Iterated birth and death process as a model of radiation cell survival

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Abstract

The iterated birth and death process is defined as an $n$-fold iteration of a stochastic process consisting of the combination of instantaneous random killing of individuals in a certain population with a given survival probability $s$ with a Markov birth and death process describing subsequent population dynamics. A long-standing problem of computing the distribution of the number of clonogenic tumor cells surviving a fractionated radiation schedule consisting of $n$ equal doses separated by equal time intervals $\tau$ is solved within the framework of iterated birth and death processes. For any initial tumor size $i$, an explicit formula for the distribution of the number $M$ of surviving clonogens at moment $\tau$ after the end of treatment is found. It is shown that if $i \to \infty$ and $s \to 0$ so that $is^n$ tends to a finite positive limit, the distribution of random variable $M$ converges to a probability distribution, and a formula for the latter is obtained. This result generalizes the classical theorem about the Poisson limit of a sequence of binomial distributions. The exact and limiting distributions are also found for the number of surviving clonogens immediately after the $n$th exposure. In this case, the limiting distribution turns out to be a Poisson distribution.

Keywords: Birth and death process; Branching process; Clonogenic tumor cell; Fractionated cancer radiotherapy; Limiting distribution; Probability distribution; Probability generating function; Tumor recurrence

1. Introduction

The purpose of this work is to solve, under natural biological assumptions, the following problem of major theoretical and practical importance in radiation oncology that was posed in [1] as early as in 1990: What is the distribution of the number of clonogenic tumor cells surviving
fractionated radiation? Lack of theoretical results leading to a closed-form analytic expression for this distribution, even under very simplistic models of cell kinetics between radiation exposures, was the most critical deterrent to evaluating and increasing the efficacy of existing clinical practices of cancer treatment and to developing relevant methods of statistical data analysis.

We proceed from the following model of tumor population kinetics, see e.g. [2]. A tumor initially comprising a non-random number $i$ of clonogenic cells is exposed to a fractionated radiation schedule consisting of $n$ instantaneously delivered equal doses $D$ separated by equal time intervals $s$. It is assumed that every clonogen survives each exposure to the dose $D$ with the same probability $s = s(D)$, given that it survived the previous exposures, and independently of other clonogens. Observe that it is not supposed that all cells forming a tumor are necessarily clonogenic. We also assume that irradiated tumor cells are killed instantaneously. According to a common radiobiological convention, a tumor cell is killed if it is incapable of producing a viable clone. Between the exposures, clonogens proliferate or die spontaneously independently of each other with constant rates $\lambda > 0$ and $\nu \geq 0$ (defined in the sense of Markov processes), respectively. Finally, it is assumed that cell death between radiation exposures is instantaneous, and that descendants of a clonogenic cell are clonogenic.

Similar models arise when a tumor cell population is exposed to chemical or immunological agents, as well as in problems of population dynamics in the presence of emigration and external or internal killing factors.

Suppose that radiation exposures occur at time moments $0, \tau, \ldots, (n-1)\tau$. Let $M$ be the random number of clonogens (including the original clonogenic cells and their descendants) that are alive at time $nt$, that is, at time $\tau$ after the $n$th exposure. Random variable (r.v.) $M$ can be viewed as the final state of a stochastic process defined as the $n$-fold iteration of the combination of exposure to the dose $D$ with the homogeneous birth and death Markov process with the birth rate $\lambda$ and death rate $\nu$. This $n$-stage stochastic process will be referred to in what follows as the iterated birth and death process. Also, denote by $L$ the number of surviving clonogens immediately after delivery of the $n$th fraction of radiation. Although r.v. $L$ is biologically more natural than $M$, the latter is more tractable mathematically.

Alternatively, r.v.s $M$ and $L$ can be characterized in terms of the Galton–Watson branching process (see e.g. [3, Chapter 1], and [4, Chapter 2]). Denote by $Z_\tau$ the state at time $\tau$ of the homogeneous birth and death Markov process with the birth rate $\lambda$, death rate $\nu$, and initial population size $i = 1$ (that can be also viewed as a continuous time branching process with the probabilities of no and two offspring equal to $\nu/(\lambda + \nu)$ and $\lambda/(\lambda + \nu)$, respectively). Then the distribution of r.v. $M$ coincides with the distribution of the $n$th generation size in the Galton–Watson process where the initial population size follows the binomial distribution $B(i, s)$ and the offspring distribution is $B(Z_\tau, s)$. In what follows, however, we will use the iterated birth and death process approach because it is more straightforward and technically simple.

Most of the previous theoretical work was related to the case $\lambda = \nu = 0$, where no cell proliferation and cell death occur between radiation exposures, and was primarily focused on the extinction probability $\bar{p}_0 := \text{Pr}(L = 0)$ (which is also referred to in radiation oncology as the tumor control probability). In this case, the probability that a given clonogenic cell will survive the $n$-dose
irradiation schedule is equal to $s^n$. Hence, $M = L$, and these r.v.s follow the binomial distribution $B(i, s^n)$. The initial number $i$ of clonogenic cells in a tumor is typically very large (1 cm$^3$ of a solid tumor contains about $10^9$ cells [5]; also, a clinically detectable tumor is estimated to contain at least $10^5$ clonogenic cells probably ranging up to $10^9$ cells or even more [6]). Furthermore, the survival probability $s^n$ is small because the dose $D$, usually 1–2 Gy, and the number of fractions $n$, normally 20–40, are chosen to achieve just that. Therefore, the distribution $B(i, s^n)$ is close to the Poisson distribution with parameter $\theta = is^n$. It is this Poisson approximation that is used for planning fractionated cancer radiotherapy in current clinical practice, see e.g. [2,7,8].

The validity of this Poisson approximation was first questioned in [1]. The idea of this work was that due to cell proliferation the distribution of the number of surviving clonogens must deviate from the binomial distribution $B(i, s^n)$ which makes the approximating Poisson distribution $P(\theta)$ not well justified. Extensive numerical simulations conducted in [1] confirmed that in the absence of cell death between radiation exposures ($v = 0$) the mean and variance of r.v. $L$ are distinct from those predicted by the binomial distribution $B(i, s^n)$. On this basis, the authors made a conclusion that the distribution of r.v. $L$ cannot be approximated by a Poisson distribution. In response to this work, it was suggested in [9] to use branching stochastic processes as an adequate tool for studying the distribution of r.v. $L$ (for an extensive discussion of this idea, the reader is referred to [10, pp. 31–40]) but the model proposed in this work was too simplistic. Numerical algorithms for computing the extinction probability $\tilde{p}_0$ in the case $v = 0$ are described in [8,11]. The work [11] also contains a more general algorithm for numerical evaluation of the probability generating function (p.g.f.) of r.v. $L$. A numerical procedure for computing the extinction probability $\tilde{p}_0$ within a more elaborate model accounting not only for cell division but also for cell loss, cell differentiation, and cell cycle effects is presented in [6].

The paper [2] represents the first attempt at theoretical approach to describing the distribution of the number of surviving clonogens. It contains explicit formulas for $\tilde{p}_0 := \Pr(M = 0)$ and the p.g.f. of r.v. $M$ obtained within the framework of homogeneous birth process. The following problems are therefore of theoretical and practical interest.

**Problem 1.** Find explicit computationally feasible formulas for the distribution of the final state $M$ of the $n$-fold iterated birth and death process and for its counterpart $L$.

**Problem 2.** Compute the limiting distributions of r.v.s $M$ and $L$ when $i \to \infty$, $s \to 0$ and $is^n \to \theta$, $0 < \theta < \infty$.

In the present communication, we solve Problems 1 and 2. For an at length discussion of biomedical and statistical implications of the results of this work, the reader is referred to [12]. A model based on our findings was successfully applied to statistical analysis of data on prostate cancer post-treatment survival [13].

The structure of the paper is as follows. In Section 2, we compute p.g.f. of the iterated birth and death process and derive some of the immediate consequences for the r.v.s $M$ and $L$. Their distribution is identified in Section 3, which leads to a solution of Problem 1. Section 4 addresses limit theorems for the iterated birth and death process that solve Problem 2. A numerical example corroborating our theoretical findings is presented in Section 5. Finally, in Section 6, we briefly discuss our results from biomedical and statistical data analysis perspectives.
2. Probability generating function of the iterated birth and death process

In this section, we will compute p.g.f. of the final state $M$ of the $n$-fold iterated birth and death process with $i$ initial cells. As a consequence, we will find p.g.f. of the number $L$ of surviving clonogens immediately after the $n$th exposure. Since p.g.f. is an indispensable tool for analysis of Markov processes with the state space $\mathbb{Z}_+$ (see e.g. [14, pp. 184–192]), we first recall some well-known facts about them.

For a non-negative integer valued r.v. $X$, denote by $\varphi_X$ its p.g.f. defined by

$$\varphi_X(z) := E(z^X) = \sum_{m=0}^{\infty} \Pr(X = m)z^m, \quad |z| \leq 1,$$

where $E$ stands for the expectation. The probabilities $\Pr(X = m)$ are related to the p.g.f. of $X$ by

$$\Pr(X = m) = \frac{D^m \varphi_X(0)}{m!}, \quad m \geq 0. \quad (1)$$

In particular, $\varphi_X(0) = \Pr(X = 0)$. Also observe that $\varphi_X(1) = 1$,

$$EX = \varphi'_X(1), \quad (2)$$

and

$$VarX = \varphi''_X(1) + \varphi'_X(1) - [\varphi'_X(1)]^2; \quad (3)$$

where $Var$ denotes the variance. The expectation and variance of $X$ can also be expressed through the logarithmic derivatives of $\varphi_X$ as follows:

$$EX = (\ln \varphi_X)'(1) \quad \text{and} \quad VarX = (\ln \varphi_X)''(1) + (\ln \varphi_X)'(1). \quad (4)$$

For a function $\phi$ whose range is contained in the domain, we denote by $\phi^{(n)}$ its $n$-fold composition with itself.

We start our calculation of p.g.f. $\varphi_M$ with the case $i = 1, n = 1$. Since each clonogenic cell survives irradiation in dose $D$ with the probability $s$, the number of survivors for a single clonogen exposed to the dose $D$ is a Bernoulli r.v. with p.g.f.

$$\beta(z) = 1 - s + sz. \quad (5)$$

According to our assumptions, expansion of a surviving clonogenic cell is governed by a homogeneous birth and death process with the birth rate $\lambda$ and death rate $v$. It was shown in [15] (see also [16, pp. 165–166]) that the state of such process at time $\tau$, that is, the size $S$ at time $\tau$ of the clone emerging from a single cell, has a generalized geometric distribution of the form

$$\Pr(S = 0) = r, \quad \Pr(S = m) = (1 - r)(1 - q)m^{-1}, \quad m \geq 1. \quad (6)$$

Parameters $r$ and $q$, $0 \leq r, q < 1$, of this distribution are related to the birth and death rates through the formulas

$$r = \frac{v(1 - \alpha)}{\lambda - xv} \quad \text{and} \quad q = \frac{\lambda(1 - \alpha)}{\lambda - xv}, \quad (6)$$
where it is denoted hereafter \( z := e^{(r-\lambda)\tau} \). P.g.f. of r.v. \( S \) is given by
\[
\varphi_S(z) = r + \sum_{m=1}^{\infty} (1-r)(1-q)^{m-1}z^m = \frac{r - (r + q - 1)z}{1 - qz}.
\] (7)

Observe that \( \lambda - z\nu = 0 \) only in the critical case \( \lambda = \nu \), that is, when \( z = 1 \). In this case,
\[
r = q = \frac{\lambda \tau}{1 + \lambda \tau} \quad \text{and} \quad \varphi_S(z) = \frac{\lambda \tau + (1 - \lambda \tau)z}{1 + \lambda \tau - \lambda \tau z},
\]
which coincides with the corresponding limits in (6) and (7). It follows from (2) and (7) that
\[
ES = \varphi'_S(1) = \frac{1 - r}{1 - q} = x^{-1}.
\] (8)

The number \( X \) of offspring of a single irradiated clonogenic cell at time \( \tau \) after exposure has p.g.f. \( \varphi = 1 - s + s\varphi_S = \beta \circ \varphi_S \), that is, in view of (5) and (7),
\[
\varphi(z) = 1 - s + s \frac{r - (r + q - 1)z}{1 - qz} = \frac{1 - s(1 - r) - [q - s(1 - r)]z}{1 - qz}.
\] (9)

Therefore, r.v. \( X \) follows a generalized geometric distribution. By (2) and (8) we have
\[
\mu := EX = \varphi'(1) = s\varphi'_S(1) = \frac{s}{x} = se^{(r-\lambda)\tau}. \tag{10}
\]

Observe that p.g.f. \( \varphi \) of r.v. \( X \) given in (9) is a fractional linear function. Conversely, every fractional linear p.g.f. of the form \( (a - bz)/(c - dz) \) with \( c, d \neq 0 \), \( c \neq d \), emerges from a generalized geometric distribution.

A standard argument about p.g.f. of a branching process (see e.g. [14, pp. 190–192]) implies that
\[
\varphi_M = [\varphi^{(n)}]^i. \tag{11}
\]

To compute the function \( \varphi^{(n)} \) explicitly, we need a more convenient formula for the p.g.f. \( \varphi \) expressed in (9) through parameters \( s(1 - r) \) and \( q \). In the generic case \( z \neq 1 \) we set
\[
\omega := \frac{1 - s(1 - r)}{q} = \frac{\lambda - \nu \alpha - s(\lambda - \nu)}{\lambda(1 - x)},
\] (12)
while in the critical case \( z = 1 \) we define by continuity \( \omega := (1 - s + \lambda \tau)/(\lambda \tau) \). It is easy to see that \( \omega \) is a fixed point of the function \( \varphi \). Since
\[
1 - \omega = \frac{(s - x)(\lambda - \nu)}{\lambda(1 - x)},
\] (13)
we have \( 0 < \omega < 1 \) for \( \mu > 1 \), \( \omega = 1 \) for \( \mu = 1 \), and \( \omega > 1 \) for \( 0 \leq \mu < 1 \). Observe that
\[
q = \frac{\mu - 1}{\mu - \omega} \quad \text{and} \quad s(1 - r) = \frac{\mu(1 - \omega)}{\mu - \omega}.
\]
This allows us to rewrite (9) in terms of parameters \( \mu \) and \( \omega \) as follows:
\[
\varphi(z) = \frac{\omega(\mu - 1) - (\omega \mu - 1)z}{\mu - \omega - (\mu - 1)z}. \tag{14}
\]
An explicit expression for the function $\varphi^{(n)}$ is given in formula (15) below. Its remarkable feature is that the action of the semigroup $\mathbb{Z}^+$ on the function $\varphi$ written in form (14) by compositions is simply $n \mapsto \mu^n$, $n \in \mathbb{Z}^+$. An equivalent but more cumbersome formula can be found in [9, p. 9], and (with a proof) in [17, pp. 296–298], [18, p. 7], and [19, p. 57]. In the case $\nu = 0$, formula (15) can be found in a slightly different form in [2].

**Proposition 1.** Suppose that $\mu \neq 1$. Then, for every natural number $n$,

$$
\varphi^{(n)}(z) = \frac{\omega(\mu^n - 1) - \omega(\mu^n - 1)z}{\mu^n - \omega - (\mu^n - 1)z}. 
$$

(15)

**Proof.** We will use induction in $n$. For $n = 1$, Eq. (15) coincides with (14). Suppose it holds for some $n \geq 1$. Then we have by (14) and (15)

$$
\varphi^{(n+1)}(z) = (\varphi^{(n)} \circ \varphi)(z) = \frac{\omega(\mu^n - 1) - (\omega \mu^n - 1)\varphi(z)}{\mu^n - \omega - (\mu^n - 1)\varphi(z)} = \frac{A_n - B_n z}{C_n - D_n z},
$$

where after an elementary calculation we find that

$$
A_n = \omega(\mu - \omega)(\mu^n - 1) - \omega(\mu - 1)(\omega \mu^n - 1) = \omega(1 - \omega)(\mu^{n+1} - 1),
$$

$$
B_n = \omega(\mu - 1)(\mu^n - 1) - (\omega \mu - 1)(\omega \mu^n - 1) = (1 - \omega)(\omega \mu^{n+1} - 1),
$$

$$
C_n = (\mu - \omega)(\mu^n - \omega) - \omega(\mu - 1)(\mu^n - 1) = (1 - \omega)(\mu^{n+1} - \omega),
$$

$$
D_n = (\mu - 1)(\mu^n - \omega) - (\omega \mu - 1)(\mu^n - 1) = (1 - \omega)(\mu^{n+1} - 1).
$$

Since $\mu \neq 1$, we also have $\omega \neq 1$. Therefore, the above formulas for $A_n$, $B_n$, $C_n$ and $D_n$ lead to the expression for $\varphi^{(n+1)}$ required in (15). This completes the proof of Proposition 1.

**Remark 1.** By passage to limit in (15) as $\mu \to 1$, we find that for $\mu = 1$

$$
\varphi^{(n)}(z) = \frac{n \lambda (1 - z) - |n \lambda (1 - z) - z(\lambda - \nu)|z}{n \lambda (1 - z) + z(\lambda - \nu) - n \lambda (1 - z)z}.
$$

According to (11) and (15), p.g.f. of r.v. $M$ is given by

$$
\varphi_M(z) = \left\{ \frac{\omega(\mu^n - 1) - (\omega \mu^n - 1)z}{\mu^n - \omega - (\mu^n - 1)z} \right\}^i.
$$

(16)

Thinking of the number of iterations $n$ as being fixed, we will also write $\varphi_M$ in the form

$$
\varphi_M(z) = \left( \frac{a - bz}{c - dz} \right)^i,
$$

(17)

where

$$
a := \omega(\mu - 1), \quad b := \omega \mu - 1, \quad c := \mu - \omega, \quad d := \mu - 1.
$$

(18)
Using (17) and (18) we evaluate the extinction probability
\[ p_0 = \Pr(M = 0) = \varphi_M(0) = \left( \frac{a}{c} \right)^i = \left[ \frac{\omega(\mu^a - 1)}{\mu^a - \omega} \right]^i. \]
In particular, in the pure birth setting \((v = 0)\), we have \(\omega = (1 - s)/(1 - \alpha)\) which leads to the following result obtained in [2]:
\[ p_0 = \left[ \frac{(1 - s)(\mu^a - 1)}{(1 - \alpha)\mu^a + s - 1} \right]^i. \]
Formula (16) allows us to find p.g.f. of r.v. \(L\). In view of \(u_M \hat{=} u^n\) and (5),
\[ \varphi_L(z) = \left[ \frac{1 - \omega - s + x\omega \mu^a - (x\omega \mu^a - s)z}{1 - \omega - s + x\mu^a - (x\mu^a - s)z} \right]^i = \left( \frac{\tilde{a} - \tilde{b}z}{\tilde{c} - dz} \right)^i, \] (19)
where
\[ \tilde{a} = 1 - \omega - s + x\omega \mu^a, \quad \tilde{b} = x\omega \mu^a - s, \quad \tilde{c} = 1 - \omega - s + x\mu^a, \quad \tilde{d} = x\mu^a - s. \] (20)
In particular, the tumor control probability \(\tilde{p}_0 = \Pr(L = 0)\) is given by
\[ \tilde{p}_0 = \left( \frac{\tilde{a}}{\tilde{c}} \right)^i = \left( \frac{1 - \omega - s + x\omega \mu^a}{1 - \omega - s + x\mu^a} \right)^i. \] (21)

From (16) and (19) we conclude that in the case \(i = 1\) r.v.s \(M\) and \(L\) follow generalized geometric distribution. In the case of continuous irradiation with an arbitrary dose rate, p.g.f. for the number of surviving clonogens at the end of treatment and the corresponding tumor control probability were computed within the framework of continuous time birth and death process in [20].

Let \(U\) be any non-negative integer valued r.v. with a p.g.f. of the form
\[ \varphi_U(z) = \frac{a - bz}{c - dz}. \]
Then
\[ EU = \varphi_U'(1) = \frac{A}{(c - d)^3} \quad \text{and} \quad \varphi_U''(1) = \frac{2dA}{(c - d)^3}, \]
where \(A := ad - bc\). Therefore, by (3)
\[ \text{Var} U = \frac{2dA}{(c - d)^3} + \frac{A}{(c - d)^2} - \frac{A^2}{(c - d)^4} = \frac{A^2 - d^2 - A}{(c - d)^4}. \]
(22)
Let also \(V := U_1 + \cdots + U_i\), where \(U_k\), \(1 \leq k \leq i\), are independent identically distributed (i.i.d.) r.v.s having the same distribution as \(U\). Then \(EV = i \cdot EU\), \(\text{Var} V = i \cdot \text{Var} U\), and
\[ \varphi_V(z) = \left( \frac{a - bz}{c - dz} \right)^i. \] (23)
For \(V = M\), a straightforward calculation based on (18) yields \(c - d = 1 - \omega\), \(c + d = 2\mu^a - \omega - 1\), and
\[ A_M := ad - bc = \mu^n(1 - \omega)^2. \] (24)

Therefore,
\[ EM = \frac{iA_M}{(c - d)^2} = i\mu^n. \] (25)

Also, invoking (22) and (13) we find that, for \( \mu \neq 1 \) and \( \omega \neq 1 \),
\[ \text{Var}M = i\mu^n(\mu^n - 1) \frac{1 + \omega}{1 - \omega} = i\mu^n(\mu^n - 1) \frac{\hat{\lambda}(2 - s - \hat{\omega}) + v(s - \hat{\omega})}{(\hat{\lambda} - v)(s - \hat{\omega})}. \] (26)

In a similar manner, for \( V = L \), we derive from (20) that \( \hat{c} - \hat{d} = 1 - \omega, \hat{c} + \hat{d} = 1 - \omega - 2s + 2\hat{\mu}^n \), and
\[ A_L := \hat{a}\hat{d} - \hat{b}\hat{c} = zA_M = z\mu^n(1 - \omega)^2. \] (27)

Hence,
\[ EL = zEM = iz\mu^n \] (28)
and, for \( \mu \neq 1 \) and \( \omega \neq 1 \),
\[ \text{Var}L = iz\mu^n \frac{1 - \omega - 2s + z\mu^n(1 + \omega)}{1 - \omega}. \] (29)

The values of \( \text{Var}M \) and \( \text{Var}L \) in the critical cases \( \mu = 1 \) or/and \( \omega = 1 \) can be easily computed by passage to appropriate limits in (26) and (29).

3. Distribution of the final state of the iterated birth and death process

In this section, we are going to compute the distribution \( p_m, m \geq 0 \), of any non-negative integer valued r.v. \( V \) with a p.g.f. of form (23). In particular, our argument applies to r.v.s \( M \) and \( L \).

We write the fractional linear function involved in (23) as follows:
\[ \frac{a - bz}{c - dz} = \frac{b}{d} \left( 1 - \frac{A}{bd} \cdot \frac{1}{z - c/d} \right), \] (30)
where \( A = ad - bc \). Then
\[ \varphi_V(z) = \left( \frac{b}{d} \right)^i \sum_{k=0}^{i} (-1)^k \binom{i}{k} \left( \frac{A}{bd} \right)^k (z - c/d)^{-k}. \]

Differentiating this equality \( m \) times and setting \( z = 0 \) we obtain on the basis of (1) that
\[ p_m = \left( \frac{b}{d} \right)^i \left( \frac{d}{c} \right)^m \sum_{k=1}^{m} \binom{i}{k} \left( \frac{k + m - 1}{m} \right) \left( \frac{A}{bd} \right)^k, \quad m \geq 0. \] (31)

Since the number \( i \) is very large, this formula can barely be used for computing the distribution of r.v. \( V \). Fortunately, the probabilities \( p_m \) can be represented in a much more efficient way (see
Proposition 4) that will allow us to find in Section 4 limiting distributions of r.v.s $M$ and $L$ when $i \to \infty$ and $s \to 0$.

Introduce the polynomials

$$P_m(x) := \sum_{k=1}^{i} \binom{i}{k} \binom{k+m-1}{m} x^k, \quad m \geq 0.$$  \hspace{1cm} (32)

Then it follows from (31) that

$$p_m = \left( \frac{b}{d} \right)^i \left( \frac{d}{c} \right)^m P_m \left( \frac{A}{bc} \right), \quad m \geq 0.$$  \hspace{1cm} (33)

From (32) we see readily that

$$P_0(x) = (1 + x)^i.$$  \hspace{1cm} (34)

Also,

$$P_1(x) = \sum_{k=1}^{i} k \binom{i}{k} x^k = x[(1 + x)^i]' = ix(1 + x)^{i-1}.$$  \hspace{1cm} (35)

Eqs. (34) and (35) invite us to define functions $Q_m$, $m \geq 0$, by

$$P_m(x) = (1 + x)^{i-m} Q_m(x), \quad m \geq 0.$$  \hspace{1cm} (36)

Then

$$Q_0(x) = 1 \quad \text{and} \quad Q_1(x) = ix.$$  \hspace{1cm} (37)

Indeed, functions $P_m$ and $Q_m$ depend on $i$. However, since in this section $i$ is assumed to be fixed, this dependence will not be shown notationally.

In the next statement we find a simple recurrence relation for polynomials $P_m$.

**Proposition 2.**

$$P_{m+1}(x) = \frac{1}{m+1} \left[ mP_m(x) + xP'_m(x) \right], \quad m \geq 0.$$  \hspace{1cm} (38)

**Proof.** According to (34) and (35), relation (38) holds for $m = 0$. In view of (32)

$$P_{m+1}(x) = \sum_{k=1}^{i} \binom{i}{k} \binom{k+m}{m+1} x^k = \sum_{k=1}^{i} \binom{i}{k} \frac{k(k+1) \cdots (k+m)}{(m+1)!} x^k, \quad m \geq 0.$$  

Hence for $m \geq 1$

$$\int x^{m-1} P_{m+1}(x) \, dx = \frac{x^m}{m+1} \sum_{k=1}^{i} \binom{i}{k} \binom{k+m-1}{m} x^k + C = \frac{x^m}{m+1} P_m(x) + C.$$  

Differentiating this equality we obtain

$$x^{m-1} P_{m+1}(x) = \frac{1}{m+1} \left[ m x^{m-1} P_m(x) + x^m P'_m(x) \right],$$  

which implies (38). Proposition 2 is proved.
From Proposition 2 we derive the following result about the functions $Q_m$, $m \geq 0$.

**Proposition 3.** \(\{Q_m\}_{m=0}^{\infty}\) is a sequence of polynomials satisfying the following recurrence relation:

\[
Q_{m+1}(x) = \frac{1}{m+1} [(m + ix)Q_m(x) + x(1 + x)Q'_m(x)], \quad m \geq 0. \quad (39)
\]

**Proof.** Using (36) we express the recurrence relation (38) in terms of the functions $Q_m$ as follows:

\[
(1 + x)^{i-m-1}Q_{m+1}(x) = \frac{1}{m+1} \left[ m(1 + x)^{i-m}Q_m(x) + (i - m)x(1 + x)^{i-m-1}Q_m(x) + x(1 + x)^{i-m}Q'_m(x) \right],
\]

which implies (39) for $m \geq 1$. In view of (37) relation (39) also holds for $m = 0$. Together with (37) this implies that every function $Q_m$, $m \geq 0$, is a polynomial of degree $m$. Proposition 3 is proved.

Our next statement provides the required formula for the polynomials $Q_m$. For $i > m$, it offers a significant computational advantage over formula (32) for the polynomials $P_m$.

**Proposition 4.**

\[
Q_m(x) = \sum_{k=1}^{m} \binom{m-1}{m-k} \binom{i+k-1}{k} x^k, \quad m \geq 1. \quad (40)
\]

**Proof.** Denote by $R_m$, $m \geq 1$, the polynomial in the right-hand side of (40). For $m = 1$, using (37) we have $R_1(x) = ix = Q_1(x)$. Therefore, it suffices to show that polynomials $R_m$, $m \geq 1$, satisfy the recurrence relation (39).

For a fixed $m \geq 1$, denote

\[
U(x) := \frac{1}{m+1} [(m + ix)R_m(x) + x(1 + x)R'_m(x)]
= \frac{1}{m+1} \left[ (m + ix) \sum_{k=1}^{m} \binom{m-1}{m-k} \binom{i+k-1}{k} x^k + x(1 + x) \sum_{k=1}^{m} \binom{m-1}{m-k} \binom{i+k-1}{k} k x^{k-1} \right].
\]

We have to check that the polynomial $U(x) = \sum_{k=1}^{m+1} u_k x^k$ coincides with the polynomial $V(x) := R_{m+1}(x) = \sum_{k=1}^{m+1} v_k x^k$, where

\[
R_{m+1}(x) = \sum_{k=1}^{m+1} \binom{m}{m-k+1} \binom{i+k-1}{k} x^k. \quad (42)
\]

From (41) and (42) we find that $u_1 = (mi + i)/(m + 1) = i = v_1$. Also,

\[
u_{m+1} = \frac{i + m}{m+1} \binom{i+m-1}{m} = \binom{i+m}{m+1} = v_{m+1}.
\]

Next, for $2 \leq k \leq m$, we have by (41)
\[ u_k = \frac{m+k}{m+1} \binom{m-1}{m-k} \binom{i+k-1}{k} + \frac{i+k-1}{m+1} \binom{m-1}{m-k+1} \binom{i+k-2}{k-1}. \]  

(43)

Observe that

\[ \binom{m-1}{m-k} = \frac{m-k+1}{m} \binom{m}{m-k+1}. \]

Similarly,

\[ \binom{m-1}{m-k+1} = \frac{k-1}{m} \binom{m}{m-k+1} \quad \text{and} \quad \binom{i+k-2}{k-1} = \frac{k}{i+k-1} \binom{i+k-1}{k}. \]

Therefore, we continue (43) to find through a simple calculation that

\[ v_k = \left( \frac{m}{m-k+1} \right) \binom{i+k-1}{k} = v_k, \quad 2 \leq k \leq m. \]

This completes the proof of Proposition 4.

The following result solves Problem 1 formulated in Section 1.

**Theorem 1.** Let \( V \) be a non-negative integer valued r.v. the p.g.f. of which has form (23) with some natural number \( i \) (in particular, this is the case for \( V = M \) and \( V = L \)). Then for the distribution of \( V \) we have

\[ p_m = \left( \frac{a}{c} \right)^i \left( \frac{b}{a} \right)^m Q_m \left( \frac{\Delta}{bc} \right), \quad m \geq 0, \]  

(44)

where \( \Delta = ad - bc \), \( Q_0(x) = 1 \), and polynomials \( Q_m, m \geq 1 \), are given in (40).

**Proof.** Since \( \varphi_V(1) = 1 \), we set \( z = 1 \) in (23) to find that \( a-b = c-d \), hence \( a = b+c-d \). Also, setting \( z = 1 \) in (30) we obtain that \( \Delta = (b-d)(d-c) \), then

\[ bc + \Delta = d(b+c-d) = ad. \]  

(45)

Now invoking formulas (33), (36) and (45) we find that

\[ p_m = \left( \frac{b}{d} \right)^i \left( \frac{d}{c} \right)^m \left( 1 + \frac{\Delta}{bc} \right)^{i-m} Q_m \left( \frac{\Delta}{bc} \right) = \left( \frac{a}{c} \right)^i \left( \frac{b}{a} \right)^m Q_m \left( \frac{\Delta}{bc} \right), \quad m \geq 0. \]

Theorem 1 is proved.

**Remark 2.** Every r.v. \( V \) with p.g.f. (23), where \( c, d \neq 0 \) and \( c \neq d \), can be represented as the sum of \( i \) independent copies of a r.v. having generalized geometric distribution. In the particular case of geometric distribution \( (a = 0) \), the distribution of r.v. \( V \) is negative binomial. Therefore, distribution (44) can (and will) be called generalized negative binomial.
4. Limit theorem for the iterated birth and death process

The following theorem establishes the form of the limiting distribution of r.v. \( M \) as \( i \to \infty \) and \( s \to 0 \). Parameters \( n \geq 1, \tau > 0, \lambda > 0 \) and \( \nu \geq 0 \) are assumed to be fixed. For \( \nu = 0, \lambda \to 0 \), this theorem gives the classical Poisson limit of a sequence of binomial distributions.

**Theorem 2.** Suppose that \( i \to \infty \) and \( s \to 0 \) so that there exists a limit
\[
\theta := \lim is^n, \quad 0 < \theta < \infty.
\] (46)

Then the distribution of r.v. \( M \) converges to the probability distribution \( \pi = \{\pi_m\}_{m=0}^{\infty} \) given by
\[
\pi_m = e^{-A} \rho^{-m} \sigma_m, \quad m \geq 0,
\] (47)

where
\[
\rho = \frac{\lambda - \chi \nu}{\lambda(1 - \chi)},
\] (48)

\[
A = \frac{\theta(\rho - 1)}{\chi^n \rho} = \frac{\theta(\lambda - \nu)}{\chi^{n-1}(\lambda - \chi \nu)},
\] (49)

\[
\sigma_0 = 1,
\]

\[
\sigma_m = \sum_{k=1}^{m} \binom{m-1}{m-k} \frac{\delta^k}{k!}, \quad m \geq 1,
\] (50)

and
\[
\delta = \frac{\theta(\rho - 1)^2}{\chi^n \rho} = \frac{\theta(\lambda - \nu)^2}{\lambda \chi^{n-2}(1 - \chi)(\lambda - \chi \nu)}.
\] (51)

**Proof.** It follows from (12) and (48) that under conditions of the theorem \( \omega \to \rho \). Note that
\[
\rho - 1 = \frac{\chi(\lambda - \nu)}{\lambda(1 - \chi)} > 0,
\]

whence \( \rho > 1 \). Recall formulas (10) and (18) to find that
\[
a \to -\rho, \quad b \to -1, \quad c \to -\rho.
\] (52)

Also, by (24), (46), (52) and (51)
\[
\frac{iA_M}{bc} \to \frac{\theta(\rho - 1)^2}{\chi^n \rho} = \delta.
\] (53)

Observe that according to (44)
\[
p_m = p_0 \left( \frac{b}{a} \right)^m Q_m \left( \frac{A_M}{bc} \right), \quad m \geq 0.
\] (54)
First, we compute the limit for \( p_0 = (a/c)^t \). Note that by (18)

\[
a \overset{c}{=} 1 + \mu^n \frac{\omega}{\mu^n} - 1.
\]

Therefore,

\[
p_0 = (a/c)^t \rightarrow e^{-A}, \quad \text{where } A = \lim_{\mu \to 1} \mu^n \frac{\omega}{\mu^n} = \frac{\theta(\rho - 1)}{\varepsilon^\rho},
\]

compare with (49). Next, invoking Proposition 4, we write

\[
Q_m \left( \frac{A_m}{bc} \right) = \sum_{k=1}^{m} \binom{m-1}{m-k} \frac{1}{k!} \prod_{j=0}^{k-1} \left( 1 + \frac{j}{i} \right) \left( \frac{iA_m}{bc} \right)^k, \quad m \geq 1.
\]

Passage to limit in this equation with (53) taken into account yields

\[
Q_m \left( \frac{A_m}{bc} \right) \rightarrow \sum_{k=1}^{m} \binom{m-1}{m-k} \frac{\delta^k}{k!} = \sigma_m, \quad m \geq 1.
\]

Finally, in view of (52), \( b/a \rightarrow 1/\rho \). Combining this with (55) and (56) we obtain from (54) the required form (47) of \( \pi_m \) for \( m \geq 1 \).

It remains to show that \( \pi \) is a proper probability distribution, that is,

\[
\sum_{m=0}^{\infty} \pi_m = 1.
\]

To this end, we will compute p.g.f. \( \varphi_\pi \) for the sequence \( \pi = \{\pi_m\}_{m=0}^{\infty} \).

By (47) and (50) we have for \(|z| < \rho\)

\[
\varphi_\pi(z) = \sum_{m=0}^{\infty} \pi_m z^m = \sum_{m=0}^{\infty} e^{-A} \left( \frac{z}{\rho} \right)^m \sigma_m = e^{-A} \left[ 1 + \sum_{m=1}^{\infty} \left( \frac{z}{\rho} \right)^m \sum_{k=1}^{m} \binom{m-1}{m-k} \frac{\delta^k}{k!} \right]
\]

\[
= e^{-A} \left[ 1 + \sum_{k=1}^{\infty} \frac{1}{k!} \sum_{m=k}^{\infty} \binom{m-1}{m-k} \left( \frac{z}{\rho} \right)^m \right]
\]

\[
= e^{-A} \left[ 1 + \sum_{k=1}^{\infty} \frac{1}{k!} \left( \frac{\delta z}{\rho} \right)^k \sum_{j=0}^{\infty} \binom{k+j-1}{j} \left( \frac{z}{\rho} \right)^j \right],
\]

where \( j := m - k \). Observe that the last sum represents the binomial series

\[
\sum_{j=0}^{\infty} \binom{k+j-1}{j} \left( \frac{z}{\rho} \right)^j \left( 1 - \frac{z}{\rho} \right)^{-k}, \quad |z| < \rho, \ k \geq 1.
\]

Therefore, using (51) we continue (58):

\[
\varphi_\pi(z) = e^{-A} \sum_{k=0}^{\infty} \frac{1}{k!} \left( \frac{\delta z}{\rho - z} \right)^k = \exp \left[ \frac{\theta(\rho - 1)}{\varepsilon^\rho} \right] \exp \left( \frac{\delta z}{\rho - z} \right)
\]

\[
= \exp \left[ - \frac{\theta(\rho - 1)}{\varepsilon^\rho} \left( 1 - \frac{(\rho - 1)z}{\rho - z} \right) \right] = \exp \left[ - \frac{\theta(\rho - 1)}{\varepsilon^\rho} \frac{1 - z}{\rho - z} \right].
\]

Setting here \( z = 1 \) we establish (57). This completes the proof of Theorem 2.
Remark 3. For the iterated pure birth process \((v = 0)\), the limiting distribution of r.v. \(M\) under conditions of Theorem 2 is given by (56) with
\[
\rho = \frac{1}{1 - \alpha}, \quad A = \frac{\theta}{\alpha^{n-1}}, \quad \delta = \frac{\theta}{\alpha^{n-2}(1 - \alpha)},
\]
where \(\alpha = e^{-\lambda t}\).

In the critical case \(\lambda = \nu > 0\) we have
\[
\rho = 1 + \frac{1}{\lambda t}, \quad A = \frac{\theta}{1 + \lambda t} \quad \text{and} \quad \delta = \frac{\theta}{\lambda t(1 + \lambda t)}.
\]

Remark 4. In view of formulas (4) Eq. (59) leads to the following expressions for the expectation and variance of the limiting distribution \(p\) of r.v. \(M\):
\[
E\pi = \frac{\theta}{\alpha^n} \quad \text{and} \quad \text{Var}\pi = \frac{\theta(\rho + 1)}{\alpha^n(\rho - 1)} = \frac{\theta[\lambda(2 - \alpha) - \nu]}{\alpha^{n+1}(\lambda - \nu)}.
\]

The same results arise when we pass to limit in formulas (25) and (26) for the expectation and variance of r.v. \(M\) when \(i \to \infty\) and \(s \to 0\) under condition (46).

By contrast to r.v. \(M\), the limiting distribution of r.v. \(L\) under the same conditions is a Poisson distribution.

Theorem 3. Let \(\tilde{p}_m, m \geq 0\), be the distribution of r.v. \(L\). Then under the conditions of Theorem 2,
\[
\tilde{p}_m \to e^{-\lambda}A^m/m!, \quad m \geq 0, \quad \text{where} \quad A = \frac{\theta}{\alpha^{n-1}}.
\]

Proof. Proceeding from (21) we easily find that
\[
\tilde{p}_0 = \left[1 + \frac{\alpha\mu(\omega - 1)}{1 - \omega - s + \alpha\mu}\right]^{-1} \to e^{-\lambda/n-1}.
\]

Next, it follows from (20), (27) and (46) that
\[
s^{-1}\tilde{b}/\tilde{a} \to \frac{1}{\rho - 1} \quad \text{and} \quad s\frac{i\lambda L}{b\tilde{c}} \to \frac{\theta(\rho - 1)}{\alpha^{n-1}}.
\]

Passage to limit as \(s \to 0\) and \(i \to \infty\) in the equality
\[
\left(\frac{\tilde{b}}{\tilde{a}}\right)^m Q_m\left(\frac{\lambda L}{b\tilde{c}}\right) = \left(s^{-1}\tilde{b}/\tilde{a}\right)^m \sum_{k=1}^{m} \binom{m-1}{m-k} s^{m-k} \prod_{j=0}^{k-1} \left(1 + \frac{j}{i}\right) \left(s\frac{i\lambda L}{b\tilde{c}}\right)^k, \quad m \geq 1,
\]
with (62) taken into account leads together with (61) to the desired conclusion (60).

Remark 5. It follows from (28) and (29) that under conditions of Theorem 2, \(EL\) and \(\text{Var}L\) converge to \(\tilde{A}\), that is, to the mean and variance of the Poisson distribution \(P(\tilde{A})\).
5. Numerical example

Theorems 2 and 3 lead to the following natural question: What are the rates of convergence of the distributions of r.v.s $M$ and $L$ to the limiting distributions (47) and (60), respectively? Sample calculations described below were designed to shed some light on this problem for r.v. $L$. A more thorough theoretical and numerical investigation will be a matter of another publication.

It follows from Theorem 3 that the distribution $P_L$ of r.v. $L$ can be approximated by the Poisson distribution $P(\tilde{\theta})$ with

$$
\tilde{\theta} := \frac{is^n}{2^n-1}.
$$

These two distributions were compared graphically and by means of computing the probability metric

$$
d(P_L, P(\tilde{\theta})) := \sup_{m \geq 0} \left| \Pr(L = m) - e^{-\tilde{\theta}m} \frac{\tilde{\theta}^m}{m!} \right|
$$

in the case when no cell death occurs between exposures ($v = 0$) and for the number of fractions $n = 30$. The common expected value $\tilde{\theta}$ of the two distributions was taken to be equal to 2; in other words, it was assumed that on the average two clonogens are alive after delivery of the last fraction of radiation.

The distributions $P_L$ and $P(\tilde{\theta})$ were graphed for $\alpha = 0.9$ and $i = 10^5, 10^7$. The corresponding value $s$ of the survival probability per fraction was computed from (63). The exact distributions of r.v. $L$ for $i = 10^5, 10^7$ and the Poisson approximation $P(\tilde{\theta})$ are represented on Fig. 1 by lines 1 (solid), 2 (dotted) and 3 (dashed), respectively. For easier visualization, all three discrete distributions were smoothed. Fig. 1 shows that, for large $i$, the Poisson distribution $P(\tilde{\theta})$ provides a good fit to the distribution $P_L$.

The distance (64) was computed for $\alpha = 0.7, 0.8, 0.9, 0.95$ and $i = 10^N$ with $N = 5, 6, 7, 8$. Results of this calculation given in Table 1 confirm that, for large $i$, the Poisson distribution $P(\tilde{\theta})$ is close to $P_L$. Furthermore, we conclude that the distance (64) monotonically tends to 0 when $i \to \infty$ for fixed $\alpha$ and monotonically decreases as $\alpha \to 1$ for fixed $i$. Observe that in the limiting case $\alpha = 1$ ($\lambda = 0$), that is, in the absence of cell proliferation and spontaneous cell death, (64) represents the distance between the binomial distributions $B(i, s^n)$ and its Poisson approximation $P(\tilde{\theta})$, $\theta = is^n$. According to the Law of Rare Events (see e.g. [14, pp. 279–281]), in this case $d(P_L, P(\tilde{\theta})) \leq is^{2n} = \tilde{\theta}^2/i$. Therefore, the distance (64) between the generalized negative binomial distribution $P_L$ and the Poisson distribution $P(\tilde{\theta})$ for $\alpha < 1$ is larger than between the corresponding binomial distribution $B(i, s^n)$ and $P(\tilde{\theta})$ in the limiting case $\alpha = 1$.

<table>
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<th>$i$</th>
<th>$\alpha = 0.7$</th>
<th>$\alpha = 0.8$</th>
<th>$\alpha = 0.9$</th>
<th>$\alpha = 0.95$</th>
</tr>
</thead>
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<td>0.122</td>
<td>0.062</td>
<td>0.031</td>
</tr>
<tr>
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<td>0.098</td>
<td>0.049</td>
<td>0.025</td>
</tr>
<tr>
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<td>0.080</td>
<td>0.040</td>
<td>0.020</td>
</tr>
<tr>
<td>$10^8$</td>
<td>0.097</td>
<td>0.067</td>
<td>0.033</td>
<td>0.019</td>
</tr>
</tbody>
</table>
6. Discussion

Our results solve the main problem raised in [1] and followed up in [6,11]. According to Theorem 1, the exact distribution of the number \( L \) of surviving clonogens belongs to the family (44) of generalized negative binomial distributions. This family does not contain binomial distributions. However, as discovered in Theorem 3, the distribution of r.v. \( L \) still converges under the natural condition (46) to the Poisson distribution (60). Therefore, the distribution of r.v. \( L \) can be approximated by the Poisson distribution \( P(\hat{\theta}) \) with \( \hat{\theta} = i s^a / x^{a-1} \). Note that \( \hat{\theta} \) is not equal to \( \hat{\lambda} = v = 0 \). This explains why the Poisson distribution \( P(\hat{\theta}) \) was rejected in [1,6,11] on the basis of numerical computations which made the authors think that any Poisson approximation is impossible. We observe also that the Poisson approximation \( P(\hat{\theta}) \) is valid not only in the absence of cell proliferation and death (\( \hat{\lambda} = v = 0 \)) but also in the more general case when their rates are equal (\( \hat{\lambda} = v \)).

It is interesting to mention that, although the distributions of r.v.s \( M \) and \( L \) are quite close when the interdose interval \( \tau \) is small, the limiting distribution (47) of r.v. \( M \) under the condition (46) is not Poisson and never reduces to it.

The model of fractionated radiation cell survival discussed in this work depends on six parameters \( n, \tau, i, s, \lambda, v \), the last four of which are unobservable. More importantly, the number of surviving clonogens is unobservable as well. To make use of the computed distribution of the size of the surviving fraction of clonogens, one has to relate it to an observable endpoint, like the time to tumor recurrence or death caused by a specific recurrent cancer. In what follows, we will

![Fig. 1. Exact distribution \( P_L \) for \( i = 10^5 \) (solid line 1), \( i = 10^7 \) (dotted line 2), and the approximating Poisson distribution \( P(\hat{\theta}) \) (dashed line 3) \( (n = 30, v = 0, x = 0.9, \hat{\theta} = 2) \)](image-url)
focus on the first possibility. Specifically, let $T$ be the time to tumor recurrence counted from the moment of delivery of the last fraction. It is assumed that r.v. $T$ is absolutely continuous.

There are two competing models of post-treatment tumor development. According to the clonogenic model introduced in [21], a recurrent tumor arises from a single clonogenic cell. Every surviving clonogen can be characterized by a latent time (called the progression time) during which it could potentially propagate into a detectable tumor. It is assumed additionally that progression times of surviving clonogens are i.i.d. r.v.s. Suppose that the number $L$ of surviving clonogens is equal to $m$. Then for the observed time $T$ to tumor recurrence we have $T = \min_{1 \leq j \leq m} T_j$, where $T_j$ is the progression time of the $j$th clonogen. Let $\varphi_L(z) = \sum_{m=0}^{\infty} \hat{p}_m z^m$ be the p.g.f. of r.v. $L$. It follows from the assumptions of the clonogenic model that the conditional survival function $F^*_L|L=m(t) := \Pr(T > t | L = m)$, $t \geq 0$, of r.v. $T$ is given by $\hat{F}^*_L|L=m = \hat{F}_1^m$, where $\hat{F}_1$ is the common survival function of the progression times of surviving clonogens. Then

$$F_T(t) = \sum_{m=0}^{\infty} \hat{F}_{T|L=m}(t) \Pr(L = m) = \sum_{m=0}^{\infty} \hat{p}_m \hat{F}_1^m(t) = \varphi_L(\hat{F}_1(t)), \quad t \geq 0. \quad (65)$$

Alternatively, the cumulative model proceeds from the assumption that all surviving clonogenic cells contribute to the resulting recurrent tumor, see for example [5]. Assume additionally that their contributions are identically distributed (but not necessarily independent). For $m \geq 0$, denote by $r_m$ the conditional hazard function of r.v. $T$ given that $L = m$. Then

$$\hat{F}_{T|L=m}(t) = \exp \left[ - \int_0^t r_m(u) \, du \right], \quad t \geq 0.$$

By our assumptions, $r_m = mr$, where $r$ is the common hazard function associated with the contributions of the surviving clonogens to the resulting detectable tumor. Then $\hat{F}_{T|L=m} = \hat{F}_2^m, m \geq 0$, where $\hat{F}_2$ is the survival function corresponding to the hazard rate $r$, and hence

$$F_T(t) = \sum_{m=0}^{\infty} \hat{p}_m \hat{F}_2^m(t) = \varphi_L(\hat{F}_2(t)), \quad t \geq 0. \quad (66)$$

Comparing (65) and (66) we conclude that, surprisingly, the distribution of the time $T$ to tumor recurrence within both models of post-treatment tumor development has the same form

$$\hat{F}_T(t) = \varphi_L(\hat{F}(t)), \quad t \geq 0, \quad (67)$$

where $\hat{F}$ is the survival function of an absolutely continuous non-negative r.v. Suppose, in particular, that r.v. $L$ follows the Poisson distribution $P(A)$. Then we derive easily from (67) that

$$\hat{F}_T(t) = e^{-AF(t)}, \quad t \geq 0, \quad (68)$$

where $F := 1 - \hat{F}$ is the corresponding cumulative distribution function. Although this form of the recurrence time distribution was originally suggested in [21] in conjunction with the clonogenic model of post-treatment tumor development, it proved to be instrumental for statistical estimation of the probability $p$ of tumor cure (also termed the cure rate) in many other settings [7,22–26]. Observe that according to (68), $p = e^{-A}$, and the positivity of $p$ is due to the fact that $\hat{p}_0 = \Pr(L = 0) > 0$. 

---

Significance of formula (67) is two-fold. First, it suggests that knowledge of the entire distribution of the number of surviving clonogens (not only of the tumor control probability $\bar{p}_0$) is critical for developing biologically motivated post-treatment survival models. Second, assuming some parametric form for the function $F$ and using for the distribution of r.v. $L$ either its exact form (44) or the Poisson approximation (60) one can in principle estimate unknown quantities $i, s$ and especially the all-important kinetic parameters $\lambda$ and $v$ from the observed times to tumor recurrence. Making use of the exact distribution of r.v. $L$ seems to be especially promising because it incorporates the known dose $D$ per fraction through survival probability $s$, and this allows to develop a regression model accounting for the variation of the dose $D$ and other clinically important covariates. Pursuing this line of reasoning presupposes, indeed, investigation into identifiability properties of the resulting survival model.

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