Submitted to J. Theoret. Biol.

UCRL-17356 c.2 rep'l.
Preprint

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AEC Contract No. W-7405-eng-48

AGE DISTRIBUTIONS OF STOCHASTICALLY DIVIDING POPULATIONS

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January 27,

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ABSTRACT

Let N(a, t) be the number of cells of age less that 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.

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 tendto 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.

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 and that $P(o) = Q(o) = o$. The behavior of each cell is assumed to be described by P and Q and to be independent of other cells.

Consider the descendants of a cell aged y at time zero. Let $n(x, y, t)$ be the number of these cells 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)

$$m(x, y, t) = F_s(1, x, y, t), \tag{1}$$

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

The probability-generating function satisfies the function equation,

$$\begin{aligned} F(s, x, y, t) = {} & Q(y+t) - Q(y) \\ & + [1 - Q(y+t) + Q(y)][1 - P(y+t) + P(y)]\, J(y+t-x) \\ & + s[1 - Q(y+t) + Q(y)][1 - P(y+t) + P(y)][1 - J(y+t+x)] \\ & + \int_{u=0}^{t} [F(s, x, o, t-u)]^2 [1 - Q(y+u) + Q(y)]\, dP(y+u), \end{aligned} \tag{3}$$

where

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

The first two terms on the right-hand side represent the probability that the original cell (aged y at time zero) dies before time t. The third and fourth terms represent the probability 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 divides not later than time t. In writing the last term we use the fact that $[F(s,x,o,t-u)]^2$ is the probability-generating function for the process starting at time $t-u$ with two cells of age zero.

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

$$\begin{aligned} m(x, y, t) = {} & [1 - Q(y+t) + Q(y)][1 - P(y+t) + P(y)][1 - J(y+t-x)] \\ & + 2 \int_{u=0}^{t} m(x, o, t-u)[1 - Q(y+u) + Q(y)]\, dP(y+u). \end{aligned} \tag{4}$$

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

$$\begin{aligned} F_{ss}(1, x, y, t) = 2 \int_{u=o}^{t} & \{[m(x, o, t-u)]^2 + F_{ss}(1, x, o, t-u)\} \\ & \times [1 - Q(y+u) + Q(y)]\, dP(y+u). \end{aligned} \tag{5}$$

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

$$w(x, y, t) = [m(x, y, t)]^2 + 2 \int_{u=o}^{t} w(x, o, t-u)[1 - Q(y+u) + Q(y)]\, dP(y+u) \qquad (6)$$

and from Eq. (2),

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

ASYMPTOTIC BEHAVIOR

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

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

and

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

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

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

In case (i), a result of Paley and Wiener (Bellman and Cooke, 1963) shows that both $m(x, o, t)$ and $w(x, o, t)$ 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 $m(x, o, t)e^t$ permits the conclusion

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

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

$$\lim_{t \to \infty} w(x, o, t)t^{-1} = \frac{1}{c} [\mu_o(x)]^2.$$

Now let $I(\alpha, y) = 2 \int_{u=o}^{\infty} e^{-\alpha u}[1 - Q(y+u) + Q(y)]\, dP(y+u).$

We then find from Eq. (4)

$$\lim_{t \to \infty} m(x, y, t) = \mu_o(x)\, I(o, y),$$

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

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

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

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

where $\alpha > 0$ is uniquely determined by the requirement, $I(\alpha, o) = 1$. Now let $\mu_\alpha(x) = \lim_{t \to \infty} m(x, o, t)e^{-\alpha t}$. The result of Paley and Wiener then shows

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

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

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

and

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

Equation (7) then yields

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

ARBITRARY INITIAL POPULATION

Let $N(x,t)$ be the number of cells of age not exceeding x in a population at time t. Then $N(x,o)$ 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 $V(x,y,t)$ of the random variable $N(x,t)$ as

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

and

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

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), $\lim_{t\to\infty} M(x,t)$

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

Footnotes and References

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

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