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The ideal free distribution and bacterial growth on two substrates

Vlastimil Křivan[a,b,*]

[a]Department of Theoretical Biology, Institute of Entomology, Branišovská 31, 370 05 České Budějovice, Czech Republic
[b]National Center for Ecological Analysis and Synthesis, 735 State Street, Santa Barbara, CA 93101-3351, USA

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Abstract

A population dynamical model describing growth of bacteria on two substrates is analyzed. The model assumes that bacteria choose substrates in order to maximize their per capita population growth rate. For batch bacterial growth, the model predicts that as the concentration of the preferred substrate decreases there will be a time at which both substrates provide bacteria with the same fitness and both substrates will be used simultaneously thereafter. Preferences for either substrate are computed as a function of substrate concentrations. The predicted time of switching is calculated for some experimental data given in the literature and it is shown that the fit between predicted and observed values is good. For bacterial growth in the chemostat, the model predicts that at low dilution rates bacteria should feed on both substrates while at higher dilution rates bacteria should feed on the preferred substrate only. Adaptive use of substrates permits bacteria to survive in the chemostat at higher dilution rates when compared with non-adaptive bacteria.

Keywords: Bacteria; Diauxie; Optimal foraging; Ideal free distribution; Population dynamics; Evolutionary ecology

0. Introduction

There is a growing realization in ecology that an understanding of the basic mechanisms that influence species coexistence cannot be achieved without considering animal behavior. Most of the classical models of population ecology do not include details of animal behavior despite the fact that it has been clearly demonstrated that animal behavior changes in response to a changing environment (e.g., with response to changing population numbers). There are clear examples where changes in population numbers cause changes in animal behavior. For example, in systems with one predator and multiple prey species, the predator switches its attacks to the most abundant prey (Murdoch, 1969; Murdoch et al., 1975). In food chains, in response to an increase in the number of top predators, the middle species in a tri-trophic food chain may decrease its activity level or undergo a habitat shift (e.g., Bolker et al., 2003; Werner and Peacor, 2003; Schmitz et al., 2004). What is less clear is whether animal behavior, in turn, influences population dynamics, i.e., whether interactions between population ecology and behavioral ecology are predominantly mutual, or one way only. Predator–prey models suggest that in two-patch environments, optimal predator foraging promotes species persistence by relaxing the apparent competition between prey species (Holt, 1977,1987,1996; Abrams and Matsuda, 1996; Gleeson and Wilson, 1986; Křivan, 1996, 1997; Fryxell and Lundberg, 1997; Křivan, 2003a,b). On the other hand, the effect of the adaptive behavior of the middle species in a food chain does not seem to lead to such strong dependencies (Křivan and Sirot, 2004) but see Abrams (1984). These theories are based on the basic postulate of evolutionary ecology which assumes that evolution works, through natural selection, toward a higher individual fitness. Thus, evolution favors those phenotypes that achieve the highest fitness and that cannot be replaced by different phenotypes with the same fitness (these phenotypes correspond to Evolutionarily Stable Strategies; Maynard Smith, 1982).

Diauxic growth (Monod, 1942) refers to the phenomenon in which bacteria growing on a mixture of two substrates utilize these substrates sequentially in two

*Corresponding author. Fax: +420 38 777 5367.
E-mail address: krivan@entu.cas.cz.

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exponential growth cycles separated by an intermediate lag period called "diauxic lag". This phenomenon gave rise to a so-called cybernetic framework which assumes that microbial regulatory processes are optimized (Kompala et al., 1984, 1986; Dhurjati et al., 1985; Ramkrishna et al., 1987; Straight and Ramkrishna, 1994a; Ramakrishna et al., 1996; Narang et al., 1997a,b,c). All these references are based on the assumption that microbes act to optimize their cellular growth rate. Although maximization of the per capita population growth rate can give an optimal bacterial foraging strategy (Kompala et al., 1984), the research on cybernetic modeling defines bacterial strategy in another way. Following microeconomic theory, these authors assumed that when presented with a multiple choice, microbes will invest available resources in order to maximize the returns from their investment. This assumption leads to a matching law which states that the fractional allocation of resources equals the fractional returns (Straight and Ramkrishna, 1994a). Thus, if r_1 and r_2 are the per capita bacterial population growth rates on two substrates then the growth on the mixture of these two substrates is described as $u_1r_1 + u_2r_2$ where $u_1 + u_2 = 1$ are controls which define allocation of critical resources for utilization of either resource. Cybernetic modeling assumes that these controls are given explicitly as $u_i = r_i/(r_1 + r_2)$. This is a special case of the input matching principle used in ecology which predicts that the number of competitors in a patch should be proportional to the total resource input received by that patch (Parker, 1978). This matching principle is a special form of the Ideal Free Distribution (IFD, Fretwell and Lucas, 1970) that describes animal distribution among several food patches. However, the input matching principle considers a very particular situation where resources continuously arrive in thesystem and then they are immediately consumed (Tregenza, 1994). Thus, there is no standing crop of resources which is certainly not the case of most systems including those in which bacteria are cultivated on several sugars either in a batch or in a chemostat. Moreover, it was shown that when resource dynamics are considered, consumers may not drive resources to the level where the matching principle holds (Křivan and Schmitz, 2003) because the IFD may dictate that consumers feed on one resource only. This means that, when applying the matching law to predict bacterial preferences for resources, such a strategy may not be evolutionarily stable (Maynard Smith, 1982).

In contrast to the results of batch culture experiments where substrates are typically assumed to be sequentially utilized (but see, Egli, 1995), in continuous cultures simultaneous utilization of different substrates typically occurs at low dilution rates while at higher dilution rates bacteria become selective and they utilize only the preferred substrate (for a review see, Ramkrishna et al., 1987; Egli, 1995; Ramakrishna et al., 1996).

In this article I will analyze a two-substrate bacteria model which assumes that bacteria feed on the substrate that maximizes bacterial fitness measured as the per capita bacterial population growth rate. In particular, I will discuss the following aspect of the model:

1. For batch growth, bacteria should use first the substrate that provides them with the highest per capita population growth rate. However, there is a critical concentration of the preferred substrate below which bacteria will feed on both substrates. Thus, at a low concentration of the preferred substrate both substrates will be used simultaneously which leads to the IFD of bacteria over the two substrates.
2. Using some experimental data taken from the literature, I will compare the predicted times when bacteria should switch from the preferred substrate to both substrates with observed times.
3. For continuous cultivation, I will analyze dependence of equilibrial species densities on the dilution rate when bacteria behave adaptively. I will show that at low dilution rates bacteria should feed on both substrates while at a higher dilution rates they should use the more profitable substrate only. Moreover, adaptive bacterial behavior allows bacteria to survive in the chemostat at dilution rates for which they would die out if they were non-adaptive (i.e., if their preferences for either substrate were fixed).

1. Model

I consider a bacterial population with biomass concentration C growing on a mixture of two substrates (e.g., sugars, carbon sources, etc.) with concentrations S_1 and S_2, respectively. The equations governing the dynamics of the model are

$$\begin{aligned}\frac{dS_1}{dt} &= D(S_{01} - S_1) - \frac{1}{Y_1}\frac{S_1}{K_1 + S_1}u_1C,\\ \frac{dS_2}{dt} &= D(S_{02} - S_2) - \frac{1}{Y_2}\frac{S_2}{K_2 + S_2}u_2C,\\ \frac{dC}{dt} &= \left(\frac{\mu_1 S_1}{K_1 + S_1}u_1 + \frac{\mu_2 S_2}{K_2 + S_2}u_2 - D\right)C. \end{aligned} \quad (1)$$

This model is general enough to describe both batch culture as well as chemostat culture. In the case of chemostat culture the model assumes that the inflow substrate concentrations are S_{01} and S_{02}, respectively, the uptake of substrates is described by the Monod equation, u_i $(u_1 + u_2 = 1)$ is a control variable which describes bacterial preference for the ith substrate, and D is the dilution rate. The batch culture is modeled by setting dilution rate D equal to zero. Here μ_i and K_i are maximum specific growth and saturation Monod constants, respectively, and Y_i is the yield of cell mass per unit of substrate S_i for the case where cells are grown on S_i alone. Controls u_i are not fixed but they change in time as substrate concentrations change. Model (1) is highly simplified. For

example, it does not take into consideration the kinetics of enzymes that are necessary for the degradation of substrates. In fact, this model assumes that the enzyme kinetics are very fast with respect to substrate degradation, which may not be true in reality. However, these simplifications lead to a tractable model (1) as we will see.

The question is whether it is possible to predict the time evolution of microbial preferences (u_i) as substrates and bacterial concentrations change. The crucial assumption is the choice of the bacterial fitness function. Following Kompala et al. (1986), I assume that bacterial fitness is proportional to the per capita population growth rate $1/C\,dC/dt$. This implies that if bacteria grow faster on substrate 1, i.e.,

$$\frac{\mu_1 S_1}{K_1+S_1} > \frac{\mu_2 S_2}{K_2+S_2} \tag{2}$$

then fitness is maximized by utilizing substrate 1 ($u_1=1$) alone, while if the opposite inequality holds than fitness is maximized by utilizing substrate 2 alone ($u_2=1$). Bacteria that mimic this strategy most closely will have a higher per capita population growth rate than those with different strategies and should therefore spread in the population.

In this article, I will always assume that the intrinsic per capita bacterial growth rate on substrate 1 is higher than that on substrate 2 (i.e., $\mu_1>\mu_2$). Because $\frac{\mu_i S_i}{K_i+S_i}\sim\mu_i$ ($i=1,2$) for high substrate concentrations, it follows that at high substrate levels, substrate 1 will be preferentially used by bacteria since inequality (2) then holds. In this sense, substrate 1 is the preferred substrate. However, which substrate will actually be used depends on the environmental conditions, i.e., on the relative proportion of the two substrates in the environment. For example, at low concentrations of the preferred substrate, the alternative substrate can be used by bacteria. The "switching" curve (which is a curve in the substrate 1–substrate 2 phase plane and a manifold in the substrate 1–substrate 2–bacteria phase space) defined by

$$\frac{\mu_1 S_1}{K_1+S_1} = \frac{\mu_2 S_2}{K_2+S_2}$$

(dashed line in Fig. 1) divides the substrate 1–substrate 2 concentration phase space in two parts.

2. Batch culture

First, I consider a batch culture which corresponds to setting the dilution rate in model (1) equal to zero (i.e., $D=0$). Fig. 1 shows the switching curve (dashed line) for the growth of *Klebsiella oxytoca* on glucose and arabinose. Below this curve, the bacterial per capita population growth rate is higher on substrate 1 (glucose) while above the curve utilizing substrate 2 (arabinose) gives a higher bacterial growth rate. Fig. 1 shows two trajectories of model (1). Let us consider the one which starts below the switching curve. As bacteria feed initially only on substrate 1, the concentration of substrate 2 does not change initially

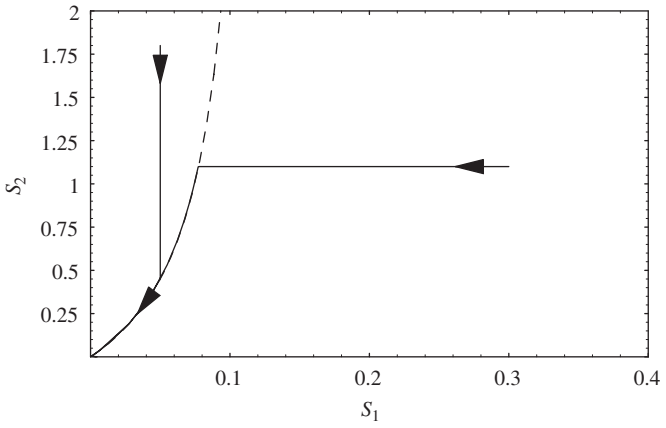

Fig. 1. Switching curve (dashed line) for the growth of *K. oxytoca* on a mixture of glucose ($\mu_1=1.08,\ K_1=0.01,\ Y_1=0.52$) and arabinose ($\mu_2=1.00,\ K_2=0.05,\ Y_2=0.5$). The two solid lines are solutions of model (1) for batch bacterial growth ($D=0$). Parameters taken from Kompala et al. (1986).

along the trajectory. As substrate 1 is used up, bacterial fitness decreases along the trajectory. When the trajectory hits the switching curve, feeding on either substrate leads to exactly the same bacterial fitness. Because trajectories that start above the switching curve also tend to the switching curve it is clear that once a trajectory hits the switching curve it cannot leave (Appendix A). As substrate concentrations cannot leave the switching curve, I can compute explicitly bacterial preferences for either substrate as a function of substrate concentrations. Calculations given in Appendix A show that along the switching curve bacterial preference for substrate 1 is

$$u_1 = \frac{Y_1(S_1\mu_1-(K_1+S_1)\mu_2)^2}{S_1^2Y_1\mu_1^2-2S_1(K_1+S_1)Y_1\mu_1\mu_2+((K_1+S_1)^2Y_1+K_1K_2Y_2)\mu_2^2}. \tag{3}$$

This gives the following IFD of bacteria across the two substrates

$$\frac{u_1}{u_2} = \frac{Y_1(S_1\mu_1-(K_1+S_1)\mu_2)^2}{K_1K_2Y_2\mu_2^2}. \tag{4}$$

Bacterial kinetics along the switching curve

$$\frac{dC}{dt} = \left(\frac{\mu_1 S_1}{K_1+S_1}u_1+\frac{\mu_2 S_2}{K_2+S_2}u_2\right)C = \frac{\mu_1 S_1}{K_1+S_1}C = \frac{\mu_2 S_2}{K_2+S_2}C$$

are again described by the Monod law.

Preference u_i for the ith substrate has theoretically two meanings. In the case of a monomorphic bacterial population it is the preference of an average individual for substrate i. In the case of a polymorphic population it is the proportion of the population feeding on substrate i. Arguments given in Egli (1995) suggest that it is more likely that the bacterial population remains monomorphic when

it uses two or more substrates, e.g., each individual bacteria utilizes both substrates simultaneously.

Model (1) allows me to estimate, for any initial concentrations of substrates and bacteria, the switching time, i.e., the first time when the corresponding trajectory hits the switching curve. To see whether actual bacteria switch optimally, I compare predicted switch times from model (1) with those given in Kompala et al. (1986). Kompala et al. (1986) gave 10 figures for growth of *K. oxytoca* on a mixture of two substrates under different initial substrate concentrations. These data are graphically presented in Figs. 6–14 and Fig. 18 in Kompala et al. (1986). I scanned these figures (see solid data points in Fig. 2, left panel) and estimated from these data the time of switching as the first time when there was a visible decrease in the slope along the bacterial growth curve. The predicted and observed times of switching are given in Table 1. The predicted time of switching is insignificantly lower (Student two sided t-test failed to reject null hypothesis at significance level 0.05; t-stat $= 0.5$, P-value $= 0.6$) than the observed time of switching. It is clear that the overall agreement is good.

The curves shown in Fig. 2 are simulations of model (1) for parameter values and initial substrate and bacterial concentrations given in Kompala et al. (1986). These parameters were estimated from the growth of *K. oxytoca* on a single substrate. The main discrepancy between the observed values and model predictions are due to diauxic lag which is not incorporated in model (1).

The time evolution of bacterial preference for the more profitable substrate 1 (glucose, u_1) is shown in Fig. 2, right panel. Initially, only glucose is used ($u_1 = 1$). As the concentration of this substrate decreases the two substrates will become equally profitable. At this time there is a sharp decrease in bacterial preference for substrate 1. This is exactly at the time when the corresponding trajectory of model (1) hits the switching curve (see Fig. 1). From then on, bacteria use both substrates and the preference for substrate 1 is given by formula (3). The preference for substrate 1 tends to increase to an asymptotic level as substrate 1 concentration converges to zero. The asymptotic preference can be computed explicitly from formula (3) to be

$$\frac{K_1 Y_1}{K_1 Y_1 + K_2 Y_2}. \tag{5}$$

This asymptotic value is 0.0025 for glucose and lactose (Fig. 2D–G), 0.05 for glucose and xylose (Fig. 2A–C), 0.17 for glucose and arabinose (Fig. 2H–I) and 0.5 for glucose and fructose (Fig. 2J).

3. Chemostat culture

Second, I consider the effect of optimal substrate switching on bacterial growth in the chemostat (in which case the dilution rate $D>0$ in model (1)). I start with analyzing equilibria of model (1). The switching curve (shown as a dashed line in Fig. 3) divides the substrate phase space in two parts: below the switching curve bacteria feed on substrate 1 only ($u_1 = 1$) while in the region above the switching curve they feed on substrate 2 only ($u_2 = 1$). At the points on the switching curve bacterial preferences are not a priori given. I will assume that when at very low concentrations (i.e., when substrate concentrations are almost equal to inflow concentrations S_{01} and S_{02} as if there were no bacteria, see model (1)) bacteria achieve a higher growth rate when feeding on substrate 1, i.e.,

$$\frac{\mu_1 S_{01}}{K_1 + S_{01}} > \frac{\mu_2 S_{02}}{K_2 + S_{02}}. \tag{6}$$

Appendix B shows that for any dilution rate D there exists at most one equilibrium at which bacteria achieve a positive concentration.

For low dilution rates ($D < \frac{\mu_2 S_{02}}{K_2 + S_{02}}$), calculations given in Appendix B show that model (1) has a non-trivial equilibrium $E^\star$ which is located on the switching curve (Fig. 3A). This equilibrium can be explicitly computed (see Appendix B)

$$\begin{aligned} S_1^\star &= \frac{DK_1}{\mu_1 - D}, \\ S_2^\star &= \frac{DK_2}{\mu_2 - D}, \\ C^\star &= S_{01} Y_1 \mu_1 + S_{02} Y_2 \mu_2 - D(K_1 Y_1 + K_2 Y_2) \\ &\quad + D^2 \left(\frac{K_1 Y_1}{D - \mu_1} + \frac{K_2 Y_2}{D - \mu_2} \right). \end{aligned} \tag{7}$$

The bacterial preferences for either substrate at population equilibrium $E^\star$ are (Appendix B)

$$u_1^\star = \frac{Y_1 \mu_1 [S_{01}\mu_1 - D(K_1 + S_{01})]}{(\mu_1 - D) C^\star}, \quad u_2^\star = 1 - u_1^\star. \tag{8}$$

Besides equilibrium $E^\star$, model (1) has two other potential equilibria. One corresponds to the case where bacteria feed on substrate 1 alone

$$E^1 = \left\{ \frac{DK_1}{\mu_1 - D}, S_{02}, \frac{Y_1 \mu_1 (S_{01}\mu_1 - D(K_1 + S_{01}))}{\mu_1 - D} \right\} \tag{9}$$

and one where bacteria feed on substrate 2 alone

$$E^2 = \left\{ S_{01}, \frac{DK_2}{\mu_2 - D}, \frac{Y_2 \mu_2 (S_{02}\mu_2 - D(K_2 + S_{02}))}{\mu_2 - D} \right\}.$$

However, neither E^1 nor E^2 is an equilibrium under the assumption that dilution rate is small because point E^1 is above the switching curve, i.e., in the region where bacteria should feed on substrate 2 alone, and point E^2 is below the switching curve, i.e., in the region of the phase space where bacteria should feed on substrate 1 alone (Fig. 3A). Thus, trajectories of model (1) which start below the switching curve tend initially to E^1 and trajectories that start above the switching curve tend initially to E^2. However, when they reach the switching curve they cannot cross it and they slide along this curve to the equilibrium $E^\star$.

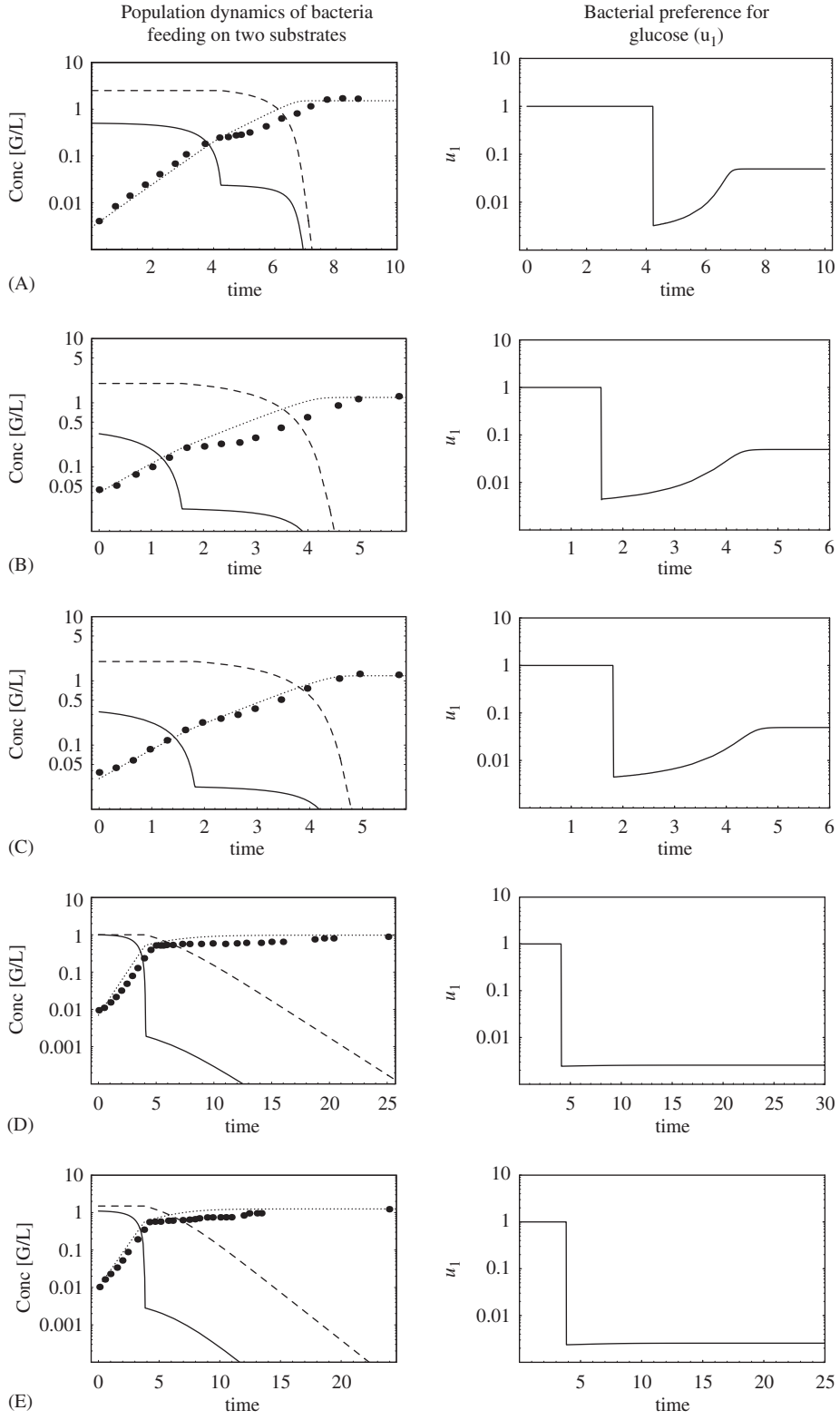

Fig. 2. The batch growth of *K. oxytoca* on two substrates (data shown as solid dots were scanned from Kompala et al. (1986)). Substrates corresponding to each panel are specified in Table 1. The lines are predictions based on model (1) for batch bacterial growth. The parameters for simulations are those given in Kompala et al. (1986) for the growth of *K. oxytoca* on a single substrate (glucose: $\mu = 1.08$, $K = 0.01$, $Y = 0.52$; arabinose: $\mu = 1.00$, $K = 0.05$, $Y = 0.5$; fructose: $\mu = 0.94$, $K = 0.01$, $Y = 0.52$; xylose: $\mu = 0.82$, $K = 0.2$, $Y = 0.5$; lactose: $\mu = 0.95$, $K = 4.5$, $Y = 0.45$). The preferred substrate (glucose, solid line), the alternative substrate (dashed line) and *K. oxytoca* (dot line) are shown in the left panel. The right panel shows predicted preference of *K. oxytoca* for the preferred substrate (u_1).

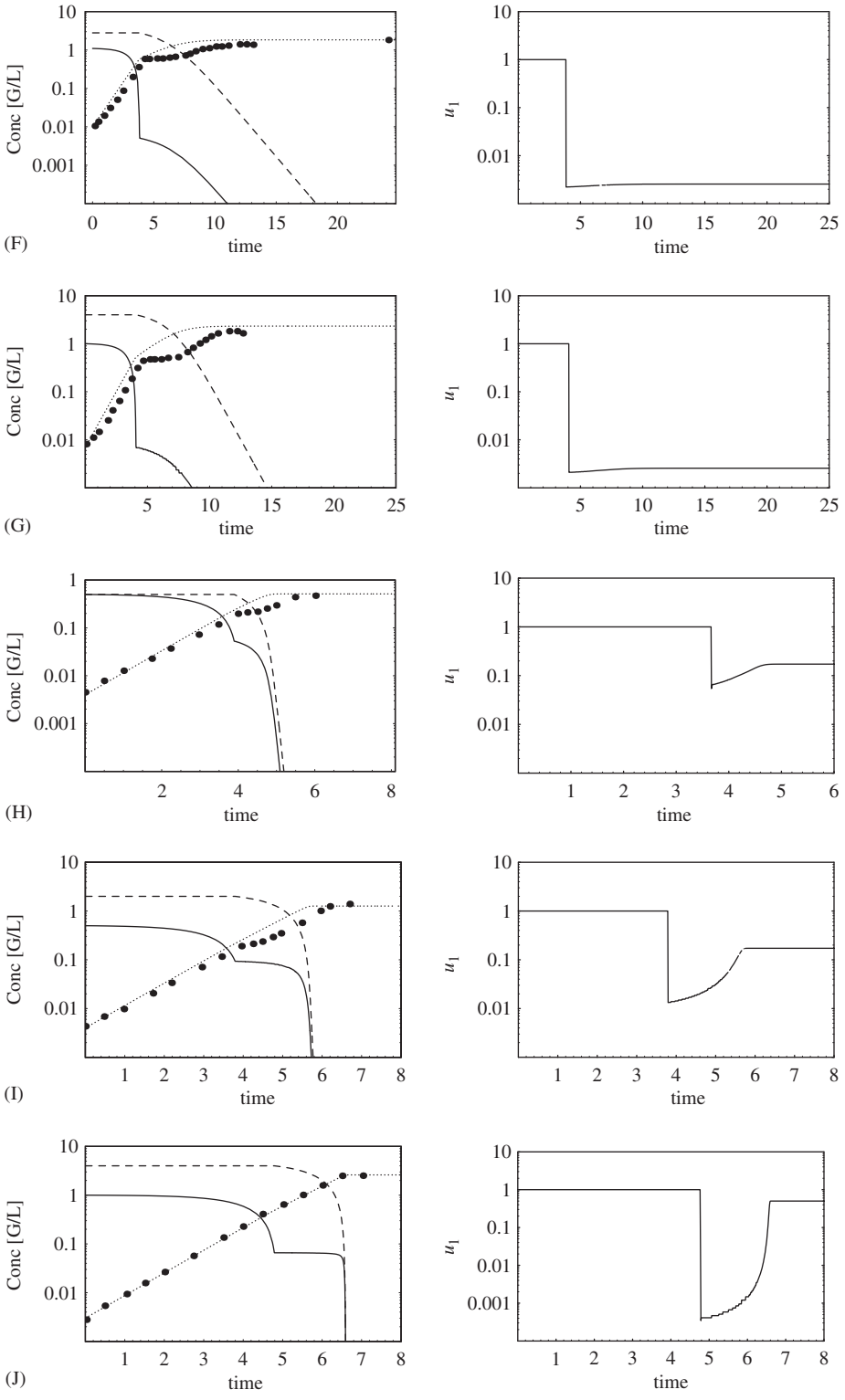

Fig. 2. (*Continued*)

For intermediate dilution rates ($\frac{\mu_2 S_{02}}{K_2+S_{02}} < D < \frac{\mu_1 S_{01}}{K_1+S_{01}}$), the point E^1 is below the switching curve and it is therefore an equilibrium of model (1) (Fig. 3B). I remark that for these dilution rates neither E^2 nor $E^\star$ are equilibria because they are not positive. Numerical simulations such as those given in Fig. 3B show that trajectories converge to E^1 in this case.

For high dilution rates ($\frac{\mu_1 S_{01}}{K_1+S_{01}} < D$) bacteria are washed out and the trajectories of model (1) converge to equilibrium $(S_{01}, S_{02}, 0)$ (Fig. 3C).

Table 1
Estimated time of switching from data given in Kompala et al. (1986) and predicted time of switching from model (1)

System in Kompala et al. (1986)	Panel in Fig. 2	Estimated time	Predicted time
glucose–xylose (Fig. 6)	A	4.2	4.2
glucose–xylose (Fig. 7)	B	1.7	1.6
glucose–xylose (Fig. 8)	C	2	1.8
glucose–lactose (Fig. 9)	D	5	4.1
glucose–lactose (Fig. 10)	E	4.2	3.8
glucose–lactose (Fig. 11)	F	4.2	3.8
glucose–lactose (Fig. 12)	G	4.6	4.2
glucose–arabinose (Fig. 13)	H	4	3.7
glucose–arabinose (Fig. 14)	I	4	3.8
glucose–fructose (Fig. 18)	J	4.5	4.8

Figure numbers refer to those given in Kompala et al. (1986).

3.1. Persistence of inflexible bacteria

In this section, I study under which conditions bacteria can survive in the system. I will consider two scenarios with respect to bacterial adaptivity. First, I assume that bacterial preferences for substrates are fixed (by which I mean that the preference for the first substrate u_1 is fixed and independent of substrate concentrations which implies that $u_2 = 1 - u_1$ is fixed too). A necessary condition for bacterial persistence is a positive bacterial growth rate at the substrate equilibrium $(S_{01}, S_{02}, 0)$. In other words, this condition requires that bacteria can invade the chemostat. This happens if the dilution rate is below an upper threshold

$$D < \frac{S_{01}\mu_1 u_1}{K_1 + S_{01}} + \frac{S_{02}\mu_2 u_2}{K_2 + S_{02}}. \tag{10}$$

Above this threshold, bacteria are washed out from the system (see model (1)). Thus, in the preference (u_1)—dilution (D) parameter space the set of those parameters for which bacteria persists in the chemostat is shown as the lower lightly shaded triangular area in Fig. 4.

3.2. Persistence of adaptive bacteria

Second, I consider adaptive bacteria that maximize their fitness. Due to assumption (6), equilibrium $(S_{01}, S_{02}, 0)$ is in the region of the substrate phase space where bacteria, when introduced in a small concentration, should consume substrate 1, i.e., $(u_1 = 1,\ u_2 = 0)$ in model (1). The condition for bacteria to invade this equilibrium is

$$D < \frac{S_{01}\mu_1}{K_1 + S_{01}}. \tag{11}$$

This threshold is always above the threshold for non-adaptive bacteria (which is given by the right handside of inequality (10)) for any fixed bacterial preferences $0 < u_i < 1,\ u_1 + u_2 = 1$. Thus, the range of dilution rates for which bacteria persist is larger for adaptive bacteria (both shaded regions in Fig. 4) when compared with non-adaptive bacteria (light shaded region in Fig. 4).

Fig. 5 compares the equilibrium species concentrations for non-adaptive (left upper panel) with adaptive (right upper panel) strategies. The bottom panel shows corresponding preference for substrate 1. This figure documents that the upper dilution threshold for bacterial extinction is higher when bacteria behave adaptively ($D \sim 1.1$) when compared with non-adaptive bacteria ($D \sim 0.75$, cf. Fig. 4 with Fig. 5). This figure also documents that at low dilution rates bacteria will feed on both substrates and bacterial preference for the better resource increases with increased dilution rate.

4. Discussion

In this article, I have constructed a population dynamical model describing bacterial growth on two substrates both in a batch and in a chemostat culture. The model assumes that bacteria instantaneously maximize their per capita population growth rate. For the batch type of cultivation, the model predicts that as the preferred substrate is used up there will be time at which both substrates provide bacteria with the same fitness. From then on bacteria will use both substrates simultaneously. There are two possibilities how to interpret this result. Either the bacterial population becomes polymorphic and each morph will feed on a single substrate only, or the population stays monomorphic in which case each individual bacteria will use both substrates simultaneously. As it was documented (for a review see, Egli, 1995), bacteria are able to simultaneously utilize several sugars and therefore, the second scenario seems to be more plausible. Whether bacteria become polymorphic or not, the model allows us to compute explicitly the preference for either substrate as a function of the two substrate concentrations using data on the bacterial growth on a single substrate only. Thus, I can predict the time at which bacteria should switch from feeding on the more profitable substrate to feeding on both substrates. Using some experimental data on bacterial growth on two substrates (Kompala et al., 1986), I tested the agreement between

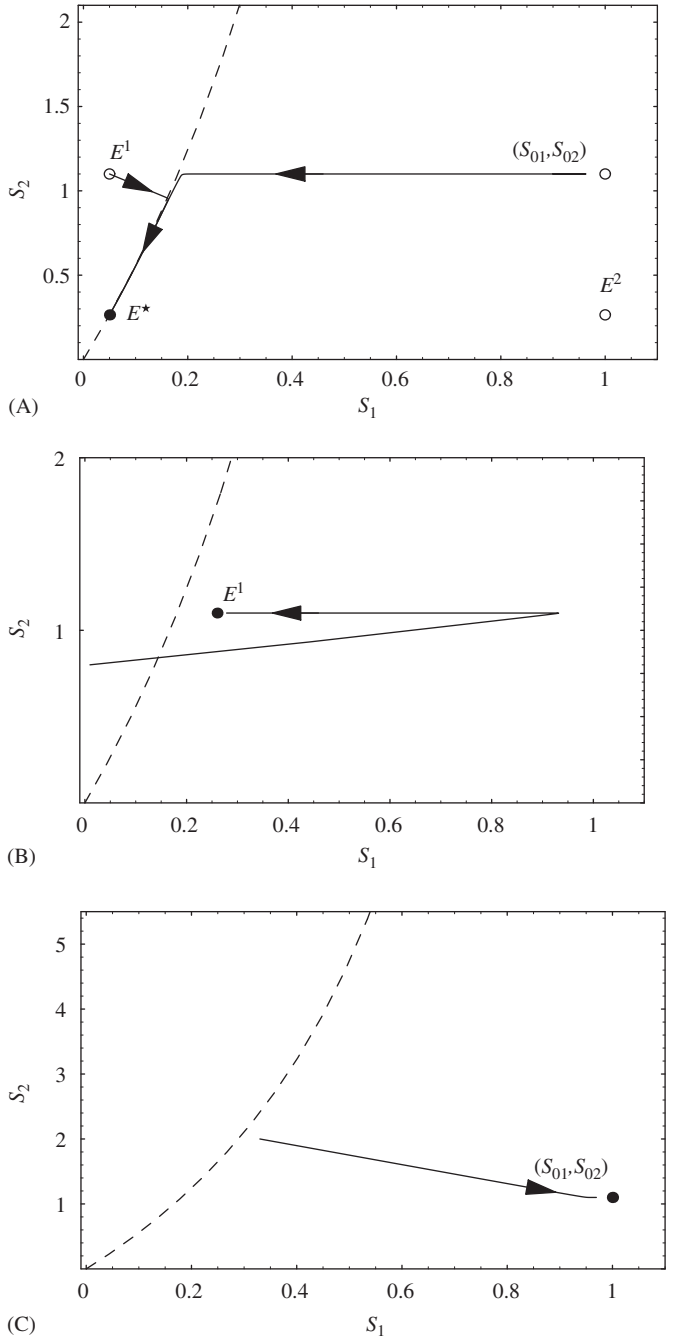

Fig. 3. Three qualitatively different possibilities for position of equilibria of model (1) for various dilution rates. (A) represents a low dilution rate ($D = 0.9$) for which trajectories of model (1) converge to the population equilibrium $E^\star$ given by formula (7) at which bacteria feed on both substrates. (B) represents an intermediate dilution rate ($D = 1.04$) for which trajectories converge to equilibrium E^1 (see formula 9) at which bacteria feed on substrate 1 only, and (C) represents a high dilution rate ($D = 1.1$) under which bacteria are washed out from the chemostat. Parameters: $S_{01} = 1$, $S_{02} = 1.1$, $K_1 = 0.01$, $K_2 = 0.05$, $Y_1 = 0.52$, $Y_2 = 0.5$, $\mu_1 = 1.08$, $\mu_2 = 1.07$.

predicted and observed times of substrate switching. The observed times of switching agree well with those that were predicted by using the model (Fig. 2, Table 1).

In the case of chemostat cultivation, the model predicts that for low dilution rates adaptive bacteria feed on both

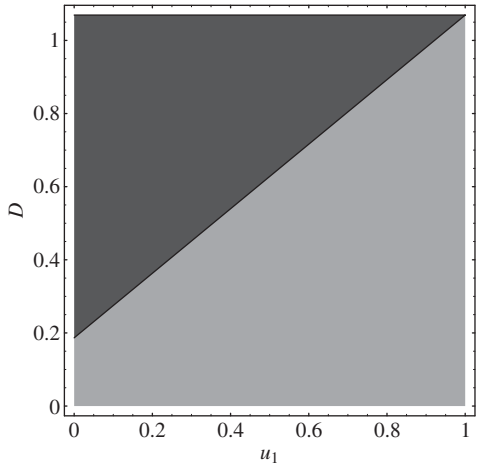

Fig. 4. Set of parameters in the bacterial preference for substrate 1—dilution rate parameter space for which bacteria persist in the chemostat. The light shaded lower triangular region delimits parameters for which non-adaptive bacteria with fixed substrate preferences survive in the chemostat. The upper dark region shows the added set of parameters for which adaptive bacteria survive in the chemostat. Parameters are those for glucose and lactose: $S_{01} = 1$, $S_{02} = 1.1$, $K_1 = 0.01$, $K_2 = 4.5$, $Y_1 = 0.52$, $Y_2 = 0.45$, $\mu_1 = 1.08$, $\mu_2 = 0.95$.

substrates while for higher dilution rates bacteria will feed on the preferred substrate only. For yet higher dilution rates, bacteria are washed out of the system. This prediction agrees qualitatively with observations (Egli, 1995). In particular, my model predicts that at low dilution rates the bacteria will feed on both substrates keeping their concentrations in the chemostat independent of the input concentrations. This qualitatively agrees with results reviewed by Egli (1995), because the residual substrate concentrations will then be directly proportional to the inflow substrate concentrations. As dilution rate increases, one substrate is completely dropped off from bacterial diet which means that the bacterial food web topology may not be fixed but it can depend on external forces (e.g., on bacterial mortality rate). At lower mortality rates, bacteria are less selective while, at higher mortality rates, they become more selective feeders. Accordingly, the food web topology changes from a food web with two substrates to a food chain (Křivan and Schmitz, 2003). Adaptive feeding also increases the range of parameters for which bacteria will persist in the chemostat when compared with inflexible bacteria with fixed food preferences. This is because substrate switching relaxes apparent competition between substrates (Holt, 1977). Indeed, at higher dilution rates, bacteria exclude the less profitable substrate from their diet and this relaxes apparent competition between substrates when compared to the situation of fixed bacterial preferences for substrates.

There is a large literature on ‘‘cybernetic modeling’’ which also describes bacterial growth on multiple substrates (Kompala et al., 1984, 1986; Dhurjati et al., 1985; Straight and Ramkrishna, 1994a,b; Ramakrishna et al.,

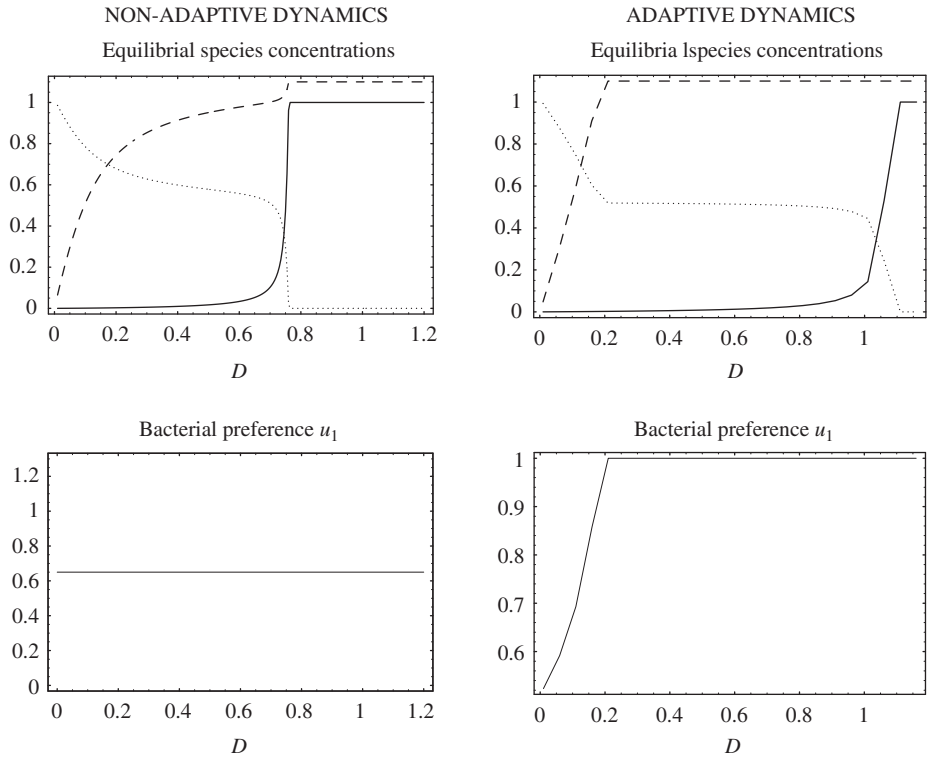

Fig. 5. The top panels show dependence of equilibria (substrate 1—solid line, substrate 2—dashed line, bacteria—dotted line) of model (1) on dilution rate D when bacteria behave adaptively (right panel) or when their preferences for substrates are fixed (left panel). The bottom panels show corresponding preferences for substrate 1. Parameters are the same as in Fig. 4.

1996; Narang et al., 1997a,b,c; Narang, 1998a, b). As in this article, cybernetic modeling is based on the assumption that microbes generally act to optimize their cellular growth rate (Kompala et al., 1984). However, there are two important differences between cybernetic models and the present work.

First, cybernetic models assume that bacterial preferences for each substrate follow the so-called input matching principle. This means that bacterial preferences for substrate i are given as $u_i = \mu_i S_i/(K_i + S_i)/[\mu_1 S_1/(K_1 + S_1) + \mu_2 S_2/(K_2 + S_2)]$. I showed that provided bacteria maximize their per capita population growth rate this assumption holds only along the switching cure, i.e., only for substrate densities for which feeding on either substrate gives the same fitness. However, if the matching principle is used for any substrate densities, then the corresponding strategy is not optimal. In the case of a batch cultivation, this problem is not so serious because, as I showed in this article, population dynamics drive substrate concentrations to the levels at which both substrates provide the same bacterial growth rate. However, in the case of chemostat I showed that for intermediate dilution rates (Fig. 3B) this is not so, because at the population equilibrium bacteria should feed on resource 1 only.

Second, in contrast to the present article, cybernetic models consider explicitly enzyme dynamics. In fact, they consider two types of control: one control regulating enzyme synthesis, the other control regulating the enzyme activity, i.e., the actual preference of microbes for either substrate. My approach to deal with multiple substrates in this article is based on a less detailed model which does not consider explicitly enzyme dynamics. However, this leads to a direct link between substrate choice and bacterial fitness (while this link involves enzyme dynamics in the case of cybernetic models), resulting in simpler models amenable to analysis. Thus, the present model is too simple to describe diauxic lag caused by delay in enzyme synthesis, but it is general and analyzable enough to describe a feedback between bacterial adaptivity and its population growth. Despite its simplicity, the agreement between model predictions and observed bacterial dynamics is pretty good which leads to some optimism about predictions of models that integrate animal behavior with population dynamics.

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Appendix A. Batch growth

Here I analyze population dynamics along the switching curve for the batch growth ($D=0$). Vector

$$n=\left\{\frac{\mu_1 K_1^2}{(K_1+S_1)^2},-\frac{\mu_2 K_2^2}{(K_2+S_2)^2}\right\}$$

is perpendicular to the switching curve in the substrate 1–substrate 2 phase space. Let f_1 and f_2 denote the vector given by the right hand side of model (1) when $u_1=1$ and $u_1=0$, respectively, are substituted. Then

$$\langle n,f_1\rangle=-\frac{CK_1^2S_1\mu_1}{Y_1(K_1+S_1)^3}$$

and

$$\langle n,f_2\rangle=\frac{CS_1\mu_1(S_1\mu_1-(K_1+S_1)\mu_2)^2}{Y_2\mu_2^2(K_1+S_1)^3},$$

where $\langle\cdot,\cdot\rangle$ denotes the scalar product. As $\langle n,f_1\rangle<0$ and $\langle n,f_2\rangle>0$ it follows that as a trajectory of model (1) reaches the switching curve it cannot leave it. The preference for substrate 1 along the switching curve can be calculated as follows. When a trajectory of model (1) moves along the switching curve

$$\frac{\mu_1 S_1(t)}{K_1+S_1(t)}=\frac{\mu_2 S_2(t)}{K_2+S_2(t)}.$$

Differentiating this equality with respect to time gives

$$\frac{\mu_1 K_1\frac{dS_1}{dt}}{(K_1+S_1)^2}=\frac{\mu_2 K_2\frac{dS_2}{dt}}{(K_2+S_2)^2}.$$

Substituting for dS_i/dt the corresponding expression from model (1) and solving for the unknown u_1 ($u_2=1-u_1$) gives bacterial preference for substrate 1 as a function of substrate concentrations

$$u_1=\frac{Y_1(S_1\mu_1-(K_1+S_1)\mu_2)^2}{S_1^2Y_1\mu_1^2-2S_1(K_1+S_1)Y_1\mu_1\mu_2+((K_1+S_1)^2Y_1+K_1K_2Y_2)\mu_2^2}.$$

Using this expression yields the IFD of bacteria over the substrates given by formula (4).

Appendix B. Chemostat growth

I study equilibria of the bacterial growth in the chemostat ($D>0$ in model (1)). The switching manifold divides the substrate–bacterial phase space into two regions. I study equilibria in both of these regions and also on the switching manifold which leads to three distinct cases. First, I consider the region of the phase space below the switching manifold where bacteria feed on substrate 1 only. Substituting $u_1=1$ in model (1) and solving for an equilibrium gives

$$E^1=\left\{\frac{DK_1}{\mu_1-D},S_{02},\frac{Y_1\mu_1(S_{01}\mu_1-D(K_1+S_{01}))}{\mu_1-D}\right\}.$$

However, this equilibrium is positive and below the switching manifold only if $\frac{\mu_1 S_{01}}{K_1+S_{01}}>D>\frac{\mu_2 S_{02}}{K_2+S_{02}}$. When the second inequality is reversed (i.e., for low dilution rates), E^1 is above the switching manifold and it is not an equilibrium of model (1). I call such an equilibrium a virtual equilibrium. Similarly, the equilibrium for population dynamics in the region of the phase space above the switching manifold where bacteria feed on substrate 2 only ($u_1=0$, $u_2=1$) is

$$E^2=\left\{S_{01},\frac{DK_2}{\mu_2-D},\frac{Y_2\mu_2(S_{02}\mu_2-D(K_2+S_{02}))}{\mu_2-D}\right\}.$$

For this equilibrium to be positive and located above the switching manifold the inequalities $\frac{\mu_2 S_{02}}{K_2+S_{02}}>D>\frac{\mu_1 S_{01}}{K_1+S_{01}}$ have to be satisfied. However, due to assumption (6), these inequalities never hold and equilibrium E^2 does not exist.

Now I search for a possible equilibrium on the switching manifold. A point on the switching manifold is an equilibrium of (1) if there exists a fixed control u_i ($i=1,2$, $0\leqslant u_i\leqslant 1$, $u_1+u_2=1$) for which the right hand side of (1) equals zero. Such a point must satisfy the following system of equations (for unknowns S_1, S_2, C, and u):

$$\begin{aligned}
&D(S_{01}-S_1)-\frac{1}{Y_1}\frac{S_1}{K_1+S_1}u_1C=0,\\
&D(S_{02}-S_2)-\frac{1}{Y_2}\frac{S_2}{K_2+S_2}u_2C=0,\\
&\left(\frac{\mu_1 S_1}{K_1+S_1}u_1+\frac{\mu_2 S_2}{K_2+S_2}u_2-D\right)C=0,\\
&\frac{\mu_1 S_1}{K_1+S_1}=\frac{\mu_2 S_2}{K_2+S_2}.
\end{aligned}$$

Solving these equations gives equilibrium $E^\star$ (see formula (7)) and the corresponding bacterial preference for substrate 1 (see formula (8)). For equilibrium $E^\star$ to exist the bacterial preference for substrate 1 ($u_1^\star$) must be between 0 and 1. When the dilution rate equals 0, the corresponding bacterial preference for substrate 1 is positive (see formula (8)) and equal to $S_{01}Y_1\mu_1/(S_{01}Y_1\mu_1+S_{02}Y_2\mu_2)$. Moreover, $u_1^\star=1$ when $D=\mu_1$ or $D=S_{02}\mu_2/(K_2+S_{02})$. Similarly, $u_1^\star=0$ when $D=\mu_2$ or $D=S_{01}\mu_1/(K_1+S_{01})$. Due to assumption (6), it is clear that $S_{02}\mu_2/(K_2+S_{02})<\min\{S_{01}\mu_1/(K_1+S_{01}),\mu_1,\mu_2\}$ and, consequently, for $D\leqslant S_{02}\mu_2/(K_2+S_{02})$ bacterial preference $u_1^\star\leqslant 1$ and equilibrium $E^\star$ exists. I summarize these results about existence of equilibria into the following three possibilities:

1. For $D<\frac{\mu_2 S_{02}}{K_2+S_{02}}$, the only equilibrium at which bacteria exist is $E^\star$.
2. For $\frac{\mu_2 S_{02}}{K_2+S_{02}}<D<\frac{\mu_1 S_{01}}{K_1+S_{01}}$, the only equilibrium at which bacteria exist is E^1.

3. For $\frac{\mu_1 S_{01}}{K_1+S_{01}} < D$, bacteria are washed out from the system.

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