

Cellular Population Dynamics.

I. Model Construction and Reformulation*

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ABSTRACT

A mathematical model of the proliferation cycle of leukemic cells is presented, based on a description in terms of stochastic point processes. The expected-value equations are integral equations of the Volterra (renewal) type. Their equivalence with a class of functional differential equations is proved.

0. INTRODUCTION

In the paper a mathematical model of cell proliferation dynamics is presented. Section 1 contains notions and results from the theory of stochastic point processes. In Sec. 2 the integral equations of growth dynamics are derived. In Sec. 3 a theorem is proved which shows that the growth equations can be replaced by certain functional differential equations. An investigation of the solutions of growth equations and some other problems are described in Part II of the paper.

1. STOCHASTIC POINT PROCESSES

In this section, the notation follows that used in the survey paper [4]. A stochastic point process (SPP) is a randomly located population or a random sequence of events in time [4, p.301]. For an exact definition some notions from measure theory are necessary. Namely, let $\mathcal{N}$ be the space of all nonnegative integer-valued measures $N(\cdot)$ defined on the σ -algebra $\mathfrak{B}(R)$ of all Borel sets of the real line R . Further let $N(A) < +\infty$ for all bounded $A \in \mathfrak{B}$, and let S be the σ -algebra generated by cylinders:

$$\{N : N(A) \leq k\} \quad (k = 0, 1, \dots, \quad A \in \mathfrak{B}). \quad (1.1)$$

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DEFINITION 1.1 [4, p. 304]

A SPP is a measurable mapping X from a probability space $(\Omega, \mathcal{A}, \mathcal{P})$ into $(\mathcal{U}, \mathcal{S})$.

Remark 1.1. The probability measure P in $(\mathcal{U}, \mathcal{S})$ is induced by X , i.e. $P = \mathcal{P}(X^{-1})$ [1].

Remark 1.2. Consider [4, p. 308] a family Ω of sequences $\omega = \{x_n\}$, $n \in Z = \{0, \pm 1, \pm 2, \dots\}$. Each x_n is treated as an "event." Then the mapping

$$N(A, \omega) \equiv \text{card}\{n : x_n \in \omega \cap A\} \quad (\omega \in \Omega, A \in \mathfrak{B}), \quad (1.2)$$

where $\text{card } C$ is the cardinality of the set C , is one-one from Ω into $\mathcal{U}$. It is possible to introduce in Ω a σ -algebra F in a way that [4, p. 309] any probability measure $\mathcal{P}$ on (Ω, F) defines a SPP. Moreover, one can prove that SPP understood as a sequence of events and SPP understood as measure-valued mapping are equivalent notions.

DEFINITION 1.2

The process $N_t \equiv N([t_0, t])$, where t_0 is a fixed point of the real line, is called the counting process of the SPP.

Remark 1.3. N_t is the number of events in $[t_0, t]$.

DEFINITION 1.3

The expectation measure (EM) $M(A)$ of the SPP is defined [4, p. 318] as

$$M(A) = E[N(A)] = \int_{\Omega} N(A, \omega) \mathcal{P}(d\omega) \quad (A \in \mathfrak{B}). \quad (1.3)$$

DEFINITION 1.4

If the EM $M(\cdot)$ is absolutely continuous with respect to the Lebesgue measure, then the expected density (ED) of a SPP is a locally integrable function $m(t)$ such that

$$M(A) = \int_A m(t) dt, \quad (A \in \mathfrak{B}) \quad (1.4)$$

or more simply,

$$M(dt) = m(t) dt. \quad (1.5)$$

DEFINITION 1.5 [4, p. 344]

A randomly shifted SPP X^s is a SPP constructed from the given SPP X so that

$$x_n^s = x_n + Y_n, \quad (1.6)$$

where $\{Y_n\}$ is a family of independent identically distributed random variables independent of $\{x_n\}$.

Remark 1.4. If $B(y) = \text{prob}(Y_n \leq y)$ and there exists a density $b = dB/dt$, then for the EM M^s of the SPP X^s it holds [4, p. 343] that

$$M^s(A) = \int_A \left[\int_R b(t-u) M(du) \right] dt \quad (1.7)$$

and the ED $m^s(t)$ exists. Furthermore, if the ED $m(t)$ of the SPP X exists,

$$m^s(t) = m(t) * b(t), \quad (1.8)$$

where the asterisk denotes convolution.

DEFINITION 1.6 [4, p. 344]

The randomly deleted SPP X^d is a SPP constructed from the SPP X so that with given probability p each event x_n is retained (independently of all other events) and with probability $1-p$ it is omitted.

Remark 1.5. For the EM of the SPP X^d it holds that

$$M^d(dt) = pM(dt), \quad (1.9)$$

and if the ED $m(t)$ exists,

$$m^d(t) = pm(t). \quad (1.10)$$

DEFINITION 1.7

The sum of the SPPs X^1 and X^2 is a SPP including events of X^1 as well as of X^2 .

Remark 1.6. For the EM of the sum of SPPs it holds that

$$M(dt) = M^1(dt) + M^2(dt), \quad (1.11)$$

and similarly for the EDs (if they exist):

$$m(t) = m^1(t) + m^2(t). \quad (1.12)$$

We now construct a simple SPP F which will be useful in further considerations. Let the number of events be finite and equal L . Each event occurs (independently) in the time interval $[t, t + dt]$ with probability $f(t)dt$. We assume $\text{supp}(f) \subset [0, h)$ for some $h > 0$, where the support of f is defined as

$$\text{supp}(f) = \overline{\{t: f(t) \neq 0\}}$$

and the bar denotes the closure of a set.

LEMMA 1.1

The EM and ED of an SPP F are given by the formulae

$$M(A) = L \int_A f(t) dt, \quad (1.13)$$

$$m(t) = Lf(t). \quad (1.14)$$

The easy proof, based on the use of Definitions 1.3 and 1.4, is omitted.

2. CONSTRUCTION OF THE MODEL

The basis on which the mathematical model is built is a structural representation of the proliferation cycle of acute lymphoblastic leukemia, due to Mauer and Evert [5, 6, 10]. Similar principles lead to the construction of more sophisticated models (see Part II). Figure 1 shows the route of each cell through the cycle. Circles denote phases of cell development; the most important are: 1, DNA synthesis (S); 3, mitosis (M); 4, resting or inactive phase (G0); 5, initial growth (G1). Phase 0 symbolizes death of the cell. Possible transfers are denoted with arrows. After leaving phase 5 each cell enters and leaves phases 1, 2, 3. In phase 3 the cell undergoes division, and each of the two daughter cells enters phase 0, 4, or 5 with probabilities m_0 ,

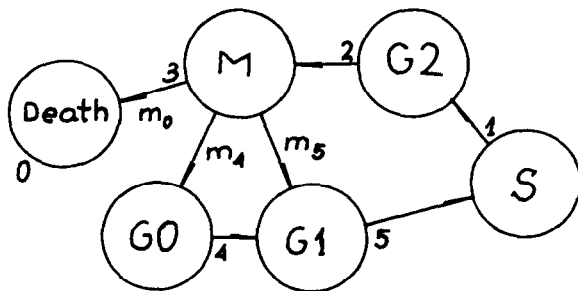


FIG. 1. Mitotic cycle of acute lymphoblastic leukemia cells. Details in text.

m_4 , m_5 respectively. From phase 4 the cell always passes to phase 5. The time spent by each cell in the i th phase is a random variable τ with given density $p_i(\tau)$. For reasons that will be clear in the sequel, the starting time for the model is chosen to be $t_0 = -2h$ (for some yet unspecified constant $h > 0$). The history of the cycle is characterized by the number N_i^0 of cells in the i th phase at $t_0 = -2h$ together with the initial distributions (ID). The ID describes the random time after which a cell occupying the i th phase at $t_0 = -2h$ leaves it (independently of all other cells). It is assumed that density $f_i(t)$ of random variable t distribution exists.

The cycle so defined is easy to simulate with the aid of various discrete simulation techniques [5, 6, 10]. Such "Monte Carlo" methods have, however, certain disadvantages. To obtain information about the moments of the process, a number of realizations must be modeled with various initial seeds for the random-number generators. In addition, in the case of population growth the number of necessary logical and arithmetical operations per unit of model time increases (exponentially [8]). The mathematical model developed in this paper describes the expected cell count and seems to be quite effective in growth-curve modeling [8]. To obtain formulae for higher moments, a more rigorous approach to SPP techniques is required, (compare [11, Chapter 5] and Sec. 4). These formulae, when obtained, may be complicated enough to be not programmable in an economic way. In this case the Monte Carlo methods would be the only reasonable tool. This interesting subject requires further research.

Consider now the balance of the i th phase (Fig. 2). Introduce SPPs X_i^+ , Y_i , G_i , X_i^- (see Fig. 1). The events of these SPPs are: the moments when cells enter phase i (for X_i^+), when cells leave phase i (for X_i^-). The SPP X_i^+ will be called the influx, and the SPP X_i^- the outflux of phase i . The SPPs Y_i and G_i are the partial outfluxes due to cells leaving phase $i-1$ (for Y_i) and leaving the initial pool of N_i^0 cells (for G_i). The SPP Y_i is X_{i-1}^+ randomly shifted (Definition 1.5), X_i^- is sum of Y_i and G_i (Definition 1.7) and G_i is a

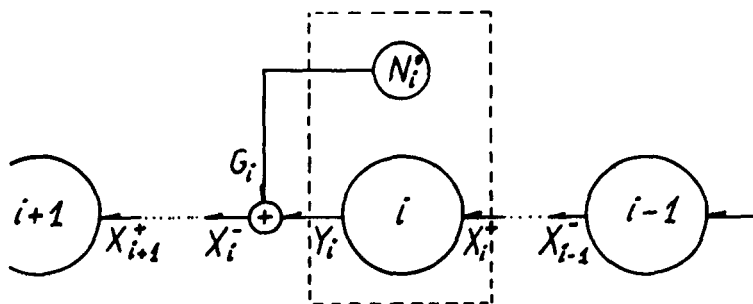


FIG. 2. Balance of i th phase of the cycle. Details in text.

SPP of the type considered in Lemma 1.1. So assuming that for all the SPPs in the cycle EDs exist, and denoting the EDs by x_i^+ , y_i , g_i , x_i^- , we have [cf. (1.8), (1.12)]

$$\left. \begin{aligned} x_i^-(t) &= y_i(t) + g_i(t), \\ y_i(t) &= x_i^+(t) * p_i(t) \end{aligned} \right\} \quad (t \geq -2h). \quad (2.1)$$

Figure 1 shows that $X_1^+ = X_5^-$, $X_2^+ = X_1^-$, $X_3^+ = X_2^-$, while X_5^+ may be treated as a randomly deleted (Definition 1.6) SPP $2X_3^-$. The SPP $2X_3^-$ is a SPP having two simultaneous events in place of each event of X_3^- . Similarly X_4^+ is randomly deleted SPP $2X_3^- - X_5^+$. Subtraction means here rejecting from $2X_3^-$ exactly those events which belong to X_5^+ , and makes sense in this particular case. EDs exist for all the G_i 's (Lemma 1.1) and thus for all the SPPs in the cycle (Remarks 1.4, 1.5, 1.6). It holds then that

$$\begin{aligned} x_1^+(t) &= x_5^-(t), \\ x_2^+(t) &= x_1^-(t), \\ x_3^+(t) &= x_2^-(t), \\ x_4^+(t) &= 2m_4 x_3^-(t), \\ x_5^+(t) &= x_4^-(t) + 2m_5 x_3^-(t). \end{aligned} \quad (2.2)$$

Writing x_i for x_i^- ($i=1,2,4,5$) and x_3 for $2x_3^-$ (which means that the dividing cell in mitosis is counted as two cells) and using (1.2), (2.2), (1.14), we obtain

$$\mathbf{x}(t) = \int_{-2h}^t \mathbf{A}(t-\tau) \mathbf{B} \mathbf{x}(\tau) d\tau + \mathbf{g}(t) \quad (t \geq -2h), \quad (2.3)$$

where

$$\mathbf{x} = \text{col}(x_i), \quad \mathbf{g} = \text{col}(g_i) = \text{col}(N_i^0 f_i), \quad (2.4)$$

$$\mathbf{A} = \text{diag}(p_i), \quad (2.5)$$

$$\mathbf{B} = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 & 0 \\ 0 & 0 & m_4 & 0 & 0 \\ 0 & 0 & m_5 & 1 & 0 \end{bmatrix}. \quad (2.6)$$

The Volterra (renewal) equation (2.3) has a well-defined forward-continuable solution in various classes of functions (compare Remark 3.1) and describes the first moment of the population growth.

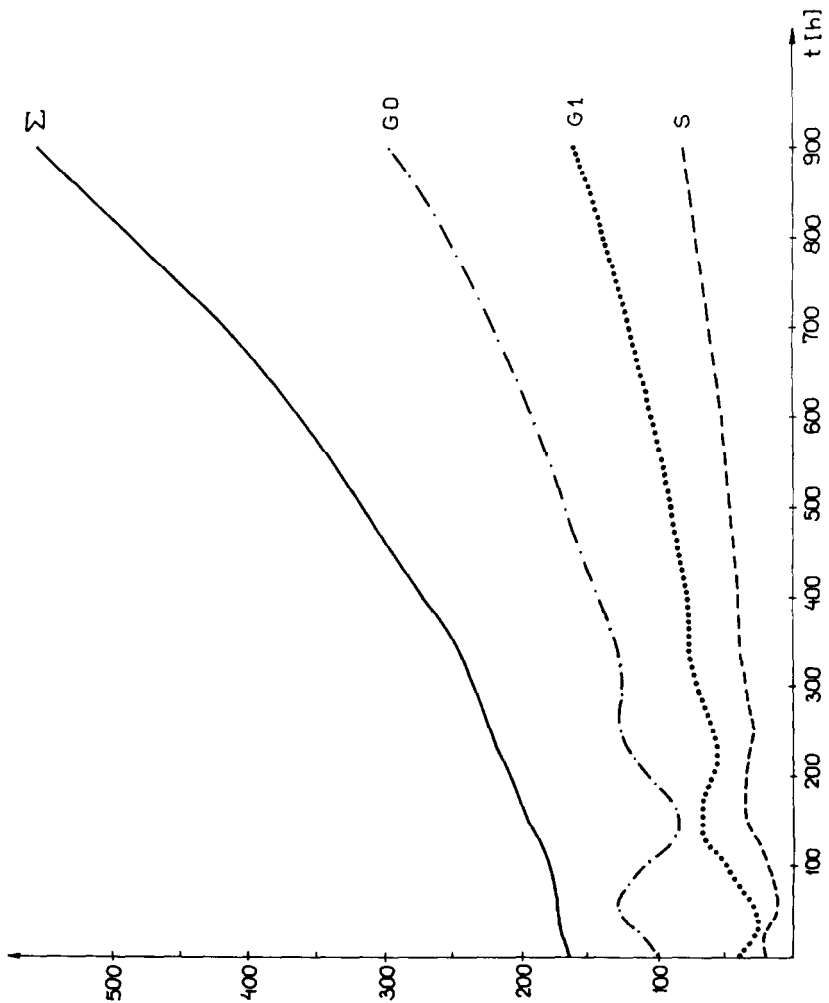


FIG. 3. Modeled growth curves. Symbol Σ denotes total number of cells. Remaining curves concern cell numbers in phases $G0$, $G1$, S .

It is not difficult to show that expected number $N_i(t)$ of cells occupying phase i is given by the equation

$$\mathbf{N}(t) = \mathbf{N}^0 = \int_{-2h}^t (\mathbf{B} - \mathbf{I}) \mathbf{x}(\tau) d\tau, \quad (2.7)$$

where $\mathbf{N} = \text{col}(N_i)$, $\mathbf{N}^0 = \text{col}(N_i^0)$, $\mathbf{I}$ = identity matrix. $N_3(t)$ equals twice the number of cells in the process of mitosis, i.e. the number of daughter cells to be present when mitosis ends. Each N_i is a combination of expected values of counting processes for outfluxes.

The cycle dynamics was modeled [8] with the use of a time-discrete version of (2.6), (2.7) with results similar to those obtained with Monte Carlo methods. An example of growth curves (taken from [8]) is depicted in Fig. 3. It is seen that the growth curves tend to the exponential and that initial oscillations occur. It will be proved in Part II that the oscillations can be eliminated if the initial distributions are chosen according to certain rules (compare [6]). The biological meaning of such choice is also clarified in Part II.

Some biologically important assumptions must be imposed on the p_i 's and f_i 's. First of all there must exist a constant $h > 0$ [the same as in (2.3)] such that

$$\text{supp}(p_i) \subset (0, h) \quad (i = 1, \dots, 5). \quad (2.8)$$

This condition means that time spent by the cell in each phase is nonzero and bounded above (with probability one). This is because in each phase (except perhaps G0, the nature of which is quite uncertain) specific biochemical processes are observed that cannot last infinitely long. For similar reasons it must hold that

$$\text{supp}(f_i) \subset [-2h, -h) \quad (i = 1, \dots, 5). \quad (2.9)$$

The functions p_i and f_i are normed probability densities; hence

$$\int_0^h p_i(t) dt = \int_{-2h}^{-h} f_i(t) dt = 1 \quad (i = 1, \dots, 5), \quad (2.10)$$

$$p_i, f_i \geq 0. \quad (2.11)$$

The formula (2.7) may be replaced by another, more convenient one.

LEMMA 2.1

Assume that the solution of (2.3) is well defined on $[-2h, \infty)$. Then for $t \geq -h$ it holds that

$$\mathbf{N}(t) = \int_0^h \mathbf{A}(u) \int_{t-u}^t \mathbf{B} \mathbf{x}(v) dv du. \quad (2.7')$$

Proof. We have [cf. (7.2)]

$$N_i(t) = N_i^0 + \int_{-2h}^t [b_i x_i^+(\tau) - x_i^-(\tau)] d\tau \quad (t \geq -2h) \quad (2.12)$$

where $b_i = 1$ ($i = 1, 2, 4, 5$), $b_3 = 2$. From (2.3), (2.4), (2.9), (2.10) it follows that

$$\int_{-2h}^t x_i^-(\tau) d\tau = b_i \int_{-2h}^t \int_{-2h}^{\tau} p_i(\tau-s) x_i^+(s) ds d\tau + N_i^0 \quad (t \geq -h) \quad (2.13)$$

Change of the order of integration in (2.13), use of (2.10), and substitution into (2.12) implies

$$N_i(t) = b_i \int_{t-h}^t x_i^+(s) \int_t^{s+h} p_i(\tau-s) d\tau ds \quad (t \geq -h). \quad (2.14)$$

We use (2.2) to obtain

$$\mathbf{N}(t) = \int_{t-h}^t \int_t^{s+h} \mathbf{A}(\tau-s) \mathbf{B} \mathbf{x}(s) d\tau ds \quad (t \geq -h). \quad (2.15)$$

Change of variables gives (2.7). The lemma is proved.

Remark 2.1. The above reasoning may be generalized to the case when the probabilities m_4, m_5, m_o are functions of time [i.e. $\mathbf{B} = \mathbf{B}(t)$] and the distribution of the phase- i residence time depends on the moment at which the cell enters phase i [i.e. $p_i(\tau) = p_i(\tau, t)$, $\mathbf{A}(\tau) = \mathbf{A}(\tau, t)$]. From the viewpoint of SPP theory, the operations of random shift and random deletion must be replaced by a more general operation of clustering [4]. This is done in [9]. The analogues of (2.3), (2.7') are then

$$\mathbf{x}(t) = \int_{-2h}^t \mathbf{A}(t-\tau, \tau) \mathbf{B}(\tau) \mathbf{x}(\tau) d\tau + \mathbf{g}(t), \quad (2.16)$$

$$\mathbf{N}(t) = \int_0^h \int_{t-u}^t \mathbf{A}(u, v) \mathbf{B}(v) \mathbf{x}(v) dv du. \quad (2.17)$$

3. REFORMULATION OF THE MODEL

In this section we prove a theorem which enables investigation of solutions of (2.3), (2.7) as solutions of a certain linear functional differential equation [7, Chapters 16–23]. The theorem holds for integral equations more general than (2.3):

THEOREM 3.1

Let:

- (1) $\hat{\mathbf{K}}(t) \in \text{BV}(-\infty, 0]$ be a real (n, n) matrix function of bounded variation without singular part, defined for $s \in (-\infty, 0]$,
- (2) $\mathbf{K}(t) \in \text{BV}[0, \infty)$, $\mathbf{K}(t) = -\mathbf{K}(-t)$,
- (3) $\text{supp}(\mathbf{K}) \subset (-h, 0)$,
- (4) $\mathbf{u} = \text{col}(u_i)$, $\mathbf{u}: [-2h, T] \rightarrow R^m$ be bounded, Lebesgue measurable and $T > 0$,
- (5) $\mathbf{B}_k$, $k = 1, \dots, m$, be real (n, n) matrices,
- (6) $\mathbf{g} = \text{col}(g_i)$, $\mathbf{g}: [-2h, T] \rightarrow R^n$ be bounded, Lebesgue measurable,
- (7) $\text{supp}(\mathbf{g}) \subset [-2h, -h)$.

Then:

(A) the integral Volterra equation

$$\mathbf{x}(t) = \int_{-2h}^t \mathbf{K}(t-\tau) \left[\sum_{k=1}^m u_k(\tau) \mathbf{B}_k \right] \mathbf{x}(\tau) d\tau + \mathbf{g}(t) \quad (*)$$

has on $[-2h, T]$ a square-integrable solution, which is absolutely continuous (AC) on $(-h, T)$,

(B) on $[0, T]$ the solution of $(*)$ satisfies

$$\mathbf{x}(t) = \int_{t-h}^t \mathbf{K}(t-\tau) \left[\sum_{k=1}^m u_k(\tau) \mathbf{B}_k \right] \mathbf{x}(\tau) d\tau, \quad (a)$$

and

(C) almost everywhere

$$\dot{\mathbf{x}}(t) = \int_{-h}^0 d_s [\hat{\mathbf{K}}(s)] \left\{ \left[\sum_{k=1}^m u_k(s+t) \mathbf{B}_k \right] \mathbf{x}(s+t) \right\}, \quad (b)$$

(D) generally, Eqs. (a) and (b) are equivalent (in the sense of solutions equal almost everywhere) for initial conditions $\boldsymbol{\varphi}$ from the subspace Φ of $C[-h, 0]$ defined as

$$\Phi = \left\{ \boldsymbol{\varphi} \in C[-h, 0] : \boldsymbol{\varphi}(0) = \int_{-h}^0 \mathbf{K}(-s) \left[\sum_{k=1}^m u_k(s) \mathbf{B}_k \right] \boldsymbol{\varphi}(s) ds \right\}, \quad (c)$$

where $C[-h, 0]$ is the Banach space of n -vector real functions continuous on $[-h, 0]$.

(E) solutions of $(*)$, (a), (b) are infinitely forward continuable (if u and g are extended onto $[-2h, \infty)$).

Remark. 3.1. The functions u_k may be treated as multiplicative controls of the system (2.3). Such controls will be introduced in Part II in connection with optimal treatment protocols for leukemia. Substitution of $m=1$, $u_1=1$, $\mathbf{K}=\mathbf{A}$, $\mathbf{B}_1=\mathbf{B}$ into (*) proves that (2.3) is a special case of (*).

Remark. 3.2. Part (A) of the theorem makes clear why the initial distributions can "spoil" the smoothness of solutions for $t \in [-2h, 0)$.

Proof of Theorem 3.1. (The words "almost everywhere" are omitted, because it is clear where they should be used.) Assumptions (2), (3), (5), (6) imply that $\mathbf{K}(t-\tau)\sum_k u_k(\tau)\mathbf{B}_k$ is square integrable on $[-2h, T] \times [-2h, T]$, and $\mathbf{g}(t)$ is square integrable on $[-2h, T]$. Therefore a square-integrable solution of (*) exists on $[-2h, T]$. The solution is bounded [assumptions (2), (6)]. Furthermore the solution is AC for $t \geq -h$ [assumptions (2), (7)], hence (A). To prove (B) it suffices to use assumptions (2), (6). We prove (D) now. Equation (b) may be rewritten (this follows from the unsymmetric Fubini theorem [3; 12, Theorem 10.3, p. 501]) as

$$\dot{\mathbf{x}}(t) = \int_{-h}^0 d_s \{ \mathbf{H}(s, t) \} \mathbf{x}(s+t), \quad (3.1)$$

where

$$\mathbf{H}(s, t) = \int_{-h}^s d_\tau \{ \hat{\mathbf{K}}(\tau) \} \left[\sum_{k=1}^m u_k(\tau+t) \mathbf{B}_k \right]. \quad (3.2)$$

For the existence of the integral in (3.2) it suffices that $\mathbf{u}$ is integrable with respect to the measure generated by $\hat{\mathbf{K}}$. From assumption (1) we know that $\hat{\mathbf{K}}$ is sum of the AC part $\tilde{\mathbf{K}}$ and jumps of amplitudes $\mathbf{K}_i$, $|\sum_i \mathbf{K}_i| < \infty$. This is depicted in Fig. 4. All u_k 's are integrable with respect to $\tilde{\mathbf{K}}$ because they are

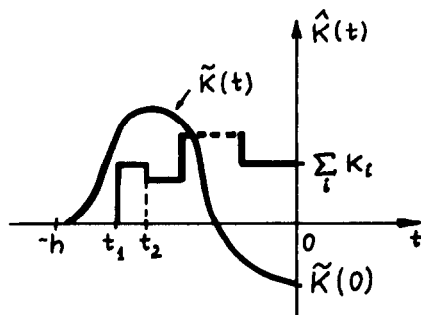


FIG. 4. Function $\hat{\mathbf{K}}(t)$. Details in the proof of Theorem 3.1.

Lebesgue integrable, and are integrable with respect to the atomic measure generated by jumps because they are bounded [12, p. 469]. Hence [12, Theorem 3.5, p. 457] $\mathbf{H}(s, t)$ is well defined. For similar reasons [12, Theorem 5.8, p. 457] $\mathbf{H}(s, t)$ is BV with respect to s and Lebesgue measurable with respect to t . Hence [7, p. 94] (3.1) is a well-defined functional differential equation (FDE) and with initial condition $\varphi(t) \in C[-h, 0]$ has an AC solution on $[0, T]$ for arbitrary $T > 0$. Equation (a) has for the initial condition $\varphi(t) \in C[-h, 0]$ a well defined solution (assumption 3) which is AC on $(0, T]$. However, at $t=0$, the solution has a jump, the amplitude of which is equal to zero if and only if $\varphi \in \Phi$ [compare (c)].

Assume now that $\mathbf{x}(t)$ is a solution of (b) with initial condition $\varphi(t)$. We have

$$\begin{aligned} \mathbf{x}(t) - \mathbf{x}(0) &= \int_0^t \int_{-h}^0 \dot{\tilde{\mathbf{K}}}(s) \left[\sum_k u_k(s + \xi) \mathbf{B}_k \right] \mathbf{x}(s + \xi) ds d\xi \\ &\quad + \sum_i \mathbf{K}_i \int_0^t \left[\sum_k u_k(\xi + t_i) \mathbf{B}_k \right] \mathbf{x}(\xi + t_i) d\xi \equiv I_1 + I_2 \quad (t \geq 0), \end{aligned} \quad (3.3)$$

where for $t = t_i$, $\tilde{\mathbf{K}}$ has jumps. Assumption (3) implies (compare Fig. 4)

$$\sum_i \mathbf{K}_i + \tilde{\mathbf{K}}(0) = \tilde{\mathbf{K}}(-h) = 0; \quad (3.4)$$

hence

$$\begin{aligned} &\frac{d}{d\xi} \left\{ - \int_{\xi-h}^{\xi} \tilde{\mathbf{K}}(s - \xi) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds \right. \\ &= \int_{\xi-h}^{\xi} \dot{\tilde{\mathbf{K}}}(s - \xi) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds - \tilde{\mathbf{K}}(0) \left[\sum_k u_k(\xi) \mathbf{B}_k \right] \mathbf{x}(\xi) \quad (\xi \geq 0). \end{aligned} \quad (3.5)$$

Integration of (3.5) implies

$$\begin{aligned} I_1 &= - \int_0^t \frac{d}{d\xi} \int_{\xi-h}^{\xi} \tilde{\mathbf{K}}(s - \xi) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds d\xi + \int_0^t \tilde{\mathbf{K}}(0) \left[\sum_k u_k(\xi) \mathbf{B}_k \right] \mathbf{x}(\xi) d\xi \\ &= - \int_{t-h}^t \tilde{\mathbf{K}}(s - t) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds + \int_{-h}^0 \tilde{\mathbf{K}}(s) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds \\ &\quad + \tilde{\mathbf{K}}(0) \int_0^t \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds. \end{aligned} \quad (3.6)$$

Similarly, changing variables in (3.3),

$$I_2 = \sum_i \mathbf{K}_i \left(\int_0^t - \int_{t+t_i}^t + \int_{t_i}^0 \right) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds. \quad (3.7)$$

Finally, using (3.3), (3.4), (3.6), (3.7), we show that

$$\begin{aligned} \mathbf{x}(t) - \mathbf{x}(0) = & - \int_{t-h}^t \hat{\mathbf{K}}(s-t) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds \\ & + \int_{-h}^0 \hat{\mathbf{K}}(s) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds. \end{aligned} \quad (3.8)$$

Knowing that $\mathbf{x}(t)$ restricted to $[-h, 0]$ equals $\boldsymbol{\varphi}(t)$, we obtain

$$\mathbf{x}(t) = - \int_{t-h}^t \hat{\mathbf{K}}(s-t) \left[\sum_k u_k(s) \mathbf{B}_k \right] \mathbf{x}(s) ds + \boldsymbol{\Psi}_0, \quad (3.9)$$

$$\boldsymbol{\Psi}_0 = \int_{-h}^0 \hat{\mathbf{K}}(s) \left[\sum_k u_k(s) \mathbf{B}_k \right] \boldsymbol{\varphi}(s) ds + \boldsymbol{\varphi}(0). \quad (3.10)$$

If $\boldsymbol{\varphi} \in \Phi$, we have $\boldsymbol{\Psi}_0 = 0$ and we can write (3.9) in form of (a). Conversely, if $\boldsymbol{\varphi} \in \Phi$, then the solution of (a) is AC on $[0, T]$, and using the above reasoning we can return to (b). This proves (D). To prove (C) we must show that the solution of (*) on $[-h, 0]$ belongs to Φ . This is obviously implied by assumption (7), because there exists $\delta > 0$ such that $\text{supp}(\mathbf{g}) \subset [-2h, -h - \delta]$, the solution $\mathbf{x}(t)$ of (*) is continuous on $[-h, 0]$ and satisfies condition (c). Solutions of (a) are obviously infinitely forward continuable: hence (E). The theorem is proved.

Remark 3.3. Theorem 3.1 may be regarded as a generalized version of the convolution differentiation formula.

4. CONCLUSIONS

Theorem 3.1 permits us to investigate the solutions of the population dynamics equation with the aid of the theory of linear functional differential equations. In Part II of the paper this will be done, with emphasis on the free growth rate, population desynchronization, and choice of initial distributions for modeling. Furthermore, the optimal-control problem will be introduced.

It was noted by Professor Robert Bartoszyński of the Mathematical Institute in Warsaw that the stochastic population process described in this paper may be treated as a multitype age-dependent branching process with immigration [2, 11]. However, the formulae (2.3), (2.7), (2.7'), the generalization mentioned in Remark 2.1, and Theorem 3.1 seem to be new.

It is seen that a full probabilistic description of the process with $\mathbf{B} = \mathbf{B}(t)$, $\mathbf{A}(\tau) = \mathbf{A}(\tau, t)$ (see Remark 2.1) can be obtained using the probability generating functional techniques [4]. The results will be described in a separate paper.

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