

Lawrence Berkeley National Laboratory

Recent Work

Title

AGE DISTRIBUTIONS IN STOCHASTICALLY DIVIDING POPULATIONS

Permalink

<https://escholarship.org/uc/item/49n6p5k1>

Author

Nooney, Grove C.

Publication Date

1967-11-03

C. Z

University of California

Ernest O. Lawrence Radiation Laboratory

AGE DISTRIBUTIONS IN STOCHASTICALLY
DIVIDING POPULATIONS

Grove C. Nooney

November 3, 1967

TWO-WEEK LOAN COPY

*This is a Library Circulating Copy
which may be borrowed for two weeks.
For a personal retention copy, call
Tech. Info. Division, Ext. 5545*

RECEIVED
LAWRENCE
RADIATION
LIBRARY
DOCUMENTS

UCRL-17356 Rev.
C. Z

DISCLAIMER

This document was prepared as an account of work sponsored by the United States Government. While this document is believed to contain correct information, neither the United States Government nor any agency thereof, nor the Regents of the University of California, nor any of their employees, makes any warranty, express or implied, or assumes any legal responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by its trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof, or the Regents of the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof or the Regents of the University of California.

Submitted to
Journal of Theoretical Biology

UCRL-17356 Rev.
Preprint

UNIVERSITY OF CALIFORNIA

Lawrence Radiation Laboratory
Berkeley, California

AEC Contract No. W-7405-eng-48

AGE DISTRIBUTIONS IN STOCHASTICALLY
DIVIDING POPULATIONS

Grove C. Nooney

November 3, 1967

AGE DISTRIBUTIONS IN STOCHASTICALLY
DIVIDING POPULATIONS*

Grove C. Nooney

Lawrence Radiation Laboratory
University of California
Berkeley, California

November 3, 1967

ABSTRACT

Let $N(a, t)$ be the number of cells of age less than a in a population of mortal, dividing cells at time t . If probabilities of death and division are given as functions of cell age, then $N(a, t)$ is a random variable. The mean and variance of this random variable have the following asymptotic behavior as functions of time: If the population tends to decrease, the mean and variance tend to zero; if the population tends to increase, the mean and standard deviation tend to increase exponentially, both with the same exponent; otherwise the mean tends to a constant and the variance tends to increase in proportion to time. Similar conclusions apply when the probabilities of death and division depend on cell age and time.

INTRODUCTION

In an earlier paper (Nooney, 1967), I discussed the age distributions of continuous populations of cells from a deterministic viewpoint. The present note treats the stochastic case, in which the death and division schedules are random functions of cell age. In this case, the number of cells of age less than a in a population at time t is a random variable called the age distribution. The mean and variance of that random variable are discussed here. The method of the generating function used by Harris (1963) allows the extension of my previous results on the mean age distribution to certain discontinuous probability distributions for death or division as well as to discrete populations. In addition, I obtain the asymptotic form of the variance.

As we shall see, the gross asymptotic behavior of the mean and variance of the age distribution depends on the gross survival character of the population: If the population tends to decrease, then the mean and variance tend to zero in time; if the population tends to increase, then the mean and standard deviation tend to increase exponentially in time, both with the same exponent; otherwise the mean tends to a constant with respect to time, and the variance tends to increase in proportion to time.

It is true also that only for an asymptotically exponentially growing population can the normalized standard deviation (standard deviation divided by mean) remain bounded in time. For other populations the actual age distribution is likely to be very different from the mean, and the mean age distribution becomes a progressively worse basis for

analysis of the population as time increases. Unfortunately the latter cases include populations of bounded size, which are of major biological interest.

The derivation of the foregoing results is based on an examination of the age distributions in populations each arising from a single cell. The assumed independence of cells permits the easy extension to arbitrary initial populations.

These methods lead to analogous conclusions when the death and division schedules are random functions of both cell age and time.

THE PROBABILITY-GENERATING FUNCTION

Let $P(a)$ be the probability that a cell would divide at an age not exceeding a if no cell death were to occur, and let $Q(a)$ be the probability that a cell would die at an age not exceeding a if no cell division were to occur. Division means replacement by two replicas of age zero; death means removal from the population. I assume that P is not a lattice distribution, that $P(0) = Q(0) = 0$ and that the behavior of each cell is described by P and Q and is independent of other cells.

Consider the living descendants of a cell aged y at time zero. Let $n(x, y, t)$ be the number of these descendants of age not exceeding x at time t . Following Harris (1963), set

$$F(s, x, y, t) = \sum_{h=0}^{\infty} s^h \Pr \{n(x, y, t) = h\}$$

and call F the probability-generating function. Note that $F(1, x, y, t) = 1$.

Defining $m(x, y, t)$ and $v(x, y, t)$ to be the mean and variance, respectively, of the random variable $n(x, y, t)$, we may write (Feller, 1950)

$$m(x, y, t) = F_s(1, x, y, t), \quad (1)$$

$$v(x, y, t) = -[m(x, y, t)]^2 + m(x, y, t) + F_{ss}(1, x, y, t). \quad (2)$$

Let us denote by $p(y, t)$ the probability that a cell of age y at time zero divides not later than time t . Then

$$p(y, t) = \frac{P(y+t) - P(y)}{1 - P(y)}.$$

Let us denote by $q(y, t)$ the probability that a cell of age y at time zero dies not later than time t . Then

$$q(y, t) = \frac{Q(y+t) - Q(y)}{1 - Q(y)}.$$

From $P(0) = Q(0) = 0$ follows that $p(0, t) = P(t)$ and $q(0, t) = Q(t)$.

The probability-generating function satisfies the functional equation,

$$\begin{aligned} F(s, x, y, t) &= q(y, t)[1 - p(y, t)] + \int_{u=0}^t q(y, u) dp(y, u) \\ &+ [1 - q(y, t)][1 - p(y, t)] J(y + t - x) \\ &+ s[1 - q(y, t)][1 - p(y, t)][1 - J(y + t - x)] \\ &+ \int_{u=0}^t [F(s, x, 0, t-u)]^2 [1 - q(y, u)] dp(y, u), \end{aligned} \quad (3)$$

where

$$J(t) = \begin{cases} 1, & t > 0 \\ 0, & t \leq 0 \end{cases}.$$

The sum of the first two terms on the right-hand side is the probability that the original cell (aged y at time zero) dies before time t . The third and fourth terms are the probabilities that the original cell survives without dividing until time t under the respective conditions $y + t \geq x$ and $y + t < x$. The last term accounts for the remaining possibility: The cell survives and divides not later than time t . In writing the last term we use the fact that $[F(s, x, 0, t-u)]^2$ is the probability-generating function for the process starting at time $t-u$ with two cells of age zero. Since it was convenient in defining P and Q to proceed as though dead cells could divide, the second term must be included on the right-hand side of Eq. (3). This term is the probability that the original cell "dies" (is removed), then divides before time t and can contribute only to $\text{Pr}\{n(x, y, t) = 0\}$. The corresponding probability of division and subsequent death is included in the last term of Eq. (3).

By differentiating Eq. (3) with respect to s and using Eq. (1), we find

$$m(x, y, t) = [1 - q(y, t)] [1 - p(y, t)] [1 - J(y + t - x)] + \int_{u=0}^t m(x, 0, t-u) [1 - q(y, u)] dp(y, u). \tag{4}$$

By differentiating Eq. (3) twice with respect to s and using Eq. (1), we obtain

$$F_{ss}(1, x, y, t) = 2 \int_{u=0}^t \{ [m(x, 0, t-u)]^2 + F_{ss}(1, x, 0, t-u) \} \times [1 - q(y, u)] dp(y, u). \tag{5}$$

Now set $w(x, y, t) = F_{ss}(1, x, y, t) + [m(x, y, t)]^2$. Then from Eq. (5)

$$w(x, y, t) = [m(x, y, t)]^2 + 2 \int_{u=0}^t w(x, 0, t-u)[1 - q(y, u)] dp(y, u) \quad (6)$$

and from Eq. (2),

$$v(x, y, t) = w(x, y, t) - 2[m(x, y, t)]^2 + m(x, y, t). \quad (7)$$

ASYMPTOTIC BEHAVIOR

In Eqs. (4) and (6), set $y=0$ and find the renewal equations

$$m(x, 0, t) = [1 - Q(t)][1 - P(t)][1 - J(t-x)] + 2 \int_{u=0}^t m(x, 0, t-u)[1 - Q(u)] dP(u) \quad (8)$$

and

$$w(x, 0, t) = [m(x, 0, t)]^2 + 2 \int_{u=0}^t w(x, 0, t-u)[1 - Q(u)] dP(u). \quad (9)$$

The asymptotic behaviors of m and w are influenced by the kernel of these renewal equations, and we shall distinguish three cases, according as $2 \int_{u=0}^t [1 - Q(u)] dP(u)$ is (i) less than, (ii) equal to, or (iii) greater than unity. For cases (ii) and (iii), we shall assume the existence of

$$c = 2 \int_{u=0}^{\infty} u[1 - Q(u)] dP(u).$$

In case (i), a result of Paley and Wiener (Bellman and Cooke, 1963) shows that both $m(x, 0, t)$ and $w(x, 0, t)$ tend to zero as t tends to infinity. Equations (4) and (6) then show that $m(x, y, t)$ and $w(x, y, t)$ tend to zero for each x and y . Finally, Eq. (7) shows that $v(x, y, t)$ also tends to zero for each x and y .

In case (ii), a theorem of Ikehara (Bellman and Cooke, 1963) applied to $m(x, 0, t) e^t$ permits the conclusion

$$\lim_{t \rightarrow \infty} m(x, 0, t) = \frac{1}{c} \int_{u=0}^x [1-Q(u)][1-P(u)] du. \quad (10)$$

We set $\mu_0(x) = \lim m(x, 0, t)$. The application of a Tauberian theorem of Hardy and Littlewood (Bellman and Cooke, 1963) to Eq. (9) permits the conclusion

$$\lim_{t \rightarrow \infty} w(x, 0, t) t^{-1} = \frac{1}{c} [\mu_0(x)]^2.$$

Now let $I(a, y) = 2 \int_{u=0}^{\infty} e^{-\alpha u} [1-q(y, u)] dp(y, u)$.

We then find, from Eq. (4),

$$\lim_{t \rightarrow \infty} m(x, y, t) = \mu_0(x) I(0, y),$$

and from Eqs. (6) and (7),

$$\lim_{t \rightarrow \infty} v(x, y, t) t^{-1} = \lim_{t \rightarrow \infty} w(x, y, t) t^{-1} = \frac{1}{c} [\mu_0(x)]^2 I(0, y).$$

In case (iii) we again call on the theorem of Ikehara to find

$$\lim_{t \rightarrow \infty} m(x, 0, t) e^{-\alpha t} = \frac{\int_0^x e^{-\alpha u} [1-Q(u)][1-P(u)] du}{2 \int_{u=0}^{\infty} u e^{-\alpha u} [1-Q(u)] dP(u)},$$

where $\alpha > 0$ is uniquely determined by the requirement, $I(\alpha, 0) = 1$.

Now let $\mu_\alpha(x) = \lim_{t \rightarrow \infty} m(x, 0, t) e^{-\alpha t}$. The result of Paley and Wiener then shows

$$\lim_{t \rightarrow \infty} w(x, 0, t) e^{-2\alpha t} = \frac{[\mu_\alpha(x)]^2}{1 - I(2\alpha, 0)}$$

Turning again to Eqs. (4) and (6), we see that

$$\lim_{t \rightarrow \infty} m(x, y, t) e^{-\alpha t} = \mu_\alpha(x) I(\alpha, y),$$

and

$$\lim_{t \rightarrow \infty} w(x, y, t) e^{-2\alpha t} = [\mu_\alpha(x)]^2 \left\{ \frac{I(2\alpha, y)}{1 - I(2\alpha, 0)} + [I(\alpha, y)]^2 \right\}.$$

Equation (7) then yields

$$\lim_{t \rightarrow \infty} v(x, y, t) e^{-2\alpha t} = [\mu_\alpha(x)]^2 \left\{ \frac{I(2\alpha, y)}{1 - I(2\alpha, 0)} - [I(\alpha, y)]^2 \right\}.$$

ARBITRARY INITIAL POPULATION

Let $N(x, t)$ be the number of cells of age not exceeding x in a population at time t . Then $N(x, 0)$ describes the initial population. Since the cells are assumed to behave independently of one another, we may write the mean $M(x, t)$ and the variance $V(x, t)$ of the random variable $N(x, t)$ as

$$M(x, t) = \int_{y=0}^{\infty} m(x, y, t) dN(y, 0)$$

and

$$V(x, t) = \int_{y=0}^{\infty} v(x, y, t) dN(y, 0).$$

Insertion into these expressions of the derived asymptotic values for m and v yields the asymptotic values for M and V : In case (i), $M(x, t)$ and $V(x, t)$ tend to zero as t tends to infinity; in case (ii),

$\lim_{t \rightarrow \infty} M(x, t)$ and $\lim_{t \rightarrow \infty} V(x, t) t^{-1}$ exist and are different from zero; in case (iii), $\lim_{t \rightarrow \infty} M(x, t) e^{-\alpha t}$ and $\lim_{t \rightarrow \infty} V(x, t) e^{-2\alpha t}$ exist and are different from zero for the α determined by $I(\alpha, 0) = 1$.

THE TIME-DEPENDENT PROCESS

If the probability distributions P and Q depend on time and cell age, then results similar to the foregoing may be derived as follows. Let $P(y, a)$ and $Q(y, a)$ be the respective conditional probabilities that a cell born at time y divides or dies before achieving age a . Let $\tilde{n}(x, y, t)$ be the number at time t of living cells of age less than x that are descendants of a single cell born at time y . Define the probability-generating function for the process as

$$\tilde{F}(s, x, y, t) = \sum_{k=0}^{\infty} s^k \Pr \left\{ \tilde{n}(x, y, t) = k \right\}.$$

A functional equation for \tilde{F} is obtained as earlier for F :

$$\begin{aligned} \tilde{F}(s, x, y, y+t) &= Q(y, t)[1 - P(y, t)] + \int_{u=0}^t Q(y, u) dP(y, u) \\ &+ [1 - Q(y, t)][1 - P(y, t)] J(t-x) \\ &+ s[1 - Q(y, t)][1 - P(y, t)][1 - J(t-x)] \\ &+ \int_{u=0}^t [\tilde{F}(s, x, y+u, y+t)]^2 [1 - Q(y, u)] dP(y, u). \end{aligned} \tag{11}$$

Setting $y = -t$ yields a renewal equation for $F(s, x, -t, 0)$. That function describes the process at time zero that began at time $-t$ with a single cell of age zero. The asymptotic behavior of the process starting at

time zero with a cell of age zero is therefore described by $\tilde{F}(s, x, -t, 0)$ for large t .

Differentiating Eq. (11), we obtain renewal equations for the mean, $\tilde{m}(x, -t, 0)$, and variance, $\tilde{v}(x, -t, 0)$, of $\tilde{n}(x, -t, 0)$, and the asymptotic behavior of these statistics depends on the behavior of

$$K(t) = 2 \int_{u=0}^t [1 - Q(-t, u)] dP(-t, u).$$

Since $0 \leq K(t) \leq 2$, there exist both $\Lambda = \limsup_{t \rightarrow \infty} K(t)$ and $\lambda = \liminf_{t \rightarrow \infty} K(t)$. In analogy to the three cases for the time-independent process, these relations hold: if $\Lambda < 1$, then $\tilde{m}(x, -t, 0)$ and $\tilde{v}(x, -t, 0)$ both tend to zero; if $\Lambda = \lambda = 1$, then \tilde{m} tends to a constant, while \tilde{v} tends to become proportional to t ; if $\lambda > 1$, then \tilde{m} and \tilde{v} both increase without bound. Possible behavior of $K(t)$ not enumerated in the foregoing is described by $\lambda \leq 1 \leq \Lambda$, with $\lambda < \Lambda$. The asymptotic character of the process is here indeterminate in general, but particular behavior of \tilde{m} entails particular behavior of \tilde{v} . For instance, if \tilde{m} is bounded and bounded away from zero, then \tilde{v} increases without bound. (It can be shown that \tilde{v} is bounded from below by a monotonically increasing function that does not tend to a limit.)

As with the time-independent process, the asymptotic behavior of the time-dependent process starting with an arbitrary initial population may be obtained from these results.

FOOTNOTES AND REFERENCES

*This work was supported by the U. S. Atomic Energy Commission.

1. Bellman, Richard and Cooke, Kenneth L., Differential-Difference Equations, New York, Academic Press, Inc., 1963, Chapter 7.
 2. Feller, William, An Introduction to Probability Theory and Its Applications, New York, John Wiley and Sons, Inc., 1950, pp. 213-214.
 3. Harris, Theodore E., The Theory of Branching Processes, Berlin-Göttingen-Heidelberg, Springer Verlag, 1963.
 4. Nooney, Grove C., Age Distributions of Dividing Populations, Biophys. J. 7, 69 (1967).
-

This report was prepared as an account of Government sponsored work. Neither the United States, nor the Commission, nor any person acting on behalf of the Commission:

- A. Makes any warranty or representation, expressed or implied, with respect to the accuracy, completeness, or usefulness of the information contained in this report, or that the use of any information, apparatus, method, or process disclosed in this report may not infringe privately owned rights; or
- B. Assumes any liabilities with respect to the use of, or for damages resulting from the use of any information, apparatus, method, or process disclosed in this report.

As used in the above, "person acting on behalf of the Commission" includes any employee or contractor of the Commission, or employee of such contractor, to the extent that such employee or contractor of the Commission, or employee of such contractor prepares, disseminates, or provides access to, any information pursuant to his employment or contract with the Commission, or his employment with such contractor.

