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ON THE WAITING TIME TO ESCAPE

MARIA CONCEIÇÃO SERRA,* *Chalmers University of Technology*

Abstract

The mathematical model we consider here is a decomposable Galton–Watson process with individuals of two types, 0 and 1. Individuals of type 0 are supercritical and can only produce individuals of type 0, whereas individuals of type 1 are subcritical and can produce individuals of both types. The aim of this paper is to study the properties of the waiting time to escape, i.e. the time it takes to produce a type-0 individual that escapes extinction when the process starts with a type-1 individual. With a view towards applications, we provide examples of populations in biological and medical contexts that can be suitably modeled by such processes.

Keywords: Decomposable Galton–Watson branching process; probability generating function

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1. Introduction

In many biological and medical contexts we find populations that, due to the small reproductive ratio of the individuals, will become extinct after some time. However, sometimes changes occur during the reproduction process that lead to an increase of the reproductive ratio, making it possible for the population to escape extinction. In this work we use the theory of branching processes to model the evolution of this kind of population.

Cancer cells subjected to chemotherapy are an example of such a population. When the cells are subjected to chemotherapy, their capacity for division is reduced, hopefully leading to the extinction of tumour cells. Yet mutations may lead to another kind of cell that is resistant to the chemotherapy. Thus, the population of this new type of cell has a larger reproductive ratio and might escape extinction.

Another example can be found in epidemics like HIV or SARS. Imagine a virus of one host species that is transferred to another host species where it has a small reproductive mean and, therefore, the extinction of its lineage is certain. Mutations occurring during the reproduction process could still lead to a virus capable of initiating an epidemic in the new host species.

The goal of this article is to use a two-type Galton–Watson branching processes (GWBP) to study properties of populations of this sort. We assume that the process starts with a single subcritical individual that gives birth to individuals of the same type, but whose descendents, through mutation, can become supercritical and are therefore capable of establishing a population that has a positive probability of escaping extinction.

In Section 2 we introduce the model, the main reproduction parameters of the process, and give some references to theoretical and applied works. Section 3 contains the main results and proofs. Using probability generating functions, we derive properties of the distribution of the

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* Postal address: Department of Mathematical Statistics, Chalmers University of Technology, SE-412 96 Göteborg, Sweden. Email address: mcserra@math.chalmers.se

waiting time to produce an individual that escapes extinction. We prove that it has a point mass at ∞ and compute the tail probabilities and its expectation (conditioned on being finite). We also show that, in the long run, the population size of this process grows like that of a single-type GWBP with a delay.

2. Description of the model

Consider a two-type GWBP $\{(Z_n^{(0)}, Z_n^{(1)}),\ n \in \mathbb{N}_0\}$, where $Z_n^{(0)}$ and $Z_n^{(1)}$ respectively denote the number of individuals of type 0 and of type 1 in the nth generation, and $\mathbb{N}_0$ is the set of nonnegative integers. Suppose that individuals of type 1 are subcritical, i.e. have reproduction mean m, $0 < m < 1$, and that each one of their descendents can mutate, independently of the others, to type 0 with probability u, $0 < u < 1$. Individuals of type 0 are supercritical, i.e. have reproduction mean m_0, $1 < m_0 < \infty$, and there is no backward mutation. For this particular two-type GWBP, the first moment matrix is of the form

$$\boldsymbol{A} = \begin{bmatrix} m_0 & 0 \\ mu & m(1-u) \end{bmatrix}.$$

Unless stated otherwise, we assume that the process starts with just one individual, of type 1, i.e. $Z_0^{(0)} = 0$ and $Z_0^{(1)} = 1$. The probability generating function of the reproduction law of type-i individuals will be denoted by f_i, $i \in \{0, 1\}$, and the joint probability generating function of $(Z_1^{(0)}, Z_1^{(1)})$ is given by

$$\begin{aligned} F(s_0, s_1) = \mathrm{E}\Big[s_0^{Z_1^{(0)}} s_1^{Z_1^{(1)}}\Big] &= \sum_{k=0}^{\infty} p_k^{(1)} \sum_{j=0}^{k} \binom{k}{j} s_0^j u^j s_1^{k-j} (1-u)^{k-j} \\ &= f_1(s_0 u + (1-u)s_1), \qquad (s_0, s_1) \in [0, 1]^2, \end{aligned} \tag{2.1}$$

where $\{p_k^{(1)},\ k \in \mathbb{N}_0\}$ represents the reproduction law of type-1 individuals.

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 (1971). For recent books, with emphasis on applications, see Axelrod and Kimmel (2002) and also Haccou *et al.* (2005). 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).

3. Main results

3.1. Number of mutants and the probability of extinction

Consider the sequence of random variables $\{I_n,\ n \in \mathbb{N}_0\}$, with I_n being the total number of mutants produced until generation n (inclusive), and let I be the random variable that represents the number of mutants in the whole process. By *mutant* we mean an individual of type 0 whose mother is of type 1.

It is obvious that the sequence I_n converges pointwise to the random variable I. In our first theorem, we use this convergence to establish a functional equation for the probability generating function of I, denoted by f_I.

Theorem 3.1. *The probability generating function of I satisfies the functional equation*

$$f_I(s) = f_1(us + (1-u) f_I(s)), \tag{3.1}$$

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

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Proof. First we establish a recursive relation for the probability generating functions of the random variables I_n, denoted by f_{I_n}. We find that, for all $n \geq 1$,

$$\begin{aligned} f_{I_n}(s) &= \mathrm{E}[s^{I_n}] \\ &= \mathrm{E}[\mathrm{E}[s^{I_n} \mid Z_1^{(0)}, Z_1^{(1)}]] \\ &= \mathrm{E}\Big[\mathrm{E}\Big[s^{Z_1^{(0)}+\sum_{i=1}^{Z_1^{(1)}} I_{n-1}^i} \,\Big|\, Z_1^{(0)}, Z_1^{(1)}\Big]\Big] \\ &= \mathrm{E}\Big[s^{Z_1^{(0)}} \mathrm{E}[s^{I_{n-1}}]^{Z_1^{(1)}}\Big] \\ &= F(s, f_{I_{n-1}}(s)) \\ &= f_1(su + (1-u) f_{I_{n-1}}(s)), \end{aligned} \tag{3.2}$$

where the I_{n-1}^i are independent, identically distributed copies of the random variable I_{n-1}, the function F is as defined in (2.1), and $f_{I_0}(s) = 1$.

By taking the limit in relation (3.2) we obtain the functional equation (3.1).

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

$$\begin{aligned} q_0 &= \mathrm{P}[Z_n^{(0)} = Z_n^{(1)} = 0 \text{ for some } n \geq 1 \mid Z_0^{(0)} = 1,\ Z_0^{(1)} = 0], \\ q_1 &= \mathrm{P}[Z_n^{(0)} = Z_n^{(1)} = 0 \text{ for some } n \geq 1 \mid Z_0^{(0)} = 0,\ Z_0^{(1)} = 1], \end{aligned}$$

it follows, from the classical result on the extinction of branching processes, that q_0 is the smallest root of

$$q_0 = f_0(q_0)$$

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 GWBPs starting from the mutants die out. Since there are I such processes, we have

$$q_1 = \mathrm{E}[q_0^I] = f_I(q_0).$$

Obtaining an explicit expression for q_1 is not always possible; therefore, approximations are necessary for application purposes. Assuming there to be small mutation rate u, Iwasa *et al.* (2003), (2004) provided these approximations for particular reproduction laws, namely for Poisson and geometric distributions. Their results extend to an even more complex scheme of mutations leading to branching processes with more than two types of individual.

3.2. Waiting time to produce a successful mutant

Consider the random variable T, which represents the time to escape, i.e. the first generation in which a successful mutant is produced. By *successful mutant* we mean a mutant that is able to start a single-type GWBP that escapes extinction. This variable takes values in the set $\{1, 2, \dots, \infty\}$, with $T = \infty$ if no successful mutant is produced.

Theorem 3.2. *The distribution of T has the following properties:*

(i) $\mathrm{P}[T > k] = f_{I_k}(q_0)$ *for all* $k \geq 0$,

(ii) $\mathrm{P}[T = \infty] = q_1$,

(iii) $\mathrm{E}[T \mid T < \infty] = \sum_{k=0}^{\infty} (f_{I_k}(q_0) - q_1)/(1 - q_1)$.

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Proof. To prove (i), observe that $T > k$ means that all I_k mutants were unsuccessful. Therefore,

$$\mathrm{P}[T > k] = \mathrm{E}[q_0^{I_k}] = f_{I_k}(q_0).$$

To prove (ii), observe that $(T > k)_{k \geq 0}$ is a nonincreasing sequence of events and that

$$\mathrm{P}[T = \infty] = \mathrm{P}\Bigg[\bigcap_{k=0}^{\infty}(T > k)\Bigg] = \lim_{k\to\infty} \mathrm{P}[T > k] = \lim_{k\to\infty} f_{I_k}(q_0) = f_I(q_0) = q_1.$$

To prove (iii), observe that $T > 0$ and, therefore,

$$\begin{aligned}
\mathrm{E}[T \mid T < \infty] &= \sum_{k=0}^{\infty} \frac{\mathrm{P}[T > k, T < \infty]}{\mathrm{P}[T < \infty]} \\
&= \sum_{k=0}^{\infty} \frac{\mathrm{P}[T < \infty] - \mathrm{P}[T \leq k]}{1 - q_1} \\
&= \sum_{k=0}^{\infty} \frac{f_{I_k}(q_0) - f_I(q_0)}{1 - q_1},
\end{aligned}$$

with the f_{I_k} as recursively defined in (3.2).

A similar problem was considered in Bruss and Slavtchova-Bojkova (1999), where a single-type GWBP with immigration to the state 0 was used to model the repopulation of an environment. The idea is the following. Consider a population starting with a supercritical individual and let it grow according to a GWBP. If extinction occurs at time t then immigration takes place immediately after, i.e. one individual of the same kind is introduced and a new process, independent of and identically distributed to the first one, restarts. Among other results, Bruss and Slavtchova-Bojkova derived properties of the last instant of immigration, i.e. of the generation into which was introduced an immigrant that started a process that escaped extinction.

In the applications we consider, the mutants appear at random times as descendents of the subcritical individuals, and the model described above therefore does not apply.

3.3. Comparison with a single-type supercritical GWBP

In this section we prove a result that will allow us to compare the limit behavior of the sequence $Z_n^{(0)}$ with the limit behavior of a single-type supercritical GWBP. First, we recall a result on single-type GWBPs. The proof can be found in any of the classical books referred to in Section 2.

Theorem 3.3. *Let $\{Y_n,\ n \in \mathbb{N}_0\}$ be a single-type supercritical GWBP with reproduction law $\{p_k^{(0)},\ k \in \mathbb{N}_0\}$, and suppose that $Y_0 = 1$. If*

$$\sum_{k=0}^{\infty} k \log k p_k^{(0)} < \infty \tag{3.3}$$

then $Y_n/\mu^n \to W$ almost surely and in L^1, where $\mu = \sum_{k=0}^{\infty} k p_k^{(0)}$ and $\mathrm{E}[W] = 1$. Furthermore, the Laplace transform of W, ϕ_W, satisfies

$$\phi_W(\mu s) = f_0(\phi_W(s)), \qquad s \geq 0.$$

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Our result is as follows.

Theorem 3.4. *If the reproduction law of type-0 individuals satisfies condition (3.3), then*

$$\frac{Z_n^{(0)}}{m_0^n} \to U \quad \text{almost surely and in } L^1,$$

with $\mathrm{E}[U] = um/(m_0 - m(1-u)) < 1$. *Furthermore, the Laplace transform of* U, ϕ_U, *satisfies the functional equation*

$$\phi_U(m_0 s) = f_1(u\phi_W(s) + (1-u)\phi_U(s)),$$

where ϕ_W *is as in Theorem 3.3.*

Proof. Consider the sequence of random variables $\{J_n,\ n \geq 1\}$, where J_n represents the number of mutants in generation n, i.e. $J_n = I_n - I_{n-1}$. Using these variables, $Z_n^{(0)}$, $n \geq 1$, can be decomposed in the following way:

$$Z_1^{(0)} = J_1, \qquad Z_n^{(0)} = \sum_{k=1}^{n-1} \sum_{i=1}^{J_k} Y_{n-k}^i, \quad n \geq 2. \tag{3.4}$$

Here, the random variable Y_{n-k}^i represents the number of individuals in generation $n-k$ of the single-type supercritical GWBP initiated by the ith mutant of generation k. These processes are independent of each other and have the same reproduction law, namely $\{p_k^{(0)},\ k \in \mathbb{N}_0\}$.

By dividing (3.4) by m_0^n and taking expectations, we obtain

$$\begin{aligned} \mathrm{E}\left[\frac{Z_n^{(0)}}{m_0^n}\right] &= \sum_{k=1}^{n-1} \frac{1}{m_0^k} \mathrm{E}\left[\sum_{i=1}^{J_k} \frac{Y_{n-k}^i}{m_0^{n-k}}\right] \\ &= \sum_{k=1}^{n-1} \frac{1}{m_0^k} \mathrm{E}[J_k] \\ &= \sum_{k=1}^{n-1} \frac{1}{m_0^k} um[m(1-u)]^{k-1} \\ &\to \frac{um}{m_0 - m(1-u)} < 1 \quad \text{as } n \to \infty. \end{aligned} \tag{3.5}$$

The expectation of J_k is obtained by differentiation of the recursive relation (3.2). Since $\{m_0^{-n} Z_n^{(0)},\ n \geq 0\}$ is a submartingale with respect to the σ-algebra $F_n = \sigma\{Z_m^{(0)}, Z_m^{(1)}, 0 \leq m \leq n\}$ and, from (3.5), we have

$$\sup \mathrm{E}\left[\frac{Z_n^{(0)}}{m_0^n}\right] < \infty,$$

the martingale convergence theorem ensures that the sequence converges almost surely to a random variable U with $\mathrm{E}[U] < \infty$.

To prove L^1-convergence, it remains to show that

$$\mathrm{E}[U] = \frac{um}{m_0 - m(1-u)}. \tag{3.6}$$

Observe that, given $(Z_1^{(0)}, Z_1^{(1)})$, the following decomposition holds:

$$\frac{Z_n^{(0)}}{m_0^n} = \frac{1}{m_0} \sum_{i=1}^{Z_1^{(0)}} \frac{Y_{n-1}^i}{m_0^{n-1}} + \frac{1}{m_0} \sum_{j=1}^{Z_1^{(1)}} \frac{X_{n-1,j}^{(0)}}{m_0^{n-1}}. \tag{3.7}$$

In this expression the Y_{n-1}^i are as described in decomposition (3.4) and the $X_{n-1,j}^{(0)}$ are the random variables that represent the number of type-0 individuals in generation $n-1$ of the jth two-type GWBP initiated in generation 1. There are $Z_1^{(1)}$ such processes and they are independent of each other. Taking the limit in (3.7) (the existence of the limits of the sequences involved was already proved) gives

$$U = \frac{1}{m_0} \sum_{i=1}^{Z_1^{(0)}} W_i + \frac{1}{m_0} \sum_{j=1}^{Z_1^{(1)}} U_j, \tag{3.8}$$

where W_i are independent, identically distributed copies of W, as defined in Theorem 3.3, and U_j are independent, identically distributed copies of U. It is now a matter of taking expectations in (3.8) to obtain the desired result, (3.6).

Finally, proving the functional equation for the Laplace transform of U is just a matter of using (3.8). Indeed,

$$\begin{aligned}
\phi_U(s) &= \mathrm{E}[\mathrm{e}^{-sU}] \\
&= \mathrm{E}[\mathrm{E}[\mathrm{e}^{-sU} \mid Z_1^{(0)}, Z_1^{(1)}]] \\
&= \mathrm{E}\Bigg[\mathrm{E}\Bigg[\exp\Bigg(-\frac{s}{m_0}\sum_{i=1}^{Z_1^{(0)}} W_i\Bigg) \Bigg| Z_1^{(0)}, Z_1^{(1)}\Bigg] \mathrm{E}\Bigg[\exp\Bigg(-\frac{s}{m_0}\sum_{j=1}^{Z_1^{(1)}} U_j\Bigg) \Bigg| Z_1^{(0)}, Z_1^{(1)}\Bigg]\Bigg] \\
&= \mathrm{E}\Bigg[\bigg(\phi_W\bigg(\frac{s}{m_0}\bigg)\bigg)^{Z_1^{(0)}} \bigg(\phi_U\bigg(\frac{s}{m_0}\bigg)\bigg)^{Z_1^{(1)}}\Bigg] \\
&= f_1\bigg(u\phi_W\bigg(\frac{s}{m_0}\bigg) + (1-u)\phi_U\bigg(\frac{s}{m_0}\bigg)\bigg).
\end{aligned}$$

With

$$\tau = \bigg|\log_{m_0}\bigg(\frac{um}{m_0 - m(1-u)}\bigg)\bigg|,$$

we conclude that there exists a random variable U^* such that

$$\frac{Z_n^{(0)}}{m_0^{n-\tau}} \to U^* \quad \text{almost surely and in } L^1,$$

with $\mathrm{E}[U^*] = 1$. This indicates that the sequence $Z_n^{(0)}$ exhibits the same limit behavior as a single-type supercritical GWBP, except with a delay τ. It remains to investigate the relation between the constant τ and the random variable that represents the delay between the two processes.

In applications, it is not only important to study the time taken to produce a successful mutant, but also the time taken for the number of type-0 individuals to reach high levels. Theorem 3.4 provides a first step in determining this.

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