

Tufail Malik · Hal Smith

A resource-based model of microbial quiescence

Received: 2 November 2005 /

Published online: 6 May 2006 – © Springer-Verlag 2006

Abstract. To analyze the ecological features of microbial quiescence, a model is proposed that involves “wake-up” rate and “sleep” rate at which the population transitions from a quiescent to an active state and back, respectively. These rates depend continuously on the resources and turn on and off at resource thresholds which may not coincide. The usual dichotomy is observed: the population is washed out under environmental stress and a single “survival” steady state exists otherwise. Proportional nutrient enrichment is used to explore analytically as well as numerically the nature of the steady state which bifurcates from the washout state.

1. Introduction

The ability of certain bacterial cells to reversibly enter a dormant (quiescent, non-viable) state has important implications for their survival particularly in environments involving stress in the form of extreme temperatures, water scarcity, or nutrient scarcity [16]. Dormancy refers to a reversible state, which may persist for extended periods, in which cells exhibit low levels of metabolic activity and do not divide. They also are more tolerant of environmental stresses than active cells. The review articles by Kaprelyants et al. [16, 17] are particularly useful. They point out the considerable controversy over definitions of “active” and “dormant” cells and the difficulties involved in determining whether cells are in particular states. These authors note that “the mechanism(s) of the transition of active cells into dormant cells are as yet little understood”. They cite internal factors such as DNA damage, or loss of components such as ribosomes or transcription factors that may play a role as may external factors such as key resources falling below a critical threshold. Indeed, a number of experimental results cited in [17] (see Table 2) involve attempts to induce dormancy by starvation.

A dormant state may play a significant role in disease and human health in two ways. First, dormant cells of pathogens may produce latent infections when resuscitated and second, dormant bacteria do not respond to many antimicrobial agents because these agents are typically effective only against growing cells. Both these factors are relevant to tuberculosis. *Mycobacterium tuberculosis* can become dormant in the host for months or years without producing disease and then revive to bring on the disease [14, 24]. It is thought that low levels of oxygen in lesions may allow *M. tuberculosis* to enter a dormant state [14]. The same issues may

pertain to the colonization of the lungs of cystic fibrosis patients by *Pseudomonas aeruginosa* [6].

Despite the uncertainties that prevail concerning dormancy, there have been considerable mathematical modeling efforts to understand its potential effects. We review a few of these below.

Jäger et al. [15] consider a chemostat-based model of single bacterial population where individual cells may be in an active (proliferating) or quiescent (non-proliferating) state with transitions between states dependent on a single limiting substrate. They assume that transitions from active state to quiescent state occur at a positive rate when substrate concentration falls below σ_2 , transition from quiescent to active state occurs at a positive rate when this concentration exceeds σ_1 . Furthermore, they assume $0 < \sigma_2 < \sigma_1$, creating a hysteresis pattern for switching between states. They find the usual dichotomy in system behavior: if environmental conditions (dilution rate, substrate feed level) are inadequate then washout of organism occurs; otherwise there is a single attracting equilibrium, although it may be of two different types, consisting of active only cells or consisting of both active and quiescent cells. An interesting feature of the model, due to the inclusion of a quiescent state, is that oscillatory convergence to equilibrium is observed. Such behavior is often observed in laboratory populations of bacteria [13] and algae [4] and therefore the ability of cells to become quiescent may partially explain the observed transient dynamics.

A generalization of this model is given in [21] where the adaptation of cells to the change in substrate concentration is considered by allowing the cells to switch between a fast and a slow nutrient uptake and growth mode. It is established that if the chemostat is inoculated with only slow growing cells the population will wash out or remain in this state as long as the nutrient level remains below a threshold level. If chemostat is inoculated with some cells in the fast growing state, even if the nutrient input concentration remains low, the population could still survive in slow growing mode, provided the dilution rate is low enough. An explanation to the experimentally observed transient oscillatory population density and hysteresis growth pattern is given and competition between two species that can switch between fast and slow nutrient uptake and growing modes is considered.

The soil crusts of desert environments harbor cyanobacteria that are dormant for the long stretches of time between brief periods of active growth brought on by infrequent rain. Inputs required for growth aside from water also arrive infrequently, often by dust storms. Yet somehow, an apparently diverse community of organisms persist in these environments. Given our relative ignorance of microbial life in these desert crusts relative to the more well-understood aquatic environments [8, 19, 20, 22, 23] it is little wonder that there is a paucity of modeling of them. Bar et al. [3] develop a strategic model to highlight the survival value of a dormancy stage in bacteria which are subjected to frequent environmental stress conditions such as low soil humidity. They model a population in which organisms can exist in either an actively growing (high mortality) state or a dormant (low mortality) state and where transitions between the two states are mediated by the current value of the soil humidity field which in turn is depleted by actively growing organisms and replenished by a time-dependent input (rain). When humidity is low, bacteria

from the active state become dormant; when high, the reverse transition occurs. It is shown that this population outperforms a “sleepless” population, incapable of dormancy, in a temporally inhomogeneous environment characterized by one brief pulse of water every one hundred time units, in the sense that sleepless’ population density oscillates wildly, falling to near zero over significant time intervals, while the dormant-capable population density oscillates with less amplitude, remaining bounded away from zero. The prediction is that, lacking a low-mortality dormant stage, bacterial populations could not survive the lengthy inter-rain periods. Bar et al. observe that “a dormant population can overcome the hard times as Sleeping Beauty waiting to be awoken”.

Gyllenberg and Webb [12] have compiled a discussion of models they have proposed and analyzed in [9–11] to explore the role of quiescence in tumor growth. Gyllenberg and Webb [10] proposes an ordinary differential equations model for the growth of solid tumors, employing quiescence. The transition rates between an active and a quiescent state depend on tumor size; the bigger the tumor size, the higher the transition rate from the active to the quiescent state and the smaller the transition rate in the opposite direction. Three cases are analyzed. A tumor forming a necrotic center grows monotonically to its ultimate size and growth fraction – the proportion of growing cells – tends to zero. In case of “true quiescence” where dormant cells retain proliferation two subcases have been addressed. If only active cells can die, then the tumor grows as predicted in early stages similar to the one forming a necrotic center. The growth fraction still tends to zero but ultimately the tumor grows without bound. If, on the other hand, quiescent class has even very small but positive mortality, the tumor grows to a finite limit depending only on vital rates and growth fraction decreases to a strictly positive value.

In [9], [11] Gyllenberg and Webb have combined quiescence with structure. Gyllenberg and Webb [9] presents an age-size structured model with quiescence where individuals in normal state advance in both age and size, while quiescent individuals advance only in age and cannot proliferate. The growth, death and transition rates depend on age, size and state. It is established that the age-size distribution of population converges to a stable distribution. In [11], a nonlinear structured model is given which assumes the transition rates between states depend on cell size as well as the total tumor size, whereas the growth and fission depends on cell size only. “Net reproductive numbers” for very large and very small tumors are identified and it is established that if the net reproductive number of a large tumor is smaller than 1, the tumor will remain bounded. The existence of a non-trivial equilibrium and stability of the trivial equilibrium is determined by the net reproductive number for small tumors.

Arino et al. [1] discuss a linear age structured model with proliferating and quiescent population compartments. The model characterizes an individual by age and state and presents certain hypotheses on division rate and transition rates between stages under which the population exhibits the asymptotic behavior of asynchronous exponential growth.

Dormancy or Quiescence is a strategy that is useful in a risky environment. A simple game-theoretic argument makes this transparent. Imagine that bacteria are able to choose strategy *A* (active) or *D* (dormant) and then “Nature” chooses

the environment H (high nutrient), with probability p or L (low nutrient), with probability $1 - p$. The payoff matrix gives the number of surviving bacteria including off-spring

$$\begin{pmatrix} \cdot & H & L \\ A & 2 & 1 - \epsilon \\ D & 1 & 1 \end{pmatrix}.$$

An active cell divides in a high nutrient environment but it may die in a low nutrient environment (with probability ϵ) and it certainly does not divide. Dormancy is a low risk-low payoff strategy in which a cell is virtually guaranteed to survive, but not divide. The expected payoff of being active, $E(A) = 2p + (1 - p)(1 - \epsilon)$, is exceeded by the expected payoff of choosing dormancy, $E(D) = 1$ only when $p \leq \epsilon/(1 + \epsilon)$. Roughly, dormancy is the best strategy only when good times are less probable than the risk of death by getting caught active in bad times.

We construct a mathematical model of a single microbial population where individual cells can transition between an active and dormant state depending on the levels of several essential resources. By essential resources, we mean that growth ceases in the absence of any one of them. In this paper, we confine our attention to the case of a constant rate of substrate influx and outflux despite the fact that natural environments are characterized by random episodic inputs. In future work we plan to extend this work to include nonconstant inputs. However, we argue that it is important to have a baseline case where a thorough mathematical analysis is possible with which to compare the more realistic but less mathematically tractable case.

Essentially, our only hypotheses are that the growth rate of active cells and the transition rates between states depend in a monotone fashion of each resource: an increase in any resource level results in no decrease (no increase) in growth rate and rate of transition of dormant cells to active cells (rate of transition of active cells to dormant cells). However, following Jäger et al. [15], we are primarily interested in the case where the “sleep threshold”, the threshold level of resource below which active cells begin to transition to dormancy, is lower than the “wake threshold”, the threshold of resource above which dormant cells begin to transition to being active. We identify a basic reproductive number R_0 for the bacterial population which depends on resource availability, growth and removal rates and transition rates between dormancy and active states. When $R_0 < 1$, the population dies out, when $R_0 > 1$ then there is a globally attractive “survival” steady state, which may or may not include a dormant subpopulation of cells. A dormant subpopulation is present in resource-poor environments and they are not present in resource-rich environments.

2. The model and main results

The equations describing a population of bacteria consisting of active cells N and dormant cells D subsisting on m essential resources R_j are

$$\begin{aligned}
 N' &= N[f(R) - d_1] + \alpha(R)D - \beta(R)N \\
 D' &= -d_2D - \alpha(R)D + \beta(R)N \\
 R'_j &= F_j(t) - r_jR_j - c_jf(R)N, \quad 1 \leq j \leq m
 \end{aligned}
 \tag{1}$$

where $F_j(t) \geq 0$ is the flux of resource R_j into the environment, $c_j > 0$ is the fraction of bacterial biomass consisting of resource R_j ($\sum c_j = 1$), $d_1 > 0$ and $d_2 \geq 0$ are removal rates of active and dormant bacteria, respectively. We expect that dormant cells have an advantage in lower removal rates: $d_1 \geq d_2$. $R = (R_1, R_2, \dots, R_m)^t$.

In the special case that resources are supplied at a constant rate $F_j(t) = dS_j$, where $S_j > 0$ is the concentration of R_j in the feed to a well-mixed continuous culture with dilution rate d and assuming that dormant and active cells are removed at rate d (ignoring cell death), our system becomes mathematically tractable because various conservation principles become available. However, we make these assumptions merely for their effect on the subsequent mathematical analysis, not because we feel that a continuous culture environment is a particularly appropriate setting. The simplified system becomes

$$\begin{aligned}
 N' &= N[f(R) - d] + \alpha(R)D - \beta(R)N \\
 D' &= -dD - \alpha(R)D + \beta(R)N \\
 R' &= d(S - R) - cf(R)N
 \end{aligned}
 \tag{2}$$

where $c = (c_1, c_2, \dots, c_m)^t$.

In order to state the weakest possible restrictions on f , some notation is useful. Let $L = \{R = S - \tau c : 0 \leq \tau \leq \min_{1 \leq j \leq m} S_j/c_j\}$ be the portion of the ray through S in the direction $-c$ belonging to \mathbb{R}_+^m . We assume that $f : \mathbb{R}_+^m \rightarrow [0, \infty)$ is continuous and C^1 on a neighborhood of L and satisfies $\nabla f(R) \cdot c > 0$ on L . Finally, we assume that $f(R) - d < 0$ for $R = S - (\min_{1 \leq j \leq m} S_j/c_j)c$, the endpoint of L on $\partial\mathbb{R}_+^m$ at which at least one component vanishes. The hypotheses stated above involve not only f but also vectors S, c and the dilution rate d . Less general conditions, involving only f , which imply those above for every choice of $S, c > 0$ and $d > 0$ are: $\frac{\partial f}{\partial R_j}(R) \geq 0$ and $\nabla f \neq 0$ in \mathbb{R}_+^m and $f(R) = 0$ if $R_j = 0$ for some j .

Numerous forms for the growth function f are mentioned in [2,5,8], including

$$f(R) = \mu_{\max} \frac{1}{1/R_1 + 1/R_2 + \dots + 1/R_m}.
 \tag{3}$$

Liebig’s law of minimum

$$f(R) = \min\{f_1(R_1), f_2(R_2), \dots, f_m(R_m)\}
 \tag{4}$$

is popular although it is not smooth. Here $f_i(R_i)$ is usually a Monod function $f_i(R_i) = \frac{\mu_{\max}R_i}{K_i+R_i}$ and μ_{\max} is the maximum specific growth rate. Another popular choice is

$$f(R) = f_1(R_1)f_2(R_2)\dots f_m(R_m).
 \tag{5}$$

See Tilman [22,23] for a classification of the resource-dependent growth isoclines.

It will be convenient to invoke two different sets of assumptions concerning the transition rates α and β . The first set, hereafter referred to as the “smooth α and β assumptions”, say simply that the two functions are smooth, that the “wake-up rate” α does not decrease when some resource is increased, and the “sleep rate” β does not increase when some resource is increased.

Smooth α, β :

- (a) $\alpha : \mathbb{R}_+^m \rightarrow [0, \infty)$ is C^1 and $\nabla\alpha \geq 0$.
- (b) $\beta : \mathbb{R}_+^m \rightarrow [0, \infty)$ is C^1 and $\nabla\beta \leq 0$.

These hypotheses include the trivial case that both α and β are constant, independent of resource R .

However, it is biologically reasonable to modify the smoothness assumptions (a) and (b) on α and β so as to allow them to be piecewise smooth as was done in [15] for the case of a single resource. When resources are very high, there is no good reason to be dormant so it is natural to assume that $\beta = 0$ and $\alpha > 0$. However, as resources become somewhat scarce α should also vanish and, for very low resource levels, $\alpha = 0$ and $\beta > 0$. This captures the hypothesized effect that a dormant cell should not awake until a higher resource threshold is exceeded than the threshold below which an active cell goes dormant. As “resource levels” are vectors R , some care must be exercised in mathematizing this hypothesis. Below, we give an alternative set of hypotheses on α and β intended to capture this effect which we hereafter refer to as the “piecewise smooth α, β assumptions”.

Piecewise-smooth α, β :

- (a) $\alpha : \mathbb{R}_+^m \rightarrow [0, \infty)$ is continuous and $A_0 := \{R \in \mathbb{R}_+^m : \alpha(R) = 0\}$ is the closure of a compact neighborhood of 0 with a piecewise smooth boundary, ∂A_0 . In addition, we assume that $R \in A_0$ and $0 \leq S \leq R$ implies that $S \in A_0$. At all but finitely many points of ∂A_0 , the unit normal n to ∂A_0 exists and satisfies $n \geq 0$. α is C^1 except on ∂A_0 and $\nabla\alpha \geq 0$.
- (b) $\beta : \mathbb{R}_+^m \rightarrow [0, \infty)$ is continuous and $B_+ := \{R \in \mathbb{R}_+^m : \beta(R) > 0\}$ is a bounded neighborhood of 0 with a piecewise smooth boundary, ∂B_+ . In addition, we assume that $\beta(R) > 0$ and $0 \leq S \leq R$ implies that $\beta(S) > 0$. At all but finitely many points of ∂B_+ , the unit normal n to ∂B_+ exists and satisfies $n \geq 0$. β is C^1 except on ∂B_+ and $\nabla\beta \leq 0$.
- (c) The closure of B_+ is contained in the interior of A_0 .

It will be convenient for describing our results in biological terms to have some biologically-inspired terminology for the surfaces ∂A_0 and ∂B_+ in resource space. We refer to the former as the “wake threshold” since when resource levels exceed this threshold, dormant cells begin to transition to active cells. We refer to the latter as the “sleep threshold” because active cells begin to transition to dormancy when resource levels fall below this threshold.

In these terms, our assumptions say that when resource vector R lies below the sleep threshold ∂B_+ , $\alpha = 0$ and $\beta > 0$ meaning that resource levels are so low that active cells are transitioning to dormancy and dormant cells are not inclined to become active. For intermediate levels of resource, that is for R lying above the

sleep threshold ∂B_+ but below the wake threshold ∂A_0 , both $\alpha = 0$ and $\beta = 0$ meaning that resource levels are high enough that active cells are not transitioning to dormancy but not high enough to induce dormant cells to become active. For resource levels R above the wake threshold ∂A_0 , $\alpha > 0$ and $\beta = 0$ meaning that resource levels are so high that dormant cells become active and active cells do not seek dormancy. See Fig. 1 depicting this scenario when there are only two resources. In this case, the wake threshold ∂A_0 and the sleep threshold ∂B_+ are curves dividing the R_1 - R_2 -plane into three regions. We will make use of the notation concerning A_0 and B_+ and their boundaries even in the smooth α, β case. In this case, we need not worry about the smoothness of α on ∂A_0 or β on ∂B_+ .

The simplification from system (1) to system (2) allows a remarkable reduction in dimension. From (2) a simple computation yields that

$$[R + (N + D)c]' = d \{S - [R + (N + D)c]\}$$

and thus $R + (N + D)c \rightarrow S$ as $t \rightarrow \infty$. Therefore solutions of (2) are attracted to the set

$$M = \{(N, D, R) \in \mathbb{R}_+^{m+2} : R + (N + D)c = S\}$$

The restriction of the dynamics to this set is completely described by the planar system given by:

$$\begin{aligned} N' &= N[f(R) - d] + \alpha(R)D - \beta(R)N \\ D' &= -dD - \alpha(R)D + \beta(R)N, \end{aligned} \tag{6}$$

where $R = S - (N + D)c$. The domain of (6) is the triangular region

$$\Gamma = \left\{ (N, D) \in \mathbb{R}_+^2 : N + D \leq \min_{1 \leq j \leq m} S_j/c_j \right\}.$$

Lemma 1. Γ is positively invariant for (6).

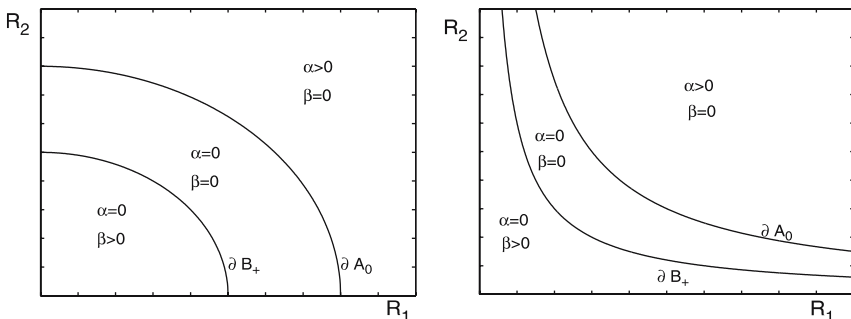


Fig. 1. Two of the possible ways the sleep threshold ∂B_+ and wake threshold ∂A_0 divide the resource plane into three regions; values of α and β in the three regions

Proof. $(N + D)' = Nf(R) - d(N + D) \leq (N + D)(f(R) - d) < 0$ when $N + D = \min_{1 \leq j \leq m} S_j/c_j$ where $R = S - (\min_{1 \leq j \leq m} S_j/c_j)c$, by the hypotheses on f . □

Equation (6) can be expressed in vector form, with $U = (N, D)^t$, as

$$U' = \begin{pmatrix} f(R) - d - \beta(R) & \alpha(R) \\ \beta(R) & -d - \alpha(R) \end{pmatrix} U.$$

A calculation shows that the determinant of the coefficient matrix is $-d G(R)$ where

$$G(R) := \left(1 + \frac{\alpha(R)}{d}\right) (f(R) - d) - \beta(R). \tag{7}$$

The basic reproductive number for our model is given by

$$R_0 := f(S) \cdot \frac{1}{d} \cdot \frac{\alpha(S) + d}{\alpha(S) + \beta(S) + d}.$$

It captures the number of daughter cells that a single hypothetical cell, introduced into the sterile steady state $E_0 = (0, 0)$ of (6), leaves before being washed out of the system. The last quotient reflects the fraction of the cell’s residence time spent as an active (versus dormant) cell. It is readily seen that $R_0 > 1$ ($R_0 < 1$) is equivalent to $G(S) > 0$ ($G(S) < 0$).

Equation (6) has three potential steady states,

$$E_0 := (0, 0), \quad E_C := (\hat{N}, \hat{D}), \quad \text{and} \quad E_N := (\bar{N}, 0)$$

We refer to E_C as the coexistence state since both dormant and active cells coexist; we call E_N the active-only state. We define $R_N := S - \bar{N}c$ and $R_C := S - (\hat{N} + \hat{D})c$.

Of course, E_0 always exists but the other two steady states can exist only when $G(R) = 0$ where $R = R_C$ for E_C and $R = R_N$ for E_N . We will establish that there is at most one E_N (one E_C), that E_N and E_C never exist simultaneously, and that one of them exists when $R_0 > 1$. There is a simple criterion for determining which one exists when $R_0 > 1$. Since $R + (N + D)c = S$ there is a simple relation between the biomass $\tau = N + D$ that can be supported at a particular resource R . Viewing biomass τ as a parameter, we determine its value such that the ray $R = S - \tau c$ meets the “growth threshold” surface

$$f(R) - d = 0.$$

If it meets the growth threshold at a resource level $\tilde{R} = S - \tau c$ below the sleep threshold, then E_C exists. If it meets the growth threshold at a resource level $\tilde{R} = S - \tau c$ above the sleep threshold, then E_N exists. Let us make this more precise. The function $h : [0, \min_j S_j/c_j] \rightarrow \mathbb{R}$ defined by

$$h(\tau) = f(S - \tau c) - d$$

is strictly decreasing since $\nabla f \cdot c > 0$, satisfies $h(0) > 0$, since $R_0 > 1$, and $h(\min_j S_j/c_j) < 0$ by our hypotheses on f . Therefore, there is a unique $\tau^* > 0$

such that $h(\tau^*) = 0$. If $\beta(S - \tau^*c) = 0$, then E_N exists and $\bar{N} = \tau^*$. If $\beta(S - \tau^*c) > 0$, then E_C exists. It is worth mentioning that E_N cannot exist if $\beta(S) > 0$.

Our first result gives a global analysis of the behavior of the planar system (6).

Theorem 1. *Let E denote the set of equilibria of (6).*

- (a) $R_0 < 1$ implies that $E = \{E_0\}$ and E_0 is a global attractor.
- (b) $R_0 > 1$ implies that $E = \{E_0, E_C\}$ or $E = \{E_0, E_N\}$; the nontrivial steady state is a global attractor provided that $N(0) > 0$.

Corresponding to the equilibria E_0, E_N, E_C of (6), there are equilibria e_0, e_N and e_C of (2). They are given by $e_0 = (E_0, S)$, $e_N = (E_N, R_N)$ and $e_C = (E_C, R_C)$. In our main result below, we show that the dynamics of (2) are the same as those of (6).

Theorem 2. *Assume that S does not belong to the wake threshold ∂A_0 . If e denotes the set of equilibria of (2), then*

- (a) $R_0 < 1 \Rightarrow e = \{e_0\}$ and e_0 is a global attractor.
- (b) $R_0 > 1 \Rightarrow e = \{e_0, e_C\}$ or $e = \{e_0, e_N\}$. The nontrivial steady state is a global attractor provided that $N(0) > 0$.

It is natural to consider the changes in the behavior of our model as the environment undergoes proportional nutrient enrichment:

$$S = \eta u, \quad \eta \geq 0$$

where $u > 0$ is a positive unit vector. We may view η is a bifurcation parameter. We assume that $\nabla f \cdot u > 0$ holds.

Suppose first that the growth threshold $f - d = 0$ lies entirely below the sleep threshold, i.e., in B_+ . Now $G(S) = G(\eta u)$ will vanish at a unique $\eta_0 > 0$ and satisfy $G(\eta u) > 0$ for all $\eta > \eta_0$ since $d/d\eta G(\eta u) > 0$ when $f - d \geq 0$. Because $f - d = 0$ lies in B_+ , it follows that $\beta(\eta u - \tau^*c) > 0$ (recall $\eta u - \tau^*c$ lies on the growth threshold) so E_C exists whenever $\eta > \eta_0$. Proportionate enrichment of the environment leads to the bifurcation of E_C from E_0 when the growth threshold lies in B_+ , E_C exists for all $\eta > \eta_0$.

Now suppose that the growth threshold lies beyond the sleep threshold, that is, it lies outside of the closure of B_+ . Then the growth threshold $f - d = 0$ and $G = 0$ coincide. Again, for the same reasons as above, there is exactly one $\eta_0 > 0$ where $G(\eta_0 u) = 0$ and $G(\eta u) > 0$ for $\eta > \eta_0$. But now, $\beta(\eta u - \tau^*c) = 0$ so E_N exists whenever $\eta > \eta_0$. Proportionate enrichment of the environment leads to the bifurcation of E_N from E_0 when the growth threshold lies beyond the sleep threshold, E_N exists for all $\eta > \eta_0$.

Of course, there is no reason why the growth threshold curve cannot cross into and out of B_+ , thereby allowing for a more complicated bifurcation picture.

We explore three scenarios numerically. Let us assume for definiteness, although one can argue more generally, that there are only two resources R_1 and R_2 and consider Michaelis-Menten kinetics: $f_i(R_i) = \mu_{\max} R_i / K_i + R_i$. Let us take piecewise

Table 1.

m	5
K_1	20
K_2	10
c_1	0.4
c_2	0.6
$N(0)$	0.4
$D(0)$	0.4
$R_1(0)$	0.4
$R_2(0)$	0.6

smooth wake-up and sleep rates $\alpha(R_1, R_2) = \max(f_1(R_1)f_2(R_2) - 0.7, 0)$ and $\beta(R_1, R_2) = -\min(f_1(R_1)f_2(R_2) - 0.5, 0)$. The corresponding regions A_0 and B_+ are shown in Figs. 2a, 3a and 4a, whose boundaries are determined by the wake threshold $\partial A_0 = \{(R_1, R_2) : f_1(R_1)f_2(R_2) - 0.7 = 0\}$ and the sleep threshold $\partial B_+ = \{(R_1, R_2) : f_1(R_1)f_2(R_2) - 0.5 = 0\}$ respectively. To incorporate proportional enrichment, three colinear supply vectors, $S = (1, 2)$, $S = (3, 6)$ and $S = (12, 24)$ are used that mimic a ‘resource-poor’ environment, a ‘resource-moderate’ environment and a ‘resource-rich’ environment, respectively. Other values used for simulations are given in the following table. Various scales along the vertical axis and c_i have been chosen to illuminate the range of possible dynamical behavior for the model. Other parameter values have been obtained from [15].

First, consider the growth function $f(R_1, R_2) = f_1(R_1)f_2(R_2)$ and let dilution rate $d = 0.3$, so that the growth threshold curve lies entirely below the sleep threshold (see Fig. 2a).

It is evident from simulations shown in Figure 2b that in the resource-poor environment the population is eventually washed out, and in resource-moderate

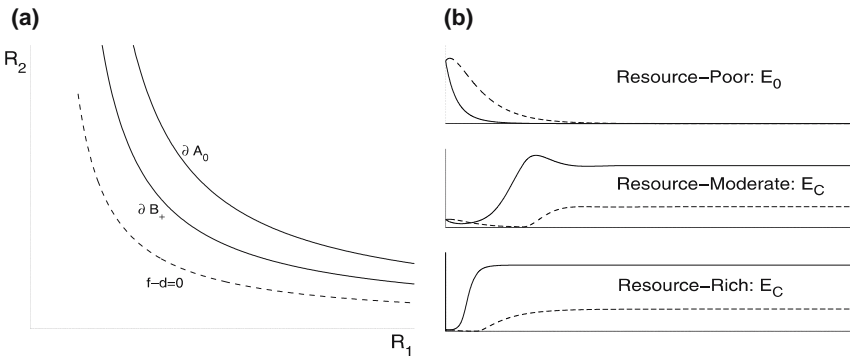


Fig. 2. **a** Growth threshold below the sleep threshold. **b** Time evolution of active (*solid line*) and dormant (*dashed line*) population. Population tends to extinction in a resource-poor environment (*top*) and to coexistence in resource-moderate (*middle*) and resource-rich (*bottom*) environments

and resource-rich environments, the population tends to the coexistence steady state.

Now let us consider the same growth function $f(R_1, R_2) = f_1(R_1)f_2(R_2)$ but $d = 0.9$ so that the growth threshold curve lies outside B_+ , as shown in Fig. 3a. In this case it is clear from simulations in Fig. 3b that the population is washed out in a resource-poor environment, and it tends to an active only steady state in the resource-moderate and resource-rich environments.

We explore the situation where the growth threshold curve enters into and leaves B_+ with the non-smooth growth function

$$f(R_1, R_2) = \min(f_1(R_1), f_2(R_2)).$$

The growth threshold curve $f - d = 0$, with $d = 0.3$ crosses into and out of B_+ as shown in Fig. 4a.

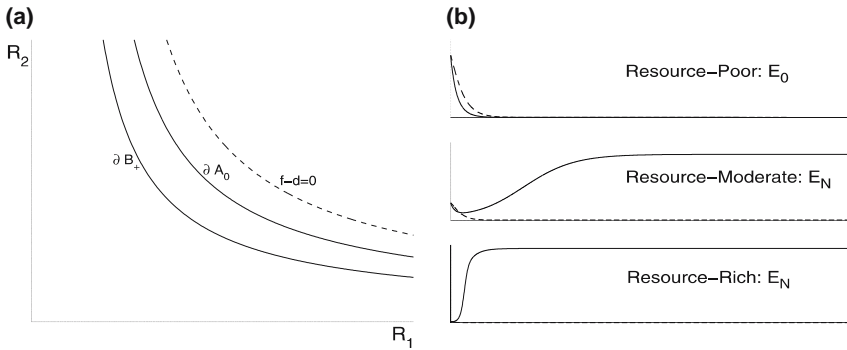


Fig. 3. **a** Growth threshold beyond the sleep threshold. **b** Population tends to extinction in a resource-poor environment (*top*), and to active only steady state in resource-moderate (*middle*) and resource-rich (*bottom*) environments

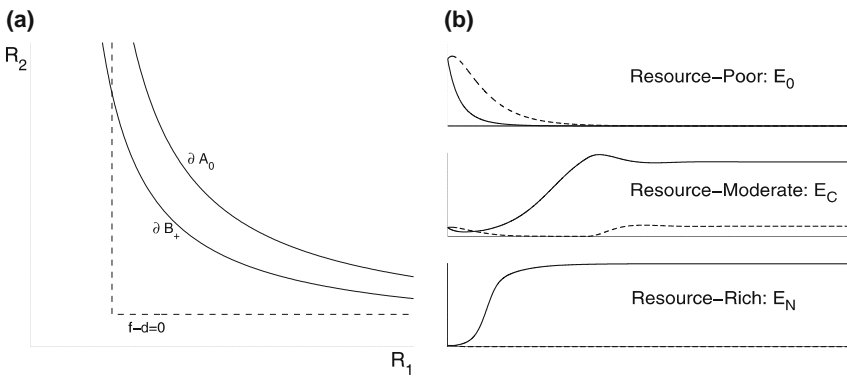


Fig. 4. **a** Growth threshold curve crossing into and out of the region B_+ . **b** The population tends to wash out steady state in a resource-poor environment (*top*), to coexistence in a resource-moderate environment (*middle*) and active only steady state in a resource-rich environment (*bottom*)

The evolution of population in the three types of environments is shown in Figure 4b. In the resource-poor environment, the population is washed out. In a resource-moderate environment, we observe coexistence steady state. In a resource-rich environment, the active only steady state bifurcates out of the coexistence steady state.

3. Discussion

The model of quiescence studied here extends the one proposed in [21] for a single resource, by allowing transition rates between states to depend on any number of complementary resources and by assuming somewhat weaker conditions on the specific growth function. A basic reproductive number R_0 , which depends on the specific growth rate $f(S)$ at the feed concentration vector S of the resources, on the residence time $1/d$, and on the fraction of that time spent in the active (dividing) state, is identified in this paper. The population is shown to wash out in when $R_0 < 1$ and to tend to a unique survival steady state when $R_0 > 1$. The survival steady state may take one of two forms, depending mainly on the resource supply S . If S is just large enough that $R_0 > 1$ but not too large the survival steady state consists of both active and quiescent cells. If S is large, all cells are active at the survival steady state.

As in [15], transient oscillations are observed as population levels approach the survival steady state (Figs. 2b, 3b and 4b), a phenomenon often observed in laboratory cultures of bacteria [13] and algae [4].

It is worth mentioning that the assumption $d_1 = d_2$, one of the those made to obtain the simplified system 6, and also employed in [15], removes an advantage that the quiescent cells are believed to have relative to active cells. Nevertheless this assumption is typically made for continuous culture studies, and brings with it tremendous tractability from the standpoint of mathematical analysis and paves the way to explore the features of quiescence-capable microbial population to an extent which would not be possible otherwise.

As mentioned in the introduction, dormancy is expected to be a particularly advantageous strategy in a highly variable and unpredictable environment. Therefore, it is more realistic to include time dependent resource supply since. However keeping in mind the expected complexity, a natural next step would be to introduce a periodic nutrient supply, mimicking for instance a natural environment with periodic pulses of rain separated by long dry spans. We would like to mention that some effort has already been put in this direction and initial numerical results seem promising, agreeing with those of [3] even though [3] proposes a different model. The purpose this work is expected to serve is to provide a baseline case where a thorough mathematical analysis is possible with which one could compare the more realistic but less mathematically tractable case.

4. Appendix

In this appendix we give the proofs of our results.

Lemma 2. *If $R_0 \leq 1$ then $E_0 := (0, 0)$ is the only steady state of (6); if $R_0 > 1$ then besides $E_0 := (0, 0)$, precisely one of $E_C := (\hat{N}, \hat{D})$ or $E_N := (\bar{N}, 0)$ exist, where $\hat{N}, \hat{D}, \bar{N} > 0$. If $h : [0, \min_j S_j/c_j] \rightarrow \mathbb{R}$ defined by*

$$h(\tau) = f(S - \tau c) - d$$

then when $R_0 > 1$ there is a unique $\tau^ \in (0, \min_j S_j/c_j)$ where $h(\tau^*) = 0$ and $\tau^* > 0$. If $\beta(S - \tau^*c) = 0$ then E_N exists; if $\beta(S - \tau^*c) > 0$ then E_C exists.*

Proof. We observed above that $dh/d\tau < 0$ so h is strictly decreasing.

By (6), $E_N = (\bar{N}, 0)$ exists ($\bar{N} > 0$) if and only if $f(S - \bar{N}c) = d$ and $\beta(S - \bar{N}c) = 0$. Equivalently, $h(\tau^*) = 0$ and $S - \tau^*c \notin B_+$ where $\tau^* := \bar{N}$. Clearly, $R_0 > 1$ if E_N exists since $f(S) > d$.

$E_C = (\hat{N}, \hat{D})$ exists if and only if

$$f(S - (\hat{N} + \hat{D})c) = d + \frac{d\beta(S - (\hat{N} + \hat{D})c)}{d + \alpha(S - (\hat{N} + \hat{D})c)}$$

and $\beta(S - (\hat{N} + \hat{D})c) > 0$. Equivalently, $G(S - \tau c) = 0$ and $S - \tau c \in B_+$ where $\tau := \hat{N} + \hat{D}$. In that case, \hat{N} and \hat{D} are uniquely determined by $\tau := \hat{N} + \hat{D}$ and $\hat{D}/\hat{N} = \beta/(\alpha + d)$ evaluated at $R = S - \tau c$. Since $f(S - (\hat{N} + \hat{D})c) > d$ it follows that $f(S) > d$ and so $G(S) > 0$ because $d/d\eta G(S - \eta c) < 0$ so long as $f \geq d$. Therefore, $R_0 > 1$.

If $R_0 > 1$ then $h(0) > 0$ and since $h(\min_j S_j/c_j) < 0$ by hypothesis there is a unique $\tau^* > 0$ such that $h(\tau^*) = 0$. If $\beta(S - \tau^*c) = 0$ then E_N exists with $\bar{N} = \tau^*$. If $\beta(S - \tau^*c) > 0$ then E_N cannot exist since $h(\bar{N}) = 0$ so by uniqueness $\bar{N} = \tau^*$, contradicting that $\beta(S - \bar{N}c) = 0$. If $\beta(S - \tau^*c) > 0$ and $h(\tau^*) = 0$ then $f(S - \tau c) > d$ for $\tau < \tau^*$ so $\tau \rightarrow G(S - \tau c)$ is strictly decreasing for $\tau < \tau^*$. Since $G(S - \tau^*c) < 0$ and $G(S) > 0$ ($R_0 > 1$) there is a unique $\tau \in (0, \tau^*)$ such that $G(S - \tau c) = 0$. Obviously, $\beta(S - \tau c) \geq \beta(S - \tau^*c) > 0$ so E_C exists and $\hat{N} + \hat{D} = \tau$ when $R_0 > 1$. □

Lemma 3. E_0 is locally asymptotically stable if $G(S) < 0$ ($R_0 < 1$) and a saddle point if $G(S) > 0$ ($R_0 > 1$). In the latter case, the stable manifold of E_0 lies outside Γ if $S \notin A_0$ and it is the portion of the D -axis in Γ if $S \in A_0$.

E_C is locally asymptotically stable when it exists. E_N is locally asymptotically stable when it exists and when $R_N \notin \partial B_+$.

Proof. The Jacobian matrix of (6) at a point (N, D) is given by

$$J = \begin{pmatrix} f - d - \beta + N(f_N - \beta_N) + D\alpha_N & \alpha + D\alpha_D + N(f_D - \beta_D) \\ \beta + N\beta_N - D\alpha_N & -d - \alpha - D\alpha_D + N\beta_D \end{pmatrix}$$

where f, α, β and their partials are evaluated at (N, D) . Note that $f_N(R) = f_D(R) = \nabla f(S - (N + D)c) \cdot (-c) < 0$. Likewise, $\alpha_N(R) = \alpha_D(R) \leq 0$ and $\beta_N(R) = \beta_D(R) \geq 0$.

The Jacobian J at E_0 is

$$J_0 = \begin{pmatrix} f - d - \beta & \alpha \\ \beta & -d - \alpha \end{pmatrix}$$

where f, α, β are evaluated at E_0 . The determinant and the trace of J_0 are given, respectively, by

$$\det J_0 = -d[f - d - \beta] - \alpha f + \alpha d = -dG$$

$$\text{trace } J_0 = f - 2d - \alpha - \beta = G - \frac{\alpha f}{d} - d$$

$G(S) < 0$ implies that the determinant is positive and the trace is negative, implying that E_0 is asymptotically stable. Clearly, $G(S) > 0$ implies that E_0 is a saddle point. If $S \notin A_0$, a computation shows that the eigenvector corresponding to the negative eigenvalue is $(1, p)$ where $p < 0$. If $S \in A_0$, the eigenvector is $(0, 1)$. Thus in former case, the stable manifold enters E_0 from the second and fourth quadrants. In latter case, since $S \in A_0$ and $0 \leq R(t) \leq S$ for all $t > 0$, therefore by assumption (a), $R(t) \in A_0$ for all $t > 0$, therefore $\alpha(R) = 0$ and (6) becomes

$$N' = N[f(R) - d] - \beta(R)N$$

$$D' = -dD + \beta(R)N$$

Now for a trajectory with $N(0) = 0, N(t) \equiv 0$ and $D(t) \rightarrow 0$, so it is attracted to E_0 . Thus the stable manifold of E_0 is the portion of the D -axis in Γ .

The Jacobian J at E_C becomes

$$J_C = \begin{pmatrix} f - d - \beta + \hat{N}f_N - \hat{N}\beta_N + \hat{D}\alpha_N & \alpha + \hat{D}\alpha_D + \hat{N}f_D - \hat{N}\beta_D \\ \beta + \hat{N}\beta_N - \hat{D}\alpha_N & -d - \alpha - \hat{D}\alpha_D + \hat{N}\beta_D \end{pmatrix}$$

where f, α, β and their partials are evaluated at $E_C = (\hat{N}, \hat{D})$. Using the condition of existence of E_C , we have

$$J_C = \begin{pmatrix} -\frac{\alpha\beta}{d+\alpha} + \hat{N}f_N - \hat{N}\beta_N + \hat{D}\alpha_N & \alpha + \hat{D}\alpha_D + \hat{N}f_D - \hat{N}\beta_D \\ \beta + \hat{N}\beta_N - \hat{D}\alpha_N & -d - \alpha - \hat{D}\alpha_D + \hat{N}\beta_D \end{pmatrix}$$

Thus the determinant is given by:

$$\det J_C = -\frac{d\beta\hat{D}\alpha_D}{d+\alpha} + \frac{d\beta\hat{N}\beta_D}{d+\alpha} - d\hat{N}f_N - \alpha\hat{N}f_N + d\hat{N}\beta_N - d\hat{D}\alpha_N - \beta\hat{N}f_D > 0.$$

Note that each summand is nonnegative and $f_N < 0$ implies the strict inequality. The trace is given by:

$$\text{trace } J_C = -\frac{\alpha\beta}{d+\alpha} + \hat{N}f_N - d - \alpha < 0.$$

We therefore conclude that the 'coexistence' steady state E_C , when it exists, is asymptotically stable.

The Jacobian J_N at E_N becomes

$$J_N = \begin{pmatrix} f - d - \beta + \bar{N}(f_N - \beta_N) & \alpha + \bar{N}(f_D - \beta_D) \\ \beta + \bar{N}\beta_N & -d - \alpha + \bar{N}\beta_D \end{pmatrix}$$

where f, α, β and their partials are evaluated at $S - c\bar{N}$. Using condition of existence of $(\bar{N}, 0)$,

$$J_N = \begin{pmatrix} \bar{N}(f_N - \beta_N) & \alpha + \bar{N}(f_D - \beta_D) \\ \bar{N}\beta_N & -d - \alpha + \bar{N}\beta_D \end{pmatrix}$$

Therefore

$$\begin{aligned} \det J_N &= \bar{N}(d\beta_N - (d + \alpha)f_N) > 0 \\ \text{trace } J_N &= \bar{N}f_N - d - \alpha < 0 \end{aligned}$$

Each summand in the expression of the determinant is nonnegative and $f_N < 0$ implies the strict inequality since α vanishes in a neighborhood of E_N . E_N is asymptotically stable. \square

Lemma 4. *Equation (6) has no periodic orbits or heteroclinic cycles.*

Proof. Using Dulac’s function $1/ND$, and the fact that $\alpha_N \equiv \alpha_D$ and $\beta_N \equiv \beta_D$,

$$\begin{aligned} \nabla \cdot \frac{1}{ND}(N', D') &= \frac{f_N}{D} + \frac{\alpha_N}{N} - \frac{\alpha}{N^2} - \frac{\beta_N}{D} - \frac{\alpha_D}{N} + \frac{\beta_N}{D} - \frac{\beta}{D^2} \\ &= \frac{f_N}{D} - \frac{\alpha}{N^2} - \frac{\beta}{D^2} \\ &< 0 \end{aligned}$$

The above argument gives the desired conclusion in case that α and β are C^1 .

We have to be more careful if our piecewise smooth hypotheses hold. In the case of piecewise smooth α and β , system (6) may not be smooth everywhere in Γ since $R = S - (N + D)c$ may belong to ∂A_0 where $\alpha(S - (N + D)c)$ is not smooth or to ∂B_+ where $\beta(S - (N + D)c)$ is not smooth. Our assumptions guarantee that the line $R = S - \tau c$ can meet ∂A_0 in at most one point (or value of τ) which, if it exists, we label τ_0 . Similarly, this line may meet ∂B_+ at most once and we label τ_+ the corresponding value of τ . If the line meets both ∂A_0 and ∂B_+ then $\tau_0 < \tau_+$ by hypothesis (c). Therefore, in the worst case, system (6) fails to be C^1 in Γ only along two lines $N + D = \tau_0$ and $N + D = \tau_+$. Since a periodic orbit or heteroclinic cycle may exist only if $R_0 > 1$ and E_C exists, we may as well assume E_C exists. Recall $\hat{N} + \hat{D} = \tau$ and $E_C \in B_+$ so $\tau > \tau_+$. In the argument below, we will assume the worst case scenario that both lines $N + D = \tau_0$ and $N + D = \tau_+$ belong to Γ , i.e., $\tau_+ < \min_{1 \leq j \leq m} S_j/c_j$. The argument is similar and simpler if neither or only one line meets Γ .

In order to show that a periodic orbit in Γ intersects a straight line $N + D = \tau$ at most twice, and exactly once for the maximal (minimal) value of τ , let us consider the variables

$$u = D/N, \quad v = N + D.$$

The inverse transformation is

$$N = \frac{v}{1 + u}, \quad D = \frac{uv}{1 + u}$$

The system (6) in uv -variables becomes

$$\begin{aligned} u' &= \beta + u(\beta - \alpha - \alpha u - f) \\ v' &= v \left(\frac{f}{1 + u} - d \right) \end{aligned} \tag{8}$$

where α, β, f are functions of v only and the domain in the phase plane is $\{(u, v) : u \geq 0, 0 \leq v \leq v_{\max}\}$ where $v_{\max} = \min_j S_j/c_j$. The two lines $N + D = \tau_0$ and $N + D = \tau_+$ are transformed into the lines $v = \tau_0$ and $v = \tau_+$ parallel to the u -axis in the uv -plane. This divides the uv -plane into three regions ω_1, ω_2 and ω_3 where

$$\begin{aligned} \omega_1 &= \{(u, v) : u \geq 0, 0 \leq v \leq \tau_0\}, \\ \omega_2 &= \{(u, v) : u \geq 0, \tau_0 \leq v \leq \tau_+\}, \\ \omega_3 &= \{(u, v) : u \geq 0, \tau_+ \leq v \leq v_{\max}\} \end{aligned}$$

These regions are shown in Figure 5. Note that when $(u, v) \in \omega_1$ then the resource vector $S - vc$ is in the region outside A_0 , so $\alpha > 0, \beta = 0$. Similarly when $(u, v) \in \omega_2$, then $\alpha = \beta = 0$ and when $(u, v) \in \omega_3$ then $\alpha = 0, \beta > 0$.

As either α or β or both vanish, the $u' = 0$ nullcline consists of $u = 0$ in $\omega_1 \cup \omega_2$ and the graph

$$u = \frac{\beta(S - vc)}{f(S - vc) - \beta(S - vc)}, \quad \tau_+ \leq v$$

in ω_3 . Along this graph, u is a strictly increasing, continuous function of v , vanishing at $v = \tau_+$ and has an asymptote $v = v_a$ in ω_3 where $f(S - v_a c) = \beta(S - v_a c)$. See Fig. 5.

The $v' = 0$ nullclines are given by

$$v = 0,$$

and

$$u = \frac{f(S - vc) - d}{d}, \quad 0 \leq v \leq \tau^*. \tag{9}$$

Note that along (9), u is a strictly decreasing function of v and meets the v -axis at $(0, \tau^*)$ where $f(S - \tau^* c) = d$.

System (8) has the steady state $E_c = (\hat{u}, \hat{v}) \in \omega_3$ in addition to the trivial steady state, where $\hat{v} < \tau^*$ (see Fig. 5). The periodic orbit, if one exists, must enclose (\hat{u}, \hat{v}) .

The following discussion is valid regardless of the relationship between v_a and τ^* . Let $U := \{(u, v) : \hat{v} < v \leq v_{\max}, v' = 0\}$ and $L := \{(u, v) : 0 \leq v < \hat{v}, v' = 0\}$ be two subsets of the nullcline $v' = 0$. Note that $u' > 0$ in U and $u' < 0$ in L . Clearly the intersections of any orbit with the $v' = 0$ nullcline in positive time must alternate between U and L . A periodic orbit, if it exists, will have extreme values of v on $U \cup L$. Since (\hat{u}, \hat{v}) must be enclosed by the periodic orbit, the global maximum value of v must be in U , and the global minimum in L . We claim

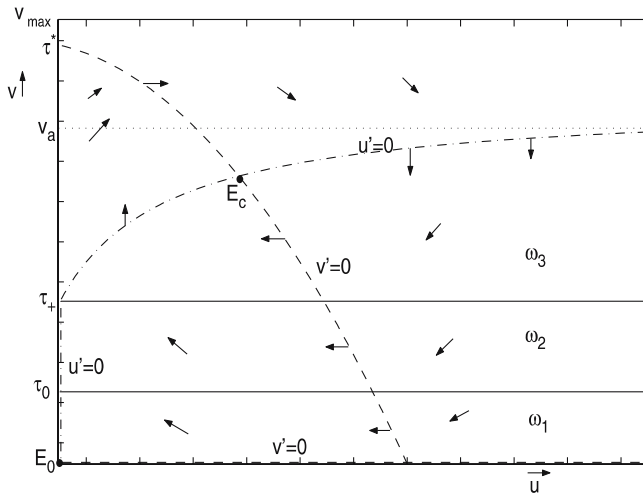


Fig. 5. Vector field in the uv -plane

there are no other local extrema. Suppose M is the global maximum lying on a horizontal line $v = v_M$. Thus $M \in U$ and the next intersection of the periodic orbit with the $v' = 0$ nullcline must be in L at a point m that lies on a horizontal line $v = v_m$. The next intersection must be in U , say at a point M_1 . If $M_1 \neq M$, then to preserve periodicity, the orbit must pass through M again in positive time, so it must intersect itself, thereby violating the uniqueness of solutions. Therefore the only intersection of the periodic orbit with U is the point M . Likewise, the only intersection of the periodic orbit with L is m . In other words, the periodic orbit touches two lines $v = v_M$ and $v = v_m$ tangentially at one point each, and it intersects all horizontal lines $v = v$ with $v_m < v < v_M$ transversally exactly twice – once with $v' > 0$ and once with $v' < 0$.

We may now draw conclusions about the original ND -system.

A periodic orbit in Γ can intersect a straight line $N + D = \tau$ at most twice. There is a unique straight line $N + D = \tau_M$ such that the periodic orbit has a maximum value of $N + D$ on it, and a unique straight line $N + D = \tau_m$ such that the periodic orbit has a minimum value of $N + D$ on it. $(N + D)'|_{\tau_M} = (N + D)'|_{\tau_m} = 0$ and the periodic orbit touches the two lines tangentially at these two points. For all other lines $N + D = \tau$ with $\tau_m < \tau < \tau_M$, the periodic orbit intersects transversally at exactly two points, one with $(N + D)' > 0$ and the other with $(N + D)' < 0$. The possibility of the periodic orbit lying entirely in the region $N + D > \tau_+$ has already been ruled out by the Dulac's criterion. The other possible occurrences of a periodic orbit with reference to the lines $N + D = \tau_0$ and $N + D = \tau_+$ are summarised in Fig. 6a and the worst of them is depicted in Fig. 6b and discussed below, in which a periodic orbit O transversally intersects both lines at exactly two points each, once with $(N + D)' > 0$ and once with $(N + D)' < 0$. This results in the formation of three simply connected regions labeled I, II and III in Fig. 6b.

Since system (6) fails to be C^1 along the two lines we can construct Jordan curves in the three regions as follows.

In region I, the Jordan curve is $L_1 \cup O_1$ where L_1 is a line parallel to and a distance δ away from $N + D = \tau_0$ with endpoints on O inside region I (where δ can be made arbitrarily small) and O_1 is the portion of O in region I extending between these two points. In region II, the Jordan curve is $L_2 \cup O_2 \cup L_3 \cup O_4$. Here $L_2(L_3)$ is a line parallel to and a distance δ away from $N + D = \tau_0(\tau_+)$ inside region II with endpoints on O and O_2 and O_4 are portions of O extending between these points inside region II. Likewise, a third Jordan curve in region III is $L_4 \cup O_3$ where L_4 is a line parallel to and a distance δ away from $N + D = \tau_+$ with endpoints on O inside region III and O_3 is the portion of O in region III extending between these two points.

Let the regions enclosed by these Jordan curves be denoted as I_δ, II_δ and III_δ respectively. Let dA denote the element of area, \mathbf{n} denote the unit normal on the curve and dl the element of arc length along the curve. We have that

$$\oint_O \frac{1}{ND}(N', D') \cdot \mathbf{n}dl = 0$$

On the other hand,

$$\begin{aligned} \oint_O \frac{1}{ND}(N', D') \cdot \mathbf{n}dl &= \oint_{L_1 \cup O_1} \frac{1}{ND}(N', D') \cdot \mathbf{n}dl \\ &+ \oint_{L_2 \cup O_2 \cup L_3 \cup O_4} \frac{1}{ND}(N', D') \cdot \mathbf{n}dl \\ &+ \oint_{L_4 \cup O_3} \frac{1}{ND}(N', D') \cdot \mathbf{n}dl + E_\delta \end{aligned}$$

where E_δ is an error introduced due to off-setting the lines L_i each δ distance from the two lines $N + D = \tau_0$ and $N + D = \tau_+$ while approximating the integral

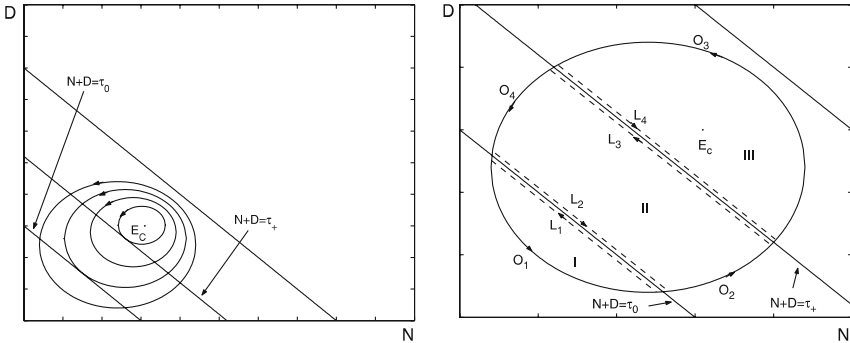


Fig. 6. a Possible occurrences of a periodic orbit inside Γ . **b** Jordan curves.

along the closed curve O as a sum of the integrals along the three Jordan curves. Therefore E_δ depends on δ . Note that E_δ is small and as $\delta \rightarrow 0$, $E_\delta \rightarrow 0$.

By Green’s Theorem, we get

$$\oint_O \frac{1}{ND}(N', D') \cdot \mathbf{n}d\mathbf{l} = \int_{I_\delta} \int \nabla \cdot \frac{1}{ND}(N', D')dA + \int_{II_\delta} \int \nabla \cdot \frac{1}{ND}(N', D')dA + \int_{III_\delta} \int \nabla \cdot \frac{1}{ND}(N', D')dA + E_\delta$$

Each of the double integrals is negative, and as $\delta \rightarrow 0$, it becomes more negative, and $E_\delta \rightarrow 0$. Thus the integral is negative! This contradiction implies that no periodic orbit can exist in Γ . □

Proof. (Theorem1)

If $R_0 < 1$ Lemma 3 implies that $E = \{E_0\}$ and that E_0 is locally stable. It is globally attractive by the Poincaré–Bendixson theory since there are no other equilibria in the positively invariant set Γ .

If $R_0 > 1$ then $G(S) > 0$ and by Lemma 3 E_0 is a saddle whose stable manifold lies outside Γ . Since Γ is bounded and positively invariant, the Poincaré–Bendixson theory implies that there exists another equilibrium. Thus, either $E = \{E_0, E_N\}$ or $E = \{E_0, E_C\}$ since both E_N and E_C cannot exist. By Lemma 4 and the Poincaré–Bendixson theory, the nontrivial equilibrium is the global attractor. □

Proof. (Theorem2)

To prove this, we will use Theorem F.1 of [18]. Define

$$\Sigma := S - [R + (N + D)c]$$

Then (2) can be written in terms of the variables N, D, Σ as follows

$$\begin{aligned} N' &= N[f(R) - d] + \alpha(R)D - \beta(R)N \\ D' &= -dD - \alpha(R)D + \beta(R)N \\ \Sigma' &= -d\Sigma \end{aligned} \tag{10}$$

where $R = S - \Sigma - (N + D)c$. This system is restricted to the positively invariant set $\tilde{\Gamma} = \{(N, D, \Sigma) | N, D \geq 0, \Sigma + (N + D)c \leq S\}$. The trivial, active only and coexistence steady states of (10) are $\sigma_0 = (E_0, 0)$, $\sigma_N = (E_N, 0)$ and $\sigma_C = (E_C, 0)$. Let σ denote the set of rest points of (10).

The matrix A of Theorem F.1 of [18] is $\text{diag}_{m \times m}(-d)$ and clearly (H1) is satisfied. By Theorem 1, (6) has either one or two rest points. E_0 is hyperbolic since $R_0 \neq 1$ (and so $G(S) \neq 0$), implying that the Jacobian J_0 has a nonzero determinant. E_N and E_C , whenever they exist, are also hyperbolic since $\nabla f \cdot c > 0$. Thus the hyperbolicity hypothesis (H2) is satisfied. If $R_0 < 1$, then E_0 is asymptotically stable and thus has a two-dimensional stable manifold. If $R_0 > 1$, then E_0 has a one-dimensional stable manifold. E_N or E_C , whichever of the two exists, has a two-dimensional stable manifold. Thus (H3) is satisfied. Theorem 1 establishes

(H4) by showing that every solution of (6) converges to a steady state. Finally, (H5) is satisfied due to Lemma 4.

Theorem F.1 of [18] therefore allows us to conclude that if $(N(t), D(t), \Sigma(t))$ is a solution of (10), then

$$\lim_{t \rightarrow \infty} (N(t), D(t), \Sigma(t)) = \sigma_i$$

where $\sigma_i = \sigma_0, \sigma_N$ or σ_C if the set of rest points of (6) is $\{E_0\}, \{E_0, E_N\}$ or $\{E_0, E_C\}$ respectively. This is equivalent to concluding the following:

If $R_0 < 1$, then $\sigma = \{\sigma_0\}$ and all trajectories of (10) are attracted to σ_0 . Therefore $e = \{e_0\}$ and all trajectories of (2) are attracted to e_0 .

If $R_0 > 1$, then $\sigma = \{\sigma_0, \sigma_N\}$ or $\{\sigma_0, \sigma_C\}$ and all trajectories of (10) converge to the nontrivial steady state except for those with initial conditions on the stable manifold of σ_0 . Therefore $e = \{e_0, e_N\}$ or $\{e_0, e_C\}$ and all trajectories of (2) converge to the nontrivial steady state except for those starting on the stable manifold of e_0 .

Now σ_0 has an $(m + 1)$ -dimensional stable manifold. If $S \in A_0$, the tangent space of the stable manifold of σ_0 is spanned by the $(m + 1)$ -vectors

$$\begin{pmatrix} 0 \\ 1 \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ e_1 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ e_2 \end{pmatrix}, \dots, \begin{pmatrix} 0 \\ 0 \\ e_m \end{pmatrix}$$

where $\mathbf{0} = (0, \dots, 0)^t \in \mathbb{R}^m$ and $\{e_1, \dots, e_m\}$ is the standard basis for \mathbb{R}^m , and by

$$\begin{pmatrix} 1 \\ p \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ e_1 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ e_2 \end{pmatrix}, \dots, \begin{pmatrix} 0 \\ 0 \\ e_m \end{pmatrix}, \quad \text{with } p < 0$$

if $S \notin A_0$.

In the former case, since $S \in A_0$ and $S \notin \partial A_0$ by assumption, if $(N(t), D(t), \Sigma(t))$ is a solution belonging to the stable manifold of σ_0 then $R(t) \rightarrow S$, so $R(t) \in A_0$ for large t , and therefore $\alpha(R) = 0$ and (10) becomes

$$\begin{aligned} N' &= N[f(R) - d] - \beta(R)N \\ D' &= -dD + \beta(R)N \\ \Sigma' &= -d\Sigma \end{aligned}$$

For a solution with $N(0) = 0, N(t) \equiv 0, D(t) \rightarrow 0$ and $\Sigma(t) \rightarrow 0$ and so it is attracted to σ_0 . Therefore the stable manifold of σ_0 is the portion of the $N = 0$ face in $\bar{\Gamma}$ because $D(0)$ and $\Sigma(0)$ can be arbitrarily chosen. Equivalently, the stable manifold of e_0 is the $N = 0$ face of \mathbb{R}_+^{m+2} as $N(0) = 0 \Rightarrow N(t) \equiv 0, D(t) \rightarrow 0$ and $R(t) \rightarrow S$ so a trajectory starting in the $N = 0$ face is attracted to e_0 .

In the latter case, suppose the codimension one, local stable manifold of σ_0 is given by $\phi(N, D, \Sigma) = 0, \phi(0, 0, \mathbf{0}) = 0$. If $(N(t), D(t), \Sigma(t))$ is a solution belonging to the stable manifold, then $\phi_N N' + \phi_D D' + \phi_\Sigma \Sigma' = 0$ for all large t . Since the tangent space of the stable manifold is spanned by the vectors given above, $\nabla\phi(0, 0, \mathbf{0}) = (-p, 1, \mathbf{0})$ and thus $D'(t)/N'(t) \rightarrow p, t \rightarrow \infty$. (Note that

the determinant of the coefficient matrix for the N and D equations is $-dG(R(t))$ and $R(t) \rightarrow S$ so $G(R(t)) > 0$ because $G(S) > 0$ which implies that N' and D' cannot be both identically zero.) Since $D(t) \rightarrow 0$ and $N(t) \rightarrow 0$, by L'Hospital's Rule, $D(t)/N(t) \rightarrow p < 0$. Therefore, the stable manifold of σ_0 cannot contain any solutions with N and D nonnegative.

We therefore conclude that the nontrivial steady state is the global attractor for all trajectories of (2) in $R_+^{m+2} - \{e_0\}$ with $N(0) > 0$. \square

Acknowledgements. Supported by NSF Grant DMS 0414270,

References

1. Arino, O., Sanchez, E., Webb, G.F.: Necessary and sufficient conditions for asynchronous exponential growth in age structured cell populations with quiescence. *J Math Anal Appl* **215**(2), 499–513 (1997)
2. Bailey, J.E., Ollis, D.: *Biochemical engineering fundamentals*, 2nd ed. NY: McGraw Hill 1986
3. Bär, M., von Hardenberg, J., Meron, E., Provenzale, A.: Modelling the survival of bacteria in drylands: the advantage of being dormant. *Proc R Soc Lond B* **269**, 937–942 (2002)
4. Cunningham, A., Maas, P.: Time lag and nutrient storage effects in the transient growth response of *Chlamydomonas reinhardtii* in nitrogen-limited batch and continuous culture. *J Gen Microbiol* **104**, 227–231 (1978)
5. De Groot, W.T.: Modelling the multiple nutrient limitation of algal growth. *Ecol Model* 99–119 (1983)
6. Drenkard, E., Ausubel, F.M.: *Pseudomonas* biofilm formation and antibiotic resistance are linked to phenotypic variation. *Nature* **416**, 740–743 (2002)
7. Grover, J.P.: Constant and variable yield models of population growth: responses to environmental variability and implications for competition. *J Theor Biol* **158**, 409–28 (1992)
8. Grover, J.P.: *Resource competition. Population and community biology series 19.* New York: Chapman and Hall 1997
9. Gyllenberg, M., Webb, G.F.: Age-size structure in populations with quiescence. *Math Biosci* **86**, 67–95 (1987)
10. Gyllenberg, M., Webb, G.F.: Quiescence as an explanation of Gompertzian tumor growth. *Growth Dev Aging* **53**, 25–33 (1989)
11. Gyllenberg, M., Webb, G.F.: A nonlinear structured population model of tumor growth with quiescence. *J Math Biol* **28**, (6), 671–694 (1990)
12. Gyllenberg, M., Webb, G.F.: Quiescence in structured population dynamics: applications to tumor growth. *Mathematical population dynamics* (New Brunswick, NJ, 1989), 4562, *Lecture Notes in Pure and Appl math*, 131. New York: Dekker, 1991
13. Hansen, S.R., Hubbell, S.P.: Single nutrient microbial competition: agreement between theoretical and experimental forecast outcomes. *Science* **207**, 1491–1493 (1980)
14. Hu, Y., Butcher, P.D., Mangan, J.A., Rajandream, M-A., Coates, A.: Regulation of hmp gene transcription in *Mycobacterium tuberculosis*: effects of Oxygen limitation and nitrosative and oxidative stress. *J Bacteriol* **181**, 3486–3493 (1999)
15. Jäger, W., Krömker, S., Tang, B.: Quiescence and transient growth dynamics in chemostat models. *Math. Bio. sci.* **119**, 225–239 (1994)
16. Kaprelyants, A.S., Gottschal, J.C., Kell, D.B.: Dormancy in non-sporulating bacteria. *FEMS Microbiol. Rev* **10**(3–4), 271–286 (1993)

17. Kell, D.B., Kaprelyants, A.S., Weichart, D.H., Harwood, C.R., Barer, M.R.: Viability and activity in readily culturable bacteria: a review and discussion of the practical issues. *A van Leeuwenhoek* **73**, 169–187 (1998)
18. Smith, H.L., Waltman, P.: *The theory of the chemostat*. Cambridge: Cambridge University Press 1995
19. Sommer, U.: The paradox of the plankton: fluctuations of phosphorus availability maintain diversity of phytoplankton in flow-through cultures. *Limnol Oceanogr* **29**, 633–636 (1984)
20. Sommer, U.: Competition and coexistence. *Nature* **402**, 366–367 (1999)
21. Tang, B., Sitomer, A., Jackson, T.: Population dynamics and competition in chemostat models with adaptive nutrient uptake. *J Math Biol* **35**, 453–479 (1997)
22. Tilman, D.: *Resource competition and community structure*. Princeton: Princeton University Press 1982
23. Tilman, D.: *Dynamics and structure of plant communities*. Princeton: Princeton University Press 1988
24. Wayne, L.G., Hayes, L.G.: An in vitro model for sequential study of shift-down of *Mycobacterium tuberculosis* through two stages of nonreplicating persistence. *Infect Immun* **64**, (6), 2062–2069 (1996)