Applied Probability Trust (9 October 2005)

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 two types of individuals, 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 processes; probability generating functions

2000 Mathematics Subject Classification: Primary 60J85

Secondary 60J80

1. Introduction

In many biological and medical contexts we find populations that, due to a small reproductive ratio of the individuals, will get extinct after some time. Yet, 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 populations.

Cancer cells submitted to chemotherapy are an example of such populations. In fact, when submitted to chemotherapy, the capacity of division of the cells is reduced, hopefully leading to the extinction of tumour cells. Yet mutations may lead to another

* Postal address: Department of Mathematical Statistics, Chalmers University of Technology, SE-412 96 Göteborg, Sweden

kind of cells that are resistant to the chemotherapy. Thus, the population of this new type of cells has a larger reproductive ratio and can 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. Yet, mutations occurring during the reproduction process can lead to a virus which is 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 (G.W.B.P.) to study properties of the populations described above. We assume that the process starts with just one subcritical individual that gives birth to individuals of the same type but, through mutation, her descendents can become supercritical and therefore capable of initiating 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 theoretical and applied references.

Section 3 contains the main results and proofs. Based on probability generating functions, we derive properties of the distribution of the waiting time to produce an individual that escapes extinction. We prove that it has a point mass at ∞, 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 as the one of a single-type G.W.B.P., with a delay.

2. Description of the model

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

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

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

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

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, Jagers and Vatutin (2005). For a nice example on how branching processes can be used to solve important problems in biology and medicine, the reader should take a look at the papers of Iwasa, Michor and Nowak (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 (included), 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 random variable I. The first theorem of this paper uses this convergence to establish a functional equation for the p.g.f. of I, denoted by f_I.

Theorem 3.1. *The p.g.f. of I satisfies the following functional equation*

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

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

Proof. First we establish a recursive relation for the p.g.f.'s of the random variables I_n, denoted by f_{I_n}.

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

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

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 following notation:

$$q_0 = P[Z_n^{(0)} = Z_n^{(1)} = 0, \text{for some } n \geq 1 | Z_0^{(0)} = 1,\, Z_0^{(1)} = 0]$$

and

$$q_1 = P[Z_n^{(0)} = Z_n^{(1)} = 0, \text{for some } n \geq 1 | Z_0^{(0)} = 0,\, Z_0^{(1)} = 1],$$

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

$$q_0 = f_0(q_0) \tag{3.3}$$

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 G.W.B.P. starting from the mutants die out. Since there are I such processes, then

$$q_1 = E[q_0^I] = f_I(q_0). \tag{3.4}$$

Obtaining explicit expressions for q_1 is not always possible and therefore approximations are necessary for application purposes. Assuming small mutation rate u, the authors of [6] and [7] provide these approximations for particular reproduction laws, namely Poisson and geometric distribution. Their results extend to an even more complex scheme of mutations leading to branching processes with more than two types of individuals.

3.2. Waiting time to produce a successful mutant

Consider the random variable T that represents the time to escape, i.e. the first generation where a *successful mutant* was produced. By *successful mutant* we mean a mutant that was able to start a single-type G.W.B.P. that escaped extinction. This variable assumes values in the set $\{1, 2, \ldots, \infty\}$, with $T = \infty$ if no successful mutant was produced.

Theorem 3.2. *The distribution of T satisfies the following:*

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

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

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

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

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

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

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

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

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

with the f_{I_k} defined recursively by (3.2) in the proof of Theorem 3.1. □

A similar problem was considered in [3] where a single-type G.W.B.P. with immigration in the state 0 is used to model the re-population of an environment. The idea is the following. Consider a population starting with a supercritical individual and let it grow according to a G.W.B.P.. 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, i.i.d. with the first one, restarts. Among others results, the authors derive properties of the last instant of immigration, i.e. of the generation where an immigrant that started a process that escaped extinction was introduced.

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

3.3. Comparison with a single-type supercritical G.W.B.P.

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 G.W.B.P..

First we recall a result on single-type G.W.B.P.. The proof can be found in any of the classical books referred in Section 2.

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

$$\sum_{k=0}^{\infty} k \log k \, p_k^{(0)} < \infty \tag{3.5}$$

then

$$\frac{Y_n}{\mu^n} \to W \quad a.s. \text{ and in } L^1$$

where $\mu = \sum_{k=0}^{\infty} k \, p_k^{(0)}$ and $E[W] = 1$. Furthermore, the Laplace transform of W, ϕ_W, satisfies

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

Our result is the following.

Theorem 3.4. *If the reproduction law of type 0 individuals satisfies condition* (3.5), *then*

$$\frac{Z_n^{(0)}}{m_0^n} \to U \quad a.s. \text{ and in } L^1$$

with $E[U] = \frac{um}{m_0 - m(1-u)} < 1$. 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:

$$\begin{cases} Z_1^{(0)} = J_1 \\ Z_n^{(0)} = \displaystyle\sum_{k=1}^{n-1} \sum_{i=1}^{J_k} Y_{n-k}^i, \quad n \geq 2, \end{cases} \tag{3.6}$$

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

Dividing (3.6) by m_0^n and taking expectations we get

$$\begin{aligned} E\left[\frac{Z_n^{(0)}}{m_0^n}\right] &= \sum_{k=1}^{n-1} \frac{1}{m_0^k}\, E\left[\sum_{i=1}^{J_k} \frac{Y_{n-k}^i}{m_0^{n-k}}\right] \\ &= \sum_{k=1}^{n-1} \frac{1}{m_0^k} E[J_k] \\ &= \sum_{k=1}^{n-1} \frac{1}{m_0^k} um[m(1-u)]^{k-1} \\ &\underset{n\to\infty}{\longrightarrow} \frac{um}{m_0 - m(1-u)} < 1 \end{aligned} \tag{3.7}$$

The expectation of J_k is obtained by differentiation of the recursive relation (3.2).

Since $\left\{m_0^{-n} Z_n^{(0)}, n \geq 0\right\}$ 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 (3.7),

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

the martingale convergence theorem ensures that the sequence converges a.s. to a random variable, U, and $E[U] < \infty$.

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

$$E[U] = \frac{um}{m_0 - m(1-u)}. \tag{3.8}$$

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

$$\frac{Z_n^{(0)}}{m_0^n} = \frac{1}{m_0} \sum_{i=1}^{Z_1^{(0)}} \frac{Y_{n-1}^i}{m_0^{n-1}} + \frac{1}{m_0} \sum_{j=1}^{Z_1^{(1)}} \frac{X_{n-1,j}^{(0)}}{m_0^{n-1}} \tag{3.9}$$

where the Y_{n-1}^i are as described in decomposition (3.6) 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 j^{th} two-type G.W.B.P. initiated in generation 1. There are $Z_1^{(1)}$ such processes and they are independent of each other. Taking the limit in (3.9), (the existence of the limits of the sequences involved was already proved) gives

$$U = \frac{1}{m_0} \sum_{i=1}^{Z_1^{(0)}} W_i + \frac{1}{m_0} \sum_{j=1}^{Z_1^{(1)}} U_j \tag{3.10}$$

where W_i are i.i.d. copies of W, as defined in Theorem 3.3, and U_j are i.i.d. copies of U. It is now a matter of taking expectation in (3.10) to obtain the desired (3.8).

Finally, to prove the functional equation for the Laplace transform of U, is just a matter of using (3.10). In fact,

$$\begin{aligned}
\phi_U(s) &= E\left[e^{-sU}\right] = E\left[E\left[e^{-sU} \mid Z_1^{(0)}, Z_1^{(1)}\right]\right] \\
&= E\left[E\left[e^{-\frac{s}{m_0}\sum_{i=1}^{Z_1^{(0)}} W_i} \mid Z_1^{(0)}, Z_1^{(1)}\right] E\left[e^{-\frac{s}{m_0}\sum_{j=1}^{Z_1^{(1)}} U_j} \mid Z_1^{(0)}, Z_1^{(1)}\right]\right] \\
&= E\left[\left[\phi_W\left(\frac{s}{m_0}\right)\right]^{Z_1^{(0)}} \left[\phi_U\left(\frac{s}{m_0}\right)\right]^{Z_1^{(1)}}\right] \\
&= f_1\left(u\phi_W\left(\frac{s}{m_0}\right) + (1-u)\phi_U\left(\frac{s}{m_0}\right)\right) \qquad (3.11)
\end{aligned}$$

□

Taking $\tau = \left|\log_{m_0}\left(\frac{um}{m_0 - m(1-u)}\right)\right|$, we can conclude that there exists a random variable U^* such that

$$\frac{Z_n^{(0)}}{m_0^{n-\tau}} \to U^* \quad \text{a.s. and in } L^1$$

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

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

Acknowledgements

To author would like to thank Patsy Haccou, Peter Jagers and Serik Sagitov for many helpful discussions and careful reading of this manuscript. Also to the Center of Mathematics of the University of Minho, Portugal, and to the Portuguese Foundation for Science and Technology for supporting the stay at Chalmers University.

References

[1] Athreya, K. and Ney, P. (1972). *Branching Processes.* Springer, Berlin.

[2] Axelrod, D.E. and Kimmel, M. (2002). *Branching Processes in Biology.* Springer-Verlag, New York.

[3] Bruss, F.T. and Slavtchova-Bojkova, M. (1999). On waiting times to populate an environment and a question of statistical inference. *J. Appl. Prob.* **36,** 261-267.

[4] Haccou, P., Jagers, P. and Vatutin, V.A. (2005). *Branching Processes: Variation, Growth and extinction of populations.* Cambridge University Press.

[5] Harris, T.E. (1963). *The Theory of Branching Processes.* Springer-Verlag, Berlin.

[6] Iwasa, Y., Michor, F. and Nowak, M. (2003) Evolutionary dynamics of escape from biomedical intervention. *Proc. Roy. Soc. London* **B 270,** 2573-2578.

[7] Iwasa, Y., Michor, F. and Nowak, M. (2004) Evolutionary dynamics of invasion and escape. *J. Theor. Biology* **226, Issue 2,** 205-214.

[8] Mode, C. (1971). *Multitype Branching Processes: Theory and Applications.* Elsevier, New York.