

## COMPARISON OF APPROACHES TO MODELING OF CELL POPULATION DYNAMICS\*

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**Abstract.** This paper reviews structured cell population models. A typical formulation is the partial differential equation (PDE)

$$\frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial(gp)}{\partial a} = B - D,$$

the Lotka–von Förster equation, generalized by Webb, where  $t$  is the chronological time,  $a$  is cell age,  $p = p(a, t)$  is the population density, and  $g$  is the cell growth rate, while  $B$  and  $D$  are birth and death terms, respectively. Essentially, it is a transport equation with additional nonlocal boundary conditions.

Another approach, apparently not involving a transport equation, and related to the theory of branching processes has been originally derived by Kimmel and analyzed by the authors. It is shown that this latter approach fits in the framework of PDE models and has comparable generality.

The relationships between both types of models are generally nontrivial and seem important for their applicability.

**Key words.** population dynamics, structured populations, branching process, PDE population model, cell growth, unequal division of cells

**AMS subject classifications.** primary, 92A15, 60J80; secondary, 35Q99, 39B99

**1. Introduction.** Our goal in this paper is to compare different approaches followed in the mathematical modeling of cell proliferation. Two basic problems are discussed: which approach represents greater generality, and which approach is better warranted by data. We concentrate on a particular model of cell cycle, but the considerations are valid for a more general class of models. Technically, we are relating our basic model to the two trends predominant in the literature: (i) the branching process approach and (ii) the partial differential equations approach.

We demonstrate how the branching processes with continuous state space can be used to derive our basic model in a more rigorous manner. In this derivation, a major role is played by an unsymmetric version of the Fubini theorem for Stieltjes integrals.

Then we show that, under the assumptions of our basic model, we can as well describe the dynamics of cells in all their stages in terms of a partial differential equation (PDE) with age and size structure, arbitrary growth function, and nonlocal boundary conditions. This assures us that our approach to modeling cell populations represents generality comparable to that achieved by the PDE approach.

In the remainder of the paper, we consider the special case of our basic model in which the cell cycle duration is determined by the birthsize of the cell. We discuss the existence of a growth function associated with this model and derive a PDE verified by the population density. The conclusion is that the form of birth and death terms used frequently in modeling population dynamics is not unique and that a PDE model without explicit age structure may not represent sufficient generality.

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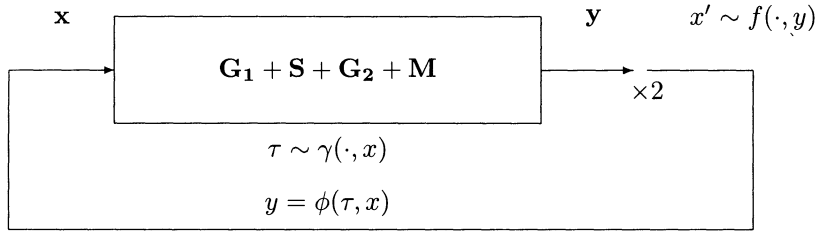


FIG. 1. Schematic diagram of the basic model.

*Notation.* We will use the following less standard notation: (i) If  $f$  is a function of two real variables, then  $f(\cdot, y)$  denotes the resulting function of the first variable when the second variable is fixed and equal to  $y$ ; (ii)  $\int a(x, y) d_x b(x, y)$  denotes the Lebesgue–Stieltjes integral of function  $a(\cdot, y)$  with respect to the measure generated by function  $b(\cdot, y)$ , with  $y$  fixed.

**1.1. The basic model.** We consider a quasi-probabilistic model of the cell cycle in which the main determinant of cell generation time is  $x$ , the amount of a cell constituent present in the daughter cell immediately after division;  $x$  may denote either total cell mass or the amount of a selected substance, for example, RNA as in [18], of supposed critical importance for cell growth. We follow cells with various amounts of this constituent. Readers interested in the physical behavior of cell growth may find [1] useful.

There are two sources of variability in the model. The first is unequal division of cells in mitosis; daughter cells of unequal size have different  $x$ . The second is an independent additional variability in the duration of cell cycle, caused mainly by stochastic character of processes in the  $G_1$  phase; generally, for two unrelated daughter cells with identical  $x$ , the duration of cell cycle may be different. This latter variability is superimposed on a deterministic law of cell growth.

We proceed as in [18] and [6].

1. Suppose that a mitotic cell just before division has mass  $y$ . The density of probability of the daughter cell’s mass  $x$ , conditional on  $y$ , is denoted by  $f(x, y)$ . It is necessary that  $f(x, y) = 0$ , whenever  $x > y$ , and that  $f(y - x, y) = f(x, y)$ .

2. The fate of the daughter cell produced during division, which reenters the cycle with birthmass  $x$ , is described in probabilistic terms as follows: (a) the time  $\tau$  it spends in the cycle is a random variable with conditional distribution density  $\gamma(\tau, x)$ , given  $x$ ; (b) the mass  $y$  of this cell when it reenters division is a function  $\phi(\tau, x)$  of the time it spends in the cycle and of its birthmass  $x$ .

These hypotheses are depicted in Fig. 1.

An important special case is obtained assuming the variant of assumption 2 as in [18] and [3] where the fate of the daughter cell is determined by its birthmass  $x$ : (a) the time  $\tau$  it spends in the cycle is a function of  $x$ ,  $\tau = \psi(x)$ ; (b) the mass  $y$  of the cell when it reenters division is a function of  $x$ ,  $y = \varphi(x)$ .

Formally, these assumptions are equivalent to letting  $\gamma(\tau, x) = \delta[\tau - \psi(x)]$  and  $\phi(\tau, x) = \varphi(x)$ , where  $\delta$  is the Dirac delta distribution concentrated at 0.

We proceed to specifying the basic hypotheses on functions  $f$ ,  $\gamma$ , and  $\phi$ , below, which formalize the requirements of cell cycle dynamics:

$(H_f)$   $f \in L^1_{\text{loc}}(\mathbf{R}_+^2)$ ;  $f \geq 0$ ;  $\int f(x, y) dx = 1$ ;  $f(y - x, y) = f(x, y)$ ;

$(H_\gamma)$   $\gamma \in L^1_{\text{loc}}(\mathbf{R}_+^2)$ ;  $\int \gamma(\tau, x) d\tau = 1$ ;  $\gamma \geq 0$ , and there exist two continuous decreasing functions  $\tau_1$  and  $\tau_2$  such that  $\lim_{\xi \rightarrow \infty} \tau_1(\xi) > 0$ ;  $\tau_1 < \tau_2$ , and  $\gamma(\tau, \xi)$  is positive if and only if  $\tau \in (\tau_1(\xi), \tau_2(\xi))$ ;

$(H_\phi)$   $\phi \in C^1(\mathbf{R}_+^2)$ ;  $\phi \geq 0$ ;  $\phi(\cdot, \xi)$  and  $\phi(\tau, \cdot)$  are increasing.

The assumptions on  $f$  express the fact that  $f(\cdot, y)$  is the density of the conditional distribution of the mass of the daughter cell, provided that the mass of the mother cell is  $y$ .

The assumptions on  $\gamma$  express the fact that  $\gamma(\cdot, x)$  is the density of the conditional distribution of the cell cycle duration given the birthmass of the cell  $x$ . The support property takes into account the requirements that

- cell cycle time varies only in certain limits,
- it should be in inverse relationship to the birthmass, and
- a minimum cell cycle time is required even for cells with large birthmass.

The assumptions on  $\phi$  express the fact that the mass at division of the cell is larger for cells with higher birthmass and cells that stay longer in the cycle.

It is possible to construct a similar model of cell cycle with not very different properties under the assumption that function  $\phi$  is not increasing in  $x$ , but either decreasing in  $x$ , or it does not depend on  $x$ . However, the variant chosen here is experimentally confirmed; see the model of CHO cells in [18], as well as the models in [20].

The assumptions that  $f$  and  $\gamma$  are positive on the entire corresponding intervals are technical.

In the special case defined by assumptions  $\gamma(\tau, x) = \delta[\tau - \psi(x)]$  and  $\phi(\tau, x) = \varphi(x)$ , the hypotheses  $(H_\gamma)$  and  $(H_\phi)$  are replaced by  $(H'_\psi)$  and  $(H'_\varphi)$  as follows:

$(H'_\psi)$   $\psi \in C^1(\mathbf{R}_+^2)$ ;  $\psi \geq 0$ ;  $\psi$  is decreasing,

$(H'_\varphi)$   $\varphi \in C^1(\mathbf{R}_+^2)$ ;  $\varphi \geq 0$ ;  $\varphi$  is increasing.

**1.2. Functions describing populations.** In cell population dynamics, a major role is played by different groups of functions employed to describe the status of the population. One group includes the distributions of cells, at a given time  $t$ , with respect to cell age  $a$ , and with respect to a structural variable  $x$ , frequently cell size. The other group includes the cumulative counting functions of cells born not later than  $t$ , with the birthsizes not exceeding  $x$ , and derivatives of these counting functions. We list these functions in Table 1.

Two remarks are due. First, the physical dimension of  $p(t, a, x)$  is cells  $\times$  age $^{-1}$   $\times$  size $^{-1}$  (and of  $q(t, x)$  cells  $\times$  size $^{-1}$ ). The dimension of  $n(t, x)$  is cells  $\times$  time $^{-1}$   $\times$  size $^{-1}$ . In other words,  $p(t, a, x)$  and  $n(t, x)$  are intrinsically different. Second, the variable  $x$  in  $p(t, a, x)$  denotes the actual size of a cell of age  $a$  present at time  $t$  in any point of the cell cycle, while in  $n(t, x)$ ,  $x$  is the birthsize (size at age  $a = 0$ ) of a daughter cell.

Descriptions of the cell population dynamics in the terms of functions  $n(t, x)$  and  $p(t, a, x)$  follow the two major traditions of population dynamics, the branching process approach and the quasi-probabilistic approach of the partial differential transport equation. We will show that, for our basic linear model, both descriptions are usually equivalent, although exceptions exist, and difficulties are not trivial.

Let us also remark that, experimentally, it is frequently easier to obtain distributions of structural variables like  $x$ , than to obtain those of cell age  $a$ . Therefore, usually, only functions  $q$  are available from the measurements. In [18] the measurements include the birth rate density  $n(t, x)$  and its prevision counterpart  $m(t, x)$ .

TABLE 1  
*Functions describing dynamics of cell populations.*

Symbol	Name	Interpretation
$p(t, a, x)$	Age-size density	$\int_{a_1}^{a_2} \int_{x_1}^{x_2} p(t, a, x) dx da$ is the number of cells with ages from $(a_1, a_2)$ and sizes from $(x_1, x_2)$ , at time $t$
$q(t, x)$	Size density	$\int_{x_1}^{x_2} q(t, x) dx$ is the number of cells with sizes from $(x_1, x_2)$ , at time $t$ , $q(t, x) = \int_0^\infty p(t, a, x) da$
$N(t, x)$	Counting function of births	$N(t, x)$ is the number of cells born in $[0, t]$ with sizes from $[0, x]$
$n(t, x)$	Size density of birth rate	$\int_{t_1}^{t_2} \int_{x_1}^{x_2} n(t, x) dx dt$ is the number of cells with sizes from $(x_1, x_2)$ born in time interval $(t_1, t_2)$ , $n(t, x) = \frac{\partial^2 N(t, x)}{\partial x \partial t}$ if $N$ is regular enough

For these reasons, the question of which description to choose in the model is quite nontrivial.

**1.3. Basic equations of cell population dynamics.** In this section, we list the most important equations we will consider. First, based on the branching process approach, we will derive the integral equation for  $N(t, x; z)$ . The additional argument  $z$  in  $N$  means that we consider a population started at time  $t = 0$  by a single cell born at size  $z$

$$(1) \quad N(t, x; z) = 2 \int_0^t \int_0^{\phi(\tau, z)} h(\xi, \tau, z) N(t - \tau, x; \xi) d\xi d\tau + \mathbf{1}(x - z).$$

A dual form of this equation is

$$(2) \quad N(t, x; z) = 2 \int_0^t \int_0^\infty H(x, t, \xi) d_\xi N(t - \tau, \xi; z) d\tau + \mathbf{1}(x - z).$$

Function  $h(\xi, \tau, z) = f[\xi, \phi(\tau, z)]\gamma(\tau, z)$ , while  $H(x, t, \xi) = \int_0^x h(\eta, \tau, \xi) d\eta$ , and

$$\mathbf{1}(x) = \begin{cases} 1; & x \geq 0, \\ 0; & x < 0. \end{cases}$$

Under additional assumptions, (2) is reduced to

$$(3) \quad n(t, x) = 2 \int_0^\infty \int_0^\infty h(x, \tau, \xi) n(t - \tau, \xi) d\xi d\tau,$$

the equation of our basic model, derived in [6]. Equations (1)–(3) define expected values of a branching process. The duality between (1) and (2) is itself interesting.

The major result of this paper is that, under additional assumptions, (3) is equivalent to the PDE with nonlocal boundary conditions

$$(4) \quad \frac{\partial p(t, a, x)}{\partial t} + \frac{\partial p(t, a, x)}{\partial a} + \frac{\partial [g(a, x)p(t, a, x)]}{\partial x} = -D(a, x)p(t, a, x),$$

$$p(t, 0, x) = 2 \int_0^\infty \int_0^\infty f(x, y) D(a, y) p(t, a, y) dy da,$$

where  $g$  is the cell growth rate and  $D$  is a death term. Functions  $p(t, a, x)$  and  $n(t, x)$  are isomorphically related to each other. Functions  $h, H, g,$  and  $D$  present in the equations are interrelated. Equivalence between (3) and (4) is important, since (4) seems to be the most general equation of its kind present in the literature.

One of the important problems encountered in proving the equivalence of (3) and (4) is the existence of function  $g$ , called the growth function of cells. Function  $g$  does not necessarily exist for a given choice of functions  $\gamma$  and  $\phi$ , and its existence is particularly problematic in the special case of our basic model in which the duration of the cell cycle is strictly determined by the birthsize of cell. We analyze this question in depth.

Eventually, we demonstrate that it is not possible to write a self-contained transport equation for our basic model using only function  $q(t, x)$ .

**2. The branching process approach.**

**2.1. Derivation and duality between the backward and the forward equations.** One of the convenient frameworks used to derive relationships for cell populations is the theory of branching processes [9]. Let us consider a population developing according to assumptions of the basic model, initiated by the birth at time  $t = 0$  of a single particle of size  $z$ . Let  $\mathcal{N}(t, x; z)$  denote the cumulative count of cells born in the time interval  $[0, t]$ , with birth sizes from  $[0, x]$ . The initial cell, after the random time  $\tau$  (the distribution of which is  $\gamma(\tau, z)$ ), divides into two cells, with sizes  $z'$  and  $z''$ . The distribution densities of  $z'$  and  $z''$ , conditional on  $\tau$ , are identical, due to symmetry of  $f$ , and equal to  $f(\cdot, \phi(\tau, z))$ . Each of these two cells initiates at time  $t = \tau$  a new population subprocess. The whole process is the union of the initial cell and these two secondary subprocesses. Therefore, the number of cells with sizes  $\leq x$  born up to time  $t$  in the process started at time 0 by a single cell of size  $z$  is equal to the sum of the numbers of cells with sizes  $\leq x$  born up to time  $t$  in the two subprocesses initiated at time  $\tau$  by the two daughters of the ancestor cell. If the first daughter cell born at  $\tau$  has the initial size  $z'$  and the other born at the same moment has the initial size  $z''$ , then their respective cumulative birth counts from  $\tau$  to  $t$  are equal to  $\mathcal{N}(t - \tau, x; z')$  and  $\mathcal{N}(t - \tau, x; z'')$ , respectively. Taking into account that the cumulative birth count before  $\tau$  including birthsizes  $\leq x$  is equal to 1 or 0 depending on the size of the ancestor cell, we obtain

$$(5) \quad \mathcal{N}(t, x, z) = \begin{cases} \mathcal{N}(t - \tau, x, z') + \mathcal{N}(t - \tau, x, z'') + 1; & \tau \leq t, \quad z \leq x, \\ \mathcal{N}(t - \tau, x, z') + \mathcal{N}(t - \tau, x, z''); & \tau \leq t, \quad z > x, \\ 1; & \tau > t, \quad z \leq x, \\ 0; & \tau > t, \quad z > x \end{cases}$$

or, more concisely,

$$(6) \quad \mathcal{N}(t, x; z) = [\mathcal{N}(t - \tau, x; z') + \mathcal{N}(t - \tau, x; z'')] \mathbf{1}(t - \tau) + \mathbf{1}(x - z),$$

where

$$\mathbf{1}(x) = \begin{cases} 1; & x \geq 0, \\ 0; & x < 0. \end{cases}$$

Let  $N(t, x; z)$  denote the expected (mean) number of cells with sizes from  $[0, x]$ , born in the interval  $[0, t]$ , i.e.,  $N(t, x; z) = \mathcal{E}[\mathcal{N}(t, x; z)]$ . Taking expectations with

respect to random variables  $\tau$ ,  $z'$ , and  $z''$  (remembering that  $z'$  and  $z''$  are identically distributed), we obtain

$$(7) \quad \begin{aligned} N(t, x; z) &= 2 \int_0^t \int_0^{\phi(\tau, z)} h(\xi, \tau, z) N(t - \tau, x; \xi) d\xi d\tau + \mathbf{1}(x - z), \\ x, t, z &\in \mathbf{R}_+, \end{aligned}$$

where  $h(\xi, \tau, z) = f[\xi, \phi(\tau, z)]\gamma(\tau, z)$ . Under the basic hypotheses of the model,  $N(t, x; z) < \infty$  exists (Theorem 1). Equation (3) (the “backward” equation of the process) is inconvenient, since the expectation of the process initiated by a cell of size  $z$  is expressed in the terms of expectations of different processes initiated by particles of sizes  $\xi$ ,  $\xi \in [0, \phi(t, z)]$ . Fortunately, it is equivalent to a dual “forward” equation

$$(8) \quad N(t, x; z) = 2 \int_0^t \int_0^\infty H(x, \tau, \xi) d\xi N(t - \tau, \xi; z) d\tau + \mathbf{1}(x - z),$$

where  $H(x, t, \xi) = \int_0^x h(\eta, \tau, \xi) d\eta$ . The equivalence of (7) and (8) is demonstrated by comparing successive approximations of solutions of (7) and (8), using the method in [13] and [14].

Let us define the successive approximations  $N_0, N_1, N_2, \dots$  of the solution of (7) and the corresponding successive approximations  $\tilde{N}_0, \tilde{N}_1, \tilde{N}_2, \dots$  of the solution of (8). We begin with

$$N_0(t, x; z) = \mathbf{1}(x - z) = \tilde{N}_0(t, x; z),$$

and, for  $i = 0, 1, \dots$ ,

$$N_{i+1}(t, x; z) = 2 \int_0^t \int_0^\infty h(\xi, \tau, z) N_i(t - \tau, x; \xi) d\xi d\tau + \mathbf{1}(x - z),$$

$$\tilde{N}_{i+1}(t, x; z) = 2 \int_0^t \int_0^\infty H(x, \tau, \xi) d\xi \tilde{N}_i(t - \tau, \xi; z) d\tau + \mathbf{1}(x - z).$$

Using induction, we demonstrate that  $N_i(t, x; z) = \tilde{N}_i(t, x; z)$ , for all  $i \geq 0$ . First, let us note that

$$N_1(t, x, z) = 2 \int_0^t H(x, \tau, z) d\tau + \mathbf{1}(x - z) = \tilde{N}_1(t, x, z).$$

For induction, let us assume that  $N_{i+1} = \tilde{N}_{i+1}$  and  $N_i = \tilde{N}_i$ . Let us consider  $N_{i+2}$ ,

$$N_{i+2}(t, x; z) = 2 \int_0^t \int_0^\infty h(\xi, \tau, z) N_{i+1}(t - \tau, x; \xi) d\xi d\tau + \mathbf{1}(x - z).$$

By the induction hypothesis,  $N_{i+1} = \tilde{N}_{i+1}$ , and then, using the definition of  $\tilde{N}_{i+1}$ , we obtain

$$2 \int_0^t \int_0^\infty h(\xi, \tau, z) \left\{ 2 \int_0^{t-\tau} \int_0^\infty H(x, \sigma, \xi) d\eta \tilde{N}_i(t - \tau - \sigma, \eta; \xi) d\sigma + \mathbf{1}(x - \xi) \right\} d\xi d\tau + \mathbf{1}(x - z).$$

Using the fact that  $N_i = \tilde{N}_i$  and expressions for  $N_1$  and  $N_0$  yields

$$4 \int_0^t \int_0^\infty h(\xi, \tau, z) \left\{ \int_0^{t-\tau} \int_0^\infty H(x, \sigma, \eta) d_\eta N_i(t - \tau - \sigma, \eta; \xi) d\sigma \right\} d\xi d\tau + N_1(t, x; z) \\ + N_0(t, x; z),$$

while a change of the integration order with respect to  $\sigma$  and  $\xi$  yields

$$4 \int_0^t \int_0^{t-\tau} \left\{ \int_0^\infty \int_0^\infty h(\xi, \tau, z) H(x, \sigma, \eta) d_\eta N_i(t - \tau - \sigma, \eta; \xi) d\xi \right\} d\sigma d\tau + N_1(t, x; z) \\ + N_0(t, x; z).$$

The unsymmetric Fubini theorem of [7] is used to change the integration order with respect to  $\xi$  and  $\eta$ , and the ordinary Fubini theorem to change the order with respect to  $\sigma$  and  $\tau$ ,

$$4 \int_0^t \int_0^{t-\sigma} \int_0^\infty H(x, \sigma, \eta) d_\eta \left\{ \int_0^\infty h(\xi, \tau, z) N_i(t - \tau - \sigma, \eta; \xi) d\xi \right\} d\tau d\sigma + \tilde{N}_1(t, x; z) \\ + \tilde{N}_0(t, x; z).$$

The unsymmetric Fubini theorem used again to change the integration order with respect to  $\eta$  and  $\tau$ , and the definition of  $\tilde{N}_0$  and  $\tilde{N}_1$ , yield

$$2 \int_0^t \int_0^\infty H(x, \sigma, \eta) d_\eta \left\{ 2 \int_0^{t-\sigma} \int_0^\infty h(\xi, \tau, z) N_i(t - \tau - \sigma, \eta; \xi) d\xi d\tau + \mathbf{1}(\eta - z) \right\} d\sigma \\ + \mathbf{1}(x - z).$$

However, the function under  $d_\eta$  is equal to  $N_{i+1}$ . By the induction hypothesis,  $N_{i+1} = \tilde{N}_{i+1}$ , and we obtain

$$2 \int_0^t \int_0^\infty H(x, \sigma, \eta) d_\eta \tilde{N}_{i+1}(t - \sigma, \eta; z) d\tau + \mathbf{1}(x - z),$$

which is equal to  $\tilde{N}_{i+2}(t, x; z)$ . Therefore,  $N_{i+2}(t, x; z) = \tilde{N}_{i+2}(t, x; z)$ , and all the approximations are equal by induction.

The manipulations under the Stieltjes integrals are justified because of the monotonicity of expected counting functions. Both sequences of approximations are increasing and convergent, given an additional hypothesis on  $\gamma$ . The proof is provided in Appendix A.

**2.2. Remarks on duality.** Several comments are due. First, the duality of first moment equations for branching processes is typical for any process involving more than one type of object, or continuum of “types” (sizes)  $x$  as in our basic model. The forward equation enables forward continuation of the expected values, given initial conditions, as in (2) or (3). Unfortunately, no simple forward equation exists, generally, for higher moments or for distributions of the process [14].

The procedure outlined above, construction of the backward equation based on the definition of the process and then derivation of a forward equation using induction and the unsymmetric Fubini theorem, can be treated as a “working program” for derivation of population models. It was successfully employed in [4], [5], [11]–[14], [16], and [17].

**2.3. Equation for  $n(t, x)$ .** Let us consider a population initiated by  $N_0$  cells, each of which was born at a generally different time  $\sigma < 0$  with size  $z$ . The distribution density of  $\sigma$  and  $z$  is denoted by  $k(\sigma, z)$  and the respective cumulative distribution by  $K(\sigma, z)$ . For such population, the expected number of births  $N(t, x)$  is equal to

$$N(t, x) = \int_0^\infty \int_{-\infty}^0 N(t - \sigma, x; z) N_0 k(\sigma, z) d\sigma dz;$$

$N(t, x)$  is now understood as the expected number of births with sizes from  $[0, x]$  during  $(-\infty, t]$ . Using the equation above and (8), it is proved that  $N(t, x)$  satisfies

$$(9) \quad N(t, x) = 2 \int_0^\infty \int_0^\infty H(x, \tau, \xi) d_\xi N(t - \tau, \xi) d\tau + N_0 K(t, x),$$

where  $x \in \mathbf{R}_+$  and  $t \in \mathbf{R}$ .  $N(t, x)$  is absolutely continuous (AC) in both variables. This is because  $N(t, x; z)$  is AC in  $(t, x)$  except for a jump at  $x = z$ , which is “smoothed out” by integration.

The absolute continuity implies the representations

$$N(t, x) = \int_{-\infty}^t \int_0^x n(\sigma, \eta) d\eta d\sigma$$

and

$$\begin{aligned} & 2 \int_0^\infty \int_0^\infty H(x, \tau, \xi) d_\xi N(t - \tau, \xi) d\tau \\ &= 2 \int_0^\infty \int_0^\infty H(x, \tau, \xi) d_\xi \left[ \int_{-\infty}^{t-\tau} \int_0^\xi n(\sigma, \eta) d\eta d\sigma \right] d\tau \\ &= 2 \int_0^\infty \int_0^\infty H(x, \tau, \xi) \int_{-\infty}^{t-\tau} n(\sigma, \xi) d\sigma d\xi d\tau \\ &= 2 \int_0^\infty \int_0^\infty \left[ \int_0^x h(\eta, \tau, \xi) d\eta \right] \int_{-\infty}^t n(\sigma - \tau, \xi) d\sigma d\xi d\tau \\ &= 2 \int_{-\infty}^t \int_0^x \left[ \int_0^\infty \int_0^\infty h(\eta, \tau, \xi) n(\sigma - \tau, \xi) d\xi d\tau \right] d\eta d\sigma. \end{aligned}$$

Comparison of terms under  $\int_{-\infty}^t \int_0^x$  yields

$$n(t, x) = 2 \int_0^\infty \int_0^\infty h(x, \tau, \xi) n(t - \tau, \xi) d\xi d\tau + N_0 k(t, x),$$

for  $t \in \mathbf{R}$ ,  $x \in \mathbf{R}_+$ . For  $t \geq 0$ , this gives (3).

Results of this section are summarized in the form of a theorem.

**THEOREM 1.** *Under the basic hypotheses  $(H_f)$ ,  $(H_\phi)$ , and  $(H_\gamma)$  and an additional hypothesis*

$$(H_*) \quad \gamma(\tau, z) \leq g(\tau), g \in L^1[0, \infty),$$

*there exists a unique solution  $N(t, x; z)$ ,  $t, x, z \geq 0$  of the backward equation (1). Function  $N(t, x; z)$  is nonnegative, nondecreasing and absolutely continuous in  $t$  and  $x$ , and bounded measurable in  $z$ . Uniqueness is understood in the  $L^1$ -equivalence class sense. Function  $N(t, x; z)$  also satisfies the forward equation (2) and is its unique*



solution in the class of functions nonnegative, nondecreasing in  $x$ , and bounded on finite intervals of  $t$ .

Function  $N(t, x) = \int_0^\infty \int_{-\infty}^0 N(t - \sigma, x; z) N_0 k(\sigma, z) d\sigma dz$  is absolutely continuous and has density  $n(t, x)$ , which satisfies (3) for  $t \geq 0$ .

Proof of Theorem 1 is presented in Appendix A.

*Remark.* Hypothesis  $(H_*)$  disallows certain variants of the model that are not desirable. For example, it excludes the possibility that  $\lim_{\xi \rightarrow \infty} \gamma(\tau, \xi) = \delta(\tau - T)$  (a Dirac delta). This would mean that, for cells large enough, the cell lifespan becomes a constant. In such situations, the approximations, which are equal to average cell numbers in successive cell generations, might indeed never converge, since generations might cease to overlap.

**3. The basic model in the PDE form.** Our goal in this section is to compare different approaches followed in the mathematical modeling of cell proliferation. First, we consider our basic model, which can be called a model with transition probability and unequal division. This model revolves around the dynamics of daughter cells. We will show that, under the assumptions of the basic model, we can describe as well the dynamics of cells in all their stages in terms of a PDE with nonlocal boundary conditions. This result is very close to an earlier result by Webb [21] obtained under slightly more restrictive assumptions.

**3.1. Remarks about the basic model.** The important feature of our basic model is the assumption that the size of a cell at division is a function  $\phi$  of its lifespan  $\tau$  and its birthsize  $\xi$ . Since the lifespan  $\tau$  is a random variable that can assume, in principle, values from  $[0, \infty)$ , then  $\phi$  can indeed be interpreted as giving cell size at any age  $\tau$  not necessarily at the age of division. We will assume this interpretation. As we will see, function  $\phi$  can be defined in the PDE formulation (4), but there it is derived from the existence of a growth function  $g$  that governs the evolution of the size of cells through their cycle, an assumption that is not made in our basic model. In brief,  $\phi(\tau, \xi)$  is the size at age  $\tau$  of a cell that was born with size  $\xi$ .

We will show that the model fits essentially in the general framework considered by Webb [21], and appears as an extension of Webb's result to the case where the growth function  $g$  depends on both age and size.

The basic model describes the evolution in time of the density with respect to time and size of the daughter cells. This leads to the equation

$$(10) \quad n(t, x) = 2 \int_0^\infty \int_0^\infty f[x, \phi(\tau, \xi)] \gamma(\tau, \xi) n(t - \tau, \xi) d\xi d\tau,$$

which is equivalent to (3) in §1.3 (see also Theorem 1 in §2.3).

Existence of solutions and a semigroup property in a space  $L^1(Q)$ , where  $Q$  is a certain rectangle in  $(-\infty, 0) \times (0, \infty)$ , is obtained under a set of assumptions, some of them mainly motivated by the study of asymptotic properties of solutions [6]. Denoting  $n_t$  the translation over  $Q$  of the restriction of  $n$  to the set  $\{(t + \tau, \xi) : (\tau, \xi) \in Q\}$ , then the semigroup is just the family of transformations  $n_0 \rightarrow n_t$ . The initial value problem can be stated as the problem of finding  $n$  such that (5) holds for  $t \geq 0$  and

$$(11) \quad n(\tau, \xi) = n_0(\tau, \xi) \quad \text{for almost every } (\tau, \xi) \in Q,$$

where  $n_0$  is the initial condition  $n_0 \in L_1(Q)$ .

We call problems (10), (11) the equation for daughter cells and denote it (DCE). We refer the reader to the Introduction for precise assumptions on  $f$ ,  $\gamma$ , and  $\phi$ . We add two properties to be verified by  $\phi$ :

$(H_\phi)'$   $\phi$  verifies  $(H_\phi)$ , and, moreover,  $\phi$  is  $C^1$  and  $\partial\phi/\partial x > 0$ .

As a final word about the model, it should be pointed out that cell death is not considered in any real sense. This is done for simplicity and does not seem to be a serious restriction. One way to include death among cells of a given size at a certain time into account is by multiplying the density function of the cells of this size at that time by a death rate. This does not introduce any significant difficulty in existence theory of solutions.

**3.2. Basic relations verified by the age-size density.** We want to describe the population in terms of a function  $p(t, a, x)$  that at each time  $t$  gives the population density with respect to age and size. This means that, provided that  $p$  satisfies some integrability requirements,  $\int_{a_1}^{a_2} \int_{x_1}^{x_2} p(t, a, x) dx da$  is the number of cells that at time  $t$  are in the cycle, with age between  $a_1$  and  $a_2$  and size between  $x_1$  and  $x_2$ . Generally, if  $\Omega$  is a measurable subset of  $R^2$ , then we may denote  $P(t, \Omega)$  the integral of  $p(t, \cdot, \cdot)$  over  $\Omega$ .  $P(t, \Omega)$  is the number of cells such that the pair  $(a, x)$ , defined by the age and the size of the cell at time  $t$ , lies in  $\Omega$ . Our first task will be to relate  $p$  and  $n$ . Define

$$\bar{\Gamma}(\tau, x) = \int_{\tau}^{\infty} \gamma(a, x) da.$$

$\bar{\Gamma}(\tau, x)$  is the probability for a cell of birthsize equal to  $x$  to survive at least until age  $\tau$ . For each  $x$ ,  $\bar{\Gamma}(\tau, x)$  approaches 0 as  $\tau$  goes to  $\infty$ .  $\bar{\Gamma}$  is known as the tail of the probability distribution of  $\tau$ .

We denote  $\phi^{-1}$  as the inverse of  $\phi$  with respect to the second variable, that is,

$$(12) \quad \phi^{-1}(\tau, y) = x \iff y = \phi(\tau, x).$$

Similarly, we write  $\phi'$  or  $(\phi^{-1})'$  to denote the partial derivative of  $\phi$  or  $\phi^{-1}$  with respect to the second variable.

LEMMA 1. *We have*

$$(13) \quad p(t, a, x) = n[t - a, \phi^{-1}(a, x)] \bar{\Gamma}[a, \phi^{-1}(a, x)] (\phi^{-1})'(a, x).$$

*Remark.* In [6] it has been assumed that  $\gamma$  has a support determined by two functions  $\tau_1$  and  $\tau_2$ ; that is,  $\gamma(\tau, \xi) > 0$  if and only if  $\tau_1(\xi) < \tau < \tau_2(\xi)$ , where  $\tau_1$  and  $\tau_2$  are continuous, decreasing, and  $\tau_1(\infty) > 0$ . Introducing the inverse functions  $\xi_1$  and  $\xi_2$  of  $\tau_1$  and  $\tau_2$ , the support can be expressed in terms of  $\xi_1$  and  $\xi_2$ . For the function  $\bar{\Gamma}$ , this yields that  $\bar{\Gamma}(\tau, \xi) > 0$  if and only if  $\tau < \tau_2(\xi)$  or equivalently if and only if  $\xi < \xi_2$ . We can also see that  $\bar{\Gamma}(\tau, \xi) = 0$  implies that  $\gamma(\tau, \xi) = 0$ .

If we consider  $\bar{\Gamma}[a, \phi^{-1}(a, x)]$ , then the support of this function can be described as the set of  $(a, x)$  such that  $\phi^{-1}(a, x) < \xi_2(a)$ ; that is,  $x < \phi[a, \xi_2(a)]$ . So, in this situation, we can draw the following consequence regarding the support of  $p$ :  $p(t, a, x) = 0$  for  $x > \phi[a, \xi_2(a)]$ .

*Proof of the lemma.* To prove expression (13), let us select an arbitrary rectangle  $R = (a_1, a_2) \times (x_1, x_2)$ . We will evaluate the number of cells with parameters inside  $R$  at time  $t$ , first in terms of  $p$ , then in terms of  $n$ . In terms of  $p$ , it is just  $P(t, R)$ . Now, for each  $(a, x) \in R$ , the parameters for the corresponding cells at birth are  $t_0 = t - a$ , (the birthdate of the cell), and  $x_0 = \phi^{-1}(a, x)$  (the birthsize of the cell). The map

$$(a, x) \rightarrow (t_0, x_0)$$

gives the region  $R_0$  of the parameters where the cells came from whose parameters are in  $R$  at time  $t$ . To obtain the number of cells in terms of  $n$ , we must integrate  $n$  over the transformed region  $R_0$ . In fact, however, not all the cells starting in  $R_0$  will arrive in  $R$  at time  $t$ . Some cells divide before this time. The density with respect to  $t_0, x_0$  of cells that survive until time  $t$  (or, equivalently, the cells that do not divide before  $t$ ) is

$$n(t_0, x_0)\bar{\Gamma}(t - t_0, x_0).$$

So, we have

$$P(t, R) = \int \int_{R_0} n(t_0, x_0)\bar{\Gamma}(t - t_0, x_0)dt_0dx_0.$$

The last step consists in rewriting the right-hand side of the above equality in terms of the variables  $(a, x)$ . This simply means a change of variables inside the integral. The determinant of the Jacobian matrix of the transformation can be easily computed as a function of  $a$  and  $x$ : it is  $(\phi^{-1})'(a, x)$ . We arrive at the following:

$$P(t, R) = \int \int_R n[t - a, \phi^{-1}(a, x)]\bar{\Gamma}[a, \phi^{-1}(a, x)](\phi^{-1})'(a, x)dadx.$$

This being true for each  $R$  yields the equality of the functions inside the integrals; therefore, the proof of expression (13) is complete.

*Remark.* Equality (13) must be understood in the  $L^1$  sense. On the right-hand side, the map  $(a, x) \rightarrow n[t - a, \phi^{-1}(a, x)]\bar{\Gamma}[a, \phi^{-1}(a, x)](\phi^{-1})'(a, x)$  defines an  $L^1$  class for each  $t$ . Moreover, the dependence of this class on  $t$  is continuous:  $t$  acts as a translation. An indirect consequence is that the map  $t \rightarrow p(t, \cdot, \cdot)$  is also continuous from  $\mathbf{R}_+$  into  $L^1$ .

**3.3. The PDE associated with the basic model.** To derive an equation for  $p$ , we consider a domain  $R$  in the space of parameters  $(a, x)$  and we express the variation of the population lying in that region  $R$  when time varies from  $t$  to  $t + h$ . In the absence of birth or death terms, the variation would be equal to 0 if, at time  $t + h$ , we integrated  $p$  over the transformed region. The transformed region is given as the image of  $R$  under the map

$$(14) \quad (a, x) \rightarrow \{a + h, \phi[a + h, \phi^{-1}(a, x)]\}.$$

This map associates to each pair  $(a, x)$  that characterizes a certain cell at a time  $t$  the value of these parameters for this same cell at time  $t + h$ , provided that this cell did not divide in the meantime. Let us denote  $A_h$  as the map defined by (14) and consider

$$\frac{\int \int_{A_h(R)} p(t + h, a, x)dadx - \int \int_R p(t, a, x)dadx}{h}.$$

This can be written in the form

$$\int \int_R \frac{p[t + h, A_h(a, x)]|DA_h(a, x)| - p(t, a, x)}{h}dadx.$$

Here  $|DA_h|$  denotes the determinant of the Jacobian matrix of  $A_h$ . In the absence of any birth or death term, this difference is equal to 0. If we assume  $p$  smooth enough

for the partial derivatives to be taken, we obtain, when letting  $h$  go to 0, the integral of a function that we denote  $\mathcal{D}p(t, a, x)$ . We call the operator  $\mathcal{D}p$  the transport equation associated with the cell growth. We can easily check the following lemma.

LEMMA 2. *It holds that*

$$(15) \quad \mathcal{D}p(t, a, x) = \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial \left\{ p \frac{\partial \phi[a, \phi^{-1}(a, x)]}{\partial a} \right\}}{\partial x}.$$

The complete equation is of the form  $\mathcal{D}p = B - D$ , where  $B$  denotes the density of daughter cells and  $D$  is the density of cells leaving the cycle. Note that, with respect to  $t$ ,  $B$  and  $D$  are rates per unit of time.

For  $a > 0$ ,  $B = 0$ . All cells are born with age  $a = 0$ . So, we are concerned only with the “death” term  $D$  associated with withdrawal of divided mother cells from the cycle.

LEMMA 3. *It holds that*

$$(16) \quad D = p(t, a, x) \frac{\gamma[a, \phi^{-1}(a, x)]}{\bar{\Gamma}[a, \phi^{-1}(a, x)]}$$

and  $D = 0$ , when  $\bar{\Gamma}[a, \phi^{-1}(a, x)] = 0$ .

*Proof.* Let us remember that  $D$  is a rate with respect to time. Let  $t, h > 0$  be given. Select a region  $R = (a_1, a_2) \times (x_1, x_2)$ . We want to evaluate the number of cells that will divide in the time interval  $(t, t + h)$  having at time  $t$  an age  $a$  and a size  $x$  such that  $(a, x) \in R$ . As in the proof of Lemma 1, we first relate these cells to daughter cells. The region of parameters for those daughter cells is again the set  $R_0$  given in the proof of Lemma 1. Now, for any region  $R_0$  in the space of parameters of daughter cells, we can estimate the number of cells in this region that divide in the time interval  $(t, t + h)$ , the only restriction on  $t$  being that  $t$  be larger than any of the birthdates  $t_0$  in  $R_0$ . Namely, for each  $(t_0, x_0) \in R_0$ , the fraction of the daughter cells born at  $t_0$  with size  $x_0$  that will divide in the age interval  $(t - t_0, t - t_0 + h)$  is equal to

$$\int_0^h \gamma(t - t_0 + s, x_0) ds;$$

therefore, the density function that yields the number of cells born in a given region  $R_0$  that will divide between  $t$  and  $t + h$  is equal to

$$\left[ \int_0^h \gamma(t - t_0 + s, x_0) ds \right] n(t_0, x_0),$$

and the actual number of cells dividing in this time interval from cells born in  $R_0$  is the integral of the above density over  $R_0$ . Dividing by  $h$  and letting  $h$  go to 0, we obtain the rate density function

$$\gamma(t - t_0 + s, x_0)n(t_0, x_0).$$

Now, if  $R_0$  is the region obtained by transformation from a region  $R$  in the space of age and size parameters, changing the variables inside the integral of  $\gamma(t - t_0 + s, x_0)n(t_0, x_0)$  will lead us to a density function with respect to age and size. This is the function  $D$  we are seeking. From the proof of Lemma 1, we have  $t_0 = t - a$ ,

$x_0 = \phi^{-1}(a, x)$ , and the determinant of the transformation is  $(\phi^{-1})'(a, x)$ . We arrive at

$$D = \gamma[a, \phi^{-1}(a, x)]n[t - a, \phi^{-1}(a, x)](\phi^{-1})'(a, x).$$

We now conclude the proof of Lemma 3. There are two cases: Either  $\bar{\Gamma}[a, \phi^{-1}(a, x)] > 0$ , in which case we obtain expression (16) from the above expression using the expression of  $n$  in terms of  $p$  given in Lemma 1 (expression (13)) or  $\bar{\Gamma}[a, \phi^{-1}(a, x)] = 0$ ; then, as we noted in the remark following Lemma 1, we also have  $\gamma[a, \phi^{-1}(a, x)] = 0$ . Therefore, the above expression shows that  $D = 0$ . The proof is complete.

We introduce the following hazard function of distribution  $\gamma$ :

$$(17) \quad \beta(\tau, \xi) = \begin{cases} \frac{\gamma(\tau, \xi)}{\bar{\Gamma}(\tau, \xi)}; & \bar{\Gamma}(\tau, \xi) > 0, \\ 0; & \bar{\Gamma}(\tau, \xi) = 0. \end{cases}$$

Combining (15) and (16), we arrive at the equation

$$(18) \quad \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial \{p \frac{\partial \phi[a, \phi^{-1}(a, x)]}{\partial a}\}}{\partial x} = -\beta[a, \phi^{-1}(a, x)]p(t, a, x).$$

To make this equation complete, it is necessary to specify initial values  $p(0, \cdot, \cdot)$  and a boundary condition  $p(t, 0, x)$ .

We will now see that the boundary condition can be stated in terms of an integral operator in  $p$ . Note first that  $\phi(0, x) = x$ , so that  $\phi^{-1}(0, x) = x$  and  $(\phi^{-1})'(0, x) = 1$ . We also check that  $\bar{\Gamma}(0, x) = 1$ . Letting  $a = 0$  in expression (7), we then find that

$$p(t, 0, x) = n(t, x).$$

Using expressions (10) and (13), we arrive at

$$(19) \quad p(t, 0, x) = 2 \int_0^\infty \int_0^\infty f(x, y)\beta[a, \phi^{-1}(a, x)]p(t, a, y)dyda.$$

Equations (18) and (19) together are the PDE formulation of our proliferation problem. It is very much like the general model derived in [21]. The main difference is in the nature of function  $\phi$ , which in [21] is the flow generated by the growth function.

However, as we will now see, it is possible to view such a function  $\phi$  as being associated with a nonautonomous ordinary differential equation. Therefore, surprisingly enough, our basic model fits in the general frame considered in [21] and appears essentially as an extension of Webb's result to the case where the growth function depends on both age and size.

We may note first that  $\phi$  defines an evolution operator on  $\mathbf{R}_+$ . Let  $X$  be such that

$$X(t, s, x) = \phi[t, \phi^{-1}(s, x)], \quad t, s \geq 0, \quad x \geq 0.$$

Then a straightforward computation shows that

$$X[t, s, X(s, r, x)] = X(t, r, x) \quad \text{for each } t, s, \quad r \geq 0, \quad \text{and } x \geq 0,$$

$$X(t, t, x) = x \quad \text{for each } t \geq 0, \quad x \geq 0.$$

Function  $\phi$  has a partial derivative with respect to its first variable. Then  $X$  also has a partial derivative with respect to its first argument. If we define

$$g(a, x) = \frac{\partial\phi[a, \phi^{-1}(a, x)]}{\partial a},$$

then we have

$$\frac{\partial X(t, s, x)}{\partial t} = g[t, X(t, s, x)].$$

In terms of  $g$ , (18) and (19) read as

$$(20) \quad \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial [pg(a, x)]}{\partial x} = -\beta[a, X(0, a, x)]p(t, a, x).$$

$$(21) \quad p(t, 0, x) = 2 \int_0^\infty \int_0^\infty f(x, y)\beta[a, X(0, a, y)]p(t, a, y)dyda.$$

The initial value condition for this problem is a function  $p_0$  defined on some subset of  $\mathbf{R}_+ \times \mathbf{R}_+$ , and  $p$  must satisfy the following:

$$(22) \quad p(0, a, x) = p_0(a, x) \quad \text{a.e. in } (a, x).$$

We will call problem (20)–(22) the equation for all cells and refer to it as (ACE).

The main conclusion of the above considerations is that problems (DCE) and (ACE) are equivalent to each other. This will be stated as a theorem after a few remarks regarding the phase space framework associated with each of these problems. In [6] we deal with functions that have support in a set of the form  $(\infty, 0) \times (A_1, A_2)$ , where  $0 < A_1 < A_2 < \infty$ . As shown there, this implies that the part of  $n_0$  that really plays a role in the computation of  $n$  is the restriction of  $n_0$  to a bounded rectangle, which we beforehand denoted  $Q$ . Therefore, the phase space for (DCE) can be taken as  $L^1(Q)$ . We may drop the restriction about the support of  $n_0$ , even though it has very clear biological interpretation. This has been done by Webb [21] for the general model and also by Grabosch [8] for the Dirac transition probability model. It is then natural to consider a space of weighted integrable functions as a phase space, for example, functions that do not grow faster than some exponential.

We will not go into more details regarding this question. Let us assume that the (DCE) problem has been stated in some space of integrable functions on  $(-\infty, 0) \times (0, \infty)$  that we will further denote  $E$ .

The relation

$$(23) \quad p_0(a, x) = n_0[-a, \phi^{-1}(a, x)]\bar{\Gamma}[a, \phi^{-1}(a, x)](\phi^{-1})'(a, x),$$

which we derive from (13), taking  $t = 0$ , yields the relationship between the initial conditions of the (DCE) problem and the (ACE) problem and thus the appropriate phase space for the latter problem. What we obtain is again a space of weighted integrable functions, this time on the product  $\mathbf{R}_+ \times \mathbf{R}_+$ , isomorphically related to  $E$  by the transformation shown in expression (15). We denote it as  $\tilde{E}$ .

**THEOREM 2.** *The (DCE) problem (that is, (10), with expression (11) as an initial value, with  $E$  as a phase space) and the (ACE) problem (that is, (20), with the nonlocal boundary condition (21) and expression (22) as an initial value, with  $\tilde{E}$  as a phase space) are equivalent to each other. Each solution of (DCE) is associated with one*

solution of (ACE), and vice versa. Initial values correspond to each other through the map defined by formula (23), and solutions correspond to each other through the map defined by formula (13).

In mathematical terms, Theorem 2 has the following consequence: It shows that the functional PDE defined as the (ACE) problem can be reduced to a difference-integral equation in  $n$  and it provides an explicit relationship between both problems. Therefore, it also shows that the (ACE) problem can be solved and gives a method to solve it.

**4. Model with Dirac function transition probability (special case of the basic model).**

**4.1. Remarks about the model.** We now consider the special case of our basic model, originally studied in [18] and employed as a description of dynamics of the cell cycle of the Chinese hamster ovary cells. In this model, it is assumed that the life length of each cell and its size when it divides are functions  $\psi$  and  $\varphi$  of its initial size. Using the notation of §1, this means that

$$(24) \quad \gamma(\tau, \xi) = \delta[\tau - \psi(\xi)],$$

where  $\delta$  is the Dirac distribution with support at the origin. In that situation, we have

$$(25) \quad \bar{\Gamma}(\tau, \xi) = \begin{cases} 1; & \tau < \psi(\xi), \\ 0; & \tau \geq \psi(\xi). \end{cases}$$

Under the above assumptions, no information is available on the way the size is growing during cell's progression through the cell cycle. Therefore, it is unlikely that this model can be used to build the function  $p(t, a, x)$ . In the next paragraph, we will assume that we know a little more about the model, namely, that there is a growth flow  $\phi$ . Note that, if  $\phi$  exists, it is related to  $\varphi$  and  $\psi$  by the identity

$$(26) \quad \varphi(\xi) = \phi[\psi(\xi), \xi].$$

We will then derive a PDE in that case. In the last paragraph, we consider the question of existence of such a function  $\phi$ , knowing  $\varphi$  and  $\psi$ . In fact, it will be necessary to restrict the search to functions  $\phi$  satisfying an autonomous ordinary differential equation. Let us note that (10) now reads as

$$(27) \quad n(t, x) = 2 \int_0^\infty f[x, \varphi(z)]n[t - \psi(z), z]dz.$$

**4.2. The PDE formulation.** Let us assume that there exists a function  $\phi$ , which verifies  $(H_\phi)'$  and is understood as the size at age  $\tau$  of cells starting from size  $\xi$ .  $\phi$  is the growth flow. Of course,  $\phi$  does not have the same meaning as in §3. The size at division is determined in terms of the initial size. For consistency, we assume that  $\varphi$ ,  $\psi$ , and  $\phi$  are connected through expression (26). Let  $p(t, a, x)$  denote the density with respect to age  $a$  and size  $x$  at time  $t$ . The same arguments as in the proof of Lemma 1 lead to

$$(28) \quad p(t, a, x) = n[t - a, \phi^{-1}(a, x)](\phi^{-1})'(a, x); \quad a < \psi \circ \phi^{-1}(a, x),$$

$$(29) \quad p(t, a, x) = 0; \quad a > \psi \circ \phi^{-1}(a, x),$$

which, indeed, can be written as a single expression using  $\bar{\Gamma}$

$$(30) \quad p(t, a, x) = n[t - a, \phi^{-1}(a, x)]\bar{\Gamma}[a, \phi^{-1}(a, x)](\phi^{-1})'(a, x).$$

In conclusion, expression (13) applies without any change to this situation. To derive a PDE verified by  $p$ , we proceed as in §3.3. First, we determine the transport equation associated with cell growth. As in Lemma 2, we do it by computing the variation of the population lying in a region  $R$  of the  $(a, x)$ -space between  $t$  and  $t + h$ , the variation that would be due to the cell growth only. This yields (15) in the region  $a < \psi \circ \phi^{-1}(a, x)$  and 0 elsewhere. Now, the  $D$  term is equal to 0 everywhere except on the line  $a = \psi \circ \phi^{-1}(a, x)$ , and, as before, the  $B$  term is equal to 0 for  $a > 0$ . These considerations lead us to

$$(31) \quad \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial \{p \frac{\partial \phi[a, \phi^{-1}(a, x)]}{\partial a}\}}{\partial x} = 0$$

for  $a < \psi \circ \phi^{-1}(a, x)$ , and  $p(t, a, x) = 0$  for  $a > \psi \circ \phi^{-1}(a, x)$ . From (28), we deduce that  $p(t, 0, x) = n(t, x)$ . Using (27), we obtain a difference-integral equation for  $p(t, 0, x)$ , namely,

$$(32) \quad p(t, 0, x) = 2 \int_0^\infty f[x, \varphi(z)]p[t - \psi(z), 0, z]dz.$$

The (ACE) problem is the combination of (31), boundary condition (32), and initial value equation

$$(33) \quad p(0, a, x) = p_0(a, x),$$

where  $p_0$  is related to  $n_0$  by expression (30) taken at  $t = 0$ .

**4.3. The existence of the growth flow.** We just saw that, if we assume that a growth flow exists, then it is still possible to derive an equation for the age-size density function. In this paragraph, we consider the question of existence and possibly uniqueness of such a growth flow for given  $\varphi$  and  $\psi$ . Regarding uniqueness, expression (26) shows that it certainly does not hold if we do not impose further restrictions on  $\phi$ . In fact, for given  $\varphi$  and  $\psi$ , expression (26) determines  $\phi$  on a one-dimensional submanifold only. On the other hand, we know from §3 that if it exists the growth flow can be associated with a nonautonomous differential equation. We will set the problem as the problem of finding the right-hand side of the differential equation. We will restrict our attention to the autonomous case.

We address the following question, given  $\varphi$  and  $\psi$  as defined above. Does there exist a growth function  $g$  such that the equation

$$(34) \quad \frac{dx}{dt} = g[x(t)]$$

has, for each  $\xi \geq 0$ , one and only one solution defined on  $\mathbf{R}_+$ , and

$$\phi[\psi(\xi), \xi] = \varphi(\xi) \quad \text{for each } \xi \geq 0,$$

where  $\phi(\tau, \xi)$  denotes the value at time  $\tau$  of the solution of (34) starting from  $\xi$  at time 0?



Before we start, let us recall the basic conditions verified by  $\varphi$  and  $\psi$ . We assume that  $\varphi$  is increasing,  $\varphi(0) = 0$  and  $\varphi(x) \geq x$  for  $x \geq 0$ , while  $\psi$  is decreasing,  $\psi(\infty) \geq 0$ ,  $\varphi$  and  $\psi$  are continuous. Further conditions will be introduced later.

Relation (26) can be written in a different way by expressing the fact that it took the time  $\tau(\xi)$  for the solution to go from  $\xi$  to  $\varphi(\xi)$ . For this formulation, let us select an antiderivative  $G$  of  $1/g$ ; that is,

$$(35) \quad G(x) = \int_{\alpha}^x \frac{d\xi}{g(\xi)}.$$

We choose  $\alpha > 0$  because, in most cases, we expect that  $g(0) = 0$ , which means that the integral of  $1/g$  from 0 to  $x$  might be unbounded. In terms of  $G$ , expression (26) reads as

$$(36) \quad \psi(\xi) = G[\varphi(\xi)] - G(\xi),$$

which leads to the functional equation

$$(37) \quad \psi = G \circ \varphi - G.$$

This is the equation to consider. The unknown function  $G$  should be at least  $C^1$  on  $\mathbf{R}^+ - \{0\}$ , increasing and such that (36) holds on  $\mathbf{R}^+ - \{0\}$ .

Let us make the assumptions on  $\varphi$  and  $\psi$  more specific. Remember that  $\varphi$  is the size just before division of a cell born with size  $x$ . We expect that  $\varphi(x) > x$ . If, however, there is  $\bar{x} > 0$  such that  $\varphi(\bar{x}) = \bar{x}$ , then the cell cycle length for cells born with size  $\bar{x}$  is expected to be 0, that is,  $\psi(\bar{x}) = 0$ . Then, for  $x > \bar{x}$ , we will have  $\psi(x) = 0$ , also; therefore  $\varphi(x) = x$ . This means that cells of size not less than  $\bar{x}$  do not grow, do not divide, and do not enter the dynamics in which we are interested. Thus, we can safely work on the interval  $[0, \bar{x})$ . This includes the cases where  $\bar{x} = \infty$  and  $\psi(\infty) = 0$ .

We will henceforth be concerned only with finding  $G$  on  $[0, \bar{x})$ , where  $\bar{x}$  is the first value for which  $\varphi(\bar{x}) = \bar{x}$  and consequently where  $\psi(\bar{x}) = 0$ , admitting the possibility of  $\bar{x} = \infty$ .

Let us turn to (37). Let us observe first that, if a function  $G$  exists, then  $G(0) = -\infty$ . In fact, as  $x$  goes to 0,  $\varphi(x)$  approaches 0, too, and  $\psi(x)$  stays away from 0. So, the difference of the values of  $G$  at points  $x$  and  $\varphi(x)$  that go jointly to 0 stays far from 0. Therefore it is impossible that  $G$  has a finite limit at 0, and, since it is increasing, it must diverge to  $-\infty$ . For each  $n \in \mathbf{N}$ , let us denote  $\theta_n = \psi + \psi \circ \varphi + \dots + \psi \circ \varphi^{n-1}$ . If  $G$  is a solution of (37), we have, for each  $n$ ,

$$G \circ \varphi^n = G + \theta_n.$$

From the facts that  $\theta_n$  is decreasing and  $G + \theta_n$  is increasing, we can deduce an estimate for  $\theta_n$ . Let  $x, y$  be such that  $0 < x < y < \bar{x}$ . Then

$$0 \leq \theta_n(x) - \theta_n(y) \leq G(y) - G(x),$$

which, in view of the monotonicity of each function  $\psi \circ \varphi^n$ , yields the convergence of the series of differences  $\psi \circ \varphi^j(x) - \psi \circ \varphi^j(y)$ , that is,

$$\sum_{j \geq 0} [\psi \circ \varphi^j(x) - \psi \circ \varphi^j(y)] \leq G(y) - G(x).$$

It may be worth noting that with the assumptions of monotonicity made on  $\varphi$  and  $\psi$ , the series of the differences  $\psi \circ \varphi^j(x) - \psi \circ \varphi^j(y)$  converges pointwise on the interval  $(0, \bar{x})$ . This is always true, even if no function  $G$  can be found. In fact, for each  $0 < x < y < \bar{x}$ , there exists  $n \geq 1$  such that  $x < y < \varphi^n(x)$ . We can then bound the sum of the  $N$  first terms of the series by the sum of the  $N$  first terms of  $\psi \circ \varphi^j(x) - \psi \circ \varphi^{j+n}(x)$ , which is bounded above by  $\sum_{k=0}^{n-1} \psi \circ \varphi^k(x)$ .

Let us choose a point  $x_0, 0 < x_0 < \bar{x}$  and define a function  $\mathcal{G}$

$$(38) \quad \mathcal{G}(x) = \sum_{j \geq 0} [\psi \circ \varphi^j(x_0) - \psi \circ \varphi^j(x)].$$

$\mathcal{G}$  is well defined on  $(0, \bar{x})$  and verifies (37). By construction,  $\mathcal{G}$  is increasing. Let us note that, if we move  $x_0$  to another position  $x_1$  and define  $\mathcal{G}_1$  accordingly, then  $\mathcal{G} - \mathcal{G}_1 = \text{constant}$ . Of course,  $\mathcal{G}$  is our candidate as a solution of (37). As noted above, such a function  $\mathcal{G}$  can always be defined. However, the function  $G$  we are seeking has smoothness properties that  $\mathcal{G}$  does not necessarily enjoy. We will now describe the properties that  $\mathcal{G}$  should have if a function  $G$  is to exist.

Let us note the inequality

$$(39) \quad |\mathcal{G}(x) - \mathcal{G}(y)| \leq |G(x) - G(y)|,$$

verified for each  $0 < x, y < \bar{x}$ .

Using (39), we can easily see that a necessary condition for  $G$  to exist, being continuous on  $(0, \bar{x})$  is that  $\mathcal{G}$  be continuous on the same interval. If we require continuity only, then we can take  $G = \mathcal{G}$ . Similarly, a necessary condition for  $G$  to exist, being locally Lipschitz continuous on  $(0, \bar{x})$ , is that  $\mathcal{G}$  be locally Lipschitz continuous, also. Moreover, if we assume that  $\varphi$  and  $\psi$  are differentiable, then a necessary condition for  $G$  to be locally Lipschitz continuous is that the series of the derivatives  $(\psi \circ \varphi^j)'$  converge pointwise on  $(0, \bar{x})$  and its sum be locally uniformly bounded on this interval.

We will now state sufficient conditions that give  $H$  the smoothness properties required for  $G$ .

**THEOREM 3.** *Suppose that the series of the first and second derivatives of  $\psi \circ \varphi^j$  converge uniformly on each bounded closed interval contained in  $(0, \bar{x})$ . Then a function  $G$  exists, which verifies (37), is increasing, and  $C^2$  on  $(0, \bar{x})$ .*

*Proof.* We must only check that the function  $\mathcal{G}$  defined by expression (38) enjoys all the properties stated in the theorem. We already noted that  $\mathcal{G}$  is increasing and, of course, is a solution of (37). It is easy to see that, with the assumptions made in the theorem,  $\mathcal{G}$  is differentiable, and its derivative is the sum of the series of the first derivatives of  $\psi \circ \varphi^j$ , and the derivative is continuously differentiable.

*Remark.* If the series  $\psi \circ \varphi^j$  itself converges, then any solution of (37) must be bounded near to  $\bar{x}$  and therefore must have a finite limit at  $\bar{x}$ . In this situation,  $G$  is uniquely determined up to the addition of a constant. If we are assuming that the series  $\psi \circ \varphi^j$  converges but do not make an assumption for the derivatives, we still have  $G$  uniquely determined. It may then happen that the growth function  $g$  derived from  $G$  will be continuous but not differentiable. It may happen that  $\varphi$  and  $\psi$  will be chosen so that  $G$  cannot be differentiated. In other words, it may happen that  $\varphi$  and  $\psi$  are not related to any growth function.

As a complement to §3, let us state the (ACE) problem at which we arrive, provided that we can find a growth function  $g$ . Note that in this situation,  $\phi$  is just the flow generated by (34) so that, if we keep the notation of §3,  $\phi = X$ , and

$\phi^{-1}(a, x) = X(-a, x)$ . The (ACE) problem is defined by the following three relations satisfied simultaneously:

$$(40) \quad \begin{aligned} \frac{\partial p}{\partial t} + \frac{\partial p}{\partial a} + \frac{\partial(pg)}{\partial x} &= 0, & a < \psi \circ X(-a, x); \\ p &= 0, & a \geq \psi \circ X(-a, x); \end{aligned}$$

$$(41) \quad p(t, 0, x) = 2 \int_0^\infty f[x, \varphi(z)]p[t - \psi(z), 0, z]dz;$$

$$(42) \quad p(0, a, x) = p_0(a, x).$$

## 5. PDE formulation without age structure.

**5.1. Introductory remarks.** Another frequently used equation of cell population dynamics is

$$(43) \quad \frac{\partial q}{\partial t} + \frac{\partial[g(x)q]}{\partial x} = B - D$$

[19, p. 186], where  $q(t, x)$  is the cell population density with respect to the cell size  $x$ ;  $P(t) = \int_0^\infty q(t, x)dx$  is the total cell count at time  $t$ ; and  $g(x)$  is the growth function. The growth function determines the evolution of cell size during the cell cycle, through the differential equation (34) of §4.  $X(t, x)$  is the flow associated with (34), assuming that  $g$  verifies hypotheses yielding existence and uniqueness of solutions of (34). Equation (43) is the analogue of  $\mathcal{D}p = B - D$ , which is stated after Lemma 2 in §4.

The left-hand side of (43) is a transport equation associated with cell growth. It is balanced on the right-hand side by the birth rate minus the death rate. The dependence of these two quantities upon  $q$  is not known. A commonly admitted view (or hypothesis) is that they are proportional to the actual population density. Neglecting the natural mortality and denoting by  $b(x)$  the “fission” [19, p. 47], or rather division, rate of cells of size  $x$ , we then have  $B(t, x) = 4b(2x)q(t, 2x)$  and  $D(t, x) = b(x)q(t, x)$ . This leads to equation

$$(44) \quad \frac{\partial q}{\partial t} + \frac{\partial[g(x)q]}{\partial x} = 4b(2x)q(t, 2x) - b(x)q(t, x).$$

That  $B$  and  $D$  should be of the above form is not obvious. Now we consider the special case of our basic model, as considered in §4. This proves to be one of the examples for which  $B$  and  $D$  have a different form.

We assume that a growth function  $g$  can be associated with the equation. We may, for example, suppose that  $\varphi$  and  $\psi$  verify the conditions of Theorem 2 or even that  $g$  and  $\varphi$  are given and  $\psi$  is derived from them. The distinctive feature of the model is that, instead of assuming that division occurs on a fraction  $b(x)$  of cells of size  $x$  no matter at which point of their cycle some may be, we consider that division occurs when cells reach a critical size determined by their birth size.

We will express the rates  $B$  and  $D$  in terms of  $n$ , so that we arrive at an equation having  $q$  in the transport part and  $n$  in the birth-death balance. Replacing  $n$  by  $q$  in the balance part is left by us as an open problem.

The final remark of this section concerns the derivation of an equation in  $q$  by direct integration of the equation in  $p$  given at the end of §3. As stated in §1,

$$q(t, x) = \int_0^\infty p(t, a, x) da.$$

Some terms of the transport equation integrate easily: such is the case for  $\partial p/\partial t$  and  $\partial p/\partial a$ . However, the computation of  $(\partial/\partial x)(pg)$  requires more care. The jump of  $p$  at  $a = \psi \circ X(-a, x)$  introduces a  $\delta$  function when integrating on 0 to  $\infty$ . So we will proceed from  $q$ .

**5.2. The PDE formulation including functions  $q(t, x)$  and  $n(t, x)$ .** The relations between  $q$  and  $n$  are expressed in the following theorem.

**THEOREM 4.** *Let  $q$  and  $n$  denote, respectively, the population density with respect to size and the size density of the birth rate. Then  $q$  and  $n$  verify the following equations:*

$$(45) \quad \frac{\partial q}{\partial t} + \frac{\partial [g(x)q]}{\partial x} = n(t, x) - n[t - \psi \circ \varphi^{-1}(x), \varphi^{-1}(x)](\varphi^{-1})'(x),$$

$$(46) \quad q(t, x) = \int_{t-\psi \circ \varphi^{-1}(x)}^t n[s, X(s-t, x)] \frac{\partial X(s-t, x)}{\partial x} ds.$$

The form of the  $B$  and  $D$  terms is different from that commonly assumed. Also, a closed-form equation for  $q$  is difficult to derive, although, given  $n$ , it can be computed. These remarks suggest that use of  $q$  in modeling may be impractical in some cases.

**6. Remarks.** The motivation for this work has been a desire to unify approaches to modeling dynamics of structured cell populations, developed by others and by ourselves, stemming from two different mathematical roots: PDEs and branching processes.

In the branching-processes approach, the leading role is played by counting processes of births and deaths of particles (cells). The expectations of the counting processes are obtained as solutions of the forward or backward equation, the equivalence of which hinges on repeated application of the unsymmetric Fubini theorem.

In the PDE approach, an additional structural variable, particle (cell) age, is required. If the age variable is employed, the resulting PDE is proved equivalent to the forward equation of the branching process, provided that the existence of the density of the expected counting process of deaths is assumed. In this approach, an important role is also played by the growth function. In this paper, we slightly generalized this notion and provided proof of its existence.

A frequent approach to model population dynamics is to use the PDE without the age variable. In this case, the existence of the branching process counterpart is not obvious. This casts some doubt on the validity of such models to describe structured cell populations.

Another paper known to us, which considers the question of relationships between the stochastic and deterministic approaches, has been recently written by Jagers [10].

**Appendix A. Proof of Theorem 1.** We start from convergence of approximations  $N_i(t, x; z)$ . Each  $N_i$  can be represented as  $N_i = \sum_{j=0}^i M_j$ , where  $M_0(t, x; z) = \mathbf{1}(x-z)$  and

$$(47) \quad M_{j+1}(t, x; z) = 2 \int_0^t \int_0^\infty h(\xi, \tau, z) M_j(t-\tau, x, \xi) d\xi d\tau.$$

Let us define

$$m_j(t, x) = \sup_{\tau \in [0, t]} |M_j(\tau, x, z)|.$$

We have  $m_0(t, x) = 1$ , and, based on iteration of (47) and on the fact that  $\int_0^\infty h(\xi, \tau, z)d\xi = \gamma(\tau, z)$ ,

$$m_j(t, x) \leq 2^j g_j(t), \quad j \geq 1, \quad t \geq 0,$$

where

$$g_1(t) = \sup_z \int_0^t \gamma(\tau, z) d\tau,$$

$$g_{j+1}(t) = \sup_z \int_0^t \gamma(\tau, z) g_j(t - \tau) d\tau.$$

The series  $\sum_{j \geq 1} 2^j g_j(t)$  converges if (for example) hypothesis  $(H_*)$  is satisfied. The limit  $\lim_{i \rightarrow \infty} \bar{N}_i$  is a solution of the backward equation (1).

For the proof of the uniqueness, let us assume that two solutions of the backward equation (1) are  $N^{(1)}$  and  $N^{(2)}$ . Then  $Z = N^{(1)} - N^{(2)}$  satisfies

$$(48) \quad Z(t, x; z) = 2 \int_0^t \int_0^\infty h(\xi, \tau, z) Z(t - \tau, x, \xi) d\xi d\tau.$$

Iterating the solution of (48) and using estimates as above shows that  $Z(t, x; z) = 0$ .

That the solution of the forward equation (2) is unique (in its class) is demonstrated by considering an equation for  $Z = N^{(1)} - N^{(2)}$  dual to (48), below:

$$(49) \quad Z(t, x; z) = 2 \int_0^t \int_0^\infty H(x, \tau, \xi) d\xi Z(t - \tau, \xi; z) d\tau.$$

Since  $Z(t, \cdot, z)$  is absolutely continuous (by absolute continuity of  $H(\cdot, t, \xi)$ ; see above), the following is verified:

$$(50) \quad \int_0^x \zeta(t, y; z) dy = 2 \int_0^t \int_0^\infty \left[ \int_0^x h(y, \tau; \xi) dy \right] \zeta(t - \tau, \xi; z) d\xi d\tau.$$

Since  $Z(t, \cdot, z)$  is a difference of two nondecreasing functions,  $|\zeta(t, \cdot; z)|$  is integrable and  $\int_0^\infty |\zeta(t, y; z)| dy$  is bounded on finite intervals of  $t$ . Therefore, (50) implies that

$$(51) \quad \bar{Z}(t, z) \leq A \int_0^t \bar{Z}(\tau, z) d\tau, \quad \bar{Z}(t, z) = \sup_{u \in [0, t]} \int_0^\infty |\zeta(u, y; z)| dy.$$

Iterating inequality (51), we obtain  $\bar{Z}(t, z) \leq (A^j/j!) \bar{Z}(t, z)$  for any  $j \geq 1$ , and thus  $\bar{Z}(t, z) = 0$ . This yields uniqueness of solution of the forward equation (2).

**Appendix B. Proof of Theorem 4.** To prove expression (45), we must only identify the  $B$  and  $D$  terms of (43). By definition of  $n$ , we have

$$(52) \quad B = n(t, x).$$

Now it is necessary to find an expression of  $D$  in terms of  $n$ . Let us select in the product  $\mathbf{R} \times \mathbf{R}$  a set of the form  $(t_1, t_2) \times \Omega$ . We want to estimate the number of cells that, during the time interval  $(t_1, t_2)$ , leave the set  $\Omega$ : These are cells that divide during this time interval at a size  $x \in \Omega$ . Here, we assume that  $\Omega$  is so small that it does not contain at the same time  $x$  and  $\varphi(x)$ . For each pair  $(t, x) \in (t_1, t_2) \times \Omega$  such that a cell of size  $x$  divides at time  $t$ , the initial size  $x_0$  of such a cell is  $x_0 = \varphi^{-1}(x)$ , and the time when this cell was born is  $t_0 = t - \psi \circ \varphi^{-1}(x)$ .

So the pairs  $(t_0, x_0)$  that correspond to cells born at time  $t_0$  with size  $x_0$ , which divide at some time between  $t_1$  and  $t_2$  with size in  $\Omega$ , fill the domain

$$\Delta = \{(t_0, x_0) : x_0 \in \varphi^{-1}(\Omega), t_1 - \psi(x_0) < t_0 < t_2 - \psi(x_0)\}.$$

The number of such cells is given by the double integral

$$\int \int_{\Delta} n(t_0, x_0) dt_0 dx_0 = \int_{\varphi^{-1}(\Omega)} \left[ \int_{t_1 - \psi(x_0)}^{t_2 - \psi(x_0)} n(t_0, x_0) dt_0 \right] dx_0.$$

After the change of variables  $(t_0, x_0) \rightarrow (t, x)$ , defined by

$$\begin{aligned} x_0 &= \varphi^{-1}(x), \\ t_0 &= t - \psi \circ \varphi^{-1}(x), \end{aligned}$$

we arrive at

$$\int_{\Omega} \int_{t_1}^{t_2} n[t - \psi \circ \varphi^{-1}(x), x] (\varphi^{-1})'(x) dt dx.$$

This expression should be equal to the integral of  $D$  over the product  $(t_1, t_2) \times \Omega$ , for each admissible  $\Omega$  and each interval  $(t_1, t_2)$ , implying the equality of the functions inside the integral. Therefore, we can conclude that

$$D = n[t - \psi \circ \varphi^{-1}(x), x] (\varphi^{-1})'(x).$$

Based on this relation, we deduce (45).

We turn now to (46), the computation of  $q$  in terms of  $n$ . Remember that  $q$  is a density with respect to  $x$ . For each measurable subset  $\Omega$ ,  $\int_{\Omega} q(t, x) dx$  is the number of cells with size  $x \in \Omega$  that are in the cycle at time  $t$ . We want to express this quantity in terms of  $n$ . We must only evaluate the number of cells born before  $t$ , whose size at time  $t$  is less than the size at division and which lies in  $\Omega$ . Let us first determine the pairs  $(t_0, x_0)$  for such cells. For each  $x \in \Omega$  such that  $x$  is the size of a cell that at time  $t$  is not ready to divide, the initial size  $x_0$  must be such that

$$\varphi^{-1}(x) < x_0 < x.$$

Now, in terms of  $(t_0, x_0)$ , we have  $x = X(t - t_0, x_0)$  or, equivalently,  $x_0 = X(t_0 - t, x)$ . So the condition on  $x_0$  can be expressed as a condition on  $t_0$ , namely,

$$\varphi^{-1}(x) < X(t_0 - t, x) < x,$$

which is equivalent to

$$\tau(t, x) < t_0 < t.$$

$\tau(t, x)$  is the time  $\tau < t$  such that  $\varphi^{-1}(x) = X(\tau - t, x)$ , which, in view of (15), yields  $t - \tau = \psi \circ \varphi^{-1}(x)$ , that is,

$$(53) \quad \tau = t - \psi \circ \varphi^{-1}(x).$$

Let us denote by  $\Delta$  the set of admissible values  $(t_0, x_0)$

$$\Delta = \{(t_0, X(t_0 - t, x)) : x \in \Omega, \tau(t, x) < t_0 < t\}.$$

We will now evaluate  $\int \int_{\Delta} n(t_0, x_0) dt_0 dx_0$ , in terms of the variables  $(t_0, x)$ . Note that the determinant of the Jacobian matrix of the transformation of  $(t_0, x) \rightarrow (t_0, x_0)$  defined by  $x_0 = X(t_0 - t, x)$  is equal to  $\partial X(t_0 - t, x)/\partial x$ . This yields

$$\int \int_{\Delta} n(t_0, x_0) dt_0 dx_0 = \int_{\Omega} \left[ \int_{\tau(t,x)}^t n[s, X(s - t, x)] \frac{\partial X(s - t, x)}{\partial x} ds \right] dx.$$

However, this is also equal to  $\int_{\Omega} q(t, x) dx$ . Since this equality is true for each  $\Omega$ , we can conclude that the integrands are equal, which, in view of (53), yields expression (46).

The formal manipulations carried out above do not guarantee the existence of  $q$  satisfying the system (45), (46). In summary, we first wrote the equation satisfied by  $q$ , then, assuming that  $q$  exists, we used its properties as a population density to express it in terms of  $n$ . Having  $q$  as a function of  $n$ , which, by the theory developed for example in [15], exists, we will now check that  $q$  is indeed a solution of (45).

We assume sufficient regularity on  $n$  so that all the partial differentiations needed in the next computations can be performed. Let us recall expression (46) where

$$q(t, x) = \int_{t-\psi \circ \varphi^{-1}(x)}^t n[s, X(s - t, x)] \frac{\partial X(s - t, x)}{\partial x} ds.$$

Taking the partial derivative of the right-hand side with respect to  $t$ , we obtain

$$\begin{aligned} n(t, x) - n\{t - \psi \circ \varphi^{-1}(x), X[-\psi \circ \varphi^{-1}(x), x]\} \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x} \\ + \int_{t-\psi \circ \varphi^{-1}(x)}^t \frac{\partial}{\partial t} \left\{ n[s, X(s - t, x)] \frac{\partial X(s - t, x)}{\partial x} \right\} ds. \end{aligned}$$

Taking now the partial derivative with respect to  $x$  of  $g(x)q(t, x)$ , we obtain

$$\begin{aligned} (\psi \circ \varphi^{-1})'(x)g(x)n\{t - \psi \circ \varphi^{-1}(x), X[-\psi \circ \varphi^{-1}(x), x]\} \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x} \\ + \int_{t-\psi \circ \varphi^{-1}(x)}^t \frac{\partial}{\partial x} \left\{ g(x)n[s, X(s - t, x)] \frac{\partial X(s - t, x)}{\partial x} \right\} ds. \end{aligned}$$

We will first check the quantities outside the integrals and show that they yield the right-hand side of (45). Summing up all the terms outside the integrals, we obtain

$$\begin{aligned} n(t, x) - n\{t - \psi \circ \varphi^{-1}(x), X[-\psi \circ \varphi^{-1}(x), x]\} \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x} \\ + (\psi \circ \varphi^{-1})'(x)g(x)n\{t - \psi \circ \varphi^{-1}(x), X[-\psi \circ \varphi^{-1}(x), x]\} \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x}. \end{aligned}$$

Writing the last two terms together yields

$$n(t, x) - n\{t - \psi \circ \varphi^{-1}(x), X[-\psi \circ \varphi^{-1}(x), x]\} \\ \cdot \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x} [1 - (\psi \circ \varphi^{-1})'(x)g(x)].$$

We will next show that

$$(54) \quad \frac{\partial X[-\psi \circ \varphi^{-1}(x), x]}{\partial x} [1 - (\psi \circ \varphi^{-1})'(x)g(x)] = (\varphi^{-1})'(x).$$

Note that, if we accept this, then we obtain the desired conclusion for the terms outside the integrals. To derive (54), we start from expression (33)

$$X[\psi(x), x] = \varphi(x).$$

By differentiation, this leads to

$$g\{X[\psi(x), x]\}\psi'(x) + (\partial/\partial x)X[\psi(x), x] = \varphi'(x).$$

Substituting  $\varphi^{-1}$  for  $x$  into this expression and dividing both sides by  $\varphi' \circ \varphi^{-1}(x) = [(\varphi^{-1})'(x)]^{-1}$ , we find that

$$1 - g(x)(\psi \circ \varphi^{-1})'(x) = (\partial/\partial x)X[\psi \circ \varphi^{-1}(x), \varphi^{-1}(x)](\varphi^{-1})'(x).$$

The conclusion then follows from the standard identity  $(\partial/\partial x)X[-t, X(t, y)] = [(\partial/\partial x)X(t, y)]^{-1}$ , applied to  $t = \psi \circ \varphi^{-1}(x)$ ,  $y = \varphi^{-1}(x)$ : by multiplication of both sides of the above equality by  $(\partial/\partial x)X[-\psi \circ \varphi^{-1}(x), x]$ , we reduce the right-hand side to  $(\varphi^{-1})'(x)$ . As a result, we are left with

$$\int_{t-\psi \circ \varphi^{-1}(x)}^t \left\{ \frac{\partial}{\partial t} \left\{ n[s, X(s-t, x)] \frac{\partial X(s-t, x)}{\partial x} \right\} \right. \\ \left. + \frac{\partial}{\partial x} \left\{ g(x)n[s, X(s-t, x)] \frac{\partial X(s-t, x)}{\partial x} \right\} \right\} ds.$$

We want to show that this quantity is equal to zero. It is enough to show that the integrand is equal to zero. Introducing the function

$$(55) \quad \nu(t, x) = \int_0^x n(t, y)dy,$$

the first term of the integrand is reduced to

$$(\partial/\partial t)(\partial/\partial x)\{\nu[s, X(s-t, x)]\}.$$

We will now show that the other term is equal to

$$-(\partial/\partial x)(\partial/\partial t)\{\nu[s, X(s-t, x)]\},$$

which, in view of our assumptions of  $n$  being smooth enough, will allow us to conclude that the integrand is equal to zero.

For that computation, we will write  $g(x)(\partial/\partial x)X(s-t, x)$  in a different form. Note that, differentiating the identity  $x = X[t, X(-t, x)]$  with respect to  $x$ , we obtain

$$g(x)(\partial/\partial x)X(t, x) = g[X(t, x)].$$

Substituting the above right-hand side for  $g(x)(\partial/\partial x)X(s-t, x)$  inside  $g(x)n[s, X(s-t, x)](\partial/\partial x)X(s-t, x)$ , we arrive at  $n[s, X(s-t, \partial x)]g[X(s-t, x)]$ , which, in terms of  $\nu$ , reads as  $-(\partial/\partial t)\{\nu[s, X(s-t, x)]\}$ . This concludes the proof of Theorem 4.



## REFERENCES

- [1] B. ALBERTS ET AL., *Molecular Biology of the Cell*, Garland, New York, 1989, pp. 727–786.
- [2] O. ARINO, D. E. AXELROD, AND M. KIMMEL, EDs., *Mathematical Population Dynamics*, Lecture Notes in Pure and Appl. Math., Marcel Dekker, New York, 1991.
- [3] O. ARINO AND M. KIMMEL, *Asymptotic analysis of a cell cycle model based on unequal division*, SIAM J. Appl. Math., 47 (1987), pp. 128–145.
- [4] ———, *Asymptotic behavior of a nonlinear functional-integral equation of cell kinetics with unequal division*, J. Math. Biol., 27 (1989), pp. 341–354.
- [5] ———, *Asymptotic behavior of nonlinear semigroup describing a model of selective growth regulation*, J. Math. Biol., 29 (1991), pp. 289–314.
- [6] O. ARINO, M. KIMMEL, AND M. ZERNER, *Analysis of a cell population model with unequal division and random transition*, in *Mathematical Population Dynamics*, O. Arino, D. E. Axelrod, and M. Kimmel, eds., Lecture Notes in Pure and Appl. Math., Marcel Dekker, New York, 1991, pp. 3–12.
- [7] R. H. CAMERON AND W. T. MARTIN, *An unsymmetric Fubini theorem*, Bull. Amer. Math. Soc., 47 (1941), pp. 121–125.
- [8] A. GRABOSCH, *Translation semigroups and their linearizations on spaces of integrable functions*, Trans. Amer. Math. Soc., 311 (1989), pp. 357–390.
- [9] T. E. HARRIS, *The Theory of Branching Processes*, Springer, Berlin, 1963.
- [10] P. JAGERS, *The Deterministic Evolution of General Branching Populations*, 25, Dept. of Mathematics, Chalmers University of Technology, The University of Göteborg, Göteborg, Sweden, 1992, preprint.
- [11] M. KIMMEL, *Cellular population dynamics, I: Model construction and reformulation*, Math. Biosci., 48 (1980), pp. 211–224.
- [12] ———, *Cellular Population Dynamics, II: Investigation of Solutions*, Math. Biosci., 48 (1980), pp. 225–239.
- [13] ———, *Equivalence result for integral equations with applications to branching processes*, Bull. Math. Biol., 44 (1981), pp. 1–15.
- [14] ———, *The point process approach to age- and time-dependent branching processes*, Adv. in Appl. Probab., 15 (1983), pp. 1–20.
- [15] ———, *Metabolic events in the cell cycle of malignant and normal cells*, in *Cancer Modeling*, J. R. Thompson and B. W. Brown, eds., Marcel Dekker, New York, pp. 215–235.
- [16] M. KIMMEL AND O. ARINO, *Cell cycle kinetics with supramitotic control, two cell cycles, and unequal division: A model of transformed embryonic cells*, Math. Biosci., 105 (1991), pp. 47–79.
- [17] M. KIMMEL AND D. E. AXELROD, *Mathematical model of the dynamics of unequal division, growth regulation and colony size of mammalian cells*, J. Theoret. Biol., 1991, to appear.
- [18] M. KIMMEL, Z. DARZYNKIEWICZ, O. ARINO, AND F. TRAGANOS, *Analysis of a cell cycle model based on unequal division of metabolic constituents to daughter cells during cytokinesis*, J. Theoret. Biol., 110 (1984), pp. 637–664.
- [19] J. A. J. METZ AND O. DIEKMANN, EDs., *The Dynamics of Physiologically Structured Populations*, Lecture Notes in Biomath., 68, Springer-Verlag, New York, 1986.
- [20] R. G. STAUDTE, M. GUIGUET, AND M. C. D'HOOGHE, *Additive models for dependent cell populations*, J. Theoret. Biol., 109 (1984), pp. 127–146.
- [21] G. F. WEBB, *Random transitions, size control, and inheritance in cell population dynamics*, Math. Biosci., 85 (1987), pp. 71–91.