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ON THE STABLE SIZE DISTRIBUTION OF POPULATIONS REPRODUCING BY FISSION INTO TWO UNEQUAL PARTS

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A nonlinear model describing the dynamics of a continuous culture of cells characterized by their size only, and reproducing by fission into unequal parts is formulated. It is assumed that cells grow proportionally to their size. Using techniques from dynamical systems theory, we establish results concerning the existence of a globally stable equilibrium.

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INTRODUCTION

It is generally accepted by cell biologists that cell size is one of the most decisive parameters as far as the individual dynamic behaviour of a cell is concerned. (See [1,2,3,4,8,15,16,20,21].) In addition cell size is an attractive parameter because of the relative ease and precision with which it can be measured. During the past twenty years size distributions of cell populations have become of increasing interest, because the instrumentation for obtaining them has improved considerably. (See [2,4,21].)

One of the main purposes of studying theoretical growth models of cell populations is to compare the analytical results with the experimental data in order to test the validity of the model. In other words: to derive information about the dynamics of the individual (growth, death, division) from the dynamics of the population as a whole. One of the main problems is to find a model which is general enough to give an acceptable description of the biological reality and which does not contain too many parameters. In this context our contribution must be seen as an attempt to describe some features of proliferating cell populations and to provide some additional insight in this complex sub-area of structured population dynamics.

In this paper we consider a continuous culture (see [12]) of proliferating cells which are assumed to be characterized by their size alone. Here "size" can be replaced by any other quantity obeying a physical conservation law, for instance weight or protein content. We assume that the growth of an individual is proportional to its size (exponential growth). (See [1,2,3,4,15]). In general this assumption is very restrictive. However Anderson et al [1,2,3,4] concluded from their measurements of mammalian cells in suspension cultures that the cell size growth rate is approximately proportional to cell size. The reason for restricting ourselves to the case of exponential growth becomes perfectly clear in section 5. The idea is the following. If the growth of a cell is proportional to its size, the dynamics of the total biomass represented by the population, is described by an ordinary differential equation. As a consequence the non-linearity, which makes the model rather intractable in the most general case, can be computed à priori, i.e. without knowledge of the size distribution. Furthermore we assume that the ratio P of birth size of a daughter cell to the division size of her mother is a random variable described by a smooth probability density function, which does not depend on the division size of the mother and which is symmetric around $\frac{1}{2}$. This assumption was first suggested by Koch & Schaechter [15].

1. THE MODEL

We consider a population of cells contained whithin some completely stirred tank of volume V. The population is supplied at a constant rate Q with fresh medium containing nutrients essential for their growth, and at the same rate medium containing cells and nutrient is removed from the tank. The ratio $D = \frac{Q}{V}$ is called the dilution rate, and is a control variable of the process. We assume that one main compound S of the medium is needed to describe the dynamics of the cell population. This compound is called the growth-limiting substrate (or nutrient). In literature a population living in such environment is called a continuous culture. (See e.g. [12].)

We assume that the individuals of the cell population are characterized by their size x only. (The state of an individual is its size; see [5].) An individuals size increases deterministically according to the ordinary differential equation

$$\frac{dx}{dt} = g(x) \tag{1.1}$$

g is called the individual growth rate and, although this is not expressed in our notation, may also depend on environmental factors such as nutrient concentration. For some populations, $g(x)$ is found to be proportional to x

$$g(x) = \gamma x, \tag{1.2}$$

in which case we speak of exponential individual growth because in this case (1.1) has the solution $x(t) = x(0)e^{\gamma t}$, if γ does not depend on time t. In this paper we assume that the individual growth rate is given by (1.2) where γ is not necessarily constant, but may depend on the substrate concentration S in the tank.

Let the organisms reproduce by fission into two parts and let the probability per unit of time that a cell of size x divides be described by a function $b(x)$. The ratio p of the size at birth of a daughter cell and the size at division of her mother is a random variable with smooth probability density function $d(p)$, which does not depend on the division size of the parent. Observe that $d(p)$ has to be symmetric around $p = \frac{1}{2}$. Notice that $\int_0^1 d(p) = 1$. (We refer to [15,16,21] for more details.)

Our system can be described by two non-linear equations

$$\frac{\partial n}{\partial t}(t,x) + \frac{\partial}{\partial x}(\gamma(S)xn(t,x)) = -Dn(t,x) \tag{1.3}$$

$$-b(x)n(t,x) + 2\int_0^1 \frac{d(p)}{p} b(\frac{x}{p})n(t,\frac{x}{p})dp$$

$$\frac{dS}{dt} = -\frac{1}{\theta}\gamma(S)\int_0^\infty xn(t,x)dx + D(S^{in} - S) \tag{1.4}$$

where $n(t,x)$ is the (unknown) population density distribution, i.e. $\int_{x_1}^{x_2} n(t,x)dx$ is the number of cells with size between x_1 and x_2 at time t per unit of volume. S^{in} is the input nutrient concentration and θ is the so-called yield constant, i.e. the ratio "biomass of the organism formed/mass of substrate used". We assume that $\gamma(S)$ has the form of a hyperbola

$$\gamma(S) = \frac{mS}{k+S} \tag{H_γ}$$

This was experimentally found by Monod (See e.g [12].) m is called the maximum growth rate and k is the Michaelis-Menten constant. However, we wish to point out that this assumption is not essential for our calculations. The analysis can be carried through for more general γ.

The last two terms at the right-hand-side of (1.3) describe the population's reproduction process. The factor $\frac{1}{p}$ accounts for the fact that newborn cells with size in $(x, x+dx)$ come from a mother with size in the interval $(\frac{x}{p}, \frac{x}{p} + \frac{dx}{p})$ which is $\frac{1}{p}$ times as large. We do not give a derivation of equation (1.3) but instead refer to a paper of Frederickson et al [8].

The first expression at the right-hand-side of (1.4) accounts for the amount of substrate used by the individuals of the population for their growth (per unit of volume). Notice that

$$W(t) = \int_0^\infty xn(t,x)dx$$

is the biomass concentration. The second expression at the right-hand-side of (1.4) is the difference of input and output of substrate

From now on we assume that the following conditions are satisfied:

1^o $b(x)$ is continous on $[0,1)$ $[H_b]$
2^o $b(x)=0,\ 0\leq x\leq a,\ b(x)>0,\ a<x<1$
3^o $\lim_{x\uparrow 1}\int_a^x b(\xi)d\xi=\infty$
4^o $\frac{b(x)}{g(x)}\exp\left[-\int_a^x\frac{b(\xi)}{g(\xi)}d\xi\right]$ is bounded on $[a,1]$

1^o $d(p)=0$ outside $(\frac{1}{2}-\Delta,\frac{1}{2}+\Delta)$, where $0<\Delta<\frac{1}{2}$ $[H_d]$
2^o d is piecewise C^1 on $(\frac{1}{2}-\Delta,\frac{1}{2}+\Delta)$
with bounded derivative

Condition $[H_b]$ describes the following biological situation. Cells cannot divide before they reach a minimal size $a>0$, and they have to divide before they reach a maximal size which is normalized to be 1. The last assumption in $[H_b]$ means that the function describing the chance per unit of size that a cell will divide at size x, remains bounded. (See section 9.) In equation (1.3) one must read $b(\frac{x}{p})n(t,\frac{x}{p})=0$, if $\frac{x}{p}>1$. We introduce the following notation

$$\alpha=(\tfrac{1}{2}-\Delta)a,\quad \beta=\tfrac{1}{2}+\Delta$$

α and β can be interpreted as the minimum resp. maximum size of a newborn cell. The fact that cells with size smaller than α cannot exist is expressed by the boundary condition

$$n(t,\alpha)=0. \tag{1.5}$$

Furthermore we supply (1.3)-(1.4) with the initial conditions

$$n(0,x)=n_0(x)\geq 0 \tag{1.6}$$

$$S(0)=S_0>0 \tag{1.7}$$

The first part of this paper (sections 2,3,4) is concerned with the investigation of the corresponding linear equation in a slightly more general form. By means of an elementary transformation, it is reduced to a more tractable problem. This is done in section 2. In section 3 the asociated eigenvalue problem is treated. Section 4 is concerned with the time-dependent linear equation. We prove that its solutions can be represented by a strongly continuous semigroup. The results of section 3 are used to establish the large time behaviour of these solutions. In section 5 it is explained how equation (1.4) can be solved à priori, i.e. without knowledge of the solution of (1.3). Existence and uniqueness of solutions of the non-linear problem (1.3)-(1.7) is proved in section 6. In section 7 we state our main result which says that there exists a globally stable equilibrium. The proof of this result can be found in section 8. In section 9 we shall make some final remarks.

2. TRANSFORMATION OF THE LINEAR EQUATION.

A good starting point for our investigation is the linear equation associated with (1.3). For the sake of generality (and because it causes no extra difficulties) we shall deal with a slightly more general form of this linear equation

$$\frac{\partial n}{\partial t}(t,x)+\frac{\partial}{\partial x}(g(x)n(t,x))=-(D(x)+b(x))n(t,x) \tag{2.1}$$

$$+2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta}\frac{d(p)}{p}b(\frac{x}{p})n(t,\frac{x}{p})dp$$

$$n(t,\alpha)=0 \tag{2.2}$$

In words: we do not restrict ourselves to the case of exponential individual growth characterized by (1.2), and the death rate D (= dilution rate if it concerns a continuous culture) is allowed to depend on x. We make the following assumptions on g and D.

g is a strictly positive, continuous function on $[\alpha,1]$ $[H_g]$

D is a nonnegative, integrable function on $[\alpha,1]$. $[H_D]$

Now let us define

$$E(x)=\exp\left(-\int_{\alpha}^{x}\frac{b(\xi)+D(\xi)}{g(\xi)}d\xi\right).$$

This quantity has a clear biological interpretation. From a cohort of N individuals starting at size α, $N\cdot E(x)$ will reach size x without having died (been washed out) or divided. Observe that $E(1)=0$. Equation (2.1) is supplemented with the initial condition

$$n(0,x)=n_0(x) \tag{2.3}$$

It is suggested by the biological interpretation of $n(t,x)$ that for all $t\geq 0$, both $n(t,\cdot)$ and $b(\cdot)n(t,\cdot)$ should be integrable. We expect that, if similar conditions are imposed on the initial function $n_0(\cdot)$, together with $n_0(x)\geq 0$, a.e. on $[\alpha,1]$, then (2.1) has a solution also satisfying these conditions. However, guided by the desire for mathematical simplicity we shall impose a more restrictive condition on n_0.

$\frac{n_0(x)}{E(x)}$ is integrable on $[\alpha,1]$. $[H_{n_0}]$

It is implied by the results of section 4 that this property is inherited by the solutions $n(t,\cdot)$ of (2.1)-(2.3). With this in mind, the following transformation does not come out of the blue.

$$m(t,x)=\frac{g(x)}{E(x)}n(t,x) \tag{2.4}$$

We obtain the following initial value problem for $m(t,x)$:

$$\frac{\partial m}{\partial t}+g(x)\frac{\partial m}{\partial x}=\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta}k(p,x)m(t,\frac{x}{p})dp \tag{2.5}$$

$$m(t,\alpha)=0 \tag{2.6}$$

$$m(0,x)=\phi(x):=\frac{g(x)}{E(x)}n_0(x) \tag{2.7}$$

where

$$k(p,x)=\frac{2}{p}d(p)b(x/p)\frac{g(x)}{g(x/p)}\frac{E(x/p)}{E(x)}. \tag{2.8}$$

One should read $k(p,x)m(t,\frac{x}{p})=0$, if $\frac{x}{p}>1$.

For all $p\in[\frac{1}{2}-\Delta,\frac{1}{2}+\Delta]$, the function $k(p,\cdot)$ has support $[pa,p)$ (which is contained in $[\alpha,\beta)$) and is bounded because of assumption $[H_b\cdot 4]$.

Condition $[H_{n_0}]$ yields that ϕ is an integrable function, i.e. $\phi\in L_1[\alpha,1]$. Most of the time we shall write L_1 if we mean $L_1[\alpha,1]$. We shall look for solutions $m(t,x)$ of (2.5)-(2.7) satisfying $m(t,\cdot)\in L_1$, for all $t\geqslant 0$.

(2.5)-(2.7) can be rewritten as an abstract Cauchy problem.

$$\frac{dm}{dt}=Am,\quad t>0, \tag{2.9}$$

$$m(0)=\phi,\quad \phi\in L_1, \tag{2.10}$$

where A is the closed operator on L_1 given by

$$(A\psi)(x)=-g(x)\frac{d\psi}{dx}+\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(p,x)\psi(\frac{x}{p})dp \tag{2.11}$$

for all ψ in the domain $\mathbf{D}(A)$ of A.

$$\mathbf{D}(A)=\{\psi\in L_1|\psi \text{ is absolutely continuous and } \psi(\alpha)=0\} \tag{2.12}$$

Finally, we refer to [6] where Diekmann et al discuss a similar problem, and use the same transformation (2.4). However, they work in the space of continuous functions, whereas we do work in L_1. The reason for this becomes clear in lemma 8.1 where we prove boundedness of solutions of the nonlinear problem.

3. THE LINEAR EIGENVALUE PROBLEM

This section is entirely concerned with the investigation of the spectrum $\sigma(A)$ of the operator A given by (2.11)-(2.12). The results that we shall find can be used to characterize the behaviour of the solutions of the time-dependent linear equation (2.1)-(2.3) for $t\to\infty$.

Throughout this paper we use the following notation. For an operator L we denote by $P\sigma(L)$ the point spectrum of L. $\mathbf{N}(L)$ is the nullspace of L and $\mathbf{R}(L)$ denotes the range.

We are looking for solutions $\psi\in\mathbf{D}(A)$ of the homogeneous equation

$$\lambda\psi-A\psi=f, \tag{3.1}$$

where $f\in L_1$. Let

$$G(x)=\int_\alpha^x\frac{d\xi}{g(\xi)}\qquad \alpha\leqslant x\leqslant 1 \tag{3.2}$$

and

$$\phi(x)=e^{\lambda G(x)}\psi(x). \tag{3.3}$$

Substitution of (3.3) in (3.1) using (2.11) yields

$$\frac{d\phi}{dx}=\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta}\hat{k}_\lambda(p,x)\phi(\frac{x}{p})dp+f(x)e^{\lambda G(x)},$$

where

$$\hat{k}_\lambda(p,x) = \frac{k(p,x)}{g(x)} e^{-\lambda(G(x/p)-G(x))}. \tag{3.4}$$

Integration from α to x and using that $\phi(\alpha) = 0$ (because $\psi \in D(A)$) yields

$$\phi(x) = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \left(\int_{\alpha}^{(x,\beta)^-} \hat{k}_\lambda(p,\xi)\phi(\xi/p)d\xi \right)dp \tag{3.5}$$

$$+ \int_{\alpha}^{x} f(\xi)e^{\lambda G(\xi)}d\xi,$$

where $(x,\beta)^-$ stands for the minimum of x and β. We can write (3.5) abstractly as

$$\phi = T_\lambda\phi + U_\lambda f, \tag{3.6}$$

where T_λ and U_λ are given by

$$(T_\lambda\psi)(x) = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \left(\int_{\alpha}^{(x,\beta)^-} \hat{k}_\lambda(p,\xi)\psi(\xi/p)d\xi \right)dp, \tag{3.7}$$

$$(U_\lambda\psi)(x) = \int_{\alpha}^{x} \psi(\xi)e^{\lambda G(\xi)}d\xi, \tag{3.8}$$

for all $\psi \in L_1$.
Obviously T_λ and U_λ define bounded, linear operators from L_1 into L_1.

The following result is straightforward.

Theorem 3.1 *Let $f \in L_1$. Then $\psi \in D(A)$ is a solution of the inhomogeneous equation (3.1) if and only if ϕ given by (3.3) is a solution of (3.6).*

The advantage of this reformulation should be come dear to the reader, if we state our next result.

Theorem 3.2 *T_λ and U_λ define completely continuous operators.*

The proof of this result is evident and will be ommitted. The sense of the following definition should be clear from theorem 3.1

$$\Sigma = \{\lambda \in C \mid 1 \in P\sigma(T_\lambda)\} \tag{3.9}$$

Notice that $\sigma(T_\lambda) \setminus \{0\} = P\sigma(T_\lambda) \setminus \{0\}$ because T_λ is completely continuous.

Theorem 3.3 *$\sigma(A) = P\sigma(A) = \Sigma$. If $\lambda \notin \sigma(A)$ then the resolvent of A, $R_\lambda(A) = (\lambda I - A)^{-1}$ is completely continuous.*

Proof It is obvious from theorem 3.1 that $\Sigma = P\sigma(A)$. Now suppose that $\lambda \notin P\sigma(A)$. Consequently $1 \notin \sigma(T_\lambda)$ and we conclude that $\phi - T_\lambda\phi = U_\lambda f$ is solvable for all $f \in L_1$. From theorem 3.1 we conclude that $\lambda \in \sigma(A)$. For $\lambda \notin \sigma(A)$ the resolvent is given by $(R_\lambda(A)f)(x) = e^{-\lambda G(x)} \cdot ((I - T_\lambda)^{-1}U_\lambda f)(x)$ and from theorem 3.2 we deduce that $R_\lambda(A)$ is completely continuous. □

Most results of the remainder of this section shall be given without proof. Instead, we refer to another paper of ours [11], where a similar eigenvalue problem has been treated, and the reader will have no difficulty to see that many results of that paper can be carried through to our present case.

Theorem 3.4 *$\sigma(A)$ consists of isolated eigenvalues.*

Proof See [11, theor. 2.4]

An important quantity is the dominant eigenvalue of A, i.e. the eigenvalue with largest real part. (In practical cases the dominant eigenvalue happens to be real.) In many cases positive operator theory can be used to prove the existence of a dominant eigenvalue.

Let the positive cone L_1^+ be defined by

$$L_1^+ = \{\psi \in L_1 | \psi(x) \geq 0 \ a.e. \ \ on \ [\alpha,1]\}. \tag{3.10}$$

The dual cone of L_1^+ is L_∞^+, i.e. the subset of functions in $L_\infty[\alpha,1]$ which are nonnegative a.e. For $\lambda \in R$ we have that T_λ is positive with respect to the cone L_1^+. For the basic theory concerning positive cones and positive operators we refer to the monograph of Schaefer [19].

In [18] Sawashima introduced the very useful notion of a non-support operator (which is more restrictive than just positivity).

Definition [18] Let X^+ be a positive cone in the Banach space X and let $(X^+)^\star$ be the dual cone. A positive operator $T;X \rightarrow X$ is called non-support with respect to X^+ if for all $\psi \in X^+, \psi \neq 0$ and $F \in (X^+)^\star$, $F \neq 0$, there exists an integer p such that for all $n \geq p$ we have $F[T^n \psi] > 0$.

It can be shown with very little effort that T_λ is non-support with respect to L_1^+ for all $\lambda \in R$. As a matter of fact we have: there exists an integer p such that for all $\psi \in L_1^+$, $\psi \neq 0$ and for all $x \in (\alpha,1]$, $(T_\lambda^p \psi)(x) > 0$. (See also [11, theorem 5.1].)
From this it follows that there exists a $\phi_\lambda \in L_1^+$ and $F_\lambda \in L_\infty^+$ such that

$$T_\lambda \phi_\lambda = r_\lambda \phi_\lambda \tag{3.11a}$$

$$T_\lambda^\star F_\lambda = r_\lambda F_\lambda, \tag{3.11b}$$

where $r_\lambda = r(T_\lambda)$ is the spectral radius of T_λ and $T_\lambda^\star : L_\infty \rightarrow L_\infty$ is the adjoint of T_λ. (See [11, theorem 3.3]). If $r(T_\lambda) = 1$, then $\lambda \in P\sigma(A)$. The equation $r(T_\lambda) = 1$ has a unique solution $\lambda_d \in R$ (See [11, theorem 4.4])

Now let

$$\psi_d(x) = e^{-\lambda_d G(x)} \phi_{\lambda_d}(x), \tag{3.12}$$

where ϕ_{λ_d} is determined by (3.11a). As in [11. theorem 5.4 and theorem 6.2] it can be proved that the eigenvalue λ_d of A is algebraically simple and strictly dominant, i.e. if $\lambda \in \sigma(A)$, $\lambda \neq \lambda_d$, then $\mathrm{Re}\lambda < \lambda_d$. We summarize some of our results.

Corollary 3.5 *The operator A has a dominant eigenvalue λ_d which is algebraically simple. The corresponding eigenvector ψ_d and adjoint eigenvector F_d are positive. If $\lambda \in P\sigma(A)$ and $\lambda \neq \lambda_d$, then* $\mathrm{Re}\lambda < \lambda_d$.

Remark 3.1 The element $F_d \in L_\infty^+$ can be computed from F_{λ_d} given by (3.11b). (See [11, section 7]). However, they do not coincide.

Remark 3.2 ψ_d is absolutely continuous, because $\psi_d \in \mathbf{D}(A)$.

Remark 3.3 The fact that all eigenvectors of A are (absolutely) continuous would have permitted us to work in the space of continuous functions in stead of L_1. This is done in [11]. The results, however, remain the same.

As in [11, section 6] we can compute the characteristic equation (i.e. the equation from which all eigenvalues of A can be computed) for our problem. Let $e_j \in L_1$, $j \geq 1$ be given by the recurrent relation

$$e_1(x) \equiv 1, \quad \alpha \leqslant x \leqslant 1,$$

$$e_j(x) = -\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \Big(\int_{(x,\beta)^-}^{\beta} \hat{k}_\lambda(p,\xi) e_{j-1}(\xi/p) d\xi \Big) dp.$$

Remark 3.4 e_j does depend on λ, $j \geqslant 2$.

Let q be the smallest integer such that $\alpha \geqslant (\frac{1}{2}+\Delta)^q$ then the characteristic equation is given by

$$\pi(\lambda) := \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \Big(\int_{\alpha}^{\beta} \hat{k}_\lambda(p,\xi) \{ e_1(\frac{\xi}{p}) + \ldots + e_{q-1}(\frac{\xi}{p}) \} d\xi \Big) dp = 1 \tag{3.13}$$

(See [11, section 6])

Theorem 3.6 *$\lambda \in P\sigma(A)$ if and only if $\pi(\lambda) = 1$. In every finite vertical strip $\{\lambda \mid s \leqslant \mathrm{Re}\lambda \leqslant t\}$ where $-\infty < s < t < \infty$ there are at most finitely many elements of $\sigma(A)$.*

Proof [11, theorem 6.5 and theorem 6.6.]

Using the algebraic simplicity of the eigenvalue λ_d and the compactness of the resolvent (c.f theorem 3.3) we can give the following decomposition of the space L_1.

$$L_1 = \mathrm{N}(\lambda_d I - A) \oplus \mathrm{R}(\lambda_d I - A) \tag{3.14}$$

Let P be the projection on $\mathrm{N}(\lambda_d I - A)$ associated with this decomposition, then P is given by

$$P\phi = F_d[\phi]\psi_d, \; \phi \in L_1 \tag{3.15}$$

where the linear functional F_d is given by corollary 3.5, and satisfies

$$F_d[\psi_d] = 1. \tag{3.16}$$

For our purposes the case of exponential individual growth and constant deathrate (wash-out) is of special interest. Let $g(x) = \gamma x$ and $D(x) = D$. If $\alpha \geqslant (\frac{1}{2}+\Delta)^2$, then $\pi(\lambda)$ is given by

$$\pi(\lambda) = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \Big(\int_{\alpha}^{\beta} \hat{k}_\lambda(p,\xi) d\xi \Big) dp =$$

$$= 2 \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} d(p) \cdot p^{\frac{\lambda+D}{\gamma}} dp,$$

where we have used (2.8) and (3.4). Because of the symmetry of $d(p)$ around $p = \frac{1}{2}$ and the fact that $\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} d(p) = 1$ (which is clear from the interpretation) we have $2 \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} pd(p) = 1$. Consequently the dominant eigenvalue λ_d is determined by $\dfrac{\lambda_d + D}{\gamma} = 1$, hence $\lambda_d = \gamma - D$. This result remains valid if $\alpha < (\frac{1}{2}+\Delta)^2$. To prove this, we regard the eigenvalue problem associated with the original equation

(2.1).

$$\lambda n(x) + \frac{d}{dx}(\gamma x n(x)) = -Dn(x) - b(x)n(x) + 2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} b(\frac{x}{p}) n(\frac{x}{p}) dp$$

After multiplication with x and integration from α to 1 we arrive at

$$\lambda W - \gamma W = -DW, \text{ where}$$

$$W = W[n] = \int_{\alpha}^{1} xn(x)dx \tag{3.17}$$

can be interpreted as the biomass associated with the size distribution n. The eigenvector n_d associated with the dominant eigenvalue λ_d is given by

$$n_d(x) = \frac{E(x)}{\gamma x}\psi_d(x), \tag{3.18}$$

where ψ_d is given by (3.12). So $n_d(x)$ is positive a.e., and has a consequence $W[n_d]>0$ from which we conclude that $\lambda_d = \gamma - D$.

Let F_d be the associated adjoint eigenvector (see corollary 3.5). We shall prove that $F_d = F$, where F is given by

$$F[\phi] = \int_{\alpha}^{1} \phi(x)E(x)dx, \quad \phi \in L_1,$$

by showing that for this F we have

$$F[A\psi] = (\gamma - D)F[\psi], \text{ for all } \psi \in \mathbf{D}(A).$$

Now let $\psi \in \mathbf{D}(A)$.

$$F[A\psi] = \int_{\alpha}^{1} \{-\gamma x \frac{d\psi}{dx} + \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(p,x)\psi(\frac{x}{p})dp\} E(x)dx$$

$$= \int_{\alpha}^{1} \psi(x)\frac{d}{dx}(\gamma x E(x))dx + \int_{\alpha}^{1} \{2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} d(p)b(\frac{x}{p})E(\frac{x}{p})\psi(\frac{x}{p})dp\}dx$$

$$= (\gamma - D)\int_{d}^{1} \psi(x)E(x)dx - \int_{\alpha}^{1} b(x)E(x)\psi(x)dx + 2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}-\Delta} pd(p)dp \cdot \int_{\alpha}^{1} b(\xi)E(\xi)\psi(\xi)d\xi$$

$$= (\gamma - D)\int_{\alpha}^{1} \psi(x)E(x)dx = (\gamma - D)F[\psi]$$

where we have used that $2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} pd(p) = 1$.

We summarize our results in the following theorem.

Theorem 3.7 *If* $g(x) = \gamma x$ *and* $D(x) = D$, *for all* $x \in [\alpha,1]$, *then the dominant eigenvalue* λ_d *of* A *is given by* $\lambda_d = \gamma - D$. *The associated adjoint eigenvector* F_d *is given by* $F_d[\phi] = \int_\alpha^1 \phi(x)E(x)dx$.

4. THE LINEAR TIME-DEPENDENT PROBLEM

In this section we shall investigate the initial value problem (2.5)-(2.7), and we shall prove existence and uniqueness of solutions and determine their behaviour for large t. All the results in this section are based on semigroup methods. Readers unfamiliar with the theory of semigroups are referred to [17,22].

In section 2 we have rewritten (2.5)-(2.7) as the abstract Cauchy problem (2.9)-(2.10). We write

$$A = B + C, \tag{4.1}$$

where

$$(B\psi)(x) = -g(x)\frac{d\psi}{dx} \tag{4.2}$$

$$(C\psi)(x) = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(p,x)\psi(\frac{x}{p})dp. \tag{4.3}$$

B is an unbounded closed operator on L_1 with domain

$$\mathrm{D}(B) = \{\psi \in L_1 \mid \psi \text{ is absolutely continuous and } \psi(\alpha) = 0\},$$

and C defines a bounded operator. With little effort one can see that B generates a strongly continuous semigroup e^{tB} given by

$$(e^{tB}\psi)(x) = \psi(G^{-1}(G(x)-t)), \quad t \geq 0, \tag{4.4}$$

where G^{-1} denotes the inverse of the function G given by (3.2). One should read $G^{-1}(\tau) = 0$ if $\tau < 0$. Obviously

$$e^{tB} = 0 \quad \text{if } t \geq G(1). \tag{4.5}$$

Now a standard result from semigroup theory (See [17, Ch 3, theorem 1.1]) yields that $A = B + C$ generates a strongly continuous semigroup as well, because C is bounded. We denote this semigroup by $T(t)$.

Theorem 4.1 *A generates a strongly continuous semigroup $T(t)$.*

This proves the existence and uniqueness of solutions of the initial value problem (2.5)-(2.7). If we denote this solution by $m(t,\cdot;\phi)$ or also $m(t;\phi)$ then $m(t;\phi) = T(t)\phi$.

Remark 4.1 $m(t;\phi) = T(t)\phi$ is not a solution of (2.5)-(2.7) in the strong sense of the word. More precisely, $m(t,x;\phi)$ is not necessarily differentiable with respect to t and x seperately. (This is only true if $\phi \in \mathrm{D}(A)$). It can be shown however, that $m(t,x;\phi)$ is differentiable along the characteristics $t - G(x) =$ *constant* of the PDE given by (2.5).

$$\lim_{h \to 0} \frac{m(t+h, G^{-1}(G(x)+h)) - m(t,x)}{h} = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(p,x)m(t,\frac{x}{p})dp,$$

where $m(t,x) = m(t,x;\phi)$.

It is possible to obtain the solutions $m(t;\phi)$ explicitly as a series. Applying the variation - of - constants formula, the abstract Cauchy problem (2.9)-(2.10) leads to the integral equation

$$m(t;\phi) = e^{tB}\phi + \int_0^t e^{(t-s)B} Cm(s;\phi)ds. \tag{4.6}$$

let

$$m_0(t;\phi) = e^{tB}\phi, \tag{4.7}$$

$$m_{i+1}(t;\phi) = \int_0^t e^{(t-s)B} Cm_i(s;\phi)ds, \quad i \geqslant 0, \tag{4.8}$$

then the solution $m(t;\phi)$ is given by

$$m(t;\phi) = \sum_{i=o}^{\infty} m_i(t;\phi). \tag{4.9}$$

This series representation of the solution has a clear biological interpretation. $m_0(t;\phi)$ represents the *o'th* generation at time t, i.e. all individuals which were present at time $t=0$ and have not yet died or divided. Inductively the *i'th* generation $m_i(t;\phi)$ contains all daughters of cells of the $(i-1)'th$ generation.

For the proof of the following result we refer to [6, lemma 4.1].

Theorem 4.2 *At every (finite) time instant t only a finite number of generations are present in the population.*

The asymptotic behaviour of the solutions for large t can be determined relatively easy if one is able to prove compactness of the semigroup after finite time. Compactness of a semigroup means, among others, that the initial function is smoothened if the semigroup acts on it.

Theorem 4.3 *$T(t)$ is compact for $t \geqslant G(1)$*

Observe that $G(1)$ is the time instant at which the *o'th* generation goes extinct. (See (4.5)). Theorem 4.3 is proved in the Appendix for the case $g(x) = \gamma x$. We restrict ourselves to this situation for several reasons. First of all because this is exactly the case for which the compactness property is not fulfilled if fission occurs into two equal parts (i.e $d(p) = \delta(p - \frac{1}{2})$). (See [6, section 8] and remark 4.2 below.) Secondly, this happens to be the case that we are mainly interested in. However, it can be checked rather easily that the result remains valid for all functions g satisfying $[H_g]$.

Remark 4.2 In [6] the dynamics of a population reproducing by fission into two equal parts is investigated rigorously. In that case the semigroup is compact after finite time if some condition on the growth rate $g(x)$ is fulfilled. It is proved among others:

(i) If $g(2x) < 2g(x)$ for all x, (or $g(2x) > 2g(x)$) then $T(t)$ is compact after finite time.

(ii) $T(t)$ never becomes compact if $g(2x) = 2g(x)$ for all x. ($g(x) = \gamma x$ is an important example of this situation)

Biologically the relation $g(2x) = 2g(x)$ means that the size of the offspring of some mother does not depend on the moment of fission of that mother, yielding that the property 'equal size" is hereditary. This, of course, is not true if a cell can divide into two unequal parts.

Now let ψ_d be the eigenvector of A associated with the dominant eigenvector λ_d of A (c.f. corollary 3.5). Then

$$T(t)\psi_d = e^{\lambda_d t}\psi_d, \tag{4.10}$$

describing the action of $T(t)$ on $\mathbf{N}(\lambda_d I - A)$. For the action of $T(t)$ on $\mathbf{R}(\lambda_d I - A) = \mathbf{N}(P) = \mathbf{R}(I-P)$, where P is the projection given by (3.15), we can deduce an exponential estimate.

Lemma 4.4 *There exist positive constants ϵ and K such that for all $\phi \in L_1$*

$$||(I-P)T(t)\phi|| \leq K e^{(\lambda_d - \epsilon)t} ||\phi||$$

Proof Theorem 3.6 yields that there exists a constant $\epsilon > 0$ such that for all $\lambda \in \sigma(A)$, $\lambda \neq \lambda_d$ we have $\mathrm{Re}\lambda \leq \lambda_d - \epsilon$. From theorem 4.3 we conclude that

$$\sigma(T(t)) \setminus \{0\} = P\sigma(T(t)) \setminus \{0\} = \{e^{\lambda t} \mid \lambda \in \sigma(A)\}$$

(See [17, chapter 2, section 2.2]). Let $\hat{A}$ denote the restriction of A to $\mathbf{R}(\lambda_d I - A)$, then $\sigma(\hat{A}) = P\sigma(\hat{A}) = P\sigma(A) \setminus \{\lambda_d\} \subset \{\lambda \mid \mathrm{Re}\lambda \leq \lambda_d - \epsilon\}$. A result of Hale [10, § 7.4] completes the proof. □

Combination of this lemma and (4.10) yields the following result.

Corollary 4.5 *For all $\phi \in L_1$ we have*

$$||T(t)\phi - F_d[\phi] e^{\lambda_d t} \psi_d|| \leq K e^{(\lambda_d - \epsilon)t} ||\phi||$$

where F_d is normalized by condition (3.16).

If $\phi \geq 0, \phi \neq 0$, then $F_d[\phi] > 0$. A similar result can be stated in terms of the original problem (2.1)-(2.3). We shall do this for the case $g(x) = \gamma x, D(x) = D, x \in [\alpha, 1]$, which is of special interest to us. Let n_0 satisfy condition $[H_{n_0}]$. With $n(t; n_0)$ we denote the solution of (2.1)-(2.3). Let ϕ be given by (2.7), i.e. $\phi(x) = \frac{\gamma x}{E(x)} n_0(x)$. Theorem 3.7 yields that

$$F_d[\phi] = \int_\alpha^1 \phi(x) E(x) dx = \int_\alpha^1 \gamma x n_0(x) dx = \gamma W[n_0],$$

where W is given by (3.16) Let n_d, given by (3.17), be normalized by the condition

$$W[n_d] = 1 \tag{4.11}$$

(See (3.16).)

Corollary 4.6 *Let $g(x) = \gamma x$ and $D(x) = D$, for all $x \in [\alpha, 1]$. Let $n_0 \in L_1$ satisfy $[H_{n_0}]$, then $||n(t; n_0) - W[n_0] e^{\lambda_d t} n_d|| < M e^{(\lambda_d - \epsilon)t} ||n_0||$ where M is a positive constant not depending on n_0.*

5. THE DYNAMICS OF SUBSTRATE AND BIOMASS

An important feature of the non-linear model discussed in section 1, which also explains why we restrict ourselves to the case of exponential individual growth, is the following. If we multiply (1.3) on both sides with x and integrate over all sizes x, we find a balance equation describing the evolution of the biomass concentration. This equation turns out to be an ordinary differential equation.

$$\frac{dW}{dt} = (\gamma(S) - D)W \tag{5.1}$$

Equation (1.4) describes the evolution of the substrate concentration, and for convenience we write it down once more.

$$\frac{dS}{dt} = -\frac{1}{\theta}\gamma(S)W + D(S^{in} - S) \tag{5.2}$$

These equations are to be supplemented with the initial conditions

$$W(0) = w, \tag{5.3}$$

$$S(0) = S_0, \tag{5.4}$$

where w is the biomass represented by the initial size distribution n_0.

$$w = W[n_0] = \int_{\alpha}^{1} x n_0(x) dx \tag{5.5}$$

and $S_0 > 0$ is some fixed quantity. Summarizing we might say that the evolution of biomass and substrate concentration in the tank reactor is described by a system of two ordinary differential equations. Mathematically this means that the non-linearity $\gamma(S)$ can be computed à priori, i.e. without knowledge of the solution. The situation turns out to be much more complicated if growth of an individual is not proportional to its size.

(5.1) and (5.2) happen to be the equations originally found by Monod (See e.g [12]) and have been extensively investigated by Hsu et al [13] (They deal with the more general situation that several species are competing for nutrients) and for the following we refer to their paper.

We denote the solutions of (5.1)-(5.4) by $W(t;S_0,w)$ and $S(t;S_0,w)$.

Theorem 5.1 *[13] The solutions $W(t;S_0,w)$ and $S(t;S_0,w)$ of (5.1)-(5.4) are positive and bounded.*

System (5.1)-(5.2) always has the trivial equilibrium

$$W = 0, \quad S = S^{in}. \tag{5.6}$$

There exists a non-trivial equilibrium

$$\begin{aligned} W &= W_e = \theta(S^{in} - \frac{kD}{m-D}), \\ S &= S_e = \frac{kD}{m-D}, \end{aligned} \tag{5.7}$$

if and only if the following conditions are satisfied:

$$m > D \quad \text{and} \quad \frac{kD}{m-D} < S^{in}. \tag*{$[H_e]$}$$

Theorem 5.2 *[13] Let $S_0 > 0$ and $w > 0$. If $[H_e]$ is not satisfied, then*

$$\lim_{t\to\infty} W(t;S_0,w) = 0, \quad \lim_{t\to\infty} S(t;S_0,w) = S^{in} .$$

If $[H_e]$ is satisfied, then

$$\lim_{t\to\infty} W(t;S_0,w) = W_e, \quad \lim_{t\to\infty} S(t;S_0,w) = S_e$$

Remark 5.1 $Z(t)$ defined by $Z(t) = S(t;S_0,w) + \frac{1}{\theta}W(t;S_0,w)$ obeys the O.D.E. $\frac{dZ}{dt} = D(S^{in} - Z)$ having the general solution $Z(t) = S^{in} + C \cdot e^{-Dt}$, where C is a constant

Summarizing we might say that biomass and substrate concentration tend to a globally stable equilibrium if t becomes large. Our main question is whether a similar result holds for the size distribution. Before answering this question we have to deal with the problem of existence and uniqueness of solutions.

6. EXISTENCE AND UNIQUENESS OF SOLUTIONS

In the former section we already observed that the non-linearity $\gamma(S)$ can be computed à priori. Let

$$\gamma(t;S_0,w) = \gamma(S(t;S_0,w)) \tag{6.1}$$

If there is to be no confusion we shall write $\gamma(t)$ instead of $\gamma(t;S_0,w)$. We introduce the new time variable τ, given by

$$\tau = \tau(t) = \int_0^t \gamma(s)ds \tag{6.2}$$

and we denote its inverse by $t = t(\tau)$. Let $u(\tau,x)$ be given by

$$e^{Dt} n(t,x) = u(\tau,x) \tag{6.3}$$

then $u(\tau,x)$ obeys the equation

$$\frac{\partial u}{\partial \tau} + \frac{\partial}{\partial x}(xu(\tau,x)) = -\frac{b(x)}{\hat{\gamma}(\tau)}u(\tau,x) + 2\int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p}\frac{b(x/p)}{\hat{\gamma}(\tau)}u(\tau,\frac{x}{p})dp, \tag{6.4}$$

where

$$\hat{\gamma}(\tau) = \gamma(t(\tau)). \tag{6.5}$$

Let

$$E(\tau,x) = \exp[-\int_a^x \frac{b(y)}{\hat{\gamma}(\tau + \log y/x) y}dy]. \tag{6.6}$$

A straightforward computation shows that

$$\frac{\partial E}{\partial \tau} + x\frac{\partial E}{\partial x} = -\frac{b(x)}{\hat{\gamma}(\tau)}E(\tau,x). \tag{6.7}$$

Let $m(\tau,x)$ be given by

$$m(\tau,x) = \frac{xu(\tau,x)}{E(\tau,x)}, \tag{6.8}$$

and let

$$k(\tau,x,p) = 2d(p)\frac{b(x/p)}{\hat{\gamma}(\tau)}\frac{E(\tau,x/p)}{E(\tau,x)}. \tag{6.9}$$

Substitution of (6.8) in (6.4) yields

$$\frac{\partial m}{\partial \tau} + x\frac{\partial m}{\partial x} = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(\tau,x,p)m(\tau,\frac{x}{p})dp, \tag{6.10}$$

and m must satisfy the initial condition

$$m(0,x) = \phi(x) = \frac{x n_0(x)}{E(0,x)}, \tag{6.11}$$

and the boundary condition

$$m(\tau,\alpha) = 0\,. \tag{6.12}$$

The initial function ϕ given by (6.11) is an L_1 - function if we assume

$$\frac{n_0(x)}{E(0,x)} \text{ is integrable on } [\alpha,1]. \qquad [H_{S_0,n_0}]$$

Nota bene that $E(0,x)$ depends on S_0 and $w = W[n_0]$. This assumption is the analogue of assumption $[H_{n_0}]$ mentioned in section 2.

So, for a **fixed** initial pair S_0,n_0 the nonlinear problem stated in section 1 can be reduced to the linear (non-autonomous) problem given by (6.10)-(6.12). We call $m(\tau,x)$ a solution if m is differentiable along the characteristics of equation (6.10) (see remark 4.1) and obeys (6.10), (6.11) and (6.12). We shall prove in this section that for all $\phi \in L_1[\alpha,1]$ there does exist a unique solution of the initial value problem (6.10)-(6.12), which we write abstractly as

$$\frac{dm}{d\tau} = Bm + C(\tau)m, \quad m(0) = \phi, \tag{6.13}$$

where the unbounded closed operator B is given by

$$(B\psi)(x) = -x\frac{d\psi}{dx}$$

having a domain

$$\mathbf{D}(B) = \{\psi \in L_1 \,|\, \psi \text{ is absolutely continuous and } \psi(\alpha) = 0\},$$

and $C(\tau),\tau \geq 0$ defines a family of bounded operators on $L_1[\alpha,1]$:

$$(C(\tau)\psi)(x) = \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(\tau,x,p)m(\tau,\frac{x}{p})dp.$$

In section 4 we have seen that B generates a strongly continuous semigroup e^{tB} given by

$$(e^{tB}\psi)(x) = \psi(xe^{-t})$$

Now a result of Kato yields that $B + C(\tau)$ "generates" a unique evolution operator (or solution operator) $V(\tau,\sigma)$. (See [14, theorem 4.5]). This means that the solution of (6.10)-(6.12) is given by

$$m(\tau,\cdot;\phi) = V(\tau,0)\phi. \tag{6.14}$$

Nota bene that the family $V(\tau,\sigma)$ depends on w, and occasionally we shall write $V(\tau,\sigma;w)$ if this dependence is to be emphasized.

The solution of the non-linear equation (1.3) can be found in the following way. Let S_0,n_0 satisfy $[H_{S_0,n_0}]$, $w = W[n_0]$ and let ϕ be given by (6.11). Then the solution $n(t,x;S_0,n_0)$ of the non-linear problem (1.3)-(1.7) is given by

$$n(t,x;S_0,n_0) = e^{-Dt}\frac{E(\tau(t),x)}{x.}(V(\tau(t),0;w)\phi)(x). \tag{6.15}$$

Notice carefully that $\tau = \tau(t)$ depends on $w = W[n_0]$. Now we have proved

Theorem 6.1 *Let the initial pair S_0,n_0 satisfy condition $[H_{S_0,n_0}]$. Then the non-linear initial value problem (1.3)-(1.7) has a unique solution $n=n(t,x;S_0,n_0)$, $S=S(t;S_0,w)$ where $w=W[n_0]$*

Remark 6.1 As we did in section 4, we can represent the solution as a series, by applying a variation of constants formula to (6.13). (See the Appendix, proof of theorem 8.4)

7. THE EXISTENCE OF A GLOBALLY STABLE EQUILIBRIUM

We ended section 5 with the question whether there exists a (globally) stable size distribution. In this section we shall answer this question affirmatively. First, suppose that condition $[H_e]$ of section 5 is not satisfied. Then

$$\lim_{t\to\infty} W(t;S_0,w)=0, \quad \text{for } all \ S_0>0, w>0.$$

From this we obtain

$$||n(t;S_0,n_0)||=\int_\alpha^1 n(t,x;S_0,n_0)dx \leqslant \frac{1}{\alpha}\int_\alpha^1 xn(t,x;S_0,n_0)dx = \frac{1}{\alpha}W(t;S_0,w), \tag{7.1}$$

yielding the following result:

Corollary 7.1 *If $[H_e]$ is not satisfied, S_0 is an initial substrate concentration and n_0 is an initial size distribution such that $[H_{S_0,n_0}]$ is satisfied, then $\lim_{t\to\infty} n(t,\cdot;S_0,n_0)=0$ in the L_1 - sense.*

During the rest of this section we assume that $[H_e]$ is satisfied. Theorem 5.2 states

$$\begin{aligned} &\lim_{t\to\infty} S(t;S_0,w)=S_e \\ &\lim_{t\to\infty} W(t;S_0,w)=W_e \end{aligned} \tag{7.2}$$

with S_e and W_e given by (5.7). Suppose that for all $t\geqslant 0$

$$S(t;S_0,w)=S_e, \quad W(t;S_0,w)=W_e, \tag{$\star$}$$

(this means that $S_0=S_e$ and $w=W[n_0]=W_e$) then $\gamma(t;S_0,w)$ given by (6.1) is to be replaced by $\gamma(S_e)=D$. The solution $n(t,x;S_0,n_0)$ can be found by applying the (linear) theory of section 4, with $g(x)=\gamma(S_e)x=Dx$, and $D(x)=D$. Theorem 3.7 states that in this case the dominant eigenvalue of the generator A is 0. Let us denote the corresponding eigenvector of A by ψ_e and let $\hat{n}_e$ be given by (3.15):

$$\hat{n}_e(x)=\frac{E(x)}{Dx}\psi_e(x). \tag{7.3}$$

Corollary 4.6 states that

$$n(t,\cdot;S_0,n_0)=W_e\cdot\hat{n}_e(\cdot)+O(e^{-\epsilon t}), \quad t\to\infty \tag{7.4}$$

where $\hat{n}_e$ is normalized by the condition $W[\hat{n}_e]=1$ (See (4.11).) Let $n_e:=W_e\cdot\hat{n}_e$, then

$$W[n_e] = W_e \tag{7.5}$$

We conclude that $n(t,\cdot;S_0,n_0)$ approaches the equilibrium n_e if ($\star$) is satisfied. Theorem 5.2 states that $W(t;S_0,w)$ and $S(t;S_0,w)$ approach the equilibria W_e and S_e if t tends to infinity. We can state our main result now.

Theorem 7.2 *Let $[H_e]$ be satisfied and let the initial pair S_0, n_0 satisfy condition $[H_{S_0,n_0}]$, then*

$$\lim_{t \to \infty} n(t,\cdot;S_0,n_0) = n_e(\cdot) \text{ in } L_1-\text{sense}$$

This result is proved in the following section

It is obvious that $[H_e]$ is satisfied if and only if D is below some critical value D_{cr}. Corollary 7.1 and 7.2 have the following interpretation.
If $D < D_{cr}$ then a nontrivial steady state is reached.
If $D \geqslant D_{cr}$ then the population goes extinct.

8. PROOF OF THE MAIN RESULT

To prove corollary 7.2 we shall make use of the theory of dynamical systems. We use the following notation. Let

$$X = R\text{x}L_1[\alpha,1]. \tag{8.1}$$

We denote an element of X with $<S,n>$.

$$||<S,n>||_X = |S|+||n||_{L_1}, \ <S,n>\in X,$$

defines a norm on X, and it is obvious that with this norm X becomes a Banach space. Let the subset Z of X be given by

$$Z = \{<S_0,n_0>\in X \,|\, S_0\geq 0, n_0\in L_1^+ \text{ and the pair } S_0,n_0 \text{ obeys } [H_{S_0,n_0}]\}. \tag{8.2}$$

Let $<S_0,n_0>\in Z$ and $w = W[n_0]$, then $<S(t),n(t)> = <S(t;S_0,w),\ n(t;S_0,n_0)>$ is an element of Z, as one can see from section 6. Let $U(t){:}R^+\text{x}Z\rightarrow Z$ be defined by

$$U(t)<S_0,n_0> = <S(t),n(t)>. \tag{8.3}$$

$U(t)$ is sometimes called a *generalized dynamical system*, where the adjective "generalized" accounts for the fact that $U(t)$ is only defined on a subset of X. For $<S_0,n_0>\in Z$,

$$\Gamma^+(<S_0,n_0>) = \bigcup_{t\geq 0}\{<S(t),n(t)>\}$$

is called the orbit starting from $<S_0,n_o>$. From section 6 it is clear that $\Gamma^+(<S_0,n_0>)\subset Z$ if $<S_0,n_0>\in Z$. The following result follows immediately from theorem 5.1 and the estimate (7.1).

Lemma 8.1 *For all $<S_0,n_0>\in Z$, the orbit $\Gamma^+(<S_0,n_0>)$ is bounded.*

Boundedness of orbits is needed in order to prove precompactness.

Theorem 8.2 *For all $<S_0,n_0>\in Z$, the orbit $\Gamma^+(<S_0,n_0>)$ is precompact.*

The proof of this very important result is given in the Appendix.

The ω-limit set $\Omega(<S_0,n_0>)$ of the orbit starting from some $<S_0,n_0>\in Z$ is the set of elements $<\Sigma,\nu>\in X$ for which there exists a non-decreasing sequence $\{t_n\}$, $t_n>0$, $t_n\rightarrow\infty$ if $n\rightarrow\infty$, such that

$$||U(t_n)<S_n,n_0>-<\Sigma,\nu>||_X\rightarrow 0 \text{ as } n\rightarrow\infty.$$

Lemma 8.3 *Let $<S_0,n_0>\in Z$. For all $<\Sigma,\nu>\in\Omega(<S_0,n_0>)$ we have $\Sigma = S_e$ and $W[\nu] = W_e$.*

Proof This follows immediately from theorem 5.2.

The ω-limit set is only of practical use if every element in it is contained in the domain of the generalized dynamical system.

Lemma 8.4 *If $<S_0,n_0>\in Z$, then $\Omega(<S_0,n_0>)\subset Z$.*

Proof Let $<S_0,n_0>\in Z$ and $<\Sigma,\nu>\in\Omega(<S_0,n_0>)$ There exists a sequence $\{t_k\}$ satisfying $t_k>0$, $t_k\rightarrow\infty$ if $k\rightarrow\infty$ such that

$$U(t_k)<S_0,n_0>\rightarrow<\Sigma,\nu> \text{ if } k\rightarrow\infty.$$

This yields $n(t_k,\cdot;S_0,n_0)\rightarrow\nu$, $k\rightarrow\infty$ in L_1 - sense. Let $m(\tau,x)$ be given by

$$E(\tau,x)m(\tau,x) = e^{Dt}xn(t,x), \qquad (\star)$$

where $\tau = \tau(t) = \int_0^t \gamma(S(t';S_0,w))dt'$, $w = W[n_0]$ and $E(\tau,x)$ is given by (6.6). We denote with $t = t(\tau)$ the inverse function of $\tau = \tau(t)$. (See section 6) From the proof of theorem 8.2 in the Appendix it follows that the set $\{e^{-Dt(\tau)}m(\tau,\cdot)|\tau \geq 0\}$ is precompact in L_1. Hence there exists a subsequence $\{t_k'\}$ of $\{t_k\}$ and an element $\phi \in L_1$ such that $e^{-Dt_k'}m(\tau_k',\cdot) \to \phi$ as $k \to \infty$. Here $\tau_k' = \tau(t_k')$. Relation ($\star$) yields

$$e^{-Dt_k'}m(\tau_k',x)E(\tau_k',x) = xn(\tau_k',x).$$

If we let on both sides k tend to infinity, we obtain $\phi(x)E(x) = x\nu(x)$, where

$$E(x) = \exp(-\int_\alpha^x \frac{b(y)+D}{Dy}dy).$$

(We have used: $\hat{\gamma}(\tau_k') \to \gamma(S_e) = D$, if $k \to \infty$)

Lemma 8.1 states that $\Sigma = S_e$ and $W[\nu] = W_e$, and this yields that $<\Sigma,\nu>$ obeys condition $[H_{S_0,n_0}]$. As a consequence $<\Sigma,\nu> \in Z$ which proves the result. □

Although $U(t)$ does not define a dynamical system in the usual sense of the word ($U(t)$ only acts on a subset of X), many results from dynamical system theory remain valid.

Theorem 8.5 *For all $<S_0,n_0> \in Z$, the ω-limit set $\Omega(<S_0,n_0>)$ is non-empty, compact and invariant. Moreover $U(t)<S_0,n_0> \to \Omega(<S_0,n_0>)$ as $t \to \infty$, with respect to the norm of X.*

Proof A straightforward computation, using theorem 8.2 and lemma 8.4, shows that the proof of theorem IV.4.1 of [22] can be carried through.

Now, let $<S_0,n_0> \in Z$ and $<\Sigma,\nu> \in \Omega(<S_0,n_0>)$. (Theorem 8.4 yields that such an element $<\Sigma,\nu>$ exists). Lemma 8.3 gives us

$$S(t;\Sigma,W[\nu]) = S(t;S_e,W_e) = S_e, \qquad (8.4)$$

which means that an orbit starting from some element of $\Omega(<S_0,n_0>)$ can be found by applying the linear theory of section 4. Using $\gamma(S_e) = D$ (see section 5) theorem 3.7 states that the dominant eigenvalue satisfies $\lambda_d = 0$, in this case. We obtain

$$||n(t;\Sigma,\nu)-n_e|| \leq Me^{-\epsilon t}||\nu|| \qquad (8.5)$$

for some constants $\epsilon, M > 0$, where n_e is normalized by (7.5). Here we have used corollary 4.6. The invariance of $\Omega(<S_0,n_0>)$ yields that for all $t \geq 0$ there exists a $<\Sigma^{-t},\nu^{-t}> \in \Omega(<S_0,n_0>)$ such that $U(t)<\Sigma^{-t},\nu^{-t}> = <\Sigma,\nu>$. Hence $||<\Sigma,\nu>-<S_e,n_e>||_X =$

$$= ||U(t)<\Sigma^{-t},\nu^{-t}>-<S_e,n_e>||_X = ||n(t;\Sigma^{-t},\nu^{-t})-n_e||_{L_1} \leq$$

$$Me^{-\epsilon t}||\nu^{-t}|| \leq \frac{1}{\alpha}Me^{-\epsilon t}W[\nu^{-t}] = \frac{1}{\alpha}MW_e e^{-\epsilon t}.$$

Hence we have used that $\Sigma^{-t} = S_e$, inequality (8.5) and $W[\nu^{-t}] = W_e$. The inequality above holds for all $t \geq 0$, from which we conclude $<\Sigma,\nu> = <S_e,n_e>$. We have proved the following result.

Theorem 8.6 *For all $<S_0,n_0> \in Z$ we have $\Omega(<S_0,n_0>) = <S_e,n_e>$.*

Combining this and theorem 8.5 yields

$$U(t)<S_0,n_0>\rightarrow<S_e,n_e>,\quad t\rightarrow\infty$$

and this proves theorem 7.2.

9. CONCLUDING REMARKS

The continuous culture of micro-organisms has become a technique of great importance in microbiology. However, up till now, most of the models describing continuous culture populations do not incorporate any structure distinguishing between the individuals of such a population. The paper of Gyllenberg [9] forms an exception. He assumes that organisms can be distinguished from each other according to their age. Another exception is formed by a paper of Diekmann et al [7]. This reference will be discused below. In this paper we considered a continuous culture of cells, whose individuals are assumed to be characterized by their size only. An important feature of our (non-linear) model is its analytic solvability. This is due to several assumptions made in this paper. For instance, the developed mathematical theory fails in both of the following cases:

(i) one does not restrict oneselves to the case of exponential growth. (See section 5.)

(ii) one assumes that fission occurs into two equal parts. In this case there does not exist a stable size distribution for the associated linear problem if $g(x) = \gamma x$. (See [6, section 8].)

In this paper we assumed that division can be described by a function $b(x)$, which quantity can be interpreted as the probability per *unit of time* for a cell with size x to divide. In [7] Diekmann et al present a second possibility to describe fission. They assume the existence of a function $p(x)$ describing the chance per *unit of size* that a cell will divide at size x, i.e. $\int_{x_1}^{x_2} p(x)dx$ is the fraction of cells dividing between x_1 and x_2. They call this the *stochastic threshold model.* The following relation between g,b and p can be deduced:

$$b(x) = g(x) \cdot \frac{p(x)}{1 - \int_a^x p(\xi)d\xi}.$$

or equivalently:

$$p(x) = \frac{b(x)}{g(x)} \exp\left(-\int_a^x \frac{b(\xi)}{g(\xi)} d\xi\right).$$

(Compare this to condition $[H_b \cdot 4]$ of section 1). Both descriptions yield the same results if g only depends on x. However, if (as in our case) g depends through nutrient limitation (or any other environmental factor) on time,

$$g = \gamma(S) g(x),$$

then the non-linearity $\gamma(S)$ only causes a deformation of the time axis if one works with the stochastic threshold model. (See [7].) In that case, a change of the dilution rate D will only cause a multiplication of the total population size with some factor. In our case, a change of the dilution rate D will also cause a deformation of the shape of the stable size distribution, and this provides an experimental test of the correctness of our model.

We intend to study more general nonlinear models, describing proliferating cell populations, in the near future.

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APPENDIX

For the proof of theorem 4.3 and theorem 8.2 we need the following lemma.

Lemma *Let $K \subset L_1[\alpha,1]$ be bounded and suppose that every $\phi \in K$ is absolutely continuous and satisfies $\int_\alpha^1 |\phi'(x)|\,dx \leq M$, where M is a positive constant not depending on ϕ, then K is precompact.*

Proof We must proof that for all $\epsilon>0$ there exists a $\delta>0$ such that for all $\phi \in K$

$$\int_\alpha^1 |\phi(x+h)-\phi(x)|\,dx < \epsilon, \text{ if } |h|<\delta$$

Let $\phi \in K$ and $h>0$

$$|\phi(x+h)-\phi(x)| \leq \int_x^{x+h} |\phi'(t)|\,dt.$$

Hence

$$\int_\alpha^1 |\phi(x+h)-\phi(x)|\,dx \leq \int_\alpha^1 \{ \int_x^{x+h} |\phi'(t)|\,dt \}dx$$

$$= \int_\alpha^{\alpha+h} |\phi'(t)| \{ \int_\alpha^t dx \}dt + \int_{\alpha+h}^1 |\phi'(t)| \{ \int_{t-h}^t dx \}dt \leq h\int_\alpha^1 |\phi'(t)|\,dt$$

$$= hM < \epsilon, \text{ if } h < \frac{\epsilon}{M}.$$

A similar estimate can be found for negative h, and this proves the result. □

Proof of theorem 4.3 (for the case $g(x) = \gamma x$).

The mapping $\phi \to m_1(t;\phi)$ where m_1 is determined by (4.7)-(4.8) defines a family of bounded operators which we denote by $S_1(t)$: $m_1(t;\phi) = S_1(t)\phi$. A straight-forward computation, using (4.3), (4.4), (4.7) and (4.8) shows that

$$(S_1(t)\phi)(x) = \int_0^t \{ \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} k(p, xe^{-\gamma\tau}) \cdot \phi(\frac{x}{p}e^{-\gamma t})dp \}d\tau$$

$$= \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \phi(\frac{x}{p}e^{-\gamma t}) \cdot \{ \int_0^t k(p, xe^{-\gamma\tau})dt \}dp ,$$

where we have substituted $g(x) = \gamma x$. If p is replaced by the new variable $z = \frac{x}{p}e^{-\gamma t}$, we obtain

$$(S_1(t)\phi)(x) = xe^{-\gamma t} \int_{\frac{x}{\frac{1}{2}+\Delta}e^{-\gamma t}}^{\frac{x}{\frac{1}{2}-\Delta}e^{-\gamma t}} \frac{\phi(z)}{z^2} \cdot \{ \int_0^t k(\frac{x}{z}e^{-\gamma t}, xe^{-\gamma\tau})d\tau \}dz .$$

It is clear that $S_1(t)\phi$ is absolutely continuous. Let $(L_1(t)\phi)(x) = \frac{d}{dx}(S_1(t)\phi)(x)$. It follows directly that

$$(L_1(t)\phi)(x) = \frac{1}{x}(S_1(t)\phi)(x) +$$

$$+ xe^{-\gamma t} \int_{\frac{x}{\frac{1}{2}+\Delta}e^{-\gamma t}}^{\frac{x}{\frac{1}{2}-\Delta}e^{-\gamma t}} \frac{\phi(z)}{z^2}\{\int_0^t \frac{d}{dx}(k(\frac{x}{z}e^{-\gamma t}, xe^{-\gamma\tau}))d\tau\}dz$$

where we have used that $k(\frac{1}{2}-\Delta,\cdot) = k(\frac{1}{2}+\Delta,\cdot) = 0$ Using (2.8) we find $\frac{d}{dx}\{k(\frac{x}{z}e^{-\gamma t}, xe^{-\gamma\tau})\} =$

$$= \frac{4}{z}e^{-\gamma t}d'(\frac{x}{z}e^{-\gamma t})\cdot \frac{b(ze^{\gamma(t-\tau)})\, E(ze^{\gamma(t-\tau)})}{E(xe^{-\gamma\tau})} +$$

$$4d(\frac{x}{z})e^{-\gamma t}\ \frac{(b\cdot E)(ze^{\gamma(t-\tau)})}{E(xe^{-\gamma\tau})}\cdot\frac{b(xe^{-\gamma\tau})+D(xe^{-\gamma\tau})}{\gamma x}.$$

Observe that $ze^{\gamma(t-\tau)} \leqslant 1$ implies that $xe^{-\gamma\tau} \leqslant \frac{1}{2}+\Delta = \beta$, because $z = \frac{x}{p}e^{-\gamma t}$, for some $p \in [\frac{1}{2}-\Delta, \frac{1}{2}+\Delta]$. Let

$$\begin{aligned} D_{\max} &:= \max\{D(x) \mid x \in [\alpha,\beta]\} \\ d_{\max} &:= \max\{d(p) \mid p \in [\tfrac{1}{2}-\Delta, \tfrac{1}{2}+\Delta]\} \\ d'_{\max} &:= \max\{|d'(p)| \mid p \in [\tfrac{1}{2}-\Delta, \tfrac{1}{2}+\Delta]\} \end{aligned}$$

(Notice that $d'_{\max}$ is well-defined because of hypothesis $[H_d]$. We obtain the following estimate

$$\left|\frac{d}{dx}k(\frac{x}{z}e^{-\gamma t}, xe^{-\gamma\tau})\right| \leqslant \frac{\frac{4}{\alpha}e^{-\gamma t}d'_{\max}}{E(\beta)}\cdot b(ze^{\gamma(t-\tau)})\cdot E(ze^{\gamma(t-\tau)}) +$$

$$\frac{4d_{\max}}{E(\beta)}\cdot\frac{b(\beta)+D_{\max}}{\gamma\alpha}\cdot b(ze^{\gamma(t-\tau)})\cdot E(ze^{\gamma(t-\tau)}) := C\cdot b(ze^{\gamma(t-\tau)})\cdot E(ze^{\gamma(t-\tau)}).$$

We deduce

$$|(L_1(t)\phi)(x)| \leqslant \frac{1}{\alpha}|(S_1(t)\phi)(x)| + Ce^{-\gamma t}\int_{\frac{x}{\frac{1}{2}+\Delta}e^{-\gamma t}}^{\frac{x}{\frac{1}{2}-\Delta}e^{-\gamma t}} \frac{|\phi(z)|}{z^2}\{\int_0^t b(ze^{\gamma\tau})E(ze^{\gamma\tau})dt\}dz$$

Using that

$$\int_0^t b(ze^{\gamma\tau})E(ze^{\gamma\tau})d\tau = \int_z^{ze^{\gamma t}} \frac{b(\xi)E(\xi)}{\gamma\xi}d\xi \leqslant 1$$

we obtain

$$|(L_1(t)\phi)(x)| \leqslant \frac{1}{\alpha}|(S_1(t)\phi)(x)| + \frac{Ce^{-\gamma t}}{\alpha^2}||\phi||.$$

Consequently

$$||L_1(t)|| \leqslant \frac{1}{\alpha}||S_1(t)|| + \frac{Ce^{-\gamma t}}{\alpha^2}$$

This result and the former lemma yield the compactness of $S_1(t)$. Let $S_i(t)$ be defined by the relation

$$S_i(t)\phi = m_i(t\,;\phi).$$

Using recurrence relation (4.7)-(4.8) and the fact that the integral expression in (4.8) is a standard Riemann integral we find that $S_i(t)$ is compact for all $i \geqslant 1$, and this result holds for all $t \geqslant 0$. Now, the proof is completed by the observation

$$T(t) = \sum_{i=1}^{\infty} S_i(t)\,, \quad \text{if } t \geqslant G(1). \quad \square$$

Proof of theorem 8.2

Let Z_1 be the subset of Z containing all elements $<S_0,n_0>$ satisfying

$$S(t\,;S_0,w) \geqslant \tfrac{1}{2}S_e\,, \quad t \geqslant 0, \qquad (\star)$$

where $w = W[n_0]$,
By definition $U(t)\ Z_1 \subset Z_1\,,\quad t \geqslant 0$.
Because of theorem 5.2 every orbit $\Gamma^+(<S_0,n_0>)$ enters Z_1 for t large enough, and for that reason we may restrict ourselves to initial pairs $<S_0,n_0>$ which are element of of Z_1.

The solution operator $V(\tau,\sigma)$ which has been defined in section 6, can be represented as a series:

$$V(\tau,\sigma) = \sum_{i=0}^{\infty} V_i(\tau,\sigma).$$

and the elements of this series can be computed from the following recurrent relation:

$$V_0(\tau,\sigma) = e^{(\tau-\sigma)B},$$

$$V_{i+1}(\tau,\sigma) = \int_{\sigma}^{\tau} e^{(\tau-\tau')B}\, C(\tau')\ V_i(\tau',\sigma)d\tau'.$$

From this, it is clear that also $U(t)$ can be written as a series:

$$U(t) = \sum_{i=0}^{\infty} U_i(t)\,, \quad \text{where}$$

$$U_0(t)<S_0,n_0> \;=\; <S(t\,;S_0,w),n^0(t\,;S_0,n_0)>$$

$$U_i(t)<S_0,n_0> \;=\; <0,n^i(t\,;S_0,n_0)>, i \geqslant 1,$$

where $n^i(t,x\,;S_0,n_0)$ can be determined from (6.15).

$$n^i(t,x\,;S_0,n_0) = e^{-Dt}\,\frac{E(\tau(t),x)}{x}(V_i(\tau(t),0\,;w)\phi)(x),$$

where ϕ is given by (6.11).

$$V_0(\tau,0) = 0 \ \text{ if } \ \tau \geqslant \log\frac{1}{\alpha},$$

because

$$(V_0(\tau,0)\phi)(x) = \phi(xe^{-\tau}).$$

$$\tau(t) = \int_0^t \gamma(t')dt' = \int_0^t \gamma(S(t'\,;S_0,w))dt' \geqslant$$

$$\int_0^t \gamma(\tfrac{1}{2}S_e)dt' = \gamma(\tfrac{1}{2}S_e)t \geqslant \log\frac{1}{\alpha} \ \text{ if}$$

$$t \geqslant t_1 \stackrel{def}{=} \frac{1}{\gamma(\frac{1}{2}S_e)} \log \frac{1}{\alpha}$$

Now we can prove the following result.

Lemma *Let* $t \geqslant t_1$ *and* K *a bounded subset of* Z_1, *then* $U(t)K$ *is precompact.*

Proof If $t \geqslant t_1$, then $U_0(t)\langle S_0, n_0\rangle = \langle S(t\,;S_0,w),0\rangle$ which, together with theorem 5.1 yields that $U_0(t)$ is compact with respect to Z_1 for $t \geqslant t_1$. In a way which is very similar to the proof of theorem 4.3, it can be shown that for $i \geqslant 1$, $U_i(t)$ is compact with respect to Z_1, for all $t \geqslant 0$. The proof which is slightly more difficult, uses the fact $S(t\,;S_0,w)$ (and therefore the individual growth $\gamma(t\,;S_0,w)x$) is bounded from above and below for all $t \geqslant 0$, uniformly in $\langle S_0,n_0\rangle \in K$.

Now $\Gamma^+(\langle S_0,n_0\rangle) = \{U(t)\langle S_0,n_0\rangle \mid t \leqslant t_1\} \cup U(t_1)\{U(s)\langle S_0,n_0\rangle \mid s \geqslant 0\}$, and theorem 8.1 and the former lemma yield that $\Gamma^+(\langle S_0,n_0\rangle)$ is precompact.

References

[1] Bell, G.I. & E.C. Anderson, Cell growth and division. I. A mathematical model with applications to cell volume distributions in mammalian suspension cultures, Biophys. J. 7 (1967) 329-351.

[2] Anderson, E.C. & D.F. Petersen, Cell growth and division. II. Experimental studies of cell volume distributions in mammalian suspension cultures, Biophys. J. 7 (1967) 353-364.

[3] Bell, G.I., Cell growth and division. III. Conditions for balanced exponential growth in a mathematical model, Biophys. J 8 (1968) 431-444.

[4] Anderson, E.C., G.I. Bell, D.F. Petersen & R.A. Tobey, Cell growth and division. IV. Determination of volume growth rate and division probability, Biophys. J. 9 (1969) 246-263.

[5] Diekmann, O., The dynamics of structured populations: some examples. To appear in: Proceedings of the international conference on "Mathematics in Biology and Medicine", Bari, Italy.

[6] Diekmann, O., H.J.A.M. Heijmans & H.R. Thieme, On the stability of the cell size distribution. To appear in J. Math. Biol.

[7] Diekmann, O., H.A. Lauwerier, T.A. Aldenberg & J.A.J. Metz, Growth, fission and the stable size distribution. J. Math. Biol. 18 (1983) 135-148.

[8] Fredrickson, A.G., D. Ramkrishna & H.M. Tsuchiya, Statistics and dynamics of procaryotic cell populations, Math. Biosc. 1 (1967) 327-374.

[9] Gyllenberg, M., Nonlinear age-dependent population dynamics in continuously propagated bacterial cultures, Math. Biosc. 62 (1982) 45-74.

[10] Hale, J.K., Theory of Functional Differential Equations, Springer, 1977.

[11] Heijmans. H.J.A.M., An eigenvalue problem related to cell growth. To appear in J. Math. An. Appl.

[12] Herbert, D., R. Elsworth & R.C. Telling, The continuous culture of bacteria, a theoretical and experimental study, J. Gen. Microbiol. 14 (1956) 601-622.

[13] Hsu, S.B., S. Hubbell & P. Waltman, A mathematical theory for single-nutrient competition in continuous cultures of micro-organisms, SIAM J. Appl. Math. 32 (1977) 366-383.

[14] Kato, T., Linear evolution equations of "hyperbolic" type, J. Fac. Sci. Univ. Tokyo, Sec. I, 17 (1970) 241-258.

[15] Koch, A.L. & M. Schaechter, A model for statistics of the cell division process. J. Gen. Microbiol. 29 (1962) 435-454.

[16] Painter, P.R. & A.G. Marr, Mathematics of microbial populations, Annu. Rev. Microbiology 22 (1968) 519-548.

[17] Pazy, A., Semigroups of linear operators and applications to partial differential equations, Springer Verlag, New York (1983).

[18] Sawashima, I., On spectral properties of some positive operators, Nat. Sci. Dep. Ochanomizu Univ. 15 (1964) 53-64. sp 0.3

[19] Schaefer, H.H., Banach Lattices and positive operators, Springer, 1974.

[20] Sinko, J.W. & W. Streifer, A model for populations reproducing by fission, Ecology 48 (1967) 910-918.

[21] Voorn, W.J., Statistics of cell size in the steady state, Ph. D. Thesis, University of Amsterdam (1983).

[22] Walker, J.A., Dynamical Systems and Evolution Equations, Plenum Press, New York (1980).