Stochastic models of stem cells and their descendants under different criticality assumptions

Nam H. Nguyen and Marek Kimmel
Department of Statistics, Rice University, Houston, Texas, USA

ABSTRACT
We study time continuous branching processes with exponentially distributed lifetimes, with two types of cells that proliferate according to binary fission. A range of possible system dynamics are considered, each of which is characterized by the mutation rate of the original cells and the survival probability of the altered cells’ progeny. For each system, we derive a closed-form expression for the joint probability generating function of cell counts, and perform asymptotic analysis on the behaviors of the cell population with particular focus on probability of extinction. Part of our results confirms known properties of branching processes using a different approach while other are original. While the model is best suited for modeling the fate of differentiating stem cells, we discuss other scenarios in which these system dynamics may be applicable in real life. We also discuss the history of the subject.

ARTICLE HISTORY
Received 26 September 2021
Accepted 20 June 2022

KEYWORDS
Exact representation; multi-type branching processes; population dynamics; stochastic processes

1. Introduction
All cells existing in multicellular organisms originate from a single fertilized egg. In embryonic development, the descendants of this single cell migrate and differentiate to create diverse tissues and organs. Even in a mature organism, the functional cells which perform a range of tasks have to renew, since they are “used up,” and their building materials such as nucleic acids, proteins and others are recycled or disposed of. In most cases, this self-renewal system has a hierarchical structure, with the self-renewing stem cells (A-cells) at the top, which divide into two progeny, each of which may remain a stem cell or change (differentiate) into a committed cell (B-cell). It is known that stem cells are highly protected and that stem cells usually have exactly 2 progeny. In addition to this, under physiological conditions, the number of stem A-cells remains roughly constant, until the organism begins to age. The commitment is irreversible, and committed B-cells proliferate so that a constant flux of their
descendants is ensured. The count of the committed $B$-cells remains roughly constant, too. In the presence of a constant flux of differentiated $A$-cells, this is only possible if the fraction of $B$-cells proceeding to self-renewal after division is less than 1. If it is greater than or equal to 1, then the system increases in volume (cell count), starting from the $B$-cells. Therefore, the basic system that is interesting under physiological conditions is, in the branching process language, a critical process of $A$-cells feeding into the sub-critical process of $B$-cells. A sufficient condition for this to happen is that each $A$-cell progeny becomes (on average) a $B$-cell with probability equal to 1/2, and each $B$-cell progeny remains (on average) a $B$-cell with probability less than 1/2.

However, in the early development phase, during aging, or under other conditions in which differentiation of $B$-cells is altered, the sub-criticality of $B$-cells may not be ensured. Less likely, but not inconceivably, the $A$-cells might be sub- or super-critical (albeit just slightly). Hence, we will consider a range of possibilities. The process can be described as follows

\[
\begin{align*}
A & \rightarrow AA \quad \text{with probability } (1-\alpha)^2 \\
A & \rightarrow AB \quad \text{with probability } 2\alpha(1-\alpha) \\
A & \rightarrow BB \quad \text{with probability } \alpha^2 \\
B & \rightarrow BB \quad \text{with probability } p^2 \\
B & \rightarrow B \quad \text{with probability } 2pq \\
B & \rightarrow \emptyset \quad \text{with probability } q^2
\end{align*}
\]  

(1.1)

where $\alpha \in [0, 1]$, $p \in [0, 1]$, and $q = 1-p$. In addition, we assume that the lifetimes of $A$-cells and $B$-cells are exponentially distributed with parameters $\lambda_A$ and $\lambda_B$ respectively.

The paper is organized as follows. In Sec. 2, we introduce notations that will be used for the rest of the paper. In Sec. 3, we mention useful properties of special functions, which will be used in the mathematical derivations. In Sec. 4.1, we perform exploratory analysis to understand how cell counts behave on average over time. Section 4.2 contains the main text of the paper, where we derive closed-form expressions for the joint probability generating functions that fully describe the population dynamics at any given time. Based on the explicit results, we study the asymptotic extinction probabilities of the system under different combinations of criticalities in Sec. 4.3. In Sec. 5, we analyze the results and provide literature examples of diseases which might be, perhaps metaphorically, due to all types of deviations from the critical $A$-cells, sub-critical $B$-cells stereotype. Section 6 is the conclusion of the paper.
2. Notations

Let $F_A(x, y, t)$ be the joint probability generating function (PGF) for the number of cells at time $t$ given that the process is initiated by a single cell of type $A$. That is, let $Z_A(t)$ and $Z_B(t)$ be the number of $A$-cells and $B$-cells at time $t$ respectively. Then, $F_A(x, y, t)$ is defined as follows

$$F_A(x, y, t) = E[x^{Z_A(t)} y^{Z_B(t)}]$$

Since we start with one single cell of type $A$, the initial condition for $F_A$ is $F_A(x, y, 0) = x$. Similarly, $F_B(x, y, t)$ is the joint PGF given that the process is initiated by a single cell of type $B$. Note that cells of type $A$ mutate irreversibly to cells of type $B$. Hence, $F_B(x, y, t)$ is independent of $x$, and hence can be written more succinctly as $F_B(y, t)$. For consistency of notation, we will write $F_B(x, y, t)$ for the rest of the paper. For $F_B$, we start with one cell of type $B$, so the initial condition is $F_B(x, y, 0) = y$.

Let $h_A(x, y)$ and $h_B(x, y)$ be the progeny PGFs for cells of type $A$ and cells of type $B$ respectively. From (1.1), it follows that

$$h_A(x, y) = [(1-x)x + xy]^2$$

$$h_B(x, y) = (p + qy)^2$$

3. Special functions

Throughout the paper, we will make use of various special functions. Let $I(a, z)$ be the modified Bessel function of order $a$ evaluated at $z$. The first derivative of $I(a, z)$ is given by

$$\frac{d}{dz} I(a, z) = \frac{1}{2} (I(a-1, z) + I(a + 1, z))$$

The following recursive formulae is also useful to simplify the results

$$I(a-1, z) - I(a + 1, z) = \frac{2a}{z} I(a, z)$$

For asymptotic analysis, we need the following approximation of $I(a, z)$ when $|z|$ is large

$$I(a, z) \sim \frac{1}{\sqrt{2\pi z}} e^{z}$$

Let $M(a, b, z)$ and $W(a, b, z)$ be the Whittaker functions (first kind and second kind, respectively) with parameters $a$ and $b$ evaluated at $z$. The first derivatives are given by
\[
M'(a, b, z) = \left(\frac{1}{2} - \frac{a}{z}\right) M(a, b, z) + \frac{1}{z} \left(\frac{1}{2} + a + b\right) M(a + 1, b, z)
\]

\[
W'(a, b, z) = \left(\frac{1}{2} - \frac{a}{z}\right) W(a, b, z) - \frac{1}{z} W(a + 1, b, z)
\]

(3.4)

Let \( _1F_1(a, b, z) \) and \( U(a, b, z) \) denote the confluent hypergeometric functions (first kind and second kind, respectively) with parameter \( a \) and \( b \) evaluated at \( z \). There is a simple algebraic relationship between the Whittaker functions and the confluent hypergeometric functions

\[
M(a, b, z) = e^{-z/2} z^{a+1/2} _1F_1\left(b-a+\frac{1}{2}, 1+2b, z\right)
\]

\[
W(a, b, z) = e^{-z/2} z^{b+1/2} U\left(b-a+\frac{1}{2}, 1+2b, z\right)
\]

(3.5)

The large-\( z \) behavior of \( _1F_1(a, b, z) \) and \( U(a, b, z) \) is given by

\[
_1F_1(a, b, z) = \frac{\Gamma(b)}{\Gamma(a)} e^z z^{a-b} (1 + O(|z|^{-1}))
\]

\[
U(a, b, z) = z^{-a} (1 + O(|z|^{-1}))
\]

(3.6)

Lastly, let \( _2F_1(a, b, c, z) \) be the Gaussian hypergeometric function with parameters \( a, b \) and \( c \) evaluated at \( z \). The function is defined by the following series expansion

\[
_2F_1(a, b, c, z) = \frac{\Gamma(c)}{\Gamma(a) \Gamma(b)} \sum_{n=0}^{\infty} \frac{\Gamma(a + n) \Gamma(b + n) z^n}{\Gamma(c + n) n!}
\]

(3.7)

with convergence guaranteed within the unit circle \(|z| = 1\). The first derivative of \( _2F_1(a, b, c, z) \) is given by

\[
_2F_1'(a, b, c, z) = \frac{ab}{c} _2F_1(1 + a, 1 + b, 1 + c, z)
\]

(3.8)

Note that the parameters of the special functions above can take complex values. Details on the properties of these special functions can be found in [1, 12].

4. Results

4.1. Analysis of expectations

Let \( E_A(t) \) be the expected number of cells of type \( A \) at time \( t \). Similarly, let \( E_B(t) \) be the expected number of cells of type \( B \) at time \( t \). From (1.1), we have that \( E_A \) satisfies
\[
\frac{dE_A}{dt} = \lambda_A (1-2x) E_A
\]

Under the initial condition \( E_A(0) = 1 \), the solution is \( E_A(t) = e^{\lambda_A (1-2x)t} \). Note that \( E_A(t) \) is identically 1 when \( x = 1/2 \), which is expected from a critical process. From the dynamics of cells of type \( B \) in (1.1), we have that \( E_B(t) \) must satisfy the following first-order linear differential equation

\[
\frac{dE_B}{dt} = 2\lambda_A (1-x)e^{\lambda_A (1-2x)t} + \lambda_B (q^2-p^2) E_B
\]

At time \( t=0 \), we have no cells of type \( B \). Therefore, the initial condition is simply \( E_B(0) = 0 \). If all cells are critical (i.e., \( x = 1/2 \) and \( p = q = 1/2 \); we call this case “bi-critical”), the equation above simplifies, and the general solution is \( E_B(t) = \lambda_A t \). If the system is not bi-critical, we obtain the general solution

\[
E_B(t) = \frac{2\lambda_A (1-x)}{\lambda_A (1-2x) - \lambda_B (q^2-p^2)} e^{\lambda_A (1-2x)t} + C e^{\lambda_B (q^2-p^2)t}
\]

Under the initial condition \( E_B(0) = 0 \), the particular solution is given by

\[
E_B(t) = \frac{2\lambda_A (1-x)}{\lambda_A (1-2x) - \lambda_B (q^2-p^2)} \left( e^{\lambda_A (1-2x)t} - e^{\lambda_B (q^2-p^2)t} \right)
\]

**4.2. Explicit probability generating function solution**

To derive the explicit solution, we consider the following backward equations\[17]\:

\[
\frac{dF_A}{dt} = -\lambda_A F_A + \lambda_A h_A(F_A, F_B) \tag{4.2.1}
\]

\[
\frac{dF_B}{dt} = -\lambda_B F_B + \lambda_B h_B(F_A, F_B) \tag{4.2.2}
\]

To solve this system of backward equations, we will solve Eq. (4.2.2) for \( F_B \) first and then substitute it into Eq. (4.2.1) to obtain \( F_A \). The approach that we employ is largely inspired by \[2, 3\], which also concerned closed-form expressions for the PGFs of two-type time continuous branching processes with exponentially distributed lifetimes, but with different dynamics from ours. A two-stage model of carcinogenesis, which involved three cell types, was addressed in Denes and Krewski\[7\] by reducing the partial differential equation satisfied by the PGF to the hypergeometric differential equation of Gauss.

**Theorem 4.2.1.** Given cells of type \( A \) and \( B \) that proliferate according to dynamics (1.1), the joint PGF \( F_A(x, y, t) \) under different criticalities is given as follows.
a. (Bi-critical) Let $\mu = \frac{4k}{4h}$.

$$F_A(w) = \frac{-4}{\mu} \left[ \frac{\mu}{2\sqrt{w}} \left( \frac{-\theta}{\mu \sqrt{w}} I_0^-(w) + I_1^-(w) \right) + \frac{C}{\mu \sqrt{w}} I_0^+(w) + I_1^+(w) \right]$$

$$+ \frac{1}{2w} - \frac{\mu(1+w)}{4w} \right]$$

(4.2.3)

where $w = \frac{2^{(1-y)/4+1}}{1-y}$, $\theta = \sqrt{1-\mu}$ is a constant defined in terms of the model parameters, and $C = C(x)$ is a constant that is determined by the initial condition. Furthermore,

$$I_0^-(w) = I(\theta, \mu \sqrt{w}) \quad I_0^+(w) = I(\theta, \mu \sqrt{w})$$

$$I_1^-(w) = I(-\theta, \mu \sqrt{w}) \quad I_1^+(w) = I(\theta + 1, \mu \sqrt{w})$$

(4.2.4)

b. (Non-critical A-cells and critical B-cells) Let $\mu = \frac{4k}{4h}$.

$$F_A(w) = \frac{-4}{\mu(1-x)^2} \left[ \frac{\theta}{2w} - \theta_1 + \frac{1}{2} \left( \frac{1}{2} + \theta_1 + \theta_2 \right) M_0(w) - CW_1(w) \right]$$

$$- \frac{\mu(w + 2x(1-x)(1-w))}{2w} \right]$$

(4.2.5)

where $w = \frac{2^{(1-y)/4+1}}{1-y}$, and $\theta_1$, $\theta_2$ and $\theta$ are constants defined in terms of the model parameters

$$\theta_1 = -\frac{\mu(1-x)z}{|1-2z|}; \quad \theta_2 = \frac{1}{2} \sqrt{1-4\mu x + 4\mu x^2}; \quad \theta = |1-2z|\mu$$

$C$ is a constant that is determined by the initial condition, and

$$M_0(w) = M(\theta_1, \theta_2, \theta w); \quad M_1(w) = M(\theta_1 + 1, \theta_2, \theta w);$$

$$W_0(w) = W(\theta_1, \theta_2, \theta w); \quad W_1(w) = W(\theta_1 + 1, \theta_2, \theta w)$$

(4.2.6)
(Non-critical B-cells) Let $\mu = \frac{\lambda_B}{2a(p-q)}$.

$$F_A(z) = \frac{-z}{\mu(1-\alpha)^2} \left\{ \frac{1 + \theta_1}{2} z^{-\frac{1-\theta_1}{2}} F_0^+(z) + \frac{(1 + \theta_1 + \theta_2)^2 - \theta_3^2}{4q^2(1 + \theta_1)} z^{-\frac{1-\theta_1}{2}} F_1^+(z) \right. $$

$$+ C \left( \frac{1 - \theta_1}{2} z^{-\frac{1+\theta_1}{2}} F_0^-(z) + \frac{(1 - \theta_1 + \theta_2)^2 - \theta_3^2}{4q^2(1 - \theta_1)} z^{-\frac{1+\theta_1}{2}} F_1^-(z) \right) $$

$$\left. \sqrt{\frac{1}{2}} \left\{ \frac{1 + \theta_1}{2} z^{-\frac{1+\theta_1}{2}} F_0^+(z) + \frac{1 + \theta_2}{2z - q^2} \right\} - \frac{1}{2} \left\{ \frac{1 - \mu}{z} (2x(1-\alpha) \frac{z-p^2}{z-q^2-1} \right\} \right\} $$

(4.2.7)

where $z = \frac{yz^p}{1+y} e^{\lambda_B(pq)t}$, and $\theta_1$, $\theta_2$ and $\theta_3$ are constants in terms of the model parameters

$$\theta_1 = \frac{\mu \sqrt{q^2-4x(1-\alpha)p^2}}{q}; \quad \theta_2 = \frac{\sqrt{q^2-4x(1-\alpha)\mu(p-q)}}{q}; \quad \theta_3 = \mu |1-2x|$$

$C$ is a constant that is determined by the initial condition, and

$$F_0^+(z) = _2F_1 \left( \frac{1}{2} (1 + \theta_1 + \theta_2 + \theta_3), \frac{1}{2} (1 + \theta_1 + \theta_2 - \theta_3), 1 + \theta_1, \frac{z}{q^2} \right);$$

$$F_0^-(z) = _2F_1 \left( \frac{1}{2} (1 - \theta_1 + \theta_2 + \theta_3), \frac{1}{2} (1 - \theta_1 + \theta_2 - \theta_3), 1 - \theta_1, \frac{z}{q^2} \right);$$

$$F_1^+(z) = _2F_1 \left( 1 + \frac{1}{2} (1 + \theta_1 + \theta_2 + \theta_3), 1 + \frac{1}{2} (1 + \theta_1 + \theta_2 - \theta_3), 2 + \theta_1, \frac{z}{q^2} \right);$$

$$F_1^-(z) = _2F_1 \left( 1 + \frac{1}{2} (1 - \theta_1 + \theta_2 + \theta_3), 1 + \frac{1}{2} (1 - \theta_1 + \theta_2 - \theta_3), 2 - \theta_1, \frac{z}{q^2} \right)$$

(4.2.8)

**Proof.** (a) Under bi-criticality, we obtain the following backward equation for $B$-cells from (2.2) and (4.2.2)

$$\frac{dF_B}{dt} = \frac{\lambda_B}{4} (F_B-1)^2$$

Noting that the initial condition is $F_B(x,y,0) = y$, we have

$$F_B(x,y,t) = \frac{\lambda_Bt(1-y)/2 + 2y}{\lambda_Bt(1-y)/2 + 2}$$

(4.2.9)
Combining (2.1), (4.2.1) and (4.2.9) gives us
\[
\frac{dF_A}{dt} = -\dot{\lambda}_AF_A + \dot{\lambda}_A \left( (1-\alpha)F_A + \alpha \frac{\dot{\lambda}_B t (1-y)}{2} + 2y \right)^2
\]

We then employ the transformation \( f = F_B = \frac{\dot{\lambda}_B t (1-y)^{\frac{2}{2}} + 2y}{\lambda_B t (1-y)^{\frac{2}{2} + 2}} \), which leads to
\[
\frac{dF_A}{df} = \mu \frac{(1-\alpha)^2 F_A^2}{(1-f)^2} + \mu \frac{2\alpha(1-\alpha)f - 1}{(1-f)^2} F_A + \mu \alpha^2 \frac{f^2}{(1-f)^2}
\]
where \( \mu = \frac{4\dot{\lambda}_A}{\dot{\lambda}_B} \) is a constant. We employ another transformation, \( w = \frac{1}{1-f} \), to simplify the equation. Note that \( \frac{dw}{df} = \frac{1}{(1-f)^2} = w^2 \). Therefore, the equation becomes
\[
\frac{dF_A}{dw} = \mu(1-\alpha)^2 F_A^2 + \mu \left( 2\alpha(1-\alpha) \frac{w-1}{w} - 1 \right) F_A + \mu \alpha^2 \left( \frac{w-1}{w} \right)^2
\]

We have that \( w(t = 0) = \frac{1}{1-y} \). Hence, the initial condition becomes \( F_A \left( w = \frac{1}{1-y} \right) = x \). This is a non-linear Riccati differential equation, which is not possible to solve in general. However, in this case we can convert it to a second-order linear ODE (the Sturm-Liouville equation) and try to solve it instead\(^5\). To do this, we introduce the following short-hand notations
\[
A = \mu(1-\alpha)^2; \quad B = \mu \left( 2\alpha(1-\alpha) \frac{w-1}{w} - 1 \right); \quad C = \mu \alpha^2 \left( \frac{w-1}{w} \right)^2
\]

Following Antal and Krapivsky\(^3\), we perform the transformation \( F_A = -\frac{u'}{Au} = -\frac{1}{A} (\log u)' \). The equation becomes
\[
u'' + \gamma v' + \beta v = 0
\]
where the coefficients \( \gamma \) and \( \beta \) are given by
\[
\gamma = - \left( \frac{A'}{A} + B \right) = \mu \left( 1 + 2\alpha(1-\alpha) \frac{1-w}{w} \right);
\]
\[
\beta = AC = \mu^2 \alpha^2 (1-\alpha)^2 \left( \frac{1-w}{w} \right)^2
\]

To remove the first derivative, we use another quasi-linear transformation \( u = \Phi T \) such that \( \Phi' = -\gamma \Phi / 2 \). As we shall see, we do not need to compute the function \( \Phi \) explicitly. Finally, we arrive at an equation whose solution can be obtained explicitly
\[ T'' - \left( \frac{\mu^2(w + 4\alpha(1-\alpha)(1-w))}{4w} - \frac{\mu\alpha(1-\alpha)}{w^2} \right) T = 0 \] (4.2.10)

Since we are assuming that cells of type A behave critically, the equation above reduces to

\[ T'' - \frac{\mu}{4w} \left( \mu - \frac{1}{w} \right) T = 0 \]

The closed-form solution for the ODE above can be written as a linear combination of modified-Bessel functions of the first kind. The solution, up to a multiplicative constant, is given by

\[ T(w) = \sqrt{w} \left[ I\left( -\sqrt{1-\mu}, \mu \sqrt{w} \right) + CI\left( \sqrt{1-\mu}, \mu \sqrt{w} \right) \right] \]

where \( I(.) \) is the modified Bessel function defined in Sec. 2. Using the short-hand notations (4.2.4), we can write \( T(w) = \sqrt{w}|I_0^-(w) + CI_1^-(w)| \). To obtain an explicit expression for \( F_A \), we reverse the calculations as follows

\[ F_A(w) = -\frac{1}{A} \left( \frac{T'(w)}{T(w)} - \frac{\gamma}{2} \right) \] (4.2.11)

As we can see, we are interested in the ratio between \( T'(w) \) and \( T(w) \) and, therefore, the omitted multiplicative constant does not matter. Using formulas (3.1) and (3.2), and short-hand notations (4.2.4), we arrive at the following expression for \( T'(w) \)

\[ T'(w) = \frac{\mu}{2} \left[ \left( -\frac{\theta}{\mu \sqrt{w}} I_0^-(w) + I_1^-(w) \right) + C \left( \frac{\theta}{\mu \sqrt{w}} I_0^+(w) + I_1^+(w) \right) \right] + \frac{1}{2w} T(w) \]

where \( \theta = \sqrt{1-\mu} \). From (4.2.11), given that \( A = \frac{\mu}{4} \) and \( \gamma = \frac{\mu(1+w)}{2w} \) in the critical case, we find that \( F_A(w) \) is given by (4.2.3), where \( w = \frac{1}{1-\tau} = \frac{2\alpha\tau(1-\gamma)/4+1}{1-\gamma} \) is a function of \( t \). The initial condition \( F_A\left( w = \frac{1}{1-\gamma} \right) = x \) leads to the following expression for the constant \( C \).

\[ C = \frac{\kappa I_0^- \left( \frac{1}{1-\gamma} \right) - \left( \frac{-\theta \sqrt{1-\gamma}}{\mu} I_0^-\left( \frac{1}{1-\gamma} \right) + I_1^-(\frac{1}{1-\gamma}) \right)}{\left( \frac{\theta \sqrt{1-\gamma}}{\mu} I_0^+\left( \frac{1}{1-\gamma} \right) + I_1^+(\frac{1}{1-\gamma}) \right) - \kappa I_0^+\left( \frac{1}{1-\gamma} \right)} \] (4.2.12)

where

\[ \kappa = \frac{2-\gamma-x}{2\sqrt{1-\gamma}} - \frac{\sqrt{1-\gamma}}{\mu} \] (4.2.13)
Proofs of the remaining parts follow the same approach, and are given in details in the online supplementary material.

4.3. Asymptotic analysis

In this section, we will study the asymptotic properties of the systems we consider, with particular focus on the probability of extinction of cells in large time.

**Theorem 4.3.1.** Suppose that cells of type A and B proliferate according to dynamics (1.1).

a. **(Bi-critical)** Eventual extinction occurs with probability 1. The rate at which the population approaches extinction is proportional to the inverse of the square root of time.

b. **(Non-critical A cells and critical B cells)** Eventual extinction happens with probability

\[
\frac{1}{2(1-z)^2} \left[ 1 - \frac{2z(1-z)p^2}{q^2} - \sqrt{q^2 - 4z(1-z)p^2} \right].
\]

The probability of extinction approaches this limit exponentially with respect to time.

c. **(Super-critical B cells)** Assuming \( h_1 \neq C_0 \), where \( h_1 \) is defined in part (c) of Theorem 4.2.1, eventual extinction happens with probability

\[
\frac{1}{2(1-z)^2} \left[ 1 - \frac{2z(1-z)p^2}{q^2} - \sqrt{q^2 - 4z(1-z)p^2} \right].
\]

The probability of extinction approaches this limit exponentially with respect to time.

**Proof.** (a) The probability of extinction of the entire population by time \( t \), \( E(t) \), is given by \( F_A(0,0,t) \). From (4.2.13), we have that, at \( x = 0 \) and \( y = 0 \),

\[
\kappa_0 := \kappa|_{x=0,y=0} = 1 - \frac{1}{\mu}
\]

Therefore, from (4.2.12),

\[
C_0 := C|_{x=0,y=0} = \frac{\kappa_0 I_0^{-}(1) - \frac{\theta}{\mu} I_0^{-}(1) + I_1^{-}(1)}{\frac{\theta}{\mu} I_0^{+}(1) + I_1^{+}(1)} - \kappa_0 I_0^{+}(1)
\]

is a finite constant. Given that \( w = \frac{\lambda t(1-y)/4+1}{1-y} \), we have that \( w_0 := w|_{x=0,y=0} = \frac{\lambda t}{4} + 1 \). Hence, \( w_0 \to \infty \) as \( t \to \infty \). Using the large-argument approximation (3.3) for modified Bessel functions and the fact that \( C_0 \) is finite, we deduce that

\[
\frac{\left( \frac{\theta}{\mu \sqrt{w_0}} I_0^{-}(w_0) + I_1^{-}(w_0) \right) + C_0 \left( \frac{\theta}{\mu \sqrt{w_0}} I_0^{+}(w_0) + I_1^{+}(w_0) \right)}{I_0^{-}(w_0) + C_0 I_0^{+}(w_0)} \sim 1 - \frac{\theta}{\mu \sqrt{w_0}} \frac{1-C_0}{1 + C_0}
\]
for large time. Therefore, it follows that

\[
E(t) = \frac{-4}{\mu} \left[ \frac{\mu}{\sqrt{w_0}} \left( \frac{-\theta}{\mu \sqrt{w_0}} I_0^-(w_0) + I_1^-(w_0) \right) + C_0 \left( \frac{-\theta}{\mu \sqrt{w_0}} I_0^+(w_0) + I_1^+(w_0) \right) \right] \\
+ \frac{1}{2w_0} - \frac{\mu(1 + w_0)}{4w_0}
\]

\[
\sim \frac{-4}{\mu} \left[ \frac{\mu}{2 \sqrt{w_0}} \left( 1 - \frac{\theta}{\mu \sqrt{w_0}} \frac{1-C_0}{1+C_0} \right) + \frac{1}{2w_0} - \frac{\mu(1 + w_0)}{4w_0} \right]
\]

\[
\sim \frac{-4}{\mu} \left( \frac{\mu}{2 \sqrt{w_0}} - \frac{\mu}{4} \right)
\]

\[
\sim 1 - \frac{4/\sqrt{\lambda_B}}{\sqrt{t}}
\]

The theorem then follows. \(\square\)

Certain extinction of a two-type system with double criticalities has been proven in Athreya and Ney\(^4\). Hence, in the bi-critical case, our theorem agrees with established theoretical results in literature using a different approach. Detailed proofs of the remaining parts are given in the online supplementary material.

5. Discussion

5.1. Stochastic models of hematopoiesis over time

The history of stochastic models of hematopoiesis goes back to the work of Till, McCullogh, and Siminovitch in 1963\(^{27}\), who modeled proliferation of colony-forming units (CFU) and described the distribution of sizes of resulting colonies using gamma distribution and simulated (using an early IBM machine) birth-death processes. Macken and Perelson\(^{19}\), in a Springer Lecture Notes volume, proposed a series of comprehensive models of hematopoietic system in the form of a multi-type Galton-Watson process. This analysis was insightful, including probabilities of non-extinction (“completion of growth”), growth rates and the first two moments of cell counts. The results were mostly obtained using now classical theorems from Harris’s book\(^{14}\). Many original papers and reviews on stochastic models appeared since, including Dingli et al.\(^{8}\) regarding stochastic clonal expansion of hematopoietic stem cells, Kimmel and Corey\(^{18}\) and Wojdyla et al.\(^{31}\) regarding evolution of neutropenia-related leukemias, and many others. Some of them were reviewed in \([16, 30]\). A paper that features a
three-type branching process model not very unlike ours was published by Denes and Krewski[7].

Diverse aspects of the dynamics of the hematopoietic systems can be understood using deterministic or quasi-stochastic approaches. The former involves expected-value dynamics modeled using ordinary differential equation (ODE) models, while the latter involves expected frequencies modeled using integral equations or partial differential equations of transport type. A comprehensive review of both types of approaches was carried out by Pujo-Menjouet[22]. A recent paper by Dinh et al.[9] shows how stochasticity is important in prediction of outcomes of treatments for leukemias (for the deterministic model related to the latter paper, see Stiehl et al.[25]).

5.2. Review of biologically relevant cases

We will limit the review to the hemopoietic (blood cell production) system in the Human and in laboratory animals such as the Mouse. The $A$-cells here are the hemopoietic stem cells (HST), while the $B$-cells are the committed multipotent progenitors (CMP), which have the ability to feed into more specialized compartments, with probability $p$ for each progeny cell following division. CMP’s have self-renewal capacity, with probability $q$ for each progeny cell following division, but they mainly serve the role of transitional cells[30]. Analogies with other hierarchical cell production systems, such as the neurogenic progenitors in the brain[28], urothelial cells in the urinary bladder[29], and others, are immediate. However, it should be noted that, except for the neurogenesis, no other cell production system seems to reach the sophistication level of higher mammals hematopoiesis. Please note that we do not consider transients caused by regulatory feedbacks, such as the interferon $\gamma$ feedback in hematopoiesis[15], which appears when the system is under stress.

**Normal adult hematopoiesis:** In this case, stabilization of the mean HSC and CMP counts is essential[23]. This is only achieved if the $A$-cells are critical ($\alpha = 1/2$) and the $B$-cells are sub-critical ($p > q$).

**Normal fetal hematopoiesis:** In this case, growth of the mean HSC and CMP counts is essential[31]. This type of hematopoiesis occurs in the Human over the last 3 months of fetal development. This may be achieved if the $A$-cells are super-critical ($\alpha > 1/2$) and the $B$-cells are sub-critical, critical or super-critical. In each of the 3 cases, the relative proportion of HSC to CMP is changing differently with time. The probability of extinction in any finite time depends on the type of proliferation of $B$-cells. Inroads into understanding this process have been obtained using mosaic mice methodology[10].

**Normal aging hematopoiesis:** In this case, the mean HSC count is decreasing but the CMP count should be prevented from falling too fast[23]. This type of hematopoiesis occurs in the Human at age greater
than about 70. This may be achieved if the $A$-cells are sub-critical ($\alpha > 1/2$) and the $B$-cells are super-critical ($p < q$).

**Repopulation following bone marrow transplant:** This case is not very dissimilar from the fetal hematopoiesis, as the main purpose is growth of the mean HSC and CMP counts. An interesting twist is that the transplant has to include a mix of some HSC and much more CMP, since transplanting HSC alone will not allow building up of hematopoiesis in a short time; growth of the mean HSC and CMP counts is essential\[^{26}\]. Our model allows ballpark computations of this mix, given the minimum count of CMPs to be present after a fixed time from the transplant to prevent subject’s death.

**Cyclic neutropenias:** Mathematically interesting cases coincide frequently with biological reality. For example, in the bi-critical case, we expect large oscillations, observed in diseases such as cyclic neutropenias\[^{21}\]. In the historic paper by Mackey and Glass\[^{20}\], cyclic hematopoiesis is attributed to defects in feedback governing stem cell activation, but the strong stochastic component may be better explained by criticality.

### 5.3. Distributions of cell lifetimes

Methods, which we used to obtain our theorems, are typical for a linear birth-and-death process\[^{13}\]. As it is known, the latter is mathematically identical to a binary fission branching process with exponential lifetimes, which traditionally is considered not appropriate for modeling cell populations. Indeed, in laboratory cell populations, the sojourn times in different cell cycle phases are usually of finite duration, and in some bacteria, cell divisions are almost synchronous, as attested by a voluminous literature of the subject (e.g., Kimmel and Axelrod’s monograph\[^{17}\]). However, the situation is different in cancer and physiological control systems. For example, in lung cancer, time to doubling of cell populations is of the order of several weeks\[^{11}\]. In hematopoietic stem cells, it may be even longer\[^{6}\]. Much of this time is waiting for “permission” to divide (in healthy cells) or finishing of multiple rounds of DNA repair (in cancer cells). This part of the cell cycle is likely to be distributed exponentially, although measurements in vivo are difficult. In any case, models of physiological stem cell systems based on exponentially distributed cell lifetimes (hence expected values are described by ordinary differential equations) seem to work with considerable precision. This was demonstrated among others by measurements and mathematical models based on shortening of telomeres in hematopoietic stem cells\[^{24}\].

### 6. Conclusions

Two- and multi-type branching processes are minimalist models for normal cell production systems and cancer progression in which altered clones
play a major role. We presented closed-form solutions for biologically meaningful two-type time continuous branching processes with exponentially distributed lifetimes. We computed the probability generating functions explicitly for all possible combinations of cell-type-specific criticalities. The most practically interesting case, which arises in the dynamics of stem cells, is when the self-renewing stem cells are critical and the committed cells are sub-critical. However, as discussed previously, other system dynamics are also relevant in certain situations. While systems with non-critical dynamics are complex due to the presence of the confluent hypergeometric and Whittaker functions, solution for the bi-critical case can be expressed in terms of the relatively simple modified Bessel functions with well-defined asymptotic behaviors. Our asymptotic analyses not only reveal the large-time probability of extinction, but also describe the rate at which this probability approaches the limit. Given the closed-form solutions, other interesting asymptotic properties can be studied by considering certain scaling limits, and require further research in the future. It is also more realistic to model cancer progression using a multi-type branching process. Given the already complex nature of the explicit solutions presented in our paper, doing the same for a multi-type system may not be feasible (however, see Denes and Krewski[7]) and require a different approach.

Acknowledgments

Nam Nguyen acknowledges funding from CPRIT grant RP200383 (Dr. Wenyi Wang, PI). Marek Kimmel acknowledges funding from NIH R01HL136333 and R01HL134880 grants (Dr. Katherine King, PI).

ORCID

Nam H. Nguyen http://orcid.org/0000-0003-4990-0192

References

[1] Abramowitz, M.; Stegun, I. A. Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables, 9th ed.; Dover: New York, 1964.
[2] Antal, T.; Krapivsky, P. Exact Solution of a Two-Type Branching Process: Clone Size Distribution in Cell Division Kinetics. J. Stat. Mech. 2010, 2010(07):P07028. DOI: 10.1088/1742-5468/2010/07/P07028.
[3] Antal, T.; Krapivsky, P. Exact Solution of a Two-Type Branching Process: Models of Tumor Progression. J. Statist Mech. Theory Exp. 2011, 2011(08):P08018. DOI: 10.1088/1742-5468/2011/08/P08018.
[4] Athreya, K. B.; Ney, P. E. Branching Processes. Springer: Berlin, Heidelberg, 1972.
[22] Pujo-Menjouet, L. Blood Cell Dynamics: Half of a Century of Modelling. Math. Model. Nat. Phenom. 2016, 11, 92–115. DOI: 10.1051/mmnp/201611106.

[23] Shepherd, B. E.; Guttorp, P.; Lansdorp, P. M.; Abkowitz, J. L. Estimating Human Hematopoietic Stem Cell Kinetics Using Granulocyte Telomere Lengths. Exp. Hematol. 2004, 32, 1040–1050. DOI: 10.1016/j.exphem.2004.07.023.

[24] Sidorov, I.; Kimura, M.; Yashin, A.; Aviv, A. Leukocyte Telomere Dynamics and Human Hematopoietic Stem Cell Kinetics during Somatic Growth. Exp. Hematol. 2009, 37, 514–524. DOI: 10.1016/j.exphem.2008.11.009.

[25] Stiehl, T.; Baran, N.; Ho, A. D.; Marciniak-Czochra, A. Clonal Selection and Therapy Resistance in Acute Leukaemias: Mathematical Modelling Explains Different Proliferation Patterns at Diagnosis and Relapse. J. R. Soc. Interface. 2014, 11, 20140079. DOI: 10.1098/rsif.2014.0079.

[26] Stiehl, T.; Ho, A. D.; Marciniak-Czochra, A. The Impact of cd34+ Cell Dose on Engraftment after Scts: Personalized Estimates Based on Mathematical Modeling. Bone Marrow Transplant. 2014, 49, 30–37.

[27] Till, J. E.; McCulloch, E. A.; Siminovitch, L. 1964 A Stochastic Model of Stem Cell Proliferation, Based on the Growth of Spleen Colony-Forming Cells. Proc. Natl. Acad. Sci. U.S.A., 51:29–36. DOI: 10.1073/pnas.51.1.29.

[28] Villalba, A.; Götz, M.; Borrell, V. The Regulation of Cortical Neurogenesis. Curr. Top. Dev. Biol. 2021, 142, 1–66. DOI: 10.1016/bs.ctdb.2020.10.003.

[29] Wang, C.; Trotter Ross, W.; Mysorekar, I. U. Urothelial Generation and Regeneration in Development, Injury, and Cancer. Dev. Dyn. 2017, 246, 336–343. DOI: 10.1002/dvdy.24487.

[30] Whichard, Z. L.; Sarkar, C. A.; Kimmel, M.; Corey, S. J. Hematopoiesis and Its Disorders: A Systems Biology Approach. Blood. 2010, 115, 2339–2347. DOI: 10.1182/blood-2009-08-215798.

[31] Wojdyla, T.; Mehta, H.; Glaubach, T.; Bertolusso, R.; Iwanaszko, M.; Braun, R.; Corey, S. J.; Kimmel, M. Mutation, Drift and Selection in Single-Driver Hematologic Malignancy: Example of Secondary Myelodysplastic Syndrome following Treatment of Inherited Neutropenia. PLoS Comput. Biol. 2019, 15, e1006664. DOI: 10.1371/journal.pcbi.1006664.