



Centrum voor Wiskunde en Informatica
Centre for Mathematics and Computer Science

H.J.A.M. Heijmans, J.A.J. Metz

Small parameters in structured population models
and the Trotter-Kato theorem

Department of Applied Mathematics

Report AM-R8603

June

Bibliotheek
Centrum voor Wiskunde en Informatica
Amsterdam

The Centre for Mathematics and Computer Science is a research institute of the Stichting Mathematisch Centrum, which was founded on February 11, 1946, as a nonprofit institution aiming at the promotion of mathematics, computer science, and their applications. It is sponsored by the Dutch Government through the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

Small Parameters in Structured Population Models and the Trotter-Kato Theorem

H.J.A.M. Heijmans

*Centre for Mathematics and Computer Science
P.O. Box 4079, 1009 AB Amsterdam, The Netherlands*

J.A.J. Metz

*Institute of Theoretical Biology, University of Leiden
Groenhovenstraat 5, 2311 BT Leiden, The Netherlands*

In this paper we discuss by means of two examples the justification of some (often implicit) limit arguments used in the development of structured population models. The first example considers the usual equation for size dependent population growth, in which it is implicitly assumed that discrete finitely sized young are produced from infinitesimal contributions by all potential parents. The second example shows how a pair of sink-source terms may transform into a side condition relating the appearance of individuals in the interior of the individual state space to the outflow of individuals at its boundary. The main mathematical tool in dealing with these examples is the Trotter-Kato theorem.

1980 Mathematics Subject Classification: 92A15, 35A35, 47D05.

Key Words & Phrases: structured population, limit transition, C_0 -semigroup, Trotter-Kato theorem.

Note: This report will be submitted for publication elsewhere.

1. INTRODUCTION

Models even at best are only approximations.

In population dynamics we often assume that (i) we are dealing with large numbers of individuals so that we may use deterministic models and that (ii) individuals either do not interact or if they do move sufficiently fast so that we need not take account of positive spatial factors. Both assumptions may be approximately true in many practical situations. The first type of approximation, i.e. replacing a stochastic model with a deterministic one if the numbers of individuals is sufficiently large, is supported by the limit theorems of KURTZ (1981) and the formal expansion procedures of VAN KAMPEN (1981). The second approximation is supported by limit considerations for reaction diffusion equations.

A second type of approximation has to do with our conception of the underlying individual physiological or behavioural mechanisms. Such approximations will be the subject of this paper.

Still a good deal of conceptual classification is needed concerning the translation of various supposed mechanisms on the individual level into equations governing population behaviour. As an example consider the usual equation for substrate dependent growth of a bacterial population

$$\frac{dN}{dt} = g(s)N, \quad (1.1)$$

where N is bacterial density (number per unit of volume), and s is substrate concentration. Strictly speaking (1.1) is no more than a description of observed population growth behaviour. Contrary to the usual claims it is not a representation of a mechanistic model. The alleged mechanistic underpinning is roughly: (i) assume that deaths or washout may be neglected, (ii) individuals divide after having taken up a unit amount of substrate, (iii) per capita substrate uptake rate, and therefore per capita division rate, equals $g(s)$. Moreover, this argument i.a. implies regularly occurring divisions, at least within one clan, whereas (1.1) implicitly assumes that divisions occur totally at random.

The structured population methodology as advocated in METZ & DIEKMANN (to appear) (early references are BELL & ANDERSON (1967), FREDERICKSON, RAMKRISHNA & TSUCHIYA (1967), and

SINKO & STREIFER (1967)) was specifically developed for dealing with the type of problems alluded to above. In structured population models the state of a population is assumed to be a frequency distribution over a space of individual states, spanned by quantities like size, age, nutrient reserves etc., and an equation is written down describing how this distribution changes due to continuous physiological processes, births, and deaths. (A reinstatement of (1.1) as an equation for overall population growth associated with a size structured population model under two different sets of fairly restrictive assumptions may be found in DIEKMANN et al (1984) and in HEIJMANS (1984a).)

When developing structured population models we regularly make all sorts of approximating assumptions either implicitly or explicitly. Generally these assumptions are phrased on the level of the individual whereas it is the population which is our main concern. In this paper we shall demonstrate for two specific examples the essential correctness of the implied limit arguments. The first example deals with an apparent conceptual inconsistency in the usual equations for size structured population dynamics. The second example is mainly technically motivated: it yields a mathematically rather unexpected result. We shall confine ourselves to the linear case only, as there we can use a ready made tool in the form of the Trotter-Kato theorem. A comparable problem was treated in HEIJMANS (1984b) (see also METZ & VAN BATENBURG (1984a,b)). Many more examples are treated without proof in METZ & DIEKMANN (to appear).

In the remaining part of the introduction we shall discuss the two examples from a biological point of view. In section 2 we summarize some versions of the Trotter Kato theorem. In sections 3 and 4 the two examples are dealt with in all rigorous detail. Finally in section 5 we shall return to the wider context again and discuss some open problems.

The equation for size structured population growth usually encountered in the literature (SINKO & STREIFER (1967), STREIFER (1974), VAN SICKLE (1977), MURPHY (1983), METZ & DIEKMANN (to appear)) reads

$$\begin{aligned}\frac{\partial}{\partial t}n(t,x) &= -\frac{\partial}{\partial x}(\gamma(x)n(t,x)) - \mu(x)n(t,x) \\ \gamma(x_0)n(t,x_0) &= \int r b(y)n(t,y)dy,\end{aligned}\tag{1.2}$$

where x denotes size, $n(t, \cdot)$ the size density at time t , γ the individual growth rate, μ the per capita death rate, x_0 birth size, b the size specific per capita birth rate and r is a fudge factor, introduced for convenience, which may be interpreted as the probability that a newborn survives the (infinitesimally short) nursery stage. However, if we stick to the literal interpretation of this equation we have to admit to a very non biological assumption: births occur at a finite rate in an instantaneous dependence on the present population, but without affecting specifically these individuals who happen to reproduce at that time. Apparently, the continuously growing parents can yet instantaneously create time and again additional masses x_0 , or else live newborn are created by magic out of added infinitesimal contributions from all parents together.

In an attempt to solve the implied anomaly we shall first formulate a different model which may be equally unrealistic biologically but which at least has the virtue of not violating any obvious biological constraints, and then rederive a slightly modified form of (1.2) by taking appropriate limits. In our model we assume that individuals give birth to offspring of size ϵ while concurrently their size is decreased the same amount. The corresponding population equation reads

$$\begin{aligned}\frac{\partial}{\partial t}n(t,x) &= -\frac{\partial}{\partial x}(g(x)n(t,x)) - \beta_\epsilon(x)n(t,x) + \beta_\epsilon(x+\epsilon)n(t,x+\epsilon) - \mu(x)n(t,x) \\ g(\epsilon)n(t,\epsilon) &= \int \rho_\epsilon \beta_\epsilon(y)n(t,y)dy.\end{aligned}\tag{1.3}$$

where g is again individual growth rate, β_ϵ per capita birth rate, ϵ the size of a newborn, and ρ_ϵ nursery survival. ϵ is assumed to be small and we shall consider the limit when we let formally $\epsilon \downarrow 0$. In nature usually roughly the same amount of energy is available for reproduction, which depending on

the species can either be spent on producing a few large or many small young. Therefore we set

$$\beta_\epsilon(x) = \epsilon^{-1} b(x).$$

Moreover in species with many small young, infant mortality is generally much higher than when young are large. For the sake of the argument we shall assume that these deaths all occur in the nursery. If recruitment is to stay bounded when we let ϵ go to zero we have to put

$$\rho_\epsilon = \epsilon r.$$

Formally setting

$$\beta_\epsilon(x + \epsilon)n(t, x + \epsilon) \approx \beta_\epsilon(x)n(t, x) + \frac{\partial}{\partial x}(b(x)n(t, x)),$$

and taking limits in (1.3) gives (1.2) with $\gamma(x) = g(x) - b(x)$ and $x_0 = 0$, i.e. the original growth rate is corrected by an amount corresponding to the mass loss in reproduction.

REMARK In fact, the limit equation resulting from (1.3) may differ slightly from (1.2). So far we have been rather vague about the range of possible sizes an individual may attain. If we assume that in principle x can take any value in \mathbb{R}_+ , there is no problem. However, if we assume, as we shall do in section 3, that there exists an $x_m < \infty$ such that $g(x_m) = 0$ and $g(x) > 0$ for $x < x_m$, we can just as well confine the domain of $n(t, \cdot)$ to $[\epsilon, x_m]$. Since $g(x) > 0$ for all x in that domain, there is no need for a boundary condition at the right-hand-side of it. In the limit equation (1.2), $\gamma(x_m) < 0$ and we therefore do need a boundary condition $n(t, x_m) = 0$ to prevent nonuniqueness of the solutions to (1.2) due to a possible instream of individuals at x_m . (Of course we shall eventually want to confine the domain of the limit equation to an interval $[0, \hat{x}]$ where $\gamma(\hat{x}) = 0$ and $\gamma(x) > 0$ for $x < \hat{x}$. But we cannot do this immediately as we cannot impose such a restriction on (1.3) for $\epsilon > 0$.)

Of course the present modified account also contains some troublesome points. For example, how should we interpret a birth size zero? A more detailed discussion of these points will be deferred till section 5, after we have taken a look at the mathematical side of the limit argument.

Our second example concerns size dependent cell kinetics. This example differs from the previous one in that the sizes of the daughter cells depend on the size of the dividing mother. We assume that the two daughter cells may differ in size, but that the distribution of their relative sizes, represented by the probability density $d(p)$, $d: (1/2 - \Delta, 1/2 + \Delta) \rightarrow \mathbb{R}_+$, where p is the fraction size of a daughter, is independent of the size of the mother. The population equation is

$$\frac{\partial}{\partial t} n(t, x) = -\frac{\partial}{\partial x}(g(x)n(t, x)) - b_\epsilon(x)n(t, x) + 2 \int_0^1 \frac{d(p)}{p} b_\epsilon\left(\frac{x}{p}\right) n(t, \frac{x}{p}) dp. \quad (1.4)$$

g denotes the individual growth rate and b_ϵ the size specific division rate. It is assumed that individuals who have passed size 1 are no larger capable of dividing, i.e. $b_\epsilon(x) = 0$ for $x > 1$, but either differentiate or die.

Now assume that $b_\epsilon(x) = 0$ outside $(1 - \epsilon, 1)$ but that yet for $\epsilon \downarrow 0$ the quantity $\int_{1-\epsilon}^1 \frac{b_\epsilon(y)}{g(y)} dy$ converges to a number larger than zero. This means that the probability that a newborn cell is eventually going to divide

$$\pi_\epsilon = 1 - \exp\left(-\int_{1-\epsilon}^1 \frac{b_\epsilon(y)}{g(y)} dy\right) \quad (1.5)$$

converges to a value $\pi_0 > 0$. In the limit cells will only divide on reaching $x = 1$, and they do so with probability π_0 . The corresponding population equation is

$$\frac{\partial}{\partial t} n(t, x) = -\frac{\partial}{\partial x} (g(x)n(t, x)) + 2d(x)\pi_0 g(1)n(t, 1). \quad (1.6)$$

This limit model may be used as a convenient approximation when cell division occurs only in a very narrow size window.

2. THE TROTTER-KATO THEOREM AND SOME OTHER RESULTS FROM SEMIGROUP THEORY

In this section we mention some known results from the theory of strongly continuous semigroups. For details and proofs we refer to the book of PAZY (1983).

Let $\{T(t)\}_{t \geq 0}$ be a strongly continuous (or C_0 -) semigroup of linear operators on some Banach space X . Let A be a linear operator on X with domain $D(A)$. For $M \geq 0, \omega \in \mathbb{R}$ we define $G(M, \omega)$ as the class of all operators A which are the generator of a C_0 -semigroup $\{T(t)\}_{t \geq 0}$ satisfying

$$\|T(t)\| \leq M e^{\omega t}, \quad t \geq 0.$$

The *Hille-Yosida theorem* says that any closed, densely defined linear operator A for which there exist constants $\omega \in \mathbb{R}, M \geq 0$ such that

(i) $(\omega, \infty) \subset \rho(A)$, where $\rho(A)$ is the resolvent set of A ,

(ii) $\|R(\lambda, A)^n\| \leq M/(\lambda - \omega)^n$, for all $\lambda > \omega, n = 1, 2, \dots$,

is an element of $G(M, \omega)$. Here $R(\lambda, A) = (\lambda I - A)^{-1}$ is the resolvent of A .

If A_0 is the generator of a C_0 -semigroup and $B: X \rightarrow X$ is a bounded linear operator, then $A = A_0 + B$, with domain $D(A) = D(A_0)$, is also the generator of a C_0 -semigroup. This perturbation result is used in both sections 3 and 4.

Let $\sigma(A)$ be the spectrum of A . The spectral bound $s(A)$ of a closed, linear operator A is defined as

$$s(A) = \sup\{\operatorname{Re} \lambda : \lambda \in \sigma(A)\}, \quad (2.1)$$

where the supremum of the empty set is $-\infty$, by definition. If $A \in G(M, \omega)$, then $s(A) \leq \omega$.

Assume that X is a Banach lattice (see e.g. SCHAEFER (1974)) and denote by X_+ the cone of positive elements of X . We say that $\{T(t)\}_{t \geq 0}$ is a positive semigroup if every operator $T(t), t \geq 0$, is positive, i.e. $T(t)X_+ \subseteq X_+$. If A is the generator of a positive C_0 -semigroup, then $R(\lambda, A)$ is a positive operator for every $\lambda > s(A)$, and $s(A) \in \sigma(A)$, if $\sigma(A) \neq \emptyset$. These results were proved by GREINER, VOIGT & WOLFF (1981).

The remainder of this section is devoted to the Trotter-Kato theorem, which relates the convergence of a sequence of infinitesimal generators (resp. their resolvents) to the convergence of the associated semigroups. What the word "convergence" stands for in this context can be found in the precise results below. We now give two different versions of the Trotter-Kato theorem; the first is applied in section 4 and the latter in section 3.

THEOREM 2.1 *Let A be a closed, densely defined linear operator and let $A_\epsilon \in G(M, \omega)$, $0 < \epsilon < \epsilon_0$. If for some λ with $\operatorname{Re} \lambda > \omega$ we have*

$$R(\lambda, A_\epsilon)\phi \rightarrow R(\lambda, A)\phi, \quad \epsilon \downarrow 0,$$

for all $\phi \in X$, then $A \in G(M, \omega)$. Let $\{T_\epsilon(t)\}_{t \geq 0}$ and $\{T(t)\}_{t \geq 0}$ be the semigroups generated by A_ϵ and A respectively, then for every $\phi \in X$ and $t \geq 0$,

$$T_\epsilon(t)\phi \rightarrow T(t)\phi, \quad \epsilon \downarrow 0,$$

and the convergence is uniform for t in bounded subsets of $(0, \infty)$.

THEOREM 2.2 Let $A_\epsilon \in G(M, \omega)$, $0 < \epsilon < \epsilon_0$ and assume that

(i) there is a dense subset D of X such that

$$A_\epsilon \phi \rightarrow A \phi, \quad \epsilon \downarrow 0,$$

for every $\phi \in D$,

(ii) there exists a λ with $\operatorname{Re} \lambda > \omega$ for which $(\lambda - A)D$ is dense in X .

Then the closure \bar{A} of A is an element of $G(M, \omega)$. If $\{T_\epsilon(t)\}_{t \geq 0}$ and $\{T(t)\}_{t \geq 0}$ are the semigroups generated by A_ϵ and \bar{A} respectively, then for every $\phi \in X$ and $t \geq 0$

$$T_\epsilon(t)\phi \rightarrow T(t)\phi, \quad \epsilon \downarrow 0,$$

and the convergence is uniform for t in bounded subsets of $(0, \infty)$.

REMARKS

(i) If we know, one or the other way, that the operator A in theorem 2.2 is closed, then, of course, $\bar{A} = A$.

(ii) From the proof of theorem 4.5, chapter 3, in PAZY (1983) it follows that conditions (i) and (ii) of theorem 2.2 imply that for every $\phi \in X$ and $\lambda \in \mathbb{C}$ with $\operatorname{Re} \lambda > \omega$,

$$R(\lambda, A_\epsilon)\phi \rightarrow R(\lambda, \bar{A})\phi \text{ as } \epsilon \downarrow 0.$$

(iii) In the literature several other versions of the Trotter-Kato theorem can be found. In the original paper of TROTTER (1958), it was allowed that the semigroups $\{T_\epsilon(t)\}_{t \geq 0}$ acted on different Banach spaces X_ϵ . Although this generality is useful in many applications, we don't need it in this paper.

3. FROM SIZE JUMPS TO REDUCED GROWTH

3.1 The model

We recall the model for size-structured population growth, described in the Introduction (see (1.3)).

$$\frac{\partial n}{\partial t}(t, x) + \frac{\partial}{\partial x}(g(x)n(t, x)) = -\beta_\epsilon(x)n(t, x) + \beta_\epsilon(x + \epsilon)n(t, x + \epsilon) \quad (3.1a)$$

$$g(\epsilon+)n(t, \epsilon+) - g(\epsilon-)n(t, \epsilon-) = \rho_\epsilon \int_a^1 \beta_\epsilon(x)n(t, x)dx \quad (3.1b)$$

$$g(0)n(t, 0) = 0 \quad (3.1c)$$

$$n(0, x) = \psi(x). \quad (3.1d)$$

For technical reasons we allow that possibly some individuals of the initial population have size between 0 and ϵ , and therefore we replaced (1.3b) by (3.1b) and added the boundary condition (3.1c) which guarantees that there is no influx of individuals at $x=0$. In (3.1b),

$$g(\epsilon+)n(t, \epsilon+) - g(\epsilon-)n(t, \epsilon-) = \lim_{h \downarrow 0} [g(\epsilon+h)n(t, \epsilon+h) - g(\epsilon-h)n(t, \epsilon-h)].$$

We assume that the growth rate $g(x)$ is such that individuals cannot grow beyond a maximum size which we normalize to $x=1$; see Assumption 3.1a below. As a consequence the last term at the right-hand-side of (3.1a) has to be taken zero if $x + \epsilon > 1$. Note that we have taken $\mu \equiv 0$.

A natural choice for the underlying population state space is $M[0, 1]$, i.e. the space of all Borel measures on $[0, 1]$; see METZ & DIEKMANN (to appear). However, (3.1) makes no sense for measures. There are at least two different ways to obviate this problem. The first is to integrate (3.1) with respect to x and to work with distributions (functions of bounded variation). In stead of this, we have chosen to use the so-called *backward equation*

$$\frac{\partial m}{\partial t}(t, x) - g(x) \frac{\partial m}{\partial x}(t, x) = -\beta_\epsilon(x)m(t, x) + \beta_\epsilon(x)m(t, x - \epsilon) + \rho_\epsilon \beta_\epsilon(x)m(t, \epsilon) \quad (3.2a)$$

$$m(0, x) = \phi(x), \quad (3.2b)$$

satisfied by the clan averages

$$m(t, x) = \int_0^1 \phi(\xi) N_x(t, d\xi), \quad (3.3)$$

where the measure $N_x(t, \cdot)$ represents the expected state at time t of a clan descending from an ancestral individual sized x at time zero. In (3.2b) ϕ is an arbitrary continuous function, i.e. $\phi \in X := C[0, 1]$, and we look for a solution $m_\epsilon(t, x; \phi)$ of (3.2), such that $m_\epsilon(t, \cdot; \phi) \in X$ for every $t \geq 0$. If we are able to find such a solution $m_\epsilon(t, \cdot; \phi)$ for every $\phi \in X$, then the solution $n_\epsilon(t, \cdot; \psi)$ of the *forward equation* (3.1), where $\psi \in X^* = M[0, 1]$, can be defined by means of the duality relation

$$\langle \phi, n_\epsilon(t, \cdot; \psi) \rangle = \langle m_\epsilon(t, \cdot; \phi), \psi \rangle. \quad (3.4)$$

Here $\langle \cdot, \cdot \rangle$ is the pairing between elements of X and X^* , i.e. for $\phi \in X = C[0, 1]$ and $\psi \in X^* = M[0, 1]$,

$$\langle \phi, \psi \rangle = \int_0^1 \phi(x) \psi(dx).$$

In subsections 3.2 and 3.4 we shall give a precise description of the relation between the backward and forward equation in terms of semigroups and generators.

From this point on, we shall work with the backward equation, and where necessary, interpret the results in terms of the forward equation. It turns out that this is a well-suited approach.

3.2 The semigroup solution of the backward equation

In this subsection we show that, under some reasonable assumptions, we can associate a strongly continuous semigroup of linear operators on $X = C[0, 1]$ with the initial value problem (3.2).

ASSUMPTIONS 3.1

- a) g is Lipschitz continuous on $[0, 1]$; $g(x) > 0, x \in [0, 1]$; $g(1) = 0$.
- b) β_ϵ is Lipschitz continuous on $[0, 1]$; there is an $a > \epsilon$ such that $\beta_\epsilon(x) = 0, x \in [0, a]$ and $\beta_\epsilon(x) > 0, x \in (a, 1]$.

Here a denotes the minimum size at which an individual can reproduce. We can write (3.2) as the abstract Cauchy problem:

$$\frac{dm}{dt}(t) = A_\epsilon m(t), \quad m(0) = \phi \in X, \quad (3.5)$$

where the closed, unbounded operator A_ϵ with domain

$$D(A_\epsilon) = \{\phi \in X \cap W_{loc}^{1,1}[0, 1] : g\phi' \in X\},$$

is given by

$$(A_\epsilon \phi)(x) = g(x) \frac{d\phi}{dx}(x) - \beta_\epsilon(x)\phi(x) + \beta_\epsilon(x)\phi(x - \epsilon) + \rho_\epsilon \beta_\epsilon(x)\phi(\epsilon).$$

We write A_ϵ as the sum of two operators:

$$A_\epsilon = A_0 + B_\epsilon, \quad (3.6)$$

where the closed, unbounded operator A_0 has the same domain as A_ϵ and is given by

$$(A_0\phi)(x) = g(x) \frac{d\phi}{dx}(x),$$

and where B_ϵ is a bounded operator given by

$$(B_\epsilon\phi)(x) = -\beta_\epsilon(x)\phi(x) + \beta_\epsilon(x)\phi(x - \epsilon) + \rho_\epsilon\beta_\epsilon(x)\phi(\epsilon).$$

It is quite easy to show that A_0 generates a strongly continuous semigroup $\{T_0(t)\}_{t \geq 0}$, and therefore A_ϵ , being a bounded perturbation of A_0 , also generates a strongly continuous semigroup $\{T_\epsilon(t)\}_{t \geq 0}$; see section 2.

Both $\{T_0(t)\}_{t \geq 0}$ and $\{T_\epsilon(t)\}_{t \geq 0}$ are positive semigroups, which is intuitively clear from the biological interpretation, but can also be shown rigorously; see HEIJMANS (1986). Let $\mathbf{1}$ be the element of X which is identically one on $[0,1]$. Then

$$A_\epsilon \mathbf{1} = \rho_\epsilon \beta_\epsilon.$$

Define the positive scalar ω_ϵ by

$$\omega_\epsilon = \sup\{\rho_\epsilon \beta_\epsilon(x) : x \in [0,1]\}. \quad (3.7)$$

One sees immediately that

$$0 \leq A_\epsilon \mathbf{1} \leq \omega_\epsilon \mathbf{1}.$$

We show that $A_\epsilon \in G(1, \omega_\epsilon)$. First suppose that $\omega_\epsilon < s(A_\epsilon)$, where $s(A_\epsilon)$ is the spectral bound of A_ϵ . Choose $\lambda > s(A_\epsilon)$. Then $R(\lambda, A_\epsilon)$ is a positive operator, and we get that

$$0 \leq R(\lambda, A_\epsilon) \mathbf{1} \leq \frac{1}{\lambda - \omega_\epsilon} \mathbf{1},$$

hence $\|R(\lambda, A_\epsilon)\| = \|R(\lambda, A_\epsilon) \mathbf{1}\| \leq \frac{1}{\lambda - \omega_\epsilon}$, and we find that $\|R(\lambda, A_\epsilon)\|$ remains bounded if $\lambda \downarrow s(A_\epsilon)$ which is in contradiction with

$$s(A_\epsilon) \in \sigma(A_\epsilon).$$

Therefore $\omega_\epsilon \geq s(A_\epsilon)$. Using the same arguments as above, we find that for $\lambda > \omega_\epsilon$,

$$\|R(\lambda, A_\epsilon)\| \leq \frac{1}{\lambda - \omega_\epsilon},$$

which yields that for $n = 1, 2, \dots$

$$\|R(\lambda, A_\epsilon)^n\| \leq \frac{1}{(\lambda - \omega_\epsilon)^n},$$

and it follows that $A_\epsilon \in G(1, \omega_\epsilon)$.

We end this section with some remarks about the forward equation, defined on $X^* = M[0,1]$.

Let $\psi \in X^*$. From (3.4) and the fact that $m_\epsilon(t, \cdot; \phi) = T_\epsilon(t)\phi$ we get that for every $\phi \in X$ $\langle \phi, n_\epsilon(t, \cdot; \psi) \rangle = \langle T_\epsilon(t)\phi, \psi \rangle = \langle \phi, T_\epsilon^*(t)\psi \rangle$, where $T_\epsilon^*(t)$ is the dual operator of $T_\epsilon(t)$. So we find that solutions of the forward equation can be represented as $n_\epsilon(t, \cdot; \psi) = T_\epsilon^*(t)\psi$. In the literature $\{T_\epsilon^*(t)\}_{t \geq 0}$ is called a weak * continuous semigroup; see e.g. BUTZER & BERENS (1967). Properties of $T_\epsilon^*(t)$ can be obtained from corresponding properties of $T_\epsilon(t)$; an illustration of this idea can be found in subsection 3.4.

3.3 The limit transition justified

As was argued in the Introduction of this paper, we are mainly interested in very small values of ϵ , and therefore we let ϵ go to zero.

ASSUMPTIONS 3.2

- a) $\beta_\epsilon(x) = \frac{1}{\epsilon}b(x)$, for some (Lipschitz continuous) function b on $[0,1]$.
- b) $\rho_\epsilon = \epsilon r$.

A motivation for these assumptions was given in the Introduction. Assumptions 3.1b and 3.2a together yield that b is Lipschitz continuous on $[0,1]$, $b(x)=0$ for $x \leq a$ and $b(x)>0$ for $a < x \leq 1$.

With these assumptions, equation (3.2a) becomes

$$\frac{\partial m}{\partial t}(t,x) - g(x)\frac{\partial m}{\partial x}(t,x) = -b(x)\frac{1}{\epsilon}\{m(t,x) - m(t,x-\epsilon)\} + rb(x)m(t,\epsilon),$$

and by letting $\epsilon \downarrow 0$ we get

$$\frac{\partial m}{\partial t}(t,x) - (g(x) - b(x))\frac{\partial m}{\partial x}(t,x) = rb(x)m(t,0), \quad (3.8)$$

which is the backward equation corresponding to (1.4). A striking feature of (3.8) is that the *reduced growth rate*

$$\gamma(x) = g(x) - b(x)$$

is *not* positive on the whole interval $[0,1]$: in particular $\gamma(1) = -b(1) < 0$.

In the rest of this subsection we will show how the Trotter-Kato theorem (section 2) can be used to justify the formal transition from (3.2a) to (3.8). In the next subsection we interpret these results in terms of the forward equations (1.2) (with $x_0=0$) and (1.3).

First we reformulate (3.8) supplied with initial condition (3.2b) as an abstract Cauchy problem.

$$\frac{dm}{dt}(t) = Am(t), \quad m(0) = \phi \in X, \quad (3.9)$$

where the closed operator A is given by

$$(A\phi)(x) = \gamma(x)\frac{d\phi}{dx}(x) + rb(x)\phi(0)$$

for every ϕ in its domain

$$D(A) = \{\phi \in X \cap W_{loc}^{1,1}[0,1] : \gamma\phi' \in X\}.$$

It is not difficult to show that A generates a strongly continuous positive semigroup: this, however, will also follow from the forthcoming analysis, which shows that we can apply the (Trotter-Kato) theorem 2.2. Let

$$\omega := \sup\{rb(x) : 0 \leq x \leq 1\}. \quad (3.10)$$

PROPOSITION 3.3 $A_\epsilon \in G(1, \omega)$.

PROOF. At the end of subsection 3.2 it was found that $A_\epsilon \in G(1, \omega_\epsilon)$, where $\omega_\epsilon = \sup\{\rho_\epsilon \beta_\epsilon(x) : 0 \leq x \leq 1\} = \omega$. \square

We make the following assumption.

ASSUMPTION 3.4 There exist a unique $\hat{x} \in (0, 1)$ such that $g(\hat{x}) = b(\hat{x})$.

In combination with the other assumptions of this section this means that:

$$\gamma(x) > 0, \quad 0 \leq x < \hat{x}$$

$$\gamma(x) < 0, \quad \hat{x} < x \leq 1.$$

Now let $D = C^1[0, 1]$, i.e. the subspace of X containing all continuously differentiable functions on $[0, 1]$. Clearly

$$D(A_\epsilon) \subseteq D, \quad D(A) \subseteq D.$$

PROPOSITION 3.5 $(\lambda - A)D$ is dense in X , for $\lambda \in \mathbb{R}$ sufficiently large.

PROOF. Consider for $F \in X$ the inhomogeneous equation

$$\lambda \phi(x) - \gamma(x) \phi'(x) = F(x),$$

where $\lambda \in \mathbb{R}$ is sufficiently large ($\lambda > \omega$). The solution of this equation for $0 \leq x < \hat{x}$ is given by

$$\phi(x) = \int_x^{\hat{x}} \frac{F(y)}{\gamma(y)} \exp\left\{-\lambda \int_x^y \frac{d\xi}{\gamma(\xi)}\right\} dy, \quad (*)$$

and a similar expression can be found for $\phi(x)$, if x is greater than \hat{x} . It is easy to check that $\phi \in D$ if $F \in D$. Now, for $f \in X$, the solution of

$$\lambda \phi - A\phi = f, \quad (**)$$

on $(0, \hat{x})$ is given by (*), with $F(x) = f(x) + r\phi(0)b(x)$ substituted. Hence $\phi \in D$ if $F \in D$. Let $f \in X$ and let ϕ be the solution of (**), then

$$\phi(0) = \int_0^{\hat{x}} \frac{f(y) + r\phi(0)b(y)}{\gamma(y)} \exp\left\{-\lambda \int_0^y \frac{d\xi}{\gamma(\xi)}\right\} dy.$$

We assume that $\lambda \in \mathbb{R}$ is so large that

$$\alpha_\lambda := \int_0^{\hat{x}} \frac{b(y)}{\gamma(y)} \exp\left\{-\lambda \int_0^y \frac{d\xi}{\gamma(\xi)}\right\} dy < \frac{1}{r},$$

and for $f \in X$ we define

$$H_\lambda(f) := \frac{r}{1 - \alpha_\lambda r} \int_0^{\hat{x}} \frac{f(y)}{\gamma(y)} \exp\left\{-\lambda \int_0^y \frac{d\xi}{\gamma(\xi)}\right\} dy.$$

Then the solution ϕ of (**) satisfies

$$r\phi(0) = H_\lambda(f).$$

So we get that $\phi \in D$ if $f + H_\lambda(f)b \in D$. We define $V \subseteq X$ as

$$V = \{f \in X : f + H_\lambda(f)b \in D\}.$$

Then $V \subseteq (\lambda - A)D$, and it suffices to show that V is a dense subset of X . Let $f \in X$ and define $g \in X$ as

$$g = f + H_\lambda(f)b.$$

Let $\{g_n\}$ be a sequence in D converging to g as $n \rightarrow \infty$. The solution of $g_n = f_n + H_\lambda(f_n)b$ is given by $f_n = g_n - \frac{H_\lambda(g_n)}{1 + H_\lambda(b)}b$. Now $f_n \in V$ and $f_n \rightarrow g - \frac{H_\lambda(g)}{1 + H_\lambda(b)}b = f$, $n \rightarrow \infty$. Therefore $\bar{V} = X$. \square

PROPOSITION 3.6 $A_\epsilon \phi \rightarrow A\phi$ as $\epsilon \downarrow 0$, for every $\phi \in D$.

PROOF. Let $\phi \in D$. Then

$$|(A_\epsilon \phi)(x) - (A\phi)(x)| \leq |b(x)| \cdot \left| \frac{1}{\epsilon} (\phi(x) - \phi(x - \epsilon)) - \phi'(x) \right| + r|b(x)| \cdot |\phi(\epsilon) - \phi(0)|,$$

for every $x \in [0, 1]$, and thus

$$\|A_\epsilon \phi - A\phi\| = \sup_{x \in [0, 1]} |(A_\epsilon \phi)(x) - (A\phi)(x)| \rightarrow 0, \quad \epsilon \downarrow 0. \quad \square$$

We are now ready to apply theorem 2.2, which give us the the following.

THEOREM 3.7 $A \in G(1, \omega)$, and if $\{T(t)\}_{t \geq 0}$ is the semigroup generated by A , then

$$T_\epsilon(t)\phi \rightarrow T(t)\phi, \quad \epsilon \downarrow 0,$$

for every $\phi \in X$, where the convergence is uniform for t in bounded subsets of $(0, \infty)$.

This theorem tells us that a solution of the limit equation (3.8) is indeed an approximation of solutions of equation (3.2a), presupposed that their initial condition ϕ is the same.

3.4 Interpretation and Concluding Remarks

In this subsection we interpret our results in terms of the forward equation (3.1). The abstract backward equation is written as

$$\frac{dm}{dt}(t) = A_\epsilon m(t), \quad m_\epsilon(0) = \phi \in X.$$

Since A_ϵ is closed and densely defined, the dual operator A_ϵ^* is well-defined. It is a weak * closed operator with domain $D(A_\epsilon^*)$ which is weak * dense in X^* ; see BUTZER & BERENS (1967). Now the forward equation can be reformulated as the abstract Cauchy problem

$$\frac{dn}{dt}(t) = A_\epsilon^* n(t), \quad n(0) = \psi \in X^*. \quad (3.11)$$

Its solutions are $n(t) = T_\epsilon^*(t)\psi$ (see subsection 3.2). Note that (3.11) admits all initial functions $\psi \in M[0, 1]$, whereas (3.1) only makes sense for densities.

REMARK We didn't prove that (3.1) corresponds with the abstract equation (3.11). A rigorous prove would involve the following steps:

- compute the resolvent operator $R(\lambda, A_\epsilon)$ for some $\lambda \in \rho(A_\epsilon)$
- compute its dual $R(\lambda, A_\epsilon)^* = R(\lambda, A_\epsilon^*)$
- compute the domain $D(A_\epsilon^*)$ from the relation

$$D(A_\epsilon^*) = R(R(\lambda, A_\epsilon^*)),$$

where $R(\cdot)$ denotes the range

- if $\psi \in D(A_\epsilon^*)$ compute $A_\epsilon^* \psi$ from the relation: $\langle \phi, A_\epsilon^* \psi \rangle = \langle A_\epsilon \phi, \psi \rangle$ for $\phi \in D(A_\epsilon)$
- finally use that the abstract forward equation is

$$\frac{dn}{dt}(t) = A_\epsilon^* n(t).$$

This procedure was carried out by HEIJMANS (1984b) for a different population model.

Our main result, theorem 3.7, can be restated in terms of solutions of the forward equation by using the duality relation (3.4); also see the last paragraph of subsection 3.2. One finds that for any

$$\psi \in M[0, 1],$$

$$n_\epsilon(t, \cdot; \psi) \rightarrow n(t, \cdot; \psi), \text{ as } \epsilon \downarrow 0$$

where convergence holds with respect to the weak * topology of $X^* = M[0, 1]$, and is uniform for t in bounded intervals of $(0, \infty)$.

From assumption 3.4 it follows that for $\epsilon = 0$, individuals with size larger than \hat{x} shrink towards \hat{x} , without ever reaching this critical size. All their offspring, however, obtains a birth size $x = 0$, and can never grow beyond \hat{x} . So it seems quite reasonable to study (1.2) on the subinterval $[0, \hat{x}]$ if $\epsilon \downarrow 0$.

In the Introduction of this paper, we noticed that, as a consequence of the assumption 3.2.a, the recruitment would cause an unlimited increase of the biomass if $\epsilon \downarrow 0$. For that reason we made assumption 3.2.b., i.e. a proportionally high death rate in the nursery. There is, however, an alternative to assumption 3.2.b. Suppose that $\rho_\epsilon = 1$, no matter how small ϵ is, and make

ASSUMPTION 3.8 Individuals with size x die at a rate $\mu(x) = \frac{g(x)}{x}$.

Now equation (3.1.a) takes the form

$$\frac{\partial n}{\partial t}(t, x) + \frac{\partial}{\partial x}(g(x)n(t, x)) = -\frac{g(x)}{x}n(t, x) - \beta_\epsilon(x)n(t, x) + \beta_\epsilon(x + \epsilon)n(t, x + \epsilon).$$

The following intuitive argument should convince the reader that this is indeed a good alternative.

Consider a cohort of newborns with size $x = \epsilon$. The flux through $x = a$, which is $g(a)n(t, a)$, is related to the flux through ϵ in the following way:

$$g(a)n(t, a) = g(\epsilon)n(t - \tau(\epsilon), \epsilon) \exp\left[-\int_\epsilon^a \frac{\mu(y)}{g(y)} dy\right],$$

where $\tau(\epsilon) = \int_\epsilon^a \frac{dy}{g(y)}$ is the time which an individual needs to grow from ϵ to a . Substituting assumption 3.8 we get

$$ag(a)n(t, a) = \epsilon g(\epsilon)n(t - \tau(\epsilon), \epsilon)$$

which means that the biomass flux through a is equal to the biomass flux through ϵ , $\tau(\epsilon)$ time units earlier, and therefore doesn't blow up. It is easy to check that other choices for μ can be made without essentially affecting the arguments. As a matter of fact, one might choose μ such that $\frac{\mu(x)}{g(x)} = \frac{1}{x} + f(x)$, where f is an L^1 -function. However, the choice $\frac{\mu(x)}{g(x)} = \frac{c}{x}$ where $c \neq 1$, yields completely different results. Although we did not prove it, we believe that it is also possible to apply a Trotter-Kato theorem replacing assumption 3.2b by assumption 3.8.

4. SIZE DEPENDENT CELL KINETICS

4.1 The equation and its semigroup solution

Consider the model for size dependent cell growth and division described in the Introduction. For the sake of convenience we repeat the equation.

$$\frac{\partial n}{\partial t}(t, x) + \frac{\partial}{\partial x}(g(x)n(t, x)) = -b_\epsilon(x)n(t, x) + 2 \int_0^1 \frac{d(p)}{p} b_\epsilon\left(\frac{x}{p}\right)n\left(t, \frac{x}{p}\right) dp, \quad (4.1a)$$

with $b_\epsilon = 0$ outside $(1 - \epsilon, 1)$ and $d = 0$ outside $(\frac{1}{2} - \Delta, \frac{1}{2} + \Delta)$. We assume that ϵ is so small that the size of the greatest newborn daughter cell is less than the size of the smallest mother cell, i.e.

$$\frac{1}{2} + \Delta < 1 - \epsilon.$$

Then the smallest daughter has a size x_{\min} , which satisfies

$$x_{\min} = (1 - \epsilon)(\frac{1}{2} - \Delta) > (\frac{1}{2} + \Delta)(\frac{1}{2} - \Delta) =: \alpha.$$

We impose the boundary condition

$$n(t, \alpha) = 0. \quad (4.1b)$$

Note that we might as well have taken

$$n(t, x_{\min}) = 0.$$

However, we prefer (4.1b), since α does not depend on ϵ . As the underlying population state space, we choose $X = L^1[\alpha, 1]$. Note that for this choice of X , equation (4.1) makes sense, and hence there is no need to work with the backward equation. We make the following assumptions.

ASSUMPTIONS 4.1

- a) $g \in C[\alpha, 1]$; $g(x) > 0$, $x \in [\alpha, 1]$.
- b) $d \in C[0, 1]$; $d(p) = 0$, $p \notin (\frac{1}{2} - \Delta, \frac{1}{2} + \Delta)$; $d(p) > 0$, $p \in (\frac{1}{2} - \Delta, \frac{1}{2} + \Delta)$; d is symmetric around $p = \frac{1}{2}$, and $\int_{\frac{1}{2} - \Delta}^{\frac{1}{2} + \Delta} d(p) dp = 1$.
- c) $b_\epsilon \in C[\alpha, 1]$; $b_\epsilon(x) = 0$, $x \in [\alpha, 1 - \epsilon]$; $b_\epsilon(x) > 0$, $x \in (1 - \epsilon, 1]$.

We can write (4.1) with initial condition

$$n(0, x) = \phi(x), \quad x \in [\alpha, 1] \quad (4.2)$$

where $\phi \in X$, as the abstract Cauchy problem.

$$\frac{dn}{dt}(t) = A_\epsilon n(t), \quad n(0) = \phi, \quad (4.3)$$

where the closed operator A_ϵ on X is given by

$$(A_\epsilon \phi)(x) = -\frac{d}{dx}(g(x)\phi(x)) - b_\epsilon(x)\phi(x) + 2 \int_{\frac{1}{2} - \Delta}^{\frac{1}{2} + \Delta} \frac{d(p)}{p} b_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp, \quad (4.4)$$

for any ϕ in its domain

$$D(A_\epsilon) = \{\phi \in X : g\phi \in W^{1,1}[\alpha, 1] \wedge \phi(\alpha) = 0\}. \quad (4.5)$$

Using the perturbation result for C_0 -semigroups, mentioned in section two, one easily shows that A_ϵ is the infinitesimal generator of a strongly continuous semigroup $\{T_\epsilon(t)\}_{t \geq 0}$.

PROPOSITION 4.2 *There exist constants $\omega \in \mathbb{R}$ and $M \geq 1$ (which do not depend on ϵ), such that $A_\epsilon \in G(M, \omega)$.*

PROOF. Let $\|\cdot\|$ be the L^1 -norm. Then $\|\cdot\|$ is equivalent to $\|\cdot\|'$ given by

$$\|\phi\|' = \int_{\alpha}^1 x |\phi(x)| dx, \quad \phi \in X.$$

Let for $t \geq 0$,

$$\|T_\epsilon(t)\|' = \sup\{\|T_\epsilon(t)\phi\|' / \|\phi\|' : \phi \in X, \phi \neq 0\}.$$

Since $T_\epsilon(t)$ is a positive operator, we have

$$\|T_\epsilon(t)\|' = \sup\{\|T_\epsilon(t)\phi\|'/\|\phi\|' : \phi \in X_+, \phi \neq 0\},$$

where X_+ is the cone of positive elements. If $\phi \in X_+$, then $\|T_\epsilon(t)\phi\|' = \int_\alpha^1 xn(t, x)dx$, where $n(t, x)$ is the solution of (4.1) - (4.2). If, in addition, $\phi \in D(A_\epsilon)$, then

$$\frac{d}{dt} \int_\alpha^1 xn(t, x)dx \leq \int_\alpha^1 g(x)n(t, x)dx \leq \omega \int_\alpha^1 xn(t, x)dx,$$

where $\omega > 0$ is taken so large that $g(x) \leq \omega x$, $x \in [\alpha, 1]$. So for $\phi \in D(A_\epsilon) \cap X_+$ we find that

$$\|T_\epsilon(t)\phi\|' = \int_\alpha^1 xn(t, x)dx \leq e^{\omega t} \int_\alpha^1 x\phi(x)dx = e^{\omega t} \|\phi\|'.$$

Since $D(A_\epsilon) \cap X_+$ is norm-dense in X_+ , this holds for any $\phi \in X_+$, and we find that

$$\|T_\epsilon(t)\|' \leq e^{\omega t}, \quad t \geq 0.$$

Since $\|\cdot\|'$ and $\|\cdot\|$ are equivalent norms, there exists a constant $M > 0$ such that

$$\|T_\epsilon(t)\| \leq Me^{\omega t}, \quad t \geq 0,$$

and the result is proved. \square

4.2 THE LIMIT TRANSITION AND ITS JUSTIFICATION

In this subsection we study the limit transition $\epsilon \downarrow 0$. Let π_ϵ be given by (1.5).

ASSUMPTION 4.3 There exists a real number $\pi_0 \in [0, 1]$ such that $\lim_{\epsilon \downarrow 0} \pi_\epsilon = \pi_0$. We expect that the limit equation looks as follows:

$$\frac{\partial n}{\partial t}(t, x) + \frac{\partial}{\partial x}(g(x)n(t, x)) = 2\pi_0 d(x)g(1)n(t, 1) \quad (4.6a)$$

$$n(t, \alpha) = 0, \quad (4.6b)$$

which is quite different from (4.1). We rewrite (4.6) with initial condition (4.2), as

$$\frac{dn}{dt}(t) = An(t), \quad n(0) = \phi, \quad (4.7)$$

where A is the closed operator

$$(A\phi)(x) = -\frac{d}{dx}(g(x)\phi(x)) + 2\pi_0 d(x)g(1)\phi(1) \quad (4.8)$$

with domain

$$D(A) = \{\phi \in X : g\phi \in W^{1,1}[\alpha, 1] \wedge \phi(\alpha) = 0\}. \quad (4.9)$$

The following result is not at all trivial.

THEOREM 4.4 For $\lambda \in \mathbb{R}$ large enough we have

$$R(\lambda, A_\epsilon)\phi \rightarrow R(\lambda, A)\phi, \quad \epsilon \downarrow 0,$$

for every $\phi \in X$.

PROOF. The proof consists of four steps.

1. Let the isomorphism $U_\epsilon : X \rightarrow X$ be given by

$$(U_\epsilon \phi)(x) = \frac{E_\epsilon(x)}{g(x)} \phi(x),$$

where $E_\epsilon(x) = \exp(-\int_\alpha^x \frac{b_\epsilon(y)}{g(y)} dy)$. Let

$$D = D(A) = D(A_\epsilon) = \{\phi \in X : g\phi \in W^{1,1}[\alpha, 1] \wedge \phi(\alpha) = 0\},$$

and

$$\tilde{D} = U_\epsilon^{-1} D = \{\phi \in X : \phi \in W^{1,1}[\alpha, 1] \wedge \phi(\alpha) = 0\}.$$

Let \tilde{A}_ϵ be the closed operator $U_\epsilon^{-1} A_\epsilon U_\epsilon$ with domain $D(\tilde{A}_\epsilon) = \tilde{D}$. Then \tilde{A}_ϵ is given by

$$(\tilde{A}_\epsilon \phi)(x) = -g(x) \frac{d\phi}{dx}(x) + 2 \frac{g(x)}{E_\epsilon(x)} \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} r_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp,$$

where $r_\epsilon(x) = \frac{b_\epsilon(x)}{g(x)} E_\epsilon(x)$ for $x \in [\alpha, 1]$. We define the isomorphism $U: X \rightarrow X$ by

$$(U\phi)(x) = \frac{\phi(x)}{g(x)}.$$

Let \tilde{A} be the closed operator $U^{-1} A U$ with domain $D(\tilde{A}) = U^{-1} D = \tilde{D}$. For $\phi \in D(\tilde{A})$ we have

$$(\tilde{A}\phi)(x) = -g(x) \frac{d\phi}{dx}(x) + 2\pi_0 d(x) g(x) \phi(1).$$

2. We show that for every $\phi \in \tilde{D}$,

$$\tilde{A}_\epsilon \phi \rightarrow \tilde{A} \phi \text{ as } \epsilon \downarrow 0.$$

Let $\phi \in \tilde{D}$, then

$$(\tilde{A}_\epsilon \phi)(x) - (\tilde{A}\phi)(x) = 2 \frac{g(x)}{E_\epsilon(x)} \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} r_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp - 2\pi_0 d(x) g(x) \phi(1).$$

We define $\bar{g} = \max_{x \in [\alpha, 1]} g(x)$, $\bar{d} = \max_{p \in [\frac{1}{2}-\Delta, \frac{1}{2}+\Delta]} d(p)$. Now

$$\begin{aligned} \|\tilde{A}_\epsilon \phi - \tilde{A}\phi\| &= \int_\alpha^1 \left| \frac{2g(x)}{E_\epsilon(x)} \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} r_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp - 2\pi_0 d(x) g(x) \phi(1) \right| dx \\ &= \int_{(\frac{1}{2}-\Delta)(1-\epsilon)}^{\frac{1}{2}+\Delta} |2g(x) \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} r_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp - 2\pi_0 d(x) g(x) \phi(1)| dx \\ &\leq 2\bar{g} \int_{(\frac{1}{2}-\Delta)(1-\epsilon)}^{\frac{1}{2}+\Delta} \left| \int_{\frac{1}{2}-\Delta}^{\frac{1}{2}+\Delta} \frac{d(p)}{p} r_\epsilon\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp - \pi_\epsilon d(x) \phi(1) \right| dx + 2\bar{g} |\pi_\epsilon - \pi_0| |\phi(1)|. \end{aligned}$$

This second expression at the right-hand-side can easily be estimated. We write the first expression as the sum of three integrals:

$$\int_{(\frac{1}{2}-\Delta)(1-\epsilon)}^{\frac{1}{2}+\Delta} = \int_{(\frac{1}{2}-\Delta)(1-\epsilon)}^{\frac{1}{2}-\Delta} + \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} + \int_{(\frac{1}{2}+\Delta)(1-\epsilon)}^{\frac{1}{2}+\Delta}.$$

It is the middle integral which causes most troubles, and we restrict our attention to this term. Let

$\delta > 0$.

$$\begin{aligned}
& 2\bar{g} \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} \left| \int_{\frac{1}{2}-\Delta}^{\frac{x}{\frac{1}{2}+\Delta}} \frac{d(p)}{p} r_{\epsilon}\left(\frac{x}{p}\right) \phi\left(\frac{x}{p}\right) dp - \pi_{\epsilon} d(x) \phi(1) \right| dx \\
&= 2\bar{g} \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} \left| \int_{\frac{x}{\frac{1}{2}+\Delta}}^{\frac{x}{\frac{1}{2}-\Delta}} \frac{1}{y} d\left(\frac{x}{y}\right) r_{\epsilon}(y) \phi(y) dy - \pi_{\epsilon} d(x) \phi(1) \right| dx \\
&= 2\bar{g} \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} \left| \int_{1-\epsilon}^1 \frac{1}{y} d\left(\frac{x}{y}\right) r_{\epsilon}(y) \phi(y) dy - \int_{1-\epsilon}^1 d(x) r_{\epsilon}(y) \phi(1) dy \right| dx \\
&= 2\bar{g} \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} \left| \int_{1-\epsilon}^1 \left\{ \frac{1}{y} d\left(\frac{x}{y}\right) \phi(y) - \frac{1}{1} d\left(\frac{x}{1}\right) \phi(1) \right\} r_{\epsilon}(y) dy \right| dx \\
&\leq 2\bar{g} \int_{\frac{1}{2}-\Delta}^{(\frac{1}{2}+\Delta)(1-\epsilon)} \left\{ \int_{1-\epsilon}^1 \delta r_{\epsilon}(y) dy \right\} dx \leq 2\bar{g} \cdot 2\Delta \cdot \delta.
\end{aligned}$$

Here we have chosen $\epsilon > 0$ so small that

$$\left| \frac{1}{y} d\left(\frac{x}{y}\right) \phi(y) - \frac{1}{1} d\left(\frac{x}{1}\right) \phi(1) \right| < \delta,$$

for every $x \in [\frac{1}{2}-\Delta, (\frac{1}{2}+\Delta)(1-\epsilon)]$ and $y \in [1-\epsilon, 1]$, and we used that $\int_{1-\epsilon}^1 r_{\epsilon}(y) dy = \pi_{\epsilon} \leq 1$. This shows that $\tilde{A}_{\epsilon} \phi \rightarrow \tilde{A} \phi$ as $\epsilon \downarrow 0$, for $\phi \in \tilde{D}$.

3. We show that for $\lambda \in \mathbb{R}$ large enough (in particular $\lambda > \omega$; see proposition 4.2)

$$R(\lambda, \tilde{A}_{\epsilon}) \phi \rightarrow R(\lambda, \tilde{A}) \phi, \text{ as } \epsilon \downarrow 0,$$

for every $\phi \in X$. Choose $\lambda > \omega$ so large that $\lambda \in \rho(A) = \rho(\tilde{A})$. Let $\phi \in X$, and define $\psi \in \tilde{D}$ as $\psi = R(\lambda, \tilde{A}) \phi$. Let for $\epsilon > 0$, $\phi_{\epsilon} = (\lambda - \tilde{A}_{\epsilon}) \psi$. From

$$\tilde{A}_{\epsilon} \psi \rightarrow \tilde{A} \psi, \text{ as } \epsilon \downarrow 0$$

we get $\phi_{\epsilon} \rightarrow \phi$ as $\epsilon \downarrow 0$. Since $R(\lambda, \tilde{A}_{\epsilon}) = U_{\epsilon}^{-1} R(\lambda, A_{\epsilon}) U_{\epsilon}$, we deduce from proposition 4.2 that

$$\|R(\lambda, \tilde{A}_{\epsilon})\| \leq \frac{\tilde{M}}{\lambda - \omega}, \quad \epsilon > 0.$$

Here we have used explicitly that $\pi_0 < 1$. Now

$$\lim_{\epsilon \downarrow 0} R(\lambda, \tilde{A}_{\epsilon}) \phi = \lim_{\epsilon \downarrow 0} [R(\lambda, \tilde{A}_{\epsilon})(\phi - \phi_{\epsilon}) + \psi] = \psi = R(\lambda, \tilde{A}) \phi.$$

4. We finally show that for $\lambda \in \mathbb{R}$ large enough,

$$R(\lambda, A_{\epsilon}) \phi \rightarrow R(\lambda, A) \phi, \text{ as } \epsilon \downarrow 0,$$

for every $\phi \in X$. It is easily checked that

$$U_{\epsilon} \phi \rightarrow U \phi, \quad \epsilon \downarrow 0 \text{ and } U_{\epsilon}^{-1} \phi \rightarrow U^{-1} \phi, \quad \epsilon \downarrow 0,$$

for every $\phi \in X$, and that there exists a constant $L > 0$ such that $\|U_{\epsilon}\|, \|U\|, \|U_{\epsilon}^{-1}\|, \|U^{-1}\| \leq L$, $\epsilon > 0$. For every $\phi \in X$ we have

$$\|R(\lambda, A_{\epsilon}) \phi - R(\lambda, A) \phi\| = \|U_{\epsilon} R(\lambda, \tilde{A}_{\epsilon}) U_{\epsilon}^{-1} \phi - U R(\lambda, A) U^{-1} \phi\| =$$

$$\begin{aligned}
& \| (U_\epsilon - U)(R(\lambda, \tilde{A}_\epsilon)U_\epsilon^{-1} - R(\lambda, \tilde{A})U^{-1} + R(\lambda, \tilde{A}_\epsilon)U^{-1} - R(\lambda, \tilde{A})U^{-1} + R(\lambda, \tilde{A})U^{-1})\phi \\
& + U(R(\lambda, \tilde{A}_\epsilon) - R(\lambda, \tilde{A}))(U_\epsilon^{-1} - U^{-1} + U^{-1})\phi + UR(\lambda, \tilde{A})(U_\epsilon^{-1} - U^{-1})\phi \| \\
& \leq \| U_\epsilon - U \| \| R(\lambda, \tilde{A}_\epsilon) \| \| U_\epsilon^{-1}\phi - U^{-1}\phi \| + \| U_\epsilon - U \| \| R(\lambda, \tilde{A}_\epsilon)U^{-1}\phi - R(\lambda, \tilde{A})U^{-1}\phi \| + \\
& \| (U_\epsilon - U)R(\lambda, \tilde{A})U^{-1}\phi \| + \| U \| \| R(\lambda, \tilde{A}_\epsilon) - R(\lambda, \tilde{A}) \| \| U_\epsilon^{-1}\phi - U^{-1}\phi \| + \\
& \| U \| \| (R(\lambda, \tilde{A}_\epsilon) - R(\lambda, \tilde{A}))U^{-1}\phi \| + \| U \| \| R(\lambda, \tilde{A}) \| \| U_\epsilon^{-1}\phi - U^{-1}\phi \|,
\end{aligned}$$

and all these terms go to zero as $\epsilon \downarrow 0$. \square

It is easily checked that A is a closed, linear operator with dense domain, and therefore we may apply theorem 2.1 which gives us that the solution of (4.1), (4.2) converges to that of (4.6), (4.2) as $\epsilon \downarrow 0$.

THEOREM 4.5 $A \in G(M, \omega)$, and if $\{T(t)\}_{t \geq 0}$ is the semigroup generated by A , then for every $\phi \in X$, $t \geq 0$,
 $T_\epsilon(t)\phi \rightarrow T(t)\phi$, as $\epsilon \downarrow 0$.

Moreover, the convergence is uniform with respect to t in bounded subsets of $(0, \infty)$.

5. DISCUSSION

In the previous two sections we have argued for the essential biological correctness of two simple population models by deriving them through appropriate limit arguments from more realistic and correspondingly more complicated models. Here simple means both relatively easy to handle and relatively parameters sparse. We expect these cases to be exemplary for a general procedure: (i) start imagining how any simplification works out on the level of the individual, (ii) take good care that birth rates keep behaving, (iii) translate the individual behaviour into a structured population model both before and after the simplification, (iv) use the Trotter-Kato theorem to connect the two. The upshot is that our intuition derived from the individual level appears to be essentially correct when applied to the population level, at least when we are careful. To emphasize the latter point we wish to finish with three cautionary notes.

Cautionary note (i)

Our derivations in a sense are still largely metaphorical.

What we mean by this remark is best explained by referring back to the example from section 3. Reproducing in general is much more complicated than just splitting off lumps of biomass. One also has to account for the inherent organization of anything viable. This necessarily leads to more complicated individual state spaces. The following example, adapted with considerable changes (we hope for the better) from EDELSTEIN & HADAR (1983) and CHIPOT & EDELSTEIN (1983), should make clear that a "realistic" representation of the processes on the individual level anyhow entails a very complicated state space, even when reproduction occurs by simply splitting of mass. It is only in the limiting case where the young have become infinitesimally small that the individual state can be efficiently described by size only!

Models cultured in stirred fluid media generally grow in roughly spherical pellets of densely intertwined hyphae. The kinetics of pellet formation can be understood as a balance between diffusion limited growth of pellets, abrasion at the pellet surface, and the "birth" of new pellets from viable fragments among the abrasion products. If we forget about the hyphal structure, the state of an individual pellet is just its "shape", parametrized by a function f of the two angular coordinates ϕ and θ , giving the distance of the center of gravity of the pellet to its surface (or rather an equivalence class of such functions under rigid rotation).

Pellets grow through the local transformation of absorbed nutrients into fungal biomass. The

internal gradient resulting from local absorption and diffusion of nutrients from the surrounding homogeneous medium is very steep. Therefore the accretion of mass effectively happens at the surface and locally is proportional to the available surface area. This already would cause a spherical shape since regions of smallest (or even negative) curvature push out faster.

Abrasion also makes for a spherical shape, but only roughly so. Small lumps of biomass are torn off preferentially at the more exposed "bumps". Locally, however, the detachment of a lump will lead to a distortion of the smooth spherical shape.

In the limit of infinitesimal abrasion fragments the pellets become exactly spherical, i.e. $f(\theta, \phi) = x$, independent of θ or ϕ . The growth component $\delta_g V$ of the size change of a pellet satisfies $\delta_g V \propto S$, where $V \propto x^3$ represents the volume of the pellet and $S \propto x^2$ its surface area. This transforms into $\delta_g x = a$ for some constant a . If we assume that vulnerability to abrasion of a surface element is proportional to the diameter of a pellet, the abrasion component of the size change satisfies $\delta_a V \propto x \cdot S$ or $\delta_a x = -bx$. Therefore $dx/dt = \delta_g x + \delta_a x =: \gamma(x) = a - bx$. (Note that $\gamma(0) = a > 0$! This is a common property of the so-called von Bertalanffy growth laws, a family of growth laws of well documented wide applicability (for $x > 0$).) Finally the production of new pellets of size zero equals

$$C \int_0^{\infty} x^3 n(t, x) dx.$$

Apparently the limiting form of the model can indeed be represented by (1.2), but the biologically justifying preliminary stages are considerably more complicated than the models embodied in (1.3).

Cautionary note (ii)

Our derivation only applies to finite time intervals.

This is inherent in the use of the Trotter-Kato theorem. That this is not just a technical imperfection is shown by the following example.

Consider the cell kinetics model from section 4 except that this time the half width Δ of the support of the distribution d of relative sizes of the daughter cells will play the role of the parameter ϵ in the Trotter-Kato theorem. It is not difficult to show by the same means as before that the limit model corresponds to

$$\frac{\partial}{\partial t} n(t, x) = -\frac{\partial}{\partial x} (g(x)n(t, x)) - b(x)n(t, x) + 4b(2x)n(t, 2x). \quad (5.1)$$

However, when $g(x) = ax$, i.e. individual growth is exponential, the relative size distribution will for $\epsilon > 0$ stabilize for large t (i.e. $n(t, x)/N(t) \rightarrow \tilde{n}(x)$, where $N(t) = \int n(t, x) dx$; see HEIJMANS (1984a)), whereas this is no longer the case for the solution to (5.1). When $\epsilon \downarrow 0$, convergence to the stable distribution becomes slower and slower and in the limit the relative size distribution will remain periodically dependent on time, returning some characteristics of the initial data for ever and ever (see e.g. Chapter II of METZ & DIEKMANN (to appear)).

Clearly the large time behaviour is a subject which has to be considered separately. In the example it is not difficult to show that for $\epsilon \downarrow 0$ the stable size distributions \tilde{n}_ϵ converge to the unique stable (i.e. invariant but not necessarily attractive) size distribution of the limit model. In other cases, but not the present one, also the attractivity property of the stable size distribution is retained. An interesting problem then is whether after discounting for the asymptotic population growth by multiplying the solution with $e^{-r_\epsilon t}$ where r_ϵ is the intrinsic rate of natural increase (dominant eigenvalue) associated with each model, we have uniform convergence for all $t \in (0, \infty)$.

Cautionary note (iii)

As yet the derivations are confined to the linear case, i.e. direct or indirect interactions between individuals are not allowed.

Ultimately we shall wish to prove limit theorems for the nonlinear case as well. After all, the strength of the structured population methodology is that it allows us to incorporate biologically realistic mechanisms for density dependence, like feedback through a limiting of individual growth by food shortage.

Such limit theorems could be of two kinds. Either one could take recourse to direct nonlinear extensions of the Trotter-Kato theorem, (which indeed exist for nonlinear contraction semigroups; see EVANS (1978)) or one could try to use the property that for a given course of the environment the equations of structured population models are always linear, but possibly time inhomogeneous, and combine some extension of the Trotter-Kato theorem to linear time inhomogeneous systems (if such an extension exists) with a construction technique for solutions of structured population equations which explicitly considers the population part of the equations as just a means of generating food consumption in terms of past food availability. However, all this is music of the distant future, as even full proofs of existence and uniqueness theorems for nonlinear structured population equations of any generality are still conspicuously lacking. Only the first hesitating steps towards a proof of an existence and uniqueness theorem for somewhat more general structured population models are being taken at this very moment. Therefore the present paper should only be considered as a first introduction into the fascinating problem of putting a rigorous basis under the structured population methodology.

BIBLIOGRAPHY

- G.I. BELL and E.C. ANDERSON (1967). *Cell growth and division. I. A mathematical model with applications to cell volume distributions in mammalian suspension cultures*. Biophys. J. **7**, 329-351.
- P.L. BUTZER and H. BERENS (1967), *Semigroups of Operators and Approximation*, Springer, Berlin.
- M. CHIPOT and L. EDELSTEIN (1983), *A mathematical theory of size distributions in tissue culture*, J. Math. Biol. **16**, 155-130.
- O. DIEKMANN, H.A. LAUWERIER, T. ALDENBERG and J.A.J. METZ (1983), *Growth, fission, and the stable size distribution*, J. Math. Biol. **18**, 135-148.
- O. DIEKMANN, H.J.A.M. HEIJMANS, and H.R. THIEME (1984), *On the stability of the cell size distribution*, J. Math. Biol. **19**, 227-248.
- L. EDELSTEIN and Y. HADAR (1983), *A model for pellet size distributions in submerged mycelial cultures*, J. Theor. Biol. **105**, 427-452.
- L.C. EVANS (1978), *Application of nonlinear semigroup theory to certain partial differential equations*. In: Nonlinear Evolution Equations, M.G. Crandall (ed), Academic Press, 1978.
- A.G. FREDRICKSON, D. RAMKRISHNA, and H.M. TSUCHIYA (1967), *Statistics and dynamics of pro-caryotic cell populations*, Math. Biosc. **1**, 327-374.
- G. GREINER, J. VOIGT and M. WOLFF (1981), *On the spectral bound of the generator of semigroups of positive operators*, J. Oper. Theor. **5**, 245-256.
- H.J.A.M. HEIJMANS (1984a), *On the stable size distribution of populations reproducing by fission into two unequal parts*, Math. Biosc. **72**, 19-50.
- H.J.A.M. HEIJMANS (1984b), *Holling's "hungry mantid" model for the invertebrate functional response considered as a Markov process. Part III: Stable satiation distribution*, J. Math. Biol. **21**, 115-143.
- H.J.A.M. HEIJMANS (1986), *Structured populations, linear semigroups, and positivity*, Math. Z. **191**, 599-617.
- N.G. VAN KAMPEN (1981), *Stochastic Processes in Physics and Chemistry*, North Holland, Amsterdam.
- T.G. KURTZ (1981), *Approximation of Population Processes*, SIAM, Philadelphia.
- J.A.J. METZ and F.H.D. VAN BATENBURG (1984a,b), *Holling's "hungry mantid" model for the invertebrate functional response considered as a Markov process*.

- Part I: *The full model and some of its limits*, J. Math. Biol. **22**, 209-238,
 Part II: *Negligible handling time*, J. Math. Biol. **22**, 239-257.
- J.A.J. METZ and O. DIEKMANN (to appear) *The Dynamics of Physiologically Structured Populations*, Springer Lect. Notes in Biomathematics.
- L.F. MURPHY (1983), *A nonlinear growth mechanism in size structured population dynamics*, J. Theor. Biol. **104**, 493-506.
- A. PAZY (1983), *Semigroups of Linear Operators and Applications to Partial Differential Equations*, Springer, New York.
- H.H. SCHAEFER (1974), *Banach Lattices and Positive Operators*, Springer, Berlin.
- J.W. SINKO and W. STREIFER (1967), *A new model for age-size structure of a population*, Ecology **48**, 910-918.
- W. STREIFER (1974), *Realistic models in population ecology*, In: A. Mac Fayden (ed.) *Advances in Ecological Research* **8**, 199-266.
- H.F. TROTTER (1958), *Approximation of semigroups of operators*, Pac. J. Math. **8**, 887-919.
- J. VAN SICKLE (1977), *Analysis of a distributed parameter population model based on physiological age*, J. Theor. Biol. **64**, 571-586.

MC NR

51202

ONTVANGEN 2 6 JUNI 1986