ARTICLE IN PRESS

Computational Statistics and Data Analysis ▮ (▮▮▮▮) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Computational Statistics and Data Analysis

journal homepage: www.elsevier.com/locate/csda

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

Maroussia Slavtchova-Bojkova [a,b,*], Plamen Trayanov [a], Stoyan Dimitrov [a]

[a] Faculty of Mathematics and Informatics, Sofia University "St. Kliment Ohridski", 5, J. Bourchier Blvd, 1164 Sofia, Bulgaria
[b] Institute of Mathematics and Informatics, Bulgarian Academy of Sciences, Acad. G. Bonchev Str., Bl. 8, 1113 Sofia, Bulgaria

ARTICLE INFO

Article history:
Received 19 February 2016
Received in revised form 28 December 2016
Accepted 29 December 2016
Available online xxxx

Keywords:
Decomposable branching processes
Continuous time
Mutations
Waiting time to escape mutant
Hazard function
Attaining high levels

ABSTRACT

The appearance of mutations in cancer development plays a crucial role in the disease control and its medical treatment. Motivated by the practical significance, it is of interest to model the event of occurrence of a mutant cell that will possibly lead to a path of indefinite survival. A two-type branching process model in continuous time is proposed for describing the relationship between the waiting time till the first escaping extinction mutant cell is born and the lifespan distribution of cells, which due to the applied treatment have small reproductive ratio. A numerical method and related algorithm for solving the integral equations are developed, 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.

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 to the first mutation appearance that found a family line that does not die out and the time required for attaining high levels of the mutation type cells, is of clinical importance since the extent of resistance determines the choice of the therapy and patient diagnosis.

We are modelling 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 a new type of cells, called type 0. 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,

* Corresponding author at: Faculty of Mathematics and Informatics, Sofia University "St. Kliment Ohridski", 5, J. Bourchier Blvd, 1164 Sofia, Bulgaria.
E-mail address: bojkova@fmi.uni-sofia.bg (M. Slavtchova-Bojkova).

http://dx.doi.org/10.1016/j.csda.2016.12.013
0167-9473/

Please cite this article in press as: Slavtchova-Bojkova, M., et al., Branching processes in continuous time as models of mutations: Computational approaches and algorithms. Computational Statistics and Data Analysis (2017), http://dx.doi.org/10.1016/j.csda.2016.12.013

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 noting 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 lifespan of a cell is not deterministic but random by nature (see Freise et al., 2008; Krzyzanski et al., 2008). 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., 2000). This means that modelling the cellular lifespan 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 lifespan, 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 branching process (BP), meaning that the probability 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 (1963), Athreya and Ney (1972), Jagers (1975), and Mode (1985). For recent books, with emphasis on biological applications, see Kimmel and Axelrod (2002), Haccou et al. (2007) and also Durrett (2015), especially for branching modelling 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. (2003, 2004).

This paper is organized as follows: Section 2 introduces the branching process model with two types of cells in continuous time and the basic functional 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 (2016). The aim of the next Section 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 study 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 5).

Another interesting and new result in Section 4 is the new algorithm developed for numerical approximation of the distribution of waiting time to 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 lifespan distributions, including smoothed empirical distributions. In Section 5 we presented two examples illustrating the features of the hazard function. Finally, in Section 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 paper with some concluding remarks.

2. Notations, model description and functional 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 (1975) and more theoretically by Athreya and Ney (1972). 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 a 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 distribution $G(t) = P(\tau \leq t)$ of the lifespan τ of each cell.

Provided 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 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

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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 type 0 cells, which can only reproduce themselves. 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, 1972; Mode, 1971), 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.

2.1. Preliminary theoretical results

As we will use some previously obtained results (see Slavtchova-Bojkova, 2016) 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, 2016) 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:

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

and

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

where

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

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, 2016):

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

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

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

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

Remark 1. As an immediate consequence of functional equation (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 (3), using that $Var[I] = h_I''(1) + h_I'(1) - h_I'(1)^2$, it is easy to find that $Var[I] = \frac{u m_1 (1-u)(1-m_1)^2 + u^2\sigma^2}{[1 - m_1(1-u)]^3}$ (the same as in Serra and Haccou, 2007), where σ is the variance of the offspring distribution of type 1 cells.

Moreover, from (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, 1975, 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 2 (*Slavtchova-Bojkova, 2016*)**.** *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) $\mathbb{E}(T | T < \infty) = \frac{1}{1 - q_1} \int_0^\infty [h_{I(t)}(q_0) - q_1] dt$,

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where Q_t are defined by

$$Q_t = 1 - G_1(t) + \int_0^t f_1(uq_0 + (1-u)Q_{t-y})\,\mathrm{d}G_1(y) \tag{5}$$

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 4.

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 is 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

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

where $A = f'(1)$. This way the BHBP$-(f(s), G(t))$ is called subcritical, critical or supercritical if $\alpha < 0$ ($A < 1$) (in case it exists), $\alpha = 0$ ($A = 1$) or $\alpha > 0$ ($A > 1$), respectively (see Jagers, 1975, 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 Athreya and Ney, 1972, 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 3 (*See Athreya and Ney, 1972, Theorem IV.2, p. 172*)**.** *Assume that $A > 1$.*

(i) *If $\sum p_{ij} \log j = \infty$ then $W(t) \equiv Z(t)/c'e^{\alpha t} \to 0$ in probability;*
(ii) *If $\sum p_{ij} \log j < \infty$ 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*

$$\varphi_W(\lambda) = \int_0^\infty f[\varphi_W(\lambda e^{-\alpha y})]\,\mathrm{d}G(y) \tag{6}$$

  in the class

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

  (c) $\mathbb{P}(W = 0) = q \equiv \mathbb{P}(Z(t) = 0$ *for some* $t)$;
  (d) *The distribution of W is absolutely continuous on* $(0, \infty)$.

3. Theoretical results

The aim in this section is to study the asymptotic behaviour of the mutant cell population and 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 in distribution of the properly normalized BP and characterizing its limit random variable as well. This result could be interpreted as the first step towards analysis of the probability of attaining high levels of the same cell population. After that we also studied the distribution of the joint event that a "successful" mutant does not appear and no cells of type 1 exist at time t and an integral equation is obtained.

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

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

$$\sum p_{0j} \log j < \infty, \tag{8}$$

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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 functional equation*

$$\phi_U(\lambda) = \int_0^\infty f_1(u\varphi_{W^0}(\lambda e^{-\alpha_0 y}) + (1-u)\phi_U(\lambda e^{-\alpha_0 y}))\, \mathrm{d}G_1(y) \tag{9}$$

where φ_{W^0} *satisfies*

$$\varphi_{W^0}(\lambda) = \int_0^\infty f_0[\varphi_{W^0}(\lambda e^{-\alpha_0 y})]\, \mathrm{d}G_0(y) \tag{10}$$

and α_0 *is the Malthusian parameter, defined as the smallest non-negative root of the equation* $m_0 \int_0^\infty e^{-\alpha_0 t}\, \mathrm{d}G_0(t) = 1$.

Proof. First we will prove the convergence in distribution of the process $Z^0(t)/e^{\alpha_0 t}$. Secondly, we will establish the functional 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

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

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 Eq. (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

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

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, 1971, Theorem 1, p. 409) and from Theorem 2 (see Slavtchova and Yanev, 1990, p. 39)

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

Therefore, as $t \to \infty$

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

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

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

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To obtain Eq. (9) we will use the functional equation (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 (2) when $Z^1(t) = 0$:

$$F_1(t; s_0, 1) = \mathbb{E}(s_0^{Z^0(t)} | Z^0(0) = 0, Z^1(0) = 1) = 1 - G_1(t) + \int_0^t f_1(uF_0(t-y; s_0) + (1-u)F_1(t-y; s_0, 1))\, \mathrm{d}G_1(y). \tag{14}$$

Substituting $s_0 = e^{-\lambda/e^{\alpha_0 t}}$ in (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:

$$\begin{aligned}
&\mathbb{E}(e^{-\lambda Z^0(t)/e^{\alpha_0 t}} | Z^0(0) = 0, Z^1(0) = 1) = 1 - G_1(t) \\
&\quad + \int_0^t f_1(uF_0(t-y; e^{-\lambda/e^{\alpha_0 t}}) + (1-u)F_1(t-y; e^{-\lambda/e^{\alpha_0 t}}, 1))\, \mathrm{d}G_1(y) \\
&= 1 - G_1(t) + \int_0^t f_1 \left(u\mathbb{E}\left[e^{-\frac{\lambda Z^0(t-y)}{e^{\alpha_0 (t-y)}} e^{-\alpha_0 y}} | Z^0(0) = 1 \right] \right. \\
&\quad \left. + (1-u)\mathbb{E}\left[e^{-\frac{\lambda Z^0(t-y)}{e^{\alpha_0 (t-y)}} e^{-\alpha_0 y}} | Z^0(0) = 0, Z^1(0) = 1 \right] \right) \mathrm{d}G_1(y).
\end{aligned} \tag{15}$$

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

$$\phi_U(\lambda) = \int_0^\infty f_1(u\varphi_{W^0}(\lambda e^{-\alpha_0 y}) + (1-u)\phi_U(\lambda e^{-\alpha_0 y}))\, \mathrm{d}G_1(y),$$

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 Eqs. (6) and (7). □

The result of Theorem 4 is a continuous analogue of Theorem 3.4 in discrete time established in Serra (2006). However, it is only the first step towards finding the probability of attaining high levels by the process $Z^0(t)$.

Theorem 2 shows the probability $Q_t = \mathbb{P}(T > t)$ (a "successful" mutant has not been born by time t) satisfies the integral equation (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 5. *The joint probability that "successful" mutant has not been born and we do not have cells of type* 1 *(with subcritical reproduction rate, $m_1 < 1$) at time t satisfies the following integral equation:*

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

Proof. Using the law of total probability we can write

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

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

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

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Remark 2. The integral equations (5) and (16) are not renewal equations, although they look similar, and we cannot apply the renewal theory (see Mitov and Omey, 2014b,a) 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 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 $T \le t \mid Z^1(t) = 0$ with positive probability.

4. Numerical approximations to the integral equations

In general we might not have an analytic 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 Eq. (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 analytic 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, 2014a) and finding the renewal function (see Xie, 1989; Bartholomew, 1963), Eqs. (5) and (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 4.3. The presented approximations are suitable when the distribution of life length $G_1(t)$ has smooth density function and $G_1(0+) = 0$.

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

The probability that a "successful" mutant is not born before time t 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 Eq. (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

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

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 Eq. (5)) numerically by applying the right rectangle rule. If we do this and use that $Q_0 = 1$ from Eq. (17), we get

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

For $t = 2h$ we can divide the integral in Eq. (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

$$Q_{2h} \approx 1 - G_1(2h) + f_1(uq_0 + (1-u)Q_h) \cdot [G_1(h) - G_1(0)] + f_1(uq_0 + (1-u)Q_0) \cdot [G_1(2h) - G_1(h)]. \tag{19}$$

But we already know Q_0 and Q_h from Eqs. (17) and (18), so after substituting them in Eq. (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:

$$\int_0^{kh} f_1(uq_0 + (1-u)Q_{kh-y})\,\mathrm{d}G_1(y) = \sum_{n=1}^{k} \left(\int_{(n-1)h}^{nh} f_1(uq_0 + (1-u)Q_{kh-y})\,\mathrm{d}G_1(y) \right).$$

Then we can apply the right rectangle rule and get the following approximation:

$$Q_{kh} \approx 1 - G_1(kh) + \sum_{n=1}^{k} \left(f_1\left(uq_0 + (1-u)Q_{(k-n)h}\right) \cdot [G_1(nh) - G_1((n-1)h)] \right), \tag{20}$$

in which Q_{kh} depends on the previous values $Q_{(k-n)h}$, for all $n = 1, \ldots, k$. By applying Eq. (20) consecutively for $k = 0, 1, \ldots, t/h$, we estimate the function $Q_.$ in the interval $[0, t]$.

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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 (16), similar to Eq. (5). By applying the same technique as in Section 4.1 we can derive the following approximation for $\mathbb{P}(T > t, Z^1(t) = 0)$:

$$\begin{aligned}\mathbb{P}(T > kh, Z^1(kh) = 0) &= \int_0^{kh} f_1(uq_0 + (1-u)\mathbb{P}(T > kh - y, Z^1(kh - y) = 0))\, \mathrm{d}G_1(y)\\ &= \sum_{n=1}^{k} \int_{(n-1)h}^{nh} f_1(uq_0 + (1-u)\mathbb{P}(T > kh - y, Z^1(kh - y) = 0))\, \mathrm{d}G_1(y)\\ &\approx \sum_{n=1}^{k} f_1(uq_0 + (1-u)\mathbb{P}(T > (k-n)h, Z^1((k-n)h) = 0)) \cdot [G_1(nh) - G_1((n-1)h)]. \end{aligned} \tag{21}$$

When $k = 0$ we have $\mathbb{P}(T > 0, Z^1(0) = 0) = 0$. Then by applying Eq. (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 Eq. (21).

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

$$g(t) = \frac{F_T'(t)}{\mathbb{P}(T > t, Z^1(t) > 0)}, \tag{22}$$

where $F_T'(t)$ is the probability density function of T. The denominator $\mathbb{P}(T > t, Z^1(t) > 0)$ in Eq. (22) satisfies

$$\begin{aligned}\mathbb{P}(T > t, Z^1(t) > 0) &= \mathbb{P}(T > t) - \mathbb{P}(T > t, Z^1(t) = 0)\\ &= 1 - F_T(t) - \mathbb{P}(T > t, Z^1(t) = 0). \end{aligned} \tag{23}$$

In Section 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 Section 4.2 we have calculated the probability $\mathbb{P}(T > t, Z^1(t) = 0)$. Substituting them in Eq. (22) and applying (23) gives us the approximation for the function $g(t)$.

Remark 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 Eqs. (5) and (22), which show the distribution of T depends on q_0, but not on the particular form of $f_0(s)$. Notice also that Eqs. (5) and (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).

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 $1 - G_1(t) \sim \mathrm{Exp}(10)$, i.e. exponential distribution with mean 10. As **Example 2** we will consider a BP with truncated normal distribution for the life length, $G_1(t) \sim \mathrm{N}_+(10, 2.5)$, 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

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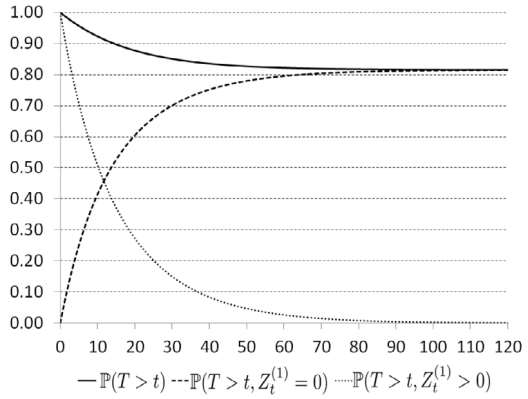

Fig. 1. Distribution of T when the life length is Exp(10), Example 1.

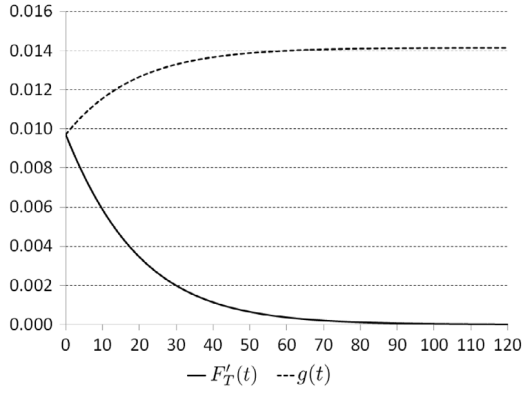

Fig. 2. The hazard function $g(t)$, when the life length is Exp(10), Example 1.

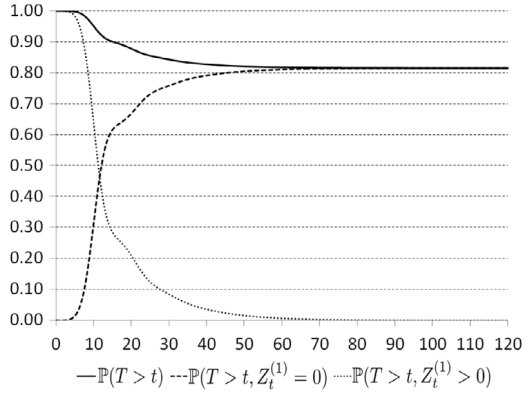

Fig. 3. Distribution of T when the life length is truncated $N_+(10, 2.5)$, Example 2.

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.

The results from applying the numerical method in Example 1 are presented in Figs. 1 and 2. The results for Example 2 are presented in Figs. 3 and 4. 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 Fig. 1 we can see that $\mathbb{P}(T > t)$ is decreasing with time towards a constant value $\mathbb{P}(T = \infty)$. The probability that "successful" mutant never occurs in the population is estimated numerically at $\mathbb{P}(T = \infty) = 0.82$. 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

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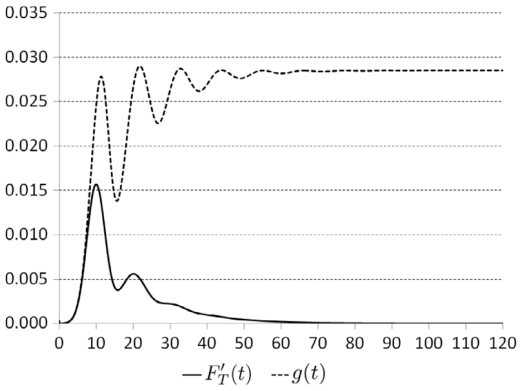

Fig. 4. The hazard function $g(t)$, when the life length is truncated $N_+(10, 2.5)$, Example 2.

is increasing with time towards 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 Fig. 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 towards 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 Figs. 3 and 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 is 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 age 20. 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. Table 1 shows $\mathbb{P}(T = \infty)$ for different values of u and q_0. 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 Figs. 1–4 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.

6. On the attaining of high levels. Simulation of the two-type BHBP

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). Let $T_x = \sup_{t\geq 0}\{t : Z^0(t) < x | Z^0(0) = 0, Z^1(t) = 1\}$ be the amount of time before the number of alive type 0 cells becomes x or more. Here, the goal of our simulation will be to obtain some empirical results concerning T_x.

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. Actually, the set of the birth–death moments for a certain realization of the BHBP is not known in advance.

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Table 1
Probability a "successful" mutant never appears, $\mathbb{P}(T = \infty)$, as a function of u and q_0.

		Extinction probability (q_0)										
		0.00	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1.00
Mutation probability (u)	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	0.10	0.84	0.85	0.86	0.88	0.89	0.91	0.92	0.94	0.96	0.98	1.00
	0.20	0.77	0.78	0.80	0.82	0.83	0.86	0.88	0.90	0.93	0.96	1.00
	0.30	0.72	0.74	0.75	0.77	0.80	0.82	0.85	0.88	0.92	0.96	1.00
	0.40	0.69	0.71	0.72	0.75	0.77	0.80	0.83	0.86	0.90	0.95	1.00
	0.50	0.67	0.68	0.70	0.72	0.75	0.78	0.81	0.85	0.89	0.94	1.00
	0.60	0.65	0.66	0.68	0.71	0.73	0.76	0.80	0.84	0.89	0.94	1.00
	0.70	0.64	0.65	0.67	0.69	0.72	0.75	0.79	0.83	0.88	0.94	1.00
	0.80	0.63	0.64	0.66	0.68	0.70	0.74	0.78	0.82	0.87	0.93	1.00
	0.90	0.63	0.63	0.65	0.67	0.69	0.73	0.77	0.81	0.87	0.93	1.00
	1.00	0.62	0.63	0.64	0.66	0.68	0.72	0.76	0.81	0.86	0.93	1.00

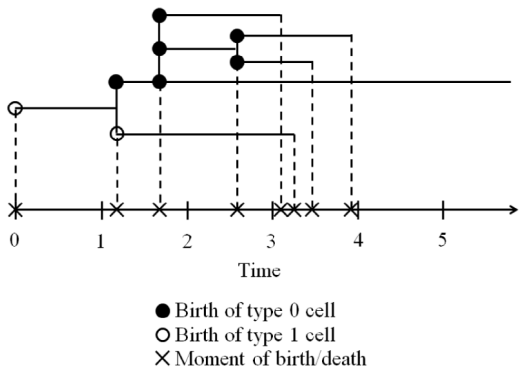

Fig. 5. Example of a two-type BHBP. The algorithm traverses through the birth–death moments, denoted with 'X', consecutively.

A natural solution to this problem is to keep an array of the birth–death moments for all the cells in the population and to traverse only through these moments. 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 Fig. 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. On the other hand, in continuous time we begin the simulation of a two-type BHBP with a single cell of type 1 born at time 0. The lifespan of the cell is generated according to exponential distribution with a certain parameter. We move to the death moment of this first cell and continue by repetition of the following steps: every time when a cell dies, we first generate the number of its children, as well as their types. If the type of the dying cell is 0, the types of all its children are directly set to 0. Otherwise, the default type of a children is 1. For each of them, a mutation to type 0 with a certain probability of mutation fixed in advance is simulated. After the types are determined, we generate the lifespans of the cells according to their types, respectively. These lifespans give us the death moments for the considered cells. At the end, we add the latter death moments to the sorted array of all the birth–death moments and we set the new current moment to be the smallest element of the obtained array greater than the actual current moment. The check whether we have reached the predetermined level x of type 0 cells is performed immediately after the types' generation for the children of a cell is completed. If the level x is reached, the described cycle is interrupted. We should note that in continuous settings we could have cells having time of birth during the lifespan of other cells, every time when the lifespan of a type 0 cell is generated. That is why we have to perform additional computational procedure which lists all of the birth–death moments lying during this lifespan and increases the number of alive type 0 cells by 1 for all of these moments. We have to admit that, due to this additional procedure, the execution time of the algorithm is increasing in comparison to the one for GWBP in discrete time.

We provide simulation results concerning the r.v. T_x in continuous time settings. Recall that by the r.v. T_x we denote the time until the number of 0 type cells crosses the 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.

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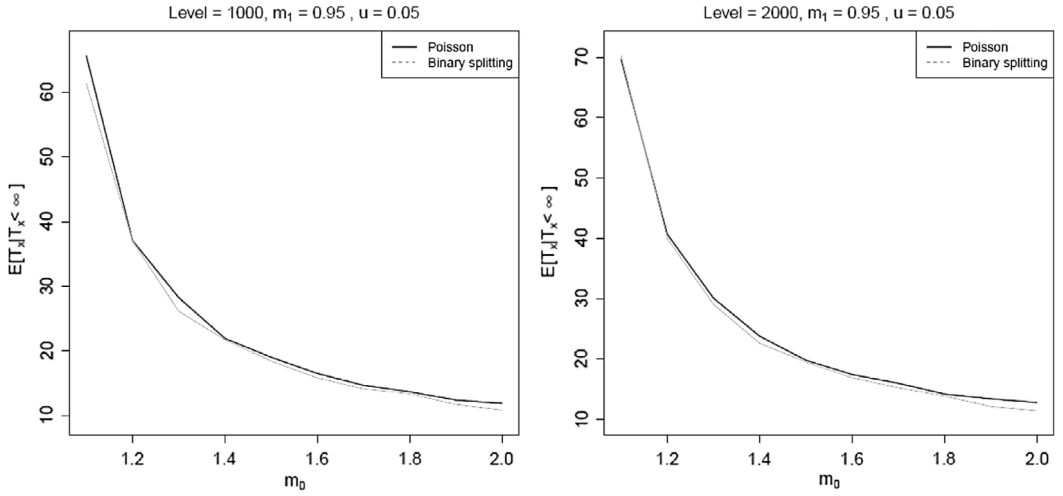

Fig. 6. Simulation results for the time T_x, elapsing until a level x of "mutants" is attained.

6.2. Estimation results for $\mathbb{E}[T_x \mid T_x < \infty]$

Using the described approach in Section 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 Fig. 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 Fig. 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.

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. This quantity sheds light on the time until the situation becomes critical, once a successful invasion has occurred (see Serra and Haccou, 2007). 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 Fig. 7. One may observe that the time needed increases when the level x increases. Another obvious observation is that as the level x increases, the modal class for the histogram is more clearly distinguished. 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.

7. Concluding remarks

The presented branching model has several possible applications:

Firstly, the results allow us to calculate the distribution of T (the waiting time until the first "successful" mutant occurs) numerically, which is important in determining how long we could wait before performing another chemotherapy. As it is shown, the distribution of T depends on the lifespan distribution of type 1 cells (which could depend on the type of cancer and the type of treatment) and can vary significantly. This is observed in Figs. 2 and 4, where we can see that the probability density function (p.d.f.) of T could have several peaks and troughs or none at all, depending on the lifespan distribution of type 1 cells. The particular shape of the p.d.f. and the hazard function $g(t)$ determine the most appropriate time to perform another chemotherapy.

Secondly, the hazard function $g(t)$ represents the probability density for the first "successful" mutant's 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 $\mathbb{P}(T = \infty \mid T > t)$.

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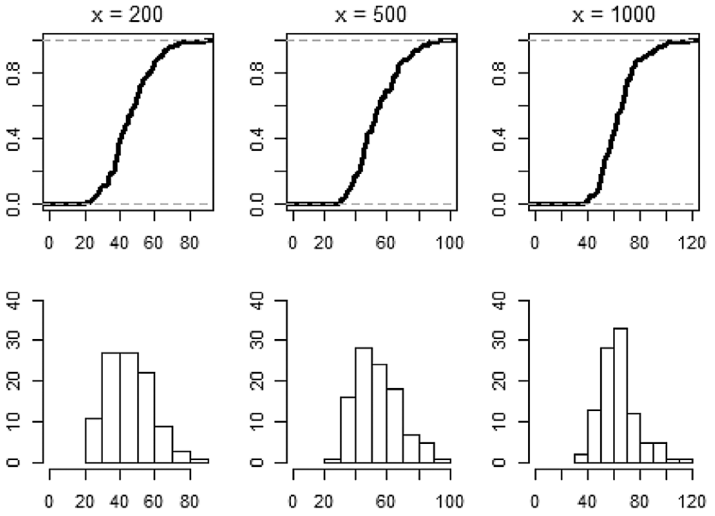

Fig. 7. Histograms and empirical cumulative distribution functions of $T_x \mid T_x < \infty$ for $x = 200, 500, 1000$.

Thirdly, the model also allows finding 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 5. We have used Matlab for implementing the numerical methods and the R programming language for performing the simulations (see R Development Core Team, 2011).

Acknowledgements

The research is supported by the National Fund for Scientific Research at the Ministry of Education and Science of Bulgaria, Grant No. DFNI-I02/17 and partially supported by the financial funds allocated to the Sofia University "St. Kl. Ohridski", Grant No. 047/2016 and Ministerio de Economía y Competitividad and the FEDER through the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, grant MTM2015-70522-P, Spain.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.csda.2016.12.013.

References

Athreya, K., Ney, P., 1972. Branching Processes. Springer Verlag.
Bartholomew, D., 1963. An approximate solution to the integral equation of renewal theory. J. R. Stat. Soc. Ser. B Stat. Methodol. 25 (2), 432–441.
Doney, R., 1971. The total progeny of a branching process. J. Appl. Probab. 8, 407–412.
Durrett, R., 2015. Branching Process Models of Cancer. Springer.
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.
Haccou, P., Jagers, P., Vatutin, V., 2007. Branching Processes: Variation, Growth and Extinction of Populations. Cambridge University Press.
Harris, T., 1963. The Theory of Branching Processes. Springer.
Iwasa, Y., Michor, F., Nowak, M., 2003. Evolutionary dynamics of escape from biomedical intervention. Proc. Biol. Sci. B 270 (1533), 2573–2578.
Iwasa, Y., Michor, F., Nowak, M., 2004. Evolutionary dynamics of invasion and escape. J. Theoret. Biol. 226 (2), 205–214.
Jagers, P., 1975. Branching Processes with Biological Applications, first ed. John Wiley & Sons Ltd..
Kimmel, M., Axelrod, D., 2002. Branching Processes in Biology. Springer.
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.
Lodish, H., Berk, A., Zipursky, L., Matsudaira, P., Baltimore, D., Darnell, J., 2000. Molecular Cell Biology, fourth ed. W. H. Freeman.
Mitov, K., Omey, E., 2014a. Intuitive approximations for the renewal function. Statist. Probab. Lett. 84, 72–80.
Mitov, K., Omey, E., 2014b. Renewal Processes. Springer.
Mode, C., 1971. Multitype Branching Processes: Theory and Applications. Elsevier, New York.
Mode, C., 1985. Stochastic Processes In Demography and their Computer Implementation. Springer.

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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.
Serra, M., 2006. On waiting time to escape. J. Appl. Probab. 43, 296–302.
Serra, M., Haccou, P., 2007. Dynamics of escape mutants. Theor. Popul. Biol. 72, 167–178.
Slavtchova, M., Yanev, N., 1990. Convergence in distribution of supercritical Bellman–Harris branching processes with state-dependent immigration. Math. Balkanica (N.S.) 4 (1), 35–42.
Slavtchova-Bojkova, M., 2016. On two-type decomposable branching processes in continuous time and time to escape extinction. In: del Puerto, I.M., et al. (Eds.), Branching Processes and their Applications. In: Lecture Notes in Statistics-Proceedings, vol. 219. Springer, pp. 319–329.
Xie, M., 1989. On the solution of renewal-type integral equations. Comm. Statist. Simulation Comput. 18 (1), 281–293.

Please cite this article in press as: Slavtchova-Bojkova, M., et al., Branching processes in continuous time as models of mutations: Computational approaches and algorithms. Computational Statistics and Data Analysis (2017), http://dx.doi.org/10.1016/j.csda.2016.12.013