dK(u)\\ &+\int_0^t\mathfrak{F}(t-u,\mathbf{s}_1)(\int_{t-u}^{t+\tau-u}\Phi(t+\tau-u-x,\mathbf{s}_2)dV(x))dK(u),\end{aligned}$$

with initial condition $\Phi(0,\tau,\mathbf{s}_1,\mathbf{s}_2)=\mathbb{E}\mathbf{s}_2^{\mathbf{Z}(\tau)}=\Phi(\tau,\mathbf{s}_2)$, where $\mathfrak{F}(t,\tau,\mathbf{s}_1,\mathbf{s}_2)=\mathbb{E}[\mathbf{s}_1^{\mathbf{Z}(t)}\mathbf{s}_2^{\mathbf{Z}(t+\tau)}|\mathbf{Z}(0)=\mathbf{Y}_i]$, $\mathfrak{F}(0,\tau,\mathbf{s}_1,\mathbf{s}_2)=\mathfrak{F}(\tau,\mathbf{s}_2)$ and $\mathfrak{F}(0,0,\mathbf{s}_1,\mathbf{s}_2)=f(\mathbf{s}_2)$ with $V(t)=\mathbb{P}(\sigma_i\le t)$.

Denote the moments

$$\begin{aligned}M_{01}^{(k)}(t) &= \left.\frac{\partial\Phi_0(t,\mathbf{s})}{\partial s_k}\right|_{\mathbf{s}=\mathbf{1}}=\mathbb{E}X^{(k)}(t),\\ M_{02}^{(k,l)}(t) &= \left.\frac{\partial^2\Phi_0(t,\mathbf{s})}{\partial s_k\partial s_l}\right|_{\mathbf{s}=\mathbf{1}}=\mathbb{E}X^{(k)}(t)X^{(l)}(t),\end{aligned}$$

$$\begin{aligned}M_{1}^{(k)}(t) &= \left.\frac{\partial\Phi(t,\mathbf{s})}{\partial s_k}\right|_{\mathbf{s}=\mathbf{1}}=\mathbb{E}Z^{(k)}(t),\\ M_{2}^{(k,l)}(t) &= \left.\frac{\partial^2\Phi(t,\mathbf{s})}{\partial s_k\partial s_l}\right|_{\mathbf{s}=\mathbf{1}}=\mathbb{E}Z^{(k)}(t)Z^{(l)}(t),\end{aligned}$$

$$\begin{aligned}M_{0n}^{(k)}(t) &= \left.\frac{\partial^n\Phi_0(t,\mathbf{s})}{\partial s_k^n}\right|_{\mathbf{s}=\mathbf{1}}\equiv\mathbb{E}[X^{(k)}(t)]^n,\\ M_{n}^{(k)}(t) &= \left.\frac{\partial^n\Phi(t,\mathbf{s})}{\partial s_k^n}\right|_{\mathbf{s}=\mathbf{1}}\equiv\mathbb{E}[Z^{(k)}(t)]^n,\end{aligned}$$

$$\begin{aligned}A_{kn}^{(l)}(t) &= \left.\frac{\partial^n F_k(t,\mathbf{s})}{\partial s_l^n}\right|_{\mathbf{s}=\mathbf{1}}\equiv\mathbb{E}[\hat{Z}_k^{(l)}(t)]^n,\\ B_{m}^{(k,l)}(t) &= \left.\frac{\partial^2 F_m(t,\mathbf{s})}{\partial s_k\partial s_l}\right|_{\mathbf{s}=\mathbf{1}}\equiv\mathbb{E}[\hat{Z}_m^{(k)}\hat{Z}_m^{(l)}],\end{aligned}$$

where to simplify the notations we introduced $\mathbb{E}[\hat{Z}_k^{(l)}(t)]^n$, $\mathbb{E}[Z^{(k)}(t)]^n$, $\mathbb{E}[X^{(k)}(t)]^n$ as a notation for the corresponding factorial moments of $\hat{Z}_k^{(l)}(t), Z^{(k)}(t), X^{(k)}(t)$, respectively.

Under the Assumption I by differentiating (A.4)–(A.7) and setting $\mathbf{s}=\mathbf{s}_1=\mathbf{s}_2=\mathbf{1}$ one obtains

$$M_{01}^{(k)}(t)=\int_0^t M_{01}^{(k)}(t-u)dG_0(u)+c_0'\int_0^t M_1^{(k)}(t-u)dG_0(u), \tag{A.8}$$

$$M_{02}^{(k,l)}(t) = \int_0^t M_{02}^{(k,l)}(t-u)dG_0(u)+c_0'\int_0^t M_2^{(k,l)}(t-u)dG_0(u)$$

$$
\begin{aligned}
&+ \quad c_0' \int_0^t M_{01}^{(l)}(t-u) M_1^{(k)}(t-u) dG_0(u) \\
&+ \quad c_0'' \int_0^t M_1^{(l)}(t-u) M_1^{(k)}(t-u) dG_0(u) \\
&+ \quad c_0' \int_0^t M_1^{(l)}(t-u) M_{01}^{(k)}(t-u) dG_0(u),
\end{aligned} \tag{A.9}
$$

$$
M_1^{(k)}(t) = \int_0^t M_1^{(k)}(t-u) dL(u) + \int_0^t \sum_{i=1}^{p} \beta_i A_{k1}^{(i)}(t-u) dK(u), \tag{A.10}
$$

$$
\begin{aligned}
M_2^{(k,l)}(t) &= \int_0^t \sum_{i=1}^{p} \sum_{j=1}^{p} n_{ij} A_{l1}^{(j)}(t-u) A_{k1}^{(i)}(t-u) dK(u) \\
&+ \int_0^t \sum_{i=1}^{p} \nu_i B_i^{(kl)}(t-u) dK(u) + \int_0^t M_2^{(k,l)}(t-u) dL(u),
\end{aligned} \tag{A.11}
$$

$$
\begin{aligned}
N_0^{(k,l)}(t,\tau) &= \int_0^t N_0^{(k,l)}(t-u,\tau) dG_0(u) \\
&+ \quad c_0' \int_0^t M_{01}^{(k)}(t-u) M_1^{(l)}(t+\tau-u) dG_0(u) \\
&+ \quad c_0' \int_0^t M_{01}^{(l)}(t+\tau-u) M_1^{(k)}(t-u) dG_0(u) \\
&+ \quad c_0'' \int_0^t M_1^{(k)}(t-u) M_1^{(l)}(t+\tau-u) dG_0(u) \\
&+ \quad c_0' \int_0^t N_2^{(k,l)}(t-u,\tau) dG_0(u),
\end{aligned} \tag{A.12}
$$

where $N_2^{(k,l)}(t,\tau) = \mathbb{E}[Z^{(k)}(t) Z^{(l)}(t+\tau)], \quad \tau > 0.$

1.4 Preliminary results

In addition to its own intrinsic interest, the asymptotics of the moments of the multidimensional BHBPIOR, plays a key role for establishing limit theorems. We concentrate our study on the non-critical cases.

I. Subcritical case.

Before stating the results about the moments of the processes of interest we need the following preliminary lemmas.

Lemma A.1 *Let* $\hat{\mathbf{Z}}_k(t)$ *be the vector of the number of particles alive at time* t, $k = 1, \ldots, p$, *starting with one new particle of type* k *in a subcritical multi-type BHBP satisfying the Assumptions I and II. Then, if* $\int_0^\infty y e^{-n\alpha_0 y} dG^{(i)}(y) < \infty$, $\int_0^\infty y e^{-n\alpha_0 y} dG_0(y) < \infty$ *and all moments of* $h^{(k)}(\mathbf{s})$, $k = 1, \ldots, p$ *exist at* $\mathbf{s} = \mathbf{1}$, *for* $n \geq 1$, *as* $t \to \infty$,

$$A_{kn}^{(l)}(t) \sim \bar{A}_{kn}^{(l)} \exp^{\alpha_0 n t}, \tag{A.13}$$

where $0 < \bar{A}_{kn}^{(l)} < \infty$.

Proof. We will establish the result using induction on n.

For $n = 1$ it is known (see Sevastyanov, Th.VIII.3, p.312) that for the subcritical multi–type BHBP, as $t \to \infty$

$$A_{k1}^{(l)}(t) \sim \bar{A}_{k1}^{(l)} \exp^{\alpha_0 t}, \tag{A.14}$$

where

$$\bar{A}_{k1}^{(l)} = \frac{u_k v_l \int_0^\infty e^{-\alpha_o u}[1 - G^{(l)}(u)]du}{\sum_{k,l=1}^{p} M_{\alpha_0 k}^{l} u_k v_l}, \tag{A.15}$$

u_i and v_j are the i-th and j-th components of the right and left eigenvectors respectively, corresponding to the Perron root ρ of the matrix $E - \hat{M}$ and $M_{\alpha_0 k}^{l} = m_{kl} \int_0^\infty e^{-\alpha_o u} dG^{(k)}(u)$. Denoting

$$Q_i(t, \mathbf{s}) = 1 - F_i(t, \mathbf{s}), \tag{A.16}$$

after expanding the integrand on the right hand side of (A.4) in a Taylor series we obtain componentwise

$$\begin{aligned} Q_i(t, \mathbf{s}) &= (1 - s_i)(1 - G^{(i)}(t)) + \int_0^t \sum_{j=1}^{p} Q_j(t - u, \mathbf{s}) m_{ij} dG^{(i)}(u) \\ &- \sum_{k=2}^{\infty} \frac{1}{k!}(-1)^k \sum_{l_1, \ldots, l_k = 1}^{p} \frac{\partial^k h^{(i)}(\mathbf{1})}{\partial s_{l_1} \ldots \partial s_{l_k}} \int_0^t \prod_{r=1}^{k} Q_{l_r}(t - u, \mathbf{s}) dG^{(i)}(u). \end{aligned} \tag{A.17}$$

Writing (A.17) in vector form, taking Laplace transforms and re-inverting, it follows that

$$\begin{aligned} Q_i(t, \mathbf{s}) &= \int_0^t \sum_{j=1}^{p} (1 - s_j)(1 - G^{(j)}(t - u)) dK_{ij}(u) \\ &- \sum_{k=2}^{\infty} \frac{1}{k!}(-1)^k \int_0^t \sum_{l_1, \ldots, l_k = 1}^{p} \prod_{r=1}^{k} Q_{l_r}(t - u, \mathbf{s}) \sum_{j=1}^{p} \frac{\partial^k h^{(j)}(\mathbf{1})}{\partial s_{l_1} \ldots \partial s_{l_k}} dR_{ij}(u), \end{aligned} \tag{A.18}$$

where $K_{ij}(t) = \sum_{n=0}^{\infty} H_{ij}^{(n)}(t)$, $R_{ij}(t) = \sum_{n=0}^{\infty} G^{(j)} * H_{ij}^{(n)}(t)$, and $F * G$ denotes convolution.

To compute $A_{k2}^{(l)}(t) \equiv \mathbb{E}[\hat{Z}_k^{(l)}(t)(\hat{Z}_k^{(l)}(t) - 1)] = \frac{\partial^2 Q_k(t,\mathbf{1})}{\partial s_l^2}$ for large t, using the fact that $Q_i(t, \mathbf{1}) \equiv 0$ for all $1 \le i \le p$, after differentiating (A.18) at $\mathbf{s} = \mathbf{1}$ we have

$$A_{k2}^{(l)}(t) = \frac{2}{2!} \sum_{l_1,l_2=1}^{p} \int_0^t A_{l_1 1}^{(l)}(t-u) A_{l_2 1}^{(l)}(t-u) \sum_{j=1}^{p} \frac{\partial^2 h^{(j)}(\mathbf{1})}{\partial s_{l_1} \partial s_{l_2}} dR_{kj}(u). \tag{A.19}$$

Using (A.14) and (A.15) it is clear that $A_{k2}^{(l)}(t) \sim \bar{A}_{k2}^{(l)} e^{2\alpha_0 t}$, $t \to \infty$, where $0 < \bar{A}_{k2}^{(l)} < \infty$. Assume the result of the theorem for $n-1$. Then, considering orders of magnitude of t, $(t \to \infty)$, it follows by the induction hypothesis that the asymptotic behaviour of $\mathbb{E}[Z_k^{(l)}(t)]^n$ is determined solely from the n-th derivatives with respect to s_l of the term

$$\frac{(-1)^2}{2!} \sum_{j=1}^{p} \sum_{l_1,l_2=1}^{p} \frac{\partial^2 h^{(j)}(\mathbf{1})}{\partial s_{l_1} \partial s_{l_2}} \int_0^t Q_{l_1}(t-u, \mathbf{s}) Q_{l_2}(t-u, \mathbf{s}) dR_{kj}(u)$$

in (A.18), evaluated at $\mathbf{s}= \mathbf{1}$.

By Leibnitz's rule for successive differentiation, since $Q_l(t, \mathbf{1}) \equiv 0$, $1 \le l \le p$,

$$\frac{\partial^n Q_r(t,\mathbf{1}) Q_m(t,\mathbf{1})}{\partial s_l^n} = \sum_{k=1}^{n} \binom{n}{k} \frac{\partial^k Q_r(t,\mathbf{1})}{\partial s_l^k} \frac{\partial^{n-k} Q_m(t,\mathbf{1})}{\partial s_l^{n-k}}. \tag{A.20}$$

Then using the induction hypothesis one obtains $A_{kn}^{(l)}(t) \sim \bar{A}_{kn}^{(l)} e^{n\alpha_o t}$ as $t \to \infty$, where $0 < \bar{A}_{kn}^{(l)} < \infty$, proving Lemma A.1. ♢

Lemma A.2 *Let $\mathbf{Z}(t)$ be the vector of the number of particles alive at time t in a sub-critical case BHBPIO. Then, under the assumptions of Lemma A.1 and if all moments of $f(\mathbf{s})$ exist at $\mathbf{s} = \mathbf{1}$, for $n \ge 1$*

$$M_n^{(k)}(t) \sim R_{kn} < \infty, as \quad t \to \infty.$$

Proof. Denoting $W(t, \mathbf{s}) = 1 - \Phi(t, \mathbf{s})$, then by (A.16) and (A.6), it follows that

$$W(t, \mathbf{s}) = \int_0^t W(t-u, \mathbf{s}) dL(u) + \int_0^t f(1 - \mathbf{Q}(t-u, \mathbf{s})) dK(u). \tag{A.21}$$

As $M_1^{(l)}(t) = -\frac{\partial W(t,\mathbf{1})}{\partial s_l} \equiv \mathbb{E}[Z^{(l)}(t)]$ after differentiating (A.21) and setting $\mathbf{s} = \mathbf{1}$ we have

$$M_1^{(l)}(t) = \int_0^t M_1^{(l)}(t-u) dL(u) + \int_0^t \sum_{i=1}^{p} \frac{\partial f(\mathbf{1})}{\partial s_i} \frac{\partial Q_i(t-u, \mathbf{s})}{\partial s_l} dK(u)$$

and via direct renewal methods, using Lemma A.1 it is not difficult to obtain, that

$$M_1^{(l)}(t) \sim \frac{\int_0^{\infty} \sum_{i=1}^{p} \beta_i A_l^{(i)}(u) du}{\nu_0} \equiv R_{l1}, l = 1, \ldots, p.$$

After second differentiation of (A.21) at $\mathbf{s} = \mathbf{1}$ we obtain the equation

$$\begin{aligned} M_2^{(l)}(t) &= \int_0^t M_2^{(l)}(t-u)dL(u) \\ &+ \int_0^t \sum_{i,j=1}^{p} \frac{\partial^2 f(\mathbf{1})}{\partial s_i \partial s_j} \frac{\partial Q_i(t-u,\mathbf{1})}{\partial s_l} \frac{\partial Q_j(t-u,\mathbf{1})}{\partial s_l} dK(u) \\ &+ \int_0^t \sum_{i=1}^{p} \frac{\partial f(\mathbf{1})}{\partial s_i} \frac{\partial^2 Q_i(t-u,\mathbf{1})}{\partial s_l^2} dK(u). \end{aligned}$$

Hence applying Lemma A.1 by similar renewal techniques (see Slavtchova [120]) it follows that

$$M_2^{(l)}(t) \sim R_{l2} < \infty, \quad t \to \infty.$$

The rest of the proof is straightforward using the fact that the higher moments of $\mathbf{Z}(t)$ satisfy renewal type equations to which we can apply renewal methods and Lemma A.1.

We can now present the asymptotics of the multi–type BHBPIOR. ♢

Theorem A.1 *Under the assumptions of Lemmas A.1 and A.2 if in addition all moments of $f_0(s)$ exist at $s = 1$, then*

$$M_{0n}^{(k)}(t) \equiv \mathbb{E}[X^{(k)}(t)]^n = \frac{\partial^n \Phi_0(t,\mathbf{1})}{\partial s_k^n} \sim \{D_k t\}^n, \tag{A.22}$$

$$M_{0n}^{(kl)}(t) \equiv \mathbb{E}[X^{(k)}(t)]^{n_1}[X^{(l)}(t)]^{n_2} = \frac{\partial^n \Phi_0(t,\mathbf{1})}{\partial s_k^{n_1} \partial s_l^{n_2}} \sim {D_k}^{n_1} {D_l}^{n_2} t^n, \tag{A.23}$$

as $t \to \infty$, $n, n_1, n_2 \geq 1$, such that $n_1 + n_2 = n$, where $0 < D_k < \infty$, $k, l = 1, \ldots, p$ are explicitly computed.

Proof. Expanding the integrand on the right hand side of (A.5) in a Taylor series around $\mathbf{1}$ we have

$$\begin{aligned} \Phi_0(t,\mathbf{s}) &= 1 - G_0(t) + \int_0^t \Phi_0(t-u,\mathbf{s}) dG_0(u) \\ &- \int_0^t [1 - \Phi(t-u,\mathbf{s})]\Phi_0(t-u,\mathbf{s}) dG_0(u) \\ &+ \sum_{l=2}^{\infty} \int_0^t \frac{(-1)^l f_0^{(l)}(1)}{l!} (1 - \Phi(t-u,\mathbf{s}))^l \Phi_0(t-u,\mathbf{s}) dG_0(u). \end{aligned}$$

Taking Laplace transforms and re–inverting, it follows that

$$\Phi_0(t,\mathbf{s}) = 1 + c_0' \int_0^t [\Phi(t-u,\mathbf{s}) - 1]\Phi_0(t-u,\mathbf{s}) dH_0(u)$$

$$+ \sum_{l=2}^{\infty} \int_0^t \frac{(-1)^l f_0^{(l)}(1)}{l!} (1 - \Phi(t-u, \mathbf{s}))^l \Phi_0(t-u, \mathbf{s}) dH_0(u), \tag{A.24}$$

where $H_0(t) = \sum_{l=0}^{\infty} G_0^{*l}(t)$.

As $M_1^{(l)}(t) \equiv \mathbb{E}[Z^{(l)}(t)]$, differentiating (A.24) by s_l and setting $\mathbf{s} = \mathbf{1}$ yields

$$M_{01}^{(l)}(t) = c_0' \int_0^t M_1^{(l)}(t-u) dH_0(u). \tag{A.25}$$

Therefore from (A.26) and Lemma A.1 it follows that as $t \to \infty$

$$M_{01}^{(l)}(t) \sim c_0' \int_0^{\infty} \frac{R_{l1}}{\mu_0} du = D_l t, \tag{A.26}$$

where $D_l \equiv c_0' R_{l1}/\mu_0$, $l = 1, \ldots, p$. After second differentiating of (A.24) by s_l and setting $\mathbf{s} = \mathbf{1}$ it is not difficult to obtain

$$\begin{aligned} M_{02}^{(l)}(t) &= c_0' \int_0^t M_2^{(l)}(t-u) dH_0(u) \\ &+ 2c_0' \int_0^t M_1^{(l)}(t-u) M_{01}^{(l)}(t-u) dH_0(u) \\ &- c_0'' \int_0^t [M_1^{(l)}(t-u)]^2 dH_0(u), \end{aligned} \tag{A.27}$$

$l = 1, \ldots, p$. Then by Lemmas A.1 and A.2, applying similar renewal techniques to the equation (A.27) as in Theorem 3.1 (see Slavtchova [120]), it follows that the asymptotics of the second moment $M_{02}^{(l)}(t)$ is determined by the second term on the right side, i.e.

$$M_{02}^{(l)}(t) \sim 2c_0' \int_0^{\infty} R_{l1} D_l u du = D_l^2 t^2, \quad t \to \infty.$$

Considering orders of magnitude of t, $(t \to \infty)$, it follows by induction, using Lemmas A.1 and A.2, that for $n \geq 2$,

$$M_{0n}^{(l)}(t) \sim n c_0' \int_0^t M_1^{(l)}(t-u) M_{0n-1}^{(l)}(t-u) dH_0(u).$$

Again using induction , assume (A.22) for $n-1$. Then by the methods of Yanev and Mitov [92](Theorem 2, p. 761) one obtains, componentwise, for $n \geq 2$,

$$M_{0n}^{(l)}(t) \sim n c_0' \int_0^{\infty} \frac{R_l D_l^{n-1}}{\mu_0} du = [D_l t]^n,$$

completing the induction and establishing (A.22). The assertion (A.23) follows by the similar arguments and we omit it. ♢

II. Supercritical case.

Theorem A.2 *Under the Assumption I, if* $\rho > 1$, *then* $\lim_{t\to\infty} M_{01}^{(k)}(t)\exp\{-\alpha_0 t\} = M_{01}^{(k)}$, *where* $\alpha_0 > 0$ *is the Malthusian parameter,*

$$M_{01}^{(k)} = \frac{c_0' M_1^{(k)} \Delta(\alpha_0)}{1-\Delta(\alpha_0)}, \quad \Delta(\lambda) = \mathbb{E}e^{-\lambda T_1}, \tag{A.28}$$

$$M_1^{(k)} = \frac{\int_0^\infty e^{-\alpha_0 u} dK(u)[\sum_{l=1}^{p} \beta_l \bar{A}_{k1}^{(l)}]}{1-\int_0^\infty e^{-\alpha_0 u} dL(u)}, \tag{A.29}$$

and $\bar{A}_{k1}^{(l)}$ *are defined by* (A.15), l, $k = 1, \ldots, p$.

Theorem A.3 *Assume the conditions of Theorem A.2. Then, if* $b_{ij}^k < \infty$ *and* $n_{ij}^k < \infty$, $i, j, k = 1, \ldots, p$, *it follows that* $\lim_{t\to\infty} M_{02}^{(k)}(t)e^{-2\alpha_0 t} = M_{02}^{(k)}$, *where*

$$M_{02}^{(k)} = \frac{(c_0' M_2^{(k)} + c_0''[M_1^{(k)}]^2 + 2c_0' M_{01}^{(k)} M_1^{(k)}) \int_0^\infty e^{-2\alpha_0 u} dG_0(u)}{1-\int_0^\infty e^{-2\alpha_0 u} dG_0(u)}, \tag{A.30}$$

$M_2^{(k)} = \lim_{t\to\infty} M_2^{(k)}(t)e^{-2\alpha_0 t}$. $M_{01}^{(k)}$, $M_1^{(k)}$ *are defined by* (A.28) *and* (A.29) *respectively.*

Theorem A.4 *Let the conditions of Theorem A.3 hold. Then componentwise* $N_0^{(k)}(t,\tau) = e^{\alpha_0(2t+\tau)} M_{02}^{(k)}(1+o(1))$, *uniformly for* $\tau \geq 0$, *where* $M_{02}^{(k)}$ *is defined by* (A.30).

The proofs of Theorems A.2, A.3 and A.4 follow by the quite similar renewal approach applied to the functional equations (A.8), (A.9) and (A.12).

1.5 Limit theorems

Theorem A.5 *Under the assumptions of Theorem A.1, as* $t \to \infty$, *it is hold componentwise*

$$X^{(k)}(t)/t \xrightarrow{\mathbb{P}} D_k, k = 1, \ldots, p.$$

Proof. From A.22 and A.23 we get $\mathbb{E}\{X^{(k)}(t)/t\}^n \sim D_k$, $n \geq 1$. The method of the moments yields that $\mathbf{X}(t)/t$ converges in probability to a constant random vector, whose distribution is determined by the asymptotic moments of the process. ♢

It is interesting to mention, that while for the multi-type subcritical both BHBPIO (see Slavtchova [120]) and BHBPRI (see Kaplan [71]) there exist a stationary limit distribution, here we obtain convergence in probability to a constant random vector.

Theorem A.6 *Assume the conditions of Theorem A.4.*

(i) Then the vector process $\mathbf{W}(t) = \mathbf{X}(t)/e^{\alpha_0 t}$ *converges in mean square to a positive vector random variable* $\mathbf{W} = (W_1, \ldots, W_p)$, *whose Laplace transform (L.T.)* $\varphi(\mathbf{y}) = \mathbb{E}e^{-\mathbf{y}\mathbf{W}}$, $\mathbf{y} \geq \mathbf{0}$ *satisfies the equation:*

$$\varphi(\mathbf{y}) = \int_0^\infty \varphi(\mathbf{y}e^{-\alpha_0 u}) f_0(\psi(\mathbf{y}e^{-\alpha_0 u})) dG_0(u), \tag{A.31}$$

and $\psi(\mathbf{y})$ *is the unique solution of the equation*

$$\psi(\mathbf{y}) = \int_0^\infty \psi(\mathbf{y}e^{-\alpha_0 u})dL(u) + \int_0^\infty f(\theta(\mathbf{y}e^{-\alpha_0 u}))dK(u) - f(\mathbf{q}), \tag{A.32}$$

where $\mathbf{q} = (q_1, \ldots, q_p)$ *with* $q_k = \lim\limits_{t\to\infty} \mathbb{P}\{\hat{\mathbf{Z}}_k(t) = \mathbf{0} | \hat{\mathbf{Z}}_k(0) = \mathbf{e}_k\}$ *and* $\theta(\mathbf{y}) = (\theta_1(\mathbf{y}), \ldots, \theta_p(\mathbf{y}))$ *have components* $\theta_i(u)$, $1 \le i \le p$, *satisfying the system of integral equations:*

$$\theta_i(u) = \int_0^\infty h^{(i)}(\theta_1(ue^{-\alpha_0 t}), \ldots, \theta_p(ue^{-a_0 t}))dG^{(i)}(t), \quad i = 1, \ldots, p. \tag{A.33}$$

(ii) Furthermore,

$$\mathbb{E}W^{(l)} = M_{01}^{(l)} \quad \textit{and} \quad Var[W^{(l)}] = M_{02}^{(l)} - [M_{01}^{(l)}]^2.$$

(iii) Moreover, there exists a scalar r.v. w *such that* $\mathbf{W} = w\mathbf{u}$ *a.s. and*

$$\mathbb{E}w = d = \frac{(\sum\limits_{l=1}^{p} \beta_l v_l)(\int_0^\infty e^{-\alpha_0 u} dG_0(u))(\int_0^\infty e^{-\alpha_0 u} dK(u))}{(1 - \int_0^\infty e^{-\alpha_0 u} dL(u))(\sum\limits_{k,l=1}^{p} M_{\alpha_0 k}^{l} u_k v_l)},$$

where $\mathbf{u}$ *is the left eigenvector of the matrix* $\hat{\mathbf{M}}$.

Proof. To prove (i) consider

$$\begin{aligned} \mathbb{E}[W^{(k)}(t+\tau) - W^{(k)}(t)]^2 &= e^{-2\alpha_0 t} M_{02}^{(k)}(t) + e^{-2\alpha_0 t} M_{01}^{(k)}(t) \\ &+ e^{-2\alpha_0(t+\tau)} M_{02}^{(k)}(t+\tau) + e^{-2\alpha_0(t+\tau)} M_{01}^{(k)}(t) \\ &+ -2e^{-\alpha_0(2t+\tau)} N_0^{(k)}(t,\tau) \end{aligned} \tag{A.34}$$

and observe that according to the Theorems A.2, A.3 and A.4 the right–hand side of (A.34) approaches zero as $t \to \infty$, uniformly in $\tau \ge 0$ for all $k = 1, \ldots, p$. By completeness of the space $L_2(\Omega, \mathbf{F}, \mathbb{P})$ there exist random variables $W^{(k)}$ such that $W^{(k)}(t) \xrightarrow{L_2} W^{(k)}$ as $t \to \infty$.

The rest of the argument is a concequence of the results of Slavtchova [120] and Mode [96]. ♢

Denote $\lim_{t\to\infty} \hat{Z}_i^{(l)}(t)/e^{\alpha_0 t} = \hat{W}_i^{(l)}$ a.s., $i, l = 1, \ldots, p$.

Theorem A.7 *Under the assumptions of Theorem A.4 if in addition*

$$\int_0^\infty \mathbb{E}[\hat{\mathbf{Z}}_i(t)/e^{\alpha_0 t} - \hat{\mathbf{W}}_i]^2 dt < \infty, \tag{A.35}$$

then

$$\lim_{t\to\infty} \mathbf{W}(t) = \mathbf{W} \quad a.s.$$

Proof. We use the representation (A.2) of the process $\mathbf{X}(t)$.

It has been proven (see Slavtchova [120], Theorem 4.3) that under the condition (A.35) $\mathbf{Z}_{ij}(t)/e^{\alpha_0 t} \to \tilde{\mathbf{W}}$ a.s. This implies that for each i there exists

$$\lim_{t\to\infty}\{\sum_{j=1}^{\nu_i}\mathbf{Z}_{ij}(t)/e^{\alpha_0 t}\} = \mathbf{W}_i \quad a.s.$$

The random vector $\mathbf{W}_i$ has L.T. $f_0(\psi(\mathbf{u}))$. It follows from the assumptions of Section 1.1 that $\{\mathbf{W}_i\}$ are i.i.d. and independent of the $\{\tau_i\}$. Define $\mathbf{W} = \sum_{i=1}^{\infty} e^{-\alpha_0\tau_i}\mathbf{W}_i$.

Proceeding as in Harris ([60], Ch. VI) assume that $h^{(i)}(\mathbf{0}) = 0$ for each $i = 1, \ldots, p$, which forces the process $\mathbf{X}(t)$ to have nondecreasing sample paths with probability 1. Therefore, it is sufficient to show that $\int_0^\infty \mathbb{E}[W^{(l)}(t) - W^{(l)}]^2 dt < \infty$. Observe that

$$[W^{(l)}(t) - W^{(l)}]^2 \le 2\left[(W^{(l)}(t) - \sum_{i=1}^{n(t)} e^{-\alpha_0\tau_i}W_i^{(l)})^2 + (\sum_{i=n(t)+1}^{\infty} e^{-\alpha_0\tau_i}W_i^{(l)})^2\right]$$

$$= 2[J_1(t) + J_2(t)].$$

From (A.2) by Schwarz's inequality,

$$J_1(t) \le \left[\sum_{i=1}^{n(t)} e^{-\alpha_0\tau_i}\right]\left[\sum_{i=1}^{n(t)} e^{-\alpha_0\tau_i}\left\{\sum_{j=1}^{\nu_i} Z_{ij}^{(l)}(t-\tau_i)/e^{\alpha_0(t-\tau_i)} - W_i^{(l)}\right\}^2\right].$$

It is not difficult to show that for the last sum we have

$$\int_0^\infty \left\{\sum_{j=1}^{\nu_i} Z_{ij}^{(l)}(t-\tau_i)/e^{\alpha_0(t-\tau_i)} - W_i^{(l)}\right\}^2 dt$$

$$= \sum_{i=1}^{\infty} e^{-\alpha\tau_i}\int_{\tau_i}^\infty \left\{\sum_{j=1}^{\nu_i} Z_{ij}^{(l)}(t-\tau_i)/e^{\alpha_0(t-\tau_i)} - W_i^{(l)}\right\}^2 dt$$

$$= \sum_{i=1}^{\infty} e^{-\alpha\tau_i}\int_0^\infty \left\{\sum_{j=1}^{\nu_i} Z_{ij}^{(l)}(t)/e^{\alpha_0 t} - W_i^{(l)}\right\}^2 dt.$$

By independence we conclude that

$$\mathbb{E}\left[\int_0^\infty J_1(t)dt\right] \le \mathbb{E}\left\{\left(\sum_{i=1}^{\infty} e^{-\alpha_0\tau_i}\right)^2\right\}\mathbb{E}\left\{\int_0^\infty \left[\sum_{j=1}^{\nu_1}(Z_{1j}^{(l)}(t)/e^{\alpha_0 t} - W_1^{(l)})\right]^2 dt\right\}.$$

Note that $\mathbb{E}\left[\sum_{i=1}^{\infty} e^{-\alpha_0\tau_i}\right]^2 < \infty$. Also by Schwarz's inequality,

$$\mathbb{E}\left\{\int_0^\infty \left[\sum_{j=1}^{\nu_1}(Z_{1j}^{(l)}(t)/e^{\alpha_0 t} - \sum_{j=1}^{\nu_i}\tilde{W}_j^{(l)})\right]^2 dt\right\} \le \mathbb{E}\{\nu_1^2\}\int_0^\infty \mathbb{E}[Z_{11}^{(l)}(t)/e^{\alpha_0 t} - \tilde{W}_1^{(l)}]^2 dt.$$

However, Slavtchova and Yanev [129] have shown that the last integral is finite under the condition (A.35). Similarly,

$$\begin{aligned}\mathbb{E}\left[\int_0^\infty J_2(t)dt\right] &\leq \mathbb{E}\left\{\left(\sum_{i=0}^{\infty} e^{-\alpha_0\tau_i}\right)\left(\sum_{i=1}^{\infty}\tau_i e^{-\alpha_0\tau_i}(W_i^{(l)})^2\right)\right\}\mathbb{E}[W_1^{(l)}]^2 \\ &\leq \delta\mathbb{E}\left(\sum_{i=1}^{\infty} e^{(-\alpha_0/2)\tau_i}\right)^2\mathbb{E}[W_1^{(l)}]^2,\end{aligned}$$

for $\delta > 0$ such that $xe^{-\alpha_0 x} \leq \delta e^{-\alpha_0 x/2}$, $x > 0$. On the other hand $\mathbb{E}[W_1^{(l)}]^2 = \mathbb{E}\left(\sum_{j=1}^{\nu_1} W_{1j}^{(l)}\right)^2 \leq \mathbb{E}\{\nu_1^2\}\mathbb{E}\{[W_1^{(l)}]^2\}$. Second moment assumption implies $\mathbb{E}\{[W_1^{(l)}]^2\} < \infty$. Therefore $\mathbb{E}\int_0^\infty J_2(t)dt < \infty$, which completes the proof. ♢

Finally, we would like to mention that it would be interesting to obtain limit results if the immigration component was not independent of the inner process.

The results from this chapter are published by Slavtchova–Bojkova in [121].

Chapter 2

LLN for subcritical BHBP with immigration

2.1 Introduction

Let us consider the following population process $\{X(t)\}_{t\geq 0}$. At the random times τ_k, $k = 1, 2, \ldots$, a random number of individuals enters the population. An individual appearing at time τ_k becomes an ancestor of Bellman–Harris branching process with immigration in the state zero (BHBPIO) $\{Z(t)\}_{t\geq 0}$. The process $X(t)$ counts the number of individuals alive at time t and we call this model, Bellman–Harris branching process with immigration at zero state and an immigration of renewal type (BHBPIOR).

The intervals between successive immigration $T_1 = \tau_1, T_2 = \tau_2 - \tau_1, \ldots$ and the number of immigrants $\nu_1, \nu_2, \ldots$, are assumed to be mutually independent random variables (i.r.v.). The r.v. T_k have common distribution function (d.f.) $G_0(t)$ and the r.v. ν_k are defined by common probability generating function (p.g.f.) $f_0(s)$. The BHBPIO $\{Z(t)\}_{t\geq 0}$ is governed by a lifetime distribution $G(t)$, an offspring p.g.f. $h(s)$, a p.g.f. $f(s)$ of the random number Y_i of immigrants in the state zero and the d.f. $K(t)$ of the duration X_i of staying in the state zero. It is assumed that $\int_0^\infty t dK(t) < \infty$.

We will use the definition of BHBPIO given by Mitov and Yanev [92]:

$$Z(t) = Z_{N(t)+1}(t - \xi(t))\mathbb{I}_{\{\xi(t)<t\}}, \xi(t) = S_{N(t)} + X_{N(t)+1}, Z(0) = 0, \tag{B.1}$$

where $\{Z_i(t)\}$ are independent Bellman–Harris branching processes starting with random number Y_i of particles, $N(t) = \max\{n \geq 0 : S_n \leq t\}$, $S_0 = 0$, $S_n = \sum_{i=1}^{n} U_i$, $U_i = X_i + \sigma_i$, $\sigma_i = \inf\{\ t : Z_i(t) = 0\}$ and $\mathbb{I}_{\{\cdot\}}$ is the indicator function.

Let us mention that the process defined by (B.1) could be interpreted as follows: starting from the zero state, the process stays at that state random time X_i with d.f. $K(t)$ and after that a random number Y_i of immigrants enters the population, according to the p.g.f. $f(s)$. The further evolution of each particle is independent and in accordance with a d.f. $G(t)$ of the life-time and the p.g.f. $h(s)$ of the offspring. Then the process hits zero after a random period σ_i, depending of the evolution of the inner BHBP $Z_i(t)$. The following evolution of the process could be presented as the replication of such i.i.d. cycles.

We introduce the following notations for the p.g.f. of the local characteristics of the processes

$$f(s) = \mathbb{E}s^{Y_1} = \sum_{k=1}^{\infty} f_k s^k, \quad h(s) = \sum_{k=0}^{\infty} p_k s^k, \quad f_0(s) = \mathbb{E}s^{\nu_1} = \sum_{k=0}^{\infty} q_k s^k.$$

It will be assumed:

(B.2) $$0 < A = h'(1) < \infty, \quad m = f'(1) < \infty, \quad m_0 = f_0'(1) < \infty,$$

(B.3) $G(t)$, $G_0(t)$ and $K(t)$ are non-lattice,

(B.4) $$0 < B = h''(1) < \infty, \quad n = f''(1) < \infty, \quad f_0''(1) = b_2 < \infty,$$

(B.5) $$r = \int_0^\infty x dG(x) < \infty, \tilde{a} = \int_0^\infty x dK(x) < \infty, r_0 = \int_0^\infty x dG_0(x) < \infty.$$

Note that $L(t) = \mathbb{P}\{X_i + \sigma_i \leq t\}$ is non-lattice with $L(0) = 0$ and denote $\mu = \int_0^\infty t dL(t)$.

Let us mention that in the critical case for the first time the BHBPIOR was studied by Weiner [136]. Later on, Slavtchova-Bojkova and Yanev [126], [127] analyzed the model $X(t)$ with two types of immigration in the non–critical cases and the problem of determining necessary and sufficient conditions for the existence of a limiting distribution were investigated. The results in the subcritical case are proved under the strong assumption of an existence of higher ($n > 2$) moments of the individual characteristics. Our results are concerning the case, where the individual characteristics are finite. The methods are quite different in the infinite moments case as might be seen in Erickson [37].

The aim of this work is to prove the convergence in probability of the subcritical BHBPIOR $X(t)$ only under assumption that the first and second moments are finite. The main result is the following theorem.

2.2 Convergence in probability

Theorem B.1 *Let us assume that* (B.2) – (B.5) *hold. If* $A < 1$, *then*

$$\frac{X(t)}{t} \xrightarrow{\mathbb{P}} c,$$

($\xrightarrow{\mathbb{P}}$ *means convergence in probability) as* $t \to \infty$, *where* $c = mm_0 r/(1 - A)\mu r_0$.

Proof. To start the proof, at first we give an equivalent representation of the process $X(t)$.

Let $\{Z_{ij}(t)_{t\geq 0}\}$ be a doubly infinite collection of independent random processes each having the same distribution as the BHBPIO $\{Z(t)\}_{t\geq 0}$. Furthermore, let all these processes be assumed to be independent of the sets of r.v. $\{\tau_i\}$ and $\{\nu_i\}$. By going to the product space, we can assume that all the above mentioned random quantities are defined on a common probability space.

Define the renewal function $n(.)$ by setting $n(t) = k$ if $\tau_k \leq t < \tau_{k+1}$, $k \geq 0$, $\tau_0 = 0$. It now follows from the assumptions in section 1, that for each $t > 0$

$$X(t) = \sum_{i=0}^{n(t)} \sum_{j=1}^{\nu_i} Z_{ij}(t - \tau_i) \quad a.s. \tag{B.6}$$

It is known for the subcritical BHBPIO $Z(t)$ (see Slavtchova and Yanev [129]), that

$$\lim_{t\to\infty} \mathbb{E}Z(t) = mr/(1 - A)\mu, \quad \mu = \int_0^\infty t dL(t),$$

and there exists stationary limit distribution, i. e.

$$\lim_{t\to\infty} \mathbb{P}\{Z(t) = k\} = \Phi_k = \mathbb{P}\{Z(\infty) = k\}, \quad \sum_{k=0}^{\infty} \Phi_k = 1, \quad \Phi(s) = \sum_{k=0}^{\infty} \Phi_k s^k,$$

$|s| \leq 1$ and

$$\mathbb{E}Z(\infty) = \Phi'(1) = mr/(1 - A)\mu \equiv a. \tag{B.7}$$

Let us denote

$$\begin{aligned} m_{ij}(t) &= \mathbb{E}Z_{ij}(t), \\ S(t) &= \frac{1}{t} \sum_{i=0}^{n(t)} \sum_{j=1}^{\nu_i} Z_{ij}(t - \tau_i), \\ S^\star(t) &= \frac{1}{t} \sum_{i=0}^{n(t)} \sum_{j=1}^{\nu_i} m_{ij}(t - \tau_i). \end{aligned}$$

To prove the theorem one need to check that for every $\varepsilon > 0$

$$\lim_{t\to\infty} \mathbb{P}\left\{\left|\frac{X(t)}{t} - c\right| > \varepsilon\right\} = 0.$$

We have the following estimation:

$$\begin{aligned} \mathbb{P}\left\{|S(t) - c| > \varepsilon\right\} &\leq \mathbb{P}\left\{|S(t) - S^\star(t)| > \frac{\varepsilon}{2}\right\} + \mathbb{P}\left\{|S^\star(t) - c| > \frac{\varepsilon}{2}\right\} \\ &= I_1 + I_2. \end{aligned}$$

Applying the Chebishev's inequality for I_1 we obtain

$$I_1 \leq \frac{\mathrm{Var}[S(t) - S^\star(t)]}{\varepsilon^2}. \tag{B.8}$$

Denote $F_t = \sigma(\tau_i, \nu_i, i = 1, 2, \ldots, n(t); n(t))$. Using that

$$\mathbb{E}[S(t) - S^\star(t)] = \mathbb{E}\{\mathbb{E}[S(t) - S^\star(t)|F_t]\} = 0,$$

for the variance we have

$$\begin{aligned} \mathrm{Var}[S(t) - S^\star(t)] &= \mathbb{E}[S(t) - S^\star(t)]^2 \\ &= \mathbb{E}\{\mathbb{E}[S(t) - S^\star(t)]^2|F_t\} \\ &= \frac{1}{t^2}\mathbb{E}\left[\sum_{i=0}^{n(t)}\sum_{j=1}^{\nu_i}\mathrm{Var}Z_{ij}(t-\tau_j)\right]. \end{aligned} \tag{B.9}$$

Set $d = \sup_t \mathbb{E}\left(Z_{ij}(t) - m_{ij}(t)\right)^2$. Using Wald's inequality and the fact that $|\mathrm{Var}Z_{ij}(t-\tau_i)| < d < \infty$, as $t \to \infty$, from (B.8) and (B.9) we obtain

$$\mathrm{Var}[S(t) - S^\star(t)] = \mathbb{E}[S(t) - S^\star(t)]^2$$

$$= \mathbb{E}\left(\mathbb{E}\left(\left(S(t) - S^\star(t)\right)^2|F_t\right)\right)$$

$$= \frac{1}{t^2}\mathbb{E}\sum_{i=0}^{n(t)}\sum_{j=1}^{\nu_i}\mathbb{E}\left(\left(Z_{ij}(t-\tau_i) - m_{ij}(t-\tau_i)\right)^2|F_t\right)$$

$$\leq \frac{d}{t^2}\mathbb{E}\sum_{i=0}^{n(t)}\nu_i = \frac{d}{t^2}\mathbb{E}n(t)\mathbb{E}\nu_1 \leq \frac{2d\mathbb{E}\nu_1}{t\mathbb{E}\tau_1}$$

for all sufficiently large t, since

$$n(t)/t \xrightarrow{\mathbb{P}} 1/\mathbb{E}\tau_1$$

and

$$\mathbb{E}n(t)/t \to 1/\mathbb{E}\tau_1, \text{ as } t \to \infty.$$

Thus,

$$I_1 \xrightarrow{\mathbb{P}} 0, \text{ as } t \to \infty. \tag{B.10}$$

Now, note only that $c = a\mathbb{E}\nu_1/\mathbb{E}\tau_1$, where a is defined by (B.7). One has

$$S^\star(t) - c = \frac{1}{t}\sum_{i=0}^{n(t)}\sum_{j=1}^{\nu_i} m_{ij}(t-\tau_i) - c$$

$$= \frac{1}{t}\sum_{n(t-T)}^{n(t)}\sum_{j=1}^{\nu_i} m_{ij}(t-\tau_i) + \frac{1}{t}\sum_{i=0}^{n(t-T)}\sum_{j=1}^{\nu_i}\left(m_{ij}(t-\tau_i) - a\right) +$$

$$+a\left(\frac{1}{t}\sum_{i=0}^{n(t-T)}\nu_i - \frac{\mathbb{E}\nu_1}{\mathbb{E}\tau_1}\right) \equiv I_3 + I_4 + I_5.$$

Now

$$0 \le I_3 \le \frac{R_1}{t} \sum_{n(t-T)}^{n(t)} \nu_i, \quad a.s.$$

where $R_1 = \sup_t m_{ij}(t) < \infty$.

Let $T = o(t) \to \infty$, $t \to \infty$. Therefore,

$$\mathbb{P}\{I_3 > \varepsilon\} \le \frac{R_1}{\varepsilon t}\mathbb{E} \sum_{n(t-T)}^{n(t)} \nu_i = \frac{R_1}{\varepsilon t}\mathbb{E}\nu_1 \mathbb{E}\left(n(t) - n(t-T)\right) = o(1), \tag{B.11}$$

as $t \to \infty$.

Denoting

$$r(T) = \sup_{x \ge T} \left|m_{ij}(x) - a\right|,$$

we see that

$$|I_4| \le \frac{r(T)}{t} \sum_{i=0}^{n(t-T)} \nu_i$$

and, therefore, for any fixed $\varepsilon > 0$

$$\mathbb{P}\{|I_4| > \varepsilon\} \le \frac{r(T)}{t}\ \mathbb{E} \sum_{i=0}^{n(t-T)} \nu_i = \frac{r(T)\mathbb{E}\nu_1}{t}\mathbb{E}n(t-T) \le R_2 r(T) \to 0 \tag{B.12}$$

as first $t \to \infty$ and then $T \to \infty$ and $R_2 = \mathbb{E}\nu_1/\mathbb{E}\tau_1$. Finally, by the law of the large numbers and the renewal theorem (see Feller [42], Section XI.6)

$$\frac{1}{t} \sum_{i=0}^{n(t-T)} \nu_i = \frac{n(t-T)}{t} \frac{1}{n(t-T)} \sum_{i=0}^{n(t-T)} \nu_i \to \frac{\mathbb{E}\nu_1}{\mathbb{E}\tau_1} \text{ a.s.}$$

and, therefore,

$$I_5 \xrightarrow{\mathbb{P}} 0 \tag{B.13}$$

as $t \to \infty$. From (B.10) – (B.13) the desired statement follows. ♢

The results from this chapter are published by Slavtchova–Bojkova in [122].

Chapter 3

LLN and CLT for subcrittical BHBP and BGWBP

3.1 Introduction

How does immigration at recurrent random epochs affect the long run behavior of populations which would otherwise become extinct because their reproductive pattern is subcritical? This question will be investigated hereafter for some classical branching processes, namely simple Galton–Watson processes (discrete time) and Bellman–Harris processes (continuous time), and for a certain immigration pattern. Thus individuals of the considered populations have i.i.d. lifetimes (identically 1 in the discrete–time case) and produce independent numbers of offspring at their death with a common subcritical distribution. Immigration is assumed to occur at an independent sequence of renewal epochs, the number of immigrants being i.i.d., and further whenever a subpopulation stemming from one of these immigrants or one of the ancestors dies out, possibly after a delay period. The number of immigrants at these extinction epochs as well as the delay periods are each sequences of i.i.d. random variables, too.

If only the second type of state–dependent immigration occurs then, by subcriticality, the resulting branching process is easily seen to be a strongly regenerative process (see e.g. Thorisson [135]) whose successive extinction times constitute regeneration epochs with finite mean. It therefore converges in distribution to a limiting variable with positive mean, see Proposition C.1. Since additional immigration at successive renewal epochs leads to a compound of such processes a linear growth behavior is to be expected, at least under some mild regularity conditions. Our main results are a confirmation of this conjecture and a central limit theorem for the considered branching processes. The focus will be on the continuous-time case because corresponding results in discrete time are then obtained by almost trivial adjustments of the arguments. Essential tools will be the theory of regenerative processes, renewal theory and occupation measures. This is in contrast to earlier related work using the "classical" analytic approach towards such processes based upon generating functions, Laplace transforms and integral equations.

The described immigration patterns for Bellman-Harris or Galton–Watson processes have been discussed in a number of papers. The Galton–Watson process with immigration at 0 (Foster–Pakes model) was first studied by Foster [43] and Pakes [102], [104],

[106], later by Mitov and Yanev [92] under additional assumptions. Its continuous time analog was studied by Yamazato [143] and Mitov and Yanev [92]. Jagers [67] and Pakes and Kaplan [109] provided results for Bellman–Harris processes with immigration of the second type (at renewal epochs). Results for both immigration types appeared in Weiner [136], but a combination of them was first investigated by Slavtchova–Bojkova and Yanev [126] and Slavtchova–Bojkova [122]. The last reference proves Theorem C.2 below under stronger conditions and by analytic means. Some of the afore–mentioned articles deal with the case of critical reproduction. Immigration at 0 then still entails that the branching process is strongly regenerative but with cycles of infinite mean length. This in turn causes a drastic change as to its asymptotic behavior which will not be an issue here.

Following Mitov and Yanev [92] and the above informal description, a *Bellman–Harris process with immigration at 0 (BHPIO)* $(Z(t))_{t\geq 0}$ is a continuous–time age–dependent branching process whose model parameters are an individual lifetime distribution G with $G(0) = 0$, an offspring distribution $(p_j)_{j\geq 0}$ with p.g.f. $f(s)$, a number of immigrants distribution $(g_j)_{j\geq 0}$ with p.g.f. $g(s)$, and finally a distribution D of the delay times elapsing after extinction epochs before new immigrants enter the population. The discrete-time variant $(Z(n))_{n\geq 0}$, where $t \in [0, \infty)$ is replaced with $n \in \mathbb{N}_0$, and where $G = \delta_1$ (Dirac measure at 1) and D is a distribution on $\mathbb{N}_0$, will be called a *Galton–Watson process with immigration at 0 (GWPIO).*

In order to extend the previous model by an additional immigration pattern at renewal epochs let $Z_{ij} = (Z_{ij}(t))_{t\geq 0}$ for $i \geq 0$, $j \geq 1$ be independent BHPIO with one ancestor and the same model parameters as $(Z(t))_{t\geq 0}$. Let $(\sigma_n)_{n\geq 0}$ be a zero-delayed renewal process with increment distribution F and $(Y_n)_{n\geq 1}$ a sequence of i.i.d. integer-valued random variables with common distribution $(h_j)_{j\geq 0}$ and p.g.f. $h(s)$. The Y_n are supposed to be the numbers of individuals entering the population at times σ_n. A further integer-valued random variable Y_0 gives the number of ancestors of the considered population. It is assumed that $(\sigma_n)_{n\geq 0}$, $(Y_n)_{n\geq 1}$, Y_0 and all Z_{ij} are mutually independent. A *Bellman-Harris process with immigration at zero and immigration of renewal type (BHPIOR)* $(X(t))_{t\geq 0}$ is then obtained as

$$X(t) \stackrel{\text{def}}{=} \sum_{i=0}^{N(t)} Z_i(t - \sigma_i), \quad t \geq 0, \tag{C.1}$$

where $Z_i(t) \stackrel{\text{def}}{=} 0$ for $t < 0$, $N(t) \stackrel{\text{def}}{=} \sup\{n \geq 0 : \sigma_n \leq t\}$, and

$$Z_i(t) \stackrel{\text{def}}{=} \sum_{j=1}^{Y_i} Z_{ij}(t), \quad t \geq 0, \tag{C.2}$$

is a BHPIO with Y_i ancestors. Its discrete time variant, where the Z_i are GWPIO and $(\sigma_n)_{n\geq 0}$ forms a discrete renewal process, is called a *Galton–Watson process with immigration at zero and immigration of renewal type (GWPIOR).*

3.2 Results

In order to formulate our results some further notation is needed. Let $(Z(t))_{t\geq 0}$ be a BHPIO (or GWPIO with $t \in \mathbb{N}_0$) as described in the Introduction. Define

$$m \stackrel{\text{def}}{=} \sum_{k\geq 1} kp_k = f'(1), \quad m_G \stackrel{\text{def}}{=} \int_0^\infty t\, G(dt),$$

and similarly m_F and m_D. Let the p-th moments of $(p_k)_{k\geq 0}, G, F, D$ be denoted as $m_p, m_{G,p}$, $m_{F,p}$ and $m_{D,p}$, respectively. Put $\mathbb{P}_k \stackrel{\text{def}}{=} \mathbb{P}(\cdot|Z(0) = k)$ for $k \geq 0$ and $\mathbb{P}^* \stackrel{\text{def}}{=} \sum_{k\geq 0} g_k \mathbb{P}_k$, so that the initial distribution of $(Z(t))_{t\geq 0}$ under $\mathbb{P}^*$ is $(g_k)_{k\geq 0}$. We will simply write $\mathbb{P}$ in assertions where the distribution of $Z(0)$ does not matter. Let T_1 be the first extinction epoch of $(Z(t))_{t\geq 0}$ after 0, defined as

$$T_1 \stackrel{\text{def}}{=} \inf\{t > 0 : Z(t-) > 0 \text{ and } Z(t) = 0\}$$

in continuous time (and as $\inf\{n \geq 1 : Z(n) = 0\}$ in discrete time). Note that, under each $\mathbb{P}_k$ with $k \geq 1$, $(\hat{Z}(t))_{t\geq 0} \stackrel{\text{def}}{=} (Z(t)\mathbb{I}_{\{T_1>t\}})_{t\geq 0}$ is an ordinary BHP with lifetime distribution G (or GWP with $G = \delta_1$), offspring distribution $(p_j)_{j\geq 0}$ and extinction time T_1 which has finite mean under every $\mathbb{P}_k$. Let $\Phi(s,t) \stackrel{\text{def}}{=} \mathbb{E}_1 s^{\hat{Z}(t)}$ be the p.g.f. of $\hat{Z}(t)$ under $\mathbb{P}_1$ and $m(t) \stackrel{\text{def}}{=} \mathbb{E}_1 \hat{Z}(t)$ for $t \geq 0$. Put also $\Lambda(t) \stackrel{\text{def}}{=} \mathbb{E}^* Z(t)$ and $\Lambda_2(t) = \mathbb{E}^* Z(t)^2$ for $t \geq 0$. When moving to the process $(X(t))_{t\geq 0}$ defined in (1.1) we put $Z(t) \stackrel{\text{def}}{=} Z_0(t)$ for $t \geq 0$ and retain the previous notation.

Proposition C.1 *Let $(Z(t))_{t\geq 0}$ be a subcritical BHPIO with arbitrary ancestor distribution, $g'(1) < \infty$, and $m_G < \infty$. Suppose also $m_D < \infty$, and that the convolution $G * D$ is nonarithmetic. Then $Z(t) \stackrel{d}{\to} Z(\infty)$, $t \to \infty$, for an integer-valued random variable $Z(\infty)$ satisfying*

$$\mathbb{P}(Z(\infty) = n) = \begin{cases} \dfrac{m_D}{\beta}, & \text{if} \quad n = 0, \\ \dfrac{1}{\beta}\displaystyle\int_0^\infty \mathbb{P}^*(\hat{Z}(t) = n)\, dt, & \text{if} \quad n \geq 1, \end{cases} \tag{C.3}$$

where $\beta \stackrel{\text{def}}{=} \mathbb{E}^* T_1 + m_D$ is finite. $Z(\infty)$ has p.g.f.

$$\Phi(s,\infty) = \frac{m_D}{\beta} + \frac{1}{\beta}\int_0^\infty \Big(g(\Phi(s,t)) - g(\Phi(0,t))\Big)\, dt \tag{C.4}$$

and mean $\Lambda(\infty)$ given by

$$\Lambda(\infty) = \frac{g'(1)m_G}{(1-m)\beta}. \tag{C.5}$$

Moreover,

$$\lim_{t\to\infty} \mathbb{E}_k Z(t) = \lim_{t\to\infty} \Lambda(t) = \Lambda(\infty) \tag{C.6}$$

for all $k \geq 0$. *If* $f''(1)$, $m_{G,2}$ *and* $m_{D,2}$ *are all finite, then also*

$$\lim_{t\to\infty} \mathbb{E}_k Z(t)^2 = \lim_{t\to\infty} \Lambda_2(t) = \Lambda_2(\infty) \stackrel{\text{def}}{=} \mathbb{E}Z(\infty)^2 \tag{C.7}$$

holds for each $k \geq 0$, *and*

$$\Lambda_2(\infty) = \frac{g'(1)m_G}{(1-m)\beta} + \frac{1}{\beta}\left(\frac{g'(1)f''(1)}{1-m} + g''(1)\right)\int_0^\infty m(t)^2\, dt \;<\; \infty. \tag{C.8}$$

Turning to the BHPIOR $(X(t))_{t\geq 0}$ formally introduced by (C.1), let us first point out for later use the following almost trivial consequences of the previous proposition. Each $(Z_i(t))_{t\geq 0}$ defined by (C.2) is the random sum of Y_i i.i.d. BHPIO $(Z_{ij}(t))_{t\geq 0}$ with one ancestor, and Y_i is independent of these processes. Suppose that the conditions of Proposition C.1 ensuring $Z_{ij}(t) \stackrel{d}{\to} Z(\infty)$ are satisfied and let $Z^1(\infty), Z^2(\infty), \ldots$ be i.i.d. copies of $Z(\infty)$ which are also independent of Y, a generic copy of $Y_1, Y_2, \ldots$ Then we infer for each $i \geq 1$ that

$$Z_i(t) \;\stackrel{d}{\to}\; Z^*(\infty) \;\stackrel{\text{def}}{=}\; \sum_{j=1}^{Y} Z^j(\infty), \quad t \to \infty, \tag{C.9}$$

and

$$\lim_{t\to\infty} \mathbb{E}Z_i(t) = \mathbb{E}Z^*(\infty) = h'(1)\Lambda(\infty). \tag{C.10}$$

For the last result it should be recalled that h denotes the p.g.f. of Y. If in addition to the previous assumptions $f''(1)$, $m_{G,2}$, $m_{D,2}$, $h'(1)$ and $h''(1)$ are all finite, then Proposition C.1 further implies

$$\begin{aligned} \lim_{t\to\infty} \mathbb{E}Z_i(t)^2 &= \mathbb{E}Z^*(\infty)^2 \\ &= h''(1)\Lambda(\infty)^2 + h'(1)(\Lambda_2(\infty) - \Lambda(\infty)^2) \;<\; \infty \end{aligned} \tag{C.11}$$

for each $i \geq 1$.

Theorem C.2 *Let* $(X(t))_{t\geq 0}$ *be a subcritical BHPIOR with arbitrary ancestor distribution,* $g'(1) < \infty$, $h'(1) < \infty$ *and* $m_G < \infty$. *Suppose also* $m_F < \infty$, $m_D < \infty$, *and that* $G * D$ *is nonarithmetic. Then*

$$\frac{X(t)}{t} \;\stackrel{p}{\to}\; \frac{g'(1)h'(1)m_G}{(1-m)m_F\beta}, \quad t \to \infty. \tag{C.12}$$

As already mentioned in the Introduction, the previous result was proved under stronger conditions and by different means in Slavtchova–Bojkova [122]. In fact, the conditions imposed there will lead us now to the following central limit theorem.

Theorem C.3 *Let $(X(t))_{t\geq 0}$ be a subcritical BHPIOR with arbitrary ancestor distribution, $g'(1) < \infty$, $f''(1) < \infty$, $h''(1) < \infty$ and $m_{G,2} < \infty$. Suppose also $m_F < \infty$, $m_{D,2} < \infty$, and that at least one of G or D is spread out. Then*

$$\frac{X(t) - (N(t)+1)h'(1)\Lambda(\infty)}{t^{1/2}} \xrightarrow{d} N(0, m_F \Xi(\infty)^2) \tag{C.13}$$

where

$$\Xi(\infty)^2 \stackrel{\text{def}}{=} (h''(1) - h'(1)^2)\Lambda(\infty)^2 + h'(1)(\Lambda_2(\infty) - \Lambda(\infty)^2) \tag{C.14}$$

denotes the variance of $Z^*(\infty)$, the limiting variable defined in (C.9).

As one can easily see from the proofs in the next section, all previous results persist to hold in discrete time, i.e. for GWPIO and GWPIOR. Minor adjustments are only caused by the fact that the renewal process $(\sigma_n)_{n\geq 0}$ as well as the delay periods are now integer-valued which entails that nonarithmetic renewal limits must be replaced with their arithmetic counterpart. The following results are therefore stated without proof. The attribute "1-arithmetic" is used as a shorthand expression for "arithmetic with lattice–span 1".

Proposition C.2 *Let $(Z(k))_{k\geq 0}$ be a subcritical GWPIO with arbitrary ancestor distribution and $g'(1) < \infty$. Suppose also $m_D < \infty$ and that $G * D = \delta_1 * D$ is 1-arithmetic. Then $Z(k) \xrightarrow{d} Z(\infty)$, $t \to \infty$, for an integer-valued random variable $Z(\infty)$ satisfying*

$$\mathbb{P}(Z(\infty) = n) = \begin{cases} \dfrac{m_D}{\beta}, & \text{if } \ n = 0, \\ \dfrac{1}{\beta} \displaystyle\sum_{k\geq 0} \mathbb{P}^*(\hat{Z}(k) = n), & \text{if } \ n \geq 1, \end{cases} \tag{C.15}$$

where $\beta \stackrel{\text{def}}{=} \mathbb{E}^* T_1 + m_D$. $Z(\infty)$ has p.g.f.

$$\Phi(s, \infty) = \frac{m_D}{\beta} + \frac{1}{\beta} \sum_{k\geq 0} \Big(g(\Phi(s,k)) - g(\Phi(0,k)) \Big) \tag{C.16}$$

and mean $\Lambda(\infty)$ given by (C.5) *with $m_G = 1$. Moreover,*

$$\lim_{k\to\infty} \mathbb{E}_j Z(k) = \lim_{k\to\infty} \Lambda(k) = \Lambda(\infty) \tag{C.17}$$

for all $j \geq 0$. If $f''(1)$ and $m_{D,2}$ are finite, then also

$$\lim_{k\to\infty} \mathbb{E}_j Z(k)^2 = \lim_{k\to\infty} \Lambda_2(k) = \Lambda_2(\infty) \tag{C.18}$$

holds for each $j \geq 0$, and

$$\Lambda_2(\infty) = \frac{g'(1)}{(1-m)\beta} + \frac{1}{\beta(1-m^2)} \left(\frac{g'(1) f''(1)}{1-m} + g''(1) \right). \tag{C.19}$$

Theorem C.4 *Let $(X(k))_{k\geq 0}$ be a subcritical GWPIOR with arbitrary ancestor distribution and $g'(1) < \infty$, $h'(1) < \infty$. Suppose also $m_F < \infty$, $m_D < \infty$, and that $G * D$ is 1-arithmetic. Then* (C.12) *remains true with $m_G = 1$ and $t \to \infty$ through the integers.*

Theorem C.5 *Let $(X(k))_{k\geq 0}$ be a subcritical GWPIOR with arbitrary ancestor distribution, $g'(1) < \infty$, $h''(1) < \infty$ and $f''(1) < \infty$. Suppose also $m_F < \infty$, $m_{D,2} < \infty$ and that $G * D$ is 1-arithmetic. Then* (C.13) *remains true as $t \to \infty$ through the integers.*

3.3 Proofs

Proof of Proposition C.1. Let $T_1, T_2, \ldots$ and $X_1, X_2, \ldots$ denote the successive extinction epochs and delay times of $(Z(t))_{t\geq 0}$. Obviously, $(Z(t))_{t\geq 0}$ is a classical regenerative process (see Asmussen [9] Ch. V) with regeneration times $T_n + X_n$, $n \geq 1$. So cycles start (and end) at successive immigration epochs (the first one at 0). They are independent and for $n \geq 2$ also identically distributed with mean β the finiteness of which we will show at the end of this proof. Since, by assumption, $G * D$ and thus the distribution of $T_1 + X_1$ are nonarithmetic, the ergodic theorem for regenerative processes (see Asmussen [9], Theorem. V.1.2) gives $Z(t) \xrightarrow{d} Z(\infty)$ with

$$\mathbb{P}(Z(\infty) = n) = \frac{1}{\beta}\,\mathbb{E}^*\bigg(\int_0^{T_1+X_1} \mathbb{I}_{\{Z(t)=n\}}\; dt\bigg) \tag{C.20}$$

for $n \in \mathbb{N}_0$. It follows directly from (C.20) that

$$\mathbb{P}(Z(\infty) = 0) = \frac{m_D}{\beta}.$$

For $n \geq 1$, we obtain

$$\begin{aligned}\mathbb{P}(Z(\infty) = n) &= \frac{1}{\beta}\,\mathbb{E}^*\bigg(\int_0^{T_1} \mathbb{I}_{\{\hat{Z}(t)=n\}}\; dt\bigg)\\ &= \frac{1}{\beta}\int_0^{\infty} \mathbb{P}^*(\hat{Z}(t) = n)\; dt\end{aligned}$$

completing the proof of (C.3). Now

$$\begin{aligned}\Phi(s,\infty) &= \frac{m_D}{\beta} + \frac{1}{\beta}\sum_{n\geq 1}\int_0^{\infty} s^n\,\mathbb{P}^*(\hat{Z}(t) = n)\; dt\\ &= \frac{m_D}{\beta} + \frac{1}{\beta}\int_0^{\infty}\sum_{k\geq 0} g_k \sum_{n\geq 1} s^n\,\mathbb{P}_k(\hat{Z}(t) = n)\; dt\\ &= \frac{m_D}{\beta} + \frac{1}{\beta}\int_0^{\infty}\sum_{k\geq 0} g_k\Big(\Phi(s,t)^k - \Phi(0,t)^k\Big)\; dt\\ &= \frac{m_D}{\beta} + \frac{1}{\beta}\int_0^{\infty}\Big(g(\Phi(s,t)) - g(\Phi(0,t))\Big)\; dt\end{aligned}$$

for $s \in [0,1)$. As to $\Lambda(\infty) = \Phi'(1,\infty)$, where the prime means of course differentiation with respect to the first argument of Φ, we get

$$\Lambda(\infty) = \frac{1}{\beta}\int_0^{\infty} g'(1)\Phi'(1,t)\; dt = \frac{g'(1)}{\beta}\int_0^{\infty} m(t)\; dt$$

and then further for $I \stackrel{\text{def}}{=} \int_0^{\infty} m(t)\, dt$, by conditioning upon the ancestor's death time ν and offspring number,

$$I = \mathbb{E}_1\bigg(\int_0^{\infty} \hat{Z}(t)\; dt\bigg)$$

$$\begin{aligned} &= m_G + \mathbb{E}_1\Big(\int_\nu^\infty \hat{Z}(t)\ dt\Big) \\ &= m_G + \sum_{k\geq 0} p_k \int_0^\infty \mathbb{E}_k \hat{Z}(t)\ dt \\ &= m_G + mI. \end{aligned}$$

We used $\mathbb{E}_k\hat{Z}(t) = k\,m(t)$ for the final equality. This shows $I = \frac{m_G}{1-m}$ and thus $\Lambda(\infty) = \frac{g'(1)m_G}{(1-m)\beta}$, i.e. (C.5).

Turning to (C.6), put $S_0 \stackrel{\text{def}}{=} 0$, $S_n \stackrel{\text{def}}{=} T_n + X_n$ for $n \geq 1$, and notice that $(S_n)_{n\geq 0}$ is a zero-delayed nonarithmetic renewal process under $\mathbb{P}^*$. Denote by $\mathbb{U}$ the associated renewal measure and put further

$$\begin{aligned} Q_1 &\stackrel{\text{def}}{=} \sum_{k\geq 1} k p_k\, \mathbb{P}_1(\nu \in \cdot | \hat{Z}(\nu) = k), \\ Q_2 &\stackrel{\text{def}}{=} \sum_{k\geq 2} k(k-1) p_k\, \mathbb{P}_1(\nu \in \cdot | \hat{Z}(\nu) = k), \\ m_2(t) &\stackrel{\text{def}}{=} \mathbb{E}_1 \hat{Z}(t)^2, \\ v(t) &\stackrel{\text{def}}{=} \mathrm{Var}_1\, \hat{Z}(t) = m_2(t) - m(t)^2. \end{aligned}$$

Note that $\mathbb{E}^*\hat{Z}(t) = g'(1)m(t)$. It then follows that

$$\begin{aligned} \Lambda(t) &= \sum_{n\geq 1} \mathbb{E}^* Z(t) \mathbb{I}_{\{S_{n-1}\leq t\leq T_n\}} \\ &= \int_{[0,t]} \mathbb{E}^* Z(t-x) \mathbb{I}_{\{T_1 > t-x\}}\ \mathbb{U}(dx) \\ &= \int_{[0,t]} \mathbb{E}^* \hat{Z}(t-x)\ \mathbb{U}(dx) \\ &= \int_{[0,t]} g'(1) m(t-x)\ \mathbb{U}(dx). \end{aligned}$$

Since $m(t) = \int_{[0,t]} \mathbb{P}_1(\nu > t-x)\, \mathbb{V}(dx)$ (see e.g. Athreya and Ney [12], p. 151]), where ν is as given above and $\mathbb{V} = \sum_{n\geq 0} Q_1^{*n}$ denotes the *defective* renewal measure associated with Q_1, we further infer

$$\Lambda(t) = \int_{[0,t]} \int_{[0,t-y]} g'(1)\, \mathbb{P}_1(\nu > t-x-y)\ \mathbb{U}(dx)\ \mathbb{V}(dy). \tag{C.21}$$

The function $t \mapsto \mathbb{P}_1(\nu > t)$ is clearly directly Riemann integrable ($m_G < \infty$). Consequently, a combination of the key renewal theorem and the dominated convergence theorem ($\mathbb{V}([0,\infty)) = \frac{1}{1-m} < \infty$) yields

$$\lim_{t\to\infty} \Lambda(t) = \frac{\mathbb{V}([0,\infty))}{\beta} \int_0^\infty g'(1)\, \mathbb{P}_1(\nu > x)\ dx = \frac{g'(1)m_G}{(1-m)\beta} = \Lambda(\infty)$$

and thus proves (C.6) for $\mathbb{P} = \mathbb{P}^*$. The same result is then obtained for $\mathbb{P} = \mathbb{P}_k$, $k \geq 0$, because

$$\mathbb{E}_k Z(t) = \mathbb{E}_k \hat{Z}(t) \mathbb{I}_{\{T_1 > t\}} + \int_{[0,t]} \Lambda(t-x)\ \mathbb{P}_k(T_1 \in dx) \tag{C.22}$$

for all $t \geq 0$ and $k \geq 0$, and

$$\mathbb{E}_k \hat{Z}(t) \mathbb{I}_{\{T_1 > t\}} = \mathbb{E}_k \hat{Z}(t) = k\, m(t)\ \to\ 0,$$

as $t \to \infty$.

We proceed with the proof of (C.7) and (C.8) and assume from now on that $m_{G,2}$ and $m_{D,2}$ are both finite. Notice that Q_2 has total mass $f''(1)$. A standard renewal argument using $\mathrm{Var}_k\, \hat{Z}(t) = kv(t)$ leads to

$$m_2(t) = \int_{[0,t]} \mathbb{P}_1(\nu > t-x)\ \mathbb{V}(dx) + \int_{[0,t]} m(t-x)^2\ Q_2 * \mathbb{V}(dx), \tag{C.23}$$

and with this identity a straightforward calculation yields

$$\int_0^\infty m_2(t)\ dt = \frac{m_G}{1-m} + \frac{f''(1)}{1-m} \int_0^\infty m(t)^2\ dt. \tag{C.24}$$

We also compute

$$\mathbb{E}^* \hat{Z}(t)^2 = \sum_{k \geq 1} g_k \mathbb{E}_k \hat{Z}(t)^2 = \sum_{k \geq 1} g_k \big(kv(t) + k^2 m(t)^2 \big) = g'(1) m_2(t) + g''(1) m(t)^2$$

for any $t \geq 0$. It is not hard to verify that $m(t)^2$ and $m_2(t)$ are directly Riemann integrable. Using these facts we get

$$\begin{aligned}
\mathbb{E}^* Z(t)^2 &= \sum_{n \geq 1} \mathbb{E}^* Z(t)^2 \mathbb{I}_{\{S_{n-1} \leq t \leq T_n\}} \\
&= \int_{[0,t]} \mathbb{E}^* Z(t-x)^2 \mathbb{I}_{\{T_1 > t-x\}}\ \mathbb{U}(dx) \\
&= \int_{[0,t]} \mathbb{E}^* \hat{Z}(t-x)^2\ \mathbb{U}(dx) \\
&= \int_{[0,t]} \Big(g'(1) m_2(t-x) + g''(1) m(t-x)^2 \Big)\ \mathbb{U}(dx)
\end{aligned}$$

and then by appealing to the key renewal theorem

$$\lim_{t \to \infty} \mathbb{E}^* Z(t)^2 = \frac{g'(1)}{\beta} \int_0^\infty m_2(t)\ dt + \frac{g''(1)}{\beta} \int_0^\infty m(t)^2\ dt. \tag{C.25}$$

By computing $\Phi''(1, \infty) = \mathbb{E}Z(\infty)(Z(\infty) - 1)$ from (C.4) one can check that the right hand side of (C.25) also equals $\Lambda_2(\infty)$. An equation similar to (C.22) holds for $\mathbb{E}_k Z(t)^2$ and leads to the conclusion that $\lim_{t \to \infty} \mathbb{E}_k Z(t)^2 = \lim_{t \to \infty} \mathbb{E}^* Z(t)^2 = \Lambda_2(\infty)$ for each

$k \geq 0$. This completes the proof of (C.7). By plugging (C.24) into (C.25), we further obtain (C.8).

We finish this proof by showing that $\beta = \mathbb{E}^* T_1 + m_D$ is finite. Since $m_D < \infty$ by assumption we must actually verify $\mathbb{E}^* T_1 < \infty$. Note that $\mathbb{E}_k T_1 \leq k\, \mathbb{E}_1 T_1$ for each $k \geq 1$ because T_1 is distributed under $\mathbb{P}_k$ as the maximum of k independent variables with the same distribution as T_1 under $\mathbb{P}_1$. Consequently,

$$\mathbb{E}^* T_1 = \sum_{k\geq 0} g_k \mathbb{E}_k T_1 \;\leq\; \mathbb{E}_1 T_1 \sum_{k\geq 0} k g_k = g'(1)\, \mathbb{E}_1 T_1 \;<\; \infty$$

as desired. ♢

Proof of Theorem C.2. By (C.1), $X(t) = \sum_{i=0}^{N(t)} Z_i(t - \sigma_i)$. It suffices to prove (C.12) with $\mathbb{P} = \mathbb{P}^*$ because only $Z_0(t)$ in the previous sum depends on the initial distribution and clearly satisfies $t^{-1} Z_0(t) \xrightarrow{p} 0$ regardless of that distribution (choice of $\mathbb{P}$). Thus fixing $\mathbb{P} = \mathbb{P}^*$, (C.9) after Proposition C.1 gives $Z_i(t) \xrightarrow{d} Z^*(\infty)$ for each $i \geq 0$. Since the $(Z_i(t))_{t\geq 0}$ are càdlàg and independent of $(\sigma_n)_{n\geq 0}$, the Skorohod-Dudley coupling theorem (see Kallenberg [69], Th. 3.30) ensures the existence of processes $(\tilde{Z}_i(t))_{t\geq 0}$ and random variables $\tilde{Z}_i(\infty)$, $i \geq 0$, such that

(1) $\tilde{Z}_i(t) \stackrel{d}{=} Z_i(t)$ for all $t \in [0, \infty)$ and $i \geq 0$;

(2) $\tilde{Z}_0(\infty) \stackrel{d}{=} \tilde{Z}_1(\infty) \stackrel{d}{=} ... \stackrel{d}{=} Z^*(\infty)$;

(3) $\tilde{Z}_i(t) \to \tilde{Z}_i(\infty)$ a.s.

(4) the $(\tilde{Z}_i(t))_{t\in[0,\infty]}$ are mutually independent and also independent of $(\sigma_n)_{n\geq 0}$.

As an immediate consequence we get

$$\tilde{X}(t) \;\stackrel{\text{def}}{=}\; \sum_{i=0}^{N(t)} \tilde{Z}_i(t - \sigma_i) \;\stackrel{d}{=}\; X(t)$$

for each $t \in [0, \infty)$, whence it suffices to prove $t^{-1}\tilde{X}(t) \xrightarrow{p} \frac{g'(1)h'(1)m_G}{(1-m)m_F\beta}$. To this end write

$$\frac{\tilde{X}(t)}{t} = \frac{N(t)}{t}\left(\frac{1}{N(t)}\sum_{i=0}^{N(t)}\Big(\tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty)\Big) + \frac{1}{N(t)}\sum_{i=0}^{N(t)}\tilde{Z}_i(\infty)\right). \tag{C.26}$$

Note that $\frac{N(t)}{t} \to m_F^{-1}$ a.s. by the elementary renewal theorem and that

$$\frac{1}{N(t)}\sum_{i=0}^{N(t)}\tilde{Z}_i(\infty) \to h'(1)\Lambda(\infty) = \frac{g'(1)h'(1)m_G}{(1-m)\beta}$$

a.s. by the strong law of large numbers and (C.10). We are thus left with the proof of

$$\frac{1}{t}\sum_{i=0}^{N(t)}\Big(\tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty)\Big) \;\xrightarrow{p}\; 0, \quad t \to \infty. \tag{C.27}$$

Put $n(t) \stackrel{\text{def}}{=} \lfloor \frac{2t}{m_F} \rfloor$ for $t \geq 0$. Then $\mathbb{P}(N(t) > n(t)) \to 0$. Since $\tilde{Z}_i(t-\sigma_i) \to \tilde{Z}_i(\infty)$ a.s., and $\mathbb{E}_k \tilde{Z}_i(t-\sigma_i) \to \mathbb{E}_k \tilde{Z}_i(\infty)$ by (2.4) of Proposition C.1 (σ_i independent of $(\tilde{Z}_i(t))_{t\geq 0}$), a generalization of Scheffé's lemma (see e.g. Bauer [25], p. 94) implies

$$\lim_{t\to\infty} \mathbb{E}_k \Big| \tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty) \Big| = 0$$

for any $i \geq 1$ and $k \geq 0$. It follows that

$$\lim_{t\to\infty} \frac{1}{t} \sum_{i=0}^{n(t)} \mathbb{E}_k \Big| \tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty) \Big| \mathbb{I}_{\{N(t)\leq n(t)\}} = 0$$

which in combination with $\mathbb{P}(N(t) > n(t)) \to 0$ gives (C.27) for $\mathbb{P} = \mathbb{P}_k$ for any $k \geq 0$. $\diamondsuit$

In order to prove Theorem C.3 we need the following auxiliary result.

Lemma C.3 *Under the conditions of Theorem* C.3*,*

$$\Lambda(t) = \Lambda(\infty) + o(t^{-1}), \quad t \to \infty. \tag{C.28}$$

Proof. We use the same notation as in the proof of Proposition C.1. Note that $M \stackrel{\text{def}}{=} \sup_{t\in\mathbb{R}} \Lambda(t)$ is finite and that (C.21) may be rewritten as

$$\Lambda(t) = g'(1)\Big(\mathbb{V} * \mathbb{U}(t) - G * \mathbb{V} * \mathbb{U}(t) \Big), \quad t \geq 0, \tag{C.29}$$

because $\mathbb{P}_1(\nu \in \cdot) = G$. Consequently, for each $s, t \geq 0$,

$$\Lambda(t+s) - \Lambda(t) = g'(1)\Big(\mathbb{V} * \mathbb{U}((t, t+s]) - G * \mathbb{V} * \mathbb{U}((t, t+s]) \Big)$$

Now use $\lim_{t\to\infty} \Lambda(t) = \Lambda(\infty)$ to infer

$$\begin{aligned} \Big| \Lambda(t) - \Lambda(\infty) \Big| &\leq \sup_{s\geq 0} \Big| \Lambda(t+s) - \Lambda(t) \Big| \\ &\leq g'(1) \sup_{s\geq 0} \Big| \mathbb{V} * \mathbb{U}((t, t+s]) - G * \mathbb{V} * \mathbb{U}((t, t+s]) \Big| \\ &\leq g'(1) \| \mathbb{V} * \mathbb{U}(t+\cdot) - G * \mathbb{V} * \mathbb{U}(t+\cdot) \|, \end{aligned}$$

where $\| \cdot \|$ denotes total variation norm. The latter expression is indeed of the required order $o(t^{-1})$ because, by assumption, the increments of $(S_n)_{n\geq 0}$ (the renewal process associated with $\mathbb{U}$) are spread out and square integrable, see Lindvall [82], (6.8)(i) on p. 86]. This completes the proof of the lemma. $\diamondsuit$

Proof of Theorem C.3. Again it suffices to verify (C.13) under $\mathbb{P} = \mathbb{P}^*$ as one can easily check. Put $\Lambda^*(\infty) \stackrel{\text{def}}{=} \mathbb{E}Z^*(\infty) = g'(1)\Lambda(\infty)$. With this and the notation from the proof of Theorem C.2 we have the decomposition

$$\frac{\tilde{X}(t) - (N(t)+1)\Lambda^*(\infty)}{t^{1/2}}$$

$$= \frac{1}{t^{1/2}} \sum_{i=0}^{N(t)} \Big(\tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty) - \Lambda^*(t-\sigma_i) + \Lambda^*(\infty) \Big)$$
$$+ \frac{1}{t^{1/2}} \sum_{i=0}^{N(t)} \Big(\Lambda^*(t-\sigma_i) - \Lambda^*(\infty) \Big)$$
$$+ \frac{1}{t^{1/2}} \sum_{i=0}^{N(t)} (\tilde{Z}_i(\infty) - \Lambda^*(\infty)).$$

and denote the three terms on the right hand side as $A_1(t), A_2(t)$ and $A_3(t)$. The last expression $A_3(t)$ consists of i.i.d. random variables with mean zero and finite variance $\Xi(\infty)^2$ which together with $t^{-1}N(t) \to m_F^{-1}$ implies by a version of Anscombe's theorem (see Gut [51], Th. I.3.1)

$$\frac{1}{t^{1/2}} \sum_{i=0}^{N(t)} (\tilde{Z}_i(\infty) - \Lambda^*(\infty)) \ \stackrel{d}{\to} \ N(0, m_F \Xi(\infty)^2).$$

So it remains to show that $A_1(t) \stackrel{p}{\to} 0$ and $A_2(t) \stackrel{p}{\to} 0$. Let $\mathbb{U}_F$ denote the renewal measure associated with $(\sigma_n)_{n\geq 0}$. Starting with $A_1(t)$, we obtain by conditioning upon $(\sigma_n)_{n\geq 0}$ that

$$\mathbb{E}A_1(t)^2 = \frac{1}{t}\mathbb{E}\left(\sum_{i=0}^{N(t)} \mathbb{E}\left(\Big(\tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty) - \Lambda^*(t-\sigma_i) + \Lambda^*(\infty) \Big)^2 \Big| \sigma_i \right) \right)$$
$$= \frac{1}{t}\mathbb{E}\left(\sum_{i\geq 0} \mathbb{E}\left(\Big(\tilde{Z}_i(t-\sigma_i) - \tilde{Z}_i(\infty) - \Lambda^*(t-\sigma_i) + \Lambda^*(\infty) \Big)^2 \Big| \sigma_i \right) \mathbb{I}_{\{\sigma_i \leq t\}} \right)$$
$$= \frac{1}{t} \int_{[0,t]} \mathbb{E}\Big(\tilde{Z}_0(t-s) - \tilde{Z}_0(\infty) - \Lambda^*(t-s) + \Lambda^*(\infty) \Big)^2 \ \mathbb{U}_F(ds).$$

A combination of $\tilde{Z}_0(t) \to \tilde{Z}_0(\infty)$ a.s. with (2.5) yields

$$\lim_{t\to\infty} \mathbb{E}\Big(\tilde{Z}_0(t) - \tilde{Z}_0(\infty) \Big)^2 = 0$$

by another appeal to the generalization of Scheffé's lemma and thus also

$$\lim_{t\to\infty} \mathbb{E}\Big(\tilde{Z}_0(t) - \tilde{Z}_0(\infty) - \Lambda^*(t) + \Lambda^*(\infty) \Big)^2 = \lim_{t\to\infty} \mathrm{Var}\left(\tilde{Z}_0(t) - \tilde{Z}_0(\infty) \right) = 0.$$

Put $C_b \stackrel{\mathrm{def}}{=} \sup_{t\geq b} \mathbb{E}(\tilde{Z}_0(t) - \tilde{Z}_0(\infty) - \Lambda^*(t) + \Lambda^*(\infty))^2$ for $b \geq 0$. Using

$$\lim_{t\to\infty} t^{-1}\mathbb{U}_F((t-b,t]) = 0 \quad \text{and} \quad \lim_{t\to\infty} t^{-1}\mathbb{U}_F([0,t-b]) = m_F^{-1}$$

for all $b > 0$, we now infer

$$\lim_{t\to\infty} \frac{1}{t} \int_{[0,t]} \mathbb{E}\Big(\tilde{Z}_0(t-s) - \tilde{Z}_0(\infty) - \Lambda^*(t-s) + \Lambda^*(\infty) \Big)^2 \ \mathbb{U}_F(ds)$$

$$\leq \lim_{b\to\infty}\lim_{t\to\infty}\left(\frac{\mathbb{U}_F([0,t-b])}{t}C_b + \frac{\mathbb{U}_F((t-b,t])}{t}C_0\right) = 0$$

and thus $\mathbb{E}A_1(t)^2 \to 0$ which in turn shows $A_1(t) \xrightarrow{p} 0$.

As to $A_2(t)$, we first note that Lemma C.3 implies

$$|\Lambda^*(t) - \Lambda^*(\infty)| = h'(1)|\Lambda(t) - \Lambda(\infty)| \leq R(t)(t+2)^{-1}$$

for some bounded decreasing function R with supremum $\|R\|_\infty$. By further using the well–known fact that $\gamma \stackrel{\text{def}}{=} \sup_{t\geq 0}\mathbb{U}_F([t,t+1]) < \infty$ we now infer

$$\begin{aligned}
\mathbb{E}|A_2(t)| &\leq \frac{1}{t^{1/2}}\mathbb{E}\left(\sum_{i=0}^{N(t)}|\Lambda^*(t-\sigma_i) - \Lambda^*(\infty)|\right)\\
&= \frac{1}{t^{1/2}}\int_{[0,t]}|\Lambda^*(t-s) - \Lambda^*(\infty)|\,\mathbb{U}_F(ds)\\
&\leq \frac{1}{t^{1/2}}\int_{[0,t]}\frac{R(t-s)}{t-s+2}\,\mathbb{U}_F(ds)\\
&\leq \frac{\|R\|_\infty}{t^{1/2}}\left(\mathbb{U}_F([0,1]) + \sum_{n=0}^{\lfloor t\rfloor-1}\frac{1}{n+1}\,\mathbb{U}_F([t-n-1,t-n])\right)\\
&\leq \frac{\gamma\|R\|_\infty}{t^{1/2}}\Big(1+\log(t+1)\Big).
\end{aligned}$$

Since the latter expression converges to 0 as $t \to \infty$ we conclude $\mathbb{E}|A_2(t)| \to 0$ and particularly $A_2(t) \xrightarrow{p} 0$ as desired. ♢

The results from this chapter are published by Alsmeyer and Slavtchova–Bojkova in [7].

Chapter 4

LLN by means of renewal theory

4.1 Introduction

What is the effect of immigration at recurrent random epochs on the longterm behavior of populations that would otherwise become extinct because their reproductive pattern is subcritical? This question was investigated by Alsmeyer and Slavtchova–Bojkova [7] for some classical branching processes, namely simple Galton–Watson processes (discrete time) and Bellman–Harris processes (continuous time), and for a certain immigration pattern. Thus, individuals of the considered populations have i.i.d. lifetimes (identically 1 in the discrete-time case), different for each type, and produce independent numbers of individuals of different types of offspring at their death with a common subcritical reproduction. Immigration is assumed to occur both, at an independent sequence of renewal epochs, the vectors of immigrants of different types being i.i.d., and further whenever a subpopulation stemming from one of these immigrants or one of the ancestors dies out, possibly after a delay period. The vectors of immigrants at these extinction epochs as well as the delay periods are each sequences of i.i.d. random vectors and variables, also. If only the second type of state-dependent immigration occurs then, by subcriticality, the resulting branching process is easily seen to be a strongly regenerative process (see Thorisson [135]) whose successive extinction times constitute regeneration epochs with finite mean. It therefore converges in distribution to a limiting vector with positive mean (see Lemma 2.1). Because additional immigration at successive renewal epochs leads to a superposition of such processes, a linear growth behavior is to be expected, at least under some mild regularity conditions. Our main result is a confirmation of this conjecture, as it is in one-dimensional case. We state the result in the continuous–time case because corresponding results in discrete time are then obtained by almost trivial adjustments of the arguments. It again follows essentially by use of the theory of regenerative processes, renewal theory and occupation measures, that is in contrast to earlier related work using the classical analytic approach towards such processes based upon generating functions, Laplace transforms and integral equations. The described immigration patterns for Bellman-Harris or Galton- Watson processes have been discussed in a number of papers. The Galton- Watson process with immigration at 0 (Foster-Pakes model) was first studied by Foster [43] and Pakes [102], [104], [106] under varying additional assumptions. Its continuous time analog was studied by Yamazato [143] and later by Mitov and Yanev [92]. Jagers [66] and

Pakes and Kaplan [109] provided results for Bellman–Harris processes with immigration of the second type (at renewal epochs). Results for both immigration types appeared in Weiner [136], but a combination of them was first investigated by Slavtchova-Bojkova and Yanev in [126] and by the author in [122]. The last reference proves Theorem 2.1, below, under stronger conditions and by analytic means.

Following previous results of the author (see Slavtchova-Bojkova [120]) and the above informal description, a $p-$dimensional Bellman-Harris process with immigration at 0 (BHPIO) $\mathbf{Z}(t) = \left(Z^{(1)}(t), Z^{(2)}(t), \dots Z^{(p)}(t)\right)$, whose $l-$th component $Z^{(l)}(t)$ means, that there exist $Z^{(l)}(t)$ particles of type l at the moment t, $l = 1, 2, \dots, p$ is a multi-type age-dependent branching process whose model parameters are the vector of an individual lifetime distributions $\mathbf{G}(t) = \left(G^{(1)}(t), G^{(2)}(t), \dots, G^{(p)}(t)\right)$, with $\mathbf{G}(0) = \mathbf{0}$, an offspring distributions $\{\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}\}$, $\boldsymbol{\alpha} \in \mathbf{N}^p$, $l = 1, 2, \dots, p$ with multivariate p.g.f.s $f^{(l)}(\mathbf{s})$, corresponding to the offspring distribution of type l particles, a vector of immigrants distribution $\{g_{\boldsymbol{\alpha}}\}_{\boldsymbol{\alpha}\in\mathbf{N}^p}$ with p.g.f. $g(\mathbf{s})$, and finally a distribution D of the delay times elapsing after extinction epochs before new immigrants enter the population.

In order to extend the previous model by an additional immigration pattern at renewal epochs, let $\mathbf{Z}_{ij} = (\mathbf{Z}_{ij}(t))_{t\geq 0}$ for $i \geq 0$, $j \geq 1$ be independent BHPIO and with the same model parameters as $(\mathbf{Z}(t))_{t\geq 0}$. Let $(\sigma_n)_{n\geq 0}$ be a zero-delayed renewal process with increment distribution F and $(\mathbf{Y}_n)_{n\geq 1}$ a sequence of i.i.d. integer-valued random vectors with common distribution $(h_{\boldsymbol{\alpha}})_{\boldsymbol{\alpha}\in\mathbf{N}^p}$ with multivariate p.g.f. $h(\mathbf{s})$. The $\mathbf{Y}_n$ are supposed to be the vectors of individuals entering the population at times σ_n. A further integer-valued random vector $\mathbf{Y}_0$ gives the number of ancestors of the considered population. It is assumed that $(\sigma_n)_{n\geq 0}$, $(\mathbf{Y}_n)_{n\geq 0}$, $\mathbf{Y}_0$ and all $\mathbf{Z}_{ij}$ are mutually independent. A p-type Bellman-Harris process with immigration at zero and immigration of renewal type (BHPIOR) $(\mathbf{X}(t))_{t\geq 0}$ is then obtained as

$$\mathbf{X}(t) = \sum_{i=0}^{N(t)} \mathbf{Z}_i(t - \sigma_i), t \geq 0, \tag{D.1}$$

where $\mathbf{Z}_i(0) = 0$, for $t < 0$, $N(t) = \sup\{n \geq 0 : \sigma_n \leq t\}$ and

$$\mathbf{Z}_i(t) = \sum_{j=1}^{\mathbf{Y}_i} \mathbf{Z}_{ij}(t), t \geq 0, \tag{D.2}$$

is a BHPIO with $\mathbf{Y}_i$ ancestors.

4.2 Main results

In order to formulate our results some further notation is needed. Let $\mathbf{s} = (s_1, s_2, \dots s_p)$, $\mathbf{0} = (0, 0, \dots, 0)$, $\mathbf{1} = (1, 1, \dots 1)$, $\mathbf{s}^{\boldsymbol{\alpha}} = s_1^{\alpha_1} s_2^{\alpha_2} \dots s_n^{\alpha_p}$, $\boldsymbol{\delta}^{\mathbf{i}} = (\delta_1^i, \dots, \delta_j^i, \dots, \delta_p^i) = (0, \dots, 1, \dots 0)$, $\delta_j^i = \begin{cases} 0 & , \ i \neq j \\ 1 & , \ i = j \end{cases}$, $\sum\limits_{\boldsymbol{\alpha}} = \sum\limits_{\alpha_1=0}^{\infty} \sum\limits_{\alpha_2=0}^{\infty} \cdots \sum\limits_{\alpha_p=0}^{\infty}$.

Let $(\mathbf{Z}(t))_{t\geq 0}$ be a BHPIO as described in the Introduction. Define

$$\mathbf{m}_G = \left(\int_0^{\infty} tG^{(1)}(dt), \dots, \int_0^{\infty} tG^{(p)}(dt) \right),$$

and similarly m_F and m_D. Put $\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}(t) = \mathbb{P}(\mathbf{Z}(t) = \boldsymbol{\alpha} | \mathbf{Z}(0) = \boldsymbol{\delta}^{(l)})$ and $\mathbb{P}^\star = \sum_{\boldsymbol{\alpha},l} g_{\boldsymbol{\alpha}} \mathbb{P}^{(l)}_{\boldsymbol{\alpha}}$, so that the initial distribution of $(\mathbf{Z}(t))_{t\geq 0}$ under $\mathbb{P}^\star$ is $(g_{\boldsymbol{\alpha}})_{\boldsymbol{\alpha}\in\mathbf{N}}$. We will simply write $\mathbb{P}$ in assertions where the distribution of $\mathbf{Z}(0)$ does not matter. Let T_1 be the first extinction epoch of $(\mathbf{Z}(t))_{t\geq 0}$ after 0, defined as

$$T_1 = \inf\{t > 0 : \mathbf{Z}(t-) > 0 \quad \text{and} \quad \mathbf{Z}(t) = 0\}.$$

Note that, under each $\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}$, $\left(\widetilde{\mathbf{Z}}(t)\right)_{t\geq 0} = \left(\mathbf{Z}(t)\mathbb{I}_{\{T_1 > t\}}\right)_{t\geq 0}$ is a $p-$dimensional BHP with lifetime distribution $\mathbf{G}$, offspring distributions $\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}$ and extinction time T_1, which has finite mean under every $\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}$. Let $\boldsymbol{\Phi}(\mathbf{s}, t) = \left(\Phi^{(1)}(\mathbf{s}, t), \ldots, \Phi^{(p)}(\mathbf{s}, t)\right)$ be the p.g.f. of $\widetilde{\mathbf{Z}}(t)$, where $\Phi^{(l)}(\mathbf{s}, t)$ is the p.g.f under $\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}$.

Lemma D.1 *Let $(\mathbf{Z}(t))_{t\geq 0}$ be a subcritical BHPIO with arbitrary ancestor distribution, $g'(\mathbf{1}) < \infty$, and $\mathbf{m}_G < \infty$. Suppose also $m_D < \infty$, and that the convolution $G * D$ is non arithmetic. Then $\mathbf{Z}(t) \xrightarrow{d} \mathbf{Z}(\infty)$, $t \to \infty$, for an integer-valued random vector $\mathbf{Z}(\infty)$ satisfying*

$$\mathbb{P}(\mathbf{Z}(\infty) = \boldsymbol{\alpha}) = \begin{cases} \dfrac{m_D}{\beta}, & \text{if} \quad \boldsymbol{\alpha} = \mathbf{0}, \\ \dfrac{1}{\beta}\displaystyle\int_0^\infty \mathbb{P}^\star(\widetilde{\mathbf{Z}}(t) = \boldsymbol{\alpha})dt, & \text{if} \quad \boldsymbol{\alpha} \geq \mathbf{1}, \end{cases} \tag{D.3}$$

where $\beta = \mathbb{E}^\star T_1 + m_D$ is finite. $\mathbf{Z}(\infty)$ has p.g.f.

$$\boldsymbol{\Phi}(\mathbf{s}, \infty) = \frac{m_D}{\beta} + \frac{1}{\beta}\int_0^\infty (g(\boldsymbol{\Phi}(\mathbf{s}, t)) - g(\boldsymbol{\Phi}(\boldsymbol{0}, t)))dt. \tag{D.4}$$

Proof: Let $T_1, T_2, \ldots$ and $X_1, X_2, \ldots$ denote the successive extinction epochs and delay times of $(\mathbf{Z}(t))_{t\geq 0}$. Obviously, $(\mathbf{Z}(t))_{t\geq 0}$ is a classical regenerative process (see Asmussen [9], Chpt. 5) with regeneration times $T_n + X_n$, $n \geq 1$. So, cycles start (and end) at successive immigration epochs (the first one at 0). They are independent and for $n \geq 2$ also identically distributed with mean β. Because, by assumption, $G * D$ and thus the distribution of $T_1 + X_1$ are non arithmetic, the ergodic theorem for regenerative processes (see Asmussen [9], Thm. V.1.2) gives $\mathbf{Z}(t) \xrightarrow{d} \mathbf{Z}(\infty)$ with

$$\mathbb{P}(\mathbf{Z}(\infty) = (\alpha_1, \alpha_2, \ldots, \alpha_p)) = \frac{1}{\beta}\mathbb{E}^\star\left(\int_0^{T_1+X_1} \mathbb{I}_{\{Z^{(1)}(t)=\alpha_1, Z^{(2)}(t)=\alpha_2, \ldots, Z^{(p)}(t)=\alpha_p\}}dt\right). \tag{D.5}$$

It follows directly from (D.5) that

$$\mathbb{P}(\mathbf{Z}(\infty) = \mathbf{0}) = \frac{m_D}{\beta}.$$

For $\boldsymbol{\alpha} \geq \mathbf{1}$, we obtain

$$\mathbb{P}(\mathbf{Z}(\infty) = (\alpha_1, \alpha_2, \ldots, \alpha_p)) \;=\; \frac{1}{\beta}\mathbb{E}^\star\left(\int_0^{T_1} \mathbb{I}_{\{Z^{(1)}(t)=\alpha_1, Z^{(2)}(t)=\alpha_2, \ldots, Z^{(p)}(t)=\alpha_p\}}dt\right)$$

$$= \frac{1}{\beta}\int_0^\infty \mathbb{P}^\star(\widetilde{\mathbf{Z}}(t)=\boldsymbol{\alpha})dt$$

completing the proof of (D.3).

Now,

$$\begin{aligned}
\boldsymbol{\Phi}(\mathbf{s},\infty) &= \frac{m_D}{\beta}+\frac{1}{\beta}\sum_{\boldsymbol{\alpha}\in\mathbf{N}^p,\boldsymbol{\alpha}\geq\mathbf{1}}\int_0^\infty \mathbf{s}^{\boldsymbol{\alpha}}\mathbb{P}^\star(\widetilde{\mathbf{Z}}(t)=\boldsymbol{\alpha})dt\\
&= \frac{m_D}{\beta}+\frac{1}{\beta}\int_0^\infty \sum_{\boldsymbol{\alpha}\geq\mathbf{0},l} g_{\boldsymbol{\alpha}}\sum_{\boldsymbol{\alpha}\in\mathbf{N}^p,\boldsymbol{\alpha}\geq\mathbf{1}}\mathbf{s}^{\boldsymbol{\alpha}}\mathbb{P}^{(l)}_{\boldsymbol{\alpha}}(\widetilde{\mathbf{Z}}(t)=\boldsymbol{\alpha})dt\\
&= \frac{m_D}{\beta}+\frac{1}{\beta}\int_0^\infty \sum_{\boldsymbol{\alpha}\geq\mathbf{0},l} g_{\boldsymbol{\alpha}}\left(\boldsymbol{\Phi}(\mathbf{s},t)^{\boldsymbol{\alpha}}-\boldsymbol{\Phi}(\mathbf{0},t)^{\boldsymbol{\alpha}}\right)dt\\
&= \frac{m_D}{\beta}+\frac{1}{\beta}\int_0^\infty \left(g(\boldsymbol{\Phi}(\mathbf{s},t))-g(\boldsymbol{\Phi}(\mathbf{0},t))\right)dt,
\end{aligned}$$

completing the proof of (D.4). ♢

Theorem D.1 *Let $(\mathbf{X}(t))_{t\geq 0}$ be a subcritical BHPIOR with arbitrary ancestor distribution, $g'(\mathbf{1})<\infty$, $h'(\mathbf{1})<\infty$, and $\mathbf{m}_G<\infty$. Suppose also $m_D<\infty$, and $G*D$ is non arithmetic. Then*

$$\frac{\mathbf{X}(t)}{t}\xrightarrow{p}\mathbf{X}(\infty),\qquad t\to\infty, \tag{D.6}$$

where the random vector $\mathbf{X}(\infty)$ is positive and $\mathbb{E}\mathbf{X}(\infty)>\mathbf{0}$.

Proof: It suffices to prove (D.6) with $\mathbb{P}=\mathbb{P}^\star$, because only $\mathbf{Z}_0(t)$ in (D.1) depends on the initial distribution and clearly satisfies $t^{-1}\mathbf{Z}_0(t)\xrightarrow{p}\mathbf{0}$ regardless of that distribution (choice of $\mathbf{P}$). Thus, fixing $\mathbb{P}=\mathbb{P}^\star$, Lemma D.1 and equation (D.2) give $\mathbf{Z}_i(t)\xrightarrow{d}\mathbf{Z}^\star(\infty)$ for each $i\geq 0$. Because the $(\mathbf{Z}_i(t))_{t\geq 0}$ are cadlag and independent of $(\sigma_n)_{n\geq 0}$, the Skorohod–Dudley coupling theorem (see Kallenberg [69], Theorem 3.30) ensures the existence of processes $\left(\widehat{\mathbf{Z}}_i(t)\right)_{t\geq 0}$ and random variables $\widehat{\mathbf{Z}}_i(\infty)$, $i\geq 0$ such that

(1) $\widehat{\mathbf{Z}}_i(t)\stackrel{d}{=}\mathbf{Z}_i(t)$ for all $t\in[0,\infty)$ and $i\geq 0$;
(2) $\widehat{\mathbf{Z}}_0(\infty)\stackrel{d}{=}\widehat{\mathbf{Z}}_1(\infty)\stackrel{d}{=}\ldots\stackrel{d}{=}\mathbf{Z}^*(\infty)$;
(3) $\widehat{\mathbf{Z}}_i(t)\to\widehat{\mathbf{Z}}_i(\infty)$ a.s.;
(4) the $\left(\widehat{\mathbf{Z}}_i(t)\right)_{t\in[0,\infty]}$, are mutually independent and also independent of $(\sigma_n)_{n\geq 0}$.

As an immediate consequence, we get

$$\widehat{\mathbf{X}}(t)\stackrel{def}{=}\sum_{i=0}^{N(t)}\widehat{\mathbf{Z}}_i(t-\sigma_i)\stackrel{d}{=}\mathbf{X}(t),\qquad t\geq 0.$$

The rest of the proof follows by the same arguments as in Alsmeyer and Slavtchova-Bojkova [7] and for technical reasons we omit it. ♢

The results from this chapter are published by Slavtchova–Bojkova in [123].

Part II

Branching models in epidemiology

Chapter 5

Continuous time branching model

5.1 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 [12] 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. [14] Axelrod et al. [13], Kimmel [75], Kimmel et al. [76], Yakovlev and Yanev [139] and Yakovlev and Yanev [140]).

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 [1], Farrington and Grant [40], Heinzmann [56] and Pakes [107]). Gonzáles, Martinez and Slavtchova-Bojkova [48] 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 [27], Farrington et al. [41], Isham [62], Mode and Sleeman [98] and Pakes [107]. However only in few papers (see for example Andersson and Britton [4], Barbour [22], Farrington and Grant [40] and Nasell [99]) 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, Martinez and Slavtchova-Bojkova [48] 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 [4] and Ball and Donnelley [18]). 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.

5.2 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 [12] (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:

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

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.*

5.3 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 [4], Ball and Donnelley [18], Haccou, Jagers and Vatutin [52], Kimeml and Axelrod [74], Mode and Sleeman [98] and Pakes [108]). 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 [62]). 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.

5.4 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 K.1, 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.*

5.5 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.

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

Applying the monotonicity and continuity properties of the functions $v_\alpha(t)$ and t^α_p (de-

pending 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 $p^{(z)} \leq v_1(t)$.

5.6 Simulation–based method

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 [68]).

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 [40], Farrington et al. [38] and Mode and Sleeman [98]). 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 5.1 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).

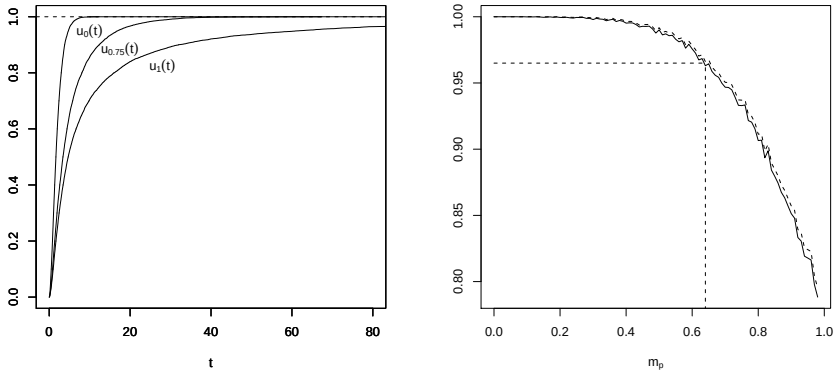

Figure 5.1: Left graphic: Behaviour of the empirical distribution functions of $u_{m_p}(\cdot)$ depending on m_p. Right graphic: Behaviour of estimated value of $u_{m_p}(15)$, jointly with an upper confidence bound at level 95%, depending on m_p (doted line).

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 $u_{m_p}(15)$, jointly with an upper confidence bound at level 95%, depending on m_p, is given in the right graphic of Figure 5.1. It is illustrated that, given $p^{(z)} = 0.965$, an approximation of $m_q(15, 0.9, 3)$ is 0.64.

Finally, in Figure 5.2 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 [112]).*

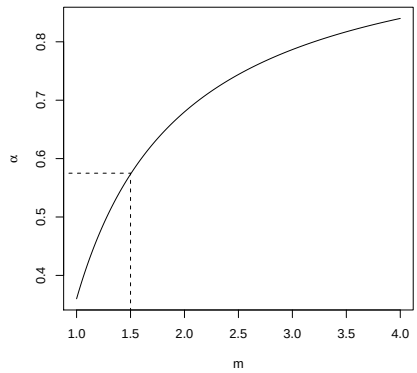

Figure 5.2: Proportion of individuals to be vaccinated depending on m and taking into account $m_q(15, 0.9, 3) = 0.64$.

5.7 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 [28], 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 K.1

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

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

and

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

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 K.2

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

1. Let α_1, α_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. ♢

5.8 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 [12] (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 $t \geq 0$. ♢

The results from this chapter are published by Gonzalez, Martinez and Slavtchova–Bojkova in [48].

Chapter 6

Sevastyanov's Branching model in epidemiological modelling

6.1 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 immunized 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 chapter 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 [4], Daley and Gani [31], Mode and Sleeman [98] or Pakes [108]).

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 [62]). 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 [32], 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 reason 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 [118]). This model is a particular case of the general branching process (see Jagers [67]), 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 [18]). 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, Martinez and Slavtchova-Bojkova [47].

The chapter has been split in 9 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 6.8 and in the subsequent section a comparison between the two policies based on the mean of the time to extinction distribution of the disease and on the quantiles of the same distribution, respectively, is made by use of simulation examples.

6.2 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.

6.3 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 [118] 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 [118]). 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 $|\alpha - \alpha^*| \leq \eta$,*

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

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 $\mu_{\alpha,z}$.*

6.4 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.

6.5 Vaccination based on the mean value

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 [118]).

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 provided in order to approximate the solution of integral equations (see for example Brunner [29] or Martinez and Slavtchova–Bojkova [86]). 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 [50] and Johnson, Susarla and Ryzin [68]).

6.6 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 [61]). 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 [101]). The left plot of Figure 6.1 shows the numbers of infected domestic birds detected each day along this period. The non-null values are also given in Table 6.1. From 20^{th} December the number of cases decreases, probably because some control measures were taken (see OIE [101]). We guess that these strategies should have started before 19^{th} December.

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

Table 6.1: Non-null values of infected domestic birds detected between 7th December 2006 and 14th 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

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 [31], Farrington and Grant [40], Farrington, Kannan and Gay [41] or Mode and Sleeman [98]). 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 [61]) – 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 7th December) is 80, and after the incubation period (in 13th and 14th 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 19th 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 6.1 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 6.2 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 into account the vaccination policy

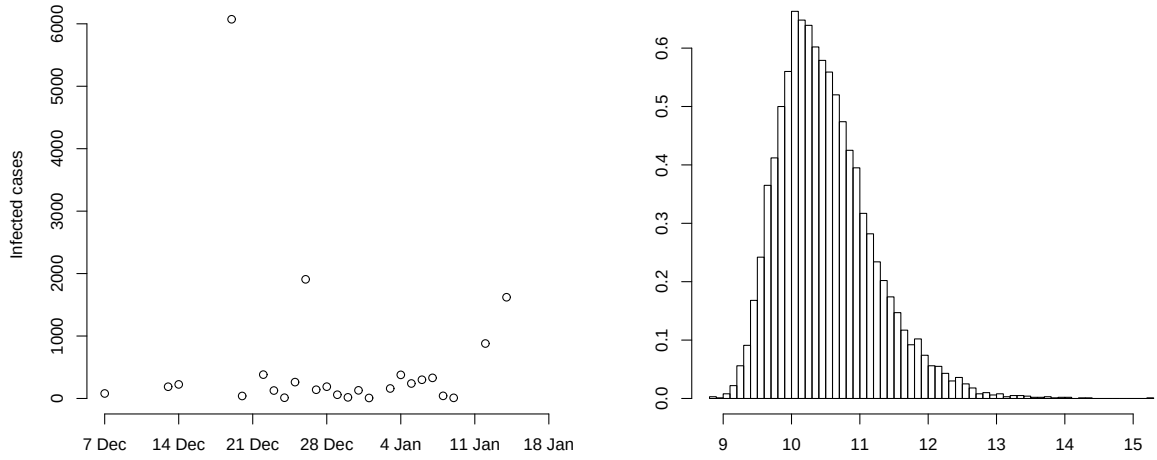

Figure 6.1: Left: Numbers of infected domestic birds detected between 7^{th} December 2006 and 14^{th} January 2007. Right: Histogram of simulated times to extinction for $\alpha = 1$.

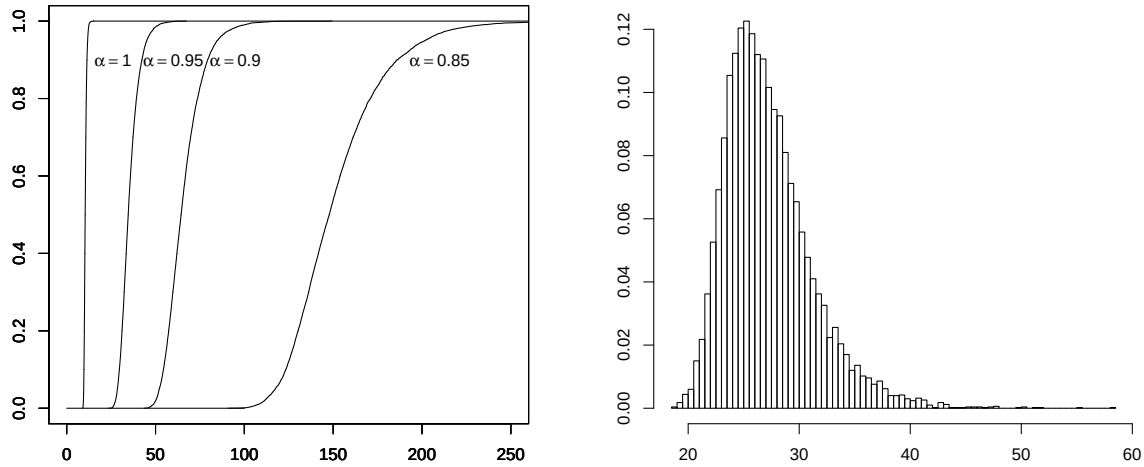

Figure 6.2: Left: Empirical d.f. of the time to extinction for $\alpha = 0.85, 0.90, 0.95$ and 1. Right: Histogram of simulated extinction times for $\alpha = 0.97$.

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 6.2 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) [112].*

6.7 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.

6.8 Proofs

In this section we provide the proofs of the results. 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 $v_{\alpha_1}(t) \leq H_{\alpha_2}^n(v_{\alpha_1}(t))$, for all $t \geq 0$ and $n \geq 1$. Then, applying Proposition F.1, for all $t \geq 0$,

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

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

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

Moreover, using again the mean value theorem,

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

and, from (F.6),

$$\begin{aligned} &|H_\alpha(H^n_{\alpha^*}(G))(t) - H_{\alpha^*}(H^n_{\alpha^*}(G))(t)| \leq \\ &\leq \int_0^t |f_\alpha(s, H^n_{\alpha^*}(G)(t-s)) - f_{\alpha^*}(s, H^n_{\alpha^*}(G)(t-s))| dG(s) \end{aligned}$$

$$\leq \ \varepsilon(1-m_\alpha).$$

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

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

and then the proof is completed. ♢

Proof of Theorem F.3

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

2. Let $\overline{\alpha}$ be such that $0 < m_{\overline{\alpha}} < m_{\alpha_{\inf}}$ and $M = \sup\{\mu_\alpha : \overline{\alpha} < \alpha \leq 1\} < \infty$. 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 $\alpha - \overline{\alpha} \leq \eta$, it follows that

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

Therefore,

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

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

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

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

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

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

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

and the proof is completed. ♢

6.9 Comparison of vaccination policies

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 [31], Farrington and Grant [40], Farrington et al. [38] or Mode and Sleeman [98]). 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 [101] and Gonzáles et al. [49]). 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 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 8.5 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 8.5, 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 8.5). Therefore, vaccinating 89% of susceptible individuals, it is

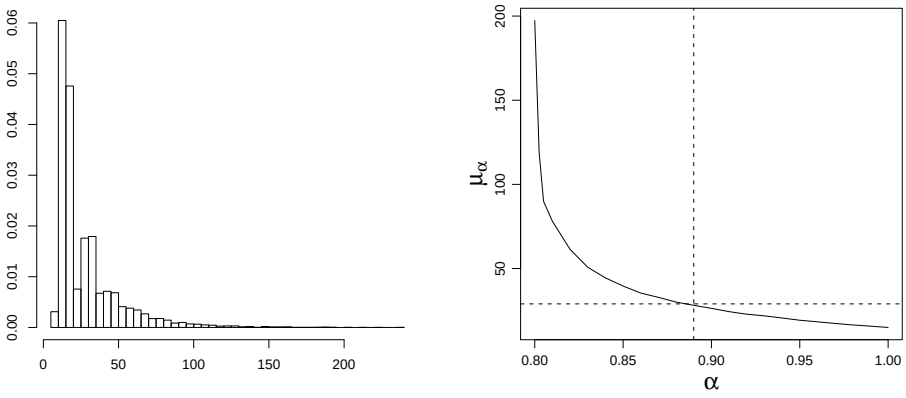

Figure 6.3: Left: Histogram of simulated extinction times for $\alpha = 0.89$. Right: Behaviour of $\mu_{\alpha,1}$ depending on α.

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 optimal vaccination coverage based on the quantiles. Indeed, in Figure 6.4, 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 6.4, 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 preferable, 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. [130]) 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

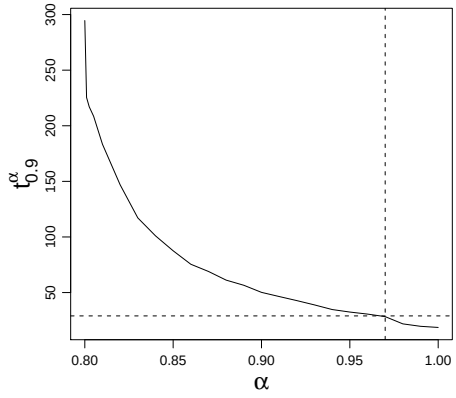

Figure 6.4: Behaviour of $t^{\alpha}_{0.9}$ depending on α.

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 [18]. 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.

The results from this chapter are published by Gonzalez, Martinez and Slavtchova–Bojkova in [49], [47] and [130].

Chapter 7

Bayesian estimation of the offspring mean

7.1 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 [5] and Heesterbeek, Dietz [55]). 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 [41]). 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 [26], Heyde [57], Farrington, Grant [40], Yanev, Tsokos [141], Farrington, et al. [41]. More complex branching process also have been applied for modeling of infectious diseases, see Marschner [85] Ball, Donnelly [18] Becker, Britton [27] González, Martinez, Slavtchova–Bojkova [48, 49] and Jacob [65].

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 allows 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. [41].

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 [112]).

Section 7.2 introduces the models of BGWBP and the total progeny, as well, in the context of the spread of infectious diseases. In Section 7.3 the Bayesian estimation approach is considered. Section 7.5 shows how these models are applied to the data on reported cases of mumps in Bulgaria.

7.2 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 [67] or Slavtchova–Bojkova and Yanev [131]. 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 $\{Z_n = 0, \quad \text{for some} \quad n \geq 1 \mid Z_0 = 1\}$ is called extinction. Denote the probability of extinction $q = P\{Z_n = 0, \quad \text{for some} \quad n \geq 1 \mid Z_0 = 1\}$. 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:

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

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

7.3 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 will 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 [16].

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 and Breuer [54]).

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 [53]).

7.4 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 [113], Robert and Casella [114], [115] and Hoff [58].

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.

7.5 Mumps in Bulgaria

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 [77]).

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 [111]).

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 7.1.

	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 7.1: 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 7.2.

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

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 offspring 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 7.3.

	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 7.3: 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.

The results from this chapter are published by Angelov and Slavtchova–Bojkova in [6].

Chapter 8

Crump-Mode-Jagers BP

8.1 Introduction

Branching processes have been applied widely to model epidemic spread (see for example the monographs by Andersson and Britton [4], Daley and Gani [31] and Mode and Sleeman [98] and the review by Pakes [108]. 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 [62]). Such an approximation dates back to the pioneering works of Bartlett [24] and Kendall [73] 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 [16], Ball and Donnelly [18] and Metz [87]). 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. [110]).

Before proceeding we give outline descriptions of some common branching process models (see e.g. Jagers [67]) 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 Sevastyanov 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 → Infective → 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 [55]), 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 [133]), 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. [48], [49] 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. [32] 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. [48], [49] 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. [83]. 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 chapter is to develop a methodology based on branching processes for addressing the above issues in a unified fashion.

González et al. [48], [49] 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. [32] 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. [48], [49] 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. [48], [49] 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. [48], [49] 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. [48], [49] focused on controlling the duration of the epidemic. 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. [48], [49] 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 realisation of a vaccinated process from that of the corresponding unvaccinated process. As indicated in Section 8.5, this methodology is very powerful and applicable to a broad range of processes.

In the next Section 8.2, 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 pro-

cess and give the basic coupling construction for obtaining a realisation of the vaccinated epidemic process from that of the unvaccinated process. The theoretical results of the chapter are given in Section 8.3.

8.2 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 [18] 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 $\rightarrow$ Exposed (i.e. latent) $\rightarrow$ Infective $\rightarrow$ Removed) models come under the above framework. The only difference between the above model and that in Ball and Donnelly [18] 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 $N \rightarrow \infty$ (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 [67]) 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 [18] maight be extended to epidemics other than SIR, e.g. SIS (Susceptible $\rightarrow$ Infective $\rightarrow$ Susceptible) and SIRS (Susceptible $\rightarrow$ Infective $\rightarrow$ Removed $\rightarrow$ Susceptible), by suitably generalizing the life history $\mathcal{H}$ to allow for removed individuals to become susceptible again (see e.g. Ball [17] 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*. For a previous use of pruning in a branching process framework see, for example, Aldous and Pitman [3].

Finally, we give some notation concerned with functions in $\mathcal{A}$, which will be used throughout the chapter. 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.

8.3 Monotonicity and continuity properties

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 [67], 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 $\omega \in \Omega$,*

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

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

$$|\mu^f_\alpha - \mu^f_{\alpha'}| \le \varepsilon. \tag{H.2}$$

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

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

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 $\|\alpha - \alpha'\| \le \eta$.

Proof

(a) For $n = 1, 2, \dots$ 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 $\alpha \in \mathcal{A}$,

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

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

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

whence, since f is non-negative,

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

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) $(U_1, U_2, \dots)$ is independent of Z, so, P-almost surely,

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

$$\leq 1 - (1-\delta)^{N(t)},$$

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

$$\mathrm{E}\left[1_{B^c_{N(t)}(\alpha,\alpha')}|Z\right] \leq \mathrm{E}\left[1_{B^c_{N(t)}(\alpha^0_0,\alpha^0_\delta)}|Z\right],$$

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

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

Note that $Z_{\alpha^{t_0}_{c_{\mathrm{inf}}}}$ has offspring mean m until time t_0, and $m_{c_{\mathrm{inf}}} \leq 1$ 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 $Z_{\alpha^{t_0}_{c_{\mathrm{inf}}}}$ (i.e. $N_{\alpha^{t_0}_{c_{\mathrm{inf}}}}(\infty)$) is finite almost surely. Also, $\|\tilde{\alpha} - \tilde{\alpha}'\| \leq (1 - c_{\mathrm{inf}})^{-1}\|\alpha - \alpha'\|$. The proof then proceeds as in part (a), but with Z and $N(t)$ replaced by $Z_{\alpha^{t_0}_{c_{\mathrm{inf}}}}$ and $N_{\alpha^{t_0}_{c_{\mathrm{inf}}}}(\infty)$, respectively, and α, α' replaced by $\tilde{\alpha}, \tilde{\alpha}'$.

♢

Remarks

1 Suppose that $m \leq 1$. Then $c_{\mathrm{inf}} = 0$ and it follows that $Z_{\alpha^{t_0}_{c_{\mathrm{inf}}}} = Z$ and $\mathcal{A}(c_{\mathrm{inf}}, t_0) = \mathcal{A}$. 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.

8.3.1 Monotonicity and continuity of d.f. 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*

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

(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 $\|\alpha - \alpha'\| \le \delta_{\alpha_{c_{\inf}}^{t_0},\infty}(\varepsilon)$.

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 $v_\alpha^f(x) = 1 - \mathrm{E}[\tilde{f}_x(Z_\alpha)]$.

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

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

and $\tilde{f}_x(Z_\alpha(\omega)) \le 1$ 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 $\alpha, \alpha' \in \mathcal{A}$,

$$|v_\alpha^f(x) - v_{\alpha'}^f(x)| \le \hat{\mu}_t(\|\alpha - \alpha'\|_t), \tag{H.8}$$

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

$$\hat{\mu}_t(\delta) = \mathrm{P}\left(B^c_{N(t)}(\alpha_0^0, \alpha_\delta^0)\right) = 1 - \mathrm{E}\left[(1-\delta)^{N(t)}\right] = 1 - \phi_{N(t)}(1-\delta).$$

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 $1 - \phi_{N_{\alpha_0^0}(t)}(1 - \delta_{\alpha_0^0,t}(\varepsilon)) \le \varepsilon$.

(c) The proof is similar to part (b) but with $N_{\alpha_0^0}(t)$ replaced by $N_{\alpha_{c_{\inf}}^{t_0}}(\infty)$.

$\diamondsuit$

Remark H.1 *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 $v_\alpha^f(x)$, 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 $m \le 1$ (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 $\|\alpha - \alpha'\| \le \delta_{\alpha_0^0,\infty}(\varepsilon)$.

Monotonicity and continuity of quantiles

In applications we wish to control the qua ntiles 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 $0 < p < 1$,

$$x_{\alpha,p}^f = \inf\{x : v_\alpha^f(x) \ge p\},$$

with the convention that $x_{\alpha,p}^f = \infty$ if $v_\alpha^f(x) < p$ for all $x \in [0,\infty)$. Thus $x_{\alpha,p}^f$ 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 $x_{\alpha',p}^f \le x_{\alpha,p}^f$.

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

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

(ii) v_α^f is continuous and strictly increasing at $x_{\alpha,p}^f$.

Proof

(a) By Theorem H.3(a), $\{x : v_\alpha^f(x) \ge p\} \subseteq \{x : v_{\alpha'}^f(x) \ge p\}$, which implies $x_{\alpha',p}^f \le x_{\alpha,p}^f$.

(b) Choose $t > 0$ such that $f \in \mathcal{P}_t$. Let $x_{\sup} = \limsup_{n\to\infty} x_{\alpha_n,p}^f$ and $x_{\inf} = \liminf_{n\to\infty} x_{\alpha_n,p}^f$. Suppose that (i) holds. Then by part (a), $x_{\sup} \le x_{\alpha,p}^f$. Fix $\varepsilon > 0$. Then, since $\lim_{n\to\infty} \alpha_n = \alpha$ and $\|\alpha_n - \alpha\|_t \le \|\alpha_n - \alpha\|$, there exists n_0 such that $\|\alpha_n - \alpha\|_t \le \delta_{\alpha_0^0,t}(\varepsilon)$ for all $n \ge n_0$, 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), $v_{\alpha_n}^f(x) - v_\alpha^f(x) \le \varepsilon$, for all $x \ge 0$ and for all $n \ge n_0$. In particular, setting $x = x_{\alpha_n,p}^f$ and noting that $v_{\alpha_n}^f(x_{\alpha_n,p}^f) \ge p$ since $v_{\alpha_n}^f$ is right-continuous, yields that $v_\alpha^f(x_{\alpha_n,p}^f) \ge p - \varepsilon$ for all $n \ge n_0$. Hence, $v_\alpha^f(x_{\inf}) \ge p - \varepsilon$, since v_α^f is increasing and right-continuous. This holds for all $\varepsilon > 0$,

so $v_\alpha^f(x_{\inf}) \geq p$, whence $x_{\inf} \geq x_{\alpha,p}^f$. Thus, $x_{\inf} = x_{\sup} = x_{\alpha,p}^f$, so $\lim_{n\to\infty} x_{\alpha_n,p}^f = x_{\alpha,p}^f$, as required.

Suppose that (ii) holds. First we assume that $\alpha_n \prec \alpha$ for all n. Then, by part (a), $x_{\inf} \geq x_{\alpha,p}^f$. Note that $v_\alpha^f(x_{\alpha,p}^f) = p$, since v_α^f is continuous at $x_{\alpha,p}^f$, and $v_\alpha^f(x) > p$ for all $x > x_{\alpha,p}^f$, since v_α^f is strictly increasing at $x_{\alpha,p}^f$. Fix $x > x_{\alpha,p}^f$ and let $\varepsilon = v_\alpha^f(x) - p$, 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

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

Thus $v_{\alpha_n}^f(x) \geq p$ for all $n \geq n_0$, whence $x_{\alpha_n,p}^f \leq x$ for all $n \geq n_0$, which implies that $x_{\sup} \leq x$. Since this holds for any $x > x_{\alpha,p}^f$, it follows that $x_{\sup} \leq x_{\alpha,p}^f$, which combined with $x_{\inf} \geq x_{\alpha,p}^f$ 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, $\lim_{q\to\infty} x_{\alpha_q^+,p}^f = \lim_{q\to\infty} x_{\alpha_q^-,p}^f = x_{\alpha,p}^f$. For any fixed $q \in \mathbb{N}$, $\alpha_n \prec \alpha_q^+$ for all sufficiently large n, so Theorem H.4(a) implies that $\liminf_{n\to\infty} x_{\alpha_n,p}^f \geq x_{\alpha_q^+,p}^f$. Letting $q \to \infty$ then yields that $x_{\inf} \geq x_{\alpha,p}^f$. A similar argument using the sequence $\{\alpha_q^-\}$ shows that $x_{\sup} \leq x_{\alpha,p}^f$, whence $\lim_{n\to\infty} x_{\alpha_n,p}^f = x_{\alpha,p}^f$, as required.

♢

Remark H.2 *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, $\lim_{s\to s^*} x_{\alpha_s,p}^f = x_{\alpha_{s^*},p}^f$. 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 $\mu_\alpha^f \le \mu_{\alpha'}^f$. 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 8.2 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., $\mathcal{A}^* = \{\alpha_c^0 : \ 0 \le c \le 1\}$. On this set, the total order is defined by the order of the real numbers. Another example is the set $\mathcal{A}^* = \{\alpha_{M,t_v,p_0} : \ M \ge 0, 0 \le p_0 \le 1, 0 \le t_v \le p_0^{-1}\}$, where, for $s \ge 0$,

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

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 proceeding 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 Section 8.3 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 $t_{\alpha,p} = x_{\alpha,p}^f$ 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. [77]). 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. [19] 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. [21].

8.4 Illustrative example: mumps in Bulgaria

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 (see Figure 8.1). This may be a result of a poor immunization of birth cohorts 1982-1992 (see Kojouharova et al. [77]). 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 our objective 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 we study as we show later.

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.

8.4.1 Deriving the outbreak duration

Our first task is to determine the behaviour of mumps outbreak durations in Bulgaria from 2005 to 2008, since our optimal vaccination level is based on outbreak duration. However, outbreak durations have not been registered; only the total number of new cases of infected individuals with mumps in each province has been observed (see Figure 8.2). Thus, instead, we derive the outbreak durations from this data set, taking into account the main features of mumps transmission. Mumps is a viral infectious disease of humans and spreads from person to person through the air. The period between someone being transmitted mumps and that person first showing symptoms of mumps is called the incubation period for mumps. This incubation period can be 12 to 25 days and the average is 16 to 18 days. The infectious period (i.e. when an individual is able to transmit the mumps virus to others) starts about 2 days before the onset of symptoms and usually, an individual with mumps symptoms is immediately isolated from the population (see `http:/kidshealth.org`). In view of the range of the incubation period, we consider that an outbreak is formed by the cases that appear in a province in 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. Applying this procedure for each province, we have obtained 262 outbreaks. The left plot in Figure 8.3 could represent one such outbreak initiated by one infected

individual. In this schematic representation we have considered that the infectious period is *negligible* due to the fact that infected individuals are immediately isolated when they show symptoms. The variable Z_t denotes the underlying branching process, which is not observed. The segments over/under Z_t indicates the lengths of time for which Z_t takes the corresponding values. The tick marks on the axis represent weeks, and $\bar{Z}_n$ the number of new cases observed during the n-th week. Indeed, $\bar{Z}_n$, $n \geq 0$, are the variables that are observed. In this context, by outbreak duration we mean the time elapsing between the appearance of the first case until isolation of the last one, that is the time to extinction of the branching process minus the incubation period of the first individual. Thus, a more accurate way to approximate outbreak duration from the observed data is by the total number of weeks until extinction of the virus (giving an error, due to discretization, of at most one week), yielding seven weeks in the outbreak of Figure 3 (left).

For each of the 262 outbreaks, we calculated the total number of weeks until extinction of the virus (and, also, the outbreak size i.e. total number of infected individuals). We noticed that the behaviour of these outbreak durations depends on the initial number of infected individuals. Hence, we have considered only those outbreaks which started with one infected individual, a total of 144. We checked that both outbreak duration and outbreak size were homogeneous between provinces (Kruskal-Wallis test: p-values 0.4763 and 0.4782, respectively) and consequently assumed that disease propagation in the different provinces are independent replications of the same process. Thus, the right plot in Figure 8.3 shows the histogram of outbreak duration for all 144 outbreaks started with one infected individual. We observe two different groups, outbreaks for which their duration is less than 10 weeks (comprising 134 outbreaks) and another group where the outbreak duration is greater than 10 weeks (comprising the remaining ten outbreaks). Possibly, this happens because some cases observed in a week could not come from cases of previous weeks, and then new outbreaks could have appeared overlapping in time. Hence, we consider that the outbreaks corresponding to durations of this last group may have been initiated no more than 10 weeks before. Thus, outbreak durations greater than 10 weeks have been removed from our study, and only durations less than 10 weeks have been considered in order not to overestimate the duration of the outbreaks. Nevertheless, an outbreak with apparent duration less than 10 weeks could actually be the superposition of two or more separate outbreaks, but we cannot determine this.

The left plot of Figure 8.4 shows the duration of the 134 outbreaks considered. We notice that 83% of these outbreaks have only one infected individual, so their outbreak duration is 0. The remaining 17% of outbreaks seem to have a cyclical behaviour with period given by the mean of the incubation period (approximately 2.5 weeks).

8.4.2 Modelling mumps transmission

As noted above, mumps is a contagious disease of humans that is spread from person to person through the air. The most common method of transmission is through coughing or sneezing, which can spread droplets of saliva and mucus infected with the mumps virus. Hence, when an infected person coughs or sneezes, the droplets atomize and can enter the eyes, nose, or mouth of another person. Following mumps transmission, a person does not immediately become sick. Once the virus enters the body, it travels to the back of

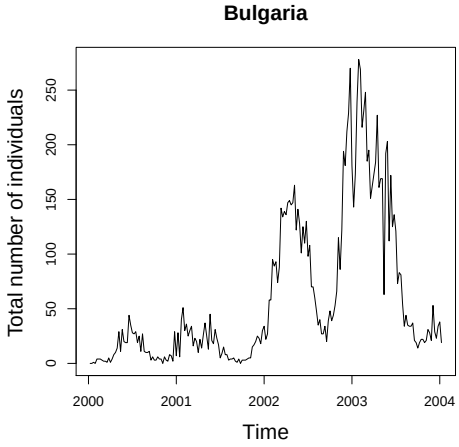

Figure 8.1: Number of new infected individuals weekly reported.

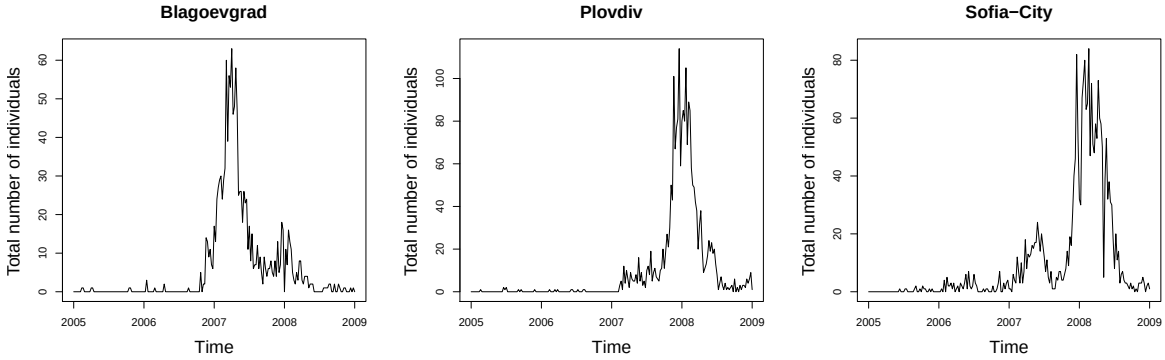

Figure 8.2: Number of new infected individuals per week for the provinces of Bulgaria with the highest incidence of mumps.

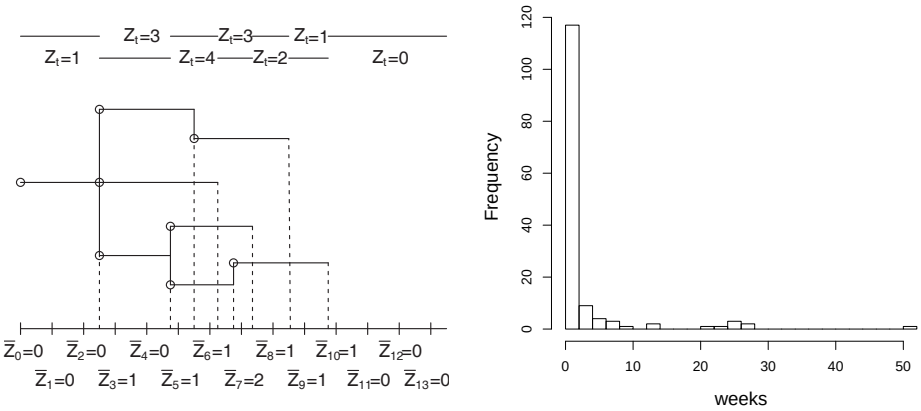

Figure 8.3: Left: Schematic representation of an outbreak. Z_t denotes the underlying branching process and $\bar{Z}_n$ the number of new cases in the n-th week. Right: Duration for outbreaks started with one infected individual.

the throat, nose and lymph glands in the neck, where it begins to multiply. As indicated previously, this period between mumps transmission and the beginning of mumps symptoms is the incubation period for mumps. People who have mumps are most contagious from 2 days before symptoms begin to 6 days after they end and transmission may occur at anytime in that period. Since an individual with mumps symptoms is immediately isolated from the population, the infectious period is very short in comparison with the incubation period, so, as indicated previously, we assume that transmission occurs only at the end point of an individual's incubation period. This assumption simplifies the mathematical model and does not influence strongly outbreak duration. As the end of the incubation period means that an individual's viral load has reached a given threshold to produce clinical signs, we assume that the mean number of individuals infected by an infected individual is constant and does not depend on the length of his/her incubation period.

An earlier analysis of these mumps data using Bienaymé-Galton-Watson branching processes is given in Angelov and Slavtchova-Bojkova [6]. However, the above observations imply that the Bellman-Harris branching process (BHBP) (see Athreya and Ney [12]) is a more appropriate model for mumps transmission and indeed it provides an improved fit to these data. Recall that a BHBP is a CMJ branching process, in which an individual reproduces only at the end of his/her life-time, according to an offspring law which is the same for all the individuals. In the epidemiological context, age is the incubation period and the reproduction law is the contagion distribution.

Next, we describe the incubation period and contagion distributions used to model mumps transmission in each outbreak in Bulgaria by means of the same BHBP (recall that we did not find any difference in the behaviour of the outbreaks in different provinces). We assume that the incubation period I follows a gamma distribution, with shape parameter $r > 0$ and rate $\gamma > 0$, so I has mean $r\gamma^{-1}$ and probability density function

$$f_I(u) = \frac{\gamma^r u^{r-1} \exp(-\gamma u)}{\Gamma(r)} \quad (u > 0),$$

where Γ is the gamma function, and that the contagion distribution follows a Poisson distribution with mean m. These distributions are appropriate for the incubation period and the number of infections, respectively (see for example Daley and Gani [31], Farrington and Grant [40], Farrington et al. [41] or Mode and Sleeman [98]). Intuitively, m, the mean number of individuals infected by an infected individual, represents the power of the virus. Taking into account that the incubation period is estimated between 12 and 25 days and the average is 16 to 18 days, we consider the gamma distribution with mean 17 and $r = 50$, which implies that the incubation period in 98.7% of individuals is between 12 and 25 days. To estimate m we consider the maximum likelihood estimator (MLE) based on the total number of births in independent extinct realisations of a BHBP. The total number of births in a BHBP has the same distribution as that in a Bienayme–Galton–Watson branching process with the same offspring distribution. In our application the offspring distribution is Poisson and it follows that the total number of births $N(\infty)$ (excluding the initial a individuals) follows a Borel–Tanner distribution with probability mass function

$$\mathrm{P}(N(\infty) = k) = \frac{am^k(a+k)^{k-1}\mathrm{e}^{-(a+k)m}}{k!} \quad (k = 0, 1, \dots).$$

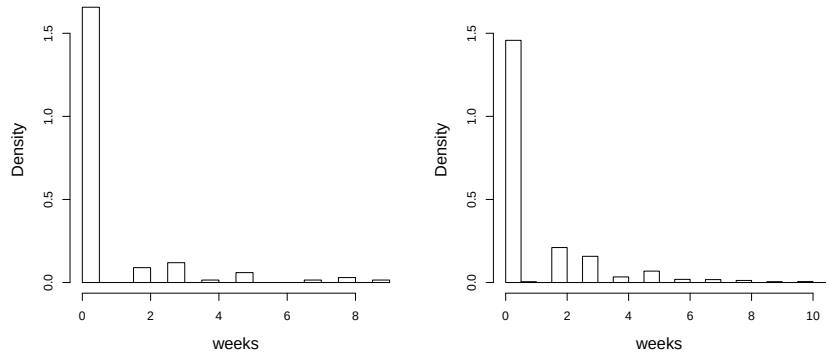

Figure 8.4: Left: Duration for outbreaks started with one infected individual without overlapping. Right: Simulated durations from a BHBP for outbreaks started with one infected individual.

(Note that, for $l = 1, 2, \ldots$, the mean number of births in the lth generation is am^l, so when $m < 1$ the expectation of this Borel-Tanner distribution is $E[N(\infty)] = a(m + m^2 + \ldots) = am(1-m)^{-1}$). It follows that the MLE of the offspring mean m, based on L independent realisations, is given by $\hat{m} = (\sum_{i=1}^{L} n^{(i)})(\sum_{i=1}^{L} a^{(i)} + n^{(i)})^{-1}$, where, for $i = 1, 2, \ldots, L$, $a^{(i)}$ and $n^{(i)}$ are respectively the initial number of individuals and the total number of births in the ith realisation (for details see Farrington et al. [41]). In our case $L = 134$, $\sum_{i=1}^{L} a^{(i)} = 134$ and $\sum_{i=1}^{L} n^{(i)} = 62$, whence $\hat{m} = 0.3163$. Note that inference based on duration of outbreaks is less sensitive to underreporting than that based on the total number of births. However, estimating the offspring law based on the time to extinction of each outbreak turns into a difficult problem in branching processes theory, even for the simplest model (see for example Farrington et al. [41]).

Applying the general theory of branching processes, since the estimated value of m is less than 1, we deduce that mumps transmission can still occur in Bulgaria, but such spread cannot lead to a large-scale epidemic. This fact is consistent with the Figures 8.1 and 8.2. Although the epidemic becomes extinct, it can have different levels of severity. One measure of severity is the mean size of an outbreak, excluding the initial case, viz. $m(1-m)^{-1}$, which in our case is estimated by 0.463. However, we are concerned with the problem of how to shorten outbreak durations by vaccination. To this end, we analyze the random variable $T_{\alpha^0_{c_{inf}}}$, the time to extinction of a BHBP with incubation period and contagion distributions as described above. Note that $c_{inf} = 0$, as $m \leq 1$, so here $T_{\alpha^0_{c_{inf}}}$ is the extinction time when there is no supplementary vaccination. The variable $T_{\alpha^0_{c_{inf}}}$ includes the incubation period of the initial individual, which is not observed in practice. Thus, from now on, we use the random variable $\widetilde{T}_{\alpha^0_{c_{inf}}}$, the difference between $T_{\alpha^0_{c_{inf}}}$ and the incubation period of the initial individual (i.e. the definition of outbreak duration given in the previous subsection) to model mumps outbreak duration in Bulgaria. The right plot in Figure 8.4 shows a histogram of $10,000$ simulated durations of outbreaks (rounded up to the nearest integer), each initiated by one infected individual and modelled by a BHBP with the above parameters. We notice that in 72.9% of these simulated

outbreaks the initial infected individual does not infect any new individual (recall 83% for real data). Moreover, the simulated outbreak durations show the same cyclical behaviour as seen in the real data.

Comparing real and simulated durations, we deduce that mumps outbreak durations in Bulgaria can be modelled by the variable $\widetilde{T}_{\alpha^0_{c_{inf}}}$ (Pearson's chi-squared test: p-value 0.2951, grouping the tail for values greater than 8).

8.4.3 Determining the optimal vaccination levels

Once we have fitted the model, in order to apply our theoretical results we have assumed that the proportion of immune individuals is constant with time, since, generally, vaccination is applied when an individual is a child and the disease spreads when he/she is a teenager. In the particular case of supplementary vaccination for Bulgarian mumps, for simplicity we assume that this vaccination process occurs simultaneously across the country (for example, in secondary schools at the same specific time). To determine the optimal vaccination levels, we denote by $\widetilde{T}_{\alpha^0_c}$ the difference between $T_{\alpha^0_c}$ and the incubation period of the initial individual, when the proportion of immune individuals in the population is c, with $0 \leq c \leq 1$. In the same way as was proved for $T_{\alpha^0_c}$ (see Corollary H.3), we deduce that $\widetilde{T}_{\alpha^0_c}$ has the same quantile properties depending on c as $T_{\alpha^0_c}$ (notice that $\widetilde{T}_{\alpha^0_c}$ is monotonically decreasing with pruning). Therefore, next we propose vaccination policies based on the quantiles of $\widetilde{T}_{\alpha^0_c}$, with $0 \leq c \leq 1$. Specifically, for fixed p and t, with $0 < p < 1$ and $t > 0$, we seek vaccination policies which guarantee that the mumps virus becomes extinct in each outbreak, with probability greater than or equal to p, not later than time t after the outbreak has been detected with z initial infected individuals, that is

$$c_{opt} = c_{opt}(z, p, t) = \inf\{c : 0 \leq c \leq 1, x^{\widetilde{T}}_{\alpha^0_c, p^{1/z}} \leq t\},$$

where $x^{\widetilde{T}}_{\alpha^0_c, p^{1/z}}$ denotes the quantile of order $p^{1/z}$ of the variable $\widetilde{T}_{\alpha^0_c}$.

As an illustration, we take $z = 5$, $p = 0.9$ and $t = 3$, being the time measured in weeks. First we justify these values. Consider the value of z. Since the number of infected individuals at the beginning of an outbreak is unknown, we bound it by the greatest number of individuals infected by one infected individual. Taking into account that the contagion distribution is Poisson and the estimate of m, we obtain the upper bound to be 5, and therefore we take $z = 5$. Moreover, we select $t = 3$, which, taking into account the features of the incubation period, guarantees that only primary and first-generation cases will be observed. Since in our situation the estimated value of m is less than 1, to approximate c_{opt}, we need to obtain the empirical distribution of $\widetilde{T}_{\alpha^0_c}$, for $0 \leq c \leq 1$, using the Monte-Carlo method described in Section 8.3.1. To this end, for each $c = 0.01k$, with $k = 0, \ldots, 100$, $100,000$ processes have been simulated and their duration calculated. The left plot in Figure 8.5 shows the behaviour of the empirical distribution function of $\widetilde{T}_{\alpha^0_c}$ for several values of c. Notice that as c increases, the outbreak duration decreases in a continuous way, in accordance with Corollaries H.1 and H.2. The right plot in Figure 8.5 shows the behaviour of $x^{\widetilde{T}}_{\alpha^0_c, 0.9^{1/5}}$ depending on c, which is in accordance with Corollary H.3. Since $x^{\widetilde{T}}_{\alpha^0_{c_{inf}}, 0.9^{1/5}} = 6.97$, our model estimates that the duration of 90% of

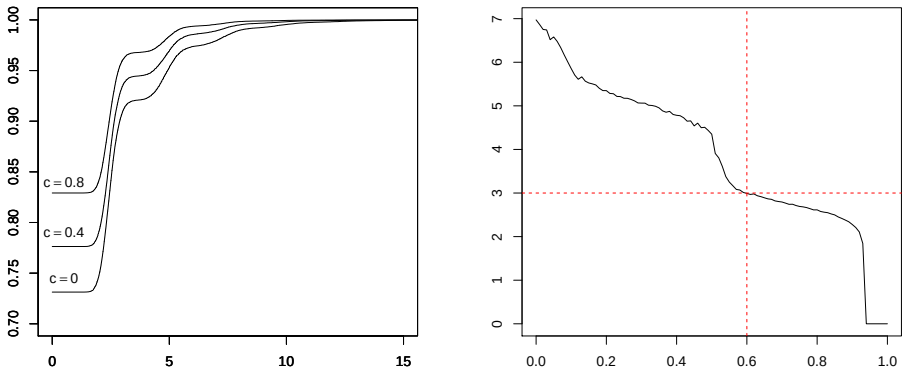

Figure 8.5: Left: Behaviour of the distribution function of $\widetilde{T}_{\alpha_c^0}$ for $c = 0, 0.4, 0.8$. Right: Behaviour of $x^{\widetilde{T}}_{\alpha_c^0, 0.9^{1/5}}$ depending on c, with $0 \leq c \leq 1$.

outbreaks in Bulgaria is less than 6.97 weeks, if vaccination is not applied (in our real data 97% of outbreaks have durations less than 6 weeks). In order to shorten the outbreak duration, from our study, we deduce that $c_{opt}(5, 0.9, 3) = 0.6$ (see right plot in Figure 8.5). Therefore, vaccinating a proportion of 60% of susceptible individuals in the target cohort, guarantees that in at least 90% of outbreaks of mumps in Bulgaria only primary and first-generation cases will be observed after the vaccination. Finally, we notice that $c_{opt}(5, 0.9, 0) = 0.94$, that is, to guarantee that at least the 90% of outbreaks do not spread after vaccination, the vaccination level should be 94% of susceptible individuals in the target cohort.

The parameters of the gamma distribution used to model the incubation period have been derived from knowledge of mumps transmission rather than estimated from data. Thus we have performed a sensitivity analysis of their influence on the optimal vaccination level. We have considered gamma distributions with mean and shape parameter r taking values in a grid (giving different probabilities for the incubation period belonging to range 12–25, which we denote as percentages of coverage), yielding the results shown in Table 8.1. One can observe that increasing the mean (holding r fixed) clearly increases the duration of the epidemic leading to higher values of c_{opt}. Moreover, increasing the shape parameter r (holding the mean fixed) decreases the variance of lifetimes and hence also the chance of long outbreak duration, leading to lower values of c_{opt}. The optimal vaccination level $c_{opt}(5, 0.9, 3)$ is fairly stable in the vicinity of the chosen values of 17 and 50 for the mean and shape parameter r, respectively.

Remark H.3 *From a computational point of view it is interesting to note that to find optimal vaccination policies, the simulation method based on* pruning*, described at the end of Section 8.3.1, has proved to be at least 17% faster than those in González et al. [48], [49], which are also simulation–based methods but work directly with the distribution of the extinction time. For the BHBP there exist other methods to approximate the distribution function of the time to extinction based on solving numerically an associated*

		Shape parameter r				
mean		30	40	50	60	70
16	% Coverage	92.2	95.3	97.1	98.8	98.8
	$c_{opt}(5, 0.9, 3)$	0.60	0.57	0.56	0.54	0.54
16.5	% Coverage	93	96.6	98.1	98.9	99.4
	$c_{opt}(5, 0.9, 3)$	0.63	0.60	0.58	0.56	0.55
17	% Coverage	94.9	95.5	98.7	99.3	99.6
	$c_{opt}(5, 0.9, 3)$	0.66	0.64	0.60	0.58	0.57
17.5	% Coverage	95.4	97.9	99	99.5	99.8
	$c_{opt}(5, 0.9, 3)$	0.70	0.67	0.65	0.62	0.61
18	% Coverage	95.3	97.8	99	99.5	99.8
	$c_{opt}(5, 0.9, 3)$	0.73	0.71	0.68	0.65	0.64

Table 8.1: Sensitivity analysis on the mean and shape parameter of the gamma incubation distribution

integral equation (see Martinez and Slavtchova-Bojkova [86], which includes comparison with simulation-based methods). Unlike the latter approach, the Monte-Carlo method proposed in Section 8.3.1 is easily extended to time-dependent vaccination processes. All the computations and simulations have been made with the statistical computing and graphics language and environment **R** *("GNU S", see [112]).*

8.5 Concluding comments

The coupled pruning technique for proving monotonicity and continuity properties of functions defined on CMJ branching processes depending on the vaccination function α is both simple and powerful. It is clear that the proofs generalise easily to more general branching processes, such as multitype CMJ branching processes, time-inhomogeneous branching processes and branching processes in a random environment. The function α does not have to represent vaccination. It could represent any control of disease propagation that has the effect of reducing either the number of susceptibles or the probability that a contacted susceptible becomes infected. However, for the coupled pruning technique to work it is necessary that, in the branching process setting, the control affects only the probability that a birth is aborted and not the intrinsic reproduction law of the branching process. Thus, for example, the method cannot be applied to density-dependent processes, such as population size dependent branching processes, if the density dependence relates to the size of the unvaccinated population rather than the total population size.

Given that the results in the Bulgarian mumps illustration are based on simulation alone, it may seem more appropriate to use an epidemic model rather than a branching process that approximates such a model. However, there are several advantages in using the simpler branching process formulation. First, branching process models can be fitted directly to the data more easily; in particular they do not require knowledge of the size of the population in which the outbreaks are occurring. Secondly, the coupled pruning

technique enables the monotonicity and continuity properties pertaining to vaccination functions to be proved easily. Thirdly, the coupled pruning technique yields an associated Monte–Carlo method for determining optimal vaccination processes. It is not immediately clear if and how the pruning argument can be extended to epidemic models in a useful way; this is a topic for future research.

The framework for optimal vaccination policies studied in Section 8.3.1 can be extended to include alternative formulations of optimal policies. For example, one may define a cost $c(\alpha)$ associated with each vaccination process $\alpha \in \mathcal{A}$ and then seek vaccination processes from a subset $\mathcal{A}^*$ of $\mathcal{A}$ which either (i) minimise $c(\alpha)$ subject to $\mu_\alpha^f \leq b$ or (ii) minimise μ_α^f subject to $c(\alpha) \leq c_0$, where c_0 is specified. Provided the cost function $c(\alpha)$ is suitably monotonic and continuous in α and $\mathcal{A}^*$ is totally ordered, Theorems H.1 and H.2 imply the existence of unique such optimal vaccination processes and it should be possible to extend the Monte-Carlo algorithm at the end of Section 8.3.1 to estimate the optimal vaccination processes. Optimal vaccination policies that permit vaccination costs to be taken into account are especially relevant in animal vaccination.

The results from this chapter are published by Ball, Gonzalez, Martinez and Slavtchova–Bojkova in [19].

Chapter 9

Total progeny of Crump-Mode-Jagers BP

9.1 Introduction

In an epidemic context, the total number of infected individuals in a population is a useful tool for public health authorities in order to determine the infection level of a disease. Clearly, the total number of individuals that are infected is a key measure of the impact of an epidemic on the population within which it is spreading. Further, from an inferential viewpoint, surveillance systems typically provide more reliable information on the total number of individuals infected than on the precise temporal pattern of spread of an epidemic, so statistical analysis is often based on total infection data. This chapter is concerned with the study of the total size of an outbreak for epidemic models of diseases which follow an SIR (Susceptible–Infectious–Recovered) scheme in a closed, homogenously mixing population or some of its extensions, for example an SEIR (Suscpetible–Exposed–Infectious–Recovered) scheme. When the population is homogeneously mixing and the number of infected individuals is small in relation to the total size of the susceptible population, it is well known that the number of infected individuals in such an epidemic may be well approximated by a single-type branching process, at least during its early stages (see, for example, Jagers [67], Chapter 3). This approximation has a long history going back to the pioneering works of Bartlett [24] and Kendall [73], and can be made mathematically precise by considering a sequence of epidemics, indexed by the population size, and showing convergence of the process of infected individuals to a branching process as the population size tends to infinity (see, for example, Ball and Donnelly [18], where such convergence of a very general epidemic model to a Crump–Mode–Jagers (CMJ) branching process - see Jagers [67] - is proved). Hence, 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. Throughout the chapter, we assume that Z is non-explosive, i.e., that $\mathrm{P}(Z(t) < \infty) = 1$ for any $t \in (0, \infty)$. Conditions which guarantee this property may be found in [67], Section 6.2.

A key tool in controlling the spread of an epidemic is vaccination and there have been numerous mathematical studies of the effect of vaccination on disease dynamics. The

majority of such studies using stochastic models have been concerned with the situation where a specified fraction of the population is vaccinated prior to an outbreak, though see Keeling and Rohani [72], Chapter 8, for examples of analysis of more general vaccination policies in a deterministic setting. Recently, Ball et al. [19] have developed a framework for analysing time–dependent vaccination policies for epidemics which are modelled by a CMJ branching process. More specifically, a vaccination process is described by a function $\alpha : [0, \infty) \to [0, 1]$, such that $\alpha(t)$ represents the proportion of the population which is immune at time t ($t \geq 0$). Thus, since the population is homogeneously mixing, the probability that a contact at time t is with a non-immune individual is $1 - \alpha(t)$. (Modelling an epidemic as a CMJ branching process implies implicitly that changes in the susceptible population owing to infection of individuals are ignored.) For perfect vaccines, i.e. ones which confer lifelong immunity immediately with probability one, $\alpha(t)$ is given by the proportion of the population that has been vaccinated (i.e. the vaccination coverage) by time t. For imperfect vaccines, the vaccination coverage 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_I, otherwise it has no effect), then $\alpha(t) = \varepsilon_I \widetilde{\alpha}(t)$, where $\widetilde{\alpha}(t)$ is the vaccination coverage at time t. Note that α is necessarily nondecreasing in t if the immunity conferred by vaccination does not wane.

Given a CMJ branching process Z and a vaccination process α, we denote by $Z_\alpha = \{Z_\alpha(t) : t \geq 0\}$ the vaccinated version of Z, in which each birth in Z is aborted independently, with probability $\alpha(t)$ if the birth time is at time t. Note that if a birth in Z is aborted in Z_α, then none of the descendents in Z of the aborted individual appear in Z_α. Hence, coupled realizations of Z and Z_α may be constructed by *pruning*, i.e. deleting individuals in Z and all of their descendants. In Ball et al. [19], such coupling was used to prove stochastic monotonicity and continuity properties, with respect to the vaccination process α, for functions defined on a CMJ branching process, first in a general context, i.e. for generic functions, and then specialized to the extinction time. However, these properties have not yet been explicitly obtained for the total progeny. Thus, in this chapter we establish explicitly these properties for the total number of infected individuals of the epidemic. To this end, we apply the general results given in the work of Ball et al. [19], since total progeny is monotonically decreasing with pruning. In Section 9.2, we deduce the monotonicity and continuity properties of the mean and quantiles of the total progeny. After that, in Section 9.3, we present a simulated example, showing how to obtain in practice optimal vaccination policies (based on the results given in the previous section) to control the spread of a disease. The example is motivated by an outbreak of avian influenza virus in humans that occurred in Indonesia in 2006.

We end the introduction by describing some notation that will be used in the sequel. Let $\mathcal{A}$ be the space of all functions $\alpha : [0, \infty) \to [0, 1]$. For any $c \in [0, 1]$ and any $t_0 \geq 0$, we define the function $\alpha_c^{t_0} \in \mathcal{A}$ by

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

which means that a proportion c of the population is vaccinated at time t_0. Thus, for example, α_c^0 denotes the constant function equal to c and α_0^0 denotes the constant function

equal to 0. Moreover, let $c_{\text{inf}} = \max(0, 1 - m^{-1})$, where m is the offspring mean for Z. Thus, if $m > 1$, then c_{inf} is the critical vaccination coverage, i.e. the minimum proportion of the population that should be vaccinated (at one single time) for the process to become critical, that is to assure the epidemic will go extinct with probability one. Note that the offspring mean of $Z_{\alpha^0_{c_{\text{inf}}}}$ is less than or equal to 1.

Also, for $t_0 \geq 0$ and $c \in [0, 1]$, let

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

Finally, for $\alpha, \alpha' \in \mathcal{A}$, write $\alpha \prec \alpha'$ if $\alpha(t) \leq \alpha'(t)$ for all $t \in [0, \infty)$ and let $\|\alpha - \alpha'\| = \sup_{t\in[0,\infty)} |\alpha(t) - \alpha'(t)|$.

9.2 Monotonicity and continuity properties

For a given vaccination strategy, $\alpha \in \mathcal{A}$, we denote by $N_{\alpha,z}(\infty)$ the total number of births of the process Z_α when $Z(0) = z$, with $z \geq 1$, that is the total number of infected individuals in an outbreak when the vaccination process is defined by α. This random variable is discrete, and in particular cases its probability distribution can be derived. For example, when the proportion of immune individuals in the population is constant with time, $N_{\alpha,z}(\infty)$ follows the Borel-Tanner distribution in some situations (see Farrrington et al. [41]). However, when a vaccination policy is time dependent, it is not easy to obtain the probability distribution of $N_{\alpha,z}(\infty)$ in a closed form.

Next we study monotonicity and continuity properties of the mean and quantile of the total number of infected individuals depending on the vaccination function α. To this end, since individuals infect independently of each other, we have that

$$N_{\alpha,z}(\infty) = N^{(1)}_{\alpha,1}(\infty) + N^{(2)}_{\alpha,1}(\infty) + \ldots + N^{(z)}_{\alpha,1}(\infty),$$

where $N^{(i)}_{\alpha,1}(\infty)$ $(i = 1, 2, \ldots, z)$ are independent random variables with the same distribution as $N_{\alpha,1}(\infty)$. Hence

$$\mathrm{E}[N_{\alpha,z}(\infty)] = z\mu^N_\alpha,$$

where μ^N_α denotes the expectation of $N_{\alpha,1}(\infty)$, i.e. the mean number of infected individuals when the outbreak starts with one infected individual and the vaccination process is defined by α. Therefore, to analyze the behaviour of $\mathrm{E}[N_{\alpha,z}(\infty)]$, for any z, it is sufficient to study μ^N_α. Applying Theorem 3.1 and an obvious extension of Theorem 3.2(b) in Ball et al. [19], we deduce the following properties of μ^N_α.

Theorem I.1

(a) If $\alpha, \alpha' \in \mathcal{A}$ satisfy $\alpha \prec \alpha'$, then $\mu^N_\alpha \geq \mu^N_{\alpha'}$.

(b) Fix $t_0 \geq 0$ and $c \in (c_{\text{inf}}, 1]$. Then, for each $\varepsilon > 0$, there exists $\eta = \eta(\varepsilon) > 0$ such that for all $\alpha, \alpha' \in \mathcal{A}(c, t_0)$ satisfying $\|\alpha - \alpha'\| \leq \eta$,

$$|\mu^N_\alpha - \mu^N_{\alpha'}| \leq \varepsilon. \tag{I.1}$$

Remark I.1

(a) Notice that, under the conditions of Theorem I.1, $\mu^N_{\alpha_c^{t_0}} < \infty$. *Indeed, it is easy to obtain that, almost surely,*

$$N_{\alpha_c^{t_0}}(\infty) \leq N(t_0) + \sum_{i=1}^{Z(t_0)} N^{(i)}_{\alpha_c^0,1}(\infty),$$

where $N(t_0)$ *represents the total number of new infections in* $(0, t_0)$. *Therefore,*

$$\mu^N_{\alpha_c^{t_0}} \leq \mathrm{E}[N(t_0)] + \mathrm{E}[Z(t_0)]\mu^N_{\alpha_c^0}.$$

The conditions which guarantee that the process is not explosive, imply that $\mathrm{E}[N(t_0)]$ *and* $\mathrm{E}[Z(t_0)]$ *are finite. Moreover,* $\mu^N_{\alpha_c^0}$ *is also finite since* $Z_{\alpha_c^0}$ *is a subcritical process.*

(b) If Z *is subcritical, so* $c_{\inf} = 0$, *then Theorem 3.2(b) in Ball et al. [19] implies that for each* $\varepsilon > 0$, *there exists* $\eta = \eta(\varepsilon) > 0$ *such that (I.1) holds for all* $\alpha, \alpha' \in \mathcal{A}$.

Notice that, in general, $\mathrm{P}(N_{\alpha,1}(\infty) \leq \mu^N_\alpha) \geq 0.5$, because of the skewness of the distribution of the total progeny of the vaccinated CMJ branching process. Hence, if the vaccination policy α is applied, more than half of the outbreaks would have total size less than the mean μ^N_α, which may be sufficient protection for the population as a whole if the infectious disease is not too harmful for individuals. On the other hand, when the infectious disease is highly detrimental, we would like to control with high probability the total number of infected individuals and consequently consider vaccination policies based on quantiles of the total size distribution. Thus, fix $\alpha \in \mathcal{A}$, and define, for $0 < p < 1$,

$$x^N_{\alpha,p} = \inf\{x : \mathrm{P}(N_{\alpha,z}(\infty) \leq x) \geq p\},$$

with the convention that $x^N_{\alpha,p} = \infty$ if $\mathrm{P}(N_{\alpha,z}(\infty) \leq x) < p$ for all $x \in [0, \infty)$. Thus $x^N_{\alpha,p}$ is the quantile of order p of the random variable $N_{\alpha,z}(\infty)$. Since this variable is not derived from $N_{\alpha,1}(\infty)$, then the next result about the monotonicity and continuity properties of $x^N_{\alpha,p}$, deduced from Theorem 3.4 in Ball et al. [19], depends on z, for any $z > 0$.

Theorem I.2 *Suppose that* $p \in (0, 1)$.

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

(b) Fix $t_0 \geq 0$ *and* $\alpha \in \mathcal{A}(c_{\inf}, t_0)$, *and let* $\{\alpha_n\}$ *be any sequence in* $\mathcal{A}$ *satisfying* $\alpha \prec \alpha_n$ *for all* n *and* $\lim_{n\to\infty} \|\alpha_n - \alpha\| = 0$. *Then* $\lim_{n\to\infty} x^N_{\alpha_n,p} = x^N_{\alpha,p}$.

Remark I.2

(a) Notice that $Z_{\alpha_{c_{\inf}}^{t_0}}$ *has offspring mean* m *until time* t_0, *and offspring mean* $m_{c_{\inf}} \leq 1$ *after time* t_0. *Thus, since* Z *is non-explosive, the total progeny of* $Z_{\alpha_{c_{\inf}}^{t_0}}$ *is finite almost surely, and therefore* $\mathrm{P}(N_{\alpha,z}(\infty) < \infty) = 1$ *and* $x^N_{\alpha,p} < \infty$, *for all* $\alpha \in \mathcal{A}(c_{\inf}, t_0)$ *and* $p \in (0, 1)$.

(b) Since $N_{\alpha,z}(\infty)$ is a discrete random variable for each α and z, then $x^N_{\alpha,p}$ is a step function depending on α.

Finally, from the above monotonicity and continuity properties of the mean and quantiles of $N_{\alpha,z}(\infty)$, and in the same way as it was described in Section 3.5 in Ball et al. [19], we propose how to choose optimal αs based on the total number of infected individuals. In particular, for fixed M, t_v and p_0, with $M \geq 0$, $0 \leq p_0 \leq 1$ and $0 \leq t_v \leq p_0^{-1}$, we define the function α_{M,t_v,p_0}, where, for $s \geq 0$,

$$\alpha_{M,t_v,p_0}(s) = \begin{cases} 0, & \text{if } s \leq M \\ p_0(s-M), & \text{if } M < s \leq M + t_v \\ t_v p_0, & \text{if } M + t_v < s. \end{cases} \tag{I.2}$$

This function 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. In practice, M and p_0 are usually known before vaccination begins, in which case the vaccination function α_{M,t_v,p_0} can be parameterized through t_v alone. Hence, for fixed M and p_0, let $\alpha_{t_v} = \alpha_{M,t_v,p_0}$ and $\mathcal{A}^* = \{\alpha_{t_v} : c_{\inf} p_0^{-1} \leq t_v \leq p_0^{-1}\}$. Since $\mathcal{A}^*$ is a subset of $\mathcal{A}(c_{\inf}, M + c_{\inf} p_0^{-1})$, then Theorems I.1 and I.2 ensure that, for each $b \geq 0$ and $p \in (0,1)$, optimal vaccination policies based on the mean and quantiles exist and are unique, provided that $\{\alpha \in \mathcal{A}^* : z\mu^N_{\alpha_{t_v}} \leq b\}$ and $\{\alpha \in \mathcal{A}^* : x^N_{\alpha_{t_v},p} \leq b\}$ are non-empty. Then, we denote by $\alpha_{t^N_{\text{opt},\mu,b}}$ and $\alpha_{t^N_{\text{opt},p,b}}$, the corresponding optimal policies based on the mean and quantiles, respectively, where

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

Notice that these optimal policies depend on M and p_0, which have been fixed previously. Moreover, $x^N_{\alpha_{t^N_{\text{opt},p,b}},p} \leq b$, though equality is not guaranteed since $N_{\alpha_{t^N_{\text{opt},p,b}},z}(\infty)$ is a discrete random variable. On the other hand, $z\mu^N_{t^N_{\text{opt},\mu,b}} = b$, if $t^N_{\text{opt},\mu,b} > c_{\inf} p_0^{-1}$.

9.3 Simulated example

To illustrate how to obtain optimal vaccination strategies based on the mean and quantiles of the total size of an outbreak, we present a simulation study which has been motivated by an outbreak of avian influenza in humans that occurred in Indonesia in 2006. The spread of this disease can be considered as an SEIR epidemic and therefore its early spread can be approximated by a CMJ branching process. In our simulations, we consider an offspring mean of 1.14, so the corresponding CMJ process is supercritical and hence a vaccination strategy (or some other mitigation measure) should be applied in order to control the outbreak. It is known (see Yang et al.[142]) that for the transmission of the avian influenza in humans, the latent period (the period elapsing between infection of an individual and the beginning of his/her infectious period) has a probable range of 3–7 days and the infectious period has a probable range of 5–13 days. So, in our

study we assume that the latent and infectious periods are independent random variables which follow gamma distributions with means 5 and 9, and shape parameters 23 and 19, respectively. Hence, approximately 95% of incubation periods are between 3 and 7 days and approximately 95% of infectious periods are between 5 and 13 days. Furthermore, we assume that during the infectious period, infections occur according to a homogeneous Poisson process, independently of the duration of incubation and infectious periods. Since the mean of the infectious period is 9 days and the offspring mean is 1.14, we assume that this Poisson process has rate $1.14/9 = 0.126667$. These kind of distributions are appropriate for latent and infectious periods, and for the number of infections made by a typical infective (see for example Daley and Gani [31], Farrington and Grant [40], Farrington et al. [41] or Mode and Sleeman [98]). In Yang et al. [142], the spread of avian influenza in humans is modelled using a households epidemic model (Ball et al. [21]) and the local (i.e. within–household) basic reproduction number R_0 is estimated to be 1.14. For homogeneously mixing epidemic models, R_0 is given by the offspring mean of the corresponding approximating CMJ branching process (Ball and Donnelly [18]). The definition of R_0 is more complicated for epidemic models with household structure (Pellis et al. [110]). Moreover, it is possible for the epidemic in the population at large to be subcritical when the local reproduction number is greater than one, and vice versa. Thus, although our choice of 1.14 for the offspring mean of the CMJ process used to model the early spread of the disease corresponds to the estimate of the local reproduction number in Yang et al. [142], it may well not reflect the true R_0 for a homogeneously mixing model of avian influenza in humans. Finally, all the simulations start with a single index patient.

Assuming the previous modelling and taking into account the kind of vaccination policies defined by ((I.2)), we seek an optimal vaccination strategy belonging to the set

$$\mathcal{A}^* = \{\alpha_{M,t_v,0.01} \in \mathcal{A} : M \in \mathbb{N} \cup \{0\},\ 13 \leq t_v \leq 100\},$$

where, for $s \geq 0$,

$$\alpha_{M,t_v,0.01}(s) = \begin{cases} 0, & \text{if } s \leq M \\ 0.01(s-M), & \text{if } M < s \leq M + t_v \\ 0.01t_v, & \text{if } M + t_v < s. \end{cases}$$

We recall that M represents the number of days until the vaccination process starts, 0.01 (1%) determines the proportion of individuals vaccinated per day during the vaccination process and t_v indicates the duration of the vaccination process (in days). Notice that 13 is the smallest value of t_v such that the vaccinated process becomes subcritical. On the other hand, when $t_v = 100$, all individuals are vaccinated during the vaccination process, minimizing the propagation of the virus.

The left plot in Figure 9.1 shows the behaviour of $\mu^N_{\alpha_{M,100,0.01}}$, for $M \in \{0, 1, \ldots, 21\}$, which has been estimated by using the Monte-Carlo simulation-method described in Section 3.5 in Ball et al. [19]. Specifically, we have simulated 10 000 processes and from them we have estimated $\mu^N_{\alpha_{M,t_v,0.01}}$, for each $M \in \{0, 1, \ldots, 21\}$ and $t_v \in \{13 + k : k = 0, 1, \ldots, 87\}$. Notice that, by Theorem I.1(a), when M increases the mean of the total number of infected individuals also increases. We observe that for M greater than 11 (vertical dotted line in the plot), the mean of the total number of new infected individuals in

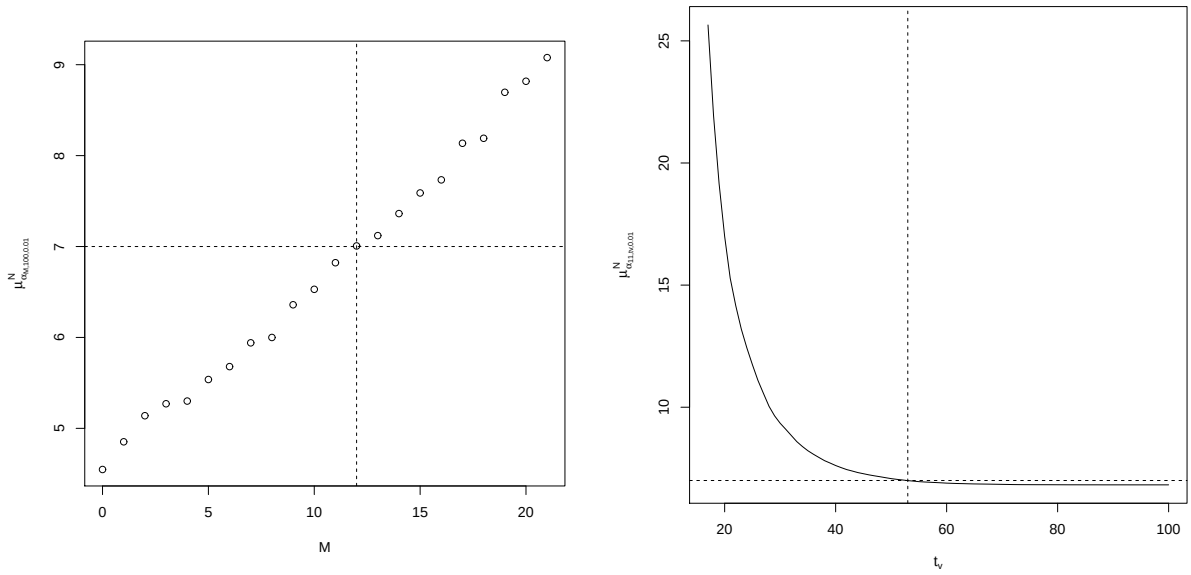

Figure 9.1: Left: Behaviour of estimated value of $\mu^N_{\alpha_{M,100,0.01}}$ depending on M. Right: Behaviour of estimated value of $\mu^N_{\alpha_{11,t_v,0.01}}$ depending on t_v.

M	0	1	2	3	4	5	6	7	8	9	10	11
$t^N_{opt,M,\mu,7}$	29	31	32	33	33	35	36	38	38	42	45	53

Table 9.1: Estimated optimal duration of vaccination depending on M.

an outbreak started with one infected individual is greater than 7 (horizontal dotted line in the plot), the size of the outbreak detected in Indonesia (see Yang et al. [142]). Hence, for each $M \in \{0, 1, \ldots, 11\}$, the optimal duration of the vaccination based on the mean, $t^N_{\text{opt},M,\mu,7}$, is given by

$$t^N_{\text{opt},M,\mu,7} = \inf\{t_v : \ \mu^N_{\alpha_{M,t_v,0.01}} \leq 7\}.$$

Table 9.1 shows the estimated optimal duration of vaccination depending on the number of days until the vaccination process starts. One can observe that these optimal durations increase when M increases.

Now, we focus our attention on M equal to 11 (the most unfavourable situation). The right plot in Figure 9.1 shows the behavior of the estimates of $\mu^N_{11,t_v,0.01}$, which decreases in a continuous way when t_v increases, by Theorem I.1. We find that the optimal duration of vaccination, again to guarantee a mean number of infected individuals no greater than 7, is 53 days (which means that at the end of the vaccination process, we have vaccinated 53% of susceptible individuals), so vaccination ceases 64 days (more than two months) after the start of an outbreak. The left plot in Figure 9.2 shows the distribution of the total number of infected individuals in the outbreak after applying this optimal vaccination procedure. Obviously, although the mean of this distribution is 7 (dotted line in the plot), there exists

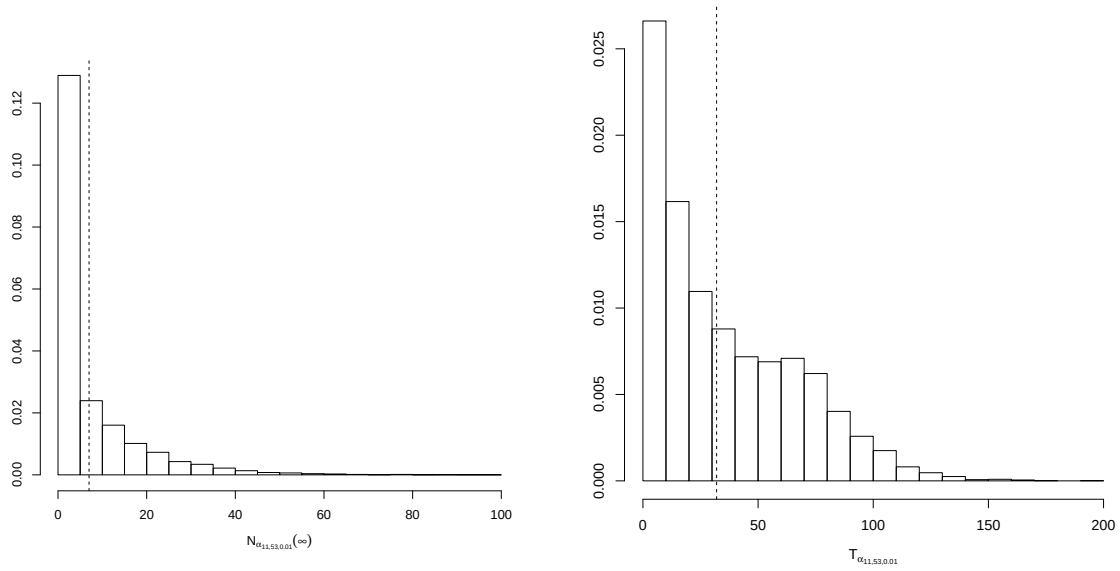

Figure 9.2: Left: Histogram of simulated total number of new infected individuals for $M = 11$ and $t_v = 53$. Right: Histogram of simulated time to extinction for $M = 11$ and $t_v = 53$.

a positive probability that more than 7 individuals are infected by the virus, which is less than 0.5, because of the skewness of the distribution. Indeed, $x^N_{\alpha_{11,53,0.01},0.703}$ is estimated by 7, that is, vaccinating 53% of susceptible individuals guarantees that at least 70.3% of new outbreaks infect no more than 7 individuals. Table 9.2 quantifies this probability as well as the probabilities of being no greater than other upper bounds. The greater that probability is, the greater will be the total number of infected individuals. Hence, when the vaccination policy $\alpha_{11,53,0.01}$ is applied, more than 90% of new outbreaks infect no more than 25 individuals. Moreover, the right plot in Figure 9.2 shows the distribution of the time to extinction of outbreaks started with one infected individual when one applies this policy. We estimate that 55.7% of the outbreaks become extinct before 32 days (dotted line in the plot), the observed value for the outbreak detected in Indonesia (see Yang et al.[142]).

For fixed $p = 0.90$, a high probability, $x^N_{\alpha_{11,t_v},0.01,0.90}$ decreases as a step function in t_v, according to Theorem I.2. The left plot in Figure 9.3 shows this behavior. Finally, notice that, although ultimately all susceptible individuals are vaccinated, at least 10% of new outbreaks infect more than 20 individuals, since this particular vaccination strategy takes a time (100 days) to be completely applied (in general, because $M > 0$ and $p_0 \neq 1$). Moreover, since $t^N_{opt,0.90,20}$ is estimated by 64, we deduce that the optimal vaccination coverage is 64%. The same behaviour is found for $p = 0.95$, where $t^N_{\text{opt},0.95,29}$ is estimated by 55, see right plot in Figure 9.3.

Remark I.3 *For the computer simulations, we used the language and environment for statistical computing and graphics* **R** *("GNU S") (see [112]).*

The results from this chapter are published by Ball, Gonzalez, Martinez and Slavtchova–

x	7	15	25	50	75	100
$\mathrm{P}(N_{\alpha_{11,53,0.01}}(\infty) \leq x)$	0.703	0.845	0.932	0.992	0.998	1

Table 9.2: Estimated probabilities of the total number of infected individuals, after applying optimal vaccination policy $\alpha_{11,53,0.01}$.

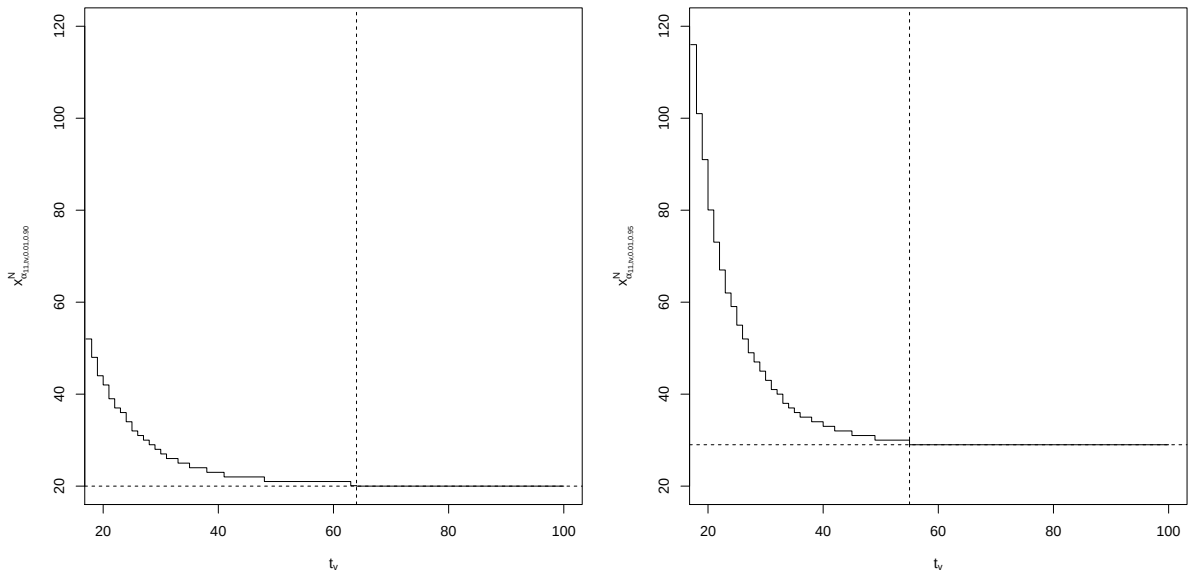

Figure 9.3: Left: Behaviour of estimated value of $x^N_{\alpha_{11,t_v,0.01},0.90}$ depending on t_v. Right: Behaviour of estimated value of $x^N_{\alpha_{11,t_v,0.01},0.95}$ depending on t_v.

Bojkova in [20].

Part III

BP in cancer modelling

Chapter 10

Two–type decomposable branching processes

10.1 Introduction

This chapter is concerned with applications of branching models in different medical, biological and environmental contexts where we find a general pattern of populations that, due to a small reproductive ratio of the individuals/cells, will extinct after some time, but as a result of a random occurrence of mutations this trend could be changed dramatically. Such populations are, for example, the viruses which may become resistant after antibiotics treatment, some insects populations after hybridization and others. Our leading example will be the appearance of cancer cells after chemotherapy and we will now be interested in the most basic question regarding the evolutionary dynamics of cancer cells: how long does it take for a population to generate a single cell that will start a pathway with indefinite survival? Or in other words what is the probability of success or failure of the anti-cancer therapy? A typical situation of such populations is observed after chemotherapy (see e. g. Iwasa et al. [63], [64] and Nowak et al. [100] together with references therein). The chemotherapy reduces the capacity of division of the cancer cells, which should lead to the destruction of tumors. However, sometimes mutations in the cells provide resistance to the therapy. This new type of cells has a higher reproduction and can avoid extinction.

Having in mind all the examples given above, it is of outstanding importance to have good estimates of the probability of escaping extinction and related aspects, such as the distribution of number of mutations which implies escaping extinction, the distribution of waiting times until escape. It was done in discrete–time setting by Serra and Haccou [117] and Serra [116] using discrete–time Galton–Watson branching processes (GWBP) and as pointed out there mathematically discrete–time models are much easier to handle than their continuous counterparts. In this chapter we will generalize and expand some of these estimates in continuous–time setting using age–dependent branching processes. Although, that at first glance mathematically this seems a methodological step, it turns out to be not that easy to tackle such problems in a general setting.

Let us shortly remind that branching processes have been intensively studied during the last decades. Classical references are the books of Harris [60], Athreya and Ney

[12], Jagers [67], and Mode [97]. For recent books, with emphasis on applications, see Axelrod and Kimmel [74], Haccou et al. [52] and also Durrett [35], especially for branching modeling in cancer. For a nice example of how branching processes can be used to solve important problems in biology and medicine, the reader is referred to the papers of Iwasa et al. [63], [64]. The close–related research related to the waiting times to extinction are some results of the author reviewed in the paper [124].

This chapter is organized as follows: Section 10.2 introduces the branching process model with two types of cells in continuous time. Section 10.3 contains the main results and proofs. In Theorem J.1 we prove the basic integral equations for probability generating function (p.g.f.) of the process itself. In Theorem J.2 of Subsection 10.3.2 we obtain the p.g.f. of both the number of mutations occurred up to time t and the number of mutations to the escape type cells in the whole process. In the reminder of this section we studied the distribution of the waiting time T, which is actually the first moment in time when a mutation cell will start the lineage that will never go extinct (Theorem J.3). More precisely we obtain its distribution, which is actually degenerate at infinity and the conditional expectation of T, conditioned of being finite. As a consequence of the results in Theorem J.3 we show how one can obtain the probability of immediate escape from extinction in terms of modified hazard function of the random variable T, conditioned in addition on non–extinction of the process of type 1 cells, which have subcritical reproduction. Finally, we end with some concluding remarks and topics for further research.

10.2 Formulation of the model

We will first outline an age–dependent branching process with one type of cells. Consider a cell proliferation process starting at time 0 with a single progenitor of type 1 of age 0 whose life-length τ has distribution $G(t) = P(\tau \leq t)$, $G(0^+) = 0$, i.e. $Z(0) = 1$. With probability p_k, $k \geq 0$ it produces at the end of its life k similar cells of age 0, which reproduce independently with the same distribution of the life–length τ and reproduction distribution $\{p_k, k \geq 0\}$, $\sum_{k=0}^{\infty} p_k = 1$. Provided that there is at least one offspring, the death–and–reproduction process is repeated, and continues as long as individuals/cells exist. The single–type process $\{Z(t), t \geq 0\}$ or the so–called Bellman–Harris branching process (BHBP) together with proper biological applications is studied by Jagers [67] and more theoretically by Athreya and Ney [12].

Now we present a two–type decomposable age–dependent branching model (also known as BHBP with two types of cells) $\{Z^0(t), Z^1(t), t \geq 0\}$, where $\{Z^0(t), t \geq 0\}$ and $\{Z^1(t), t \geq 0\}$ denote the number of cells of type 0 and type 1 at time t respectively. Suppose that cells of type 1 are subcritical, i.e. have reproduction mean m_1, $0 < m_1 < 1$, and that each one of their descendants can mutate at birth, independently of the others, to type 0 cells with probability u, $0 < u < 1$. Individuals/cells of type 0 are supercritical, i.e. have reproduction mean m_0, $1 < m_0 < \infty$, and there is no backward mutation. Let us mention here that if no mutation appear ($u = 0$) then the process will be described by two independent classical single–type BHBP.

By $G_i(t) = P(\tau_i \leq t)$, $G_i(0^+) = 0$, $i = 0, 1$ we denote the distribution of the life–

lengths τ_i of the cells of type 0 and type 1 and by ν_i, $i = 0, 1$ the offspring of type i cells, $i = 0, 1$.

Let us introduce the following notations:

$F_i(t; s_0, s_1) = \mathbb{E}(s_0^{Z^0(t)} s_1^{Z^1(t)} | Z^i(0) = 1, Z^j(0) = 0, j \neq i)$, for $i = 0, 1$,

$\mathbf{F}(t; \mathbf{s}) = (F_0(t; \mathbf{s}), F_1(t; \mathbf{s}))$, $\mathbf{s} = (s_0, s_1)$.

Unless stated otherwise, we assume that the process starts with just one cell of type 1, i.e. $Z^0(0) = 0$ and $Z^1(0) = 1$. The p.g.f. of the offspring ν_i of type i cells will be denoted by $f_i(s)$, $i = 0, 1$.

Similar results of the discrete version of the two-type branching process, i.e. GWBP are obtained by Serra [116] and Haccou and Serra [117], where the distribution of the waiting time to produce a cell that will escape extinction, is studied.

10.3 Main results

10.3.1 Basic integral equation

In the following theorem we will obtain the basic integral equation for the p.g.f. of the age–dependent branching process defined in Section 10.2.

Theorem J.1 *The p.g.f.* $\mathbf{F}(t; s_0, s_1)$ *satisfies the following integral equations*

$$\text{(J.1)} \quad F_1(t; s_0, s_1) = s_1(1 - G_1(t)) + \int_0^t f_1(uF_0(t-y; s_0) + (1-u)F_1(t-y; s_0, s_1))dG_1(y),$$

and

$$\text{(J.2)} \qquad F_0(t; s_0, s_1) \equiv F_0(t; s_0) = s_0(1 - G_0(t)) + \int_0^t f_0(F_0(t-y; s_0))dG_0(y),$$

where

$$F_i(0; s_0, s_1) = s_i, |s_i| \leq 1, i = 0, 1.$$

Proof. We start with a derivation of the basic integral equation ((J.1)). A decomposition of the sample space Ω in accordance with the life–length τ_1 and number ν_1 of offspring of the initial cell of type 1 suggests the relation:

$$
\begin{aligned}
&F_1(t;s_0,s_1) = \mathbb{E}\left(\mathbb{E}(s_0^{Z^0(t)}s_1^{Z^1(t)}|Z^1(0)=1,Z^0(0)=0,\{\tau_1,\nu_1\})\right)\\
&= s_1(1-G_1(t))\\
&+\int_0^t dG_1(y)\sum_{j=0}^{\infty}p_{1j}\sum_{k=0}^{j}\binom{j}{k}\mathbb{E}(s_0^{Z^0(t-y)}u^k s_1^{Z^1(t-y)}(1-u)^{j-k}|Z^0(0)=k,Z^1(0)=j-k)\\
&= s_1(1-G_1(t))\\
&+\int_0^t dG_1(y)\sum_{j=0}^{\infty}p_{1j}\sum_{k=0}^{j}\binom{j}{k}u^k(1-u)^{j-k}(\mathbb{E}(s_0^{Z^0(t-y)}|Z^0(0)=1,Z^1(0)=0))^k\times\\
&(\mathbb{E}(s_0^{Z^0(t-y)}s_1^{Z^1(t-y)}|Z^0(0)=0,Z^1(0)=1))^{j-k}\\
&= s_1(1-G_1(t))+\int_0^t f_1(uF_0(t-y;s_0)+(1-u)F_1(t-y;s_0,s_1))dG_1(y),
\end{aligned}
$$

where $\{p_{1k}, k\geq 0\}$ is the distribution of the offspring of type 1 cells. Equation ((J.2)) is derived in a similar way. Notice that this equation is the integral equation obtained for the classical BHBP. ♢

Note that when G_1 is the unit step function

$$G_1(t) = \begin{cases} 0, & \text{for } t<1,\\ 1, & \text{for } t\geq 1,\end{cases}$$

then ((J.1)) reduces to a functional iteration formula for $F(n;s_0,s_1)$ obtained by Serra in [116]; while if

$$G_1(t) = \begin{cases} 0, & \text{for } t<0,\\ 1-e^{-\lambda t}, & \text{for } t\geq 0,\end{cases}$$

then we have a two–type Markov branching process allowing mutations.

Let us mention here that the result in continuous time is rather different from that of Serra [116] using GWBP, where actually the p.g.f. of the process is reduced to the single–type GWBP and after that is used significantly to study the distribution of the number of mutations. On the other hand, here we would like to point out that using equations ((J.1)) and ((J.2)) one can study the asymptotic properties of the mean, variance and higher moments of types 0 and 1 cells when $t\to\infty$, which is left for a later stage.

10.3.2 Mutants and probability of extinction

Unless mutations occur, the process of interest will be a single–type subcritical BHBP and it is the appearance of mutants that makes the study of such populations an interesting task. That is why it is important to study the total number of mutations that occur in the whole process. This random quantity will play a crucial role in determining the extinction probability of the process.

Consider the random variable (r.v.) $I(t)$, $t\geq 0$, being the total number of mutants produced until time t (inclusive), and let I be the r.v. that represents the number of

mutants in the whole process. By mutant we mean a cell of type 0, whose mother is of type 1. It is obvious that the sequence of r.v. $I(t), t \geq 0$, converges pointwise to the r. v. I. In our next theorem, we use this convergence to establish a functional and integral equation for the p.g.f. of I, denoted by $h_I(s)$ and of $I(t)$, denoted by $h_{I(t)}(s)$, respectively.

Theorem J.2 *The p.g.f. $h_I(s)$ of I and $h_{I(t)}(s)$ of $I(t)$ satisfy the equations*

$$h_I(s) = f_1(us + (1-u)h_I(s)), \tag{J.3}$$

$$h_{I(t)}(s) = 1 - G_1(t) + \int_0^t f_1(us + (1-u)h_{I(t-y)}(s))dG_1(y), \tag{J.4}$$

for all $s \in [0,1]$.

Proof. First we establish a recursive relation for the p.g.f. of the r.v. $I(t), t \geq 0$. We will use again a decomposition of the sample space Ω in accordance with the life–length τ_1 and the number of offspring ν_1 of the initial cell of type 1. It is clear that $I(t) = 0$, if $\tau_1 > t$ with probability $1 - G_1(t)$, and $I(t) = \nu_{10} + \sum_{i=1}^{\nu_1 - \nu_{10}} I(t - \tau_1)$, when $\tau_1 \leq t$, where $\nu_{10} \in Bi(\nu_1, u)$ is the number of mutations between the descendants and $\nu_1 - \nu_{10}$ is the number of type 1 cells, produced by the initial cell. Therefore

$$\begin{aligned}
&\mathbb{E}(s^{I(t)}|Z^1(0) = 1, Z^0(0) = 0) \\
&= (1 - G_1(t))s^0 + \int_0^t dG_1(y)\mathbb{E}\left(s^{\nu_{10} + \sum_{i=0}^{\nu_1 - \nu_{10}} I_i(t-y)}\right) \\
&= 1 - G_1(t) + \int_0^t dG_1(y)\mathbb{E}\left(s^{\nu_{10}} \times s^{\sum_{i=0}^{\nu_1 - \nu_{10}} I_i(t-y)}\right) \\
&= 1 - G_1(t) + \int_0^t dG_1(y)\mathbb{E}\left[\mathbb{E}\left(s^{\nu_{10}} \times s^{\sum_{i=0}^{\nu_1 - \nu_{10}} I_i(t-y)}\right)|(\nu_1, \nu_{10})\right] \\
&= 1 - G_1(t) + \int_0^t \left[\sum_{j=0}^{\infty} p_{1j} \sum_{k=0}^{j} \binom{j}{k} u^k (1-u)^{j-k} s^k \times \mathbb{E}s^{\sum_{i=0}^{j-k} I_i(t-y)}\right] dG_1(y) \\
&= 1 - G_1(t) + \int_0^t \left[\sum_{j=0}^{\infty} p_{1j} \sum_{k=0}^{j} \binom{j}{k} u^k (1-u)^{j-k} s^k \times (h_{I(t-y)}(s))^{j-k}\right] dG_1(y) \\
&= 1 - G_1(t) + \int_0^t f_1(us + (1-u)h_{I(t-y)}(s))dG_1(y),
\end{aligned}$$

where $I_i(t)$ are independent identically distributed copies of $I(t)$ and $h_{I(0)}(s) = 1$. After that, using the techniques of embedded generation process (see Athreya and Ney, p. 141 [12]) we obtain that the result of the number of mutations in the whole process proved by Serra [116] for Galton–Watson branching processes remains true for age–dependent branching processes. ♢

We now proceed to determine the probability of extinction. Using the notation

$$q_0 = \mathbf{P}[Z^0(t) = Z^1(t) = 0 \text{ for some } t > 0 | Z^0(0) = 1, Z^1(0) = 0],$$

$$q_1 = \mathbf{P}[Z^0(t) = Z^1(t) = 0 \text{ for some } t > 0 | Z^0(0) = 0, Z^1(0) = 1],$$

it follows, from the classical result on the extinction of branching processes, that q_0 is the smallest root of the equation $q_0 = f_0(q_0)$ in the interval $[0, 1]$. To determine q_1, notice that extinction of the process occurs if and only if all the supercritical single–type BHBP starting from the mutants die out, since $m_1 < 1$. Therefore, since there are I such processes, we have

$$q_1 = \mathbf{E}[q_0^I] = h_I(q_0).$$

Then, we deduce that $q_1 < 1$, since $m_0 > 1$ and $q_0 < 1$. Let us remind that assuming small mutation rate u, Iwasa et al. [63], [64] provided approximations for particular reproduction laws, namely for Poisson and geometric distributions. Their results extend to even more complex scheme of mutations leading to branching processes with more than two types of individuals.

10.3.3 Time to escape extinction

Now, we consider the r. v. T, which represents the time to escape extinction, i.e. the first time in which a successful mutant is produced. By successful mutant we mean a mutant that is able to start a single–type BHBP that allows indefinite survival. This variable takes values in the set $(0, +\infty]$, with $T = \infty$, if no successful mutant is produced.

Theorem J.3 *The distribution of T has the following properties:*
(i) $\mathbb{P}(T > t) = h_{I(t)}(q_0) \equiv Q_t$, *for* $t > 0$,
(ii) $\mathbb{P}(T = \infty) = q_1$,
(iii) $\mathbb{E}(T | T < \infty) = \dfrac{1}{1 - q_1} \displaystyle\int_0^\infty [h_{I(t)}(q_0) - q_1] dt$,
where Q_t are defined by

$$Q_t = 1 - G_1(t) + \int_0^t f_1(uq_0 + (1 - u)Q_{t-y}) dG_1(y)$$

with $Q_0 = 1$.

Proof. To prove (i), observe that $T > t$ means that all mutants that occurred up to time t were unsuccessful. Therefore,

$$\mathbb{P}(T > t) = \mathbb{E}(q_0^{I(t)}) = h_{I(t)}(q_0).$$

To prove (ii), observe that $(T > t)_{t\geq 0} \downarrow (T = \infty)$ and it implies

$$\mathbb{P}(T > t)_{t\geq 0} \downarrow \mathbb{P}(T = \infty).$$

Then from (i)

$$\lim_{t\to\infty} \mathbb{P}(T > t) = \lim_{t\to\infty} h_{I(t)}(q_0)$$

and as $I(t)$ converges pointwise to I, it follows

$$\mathbb{P}(T = \infty) = \lim_{t\to\infty} h_{I(t)}(q_0) = h_I(q_0) = q_1.$$

For proving (iii) observe that $T > 0$ and, therefore,

$$\begin{aligned}
\mathbb{E}(T|T < \infty) &= \int_0^\infty (1 - \mathbb{P}(T \leq t|T < \infty))dt \\
&= \int_0^\infty (1 - \frac{\mathbb{P}(T \leq t, T < \infty)}{1 - q_1})dt \\
&= \frac{1}{1 - q_1} \int_0^\infty (1 - q_1 - \mathbb{P}(T \leq t))dt \\
&= \frac{1}{1 - q_1} \int_0^\infty (\mathbb{P}(T > t) - q_1)dt \\
&= \frac{1}{1 - q_1} \int_0^\infty (h_{I(t)}(q_0) - q_1)dt,
\end{aligned}$$

with $h_{I(t)}(s)$ defined by equation ((J.4)). ♢

10.3.4 Immediate risk of escape

Another natural characterization of the appearance of a successful mutant is the probability of producing a successful mutant in a very short time interval dt after time t, given that it has not been produced yet, called immediate risk of escape extinction. We will show in this subsection how one can compute this probability theoretically using the results of Theorem J.3.

In general one could use the hazard function of the variable T, defined by $\mathbb{P}(T \in (t, t + dt)|T > t)$, but in this case we need to modify this function, as it is done in discrete–time setting (see Serra and Haccou [117]). It is due to the fact that the r. v. T has a defective distribution ($T = \infty$ when no successful mutant is produced) and in fact, if there are no subcritical individuals (i.e. of type 1) alive at time t, the probability of producing a successful mutant immediately after this moment is zero. That is why we will use the following modification of the standard hazard function:

(J.5) $$g(t)dt = \mathbb{P}(T \in (t, t + dt|T > t, Z^1(t) > 0)).$$

We have

$$\begin{aligned}
g(t)dt &= \frac{\mathbb{P}(T \in (t, t + dt))}{\mathbb{P}(T > t, Z^1(t) > 0)} \\
&= \frac{\mathbb{P}(T \in (t, t + dt))}{\mathbb{P}(T > t) - \mathbb{P}(T > t, Z^1(t) = 0)}.
\end{aligned}$$

The probabilities $\mathbb{P}(T > t)$ and $\mathbb{P}(T \in (t, t + dt))$ are computed using Theorem J.3. The second term in the denominator satisfies the following recursive formula:

$$\begin{aligned}
&\mathbb{P}(T > t, Z^1(t) = 0) = \mathbb{P}(T > t, Z^1(t) = 0|\tau_1 < t)\mathbb{P}(\tau_1 < t) \\
&+ \mathbb{P}(T > t, Z^1(t) = 0|\tau_1 \geq t)\mathbb{P}(\tau_1 \geq t) \\
&= \int_0^t \mathbb{P}(T > t, Z^1(t) = 0|\tau_1 = y) dG_1(y) \\
&= \int_0^t \sum_{j=0}^{\infty} p_{1j} \sum_{k=0}^{j} \binom{j}{k} (uq_0)^k \left((1-u)\mathbb{P}(T > t, Z^1(t) = 0)\right)^{j-k} dG_1(y) \\
&= \int_0^t f_1(uq_0 + (1-u)\mathbb{P}(T > t - y, Z^1(t - y) = 0)) dG_1(y),
\end{aligned}$$

using that τ_1 is the life–time and $\{p_{1k}, k \geq 0\}$ is the distribution of the offspring of the initial cell of type 1 and clearly the second conditional probability term is equal to 0.

Let us remind here that we receive the similar recursive formula as that established by Serra and Haccou [117].

Indeed, from

$$\mathbb{P}(T > t, Z^1(t) = 0) = \int_0^t f_1(uq_0 + (1-u)\mathbb{P}(T > t - y, Z^1(t - y) = 0)) dG_1(y) \tag{J.6}$$

when

$$G_1(t) = \begin{cases} 0, & \text{for } t < 1, \\ 1, & \text{for } t \geq 1, \end{cases}$$

we obtain that

$$\mathbb{P}(T > n, Z^1(n) = 0) = f_1(uq_0 + (1-u)\mathbb{P}(T > n - 1, Z^1(n - 1) = 0)), \quad n \geq 1,$$

which is exactly the result in Serra and Haccou [117].

So, the modified hazard function is given by

$$\begin{aligned}
g(t)dt &= \frac{\mathbb{P}(T \in (t, t + dt))}{\mathbb{P}(T > t) - \mathbb{P}(T > t, Z^1(t) = 0)} \\
&= \frac{Q_t' dt}{Q_t - \mathbb{P}(T > t, Z^1(t) = 0)}
\end{aligned}$$

where $\mathbb{P}(T > t, Z^1(t) = 0)$ satisfies equation ((J.6)).

10.4 Concluding remarks

First, we would like to conclude that this study is the first step towards the expanding of the theory and methods using continuous–time counterparts of the discrete–time GWBP for different schemes leading to mutations. In the context of cancer dynamics, resistance to the anti–cancer therapy and the possible appearance of metastasis we are tackling the

problems of the distribution of the first moment of the occurrence of "successful" mutant together with the growth of the population of the mutant cells. Let us mention here that once the results are proved for models with one type of mutation, they could be extended to more than one type and different mutation schemes, including backward and/or forward mutations. Moreover, the branching models with continuous–time are more realistic and reveal more adequately and accurately the behavior of cell populations with overlapping generations.

Secondly, we found the analytical decisions in terms of p.g.f. of these r.v.s, which could be used subsequently to derive their moments and corresponding limit theorems for the BHBP driving the development of the real process, which might be considered per se as an innovation in application of branching theory. In this connection, the following questions for further research could be pointed out: to study the distribution of the waiting time to attain certain levels of the branching processes in continuous–time setting and to obtain limiting results for its distribution.

Thirdly, we obtain also a theoretical formulae for immediate risk of avoiding extinction that could be used later on for the comparison of the behavior of the modified hazard function for different offspring distributions.

Finally, the results proved generalize the similar ones obtained by Serra [116], Serra and Haccou [117] and those for the exponential models of growth developed by Iwasa et al. [63], [64] and Durrett [35], as well.

The results from this chapter are published by Slavtchova–Bojkova in [125].

Chapter 11

Branching processes in continuous time as models of mutations: computational approaches and algorithms

11.1 Introduction

The motivation for this study comes from the occurrence of mutant type cells after chemotherapy treatment of cancer and we will now be tackling some basic questions regarding the evolutionary dynamics of cancer cells using branching processes theory. In a cancer research context, the distribution of both - the waiting time of the first mutation that founds a family line that does not die out and the time for attaining high level of the mutation type cell population, are of clinical importance since the extent of resistance determines the choice of the therapy and patient diagnosis.

We are modeling a situation, where after local eradication of cancer in a given organism and application of proper therapy, there are cured cells, called type 1 cells, which due to the applied treatment have a reduced capacity for division. In this sense, if the treatment is successful, the applied therapy will lead to the destruction of the tumour. However, during the reproduction phase of the treated cells, a mutation could appear. That results in the appearance of new type of cells, called type 0 cells. The type 0 cells differ from the initial type 1 cells, mainly by their high reproduction rate, which implies they are resistant to the applied therapy. Moreover, what is essential here, is that some of the mutants, called "successful" mutants or cells of escape type, may start a lineage that could avoid extinction. The two-type branching process model is a natural candidate for mathematical model of this real world situation because of the basic pattern of independent cell evolution, consisting of birth, life, reproduction and death. The process starts with one or more cells of type 1 with low capacity for division and, with certain small probability, it is possible that these cells could mutate and lead to the appearance of type 0 cells. Let us mention also that cells of type 0 could not produce cells of type 1, so the resulting branching process is reducible. In addition, it is worth noticing that if a mutation does not occur, then there will be only one type of cells in the organism, which

correspond to the single-type branching process model. On the other hand, every mutant cell of type 0 starts an independent branching process with high reproduction rate of cells.

The use of a branching process model in continuous time is basically motivated by the studies which have shown that the life time of a cell is not deterministic but random by nature (see Freise et al.[44], Krzyzanski et al.[80]). Moreover, different types of cells have different life spans and they could depend on external factors like nutrition or stress in the environment (see Lodish et al. [84]). This means that modeling the cellular life time as a continuous random variable is a more suitable approach. That is why we consider the two-type decomposable branching process as a model in which every cell lives independently, has a continuously distributed life time, specific for each type, and at the end of its life it reproduces independently of the life length or dies. This model is known in the branching processes literature as a decomposable two-type Bellman–Harris branching process (BHBP) or age-dependent BP, meaning that the probability that a cell living at time t dies in the interval $(t, t + dt)$ is, in general, a non-constant function of t.

Branching processes have been intensively studied during the last decades. Classical references are the books of Harris [60], Athreya and Ney [12], Jagers [67], and Mode [96]. For recent books, with emphasis on biological applications, see Kimmel and Axelrod [74], Haccou et al. [52] and also Durrett [35], especially for branching modeling in cancer. For a nice example of how branching processes can be used to solve important problems in biology and medicine, the reader is referred to the papers of Iwasa et al. [63], [64].

This chapter is organized as follows: Section 11.2 introduces the branching process model with two types of cells in continuous time and the basic integral equations for probability generating function (p.g.f.) of the process itself and of both the number of mutations occurred up to time t and the number of mutations to the escape type cells in the whole process, obtained by Slavtchova–Bojkova [125]. The aim of the next Section 11.3 is to prove an analogue of the classical limit result of Kesten and Stigum for the continuous time counterpart of the two-type Galton–Watson BP revealing the limit behaviour of the mutant cell population and characterizing its limit random variable as well. This result is also the first step towards analysis of the probability of attaining high levels of the same cellular population. In the remainder of this section we studied the distribution of the event that jointly the first "successful" mutant does not appear and no cells of type 1 exist at time t and an integral equation is obtained (Theorem K.5).

Another interesting and new result in Section 11.4 is the new algorithm developed for the numerical approximation of the distribution of waiting time to the appearance of the "successful" mutant. It is important that in comparison with the non-decomposable branching processes here the integral equations obtained are not of renewal type, making the task rather different from the existing methodologies for finding solutions of such equations. The final goal is to investigate the behaviour of the hazard function for the waiting time to appearance of the first "successful" mutant. What is surprising in continuous time is that the hazard function depends strongly on the chosen type of the life length distribution and it could be very simple (as in the case of exponentially distributed life length) or much more complex (as in the case of trimmed normal distribution). That is why the use of BHBP, where life length is continuous random variable, gives us opportunity to investigate much more complex hazard functions than the one in Galton–Watson BP. The numerical approach for calculating the distribution of the waiting time until "successful"

mutant arrives and the associated hazard function is suitable for a wide range of different life time distributions, including smoothed empirical distributions. In Section 11.5 we presented two examples illustrating the features of the hazard function. Finally, in Section 11.6 an approach to simulation of the two-type BHBP is described. Experimental results for the expectation and the distribution of the time to attain high levels by the mutant cells are provided. We end the chapter with some concluding remarks.

11.2 Notations, model and integral equations

We will first define the BHBP $\{Z(t), t \geq 0\}$ with one type of cells. The single-type BHBP together with proper biological applications is studied by Jagers [67] and more theoretically by Athreya and Ney [12]. Consider a cell proliferation process, which without loss of generality is starting at time 0 with a single progenitor of age 0, i.e. $Z(0) = 1$, whose life length τ has distribution $G(t) = P(\tau \leq t)$, $G(0^+) = 0$. From mathematical point of view the results could be generalized for more than one cell at the beginning - random or non-random number. At the end of its life, it produces k similar cells of age 0, $k \geq 0$, with probability p_k, which are living and reproduce independently with the same distribution of the life length τ and reproduction distribution $\{p_k\}_{k\geq 0}$, $\sum_{k=0}^{\infty} p_k = 1$. For the sake of brevity we will denote from now on by the couple $(f(s), G(t))$ a BHBP with probability generating function (p.g.f.) $f(s)$ of the offspring distribution $\{p_k\}_{k\geq 0}$, and the distribution $G(t) = P(\tau \leq t)$ of the life time τ of each cell.

Provided that there is at least one offspring, the death-and-reproduction process is repeated, and continues as long as cells exist. So, starting with initial number of $Z(0)$ cells, the process $Z(t)$ is interpreted as the number of existing cells in the population at time $t > 0$.

Now, in order to introduce the mutations during the reproduction process, we present a two-type decomposable BHBP $\{Z^0(t), Z^1(t), t \geq 0\}$, where $\{Z^0(t), t \geq 0\}$ and $\{Z^1(t), t \geq 0\}$ denote the number of cells of type 0 and type 1 at time t respectively. Suppose that cells of type 1 are subcritical, i.e. have reproduction mean m_1, $0 < m_1 < 1$, and that each one of their descendants can mutate at birth, independently of the others, to type 0 cells with probability u, $0 < u < 1$. Cells of type 0 are supercritical, i.e. have reproduction mean m_0, $1 < m_0 < \infty$, and there is no backward mutation. Let us mention here that if no mutation appear ($u = 0$) then the process will be described by two independent classical single-type BHBP.

From theoretical standpoint however, it is important to emphasize here that the processes of interest are decomposable and consist of two sets of types: type 1 cells, which can reproduce themselves and with positive probability eventually can mutate to type 0 cells, forms one class. Another class is consisting of 0 type cells, which can reproduce themselves only. This class is final, i.e. once the process hits it, will stay there. While for the non-decomposable multi-type BHBP there are well-known results about the probability of extinction and limit theorems for their asymptotic behaviour, as well (see Athreya and Ney [12], Mode [96]), for their decomposable counterparts the approach turns out to be particular in any specific case. That is why our investigation proposes new methodology

with respect to both the model and the techniques used.

11.2.1 Preliminary theoretical results

As we will use some previously obtained results (see Slavtchova–Bojkova [125]) for the problems under this study, that is why we will shortly remind them in what follows.

By $G_i(t) = \mathbb{P}(\tau_i \leq t)$, $G_i(0^+) = 0$, we denote the distribution of the life lengths τ_i, by ν_i, the offspring of type i cells and by $f_i(s)$ the p.g.f. of the offspring ν_i, corresponding to the distributions $\{p_{ik}\}_{k\geq 0}$, of type i, $i = 0, 1$ cells.

For the p.g.f. of the process $\{Z^0(t), Z^1(t), t \geq 0\}$ it is proved (see Slavtchova–Bojkova [125]) that $F_i(t; s_0, s_1) = \mathbb{E}(s_0^{Z^0(t)} s_1^{Z^1(t)} | Z^i(0) = 1, Z^j(0) = 0, j \neq i)$ for $i = 0, 1$ satisfy the following system of integral equations:

$$F_0(t; s_0, s_1) \equiv F_0(t; s_0) = s_0(1 - G_0(t)) + \int_0^t f_0(F_0(t-y; s_0))dG_0(y), \tag{K.1}$$

and

$$F_1(t; s_0, s_1) = s_1(1-G_1(t)) + \int_0^t f_1(uF_0(t-y; s_0) + (1-u)F_1(t-y; s_0, s_1))dG_1(y), \tag{K.2}$$

where

$$F_i(0; s_0, s_1) = s_i, |s_i| \leq 1, i = 0, 1.$$

Concerning the probability of extinction/survival of type i cells, $i = 0, 1$ it turned out that its behaviour depends on the total number of mutations that appear in the whole process. Given that $Z^0(0) = 0, Z^1(0) = 1$, for the random variable (r.v.) $I(t)$, $t \geq 0$, being the total number of mutants produced until time t (inclusive) and the r.v. I being the number of mutants in the whole process, it is established (see Slavtchova–Bojkova [125]):

Theorem K.1 *The p.g.f. $h_I(s)$ of I and $h_{I(t)}(s)$ of $I(t)$ satisfy the functional and integral equations respectively*

$$h_I(s) = f_1(us + (1-u)h_I(s)), \tag{K.3}$$

$$h_{I(t)}(s) = 1 - G_1(t) + \int_0^t f_1(us + (1-u)h_{I(t-y)}(s))dG_1(y), \tag{K.4}$$

for all $s \in [0, 1]$.

Remark K.1 *As an immediate consequence of functional equation* (K.3)*, by differentiating and replacing s by* 1*, it yields $\mathbb{E}[I] = \frac{m_1 u}{1-m_1(1-u)}$. By second differentiating of* (K.3)*, using that $Var[I] = h_I''(1) + h_I'(1) - h_I'(1)^2$, it is easy to find that $Var[I] = \frac{um_1(1-u)(1-m_1)^2 + u^2\sigma^2}{[1-m_1(1-u)]^3}$ (the same as in Serra and Haccou [117]), where σ is the variance of the offspring distribution of type* 1 *cells.*

Moreover, from (K.4) by differentiating and taking $s = 1$ one can obtain equations for the moments of the number of mutants at time t, which is left for further study.

Now, for the probability of extinction/survival of type i cells, $i = 0, 1$, we have, that $q_0 = \mathbb{P}[Z^0(t) = Z^1(t) = 0 \text{ for some } t > 0 | Z^0(0) = 1, Z^1(0) = 0]$, is the smallest root of the equation $q_0 = f_0(q_0)$ in the interval $[0, 1]$ (see Jagers [67], p. 140). Having in mind that $q_1 = \mathbb{P}[Z^0(t) = Z^1(t) = 0 \text{ for some } t > 0 | Z^0(0) = 0, Z^1(0) = 1]$, then the extinction of the process occurs, if and only if, all the supercritical (meaning that $m_0 > 1$) single-type BHBP starting from the mutants die out, since $m_1 < 1$. Therefore, $q_1 = \mathbb{E}[q_0^I] = h_I(q_0)$.

Let us recall that by "successful" mutant we mean a mutant that is able to start a single-type BHBP that allows indefinite survival. We will be interested in the distribution of the r. v. T, meaning the waiting time until first "successful" mutant appears. This variable takes values in the set $(0, +\infty]$, with $T = \infty$, if no "successful" mutant is produced. Having in mind the special role of T in the further investigations of the recurrence time of cancer we also recall the following result:

Theorem K.2 *(Slavtchova–Bojkova [125]) The distribution of T has the following properties:*

(i) $\mathbb{P}(T > t) = h_{I(t)}(q_0) \equiv Q_t, \quad for \quad t > 0,$

(ii) $\mathbb{P}(T = \infty) = q_1,$

(iii) $\mathbb{E}(T | T < \infty) = \dfrac{1}{1 - q_1} \displaystyle\int_0^\infty [h_{I(t)}(q_0) - q_1] dt,$

where Q_t are defined by

$$Q_t = 1 - G_1(t) + \int_0^t f_1(uq_0 + (1 - u)Q_{t-y}) dG_1(y) \tag{K.5}$$

with $Q_0 = 1$ and q_0 and q_1 are the extinction probabilities of the process, starting with one cell of type 0 and one cell of type 1, respectively.

We will apply this result in Section 11.4.

11.2.2 Comparison with single-type BHBP

It is important to recall the known results in one dimensional case, or otherwise for the single-type BHBP because if there are no mutations, then $Z^1(t)$ will be exactly a single-type BHBP and in what follows we present the well-known limit theorem for these processes, normalized by their expected value. It is convenient to point out here that in supercritical case the BHBP are characterized by exponentially growing expected value, where the rate of growth is the so-called Malthusian parameter of the processes, which we will introduce in what follows. But, on the contrary, if there appears a mutation, then it will lead to a new two-type BHBP, different from the single-type BHBP. However, the result for the single-type case is useful for revealing the limit behaviour of the two-type one.

It is well-known, that in continuous time the behaviour of single-type BHBP $\{Z(t), t \geq 0\}$, and of other more generalized BP in continuous time as well, is driven not only by

the offspring mean (reflecting the capacity of a cell for division), but also by so-called Malthusian parameter. The Malthusian parameter α of BHBP – $(f(s), G(t))$ is defined as the root of the equation

$$A\int_0^\infty e^{-\alpha t}dG(t) = 1,$$

where $A = f'(1)$. This way the BHBP – $(f(s), G(t))$ is called subcritical, critical or supercritical if $\alpha < 0 \quad (A < 1)$ (in case it exists), $\alpha = 0 \quad (A = 1)$ or $\alpha > 0 \quad (A > 1)$, respectively (see Jagers [67], p. 131, p. 132, p. 156).

With the following result we would like to investigate the time for the mutation cells to reach high levels. First let us remind that $\mathbb{E}[Z(t)] \sim ce^{\alpha_0 t}$, as $t \to \infty$, for some proper constant $c \in \mathbb{R}$ (see Atreya and Ney [12], Theorem 5.3A, p. 152). Also we need to recall the classical result for supercritical BHBP, namely the analogue of Kesten and Stigum theorem, which is the refinement of the estimates of the growth of processes on the set of non-extinction.

Theorem K.3 *(see Athreya and Ney [12], Theorem IV.2, p. 172) Assume that $A > 1$.*

(i) If $\sum p_j jlogj = \infty$ then $W(t) \equiv Z(t)/c'e^{\alpha t} \to 0$ in probability;

(ii) If $\sum p_j jlogj < \infty$ then $W(t)$ converges in distribution to a non-negative r.v. W having the following properties:

a) $\mathbb{E}[W] = 1$;

b) The Laplace transform $\varphi_W(\lambda) = \mathbb{E}e^{-\lambda W}, \lambda \geq 0$, is the unique solution of the equation

$$\varphi_W(\lambda) = \int_0^\infty f[\varphi_W(\lambda e^{-\alpha y})]dG(y) \tag{K.6}$$

in the class

$$C = \{\varphi : \varphi(\lambda) = \int_0^\infty e^{-\lambda t}dF(t), F(0+) < 1, \int_0^\infty tdF(t) = 1\}; \tag{K.7}$$

c) $\mathbb{P}(W = 0) = q \equiv \mathbb{P}(Z(t) = 0 \quad for\ some \quad t)$;

d) The distribution of W is absolutely continuous on $(0, \infty)$.

11.3 Theoretical results

In the next theorem we will establish a limit result (in distribution) for the process $Z^0(t)/\mathbb{E}Z^0(t)$.

Theorem K.4 *If the reproduction law $\{p_{0k}\}_{k\geq 0}$ of type 0 cells satisfies the following condition:*

$$\sum p_{0j} jlogj < \infty, \tag{K.8}$$

then there exists $\lim_{t\to\infty} Z^0(t)/e^{\alpha_0 t} = U$ in distribution. Moreover, the Laplace transform ϕ_U of U satisfies the integral equation

$$\phi_U(\lambda) = \int_0^\infty f_1(u\varphi_{W^0}(\lambda e^{-\alpha_0 y}) + (1-u)\phi_U(\lambda e^{-\alpha_0 y}))dG_1(y) \tag{K.9}$$

where φ_{W^0} *satisfies*

$$\varphi_{W^0}(\lambda) = \int_0^\infty f_0[\varphi_{W^0}(\lambda e^{-\alpha_0 y})] dG_0(y) \tag{K.10}$$

and α_0 *is the Malthusian parameter, defined as the smallest non-negative root of the equation* $m_0 \int_0^\infty e^{-\alpha_0 t} dG_0(t) = 1$.

Proof.

First we will prove the convergence in distribution of the process $Z^0(t)/e^{\alpha_0 t}$. Secondly, we will establish the integral equation for the limit r.v.

Let us notice here that due to the assumption of independence in cells evolution, with every newly born mutant (meaning that the mother cell is of type 1) cell i of type 0 starts an independent single-type $Z_i^0(t), Z_i^0(0) = 1$ BHBP with supercritical reproduction rate $m_0 > 1$, where $i = 1, 2, \ldots, I(t)$. Moreover all these processes are identically distributed as the BHBP- $(f_0(s), G_0(t))$. Having in mind that $Z^1(0) = 1$, then we obtain

$$Z^0(t) = \sum_{i=0}^{I(t)} Z_i^0(t - \delta_i)\mathbb{I}_{\delta_i \le t}, \quad \text{where} \quad \delta_i \quad \text{is the birth time of the} \quad i-\text{th} \quad \text{mutant.}$$

In what follows we will decompose every BHBP $\{Z_i^0(t - \delta_i)\}$ as a difference of the total number of cells born up to time t and the total number of cells died up to time t.

Let $\eta_i^0(t - \delta_i)$ be the total number of cells of type 0 born up to time t in the process $Z_i^0(t - \delta_i)$ with $Z_i^0(0) = 1$ and $\mu_i^0(t - \delta_i)$ be the number of type 0 cells that died up to time t in the same process. Let us denote

$$S_1(t) = \sum_{i=1}^{I(t)} \eta_i^0(t - \delta_i)\mathbb{I}_{\delta_i \le t},$$

$$S_2(t) = \sum_{i=1}^{I(t)} \mu_i^0(t - \delta_i)\mathbb{I}_{\delta_i \le t},$$

where $I(t)$ is the total number of mutants produced until time t, satisfying equation (K.4) and $I(t)$ is independent of $\{\eta_i^0(t - \delta_i)\}$ and $\{\mu_i^0(t - \delta_i)\}$.

Then for the number $Z^0(t)$ of cells of type 0 existing at the moment t, we have the representation

$$Z^0(t) = S_1(t) - S_2(t), \tag{K.11}$$

taking into account that the two-type process $\{Z^0(t), Z^1(t), t \ge 0\}$ is such that $Z^0(0) = 0, Z^1(0) = 1$.

Under the conditions of the present theorem $I(t) \to I$, as $t \to \infty$ pointwise and $\mathbb{E}[I] < \infty$.

On the other hand, we have for $i \ge 1$

$$\frac{\eta_i^0(t)}{e^{\alpha_0 t}} \to H_i, \quad \text{in distribution,}$$

(see Doney [34], Theorem 1, p. 409) and from Theorem 2 (see Slavtchova–Bojkova and Yanev [119], p. 39)

$$\frac{\mu_i^0(t)}{e^{\alpha_0 t}} \to \tilde{H}_i, \quad \text{in distribution,} \quad \text{as} \quad t \to \infty.$$

Therefore as $t \to \infty$

$$\frac{S_1(t)}{e^{\alpha_0 t}} \to \sum_{i=1}^{I} H_i, \quad \text{in distribution,} \tag{K.12}$$

$$\frac{S_2(t)}{e^{\alpha_0 t}} \to \sum_{i=1}^{I} \tilde{H}_i, \quad \text{in distribution.} \tag{K.13}$$

From (K.11), (K.12) and(K.13) it follows that the process $Z^0(t)/e^{\alpha_0 t}$ converges in distribution to a certain r.v. U, say.

To obtain equation (K.9) we will use the integral equation (K.2) of the p.g.f. of the $\{Z^0(t), Z^1(t), t \geq 0\}$. First we will consider the equation for $Z^0(t)$ obtained from (K.2) when $Z^1(t) = 0$:

$$\begin{aligned} F_1(t; s_0, 1) &= \mathbb{E}(s_0^{Z^0(t)} | Z^0(0) = 0, Z^1(0) = 1) = 1 - G_1(t) \\ &+ \int_0^t f_1(uF_0(t-y; s_0) + (1-u)F_1(t-y; s_0, 1))dG_1(y). \end{aligned} \tag{K.14}$$

Substituting $s_0 = e^{-\lambda/e^{\alpha_0 t}}$ in (K.14) we will get for the Laplace transform $\mathbb{E}e^{-\lambda Z^0(t)/e^{\alpha_0 t}}$ of the normalized process $Z^0(t)/e^{\alpha_0 t}$ the following equation:

(K.15)

$$\mathbb{E}(e^{-\lambda Z^0(t)/e^{\alpha_0 t}} | Z^0(0) = 0, Z^1(0) = 1) = 1 - G_1(t)$$

$$+ \int_0^t f_1(uF_0(t-y; e^{-\lambda/e^{\alpha_0 t}}) + (1-u)F_1(t-y; e^{-\lambda/e^{\alpha_0 t}}, 1))dG_1(y) =$$

$$1 - G_1(t) +$$

$$\int_0^t f_1(u\mathbb{E}[e^{-\frac{\lambda Z^0(t-y)}{e^{\alpha_0(t-y)}}e^{-\alpha_0 y}} | Z^0(0) = 1] + (1-u)\mathbb{E}[e^{-\frac{\lambda Z^0(t-y)}{e^{\alpha_0(t-y)}}e^{-\alpha_0 y}} | Z^0(0) = 0, Z^1(0) = 1])G_1(y)$$

The rest of the argument follows by having in mind the result of Theorem K.2 and the established existence of the limit of $Z^0(t)/e^{\alpha_0 t}$. Taking limit as $t \to \infty$ in (K.15) we have

$$\phi_U(\lambda) = \int_0^\infty f_1(u\varphi_{W^0}(\lambda e^{-\alpha_0 y}) + (1-u)\phi_U(\lambda e^{-\alpha_0 y}))dG_1(y),$$

where φ_{W^0} is the Laplace transform of the r.v. $W^0 = \lim_{t\to\infty} \frac{Z^0(t)}{e^{\alpha_0 t}}$ and satisfies equations (K.6) and (K.7). ♢

The result of Theorem K.4 is a continuous analogue of Theorem 3.4 in discrete time established in Serra [116]. It is however, only the first step towards finding the probability of attaining high levels by the process $Z^0(t)$.

Theorem K.2 shows the probability $Q_t = \mathbb{P}(T > t)$ (a "successful" mutant has not been born by time t) satisfies the integral equation (K.5). In the next theorem we will prove that similar integral equation could be derived for $\mathbb{P}(T > t, Z^1(t) = 0)$.

Theorem K.5 *The joint probability that "successful" mutant has not been born yet and we do not have cells of type* 1 *(with subcritical reproduction rate, $m_1 < 1$) satisfies the following integral equation:*

$$\text{(K.16)} \quad \mathbb{P}(T > t, Z^1(t) = 0) = \int_0^t f_1(uq_0 + (1-u)\mathbb{P}(T > t-y, Z^1(t-y) = 0))\,\mathrm{d}G_1(y).$$

Proof.

Using the law of total probability we can write

$$\begin{aligned}\mathbb{P}(T > t, Z^1(t) = 0) &= \mathbb{P}(T > t, Z^1(t) = 0 \mid \tau_1 < t)\mathbb{P}(\tau_1 < t)\\ &\quad + \mathbb{P}(T > t, Z^1(t) = 0 \mid \tau_1 > t)\mathbb{P}(\tau_1 > t)\\ &= \mathbb{P}(T > t, Z^1(t) = 0 \mid \tau_1 < t)\mathbb{P}(\tau_1 < t)\\ &= \int_0^t \mathbb{P}(T > t, Z^1(t) = 0 \mid \tau_1 = y)\,\mathrm{d}G_1(y).\end{aligned}$$

If the initial cell of type 1 dies at time y it produces offspring at time $t = y$ with p.g.f. $f_1(s)$. Then the event "we do not have a successful mutant and we do not have a cell of type 1 at time t" is equivalent to the event "every cell from the offspring of the ancestor is either a mutant at the moment t or will lead to a generation of mutants only after the moment t and all of the produced mutants will start a BP that goes extinct". This happens if and only if all the mutants from the offspring of the initial cell lead to extinction (with probability q_0 for each) and all cells that are not mutants start a BP at time $t = y$ that will convert to mutants only to time t, all of which will be "unsuccessful" (which has probability $\mathbb{P}(T > t - y, Z^1(t-y) = 0)$).

The probability for mutation is u, so the probability for an offspring cell to become an "unsuccessful" mutant is uq_0 and the probability to be normal cell but lead to "unsuccessful" mutants only is $(1-u)\mathbb{P}(T > t-y, Z^1(t-y) = 0)$. Then the probability for all of the offspring cells (born at time y) to be either unsuccessful mutants or convert to "unsuccessful" mutants only to time t is $f_1(uq_0 + (1-u)\mathbb{P}(T > t-y, Z^1(t-y) = 0))$. So we can write

$$\begin{aligned}\mathbb{P}(T > t, Z^1(t) = 0) &= \int_0^t \mathbb{P}(T > t, Z^1(t) = 0 \mid \tau_1 = y)\,\mathrm{d}G_1(y)\\ &= \int_0^t f_1(uq_0 + (1-u)\mathbb{P}(T > t-y, Z^1(t-y) = 0))\,\mathrm{d}G_1(y).\end{aligned}$$

♢

Remark K.2 *The integral equations* (K.5) *and* (K.16) *are not renewal equations, although they look similar, and we cannot apply the renewal theory (see Mitov and Omey [91]) for their solution or asymptotic behaviour. However, these two integral equations can be solved numerically. We also know that* $\mathbb{P}(T > t) \to \mathbb{P}(T = \infty)$ *and* $\mathbb{P}(T > t, Z^1(t) = 0) \to \mathbb{P}(T = \infty)$ *as* $t \to \infty$.

Remark K.3 *We have that* $\mathbb{P}(T > t, Z^1(t) = 0) = \mathbb{P}(T = \infty, Z^1(t) = 0)$ *for every* $t \in \mathbb{R}$ *due to the fact that we cannot have a "successful" mutant after time* t *if we do not have any cells of type* 1 *left. Note that* $\mathbb{P}(T = \infty, Z^1(t) = 0) = \mathbb{P}(T = \infty \mid Z^1(t) = 0)\mathbb{P}(Z^1(t) = 0)$, *where* $\mathbb{P}(T = \infty \mid Z^1(t) = 0) < 1$ *since it could also happen that* $T \leq t \mid Z^1(t) = 0$ *with positive probability.*

11.4 Approximations to the integral equations

In general we might not have an analytical form of the function $G_1(t)$, because it could be derived from the data by using smoothing techniques (for example, kernel smoothing). This means we need to use a numerical method for solving equation (K.5). What we gain by using a numerical method is that it does not require to find the theoretical solution and works not only for exponentially distributed life length, but also for much larger class of distributions that have smooth probability density functions. Although it is possible to estimate Q_t for each t without an analytical form of the function $G_1(.)$, the values of that function at $0, h, 2h, \ldots, t$ are needed to apply that method.

Despite there are many numerical methods for solving renewal equations in literature (see Mitov and Omey [90]) and finding the renewal function (see Xie [137] and Bartholomew [23]), the equations (K.5) and (K.16) are not renewal ones and we need to use another approach. This section presents numerical solutions to the integral equations for $\mathbb{P}(T > t)$ and $\mathbb{P}(T > t, Z^1(t) = 0)$, which are then used for calculating the hazard function, defined in Section 11.4.3. The presented approximations are suitable when the distribution of life length $G_1(t)$ has smooth density function and $G_1(0+) = 0$.

11.4.1 Numerical approximation for $\mathbb{P}(T > t)$

The probability for every mutant to time t to initiate a process that eventually goes extinct is $Q_t = \mathbb{P}(T > t) = 1 - F_T(t)$, where $F_T(t)$ denotes the cumulative distribution function of the r.v. T. The algorithm presented below describes the numerical approach for solving equation (K.5).

First consider the initial moment, $t = 0$, when the branching process starts with a single cell of type 1. Assuming $G_1(0+) = 0$, we have that

$$Q_0 = \mathbb{P}(T > 0) = 1 - G_1(0) = 1, \tag{K.17}$$

i.e. $Q_0 = 1$. This assumption for the distribution of life length $G_1(t)$ is actually quite natural because it states that the newly born cells do not die instantly after birth.

Secondly for $t = h$ we can estimate the integral $\int_0^h f_1(uq_0 + (1-u)Q_{h-y})\,\mathrm{d}G_1(y)$ (see equation (K.5)) numerically by applying the right rectangle rule. If we do this and use that $Q_0 = 1$ from equation (K.17), we get

$$\begin{aligned} Q_h &\approx 1 - G_1(h) + f_1(uq_0 + (1-u)Q_{h-h}) \cdot G_1(h) \\ &= 1 - G_1(h) + f_1(uq_0 + 1 - u) \cdot G_1(h). \end{aligned} \tag{K.18}$$

For $t = 2h$ we can divide the integral in equation (K.5) in two parts:

$$\begin{aligned} \int_0^{2h} f_1(uq_0 + (1-u)Q_{2h-y})\,\mathrm{d}G_1(y) = &\int_0^h f_1(uq_0 + (1-u)Q_{2h-y})\,\mathrm{d}G_1(y) \\ &+ \int_h^{2h} f_1(uq_0 + (1-u)Q_{2h-y})\,\mathrm{d}G_1(y). \end{aligned}$$

For each of the two parts we can use the right rectangle rule to approximate the integrals and we get

$$\begin{aligned} Q_{2h} \approx 1 - G_1(2h) &+ f_1(uq_0 + (1-u)Q_h) \cdot [G_1(h) - G_1(0)] \\ &+ f_1(uq_0 + (1-u)Q_0) \cdot [G_1(2h) - G_1(h)]. \end{aligned} \tag{K.19}$$

But we already know Q_0 and Q_h from equations (K.17) and (K.18), so after substituting them in equation (K.19) we can find Q_{2h}.

We will consider now a more general case $t = kh$ and see how we can calculate $\mathbb{P}(T > kh)$. As in the previous case of $k = 2$, we can divide the integral in k smaller parts:

$$\begin{aligned} &\int_0^{kh} f_1(uq_0 + (1-u)Q_{kh-y})\,\mathrm{d}G_1(y) = \\ &= \sum_{n=1}^{k} \left(\int_{(n-1)h}^{nh} f_1(uq_0 + (1-u)Q_{kh-y})\,\mathrm{d}G_1(y) \right). \end{aligned}$$

Then we can apply the right rectangle rule and get the following approximation:

$$\begin{aligned} Q_{kh} \approx\ & 1 - G_1(kh) + \\ &+ \sum_{n=1}^{k} \left(f_1\left(uq_0 + (1-u)Q_{(k-n)h}\right) \cdot [G_1(nh) - G_1((n-1)h)] \right), \end{aligned} \tag{K.20}$$

in which Q_{kh} depends on the previous values $Q_{(k-n)h}$, for all $n = 1, \ldots, k$. By applying equation (K.20) consecutively for $k = 0, 1, \ldots, t/h$, we estimate the function $Q_\cdot$ in the interval $[0, t]$.

11.4.2 Numerical approximation for $\mathbb{P}(T > t, Z^1(t) = 0)$

The probability $\mathbb{P}(T > t, Z^1(t) = 0)$ satisfies the integral equation (K.16), similar to equation (K.5). By applying the same technique as in Subsection 11.4.1 we can derive the following approximation for $\mathbb{P}(T > t, Z^1(t) = 0)$:

(K.21)

$$\mathbb{P}(T > kh, Z^1(kh) = 0) = \int_0^{kh} f_1(uq_0 + (1-u)\mathbb{P}(T > kh - y, Z^1(kh - y) = 0))\,\mathrm{d}G_1(y)$$

$$= \sum_{n=1}^{k} \int_{(n-1)h}^{nh} f_1(uq_0 + (1-u)\mathbb{P}(T > kh - y, Z^1(kh - y) = 0))\,\mathrm{d}G_1(y)$$

$$\approx \sum_{n=1}^{k} f_1(uq_0 + (1-u)\mathbb{P}(T > (k-n)h, Z^1((k-n)h) = 0)) \cdot [G_1(nh) - G_1((n-1)h)].$$

When $k = 0$ we have $\mathbb{P}(T > 0, Z^1(0) = 0) = 0$. Then by applying equation (K.21) consecutively for $k = 0, 1, \ldots, t/h$ we find the probability $\mathbb{P}(T > t, Z^1(t) = 0)$, i.e. the solution to equation (K.21).

11.4.3 Numerical approximation for hazard function

In literature the hazard function is defined as the probability for an instantaneous failure, on the condition it has not happened yet. In the context of the event of occurrence of the first "successful" mutant, this standard definition represents the probability for the instantaneous first "successful" mutant to be born, given it has not been born yet. However, if we have no longer cells of type 1 left in the population, then the probability for such mutant to appear is zero. That is why we will consider a slightly modified definition of hazard function, where it represents the probability for the instantaneous appearance of the first "successful" mutant, provided it has not appeared yet and there is still a positive chance for it to appear. We define the hazard function as $g(t)dt = \mathbb{P}(T \in [t, t + dt]|T > t, Z^1(t) > 0)$, which can be written in the form

(K.22)
$$g(t) = \frac{F_T'(t)}{\mathbb{P}(T > t, Z^1(t) > 0)},$$

where $F_T'(t)$ is the probability density function of T. The denominator $\mathbb{P}(T > t, Z^1(t) > 0)$ in equation (K.22) satisfies

(K.23)
$$\begin{aligned}\mathbb{P}(T > t, Z^1(t) > 0) &= \mathbb{P}(T > t) - \mathbb{P}(T > t, Z^1(t) = 0)\\ &= 1 - F_T(t) - \mathbb{P}(T > t, Z^1(t) = 0).\end{aligned}$$

In Subsection 11.4.1 we have calculated the function $F_T(t)$, from which we can also calculate the derivative $F_T'(t)$. By applying the numerical method we have calculated the values $F_T(h), F_T(2h), \ldots, F_T(t)$ from which we can approximate the derivative $F'(kh) \approx$

$(F_T((k+1)h) - F_T(kh))/h$. In Subsection 11.4.2 we have calculated the probability $\mathbb{P}(T > t, Z^1(t) = 0)$. Substituting them in equation (K.22) and applying (K.23) gives us the approximation for the function $g(t)$.

Remark K.4 *Notice that we do not require explicit form for the offspring p.g.f. of type* 0 *cells. All p.g.f. that correspond to the same probability for extinction q_0 produce the same distribution of T and the same hazard function $g(t)$. This follows from equations* (K.5) *and* (K.22)*, which show the distribution of T depends on q_0, but not on the particular form of $f_0(s)$. Notice also that equations* (K.5) *and* (K.16) *do not require to have explicit form for $G_0(t)$, i.e. the appearance of "successful" mutants does not depend on the life length of the mutant (type* 0*).*

11.5 Application. Two interesting examples

We consider two examples of BHBP, both starting with a single cell of type 1, having the same p.g.f. of the offspring distribution for type 1 cells, the same mutation probability and the same extinction probability for type 0 cells. The only difference between the two examples will be the choice of different life length distribution. This will allow us to investigate the effect of choosing different life length models on the shape of the hazard function $g(t)$.

We will first define the parameters of the BP that will be kept the same for both examples. The type 1 cells represent subcritical BP but they have a probability $u = 0.20$ for mutation to type 0, which has supercritical reproduction. Let the offspring p.g.f. for type 1 cells be $f_1(s) = 0.625 + 0.375s^2$, which means that type 1 cell could either have 0 offspring with probability 0.625 or 2 descendants with probability 0.375. Let the extinction probability of BP, starting with a type 0 cell, be $q_0 = 0.30$.

As **Example 1** we will consider a BP with exponential distribution for the life length of cells of type 1 - $G_1(t) \sim \text{Exp}(10)$, i.e. exponential distribution with mean 10. As **Example 2** we will consider a BP with truncated normal distribution for the life length, $G_1(t) \sim \text{N}_+(10, 2.5)$, i.e. normal distribution, conditional on $[0, +\infty)$, that has mean 10 and standard deviation of 2.5. The use of truncated normal distribution is strictly necessary because otherwise the life length could become negative. Although truncating is theoretically required, the choice of small standard deviation makes the truncated normal distribution very similar to the original one. With expected life length of 10 time units and standard deviation of 2.5 time units, the probability for a negative realization is less than 10^{-4} . Thus the expected life length of the truncated normal distribution is very close to 10 time units.

In Figures 11.1 and 11.2 are presented the results from applying the numerical method in Example 1. In Figures 11.3 and 11.4 are presented the results of Example 2. The two examples have the same parameters, the same expected life length of 10 time units, but they have very different functional forms for the life length distribution.

In Figure 11.1 we can see that $\mathbb{P}(T > t)$ is decreasing with time toward a constant value $\mathbb{P}(T = \infty)$. The probability that "successful" mutant never occurs in the population is $\mathbb{P}(T = \infty) = 0.82$. The probability $\mathbb{P}(T > t, Z^1(t) = 0)$ that "successful" mutant is not born yet and we no longer have any cells of type 1 left in the population is increasing

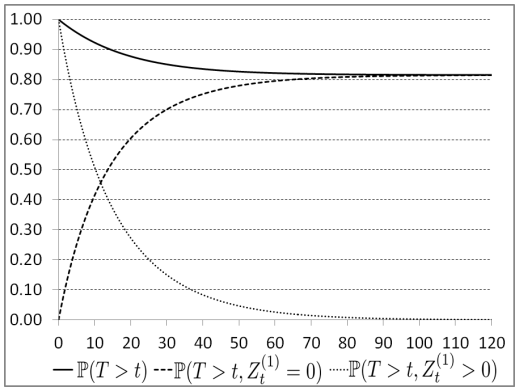

Figure 11.1: Distribution of T when the life length is Exp(10), Example 1.

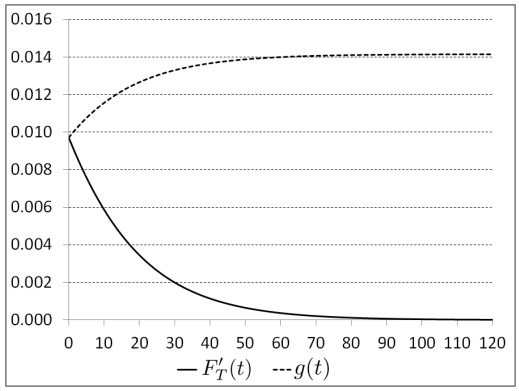

Figure 11.2: The hazard function $g(t)$, when the life length is Exp(10), Example 1.

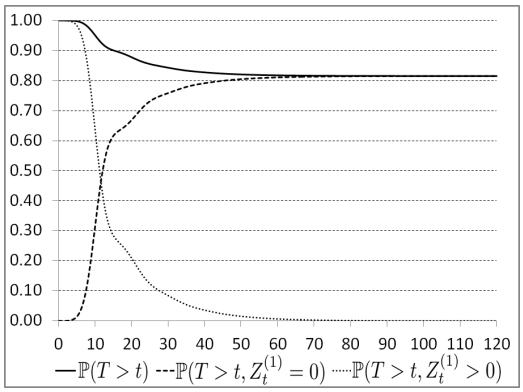

Figure 11.3: Distribution of T when the life length is truncated $\mathrm{N}_+(10, 2.5)$, Example 2.

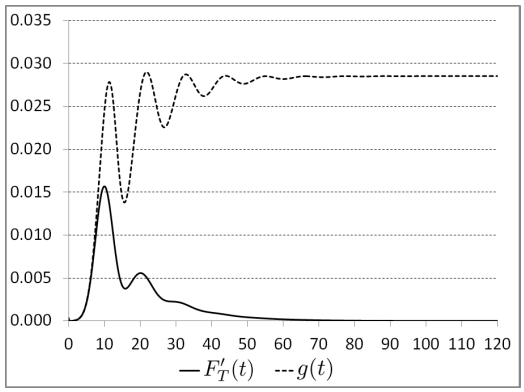

Figure 11.4: The hazard function $g(t)$, when the life length is truncated $\mathrm{N}_+(10, 2.5)$, Example 2.

with time toward the same constant value $\mathbb{P}(T = \infty) = 0.82$. This is a quite intuitive and expected result, taking into account that type 1 BP is subcritical and $\mathbb{P}(Z^1(t) = 0) \to 1$ a.s. as $t \to \infty$.

In Figure 11.2 is presented $F_T'(t)$, the probability density function of the waiting time until "successful" mutant is born. We can see it is around 0.01 in the beginning and gradually decreases toward 0, in such a way that the area below it is around 0.18, i.e. the probability "successful" mutant exists. We could conclude then the most probable time for the first "successful" mutant to be born is in the beginning. The hazard function $g(t)$ represents the conditional probability density for "successful" mutant to be born at time t, if it is not born yet and we still have cells of type 1 alive. Because of the fact that $\mathbb{P}(T > 0, Z^1(0) > 0) = 1$ we have $g(0) = F'(0)$.

If we now compare the two examples we see some similarities. For example, changing the life length distribution to normal does not change $\mathbb{P}(T = \infty)$. In fact, if we consider a Galton–Watson process where the distribution of life length is non-stochastic, a unit time, then we will arrive at the same $\mathbb{P}(T = \infty) = 0.82$. This is because the Galton–Watson

process is embedded in the BHBP. Thus the limits of $\mathbb{P}(T > t)$, $\mathbb{P}(T > t, Z^1(t) = 0)$ and $\mathbb{P}(T > t, Z^1(t) > 0)$ are exactly the same as in the two examples and they do not depend on the life length distribution.

In case of trimmed normally distributed life length (see Figures 11.3 and 11.4) with average 10 and standard deviation 2.5 the probability to have a "successful" mutant is close to 0 when $t \in [0, 4]$. The reason is that such cell has a chance of being born only when the initial cell of type 1 dies, which is less than 0.01 for $t \in [0, 4]$. When time approaching 10, the probability for the initial cell to die is at its peak, so the probability to produce a "successful" mutant while dying is also climbing. If the initial cell is not successful in producing a mutant while dying, then this could happen during the life period of its offspring, which will die around 20^{th} time unit. But because the process is subcritical, the expected number of descendants is declining with time and these "peaks" in $F'_T(t)$ are subsiding, tending to zero. This "wave-like" behaviour is also evident in the hazard function $g(t)$ and it is caused again by the peak in probability of dying at age 10, which causes peak in the probability of "successful" mutant being produced.

Another use of the numerical approach is to investigate how the hazard function $g(t)$ and the distribution of T change when we choose different model parameters. For example, if we increase the mutation probability u from 0.20 to 0.50, then $\mathbb{P}(T = \infty)$ decreases from 0.82 to 0.72. If we increase the probability for extinction q_0 to 0.90 (from 0.30) then $\mathbb{P}(T = \infty)$ increases to 0.96. If we decrease the expected number of offspring for type 1 cells, making the probability for 2 offspring only 0.10 (from 0.375), then $\mathbb{P}(T = \infty)$ increases to 0.97. Changing these parameters and the lifespan distribution of type 1 cells also significantly affects the shape of the functions presented in Figures 11.1-11.4 and the speed at which they converge, i.e. their asymptotic behaviour. The theoretical and numerical results allow us to study how different model parameters affect the properties of the branching process.

11.6 On the attaining of high levels

11.6.1 Simulation studies and an algorithm

The task to simulate a two-type BP in continuous time is very similar to that of simulating it in discrete time settings (two-type GWBP). Here, the goal of the simulation will be to obtain some empirical results concerning the amount of time $T_x = \sup_{t \geq 0}\{t : Z^0(t) < x | Z^0(0) = 0, Z^1(t) = 1\}$, before the number of alive type 0 cells becomes x or more.

Having either continuous or discrete time, one would need to traverse over all of the birth moments in the process sequentially and to count the number of type 0 cells born among them. The algorithm must stop at the first such moment where the predetermined level x of type 0 cells is reached (or stop in case of extinction). While in discrete time we can only traverse through the integer time moments since the possible moments of birth of cells are integers, this is not the case in continuous time. Indeed, in the case of BHBP, the cells can have non-integer life length and as a result, we do not have a set of possible birth moments known in advance. Every positive real number could be a moment of birth for a cell. A natural solution to this problem is to keep an array of the birth-death times for the cells in the population, sorted in ascending order and to traverse only through

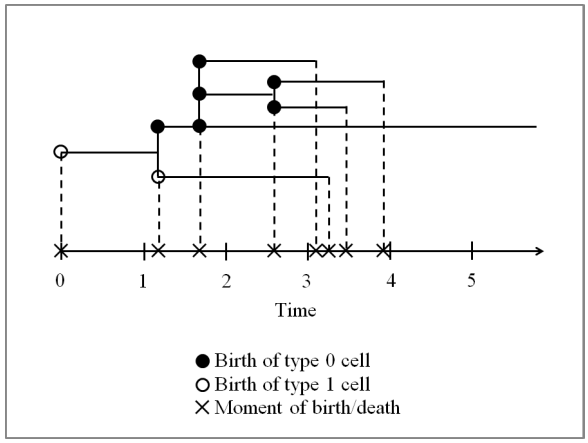

Figure 11.5: Example of a two-type BHBP. The algorithm traverses through the birth-death moments, denoted with 'X', consecutively

the moments in it. The size of the array will be finite, since $T_x < \infty$ with probability 1, given the non-extinction of the population, and the total number of generated cells in a bounded time interval is finite. An example is shown in Figure 11.5. The birth-death times are marked with a cross over the time line.

Counting the number of type 0 cells in discrete settings is relatively easy. When we have a two-type GWBP each cell has lifespan of length 1. Therefore, when a new type 0 cell is born at a certain time moment i, we have to increase the number of alive type 0 cells by 1 only for that integer time moment i, because the cell dies at the next moment $i+1$ and there are no cell born between these two moments. However, in continuous time, the latter is quite possible. We could have such cells having times of birth during the lifespan of the considered type 0 cell. Thus, every time when a type 0 cell is generated in continuous settings, we have to perform additional computational procedure which lists all of the birth-death moments lying in the interval of living for the newly born type 0 cell.

It is worth noting that this affects the time efficiency of the algorithm, making it significantly slower then its analogue in discrete time. This is supported by the results of our simulation. Running the algorithm in continuous time and for the same levels 10^4 and 10^5, as those used in Serra and Haccou [117] for the discrete case, required impractically big amount of time.

We provide simulation results concerning the r.v. T_x in continuous time settings. Recall that with T_x we denote the r.v. representing the time for the number of escape type cells to cross level x in the two-type BHBP. It is possible that T_x might be infinite, hence we considered T_x conditioned on $T_x < \infty$, i.e. the realizations when the population goes extinct before the number of type 0 cells to reach level x are neglected. The results would be the same if we considered T_x conditioned on non-extinction, because if the population does not extinct, the probability of reaching level x is 1, for arbitrary big values of x.

11.6.2 Estimation results for $\mathbb{E}[T_x \mid T_x < \infty]$

Using the described approach in Subsection 11.6.1, in particular, we evaluated $E[T_x \mid T_x < \infty]$ by using the crude Monte Carlo approach. The values of this expectation are plotted in Figure 11.6 for two high levels of x, 1000 and 2000, and processes with Poisson and binary splitting reproduction laws for the offspring of type 0 cells. The latter distribution is over the values 0 and 2 only, which means that type 0 cell could either has 0 or 2 descendants. We considered different values in the interval $[1.1, 2]$ for the reproduction mean m_0 of the type 0 cells. The type 1 cells have exponential distribution for the offspring with parameter m_1 fixed to 0.95. The mutation probability u equals to 0.05. Further, we assumed that the life length of every cell is exponentially distributed with mean 1 time unit. As in the previous section we consider a BHBP starting with a single-type 1 cell. We simulated 200 processes for each value of m_0.
From Figure 11.6 we can see that, as expected, the time to cross level x increases with x and decreases as the reproduction mean m_0 increases. We also observe that, as in the discrete settings, for such different reproduction laws, like Poisson and binary splitting, the $E[T_x \mid T_x < \infty]$ has quite similar behaviour regarding this problem.

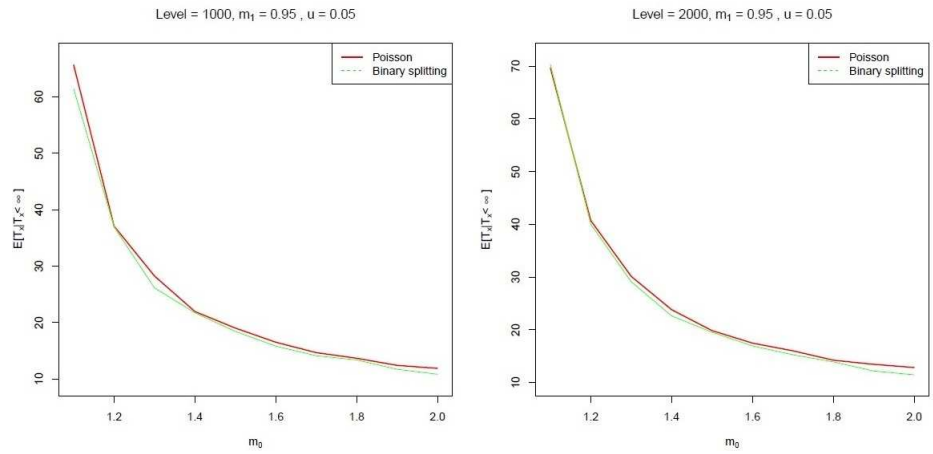

Figure 11.6: Simulation results for the time T_x, elapsing until a level x of "mutants" is attained.

11.6.3 On the distribution of T_x

Another question of interest is the distribution of T_x, conditioned on $T_x < \infty$, for the case where the expected numbers of offspring of the supercritical mutant cells are close to 1 (see Serra and Haccou [117]). We obtain the empirical distribution of the latter r. v., from 100 samples, for $m_0 = 1.1$ and when x has values $200, 500$ and 1000, respectively. The other parameters were the same as those described in the previous subsection. The cumulative distribution functions and the corresponding histograms in these three cases are shown in Figure 11.7. An object of future work could be the investigation of an appropriate distribution law for T_x (conditioned on $T_x < \infty$) with parameters depending on the level x.

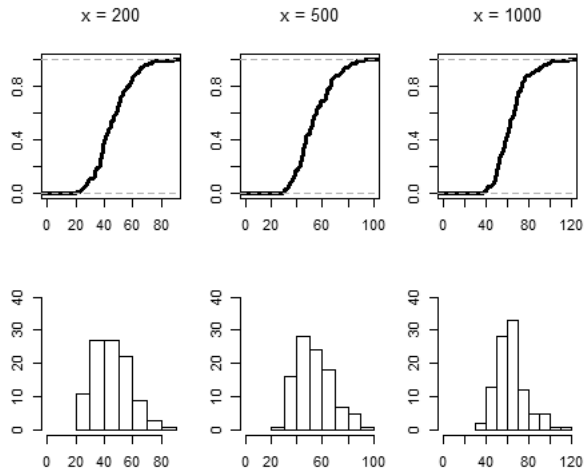

Figure 11.7: Histograms and empirical cumulative distribution functions of $T_x \mid T_x < \infty$ for $x = 200, 500, 1000$.

11.7 Concluding remarks

We are tackling the common event of metastasis of cancer after local elimination followed possibly by proper treatment (independently of the type of cancer). In this case, another therapy might be needed. First, one of the questions that naturally arises is what is the waiting time to next treatment. If we know the distribution of the time T until the first "successful" mutant occurs, then we could determine how long we could wait before performing another chemotherapy. The results have shown that the distribution of T depends on the lifespan distribution of type 1 cells and the results vary significantly on the choice of distribution (which could depend on the type of cancer and the type of treatment). In Figures 11.2 and 11.4 we have shown that the p.d.f. of T could have several peaks and troughs and knowing the particular form of the p.d.f. and the hazard function $g(t)$ will give us knowledge on the most appropriate time to perform another chemotherapy.

Secondly, the hazard function $g(t)$ represents the probability density for the first "successful" mutant appearance, given that it has not appeared yet, but we still have cells of type 1 left in the organism. From the particular distribution of T we can also calculate the conditional probability that a person will not develop aggressive cancer if he has not developed it yet $\mathbb{P}(T = \infty \mid T > t)$.

Third, the model also allows to find the probability a person who decided not to be treated again will not develop cancer ($\mathbb{P}(T = \infty)$), which does not depend on the particular lifespan distribution. In addition, we are interested in the waiting time it takes to reach a certain level of cancer cells, so they can be medically detected.

Finally, the presented theoretical results provide a continuous time branching model for studying the dynamics of cancer development, the factors affecting the process and their influence and importance. Choosing different parameters in the model allows us to investigate their effect on the properties of the branching process. Moreover, the numerical approach and simulations allow the model to be tailored to the real data available for the

particular kind of cancer and chemotherapy which will be our next goal.

Remark K.5 *We have used Matlab for implementing the numerical methods and the R programming language for performing the simulations (see [112]).*

The results from this chapter are published by Slavtchova–Bojkova, Trayanov and Dimitrov in [132].

Bibliography

[1] Agresti, A. (1974). Bounds on the extinction time distribution of a branching process. Adv. Appl. Probab. **6,** 332–335.

[2] Ahsanullah, M., Yanev, G.P. (2008). Records and Branching Processes. Nova Science Publishers.

[3] Aldous, D., Pitman, J. (1998). Tree–valued Markov chains derived from Galton–Watson processes. Ann. Inst. Henri Poincare Probab. Stat. **34** 637–686.

[4] Andersson, H., Britton, T. (2000). Stochastic epidemic models and their statistical analysis. Lecture Notes in Statistics **151,** Springer–Verlag.

[5] Anderson, R. M., May, R. M. (1991). Infectious Diseases of Humans: Dynamics and Control, Oxford University Press.

[6] Angelov, A., Slavtchova–Bojkova, M. (2012). Bayesian estimation of the offspring mean in branching processes: Application to infectious disease data. Computers and Mathematics with Applications, **64,** 229–235.

[7] Alsmeyer, G., Slavtchova-Bojkova M. (2005). Limit theorems for subcritical age–dependent branching processes with two types of immigration. Stochastic Models, **21,** 133–147.

[8] Alsmeyer, G., Gutiérrez, C., Martinez, R. (2011). Limiting genotype frequencies of Y–linked genes through bisexual branching processes with blind choice. J. Theor. Biol., **275**, 42–51.

[9] Asmussen, S. (1987). Applied Probability and Queues. Wiley, New York.

[10] Asmussen, S., Hering, H. (1983). Branching Processes. Birkhauser.

[11] Athreya, K. (1969). On the suprecritical one dimensional age–dependent branching processes. Ann. Math. Statist., **40,** 743–763.

[12] Athreya, K., Ney, P. (1972). Branching processes. Springer Verlag.

[13] Axelrod, D. E., Gusev, Y. and Gamel, J. W. (1997). Ras–oncogene transformed and non–transformed cell population are each heterogeneous but respond differently to the chemotherapeutic drug cytosine arabinoside (Ara–C). Cancer Chemotherapy and Pharmacology, **29,** 445–451.

[14] Axelrod, D. E., Gusev, Y., Kuczek, T. (1993). Persistence of cell cycle times over many generations as determined by heriatability of colony sizes of ras oncogene–transformed and non-transformed cells. Cell Proliferation, **26,** 235–249.

[15] Bienaymé, I. J. (1845). De la loi de multiplication et de la duree de familles. Soc. Philomat. Paris Extrats Ser. **5**, p. 37.

[16] Ball, F., (1983). The threshold behaviour of epidemic models, Journal of Applied Probability, **20,** 227–241.

[17] Ball, F. (1999). Stochastic and deterministic models for SIS epidemics among a population partitioned into households. Math. Biosci. **156,** 41–67.

[18] Ball, F., Donnelley, P. (1995). Strong approximations for epidemic models. Stochastic Process. Appl., **55,** 1–21.

[19] Ball, F., González, M., Martinez, R., Slavtchova-Bojkova, M. (2014). Stochastic monotonicity and continuity properties of functions defined on Crump–Mode–Jagers branching processes, with application to vaccination in epidemic modelling. Bernoulli **20:4**, 2076–2101.

[20] Ball, F., González, M., Martinez, R., Slavtchova-Bojkova, M. (2016). Total progeny of Crump–Mode–Jagers branching processes: an application to vaccination in epidemic modeling, Branching Processes and their Applications. Lecture Notes in Statistics-Proceedings (del Puerto, I.M., et al eds.), Springer, **219**, 257–267.

[21] Ball, F., Mollison, D., Scalia-Tomba, G. (1997). Epidemics with two levels of mixing. Ann Appl Probab **7:1**, 46–89.

[22] Barbour, A. D. (1975). The duration of the closed stochastic epidemic. Biometrika, **62,** 477–482.

[23] Bartholomew, D. (1963). An approximate solution to the integral equation of renewal theory. J. Royal Statist. Soc., B 25(2), 432–441.

[24] Bartlett, M. S. (1955). An Introduction to Stochastic Processes, 1st ed., Cambridge University Press.

[25] Bauer, H. (1992). Maß- und Integrationstheorie (2. Ed.). De Gruyter, Berlin.

[26] Becker, N. (1974). On parametric estimation for mortal branching processes, Biometrika, **61,** 393–399.

[27] Becker, N., Britton, T. (2004). Estimating vaccine efficacy from small outbreaks. Biometrika, **91**(2), 363–382.

[28] Billingsley, P. (1986). Probability and Measure. John Wiley and Sons, Inc.

[29] Brunner, H. (2004). Collocation methods for Volterra integral and related functional differential equations. Cambridge University Press.

[30] Chow, Y.S., Teicher, H. (1978). Probability Theory, Springer-Verlag, New York.

[31] Daley, D. J., Gani, J. (1999). Epidemic modelling: An introduction. Cambridge University Press.

[32] De Serres, G., Gay, N. J., Farrington, C. P. (2000). Epidemiology of transmissible diseases after elimination. Am. J. Epidemiol. **151,** 1039–1048

[33] Devroye, L. (1998). Branching processes and their applications in the analysis of tree structures and tree algorithms. Probabilistic Methods for Algorithmic Discrete Mathematics, (M. Habib, C. McDiarmid, J. Ramirez-Alfonsin and B. Reed, eds.), **16**, 249–314, Springer–Verlag, Berlin.

[34] Doney, R. (1971). The total progeny of a branching process. J. Appl. Prob., 8, 407–412.

[35] Durrett, R. (2015). Branching Process Models of Cancer. Springer.

[36] Epps, T.W. (2009). Quantitative finance: its development, mathematical foundations, and current scope. John Wiley and Sons, Inc.

[37] Erickson, K. B. (1970). Strong renewal theorem in the infinite mean case, Trans. Amer. Math. Soc., **151**, 263–291.

[38] Farrington, C., Andrews N. (2003) Monitoring the Health of Populations. Chapter Outbreak Detection: Application to Infectious Disease Surveillance, Oxford University Press.

[39] Farrington, C., Andrews N., Beale A., Catchpole M. (1996) A statistical algorithm for the early detection of outbreaks of infectious disease. Journal of the Royal Statistical Society. Series A. **159,** 547–563.

[40] Farrington, C., Grant, A. (1999). The distribution of time to extinction in subcritical branching processes: applications to outbreaks of infectious disease. J. Appl. Probab., **36,** 771–779.

[41] Farrington, C. P., Kanaan, M. N., Gay, N. J. (2003). Branching process models for surveillance of infectious diseases controlled by mass vaccination. Biostatistics, **4(2),** 279–295.

[42] Feller, W. (1971). An Introduction to Probability Theory and Its Applications. John Wiley and Sons. New York. 2nd ed.. **2**.

[43] Foster, J. H. (1971). A limit theorem for a branching process with state-dependent immigration. Ann. Math. Stat. **42,** 1773-1776.

[44] Freise, K., Widness, J., Schmidt, R., Veng–Pedersen, P. (2008). Modeling time variant distributions of cellular lifespans: increases in circulating reticulocyte lifespans following double phlebotomies in sheep. J Pharmacokinet Pharmacodyn, 35(3), 285–323.

[45] Galton, F., Watson, H. W. (1874). On the probability of the extinction of families. J. Roy. Anthrop. Soc. London, **4**, 138–144.

[46] González, M., del Puerto, I. M., Martinez, R., Molina, M., Mota, M., Ramos, A. (2010). Workshop on Branching Processes and Their Applications. ,Lecture Notes in Statistics, **197**, Springer–Verlag.

[47] González, M., Martinez, R., Slavtchova–Bojkova, M. (2009). Age–dependent branching processes as models of infectious diseases. Compt. Rend. de l'Acad. Bulgare des Sci. **62(5)**, 541–550.

[48] González M., Martinez R., Slavtchova–Bojkova M. (2010a). Stochastic monotonicity and continuity properties of the extinction time of Bellman–Harris branching processes: an application to epidemic modelling. Jour. Appl. Prob., **47**, 58–71.

[49] González M., Martinez R., Slavtchova–Bojkova M. (2010b). Time to extinction of Infectious diseases through age–dependent branching models. Lecture Notes in Statistics - Proceedings. **197,** 241–256.

[50] Guttorp, P. (1991). Statistical Inference for Branching Processes. John Wiley and Sons, Inc.

[51] Gut, A. (1988). Stopped Random Walks. Limit Theorems and Applications. Springer, New York.

[52] Haccou, P., Jagers, P., Vatutin, V. (2007). Branching processes: variation, growth and extinction of populations. Cambridge University Press.

[53] Haight F. A. (1961). A distribution analogous to the Borel–Tanner, Biometrika, **48,** 167–173.

[54] Haight F. A., Breuer M. A. (1960). The Borel–Tanner distribution, Biometrika , **47,** 143–150.

[55] Heesterbeek J. A. P., Dietz K. (1996). The concept of R_0 in epidemic theory, Statistica Nederlandica, **50,** 89–110.

[56] Heinzmann, D. (2009). Extinction times in multitype Markov branching processes. J. Appl. Probab . **46(1),** 296–307.

[57] Heyde C. C. (1979). On assessing the potential severity of an outbreak of a rare infectious disease: a Bayesian approach, Australian Journal of Statistics, **21,** 282–292.

[58] Hoff P.D., (2009). A First Course in Bayesian Statistical Methods, Springer.

[59] Höhle, R., (2005). The R-package "surveillance". Sonderforschungsbereich 386.

[60] Harris, T. (1963). The theory of branching processes. Springer.

[61] IDSA: Avian influenza (bird flu): agricultural and wildlife considerations. Infectious Diseases Society of America. (2007)
http://www.idsociety.org/pandemicinfluenza.htm.

[62] Isham, V. (2005). Stochastic models for epidemics. Celebrating statistics papers in honour of Sir David Cox on his 80th birthday (Davison, A.C., Dodge, Y. and Wermuth, N., eds.), Chapter 1, Oxford University Press.

[63] Iwasa, Y., Michor, F., Nowak, M. (2003). Evolutionary dynamics of escape from biomedical intervention. Proc. Biol. Sci., B 270(1533), 2573–2578.

[64] Iwasa, Y., Michor, F., Nowak, M. (2004). Evolutionary dynamics of invasion and escape. J. Theor. Biol., 226(2), 205–214.

[65] Jacob C., (2010). Branching processes: their role in epidemiology, International Journal of Environmental Research and Public Health, **7,** 1186–1204.

[66] Jagers, P. (1968). Age–dependent branching processes allowing immigration. Theory Probab. Appl. **13**, 225–236.

[67] Jagers, P. (1975). Branching Processes with Biological Applications. (1st ed.). John Wiley & Sons Ltd.

[68] Johnson, R., Susarla, V. and Van Ryzin J. (1979). Bayesian nonparametric estimation for age–dependent branching processes. Stochastic Process. Appl. **9(3),** 307–318.

[69] Kallenberg, O. (2002). Foundations of Modern Probability (2nd Ed.). Springer, New York.

[70] Kaplan, N. and Pakes A. (1974). Supercritical age-dependent branching processes with immigration. Stoch. Proc. and Appl. **2,** 371–389.

[71] Kaplan, N. (1974). Multidimensional age–dependent branching processes allowing immigration: the limiting distribution. Jour. of Appl. Prob. **11,** 225–236.

[72] Keeling, M.J., Rohani, P. (2008). Modeling Infectious Diseases in Humans and Animals. Princeton University Press.

[73] Kendall, D.G., (1956). Deterministic and stochastic epidemics in closed populations, Proc. 3rd. Berkeley Symp. on Math. Statist. Prob., **4,** 149–165, University of California Press.

[74] Kimmel, M., Axelrod, D. (2002). Branching Processes in Biology. Springer. New York.

[75] Kimmel, M. (1985). Nonparametric analysis of stathmokinesis. Math. Biosci. **74,** 111–123.

[76] Kimmel, M. and Traganos, F. (1986). Estimation and prediction of cell cycle speciffic effects of anticancer drugs. Math. Biosci. **80,** 187–208.

[77] Kojouharova, M., Kurchatova A., Marinova L., Georgieva T. (2007). Mumps outbreak in Bulgaria, 2007: a preliminary report. Eurosurveillance, **12**.

[78] Kolmogorov, A. N. (1938). Zur Losung einer biologischen Aufgabe. Tomsk State Univ., **2**, 1–6. (in Russian).

[79] Kolmogorov, A. N., Dmitriev, N. A. (1947). Branching Random Processes, Dokl. Acad. Nauk (Pro. Acad. Sci. USSR) **56**, 7–10. (in Russian).

[80] Krzyzanski, W., Perez-Ruixo, J., Vermeulen, A. (2008). Basic pharmacodynamic models for agents that alter the lifespan distribution of natural cells. J Pharmacokinet Pharmacodyn, 35(3), 349–377.

[81] Kulkarni, M. V., Pakes A. G. (1983) Total progeny of a simple branching process with state dependent immigration, J. Appl. Prob., **20,** 472-482.

[82] Lindvall, T. (1992). Lectures on the Coupling Method. Wiley, New York.

[83] Lloyd-Smith, J.O., George, D., Pepin, K.M., Pitzer, V.E., Pulliam, J.R.C., Dobson, A.P., Hudson, P.J. and Grenfell, B.T. (2009). Epidemic dynamics at the human–animal interface. Science **326,** 1362–1367.

[84] Lodish, H., Berk, A., Zipursky, L., Matsudaira, P., Baltimore, D., Darnell, J. (2000). Molecular Cell Biology. (4th ed.). W. H. Freeman.

[85] Marschner I.C. (1992). The effect of preferential mixing on the growth of an epidemic, Mathematical Biosciences, **109,** 39–67.

[86] Martinez, R., Slavtchova-Bojkova, M. (2005). Comparison between numerical and simulation methods for age–dependent branching models with immigration. Pliska Stud. Math. Bulgar. **17,** 147-154.

[87] Metz, J. (1978). The epidemic in a closed population with all susceptibles equally vulnerable; some results for large susceptible populations and small initial infections. Acta Biotheoretica **27,** 75–123.

[88] Mitov, K.V. (1995). Some results for multitype Bellman–Harris branching processes with state–dependent immigration. Lecture Notes in Statistics. **99**, C.C. Heyde (Ed.), Branching Processes, First World Congress, Springer Verlag, New York.

[89] Mitov, K.V. (1989). Multitype Bellman-Harris branching processes with state–dependent immigration. Proc. of the Eighteen Spring Conf. of UBM, 423-428.

[90] Mitov, K., Omey, E. (2014a). Intuitive approximations for the renewal function. Statistics and Probability Letters, **84**, 72–80.

[91] Mitov, K., Omey, E. (2014b). Renewal Processes. Springer.

[92] Mitov, K. V. and Yanev N. M. (1985). Bellman–Harris Branching processes with state–dependent immigration. J. Appl. Prob. **22,** 757-765.

[93] Mitov, K. V. and Yanev N. M. (1989). Bellman–Harris branching processes with a special type of state–dependent immigration. Adv. Appl. Prob. **21,** 270–283.

[94] Mitov, K., Yanev, N. M. (2009) Bbranching stochastic processes: regulation, regeneration, estimation, applications, 2009, Pliska Stud. Math. Bulgar. **19**, 5-58.

[95] Mitova–Bobcheva M., Slavtchova–Bojkova M., Kojouharova M., Kurchatova A. (2011). Analysing and monitoring surveillance data of munmps in Bulgaria. Pliska Stud. Math. Bulgar. **20,** 149–154.

[96] Mode, C. (1971). Multitype branching processes: Theory and Applications. Elsevier, New York.

[97] Mode, C. (1985). Stochastic Processes In Demography and Their Computer Implementation. Springer.

[98] Mode, C. J. and Sleeman, C. K. (2000). Stochastic processes in epidemiology. World Scientific.

[99] Nasell, I. (2002). Stochastic models of some endemic infections. Math. Biosci. **179,** 1–19.

[100] Nowak, M.A., Michor, F., Komarova, N.L., Iwasa, Y. (2004). Evolutionary dynamics of tumor suppressor gene inactivation. Proc. Natl. Acad. Sci. USA **101**, 10635–10638.

[101] OIE: Report reference 1828/TY-DT. (2007). World Organization for Animal Health. http://www.oie.int.

[102] Pakes, A. G. (1971). A branching processes with a state–dependent immigration component. Adv. Appl. Prob. **3,** 301–314.

[103] Pakes A. G. (1971) Some limit theorems for the total progeny of a branching process, Adv. Appl. Prob., **3,** 176-192.

[104] Pakes, A. G. (1972). Limit theorems for an age–dependent branching process with immigration. Math. Biosci. **14**, 221–234.

[105] Pakes, A. G. (1975). Some results for non-supercritical Galton-Watson processes with immigration. Math. Biosci. **24,** 71–92.

[106] Pakes, A. G. (1978). On the age distribution of a Markov chain. J. Appl. Probab. **15**, 65–77.

[107] Pakes, A. (1989). On the asymptotic behaviour of the extinction time of the simple branching process. Adv. Appl. Probab. **21,** 470–472.

[108] Pakes, A. (2003). Biological applications of branching processes. Handbook of Statistics Vol. 21 Stochastic Processes: Modelling and Simulation (Shanbhag, D.N. and Rao, C.R., eds.), Chapter 18, 693–773, Elsevier Science B.V.

[109] Pakes, A.G., Kaplan, N. (1974). On the subcritical Bellman–Harris process with immigration. J. Appl. Probab. **11**, 652–668.

[110] Pellis, L., Ball, F. and Trapman, P. (2012). Reproduction numbers for epidemic models with households and other social structures. I. Definition and calculation of R_0. Math. Biosci. **235:1,** 85–97.

[111] Plummer, M., Best, N., Cowles, K., Vines, K. (2010). coda: Output analysis and diagnostics for MCMC. R package version 0.13-5. http://CRAN.R-project.org/package=coda.

[112] R Development Core Team (2011). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing Vienna, Austria. ISBN 3-900051-07-0.

[113] Robert, C. (2007). The Bayesian Choice, 2nd edition, Springer.

[114] Robert, C., Casella, G. (2004). Monte Carlo Statistical Methods, 2nd edition, Springer.

[115] Robert, C., Casella, G. (2010). Introducing Monte Carlo Methods with R, Springer.

[116] Serra, M. (2006). On waiting time to escape. J. Appl. Prob., 43, 296–302.

[117] Serra, M., Haccou, P. (2007). Dynamics of escape mutants. Theor. Popul. Biol., 72, 167–178.

[118] Sevastyanov, B. A. (1971). Branching processes , Mir, Moscow.

[119] Slavtchova, M., Yanev, N. (1990). Convergence in distribution of supercritical Bellman—Harris branching processes with state–dependent immigration. Mathematica Balkanica, New series, 4(1), 35–42.

[120] Slavtchova, M. N. (1991). Limit theorems for multitype Bellman–Harris branching processes with state–dependent immigration. Serdica. **17,** 144–156.

[121] Slavtchova–Bojkova, M. (1996). Multi–type age–dependent branching processes with state–dependent immigration, In: Proc. of Athens Conf. on Applied Prob. and Time series, Edts: C.C.Heyde, Yu. Prohorov, R. Pyke and S. Rachev, Lecture Notes in Statistics, Springer, Berlin, **114,** 192–205.

[122] Slavtchova–Bojkova, M. (2002). On the subcritical age–dependent branching process with two types of immigration. Proc. 31st Spring Conf. of the Union of Bulgarian Mathematicians, Borovets, 187–192.

[123] Slavtchova–Bojkova, M. (2011). A limit theorem for multi–type subcritical age–dependent branching process with two types of immigration. Proc. 40th Spring Conf. of the Union of Bulgarian Mathematicians, Borovets, 314–319.

[124] Slavtchova-–Bojkova, M. (2013). Time to extinction in branching processes and its application in epidemiology, Pliska Stud. Math. Bulgar. **22,** 101-–126.

[125] Slavtchova–Bojkova, M. (2016). On two-type decomposable branching processes in continuous time and time to escape extinction. Branching Processes and their Applications. Lecture Notes in Statistics-Proceedings (del Puerto, I.M., et al eds.), Springer, 219, 319–329.

[126] Slavtchova–Bojkova, M., Yanev, N. (1994). Non–critical branching processes with two types of state–dependent immigration. Compt. Rend. de l'Acad. Bulgar. des Sci., **47** 13–16.

[127] Slavtchova–Bojkova M., Yanev N. (1994). Limit theorems for age–dependent branching processes with state–dependent immigration. Preprint, Institute of Mathematics and Informatics, Bulgarian Academy of Sciences.

[128] Slavtchova-Bojkova, M., Yanev, N. (1995). Age–dependent branching proceses with state–dependent immigration. Lecture Notes in Statistics. **99**, C.C. Heyde (Ed.), Branching Processes, First World Congress, Springer Verlag, New York.

[129] Slavtchova, M., Yanev, N. (1991). Non–Critical Bellman–Harris branching processes with state–dependent immigration. Serdica **17,** 67–79.

[130] Slavtchova–Bojkova, M., Gonzalez, M., Martinez, R. (2010c). Age-dependent branching processes for surveillance of vaccine–preventable diseases with incubation period, Frontiers in Systems Biology, Front. Psychiatry. **1:127,** DOI 10.3389/fpsyt.2010.00127.

[131] Slavtchova–Bojkova, M., Yanev, N. M. (2007). Branching Stochastic Processes, Sofia University Press "St. Kliment Ohridski", ISBN 978-954-07-2601-4. (in Bulgarian).

[132] Slavtchova–Bojkova, M., Trayanov, P., Dimitrov, S. (2017). Branching processes in continuous time as models of mutations: Computational approaches and algorithms. Computational Statistics and Data Analysis http://dx.doi.org/10.1016/j.csda.2016.12.013l

[133] Smith, C.E.G. (1964). Factors in the transmission of virus infections from animal to man. Scientific Basis of Medicine Annual Review 125–150. London: Athlone Press.

[134] Stroup, D., Williamson, G., Herndon, J., Karon, J. (1989). Detection of aberrations in the occurrence of notifiable diseases surveillance data. Statistics in Medicine.**8,** 323–329.

[135] Thorisson, H. (2000). Coupling, Stationarity, and Regeneration. Springer, New York.

[136] Weiner, H. (1991). Age–dependent branching Processes with two types of immigration. Journal of Information and Optimization Sciences **2,** 207–218.

[137] Xie, M. (1989). On the solution of renewal–type integral equations. Communications in Statistics - Simulation and Computation, 18(1), 281–293.

[138] Yakovlev, A.Yu., Yanev, N.M., (1989). Transient Processes in Cell Proliferation Kinetics. Lecture Notes in Biomathematics, **82**, Springer–Verlag, New York.

[139] Yakovlev, A., Yanev, N. (2006). Branching stochastic processes with immigration in analysis of renewing cell populations. Math. Biosci. **203,** 37–63.

[140] Yakovlev, A. and Yanev, N. (2007). Age and residual lifetime distributions for branching processes. Statist. Probab. Lett. **77(5),** 503–513.

[141] Yanev, G.P., Tsokos, C.P., (1999). Decision–theoretic estimation of the offspring mean in mortal branching processes, Communications in Statistics: Stochastic Models, **15,** 889–902.

[142] Yang, Y., Halloran, M., Sugimoto, J., Longini, I. (2007) Detecting human–to–human transmission of avian influenza A (H5N1). Emerging Infectious Diseases **13:9,** 1348–1353.

[143] Yamazato, M. (1975). Some results on continuous time branching processes with state–dependent immigration. J. Math. Soc. Japan **27,** 479–496.