Biomath Communications

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Analysis of a Bioreactor Model with Microbial Growth Phases and Spatial Dispersal [1]

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Abstract

We consider a batch mode bioreactor model proposed by Alt and Markov (2012). The model is developed using the fact that the bacterial growth undergoes four phases: lag, log, stationary and death phase. First we modify the model by introducing additional (the so-called transport) terms to describe continuously stirred bioreactor dynamics. For this model we compute the equilibrium points and study their asymptotic stability. Some basic properties of the solutions like uniform boundedness and uniform persistence are also established. Then we extend the model by adding diffusion terms to the equations. The latter reaction diffusion equations are studied numerically. Thereby, solutions in the form of travelling waves are found.

Keywords: Continuously stirred bioreactor model, Reaction diffusion equations, Travelling wave solutions

[1]**Citation:** T. Ivanov, N. Dimitrova, Analysis of a Bioreactor Model with Microbial Growth Phases and Spatial Dispersal. Biomath Communications 2/2 (2015) `http://dx.doi.org/10.11145/j.bmc.2016.01.111`

1 Introduction

A new approach to the mathematical modelling of microbial growth is proposed in [5]. This approach is based on the fact that bacterial growth in batch culture can be modelled using four different phases:

(i) lag phase: bacteria adapt themselves to growth conditions. The bacteria are maturing and not yet able to divide.

(ii) log phase is the period characterized by cell doubling. If growth is not limited, doubling will continue at a constant growth rate thus the number of cells and the rate of population increase doubles with each consecutive time period.

(iii) stationary phase: the growth rate slows down as a result of nutrient depletion and accumulation of toxic products. This phase is reached as the bacteria begin to exhaust the available resources. In this phase the bacterial growth is equal to the rate of bacterial death.

(iv) death phase: bacteria run out of nutrient substrate and die.

More details about bacterial growth phases and their modeling can be found in [1], [5] and the references therein.

The batch mode bioreactor model with microbial growth phases proposed in [1] is described by the following nonlinear ordinary differential equations

$$\begin{aligned}\frac{ds}{dt} &= -k_1 u_1 s - (\alpha + \beta) u_2 s \\ \frac{du_1}{dt} &= -k_1 u_1 s + k_2 u_2 + \alpha u_2 s - \gamma_1 u_1 \\ \frac{du_2}{dt} &= k_1 u_1 s - k_2 u_2 + \beta u_2 s - \gamma_2 u_2,\end{aligned} \tag{1}$$

where

s is the substrate concentration;

u_1 is the concentration of bacteria in lag and stationary phase;

u_2 is the concentration of (vital, active) bacteria in log phase;

$k_1 s u_1$ represents the consumption of s by bacteria u_1 and the transition of bacteria u_1 into bacteria u_2;

$\alpha s u_2$ models a part of bacteria u_2 passing into bacteria u_1;

$\beta s u_2$ represents the consumption of s by bacteria u_2 and the increase of the biomass u_2 due to nutrition and reproduction;

$k_2 u_2$ describes the random transition of bacteria from type u_2 into type u_1;

$\gamma_i u_i$ describes the decay of bacteria u_i, $i = 1, 2$.

It is assumed that all parameters in the model are positive.

2 The continuously stirred bioreactor model

We modify the model (1) by adding terms describing the inlet of substrate in the bioreactor:

$$\begin{aligned} \frac{ds}{dt} &= -k_1 u_1 s - (\alpha + \beta) u_2 s + d_r (s^0 - s) \\ \frac{du_1}{dt} &= -k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 \\ \frac{du_2}{dt} &= k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2. \end{aligned} \tag{2}$$

Here d_r denotes the dilution rate, $d_r > 0$, and s^0 is the input substrate concentration in the bioreactor. The parameters γ_1 and γ_2 from (1) are assumed now to be equal, $\gamma_1 = \gamma_2$, interpreted as wash-out of bacteria and denoted in (2) by d_r. After possible rescaling of the first equation by means of $s := s/s^0$, we may assume that $s^0 = 1$ and consider further the model in the following form

$$\begin{aligned} \frac{ds}{dt} &= -k_1 u_1 s - (\alpha + \beta) u_2 s + d_r (1 - s) \\ \frac{du_1}{dt} &= -k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 \\ \frac{du_2}{dt} &= k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2. \end{aligned} \tag{3}$$

For biological evidence we also assume that the following inequality is fulfilled:

$$\max\{k_1,\ k_2\} < \beta. \tag{4}$$

2.1 Basic properties of the solutions

We consider the model (3) under the assumption (4).

Proposition 2.1. *The positive octant*

$$\Omega = \{(s, u_1, u_2) \in R^3 : s > 0, u_1 > 0, u_2 > 0\}$$

is positively invariant set for (3).

Proof. The boundary of Ω satisfies the following properties.

If $s(\tau) = 0$ for some $\tau \geq 0$ then $\dfrac{ds}{d\tau} = d_r > 0$.

If $u_1(\tau) = 0$ for some $\tau \geq 0$ then $\dfrac{du_1}{d\tau} = u_2(\tau)(k_2 + \alpha s(\tau)) \geq 0$ with $\dfrac{du_1}{d\tau} = 0$ if and only if $u_2(\tau) = 0$.

If $u_2(\tau) = 0$ for some $\tau \geq 0$ then $\dfrac{du_2}{d\tau} = k_1 s(\tau) u_1(\tau)$ with $\dfrac{du_2}{d\tau} = 0$ if and only if $u_1(\tau) = 0$.

Thus the vector field points inside Ω along the whole boundary of Ω without the line $\{u_1 = u_2 = 0, s > 0\}$, which itself is invariant for the system (3).

The right-hand side of (3) is continuously differentiable, thus local existence and uniqueness of solutions follow immediately. □

Proposition 2.2. *All nonnegative solutions of the model (3) are uniformly bounded and thus exist for all time $t > 0$.*

Proof. Since $s(t) > 0$, $u_1(t) > 0$, $u_2(t) > 0$ holds true in Ω, any solution $(s(t), u_1(t), u_2(t))$ satisfies the inequality $\dfrac{ds}{dt} \leq d_r(1 - s(t))$ and therefore $\limsup_{t\to\infty} s(t) \leq 1$. Further,

$$\frac{ds}{dt} + \frac{du_1}{dt} + \frac{du_2}{dt} = -k_1 s u_1 + d_r(1 - s - u_1 - u_2) \leq d_r(1 - s - u_1 - u_2),$$

which implies $\limsup_{t\to\infty}(s(t) + u_1(t) + u_2(t)) \leq 1$. Since all solutions are nonnegative in Ω, it follows that any positive solution is bounded, exists for for all $t \in [0, +\infty)$ and enters the bounded set $\{(s, u_1, u_2) \geq 0, s + u_1 + u_2 \leq 1\}$. This means that the system (3) is dissipative in the closure $\overline{\Omega}$. □

2.2 Equilibrium points and their local stability

The equilibrium points of the model (3) are solutions of the nonlinear system

$$-k_1 u_1 s - (\alpha+\beta) u_2 s + d_r(1-s) = 0 \tag{5}$$
$$-k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 = 0 \tag{6}$$
$$k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2 = 0. \tag{7}$$

Obviously, $E_0 = (1, 0, 0)$ is always an equilibrium point of the model; it is called wash-out equilibrium.

By adding equation (5) to (7), equation (6) to (7) we obtain the system

$$-k_1 s u_1 - (\alpha+\beta) u_2 s + d_r(1-s) = 0 \tag{8}$$
$$-k_2 u_2 - \alpha s u_2 + d_r(1-s-u_2) = 0 \tag{9}$$
$$(\alpha+\beta) s u_2 - d_r(u_1+u_2) = 0. \tag{10}$$

We express u_1 from (10) as

$$u_1 = u_2\left(\frac{\alpha+\beta}{d_r}s - 1\right); \tag{11}$$

equation (9) delivers

$$u_2 = \frac{d_r(1-s)}{\alpha s + k_2 + d_r}. \tag{12}$$

Then substituting u_1 from (11) and u_2 from (12) into (8) we obtain the following quadratic equation with respect to s:

$$\frac{k_1}{d_r}(\alpha+\beta)s^2 - (k_1-\beta)s - (k_2+d_r) = 0. \tag{13}$$

The discriminant Δ_s of the latter is given by

$$\Delta_s = (k_1-\beta)^2 + 4\frac{k_1}{d_r}(\alpha+\beta)(k_2+d_r) > 0,$$

thus the quadratic equation (13) possesses two real roots, one positive and one negative. We denote the positive root by s^*, i. e.

$$s^* = \frac{d_r(k_1 - \beta + \sqrt{\Delta_s})}{2k_1(\alpha+\beta)}. \tag{14}$$

According to Proposition 2.2 the steady state component s^* should satisfy $s^* < 1$. The latter inequality is equivalent with the quadratic inequality (with respect to d_r)

$$d_r^2 + (k_1 + k_2 - \beta)d_r - k_1(\alpha+\beta) < 0.$$

Its discriminant is $\Delta_d = (k_1 + k_2 - \beta)^2 + 4k_1(\alpha+\beta) > 0$; hence there are two real roots with respect to d_r, one positive and one negative; denote by $\bar{d}_r$ the positive root, i. e.

$$\bar{d}_r = \frac{1}{2}(\beta - k_1 - k_2 + \sqrt{\Delta_d}).$$

Then for $0 < d_r < \bar{d}_r$ we have $s^* < 1$.

From (12) we find

$$u_2^* = \frac{d_r(1-s^*)}{\alpha s^* + k_2 + d_r}.$$

Clearly, $u_2^* > 0$ if $d_r < \bar{d}_r$ holds true. Further, by replacing $u_2 = u_2^*$ and $s = s^*$ in (11) we find

$$u_1^* = u_2^* \left(\frac{\alpha+\beta}{d_r} s^* - 1 \right).$$

Obviously, $u_1^* > 0$ if and only if $s^* > \dfrac{d_r}{\alpha+\beta}$; it can be easily seen from (14) that the latter inequality is always satisfied.

We summarize the above calculations in the following proposition.

Proposition 2.3. *If $d_r < \bar{d}_r$, then the model (3) possesses two equilibrium points: the wash-out steady state $E_0 = (1, 0, 0)$ and the positive (internal) equilibrium $E^* = (s^*, u_1^*, u_2^*)$. If $d_r > \bar{d}_r$ then the wash-out steady state E_0 is the unique equilibrium point of the model.* □

Remark 2.1. *When* $d_r = \bar{d}_r$, *then* $s^* = 1$ *holds true. In this case* E_0 *and* E^* *coincide and a bifurcation (with respect to the parameter* d_r*) of the steady states may occur.*

In what follows we shall investigate the local asymptotic stability of the equilibrium points.

Proposition 2.4. *If* $d_r < \bar{d}_r$, *then* E^* *is locally asymptotically stable equilibrium and* E_0 *is a saddle point. If* $d_r > \bar{d}_r$ *then the unique equilibrium point* E_0 *is locally asymptotically stable.*

Proof. The Jacobian matrix of the model (3) is

$$J(s, u_1, u_2) = \begin{pmatrix} -k_1u_1 - (\alpha+\beta)u_2 - d_r & -k_1 s & -(\alpha+\beta)s \\ -k_1u_1 + \alpha u_2 & -k_1 s - d_r & k_2 + \alpha s \\ k_1u_1 + \beta u_2 & k_1 s & -k_2 + \beta s - d_r \end{pmatrix}$$

The eigenvalues of $J(E_0)$ are the roots of the characteristic polynomial $|J(E_0) - \lambda I| = 0$ (I denotes the (3×3)–unit matrix), which is given by

$$\begin{aligned}(d_r + \lambda)[\lambda^2 &+ (2d_r + k_1 + k_2 - \beta)\lambda \\ &+ (d_r^2 + (k_1 + k_2 - \beta)d_r - k_1(\alpha+\beta))] = 0.\end{aligned}$$

Obviously, $\lambda_3 = -d_r < 0$ is one of the eigenvalues of $J(E_0)$. The other two eigenvalues λ_1, λ_2 are solutions of the quadratic equation (the term in the square brackets above) and satisfy the relations

$$\begin{aligned}\lambda_1\lambda_2 &= d_r^2 + (k_1 + k_2 - \beta)d_r - k_1(\alpha+\beta), \\ \lambda_1 + \lambda_2 &= -2d_r + \beta - k_1 - k_2.\end{aligned}$$

When $d_r < \bar{d}_r$ then $\lambda_1\lambda_2 < 0$ and hence E_0 is a saddle equilibrium point. If $d_r > \bar{d}_r$ then $\lambda_1\lambda_2 > 0$, i. e. both eigenvalues are of equal signs; moreover, the inequality $d_r > \bar{d}_r$ implies $2d_r > \beta - k_1 - k_2$ thus $\lambda_1 + \lambda_2 < 0$ holds true. In this case E_0 is locally asymptotically stable equilibrium point.

To prove the local stability of E^* we shall use the Routh-Hurwitz criterion. The eigenvalues of $J(E^*) = (J_{ij})_{i,j=1}^3$ are the roots of the cubic polynomial

$$g(\lambda) = -\lambda^3 + a\lambda^2 - b\lambda + c,$$

where the coefficients a, b and c are presented by

$$\begin{array}{rcl} a & = & \mathrm{tr}J(E^*) \;=\; J_{11}+J_{22}+J_{33} \\ b & = & \det\begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22}\end{pmatrix} + \det\begin{pmatrix} J_{22} & J_{23} \\ J_{32} & J_{33}\end{pmatrix} + \det\begin{pmatrix} J_{11} & J_{13} \\ J_{31} & J_{33}\end{pmatrix} \\ c & = & \det J(E^*). \end{array}$$

According to the Routh-Hurwitz criterion [7], the necessary and sufficient condition for $g(\lambda)$ to possess three roots with negative real parts is $a<0$, $c<0$ and $ab<c$.

Using the fact that s^* is the root of (13) it is straightforward to see that

$$a = -\left(2d_r + k_1u_1^* + (\alpha+\beta)u_2^* + \frac{k_1}{d_r}(\alpha+\beta)s^{*2}\right) < 0. \qquad (15)$$

Denote for simplicity

$$G_1 = \det\begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22}\end{pmatrix}, G_2 = \det\begin{pmatrix} J_{22} & J_{23} \\ J_{32} & J_{33}\end{pmatrix}, G_3 = \det\begin{pmatrix} J_{11} & J_{13} \\ J_{31} & J_{33}\end{pmatrix}$$

and further

$$G_4 = \det\begin{pmatrix} J_{21} & J_{23} \\ J_{31} & J_{33}\end{pmatrix}, G_5 = \det\begin{pmatrix} J_{21} & J_{22} \\ J_{31} & J_{32}\end{pmatrix}.$$

It is easy to see that

$$\begin{array}{rcl} G_1 & = & k_1d_ru_1^* + d_r(\alpha+\beta)u_2^* + k_1d_rs^* + k_1(2\alpha+\beta)s^*u_2^* + d_r^2, \\ G_2 & = & -k_1(\alpha+\beta)s^{*2} + d_r(k_1-\beta)s^* + d_r(k_2+d_r) = 0, \\ G_3 & = & (k_2+d_r)(k_1u_1^* + (\alpha+\beta)u_2^*) - \beta d_rs^* + \alpha k_1s^*u_1^* + d_r(d_r+k_2). \end{array}$$

Then we have

$$\begin{array}{rcl} b & = & G_1 + G_3 \\ & = & (k_2+2d_r)(k_1u_1^* + (\alpha+\beta)u_2^*) + k_1(\alpha+\beta)s^{*2} \\ & & +k_1(2\alpha+\beta)s^*u_2^* + \alpha k_1s^*u_1^* + d_r^2. \end{array}$$

Further,

$$\begin{aligned} G_4 &= -k_1 u_1^* \left((\alpha+\beta)s^* - d_r\right) - u_2^* \left(\alpha d_r + k_2(\alpha+\beta)\right) < 0, \\ G_5 &= k_1(\alpha+\beta)s^* u_2^* + d_r(k_1 u_1^* + \beta u_2^*) > 0. \end{aligned}$$

Then

$$c = k_1 s^* \, G_4 - (\alpha+\beta)G_5 < 0.$$

Finally, straightforward (but rather lengthy) calculations deliver

$$\begin{aligned} ab - c &= -\left\{ \frac{k_1}{d_r}(\alpha+\beta)^2 s^{*4} + (k_2 + 2d_r)(k_1 u_1^* + (\alpha+\beta)u_2^*)^2 \right. \\ &\quad + \frac{k_1^2}{d_r}\alpha(\alpha+\beta)s^{*3}u_1^* + \frac{k_1^2}{d_r}(\alpha+\beta)(2\alpha+\beta)s^{*3}u_2^* \\ &\quad + \alpha k_1(k_1 u_1^* + (\alpha+\beta)u_2^*)s^* u_1^* + k_1(2\alpha+\beta)(k_1 u_1^* + (\alpha+\beta)u_2^*)s^* u_2^* \\ &\quad + 3k_1 d_r(\alpha+\beta)s^{*2} + k_1(\alpha+\beta)\left(\frac{k_2}{d_r}(\alpha+\beta) + 3\alpha + k_1\right) s^{*2}u_2^* \\ &\quad + \left((\alpha+\beta)(7k_1 d_r + k_1 k_2 + \beta d_r) + k_1 d_r(\beta - k_1)\right) s^* u_2^* \\ &\quad \left. + \frac{k_1^2}{d_r}(k_2 + 2d_r)(\alpha+\beta)u_1^* + d_r(5d_r + 2k_2)(\alpha+\beta-k_1)u_2^* + 2d_r^3 \right\}. \end{aligned}$$

Taking into account (4) it follows that $ab - c < 0$ is valid. Therefore if E^* exists, it is locally asymptotically stable. □

2.3 Global properties of the solutions

We shall show first that there exists a uniform lower bound of $s(t)$.

Proposition 2.5. *The following inequality holds true:*

$$\lim\ inf_{t\to\infty} s(t) \geq \frac{d_r}{k_1 + \alpha + \beta + d_r}.$$

Proof. Using the fact that $u_i(t) \leq 1$, $i = 1, 2$, we obtain from the first equation of (3)

$$\begin{aligned} \frac{ds}{dt} &= -(k_1 u_1 + (\alpha+\beta)u_2 + d_r)s + d_r \\ &\geq -(k_1 + \alpha + \beta + d_r)s + d_r, \end{aligned}$$

which means that $\lim\ \inf_{t\to\infty} s(t) \geq \dfrac{d_r}{k_1+\alpha+\beta+d_r}$. $\square$

Remark 2.2. *Denote* $C_s = \dfrac{d_r}{k_1+\alpha+\beta+d_r}$. *Obviously,* $0 < C_s < 1$ *is valid. Moreover, any constant* $\widetilde{C}_s$ *satisfying* $0 < \widetilde{C}_s < C_s$ *can be used as a lower bound of* $s(t)$*.*

Denote $u = \dfrac{u_1}{u_2}$; then from the second and third equation of (3) we obtain

$$\frac{du}{dt} = -k_1 s u^2 - \left((k_1+\beta)s - k_2\right)u + \alpha s + k_2. \tag{16}$$

Proposition 2.6. *There exist positive constants* C_u^l *and* C_u^b *such that* $C_u^l \leq \lim\ inf_{t\to\infty} u(t)$ *and* $\lim\ sup_{t\to\infty} u(t) \leq C_u^b$ *are satisfied.*

Proof. Since $s(t) \leq 1$ for all $t > 0$ holds true, we have from (16) that

$$\frac{du}{dt} \geq -k_1 u^2 - (k_1+\beta-k_2)u + k_2.$$

We can compare the solution of the above differential inequality with the solution of the Riccati equation

$$\frac{dz}{dt} = -k_1 z^2 - (k_1+\beta-k_2)z + k_2. \tag{17}$$

Consider the quadratic equation $-k_1 z^2 - (k_1+\beta-k_2)z + k_2 = 0$ and denote by $\underline{z}$ its positive root:

$$\underline{z} = \frac{1}{2k_1}\left(-k_1-\beta+k_2+\sqrt{\Delta_1}\right), \quad \Delta_1 = (k_1+\beta-k_2)^2 + 4k_1k_2 > 0.$$

Then $\underline{z}$ represents a particular solution of (17). The variable change $\zeta = \dfrac{1}{z-\underline{z}}$ transforms the Riccati equation (17) into a linear one

$$\frac{d\zeta}{dt} = (k_1+\beta-k_2+2k_1\underline{z})\zeta + k_1,$$

which solution can be easily computed to be

$$\zeta(t) = \frac{k_1}{\sqrt{\Delta_1}}(-1 + e^{\sqrt{\Delta_1}\,t}).$$

Then

$$z(t) = \underline{z} + \frac{1}{\zeta(t)} = \underline{z} + \frac{\sqrt{\Delta_1}e^{-\sqrt{\Delta_1}\,t}}{k_1(1 - e^{-\sqrt{\Delta_1}\,t})} \geq \underline{z}.$$

We obtain that $u(t)$ satisfies the inequality

$$C_u^l \leq \lim\ \inf_{t\to\infty} u(t) \ \text{ with } \ C_u^l = \underline{z}.$$

The uniform upper boundedness of $u(t)$ can be easily obtained using a similar approach. By means of Propositions 2.2 and 2.5 we have $0 < C_s \leq s(t) \leq 1$ and thus

$$\frac{du}{dt} \leq -k_1 C_s u^2 + (k_2 - (k_1 + \beta)C_s)u + \alpha + k_2,$$

which solutions can be again compared with the solutions of the Riccati equation

$$\frac{dz}{dt} = -k_1 C_s z^2 + (k_2 - (k_1 + \beta)C_s)z + \alpha + k_2. \tag{18}$$

Denote by $\bar{z} = \dfrac{-(k_1 + \beta)C_s + k_2 + \sqrt{\Delta_2}}{2k_1 C_s} > 0$ with $\Delta_2 = (k_2 - (k_1 + \beta)C_s)^2 + 4k_1 C_s(\alpha + k_2)$ a particular solution of (18). Then it can be easily seen as above that the following inequality is satisfied

$$\lim\ \sup_{t\to\infty} u(t) \leq C_u^b \ \text{ with } \ C_u^b = \bar{z}.$$

It remains to be shown that $C_u^l \leq C_u^b$ is valid. Using the particular expressions of the constants C_u^l and C_u^b, we have to show that

$$C_s^2(k_2 - (k_1 + \beta))^2 \leq (k_2 - C_s(k_1 + \beta))^2 \tag{19}$$

is fulfilled. If $k_2 \geq k_1 + \beta \geq C_s(k_1 + \beta)$ or $0 < -(k_2 - (k_1 + \beta)) \leq k_2 - C_s(k_1 + \beta)$ then (19) is obviously satisfied. In the case $0 <$

$k_2 - C_s(k_1+\beta) \leq -(k_2-(k_1+\beta))$ we can always choose a sufficiently small positive constant $\widetilde{C}_s < C_s$ (see Remark 2.2), so that $0 < -(k_2 - (k_1+\beta)) < k_2 - \widetilde{C}_s(k_1+\beta)$ holds true. This proves the proposition. □

Theorem 2.1. *If $d_r > \bar{d}_r$ then the wash-out equilibrium point $E_0 = (1,0,0)$ is globally asymptotically stable for the model (3).*

Proof. First we prove that $\lim_{t\to\infty} u_2(t)$ exists and is equal to zero. If $u_2(t)$ does not tend to a limit then $0 < \liminf_{t\to\infty} u_2(t) < \limsup_{t\to\infty} u_2(t) = \bar{u}_2$. Using the Fluctuation Lemma [4] there exists a sequence $t_m \to +\infty$ such that $\dot{u}_2(t_m) = 0$ for all m and $\lim_{m\to\infty} u_2(t_m) = \limsup_{t\to\infty} u_2(t) = \bar{u}_2$. Proposition 2.6 implies $\lim_{m\to\infty} u_1(t_m) = \limsup_{t\to\infty} u_1(t) = \bar{u}_1 > 0$; from equation (16) we obtain that $\lim_{m\to\infty} u(t_m) = \bar{u} = \dfrac{\bar{u}_1}{\bar{u}_2} > 0$. Applying Barbălat's Lemma [3] we obtain

$$0 = \lim_{m\to\infty} \dot{u}_2(t_m) = \lim_{m\to\infty} [(k_1 u_1(t_m) + \beta u_1(t_m))s(t_m) - (k_2+d_r)s(t_m)],$$

and thus

$$\lim_{m\to\infty} s(t_m) = \bar{s} = \frac{k_2+d_r}{k_1\bar{u}+\beta}.$$

According to Proposition 2.2 we have $\bar{s} \leq 1$; the last inequality is equivalent with

$$d_r \leq k_1\bar{u} + \beta - k_2.$$

Proposition 2.6 implies the existence of a sufficiently small constant $\widetilde{C}_s$ such that

$$\begin{aligned}
d_r &\leq k_1 \frac{-(k_1+\beta)\widetilde{C}_s + k_2 + \sqrt{\Delta_2}}{2k_1\widetilde{C}_s} + \beta - k_2 \\
&= \frac{1}{2\widetilde{C}_s}\left(\beta\widetilde{C}_s - k_1\widetilde{C}_s + k_2(1-2\widetilde{C}_s) + \sqrt{\Delta_2}\right) \\
&= \frac{1}{2}\left(\beta - k_1 + k_2\left(\frac{1}{\widetilde{C}_s} - 2\right) + \sqrt{\frac{1}{\widetilde{C}_s^2}(k_2-k_1-\beta)^2 + 4\frac{k_1}{\widetilde{C}_s}(\alpha+k_2)}\right) \\
&\leq \frac{1}{2}(\beta - k_1 - k_2 + \sqrt{\Delta_d} = \bar{d}_r.
\end{aligned}$$

This is a contradiction with the assumption that $d_r > \bar{d}_r$. Therefore, there exists $\lim_{t\to\infty} u_1(t) = \lim_{t\to\infty} u_2(t) = 0$. Using the theory of the asymptotically autonomous dynamical systems [6], we can consider the model (3) on the invariant set $u_1 = u_2 = 0$; on this set the system (3) takes the form $\dot{s} = d_r(1 - s)$, and hence $s(t)$ tends to 1 as $t \to \infty$. Therefore, $E_0 = (1, 0, 0)$ is globally asymptotically stable equilibrium of the model. □

Corollary 2.1. *If $d_r < \bar{d}_r$ holds true, then the system (3) is uniformly persistent.*

Proof. It follows from Proposition 2.6 that either $u_1(t)$ and $u_2(t)$ tend to zero as $t \to +\infty$ or both are persistent, i. e. there exist positive constants c_i, such that $\lim\inf_{t\to+\infty} u_i(t) \geq c_i$, $i = 1, 2$ (see [2]). Suppose that $u_2(t) \to 0$ as t tends to ∞; then $u_1(t)$ will also tend to 0 as $t \to \infty$. As in the proof of Theorem 2.1 we obtain that $s(t)$ must tend to 1; this will mean that E_0 is asymptotically stable for (3), but it is not. The contradiction proves the corollary. □

3 Reaction diffusion system. Travelling wave solution

The model (3) describes bacterial growth in a continuously stirred bioreactor, when the culture medium is perfectly homogeneous. Such a hypothesis is not valid for a tubular bioreactor. Consider the bioreactor as a long and narrow tube; let the input pump, feeding the tank with substrate, be at the narrow end of the tube. Under these assumptions, the environment cannot remain homogeneous anymore, and the dynamics of bacterial growth depend on spatiotemporal conditions.

We introduce diffusion terms in equations (3) to describe the spatial dispersal of the bacteria. As a first approximation we consider the one dimensional case with x being the spatial variable. We obtain the reaction diffusion system

$$
\begin{aligned}
\frac{\partial s}{\partial t} &= D\frac{\partial^2 s}{\partial x^2} - k_1 u_1 s - (\alpha+\beta) u_2 s + d_r(1-s) \\
\frac{\partial u_1}{\partial t} &= D\frac{\partial^2 u_1}{\partial x^2} - k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 \\
\frac{\partial u_2}{\partial t} &= D\frac{\partial^2 u_2}{\partial x^2} + k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2,
\end{aligned}
\tag{20}
$$

where D denotes the diffusion coefficient.

We look for a travelling wave solution of (20), namely:

$$
\begin{aligned}
s &= \bar{s}(\xi) \\
u_1 &= \bar{u}_1(\xi), \\
u_2 &= \bar{u}_2(\xi)
\end{aligned}
\tag{21}
$$

where

$$\xi = x + qt, \quad q = \mathit{const} \text{ is the speed of the wave.}$$

Upon substituting (21) into (20) and omitting the bars for notational simplicity, we obtain the following system of ordinary differential equations of second order

$$
\begin{aligned}
q\frac{ds}{d\xi} &= D\frac{d^2 s}{d\xi^2} - k_1 u_1 s - (\alpha+\beta) u_2 s + d_r(1-s) \\
q\frac{du_1}{d\xi} &= D\frac{d^2 u_1}{d\xi^2} - k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 \\
q\frac{du_2}{d\xi} &= D\frac{d^2 u_2}{d\xi^2} + k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2.
\end{aligned}
\tag{22}
$$

Let l, w_1 and w_2 denote respectively $ds/d\xi$, $du_1/d\xi$ and $du_2/d\xi$. Then we can rewrite (22) as a first-order system

$$
\begin{aligned}
\frac{ds}{d\xi} &= l \\
\frac{dl}{d\xi} &= \frac{1}{D}[k_1u_1s + (\alpha+\beta)u_2s - d_r(1-s) + ql] \\
\frac{du_1}{d\xi} &= w_1 \\
\frac{dw_1}{d\xi} &= \frac{1}{D}[k_1u_1s - k_2u_2 - \alpha u_2s + d_ru_1 + qw_1] \\
\frac{du_2}{d\xi} &= w_2 \\
\frac{dw_2}{d\xi} &= \frac{1}{D}[-k_1u_1s + k_2u_2 - \beta u_2s + d_ru_2 + qw_2].
\end{aligned}
\tag{23}
$$

Proposition 3.1. *The equilibrium point $\widehat{E}_0 = (1,0,0,0,0,0)$ is a locally asymptotically unstable equilibrium for the system (23).*

Proof. The Jacobian matrix of (23) is

$$
\begin{aligned}
J &= J(s,l,u_1,w_1,u_2,w_2) \\
&= \begin{pmatrix}
0 & 1 & 0 & 0 & 0 & 0 \\
\frac{d_r+u_2(\alpha+\beta)+u_1k_1}{D} & \frac{q}{D} & \frac{sk_1}{D} & 0 & \frac{s(\alpha+\beta)}{D} & 0 \\
0 & 0 & 0 & 1 & 0 & 0 \\
\frac{-u_2\alpha+u_1k_1}{D} & 0 & \frac{d_r+sk_1}{D} & \frac{q}{D} & \frac{-s\alpha-k_2}{D} & 0 \\
0 & 0 & 0 & 0 & 0 & 1 \\
\frac{-u_2\beta-u_1k_1}{D} & 0 & -\frac{sk_1}{D} & 0 & \frac{d_r-s\beta+k_2}{D} & \frac{q}{D}
\end{pmatrix}
\end{aligned}
$$

One of the eigenvalues of J, evaluated at $\widehat{E}_0 = (1,0,0,0,0,0)$ is

$$\tilde{\lambda}_1 = \frac{q+\sqrt{4d_rD+q^2}}{2D}$$

$\tilde{\lambda}_1$ is obviously positive when $q > 0$ holds true; otherwise we have

$$\tilde{\lambda}_1 = \frac{q+\sqrt{4d_rD+q^2}}{2D} > \frac{-|q|+\sqrt{q^2}}{2D} = 0.$$

Therefore $\widehat{E}_0$ is an unstable equilibrium. □

Proposition 3.2. *If $d_r < \bar{d}_r$, then $\widehat{E}^* = (s^*, 0, u_1^*, 0, u_2^*, 0)$ is an equilibrium point for (23), which is locally asymptotically unstable.*

Proof. It is straightforward to see that $\widehat{E}^*$ is an equilibrium point of (23). Further, the characteristic equation of the $J(s, l, u_1, w_1, u_2, w_2)$, evaluated in $\widehat{E}^*$, i. e. $|J(\widehat{E}^*) - \hat{\lambda} I| = 0$, can be presented in the form

$$-\lambda^3 + a\lambda^2 - b\lambda + c = 0, \tag{24}$$

where $\lambda = \hat{\lambda}(q - \hat{\lambda})$, and the coefficients a, b and c are computed as in Proposition 2.4. We know from Proposition 2.4, that (24) possesses three roots (with respect to λ) with negative real parts. Let λ_1 be a real root of (24); then λ_1 must be negative. In this case $\hat{\lambda}$ satisfies the equation

$$\hat{\lambda}^2 - q\hat{\lambda} + \lambda_1 = 0,$$

whose roots $\hat{\lambda}_1$ and $\hat{\lambda}_2$ are real and of opposite signs due to $\hat{\lambda}_1\hat{\lambda}_2 = \lambda_1 < 0$. Hence, $\widehat{E}^*$ is a saddle equilibrium point for (23). □

Therefore, system (23) possesses two saddle equilibrium points $\widehat{E}^*$ and $\widehat{E}_0$. Our goal is to find a heteroclinic orbit between these two equilibrium points, which will correspond to a travelling wave solution of (22). Such an orbit (if exists) should satisfy the boundary conditions

$$\begin{aligned}
&s(-\infty) = 1,\\
&l(-\infty) = u_1(-\infty) = w_1(-\infty) = u_2(-\infty) = w_2(-\infty) = 0;\\
&s(+\infty) = s^*,\ u_1(+\infty) = u_1^*,\ u_2(+\infty) = u_2^*,\\
&l(+\infty) = w_1(+\infty) = w_2(+\infty) = 0.
\end{aligned}$$

A numerical example in the next section illustrates the existence of such a heteroclinic orbit and thus the existence of a travelling wave solution.

Remark 3.1 The speed q of the wave can be obtained approximately using the following heuristic arguments. Let us consider in (20) the wave front at its leading edge, i. e. in the area where $u_1 \approx 0$,

$u_2 \approx 0$, $s = 1$. After linearization of the third equation in (20) we obtain

$$\frac{\partial u_2}{\partial t} = D\frac{\partial^2 u_2(x,t)}{\partial x^2} - k_2 u_2 + \beta u_2 - d_r u_2 \tag{25}$$

Equation (25) coincides with the Kolmogorov-Petrovskii-Piskunov-Fisher equation [8], therefore

$$q \approx 2\sqrt{D(\beta - k_2 - d_r)}.$$

The travelling wave solution exists if and only if $\beta - k_2 - d_r > 0$ or equivalently $0 < d_r < \beta - k_2$ (see (4)); it can also be easily checked that $\beta - k_2 < \bar{d}_r$ holds true.

4 Numerical simulations

We consider the following values for the model constants taken from [1]:

$$k_1 = 0.05, \quad k_2 = 0.85, \quad \alpha = 1.35, \quad \beta = 1.5.$$

Within these values we obtain $\bar{d}_r = 0.7822$. Let us choose $d_r = 0.5$. Then the equilibrium

$$E^* = (0.8039850335, 0.1441799143, 0.04024320293).$$

is locally asymptotically stable, E_0 is a saddle point for the model.

Figure 1 demonstrates the asymptotic stability of E^*, visualizing three solutions of the model (3) with three different initial conditions.

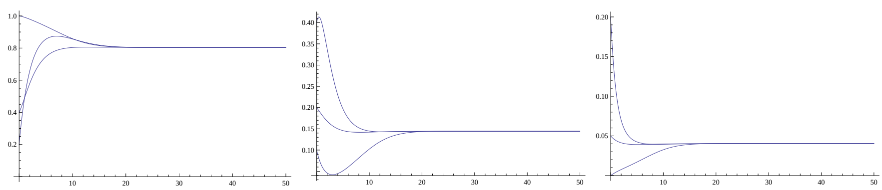


Figure 1: Solutions (from left to rigth) $s(t)$, $u_1(t)$ and $u_2(t)$ of (3) with three different initial points

We consider now the model (20) where the spatial variable x is in the interval $[0, X]$ with the following boundary conditions, modeling a closed biological system

$$\begin{aligned} \frac{\partial s}{\partial x}(0,t) = \frac{\partial s}{\partial x}(X,t) = 0, \\ \frac{\partial u_1}{\partial x}(0,t) = \frac{\partial u_1}{\partial x}(X,t) = 0, \\ \frac{\partial u_2}{\partial x}(0,t) = \frac{\partial u_2}{\partial x}(X,t) = 0, \\ t \geq 0 \end{aligned} \tag{26}$$

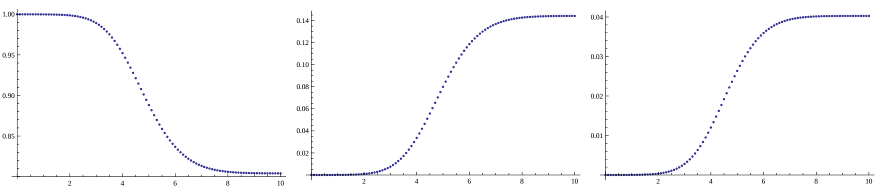
and initial conditions:

$$s(x,0) = 1,\ 0 \leq x \leq X$$

$$u_1(x,0) = \begin{cases} 0.75 & x \geq 0.95X \\ 0 & 0 \leq x < 0.95X \end{cases}$$

$$u_2(x,0) = 0,\ 0 \leq x \leq X$$

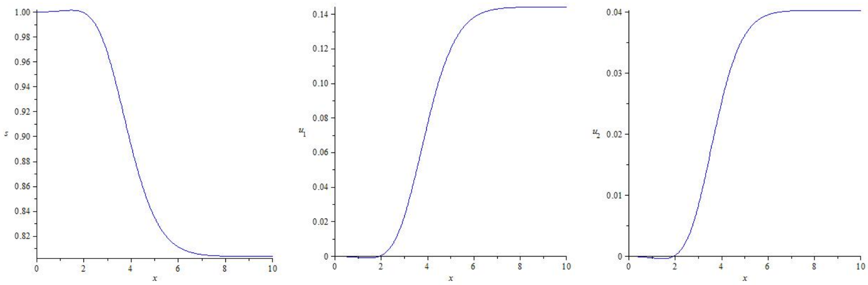
We take the diffusion coefficient to be $D = 0.05$ and $X = 10$. We obtain the wave profiles, shown in Figure 2. Those correspond to the results, obtained in Section 2: the wave solution connects the stationary points of the nondistributed system (3).



(a) $s(x,t)$ (b) $u_1(x,t)$ (c) $u_2(x,t)$

Figure 2: A travelling wave solution of the system (20), connecting the stationary points (1,0,0) and (0.803998,0.144175,0.040262)

Using the formula from Remark 3.1, we obtain the estimate $q \approx 0.173205$. Given this estimate, we show that the solutions of the ODE system (3) correspond to the wave profile of the solution, obtained from the original reaction-diffusion system (20) and thus, showing the existence of a heteroclinic orbit between the two equilibrium points in (23), see Figure 3.



(a) $s(\xi)$ (b) $u_1(\xi)$ (c) $u_2(\xi)$

Figure 3: Solutions for $s(\xi)$, $u_1(\xi)$ and $u_2(\xi)$ in (23), corresponding to the heteroclinic orbit, connecting the stationary points $\widehat{E_0}$ and $\widehat{E^*}$

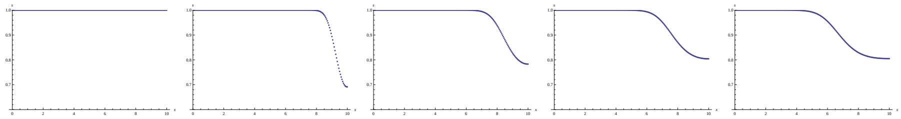
Our numerical experiments suggest that in the case when the internal equilibrium $E^* = (s^*, u_1^*, u_2^*)$ exists the solution of the system (20) behaves like the travelling wave solutions for some period of time when the initial conditions are "forgotten" and the boundary conditions have not started acting yet. Let us illustrate this with the following example. We consider the model (20) with boundary conditions (26) and the following initial conditions:

$$s(x,0) = 1,\ 0 \le x \le X;$$

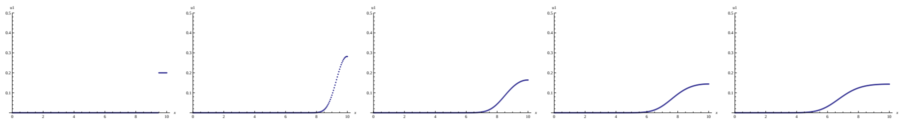
$$u_1(x,0) = \begin{cases} 1 & x \ge 0.95X \\ 0 & 0 \le x < 0.95X; \end{cases}$$

$$u_2(x,0) = \begin{cases} 0.15 & x \ge 0.95X \\ 0 & 0 \le x < 0.95X. \end{cases}$$

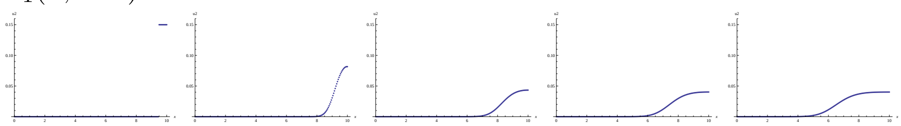
In Figure 4 the solution is plotted for different values of t, in order to show how it converges to the wave profile, that we have already discussed.



(a) Numerical approximation for $s(x, 0)$, $s(x, 2.5)$, $s(x, 7.5)$, $s(x, 12.5)$, $s(x, 17.5)$



(b) Numerical approximation for $u_1(x, 0)$, $u_1(x, 2.5)$, $u_1(x, 7.5)$, $u_1(x, 12.5)$, $u_1(x, 17.5)$



(c) Numerical approximation for $u_2(x, 0)$, $u_2(x, 2.5)$, $u_2(x, 7.5)$, $u_2(x, 12.5)$, $u_2(x, 17.5)$

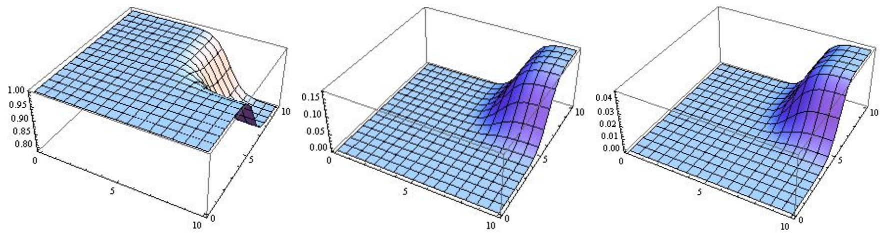
Figure 4: Convergence of the solutions of the model (20) to the travelling wave solution

Let us now study the two-dimensional case. Introducing a second spatial variable y, the model takes the form:

$$\begin{aligned} \frac{\partial s}{\partial t} &= D\frac{\partial^2 s}{\partial x^2} + D\frac{\partial^2 s}{\partial y^2} - k_1 u_1 s - (\alpha + \beta) u_2 s + d_r(1 - s) \\ \frac{\partial u_1}{\partial t} &= D\frac{\partial^2 u_1}{\partial x^2} + D\frac{\partial^2 u_1}{\partial y^2} - k_1 u_1 s + k_2 u_2 + \alpha u_2 s - d_r u_1 \\ \frac{\partial u_2}{\partial t} &= D\frac{\partial^2 u_2}{\partial x^2} + D\frac{\partial^2 u_2}{\partial y^2} + k_1 u_1 s - k_2 u_2 + \beta u_2 s - d_r u_2. \end{aligned} \tag{27}$$

We solve this system numerically to obtain the wave profiles visualized in Figure 5.

One more step to understanding the effect of the diffusion is to compare models (3) and (20). Let us note that the first one describes a stirred bioreactor and the second one – an unstirred bioreactor. The



(a) $s(x, y, t)$ (b) $u_1(x, y, t)$ (c) $u_2(x, y, t)$

Figure 5: A travelling wave solution of (27)

comparison between the two models can give us a better understanding of the difference between the two processes.

We introduce the notation

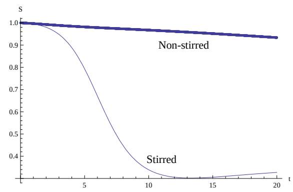
$$S(t) := \frac{1}{X}\int_0^X s(x,t)dx$$
$$U_1(t) := \frac{1}{X}\int_0^X u_1(x,t)dx$$
$$U_2(t) := \frac{1}{X}\int_0^X u_2(x,t)dx,$$

where $s(x,t)$, $u_1(x,t)$ and $u_2(x,t)$ are the solutions of (20). Those are the total amounts of the substrate, bacteria in lag and bacteria in log phase, respectively, in the unstirred bioreactor at time t (assuming a unit volume).

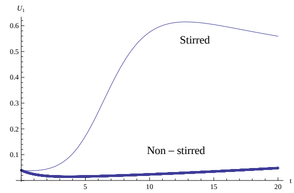
The corresponding quantities for the model (3) (i. e. the continuously stirred bioreactor model) are exactly the values of the solution at time t.

5 Conclusion

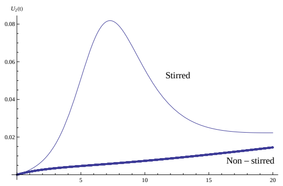
The paper is devoted to studying a bioreactor model describing microbial competition between bacteria in different growth phases. Originally the model was proposed in [1] for a batch culture. This model is



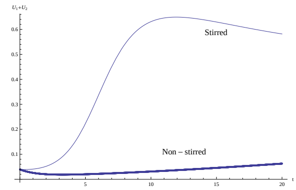
(a) $S(t)$



(b) $U_1(t)$



(c) $U_2(t)$



(d) $U_1(t) + U_2(t)$

modified here by introducing first additional terms to describe a homogeneous continuously stirred bioreactor dynamics (3). The analysis of the latter model includes computation of the equilibrium points and studying their asymptotic stability. Basic properties of the solutions like uniform boundedness and uniform persistence are also established. In a second step the model is extended by adding diffusion terms to the equations of (3) to describe the spatial dispersal of the bacteria, i. e. to take into account the nonhomogeneity conditions in the bioreactor. For the latter model, solutions in the form of travelling waves are found. Results from numerical simulations are provided as demonstrations of the theoretical studies as well as for comparison between the two models.

Acknowledgments

The work of the first author has been partially supported by the Sofia University "St. Kl. Ohridski" under contract No. 075/2015. The work of the second author has been partially supported by the Sofia University "St. Kl. Ohridski" under contract No. 08/26.03.2015.

References

[1] R. Alt, S. Markov: Theoretical and computational studies of some bioreactor models. Computers and Mathematics with Applications (2012) 64, 3 : 350–360.

[2] G. Butler, H. I. Freedman, P. Waltman: Uniformly persistent systems. Proc. Amer. Math. Soc. (1986) 96 : 425–430.

[3] K. Golpalsamy: Stability and oscillations in delay differential equations of population dynamics. *Kluwer Academic Publishers* Dordrect, 1992.

[4] W. M. Hirsch, H. Hanisch, J.-P. Gabriel: Differential equation models of some parasitic infections: methods for the study of asymptotic behavior. Comm. Pure Appl. Math. (1985) 38 : 733–753.

[5] S. Markov: On the mathematical modelling of microbial growth: some computational aspects. Serdica Journal of Computing (2011) 5, 2 : 153–168.

[6] K. Mischaikov, H. Smith, H. Thieme: Asymptotically autonomous semiflows: chain recurrence and Lyapunov functions. TAMS (1995) 347, 5 : 1669–1685.

[7] Bl. Sendov, A. Andreev, N. Kjurkchiev: Numerical solution of polynomial equations. In: *Handbook of Numerical Analysis, Vol. III*, eds. P. G. Ciarlet et al., North-Holland, Amsterdam, 1994, 625–778.

[8] V. Volpert, S. Petrovskii: Reaction-diffusion waves in Biology. Physics at Life Reviews (2009) 6 : 267–310.