

ON A MIXED PROBLEM FOR THE M'KENDRICK-VON FOERSTER EQUATION*

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Abstract. A mixed problem for the M'Kendrick-Von Foerster equation is solved explicitly: existence, uniqueness and regularity theorems are proved as well as several integral formulas.

This theory provides us with an effective means to analyze microbial population dynamics and the underlying cellular physiological changes, taking into consideration that one can calculate the main microbiological quantities from experimental data.

1. Introduction. In his epidemiological study of age-structured populations M'Kendrick [7] introduced a partial differential equation of the type

$$\frac{\partial u}{\partial a} + \frac{\partial u}{\partial t} = -\lambda u,$$

which was rediscovered by Scherbaum and Rasch [9] and studied by Von Foerster [12] in the kinetics of cellular proliferation (cf. [8] and [11]). We use the differential operator D_c according to, say, Gurtin [2] in order to extend the class of functions to be treated in the equation. We shall call the equation the M'Kendrick-Von Foerster equation. The existence and uniqueness of solution to this equation under an integral birth law (a kind of boundary condition) have been studied by not a few investigators, e.g., Gurtin and MacCamy [3], Sinestrari [10]. On the other hand, a birth law different from the integral type is imposed on this equation in application to the age-dependent population dynamics of a homogeneous cohort of microorganisms. Few theoretical treatments of this case have been published so far.

Though microbial culture in the period of steady growth, i.e. with constant generation time, has been treated by many authors, there have been few rigorous treatments of time-dependent generation time. In our previous papers [1, 13] we explicitly introduced the concept of time-dependent generation time (assumed to be the same for all the cells) and, using it, analyzed microbial proliferation in the period of *non-steady* growth. The period with constant generation time was described as a special case in this framework.

Our theory as presented in the first paper [1] had several restrictions. Among those were the following: (i) the death rate of the cells was assumed to be zero; (ii) the increase of biomass of a cell per unit biomass per unit time ("individual growth rate") was assumed to be independent of time and the same for all the cells; (iii) the initial time had to be in the

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logarithmic phase; (iv) the length of time interval treated in the theory was such that a cell could divide at most once during it. We applied the theory to the growth data [6] of *Bacillus subtilis* and obtained some new results which might be very difficult to obtain directly from microbiological experiments. In our second paper [13] the restrictions (iii) and (iv) were completely eliminated and the death rate of the cells was supposed to be a constant, not necessarily zero. The restriction (ii) remained unaltered.

In the present paper the death rate and the individual growth rate are allowed to vary with the time, though they are still assumed to be the same for all the cells. The definition of time-dependent generation time is made more rigorous and rendered fitter for practice. Some functions treated separately in the previous papers are now unified as the solution of a mixed problem for the M'Kendrick–Von Foerster equation. We solve the mixed problem explicitly. Some results on regularity of the solutions are obtained. According to the theory, we can calculate the solutions (which are functions of two variables) given the function representing the time-dependent generation time; this function is fundamental in the sense that it determines the shape of the domain in which the equation is considered. Further, we get several important integral formulas by which we can calculate the integrals of the solutions with respect to the first variable. For application of the theory to experimental data, the inverse problem must be solved; that is, the problem of finding a function representing the time-dependent generation time (which is of fundamental importance in our theory), given the definite integral of the solution with respect to the first variable as a function of the second variable. We also solve this inverse problem.

Though the assumption that all cells have the same generation time at each instant deviates somewhat from reality, it greatly simplifies the formulation and allows us to get formulas describing essential aspects of cellular growth. Also, our theory is ready to be applied to the analysis of experimental data. As is shown in Sec. 3, the main microbiological quantities (for example, the age distribution and the time-dependent generation time) can be calculated from observed growth curves of cell number and cell biomass. A reader more interested in biological significance and applications than in mathematical details had better read Sec. 3 first and consult Sec. 2 when necessary.

2. A mixed problem for the M'Kendrick–Von Foerster equation

2.1 Preliminaries. Let Ω be a subset of \mathbb{R}^2 satisfying the characteristic line condition (cf. [1]):

$$(a, t) \in \Omega, \quad h \in \mathbb{R}, \quad (a + h, t + h) \in \Omega, \quad 0 < \theta < 1 \Rightarrow (a + \theta h, t + \theta h) \in \Omega.$$

We shall say that a real-valued¹ function v defined on Ω is characteristically differentiable at a point $(a, t) \in \Omega$ if

$$\lim_{h \rightarrow 0} \frac{v(a + h, t + h) - v(a, t)}{h}$$

exists. This limit is denoted by $D_c v(a, t)$. (See, e.g., [2].) If v is partially differentiable in an open neighborhood of (a, t) contained in Ω and at least one of the partial derivatives $\partial v / \partial a$

¹ We assume in the present paper that functions are real-valued unless otherwise stated.

and $\partial v/\partial t$ is continuous at (a, t) , then we have

$$D_c v(a, t) = \left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t} \right) v(a, t).$$

Let t_0 be a real number and g_0 a positive one. We consider a positive continuous function g defined on the interval $[t_0, \infty)$ such that $g(t_0) = g_0$ and

$$t_0 \leq t < t' \Rightarrow g(t') - g(t) < t' - t. \tag{1}$$

PROPOSITION 1. Condition (1) implies that

$$\Omega \equiv \{(a, t) \in \mathbb{R}^2 \mid t \geq t_0, 0 \leq a \leq g(t)\} \tag{2}$$

satisfies the characteristic line condition.

Proof. Suppose that $(a, t) \in \Omega$ and $(a + h, t + h) \in \Omega$. We shall show that $(a + \theta h, t + \theta h) \in \Omega$ for $0 < \theta < 1$. Without loss of generality, one can suppose that $h > 0$. It is clear that $t + \theta h > t_0$ and $a + \theta h > 0$. If there exists some θ_0 such that $0 < \theta_0 < 1$ and $a + \theta_0 h > g(t + \theta_0 h)$, setting

$$\begin{aligned} \theta_1 &= \sup\{\theta \in [0, \theta_0) \mid a + \theta h \leq g(t + \theta h)\} \\ \theta_2 &= \inf\{\theta \in (\theta_0, 1] \mid a + \theta h \leq g(t + \theta h)\}, \end{aligned}$$

we have $0 \leq \theta_1 \leq \theta_0 \leq \theta_2 \leq 1$. By the continuity of g ,

$$a + \theta_1 h = g(t + \theta_1 h), \quad a + \theta_2 h = g(t + \theta_2 h).$$

Hence, $\theta_1 < \theta_0 < \theta_2$. We therefore reach a relation

$$(\theta_2 - \theta_1)h = g(t + \theta_2 h) - g(t + \theta_1 h),$$

which contradicts the condition (1). Q.E.D.

We define $b(t) \equiv t - g(t)$ for $t \geq t_0$. Then, b is a strictly increasing continuous function on $[t_0, \infty)$ such that

$$b(t) < t \quad \text{for } t \geq t_0 \tag{3}$$

$$b(t_0) = t_0 - g_0 (\equiv t_{-1}). \tag{4}$$

We put

$$b_\infty \equiv \sup_{t \geq t_0} b(t) \quad (\leq \infty).$$

Since the range of the strictly increasing continuous function b is $[t_{-1}, b_\infty)$, there exists an inverse function b^{-1} of b defined on $[t_{-1}, b_\infty)$. b^{-1} is a strictly increasing continuous function such that

$$b^{-1}(s) > s \quad \text{for } t_{-1} \leq s < b_\infty, \quad b^{-1}(t_{-1}) = t_0.$$

Let us recursively define a strictly increasing sequence $\{t_n\}_{1 \leq n < \zeta}$ of extended real numbers (i.e., elements of $\{-\infty\} \cup \mathbb{R} \cup \{\infty\}$) as follows:

$$\begin{aligned} t_n &= b^{-1}(t_{n-1}) & \text{if } t_{-1} \leq t_{n-1} < b_\infty \\ &= \infty & \text{if } b_\infty \leq t_{n-1} < \infty \\ &= \text{undefined} & \text{if } t_{n-1} = \infty. \end{aligned}$$

If there exists an n_0 such that $t_{n_0-1} = \infty$, then the sequence $\{t_n\}$ terminates at $n = n_0 - 1$ and ζ is defined as n_0 . Otherwise the sequence is infinite and we define $\zeta = \infty$. It is clear that

$$[t_{-1}, \infty) = \bigcup_{0 \leq n < \zeta} [t_{n-1}, t_n) \quad (\text{disjoint union}). \tag{5}$$

For later purposes we introduce the notation

$$\Omega_n \equiv \{(a, t) \in \Omega \mid t_{n-1} \leq t - a < t_n\} \quad \text{for } 0 \leq n < \zeta. \tag{6}$$

Since $(a, t) \in \Omega$ implies $t - a \geq b(t) \geq t_{-1}$, we have

$$\Omega = \bigcup_{0 \leq n < \zeta} \Omega_n \quad (\text{disjoint union}). \tag{7}$$

We define recursively a sequence of functions b_n defined on $[t_{n-1}, \infty)$ as follows:

$$\begin{aligned} b_0(t) &= t && \text{for } t \geq t_{-1}, \\ b_n(t) &= b_{n-1}(b(t)) && \text{for } 1 \leq n < \zeta, t \geq t_{n-1}. \end{aligned}$$

Since $t \geq t_{n-1}$ implies $b(t) \geq t_{n-2}$, b_n is a well-defined strictly increasing continuous function on $[t_{n-1}, \infty)$. The following formulas are immediate consequences of the definitions of $\{t_n\}_{-1 \leq n < \zeta}$ and $\{b_n\}_{0 \leq n < \zeta}$:

$$\begin{aligned} b_1(t) &= b(t) && \text{for } t \geq t_0, \\ b_n(t) &= b_{n-k}(b_k(t)) && \text{for } t \geq t_{n-1}, 0 \leq k \leq n < \zeta, \end{aligned} \tag{8}$$

$$b_n(t_k) = b_{n-j}(t_{k-j}) \quad \text{for } 0 \leq j \leq n < \zeta, n - 1 \leq k < \zeta,$$

$$b_n(t_{n-1}) = b_0(t_{-1}) = t_{-1}, \tag{9}$$

$$b_n(t_n) = b_0(t_0) = t_0, \tag{10}$$

$$1 \leq n < \zeta, \quad t_{n-1} \leq t < t_n \Rightarrow \begin{cases} t_{-1} \leq b_n(t) < t_0 \\ t_{n-2} \leq b(t) < t_{n-1}, \end{cases} \tag{11}$$

$$t_n = \sup\{t \in [t_0, \infty) \mid b(t) < t_{n-1}\} \quad \text{for } 1 \leq n < \zeta. \tag{12}$$

2.2 Solution of a Mixed Problem for the M'Kendrick-Von Foerster Equation

THEOREM 1. Let $g, \Omega, b, \{t_n\}_{-1 \leq n < \zeta}$ and $\{b_n\}_{0 \leq n < \zeta}$ be as in Sec. 2.1 and κ be a continuous function defined on $[t_0, \infty)$, w an arbitrary function on $(0, g_0]$ and β an arbitrary one on $[t_0, \infty)$. Then, there exists a unique solution $v(a, t)$ on Ω of the mixed problem

$$\begin{aligned} \text{(F)} \quad & D_c v(a, t) = \kappa(t)v(a, t) \quad \text{for } (a, t) \in \Omega, \\ \text{(I)} \quad & v(a, t_0) = w(a) \quad \text{for } 0 < a \leq g_0, \\ \text{(B)} \quad & v(0, t) = \beta(t)v(g(t), t) \quad \text{for } t \geq t_0. \end{aligned} \tag{13}$$

The unique solution $v(a, t)$ is given by the following formula:

$$\text{(S)} \quad v(a, t) = K(t)p(t - a) \quad \text{for } (a, t) \in \Omega,$$

where

$$K(t) = \exp \int_{t_0}^t \kappa(\tau) d\tau \quad \text{for } t \geq t_0 \tag{14}$$

and p is a function on $[t_{-1}, \infty)$ defined as

$$p(t) = w(t_0 - b_n(t)) \prod_{j=0}^{n-1} \beta(b_j(t)) \quad \text{for } 0 \leq n < \zeta, t_{n-1} \leq t < t_n \tag{15}$$

under the convention

$$\prod_{j=0}^{n-1} \beta(b_j(t)) = 1 \quad \text{if } n = 0. \tag{16}$$

Proof. By the transformation

$$v(a, t) = K(t)f(a, t),$$

Eq. (F) is equivalent to the equation

$$D_c f(a, t) = 0 \quad \text{for } (a, t) \in \Omega.$$

Further, a function f on Ω satisfies this equation if and only if there exists a function p defined on $[t_{-1}, \infty)$ such that

$$f(a, t) = p(t - a) \quad \text{for } (a, t) \in \Omega.$$

The mixed problem (13) is, therefore, equivalent to the following problem with respect to p :

$$\begin{aligned} \text{(I')} \quad & p(t_0 - a) = w(a) \quad \text{for } 0 < a \leq g_0, \\ \text{(B')} \quad & p(t) = \beta(t)p(b(t)) \quad \text{for } t \geq t_0. \end{aligned} \tag{17}$$

So we have only to show that (15) gives a unique solution of the problem (17). First we show the uniqueness. Suppose that both functions p_1 and p_2 defined on $[t_{-1}, \infty)$ are solutions of (17). We shall show by mathematical induction on n that p_1 and p_2 coincide on $[t_{n-1}, t_n)$.

1. For $n = 0$, we have $p_i(t) = p_i(t_0 - (t_0 - t)) = w(t_0 - t) (i = 1, 2; t_{-1} \leq t < t_0)$ by (I'). We obtain, therefore,

$$p_1(t) = p_2(t) \quad \text{for } t_{-1} \leq t < t_0.$$

2. Let $1 \leq n < \zeta$ and suppose that $p_1(t) = p_2(t)$ for $t_{n-2} \leq t < t_{n-1}$. For $t_{n-1} \leq t < t_n$, we have $t_{n-2} \leq b(t) < t_{n-1}$ by (11). We have, therefore, by the induction hypothesis, $p_1(b(t)) = p_2(b(t))$. Hence, we obtain, using (B'),

$$p_1(t) = p_2(t) \quad \text{for } t_{n-1} \leq t < t_n,$$

which completes the induction.

Secondly, we show that (15) is a solution of (17). From (10), (11) and the definitions of $\{t_n\}$ and $\{b_n\}$, it is clear that $t_0 - b_n(t)$ and $b_j(t)$ belong to the domains of definition of w and β , respectively, for $0 \leq n < \zeta, t_{n-1} \leq t < t_n$ and $0 \leq j \leq n - 1$. Hence, p is a well-defined function on $[t_{-1}, \infty)$ by (5). For $0 < a \leq g_0$, we have

$$p(t_0 - a) = w(t_0 - b_0(t_0 - a)) = w(a),$$

which is nothing other than (I'). Since for any $t \geq t_0$ there exists an integer n such that

$1 \leq n < \zeta$ and $t_{n-1} \leq t < t_n$, we have by (11)

$$\begin{aligned} p(b(t)) &= w(t_0 - b_{n-1}(b(t))) \prod_{j=0}^{n-2} \beta(b_j(b(t))) \\ &= w(t_0 - b_n(t)) \prod_{j=0}^{n-2} \beta(b_{j+1}(t)). \end{aligned}$$

Hence,

$$\begin{aligned} \beta(t)p(b(t)) &= \beta(b_0(t))w(t_0 - b_n(t)) \prod_{j=1}^{n-1} \beta(b_j(t)) \\ &= w(t_0 - b_n(t)) \prod_{j=0}^{n-1} \beta(b_j(t)) = p(t). \end{aligned}$$

Thus p satisfies (B') as well. Q.E.D.

Remark. It is clear from the explicit expression (S) with (14) and (15) of the solution that $\beta \geq 0$ and $w \geq 0$ imply $v \geq 0$. Furthermore, if we denote by \tilde{v} the unique solution of the mixed problem (13) considered for $\tilde{\kappa}$, \tilde{w} and $\tilde{\beta}$ in place of κ , w and β , respectively, such that $\kappa \leq \tilde{\kappa}$, $w \leq \tilde{w}$ and $0 \leq \beta \leq \tilde{\beta}$, the inequality $v \leq \tilde{v}$ holds.

We proceed now to regularity of the solution v of (13). The regularity of v is reduced by the relation (S) to those of K and p . The regularity of K being obvious, we examine that of p . In the following three propositions, we suppose that the assumptions in Theorem 1 remain intact. From the expression (15), we have

PROPOSITION 2. If β is right-continuous and w left-continuous, then p is right-continuous.

PROPOSITION 3. Let n be such that $1 \leq n < \zeta$ and let β be left-continuous at t_j for all j such that $1 \leq j \leq n-1$. Then $w(0+) = \beta(t_0)w(g_0)$ implies the left-continuity of p at t_{n-1} . Moreover, when $\beta(t_j) \neq 0$ for $1 \leq j \leq n-1$, the converse is also true. (When there exists $\lim_{h \downarrow 0} f(a+h)$, this limit is denoted by $f(a+)$. Similarly we use the notation $f(a-) = \lim_{h \downarrow 0} f(a-h)$.)

Proof. For $t_{n-2} \leq t < t_{n-1}$, we have

$$p(t) = w(t_0 - b_{n-1}(t)) \prod_{j=0}^{n-2} \beta(b_j(t)).$$

Hence,

$$p(t_{n-1}-) = w(0+) \prod_{j=0}^{n-2} \beta(b_j(t_{n-1})).$$

On the other hand, we have

$$p(t_{n-1}) = w(g_0)\beta(t_0) \prod_{j=0}^{n-2} \beta(b_j(t_{n-1})).$$

These two formulas show the desired results. Q.E.D.

PROPOSITION 4. Let r be a non-negative integer and let both g and β belong to $C^r[t_0, \infty)$ (i.e., the set of all real-valued functions of class C^r on the interval $[t_0, \infty)$).² Then, $p \in C^r[t_{-1}, \infty)$ if and only if the following two conditions are fulfilled:

- (i) $w \in C^r(0, g_0]$,
- (ii) w satisfies for $0 \leq i \leq r$

$$(B_i) \quad w^{(i)}(0+) = (-1)^i i! \sum_{v=0}^i \frac{\beta^{(i-v)}(t_0)}{(i-v)!} \sum_{k=0}^v (-1)^k w^{(k)}(g_0) \sum_{\alpha \in A_{v,k}} G(b, \alpha),$$

where

$$A_{v,k} = \left\{ \alpha = (\alpha_1, \dots, \alpha_v) \mid \alpha_1, \dots, \alpha_v \text{ are non-negative integers} \right. \\ \left. \text{such that } \sum_{l=1}^v \alpha_l = k \text{ and } \sum_{l=1}^v l\alpha_l = v \right\}$$

for $0 \leq k \leq v$, and

$$G(b, \alpha) = \prod_{l=1}^v \frac{1}{\alpha_l!} \left\{ \frac{b^{(l)}(t_0)}{l!} \right\}^{\alpha_l} \quad \text{for } \alpha \in A_{v,k}.$$

Note that if $v = 0$ then $(\alpha_1, \dots, \alpha_v)$ is a multi-index of length 0. Since there exists a unique multi-index of length 0, $A_{0,0}$ is a singleton and $\sum_{\alpha \in A_{0,0}} G(b, \alpha) = 1$, under the convention that if α is the multi-index of length 0, then $\sum_{l=1}^v \alpha_l = 0$, $\sum_{l=1}^v l\alpha_l = 0$ and $G(b, \alpha) = 1$. For $v \geq 1$ we have $A_{v,0} = \emptyset$ and $\sum_{\alpha \in A_{v,0}} G(b, \alpha) = 0$.

Proof. By the formula (15), $p \in C^r[t_{-1}, \infty)$ if and only if

- (i) $w \in C^r(0, g_0]$ and
- (ii') $p^{(i)}(t_{n-1}-) = p^{(i)}(t_{n-1}+)$ for $1 \leq n < \zeta, 0 \leq i \leq r$.

The condition (ii') is equivalent to

$$p^{(i)}(t_0-) = p^{(i)}(t_0+) \quad \text{for } 0 \leq i \leq r$$

by (B'). Since we have

$$p(t) = w(t_0 - b(t))\beta(t) \quad \text{for } t_0 \leq t < t_1,$$

we obtain, by Leibniz' formula concerning the derivative of the product of functions and Faa di Bruno's formula concerning that of the composite function,

$$p^{(i)}(t) = \sum_{v=0}^i \binom{i}{v} \beta^{(i-v)}(t)v! \sum_{k=0}^v \sum_{\alpha \in A_{v,k}} w^{(k)}(t_0 - b(t))G(-b, \alpha)$$

for $t_0 \leq t < t_1$. Hence,

$$p^{(i)}(t_0+) = \sum_{v=0}^i \frac{i!}{(i-v)!} \beta^{(i-v)}(t_0) \sum_{k=0}^v w^{(k)}(g_0)(-1)^k \sum_{\alpha \in A_{v,k}} G(b, \alpha).$$

² When r is zero, it is nothing other than the set of all real-valued continuous functions on this interval.

On the other hand, since

$$p(t) = w(t_0 - t) \quad \text{for } t_{-1} \leq t < t_0,$$

we have

$$p^{(i)}(t) = (-1)^i w^{(i)}(t_0 - t).$$

We obtain, therefore,

$$p^{(i)}(t_0 -) = (-1)^i w^{(i)}(0 +). \quad \text{Q.E.D.}$$

Remark. We shall write down for the reader the concrete form of (B_i) when $i = 0$ and 1 :

$$(B_0) \quad w(0 +) = \beta(t_0)w(g_0),$$

$$(B_1) \quad w'(0 +) = \beta(t_0)b'(t_0)w'(g_0) - \beta'(t_0)w(g_0).$$

We obtain, by (S) and Proposition 4, the following

COROLLARY. Let r be a non-negative integer, $g, \beta \in C^r[t_0, \infty)$ and $\kappa \in C^{r-1}[t_0, \infty)$. Then, $v \in C^r(\Omega)$ if and only if

- (i) $w \in C^r(0, g_0]$ and
- (ii) w satisfies (B_i) for $0 \leq i \leq r$.

Remark. When $r = 0$, we suppose that $\kappa \in C^0[t_0, \infty)$, which is the basic assumption on κ throughout this paper.

2.3 Integrals of the type $\int_{a_1}^{a_2} v(a, t) da$. We use the same notation as in 2.1 and 2.2. If the function p on $[t_{-1}, \infty)$ defined by (15) is locally integrable, i.e. integrable in Lebesgue's sense,³ on any bounded closed set contained in $[t_{-1}, \infty)$, then we can consider the integral

$$P(t) \equiv \int_{t_{-1}}^t p(\tau) d\tau \quad \text{for } t \geq t_{-1}.$$

P is then a continuous function on $[t_{-1}, \infty)$. In this case, $v(a, t) = K(t)p(t - a)$ is integrable with respect to a on the interval $(0, g(t)]$ for any fixed $t \geq t_0$, and we have

$$\begin{aligned} V_1(t) &\equiv \int_0^{g(t)} v(a, t) da = K(t) \int_{b(t)}^t p(\tau) d\tau \\ &= K(t)\{P(t) - P(b(t))\}. \end{aligned} \quad (18)$$

Then V_1 is continuous on $[t_0, \infty)$. When a constant C_0 and a continuous function σ on $[t_0, \infty)$ are given in addition, and we put

$$V_2(t) \equiv C_0 + \int_{t_0}^t \sigma(\tau)V_1(\tau) d\tau \quad \text{for } t \geq t_0,$$

then we have

$$V_2 \in C^1[t_0, \infty), \quad \frac{d}{dt} V_2(t) = \sigma(t)V_1(t), \quad V_2(t_0) = C_0.$$

$V(t)$ defined as $V_1(t) + V_2(t)$ is therefore a continuous function on $[t_0, \infty)$.

If β is right-continuous and w left-continuous, then p is right-continuous by Proposition

2. Hence, P , if it exists, is right-differentiable and its right derivative D^+P is equal to p , which is verified by

$$\left| \frac{P(t+h) - P(t)}{h} - p(t) \right| \leq \frac{1}{h} \int_t^{t+h} |p(\tau) - p(t)| d\tau \quad \text{for } h > 0. \tag{19}$$

If we assume, in addition, that g is right-differentiable, V_1 also is right-differentiable by (18):

$$D^+V_1(t) = \kappa(t)V_1(t) + K(t)\{p(t) - p(b(t))D^+b(t)\} \quad \text{for } t \geq t_0. \tag{20}$$

We have, therefore,

$$D^+V(t) = \{\kappa(t) + \sigma(t)\}V_1(t) + K(t)\{p(t) - p(b(t))D^+b(t)\}. \tag{21}$$

PROPOSITION 5. Let $r \geq 1, g \in C^r[t_0, \infty), \beta \in C^{r-1}[t_0, \infty)$ and $\kappa \in C^{r-1}[t_0, \infty)$. If

- (i) $w \in C^{r-1}(0, g_0]$ and
- (ii) w satisfies (B_i) for $0 \leq i \leq r - 1$,

then $V_1 \in C^r[t_0, \infty)$.

Proof. By Proposition 4, $p \in C^{r-1}[t_{-1}, \infty)$. Hence, p is locally integrable and $P \in C^r[t_{-1}, \infty)$. We have, therefore, the conclusion by (18). Q.E.D.

Hereafter we investigate the case in which g is right-differentiable and $\beta = \gamma D^+b$ with a suitable constant γ .

PROPOSITION 6. If g is right-differentiable, then the relation $\beta = \gamma D^+b$ implies

$$\prod_{j=0}^{n-1} \beta(b_j(t)) = \gamma^n D^+b_n(t) \quad \text{for } 0 \leq n < \zeta, t \geq t_{n-1}.$$

Proof. We prove this formula by mathematical induction on n . The case in which $n = 0$ is trivial under the convention (16). Let n be such that $1 \leq n < \zeta$ and suppose that the relation

$$\prod_{j=0}^{n-2} \beta(b_j(t)) = \gamma^{n-1} D^+b_{n-1}(t)$$

holds for $t \geq t_{n-2}$. From the definition of b_n , we have

$$D^+b_n(t) = D^+b_{n-1}(b(t)) \cdot D^+b(t) \quad \text{for } t \geq t_{n-1}.$$

We obtain, therefore,

$$\begin{aligned} \gamma^n D^+b_n(t) &= \gamma^{n-1} D^+b_{n-1}(b(t)) \cdot \gamma D^+b(t) \\ &= \left\{ \prod_{j=0}^{n-2} \beta(b_j(b(t))) \right\} \beta(t) = \prod_{j=0}^{n-1} \beta(b_j(t)). \end{aligned} \tag{Q.E.D.}$$

Remark. We have in this situation

$$p(t) = \gamma^n w(t_0 - b_n(t)) D^+b_n(t) \quad \text{for } 0 \leq n < \zeta, t_{n-1} \leq t < t_n. \tag{22}$$

³ In this paper we always consider integrals in Lebesgue's sense. So we shall say simply "integrable" in the following.

Using the corollary to Proposition 4, we have the following

COROLLARY. Let $r \geq 0$, $g \in C^{r+1}[t_0, \infty)$, $\beta = \gamma D^+ b$ ($D^+ b$ denotes the derivative of b) and $\kappa \in C^{r-1}[t_0, \infty)$.⁴ Then the necessary and sufficient condition for $v \in C^r(\Omega)$ is that

- (i) $w \in C^r(0, g_0]$ and
- (ii) w satisfies (B_i) for $0 \leq i \leq r$.

LEMMA 1. Let F be a continuous right-differentiable function defined on $[s_0, s_1]$. If $D^+ F$ is right-continuous and integrable on $[s_0, s_1]$, then we have

$$\int_{s_0}^{s_1} D^+ F(\tau) \, d\tau = F(s_1) - F(s_0).$$

Proof. Since $D^+ F$ is right-continuous and integrable,

$$H(s) \equiv \int_{s_0}^s D^+ F(\tau) \, d\tau \quad (s_0 \leq s \leq s_1)$$

is a continuous right-differentiable function and we have, similarly to (19),

$$D^+ H = D^+ F.$$

$H - F$ is, therefore, a continuous right-differentiable function defined on $[s_0, s_1]$ whose right derivative vanishes. Hence $H - F$ is constant:

$$H(s_1) - F(s_1) = H(s_0) - F(s_0) = -F(s_0). \quad \text{Q.E.D.}$$

LEMMA 2. If F is a continuous, monotone increasing and right differentiable function defined on $[s_0, s_1]$, then $D^+ F$ is integrable on $[s_0, s_1]$.

Proof. Since F is monotone increasing, it is differentiable almost everywhere and we have

$$\int_{s_0}^{s_1} DF(\tau) \, d\tau \leq F(s_1) - F(s_0),$$

where $DF(\tau)$ denotes the differential coefficient at almost all $\tau \in [s_0, s_1]$ (cf. [3]). We obtain, therefore,

$$0 \leq \int_{s_0}^{s_1} D^+ F(\tau) \, d\tau = \int_{s_0}^{s_1} DF(\tau) \, d\tau < \infty. \quad \text{Q.E.D.}$$

If g is a positive continuous right-differentiable function on $[t_0, \infty)$ such that the conditions $g(t_0) = g_0$ and (1) hold and $D^+ g$ is right-continuous, and β is a function on $[t_0, \infty)$ and γ is a constant such that $\beta = \gamma D^+ b$ where $b(t) = t - g(t)$ for $t \geq t_0$, and w is a left-continuous integrable function on $(0, g_0]$, then we say that the quadruple (g, β, γ, w) satisfies the condition (R).

LEMMA 3. Let (g, β, γ, w) satisfy the condition (R). Then p defined by (15) (hence by (22)) is locally integrable and its integral on $[t_{-1}, t)$ is given by

$$P(t) \equiv \int_{t_{-1}}^t p(\tau) \, d\tau = \sum_{j=0}^n \gamma^j W(g_0) - \gamma^n W(t_0 - b_n(t)) \quad \text{for } 0 \leq n < \zeta, t_{n-1} \leq t < t_n,$$

⁴ For the case in which r equals zero, under the same convention as in the remark on the corollary to Proposition 4.

where

$$W(a) \equiv \int_0^a w(\xi) d\xi \quad \text{for } 0 < a \leq g_0.$$

Proof. We fix for the moment an integer n such that $0 \leq n < \zeta$ and put

$$F(t) = -W(t_0 - b_n(t)) \quad \text{for } t_{n-1} \leq t < t_n.$$

F is then a continuous right-differentiable function defined on $[t_{n-1}, t_n)$ and we have

$$D^+ F(t) = w(t_0 - b_n(t))D^+ b_n(t)$$

which is right-continuous by the assumptions on g and w . We put

$$\tilde{W}(a) \equiv \int_0^a |w(\xi)| d\xi \quad \text{for } 0 < a \leq g_0,$$

$$\tilde{F}(t) \equiv -\tilde{W}(t_0 - b_n(t)) \quad \text{for } t_{n-1} \leq t < t_n.$$

\tilde{F} is then continuous, montone increasing and right-differentiable, and we have

$$D^+ \tilde{F}(t) = |w(t_0 - b_n(t))| D^+ b_n(t) = |D^+ F(t)|.$$

If $t_{n-1} \leq t < t_n$, then $D^+ \tilde{F}$ is integrable on $[t_{n-1}, t)$ by Lemma 2, and so is $D^+ F$. We obtain, therefore, by Lemma 1

$$\int_{t_{n-1}}^t D^+ F(\tau) d\tau = F(t) - F(t_{n-1}) \quad \text{for } t_{n-1} \leq t < t_n.$$

Hence p is integrable on $[t_{n-1}, t)$ and

$$\int_{t_{n-1}}^t p(\tau) d\tau = \gamma^n \{W(g_0) - W(t_0 - b_n(t))\}.$$

When t_n is finite, we have $F(t_n-) = \tilde{F}(t_n-) = 0$ by $W(0+) = \tilde{W}(0+) = 0$. In this case, therefore, we can define $F(t_n) = \tilde{F}(t_n) = 0$ and choose t_n as t in the above argument and obtain

$$\int_{t_{n-1}}^{t_n} p(\tau) d\tau = \gamma^n W(g_0) \quad \text{for } 0 \leq n < \zeta.$$

Hence,

$$\int_{t-1}^{t_{n-1}} p(\tau) d\tau = \sum_{j=0}^{n-1} \int_{t_{j-1}}^{t_j} p(\tau) d\tau = \sum_{j=0}^{n-1} \gamma^j W(g_0).$$

Thus we get an integral formula

$$\begin{aligned} P(t) &= \int_{t-1}^{t_{n-1}} p(\tau) d\tau + \int_{t_{n-1}}^t p(\tau) d\tau \\ &= \sum_{j=0}^{n-1} \gamma^j W(g_0) + \gamma^n \{W(g_0) - W(t_0 - b_n(t))\} \quad \text{for } t_{n-1} \leq t < t_n. \quad \text{Q.E.D.} \end{aligned}$$

THEOREM 2. Let (g, β, γ, w) satisfy the condition (R). Then $v(a, t)$ given by the formula (S) is

integrable with respect to a on $(0, g(t)]$ for any fixed $t \geq t_0$ and its integral is

$$(J) \quad V_1(t) \equiv \int_0^{g(t)} v(a, t) da = K(t)E(t),$$

where

$$E(t) \equiv \gamma^{n-1} \{ \gamma W(g_0) - (\gamma - 1)W(t_0 - b_n(t)) \} \quad \text{for } 1 \leq n < \zeta, t_{n-1} \leq t < t_n \quad (23)$$

(W is the same as in Lemma 3), and K is defined by (14).

Proof. We have, by (11) and Lemma 3,

$$P(b(t)) = \sum_{j=0}^{n-1} \gamma^j W(g_0) - \gamma^{n-1} W(t_0 - b_n(t)) \quad \text{for } 1 \leq n < \zeta, t_{n-1} \leq t < t_n. \quad (24)$$

Hence,

$$P(t) - P(b(t)) = \gamma^n W(g_0) - (\gamma^n - \gamma^{n-1})W(t_0 - b_n(t)).$$

We therefore have

$$E(t) = P(t) - P(b(t)) \quad \text{for } t \geq t_0. \quad (25)$$

Combining (18) with (25), we obtain the formula (J). Q.E.D.

Remark. We have, using (9),

$$E(t_{n-1}) = \gamma^{n-1} W(g_0) \quad \text{for } 1 \leq n < \zeta. \quad (26)$$

Especially, when $n = 1$,

$$E(t_0) = W(g_0), \quad (27)$$

and

$$V_1(t_0) = W(g_0). \quad (28)$$

When t_n is finite, we have, by $W(0+) = 0$,

$$E(t_n-) = \gamma^n W(g_0), \quad (29)$$

which proves the continuity of E , together with (26).

COROLLARY. Let (g, β, γ, w) satisfy the condition (R). Then E defined by (23) satisfies

$$E(t) = \gamma E(b(t)) \quad \text{for } t \geq t_1, \quad (30)$$

and V_1 defined by (J) satisfies

$$V_1(t) = \gamma V_1(b(t)) \exp \int_{b(t)}^t \kappa(\tau) d\tau \quad \text{for } t \geq t_1. \quad (31)$$

E , V_1 and V are right-differentiable and their right derivatives are right-continuous and the following relations hold:

$$D^+ E(t) = p(t) - p(b(t)) D^+ b(t) = \gamma^{n-1} (\gamma - 1) w(t_0 - b_n(t)) D^+ b_n(t) \quad (32)$$

$$\text{for } 1 \leq n < \zeta, t_{n-1} \leq t < t_n,$$

$$D^+ V_1(t) = \kappa(t) V_1(t) + K(t) D^+ E(t) \quad \text{for } t \geq t_0, \quad (33)$$

$$D^+ V(t) = \{\kappa(t) + \sigma(t)\} V_1(t) + K(t)D^+ E(t) \quad \text{for } t \geq t_0, \tag{34}$$

$$K(t)D^+ E(t): v(0, t) = D^+ E(t): p(t) = (\gamma - 1): \gamma \quad \text{for } t \geq t_0. \tag{35}$$

If $E(t) \neq 0$, then

$$\frac{1}{E(t)} D^+ E(t) = \frac{(\gamma - 1)w(t_0 - b_n(t))D^+ b_n(t)}{\gamma W(g_0) - (\gamma - 1)W(t_0 - b_n(t))} \tag{36}$$

for $1 \leq n < \zeta, t_{n-1} \leq t < t_n$,

$$\frac{1}{V_1(t)} D^+ V_1(t) = \kappa(t) + \frac{(\gamma - 1)w(t_0 - b_n(t))D^+ b_n(t)}{\gamma W(g_0) - (\gamma - 1)W(t_0 - b_n(t))} \tag{37}$$

for $1 \leq n < \zeta, t_{n-1} \leq t < t_n$.

If $\gamma \neq 1$, then we have

$$v(a, t) = \frac{\gamma}{\gamma - 1} K(t)D^+ E(t - a) \quad \text{for } (a, t) \in \Omega. \tag{38}$$

Proof. (30) is an immediate consequence of (23). (30) is rewritten as (31) in terms of V_1 . (32) is obtained from (25) and (22). The expression (33) is obvious by (J). (33) implies (34). We have, by (32) and (B'),

$$\gamma D^+ E(t) = \gamma p(t) - p(b(t))\beta(t) = (\gamma - 1)p(t),$$

which proves (35) with the aid of (S). (36) and (37) are easy to derive. (38) is shown by (S) and (35). Q.E.D.

PROPOSITION 7. Let $r \geq 1, g \in C^r[t_0, \infty), \kappa \in C^{r-1}[t_0, \infty)$ and $\beta = \gamma Db$. If

- (i) $w \in C^{r-1}(0, g_0]$ and
- (ii) w satisfies (B_i) for $0 \leq i \leq r - 1$,

then $V_1 \in C^r[t_0, \infty)$.

Proof. Since $\beta \in C^{r-1}[t_0, \infty)$, one can apply Proposition 5. Q.E.D.

PROPOSITION 8. Let (g, β, γ, w) satisfy the condition (R). Then the following integral formula holds:

$$(B'') \quad \int_0^h v(a, t + h) da = \gamma \left(\exp \int_t^{t+h} \kappa(\tau) d\tau \right) \int_{g(t+h)-h}^{g(t)} v(a, t) da$$

for $t \geq t_0, 0 \leq h \leq g(t + h)$.

Proof. The left-hand side of (B'') is equal to

$$\int_0^h K(t + h)p(t + h - a) da = K(t + h) \int_t^{t+h} p(\tau) d\tau$$

$$= K(t + h)\{P(t + h) - P(t)\}.$$

On the other hand, the right-hand side of (B'') is equal to

$$\gamma \frac{K(t + h)}{K(t)} \int_{g(t+h)-h}^{g(t)} K(t)p(t - a) da = \gamma K(t + h) \int_{b(t)}^{b(t+h)} p(\tau) d\tau.$$

$$= \gamma K(t + h)\{P(b(t + h)) - P(b(t))\}.$$

Since we have by (24)

$$P(t + h) - \gamma P(b(t + h)) = W(g_0) \quad \text{for } t \geq t_0 \text{ and } h \geq 0,$$

we obtain

$$P(t + h) - P(t) = \gamma \{P(b(t + h)) - P(b(t))\}. \quad \text{Q.E.D.}$$

Proposition 8 shows that the unique solution v of the mixed problem (F) (I) (B) satisfies (B'') under the condition (R). Conversely, we can show that, for any continuous function v on Ω , (B'') implies (B). In fact, the implication is shown for a wider class of v 's:

PROPOSITION 9. Let v be a function defined on Ω and fix a $t \geq t_0$. Assume that, for some $\varepsilon > 0$, v restricted on

$$\{(a, \tau) \in \Omega \mid 0 \leq a \leq \tau - t, t \leq \tau < t + \varepsilon\}$$

is continuous at $(0, t)$ and integrable with respect to a on $(0, \tau - t]$ for each fixed $\tau \in [t, t + \varepsilon)$ and that $v(a, t)$ as a function of a is left-continuous at $a = g(t)$ and integrable on $(0, g(t)]$. Furthermore, we assume that g is right-differentiable at t . Under these assumptions, if v satisfies (B''), then it also satisfies (B).

Proof. For $0 < h < \varepsilon$, we have

$$\left| \frac{1}{h} \int_0^h v(a, t + h) da - v(0, t) \right| \leq \frac{1}{h} \int_0^h |v(a, t + h) - v(0, t)| da.$$

Hence, by the restricted continuity of v at $(0, t)$ as stated above,

$$\lim_{h \downarrow 0} \frac{1}{h} \int_0^h v(a, t + h) da = v(0, t).$$

On the other hand, we have,

$$\begin{aligned} \frac{1}{h} \int_{g(t+h)-h}^{g(t)} v(a, t) da &= \left\{ 1 - \frac{g(t+h) - g(t)}{h} \right\} \\ &\quad \times \frac{1}{g(t) - \{g(t+h) - h\}} \int_{g(t+h)-h}^{g(t)} v(a, t) da. \end{aligned}$$

Since $v(a, t)$ is left-continuous with respect to a at $g(t)$, we have

$$\lim_{h \downarrow 0} \frac{1}{h} \int_{g(t+h)-h}^{g(t)} v(a, t) da = \{1 - D^+ g(t)\} v(g(t), t).$$

We obtain, therefore, by (B'')

$$v(0, t) = \gamma D^+ b(t) \cdot v(g(t), t). \quad \text{Q.E.D.}$$

Remark. In this sense we can say that (B'') is an integral version of the boundary condition (B). Note that, under the condition (R), v defined by (S) satisfies the hypotheses in Proposition 9, by Proposition 2. Thus, under the condition (R), (S) gives also a unique solution of the problem (F) (I) (B'').

2.4 *Inverse problem.* When b, W and γ are given, E is determined by (23). In this section we investigate this correspondence between b, W and E with a parameter γ .

Let b be a strictly increasing continuous function defined on $[t_0, \infty)$ satisfying (3) and (4). The procedure in Sec. 2.1 defines the sequence of numbers $\{t_n\}_{-1 \leq n < \zeta}$ and that of functions $\{b_n\}_{0 \leq n < \zeta}$. Let W be a function defined on $(0, g_0]$ and γ a constant. A function E on $[t_0, \infty)$ is then defined by the formula (23). We denote this relation by $Y(b, W) = E$. E satisfies (26), (27), (29) and (30). If E is strictly increasing and $W(g_0) > 0$, then we have $\gamma > 1$ by (26), because $\{t_n\}$ is strictly increasing. Moreover, if $b_\infty \geq t_0$, then W also is strictly increasing. Conversely, if $\gamma > 1$ and W is strictly increasing, then E is strictly increasing on $[t_{n-1}, t_n)$ for each n such that $1 \leq n < \zeta$. When t_n is finite and the limit $W(0+)$ exists, we have

$$E(t_n -) = \gamma^{n-1} \{ \gamma W(g_0) - (\gamma - 1)W(0+) \}.$$

If we assume $W(0+) \geq 0$ in addition, then E is strictly increasing on the whole interval $[t_0, \infty)$. We have, therefore, proved

PROPOSITION 10. Under the assumptions $b_\infty \geq t_0$ and $W > 0$, the following two conditions are equivalent:

- (i) $\gamma > 1$ and W is strictly increasing,
- (ii) E is strictly increasing.

Furthermore, when the above conditions are satisfied, E is continuous if and only if W is continuous and $W(0+) = 0$.

Next, we consider an inverse problem: we seek a function b such that $Y(b, W) = E$ when W and E are given.

THEOREM 3. Let $g_0 > 0$ and $\gamma > 1$. Suppose that W is a strictly increasing continuous function defined on $(0, g_0]$ satisfying $W(0+) = 0$ and that E is a strictly increasing continuous function defined on $[t_0, \infty)$ satisfying $E(t_0) = W(g_0)$. Then there exists a unique solution b of the equation

$$Y(b, W) = E$$

such that (3) and (4) hold. The unique solution b is given by the formula

$$\begin{aligned} b(t) &= t_0 - W^{-1} \left(\frac{\gamma E(t_0) - E(t)}{\gamma - 1} \right) \quad \text{if } t_0 \leq t < \tilde{t}_1 \\ &= E^{-1} \left(\frac{1}{\gamma} E(t) \right) \quad \text{if } t \geq \tilde{t}_1, \end{aligned} \tag{39}$$

where

$$\tilde{t}_1 \equiv \sup \{ t \in [t_0, \infty) \mid E(t) < \gamma E(t_0) \} (\leq \infty). \tag{40}$$

Proof. We show first that b defined by (39) gives a solution of $Y(b, W) = E$. Noting that, for $t \geq t_0$, $t < \tilde{t}_1$ is equivalent to $E(t) < \gamma E(t_0)$, b given by (39) is a well-defined function on $[t_0, \infty)$ satisfying (3) and (4). It is clear that b is strictly increasing and continuous on both of the intervals $[t_0, \tilde{t}_1)$ and $[\tilde{t}_1, \infty)$. When \tilde{t}_1 is finite, we have

$$\begin{aligned} b(\tilde{t}_1) &= E^{-1} \left(\frac{1}{\gamma} E(\tilde{t}_1) \right) = t_0, \\ b(\tilde{t}_1 -) &= t_0 - W^{-1} \left(\frac{\gamma E(t_0) - E(\tilde{t}_1 -)}{\gamma - 1} \right) = t_0. \end{aligned}$$

b is therefore a strictly increasing continuous function on the whole interval $[t_0, \infty)$. We construct $\{t_n\}_{-1 \leq n < \zeta}$ and $\{b_n\}_{0 \leq n < \zeta}$ by the procedure in Sec. 2.1. We have then by (12)

$$t < t_1 \Leftrightarrow b(t) < t_0 \Leftrightarrow t < \tilde{t}_1.$$

Hence we obtain

$$t_1 = \tilde{t}_1. \quad (41)$$

Next we shall show by mathematical induction on n that

$$E(t_{n-1}) = \gamma^{n-1} E(t_0) \quad \text{for } 1 \leq n < \zeta.$$

It is trivial when $n = 1$. Let $2 \leq n < \zeta$ and suppose that $E(t_{n-2}) = \gamma^{n-2} E(t_0)$. By (12), (41) and the definition of b , $t < t_{n-1}$ if and only if (i) $t < t_1$ or (ii) $t \geq t_1$ and $E^{-1}[(1/\gamma) E(t)] < t_{n-2}$. Hereupon we have

$$E^{-1}\left(\frac{1}{\gamma} E(t)\right) < t_{n-2} \Leftrightarrow E(t) < \gamma E(t_{n-2}) \Leftrightarrow E(t) < \gamma^{n-1} E(t_0)$$

by the induction hypothesis. We therefore obtain

$$E(t_{n-1}) = \gamma^{n-1} E(t_0),$$

which completes the induction. By mathematical induction again, we have

$$b_{n-1}(t) = E^{-1}\left(\frac{1}{\gamma^{n-1}} E(t)\right) \quad \text{for } 1 \leq n < \zeta, t \geq t_{n-1}.$$

Since $t_0 \leq b_{n-1}(t) < t_1$ for $t_{n-1} \leq t < t_n$, we have

$$b_n(t) = b(b_{n-1}(t)) = t_0 - W^{-1}\left(\frac{\gamma E(t_0) - E(b_{n-1}(t))}{\gamma - 1}\right).$$

Hence

$$W(t_0 - b_n(t)) = \frac{1}{\gamma - 1} \left\{ \gamma E(t_0) - \frac{1}{\gamma^{n-1}} E(t) \right\}.$$

We therefore obtain

$$E(t) = \gamma^{n-1} \{ \gamma E(t_0) - (\gamma - 1) W(t_0 - b_n(t)) \} \quad \text{for } 1 \leq n < \zeta, t_{n-1} \leq t < t_n,$$

which is nothing other than the relation $Y(b, W) = E$.

In order to prove the uniqueness of solution of $Y(b, W) = E$, suppose that b is an arbitrary solution of $Y(b, W) = E$. b determines $\{t_n\}_{-1 \leq n < \zeta}$ and $\{b_n\}_{0 \leq n < \zeta}$ by the procedure in Sec. 2.1. We have $E(t) < \gamma E(t_0)$ for $t_0 \leq t < t_1$ by (23). When t_1 is finite, $E(t_1) = \gamma E(t_0)$. Hence for $t \geq t_0$

$$t < t_1 \Leftrightarrow E(t) < \gamma E(t_0) \Leftrightarrow t < \tilde{t}_1.$$

This equivalence shows $t_1 = \tilde{t}_1$. We have, then,

$$E(t) = \gamma W(t_0 - b(t)) - (\gamma - 1) W(t_0 - b(t)) \quad \text{for } t_0 \leq t < \tilde{t}_1.$$

Hence

$$b(t) = t_0 - W^{-1} \left(\frac{\gamma E(t_0) - E(t)}{\gamma - 1} \right) \quad \text{if } t_0 \leq t < \tilde{t}_1.$$

We have by (30)

$$b(t) = E^{-1} \left(\frac{1}{\gamma} E(t) \right) \quad \text{if } t \geq \tilde{t}_1. \quad \text{Q.E.D.}$$

Remark 1. (41) shows that \tilde{t}_1 defined by (40) equals t_1 determined by b through the procedure in 2.1.

Remark 2. Since g and w correspond one-to-one to b and W , respectively, we can consider the equation

$$\tilde{Y}(g, w) = E$$

similarly as $Y(b, W) = E$ and obtain results parallel to those of Theorem 3.

3. Application to microbial population dynamics.

3.1. Main results in application of the abstract theory. We shall apply the theory in Sec. 2 to the analysis of microbial growth in a batch culture.

Let t and a represent time and cell age, respectively. The age of a cell is defined as the time having elapsed since the last division of the cell.

Generation time.

Assumption I. At any time t there exists a maximum value $g(t)$ of the cell ages in the culture. Each of the cells whose age has reached $g(t)$ at time t divides into two equal sister cells. The other cells do not divide at time t . $g(t)$ satisfies the condition (1).

In the period of steady growth, $g(t)$ does not depend upon t , being equal to the time length between two successive divisions of a cell, that is, generation time. Indeed, $g(t)$ defined in Assumption I is a generalization of generation time into the case in which generation time varies with the time. Assumption I means that all the cells in the culture have the same generalized generation time $g(t)$ at time t . (In this paper we shall simply call $g(t)$ generation time at time t .)

From the definition of $g(t)$, $g(t') - g(t) \leq t' - t$ for $t_0 \leq t < t'$, where t_0 is the initial time. Without the condition (1) in Sec. 2, it would be possible that the increase in generation time would be equal to the lapse of time during the time interval $[t, t']$, i.e., $g(\tau) = \tau + \text{const.}$ ($t \leq \tau \leq t'$). In such a period there would be no cell whose age newly reaches $g(\tau)$, and, accordingly, no cell division would occur (cf. boundary condition (B)). We assume (1) as we treat, for the present, only the period at each instant of which more or less cell divisions do occur.

M'Kendrick-Von Foerster equation. The number of viable cells of age a between a_1 and a_2 at time t is expressed in terms of the density function $u(a, t)$ of viable cell number with respect to a at time t as

$$\int_{a_1}^{a_2} u(a, t) da.$$

Assumption II. At any time t , all the viable cells of age a have the same biomass $m(a, t)$.

$u(a, t)$ and $m(a, t)$ are defined on Ω (cf. (2)) and supposed to be characteristically differentiable (cf. Sec. 2.1.). This supposition is reasonable so far as there is no drastic environmental change in the culture, because the growth trajectory of a cell is represented by a characteristic line in the (a, t) -plane. The quantity

$$-\frac{1}{u(a, t)} D_c u(a, t)$$

is the decreasing rate per unit time of number of the cells of age a at time t . In most cases it is a function of a, t and $u(a, t)$. We denote the function by $\lambda(a, t, u(a, t))$ and call it the "loss function". Then u satisfies the M'Kendrick-Von Foerster equation

$$(F_u) \quad D_c u = -\lambda u \quad \text{on } \Omega.$$

In the case of batch culture, λ becomes death rate per unit time, because there is no decrease (or increase) by migration in cell number. As the increase and the decrease in cell number caused by cell division occur only at $a = 0$ and $a = g(t)$, respectively, they will be formulated as a boundary condition later. The expression

$$\frac{1}{m(a, t)} D_c m(a, t)$$

represents the biomass growth rate per unit time of a cell of age a at time t . In most cases it is a function of a, t and $m(a, t)$ (Moreover, it may seem very probable that the biomass growth rate depends also on $u(a, t)$. In the present paper, however, we assume that it is independent of $u(a, t)$.) We denote the function by $\mu(a, t, m(a, t))$ and call it the "individual growth function". Then m satisfies the M'Kendrick-Von Foerster equation

$$(F_m) \quad D_c m = \mu m \quad \text{on } \Omega.$$

Assumption III. λ and μ are functions of only one variable t .

The integral $\int_{a_1}^{a_2} m(a, t)u(a, t) da$ represents the total mass of the viable cells of age a between a_1 and a_2 at time t . As we have

$$\begin{aligned} & \frac{1}{m(a, t)u(a, t)} D_c \{m(a, t)u(a, t)\} \\ &= \frac{1}{m(a, t)} D_c m(a, t) + \frac{1}{u(a, t)} D_c u(a, t) \\ &= \mu(a, t, m(a, t)) - \lambda(a, t, u(a, t)), \end{aligned}$$

mu also satisfies the M'Kendrick-Von Foerster equation

$$(F_{mu}) \quad D_c(mu) = (\mu - \lambda)mu \quad \text{on } \Omega$$

under Assumption III.

Boundary condition. Let $(a, t) \in \Omega$ and h be a positive number such that $(a + h, t + h) \in \Omega$. Then

$$(F_u') \quad u(a + h, t + h) = u(a, t) \exp \left\{ - \int_t^{t+h} \lambda(\tau) dt \right\}.$$

This is an integral version of the equation (F_u). The cells which divide during the time interval $[t, t + h)$ are those which have at time t the age a such that $g(t + h) - h < a \leq g(t)$ and survive until their time of division. We divide $[t, t + h)$ into sufficiently small intervals $[\tau_{j-1}, \tau_j)$ ($j = 1, \dots, n; \tau_0 = t, \tau_n = t + h$) and write an arbitrary point of $[\tau_{j-1}, \tau_j)$ as s_j . Denoting the ages at time t of the cells dividing at the times τ_{j-1} and τ_j by a_{j-1} and a_j , respectively (Fig. 1), we consider the cells having at time t the age a such that $a_j < a \leq a_{j-1}$. Their number is expressed as

$$\int_{a_j}^{a_{j-1}} u(a, t) da.$$

The number of the cells which survive till s_j is

$$\int_{a_j + s_j - t}^{a_{j-1} + s_j - t} u(a, s_j) da.$$

It becomes

$$\int_{a_j}^{a_{j-1}} u(a + s_j - t, t + s_j - t) da$$

by change of variable of integration from a to $a - (s_j - t)$. It is equal to

$$\int_{a_j}^{a_{j-1}} u(a, t) da \cdot \exp\left\{-\int_t^{s_j} \lambda(\tau) d\tau\right\}$$

by the equation (F_u'). This number doubles by the division at time s_j , and the number of the cells which survive till $t + h$ is

$$\begin{aligned} 2 \int_{a_j}^{a_{j-1}} u(a, t) da \cdot \exp\left\{-\int_t^{s_j} \lambda(\tau) d\tau\right\} \cdot \exp\left\{-\int_{s_j}^{t+h} \lambda(\tau) d\tau\right\} \\ = 2 \int_{a_j}^{a_{j-1}} u(a, t) da \cdot \exp\left\{-\int_t^{t+h} \lambda(\tau) d\tau\right\}. \end{aligned}$$

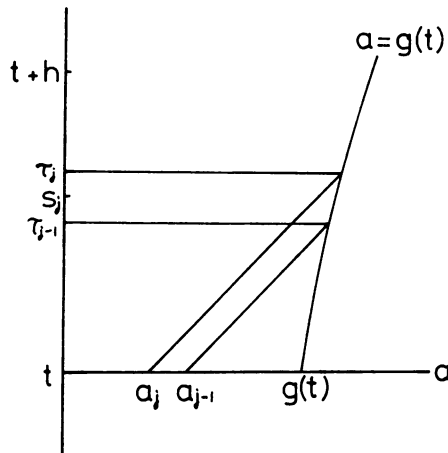


FIG. 1. Relation between the time of division of a cell and its cell age at t .

Summing up with regard to all the cells having at time t the age a such that $g(t+h) - h < a \leq g(t)$, we get

$$2 \sum_{j=1}^n \int_{a_j}^{a_{j-1}} u(a, t) da \cdot \exp \left\{ - \int_t^{t+h} \lambda(\tau) d\tau \right\} \\ = 2 \int_{g(t+h)-h}^{g(t)} u(a, t) da \cdot \exp \left\{ - \int_t^{t+h} \lambda(\tau) d\tau \right\}.$$

As this is the number of the viable cells of age a between 0 and h at time $t+h$, we get the following equation:

$$\int_0^h u(a, t+h) da = 2 \int_{g(t+h)-h}^{g(t)} u(a, t) da \cdot \exp \left\{ - \int_t^{t+h} \lambda(\tau) d\tau \right\}.$$

This is the integral version (B'') of the boundary condition (B) in the case in which $v = u$, $\gamma = 2$ and $\kappa = -\lambda$ (cf. Sec. 2.3). Supposing that $g(t)$ is right-differentiable and $u(a, t)$ satisfies the hypotheses of Proposition 9, we get the boundary condition:

$$(B_u) \quad u(0, t) = 2\{1 - D^+g(t)\}u(g(t), t) \\ = 2D^+b(t) \cdot u(g(t), t) \quad \text{for } t \geq t_0$$

applying Proposition 9. It follows from this derivation that the point $(0, t)$ in the (a, t) -plane belongs rather to the infinitesimal future of t than to t itself. If $g(t)$ were supposed to be of class C^1 , $V_1(t)$ (corresponding to $N_1(t)$ or $M_1(t)$ in this section, cf. Table I) would also be of class C^1 , by Proposition 7, under the assumption that $w(a)$ (corresponding to $\phi(a)$ or $\psi(a)\phi(a)$ in this section) is continuous on $(0, g_0]$ and satisfies (B_0). Hence, it would follow that observed functions $N_1(t)$ and/or $M_1(t)$ not belonging to the class C^1 could not be treated in the theory. In practice, however, such data do exist, at least within the range of precision of experiment (e.g., [6]). We have shown in Sec. 2 that such data can also be treated in the theory if we loosen the restriction on $g(t)$ and only suppose that it is a right-differentiable continuous function whose right derivative is right-continuous.

The biomass of a cell with age $g(t)$ at time t is $m(g(t), t)$. From Assumption I, such a cell divides into two equal sister cells of age 0 and we get the boundary condition:

$$(B_m) \quad m(0, t) = \frac{1}{2} m(g(t), t) \quad \text{for } t \geq t_0.$$

The boundary condition for the function $m(a, t)u(a, t)$ is, each side of (B_u) being multiplied by the corresponding side of (B_m),

$$(B_{mu}) \quad m(0, t)u(0, t) = D^+b(t) \cdot m(g(t), t)u(g(t), t) \quad \text{for } t \geq t_0.$$

Initial condition.

$$(I_u) \quad u(a, t_0) = \phi(a),$$

$$(I_m) \quad m(a, t_0) = \psi(a),$$

$$(I_{mu}) \quad m(a, t_0)u(a, t_0) = \psi(a)\phi(a) \quad \text{for } 0 < a \leq g_0 = g(t_0).$$

As stated above in the derivation of the boundary condition (B_u) , $(0, t_0)$ is considered a point belonging to the infinitesimal future of t_0 , and so $a = 0$ is omitted from the range of a in the initial condition. Since u and mu are density functions, a point in the range of variable may be omitted when one considers their integrals. If 0 were included in the range of a , then we would have from (I_u) and (I_m) ,

$$\phi(0) = u(0, t_0) = 2D^+ b(t_0) \cdot u(g_0, t_0) = 2D^+ b(t_0) \cdot \phi(g_0),$$

$$\psi(0) = m(0, t_0) = \frac{1}{2} m(g_0, t_0) = \frac{1}{2} \psi(g_0).$$

$\phi(a)$ and $\psi(a)$ could therefore no longer be arbitrary functions. These conditions for ϕ and ψ are no other than the boundary condition (B_0) in the corollary to Proposition 4, which assures the continuity of the solutions u and m . If only a point $a = 0$ is omitted, any function can be taken for $\psi(a)$. As for $\phi(a)$, we assume only the following.

Assumption IV. For any a_1 and a_2 such that $0 \leq a_1 < a_2 \leq g_0$, the integral

$$\int_{a_1}^{a_2} \phi(a) da$$

is positive.

Solution of the mixed problems. From the forms of the partial differential equations (F_u) , (F_m) and (F_{mu}) , the boundary conditions (B_u) , (B_m) and (B_{mu}) , and the initial conditions (I_u) , (I_m) and (I_{mu}) which u , m and mu satisfy, respectively, it is clear that Theorem 1 can be applied to these mixed problems $(F_*) (I_*) (B_*)$ ($*$ = u , m or mu). The correspondence of the notations involved in the application of Theorems 1 and/or 2 to each of these cases is shown in Table I. γ corresponds to the ratio of the quantity in question after a cell division to that before the division. Treating division into two equal sister cells, we must choose $\gamma = 2$ for u and $\gamma = 1$ for mu . The theory in Sec. 2 can be applied to the cases in which some other values must be taken for γ .

Thus, the assumptions and conclusions in the application of Theorem 1 to these cases are summarized as follows:

Assumptions:

g is a positive, continuous and right-differentiable function defined on $[t_0, \infty)$ such that

$$t_0 \leq t < t' \Rightarrow g(t') - g(t) < t' - t,$$

λ and μ are real-valued continuous functions defined on $[t_0, \infty)$,

ϕ is a real-valued integrable function on $(0, g_0]$ which conforms to Assumption IV,

ψ is an arbitrary real-valued function defined on $(0, g_0]$.

TABLE I. Correspondence of the notations involved in the application.

v	κ	β	γ	w	W	E	V_1	σ	C_0	V_2	V
u	$-\lambda$	$2D^+ b$	2	ϕ	Φ	E_u	N_1	λ	$N_2(t_0)$	N_2	N
m	μ	$\frac{1}{2}$		ψ							
mu	$\mu - \lambda$	$D^+ b$	1	$\psi\phi$	Ψ	E_{mu}	M_1	λ	$M_2(t_0)$	M_2	M

Conclusions:

For $(a, t) \in \Omega_n (0 \leq n < \zeta)$ (cf. (2), (6) and Fig. 2),

$$(S_u) \quad u(a, t) = 2^n D^+ b_n(t - a) \cdot \phi(t_0 - b_n(t - a)) \exp \left\{ - \int_{t_0}^t \lambda(\tau) d\tau \right\}$$

$$(S_m) \quad m(a, t) = \frac{1}{2^n} \psi(t_0 - b_n(t - a)) \exp \int_{t_0}^t \mu(\tau) d\tau.$$

Under Assumption IV, we have

$$\phi(a) \geq 0 \quad \text{almost everywhere.}$$

For λ, μ and ψ , we are obliged to choose only non-negative functions from the biological viewpoint.

Integrals and related formulas. Now we shall derive integral formulas of u and mu by applying Theorem 2. If $\phi(a)$ and $\psi(a)\phi(a)$ are left-continuous and integrable on $(0, g_0]$, and $D^+ g(t)$ is right-continuous, it is clear from Theorem 2 that $u(a, t)$ and $m(a, t)u(a, t)$ are integrable with respect to a on $(0, g(t)]$ for any fixed $t \geq t_0$. Before we proceed to integral

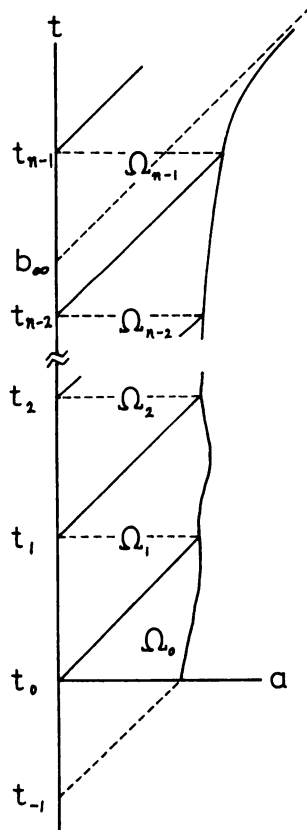


FIG. 2. The domain Ω as the disjoint union of $\{\Omega_n\}_{0 \leq n < \zeta}$ (cf. (6) and (7)) (a case in which $b_\infty < t_{n-1} < \infty$).

formulas, a remark must be made on a property of the solution $u(a, t)$. Since Assumption I says that $g(t)$ is defined as the maximum cell age in the culture, the solution $u(a, t)$ must satisfy

$$(L) \quad \int_{g(t)-\varepsilon}^{g(t)} u(a, t) da > 0$$

for any t and ε such that $t \geq t_0$, $0 < \varepsilon < g(t)$. Under Assumption IV the unique solution of the mixed problem (F_u) (I_u) (B_u) satisfies (L).

The total number $N_1(t)$ and the total biomass $M_1(t)$ of the viable cells at time t are given by

$$N_1(t) = \int_0^{g(t)} u(a, t) da, \quad M_1(t) = \int_0^{g(t)} m(a, t)u(a, t) da.$$

Putting

$$\Phi(a) \equiv \int_0^a \phi(\xi)d\xi \tag{42}$$

and

$$\Psi(a) \equiv \int_0^a \psi(\xi)\phi(\xi)d\xi, \tag{43}$$

for $0 < a \leq g_0$, we get from (28)

$$N_1(t_0) = \Phi(g_0), \quad M_1(t_0) = \Psi(g_0).$$

If we put $\gamma = 2$ and $W = \Phi$ in (23), $E(t)$ becomes

$$E_u(t) = 2^{n-1}\{2\Phi(g_0) - \Phi(t_0 - b_n(t))\} \quad \text{for } 1 \leq n < \zeta, t_{n-1} \leq t < t_n.$$

If we put $\gamma = 1$ and $W = \Psi$ in (23), $E(t)$ becomes

$$E_{mu}(t) = \Psi(g_0) \quad \text{for } t \geq t_0.$$

The expression (J) in Theorem 2 implies

$$(J_u) \quad N_1(t) = E_u(t)\exp\left\{-\int_{t_0}^t \lambda(\tau) d\tau\right\}$$

$$= 2^{n-1}\{2\Phi(g_0) - \Phi(t_0 - b_n(t))\}\exp\left\{-\int_{t_0}^t \lambda(\tau) d\tau\right\} \quad \text{for } t_{n-1} \leq t < t_n,$$

$$(J_{mu}) \quad M_1(t) = \Psi(g_0)\exp\int_{t_0}^t \{\mu(\tau) - \lambda(\tau)\}d\tau \quad \text{for } t \geq t_0.$$

From the formula (31),

$$N_1(t) = 2N_1(b(t))\exp\left\{-\int_{b(t)}^t \lambda(\tau) d\tau\right\},$$

$$M_1(t) = M_1(b(t))\exp\int_{b(t)}^t \{\mu(\tau) - \lambda(\tau)\}d\tau$$

for $t \geq t_1$. From the formula (37),

$$\frac{1}{N_1(t)} D^+ N_1(t) = \frac{\phi(t_0 - b_n(t)) D^+ b_n(t)}{2\Phi(g_0) - \Phi(t_0 - b_n(t))} - \lambda(t)$$

for $1 \leq n < \zeta, t_{n-1} \leq t < t_n$,

$$\frac{1}{M_1(t)} D^+ M_1(t) = \mu(t) - \lambda(t) \quad \text{for } t \geq t_0. \quad (44)$$

Suppose that $r \geq 1, g \in C^r[t_0, \infty)$ and $\lambda, \mu \in C^{r-1}[t_0, \infty)$. If (i) $\phi, \psi \in C^{r-1}(0, g_0]$ and (ii) ϕ and $\psi\phi$ satisfy (B_i) ($0 \leq i \leq r-1$), then we have by Proposition 7

$$N_1, M_1 \in C^r[t_0, \infty).$$

From the relation (38), u is written in terms of λ and E_u as follows:

$$u(a, t) = 2D^+ E_u(t - a) \cdot \exp\left\{-\int_{t_0}^t \lambda(\tau) d\tau\right\} \quad \text{for } (a, t) \in \Omega. \quad (45)$$

We consider the number $N_2(t)$ and the biomass $M_2(t)$ of all the dead cells in the culture at time t . In the definition of $V_2(t)$ in Sec. 2.3, if we put $C_0 = N_2(t_0)$, $\sigma(t) = \lambda(t)$ and $V_1(t) = N_1(t)$, then $V_2(t)$ becomes $N_2(t)$, and if we put $C_0 = M_2(t_0)$, $\sigma(t) = \lambda(t)$ and $V_1(t) = M_1(t)$, then $V_2(t)$ becomes $M_2(t)$. Hence we have

$$DN_2(t) = \lambda(t)N_1(t), \quad DM_2(t) = \lambda(t)M_1(t). \quad (46)$$

The total number and biomass of the cells are

$$N(t) = N_1(t) + N_2(t), \quad (47)$$

$$M(t) = M_1(t) + M_2(t), \quad (48)$$

respectively. Their right derivatives are

$$D^+ N(t) = D^+ N_1(t) + \lambda(t)N_1(t)$$

$$D^+ M(t) = D^+ M_1(t) + \lambda(t)M_1(t).$$

From the relations (32), (34) and (35), we get

$$D^+ N(t) = 2^{n-1} D^+ b_n(t) \cdot \phi(t_0 - b_n(t)) \exp\left\{-\int_{t_0}^t \lambda(\tau) d\tau\right\} = \frac{1}{2} u(0, t),$$

$$D^+ M(t) = \Psi(g_0) \mu(t) \exp\int_{t_0}^t \{\mu(\tau) - \lambda(\tau)\} d\tau. \quad (49)$$

3.2 A method to determine the functions in Sec. 3.1 from experimental data. We can perform the calculations to obtain the microbiological quantities in Sec. 3.1 from observed data. As the optical density of a cell suspension for the light of an appropriate wavelength is proportional to the biomass of the cells in unit volume, we can get $M(t)$ from the optical density measurement. $N(t)$ is given by direct counting of the cells by means of a counting chamber. $N_1(t)$ can be obtained from viable count. In some cases, $N(t), N_1(t)$ and $N_2(t)$ are obtained simultaneously by counting after staining with methylene blue. Assuming that the

initial functions $\phi(a)$ and $\psi(a)$ are known and that $M(t)$, $N(t)$ and $N_1(t)$ are observed for $t \geq t_0$, we can calculate $M_1(t)$, $M_2(t)$, $N_2(t)$, $\lambda(t)$, $\mu(t)$, $g(t)$, $u(a, t)$ and $m(a, t)$ by the following procedure. (For the case in which $\phi(a)$ and $\psi(a)$ are the theoretical functions in logarithmic phase and $\lambda = 0$, we calculated, in [1], μ , $g(t)$, $u(a, t)$ and $m(a, t)$ for $t_0 \leq t < t_1$ from the observed data [6] of $M(t)$ and $N(t)$.)

We get $N_2(t)$ from $N(t)$ and $N_1(t)$ by (47) and obtain $\lambda(t)$ from (46). (J_u) implies

$$E_u(t) = N_1(t) \exp \int_{t_0}^t \lambda(\tau) d\tau. \tag{50}$$

Thus $E_u(t)$ can be calculated from the observed data. Then $u(a, t)$ is obtained from (45). From Theorem 3, we have for $t \geq t_0$,

$$\begin{aligned} b(t) &= t_0 - \Phi^{-1}(2E_u(t_0) - E_u(t)) & (t < \tilde{t}_1) \\ &= E_u^{-1}(E_u(t)/2) & (t \geq \tilde{t}_1), \end{aligned} \tag{51}$$

where

$$\tilde{t}_1 = \sup\{t \in [t_0, \infty) \mid E_u(t) < 2E_u(t_0)\}.$$

$g(t)$ is obtained from $b(t)$. $b_n(t)$ is the n -fold composite function of $b(t)$. From (49),

$$D^+ M(t) \cdot \exp \int_{t_0}^t \lambda(\tau) d\tau = \Psi(g_0)\mu(t) \exp \int_{t_0}^t \mu(\tau) d\tau.$$

Integrating, we get

$$\begin{aligned} \int_{t_0}^t D^+ M(s) \cdot \left\{ \exp \int_{t_0}^s \lambda(\tau) d\tau \right\} ds &= \Psi(g_0) \int_{t_0}^t \mu(s) \left\{ \exp \int_{t_0}^s \mu(\tau) d\tau \right\} ds \\ &= \Psi(g_0) \left\{ \left(\exp \int_{t_0}^t \mu(\tau) d\tau \right) - 1 \right\} = M_1(t) \left\{ \exp \int_{t_0}^t \lambda(\tau) d\tau \right\} - \Psi(g_0) \quad (\text{by } (J_{mu})). \end{aligned}$$

Hence we obtain $M_1(t)$ from $M(t)$ by the following formula:

$$M_1(t) = \left[\Psi(g_0) + \int_{t_0}^t D^+ M(s) \cdot \left\{ \exp \int_{t_0}^s \lambda(\tau) d\tau \right\} ds \right] \exp \left\{ - \int_{t_0}^t \lambda(\tau) d\tau \right\}. \tag{52}$$

Then $\mu(t)$ is calculated from (44). Further, we get $M_2(t)$ from $M(t)$ and $M_1(t)$ by (48). $m(a, t)$ is calculated from b_n , ψ and μ through the use of (S_m) . Fig. 3 shows a scheme of the calculation.

When the density function of the cell number with respect to cellular volume is observable by means of a Coulter counter, one can check our theory by combining this density function with $u(a, t)$. Moreover, if cellular volume and cellular biomass have one-to-one correspondence,⁵ the density function of the cell number with respect to cellular biomass m at each instant will be known. It represents, however, the sum of the density functions of the

⁵ It is, for example, very probable that cellular biomass is approximately proportional to cellular volume.

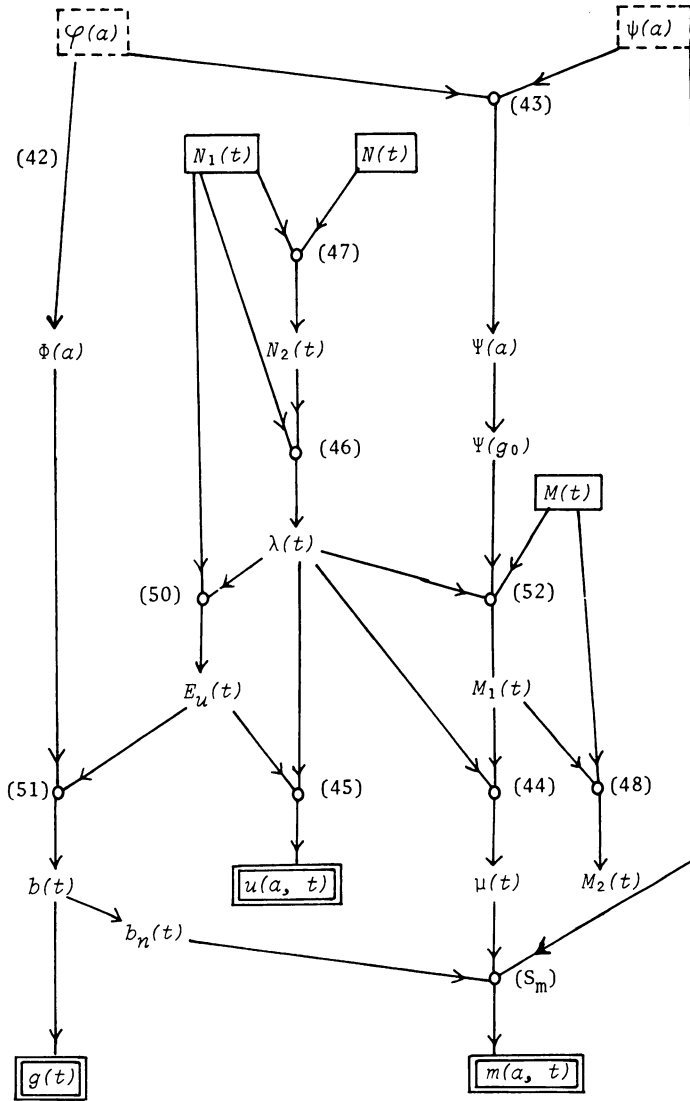


FIG. 3. A scheme for calculating the microbiological quantities in the text from experimental data. $\varphi(a)$: quantities assumed known at the initial time t_0 ; $N(t)$: data observed for $t \geq t_0$; $u(a, t)$: main microbiological quantities to be obtained through calculation; () : number of equation used for calculation.

viable and the dead cells, as the Coulter counter cannot distinguish the former from the latter. We write the density function at time t as $q(m, t)$. The similar functions for the viable and the dead cells are also written as $q_1(m, t)$ and $q_2(m, t)$, respectively. Then

$$q(m, t) = q_1(m, t) + q_2(m, t). \tag{53}$$

As $\lambda(t)$ is the death rate per unit time, the density function $q_1(m, t)$ of the number of the viable cells multiplied by $\lambda(t)$ is equal to the increasing rate of the density function $q_2(m, t)$ of

the number of the dead cells. Thus

$$\begin{aligned} \frac{\partial}{\partial t} q_2(m, t) &= \lambda(t)q_1(m, t), \\ \frac{\partial^+}{\partial t} q(m, t) &= \frac{\partial^+}{\partial t} q_1(m, t) + \lambda(t)q_1(m, t). \end{aligned}$$

If $q_1(m, t)$ is a continuous right-differentiable function of t for any fixed m and $q(m, t)$ is a continuous monotone increasing right-differentiable function of t for any fixed m such that $(\partial^+/\partial t)q(m, t)$ is right-continuous with respect to t , then we have

$$q_1(m, t) = \left[q_1(m, t_0) + \int_{t_0}^t \frac{\partial^+}{\partial s} q(m, s) \cdot \left\{ \exp \int_{t_0}^s \lambda(\tau) d\tau \right\} ds \right] \cdot \exp \left\{ - \int_{t_0}^t \lambda(\tau) d\tau \right\} \quad (54)$$

by Lemmas 1 and 2. Supposing that $m(a, t)$ is a strictly increasing absolutely continuous function of a at any fixed time $t \geq t_0$ and that $q_1(m, t)$ is locally integrable with respect to m , we have

$$\begin{aligned} \int_{a_1}^{a_2} u(a, t) da &= \int_{m(a_1, t)}^{m(a_2, t)} q_1(m, t) dm \\ &= \int_{a_1}^{a_2} q_1(m(a, t), t) \frac{\partial}{\partial a} m(a, t) da \end{aligned}$$

where $(\partial/\partial a)m(a, t)$ denotes the partial derivative of $m(a, t)$ with respect to a for almost all $a \in [a_1, a_2]$. So we obtain

$$u(a, t) = q_1(m(a, t), t) \frac{\partial}{\partial a} m(a, t) \quad (55)$$

for almost all a . If $\phi(a)$ and $q_1(m, t_0)$ are left-continuous with respect to a and m , respectively, and $\psi(a)$ is a left-differentiable function such that $D^- \psi(a)$ is left-continuous, then we have, putting $t = t_0$ in (55),

$$\phi(a) = q_1(\psi(a), t_0) D^- \psi(a) \quad (56)$$

for all a . Since $q_1(m, t_0)$ is locally integrable, (56) is written as

$$\phi(a) = \frac{d^-}{da} \{ Q_1(\psi(a)) \},$$

where

$$Q_1(m) \equiv \int_{\psi(0^+)}^m q_1(m', t_0) dm'.$$

Thus, if $\psi(a)$ is continuous, we get

$$\Phi(a) = Q_1(\psi(a)) \quad \text{for } 0 < a \leq g_0.$$

Hence,

$$\psi(a) = Q_1^{-1}(\Phi(a))$$

provided that Q_1 is strictly increasing. Hence, if $q_1(m, t_0)$ is known, each of $\phi(a)$ and $\psi(a)$ can be calculated from the other. When $q_1(m, t_0)$ is known and $q(m, t)$ is observable for $t \geq t_0$, $q_1(m, t)$ can be calculated by means of (54). Then one can convert it into $u(a, t)$ by (55), using $m(a, t)$ previously calculated from the data (i.e., known $\phi(a)$, $\psi(a)$ and observed $M(t)$, $N(t)$, $N_1(t)$). The result may be compared with previously obtained $u(a, t)$ in order to check the theory. A scheme of the calculation is shown in Fig. 4.

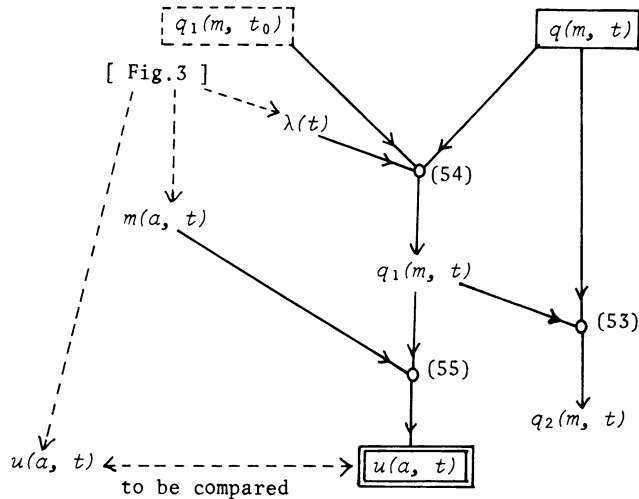


FIG. 4. A scheme for calculating $u(a, t)$ from $m(a, t)$, $\lambda(t)$ and data observed by a Coulter counter. Legend as in Fig. 3.

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