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Production, development and maturation of red blood cells
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Production, Development and Maturation of Red Blood Cells
A Mathematical Model

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The production and maintenance of the different blood components in the human body is a complex process. The essential morphological stages during the production are the pluriopotential stem cell compartment, the precursor cell compartment, and the blood cell compartment. Regulation seems to work via enzymatic control mechanisms. During the formation of red blood cells (mainly in the precursor cell stage) hemoglobin synthesis takes place. Here this process is modelled by a system of first–order partial differential equations which is then reformulated as an abstract Cauchy problem. Using a duality setting and perturbation theory we develop a general method to prove (under appropriate assumptions) global existence, uniqueness and positivity of solutions.

Keywords & Phrases : Blood production system, bone marrow, stem cells, precursor cells, red blood corpuscles, regulation, enzymatic control, structured population, state–dependent time evolution, semilinear Cauchy problem, quasilinear Cauchy problem, variation–of–constants formula, mild solution, nonlinear semigroup, positivity, linearization, linearized stability.

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1. The blood production system.

The production of the different blood components of mammalian is one of the most complex processes in man (see e.g. WINTROBE [1967]). The blood cell production system regulates the supply and maintenance of most of the blood components, such as the red blood corpuscles (erythrocytes), platelets (megakaryocytes), and some of the white blood corpuscles (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 about all essential physiological processes involved in the production process is by no means complete and the very exact regulation mechanisms 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 man every day about $2.64 \cdot 10^9$ red blood cells/kg are destructed, thus have to be replaced by new ones to maintain an approximate constant number of red blood corpuscles. The normal number of erythrocytes present in man is about $3.1 \cdot 10^{11}$ cells/kg. Moreover, sudden disturbances, which may occur due to sudden blood loss (caused by an accident, e.g.) or gain (caused by a blood transfusion, e.g.) have to be smoothed down or up in shortest possible time. Nevertheless, it happens that 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 some well described diseases such as periodic hematopoiesis, anemias or leukemias.

The main processes which have to be accomplished by the blood production system are *production, differentiation, multiplication, amplification* and *maturation*. The human blood production system can be split up in three, morphologically distinguishable, compartments, where these physiological processes take place. Indeed one can distinguish:

the self maintained stem cell compartment (located in the bone marrow);

the precursor cell compartment (located partly in the bone marrow and partly in the blood fluid);

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 towards 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. For example, in the erythrocyte line at least five morphologically different cell types are formed (proerythrocytes, basophilic erythroblasts, polychromatic erythroblasts, orthochromatic erythroblasts, reticulocytes). The total number of cells increases during the precursor stage by a factor three. In average it takes about two days for a cell to transit through this stage. Mitosis occurs only in the first precursor cell stages. The maturation level, e.g. the hemoglobin content of the cells, increases 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 compartment or blood fluid, the newly formed red blood corpuscles are completely developed. Note that for the rest of this note we restrict our attention on the erythrocyte cell line. One can observe different maturation levels, that is, a different hemoglobin content of the newly formed red blood cells. For an overview see Fig. 1.

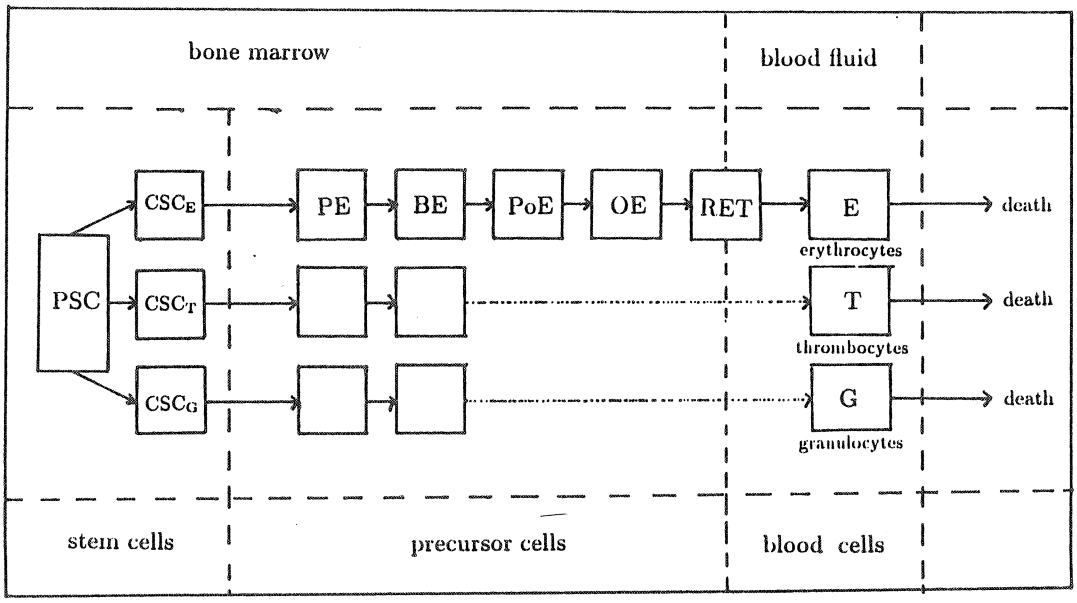

Fig. 1. The morphological structure of the (red) blood production system with several differentiation stages and its location in the bone marrow and the blood fluid. The diagram restricts to the recognizable precursors of the erythrocyte cell line. A similar development occurs in the trombocyte line and the granulocyte line, which are not specified in detail. Abbreviations used are:
PSC: pluriopotential stem cells; CSC: committed stem cells; PE: proerythroblast cells; BE: basophilic erythroblast cells; PoE: polychromatic erythroblast cells; OE: orthochromatic erythroblast cells; RET: reticolocytes; E: erythrocytes (red blood cells); T: thrombocythes (platelets); G: granulocytes (neutrophils, leukocytes)

Besides these morphological facts there is still a lot of uncertainty and speculation concerning the way how the regulation of this complex production system works. It is unquestioned that enzymes play an important role in the regulation process. For the red blood cell production the enzyme erythopoitin 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 erythropoitin by the kidney. Finally, this enzyme causes an increased influx of read blood cells into the blood. Nevertheless, it seems not to be clear what precisely leads to the raise of the influx flow, e.g., a sudden release of nearly mature precursor cells, a higher division rate of stem cells, an increased flow from the stem cell compartment to the precursor cell compartment, a faster maturation velocity, a combination of these changes, or still some other mechanism. A second enzyme which seems to be involved into the regulation of the blood cell production is chalone which is known to inhibit mitosis (see e.g. Kirk, Orr, and Forrest [1970]) and appears to influence the dynamics, resp. 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 enzymes and growth factors known to be of importance for the regulation of the other blood components. For example, in the myeloid cell line the enzyme granolopoitin and some less known colony stimulating factors CSF are involved. For the megakaryocyte line the enzyme thrombopoitin 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 the normally functioning (healthy) system cell death seems neither to occur in the stem cell compartment nor in the precursor cell stage, but it naturally occurs in the blood cell compartment. In the first two compartments cell death may arise due to some artificial disturbances of the system. Nevertheless, the physiological processes leading to the exact regulation are more–or–less unknown. We get the following schematical diagram (see Fig. 2) of the red blood cell production.

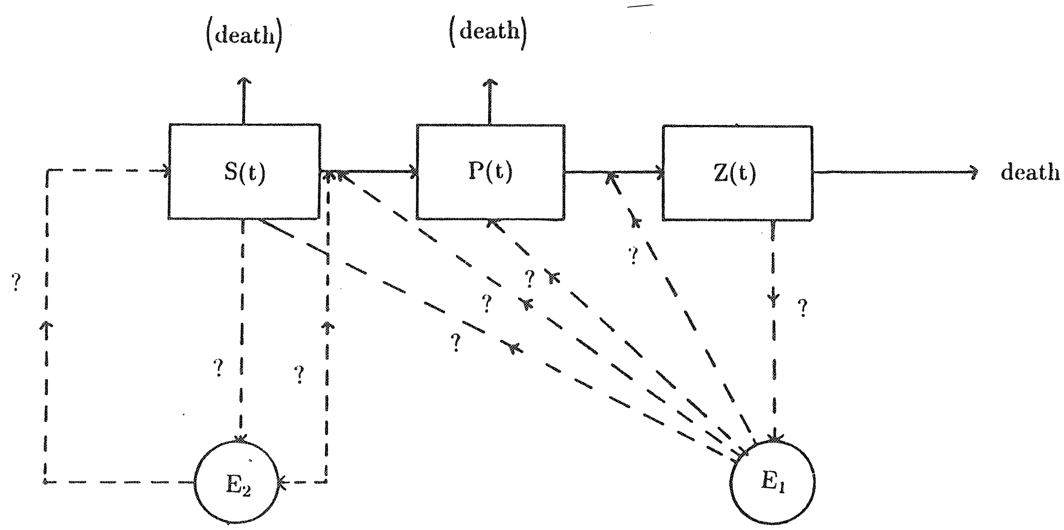

Fig. 2. Schematical diagram of the red blood production system including three different cell stages: stem cells S(t); precursor cells P(t); blood cells Z(t). Two enzymes may be involved in the regulation of the cell production. There is some kind of short range feedback (via an enzyme E_2) which regulates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

2. A mathematical model.

Many attempts have been made to describe the cell production system by some theoretical model which enables one to get at least some understanding of the observed deficiencies and to trace the mechanisms which are responsible for them. Especially we mention the investigations of MACKEY [1978], [1981], MACKEY & DÖRMER [1982], ARINO & KIMMEL [1986], HEIJMANS [1985], KIRK et al. [1970], TARBUTT & 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 & DÖRMER [1982]. We formulate a model which is based on the observation that cell maturation is a continuous process taking place mainly in the precursor cell stage. Indeed M.C. MACKEY and P. DÖRMER give a very illustrating diagram which shows the main ideas of their model (MACKEY & DÖRMER [1982, Fig. 1]).

Independently 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 an enzyme) on the number of mature cells. If there are little red blood corpuscles there is a lot of enzyme. A high amount of enzyme then leads to a high maturation velocity. We summarize these observations in Fig. 3 which shall also serve as a guide throughout the following discussion in order to formulate and illustrate our mathematical model.

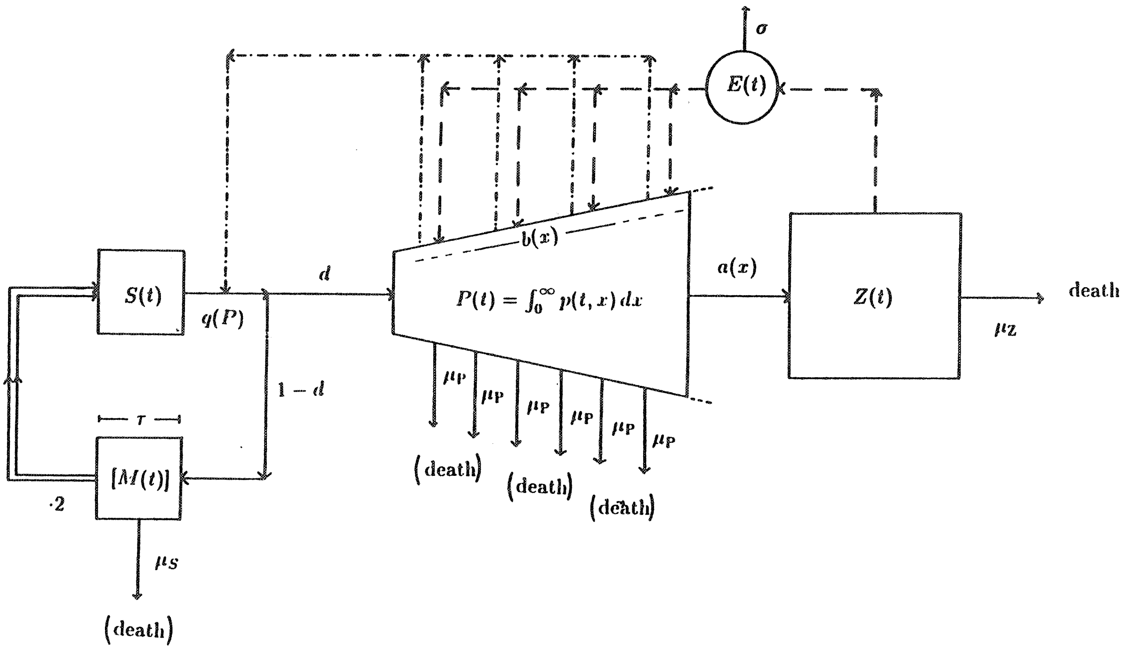

Fig. 3. Schematic outline of the model for the red blood cell production given by the differential equation system (2.5), (2.6), (2.9), (2.10), (2.11), (2.12) and (2.13). See the text for details.

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 respectively denoted by $S(t)$, $P(t)$ and $Z(t)$. 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 an enzyme, e.g. erythropoitin, 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 enzyme slows down the maturation velocity of the precursor cells. Mathematically this process can be described by an ODE for the maturation $x(t)$ of an individual precursor cell:

$$\frac{dx}{dt}(t) = \tilde{\psi}(E(t)) \cdot g(x(t)), \tag{2.1}$$

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.

Independently 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 towards 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 enzyme 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 the increase of the maturation level, and is independent of the time required to realize this increase. The death rates of precursor cells and blood cells are respectively denoted by μ_P and μ_Z. This leads us to the following system of equations for $p(t,x)$ and $Z(t)$:

$$\frac{\partial}{\partial t}p(t,x) + \tilde{\psi}(E(t))\frac{\partial}{\partial x}(g(x)p(t,x)) = b(x)p(t,x) - \tilde{\psi}(E(t))a(x)p(t,x) - \mu_P p(t,x) \tag{2.2}$$

$$\frac{d}{dt}Z(t) = -\mu_Z Z(t) + \tilde{\psi}(E(t)) \int_0^\infty a(x)p(t,x)\,dx. \tag{2.3}$$

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

$$\frac{d}{dt}E(t) = -\sigma E(t) + h(Z(t)). \tag{2.4}$$

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 M.C. MACKEY [1981] and A. ARINO & M. 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 which 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),

$$\frac{d}{dt}S(t) = 2(1-d)q(P_\tau(t))S_\tau(t)e^{-\mu_S\tau} - dq(P(t))S(t), \tag{2.5}$$

and to the following boundary condition for p,

$$\tilde{\psi}(E(t))g(0)p(t,0) = dq(P(t))S(t). \tag{2.6}$$

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 (2.6) with S constant, that is (writing $q(P)$ instead of $dq(P)S$)

$$\tilde{\psi}(E(t))g(0)p(t,0) = q(P(t)). \tag{2.7}$$

Note that the latter assumption can be justified by assuming that the time scale of equation (2.5) 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 (2.4), whence we get that $E = h(Z)/\sigma$. Thus, putting $\psi(Z) = \tilde{\psi}(h(Z)/\sigma)$, we arrive at the following system:

$$\psi(Z(t))g(0)p(t,0) = q(P(t)) \tag{2.8}$$

$$\frac{\partial}{\partial t}p(t,x) + \psi(Z(t))\frac{\partial}{\partial x}(g(x)p(t,x)) = (b(x) - \mu_P)p(t,x) - \psi(Z(t))a(x)p(t,x) \tag{2.9}$$

$$\frac{d}{dt}Z(t) = -\mu_Z Z(t) + \psi(Z(t))\int_0^\infty a(x)p(t,x)\,dx \tag{2.10}$$

$$P(t) = \int_0^\infty p(t,x)\,dx, \tag{2.11}$$

$$p(0,x) = p_0(x) \tag{2.12}$$

$$Z(0) = Z_0. \tag{2.13}$$

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.

To rewrite the system we have to devote a few words to the duality framework of dual semigroups as developed in CLÉMENT et al. [1987a,1987b,1989]. 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 (2.8)–(2.13) as the following quasilinear Cauchy problem:

$$\begin{aligned} \frac{d}{dt}u(t) &= \Psi(u(t))A_0^*u(t) + F^\times(u(t)) \\ u(0) &= u_0. \end{aligned} \qquad (\mathrm{P}_t)$$

Here $F^\times$ is a nonlinear continuous operator mapping $X^\odot$ into X^*. In (GRABOSCH & HEIJMANS [1988]) we studied the analogon 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 are going to discuss the corresponding results for our Cauchy problem (P_t) we will show that the system (2.8)-(2.13) can indeed be written in this form.

To begin with we define the "backward problem". Let $X = C_0(\mathbb{R}_+) \times \mathbb{R}$ and assume, that $g \in C(\mathbb{R}_+)$, $g(x) > 0$ a.e, and $a \in L^\infty(\mathbb{R}_+)$, $a(x) \geq 0$ a.e. We consider the operator A_0 with domain

$$D(A_0) := \{(p, Z) \in X : gp' \in C_0(\mathbb{R}_+)\} \qquad (2.14)$$

given by

$$A_0((p, Z)) := (gp' - ap, 0). \qquad (2.15)$$

It is straightforward to prove that A_0 generates a strongly continuous semigroup 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 a weak*continuous semigroup on X^*. Thus we consider the

subspace $X^{\odot} = L^1(\mathbb{R}_+) \times \mathbb{R} = \overline{D(A_0^*)}$ of X^*. Then $X^{\odot}$ 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 $\mu_P, \mu_Z \in \mathbb{R}_+$. In view of the system (2.8)–(2.13) we define a perturbation $F^{\times} : X^{\odot} \in X^*$ by

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

where Δ_0 is the Dirac measure in 0.
As a "feedback" function we define $\Psi : X^{\odot} = L^1(\mathbb{R}_+) \times \mathbb{R} \to \mathbb{R}_+ \setminus \{0\}$ by

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

One can show that with these choices for X, A_0, $F^{\times}$ and Ψ system (P_t) is an abstract reformulation of (2.8)–(2.13). 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

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

We refer to Section 3, Proposition 3.5 for the sense in which this operator gives the connection to the differential equation system (2.8)–(2.13).

3. Existence, uniqueness and regularity of solutions.

In this and the following sections we shall be dealing with the initial value problem (P_t) of Section 2. One should observe that we have to do with a quasilinear 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 modelling the influx of newborn individuals at the boundary which occur very often in structured population equations.

We assume furthermore that the function $\Psi : X^\odot \to \mathbb{R}_+$ is continuous, strictly positive and locally bounded, i.e., Ψ is bounded on bounded subsets of X^*.

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

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

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

$$\left\|B^\times(x^\odot) - B^\times(y^\odot)\right\| \leq L_B(r) \left\|x^\odot - y^\odot\right\| \tag{3.1}$$

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

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

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

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

In order to write down the right hand side of this identity one has to make sure that the integration makes sense. Using the above 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 thus defined integral 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

$$\tau_u(t) := \int_0^t \Psi(u(s))\, ds \tag{3.2}$$

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

$$t_v(\tau) := \int_0^\tau [\Psi(v(\sigma))]^{-1} d\sigma. \tag{3.3}$$

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 & HEIJMANS [1988, Def.2.4]). The following lemma is taken from the same source (Prop.2.2).

LEMMA 3.1. *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:*

$\tau_0 = \tau_u(t_0)$,	*and*	$t_0 = t_v(\tau_0)$	
$t_v(\tau_u(t)) = t$,	*and*	$v(\tau_u(t)) = u(t)$	*for* $0 \leq t \leq t_0$
$\tau_u(t_v(\tau)) = \tau$,	*and*	$u(t_v(\tau)) = v(\tau)$	*for* $0 \leq \tau \leq \tau_0$.

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 above relations hold.

From this lemma we deduce that u is a classical (resp. mild) solution of (P_t) if and only if v is a classical (resp. mild) solution of (P_τ). It is this one–to–one relation between solutions of either problems which is exploited in (GRABOSCH & HEIJMANS [1988]) to deal with the quasilinear system.

Semilinear equations of the form (P_τ) are introduced and investigated by CLÉMENT et al. [1987a,1987b,1989]. Using these results and Lemma 3.1 we can adopt the existence and uniqueness result of (GRABOSCH & HEIJMANS [1988, Thm.3.2]) to the quasilinear equation (P_t) and obtain the following result:

PROPOSITION 3.2. *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 & 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] and [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 the solutions of the problem (P_t): see CLÉMENT, HEIJMANS et al. [1987], CLÉMENT et al. [1987b,1989]. With the uniform boundedness principle one easily obtains that $D(A^{\times}) \subseteq \mathcal{F}$. But the converse also holds.

PROPOSITION 3.3. *$D(A^\times) = D(A_0^*) = \mathrm{Fav}(T_0^*) = \mathcal{F}$, 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 $x^\odot \in X^\odot$ then 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 this is explicitly mentioned.

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

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 2 this assumption is not satisfied. Thus in Section 4 we shall meet some different conditions on $F^\times$ which guarantee that the "Global Existence Assumption" holds. Under either of these assumption, $\mathcal{F}$ 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 3.4. *Let the "Global Existence Assumption" hold. 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 with $A_0 - \omega I$ and $F^\times(u)$ with $F^\times(u) + \omega\Psi(u)$). As a first step we show that for every $T > 0$ there is a constant $\omega(r,T) \in \mathbb{R}$ such that

$$\left\|u(t;x^\odot) - y(t;y^\odot)\right\| \leq Me^{\omega(r,T)t}\left\|x^\odot - y^\odot\right\|, \quad 0 \leq t \leq T, \tag{3.4}$$

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 (3.4) let $r, T > 0$, take $t \leq T$ and $\|x^\odot\|, \|y^\odot\| \leq r$. Then for every $s \leq t$ we have $\|u(s;x^\odot)\|, \|u(s;y^\odot)\| \leq Me^{\omega T}r =: R$. By the local Lipschitz continuity of $F^\times$,

$$\left\|F^\times(u(s;x^\odot)) - F^\times(u(s;y^\odot))\right\| \leq L_F(R)\left\|u(s;x^\odot) - u(s;y^\odot)\right\|.$$

Now subtracting the variation–of–constants formulas (VOC_t) for $x^{\odot}$ and $y^{\odot}$ and using Gronwall's lemma we derive that

$$\left\|u(t;x^{\odot}) - u(t;y^{\odot})\right\| \leq M \left\|x^{\odot} - y^{\odot}\right\| e^{ML_F(R)t}, \quad t \leq T.$$

Hence (3.4) follows with $\omega(r,T) := ML_F(Me^{\omega T}r)$.

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

$$\left\|u(t;x^{\odot}) - u(s;x^{\odot})\right\| \leq C(T)|t-s|. \tag{3.5}$$

Suppose that the estimate (3.5) holds for $s = 0$. Then it holds for arbitrary s and t (with $C(T)$ adapted). Namely, by (3.4), if $s \leq t$,

$$\begin{aligned}\left\|u(t;x^{\odot}) - u(s;x^{\odot})\right\| &= \left\|u(s;u(t-s;x^{\odot})) - u(s;x^{\odot})\right\| \\ &\leq Me^{\overline{\omega}(T)s}\left\|u(t-s;x^{\odot}) - x^{\odot}\right\| \\ &\leq H(T)\left\|u(t-s;x^{\odot}) - x^{\odot}\right\|.\end{aligned} \tag{3.6}$$

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

Now we prove that (3.5) holds for $s = 0$ and $t \leq T$. 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 $\|u(t_k) - x^{\odot}\| \leq Kt_k$. Let (p_k) a sequence of positive integers such that $p_k t_k \to t$ as k goes to infinity. Then, by (3.6)

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

This concludes the proof. □

In fact this result says that $A^{\times}$ is the weak*generator of the semigroup $\{T^{\odot}(t), t \geq 0\}$. 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 $X^{\odot}$, i.e., $D(A^{\odot}) = \{x^{\odot} \in D(A^{\times}) : A^{\times}x^{\odot} \in X^{\odot}\}$ and $A^{\odot}x^{\odot} = A^{\times}x^{\odot}$.

PROPOSITION 3.5. *Assume in addition to the assumptions of Proposition 3.4 that $F^{\times}/\Psi$ is continuously Fréchet–differentiable. If $x^{\odot} \in D(A^{\odot})$, then $u(\cdot\,; x^{\odot})$ is continuously differentiable and*

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

holds.

For a proof see GRABOSCH & HEIJMANS [1988, Thm.3.4].

4. GLOBAL EXISTENCE AND POSITIVITY.

In this section we shall 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 same line as in (GRABOSCH & 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, Chapter II]). Then X^* is a Banach lattice with positive cone $X_+^* = \{x^* \in X^* : \langle x, x^*\rangle \geq 0 \text{ for all } x \in X_+\}$. The thus defined order on X^* induces a natural order on the closed, linear subspace $X^{\odot}$. In general $X^{\odot}$ needs not be a sublattice of X^* (see GRABOSCH & 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

$$M^{\circ} := \{x^* \in X^* : \langle x, x^*\rangle \leq 1 \text{ for all } x \in M\} \tag{4.1}$$

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

$$M^{\circ\circ} := (M^{\circ})^{\circ} = \{x^{**} \in X^{**} : \langle x^{**}, x^*\rangle \leq 1 \text{ for all } x^* \in M^{\circ}\}. \tag{4.2}$$

LEMMA 4.1. *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):

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

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

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

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 4.2. *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

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

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

Before we are going to prove the next lemma we want to remind the reader to the notion of a *subdifferential* of a convex continuous functional on a Banach space (see e.g. CLÉMENT, HEIJMANS et al. [1987, Appendix A.1]).

DEFINITION. Let X be a Banach space, let $\Phi : X \to \mathbb{R}$ be convex and continuous and take $x \in X$. The *subdifferential* of Φ in x is given by

$$\begin{aligned} d\Phi(x) &= \{x^* \in X^* : \langle y, x^*\rangle \leq \Phi(y) \text{ for all } y \in X \text{ and } \langle x, x^*\rangle = \Phi(x)\} \\ &= \{x^* \in X^* : \langle y - x, x^*\rangle \leq \Phi(y) - \Phi(x) \text{ for all } y \in X\}. \end{aligned} \tag{4.3}$$

Here we are interested in a very special convex 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, convex functional on X^* (see GRABOSCH & HEIJMANS [1988, Lemma 4.3] for some important properties of Φ). From definition (4.3) 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 4.3. *Let $x^* \in X^*$. Then $d_*\Phi(x^*)$ is $\sigma(X^{**}, X^*)$–dense in $d\Phi(x^*)$.*

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

$$\begin{aligned} d_*\Phi(x^*) &= \{x \in X : \|x\| \leq 1, -x \geq 0, \langle x^*, x\rangle = 0\} \\ &= U_X \cap (-X_+) \cap \{x \in X : \langle x^*, x\rangle = 0\}. \end{aligned} \tag{4.4}$$

We obtain by Lemma 4.1 that $M^{\circ\circ} = U_{X^{**}} \cap (-X^{**}_+) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**}\rangle = 0\}$. But

$$U_{X^{**}} \cap (-X^{**}_+) \cap \{x^{**} \in X^{**} : \langle x^*, x^{**}\rangle = 0\} = d\Phi(x^*). \tag{4.5}$$

Since $d_*\Phi(x^*)$ is convex, as the intersection of convex sets, we obtain by the bipolar theorem (see SCHAEFER [1971, IV.Thm.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 $f : [0,1] \to X^*$ is weak*continuous and that its weak*Riemann integral $\int_0^1 f(s)\,ds$ exists. Let $\Phi : X^* \to \mathbb{R}$ be given by $\Phi(x^*) = \|(x^*)_-\|$. Then*

$$\Phi\Big(\int_0^1 f(s)\,ds\Big) \leq \int_0^1 \Phi(f(s))\,ds \leq \infty. \tag{4.6}$$

PROOF. Let $x^* := \int_0^1 f(s)\,ds$, and let $d\Phi(x^*)$ be the subdifferential of Φ in x^*, i.e., $d\Phi(x^*) = \{x^{**} \in X^{**} : \langle y^*, x^{**}\rangle \leq \Phi(y^*) \text{ for all } y^* \in X^* \text{ and } \langle x^*, x^{**}\rangle = \Phi(x^*)\}$. By Lemma 4.3 we know that $d_*\Phi(x^*) = \{x \in X : \langle y^*, x\rangle \leq \Phi(y^*) \text{ for all } y^* \in X^* \text{ and } \langle x^*, x\rangle = \Phi(x^*)\}$ 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 4.2 $s \mapsto \Phi(f(s))$ is measurable, thus integration over s yields

$$\begin{aligned} \int_0^1 \Phi(f(s))\,ds &\geq \int_0^1 \langle x, f(s) - x^*\rangle\,ds + \Phi(x^*) = \int_0^1 \langle x, f(s)\rangle\,ds - \langle x, x^*\rangle + \Phi(x^*) \\ &= \langle x, x^*\rangle - \langle x, x^*\rangle + \Phi(x^*) = \Phi(x^*) = \Phi\Big(\int_0^1 f(s)\,ds\Big). \end{aligned}$$ □

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 & HEIJMANS [1988, Lemma 4.4]).

LEMMA 4.4. *Let X be a separable Banach lattice, $0 \le x^\odot \in X^\odot$ and $F^\times$ as in Section 3. Equivalent are:*

(i) *If $x \in X_+$ with $\langle x, x^\odot \rangle = 0$, then $\langle x, F^\times(x^\odot)\rangle \ge 0$.*

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

PROOF. Without restriction we can assume that $x^\odot \in \partial X_+^*$.
We consider $\Phi : X^* \to \mathbb{R}$ given by $\Phi(x^*) = \operatorname{dist}(x^*, X_+^*)$. By Lemma 4.3 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, HEIJMANS et al. [1987, Prop.A.1.2]) 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

$$D_{F^\times(x^\odot)}\Phi(x^\odot) = \sup\{\langle F^\times(x^\odot), x\rangle : x \in d_*\Phi(x^\odot)\}. \tag{4.7}$$

Furthermore we observe that

$$\begin{aligned}\lim_{h\downarrow 0}\frac{1}{h}\operatorname{dist}(x^\odot + hF^\times(x^\odot), X_+^*) &= \lim_{h\downarrow 0}\frac{1}{h}[\operatorname{dist}(x^\odot + hF^\times(x^\odot), X_+^*) - \operatorname{dist}(x^\odot, X_+^*)]\\ &= \lim_{h\downarrow 0}\frac{1}{h}[\Phi(x^\odot + hF^\times(x^\odot)) - \Phi(x^\odot)]\\ &= D_{F^\times(x^\odot)}\Phi(x^\odot).\end{aligned} \tag{4.8}$$

After these preparations we can now prove the equivalence of (i) and (ii).
Indeed, by the formulas (4.7) and (4.8) 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 (4.4), hence to condition (i). □

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

LEMMA 4.5. *Let X be a separable Banach lattice and let $x^\odot \in X_+^\odot$. Assume that one of the equivalent conditions of Lemma 4.4 holds. Then*

$$\frac{1}{h}[T_0^\odot(h)x^\odot + \int_0^h T_0^*(s)F^\times(x^\odot)\,ds]_- \to 0 \quad \text{as } h \downarrow 0. \tag{4.9}$$

PROOF. The following estimate holds:

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

by Jensen's inequality and Lemma 4.2

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

$$+\,h\,F^{\times}(x^{\odot})]_-\|\,ds \quad \text{by (Grabosch \& Heijmans [1988, Lemma 4.3(h)])}$$

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

where the last estimate follows from the continuity of $F^{\times}$. From the subtangential condition (ii) of Lemma 4.4 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 above estimate proves the assertion. □

After these preparations we can state our main results concerning the existence of positivity preserving, resp. of global solutions of (P_t). For the analogues statements we refer to Grabosch & Heijmans [1988, Thm.4.2]

Proposition 4.6. *Let A_0 be the generator of a linear, positive 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 the following "positive–off–diagonal" property:*

$$\text{If } x \in X_+ \text{ with } \langle x, x^{\odot}\rangle = 0, \text{ then } \langle F^{\times}(x^{\odot}), x\rangle \ge 0. \tag{4.10}$$

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

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

$$F^{\times}(x^{\odot}) = F^{\times}(x_+^{\odot}) \qquad \text{for all } x^{\odot} \in X^{\odot}. \tag{4.11}$$

Namely, if this is not satisfied we define $F_0^{\times} : X^{\odot} \to X^*$ by $F_0^{\times}(x^{\odot}) := F^{\times}(x_+^{\odot})$ $(x^{\odot} \in X^{\odot})$. Then by construction $F_0(x^{\odot}) = F_0(x_+^{\odot})$. Note that $F_0^{\times}$ still satisfies (4.10). If solutions of (VOC_t) with $F^{\times}$ replaced by $F_0^{\times}$ are positivity preserving, then they coincide with solutions of the original (VOC_t) for positive initial data $x^{\odot}$.
Further we restrict to the case where $\|T_0(t)\| \le Me^{\omega t}$ with $M = 1$ for all $t \ge 0$. In the proof of Theorem 4.2 in (Grabosch & Heijmans [1988]) it is shown that the general case can always be reduced to this situation. Let $x^{\odot} \ge 0$ and let $u(t) = u(t; x^{\odot})$ be the continuous solution of (VOC_t) on $[0, t_{\max}(x^{\odot}))$. We show that $u(t) \ge 0$ or equivalently that $u_-(t) := [u(t)]_-$ is zero. For $t < t_{\max}$ we define

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

Now

$$u(t+h) = T_0^{\odot}(h)u(t) + \int_0^h T_0^*(h-s)F^{\times}(u(t+s))\,ds.$$

Using Lemma 4.5, (4.11) 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

$$\begin{aligned}
\|u_-(t+h)\| &\leq \|u(t+h) - T_0^{\odot}(h)u_+(t) - \int_0^h T_0^*(h-s)F^{\times}(u_+(t+s))\,ds\| \\
&\qquad + \|[T_0^{\odot}(h)u_+(t) + \int_0^h T_0^*(h-s)F^{\times}(u_+(t+s))\,ds]_-\| \\
&\leq \|T_0^{\odot}(h)u_-(t)\| + \|u(t+h) - T_0^{\odot}(h)u(t) - \int_0^h T_0^*(h-s)F^{\times}(u(t+s))\,ds\| \\
&\qquad + \|[T_0^{\odot}(h)u_+(t) + \int_0^h T_0^*(h-s)F^{\times}(u_+(t))\,ds]_-\| + \mathrm{o(h)} \\
&\leq e^{\omega h}\,\|u_-(t)\| + \mathrm{o(h)}.
\end{aligned}$$

Hence $\phi(t+h) \leq \phi(t) + \mathrm{o(h)}$ 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 $\phi = 0$. □

The proof of the next result can be given similarly to the proof of Theorem 4.6 in GRABOSCH & HEIJMANS [1988].

PROPOSITION 4.7. *Let A_0 be the generator of a linear, positive, bounded 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 property (4.8) and that there exists an locally Lipschitz continuous operator $F_0^{\times} : X^{\odot} \to X^*$ such that*

$$\begin{aligned}
&F^{\times}(x^{\odot}) \leq F_0^{\times}(x^{\odot}) \text{ for all } x^{\odot} \geq 0, \\
&\|F_0^{\times}(x^{\odot})\| \leq C\,\|x^{\odot}\| \text{ for all } x^{\odot} \geq 0.
\end{aligned} \tag{4.12}$$

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

PROOF. Let $x^{\odot} \geq 0$. Then $u(t;x^{\odot})$ is the continuous solution of (VOC_t), i.e.,

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

Using the first part of the assumption (4.12) and the fact that $u(t) \geq 0$ we get

$$u(t) \leq T_0^{\odot}(\tau_u(t))x^{\odot} + \int_0^t T_0^*(\tau_u(t) - \tau_u(s))F_0^{\times}(u(s))ds.$$

Since, for all $t \geq 0$, $\|T_0(t)\| \leq M$ and hence $\|T_0^*(t)\|$, $\|T_0^{\odot}(t)\| \leq M$ for some constant $M \geq 1$, we get, using the second part of assumption (4.12),

$$\|u(t)\| \leq M \|x^{\odot}\| + \int_0^t MC \|u(s)\| \, ds.$$

Now Gronwall's lemma yields that

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

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

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

Corollary 4.8. *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 (4.10),*
- *$F^{\times}$ satisfies (4.12).*

Then the following holds.

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

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

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

i.e., (P_t) is satisfied in the weak sense.*

(c) *If, in addition to the above assumptions, $F^{\times}/\Psi$ 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_t) is satisfied.*

5. Linearized (in)stability

Again we proceed as in (Grabosch & Heijmans [1988, Sec.5]), where we proved a principle of linearized (in)stability for quasilinear equations of type (P_t) 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_τ). 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 & 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 $\overline{u}$ be an equilibrium of (P_t). Then the linearization of (P_t) in $\overline{u}$ is given by

$$\frac{dw}{dt} = \Psi(\overline{u})A_0^* w + A_0^* \overline{u} \cdot \langle \Psi'(\overline{u}), w\rangle + (F^\times)'(\overline{u})w. \tag{5.1}$$

The stability properties of $\overline{u}$ for equation (P_t) are determined by the stability properties of the zero solution of the linearization (5.1). We define the operator C^* on X^* by

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

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 5.1.

(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.*

6. Final remarks.

In Section 2 we explained that our mathematical model for the blood production system (2.8)–(2.13) fits into the abstract framework provided by the abstract Cauchy problem (P_t). We point out however, that to give a rigorous proof of this correspondence would involve some lengthy though straightforward computation. Therefore all the abstract results found in Sections 3–5 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, inclusive the "positive-of-diagonal property" (4.10) and the assumptions (4.12), 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 non-negative.

In fact, the model including the delay system for S, which is given by (2.2)–(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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