Dynamics of escape mutants

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Abstract

We use multi-type Galton–Watson branching processes to model the evolution of populations that, due to a small reproductive ratio of the individuals, are doomed to extinction. Yet, mutations occurring during the reproduction process, may lead to the appearance of new types of individuals that are able to escape extinction. We provide examples of such populations in medical, biological and environmental contexts and give results on (i) the probability of escape/extinction, (ii) the distribution of the waiting time to produce the first individual whose lineage does not get extinct and (iii) the distribution of the time it takes for the number of mutants to reach a high level. Special attention is dedicated to the case where the probability of mutation is very small and approximations for (i)–(iii) are derived.
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1. Introduction

In many medical, biological and environmental contexts we find populations that, due to a small reproductive ratio of the individuals, will go extinct after some time. Yet, sometimes changes can occur during the reproduction process that lead to an increase of the reproductive ratio, making it possible for the population to escape extinction.

Cancer cells submitted to chemotherapy are an example of such populations (cf. Michor et al., 2004; Nowak et al., 2004). During chemotherapy the capacity of division of the cancer cells is reduced, which should lead to the destruction of tumors. Yet, sometimes mutations in the cells provide resistance to the therapy. This new type of cells has a higher reproduction and can escape extinction.

Another example can be found in viruses. A virus adapted to one host species that switches to another host usually has a small reproductive mean and, therefore, the

extinction of its lineage is certain. Mutations can lead to a virus capable of initiating an epidemic in the new host species. This happened for instance in HIV and SARS viruses.

More generally, in many evolutionary processes mutants may appear which are initially less viable than the resident type and thus are doomed for extinction. Additional mutations, however, may lead to a more successful type that can outcompete the resident. In this way, an evolutionary process can cross a fitness valley.

In agriculture we find situations where introgression may occur between genetically modified or cultivated organisms with wild populations (Ellstrand et al., 1999; Maan, 1987). Usually the first backcrosses are not very viable and fertile, but eventually a successful type may be produced.

Finally, an important environmental problem is the spread of insecticide resistance due to hybridization between resistant and susceptible insects. Some of the biotypes of the sweet potato whitefly, for instance, have developed resistance to certain insecticides (Byrne et al., 1994; De Barro and Hart, 2000; Guirao et al., 1997). Although matings between different biotypes are rare, hybrid formation can occur. The initial hybrids have low

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fitness. Yet, after several backcrosses between resistant and sensitive biotypes, a successful resistant hybrid may be produced.

In all the examples given above it is of vital importance to have good estimates of the probability of successful escape and related aspects, such as the distribution of numbers of escape mutations, the distribution of waiting times until escape, and the time it takes for the number of escape mutants to reach a high level. In this paper we will derive such estimates.

We will use a discrete time branching process (Jagers, 1975), known as the Galton–Watson branching process (GWBP) as a model, and therefore we assume that each individual of the population belongs to a unique generation, lives one unit of time and gives birth to a random number of individuals. The descendants will form the next generation and so on. Since we consider different kinds of individuals, with different reproductive ratio, we will use a multi-type GWBP to model their dynamics.

The assumption of discrete non-overlapping generations is obviously a simplification. Yet, mathematically, discrete models are much easier to handle than their continuous time analogs, and in some problems, like extinction, we can deduce results that also hold for the analogous continuous time process. Furthermore, our results will serve as a first step, and may be generalized at a later stage.

The structure of the paper is as follows. In Section 2 we describe the basic model for two types and derive the probability generating function of the numbers of mutations to the escape type. We demonstrate how this function can be used to determine moments of the distribution of the numbers of mutations. In Section 3 we derive expressions for the probability of extinction (and escape) of this process. Furthermore, we present approximations of these probabilities for multi-type processes with a general reproduction and mutation scheme, assuming that the mutation rates are small. We show that the results derived by Iwasa et al. (2003, 2004), for the Poisson and geometric offspring distributions can be applied more generally, and we provide a bound for the error term in the approximation. In Section 4 we study the waiting time to produce a successful mutant in a population with two types of individuals and give approximations for its distribution. Finally, in Section 5 we consider the time until the mutant population has grown to a high level.

2. The basic model

Consider a population with two types of individuals, type 0 and type 1, such that each descendant of an individual of type 1 can mutate, with probability $u \in (0, 1)$, to type 0. Mutations from type 0 to type 1 are assumed not to occur. Furthermore, we assume that individuals reproduce independently of each other and that the occurrence of mutations is also independent. We assume that individuals of type 1 have reproduction mean $0 < m < 1$ and we call them subcritical individuals. Individuals of type

0 will be called escape type and we assume they have reproduction mean $1 < m_0 < \infty$.

Notice that a single-type GWBP, starting with one individual of type 0, has positive probability of escaping extinction and this justifies the choice of calling them "escape" individuals. The choice to call type 1 "subcritical" individuals follows established mathematical terminology.

We will use a two-type GWBP, $\{(Z_n^{(0)}, Z_n^{(1)}), n \in \mathbb{N}_0\}$, to model the number of individuals in this kind of population. As usual, $Z_n^{(0)}$ and $Z_n^{(1)}$ denote the number of individuals of type 0 and of type 1, respectively, in the nth generation. Unless stated otherwise, we assume that the population starts with a single individual of type 1, i.e., $Z_0^{(0)} = 0$ and $Z_0^{(1)} = 1$. The joint probability generating function (p.g.f.) of $(Z_1^{(0)}, Z_1^{(1)})$ is given by

$$F(s_0, s_1) = f(s_0 u + (1 - u)s_1), \quad (s_0, s_1) \in [0, 1]^2, \qquad (1)$$

where f denotes the p.g.f. of the reproduction law of type 1 individuals.

Unless mutations occur, such a process will be a single-type subcritical GWBP and it is the appearance of mutants that makes the study of such populations an interesting task. Therefore it is important to study, for instance, the total number of mutations that occur in the whole process. This random quantity will play a crucial role in determining the extinction probability of the process. Let I be the random variable (r.v.) that counts the total number of mutations to the escape type in the whole process. Using (1), we can deduce that the p.g.f. of I, which will be denoted by h, satisfies the following functional equation:

$$h(s) = F(s, h(s)) = f(su + (1 - u)h(s)) \quad \forall s \in [0, 1]. \qquad (2)$$

From this functional equation we can derive the moments of I. We start by computing the mean value. Differentiating (2), we get

$$h'(s) = f'(su + (1 - u)h(s))(u + (1 - u)h'(s)) \qquad (3)$$

and replacing s by 1 in (3), and solving for $h'(1) = E[I]$, yields

$$E[I] = \frac{mu}{1 - m(1 - u)}. \qquad (4)$$

Differentiating (3), we can obtain the variance in a similar way, which leads to

$$Var[I] = h''(1) + E[I](1 - E[I])$$
$$= \frac{um(1 - u)(1 - m)^2 + u^2\sigma^2}{[1 - m(1 - u)]^3}, \qquad (5)$$

where σ^2 denotes the variance of the reproduction law of type 1 individuals.

From (4) it can be seen that, on average, less than m mutants are produced before the original type is extinct. It may come as a surprise that this upper limit holds for all u and $m < 1$, considering the fact that, if no mutations were allowed, the expectation of the total progeny of the initial individual would be $m/(1 - m)$ which is always larger than