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GROWTH, FISSION AND THE STABLE SIZE DISTRIBUTION

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Growth, fission and the stable size distribution*)

by

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ABSTRACT

A model for the growth of a size-structured population reproducing by fission and living under changing (nutrient) conditions is formulated and analysed. It is shown that the dynamics is asymptotically described by an o.d.e. total population model, while the size distribution becomes stationary.

KEY WORDS & PHRASES: *size-dependent population growth, reproduction by fission, balance equation, first order p.d.e., transformed arguments, nutrient limitation*

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*) This report will be submitted for publication elsewhere.

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1. INTRODUCTION

Individuals of a population may be characterized by many different traits such as age, weight, size, sex, color, etc. In a model for the growth of the population one usually leaves these characteristics out of consideration, both because one believes that they have a minor influence on the reproduction process only and because inclusion would make the model intractable.

A distinct exception to this rule is formed by the theory of age-dependent population growth, e.g., Lotka (1922), Keyfitz (1968), Rubinow (1978), Gurtin & MacCamy (1979), Gurney & Nisbet (1980), Prüss (1981), Gyllenberg (1982), Webb (to appear). An obvious reason for the exceptional position of age is formed by the fact that for many populations (including the human!) fertility depends on age in a rather prominent way. From a mathematical point of view too, age has a privileged position among all possible characteristics, since an individual's age increases linearly with time: $\frac{da}{dt} = 1$. A final property of age is that at birth it always has the fixed value zero.

When reproduction occurs by fission it seems appropriate to take account of the "size" of individuals (by which we mean any relevant quantity like weight, nitrate- or phosphate-content, satisfying a physical conservation law) and some new features arise. Firstly, the growth rate of individuals has to be defined (prescribed) and this opens the way to incorporate density dependence, like nutrient limitation, on the basis of a clear, well-defined biological interpretation. Secondly, the conservation law requires a relation between the size of the mother and the size of her progeny and this too makes "size" quite distinct from "age".

In recent work building on older work of Sinko & Streifer (1971) and Bell & Anderson (1967), Diekmann et al. (in preparation) have rigorously shown that in an unlimited environment a population of proliferating cells grows exponentially, while its size-distribution becomes stationary, if a certain condition on the growth rate of individuals (which excludes exponential growth of the individuals; see section 2 for more details) is satisfied. Here we shall pin-point certain assumptions which guarantee that the convergence of the size-distribution will "survive" density

dependence (while, of course, the dynamical behaviour of the total population may differ substantially from exponential growth). Possibly, these assumptions do not describe the characteristics of any "real" population of unicellular organisms. Indeed, some of the subtle differences in the way growth of individuals and reproduction by fission might be combined become very clear in the context of our mathematical formulation and we hope that this will stimulate further discussion and experiments. We welcome all critical comments and suggestions!

The aim of structured population dynamics is to use (known) properties of individuals to describe, understand and predict the dynamical behaviour of the population as a whole (see, however, the discussion in section 6). Here we shall demonstrate a situation in which all relevant information concerning the individuals can be summarized into a few computable numbers (for instance, a dominant positive eigenvalue) which enter into a total population model.

2. SOME ALTERNATIVE SPECIFICATIONS

Let the individuals of a population of cells be characterized by a variable x, which we shall call size. Let $g=g(x)$ denote the rate at which an individual's size increases: $\frac{dx_{individual}}{dt} = g(x_{individual})$. (Possibly g depends on other factors, like food supply, but this is not yet expressed explicitly in our notation.) Let $n=n(t,x)$ denote the (unknown) density function, i.e., $\int_{x_1}^{x_2} n(t,\xi)d\xi$ is the number of cells with size between x_1 and x_2 at time t. Then the effect of the growth of individuals on the change of this density function in time is described by the differential operator (see Sinko & Streifer (1967), Streifer (1974), VanSickle (1977))

$$\frac{\partial}{\partial x}\,(g(x)n(t,x)).$$

So, in the absence of reproduction and mortality, we have the first order partial differential equation (balance equation)

$$\frac{\partial n}{\partial t}\,(t,x) + \frac{\partial}{\partial x}\,(g(x)n(t,x)) = 0. \tag{2.1}$$

One possible description of reproduction by fission is the following. Suppose that each individual which reaches the size 1 (here the one is just a matter of normalization of size) splits instantaneously into two individuals of size $\frac{1}{2}$. Mathematically, this amounts to adding to (2.1) the boundary condition

$$g(\tfrac{1}{2})n(t,\tfrac{1}{2}) = 2g(1)n(t,1). \tag{2.2}$$

Alternatively one can postulate the existence of a function $b=b(x)$, which describes the rate at which cells of size x divide, and replace (2.1) by

$$\frac{\partial n}{\partial t}(t,x) + \frac{\partial}{\partial x}(g(x)n(t,x)) = -b(x)n(t,x) + 4b(2x)n(t,2x) \tag{2.3}$$

(see Sinko & Streifer (1971)), where the right-hand side contains a reproduction-sink term with argument x and a reproduction-source term with argument 2x. When multiplied with x and integrated these terms cancel, as they should because of mass-conservation. This little exercise also explains the factor 4 (it is the product of a factor 2 for the doubling of numbers and a factor 2 for the doubling of intervals; those who originate from splitting in (2x, 2x+2dx) enter into (x, x+dx). (In the present paper we shall always assume that organisms split into two exactly equal parts. In a forthcoming paper H. Heijmans (in preparation) will analyse splitting into unequal parts in a similar spirit.)

Finally, we present a third possibility, which we shall call the stochastic size threshold model. Suppose, as in the first case, that each cell has a predestinated size at which it splits, but that these splitting-sizes may differ from one cell to another. More precisely, we postulate the existence of a function $\gamma=\gamma(x)$ with the property that the chance of an arbitrary cell to split at a size between x_1 and x_2 is given by $\int_{x_1}^{x_2}\gamma(\xi)d\xi$. In the experimental literature this property is usually expressed by saying that size has to cross a stochastic threshold for the fission to occur (see Figure 1). These splitting-sizes are not hereditary; rather one should think of differences in development caused by stochastic variations in the micro-environment.

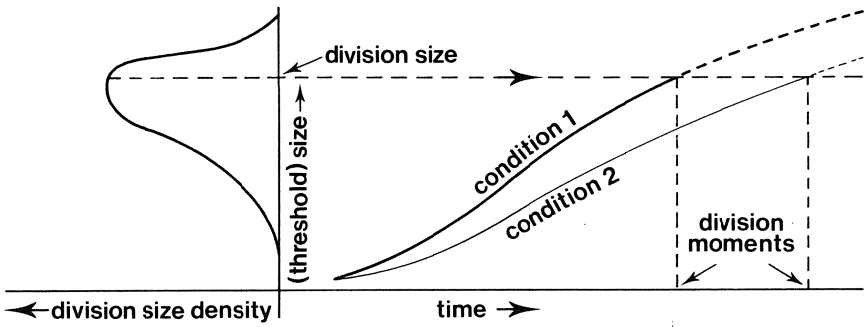

Figure 1.

A graphical representation of the "stochastic size threshold for division" model. Two different growth curves occuring under different conditions are shown, together with the corresponding division moments resulting from a particular selection of the size threshold. The figure immediately demonstrates that the distribution of the times till division will depend on the circumstances but the distribution of the sizes of dividing individuals remains constant by assumption.

In order to calculate a differential generator for n we shall have to express the rate of splitting in terms of γ. To this end we shall follow a cohort (compare Rubinow, 1978). Let α denote the infimum of the support of γ (i.e., the size at which γ starts to be different from zero). From N_0 cells passing size α at t=0

$$N(t) = N_0\left(1 - \int_{\alpha}^{x_{ind.}(t)} \gamma(\xi)d\xi\right)$$

"survive" the time-interval [0,t]. The rate of splitting $\frac{-1}{N(t)}\frac{dN}{dt}(t)$ is given by

$$\left.\frac{\gamma(x)\frac{dx}{dt}}{1-\int_{\alpha}^{x}\gamma(\xi)d\xi}\right|_{x=x_{ind.}(t)}$$

which we rewrite as $\delta(x)g(x)$, where by definition

$$\delta(x) = \frac{\gamma(x)}{1 - \int_{\alpha}^{x}\gamma(\xi)d\xi} \tag{2.4}$$

Note that $\exp -\int_{x_1}^{x_2} \delta(\xi)d\xi$ describes the chance that an arbitrary cell passing size x_1 will reach size x_2 before it splits (this property can be used as an alternative definition of this third model), while g determines how long it takes to grow from x_1 to x_2. In other words, the chance is related to the size-interval which has to be passed, but completely independent of the time needed to realize this passage. Instead of (2.3) we now have

$$\frac{\partial n}{\partial n}(t,x) + \frac{\partial}{\partial x}(g(x)n(t,x)) = -g(x)\delta(x)n(t,x) + 4g(2x)\delta(2x)n(t,2x). \tag{2.5}$$

If g is a function of x only, the equations (2.3) and (2.5) can be identified by putting $b(x) = g(x)\delta(x)$. However, if explicitly of implicitly g depends on time (for instance through food supply which is in some way coupled back to the population itself, see sections 4 and 5 for more details), the equations are quite different. Figure 2 illustrates the basic difference in analogous discrete models. In the extreme case that growth of individuals has stopped completely, (2.3) implies that fission goes on as long as individuals of size x with $b(x) > 0$ are present, whereas (2.5) implies that fission stops at once. Probably these consequences are equally unrealistic and more complicated models, involving both size and age, may be needed to avoid them.

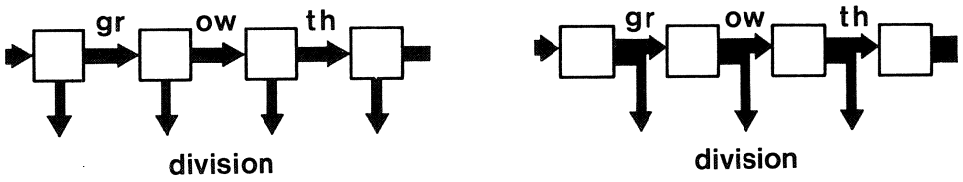

Figure 2.

A graphical representation of two discrete analogues to our second and third model formulation respectively. In the left hand model splitting occurs independent of growth. In the right hand model splitting is entirely dependent on the speed of growth. The two models are equivalent if growth stays constant over time. Otherwise they differ.

For the sake of exposition we have thus far neglected that cells may be removed from the system. In the rest of the paper we add a term $-Dn(t,x)$ to the right-hand side of the equation to account for mortality and dilution (in a chemostat). We assume that D is a constant. The assumption that D does not depend on x is essential for the approach in this paper. However, most of the results can easily be generalized to the case where D depends on time, either explicitly or implicitly.

In the next section we shall summarize some results from Diekmann et al. (in preparation) for the linear, time-invariant case of (2.3) or (2.5). The main result presented will concern the convergence to a stable stationary size distribution under the assumption

DRIG: $\quad g(2x) < 2g(x)$

for all relevant x. Here DRIG abbreviates "Decreasing Relative Individual Growth" and it tells us that two daughters together gain more mass than the undivided mother would have done. One also obtains a stable stationary distribution in the IRIG case $g(2x) > 2g(x)$, but this seems an unrealistic assumption. In the special case of exponential individual growth ($g(x)=kx$) no stable stationary distribution will evolve, however. (See Diekmann et al. (in preparation) for the details.) So throughout the paper we make hypothesis DRIG.

Subsequently, in section 4, we shall study (2.5) under the rather strong assumption that changes in the environment (like food supply) affect the growth rate through a time dependent factor β:

SNH: $\quad g = \beta(t)g(x).$

Here β is a function describing the instantaneous availability of nutrients and SNH is an abbreviation of "Structural Nutrient Hypothesis". This catch phrase stems from the fact that the assumption seems reasonable as a first approximation if the growth rate is limited by the uptake of structural nutrients, as opposed to, for example, energy uptake (the assumption ignores that nutrients may be excreted, or consumed in the basal metabolism). It will turn out that we can reduce the problem to the situation of

section 3 by a scaling of the time axis.

As a next step, in section 5, we shall relate β to the growing population itself by adding a balance equation for the substrate concentration. We shall present two examples and show that the asymptotic behaviour is completely determined by a system of ordinary differential equations (o.d.e.'s), a total population model.

In section 6 we shall summarize our main conclusions.

3. THE STABLE SIZE DISTRIBUTION

In this section we consider the equation

$$\frac{\partial n}{\partial t}(t,x) + \frac{\partial}{\partial x}(g(x)n(t,x)) = -Dn(t,x) - g(x)\delta(x)n(t,x) + 4g(2x)\delta(2x)n(t,2x). \tag{3.1}$$

where D is a nonnegative constant and δ, g are given functions which satisfy, for some number $\alpha \in (0,1)$:

H_δ: δ is a continuous function which vanishes for $x \in [0,\alpha]$ and which is positive for $x \in (\alpha,1)$. Moreover,

$$\lim_{x \uparrow 1} \int_\alpha^x \delta(\xi)d\xi = +\infty .$$

H_g: g is a strictly positive continuous function defined on $[\frac{1}{2}\alpha, 1]$.

So we assume that cells cannot divide before they have reached a minimal size $\alpha > 0$. In order to express that cells with size less than $\frac{1}{2}\alpha$ cannot exist, we supplement (3.1) with the boundary condition

$$n(t,\tfrac{1}{2}\alpha) = 0 . \tag{3.2}$$

Moreover, we assume that cells have to divide before they reach a maximal size, which we have normalized to be 1, and we let the domain of x be the interval $[\frac{1}{2}\alpha,1]$. In equation (3.1) one should read

(3.3) $\quad 4g(2x)\delta(2x)n(t,2x) = 0 \qquad \text{for } x \geq \tfrac{1}{2}\ .$

Finally, we supplement (3.1) and (3.2) with the initial condition

(3.4) $\quad n(0,x) = \phi(x) \qquad , \qquad \tfrac{1}{2}\alpha \leq x \leq 1.$

We shall call ϕ *compatible* if and only if the function

$$\phi(x)\ \exp \int_{\alpha}^{x} \delta(\xi)d\xi$$

is bounded and continuous (note that the former effectively is a condition on the rate at which ϕ should go to zero when x tends to one).

We can rewrite (3.1)-(3.2) abstractly as

(3.5) $\quad \dfrac{dn}{dt} = An - Dn,$

where A is an unbounded linear operator acting on functions of x (see Heijmans (preprint, 1982) or Diekmann et al. (in preparation) for a precise description of the space and the domain of definition of A). For the study of this evolution equation the eigenvalue problem

(3.6) $\quad An = \lambda n$

is of great importance. Heijmans (preprint, 1982) has proved the following result.

THEOREM 3.1

(i) A has a positive, algebraically simple, eigenvalue $\tilde{\lambda}$ with a corresponding eigenfunction $\tilde{n}$ which is positive on $(\tfrac{1}{2}\alpha,1]$.

(ii) All other eigenvalues of A have real part less than $\tilde{\lambda}$.

We shall call $\tilde{\lambda}$ the dominant eigenvalue. Heijmans (preprint, 1982) also shows that whenever $\alpha > \tfrac{1}{2}$, the number $\tilde{\lambda}$ is the unique real root of the *characteristic equation*

$$(3.7)\qquad 2\int_{\alpha}^{1}\delta(\xi)\, e^{-\int_{\frac{1}{2}\xi}^{\xi}(\delta(\eta)+\frac{\lambda}{g(\eta)})d\eta}\, d\xi = 1.$$

The evolution problem (3.5) with $n(0) = \phi$ compatible, has been studied by Diekmann et al. (in preparation). They show that a solution (in an appropriate "mild" sense) exists and is unique. Moreover, concerning the asymptotic behaviour for $t \to +\infty$ the following result was derived

THEOREM 3.2. Assume DRIG: $g(2x)<2g(x)$ for $x \in (\frac{1}{2}\alpha,\frac{1}{2}]$.
Then $n(t,x) = e^{(\tilde{\lambda}-D)t}(C\tilde{n}(x) + o(1))$, for $t \to +\infty$,
where C is a constant depending on ϕ only.

In other words, $\tilde{\lambda}$-D is the Malthusian parameter (intrinsic rate of natural increase) and $\tilde{n}$ the stable size distribution. The proof of this theorem is based on the decomposition of the space of functions of x into a one dimensional subspace X_d (d=dominant) spanned by $\tilde{n}$ and a complementary subspace X_n (n=negligible) which are both invariant under the solution operator of equation (3.5). The fact that the component in X_n is asymptotically negligible indeed, is due to the estimate in Theorem 3.1 (ii). We refer to Thieme (preprints, 1982) for a general approach to the problem of stable distributions.

4. A CHANGING ENVIRONMENT

As a next step we assume

SNH: $g_{individual} = \beta(t)g(x)$,

where g(x) satisfies DRIG: $g(2x) < 2g(x)$. Introducing

$$(4.1)\qquad k(t,x) = e^{Dt}\, n(t,x)$$

we find

$$(4.2)\qquad \frac{dk}{dt} = \beta(t)Ak.$$

In terms of the new time variable

$$\tau = \int_0^t \beta(\sigma)d\sigma \tag{4.3}$$

and

$$m(\tau) = k(t(\tau)) \tag{4.4}$$

we have the time-invariant problem

$$\frac{dm}{d\tau} = Am \ . \tag{4.5}$$

Consequently the results of the foregoing section yield the existence and the uniqueness of a solution as well as the asymptotic behaviour

$$m(\tau,x) = e^{\tilde{\lambda}\tau}\,(C\tilde{n}(x) + o(1)) \qquad , \qquad \tau \to +\infty \ .$$

Hence

$$n(t,x) = e^{-Dt}\, e^{\tilde{\lambda}\int_0^t \beta(\sigma)d\sigma}\,(C\tilde{n}(x) + o(1)), \quad t \to +\infty, \tag{4.6}$$

provided $\int_0^t b(\sigma)d\sigma \to +\infty$ as $t \to +\infty$. We conclude that, essentially, the time-dependent factor β causes a deformation of the time axis only.

There is a more complicated way to arrive at this result which, however, gives additional insight. Substituting

$$n(t,x) = \rho(t)\,\tilde{n}(x) + r(t,x), \tag{4.7}$$

with $r(t,\cdot)$ an element of X_n, into

$$\frac{dn}{dt} = \beta(t)An - Dn$$

we find

$$(\rho'(t) - \tilde{\lambda}\beta(t)\rho(t) + D\rho(t))\tilde{n}(x) = -\left[\frac{dr}{dt} - \beta(t)Ar + Dr\right].$$

The left-hand side belongs to X_d and the right-hand side to X_n (note that A maps X_n into itself). Since the intersection of these subspaces is $\{0\}$, both sides are zero. Consequently, ρ satisfies the o.d.e.

$$\rho'(t) = \tilde{\lambda}\beta(t)\rho(t) - D\rho(t), \tag{4.8}$$

and therefore

$$\rho(t) = \rho(0)\, e^{-Dt + \int_0^t \beta(\sigma)d\sigma}.$$

On the other hand, time scaling and Theorem 3.1(ii) imply that

$$r(t,x) = o\left(e^{-Dt + \int_0^t \beta(\sigma)d\sigma}\right), \qquad t \to +\infty,$$

and we can write

$$n(t,x) = \rho(t)\,\{\tilde{n}(x) + o(1)\}, \qquad t \to +\infty.$$

Note that $r(t,x) = 0$ for all t whenever $r(0,x) = 0$. In other words, if the initial condition is of the special form $n(0,x) = \rho(0)\tilde{n}(x)$ then $n(t,x) = \rho(t)\tilde{n}(x)$ with ρ the solution of the o.d.e. (4.8).

5. FEEDBACK: TWO CONCRETE EXAMPLES

When the growing population itself causes changes in the environment, the function β is not explicitly given, but instead we might have a (differential) equation for β in which a functional of $n(t,\cdot)$ appears. In general, the procedure of section 4 still works. For special initial conditions $n(0,x) = \rho(0)\tilde{n}(x)$ we find an autonomous system of ordinary differential equations. For general initial conditions we can use the (unknown) time variable τ (see (4.3)) to solve the partial differential equation and subsequently find β (and hence τ) from a (non-autonomous) system of ordinary differential equations. The asymptotic formula (4.6) can then be used to show that the ordinary differential system is asymptotically autonomous and this yields, finally, that the phase portrait

of the autonomous problem gives complete information about the asymptotic behaviour. We shall now make this procedure precise, but rather than doing it in general we shall treat two special examples from microbial ecology.

A standard laboratory device that is of great use for experimental investigations in microbial ecology and for the development of theory as well, is the continuous culture or chemostat. The archetype model for the chemostat is (Herbert et al., 1956)

$$\frac{dW}{dt} = p(S)W - DW \tag{5.1}$$

$$\frac{dS}{dt} = - ap(S)W + D(S^r - S), \tag{5.2}$$

where

$W(t)$ = concentration of biomass of the organism,
$S(t)$ = substrate or nutrient concentration,
$p(S)$ = population growth rate as a function of substrate concentration,
D = dilution rate, an adjustable constant,
S^r = input substrate concentration,
a = amount of nutrient per unit biomass (constant).

One easily verifies that $Z := aW + S$ satisfies $\frac{dZ}{dt} = D(S^r - Z)$, and consequently $Z(t) \to S^r$ as $t \to +\infty$. Therefore, as far as the asymptotic behaviour is concerned, we might as well replace the differential equation (5.2) for S by the algebraic equation

$$S(t) = S^r - aW(t). \tag{5.3}$$

Frequently, the function p is modelled as a hyperbola

$$p(S) = \frac{\alpha S}{k + S} \quad , \quad \text{"Monod"} \quad ,$$

but especially with toxic substances more complicated functions may arise. Apart from the wash-out state $S = S^r$, $W = 0$, steady states are found from

$$p(S) = D$$

$$aW + S = S^r,$$

and their stability is determined by the sign of $\frac{dp}{dS}$. Multi-species extensions of one-substrate systems are discussed by, e.g., Powell (1958), Hsu et al. (1977) and Aldenberg (1981). The latter paper also contains an analysis of systems with several potentially limiting nutrients.

The previous description is typical for early work in chemostat models. Williams (1971) is one of the first to make a plea for combining lumped population variables, like total biomass, numbers and nutrient concentration, with distributions of certain properties like age or size within the population. A recent reference showing what information can be gleaned from such more detailed modelling efforts is Voorn (1983).

So let us now study a continuous culture of cells which grow and reproduce according to the model discussed above:

$$\frac{dn}{dt} = \beta(S)An - Dn \tag{5.4}$$

$$S(t) = S^r - \int_{\frac{1}{2}\alpha}^{1} a\xi n(t,\xi)d\xi \ . \tag{5.5}$$

Let $m = m(\tau,x;\phi)$ denote the solution of the initial value problem

$$\frac{dm}{d\tau} = Am \quad , \quad m(0) = \phi .$$

Then, exactly as in section 4, we find

$$n(t,x) = e^{-Dt}\, m(\tau,x;\phi) \ , \tag{5.6}$$

where

$$\tau = \tau(t) = \int_0^t \beta(S(\sigma))d\sigma \tag{5.7}$$

is still to be determined (since S(t) is not known). Differentiating (5.7) and using (5.6) and (5.5) we find

$$(5.8)\qquad \frac{d\tau}{dt} = \beta\,(S^r - ae^{-Dt}\int_{\frac{1}{2}\alpha}^{1} \xi m(\tau,\xi;\phi)d\xi)\ .$$

Under appropriate assumptions on β, equation (5.8) and the initial condition $\tau(0) = 0$ define a unique solution τ. If we take for τ in (5.6) this solution we have come full circle and we have obtained the solution of the initial value problem. Since $\frac{d\tau}{dt} \geq 0$, τ approaches a limit as $t \to +\infty$. If we assume that this limit is finite, (5.8) leads to a contradiction (due to the factor e^{-Dt}) and we conclude that $\tau \to +\infty$. So the known asymptotic behaviour of m implies that

$$(5.9)\qquad n(t,x) = \rho(t)\,\{\tilde{n}(x) + o(1)\} \quad , \qquad t \to +\infty,$$

where the remainder term belongs to X_n. As before we deduce that ρ satisfies the o.d.e.

$$(5.10)\qquad \frac{d\rho}{dt} = (\tilde{\lambda}\beta(S)-D)\rho\ ,$$

where

$$(5.11)\qquad S(t) = S^r - \hat{a}\rho - o(1) \quad , \qquad t \to +\infty,$$

with

$$(5.12)\qquad \hat{a} = a\int_{\frac{1}{2}\alpha}^{1} \xi\tilde{n}(\xi)d\xi\ .$$

Therefore (5.10) is asymptotically autonomous and the asymptotic behaviour is completely described by a total population model of exactly the type (5.1),(5.3). The underlying structured model manifests itself only through the numbers $\tilde{\lambda}$ and $\int_{\frac{1}{2}\alpha}^{1} \xi\tilde{n}(\xi)d\xi$ which can be computed once $g(x)$ and $\delta(x)$ are specified.

In precisely the same way one can reduce structured multi-species multi-substrates systems to total population models. Moreover, one can incorporate refinements as in Droop's (1970) theory.

As a second example let us look at the growth of bacteria which

produce toxic metabolic substances (see, e.g. the papers by Volterra and Kostitzin reproduced in the book (pp. 47-56) by Scudo & Ziegler (1978)). Let q denote the concentration of the toxic chemical and let $\beta(q)$ describe the reduction of the individuals growth rate as a function of q. Let $h(\xi)$ denote the rate at which a cell of size ξ produces the chemical and let σ denote the rate at which the chemical disappears spontaneously by dilution or desintegration. Then

$$(5.13)\qquad \begin{cases} \dfrac{dn}{dt} = \beta(q)\, An - Dn \\ \dfrac{dq}{dt} = \displaystyle\int_{\frac{1}{2}\alpha}^{1} h(\xi)n(t,\xi)d\xi - \sigma q \ . \end{cases}$$

Reasoning exactly as before we find that the asymptotic behaviour is described by the o.d.e. system

$$(5.14)\qquad \begin{cases} \dfrac{d\rho}{dt} = (\tilde{\lambda}\beta(q) - D)\rho \\ \dfrac{dq}{dt} = c\rho - \sigma q \end{cases}$$

with

$$c = \int_{\frac{1}{2}\alpha}^{1} h(\xi)\tilde{n}(\xi)d\xi \ .$$

Under appropriate assumptions on β, $(\bar{q},\bar{\rho}) = (\beta^{-1}(\frac{D}{\tilde{\lambda}}), \frac{\sigma}{c}\beta^{-1}(\frac{D}{\tilde{\lambda}}))$ is a stable steady state. The corresponding eigenvalues are complex conjugated whenever $\sigma^2 + 4\tilde{\lambda}\beta'(\bar{q})\bar{\rho}c < 0$. So one can have an oscillatory approach towards the carrying capacity as is frequently observed (see the papers by Volterra and Kostitzin mentioned before).

We close by referring to Gyllenberg (1982) and Nisbet & Gurney (preprint, 1982) for work which is similar in spirit though different in many details.

6. CONCLUSIONS

There are several ways to model the growth of populations of unicellular organisms reproducing by fission, which live under changing conditions. We have listed several alternatives and we found that in one specific case the dynamics are asymptotically described by o.d.e. total population models, while the size distribution becomes stationary. This case is characterized by the assumption that growth of individuals and reproduction scale with the same factor when conditions change. As a remarkable consequence, the stable size distribution is independent of parameters like the dilution rate and the substrate concentration. It seems likely that other model specifications lead to stable stationary distributions too, but these will certainly depend on such parameters. This may therefore provide an experimental test of the correctness of the stochastic size threshold assumption and the structural nutrient hypothesis.

In this paper asymptotic stability of steady states is determined in two steps: (1) convergence of the size distribution, (2) convergence of total population variables. The time scales of these processes are determined by the roots of characteristic equations (the transcendental equation (3.7) for (1) and a polynomial equation corresponding to the linearization around the steady state for (2)). So, in principle, one can estimate these time scales. But to really carry this out requires a further specification of the model and numerical computations.

Our results rigorously show that the implicit assumption of a stable population structure, which underlies all total population models, is justified in a special class of models for populations which reproduce by fission, at least as far as the asymptotic behaviour is concerned. The transient behaviour also will effectively be determined by the o.d.e. for the total population variables if at least one of the following three conditions holds: (1) the size distribution of the inoculum is sufficiently near the stationary one, (2) the inoculum is sufficiently small so that the stationary size distribution is reached before the total population has grown to an appreciable size, (3) the two time scales discussed above for the convergence to the stable size distribution and the equilibrating

of the total population are sufficiently different, the first being the faster process. It is only when none of these three conditions is fulfilled that the size structure may affect the transient behaviour significantly.

As stated our results enable us to deduce parameters of total population models from properties of individuals. So in the ideal case where we can measure the growth rate of individuals as a function of substrate concentration and, in addition, the fission rate, these could be used to calculate the growth of the total population. Subsequently the model could then be tested by comparing the predicted total population level with the one that is experimentally observed, in accordance with established scientific procedure. Unfortunately, this dream probably will never come true: for micro-organisms, as opposed to, e.g., mammals, dynamic observations are almost always made at the population and not at the individual level. Therefore our main interest should be in the inverse problem. We have seen already how for the chemostat we could test the stochastic size threshold assumption and the structural nutrient hypothesis. When these are confirmed we may use formula (5.10) to deduce that at the steady state

$$\tilde{\lambda}\beta(S) = D.$$

So we can determine $\tilde{\lambda}\beta(S)$ as a function of S by systematically varying D and plotting it against the resulting steady state substrate concentration. (As $\tilde{\lambda}$ enters the subsequent calculations as a scaling parameter only we could without loss of generality set $\tilde{\lambda} = 1$, i.e. $\beta(S) = D$.) As a next step we have to relate the individual growth rate, the division rate and the stable size distribution. To this end we write the growth rate at a particular substrate concentration $\bar{S}$ as $\bar{g}(x) = \beta(\bar{S})g(x)$. In this notation, on multiplying the left and right hand sides with $\beta(\bar{S})$, the eigenvalue equation (3.6) can be written as

$$-\frac{d(\bar{g}\tilde{n})}{dx}(x) - \bar{g}(x)\delta(x)\tilde{n}(x) + 4\bar{g}(2x)\delta(2x)\tilde{n}(2x) = \tilde{\lambda}\beta(\bar{S})\tilde{n}(x) = D\tilde{n}(x).$$

If we know how to measure $\tilde{n}$ this equation can be used to calculate $\bar{g}$ given δ or δ given $\bar{g}$. Alternatively, and perhaps more relevantly, we can relate the moments of the stationary size distribution and the division size

distribution for some simple growth functions in the manner of Voorn (1983). The reason that this is possible at all stems from the fact that for the stochastic size threshold model under the structural nutrient hypothesis the technically more attractive chemostat experiment is essentially equivalent to the mathematically more tractable case of unrestricted population growth.

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