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MULTITYPE BRANCHING PROCESSES IN CONTINUOUS TIME AS MODELS OF CANCER

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A generalization of the results for two-type decomposable branching processes model in continuous time derived in [9] is obtained. More precisely, the system of integral equations for probability generating functions (p.g.f.) of the $(n+1)-$type processes is obtained. Another important result is the recursive equations satisfied by the p.g.f. of the number of mutations. The results obtained are the base for further research of probabilities of extinction and estimation of the risk of cancer recurrence.

Keywords: decomposable multi–type branching processes, continuous time, mutations.

2000 Math. Subject Classification: 60J85, 60J80.

1. INTRODUCTION

The aim of this paper stems from the attempts to model mathematically the behavior of cancer cell populations subjected to some treatment, i.e. chemotherapy, radiotherapy or another type of medical treatment. As a result of the treatment, the reproduction rate of the cancer cells decreases. In terms of the branching process theory, the reproduction of these cells acquires subcritical characteristics meaning that the mean of the offspring per progenitor is less than 1. It is well-known (see e.g. [1]) that a subcritical population goes extinct with probability 1 (or almost surely) given a sufficiently long period of time. The empirical experience, however, shows that during the division of the subcritical cells it is possible for mutations to

occur. These mutant cells may have supercritical characteristics, i.e. the mean of cells per progenitor is greater than 1, meaning that after a sufficiently long period of time either the population completely disappears with probability $0 < q < 1$, or it increases (theoretically) indefinitely with probability $1 - q$. Models in discrete time with more than one subcritical cell type and one supercritical cell type are considered in [7], [8] and others. Similar models, but in a continuous time are studied in [2], [9] and [10].

The framework of classical branching theory, on which the results in the current paper are based, is developed in the classical books [3, 1, 4, 6]. Further development on the application of branching processes in biology can be found in [5] and [2].

This work aims to expand the results in [9] and [10], in the case of more than one subcritical cell types. Let us note that considering a branching process with more than one type of subcritical cancer cells is actually of interest from a practical point of view. Cancer is a multi-stage disease and frequently metastases are observed after local eradication of the tumor and subsequent adequate treatment meaning that the cancer spreads to different parts of the body, depending on the particular type of cancer. The differences in the environment may encourage the variation in the characteristics of the cancer cells, leading to the differentiation of different types. This motivates studying a more complicated model allowing more than one type of subcritical cells.

In what follows, we will discuss the general case in which the offspring of a subcritical cell of an arbitrary type may be of any other type, i.e. from one of the subcritical types or from the supercritical one. On the other hand, we will limit ourselves to the case of one supercritical type, where the generation of supercritical type cells can only be of the supercritical type. This means we will explore a decomposable branching process (for this type of branching processes, the theoretical results are far less abundant).

The paper is organized as follows: Section 2 introduces the branching process model with $n + 1$ types of cells in continuous time. Section 3 contains the main results and proofs. In Theorem 1 we prove the basic functional equations for p.g.f. of the process itself. In Theorem 2 we obtain the p.g.f. 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.

2. FORMULATION OF THE MODEL

Before proceeding with the main model in Definition 2 let us recall:

Definition 1. An age–dependent branching process $\{Z(t), t \geq 0\}$ with one type of cells, being the number of cells alive at time t, starting at time 0 with a single progenitor of age 0, i.e. $Z(0)$, is called a Bellman–Harris branching process (BHBP), if:

(i) The life–length τ of the progenitor has distribution $G(t)=P(\tau\leq t)$, $G(0^+)=0$;

(ii) Each cell produces $k,\ k\geq 0$, similar cells of age 0 at the end of its life with probability $p_k, 0\leq p_k\leq 1$, which have the same life–length distribution $G(t)$ and reproduce independently according to $\{p_k\}$, $\sum_{k=0}^{\infty} p_k = 1$.

The single–type Bellman–Harris branching process together with proper biological applications is studied by Jagers [4] and more theoretically by Athreya and Ney [1].

Now we will state the constructive definition of the main model, as a model of a multi-stage cancer process, where type 0 is reserved for the malignant-type (supercritical) cells, characterized by high capacity of division, and the types $i,\ i=1,\ldots,n$, correspond to the successfully treated (subcritical) types of cancer cells.

Definition 2. Define the multi-type branching model of mutations with $n+1$ types of cells as follows:

(i) There are $n+1$, $n>1$ different types of cells;

(ii) Each cell type has the properties stated in the definition of the single–type BHBP (although it is not necessary for the offspring to be of the same type as the mother cell, see (iii)). Each type has a (possibly) distinctive (continuous) distribution $G_i(t)=P(\tau_i\leq t)$, $G_i(0^+)=0$, of the life–length τ_i, and (possibly) distinctive (discrete) distribution $\{p_{ik}\}$, $\sum_{k=0}^{\infty} p_{ik}=1$ of the number of cells in the offspring ν_i, $i=0,\ldots,n$;

(iii) Each of the descendants of a subcritical type $i,\ i=1,\ldots,n$, can mutate at birth, independently of other cells, to any other type, with probabilities u_{ik}, $0\leq u_{ik}\leq 1,\ k=0,\ldots,n$, $\sum_{k=0}^{n} u_{ik}=1$. Descendants of the supercritical type 0 can not mutate to another type, i. e. $u_{00}=1$, meaning that there is no backward mutation. Because of the mutation scheme of type 0 the branching process is decomposable.

(iv) Cells of type $i,\ i=1,\ldots,n$, have subcritical reproduction, i.e. for the offspring mean m_i, we have $0<m_i<1$. Cells of type 0 have supercritical reproduction, i.e. have reproduction mean m_0, with $1<m_0<\infty$;

(v) Formally, we denote $\{\mathbf{Z}(t)=(Z^0(t),Z^1(t),\ldots,Z^n(t)),t\geq 0\}$, where $\{Z^i(t),t\geq 0\}$ stands for the number of cells of type i, $i=0,\ldots,n$, at time t, respectively.

From now on, unless stated otherwise, we assume that the process starts with just one cell of type i, $i=1,\ldots,n$, i.e. $Z^0(0)=0$, $Z^i(0)=1$ and $Z^j(0)=0,\ j\neq i$.

The p.g.f. of the offspring ν_i of type i cells will be denoted by $f_i(s)$, $i = 0, \ldots, n$, and

$$f_i(s) = E(s^{\nu_i}) = \sum_{k=0}^{\infty} p_{ik} s^k, \quad |s| \leq 1.$$

In addition, we introduce the following notation for the p.g.f. of the process:

1. For each type $i = 0, \ldots, n$, we denote

$$F_i(t; s_0, \ldots, s_n) = \mathbb{E}(s_0^{Z^0(t)} \ldots s_n^{Z^n(t)} | Z^i(0) = 1, Z^j(0) = 0, j \neq i);$$

2. The p.g.f. of the whole process is

$$\mathbf{F}(t; \mathbf{s}) = (F_0(t; \mathbf{s}), \ldots, F_n(t; \mathbf{s})), \mathbf{s} = (s_0, \ldots, s_n).$$

3. MAIN RESULTS

3.1. BASIC FUNCTIONAL EQUATIONS

In the following theorem we will obtain the basic non-linear integral equations for the p.g.f. of the age–dependent branching process defined in Section 2.

Theorem 1. *The probability generating function* $\mathbf{F}(t; s_0, \ldots, s_n)$ *satisfies the following non-linear integral equations*

1. For type 0*:*

$$\begin{aligned} F_0(t; s_0, s_1, \ldots, s_n) &= F_0(t; s_0) \\ &= s_0(1 - G_0(t)) + \int_0^t f_0(F_0(t-y; s_0)) dG_0(y). \end{aligned} \tag{3.1}$$

2. For type i, $1 \leq i \leq n$*:*

$$\begin{aligned} F_i(t; s_0, s_1, \ldots, s_n) &= s_i(1 - G_i(t)) \\ &+ \int_0^t f_i\Big(u_{i0} F_0(t-y; s_0) + \sum_{k=1}^{n} u_{ik} F_k(t-y; s_0, s_1, \ldots, s_n)\Big) dG_i(y). \end{aligned} \tag{3.2}$$

Proof. 1). Let us consider the case when the process starts with one cell of type 0. The independence assumption of the cells' evolution allows us to consider our process as consisting of k separate processes, after first splitting of the initial cell, which gives us the following relation:

$$F_0(t;s_0,s_1,\dots,s_n) = E(E(s_0^{Z^0(t)}s_1^{Z^1(t)}\dots s_n^{Z^n(t)}|Z^0(0)=1,Z^j(0)=0,j\neq 0,(\tau_0,\nu_0)))$$

$$= s_0(1-G_0(t)) + \int_0^t \sum_{k=0}^{\infty} p_{0k} E(s_0^{Z^0(t-y)}s_1^{Z^1(t-y)}\dots s_n^{Z^n(t-y)}|Z^0(0)=k, Z^j(0)=0, j\neq 0) dG_0(y)$$

$$= s_0(1-G_0(t)) + \int_0^t \sum_{k=0}^{\infty} p_{0k} (E(s_0^{Z^0(t-y)}|Z^0(0)=1, Z^j(0)=0, j\neq 0))^k dG_0(y)$$

$$= s_0(1-G_0(t)) + \int_0^t \sum_{k=0}^{\infty} p_{0k} F_0(t-y;s_0)^k dG_0(y)$$

$$= s_0(1-G_0(t)) + \int_0^t f_0(F_0(t-y;s_0)) dG_0(y).$$

Notice that this equation is the integral equation obtained for the classical BHBP.

2). Consider the case where the process starts with one cell of type i, $1\leq i\leq n$. Again, using the independence assumption, a decomposition of the sample space Ω in accordance with the life–length τ_i and number ν_i of offspring of the initial cell of type i and multinomial distribution yields the relation:

$$F_i(t;s_0,s_1,\dots,s_n) = E(E(s_0^{Z^0(t)}s_1^{Z^1(t)}\dots s_n^{Z^n(t)}|Z^i(0)=1,Z^j(0)=0,j\neq i,(\tau_i,\nu_i)))$$
$$= s_i(1-G_i(t))$$
$$+ \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \frac{u_{i0}^{k_0}u_{i1}^{k_1}\dots u_{in}^{k_n}}{k_1!k_2!\dots k_n!} k! E(s_0^{Z^0(t-y)}s_1^{Z^1(t-y)}\dots s_n^{Z^n(t-y)}|Z^j(0)=k_j,\forall j) dG_i(y)$$

$$= s_i(1-G_i(t)) + \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \Big[\frac{u_{i0}^{k_0}u_{i1}^{k_1}\dots u_{in}^{k_n}}{k_1!k_2!\dots k_n!} k! E(s_0^{Z^0(t-y)}|Z^0(0)=1,Z^j(0)=0,j\neq 0)^{k_0}$$
$$\times \prod_{m=1}^{n} E(s_0^{Z^0(t-y)}s_1^{Z^1(t-y)}\dots s_n^{Z^n(t-y)}|Z^m(0)=1,Z^j(0)=0,j\neq m)^{k_m} \Big] dG_i(y)$$

$$= s_i(1-G_i(t)) + \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \Big[\binom{k}{k_0,k_1,\dots,k_n} u_{i0}F_0(t-y;s_0)]^{k_0}$$
$$\times \prod_{m=1}^{n} [u_{im}F_m(t-y;s_0,s_1,\dots,s_n)]^{k_m} \Big] dG_i(y)$$

$$= s_i(1-G_i(t)) + \int_0^t \sum_{k=0}^{\infty} p_{ik} \Big[u_{i0}F_0(t-y;s_0) + \sum_{\nu=1}^{n} u_{i\nu}F_\nu(t-y;s_0,s_1,\dots,s_n) \Big]^k dG_i(y)$$

$$= s_i(1-G_i(t)) + \int_0^t f_i\Big(u_{i0}F_0(t-y;s_0) + \sum_{\nu=1}^{n} u_{i\nu}F_\nu(t-y;s_0,s_1,\dots,s_n)\Big)dG_i(y).$$

□

3.2. NUMBER OF MUTANTS

Definition 3. In the context of the model under discussion a "mutant" cell is each cell of type 0, whose mother cell is of type i, $1{\leq}i{\leq}n$.

It is worth noticing that, at any moment of time, the random variable (r.v.) "number of cells of type 0" is rather different from the r.v. "number of mutants".

Let us denote by $I_i(t)$, $1{\leq}i{\leq}n$, the r.v. "number of mutants that occurred in the process until time t, for a process starting with one cell of type i". We denote the p.g.f. of $I_i(t), 1{\leq}i{\leq}n$ as:

$$h_{I_i(t)}(s) = E(s^{I_i(t)}), \quad |s|{\leq}1. \tag{3.3}$$

Let $I_i, 1{\leq}i{\leq}n$ be the r.v. "total number of mutant cells, that occurred in a process with one initial cell of type i, for the duration of the whole process".

The p.g.f. of $I_i, 1{\leq}i{\leq}n$ is denoted by:

$$h_{I_i}(s) = E(s^{I_i}), |s|{\leq}1. \tag{3.4}$$

Theorem 2. *The probability generating functions $h_{I_i(t)}(s)$ of $I_i(t)$ and $h_{I_i}(s)$ of I_i satisfy the integral equations:*

$$h_{I_i(t)}(s) = 1{-}G_i(t){+}\int_0^t f_i(u_{i0}s{+}u_{i1}h_{I_1(t-y)}(s){+}\cdots{+}u_{in}h_{I_n(t-y)}(s))dG_i(y), \tag{3.5}$$

$$h_{I_i}(s) = f_i(u_{i0}s + u_{i1}h_{I_1}(s) + \cdots + u_{in}h_{I_n}(s)). \tag{3.6}$$

Proof. 1). Let us consider $h_{I_i(t)}(s)$. We have

$$h_{I_i(t)}(s) = E(s^{I_i(t)}) = E(E(s^{I_i(t)}|(\tau_i,\nu_i)))$$

$$= 1 - G_i(t) + \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \Bigg[\binom{k}{k_0,k_1,\dots,k_n} u_{i0}^{k_0}u_{i1}^{k_1}\dots u_{in}^{k_n}\, s^{k_0}$$

$$\times E(s^{I_i(t-y)}|Z^j(0)=k_j, j{\neq}0)\Bigg] dG_i(y)$$

$$= 1 - G_i(t)$$

$$+ \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \Bigg[\binom{k}{k_0,k_1,\dots,k_n} u_{i0}^{k_0}u_{i1}^{k_1}\dots u_{in}^{k_n}\, s^{k_0} \prod_{m=1}^{n} E(s^{I_m(t-y)})^{k_m}\Bigg] dG_i(y)$$

$$= 1 - G_i(t)$$
$$+ \int_0^t \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \left[\binom{k}{k_0, k_1, \ldots, k_n} u_{i0}^{k_0} u_{i1}^{k_1} \ldots u_{in}^{k_n} s^{k_0} \prod_{m=1}^{n} (h_{I_m(t-y)}(s))^{k_m} \right] dG_i(y)$$
$$= 1 - G_i(t) + \int_0^t \sum_{k=0}^{\infty} p_{ik} (u_{i0}s + u_{i1} h_{I_1(t-y)}(s) + \cdots + u_{in} h_{I_n(t-y)}(s))^k dG_i(y)$$
$$= 1 - G_i(t) + \int_0^t f_i(u_{i0}s + u_{i1} h_{I_1(t-y)}(s) + \cdots + u_{in} h_{I_n(t-y)}(s)) dG_i(y).$$

2). In a similar manner, for $h_{I_i}(s)$ we obtain:

$$h_{I_i}(s) = E(s^{I_i}) = E(E(s^{I_i}|(\tau_i, \nu_i)))$$
$$= \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \left[\binom{k}{k_0, k_1, \ldots, k_n} u_{i0}^{k_0} u_{i1}^{k_1} \ldots u_{in}^{k_n} s^{k_0} E(s^{I_i}|Z^j(0) = k_j, j \neq 0) \right]$$
$$= \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \left[\binom{k}{k_0, k_1, \ldots, k_n} u_{i0}^{k_0} u_{i1}^{k_1} \ldots u_{in}^{k_n} s^{k_0} \prod_{m=1}^{n} E(s^{I_m})^{k_m} \right]$$
$$= \sum_{k=0}^{\infty} p_{ik} \sum_{\sum_0^n k_\ell = k} \left[\binom{k}{k_0, k_1, \ldots, k_n} u_{i0}^{k_0} u_{i1}^{k_1} \ldots u_{in}^{k_n} s^{k_0} \prod_{m=1}^{n} h_{I_m}(s))^{k_m} \right]$$
$$= \sum_{k=0}^{\infty} p_{ik} (u_{i0}s + u_{i1} h_{I_1}(s) + \cdots + u_{in} h_{I_n}(s))^k$$
$$= f_i(u_{i0}s + u_{i1} h_{I_1}(s) + \cdots + u_{in} h_{I_n}(s)).$$

□

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