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Production, Development, and Maturation of Red Blood Cells

A Mathematical Model

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I. INTRODUCTION

The blood production system in the human body can be considered as a structured population in at least two respects. First, it consists of several compartments, whose interaction is regulated by an unknown number of proteins. Moreover, cells within the same compartment may behave differently due to different physiological characteristics, such as hemoglobin content. In this paper we propose a structured population model in the spirit of Metz and Diekmann (1986). The basic assumption is that the cell population responsible for the production of blood cells consists of three compartments: the stem cells, the precursor cells, and the blood cells. Furthermore, we assume that the cells of the second compartment can be distinguished according to their maturation level.

Adopting the framework of dual semigroups as developed by Clément et al. (1987a,b, 1989), we reformulate our model as an abstract quasi-linear Cauchy problem. The quasi-linear character of the system is due to the assumption that the maturation velocity of cells depends, among other factors, on the concentration of some protein. In Grabosch and Heijmans (1988) we have investigated a similar Cauchy problem, but without the extra complication of dual semigroups. This duality framework is necessary to model the (nonlinear) boundary condition that describes the influx of new precursor cells from the first compartment.

In Section II we present a rather detailed discussion of the blood cell production system in the human body. In Section III we present our model and suggest some simplifications. We prove well-posedness of our model in Section IV by showing that it has a unique solution. From biological considerations it is clear that this solution has to be positive: That such is indeed the case is shown in Section V using some advanced techniques from functional analysis. In Section VI we prove the principle of linearized stability. The paper is concluded with some remarks in Section VII.

II. BLOOD PRODUCTION SYSTEM

The production of the various mammalian blood components is one of the most complex processes in humans (see, e.g., Wintrobe, 1967). The blood cell production system regulates the supply and maintenance of most blood components, such as the red blood cells (erythrocytes), platelets (megakaryocytes), and some of the white blood cells (granolocytes, neutrophils). It is well known that essential parts of the blood production system take place in the bone marrow, other parts in the blood fluid itself. Nevertheless, the knowledge about all essential physiological processes involved in the production process is by no means complete and the very exact regulation mechanisms used to maintain approximately constant cell numbers is most incomprehensible. Indeed, to maintain an approximate constant number of all different cell types, a very effective and precise regulation has to take place. For example, in humans about 2.64×10^9 red blood cells/kg are destroyed daily and have to be replaced by new ones to maintain an approximate constant number of red blood cells. The normal number of erythrocytes present in humans is about 3.1×10^{11} cells/kg. Moreover, sudden disturbances, which may occur due to sudden blood loss (e.g., caused by an accident), or gain (e.g., caused by a blood transfusion) have to be smoothed down or up in the shortest possible time. Nevertheless, sometimes this regulation fails and the system is disturbed and gets out of control. One can observe oscillating cell numbers, reduced or increased (fixed) numbers of cells, or just "randomly" varying cell numbers. These irregularities manifest as such well-described diseases as periodic hematopoiesis, anemias, and leukemias.

The main processes that have to be accomplished by the blood production system are basic production, differentiation, amplification, and maturation. The human blood production system can be split up in three (morphologically distinguishable) compartments where these physiological processes take place. One can distinguish (1) the self-maintained stem cell compartment (located in the bone marrow), (2) the precursor cell compartment (located partly in the bone marrow and partly in the blood fluid), and (3) the blood cell compartment (located in the blood fluid). The only compartment capable of self-maintenance is the stem cell compartment. Here the "production" of new cells takes place. Already at this early stage of the development a first commitment toward a special cell line, such as the erythrocyte line, is settled. Cells entering the precursor stage are still morphologically indistinguishable from each other. In the precursor or transition stage, differentiation takes place. Cells pass through several successive stages. For example, in the erythrocyte line at least five morphologically different cell types are formed in succession (proerythrocytes, basophilic erythroblasts, polychromatic erythroblasts, orthochromatic erythroblasts, reticulocytes). The total number of cells increases during the precursor stage by a factor of 3, since cells undergo division independent of their morphological type. In average it takes about 2 days for a cell to transit through the precursor cell stage. Mitosis occurs only in the first precursor cell stages. The maturation level (e.g., the hemoglobin content of the cells), increases steadily during the time spent in the precursor stage. Transition to the blood compartment occurs at a morphologically not distinguishable point of the precursor cell stage. In the last stage of our subdivision, the blood cell compartent or blood fluid, the newly formed red blood cells are completely developed. One can observe different maturation levels, that is, a different hemoglobin content of the newly formed red blood cells. For an overview of the blood production system, see Fig. 1. Note that for the rest of this note we restrict our attention to the erythrocyte cell line.

Besides those morphological facts there is still a lot of uncertainty and speculation concerning how the regulation of this complex production system works. It is unquestioned that proteins play an important role in the regulation process. For red blood cell production, the protein erythropoietin seems to be of some importance. This influence has an obvious explanation from the following observation. A decreased number of red blood cells leads to a decreased amount of hemoglobin, thus to a decrease in the arterial oxygen tension. This stimulates the release of erythropoietin by the kidney. Finally, this protein causes an increased influx of red blood cells into the blood. Nevertheless, it seems not to be clear precisely what leads to the increased influx flow: a sudden release of nearly mature precursor cells, a higher division rate of stem cells, an increased flow from the

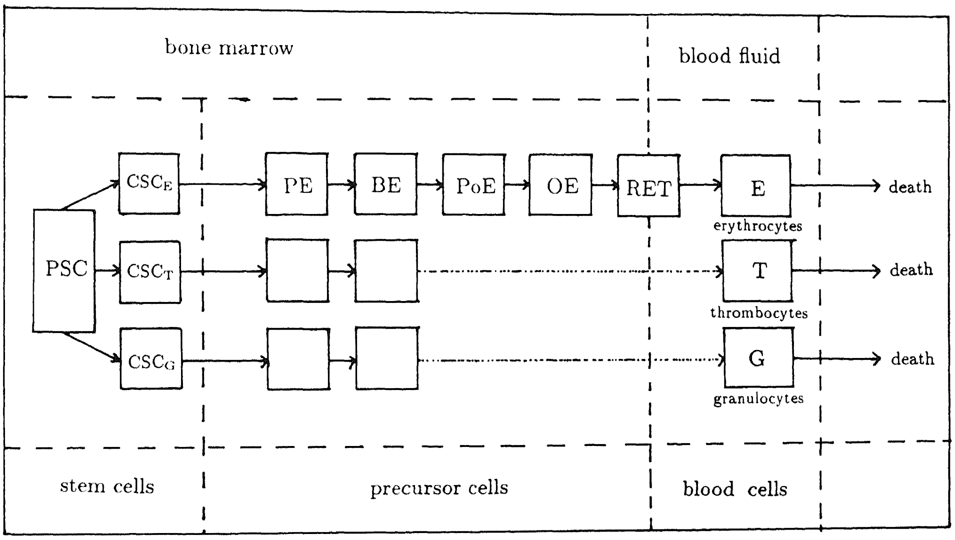

Figure 1 Morphological structure of the (red) blood production system with several differentiation stages and its location in the bone marrow and blood fluid. The diagram is restricted to the recognizable precursors of the erythrocyte cell line. A similar development occurs in the thrombocyte and granulocyte lines, which are not specified in detail. PSC, pluripotential stem cells; CSC, committed stem cells; PE, proerythroblast cells; BE, basophilic erythroblast cells; PoE; polychromatic erythroblast cells; OE, orthochromatic erythroblast cells; RET, reticulocytes; E, erythrocytes (red blood cells); T, thrombocytes (platelets); G, granulocytes (neutrophils, leukocytes).

stem cell compartment to the precursor cell compartment, a faster maturation velocity, a combination of these changes, or still another mechanism. A second protein that seems to be involved in the regulation of blood cell production is chalone, which is known to inhibit mitosis (see, e.g., Kirk et al., 1970) and appears to influence the dynamics (respectively, the production) of the stem cells (see, e.g., Kirk et al., 1970). A restricting factor for the maturation process seems to be the amount of iron available in the blood. This is clear by the fact that iron is one of the main constituents of hemoglobin. Similarly, there are some proteins and growth factors known to be of importance for the regulation of the other blood components. For example, in the myeloid cell line the protein granolopoietin and some less well known colony stimulating factors (CSFs) are involved. For the megakaryocyte line the protein thrombopoietin is of importance. The "natural" regulation mechanism for the different blood components is of course the destruction of blood cells with a cell-type specific rate and the production of new cells by the stem cells. But, as described above, there are many important steps in between which are responsible for the fine regulation. In a normally functioning (healthy) system, cell death does not seem to occur in the stem cell compartment or in the precursor cell stage, but it occurs naturally in the blood cell compartment. In the first two compartments, cell death may arise due to an artificial disturbance of the system. Nevertheless the physiological processes leading to exact regulation are more-or-less unknown. We get the schematical diagram of red blood cell production shown in Fig. 2.

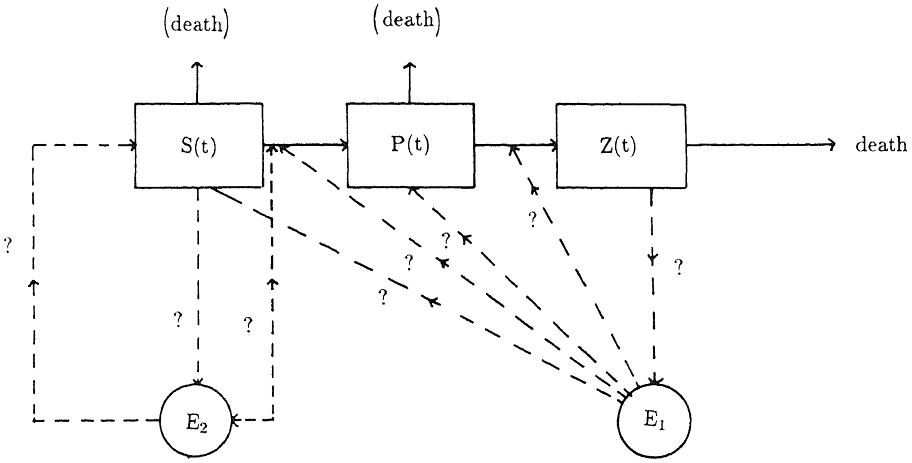

Figure 2 Schematical diagram of the red blood production system, including three different cell stages: stem cells S(t), precursor cells P(t), and blood cells Z(t). Two proteins may be involved in the regulation of cell production. There is some kind of short-range feedback (via the protein E_2) which regulates the stem cell number, and a long-range feedback (via the protein E_1) which regulates the precursor cell number. Cell loss occurs mainly in the blood cell compartment.

III. MATHEMATICAL MODEL

Many attempts have been made to describe the cell production system by a theoretical model that enables one to get at least some understanding of the observed deficiencies and to trace the mechanisms responsible for them. We mention especially the investigations of Mackey (1978, 1981), Mackey and Dörmer (1982), Arino and Kimmel (1986), Heijmans (1985), Kirk et al. (1970), Tarbutt and Blackett (1986), and Wheldon (1975).

To avoid complexity and thus to keep mathematical tractability, we try to concentrate on some (hopefully essential) features of the blood production system. Among others we are led by ideas of Mackey and Dörmer (1982). We formulate a model based on the observation that cell maturation is a continuous process taking place mainly in the percursor cell stage. Indeed, Mackey and Dörmer give a very illustrative diagram that shows the main ideas of their model (Mackey and Dörmer, 1982, Fig. 1).

Independent of the transition and maturation process in the precursor cell stage, cells undergo mitosis several times. Thus the maturation level is independent of the cell cycle position of a cell and independent of the transition between different "morphological" substages of the precursor cell stage. The velocity of maturation is supposed to depend indirectly (via a protein) on the number of mature cells. If there are few red blood cells, there is a lot of protein. A high amount of protein then leads to a high maturation velocity. We summarize these observations in Fig. 3, which will serve as a guide throughout the following discussion, in which we formulate and illustrate our mathematical model.

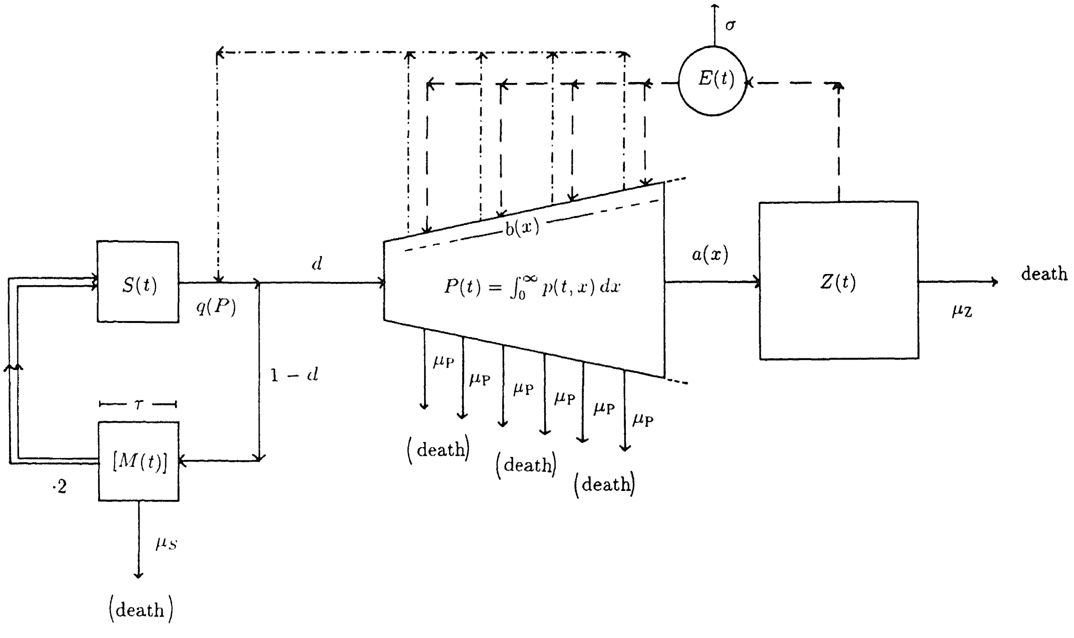

Figure 3 Schematic outline of the model for red blood cell production given by the differential equation system (2)–(6). See the text for details.

We consider three differentiation stages: the stem cell compartment, the precursor cell compartment, and finally, the blood cell compartment. The number of cells in these three compartments are denoted by $S(t)$, $P(t)$, and $Z(t)$, respectively. We assume, furthermore, that the precursor cells can be distinguished according to their maturation level x. We denote by $p(t, x)$ the density for the precursor cells with respect to the maturity level x at time t. Thus the total number of precursor cells at time t is given by $P(t) = \int_0^\infty p(t, x)\, dx$. Furthermore, we think of a protein (e.g., erythropoietin) acting in between the red blood cell compartment $Z(t)$ and the precursor cell stage $P(t)$ in such a way that a lot of protein slows down the maturation velocity of the precursor cells. Mathematically, this process can be described by an ordinary differential equation for the maturation $x(t)$ of an individual precursor cell:

$$\frac{dx}{dt}(t) = \tilde{\psi}(E(t))g(x(t)) \tag{1}$$

where $\tilde{\psi}(E)$ is a real-valued decreasing function in E. Note that we assume here that the maturation velocity can be written as the product of two terms, one depending on E and the other on x. The general case where the maturation velocity is an arbitrary function of the variables E and x would considerably complicate the mathematical analysis of the model.

Independent of the maturation process, the precursor cells undergo mitosis. The daughter cells of a dividing cell inherit the maturation level of their mother. We denote by $b(x)$ the division rate of cells with maturation level x. On the other hand, the progression or transit of precursor cells toward the blood compartment depends on the maturation level as well as on the maturation velocity, a low velocity leading to fewer cells passing to the blood cell compartment than a high velocity. To be precise, the probability per unit of time for a precursor cell with maturation level x to enter the blood cell compartment if the protein concentration is E is given by $\tilde{\psi}(E)a(x)$. In Diekmann et al. (1983) it is explained in detail that such an assumption corresponds to the situation where the probability to pass to the blood cell compartment is determined only by an increase in maturation level, and is independent of the time required to realize this increase. The death rates of precursor cells and blood cells are denoted by μ_P and μ_Z, respectively. This leads us to the following system of equations for $p(t, x)$ and $Z(t)$:

$$\begin{aligned}\frac{\partial}{\partial t}p(t,x) + \tilde{\psi}(E(t))\frac{\partial}{\partial x}(g(x)p(t,x)) &= b(x)p(t,x) - \tilde{\psi}(E(t))a(x)p(t,x) \\ &\quad - \mu_P p(t,x)\end{aligned} \tag{2}$$

$$\frac{d}{dt}Z(t) = -\mu_Z Z(t) + \tilde{\psi}(E(t))\int_0^\infty a(x)p(t,x)\, dx \tag{3}$$

Concerning the protein, we assume that it is produced by the red blood cells at the rate $h(Z(t))$, and that it disintegrates at the rate σ. This amounts to the following equation for $E(t)$:

$$\frac{d}{dt}E(t) = -\sigma E(t) + h(Z(t)) \tag{4}$$

To complete the description of the model, we need an equation governing the dynamics of the stem cell compartment, the true production centre of red blood cells, and a boundary condition at $x = 0$ describing the influx of precursor cells from the stem cell compartment.

Concerning the dynamics of S, we could follow the models of Mackey (1981) or Arino and Kimmel (1986). Depending on the number of cells in the precursor cell compartment (via the function q), cells leave a quiescent stage after division. A fraction $1 - d$ goes through the cell division process, whereas the other fraction d enters the precursor cell stage with a maturity level 0. One knows that hardly any quiescent cells die; thus we include a death rate μ_S only for the "active" part of the cell cycle of stem cells. If τ is the time duration of the cell division process, then $e^{-\mu_S\tau}$ is the fraction of cells that survive the mitotic phase, and the number of daughter cells at time t is $2(1-d)q(P_\tau(t))S_\tau(t)\,e^{-\mu_S\tau}$. Here $P_\tau(t) = P(t-\tau)$ and the same for S_τ. These assumptions would lead to the following delay equation for S (compare Fig. 3):

$$\frac{d}{dt}S(t) = 2(1-d)q(P_\tau(t))S_\tau(t)\,e^{-\mu_S\tau} - dq(P(t))S(t) \tag{5}$$

and to the following boundary condition for p:

$$\tilde{\psi}(E(t))g(0)p(t,0) = dq(P(t))S(t) \tag{6}$$

In the literature one often assumes that

$$q(P) = c\frac{\theta^n}{\theta^n + P^n}$$

for $c, \theta > 0$ and $n \in \mathbb{N}$.

To keep our model tractable, however, we assume that S is constant and that the influx of precursor cells at the boundary is given by (6) with S constant; that is [writing $q(P)$ instead of $dq(P)S$],

$$\tilde{\psi}(E(t))g(0)p(t,0) = q(P(t)) \tag{7}$$

Note that the latter assumption can be justified by assuming that the time scale of equation (5) is slow. There does, however, exist no evidence for such an assumption. Implicitly, our assumption of S being constant over time means that the processes responsible for the regulation of the stem cell population are so flexible that they can account for a stem cell population whose size remains more or less fixed.

We further simplify the model by assuming that the dynamics of E is fast compared to that of Z. In fact, we assume that E is in equilibrium [i.e. $dE/dt = 0$ in (4)], from which we get that $E = h(Z)/\sigma$. Thus, putting $\psi(Z) = \tilde{\psi}(h(Z)/\sigma)$, we arrive at the following system:

$$\psi(Z(t))g(0)p(t,0) = q(P(t)) \tag{8}$$

$$\frac{\partial}{\partial t}p(t,x) + \psi(Z(t))\frac{\partial}{\partial x}(g(x)p(t,x)) = (b(x) - \mu_P)p(t,x) - \psi(Z(t))a(x)p(t,x) \tag{9}$$

$$\frac{d}{dt} Z(t) = -\mu_Z Z(t) + \psi(Z(t)) \int_0^\infty a(x)p(t,x)\,dx \tag{10}$$

$$P(t) = \int_0^\infty p(t,x)\,dx \tag{11}$$

$$p(0,x) = p_0(x) \tag{12}$$

$$Z(0) = Z_0 \tag{13}$$

Still, the mathematical analysis of such a system requires some effort because we have three types of nonlinearities: an additive term, a boundary condition, and a state-dependent maturation velocity.

At this point we want to encourage all readers who made it up to this point to continue following the somehow tough formulation of the functional analytic framework of this system during the rest of this section, its much more straightforward mathematical analysis in Sections IV to VI, and finally, its consequences on the biological model, which are derived in Section VII. The effort should be considered as a single investment for which the reader will be rewarded at the end. The necessary mathematical prerequisites on the theory of positive operator semigroups on Banach lattices can be found in Clément et al. (1987c), Nagel (1986), and Schaefer (1971, 1974).

To rewrite system (8)–(13) we have to devote a few words to the duality framework of dual semigroups as developed in Clément et al. (1987a,b, 1989) and Butzer and Berens (1967). Let A_0 be the generator of a linear strongly (but not uniformly) continuous semigroup $\{T_0(t),\ t \geq 0\}$ of operators on a nonreflexive Banach space X. We denote by X^* the Banach space of all linear, continuous functionals on X. The dual semigroup $\{T_0^*(t),\ t \geq 0\}$ is in general only weak* continuous. Let $X^\odot$ be the closed invariant subspace of X^* on which $\{T_0^*(t),\ t \geq 0\}$ is strongly continuous or, alternatively, the closure of $D(A_0^*)$. The restriction of $\{T_0^*(t),\ t \geq 0\}$ to $X^\odot$ yields a strongly continuous semigroup $\{T_0^\odot(t),\ t \geq 0\}$. Now we can rewrite our system (8)–(13) as the following quasi-linear Cauchy problem:

$$\frac{d}{dt} u(t) = \Psi(u(t))A_0^* u(t) + F^\times(u(t)) \tag{P$_t$}$$

$$u(0) = u_0$$

Here $F^\times$ is a nonlinear continuous operator mapping $X^\odot$ into X^*. In Grabosch and Heijmans (1988) we studied the analog of (P_t) on a Banach space X. Under some rather weak assumptions we could prove the existence and uniqueness of positivity-preserving global solutions. Furthermore, we discussed the stability properties of equilibria and proved a "principle of linearized stability." Before we discuss the corresponding results for our Cauchy problem (P_t), we will show that the system (8)–(13) can indeed be written in this form.

To begin with, we define the "backward problem," which is a preadjoint version of a simple cell growth equation (see the definition of the operator $A_0^\odot$ below). We define the Cartesian product $X := C_0(\mathbb{R}_+) \times \mathbb{R}$, where $C_0(\mathbb{R}_+)$ denotes the Banach space of continuous function on $\mathbb{R}_+$ which vanish at $+\infty$ endowed with the sup norm. We assume that g is a continuous function on $\mathbb{R}_+$ with $g(x) > 0$ for every $x \in \mathbb{R}_+$ and that a is a continuous, bounded, positive function on $\mathbb{R}_+$. Next we consider the unbounded operator A_0 with domain

$$D(A_0) := \{(p, Z) \in X : gp' \in C_0(\mathbb{R}_+)\} \tag{14}$$

given by

$$A_0((p, Z)) := (gp' - ap, 0) \tag{15}$$

It is straightforward to prove that A_0 generates a strongly continuous semigroup $\{T_0(t),\ t \geq 0\}$ on X. The adjoint operator A_0^* is operating on $X^* = M(\mathbb{R}_+) \times \mathbb{R}$, where $M(\mathbb{R}_+)$ denotes the Banach space of regular Borel measures on $\mathbb{R}_+$. It is well known that $L^1(\mathbb{R}_+)$ can be considered as a closed linear subspace of $M(\mathbb{R}_+)$. For $p \in L^1(\mathbb{R}_+)$ we denote by ν_p the corresponding (absolutely continuous) measure in $M(\mathbb{R}_+)$. With these notations it is easy to check that A_0^* is given by

$$\begin{aligned} D(A_0^*) = \{(p, Z) \in L^1(\mathbb{R}_+) \times \mathbb{R}&: \text{there exists } D(gp) \in M(\mathbb{R}_+) \text{ such that} \\ &g(x)p(x) = D(gp)([0, x)) \text{ for a.e. } x \in \mathbb{R}_+\} \\ A_0^*((p, Z)) = (-D(gp) - a\nu_p, 0)& \end{aligned}$$

[Here $D(gp)$ can be interpreted as a distributional derivative of $g \cdot p$).] The operator A_0^* generates the weak* continuous semigroup $\{T_0^*(t),\ t \geq 0\}$ on X^*. Thus we consider the subspace $X^{\odot} := L^1(\mathbb{R}_+) \times \mathbb{R}$ of X^*. It is well known that $D(A_0^*)$ is dense in $X^{\odot}$ with respect to the norm in X^*. Thus $X^{\odot} = \overline{D(A_0^*)}$. It is easy to see that $X^{\odot}$ is $T_0^*(t)$-invariant for all $t \geq 0$, and if we define $T_0^{\odot}(t) = T_0^*(t)_{|X^{\odot}}$, then $\{T^{\odot}(t), t \geq 0\}$ forms a strongly continuous semigroup on $X^{\odot}$. (Actually, $X^{\odot}$ is the largest subspace of X^* with this property.) The part of A_0^* in $X^{\odot}$ is given by

$$\begin{aligned} D(A_0^{\odot}) &:= \{(p, Z) \in X^{\odot} : A_0^*((p, Z)) \in X^{\odot}\} \\ &= \{(p, Z) \in L^1(\mathbb{R}_+) \times \mathbb{R} : p \text{ absolutely continuous}, g(0)p(0) = 0\} \\ A_0^{\odot}((p, Z)) &:= A_0^*((p, Z)) = (-(gp)' - ap, 0) \end{aligned}$$

Let $b \in L^\infty(\mathbb{R}_+)$, $b(x) \geq 0$ a.e., $q \in C(\mathbb{R})$, $\psi \in C(\mathbb{R})$, $\psi \geq 0$, and μ_P, $\mu_Z \in \mathbb{R}_+$. In view of the system (8)–(13), we define a perturbation $F^\times : X^{\odot} \rightarrow X^*$ by

$$\begin{aligned} F^\times((p, Z)) = q\left(\int_0^\infty p(x)\,dx\right) \cdot \Delta_0 + (b(\cdot) - \mu_P) \cdot p, \\ -\mu_Z Z + \psi(Z) \int_0^\infty a(x)p(x)\,dx \end{aligned}$$

where Δ_0 is the Dirac measure in 0; that is, for $f \in C_0(\mathbb{R}_+)$ it is $\Delta_0(f) = f(0)$. As a "feedback" function we define $\Psi : X^{\odot} = L^1(\mathbb{R}_+) \times \mathbb{R} \rightarrow \mathbb{R}_+\backslash\{0\}$ by

$$\Psi((p, Z)) := \psi(Z)$$

One can show that with these choices for X, A_0, $F^\times$, and Ψ, the system (P_t) is an abstract reformulation of (8)–(13). Indeed, if we define the operator $A^\times$ on X^* by

$$\begin{aligned} D(A^\times) &:= D(A_0^*) \\ A^\times((p, Z)) &:= \Psi((p, Z))A_0^*((p, Z)) + F^\times((p, Z)) \end{aligned}$$

and determine (by a straightforward computation) the part of $A^\times$ in $X^{\odot}$, which we denote by $A^{\odot}$, we obtain

$$\begin{aligned} D(A^{\odot}) &:= \{(p, Z) \in D(A_0^*) : A^{\times}((p, Z)) \in X^{\odot}\} \\ &= \{(p, Z) \in L^1(\mathbb{R}_+) \times \mathbb{R}: \\ &\qquad p \text{ absolutely continuous, } \psi(Z)g(0)p(0) = q(\textstyle\int_0^{\infty} p(x)\, dx) \\ A^{\odot}((p, Z)) &:= A^{\times}((p, Z)) = \Psi((p, Z))A_0^*((p, Z)) + F^{\times}(p, Z)) \end{aligned}$$

We refer to Section IV, Proposition 4, for the sense in which this operator gives the connection to the differential equation system (8)–(13).

IV. EXISTENCE, UNIQUENESS, AND REGULARITY OF SOLUTIONS

In this and the following sections we deal with the initial value problem (P_t) of Section III. One should observe that we have to do with a quasi-linear equation due to the presence of the term $\Psi(u(t))$.

Throughout the following three sections we assume that A_0 is the infinitesimal generator of a strongly continuous semigroup $\{T_0(t), t \geq 0\}$ on the Banach space X, and that $F^{\times}$ is a nonlinear continuous operator from $X^{\odot}$ into X^*. We point out that perturbations given by a continuous additive perturbation $F^{\times}$ mapping $X^{\odot}$ into X^* enable us to consider boundary conditions modeling the influx of "newborn" individuals at the boundary, which occurs very often in structured population equations. We assume furthermore that the function $\Psi : X^{\odot} \rightarrow \mathbb{R}_+$ is continuous, strictly positive, and locally bounded, (i.e., Ψ is bounded on bounded subsets of X^*).

The easiest way to deal with the quasi-linear Cauchy problem (P_t) is to relate it to a semilinear Cauchy problem on the Banach space X^*. Let $B^{\times} : X^{\odot} \rightarrow X^*$ be defined by

$$B^{\times}(x^{\odot}) := \frac{F^{\times}(x^{\odot})}{\Psi(x^{\odot})} \qquad \text{for } x^{\odot} \in X^{\odot}$$

We assume that both $B^{\times}$ and $F^{\times}$ are locally Lipschitz continuous operators; that is, for $r \geq 0$ there exists a constant $L_B(r) \geq 0$ such that

$$\|B^{\times}(x^{\odot}) - B^{\times}(y^{\odot})\| \leq L_B(r)\|x^{\odot} - y^{\odot}\| \tag{16}$$

for all $x^{\odot}, y^{\odot} \in X^{\odot}$ with $\|x^{\odot}\| \leq r$, $\|y^{\odot}\| \leq r$, and a similar estimate for $F^{\times}$. Now consider the Cauchy problem

$$\begin{aligned} &\frac{d}{d\tau} v(\tau) = A_0^* v(\tau) + B^{\times}(v(\tau)) \\ &v(0) = x^{\odot} \in X^{\odot} \end{aligned} \tag{P$_\tau$}$$

Instead of (P_τ), one may consider the variation-of-constants formula

$$v(\tau) = T_0^{\odot}(\tau)x^{\odot} + \int_0^{\tau} T_0^*(\tau - \sigma)B^{\times}(v(\sigma))\, d\sigma \tag{VOC$_\tau$}$$

In order to write down the right-hand side of this identity, one has to make sure that the integration makes sense. Using the foregoing assumptions on A_0 and $B^{\times}$, one can easily show that the integrand is a $\sigma(X^*, X)$-continuous (short weak* continuous) and X^*-valued function. Thus one can define the integral as a weak* Riemann integral. It turns out that the integral thus defined actually takes values in the smaller space $X^{\odot} \subseteq X^*$ (see Clément et al., 1987a). The corresponding notion of differentiability is called weak* differentiability and the weak* derivative of a weak* differentiable function $u(t)$ is denoted by w^*du/dt.

A continuous differentiable function v satisfying (P_τ) is called a classical solution, whereas a continuous function v satisfying (VOC_τ) is called a mild solution of (P_τ).

We will relate solutions of (P_t) to solutions of (P_τ). To do this we need some notations. For $u \in C([0, t_0], X^*)$ and $t \in [0, t_0]$ we define

$$\tau_u(t) := \int_0^t \Psi(u(s))\, ds \tag{17}$$

and for $v \in C([0, \tau_0], X^*)$ and $\tau \in [0, \tau_0]$ we define

$$t_v(\tau) := \int_0^\tau [\Psi(v(\sigma))]^{-1}\, d\sigma \tag{18}$$

In the same way as above we call a continuously differentiable solution of (P_t) a classical solution and a continuous solution u of the corresponding variation-of-constants formula

$$u(t) = T_0^{\odot}(\tau_u(t))x^{\odot} + \int_0^t T_0^*(\tau_u(t) - \tau_u(s))F^{\times}(u(s))\, ds \tag{VOC_t}$$

a mild solution of (P_t) (see also Grabosch and Heijmans, 1988, Def. 2.4). The following lemma is taken from the same source (Prop. 2.2).

Lemma 1. To every $t_0 \geq 0$ and $u \in C([0, t_0]; X^{\odot})$ there corresponds a unique $\tau_0 \geq 0$ and a unique $v \in C([0, \tau_0]; X^{\odot})$ such that the following relations hold:

$$\begin{aligned} &\tau_0 = \tau_u(t_0) \quad \text{and} \quad t_0 = t_v(\tau_0) \\ &t_v(\tau_u(t)) = t \quad \text{and} \quad v(\tau_u(t)) = u(t) \qquad \text{for } 0 \leq t \leq t_0 \\ &\tau_u(t_v(\tau)) = \tau \quad \text{and} \quad u(t_v(\tau)) = v(\tau) \qquad \text{for } 0 \leq \tau \leq \tau_0 \end{aligned}$$

Conversely, for every $\tau_0 \geq 0$ and $v \in C([0, \tau_0]; X^{\odot})$ there corresponds a unique $t_0 \geq 0$ and a unique $u \in C([0, t_0]; X^{\odot})$ such that the foregoing relations hold.

From this lemma we deduce that u is a classical (respectively, mild) solution of (P_t) if and only if v is a classical (respectively, mild) solution of (P_τ). It is this one-to-one relation between solutions of either problems that is exploited in Grabosch and Heijmans (1988) to deal with the quasi-linear system.

Semilinear equations of the form (P_τ) are introduced and investigated by Clément et al. (1987a,b, 1989). Using these results and Lemma 1, we can adopt the existence and uniqueness result of Grabosch and Heijmans (1988, Th. 3.2) to the quasi-linear equation (P_t) and obtain the following result:

Proposition 1. For every $x^{\odot} \in X^{\odot}$ there exists a maximal $t_{\max}(x^{\odot}) > 0$ such that (P_t) has a unique mild solution $u(\cdot\,; x^{\odot})$ on $[0, t_{\max}(x^{\odot}))$ which has the semigroup property. If $t_{\max}(x^{\odot}) < \infty$, then $\lim_{t \uparrow t_{\max}} \|u(t; x^{\odot})\| = \infty$.

In the remainder of this section we state some regularity properties of the solutions. Similar results have been proved in Grabosch and Heijmans (1988, Sec. 4), where the duality framework was not adopted. The results stated here follow by a combination of the ideas in Clément et al. (1987b, Sec. 3; 1989, Sec. 3), where semilinear dual semigroups have been investigated.

We define an operator $A^{\times}$ as follows. We define $x^{\odot}$ to be in $D(A^{\times})$ if $t^{-1}(u(t;x^{\odot}) - x^{\odot})$ for $t \to 0$ weak* converges to some $y^* \in X^*$ and we set $A^{\times}x^{\odot} = y^*$. Furthermore, we define the subset $\mathcal{F}$ of $X^{\odot}$ as the set of all $x^{\odot}$ for which $\limsup_{t\downarrow 0} t^{-1}\|u(t;x^{\odot}) - x^{\odot}\| < \infty$. Note that $\mathcal{F}$ can be interpreted as a sort of Favard class for solutions of the problem (P_t): see Clément et al. (1987b,c, 1989). With the uniform boundedness principle, one easily obtains that $D(A^{\times}) \subseteq \mathcal{F}$. But the converse also holds.

Proposition 2. $D(A^{\times}) = D(A_0^*) = \mathrm{Fav}(T_0^*) = \mathcal{F}$, and

$$A^{\times}x^{\odot} = \Psi(x^{\odot})A_0^*x^{\odot} + F^{\times}(x^{\odot})$$

for $x^{\odot} \in D(A_0^*)$.

Proof: This follows along the same lines as the proof of Theorem 3.2 in Clément et al. (1987b).

If $t_{\max}(x^{\odot}) = \infty$ for every $x^{\odot} \in X^{\odot}$, we can associate a strongly continuous semigroup $\{T^{\odot}(t), t \geq 0\}$ with problem (P_t) such that $u(t;x^{\odot}) = T^{\odot}(t)x^{\odot}$, $t \geq 0$. For reference we state the following assumption. We shall not use this assumption unless stated explicitly.

Global Existence Assumption. For every $x^{\odot} \in X^{\odot}$, $t_{\max}(x^{\odot}) = \infty$ and $\|u(t;x^{\odot})\| \leq Me^{\omega t}\|x^{\odot}\|$, for some fixed constants $M \geq 1$ and $\omega \in \mathbb{R}$ and all $t \geq 0$.

As in Clément et al. (1987b), one can show that this assumption is satisfied if $F^{\times}/\Psi$ is globally Lipschitz continuous. Nevertheless, in the situation outlined in Section III, this assumption is not satisfied. Thus in Section V we shall meet some different conditions on $F^{\times}$ which guarantee that the global existence assumption holds. Under either of these assumptions, $\mathcal{F}$ can be identified with the Favard class [or "generalized domain" as Crandall (1973) called it] of the semigroup $\{T^{\odot}(t), t \geq 0\}$ associated with solutions of (P_t).

Proposition 3. Let the "global existence assumption" hold, and let the unperturbed semigroup $\{T_0(t), t \geq 0\}$ be bounded. Then $x^{\odot} \in \mathcal{F}$ if and only if the orbit $t \mapsto u(t;x^{\odot})$ is locally Lipschitz continuous. For such initial data $x^{\odot}$, the solution $u(\cdot;x^{\odot})$ is weak* continuously differentiable and satisfies

$$w^*\frac{du}{dt}(t) = \Psi(u(t))A_0^*u(t) + F^{\times}(u(t))$$

Proof: We prove that the orbit $t \mapsto u(t;x^{\odot})$ is locally Lipschitz continuous for $x^{\odot} \in \mathcal{F}$. Then the second assertion can be proved along the same lines as Theorem 3.4 in Clément et al. (1987b). Without loss of generality we may assume that $\{T_0(t), t \geq 0\}$ is bounded [otherwise, we replace A_0 by $A_0 - \omega I$ and $F^{\times}(u)$ by $F^{\times}(u) + \omega\Psi(u)$]. As a first step we show that for every $T > 0$ there is a constant $\omega(r, T) \in \mathbb{R}$ such that

$$\|u(t;x^{\odot}) - u(t;y^{\odot})\| \leq Me^{\omega(r,T)t}\|x^{\odot} - y^{\odot}\|, \qquad 0 \leq t \leq T \tag{19}$$

for all $x^{\odot}, y^{\odot} \in X^{\odot}$ with $\|x^{\odot}\|, \|y^{\odot}\| \leq r$. Here M is the bound of the semigroup $\{T_0(t), t \geq 0\}$ [i.e., $\|T_0(t)\| \leq M$], Without loss of generality we may assume that M

is the same as in the global existence assumption. To prove (19), let r, $T > 0$ and take $t \le T$ and $\|x^\odot\|$, $\|y^\odot\| \le r$. Then for every $s \le t$ we have $\|u(s; x^\odot)\|$, $\|u(s; y^\odot)\| \le Me^{\omega T} r =: R$. By the local Lipschitz continuity of $F^\times$,

$$\|F^\times(u(s; x^\odot)) - F^\times(u(s; y^\odot))\| \le L_F(R)\|u(s; x^\odot) - u(s; y^\odot)\|$$

Now subtracting the variation-of-constants formulas (VOC$_t$) for $x^\odot$ and $y^\odot$ and using Gronwall's lemma, we derive that

$$\|u(t; x^\odot) - u(t; y^\odot)\| \le M\|x^\odot - y^\odot\| e^{ML_F(R)t}, \qquad t \le T$$

Hence (19) follows with $\omega(r, T) := ML_F(Me^{\omega T} r)$.

Let $x^\odot \in \mathscr{F}$. To prove local Lipschitz continuity of the orbit $t \to u(t; x^\odot)$, we use arguments similar to those of Crandall (1973, Cor. 1). We must show that for every $T > 0$ there is a $C(T) > 0$ such that for s, $t \le T$ we have

$$\|u(t; x^\odot) - u(s; x^\odot)\| \le C(T)|t - s| \tag{20}$$

Suppose that the estimate (20) holds for $s = 0$. Then it holds for arbitrary s and t [with $C(T)$ adapted]. Namely, by (19), if $s \le t$,

$$\begin{aligned}\|u(t; x^\odot) - u(s; x^\odot)\| &= \|u(s; u(t - s; x^\odot)) - u(s; x^\odot)\| \\ &\le Me^{\bar{\omega}(T)s}\|u(t - s; x^\odot) - x^\odot\| \\ &\le H(T)\|u(t - s; x^\odot) - x^\odot\| \end{aligned} \tag{21}$$

Here $\bar{\omega}(T) := \omega(r, T)$ with $r = \max\{\|x^\odot\|, Me^{\omega T}\|x^\odot\|\}$, and $H(T) := Me^{\bar{\omega}(T)T}$.

Now we prove that (20) holds for $s = 0$ and $t \le T$. We shall write $u(t)$ instead of $u(t; x^\odot)$. Take $K > \limsup_{t\downarrow 0} t^{-1}\|u(t) - x^\odot\|$. We can choose a sequence (t_k) of positive numbers convergent to zero such that $\|u(t_k) - x^\odot\| \le Kt_k$. Let (p_k) a sequence of positive integers such that $p_k t_k \to t$ as k goes to infinity. Then, by (21),

$$\begin{aligned}\|u(t) - x^\odot\| &= \lim_{k\to\infty} \|u(p_k t_k) - x^\odot\| \\ &\le \limsup_{k\to\infty} \sum_{j=1}^{p_k} \|u(jt_k) - u((j-1)t_k)\| \\ &\le \limsup_{k\to\infty} \sum_{j=1}^{p_k} H(T)\|u(t_k) - x^\odot\| \\ &\le \limsup_{k\to\infty} \sum_{j=1}^{p_k} H(T)Kt_k \\ &= \lim_{k\to\infty} H(T)Kp_k t_k = H(T)Kt \end{aligned}$$

This concludes the proof.

In fact, this result says that $A^\times$ is the weak* generator of the semigroup $\{T^\odot(t),\ t \ge 0\}$. Under appropriate conditions on $F^\times$ the weak* solutions of (P$_t$) are C^1-solutions as well. Let $A^\odot$ be the part of $A^\times$ in $X^\odot$, that is, $D(A^\odot) = \{x^\odot \in D(A^\times) : A^\times x^\odot \in X^\odot\}$ and $A^\odot x^\odot = A^\times x^\odot$.

Proposition 4. Assume in addition to the assumptions of Proposition 3 that $F^\times/\Psi$ is continuously Fréchet differentiable. If $x^\odot \in D(A^\odot)$, then $u(\cdot; x^\odot)$ is continuously differentiable and

$$
\begin{aligned}
&\frac{d}{dt}u(t) = \Psi(u(t))A_0^*u(t) + F^{\times}(u(t)), \qquad t \in [0, t_{\max}(x^{\odot}))\\
&u(0) = x^{\odot}
\end{aligned}
$$

holds.

For a proof, see Grabosch and Heijmans (1988, Th. 3.4).

V. GLOBAL EXISTENCE AND POSITIVITY

In this section we deal with positivity and global existence of solutions. It turns out that the positivity preservingness of the solution operator can be used also to establish global existence. Again we will follow the line in Grabosch and Heijmans (1988, Sec. 4) for our proofs, but since we are dealing with weak* continuous semigroups and weak* Riemann integrals, we have to be more careful. We start with a couple of definitions and lemmas.

We will assume throughout this section that X is a Banach lattice with positive cone $X_+ = \{x \in X : x \geq 0\}$ (see Schaefer, 1984, Chap. II). Then X^* is a Banach lattice with positive cone $X_+^* = \{x^* \in X^* : \langle x, x^* \rangle \geq 0$ for all $x \in X_+\}$. The thus defined order on X^* induces a natural order on the closed, linear subspace $X^{\odot}$. In general, $X^{\odot}$ need not be a sublattice of X^* (see Grabosch and Nagel, 1989). By U_X we denote the unit ball of X. We recall from Schaefer (1971, Ch, IV.1) that for $M \subseteq X$ the polar set M° of M is defined by

$$M^\circ := \{x^* \in X^* : \langle x, x^* \rangle \leq 1 \text{ for all } x \in M\} \tag{22}$$

and the bipolar set $M^{\circ\circ}$ of M is defined by

$$M^{\circ\circ} := (M^\circ)^\circ = \{x^{**} \in X^{**}: \langle x^{**}, x^* \rangle \leq 1 \text{ for all } x^* \in M^\circ\} \tag{23}$$

Lemma 2. For $x^* \in X_+^*$ let $M := U_X \cap (-X_+) \cap \{x \in X : \langle x^*, x \rangle = 0\} \subseteq X \subseteq X^{**}$. Then the bipolar set $M^{\circ\circ}$ of M in X^{**} is

$$M^{\circ\circ} = U_{X^{**}} \cap (-X_+^{**}) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**} \rangle = 0\}$$

Proof. We consider the duality pairing $\langle X^{**}, X^* \rangle$. Let $M := U_X \cap (-X_+) \cap \{x \in X : \langle x^*, x \rangle = 0\}$. We compute the polar set M° of M. We obtain ("span" denoting the linear span)

$$
\begin{aligned}
M^\circ &= (U_X \cap (-X_+) \cap \{x \in X : \langle x^*, x \rangle = 0\})^\circ\\
&= \overline{co\{(U_X)^\circ \cup (-X_+)^\circ \cup \{x \in X : \langle x^*, x \rangle = 0\}^\circ\}}^{\sigma(X^*, X^{**})}\\
&\quad \text{by Schaefer (1971, IV.1.5, Cor. 2)}\\
&= \overline{\mathrm{co}\{U_{X^*} \cup X_+^* \cup \mathrm{span}\{x^*\}\}}^{\sigma(X^*, X^{**})}.
\end{aligned}
$$

We compute the bipolar of M in X^{**} and obtain

$$
\begin{aligned}
(M^\circ)^\circ &= \left(\overline{\mathrm{co}\{U_{X^*} \cup X_+^* \cup \mathrm{span}\{x^*\}\}}^{\sigma(X^*, X^{**})}\right)^\circ\\
&= (U_{X^*} \cup X_+^* \cup \mathrm{span}\{x^*\})^\circ\\
&= (U_{X^*})^\circ \cap (X_+^*)^\circ \cap (\mathrm{span}\{x^*\})^\circ \qquad \text{by Schaefer [1971, IV.1.3(3)]}\\
&= U_{X^{**}} \cap (-X_+^{**}) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**} \rangle = 0\}.
\end{aligned}
$$

Let x be an element of a Banach lattice X, and define $x_+ = \sup\{x, 0\}$ and $x_- = -\inf\{x, 0\}$. Then $x_+, x_- \geq 0$ and $x = x_+ - x_-$.

Lemma 3. Let X be a separable Banach lattice. If $s \mapsto f(s)$ from $[0,1] \to X^*$ is weak* continuous, then $s \mapsto \|f(s)_-\|$ is measurable.

Proof. Let $s \in [0,1]$ fixed. For any $x \in X_+$ we have $\langle f(s)_-, x\rangle = -\inf\{\langle f(s), y\rangle : 0 \leq y \leq x\}$ (see Schaefer, 1974, II.4.2, Cor. 1). By the separability of X it is enough to consider the infimum over a countable set $\{y_n \in X : n \in \mathbb{N}\}$ with $0 \leq y_n \leq x$ and $\{y_n : n \in \mathbb{N}\}$ dense in $[0,x] = \{y : 0 \leq y \leq x\}$. Since $s \mapsto \langle f(s), y_n\rangle$ is continuous (hence measurable) for all n we know that $s \mapsto \langle f(s)_-, x\rangle$ is measurable for every $x \in X_+$. The same argument applied for a second time shows that $s \mapsto \|f(s)_-\|$ is measurable since

$$\begin{aligned}\|f(s)_-\| &= \sup\{\langle f(s)_-, x_n\rangle : x_n \in U_X\} \\ &= \sup\{\langle f(s)_-, (x_n)_+\rangle - \langle f(s)_-, (x_n)_-\rangle : x_n \in U_X\}\end{aligned}$$

and $s \mapsto \langle f(s)_-, (x_n)_+\rangle - \langle f(s)_-, (x_n)_-\rangle$, being the difference of two measurable functions, is measurable.

Before we prove the next lemma we want to remind the reader of the notion of a subdifferential of a sublinear, continuous functional on a Banach space (see, e.g., Clément et al., 1987c, App. A.1.4; Nagel, 1986, Sec. A-II.2).

Definition 1. Let X be a Banach space, and let $\Phi : X \to \mathbb{R}$ be sublinear [i.e., $\Phi(x + y) \leq \Phi(x) + \Phi(y)$ for all $x, y \in X$, and $\Phi(\alpha x) = \alpha\Phi(x)$ for all $x \in X$, $\alpha \geq 0$] and continuous, and take $x \in X$. The subdifferential of Φ in x is given by

$$\begin{aligned}d\Phi(x) &= \{x^* \in X^* : \langle y, x^*\rangle \leq \Phi(y) \text{ for all } y \in X \text{ and } \langle x, x^*\rangle = \Phi(x)\} \qquad (24)\\ &= \{x^* \in X^* : \langle y - x, x^*\rangle \leq \Phi(y) - \Phi(x) \text{ for all } y \in X\}\end{aligned}$$

Here we are interested in a very special sublinear function on the dual Banach lattice X^* (where X is a Banach lattice), namely the function $\Phi : X^* \to \mathbb{R}$ given by $\Phi(x^*) = \|x^*_-\| = \text{dist}(x^*, X^*_+)$, which is a continuous, sublinear functional on X^*. [See Grabosch and Heijmans (1988, Lemma 4.3) for some important properties of Φ).] From definition (24) we obtain

$$d\Phi(x^*) = \{x^{**} \in X^{**} : \langle y^*, x^{**}\rangle \leq \Phi(y^*) \text{ for all } y^* \in X^* \text{ and } \langle x^*, x^{**}\rangle = \Phi(x^*)\}$$

We also consider a subset of $d\Phi(x^*)$ in X, the weak* subdifferential

$$d_*\Phi(x^*) := \{x \in X : \langle y^*, x\rangle \leq \Phi(y^*) \text{ for all } y^* \in X^* \text{ and } \langle x^*, x\rangle = \Phi(x^*)\}$$

and obtain the following result.

Lemma 4. Let $x^* \in X^*$. Then $d_*\Phi(x^*)$ is $\sigma(X^{**}, X^*)$-dense in $d\Phi(x^*)$.

Proof: Let $M := d_*\Phi(x^*) = \{x \in X : \langle y^*, x\rangle \leq \Phi(y^*)$ for all $y^* \in X^*$ and $\langle x^*, x\rangle = \Phi(x^*)\}$. One easily computes that

$$\begin{aligned}d_*\Phi(x^*) &= \{x \in X : \|x\| \leq 1, -x \geq 0, \langle x^*, x\rangle = 0\} \\ &= U_X \cap (-X_+) \cap \{x \in X : \langle x^*, x\rangle = 0\} \qquad (25)\end{aligned}$$

We obtain by Lemma 2 that $M^{\circ\circ} = U_{X^{**}} \cap (-X^{**}_+) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**}\rangle = 0\}$. But

$$U_{X^{**}} \cap (-X^{**}_+) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**}\rangle = 0\} = d\Phi(x^*) \qquad (26)$$

Since $d_*\Phi(x^*)$ is convex as the intersection of convex sets, we obtain by the bipolar theorem (see Schaefer, 1971, IV, Th. 1.5) that the $\sigma(X^{**}, X^*)$-closure of $d_*\Phi(x^*)$ is equal to $d\Phi(x^*)$, which proves our assertion.

We are now prepared to prove an extended version of Jensen's inequality for our special convex functional.

Jensen's Inequality. Let X be a separable Banach lattice. Assume that $f\colon [0,1] \rightarrow X^*$ is weak* continuous and that its weak* Riemann integral $\int_0^1 f(s)\,ds$ exists. Let $\Phi : X^* \rightarrow \mathbb{R}$ be given by $\Phi(x^*) = \|(x^*)_-\|$. Then

$$\Phi\left(\int_0^1 f(s)\,ds\right) \leq \int_0^1 \Phi(f(s))\,ds \leq \infty \tag{27}$$

Proof: Let $x^* := \int_0^1 f(s)\,ds$, and let $d\Phi(x^*)$ be the subdifferential of Φ in x^* [i.e., $d\Phi(x^*) = \{x^{**} \in X^{**} : \langle y^*, x^{**}\rangle \leq \Phi(y^*)$ for all $y^* \in X^*$ and $\langle x^*, x^{**}\rangle = \Phi(x^*)\}$]. By Lemma 4 we know that $d_*\Phi(x^*) = \{x \in X : \langle y, x\rangle \leq \Phi(y^*)$ for all $y^* \in X^*$ and that $\langle x^*, x\rangle = \Phi(x^*)\}$ is $\sigma(X^{**}, X^*)$-dense in $d\Phi(x^*)$. Since $d\Phi(x^*) \neq \emptyset$ by the theorem of Hahn–Banach, we also know that $d_*\Phi(x^*) \neq \emptyset$. Thus let $x \in d_*\Phi(x^*) \subseteq d\Phi(x^*)$. Since $d\Phi(x^*)$ is a subdifferential we have $\Phi(f(s)) \geq \langle x, f(s) - x^*\rangle + \Phi(x^*)$ for all $s \in [0, 1]$. By Lemma 3, $s \mapsto \Phi(f(s))$ is measurable; thus integration over s yields

$$\int_0^1 \Phi(f(s))\,ds \geq \int_0^1 \langle x, f(s) - x^*\rangle\,ds + \Phi(x^*) = \int_0^1 \langle x, f(s)\rangle\,ds - \langle x, x^*\rangle + \Phi(x^*)$$

$$= \langle x, x^*\rangle - \langle x, x^*\rangle + \Phi(x^*) = \Phi(x^*) = \Phi\left(\int_0^1 f(s)\,ds\right)$$

Now we will come to our key lemma, in which we characterize some kind of weak* subtangential property (or positive-off-diagonal property) of the operator $F^\times$ (compare Grabosch and Heijmans, 1988, Lemma 4.4).

Lemma 5. Let X be a separable Banach lattice, $0 \leq x^\odot \in X^\odot$ and $F^\times$ as in Section IV. Equivalent are:

(i) If $x \in X_+$ with $\langle x, x^\odot\rangle = 0$, then $\langle x, F^\times(x^\odot)\rangle \geq 0$.
(ii) $\lim_{h\downarrow 0}(1/h)\,\mathrm{dist}(x^\odot + hF^\times(x^\odot), X_+^*) = 0$.

Proof: Without restriction we can assume that $x^\odot \in \partial X_+^*$. We consider $\Phi : X^* \rightarrow \mathbb{R}$ given by $\Phi(x^*) = \mathrm{dist}(x^*, X_+^*)$. By Lemma 4 we know that the weak* subdifferential $d_*\Phi(x^\odot)$ of Φ in $x^\odot$ lies $\sigma(X^{**}, X^*)$-dense in the subdifferential $d\Phi(x^\odot)$ of Φ in $x^\odot$. We let $D_{F^\times(x^\odot)}\Phi(x^\odot)$ denote the Gateaux derivative of Φ at $x^\odot$ in the direction $F^\times(x^\odot)$. By Clément et al. (1987c, Prop. A.1.24) we have $D_{F^\times(x^\odot)}\Phi(x^\odot) = \sup\{\langle F^\times(x^\odot), x^{**}\rangle : x^{**} \in d\Phi(x^\odot)\}$. Since $d_*\Phi(x^\odot)$ is dense in $d\Phi(x^\odot)$ we can conclude that

$$D_{F^\times(x^\odot)}\Phi(x^\odot) = \sup\{\langle F^\times(x^\odot), x\rangle : x \in d_*\Phi(x^\odot)\} \tag{28}$$

Furthermore, we observe that

$$\lim_{h\downarrow 0} \frac{1}{h}\,\mathrm{dist}(x^\odot + hF^\times(x^\odot), X_+^*)$$

$$= \lim_{h\downarrow 0} \frac{1}{h}\left[\mathrm{dist}(x^\odot + hF^\times(x^\odot), X_+^*) - \mathrm{dist}(x^\odot, X_+^*)\right]$$

$$
\begin{aligned}
&= \lim_{h \downarrow 0} \frac{1}{h} [\Phi(x^{\odot} + hF^{\times}(x^{\odot})) - \Phi(x^{\odot})] \\
&= D_{F^{\times}(x^{\odot})} \Phi(x^{\odot})
\end{aligned}
\tag{29}
$$

After these preparations we can now prove the equivalence of (i) and (ii). Indeed, by formulas (28) and (29), condition (ii) is equivalent to $\langle F^{\times}(x^{\odot}), x\rangle \le 0$ for all $x \in d_*\Phi(x^{\odot})$. This is equivalent to $\langle F^{\times}(x^{\odot}), x\rangle \le 0$ for all $x \in X$ with $\|x\| \le 1$, $-x \ge 0$ and $\langle x, x^{\odot}\rangle = 0$ [by formula (25)], hence to condition (i).

The following lemma forms the basis for the proof of the positivity preservingness of the solution operator.

Lemma 6. Let X be a separable Banach lattice and let $x^{\odot} \in X_+^{\odot}$. Assume that one of the equivalent conditions of Lemma 5 holds. Then

$$
\frac{1}{h}\left[T_0^{\odot}(h)x^{\odot} + \int_0^h T_0^*(s)F^{\times}(x^{\odot})\, ds\right]_- \to 0 \qquad \text{as } h \downarrow 0 \tag{30}
$$

Proof: The following estimate holds:

$$
\begin{aligned}
&\frac{1}{h}\left\|\left[T_0^{\odot}(h)x^{\odot} + \int_0^h T_0^*(s)F^{\times}(x^{\odot})\, ds\right]_-\right\| \\
&= \frac{1}{h}\left\|\left[\int_0^1 T_0^*(sh)T_0^*([1-s]h)x^{\odot}\, ds + \int_0^1 T_0^*(hs)hF^{\times}(x^{\odot})\, ds\right]_-\right\| \\
&= \frac{1}{h}\left\|\left[\int_0^1 T_0^*(sh)[T_0^*([1-s]h)x^{\odot} + hF^{\times}(x^{\odot})]\, ds\right]_-\right\| \\
&\le \frac{1}{h}\int_0^1 \|[T_0^*(sh)[T_0^*([1-s]h)x^{\odot} + hF^{\times}(x^{\odot})]]_-\|\, ds
\end{aligned}
$$

by Jensen's inequality and Lemma 3

$$
\begin{aligned}
&\le \frac{1}{h}\int_0^1 e^{\omega sh}\|[T_0^*([1-s]h)x^{\odot} + hF^{\times}(T_0^*([1-s]h)x^{\odot}) - hF^{\times}(T_0^*([1-s]h)x^{\odot}) \\
&\quad + hF^{\times}(x^{\odot})]_-\|\, ds
\end{aligned}
$$

by Grabosch and Heijmans [1988, Lemma 4.3(h)]

$$
\le \frac{1}{h}\int_0^1 e^{\omega sh}\, \|[T_0^*([1-s]h)x^{\odot} + hF^{\times}(T_0^*([1-s]h)x^{\odot})]_-\|\, ds + o(1)
$$

where the last estimate follows from the continuity of $F^{\times}$. From the subtangential condition (ii) of Lemma 5 we know that for any $r \in [0, 1]$,

$$
f_h(r) := \frac{1}{h}[T_0^*(r)x^{\odot} + hF^{\times}(T_0^*(r)x^{\odot})]_- \to 0 \qquad \text{as } h \downarrow 0
$$

Moreover, $(f_h)_{h>0}$ is a directed set, since $h < k$ implies that $f_h \le f_k$ [which follows from the convexity of $x^{\odot} \mapsto \operatorname{dist}(x^{\odot}, X_+^*)$]. Thus by the theorem of Dini, $f_h(r) \to 0$ uniformly for $r \in [0, 1]$ and $h \downarrow 0$. The estimate above proves the assertion.

After these preparations we can state our main results concerning the existence of positivity preserving [respectively, of global] solutions of (P_t). For the analogous statements for the case that $F^{\times}$ takes values in $X^{\odot}$, we refer to Grabosch and Heijmans (1988, Th. 4.2).

Proposition 5. Let A_0 be the generator of a linear, positive C_0-semigroup $\{T_0(t), t \geq 0\}$ on a separable Banach lattice X such that $X^{\odot}$ is a Banach lattice as well. Assume that $F^{\times} : X^{\odot} \to X^*$ satisfies the following positive-off-diagonal property:

$$\text{If } x \in X_+ \text{ with } \langle x, x^{\odot}\rangle = 0, \text{ then } \langle F^{\times}(x^{\odot}), x\rangle \geq 0 \tag{31}$$

Then $x^{\odot} \geq 0$ implies that $u(t; x^{\odot}) \geq 0$ for all $t \in [0, t_{\max}(x^{\odot}))$.

Proof: First we observe that we may restrict ourselves to the case that $\Psi \equiv 1$. Furthermore, we may assume without loss of generality that

$$F^{\times}(x^{\odot}) = F^{\times}(x^{\odot}_+) \qquad \text{for all } x^{\odot} \in X^{\odot} \tag{32}$$

Namely, if this is not satisfied, we define $F^{\times}_0 : X^{\odot} \to X^*$ by $F^{\times}_0(x^{\odot}) := F^{\times}(x^{\odot}_+)$ ($x^{\odot} \in X^{\odot}$). Then, by construction, $F_0(x^{\odot}) = F_0(x^{\odot}_+)$. Note that $F^{\times}_0$ still satisfies (31). If solutions of (VOC$_r$) with $F^{\times}$ replaced by $F^{\times}_0$ are positivity preserving, they coincide with solutions of the original (VOC$_r$) for positive initial data $x^{\odot}$.

Further, we restrict ourselves to the case where $\|T_0(t)\| \leq Me^{\omega t}$ with $M = 1$ for all $t \geq 0$. In the proof of Theorem 4.2 in Grabosch and Heijmans (1988) it is shown that the general case can always be reduced to this situation. Let $x^{\odot} \geq 0$ and let $u(t) = u(t; x^{\odot})$ be the continuous solution of (VOC$_r$) on $[0, t_{\max}(x^{\odot}))$. We show that $u(t) \geq 0$ or, equvialently, that $u_-(t) := [u(t)]_-$ is zero. For $t < t_{\max}$ we define

$$\phi(t) := e^{-\omega t}\|u_-(t)\|$$

Now

$$u(t+h) = T^{\odot}_0(h)u(t) + \int_0^h T^*_0(h-s)F^{\times}(u(t+s))\,ds$$

Using Lemma 6, formula (32), and the fact that for $x^{\odot}$, $y^{\odot} \in X^{\odot}$ we have $\|x^{\odot} - y^{\odot}\| \geq \|x^{\odot}_-\| - \|y^{\odot}_-\|$, we get

$$\begin{aligned}
\|u_-(t+h)\| \leq {} & \left\| u(t+h) - T^{\odot}_0(h)u_+(t) - \int_0^h T^*_0(h-s)F^{\times}(u_+(t+s))\,ds \right\| \\
& + \left\| \left[T^{\odot}_0(h)u_+(t) + \int_0^h T^*_0(h-s)F^{\times}(u_+(t+s))\,ds \right]_- \right\| \\
\leq {} & \|T^{\odot}_0(h)u_-(t)\| + \Bigg\| u(t+h) - T^{\odot}_0(h)u(t) \\
& - \int_0^h T^*_0(h-s)F^{\times}(u(t+s))\,ds \Bigg\| \\
& + \left\| \left[T^{\odot}_0(h)u_+(t) + \int_0^h T^*_0(h-s)F^{\times}(u_+(t))\,ds \right]_- \right\| + o(h) \\
\leq {} & e^{\omega h}\|u_-(t)\| + o(h)
\end{aligned}$$

Hence $\phi(t+h) \leq \phi(t) + o(h)$ for $h \downarrow 0$ and $t < t_{\max}$. In other words,

$$D_+\phi(t) := \liminf_{h \downarrow 0} \frac{1}{h}(\phi(t+h) - \phi(t)) \leq 0$$

Since $\phi(0) = \|u_-(0)\| = \|x^{\odot}_-\| = 0$, a well-known result from the theory of differential inequalities (see, e.g., Martin, 1976, Lemma 7.4, p. 260) implies that $\phi = 0$.

The proof of the next result can be given similarly to the proof of Theorem 4.6 in Grabosch and Heijmans (1988).

Proposition 6. Let A_0 be the generator of a linear, positive, bounded C_0-semigroup $\{T_0(t),\ t \ge 0\}$ on a separable Banach lattice X such that $X^\odot$ is a Banach lattice as well. Assume that $F^\times : X^\odot \to X^*$ satisfies property (31) and that there exists an locally Lipschitz continuous operator $F_0^\times : X^\odot \to X^*$ such that

$$\begin{aligned} &F^\times(x^\odot) \le F_0^\times(x^\odot) \qquad \text{for all } x^\odot \ge 0 \\ &\|F_0^\times(x^\odot)\| \le C\|x^\odot\| \qquad \text{for all } x^\odot \ge 0 \end{aligned} \tag{33}$$

Then $t_{\max}(x^\odot) = \infty$ for all $x^\odot \ge 0$, and $\|u(t;x^\odot)\| \le Me^{\omega t}$ for some constants $M \ge 1$ and $\omega \in \mathbb{R}$.

Proof: Let $x^\odot \ge 0$. Then $u(t;x^\odot)$ is the continuous solution of (VOC$_r$), that is,

$$u(t) = T_0^\odot(\tau_u(t))x^\odot + \int_0^t T_0^*(\tau_u(t) - \tau_u(s))F^\times(u(s))\,ds$$

Using the first part of the assumption (33) and the fact that $u(t) \ge 0$, we get

$$u(t) \le T_0^\odot(\tau_u(t))x^\odot + \int_0^t T_0^*(\tau_u(t) - \tau_u(s))F_0^\times(u(s))\,ds$$

Since, for all $t \ge 0$, $\|T_0(t)\| \le M$ and hence $\|T_0^*(t)\|$, $\|T_0^\odot(t)\| \le M$ for some constant $M \ge 1$, we get, using the second part of assumpion (33),

$$\|u(t)\| \le M\|x^\odot\| + \int_0^t MC\|u(s)\|\,ds$$

Now Gronwall's lemma yields that

$$\|u(t)\| \le M\|x^\odot\|e^{MCt}$$

for $t < t_{\max}(x^\odot)$. From this, the assertion follows easily.

We collect the main results of this and the preceding section.

Corollary 1. Let A_0 be the generator of a linear, positive, bounded C_0-semigroup on the Banach space X, and assume that

$\Psi : X^\odot \to \mathbb{R}_+$ is continuous, strictly positive, and locally bounded.
$B^\times = F^\times/\Psi$ is locally Lipschitz continuous.
$F^\times$ is locally Lipschitz continuous.
$F^\times$ satisfies the positive-off-diagonal property (31).
$F^\times$ satisfies (33).

Then the following hold.

(a) There exists a unique continuous positive solution $u(\cdot;x^\odot)$ of (VOC$_r$) for every $x^\odot \ge 0$. Moreover, $t_{\max}(x^\odot) = \infty$ for all $x^\odot \ge 0$ and $\|u(t;x^\odot)\| \le Me^{\omega t}\|x^\odot\|$ for certain constants $M \ge 1$, $\omega \in \mathbb{R}$.

(b) If, furthermore, $x^\odot \in D(A_0^*)$, then $t \to u(t;x^\odot)$ is locally Lipschitz continuous, weak* continously differentiable, and

$$w^* \frac{du}{dt}(t) = \Psi(u(t))A_0^* u(t) + F^{\times}(u(t))$$

That is, (P_r) is satisfied in the weak* sense.

(c) If, in addition to the assumptions above, $F^{\times}/\Psi$ is continuously Fréchet differentiable and $x^{\odot} \in D(A^{\odot})$, that is, $x^{\odot} \in D(A_0^*)$ and $\Psi(x^{\odot})A_0^* x^{\odot} + F^{\times}(x^{\odot}) \in X^{\odot}$, then $u(\cdot\,; x^{\odot})$ is continuously differentiable and (P_r) is satisfied.

VI. LINEARIZED (IN)STABILITY

Again we proceed as in Grabosch and Heijmans (1988, Sec. 5), where we proved a principle of linearized (in)stability for quasi-linear equations of type (P_r) on a Banach space X. Similar to that situation we can first consider semilinear equations and prove a principle of linearized (in)stability using the variation-of-constants formula (VOC_T). Again we have to pay attention to the sense in which the integral sign has to be understood, namely as a weak* Riemann integral. Nevertheless, all proofs from Grabosch and Heijmans (1988, Sec. 5) (see also Clément et al., 1987b) carry over without major problems. The same is true for the analysis of the quasilinear equation.

Thus let $\bar{u}$ be an equilibrium of (P_r). Then the linearization of (P_r) in $\bar{u}$ is given by

$$\frac{dw}{dt} = \Psi(\bar{u})A_0^* w + A_0^* \bar{u} \cdot \langle \Psi'(\bar{u}), \omega \rangle + (F^{\times})'(\bar{u})w \tag{34}$$

The stability properties of $\bar{u}$ for equation (P_r) are determined by the stability properties of the zero solution of the linearization (34). We define the operator C^* on X^* by

$$C^* x^{\odot} = \Psi(\bar{u})A_0^* x^{\odot} + \langle \Psi'(\bar{u}), x^{\odot} \rangle \cdot A_0^* \bar{u} + (F^{\times})'(\bar{u})x^{\odot}$$

with domain $D(C^*) = D(A_0^*)$. Then the part $C^{\odot}$ of C^* in $X^{\odot}$ generates a strongly continuous semigroup $\{S(t),\ t \geq 0\}$ on $X^{\odot}$. We obtain the following (in)stability result, which splits up into two parts.

Proposition 7.

(a) Let the growth bound $\omega(S(t)) = \omega(C^{\odot}) < 0$ and $0 \leq \xi < -\omega(C^{\odot})$. Then there exists $\delta > 0$ such that for $\|x^{\odot}\| \leq \delta$ we have $t_{\max}(x^{\odot}) = \infty$ and $\lim_{t \to \infty} e^{\xi t} \|u(t; x^{\odot})\| = 0$.

(b) Assume that $X^{\odot} = X_1^{\odot} \oplus X_2^{\odot}$, where $X_i^{\odot}$ is invariant under $S(t)$ and $\dim X_1^{\odot} < \infty$. Let $S_i(t)$ denote the restriction of $S(t)$ to $X_i^{\odot}$ and $C_i^{\odot}$ the corresponding generator $(i = 1, 2)$. If $\omega(C_2^{\odot}) < \min\{\mathrm{Re}\,\lambda : \lambda \in \sigma(C_1^{\odot})\}$ and $0 < s(C_1^{\odot}) = \max\{\mathrm{Re}\,\lambda : \lambda \in \sigma(C_1^{\odot})\}$, then there exists $\epsilon > 0$, a sequence $(t_n) \subseteq \mathbb{R}_+$, $t_n \to \infty$, and a sequence $(x_n^{\odot}) \subseteq X^{\odot}$, $x_n^{\odot} \to 0$ such that $t_{\max}(x_n^{\odot}) > t_n$ and $\|u(t_n; x_n^{\odot})\| \geq \epsilon$ for n large enough.

VII. FINAL REMARKS

In Section III we explained that our mathematical model for the blood production system (8)–(13) fits into the abstract framework provided by the abstract Cauchy problem (P_r). Therefore, all the abstract results found in Sections IV to VI can be applied to our model. The abstract assumptions can easily be translated into conditions on the parameters of the model, in particular $q(P)$ and $\psi(Z)$. In fact, all the assumptions made in the paper, including the positive-off-diagonal property (31) and the assumptions (33), are found to be true if

ψ is strictly positive, locally bounded and continuously differentiable.
g is strictly positive and continuous.
q is continuously differentiable, $q(P) \geq 0$ for $P \geq 0$ and $q(P) \leq LP$, $P \geq 0$ for some constant $L > 0$.
$a, b \in L_\infty(\mathbb{R}_+)$ and nonnegative.

In fact, the model including the delay system for S, which is given by (2)–(5), also fits into our abstract framework. Nevertheless, the presence of the delay term makes the choice of the state space quite involved.

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REFERENCES

Arino, O., and Kimmel, M. (1986). Stability Analysis of Models of Cell Production Systems. *Math. Model. 7*: 1269–1300.

Butzer, P. L., and Berens, H. (1967). Semi-groups of Operators and Approximation. Springer-Verlag, Berlin.

Clément, Ph., Diekmann, O., Gyllenberg, M., Heijmans, H., and Thieme, H. (1987a). Perturbation Theory for Dual Semigroups. I. The Sun-Reflexive Case. *Math. Ann. 277*: 709–725.

Clément, Ph., Diekmann, O., Gyllenberg, M., Heijmans, H., and Thieme, H. (1987b). Perturbation Theory for Dual Semigroups. III. Nonlinear Lipschitz Continuous Perturbations in the Sun-Reflexive Case, in *Proc. Volterra Integro Differential Equations in Banach Space and Applications*, Trento, 1987.

Clément, Ph., Heijmans, H. J. A. M., Angenent, S., van Duijn, C. J., and de Pagter, B. (1987c). One-Parameter Semigroups, *CWI Monographs 5*. North-Holland, Amsterdam.

Clément, Ph., Diekmann, O., Gyllenberg, M., Heijmans, H., and Thieme, H. (1989). Perturbation Theory for Dual Semigroups. IV. The Intertwining Formula and the Canonical Pairing, in *Trends in Semigroups and Applications* (Ph. Clément et al., eds. Marcel Dekker, New York.

Crandall, M. G. (1973). A Generalized Domain for Semigroup Generators. *Proc. Am. Math. Soc. 37*: 434–440.

Diekmann, O., Lauwerier, H. A., Aldenberg, T., and Metz, J. A. J. (1983). Growth Fission, and the Stable Size Distribution. *J. Math. Biol. 18*: 135–148.

Grabosch, A., and Heijmans, H. J. A. M. (1988). *Cauchy Problems with State-Dependent Time Evolution*, CWI Report AM-R8813 (revised version). North-Holland, Amsterdam.

Grabosch, A., and Nagel, R. (1989). Order Structure of the Semigroup Dual: A Counterexample. *Indag. Math. A92*: 199–201.

Heijmans, H. J. A. M. (1985). Dynamics of Structured Populations (in particular; Chapter VI). Ph.D. thesis, Amsterdam.

Kirk, J., Orr, J. S., and Forrest, J. (1970). The Role of Chalone in the Control of the Bone Marrow Stem Cell Population. *Math. Biosci. 6*: 129–143.

Mackey, M. C. (1978). Unified Hypothesis for the Origin of Aplastic Anemia and Periodic Hematopoiesis. *Blood 51*: 941–956.

Mackey, M. C. (1981). Some Models in Hematopoiesis: Predictions and Problems, in *Biomathematics and Cell Kinetics* (M. Rotenberg, ed.), Elsevier North-Holland Biomedical Press, Amsterdam, pp. 23–38.

Mackey, M. C., and Dörmer, P. (1982). Continuous Maturation of Proliferating Erythroid Precursors. *Cell Tissue Kinet. 15*: 381–392.

Martin, R. H. (1976). Nonlinear Operators and Differential Equations in Banach Spaces. Wiley, New York.

Metz, J. A. J., and Diekmann, O. (eds.) (1986). Dynamics of Physiologically Structured Populations, Lecture Notes in Biomathematics 86. Springer-Verlag, Berlin.

Nagel, R. (ed.) (1986). One-Parameter Semigroups of Positive Operators, Lecture Notes in Mathematics 1184. Springer-Verlag, Berlin.

Schaefer, H. H. (1971). Topological Vector Spaces. Springer-Verlag, Berlin.

Schaefer, H. H. (1974). Banach Lattices and Positive Operators. Springer-Verlag, Berlin.

Tarbutt, R. G., and Blackett, N. M. (1986). Cell Population Kinetics of the Recognizable Erythroid Cells in the Rat. *Cell Tissue Kinet. 1*: 65–80.

Wheldon, T. E. (1975). Mathematical Models of Oscillatory Blood Cell Production. *Math. Biosci. 24*: 289–305.

Wintrobe, M. M. (1967). Clinical Hematology, 6th ed. Lea & Febiger, Philadelphia.