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

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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.

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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,

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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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