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Some Remarks on Changing Populations*,**

Ernesto Trucco

Division of Biological and Medical Research, Argonne National
Laboratory, Argonne, Illinois

This paper represents a summary of my recent work on the dynamics of cellular populations. I have deliberately chosen the title to be the same as that of an article written in 1959 by H. Von Foerster(1) which contains the essential points of the theory in an intuitive (rather than strictly rigorous) manner. Actually, of course, there is a vast literature on these problems, going back to the work of A. J. Lotka, summarized in his book, reference(2).

By *deme* (see(3)) we mean the totality of cells in a cellular population answering a well-defined but necessarily incomplete *state description*, i. e., all the cells of a given *type* (cf.(4,5)). The equation derived by H. Von Foerster for the age density function, $n(t, a)$, of a deme is similar to the continuity equation in hydrodynamics. It has the form

$$\frac{\partial n}{\partial t}+\frac{\partial n}{\partial a}=-\lambda n, \quad \cdots\cdots (1)$$

where $n(t, a)da$ represents the number of cells with ages in the range $(a\cdots a+da)$ at time t (t and a denote time and cellular age, respectively). The quantity λ, called the *loss function*, measures the probability that a cell will leave the deme during the time interval dt for any cause whatever.

Later, and independently, P-E. E. Bergner(6)* as well as A. G. Fredrickson and H. M. Tsuchiya(7)† obtained and used essentially the same formulation. The latter authors also made specific assumptions about the various contributions to the loss function.

We assume quite generally that λ is the sum of three terms

$$\lambda=\mu+\rho+\tau . \quad \cdots\cdots (2)$$

These correspond to three mutually exclusive events: mitosis, permanent removal, and emigration (for details see(3)). μ is called the *generation coefficient*. The quantity $n(t, 0)\equiv\alpha(t)$ represents the *generalized birth rate* or *influx function*.

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* I am much obliged to Dr. Bergner for allowing me to read his manuscript before publication.

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† In my paper(3) Fredrickson and Tsubhiya's article(7) is referred to as an "unpublished manuscript." Professor Tsuchiya kindly informed me that this work had appeared in the A. I. Ch. E. Journal.

For a deme of cells dividing by binary fission without influx from a precursor population, it is postulated that

$$\alpha(t)=2\int_{a=0}^{\infty}\mu\cdot n\mathrm{d}a. \qquad (3)$$

We also put $n(0,a)\equiv\beta(a)$; this is the *initial age distribution*. The solution of equation (1) is completely determined if $\alpha(t)$, $\beta(a)$, and λ are known. The total number of cells in the deme, $N(t)$, is given by

$$N(t)=\int_{a=0}^{\infty}n(t,a)\mathrm{d}a, \qquad (4)$$

and we have

$$\frac{\mathrm{d}N}{\mathrm{d}t}=\alpha(t)-\int_{a=0}^{\infty}\lambda n\,\mathrm{d}a. \qquad (5)$$

The function

$$f\equiv\frac{\lambda n}{\int_{a=0}^{\infty}\lambda n\,\mathrm{d}a} \qquad (6)$$

which depends on time, age, and possibly other parameters specifying the system, is called the *Uhlhorn probability density*. Its first moment with respect to the variable a,

$$\bar{l}=\int_{a=0}^{\infty}af\,\mathrm{d}a, \qquad (7)$$

gives the average age of the cells disappearing from the deme during the time interval dt. It is shown in[8] that equation (7) is equivalent to a relation derived by U. Uhlhorn (unpublished) and quoted without proof by P-E. E. Bergner (reference[9], page 976).

The general solution of equation (1) can be found very easily if the loss function, λ, depends only on t and a, but not on n. This, of course, is a very restrictive assumption. The corresponding hypotheses in the stochastic treatment of population dynamics are those of a multiplicative or branching process (T. E. Harris[4,5,10], and J. E. Moyal[11,12]). In other words, the behavior of one cell is not influenced by the presence of other cells. The function $n(t,a)$ is then given by equation (9) of reference[8]. Two special cases of this result are of interest.

1) Suppose that λ depends explicitly on t and $N(t)$, but not on a or n. In the present formalism the age variable specifies the structure or the *constitution* of the deme (reference[2], pp. 44–45, see also[13]). Therefore, by suppressing all age

dependence of the loss function we are essentially considering what H. M. Tsuchiya[14] has called a completely unstructured model. For simplicity, let λ be a function of N only:

$$\lambda = g(N) = m(N) + r(N), \quad \cdots\cdots\cdots (8)$$

where m is the generation coefficient $[m=\mu]$ while r represents losses from death or emigration. $N(t)$ is expressed in terms of n by equation (4). Then (3) determines the birth rate:

$$\alpha(t) = 2m(N)\cdot N, \cdots\cdots\cdots (9)$$

and from (5) we obtain

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \alpha(t) - g(N)\cdot N = N\cdot[m(N) - r(N)]. \cdots\cdots\cdots (10)$$

Equations of the form (10) are frequently used in population dynamics; this is the familiar formulation stating that the behavior of the population depends only on the total number of cells, $N(t)$. In fact, the problem will be solved completely if $N(t)$ is found from the ordinary differential equation (10) with the initial condition $N_0 \equiv N(0) = \int_{a=0}^{\infty} \beta(a)\mathrm{d}a$. Once $N(t)$ has been determined, the loss function, $g(N(t))$, becomes a known function of t only and the age density can be computed from equation (9) of[3]. The result is

$$n(t,a) = \left\{\begin{array}{ll} \dfrac{\alpha(T)}{R(T)}R(t) = 2m(N(T))\cdot N(T)\cdot\dfrac{R(t)}{R(T)} & \text{for} \quad t>a \\ \beta(a-t)\cdot R(t) & \text{for} \quad a>t, \end{array}\right\} \cdots (11)$$

where $T = t - a$ and $R(t) = \exp\left[-\int_{y=0}^{t} g(N(y))\mathrm{d}y\right]$.

Notice that this solution is consistent, in the sense that on computing $\int_{a=0}^{t} n(t,a)\mathrm{d}a + \int_{a=t}^{\infty} n(t,a)\mathrm{d}a$, with $n(t,a)$ given by (11), we obtain $N(t)$. This can readily be verified using the fact that $\dfrac{\alpha(T)}{R(T)} = \dfrac{\mathrm{d}}{\mathrm{d}T}\left[\dfrac{N(T)}{R(T)}\right]$. As an example, the *logistic equation* is obtained by taking $m(N) = A = \text{constant} > 0$, and $r(N) = B\cdot N$, where B is a positive constant. This gives: $\alpha(t) = 2AN$, $\mathrm{d}N/\mathrm{d}t = AN - BN^2$, $N(t) = AN_0/[BN_0 + (A - BN_0)\exp(-At)]$, and $R(t) = (N(t)/N_0)\exp(-2At)$.

2) A second simple situation is that in which λ depends on age only:

$$\lambda = \theta(a) = \mu(a) + \rho(a) + \tau(a) \geq 0. \quad \cdots\cdots\cdots (12)$$

I call these *intrinsic loss functions*. From equation (9) of[3] we now have

$$n(t,a)=\left\{\begin{array}{ll}\alpha(t-a)\cdot\varphi(a) & \text{for}\quad t>a\\ \dfrac{\beta(a-t)}{\varphi(a-t)}\cdot\varphi(a) & \text{for}\quad a>t,\end{array}\right\}\cdots\cdots\cdots(13)$$

where

$$\varphi(a)=\exp\left[-\int_{x=0}^{a}\theta(x)\mathrm{d}x\right]\cdots\cdots(14)$$

[It is assumed that the integral $\int_{x=0}^{\infty}\theta(x)\mathrm{d}x$ diverges.] In particular, the steady state solution, $\bar{n}(a)$, is given by $\bar{n}(a)=\alpha_0\cdot\varphi(a)=\beta(a)$, α_0 being a constant. Thus, the Uhlhorn probability density *for the steady state* becomes

$$f(a)=\theta(a)\cdot\varphi(a)=-\frac{\mathrm{d}\varphi(a)}{\mathrm{d}a}\equiv\delta(a).\cdots\cdots(15)$$

[The notation $\delta(a)$ was originally introduced by H. Von Foerster; $\delta(a)$ should not be confused with a Dirac delta function.] The first moment, D, of $\delta(a)$ is the *mean life span*; it represents the average age of cells leaving the deme if there is a constant influx, α_0, of newborn cells. This is equivalent to a *congenerate sample* in the sense of Von Foerster (reference[1], p. 387). Thus we have

$$D=\int_{a=0}^{\infty}a\delta(a)\mathrm{d}a=\int_{a=0}^{\infty}\varphi(a)\mathrm{d}a=\bar{N}/\alpha_0,\cdots\cdots(16)$$

where $\bar{N}=\int_{a=0}^{\infty}\bar{n}(a)\mathrm{d}a$. Notice that our assumption $\lambda=\theta(a)$ excludes the occurrence of correlation between the life spans of related cells, e. g. sister cells, whereas in fact such a correlation is frequently observed (E. O. Powell[15], H. E. Kubitschek[16]).

If λ is given by equation (12), the birth rate, $\alpha(t)$, can be obtained from an integral equation of the renewal type. Inserting the expression (13) for $n(t,a)$ into equation (3) we find

$$\alpha(t)=G(t)+2\int_{a=0}^{t}\mu(a)\alpha(t-a)\varphi(a)\mathrm{d}a\cdots\cdots(17)$$

with

$$G(t)=2\int_{a=t}^{\infty}\mu(a)\frac{\beta(a-t)}{\varphi(a-t)}\varphi(a)\mathrm{d}a.\cdots\cdots(18)$$

The solution of equation (17) for some simple special cases is discussed in reference[8].

Assume that the intrinsic loss function, $\theta(a)$, is the sum of two terms corresponding to mutually exclusive mechanisms of cell removal, say

$\theta(a)=\theta_1(a)+\theta_2(a)$. Define $\varphi_i(a)=\exp\left[-\int_{x=0}^{a}\theta_i(x)\mathrm{d}x\right]$ and $\delta_i(a)=\theta_i(a)\varphi_i(a)$, for $i=1,2$. Then we have $\varphi(a)=\varphi_1(a)\cdot\varphi_2(a)$, and

$$\delta(a)=\delta_1(a)\left[1-\int_{x=0}^{a}\delta_2(x)\mathrm{d}x\right]+\left[1-\int_{x=0}^{a}\delta_1(x)\mathrm{d}x\right]\delta_2(a).$$

Some examples of these relations are given in reference[18].

A further application of the Von Foerster formalism with intrinsic loss function is the equation derived first by Y. Maruyama[17]* and later by E. O. Powell[15] for the exponential growth of a bacterial population without losses from death or migration. It is also assumed that the generation coefficient, μ, depends on age only. Thus we have

$$\lambda=\theta(a)=\mu(a). \quad\cdots\cdots(19)$$

We put as before

$$\varphi(a)=\exp\left[-\int_{x=0}^{a}\mu(x)\mathrm{d}x\right] \quad\cdots\cdots(20)$$

and

$$\delta(a)=\mu(a)\varphi(a)=-\frac{\mathrm{d}\varphi(a)}{\mathrm{d}a}. \quad\cdots\cdots(21)$$

The *Maruyama-Powell age density function* is defined to be

$$n(t,a)=2cN_0\mathrm{e}^{ct}\mathrm{e}^{-ca}\varphi(a) \qquad [N_0=\text{constant}>0], \quad\cdots\cdots(22)$$

where the positive constant c is determined uniquely by the equation

$$2\int_{a=0}^{\infty}\mathrm{e}^{-ca}\delta(a)\mathrm{d}a=1. \quad\cdots\cdots(23)$$

It is easily seen that the expression (22) for the age density $n(t,a)$ satisfies equations (1) and (3). From (4), (22), and (23) we obtain $N(t)=N_0\mathrm{e}^{ct}$, so that the value of c found from (23) is related to T, the mean doubling time of the culture, by the equation $cT=\ln 2$. The properties of $n(t,a)$, as given by equation (22), and of the Uhlhorn probability density derived from it, are discussed at the end of reference[8]. Notice that in this case the Uhlhorn function coincides with Powell's "carrier distribution." According to Powell (page 497 of[15]), the carrier distribution governs the generation times for the immediate ancestors (mothers) of the cells actually extant at any given time. The meaning of this statement is not

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** Maruyama's name is not mentioned in my paper[8] because I did not know the contents of his article[17]. I am very grateful to Dr. Maruyama for supplying this reference which could not be obtained in the United States. It should be pointed out that the results of Maruyama and Powell are already contained in the earlier work of Harris, T. E. (e.g., reference[4], Theorem 12).

quite clear to me.

A special case of equation (22) is obtained when all the cells have identical generation time, say D. This is approximately true in many cases and has been called *equivivancy* by H. Von Foerster. Then we have $\varphi(a)=1$ for $0 \leq a < D$, $\varphi(a)=0$ for $a > D$, and (22) reduces to

$$n(t,a)=\begin{cases} 2cN_0 e^{ct} e^{-ca} & \text{for} \quad 0 \leq a < D \\ 0 & \text{for} \quad a > D, \end{cases} \quad \cdots\cdots\cdots (24)$$

with $c=(1/D)\ln 2$.

A very simple but interesting application of equation (24) is given in reference[18].

Consider again a population characterized by equations (19)-(21), but assume now that $\beta(a)=\bar{\delta}(a-y)$, where $\bar{\delta}$ denotes the Dirac delta function and y is a non-negative constant. Formally, this means that at time zero there is *one* cell of age y (even though the theory is applicable only for large populations). Put

$$M(t,y,x)=\int_{a=0}^{x} n(t,a)\,\mathrm{d}a, \quad \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (25)$$

which is the equivalent of the quantity $M(t,y,x)$ introduced by T. E. Harris in his theory of branching processes [reference[4], equation (5.13)]. We shall show that the function $M(t,y,x)$ defined by (25) satisfies the integral equation

$$M(t,y,x)=J(x-y-t)\frac{\varphi(y+t)}{\varphi(y)}+2\int_{u=0}^{t}\frac{\delta(u+y)}{\varphi(y)}M(t-u,0,x)\,\mathrm{d}u, \quad \cdots (26)$$

where $J(\xi)=0$ if $\xi \leq 0$ and $J(\xi)=1$ if $\xi > 0$. This is the same as equation (5.23) of reference[4].

Remembering the assumption on $\beta(a)$, equation (18) now becomes

$$G(t)=2\frac{\delta(t+y)}{\varphi(y)}, \quad \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (27)$$

and equation (17) can be written in the form

$$\alpha(t)=G(t)+(2\delta * \alpha), \quad \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (28)$$

where the symbol * denotes convolution. The solution of the integral equation (28) is given by

$$\alpha(t)=G(t)+(G * Q), \quad \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (29)$$

where Q, the resolvent kernel, is itself a solution of the equation

$$Q(t)=2\delta(t)+(2\delta * Q). \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (30)$$

If $y=0$ we have $G(t)=2\delta(t)$, in which case the two equations (28) and (30) have the same form. This means that $Q(t)=[\alpha(t)]_{y=0}$, and therefore, using equation (13):

$$M(t,0,x)=\int_{a=0}^{\sigma}Q(t-a)\varphi(a)\mathrm{d}a+J(x-t)\varphi(t), \cdots\cdots\cdots\cdots\cdots\cdots\cdots (31)$$

where σ is the smaller of the two numbers x and t. In particular,

$$M(t,0,x)=M(t,0,t)+\varphi(t) \quad \text{if} \quad x>t. \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (32)$$

Assume now $x<t$. Then we have from equations (13) and (29)

$$M(t,y,x)=\int_{a=0}^{x}\varphi(a)\,[G(t-a)+\int_{u=0}^{t-a}G(u)Q(t-a-u)\mathrm{d}u]\,\mathrm{d}a,$$

or, inverting the order of the integrations over a and u, and using equation (31),

$$M(t,y,x)=\int_{a=0}^{x}\varphi(a)G(t-a)\mathrm{d}a+\int_{u=0}^{t-x}G(u)M(t-u,0,x)\mathrm{d}u$$

$$+\int_{u=t-x}^{t}G(u)M(t-u,0,t-u)\mathrm{d}u.$$

In the last integral, $M(t-u,0,t-u)$ can be replaced by $M(t-u,0,x)-\varphi(t-u)$, according to equation (32), and so we are left with

$$M(t,y,x)=\int_{u=0}^{t}G(u)M(t-u,0,x)\mathrm{d}u. \cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots\cdots (33)$$

This is the same as (26) if $x<t$.

The case $x>t$ is treated in a similar manner, remembering that

$$\int_{a=t}^{x}n(t,a)\mathrm{d}a=\left\{\begin{array}{ll}[1/\varphi(y)]\varphi(y+t) & \text{if} \quad t+y<x, \\ 0 & \text{otherwise.}\end{array}\right\} \cdots\cdots\cdots\cdots (34)$$

Thus we see that the quantity $M(t,y,x)$ computed from the Von Foerster equation coincides with the expected value $M(t,y,x)$ obtained from the theory of branching processes.

In general, the age of cells is not a variable that can be measured directly. It would be interesting to extend the theory assuming that cellular types are characterized by quantities other than age. The type would then be represented as a point or *state vector* in an abstract space[11,12]. No equations of motion are known for these representative points, so that we can only try to develop their statistics without the corresponding mechanics (cf. the introductory remarks in E. H. Kerner's paper, reference[19]).

O. Scherbaum and G. Rasch[20] as well as Fredrickson and Tsuchiya (reference[7], page 464) discuss the distribution of size, s, within a cellular population. D. G. Oldfield[21] has attempted a generalization of the Von Foerster equation by straightforward analogy with the continuity equation of hydrodynamics.

In principle, the statistical theory of cellular (or other) systems is completely developed by J. E. Moyal[11], where no restrictions of any kind are imposed on the state space. It is assumed in most cases that the stochastic population process is Markovian and is therefore characterized by a transition probability $P(A, t/x, s)$. This is the probability of transition from state x at time s to some state y in the set A at time t, satisfying the so-called Chapman-Kolmogorov equation. Theoretically these assumptions are not a severe restriction because almost any process can be made Markovian by appropriate choice of the states [see reference[5], pp. 59–60]. In practice, however, the states are more or less prescribed by the nature of the system.

J. E. Moyal[22] also gives a theory of Markov processes in which transitions may be sudden ["jumps"] or continuous. For example, a change in number of cells is always a jump, but variations in size are usually continuous. The possibility of using Moyal's very general results for biological applications deserves serious study.

Note added in proof:

After completing the present manuscript I was informed by Dr. C. F. Mountain that, due to several unforeseen difficulties, the Proceedings of the Second Annual Symposium on Biomathematics and Computer Science in the Life Sciences cannot be published. Therefore, reference[13] of this paper will not appear in print.

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