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A size-structured model of bacterial growth and reproduction

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We consider a size-structured bacterial population model in which the rate of cell growth is both size- and time-dependent and the average per capita reproduction rate is specified as a model parameter. It is shown that the model admits classical solutions. The population-level and distribution-level behaviours of these solutions are then determined in terms of the model parameters. The distribution-level behaviour is found to be different from that found in similar models of bacterial population dynamics. Rather than convergence to a stable size distribution, we find that size distributions repeat in cycles. This phenomenon is observed in similar models only under special assumptions on the functional form of the size-dependent growth rate factor. Our main results are illustrated with examples, and we also provide an introductory study of the bacterial growth in a chemostat within the framework of our model.

Keywords: bacterial growth; size structure; stable size distribution; size distribution cycle; average cell size; chemostat

MSC: 35F10; 35F15; 37N25; 46N60; 92D25

1. Introduction

When a bacterial population grows, there are two fundamental types of ‘growth’ that take place: growth in biomass and growth in cell number. The former type of growth results from the increase in mass of individual cells and the latter type results from binary fission. In his pioneering work on bacterial growth, Monod [19] pointed out that

When the average size of cells does not change in the time interval considered, the increase in bacterial density is proportional to the increase in cell concentration. Whether growth is estimated in terms of one variable of the other, the growth rate is the same. However, as established particularly by the classical studies of Henri, the average size of the cells may vary considerably from one phase to another of a growth cycle. It follows that the two variables, cell concentration and bacterial density, are not equivalent. Much confusion has been created because this important distinction has been frequently overlooked.

The benefit gained by ‘overlooking’ the distinction between biomass and cell number is that this simplification allows for the formulation of tractable mathematical models in which the state of a population can be described by a single time-dependent variable. Such models essentially view the population as a single ‘blob’ whose mass (or some other particular characteristic) is continuously

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changing. Models that do distinguish between growth in biomass and growth in cell number must include separate mechanisms for describing cell growth and fission. Such *size-structured* models were first developed by Sinko and Streifer [22,23], Bell [3] and Bell and Anderson [4] and were later modified and investigated extensively by Diekmann *et al.* [7,8] and Metz and Diekmann [17].

The model that we develop and analyse in this paper is a size-structured model that is similar to the model studied in [7,8,17]. The major difference is that our model contains a balance law (a linear partial differential equation) that describes only the cell growth process. The reproductive process is described by a parameter, q , which we call the per capita reproductive quota, and which is introduced as a boundary condition to accompany the balance law. In contrast, both the growth and reproductive processes are described by a single balance law in the model studied in [7,8,17]. The different modelling approach that we use is found to result in different dynamics. We find that the cell size distributions that occur in all solutions of our model repeat in cycles, whereas the generic behaviour of solutions of the model in [7,8,17] is the convergence of all solutions to a stable size distribution (with cyclic distributions occurring only under certain assumptions on the cell growth rate). The different dynamics that we find at the distribution level also results in different dynamics at the overall population level. In particular, we find that, in accordance with the observations of Monod given above, our model admits solutions for which the average cell size does not remain constant (or approach a constant value as $t \rightarrow \infty$).

The remainder of this paper is organized as follows. In Section 2, we formulate our model and make some preliminary observations. The general solution of the model is constructed in Section 3, and the behaviour of the general solution is described in terms of the model parameters in Section 4. Two examples that illustrate our results are provided in Section 5. In Section 6, we adapt our model to a chemostat setting and provide a preliminary analysis of this chemostat model. A summary and discussion that compares our model to the model studied in [7,8,17] is given in Section 7.

2. Formulation of the model

To formulate our model of bacterial growth and reproduction, we begin by assuming that all cells in the population are born with size $m > 0$ and grow to size $2m$, at which point they undergo fission. We also assume that cell growth takes place according to a law of the form

$$x'(t) = f(t)g(x(t)), \quad (1)$$

where x denotes the cell size. To model the reproductive process, we assume that the average number of viable daughter cells produced by each mother cell is constant throughout time. Since each mother cell produces either 2 or 1 or 0 daughter cells that will eventually themselves become mother cells, we assume that this constant, q , satisfies $0 < q \leq 2$ (with the typical case being $q = 2$). In addition, we assume that cells are removed from the population at a constant per capita rate $D \geq 0$. This assumption is valid, for example, in a chemostat setting in which the natural (size- and age-specific) death rates of bacterial cells are regarded as being negligible in comparison with the removal (washout) rate. The terminology that we will use and our model hypotheses are formally stated as follows:

(H_m) The *minimum cell size*, m , satisfies $m > 0$.

(H_g) The *size-dependent growth factor*, $g : [m, 2m] \rightarrow [a, b]$, where $0 < a < b$ is of class C^1 .

(H_f) The *time-dependent growth factor*, $f : [0, \infty) \rightarrow [\alpha, \beta]$, where $0 < \alpha < \beta$ is continuous.

(H_q) The *per capita reproductive quota*, q , satisfies $0 < q \leq 2$.

(H_D) The *per capita removal rate*, D , satisfies $D \geq 0$.

Throughout our work, we will use the term ‘size’ to mean cell biomass. Thus m and x have units of mass. In addition, we will assume that g has units of mass and that f has units of time^{-1} . In H_q , the term ‘per capita’ refers to the average number of daughters produced per mother and hence q has units of number/number (or no units). In H_D , the term ‘per capita’ refers to the percentage of the population that is removed per unit of time and thus D has units of $(\text{number/number})(\text{time}^{-1}) = \text{time}^{-1}$.

Equation (1) together with hypotheses H_g and H_f implies that a cell that is born with size m at a given time t will (if it is viable and is not removed from the population) reach size $2m$ and undergo fission at time t^* where

$$\int_t^{t^*} f(w) \, dw = \int_m^{2m} \frac{du}{g(u)} := G.$$

Hypothesis H_f guarantees that the lifespan, $t^* - t$, of any cell is bounded above by $G/\alpha < \infty$ and bounded below by $G/\beta > 0$. In addition, we note that H_f and H_g are very non-restrictive on the functional forms that can be assumed by the time-dependent and size-dependent growth factors.

As is customary, we define $\rho(t, x)$ to be the density with respect to the cell size, x , of the population at time t . Thus ρ has units of number/mass. We take the domain of ρ to be the closed set $\Omega = [0, \infty) \times [m, 2m]$. At any time $t \geq 0$, the total number of cells in the population, $P(t)$, and the total biomass of the population, $B(t)$, are

$$P(t) = \int_m^{2m} \rho(t, x) \, dx, \quad B(t) = \int_m^{2m} x\rho(t, x) \, dx.$$

By incorporating H_m – H_D , we obtain the model

$$f(t)(g(x)\rho(t, x))_x + \rho_t(t, x) + D\rho(t, x) = 0, \quad (t, x) \in \Omega, \quad (2a)$$

$$g(m)\rho(t, m) = qg(2m)\rho(t, 2m), \quad t \geq 0, \quad (2b)$$

$$\rho(0, x) = \phi(x), \quad x \in [m, 2m]. \quad (2c)$$

Equation (2a), which gives a balance law for cell growth and removal, can be derived using the approach of Diekmann *et al.* [8, p. 247]. These authors give the derivation in the case that the cell growth rate depends only on cell size, x , and not explicitly on t , but their derivation is easily modified to yield Equation (2a) in the non-autonomous case. The balance law derived in [8] also includes terms that account for removal of larger cells and creation of smaller cells due to fission, but we do not include these terms because the reproductive process in our model is described completely by the boundary condition (2b), for which we provide a derivation in the appendix. The initial size distribution, ϕ , is assumed to be a function of class C^1 with $\phi(x) \geq 0$ for all $x \in [m, 2m]$. Throughout this paper, the term ‘distribution’ will always refer to a function of this class.

Our objective is to describe the behaviour of all solutions of model (2). We will investigate the behaviour of solutions at both the *population level* and the *distribution level*. By behaviour at the population level, we mean the evolution over time of the total population, P , and the total biomass, B . By behaviour at the distribution level, we mean the evolution over time of the size distributions, $\rho(t, \cdot)$, where for each $t \geq 0$, $\rho(t, \cdot)$ is the distribution that has value $\rho(t, x)$ for each $x \in [m, 2m]$.

2.1. Some basic observations

If ρ is a positive-valued solution of model (2), then

$$P'(t) = \int_m^{2m} \rho_t(t, x) dx = f(t)g(m)\rho(t, m) - f(t)g(2m)\rho(t, 2m) - DP(t)$$

and by Equation (2b)

$$P'(t) = (q - 1)f(t)g(2m)\rho(t, 2m) - DP(t).$$

Two immediate (and reasonable) implications of the above equation are that (1) the number of cells in the population decreases monotonically to zero if $q < 1$ or if $q = 1$ and $D > 0$ and (2) the population remains constant if $q = 1$ and $D = 0$.

In addition, the biomass satisfies

$$B'(t) = \int_m^{2m} x\rho_t(t, x) dx = -f(t) \int_m^{2m} x(g(x)\rho(t, x))_x dx - DB(t)$$

and by integration by parts and Equation (2b), we obtain

$$B'(t) = f(t) \int_m^{2m} g(x)\rho(t, x) dx - (2 - q)mf(t)g(2m)\rho(t, 2m) - DB(t).$$

The first term on the right of the above equation accounts for the increase in biomass due to cell growth, the second term accounts for the change in biomass due to fission, and the final term accounts for removal. The second term is zero if $q = 2$ because biomass is conserved during the fission process in this case.

3. The general solution

To set the stage for constructing the general solution of model (2), we define

$$G := \int_m^{2m} \frac{du}{g(u)}, \quad A_f(t) = \frac{1}{t} \int_0^t f(w) dw.$$

Our construction of the general solution proceeds in three stages: (1) we transform the model by making a change of variables. (2) We identify an important family of solutions that correspond to invariant size distributions and analyse the behaviour of this family of solutions. (3) We construct the general solution in terms of the transformed variables and then translate back to the original variables.

3.1. Change of variables

Model (2) can be simplified by introducing new variables, τ and ξ , defined as

$$\tau = \int_0^t f(w) dw, \quad \xi = \int_m^x \frac{du}{g(u)}$$

and by then defining a new density function

$$\sigma(\tau, \xi) = e^{D\tau} g(x)\rho(t, x), \quad \tau \geq 0, \quad \xi \in [0, G].$$

Since $dt/d\tau = 1/f(t)$, $dx/d\xi = g(x)$, $\tau(0) = 0$, $\xi(m) = 0$, and $\xi(2m) = G$, it can be seen that σ satisfies

$$\sigma_\xi(\tau, \xi) + \sigma_\tau(\tau, \xi) = 0, \quad \tau \geq 0, \quad \xi \in [0, G], \tag{3a}$$

$$\sigma(\tau, 0) = q\sigma(\tau, G), \quad \tau \geq 0, \tag{3b}$$

$$\sigma(0, \xi) = (g\phi)(x(\xi)) := \psi(\xi), \quad \xi \in [0, G]. \tag{3c}$$

In Equation (3c), we have used the notation $(g\phi)(x(\xi))$ to denote the product $g(x(\xi))\phi(x(\xi))$. This abbreviated notation will be used throughout the remainder of the paper.

3.2. Invariant size distributions

We say that a distribution $\psi \geq 0$ is an *invariant size distribution* (or, for brevity, an *invariant distribution*) on $[0, G]$ if system (3) admits a solution of the form $\sigma(\tau, \xi) = T(\tau)\psi(\xi)$. Clearly $\psi \equiv 0$ is an invariant distribution. By separation of variables, we find that any non-zero invariant distribution must satisfy

$$-\frac{\psi'(\xi)}{\psi(\xi)} = \frac{T'(\tau)}{T(\tau)} = \gamma,$$

for some constant γ . Hence, $\psi(\xi) = Ke^{-\gamma\xi}$, where $K \neq 0$ and γ is such that

$$\psi(0) = q\psi(G) \Leftrightarrow \gamma = \gamma^* := \frac{\ln(q)}{G}.$$

The solutions of Equation (3) corresponding to invariant distributions are thus given for arbitrary $K \geq 0$ by

$$\sigma(\tau, \xi) = K \exp(\gamma^*(\tau - \xi)), \quad \tau \geq 0, \quad \xi \in [0, G],$$

or by $\sigma(\tau, \xi) = T(\tau)\psi(\xi)$, where

$$\psi(\xi) = K \exp\left(-\frac{\ln(q)}{G}\xi\right), \tag{4a}$$

$$T(\tau) = \exp\left(\frac{\ln(q)}{G}\tau\right). \tag{4b}$$

In terms of the original variables from model (2), solutions corresponding to invariant distributions can be expressed as

$$\rho(t, x) = \frac{e^{-Dt}\sigma(\tau, \xi)}{g(x)} = \frac{Ke^{-Dt}}{g(x)} \exp\left(\gamma^*\left(\int_0^t f(w) dw - \int_m^x \frac{du}{g(u)}\right)\right)$$

or, alternatively, as $\rho(t, x) = \pi(t)\phi(x)$, where

$$\phi(x) = \frac{K}{g(x)} \exp\left(-\gamma^* \int_m^x \frac{du}{g(u)}\right), \tag{5a}$$

$$\pi(t) = \exp((\gamma^* A_f(t) - D)t). \tag{5b}$$

Since the total population at time t is

$$P(t) = \pi(t) \int_m^{2m} \phi(x) dx,$$

it can be seen from Equation (5b) that

$$P(t)(\langle, =, \rangle)P(0)$$

depending (respectively) on whether

$$\gamma^* A_f(t)(\langle, =, \rangle)D.$$

Clearly, the function f plays a prominent role in determining the population-level behaviour. Depending on f , the population might grow without bound, decay to zero, or persist in the sense that

$$0 < \underline{\lim}_{t \rightarrow \infty} P(t) \leq \overline{\lim}_{t \rightarrow \infty} P(t) < \infty.$$

Persistence can occur (but is not assured to occur) only if $\lim_{t \rightarrow \infty} A_f(t) = DG/\ln(q)$. When viewed at the population level, model (2) is essentially a non-autonomous model with f as the ‘forcing’ or ‘control’ factor.

At the distribution level, Equation (5a) implies that ϕ can have an extremum at any value of x , where $g'(x) = -\gamma^* = -\ln(q)/G$. It is thus clearly possible to construct functions, g , for which ϕ has one or more extrema in $[m, 2m]$. This observation is relevant to solving the ‘inverse problem’ of finding appropriate g (and other model parameters) that will fit a given empirically observed distribution. Solving the inverse problem has been found to be problematic in some other size-structured bacterial population models. For example, the model of Cushing [6] discussed in Smith and Waltman [26, Chapter 9] was shown to admit only monotone-decreasing invariant distributions and this precluded being able to fit the model to the unimodal invariant distributions observed in the experiments of Williams [28]. In the present model, the size-dependent growth factor, $g(x)$, can be reconstructed directly from the invariant distribution, $\phi(x)$, by solving Equation (5a):

$$g(x) = \frac{K - \gamma^* \int_m^x \phi(u) du}{\phi(x)}.$$

3.3. The general solution

Any solution, $\sigma(\tau, \xi)$, of Equation (3a) remains constant along the characteristic curves $\tau = \xi + \text{Const}$. If $\sigma(\tau, \xi)$ also satisfies Equation (3b), then for all $\tau \geq 0$, we have

$$\lim_{\epsilon \rightarrow 0_+} \sigma(\tau + \epsilon, \epsilon) = q \lim_{\epsilon \rightarrow 0_+} \sigma(\tau - \epsilon, G - \epsilon).$$

Hence, in order to obtain classical solutions of system (3) on the strip $[0, \infty) \times [0, G]$, we find it to be convenient to first construct solutions that exist globally for all $\tau \geq 0$ and all $\xi \in R$. To do this, we first require that the initial distribution, ψ , in Equation (3c) satisfies the compatibility conditions

$$\psi(0) = q\psi(G), \tag{6a}$$

$$\psi'(0) = q\psi'(G), \tag{6b}$$

and we then extend ψ to the entire real line by defining

$$\psi_q(\xi - nG) = q^n \psi(\xi), \quad \xi \in [0, G), \quad n \in Z.$$

The general solution can then simply be expressed as

$$\sigma(\tau, \xi) = \psi_q(\xi - \tau), \quad \tau \geq 0, \quad \xi \in R.$$

By construction, the restriction of σ to the strip $[0, \infty) \times [0, G]$ is a solution of Equation (3).

Now we can express the general solution in terms of the original variables. Since $\psi(\xi) = (g\phi)(x(\xi))$ and $dx/d\xi = g(x(\xi))$, the compatibility conditions (6) correspond to the following compatibility conditions for ϕ :

$$(g\phi)(m) = q(g\phi)(2m), \tag{7a}$$

$$(g(g\phi)')(m) = q(g(g\phi)')(2m). \tag{7b}$$

At this point, we introduce two auxiliary extensions. We let $g_m(x)$ be the m -periodic extension of g from $[m, 2m)$ onto R . We also extend the initial distribution, ϕ , by defining $\phi_q(x - nm) = \phi^n(x)$ for all $x \in [m, 2m)$ and all $n \in Z$. The (global) characteristics now take the form

$$\int_0^t f(w) dw - \int_m^x \frac{du}{g_m(u)} = \text{Const.} \tag{8}$$

These characteristics are continuous, but not necessarily smooth since the extension g_m may have jump discontinuities at $x = nm, n \in Z$. Furthermore, due to the m -periodicity of g_m , any translate of a characteristic by m units in the x -direction is another characteristic.

Let $X(t, x)$ be the point of intersection of the characteristic passing through (t, x) with the x -axis. Due to Equation (8), $X(t, x)$ must satisfy

$$\int_0^t f(w) dw = \int_{X(t,x)}^x \frac{du}{g_m(u)}$$

and hence $X(t, x)$ is determined uniquely. It is also clear that $X(t, x)$ is an increasing function of x , a decreasing function of t , and that $X(t, x) < x$ for all $t > 0$. In terms of $X(t, x)$, the general solution of Equation (2) can be expressed as

$$\rho(t, x) = \frac{(\phi_q g_m)(X(t, x))}{g_m(x)} e^{-Dt}. \tag{9}$$

We note that although the solution (9) is defined globally (for all $t \geq 0$ and all $x \in R$), its restriction to the set $\Omega = [0, \infty) \times [m, 2m]$ is the solution of Equation (2) with initial distribution ϕ . This solution is classical if and only if the compatibility conditions (7) are satisfied.

4. Behaviour of solutions

We are now prepared to study the population and distribution-level behaviour of all solutions of Equation (2). Throughout the remainder, we assume that the initial distribution, ϕ , satisfies the compatibility conditions (7) and hence that ρ , as defined by Equation (9), satisfies Equation (2) in the classical sense throughout Ω .

4.1. Population-level dynamics

In Section 3.2, it was seen that solutions of Equation (2) that correspond to invariant distributions have the form $\rho(t, x) = \pi(t)\phi(x)$, where

$$\pi(t) = \exp\left(\left(\frac{\ln(q)}{G} A_f(t) - D\right)t\right).$$

In this section, we will show that $\pi(t)$ governs the dynamics of the total population for all solutions of Equation (2).

The total population is given by

$$P(t) = \int_m^{2m} \rho(t, x) dx = e^{-Dt} \int_m^{2m} \frac{\sigma(\tau, \xi)}{g(x)} dx = e^{-Dt} \int_0^G \sigma(\tau, \xi) d\xi,$$

since $dx/d\xi = g(x)$. By the definition of $\tau = tA_f(t)$, we have that

$$\pi(t) = \exp\left(\frac{\ln(q)}{G}\tau - Dt\right) = q^{(\tau/G)}e^{-Dt}.$$

Hence, we can express the ratio $P(t)/\pi(t)$ as

$$\frac{P(t)}{\pi(t)} = q^{-\tau/G} \int_0^G \sigma(\tau, \xi) d\xi = q^{-(\tau/G)} \int_0^G \psi_q(\xi - \tau) d\xi.$$

THEOREM 1 *Let ρ be the solution of Equation (2) corresponding to the initial distribution ϕ and*

$$P(t) = \int_m^{2m} \rho(t, x) dx > 0, \quad B(t) = \int_m^{2m} x\rho(t, x) dx > 0.$$

Then

(i) For all $t \geq 0$,

$$\min(q, q^{-1})P(0) \leq \frac{P(t)}{\pi(t)} \leq \max(q, q^{-1})P(0). \quad (10)$$

(ii) If $q \neq 1$, the ratio $P(t)/\pi(t)$ remains constant if and only if the solution ρ corresponds to an invariant distribution. If $q = 1$, the ratio $P(t)/\pi(t)$ remains constant for all solutions of Equation (2).

(iii) For all $t \geq 0$,

$$\frac{1}{2} \min(q, q^{-1})B(0) \leq \frac{B(t)}{\pi(t)} \leq 2 \max(q, q^{-1})B(0). \quad (11)$$

Proof First we will prove claim (i) in the case $q \geq 1$: let $\tau = nG + \tau_0$, where $\tau_0 \in [0, G)$ and n is a non-negative integer. Since $\psi_q(\xi - G) = q\psi_q(\xi)$ for all $\xi \in R$, we observe that

$$\begin{aligned} \int_0^G \psi_q(\xi - \tau_0) d\xi &= \int_{-\tau_0}^0 \psi_q(\xi) d\xi + \int_0^{G-\tau_0} \psi_q(\xi) d\xi \\ &= q \int_{G-\tau_0}^G \psi_q(\xi) d\xi + \int_0^{G-\tau_0} \psi_q(\xi) d\xi. \end{aligned}$$

Thus, since $q \geq 1$ and $P(0) = \int_0^G \psi_q(\xi) d\xi$, we obtain

$$P(0) \leq \int_0^G \psi_q(\xi - \tau_0) d\xi \leq qP(0). \quad (12)$$

Next, since $q^n \psi_q(\xi - \tau_0) = \psi_q(\xi - \tau)$ for all $\xi \in R$, we observe that

$$q^{-\tau_0/G} \int_0^G \psi_q(\xi - \tau_0) d\xi = q^{-(\tau/G)} \int_0^G \psi_q(\xi - \tau) d\xi = \frac{P(t)}{\pi(t)}$$

and since $q^{-1} \leq q^{-\tau_0/G} \leq 1$, we thus have

$$q^{-1} \int_0^G \psi_q(\xi - \tau_0) d\xi \leq \frac{P(t)}{\pi(t)} \leq \int_0^G \psi_q(\xi - \tau_0) d\xi. \tag{13}$$

By combining Equations (12) and (13), we obtain

$$q^{-1} P(0) \leq \frac{P(t)}{\pi(t)} \leq q P(0)$$

which completes the proof of claim (i) in the case $q \geq 1$. A similar argument shows that (i) also holds when $q < 1$.

To prove claim (ii), we first note that the second assertion of (ii) follows immediately from Equation (10). Hence, we will assume that $q \neq 1$. For any solution, σ , that corresponds to an invariant distribution, ψ , of Equation (3), we have by Equation (4a) and the definition of ψ_q that $\psi_q(\xi) = K \exp(-(\ln(q)/G)\xi)$. Therefore

$$\frac{P(t)}{\pi(t)} = q^{-\tau/G} \int_0^G K \exp\left(-\frac{\ln(q)}{G}(\xi - \tau)\right) d\xi = K \int_0^G \exp\left(-\frac{\ln(q)}{G}\xi\right) d\xi$$

remains constant for all $t, \tau \geq 0$. To prove the converse, suppose that ψ is such that

$$q^{-\tau/G} \int_0^G \psi_q(\xi - \tau) d\xi = \text{Const.}$$

Then, by differentiation, we find that

$$-\frac{\ln(q)}{G} \int_0^G \psi_q(\xi - \tau) d\xi + \psi_q(-\tau) - \psi_q(G - \tau) = 0$$

holds for all $\tau \geq 0$. Substituting $\psi_q(-\tau) = q\psi_q(G - \tau)$ and differentiating one more time, we obtain

$$(q - 1)\psi'_q(G - \tau) = -(q - 1)\frac{\ln(q)}{G}\psi_q(G - \tau), \quad \tau \geq 0,$$

which, since $q \neq 1$, implies that $\psi_q(\xi) = K \exp(-(\ln(q)/G)\xi)$, $\xi \leq G$, is an invariant distribution.

To complete the proof, we note that claim (iii) follows immediately from Equation (10) and the fact that $mP(t) \leq B(t) \leq 2mP(t)$ for all $t \geq 0$. ■

Theorem 1 tells us that the population-level behaviour of all solutions of Equation (2) is determined by the time evolution of $\pi(t)$, which is in turn determined by the parameters f, g, q , and D . If these parameters are such that $\pi(t) \rightarrow 0(\infty)$ as $t \rightarrow \infty$, then also $P(t) \rightarrow 0(\infty)$ as $t \rightarrow \infty$. If $\pi(t)$ is bounded, then so is $P(t)$, and we obtain an estimate on its bounds in terms of m, g, q , and ϕ . Since $\pi(t)$ does not depend on ϕ , the population-level behaviour of all solutions is qualitatively the same (not dependent on the initial size distribution). In many models of structured population dynamics, the distribution-level behaviour of all solutions is also found to be the same in that all solutions are seen to converge to an invariant distribution as $t \rightarrow \infty$. In what follows, we will see that this behaviour does not occur in model (2).

4.2. Distribution-level dynamics

It will now be shown that the size distributions of all solutions of Equation (2) occur in cycles. Since $\psi_q(\xi - G) = q\psi_q(\xi)$ for all $\xi \in R$, we have

$$\sigma(\tau + G, \xi) = \psi_q(\xi - \tau - G) = q\psi_q(\xi - \tau) = q\sigma(\tau, \xi)$$

for all $\tau \geq 0$ and $\xi \in R$. It follows that

$$\begin{aligned} \rho(t(\tau + G), x(\xi)) &= \frac{e^{-Dt(\tau+G)}\sigma(\tau + G, \xi)}{g(x(\xi))} \\ qe^{D(t(\tau)-t(\tau+G))} \frac{e^{-Dt(\tau)}\sigma(\tau, \xi)}{g(x(\xi))} &= qe^{D(t(\tau)-t(\tau+G))}\rho(t(\tau), x(\xi)). \end{aligned}$$

Equivalently,

$$\frac{\rho(t(\tau + G), x)}{\rho(t(\tau), x)} = qe^{D(t(\tau)-t(\tau+G))}.$$

We recall that by definition of $t(\tau)$,

$$G = (\tau + G) - \tau = \int_0^{t(\tau+G)} f(w) \, dw - \int_0^{t(\tau)} f(w) \, dw = \int_{t(\tau)}^{t(\tau+G)} f(w) \, dw.$$

The above observations can be summarized in the following statement.

THEOREM 2 *If ρ is a solution of Equation (2) and $0 \leq t_1 < t_2$ are such that*

$$\int_{t_1}^{t_2} f(w) \, dw = G,$$

then $\rho(t_2, \cdot) \sim \rho(t_1, \cdot)$, meaning that there exists a constant $C > 0$ such that $\rho(t_2, x) = C\rho(t_1, x)$ for all $x \in [m, 2m]$.

Theorem 2 tells us that, for any given compatible ϕ , all possible size distributions that are achieved by the corresponding solution of Equation (2) occur in the interval $[0, t(G))$. These same distributions then occur again (in the sense of equivalence) in each of the intervals $[t(nG), t((n + 1)G))$. In particular, no solutions converge to invariant distributions (other than those solutions that actually correspond to invariant distributions). Furthermore, for a given ϕ , the actual size distributions that occur do not depend on f but the frequencies with which these distributions repeat themselves do depend on f . If f_1 and f_2 are two different functions (both satisfying H_f) and ρ_1 and ρ_2 are the corresponding solutions of Equation (2) with $\rho_1(0, \cdot) = \rho_2(0, \cdot) = \phi$, then for any $t \geq 0$, we will have $\rho_2(t^*, \cdot) \sim \rho_1(t, \cdot)$ for infinitely many $t^* \geq 0$. However, the population-level behaviour (growth, decay, or boundedness) of ρ_1 and ρ_2 might differ greatly depending on the behaviour of f_1 and f_2 .

5. Examples

To illustrate the results given in Sections 3 and 4, we now consider two examples. In each of these examples, we assume that $f(t)$ is constant for all $t \geq 0$. Each example could easily be modified to allow other choices of $f(t)$, but we do not do so here for the sake of brevity.

5.1. Size-proportional growth rate

Assume that cells grow according to $x'(t) = kx$, where $k > 0$ is constant. In this case, we can take $f(t) = k$ and $g(x) = x$ to obtain

$$\tau = \int_0^t k \, dw = kt, \quad \xi = \int_m^x \frac{du}{u} = \ln(x/m), \quad G = \int_m^{2m} \frac{du}{u} = \ln(2), \quad \gamma^* = \frac{\ln(q)}{\ln(2)}.$$

The invariant distributions for system (3) are

$$\psi(\xi(x)) = K \exp(-\gamma^* \ln(x/m)) = K \left(\frac{m}{x}\right)^{\gamma^*} = K \left(\frac{m}{x}\right)^{\ln(q)/\ln(2)},$$

and the corresponding invariant distributions for system (2) are

$$\phi(x) = K \frac{\psi(\xi(x))}{x} = \frac{K}{m} \left(\frac{m}{x}\right)^{(\ln(q)/\ln(2))+1}.$$

These invariant distributions are monotone increasing if $q < 1/2$, monotone decreasing if $q > 1/2$, and constant if $q = 1/2$. Thus, there are no ‘exotic’ invariant distributions when a size-proportional growth rate is assumed.

The compatibility conditions (7) from which classical solutions of Equation (2) can be constructed are

$$\begin{aligned} \phi(m) &= 2q\phi(2m), \\ \phi'(m) &= 4q\phi'(2m), \end{aligned}$$

and the exponential growth factor is

$$\pi(t) = \exp\left(\left(\frac{\ln(q)}{\ln(2)}k - D\right)t\right).$$

By Theorem 1 we obtain

- (1) If $k \ln(q) < D \ln(2)$, then $\lim_{t \rightarrow \infty} P(t) = 0$.
- (2) If $k \ln(q) > D \ln(2)$, then $\lim_{t \rightarrow \infty} P(t) = \infty$.
- (3) If $k \ln(q) = D \ln(2)$ (implying that $q \geq 1$), then

$$q^{-1}P(0) \leq P(t) \leq qP(0), \quad t \geq 0.$$

To investigate statement 3 a bit further, we will show that the critical case $k \ln(q) = D \ln(2)$ does not imply that either the population, $P(t)$, or the biomass, $B(t)$, remains constant. In fact, we will show that both $P(t)$ and $B(t)$ are periodic functions of period $\ln(2)/k$ which are, in general, not constant.

As we did previously, it is more convenient to work with P and B as functions of τ :

$$P(\tau) = q^{-\tau/G} \int_0^G \psi_q(\xi - \tau) \, d\xi, \quad B(\tau) = m q^{-\tau/G} \int_0^G e^\xi \psi_q(\xi - \tau) \, d\xi.$$

We find immediately that

$$\begin{aligned} P(\tau + G) &= q^{-(\tau/G)-1} \int_0^G \psi_q(\xi - \tau - G) \, d\xi \\ &= q^{-(\tau/G)-1} \int_0^G q \psi_q(\xi - \tau) \, d\xi = P(\tau), \end{aligned}$$

and similarly, we have that $B(\tau + G) = B(\tau)$ for all $\tau \geq 0$. In addition, by Theorem 2 and due to the fact that $t = \tau/k$, we conclude that $P(t)$ and $B(t)$ are both periodic of period $G/k = \ln(2)/k$.

Assuming that $q \neq 1$ (and hence $D \neq 0$), we obtain from part (ii) of Theorem 1 that $P(t)$ does not remain constant unless ϕ is an invariant distribution. A similar argument, which requires the assumption that $k \neq D$ and $q \neq 2$, shows that $B(t)$ does not remain constant unless ϕ is an invariant distribution. The two subcases of the critical case which have to be checked separately are (1) $q = 1$, $D = 0$ and (2) $q = 2$, $k = D$. In the former subcase, $P(t)$ remains constant and $B(t)$ is periodic (and not constant unless ϕ is an invariant distribution). In the latter subcase, $B(t)$ remains constant and $P(t)$ is periodic (and not constant unless ϕ is an invariant distribution).

5.2. Constant growth rate

If cells grow according to $x'(t) = a$ (where $a > 0$ is constant), then we can take $f(t) = 1$ and $g(x) = a$. In this case,

$$\tau = \int_0^t dw = t, \quad \xi = \int_m^x \frac{du}{a} = \frac{x-m}{a}, \quad G = \int_m^{2m} \frac{du}{a} = \frac{m}{a}, \quad \gamma^* = \frac{a \ln(q)}{m}.$$

The invariant distributions of Equations (3) and (2), respectively, are

$$\psi(\xi(x)) = K \exp\left(-\gamma^* \frac{x-m}{a}\right) = K q^{(m-x)/m}, \quad \phi(x) = \frac{K}{a} q^{(m-x)/m}.$$

These invariant distributions are monotone increasing if $q < 1$, monotone decreasing if $q > 1$, and constant if $q = 1$. Thus, as in the previous example, there are only monotone invariant distributions.

In addition, the compatibility conditions are

$$\begin{aligned} \phi(m) &= q\phi(2m), \\ \phi'(m) &= q\phi'(2m), \end{aligned}$$

and the exponential growth factor is

$$\pi(t) = \exp\left(\left(\frac{a \ln(q)}{m} - D\right)t\right).$$

By Theorem 1, the population-level behaviour of solutions is

- (1) If $a \ln(q) < Dm$, then $\lim_{t \rightarrow \infty} P(t) = 0$.
- (2) If $a \ln(q) > Dm$, then $\lim_{t \rightarrow \infty} P(t) = \infty$.
- (3) If $a \ln(q) = Dm$ (implying that $q \geq 1$), then

$$q^{-1}P(0) \leq P(t) \leq qP(0), \quad t \geq 0.$$

A noteworthy feature of this example is that the minimum cell size, m , is found to have a role in determining the population-level behaviour. For given $D > 0$, $a > 0$, and $q > 1$, we will have $a \ln(q) < Dm$ (and $P(t) \rightarrow 0$) if m is sufficiently large and $a \ln(q) > Dm$ (and $P(t) \rightarrow \infty$) if m is sufficiently small. The intuitive reason for this is that, with a constant cell growth rate, smaller cells take less time (than do larger cells) to reach maturity and are thus able to reproduce at a rate that exceeds the removal rate.

6. Application to the chemostat

The standard unstructured model for microbial growth in a chemostat is

$$B'(t) = \mu(S(t))B(t) - DB(t), \quad (14a)$$

$$S'(t) = D(S_f - S(t)) - Y^{-1}\mu(S(t))B(t), \quad (14b)$$

where $B(t)$ is the concentration of biomass in the chemostat culture vessel and $S(t)$ is the concentration of a growth-limiting substrate. This model is based on the work of Monod who postulated that the per capita rate of increase in biomass of a bacterial population in batch culture depends on $S(t)$ according to $B'(t) = \mu(S(t))B(t)$, where μ is usually assumed to be a 'Monod function' of the form $\mu(S) = \mu_m S / (K_h + S)$. (μ_m is the maximal specific growth rate and K_h is the half-saturation constant.) Another of Monod's postulates for the batch culture was that the rate of consumption of substrate is proportional to the rate of increase of biomass. Thus $S'(t) = -Y^{-1}\mu(S(t))B(t)$, where Y is the yield constant (defined to be the ratio of biomass formed per substrate consumed). Model (14) is obtained by adapting Monod's batch culture model to a chemostat setting by including the parameters

$$S_f = \text{concentration of substrate in the fresh medium input}$$

and

$$D = \frac{\text{flow rate of chemostat}}{\text{volume of culture vessel}}.$$

The generic behaviour of solutions of model (14) is the convergence of both the biomass and the substrate to steady-state values as $t \rightarrow \infty$. Specifically, if $\mu(S_f) < D$, then $(B(t), S(t)) \rightarrow (0, S_f)$; whereas if $\mu(S_f) > D$, then $(B(t), S(t)) \rightarrow (Y(S_f - \lambda), \lambda)$, where λ , which is called the break-even substrate concentration, is defined by $\mu(\lambda) = D$. A more detailed introduction to the mathematics of the chemostat can be found in Smith and Waltman [26]. In addition, a very complete historical discussion of the chemostat from a combined theoretical/empirical perspective is given in Panikov [20, Chapter 1].

To model a bacterial population in a chemostat within the framework of the size-structured model (2), we begin with the assumption that cell size increases according to a law of the form $x'(t) = \mu(S(t))g(x(t))$, where μ is a Monod function. The equations that describe growth and reproduction are thus

$$\mu(S(t))(g(x)\rho(t, x))_x + \rho_t(t, x) + D\rho(t, x) = 0, \quad (15)$$

$$g(m)\rho(t, m) = qg(2m)\rho(t, 2m). \quad (16)$$

In order to model the consumption of substrate, we adopt Monod's postulate that the rate of consumption of substrate is proportional to the rate of addition of new biomass. If ρ is a solution of Equations (15) and (16), then by the discussion given in Section 2.1, the rate of addition of biomass due to cell growth is $\mu(S(t)) \int_m^{2m} g(x)\rho(t, x) dx$. We thus model the consumption of substrate by

$$S'(t) = D(S_f - S(t)) - Y^{-1}\mu(S(t)) \int_m^{2m} g(x)\rho(t, x) dx. \quad (17)$$

For given initial data $S(0) = S_0 \geq 0$ and $\rho(0, \cdot) = \phi$ (assumed to satisfy the compatibility conditions (7)), the size distribution and substrate dynamics are described by Equations (15)–(17).

Consequently, the population-level dynamics are described by

$$B'(t) = \mu(S(t)) \left(\int_m^{2m} g(x)\rho(t, x) dx - (2 - q)mg(2m)\rho(t, 2m) \right) - DB(t) \quad (18)$$

and

$$P'(t) = (q - 1)\mu(S(t))g(2m)\rho(t, 2m) - DP(t). \quad (19)$$

It should be noted that in Equations (18) and (19), $B(t)$ has units of mass and $P(t)$ has units of cell number. We can convert to units of concentration by setting $\tilde{\rho} = \rho/V$, $\tilde{B} = B/V$, and $\tilde{P} = P/V$, where V is the volume of the chemostat culture vessel. By rewriting Equations (18) and (19) in terms of $\tilde{\rho}$, \tilde{B} , and \tilde{P} and then again renaming $\rho = \tilde{\rho}$, $B = \tilde{B}$, and $P = \tilde{P}$, the same equations are obtained but with $B(t)$ and $P(t)$ having units of concentration.

A general study of model (15)–(19) will be the subject of a future investigation. In order to pave the way for this future work, we will examine the chemostat dynamics that arise from the model in the important case of perfect reproductive efficiency ($q = 2$) and size-proportional growth rate ($g(x) = x$). In this case, Equations (15)–(17) take the form

$$\mu(S(t))(x\rho(t, x))_x + \rho_t(t, x) + D\rho(t, x) = 0 \quad (20a)$$

$$\rho(t, m) = 4\rho(t, 2m) \quad (20b)$$

$$S'(t) = D(S_f - S(t)) - Y^{-1}\mu(S(t)) \int_m^{2m} x\rho(t, x) dx \quad (20c)$$

with initial data $S(0) = S_0 \geq 0$ and $\rho(0, \cdot) = \phi$. If (ρ, S) is a solution of system (20a)–(20c), then the biomass, $B(t) = \int_m^{2m} x\rho(t, x) dx$, and cell numbers, $P(t) = \int_m^{2m} \rho(t, x) dx$, satisfy the differential equations

$$B'(t) = (\mu(S(t)) - D)B(t), \quad (20d)$$

$$P'(t) = 2m\mu(S(t))\rho(t, 2m) - DP(t). \quad (20e)$$

We remark that Equations (20a)–(20d) were derived from the first principles by Smith in [24] by assuming the size-proportional cell growth rate ($g(x) = x$) and perfect reproductive efficiency ($q = 2$) and by then passing from a discrete version of the model to Equations (20a)–(20d). As was shown in the analysis provided in [24, p. 753], since Equations (20c) and (20d) are identical to the classical chemostat model (14), the biomass–substrate dynamics are the same in the structured model as in the unstructured model: if $\mu(S_f) > D$, then $(B(t), S(t)) \rightarrow (Y(S_f - \lambda), \lambda)$, where $\mu(\lambda) = D$. However, we should point out that the corresponding size distribution will oscillate, unless the initial distribution is invariant. Thus, the attractivity of the steady state claimed by Smith is valid only for solutions corresponding to invariant distributions, e.g. precisely those considered in [24]. However, the structured model provides a richer description of the population dynamics as we now illustrate by examining solutions for which the biomass–substrate steady state has already been achieved. To construct such solutions, we first set $S(t) \equiv \lambda$ in Equation (20a) and choose any compatible distribution ϕ , fixed but arbitrary, such that

$$\int_m^{2m} x\phi(x) dx = Y(S_f - \lambda).$$

Taking ρ to be the corresponding solution of Equations (20a) and (20b), we obtain

$$\frac{d}{dt} \left(\int_m^{2m} x\rho(t, x) dx \right) = 0$$

and thus Equations (20c) and (20d) are also satisfied by $(\rho, S) = (\rho, \lambda)$ with $S'(t) = B'(t) = 0$ for all $t \geq 0$. However, since $q = 2$ and $\pi(t) = 1$ for all $t \geq 0$, then $P(t)$ is not constant

unless ϕ is an invariant distribution. This follows from part (ii) of Theorem 1. Furthermore, since $\mu(S) \ln(q) = D \ln(2)$ corresponds to the critical case discussed in Section 5.1, we observe that $P(t)$ is in fact a periodic function of period $\ln(2)/D$. We thus obtain a scenario in which a biomass–substrate steady state has been achieved but in which the average cell size ($B(t)/P(t)$) fluctuates periodically.

7. Discussion

Early models of bacterial population dynamics attempted to describe the behaviour of such populations in terms of a single observable feature, usually the cell number or biomass. These models were improved upon by taking the population structure into account. The development of structured models has proceeded according to two fundamental approaches which we will refer to very loosely as *state structuring* and *age/size structuring*. In the state structure approach, the cell cycle is viewed as being comprised of a discrete set of states and the process by which cells transfer between these states is modelled. The most well-known model of this type is the one introduced by Smith and Martin [25] in which the cell cycle is viewed as consisting of two states, A and B , with the probabilistic time of residence in the A state and deterministic time of residence in the B state. The Smith–Martin idea has been modified and expanded upon in the work of Tyson and Hanns-gen [27], Grasman [9], Pilyugin *et al.* [21], and others. The age/size structure approach differs from the state structure approach in that it classifies cells according to age and/or body size and/or some other identifiable physical characteristics. Some structured models, such as those developed by Lasota and Mackey [16] and Basse *et al.* [2], incorporate elements of both state structure and age/size structure. A general survey of the structured cell population models is given in Arino [1].

The model (2) that we have investigated here is a size-structured model where ‘size’ is interpreted to mean cell biomass. Under very general assumptions on the model parameters, we show that the model admits classical solutions and determine the behaviour of these solutions in terms of the model parameters. This behaviour is found to be fundamentally different than that typically found in similar models. Instead of convergence of all solutions to a stable size distribution, we obtain cyclic size distributions that correspond to populations in which the average cell size fluctuates in cycles that are possibly of variable length.

A general concern in the process of mathematical modelling is the trade-off that must be made between realism and the feasibility of mathematical analysis. Model (2) incorporates the processes of bacterial growth and reproduction in a fundamental way that allows for the construction of classical solutions whose behaviour can be clearly elucidated. However, we sacrifice some realism by hypothesizing that all cells undergo fission at the same critical size ($2m$). A similar simplifying assumption was made in the model studied by Cushing [6] and Smith and Waltman [26]. This model allows for variation of size at fission but requires that all cells have the same birth size. In reality, empirical studies performed on cultures of *Escherichia coli* [10,11] have shown that the coefficient of variation for size at fission is generally around 10% to 16% and that this does not depend significantly on the medium in which the cells are being cultured. The coefficient of variation of age at fission is much larger. By assuming that all cells divide at the same size, we are able to introduce the reproductive parameter, q , which keeps track of the reproductive process and enables us to determine how the interplay between growth and reproduction governs the population dynamics.

A model that bears close resemblance to model (2) is model (21) which was studied by Diekmann *et al.* in [7,8] and by Metz and Diekmann in [17].

$$(f(t)g(x)\rho(t, x))_x + \rho_t(t, x) = -b(x)\rho(t, x) + 4b(2x)\rho(t, 2x) - D\rho(t, x), \quad (21a)$$

$$\rho \left(t, \frac{1}{2}a \right) = 0, \quad (21b)$$

$$\rho(0, x) = \phi(x). \quad (21c)$$

Model (21) contains a balance law that describes both the growth and reproductive processes and hence allows for the fact that fission can occur over a range of sizes. Specifically, the maximum possible cell size is normalized to be 1, it is assumed that cells divide into two equal parts, and the minimum size at which cells can undergo fission is assumed to be $a < 1$. This implies that all newborn cells lie in the size range $[a/2, 1/2]$ and that fission takes place only in cells that are in the size range $[a, 1]$. Cells of size x are assumed to divide with probability $b(x)$. The detailed analysis of this model given in [7,8,17] proceeds by first transforming the model into an abstract evolution equation in an appropriate Banach space and by then applying the theory of semigroups of linear operators. However, solutions of the abstract evolution equation cannot typically be transformed back into classical solutions of Equation (21) and are thus interpreted as satisfying Equation (21) only in a certain weak sense. The generic dynamical behaviour of model (21) is the convergence of all solutions to an asymptotically stable invariant size distribution in which the average cell size is constant. However, if the typical assumption of the size-proportional cell growth rate ($g(x) = x$) is made, then model (21) does *not* have a stable size distribution and all solutions have cyclic size distributions just as in model (2).

We conclude with a discussion of the modelling role of the function $g(x)$. In most studies, it is assumed that cell size increases at a size-proportional rate ($g(x) = x$). In this case, models (2) and (21) are in agreement on their predictions of the population dynamics. However, the question of whether the cell growth rate can be generally expected to be size-proportional appears to have still not been settled. Based on an extensive set of experiments performed with *Escherichia coli* and other bacteria, Kubitschek [12–15] argues that the rate of the increase in size of these bacteria is constant throughout most of the cell cycle. On the other hand, Cooper [5] strongly takes the position that the rate of cell growth is indeed size proportional. Empirical results obtained by Meyer *et al.* [18] indicate that the growth rate is probably neither constant nor size proportional but that it varies across different stages of the cell cycle and for different species. The ‘inverse problem’ of finding $g(x)$ based on empirical observations of cell size distributions is thus clearly an issue that is of interest to microbiologists. We are hopeful that size-structured models such as the ones we have introduced here can be helpful in furthering such investigations.

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Appendix. Derivation of boundary condition (2b)

For fixed $t \geq 0$ and small $h > 0$, the time that it takes for a cell that has size $2m - h$ at time t to grow to size $2m$ is $\tau(h, t)$, where

$$\int_t^{t+\tau(h,t)} f(w) dw = \int_{2m-h}^{2m} \frac{1}{g(u)} du.$$

Observe that

$$\frac{\partial \tau}{\partial h}(h, t) = \frac{1}{f(t + \tau(h, t))g(2m - h)}.$$

During the time interval $[t, t + \tau(h, t)]$, a cell that has size m will grow to size $x(t + \tau(h, t))$, where x is the solution of $x'(t) = f(t)g(x(t))$, $x(t) = m$.

Our assumption that each mother produces q daughters is thus modelled by the requirement that

$$\lim_{h \rightarrow 0^+} \frac{1}{h} \int_m^{x(t+\tau(h,t))} \rho(t + \tau(h, t), x) dx = q \cdot \lim_{h \rightarrow 0^+} \frac{1}{h} \int_{2m-h}^{2m} \rho(t, x) dx.$$

The right-hand side of the above equation is equal to $q\rho(2m, t)$. Also, by L'Hopital's rule, we have

$$\begin{aligned} \lim_{h \rightarrow 0^+} \frac{x(t + \tau(h, t)) - m}{h} &= \lim_{h \rightarrow 0^+} f(t + \tau(h, t))g(x(t + \tau(h, t))) \frac{\partial \tau}{\partial h}(h, t), \\ &= \frac{g(m)}{g(2m)}, \end{aligned}$$

which gives

$$\lim_{h \rightarrow 0^+} \frac{1}{h} \int_m^{x(t+\tau(h,t))} \rho(t + \tau(h, t), x) dx = \frac{g(m)}{g(2m)} \rho(t, m).$$

We thus require that

$$g(m)\rho(t, m) = qg(2m)\rho(t, 2m).$$