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Branching Stochastic Evolutionary Models of Cell Populations

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Abstract. This review paper surveys results on branching stochastic models with and without immigration published during the past nine years. Studies of this class of stochastic models were motivated by the quantitative analysis of the dynamics of population of cells of the central nervous system, called the terminally differentiated oligodendrocytes, and their progenitor cells. We focus on original ideas specifically developed for Sevastyanov branching processes allowing the contribution of an external cellular compartment (e.g., stem cells) via a nonhomogeneous Poisson immigration process. Limiting distributions are discribed in the subcritical, critical and supercritical cases for various immigration rates.

Keywords: Branching stochastic processes; Models of cell proliferation; Stem cells; Non-homogeneous immigration; Limiting distributions

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1 Introduction

Thomas R. Malthus (1766-1834) was one of the pioneers of Mathematical Biology. Between 1798 and 1826, he published six editions of "An Essay on the Principle of Population" in which he reported the observation that populations exhibit a propensity for growth, and articulated the principle according which they multiply geometrically. His claim has since been proven correct for populations that develop in isolation; that is, populations composed of individuals that reproduce and die independently of their environment.

Several classes of mathematical models are available to practitioners to model population dynamics. One of them uses the theory of branching processes, a family of stochastic processes initiated by Bienaymé [3], and independently formulated by Galton and Watson [5]. The properties of the celebrated Bienaymé-Galton-Watson process are now well understood, and their applications to biology well accepted since Kolmogorov's work who proved the first asymptotic result on the probability of non-extinction [20].

Kolmogorov also introduced the terminology "branching processes" when he started a seminar series on this topic at Moscow State University in 1946. The first three fundamental papers on single and multitype Markov branching processes that resulted from this initiative are worth mentioning [21, 22, 28]. Non-Markov branching processes were subsequently formulated by Bellman and Harris in 1948 [8].

For readers least familiar with these models, branching processes describe the temporal evolution of populations in which individuals, more generally objects, may reproduce during or at the end of their life time. The nature and scale of these objects are virtually unrestricted, and include elementary particles (e.g., photons, electrons), atoms, molecules, genes, cells, viruses, bacteria, animals, plants, information. As a result, these stochastic models have found many applications in a variety of fields, including Physics, Chemistry, Biology, Demography, Economics and Finance, Technology, and Computer Science. The theory and applications of branching processes is covered in many textbooks. We refer to [1, 2, 6, 7, 8, 18, 25, 26] for theoretical

aspects, and to [7, 18, 19, 29] for applications to biology.

The goal of this paper is to survey recent results on branching stochastic models based on papers published during the past nine years (see [9, 10, 11, 12, 13, 14, 15] and [23, 24, 27, 30]). We focus on original ideas specifically developed for Sevastyanov branching processes with a non-homogeneous Poisson immigration. This class of models was motivated by quantitative studies of cells of the central nervous system, called the terminally differentiated oligodendrocytes and their progenitor cells.

The paper is organized as follows. Section 2 provides a motivating example for considering Sevastyanov process as a model of cell kinetics. Section 3 defines the (single-type) Sevastyanov process without immigration. Section 4 extends the definition of the process to allow for non-homogeneous immigration. This class of stochastic processes offers a quantitative framework to study the kinetics of cell populations that are sustained by an influx of cell from an external compartment. Examples of such situations abound in cell biology. Section 5 presents properties of population dynamics captured by the model for various immigration rates. The section is divided into three subsections to consider the subcritical, critical, and supercritical cases separately. Section 6 offers concluding remarks.

2 A motivating example from stem cell biology

Adult stem cells are multipotent cells responsible for replacing damaged and dead cells of tissues and organs of the body. They are defined by two criteria: (1) they must be able to undergo self-renewing divisions to produce more stem cells of the same type via symmetric or asymmetric division; (2) they must be able to differentiate into other cell types. They share these characteristics with so-called progenitor cells which are further committed to particular lineages of the body than stem cells. Some cancer cells associated with particular malignancies (e.g., leukemia) are also able to give rise to all cell types that

exist in a tumor, and thus possess the characteristics that define normal stem cells.

Stem cells reside in a specific microenvironment called the stem cell niche with which they interact to balance stem cell quiescence with proliferation and differentiation, and to regulate their fate in response to the varying needs of the body. These niches are placed in specific anatomic locations to optimize support for regeneration and maintenance of specific tissues. For instance, hematopoietic stem cells are located in the bone marrow from where they generate all blood cells, including red blood cells and lymphocytes. Neural stem cells are committed to the neuronal lineages (e.g., oligodendrocytes, neurons, astrocytes) of the central nervous system; their niches may be found in the subventricular zone along the lateral wall of the lateral ventricles and in the subgranular zone of the hippocampal dentate gyrus [4].

The factors that control the dynamics and differentiation of stem cells are not fully understood, and the focus of experimental studies. In biomedical research, these studies are particularly important as they may lead to the discovery of novel approaches for treating the millions of people that become affected by diseases or injuries each year. Hematopoietic stem cell transplantation is one example of successful stem cell-based therapies that was developed following years of research to treat patients with cancers of the blood or bone marrow. The rarity of certain stem cells, combined with the fact that they reside in niches create bottlenecks that make them difficult to observe in human studies. Experimental observations are sometime restricted to output of the stem cell compartment, forcing scientists to infer properties of these cells from indirect observations. Mathematical models have been proposed to bridge the gap between observations and the stem cell compartment. Several classes of models have been developed to describe cell kinetics, including branching processes which are designed to capture variation in population growth that occurs from stochasticity in cell fate decision and life time duration.

In previous work, we have used these models to characterize the dynamics of multiple cellular systems, including the oligodendrocytes type-2 astrocytes (O-2A) progenitor cells and their terminally differ-

entiated progeny, known as oligodendrocytes [16, 17]. These cells produce the myelin sheath that enwraps axons in the central nervous system and are involved in signal propagation along the nerves. To model the dynamics of the population of O-2A progenitor cells, the model assumes that every cell may either divide into two new O-2A progenitor cells with probability p_2 $(0 < p_2 \leq 1)$ or either die or differentiate into an oligodendrocyte with probability $p_0 = 1 - p_2$ at the end of its life time or mitotic cycle. In other words, every O-2A progenitor cell produces a random number of offsprings (progeny) ν with a probability generating function (p.g.f.) $h(s) = \mathbf{E}(s^\nu) = p_0 + p_2 s^2$, $|s| \leq 1$. This single-type model does not distinguish cells based on any of their characteristics, but assumes that the duration of the life time is a random variable (r.v.) τ with cumulative distribution function $G(x) = P(\tau \leq x)$, $x \geq 0$.

Every cell is assumed to evolve independently of every other cell. However, the random variables τ and ν may be either dependent or independent. From a biological standpoint, the assumption that τ and ν are dependent is most natural because it allows the duration of the life time to be stochastically longer or shorter depending on the ultimate fate of the cell (e.g., division versus death or differentiation). Experimental studies have shown that the time to death, the time to differentiation, and the time to division of O-2A progenitor cells were not identically distributed, which this assumption captures. It leads to the Sevastyanov process, which is formally defined in Section 3.

3 The Sevastyanov process *(as model of cell proliferation)*

The Sevastyanov process introduced in Section 2 generalizes by allowing the number of offspring of every cell to be arbitrary. Thus, define $p_k = \mathbf{P}\{\nu = k\}$, $k = 0, 1 \ldots$, with $\sum_{k=0}^{\infty} p_k = 1$, and write $h(s) = \sum_{k=0}^{\infty} p_k s^k$. To allow dependencies between the life time and offspring, the process assumes that the joint distribution of (τ, ν) is given by $\mathbf{P}\{\tau \leq x, \nu = k\} = \int_0^x p_k(u) dG(u)$. Define the as-

sociated conditional offspring p.g.f. $h(u,s) = \sum_{k=0}^{\infty} p_k(u)s^k$, with $h(u,1) = 1$ for every $u \geq 0$. The pair (G,h) defines the characteristics of the Sevastyanov process. When τ and ν are independent, we have $h(u,\cdot) \equiv h(\cdot)$, $u \geq 0$, and the Sevastyanov process reduces to the Bellman-Harris process. If, in addition, $G(x) = 1 - e^{-x/M}$, the process is a Markov branching process, whereas when $G(x) = \mathbf{1}_{\{x \geq 1\}}$, it becomes a (discrete-time) Bienaymé-Galton-Watson process. When started from a single cell, the sample path (trajectory) of the process produces a genealogical tree rooted at the initiator cell, and, when started from multiple cells, it generates a genealogical forest.

Let $\{Z(t), t \geq 0\}$ denote the total number of cells alive at time t. Its p.g.f. $F(t,s) = \mathbf{E}[s^{Z(t)}|Z(0) = 1]$, $t \geq 0, |s| \leq 1$, satisfies the non-linear integral equation

$$F(t,s) = s(1 - G(t)) + \int_0^t h(u, F(t-u,s))dG(u), \quad F(0,s) = s.$$

Let $a(u) = h'_s(u,1)$ and $b(u) = h''_{ss}(u,1)$ denote the conditional first two factorial moments of the progeny size of any cell that divides at age u. Let $h(s) = \int_0^{\infty} h(u,s)dG(u)$, $|s| \leq 1$, denote the (unconditional) p.g.f. of the progeny size of any cell, where $a = h'(1)$ and $b = h''(1)$. Put $M = \mathbf{E}\tau = \int_0^{\infty} udG(u) < \infty$, $M_a = \int_0^{\infty} ua(u)dG(u) < \infty$, $M_b = \int_0^{\infty} b(u)dG(u) < \infty$, $M_1(t) = \mathbf{E}[Z(t)]$, $M_2(t) = \mathbf{E}[Z(t)(Z(t)-1)]$, and $W(t) = \mathbf{Var}[Z(t)]$.

Let α denote the Malthusian parameter of the process. It is defined as the solution to the equation

$$\int_0^{\infty} e^{-\alpha x} a(x)dG(x) = 1,$$

and enables classifying the Sevastyanov process as subcritical if $a < 1$ ($\alpha < 0$), critical if $a = 1$ and $b > 0$ ($\alpha = 0$), and supercritical if $a > 1$ ($\alpha > 0$). All three cases are treated in this paper.

When $(a,b) = (1,0)$, we have that $Z(\cdot) \equiv 1$ almost surely, and the total population size is an ordinary renewal process. In all other cases, the average population size grows or decays exponentially quickly as

$t \to \infty$: $\mathbf{E}[Z(t)] \sim C_\alpha e^{\alpha t}$, where $C_\alpha \in (0, \infty)$ (Malthusian average growth of population).

When $\alpha \leq 0$, we have that $P\{Z(t) \to 0\} = 1$; i.e., the population almost surely (a.s.) becomes eventually extinct in both the subcritical and critical cases. In the supercritical case ($\alpha > 0$), we have $P\{Z(t) \to 0\} = q$, where q, the probability of extinction, is the (unique) solution to the equation $h(q) = q$ that belongs to the interval $[0, 1)$. The population has therefore a strictly positive probability of (indefinite) survival.

The following limiting results were proven under additional conditions [26]:

1) If $\alpha < 0$ then $\lim_{t\to\infty} P\{Z(t) = n | Z(t) > 0\} = d_k, \sum_{k=1}^{\infty} d_k = 1$ (conditional limiting distribution).

2) If $\alpha = 0$ then $\lim_{t\to\infty} P\{Z(t)/Dt \leq x | Z(t) > 0\} = 1 - e^{-x}, x \geq 0, D = M/M_a$.

3) If $\alpha > 0$ then $\lim_{t\to\infty} Z(t)/\mathbf{E}Z(t) = \zeta$ *a.s.* and L_2, $\mathbf{E}\zeta = 1$.

4 Sevastyanov process with non-homogeneous immigration *(as model of cell proliferation induced by stem cells)*

The Sevastyanov process without immigration describes the dynamics of a population that evolves in complete isolation from external populations, a potential limitation when studying the dynamics of cellular systems that develop *in vivo*. For example, the model presented in Section 2 does not allow the differentiation of stem cells into O2-A progenitor cells, an assumption mostly only valid for *in vitro* studies. The model can be meaningfully extended by appending an immigration component to the branching process, thereby allowing a cellular influx from other compartments into the population of interest. The goal of this section is to define such a process.

Let (S_k, I_k), $k = 1, 2 \ldots$ denote independent and identically distributed (i.i.d.) random vectors where the ordered sequence $0 < S_1 < S_2 \ldots$ represent time points generated by a Poisson process $\Pi(0, t)$, and where I_k, $k = 1, 2 \ldots$, is a sequence of non-negative integer valued r.v.. In our oligodendrocyte example, the r.v. I_k represents the number of stem cells immigrating into the population of O-2A progenitor cells at time S_k by differentiating. Thus, at every time S_k, a random number I_k of i.i.d. Sevastyanov processes are initiated by the pool of immigrating stem cells.

The model that describes the arrival of new cells into the population of interest is called the immigration process. The assumption that $\Pi(0, t)$ is Poisson entails that $\mathbf{P}\{\Pi(0, t) = n\} = e^{-R(t)} R^n(t)/n!$, $n = 0, 1, 2 \ldots$, where $R(t) = \int_0^t r(x)dx$ denotes the mean measure of the process, and $r(x) > 0$ is its local intensity or immigration rate. This rate is allowed to be time-dependent, a feature that may be necessary in biological applications in order to capture some of the non-stationarity exhibited by population dynamics.

Let $\{Y(t),\ t \geq 0\}$ denote the number of cells in the population at time t as described by the combination of the immigration and Sevastyanov processes. We refer to this composite model as the Sevastyanov branching process with non-homogeneous Poisson immigration (SBPwNPI), and note that $Y(t)$ can be expressed as

$$Y(t) = \sum_{k=1}^{\Pi(0,t)} \sum_{j=1}^{I_k} Z^{(k,j)}(t - S_k) \text{ if } \Pi(0, t) > 0, \text{ and } Y(t) = 0 \text{ if } \Pi(0, t) = 0,$$

where $\{Z^{(k,j)}(t), t \geq 0\}$, $j, k = 1, 2 \ldots$, denote i.i.d. Sevastyanov processes with characteristics (G, h). Write $g(s) = \mathbf{E}(s^{I_n}) = \sum_{k=0}^{\infty} q_k s^k$ for the p.g.f. of the number of immigrants at any time S_k, and put $\gamma = g'(1-) < \infty$ and $\gamma_2 = g''(1-) < \infty$ for the associated first and second order factorial moments. Then, the p.g.f. of $Y(t)$, defined by $\Phi(t; s) = \mathbf{E}(s^{Y(t)} | Y(0) = 0)$, satisfies the following equation:

$$\Phi(t; s) = \exp\left\{ - \int_0^t r(t - u)(1 - g(F(u; s)))du \right\},$$

with $\Phi(0;s)=1$. Introduce the joint p.g.f.

$$\Phi(s_1,s_2;t,u)=\mathbf{E}[s_1^{Y(t)}s_2^{Y(t+u)}|Y(0)=0]\ \ (t,u\geq 0).$$

Then,

$$\begin{aligned}\Phi(t,u;s_1,s_2) &= \exp\left\{-\int_0^t r(x)[1-g(F(t-x,u;s_1,s_2))]dx\right. \qquad (1)\\ &\qquad \left.-\int_t^{t+u} r(y)[1-g(F(t,u-y;1,s_2))]dy\right\},\end{aligned}$$

where $F(t,u;s_1,s_2)=\mathbf{E}[s_1^{Z(t)}s_2^{Z(t+u)}|Y(0)=0]$, $t,u\geq 0$, satisfies the integral equation

$$\begin{aligned}F(t,u;s_1,s_2) &= \int_0^t h(F(t-x,u;s_1,s_2))dx\\ &\quad +s_1\int_t^{t+u} h(y;F(t+u-y;s_2))dy\\ &\quad +s_1s_2[1-G(t+u)].\end{aligned}$$

Define the moments $A(t)=\mathbf{E}[Y(t)]$, $B(t)=\mathbf{E}[Y(t)(Y(t)-1)]$, and $V(t)=\mathbf{Var}[Y(t)]$, studied in Section 5.

5 Asymptotic behaviour of the SBPwNHPI

This section presents results on limiting distributions of the population size process $\{Y(t),t\geq 0\}$ as $t\to\infty$. We consider all three (sub-, super, and critical) cases, and let the immigration rates assume different forms.

5.1 Subcritical populations

Assume first that the average number of progeny per cell is smaller than 1: $a<1$, or, equivalently, $\alpha<0$.

Theorem 1. *Assume that* $r(t) \sim re^{\rho t}$ *for some given constant* $r > 0$.
(i) If $\rho < 0$, *then* $\lim_{t\to\infty} P\{Y(t) = k|Y(t) > 0\} = q_k > 0, k = 1, 2 \ldots$.
ii) If $\rho > 0$, *then as* $t \to \infty$:
(a) LLN: $\zeta(t) = Y(t)/A(t) \to 1$ *a.s. and* L_2;
(b) CLT: $X(t) = [Y(t) - A(t)]/\sqrt{V(t)} \to N(0, \sigma^2)$ *in distribution where*

$$0 < \sigma^2 = \frac{\int_0^\infty e^{-\rho u}[\gamma M_2(u) + \gamma_2 M_1^2(u)]du}{\int_0^\infty e^{-\rho u}[\gamma M_2(u) + \gamma M_1(t)(u) + \gamma_2 M_1^2(u)]du} < 1.$$

Theorem 2. *Let* $r(t) \sim rt^\theta$ *with* $r > 0$.
(i) If $\theta < 0$ *then* $\lim_{t\to\infty} P\{Y(t) = k|Y(t) > 0\} = q_k > 0, k = 1, 2, \ldots$, *where*

$$\Psi^*(s) = \sum_{k=1}^\infty q_k s^k = 1 - \frac{\int_0^\infty (1 - g(F(u, s)))du}{\int_0^\infty (1 - g(F(u, 0)))du}, \quad 0 \le s \le 1.$$

(ii) If $\theta > 0$, *then as* $t \to \infty$:
(a) LLN: $\zeta(t) = Y(t)/A(t) \to 1$, *in* L_2. *The convergence is almost surely if* $\theta > 1$.
(b) CLT: $X(t) = [Y(t) - A(t)]/\sqrt{V(t)} \to N(0, \sigma^2)$ *in distribution as* $t \to \infty$, *where*

$$0 < \sigma^2 = 1 - \frac{\gamma \int_0^\infty M_1(u)du}{\int_0^\infty [\gamma M_2(u) + (\gamma + \ \gamma_2) M_1^2(u)]du} < 1.$$

Theorem 3. *Assume* $\lim_{t\to\infty} r(t) = r > 0$. *Then, there exists a stationary limiting distribution*

$$\lim_{t\to\infty} P\{Y(t) = k\} = Q_k > 0, k = 0, 1, 2 \ldots,$$

where

$$\Psi^*(s) = \sum_{k=0}^\infty Q_k s^k = \exp\left\{-r \int_0^\infty [1 - g(F(u, s))]du\right\}, |s| \le 1.$$

Corollary. Assume $G(t) = 1 - e^{-t/M}$, $t \geq 0$. Then, $\{Z(t), t \geq 0\}$ is a Markov branching process, and

$$\Psi^*(s) = \exp\left\{-r \int_s^1 \frac{1 - g(x)}{f(x)} dx\right\},$$

where $f(s) = (h(s) - s)/M$, and $M = \mathbf{E}\tau = \int_0^\infty u dG(u) < \infty$.

5.2 Critical populations

We now consider the critical case where $a = 1$ (i.e., $\alpha = 0$) and assume that the rate of the Poisson process is either such that $r(t) \sim t^\delta L_R(t)$ as $t \to \infty$ for some smoothly varying function (s.v.f.) $L_R(t)$, or $\int_0^\infty r(t)dt = R \in (0, \infty)$. In cell biology, the critical case describes (homeostatic) populations of cells that produce on average one cell upon completion of their life time. Since $a = \int_0^\infty a(u)dG(u) = 1$, the distribution function $G_a(t) = \int_0^t a(u)dG(u)$, $t \geq 0$, is proper on $[0, \infty)$. Define $M_a = \int_0^\infty ua(u)dG(u) = \int_0^\infty u dG_a(u)$.

Theorem 4. *Assume that M and M_a are finite. Then, as $t \to \infty$, $A(t) = \mathbf{E}[Y(t)] \sim \gamma \dfrac{M}{M_a} R(t)$ and $B(t) \sim \dfrac{\gamma M^2 b}{M_a^3(\delta + 2)} R(t)t$. Furthermore, depending on the rate at which $r(t)$ increases or decreases, the asymptotic behavior of $A(t)$ is as follows:*

$$r(t) \downarrow 0, \int_0^\infty r(t)dt = R \in (0, \infty) \quad \Rightarrow \quad A(t) \to \gamma \frac{M}{M_a} R. \tag{2}$$

$$r(t) \sim \frac{r}{t}, r > 0, \quad \Rightarrow \quad A(t) \sim \gamma \frac{M}{M_a} r \log t. \tag{3}$$

$$r(t) \sim t^\delta L_R(t), \delta \in (-1, 0] \quad \Rightarrow \quad A(t) \sim \gamma \frac{M}{M_a} \frac{t^{1+\delta}}{1 + \delta} L_R(t). \tag{4}$$

$$r(t) \uparrow r > 0, \quad \Rightarrow \quad A(t) \sim \gamma \frac{M}{M_a} rt. \tag{5}$$

$$r(t) \sim t^\delta L_R(t), \delta > 0 \quad \Rightarrow \quad A(t) \sim \gamma \frac{M}{M_a} \frac{t^{1+\delta}}{1 + \delta} L_R(t). \tag{6}$$

Theorem 5. *Let* $t \to \infty$.

(i) If $\int_0^\infty r(t)dt = R \in (0,\infty)$, *then*

$$D(t) = P\{Y(t) > 0\} = \frac{2R\gamma M_a}{bt}(1 + o(1)).$$

(ii) If $r(t) \sim \frac{r}{t}$, *then* $P\{Y(t) > 0\} = \dfrac{4M_a\gamma r \log t}{bt}(1 + o(1))$.

(iii) If $r(t) \sim t^\delta L_R(t)$, $\delta \in (-1, 0]$, *then*

$$P\{Y(t)>0\} = \frac{2M_a\gamma r(t) \log t}{b}(1 + o(1)).$$

(iv) If $r(t) \uparrow r > 0$ *or* $r(t) \sim t^\delta L_R(t), \delta > 0$, *then* $P\{Y(t) > 0\} \to 1$.

Theorem 6. *Suppose that* $r(t) \downarrow 0$ *and* $\int_0^\infty r(t)dt = R \in (0,\infty)$. *Then,* $D(t) = P\{Y(t) > 0\} \sim \dfrac{2R\gamma M_a}{bt}$ *and*

$$\lim_{t\to\infty} P\left\{Y(t)D(t) \le x | Y(t) > 0\right\} = 1 - e^{-\frac{\gamma MR}{M_a}x}, x \ge 0.$$

This result extends Kolmogorov and Yaglom's classical results in the Markov case without immigration.

Theorem 7. *Suppose that* $r(t) \sim t^\delta L_R(t)$ *and* $\delta \in (-1, 0]$. *Then,*

$$\lim_{t\to\infty} P\left\{\frac{\log Y(t)}{\log t} \le x \middle| Y(t) > 0\right\} = x, \quad x \in [0, 1].$$

Theorem 8. *Suppose that* $r(t) \uparrow r > 0$, $\theta = Mb/2M_a^2 r$, *and* $\varkappa = 2\gamma M_a/b$. *Then,*

$$\lim_{t\to\infty} P\left\{\frac{Y(t)}{rt} \le x\right\} = \frac{1}{\theta^\varkappa \Gamma(\varkappa)} \int_0^x u^{\varkappa-1} e^{-u/\theta} du, \quad x \ge 0.$$

This limiting distribution includes that established in the homogeneous Markov case by Sevastyanov (1957) as particular case.

Theorem 9. *Suppose that* $r(t) \sim t^{\delta} L_R(t), \delta > 0$. *Then, as* $t \to \infty$*:*

(i) LLN: $Y(t)/A(t) \to 1$ *in probability.*

(ii) CLT: $X(t) = (Y(t) - A(t))/\sqrt{V(t)} \xrightarrow{D} N(0,1)$.

The second result of Theorem 9 states that, as t gets large,

$$\frac{Y(t)}{r(t)t} \sim N\left(\frac{\gamma\mu}{M_a(\delta+1)}, \frac{b(\delta+1)}{M_a(\delta+2)r(t)}\right),$$

an approximation useful for asymptotic estimation and statistical inference.

Theorem 10. *Suppose that* $r(t) = L(t)/t$ *for some s.v.f.* $L(\cdot)$. *Then,* $P\{Y(t) > 0\} \sim KL^*(t)/t$, *where* $K \in (0,\infty)$, $L^*(t) = L_1(t) + R(t)$, $L_1(t) = L(t)\log t$, *and* $R(t) = \int_0^t L(x)x^{-1}dx$. *Furthermore, if* $L_1(t)/R(t) \to \rho \in [0,\infty)$ *as* $t \to \infty$, *then:*

$$\lim_{t\to\infty} P\left\{\frac{Y(t)}{Ct} \le x | Y(t) > 0\right\} = \frac{\rho}{1+\rho} + \frac{1}{1+\rho}(1 - e^{-x}), \quad (7)$$

where $C = MM_b/2M_a^2 \in (0,\infty)$, *and*

$$\lim_{t\to\infty} P\left\{\frac{\log Y(t)}{\log t} \le x | Y(t) > 0\right\} = \frac{\rho x}{1+\rho}\mathbf{1}_{\{0\le x\le 1\}} + \frac{\rho}{1+\rho}\mathbf{1}_{\{x\ge 1\}}. \quad (8)$$

Remark. This last theorem shows that two distinct limiting distributions may hold under a same set of conditions using two different normalizations. It also shows that the growth rates of sample paths that do not become extinct fall into two separate categories: (1) with probability $\frac{1}{1+\rho}$, the growth is linear with an exponentially distributed slope; (2) with probability $\frac{\rho}{1+\rho}$, the growth is parabolic with power uniformly distributed on $(0,1)$. A potential explanation of the difference between the two categories is that the first one may contain long-lived cells whereas the second one may include short-lived cells.

5.3 Supercritical populations

We finally consider the supercritical case $a > 1$ (equivalently, $\alpha > 0$), which is appropriate to model the dynamics of populations in which cells produce more than one offspring on average upon completion of their life time.

Theorem 11. *Let* $\hat{r}(\alpha) = \lim_{t\to\infty} \int_0^t r(u)e^{-\alpha u}du < \infty$. *Then* $A(t) \sim \gamma C\hat{r}(\alpha)e^{\alpha t}$ *as* $t \to \infty$ *and* $\zeta(t) = Y(t)/A(t) \xrightarrow{L_2} \zeta$ *where*

$$C = \frac{\int_0^\infty e^{-\alpha t}(1 - G(t))dt}{\int_0^\infty xe^{-\alpha x}a(x)dG(x)} < \infty,$$

ζ *is a r.v. with* $E\zeta = 1$ *and*

$$Var(\zeta) = \frac{\hat{r}(2\alpha)\left[\gamma W + (\gamma + \gamma_2)C^2\right]}{\left[C\gamma\hat{r}(\alpha)\right]^2} < \infty,$$

where

$$W = \frac{C^2\int_0^\infty (b(x) + a(x))e^{-2\alpha x}dG(x) - 1}{1 - \int_0^\infty a(x)e^{-2\alpha x}dG(x)} > 0.$$

Remark. If $r(t) = O(e^{\rho t})$ for some constant $\rho < \alpha$, then $\hat{r}(\alpha) < \infty$.

Theorem 12. *Assume* $r(t) \sim re^{\rho t}$ *with* $\rho \geq \alpha$. *Then, as* $t \to \infty$*:*

(i) LLN: $\zeta(t) = Y(t)/A(t) \xrightarrow{L_2} 1$ *and* $\zeta(t) \xrightarrow{a.s.} 1$, *where*

$$A(t) \sim e^{\rho t}\gamma r\int_0^\infty e^{-\rho u}M(u)du$$

if $\rho > \alpha$, *and* $A(t) \sim te^{\alpha t}\gamma rC$ *if* $\rho = \alpha$.

(ii) CLT:

(A) If $\alpha \leq \rho \leq 2\alpha$, *then* $X(t) = [Y(t) - A(t)]/\sqrt{V(t)} \xrightarrow{D} N(0, 1)$;

(B) If $\rho > 2\alpha$, *then* $X(t) \xrightarrow{D} N(0, \sigma^2)$ *where*

$$\sigma^2 = 1 - \frac{\gamma r\int_0^\infty e^{-\rho u}M(u)du}{r\int_0^\infty e^{-\rho u}[\gamma W(u) + (\gamma + \gamma_2)M^2(u)]du} < \infty.$$

6 Concluding remarks

We have presented a summary of results on SBPwNHPI established over the past few years, a class of branching stochastic processes that find many applications in cell biology which support its specific structure. We considered and compared its theoretical properties in all three cases (sub-, super-, and critical), and presented several limiting distributions, both conditional or non-conditional, as well as with or without a norming function. Some of these results are akin to a LLN and CLT.

Importantly, our survey demonstrated the richness of behaviors that this process is able to exhibit. This diversity is primarily generated by two factors: (1) the intensity of the reproduction law (i.e., whether the process is subcritical, critical, or supercritical), as captured by the Malthusian parameter α; and (2) the immigration rate $r(\cdot)$ which may dictate whether a population will avoid extinction, for instance. While cell populations may have a propensity for grow, they are also known for their tendencies to converge to equilibrium via a process called homeostasis. SBPwNHI are designed to capture cellular dynamics during specific phases of population growth; for example during the recovery phase subsequent to injury or stress [12]. One possible exception where growth may be unlimited is populations of cancer cells [19].

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