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Asymptotic behavior of cell populations described by two-type reducible age-dependent branching processes with non-homogeneous immigration¹

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Abstract

Stem and precursor cells play a critical role in tissue development, maintenance, and repair throughout the life. Often, experimental limitations prevent direct observation of the stem cell compartment, thereby posing substantial challenges to the analysis of such cellular systems. Two-type age-dependent branching processes with immigration are proposed to model populations of progenitor cells and their differentiated progenies. Immigration of cells into the pool of progenitor cells is formulated as a non-homogeneous Poisson process. The asymptotic behavior of the process is governed by the largest of two Malthusian parameters associated with embedded Bellman-Harris processes. Asymptotic approximations to the expectations of the total cell counts are improved by Markov compensators.

Keywords

Cell kinetics; Immigration; Limiting expectation; Oligodendrocytes

1. Introduction

Age-dependent branching processes with immigration have been proposed to describe the temporal development of populations of differentiated cells *in vivo* (Yakovlev and Yanev, 2006). Jagers (1968), Yanev (1972a, 1972b), Pakes (1972), Radcliffe (1972), Pakes and Kaplan (1974), Kaplan and Pakes (1974), and Hyrien and Yanev (2012) investigated this class of processes in the single-type case. Experimental techniques can help distinguish different cell types within tissues, and it is equally important to consider the multi-type case. For a comprehensive review of branching processes and their biological applications, the reader is referred to Jagers (1975), Yakovlev and Yanev (1989), Kimmel and Axelrod (2002), and Haccou et al. (2005). Other applications of branching processes to population dynamics and biology include Jagers and Harding (2009), Lalam and Jacob (2007), and Hyrien and Zand (2008), for example.

In the class of two-type reducible age-dependent branching processes with an immigration component formulated as a non-homogeneous Poisson process we shall express the

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asymptotic behavior of the expectation of the process in the sub-, super- and critical cases, while allowing the rate of the Poisson process to increase or decrease at various rates. To obtain these results, we shall establish asymptotic properties for solutions to renewal-type equations.

2. A motivating example: the generation of oligodendrocytes

Oligodendrocytes are cells of the central nervous system (CNS) which are responsible for the production of the myelin sheath which enwraps axons. They play a critical role in signal propagation along the nerves. They are non-dividing, terminally differentiated cells, and they eventually die. Injury to the oligodendrocyte population may be associated with demyelinating diseases such as multiple sclerosis (Blakemore, 2008; Korn, 2008). Understanding the biological processes that govern their generation and survival is essential for preventing and reverting such dysfunctions.

The production of oligodendrocytes *in vivo* is illustrated in Figure 1. Oligodendrocytes are generated by differentiation of oligodendrocyte/type-2 astrocyte (O-2A) progenitor cells (Raff et al., 1983). O-2A progenitor cells are migratory glial cells populating the CNS able to self-renew in the spinal cord. In addition to self-renewing, O-2A progenitor cells proliferate through newly formed O-2A progenitor cells that originate from differentiating lineage-committed progenitors generated by stem cells as intermediates in the production of differentiated cell types. O-2A progenitor cells arise from glial-restricted progenitor (GRP) cells (Rao et al., 1998). Finally they exit the mitotic cycle to die or to generate oligodendrocytes and astrocytes *in vitro* and *in vivo* by differentiation (Raff et al., 1983).

The proliferation of O-2A progenitor cells can be regulated by signaling molecules. For example, division is stimulated when they grow in the presence of platelet-derived growth factor (PDGF) or thyroid hormone (Noble et al., 1988; Yakovlev et al., 1999). The processes of division, death, and differentiation of O-2A progenitor cells may also be altered in a number of ways. For example, exposures to commonly used chemotherapeutic agents (e.g., carmustine, a classical drug used in the treatment of gliomas and non-Hodgkin's lymphomas) at sublethal doses disrupts the normal balance existing between cell differentiation and cell division and increase the likelihood that O-2A progenitor cells exit the mitotic cycle to undergo premature differentiation into oligodendrocytes as well as to modify the timing of these events (Dietrich et al., 2006; Hyrien et al., 2010b).

Although the generation of oligodendrocytes and of their O-2A progenitor cells is well characterized, how do they develop *in vivo* and how do they respond to their environment? One limitation to the study of such cellular systems is that the events of division, differentiation, and death cannot be observed directly during experiments without resorting to the painstaking technique of time-lapse microscopy. Other experimental techniques (such as multiparameter flow cytometry or fluorescence microscopy) permit to determine the composition of the cell population only at discrete points in time. Models designed to gain quantitative insights into the generation of oligodendrocytes from such data rested on multitype age-dependent branching processes (Yakovlev et al., 1998a, 1998b; von Collani et al., 1999; Boucher et al., 1999; Yakovlev et al., 2000; Zorin et al., 2000; Boucher et al., 2001; Hyrien et al., 2005a, 2005b, 2006b, 2010a, 2010b; Chen et al., 2011; Chen and Hyrien, 2011). These studies were limited to cells cultured *in vitro*.

A second limitation is that part of the lineage (such as stem cells) cannot always be tracked experimentally. This occurs either because these unobservable cells are too rare to be reliably detected or because sensitive markers have not been developed yet to label them. We use multi-type age-dependent branching processes with immigration to model the

dynamics of multitype cellular systems *in vivo*. The influx of these unobservable cells is described by an immigration process.

The generation of oligodendrocytes and of their O-2A progenitor cells involves O-2A progenitor cells, called type-1 cells, and oligodendrocytes, called type-2 cells. The process begins at time zero with N_{01} cells of type 1 and N_{02} cells of type 2, where N_{01} and N_{02} may either be fixed or random. New type-1 cells are generated in accordance with an immigration process formulated as a non-homogeneous Poisson process with rate $r(t)$. This immigration process represents the influx of stem/progenitor cells which differentiate into O-2A progenitor cells. Upon arrival, these immigrants are type-1 cells of age zero. Every type-1 cell either divides into two new type-1 cells with probability p_1 , or it produces a single type-2 cell (differentiation into an oligodendrocyte) with probability p_2 , or it dies with probability $p_3 = 1 - p_1 - p_2$. Every type-2 cell is mortal. The time to division, death, or differentiation of any type-1 cell is described by a non-negative random variable (r.v.) τ_1 with cumulative distribution function (c.d.f.) $G_1(x) = P(\tau_1 \leq x)$ which satisfies $G_1(0+) = 0$. The lifespan of any type-2 cell is described by a non-negative r.v. τ_2 with c.d.f. $G_2(x) = P(\tau_2 \leq x)$, $G_2(0+) = 0$. The distributions of the r.v. τ_1 and τ_2 were usually taken as two-parameter gamma distributions (Yakovlev et al., 1998a, 1998b; Boucher et al., 1999; Zorin et al., 2000; Boucher et al., 2001; Hyrien et al., 2005a, 2005b, 2006b, 2010a, 2010b; Chen et al., 2011). Finally cells are assumed to evolve independently of every other cell.

Modeling the dynamics of other cellular systems (e.g., leukemia cells or lymphocytes) may require other assumptions. For instance, cells that have reached the terminal stage (type-2) may retain their ability to self-renew through division. For this reason we shall investigate asymptotic properties for a more general process.

3. A two-type branching process with non-homogeneous immigration

In the two-type reducible Bellman-Harris process, every type-1 cell produces ξ_1 type-1 and ξ_2 type-2 cells. The offspring vector $\xi := (\xi_1, \xi_2)$ is a random vector with p.g.f.

$h_1(s_1, s_2) := E(s_1^{\xi_1} s_2^{\xi_2})$, $|s_i| \leq 1$, $i = 1, 2$. The life-span of every type-1 cell is described by a r.v. τ_1 with c.d.f. $G_1(x) := P(\tau_1 \leq x)$ satisfying $G_1(0+) = 0$. Every type-2 cell produces η_2 type-2 cells of age zero, where η_2 is a r.v. with p.g.f. $h_2(s_2) := E(s_2^{\eta_2})$, $|s_2| \leq 1$. The life-span of every type-2 cell is described by a r.v. τ_2 with c.d.f. $G_2(x) := P(\tau_2 \leq x)$, satisfying $G_2(0+) = 0$. Every cell is of age zero at birth, and it evolves independently of all other cells. The distributions G_1 and G_2 are assumed to be non-lattice.

Put $Z(t) := (Z_1(t), Z_2(t))$, $t \geq 0$, where the stochastic process $Z_k(t)$, $k = 1, 2$, denotes the total number of type- k cells at time t . Introduce the associated p.g.f.

$F_1(t; s_1, s_2) := E(s_1^{Z_1(t)} s_2^{Z_2(t)} | Z(0) = (1, 0))$ and $F_2(t; s_2) := E(s_2^{Z_2(t)} | Z_2(0) = 1)$. Then $F_1(t; s_1, s_2)$ and $F_2(t; s_2)$ satisfy:

$$\begin{cases} F_1(t; s_1, s_2) = \int_0^t h_1(F_1(t-u; s_1, s_2), F_2(t-u; s_2)) dG_1(u) + s_1(1-G_1(t)) \\ F_2(t; s_2) = \int_0^t h_2(F_2(t-u; s_2)) dG_2(u) + s_2(1-G_2(t)) \end{cases} \quad (1)$$

with initial conditions $F_1(0; s_1, s_2) = s_1$ and $F_2(0; s_2) = s_2$ (Athreya and Ney, 1972).

A biologically motivated choice for the offspring distribution is $h_1(s_1, s_2) = p_0 + p_1 s_1^2 + p_2 s_2$. The postulate is that every type-1 cell can either die with probability p_0 , divide into two type-1 cells with probability p_1 , or differentiate into a single type-2 cell with probability p_2 . An alternative model is $h_1(s_1, s_2) = p_0 + p_1 s_1^2 + p_2 s_2^2 + p_3 s_1 s_2$. The offspring p.g.f. $h_2(s_2)$ for

type-2 cells is usually assumed to take the form $h_2(s_2) = 1 - q + qs_2^2$, $0 \leq q \leq 1$, which results from the assumption that every type-2 cell either dies with probability $1 - q$ or divides into two new type-2 cells with probability q . The model of the generation of oligodendrocytes relies on $q = 0$.

$A_1(t) := E(Z_1(t)/Z_1(0) = 1)$, $A_2(t) := E(Z_2(t)/Z_1(0) = 1)$, and $B_2(t) := E(Z_2(t)/Z_2(0) = 1)$ denote expectations associated with the processes $Z_k(t)$, $k = 1, 2$. These expectations are obtained by differentiating the p.g.f. in Eq. (1). For example, $A_1(t) = \frac{\partial}{\partial s_1} F_1(t; s_1, s_2)|_{s_1=s_2=1}$. The expectations of the offspring and of the life-span distributions are denoted $a_1 := E\xi_1$, $a_2 := E\xi_2$, $b_2 := E\eta_2$, $\mu_1 := \int_0^\infty x dG_1(x)$, and $\mu_2 := \int_0^\infty x dG_2(x)$. If a_1 , a_2 , b_2 , μ_1 , and μ_2 are finite, Eq. (1) implies that $A_1(t)$, $A_2(t)$, and $B_2(t)$ satisfy the renewal-type equations:

$$A_1(t) = a_1 \int_0^t A_1(t-u) dG_1(u) + 1 - G_1(t), \quad A_1(0) = 1 \quad (2)$$

$$A_2(t) = a_1 \int_0^t A_2(t-u) dG_1(u) + a_2 \int_0^t B_2(t-u) dG_1(u), \quad A_2(0) = 0 \quad (3)$$

$$B_2(t) = b_2 \int_0^t B_2(t-u) dG_2(u) + 1 - G_2(t), \quad B_2(0) = 1. \quad (4)$$

The sequence $0 = S_0 < S_1 < S_2 < S_3 < \dots$ denote the set of ordered time points at which new cells immigrate into the population of type-1 cells. For every $t \geq 0$, define the associated point process $\Pi(t) := \sum_{k=1}^\infty 1_{\{S_k \leq t\}}$. The process $\pi(t)$ is a non-homogeneous Poisson process with rate $r(t)$ and cumulative rate $R(t) := \int_0^t r(u) du$. For every $k = 1, 2, \dots$, $U_k := S_k - S_{k-1}$ denotes the k th inter-arrival time, and $S_k := \sum_{i=1}^k U_i$, $k = 1, 2, \dots$. Let $\{I_k, k = 1, 2, \dots\}$ denote a collection of independent and identically distributed integer-valued r.v. with p.g.f. $g(s) := E(s^{I_k})$, $|s| \leq 1$, corresponding to the total number of immigrants that become type-1 cells at the times S_k . When $U_k \stackrel{\text{i.i.d.}}{\sim} \exp(r)$, $\pi(t)$ reduces to a Poisson process with cumulative rate $R(t) = rt$.

With $Y_k(t)$, $k = 1, 2$, the total number of type-1 and type-2 cells at time t under the branching process with immigration, and $Y(t) := (Y_1(t), Y_2(t))$, with $Y(0) = (0, 0)$, this process is represented as:

$$Y(t) = \begin{cases} \sum_{k=1}^{\Pi(t)} Z^k(t - S_k) & \text{if } \Pi(t) > 0 \\ 0 & \text{if } \Pi(t) = 0, \end{cases} \quad (5)$$

where $Z^k(t)$, $k = 1, 2, \dots$, are i.i.d. copies of the process $Z(t)$ started with a random number I_k of type-1 ancestors. Introduce the p.g.f. $\Psi(t; s_1, s_2) := E(s_1^{Y_1(t)} s_2^{Y_2(t)} | Y(0) = (0, 0))$, with $\Psi(0; s_1, s_2) = 1$. From Eq. (5),

$$\Psi(t; s_1, s_2) = \exp \left(- \int_0^t r(t-u) (1 - g(F_1(u; s_1, s_2))) du \right), \quad (6)$$

where the p.g.f. $F_1(u; s_1, s_2)$ satisfies the first identity in Eq. (1). The derivation of Eq. (6) follows the proof of Theorem 1 in Yakovlev and Yanev (2007). It requires a careful application of the Order Statistics Property and of a random time change. Introduce the

expectations of the process with immigration $M_k(t) := E(Y_k(t) / Y(0) = (0, 0))$, $k = 1, 2$. Differentiating both sides of Eq. (6) w.r.t. s_1 (resp. s_2) yields

$$M_k(t) = \gamma \int_0^t r(t-u) A_k(u) du, \quad M_k(0) = 0, \quad (7)$$

where $\gamma := E(I_k)$, $k = 1, 2$.

4. Asymptotic results for renewal-type equations

The moments of the process without immigration satisfy renewal-type equations of the form:

$$U(t) = \kappa \int_0^t U(t-x) dG(x) + f(t), \quad (8)$$

for some constant $\kappa > 0$, where $G(x)$ denotes the c.d.f. of a non-negative r.v. with expectation $\mu = \int_0^\infty x dG(x)$ assumed finite, and where f is a real-valued function (Athreya and Ney, 1972; Jagers, 1975). For every $\lambda \geq 0$, $\widehat{G}(\lambda) := \int_0^\infty e^{-\lambda x} dG(x)$ denotes the Laplace transform of $G(\cdot)$. The solution to Eq. (8) is unique and bounded on finite intervals whenever $\kappa \widehat{G}(0+) < 1$ (Feller, 1971, Ch. XI.1; Athreya and Ney, 1972, Ch. IV.4). The solution α to the equation $\kappa \widehat{G}(\alpha) = 1$, referred to as *Malthusian parameter*, plays a major role in the asymptotic behavior of $U(t)$. It always exists if $\kappa \geq 1$ (in which case $\alpha = 0$, with $\alpha = 0$ iff $\kappa = 1$), but that need not be the case when $\kappa < 1$. The existence of α is assumed throughout.

Define the c.d.f. $\tilde{G}(t) := \kappa \int_0^t e^{-\alpha x} dG(x)$. Its expectation is $\tilde{\mu} := \int_0^\infty x d\tilde{G}(x)$, assumed finite. Theorem A below recalls well-known asymptotic results (Harris, 1963: 161; Feller, 1971, Ch. XI.1; Athreya and Ney, 1972, Ch. IV.4; Bingham et al., 1987).

Theorem A

- i. Let $\kappa = 1$ and let f be a directly Riemann integrable (d.R.i) function.

Then, $\lim_{t \rightarrow \infty} U(t) = \frac{1}{\mu} \int_0^\infty f(x) dx$.

- ii. Let $\kappa = 1$ and $\lim_{t \rightarrow \infty} f(t) = C$, where $0 < C < \infty$. Then, $U(t) \sim \frac{Ct}{\mu}$, as $t \rightarrow \infty$

- iii. Let $\kappa < 1$ and $\lim_{t \rightarrow \infty} f(t) = C$, where $0 < C < \infty$. Then, $\lim_{t \rightarrow \infty} U(t) = \frac{C}{1-\kappa}$.

Case (i) of Theorem A is known as the Key Renewal Theorem. Further developments of renewal theory were obtained by Mitov and Yanev (2001, 2008). The results established below will be useful for investigating the asymptotic behavior of the moments of the process.

Theorem 4.1—If $f(t) \sim Ct^\rho e^{\beta t}$, $0 < C < \infty$, $\rho \geq 0$, and $\beta \in \mathbb{R}$, then

$$U(t) \sim \begin{cases} \frac{1}{\mu} e^{\alpha t} \int_0^\infty f(x) e^{-\alpha x} dx & \text{if } \alpha > \beta, \\ \frac{C}{\mu(\rho+1)} t^{\rho+1} e^{\alpha t} & \text{if } \alpha = \beta, \\ \frac{C}{1-\kappa \widehat{G}(\beta)} t^\rho e^{\beta t} & \text{if } \alpha < \beta. \end{cases} \quad (9)$$

Proof—Let $\tilde{U}(t) := e^{-\alpha t} U(t)$ and $\tilde{f}(t) := e^{-\alpha t} f(t)$, and consider the renewal equation

$$\bar{U}(t) = \bar{f}(t) + \int_0^t \bar{U}(t-x) d\tilde{G}(x). \quad (10)$$

Case $\alpha > \beta$: We have $\tilde{K}(t) \sim Ct^\rho e^{-(\alpha-\beta)t} \rightarrow 0$ as $t \rightarrow \infty$, and $\int_0^\infty \bar{f}(t) dt < \infty$, leading to $\bar{U}(t) \rightarrow \frac{1}{\bar{\mu}} \int_0^\infty \bar{f}(x) dx$ using the Key Renewal Theorem, and the result follows.

Case $\alpha = \beta$: Consider Eq. (10) with $\tilde{K}(t) \sim Ct^\rho$. From Feller (1971, Ch.XI.1), $\bar{U}(t) = \int_0^t \bar{f}(t-x) dN(x)$, where $N(t) = \sum_{k=0}^\infty \tilde{G}^{*k}(t)$, and $N(t) \sim \frac{t}{\bar{\mu}}$ as $t \rightarrow \infty$. From the change of variable $x = ty$,

$$\bar{U}(t) = \int_0^1 \bar{f}(t(1-y)) dN(ty) \sim \frac{C}{\bar{\mu}} t^{\rho+1} \int_0^1 (1-y)^\rho dy = \frac{C}{\bar{\mu}(\rho+1)} t^{\rho+1}, \quad (11)$$

which completes the proof.

Case $\alpha < \beta$: If $\beta = 0$, then $\alpha < 0$ and $\kappa < 1$. The solution to Eq. (8) is:

$$U(t) = \int_0^t f(t-z) dN_\kappa(z), \quad (12)$$

where $N_\kappa(t) = \sum_{n=0}^\infty \kappa^n G^{*n}(t)$. Theorem A (iii) implies that $\lim_{t \rightarrow \infty} N_\kappa(t) = (1 - \kappa)^{-1}$.

For every $\theta \in (0, 1)$ and $t \geq 1$, $U(t)$ is expressed as:

$$U(t) = \int_0^{t^\theta} f(t-z) dN_\kappa(z) + \int_{t^\theta}^t f(t-z) dN_\kappa(z). \quad (13)$$

The case $\rho = 0$ follows from Theorem A (iii). When $\rho > 0$, $f(t) \sim Ct^\rho$ as $t \rightarrow \infty$, and

$$\int_0^{t^\theta} f(t-z) dN_\kappa(z) \sim f(t) N_\kappa(t^\theta) \sim \frac{C}{1-\kappa} t^\rho. \quad (14)$$

For large t there exists a constant $K > 0$ such that

$$\int_{t^\theta}^t f(t-z) dN_\kappa(z) \leq K t^\rho \int_{t^\theta}^t dN_\kappa(z) = o(t^\rho). \quad (15)$$

Hence $U(t) \sim \frac{C}{1-\kappa} t^\rho$, $t \rightarrow \infty$.

Consider now the case where $\beta > 0$. By definition of α , $\Delta := \kappa \int_0^\infty e^{-\beta x} dG(x) < 1$ whenever $\alpha < \beta$. Define the c.d.f. $G^*(t) := \frac{\kappa}{\Delta} \int_0^t e^{-\beta x} dG(x)$. Introduce $U^*(t) := U(t)e^{-\beta t}$. Eq. (8) yields

$$U^*(t) = \Delta \int_0^t U^*(t-x) dG^*(x) + f^*(t), \quad (16)$$

where $f^*(t) := f(t)e^{-\beta t} \sim Ct^\rho$ as $t \rightarrow \infty$. Because $\Delta < 1$, the Malthusian parameter α^* associated with Eq. (16) is strictly negative. Applying the result obtained when $\alpha < 0$ yields $U^*(t) \sim \frac{C}{1-\Delta} t^\rho$. The assertion follows.

When $\alpha > \beta$ and $f(t) = C\rho e^{\beta t}$, $U(t) \sim \frac{C\Gamma(\rho+1)}{\mu(\alpha-\beta)\rho+1} e^{\alpha t}$.

5. Asymptotic properties for expectations of the process

We treat the asymptotic properties of the Bellman-Harris process without immigration $Z(t)$ first. The Malthusian parameters α_1 and α_2 are defined as the roots to the equations $a_1 \int_0^\infty e^{-\alpha_1 x} dG_1(x) = 1$ and $b_2 \int_0^\infty e^{-\alpha_2 x} dG_2(x) = 1$. We have $\alpha_1 = 0$ iff $a_1 = 1$, and $\alpha_2 = 0$ iff $b_2 = 1$. For $k = 1, 2$, the process $Z_k(t)$, started with a single cell of type k , is said to be subcritical if $\alpha_k < 0$ ($a_1 < 1$ or $b_2 < 1$), critical if $\alpha_k = 0$ ($a_1 = 1$ or $b_2 = 1$), and supercritical if $\alpha_k > 0$ ($a_1 > 1$ or $b_2 > 1$) (Athreya and Ney, 1972). In the critical case, $A_1(t) \equiv 1$ and $B_2(t) \equiv 1$ (Athreya and Ney, 1972), whereas in the super- and subcritical cases, $A_1(t) \sim C_1 e^{\alpha_1 t}$ and $B_2(t) \sim C_2 e^{\alpha_2 t}$, where $C_1 := \frac{a_1 - 1}{a_1 \mu_1}$ and $C_2 := \frac{b_2 - 1}{a_2 b_2 \mu_2}$, provided that the following quantities are finite: $\tilde{\mu}_1 := a_1 \int_0^\infty x e^{-\alpha_1 x} dG_1(x) = \int_0^\infty x d\tilde{G}_1(x)$, $\tilde{\mu}_2 := b_2 \int_0^\infty x e^{-\alpha_2 x} dG_2(x) = \int_0^\infty x d\tilde{G}_2(x)$ where $\tilde{G}_1(t) := a_1 \int_0^t e^{-\alpha_1 x} dG_1(x)$ and $\tilde{G}_2(t) := b_2 \int_0^t e^{-\alpha_2 x} dG_2(x)$. The two-type process $Z(t) = (Z_1(t), Z_2(t))$ is reducible, and the asymptotic behavior of $A_2(t)$ is more complex. For example, as shown in Theorem 5.1, it depends on both Malthusian parameters α_1 and α_2 .

Theorem 5.1

Let $\alpha := \max\{\alpha_1, \alpha_2\}$, $\delta := \alpha_2 - \alpha_1$, $\bar{B}_2(t) := e^{-\alpha_2 t} B_2(t)$, and $\hat{G}_1(\alpha_2) := \int_0^\infty e^{-\alpha_2 x} dG_1(x)$. If $\tilde{\mu}_1 < \infty$ and $\tilde{\mu}_2 < \infty$, then $A_2(t) \sim K_\alpha t^{\Delta(\alpha)} e^{\alpha t}$, where

$$K_\alpha \sim \begin{cases} K_1 := \frac{a_2 C_2}{a_1 \tilde{\mu}_1} & \text{if } \alpha = \alpha_1 = \alpha_2 \\ K_2 := \frac{a_2}{a_1 \tilde{\mu}_1} \int_0^\infty e^{\delta x} \bar{B}_2(x) dx & \text{if } \alpha = \alpha_1 > \alpha_2 \\ K_3 := \frac{a_2 C_2 \hat{G}_1(\alpha_2)}{1 - a_1 \hat{G}_1(\alpha_2)} & \text{if } \alpha = \alpha_1 < \alpha_2, \end{cases} \quad (17)$$

and $\Delta(\alpha) = 1$ if $\alpha_1 = \alpha_2$ and $\Delta(\alpha) = 0$ if $\alpha_1 \neq \alpha_2$.

Proof

Define $\tilde{A}_2(t) := e^{-\alpha_1 t} A_2(t)$, $\tilde{B}_2(t) := e^{-\alpha_1 t} B_2(t)$, $W(t) := a_2 \int_0^t B_2(t-u) dG_1(u)$, and $\tilde{W}(t) := e^{-\alpha_1 t} W(t)$. From Eq. (3), $\tilde{A}_2(t)$ satisfies:

$$\tilde{A}_2(t) = \int_0^t \tilde{A}_2(t-u) d\tilde{G}_1(u) + \tilde{W}(t). \quad (18)$$

Case $\delta = 0$ —We have $\tilde{W}(t) = \frac{a_2}{a_1} \int_0^t \bar{B}_2(t-u) d\tilde{G}_1(u) \rightarrow \tilde{K}_1 = \frac{a_2 C_2}{a_1}$, as $t \rightarrow \infty$. Theorem 4.1 (case $\alpha = \rho = 0$) implies that $\tilde{A}_2(t) \sim \frac{\tilde{K}_1}{\tilde{\mu}_1}$, and the result follows. If $\alpha_1 = \alpha_2 = 0$, we have $A_2(t) \sim \frac{1}{\mu_1}$ where $\mu_1 = \int_0^\infty x dG_1(x) < \infty$.

Case $\delta < 0$ —We have $\tilde{W}(t) = \frac{a_2}{a_1} e^{\delta t} \int_0^t \bar{B}_2(t-u) e^{-\delta u} d\tilde{G}_1(u)$ converges to 0 as $t \rightarrow \infty$. Applying the Key Renewal Theorem to Eq. (18) yields $\tilde{A}_2(t) \rightarrow \frac{1}{\tilde{\mu}_1} \int_0^\infty \tilde{W}(x) dx = K_2$, which completes the proof.

Case $\delta > 0$ —We have $W(t) = a_2 e^{\alpha_2 t} \int_0^t \bar{B}_2(t-u) e^{-\alpha_2 u} dG_1(u)$, hence $W(t) \sim a_2 C_2 \hat{G}_1(\alpha_2) e^{\alpha_2 t}$. We have $\hat{G}_1(\alpha_2) < \infty$ because $\alpha_2 > \alpha_1$. $A_2(t)$ is the solution to the renewal-type equation

$A_2(t) = a_1 \int_0^t A_2(t-u) dG_1(u) + W(t)$. Therefore Theorem 4.1 (case $\alpha < \beta$, $\rho = 0$) yields $A_2(t) \sim K_3 e^{a_2 t}$. In particular $K_3 = \frac{a_2}{1-a_1}$ when $a_2 = 0$.

When the model is Markovian, $G_1(t) = 1 - e^{-\beta_1 t}$ and $G_2(t) = 1 - e^{-\beta_2 t}$, the Malthusian parameters are given by $\alpha_1 = \beta_1(a_1 - 1)$ and $\alpha_2 = \beta_2(b_2 - 1)$, and $A_1(t) = e^{a_1 t}$ and $B_2(t) = e^{a_2 t}$. Then $A_2(t) = a_2 \beta_1 t e^{a_1 t}$ when $\alpha_1 = \alpha_2$, and $A_2(t) = \frac{a_2 \beta_1}{\alpha_2 - \alpha_1} (e^{\alpha_2 t} - e^{\alpha_1 t})$ when $\alpha_1 \neq \alpha_2$. Therefore, writing $\delta = \alpha_2 - \alpha_1$, $A_2(t) \sim a_2 \beta_1 t e^{a_1 t}$ if $\delta = 0$; $A_2(t) \sim -\frac{a_2 \beta_1}{\delta} e^{\alpha_1 t}$ if $\delta < 0$; $A_2(t) \sim \frac{a_2 \beta_1}{\delta} e^{\alpha_2 t}$ if $\delta > 0$. This is consistent with Theorem 5.1.

When $\alpha_1 = \alpha_2$, the asymptotic approximations to $A_2(t)$ established in Theorem 5.1 obeys the general form $A_2(t) \sim K_{i+1} e^{a_i t}$, $i = 1, 2$. These approximations do not satisfy the initial condition $A_2(0) = 0$. Better approximations for small t can be worked out from the fact that $A_2(t) = \frac{a_2 \beta_1}{|\delta|} e^{\max\{\alpha_1, \alpha_2\} t} (1 - e^{-|\delta| t})$ in the Markov case. Therefore, we propose $\Delta_t = 1 - e^{-|\delta| t}$ as a correction factor, thereby yielding the approximation $A_2(t) \sim \Delta_t K_{i+1} e^{a_i t}$, $i = 1, 2$. The correction factor Δ_t is a "Markov compensator." Its influence on the approximation vanishes at $t \rightarrow \infty$ because $\lim_{t \rightarrow \infty} \Delta_t = 1$. Computations presented in Section 6 indicate that it improves the approximation to the expectations for small values of t .

The asymptotic behavior of $M_1(t)$ and $M_2(t)$ is deduced from Eq. (7). If $\alpha_1 = 0$, then $M_1(t) = \gamma R(t)$. If $\alpha_1 > 0$ and $r(t) = r t^\theta$, $\theta > -1$, then $M_1(t) \sim \gamma r \Gamma(\theta+1) A_1(t) \alpha_1^{-(\theta+1)}$ when $\alpha_1 > 0$, and $M_1(t) \sim \gamma^{-1} r(t)$ when $\alpha_1 < 0$, where $\bar{A}_1 := \int_0^\infty A_1(x) dx < \infty$. If $\alpha_1 = 0$ and $r(t) = \frac{r}{1+t}$, then $M_1(t) \sim \gamma^{-1} r(t)$ when $\alpha_1 < 0$ and $M_1(t) \sim \gamma r E_1(\alpha_1) A(t)$ when $\alpha_1 > 0$, where $E_1(\alpha_1) := \int_0^\infty e^{-\alpha_1 x} (1+x)^{-1} dx < \infty$. If $\alpha_1 = 0$ and $r(t) = r e^{\rho t}$, $\rho > 0$, then $M_1(t) \sim \frac{\gamma r C_1}{|\rho - \alpha_1|} e^{\max\{\rho, \alpha_1\} t}$ when $\rho \neq \alpha_1$, and $M_1(t) \sim \gamma r C_1 t e^{a_1 t}$. The asymptotic behavior of $M_2(t)$ is obtained similarly using Eq. (7) and Theorem 5.1.

When $R(t) = r t$ the above results simplify as: $M_1(t) \sim \frac{\gamma r C_1}{\alpha_1} e^{a_1 t}$ when $\alpha_1 > 0$; $M_1(t) \rightarrow -\frac{\gamma r C_1}{\alpha_1}$ when $\alpha_1 < 0$; $M_1(t) = r \gamma t$ when $\alpha_1 = 0$. Furthermore, when $\alpha_1 = \alpha_2$, we have $M_2(t) \sim \frac{\gamma r K_a}{a} e^{a t}$ if $a > 0$; $M_2(t) \sim r \gamma K_a t$ if $a = 0$, and $M_2(t) \rightarrow -\frac{\gamma r K_a}{a}$ when $a < 0$. When $a = \alpha_1 = \alpha_2$, $M_2(t) \sim \frac{\gamma r K_1}{a} t e^{a t}$ if $a > 0$; $M_2(t) \sim \frac{\gamma r}{2\mu_1} t^2$ if $a = 0$; $M_2(t) \rightarrow -\frac{\gamma r K_1}{a}$ if $a < 0$. Markov compensators lead to better small- t approximations: $M_1(t) \sim \frac{\gamma r C_1}{\alpha_1} e^{a_1 t} \bar{\Delta}_t$, $\alpha_1 > 0$, $\bar{\Delta}_t = 1 - e^{-a_1 t}$, and $M_2(t) \sim \frac{\gamma r K_a}{a} e^{a t} \tilde{\Delta}_t$, $a > 0$, $\tilde{\Delta}_t = 1 - \alpha_0^{-1} (\alpha e^{-|\delta| t} - |\delta| e^{-a t})$, $a > 0$, where $\alpha_0 := \min\{\alpha_1, \alpha_2\} > 0$ and $\delta = \alpha_2 - \alpha_1$.

6. Probability of extinction

The probability of extinction of $Z(t)$ at time t is given by:

$$Q_{12}(t) := P(Z_1(t)=0, Z_2(t)=0 | Z_1(0)=1, Z_2(0)=0) = F_1(t; 0, 0), \quad (19)$$

which is fully determined through Eq. (1). The parameter a is also involved in the probability of extinction:

Theorem 6.1

Put $q_{12} := \lim_{t \rightarrow \infty} Q_{12}(t)$. Then $q_{12} = 1$ if $\alpha < 0$, and $q_{12} < 1$ if $\alpha > 0$.

Proof

Firstly the probability of extinction q_{12} satisfies $q_{12} = h_1(q_{12}, q_2)$, where $q_2 := h_2(q_2)$. The probability $q_1 := P(Z_1(t) \rightarrow 0 | Z_1(0) = 1)$ satisfies $q_1 = h_1(q_1, 1)$, where $q_1 = 1$ if $\alpha_1 < 0$ and

$q_1 < 1$ if $\alpha_1 > 0$. On one hand, $\alpha_2 = 0$ implies that $q_2 = 1$ and the identity $q_{12} = h_1(q_{12}, 1)$ implies that $q_{12} = q_1$. On the other hand, if $\alpha_2 > 0$ then $q_2 < 1$ and $q_{12} = h_1(q_{12}, q_2) < h_1(q_1, 1) = q_1 - 1$.

The asymptotic behavior of $Q_{12}(t)$ can also be derived using results from Vatutin (1977).

7. Simulations and approximations

We investigate the performance of the approximations to the expectation of the process constructed using the asymptotic properties obtained in section 5. We considered a two-type branching process with time-homogeneous immigration ($r(t) = r$) and with offspring distributions $h_1(s_1, s_2)$ and $h_2(s_2)$ given by $h_1(s_1, s_2) = p_0 + p_1 s_1^2 + p_2 s_2$ and $h_2(s_2) = q_0 + q_1 s_2^2$. We assumed the lifespans τ_1 and τ_2 to follow gamma distributions with parameters (ν_k, β_k) , $k =$

1, 2, such that $G_k(t) = \frac{\beta_k^{\nu_k}}{\Gamma(\nu_k)} \int_0^t x^{\nu_k-1} e^{-\beta_k x} dx$, $t \geq 0$. For the parameters of the lifespan distributions and for the rate of the immigration process, we took: $\nu_1 = 2$, $\beta_1 = 0.1$, $\nu_2 = 0.5$, $\beta_2 = 0.02$, and $r = 0.5$. We present results based on two sets of parameters for the offspring distributions $h_1(s_1, s_2)$ and $h_2(s_2)$: $p_0 = 0.2$, $p_1 = 0.5$, $p_2 = 0.3$, $q_0 = 0.5$, $q_1 = 0.5$ (scenario 1); and $p_0 = 0.2$, $p_1 = 0.3$, $p_2 = 0.5$, $q_0 = 0.65$, $q_1 = 0.35$ (scenario 2). Under the first scenario, $\alpha_1 = 0$ and $\alpha_2 = 0$, such that $Z_1(t)$ and $Z_2(t)$ were critical. Under the second scenario, both Malthusian parameters were negative, and the processes $Z_1(t)$ and $Z_2(t)$ were subcritical. The two models were non-Markovian.

Figure 2 shows results obtained using scenario 1 in the top two panels, and scenario 2 in the bottom two panels. For type-1 cells (left-hand side panels) and type-2 cells (right-hand side panels), it includes two sample paths of the process; the average of the 1000 sample paths (solid lines), which provides unbiased approximations to the true expectation of the process; approximations for the expected total numbers of cells relying on the asymptotic behaviors of $M_1(t)$ and $M_2(t)$ given in Section 5 (dashed lines).

In the first scenario, the asymptotic approximations worked well for both cell types, with the approximations coinciding almost perfectly with the simulation-based approximations. In the second scenario, the asymptotic approximations described the total number of cells after a long enough time correctly, but not from the start. The Markov-compensated approximations are virtually identical to $M_1(t)$ and $M_2(t)$, even for small t .

8. Conclusion

We have studied a two-type age-dependent branching process with non-homogeneous immigration to model populations of progenitor cells and their differentiated progeny. Using renewal theory, we have obtained asymptotic approximations to the expectations for the total number of cells of both types. We have improved these approximations using Markov compensators, and found the resulting approximations to be numerically accurate.

The asymptotic behavior of the process suggests that the growth of the population is primarily governed by the parameter $\alpha = \max\{\alpha_1, \alpha_2\}$. This parameter allows us to classify the two-type process as subcritical if $\alpha < 0$, critical if $\alpha = 0$, and supercritical if $\alpha > 0$. When the immigration rate is time-homogeneous ($R(t) = rt$), expectations grow exponentially in the supercritical case, converge to some constant in the subcritical case, and increase either linearly or quadratically in the critical case. When immigration varies in time, the expectations show more variety in their asymptotic behaviors as they depend on the time-varying immigration rate.

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Figure 1. Generation of oligodendrocytes (SC = stem and precursor cells; O-2A = oligodendrocyte/type-2 astrocyte progenitor cells; Oligo = oligodendrocytes).

Figure 2.

Results of simulations based on scenario 1 in the top two panels and based on scenario 2 in the bottom two panels. The left-hand side panels show the total number of type-1 cells as a function of time. The right-hand side panels show the total number of type-2 cells as a function of time. Each graph includes two sample paths of the process; the average of the 1000 sample paths (solid lines); approximations to the expected total numbers of cells computed using the asymptotic behaviors of $M_1(t)$ and $M_2(t)$ given in Section 5 (dashed lines).