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A fundamental analysis of continuous flow bioreactor and membrane reactor models with non-competitive product inhibition. III. Linear inhibition

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Keywords

continuous, fundamental, analysis, flow, bioreactor, iii, membrane, linear, reactor, models, non, competitive, product, inhibition

Disciplines

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A fundamental analysis of continuous flow bioreactor and membrane reactor models with non-competitive product inhibition. III. Linear inhibition.

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Abstract

The steady-state production of a product produced through the growth of microorganisms in a continuous flow bioreactor is presented. A generalised reactor model is used in which both the classic well-stirred bioreactor and the idealised membrane bioreactor are considered as special cases. The reaction is assumed to be governed by Monod growth kinetics subject to non-competitive product inhibition. Inhibition is modelled as a decreasing linear function of the product concentration with a finite cut-off. This reaction scheme is well documented in the literature, although a stability analysis of the governing equations has not previously been presented.

The steady-state solutions for the models have been obtained, and the stability has been determined as a function of the residence time. The key dimensionless parameter (γ) that controls the degree of non-competitive product inhibition is obtained by scaling of the equations, and its effect on the reactor performance is quantified in the limit when product inhibition is “small” and “large”. The parameter γ is the reciprocal of a scaled inhibition constant (P_m) that depends upon the substrate and product yield factors and the Monod constant ($\gamma = \frac{\alpha_s}{\alpha_p} \cdot \frac{K_s}{P_m}$).

Keywords Monod growth kinetics; stirred tank; bioreactor; membrane reactor; non-competitive product inhibition; stability analysis; steady-state models.

1 Introduction

A continuous stirred flow bioreactor is a well-stirred vessel containing microorganisms (X) through which a substrate (S) flows at a continuous rate. The microorganisms grow in the vessel through the consumption of

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the substrate to produce more microorganisms and a product (P). Unused substrate, microorganisms, and the product flow out of the reactor at the same rate at which the feed is admitted. In membrane-based bioreactors a permeable membrane, such as a microfiltration membrane, is used to physically retain microorganisms inside the reactor whilst allowing the substrate and product to move through the reactor. Entrapping the microorganisms in this manner increases their concentration compared to a flow reactor. This results in a greater conversion of the substrate, allowing for a more rapid and efficient process.

In this paper we analyze the steady-state behaviour of a biological process in a generalised bioreactor model as a function of the residence time. The parameter β defines the reactor model. When $\beta = 1$ equations (4) & (5) are the standard model for a well-stirred reactor without recycle. When $\beta = 0$ the model equations provide a simple representation of an idealised membrane reactor [1, 2]. The case ($0 < \beta < 1$) represents a number of reactor configurations. These include: a non-idealised membrane reactor, in which some of the microorganisms leave the reactor vessel in the effluent stream; a fixed-bed biological process with a large recirculation rate and with biomass detachment – β is the fraction of the biomass that is detached from the reactor by the flow – [3, page 428] and a perfusion bioreactor incorporating a cell bleed [4, 5].

The biochemical model is based upon Monod growth rate kinetics with noncompetitive product inhibition and death of the microorganisms. Several forms for non-competitive product inhibition have been suggested in the literature. These include [6, page 179]

$$\mu(S, P) = \mu(S) \cdot \frac{1}{1 + \frac{P}{K_p}}, \quad (1)$$

$$\mu(S, P) = \mu(S) \cdot \exp\left[-\frac{P}{K_p}\right], \quad (2)$$

$$\mu(S, P) = \mu(S) \cdot \left(1 - \frac{P}{P_m}\right) \mathcal{H}(P_m - P). \quad (3)$$

In these expressions $\mu(S)$ is the growth rate expression in the absence of product, K_p is the product inhibition constant, P_m is a concentration at which growth stops and \mathcal{H} is the Heaviside function. The third of these expressions can be derived as a Taylor series expansion of the second for small product concentrations. There is a clear biological difference between the linear inhibition model, equation (3), and the algebraic/exponential inhibition models, equations (1) & (2), in that in the former there is a maximum product concentration above which there is no production of the product. We are not aware of any biological interpretation associated to the difference between the algebraic and exponential models.

In earlier papers the steady-state product concentration was determined as a function of the residence time when inhibition is characterised by the first two of these expressions [7, 8]. In this paper we extend our earlier investigation by employing the third of these expressions. In section 4 we compare the results obtained using expressions 1 and 2 with those obtained using expression 3.

An example of a product that causes non-competitive inhibition is L-lactate, which is an optically active material that has diverse applications across the agrocultural, chemical, cosmetic, food, leather, pharmaceutical, and textile industries. It is a starting material in the synthesis of lactic and polylactate acid, which are used to

produce biocompatible and biodegradable plastics which have important medical applications.

The production of lactate via fermentation can produce both optically pure L- or D-lactic acid depending upon the choice of microorganism. Lactate fermentation is frequently characterised by end-product inhibition and this has been modelled in a variety of ways. The algebraic inhibition function was used by in [9]. The exponential inhibition function was used in [10, 11]. The linear inhibition function, with a threshold concentration below which inhibition does not occur, was used in [12]. The algebraic expression has also been combined with the linear expression, the latter expression including a threshold concentration at which inhibition starts [13].

Lactate inhibition has been modelled as uncompetitive inhibition [14, 15]. Assuming that the underlying specific growth rate model is Monod these uncompetitive inhibition was modelled by

$$\mu(S, P) = \frac{\mu_m S}{K_s + \left(1 + \frac{P}{K_i}\right) S}.$$

According to Ohara *et al* [9] it is uncertain how to distinguish between non-competitive and uncompetitive inhibition.

In this paper we prefer to write equation (3) in the equivalent form

$$\mu(S, P) = \mu(S) \cdot \left(1 - \frac{P}{P_m}\right) \mathcal{H}\left(1 - \frac{P}{P_m}\right).$$

This reformulation is more appealing mathematically because the argument of the Heaviside function is dimensionless.

Non-competitive product inhibition is a standard topic in biochemical engineering and is addressed in textbooks such as [16, chapter 7], [17, chapter 3.3.8] and [6, chapter 6]. Given the long history of this topic it is surprising that a stability analysis of equations (4)–(9) has not appeared in the literature.

2 Equations

In this section we write down the model equations for the concentration of microorganisms, substrate and product within a well-stirred, well aerated, bioreactor and a membrane reactor. The assumption that the reactor is well-stirred means that the substrate is instantaneously and homogeneously mixed with the reactor contents. The assumption that the reactor is well aerated means that oxygen is not a rate-limiting substance. It is also assumed that the flow through the bioreactor is sufficiently fast that cell-growth does not occur on the walls of the reactors and that operating conditions are such that the pH, temperature and other thermodynamic variables are automatically controlled so as to remain constant and spatially uniform. Finally, dead cells will accumulate in a membrane reactor. This will slowly reduce the reactor volume. This effect is not included in the current model.

2.1 The dimensional model

The model equations are

$$V \frac{dS}{dt} = F(S_0 - S) - \frac{\mu(S)}{\alpha_s} \cdot \mu(P) \cdot VX, \quad (4)$$

$$V \frac{dX}{dt} = \beta F(X_0 - X) + \mu(S) \cdot \mu(P) \cdot VX - V k_d X. \quad (5)$$

$$V \frac{dP}{dt} = F(P_0 - P) + \frac{\mu(S)}{\alpha_p} \cdot \mu(P) \cdot VX. \quad (6)$$

The specific growth rate is given by

$$\mu(S) = \frac{\mu_m S}{K_s + S}. \quad (7)$$

Non-competitive product inhibition

$$\mu(P) = \left(1 - \frac{P}{P_m}\right) \mathcal{H}\left(1 - \frac{P}{P_m}\right). \quad (8)$$

Residence time

$$\tau = \frac{V}{F}. \quad (9)$$

The terms that appear in equations (4)–(9) are defined in appendix A.

Note that in the limit that when the value of the parameter P_m approaches infinity the system (4)–(6) reduces to a simple cellmass-substrate system where the growth kinetics are Monod. This system was analysed in [18].

In equations (4)–(6) the main experimental control parameter is the residence time, given in equation (9).

2.1.1 The dimensionless model

By introducing the dimensionless variables defined in appendix A the dimensional model, equations (4)–(6), can be written in the dimensionless form

$$\frac{dS^*}{dt^*} = \frac{1}{\tau^*} (S_0^* - S^*) - \frac{S^* X^*}{1 + S^*} \cdot (1 - \gamma P^*) \mathcal{H}(1 - \gamma P^*), \quad (10)$$

$$\frac{dX^*}{dt^*} = \frac{\beta}{\tau^*} (X_0^* - X^*) + \frac{S^* X^*}{1 + S^*} \cdot (1 - \gamma P^*) \mathcal{H}(1 - \gamma P^*) - k_d^* X^*, \quad (11)$$

$$\frac{dP^*}{dt^*} = \frac{1}{\tau^*} (P_0^* - P^*) + \frac{S^* X^*}{1 + S^*} \cdot (1 - \gamma P^*) \mathcal{H}(1 - \gamma P^*), \quad (12)$$

where the parameter groups are defined in appendix A. Note that in the limit in which the scaled model (10)–(12) reduces to a simple cellmass-substrate system where the growth kinetics are Monod is the limit as γ approaches zero.

In section 3 we need the Jacobian of system (10)–(12). Assuming that $P^* < \gamma^{-1}$ this is given by

$$J(S^*, X^*, P^*) = \begin{pmatrix} -\frac{1}{\tau^*} - A & -B & C \\ A & -\frac{\beta}{\tau^*} + B - k_d^* & -C \\ A & B & -\frac{1}{\tau^*} - C \end{pmatrix},$$

$$A = \frac{1}{(1 + S^*)^2} \cdot X^* (1 - \gamma P^*),$$

$$B = \frac{S^*}{1 + S^*} (1 - \gamma P^*),$$

$$C = \frac{S^* X^*}{1 + S^*} \cdot \gamma.$$

From now on we assume that the growth medium fed into the bioreactor is sterile, i.e. the concentration of microorganisms flowing into the reactor is zero ($X_0 = X_0^* = 0$), and that no product flows into bioreactor, i.e. $P_0 = P_0^* = 0$. Furthermore, we assume that the dimensionless residence time, the dimensionless substrate concentration in the feed, the dimensionless maximum product concentration and the dimensionless death rate ($\tau^* > 0$, $S_0^* > 0$, $\gamma > 0$ and $k_d^* > 0$ respectively).

3 Results

Using the method outlined in [7, appendix B] it can be shown that the region defined below is positively invariant.

$$\begin{aligned} 0 &\leq S^* (t^* = 0) \leq S_0^*, \\ 0 &\leq X^* (t^* = 0), \\ 0 &\leq P^* (t^* = 0) \leq \gamma^{-1}. \end{aligned}$$

This means that if the initial concentrations satisfy the above constraints then the solution of system (10)–(12) satisfies the constraints for all time $t^* \geq 0$. In appendix B we show that a solution starting at any physically meaningful initial condition, i.e. the initial coordinates are all strictly non-negative, outside the invariant region eventually enters the invariant region, i.e. the invariant region is attracting. The significance of this result is that we are free to drop the Heaviside function from the model, as the solution is guaranteed to enter the invariant region.

In section 3.1 it is shown that there are two steady-state solution branches. These are a washout branch and a no-washout branch. The conditions for the latter to be physically meaningful are derived. The term ‘washout branch’ is used in this paper to denote a solution in which cells are removed from the system faster than they grow and hence their steady-state value is zero. By ‘remove’ we include both removal due to flow and removal due to cell death.

In section 3.2 the stability of the steady-state solutions are determined. When the washout solution is locally stable it can be shown to be globally stable. For sufficiently small values of the feed concentration (S_0^*) the

washout branch is stable for all values of the residence time (τ^*). When the washout branch is not globally stable for all values of the residence then there is a critical value of the residence time, $\tau_{\text{cr}}^* > 0$, at which a transcritical bifurcation occurs. Washout occurs for $\tau^* < \tau_{\text{cr}}^*$ and the no-washout solution branch is locally stable for $\tau^* > \tau_{\text{cr}}^*$. In section 3.3 an approximate solution is obtained for the substrate concentration for values of the residence time slightly higher than the critical value ($\tau^* - \tau_{\text{cr}}^* \ll 1$). In section 3.4 approximate solutions are obtained for small values of the dimensionless product inhibition constant ($\gamma \ll 1$). These are further simplified in the limit of high residence time. In section 3.5 asymptotic solutions for large residence times are stated for arbitrary values of the inhibition constant. These are further simplified for the case of large product inhibition ($\gamma \gg 1$).

3.1 Steady-state solution branches

The steady-state solutions are given by

Washout branch

$$(S^*, X^*, P^*) = (S_0^*, 0, 0), \quad (13)$$

No-washout branch

$$(S^*, X^*, P^*) = \left(\hat{S}^*, \frac{S_0^* - \hat{S}^*}{\beta + k_d^* \tau^*}, S_0^* - \hat{S}^* \right), \quad (14)$$

where \hat{S}^* is a root of the equation

$$\mathcal{G}(\hat{S}^*) = a\hat{S}^{*2} + b\hat{S}^* + c = 0. \quad (15)$$

The coefficients a , b and c are defined by

$$\begin{aligned} a &= \tau^*, \\ b &= (1 - k_d^*)\gamma^{-1}\tau^* - S_0^*\tau^* - \beta\gamma^{-1}, \\ c &= -(k_d^*\tau^* + \beta)\gamma^{-1}. \end{aligned}$$

Note that the coefficient of \hat{S}^{*2} is strictly positive ($a > 0$) and the constant term is strictly negative ($c < 0$) as by assumption we have: $k_d^* > 0$, $\tau^* > 0$ and $\gamma > 0$. Thus equation (15) has one root that is positive and one root that is negative. Consequently, the required value for \hat{S}^* is given by

$$\hat{S}^* = \frac{-b + \sqrt{b^2 - 4ac}}{2a}. \quad (16)$$

Differentiating equation (16) we obtain

$$\frac{dS^*}{d\tau} = \frac{\beta}{2\gamma\tau^{*2}} \left[\frac{b}{\sqrt{b^2 - 4ac}} - 1 - \frac{2\tau^*}{\sqrt{b^2 - 4ac}} \right] \leq 0 \quad (\text{as } c < 0).$$

When $\beta = 0$, corresponding to an idealised membrane reactor, the substrate concentration does not depend upon the residence time. When $0 < \beta \leq 1$ the substrate concentration is a decreasing function of the residence

time. It follows from equation (14) that the product concentration is then an increasing function of the residence time.

The no-washout branch is only physically meaningful when the substrate, cell-mass and product concentrations are positive ($S^* > 0$, $X^* > 0$, $P^* > 0$). We have already established that $\hat{S}^* > 0$. Thus from equation (14) we need to find the condition for $\hat{S}^* < S_0^*$. This requires

$$\tau^* > \frac{(1 + S_0^*)\beta}{S_0^*(1 - k_d^*) - k_d^*},$$

provided that

$$0 < k_d^* < \frac{S_0^*}{1 + S_0^*}.$$

An alternative formulation of this, which will be helpful in subsequent sections, is

$$S_0^* > \frac{k_d^*}{1 - k_d^*} \quad (17)$$

provided that

$$0 < k_d^* < 1. \quad (18)$$

At the critical value

$$\tau^* = \tau_{cr}^* = \frac{(1 + S_0^*)\beta}{(1 - k_d^*)S_0^* - k_d^*},$$

the washout and no-washout solution branches intersect at a transcritical bifurcation. (The bifurcation point is known as a transcritical bifurcation because for values of the residence time either slightly higher or slightly lower than the critical value there are two steady-state solutions in the neighbourhood of the bifurcation point. However, at the critical value there is only one steady-state solution).

3.2 Stability of the steady-state solutions

In section 3.2.1 the local stability of the washout solution branch is determined. Using the method of Butler [19], it can be shown that when the washout solution is locally stable it is globally stable. Furthermore, when the stability of the washout solution is undetermined, because of the presence of a zero eigenvalue, it remains globally stable. In section 3.2.2 the nowashout solution branch is shown to be locally stable whenever it is physically meaningful.

3.2.1 Stability of the washout solution

The Jacobian matrix evaluated at the washout steady-state solution is given by

$$J(S_0^*, 0, 0) = \begin{pmatrix} -\frac{1}{\tau^*} & -\frac{S_0^*}{1+S_0^*} & 0 \\ 0 & -\frac{\beta}{\tau^*} + \frac{S_0^*}{1+S_0^*} - k_d^* & 0 \\ 0 & \frac{S_0^*}{1+S_0^*} & -\frac{1}{\tau^*} \end{pmatrix}.$$

The eigenvalues of this matrix are

$$\begin{aligned}\lambda_1 &= -\frac{1}{\tau^*} < 0, \\ \lambda_2 &= -\frac{\beta^*}{\tau^*} + \frac{S_0^*}{1+S_0^*} - k_d^*, \\ \lambda_3 &= -\frac{1}{\tau^*} < 0.\end{aligned}$$

If $\beta = 0$ then the steady-state solution is always stable if

$$k_d^* > \frac{S_0^*}{1+S_0^*}$$

and it is always unstable if

$$k_d^* < \frac{S_0^*}{1+S_0^*}.$$

(When $\beta = 0$ there are no cells leaving the system. Under these circumstances the washout solution branch can alternatively be called the death solution branch).

If $0 < \beta \leq 1$ then the washout steady-state is always stable when

$$\begin{aligned}k_d^* &\geq 1, \\ \Rightarrow \frac{k_d}{\mu_m} &\geq 1, \\ \Rightarrow k_d &\geq \mu_m.\end{aligned}$$

This inequality makes sense ‘physically’ because it shows that the washout steady-state is always stable if the death rate is greater than, or equal to, the maximum growth rate.

If $k_d^* < \frac{S_0^*}{1+S_0^*}$ and $0 < \beta \leq 1$ then the washout steady-state is stable provided

$$\tau^* < \frac{(1+S_0^*)\beta}{S_0^* - k_d^*(1+S_0^*)}.$$

Using the method outlined in [7, page 100] it can be shown that when the washout solution solution is locally stable it is in fact globally stable. Furthermore, the steady-state remains globally stability when $\lambda_2 = 0$.

3.2.2 Local stability of the no-washout solution

As noted in section 2.1.1 the Jacobian matrix for the no-washout branch can be written in the form

$$J(S^*, X^*, P^*) = \begin{pmatrix} -\frac{1}{\tau^*} - A & -B & C \\ A & 0 & -C \\ A & B & -\frac{1}{\tau^*} - C \end{pmatrix} \quad (19)$$

The characteristic polynomial of this matrix is given by

$$p(\lambda) = -\left(\lambda + \frac{1}{\tau^*}\right) \left[\lambda^2 + \left(A + C + \frac{1}{\tau^*}\right) \lambda + (A + C)B \right].$$

It follows that along the no-washout branch there is an eigenvalue

$$\lambda_1 = -\frac{1}{\tau^*} < 0.$$

The remaining two eigenvalues are the roots of the quadratic equation

$$\lambda^2 + \left(A + C + \frac{1}{\tau^*}\right)\lambda + (A + C)B = 0. \quad (20)$$

It follows from the definition of A , B and C in section 2.1.1 that these quantities are positive for physically meaningful solutions. Thus the coefficient of λ and the constant term in equation (20) are positive. Therefore the two eigenvalues determined by equation (20) are strictly negative. Consequently the no-washout branch is stable whenever it is physically meaningful.

Observe that there is a zero eigenvalue when $A = C = X^* = 0$, which is when $S^* = S_0^*$ and $P^* = 0$, i.e. when the no-washout branch and the washout branch intersect at a transcritical bifurcation. This happens at the parameter value

$$\tau_{\text{cr}}^* = \frac{(1 + S_0^*)\beta}{S_0^* - k_d^*(1 + S_0^*)}. \quad (21)$$

This value of the residence time represents the maximum residence time at which the treatment process fails. At lower residence times microorganisms are removed from the system at a rate greater than their maximum growth rate, resulting in process failure. At residence times lower (higher) than the transcritical value the washout (no-washout) solution is the only stable solution. Note that the critical value of the residence time is independent of the dimensionless product concentration at which growth stops (γ). The critical value of the dimensionless residence time τ_{cr}^* corresponds to a critical dimensional residence time given by

$$\tau_{\text{cr}} = \frac{(\mu_m - k_d)S_0 - K_s k_d}{K_s + S_0}.$$

Steady-state diagrams showing how the dimensionless substrate concentration (S^*), the dimensionless microorganism concentration (X^*) and the dimensionless product concentration (P^*) change as the dimensionless residence time is varied are shown in figures 1–3; only physically meaningful solutions have been plotted. That is in figures 1–3 the stable solution for sufficiently low residence times ($\tau^* < \tau_{\text{tr}}^*$) are the lines $S^* = S_0^* = 1$, $X^* = 0$ and $P^* = 0$ respectively.

3.3 Approximate solution near the transcritical bifurcation

At

$$\tau^* = \tau_{\text{cr}}^* = \frac{(1 + S_0^*)\beta}{(1 - k_d^*)S_0^* - k_d^*},$$

a transcritical bifurcation occurs when the washout solution branch and the no-washout solution branch intersect at the point

$$(S^*, X^*, P^*, \tau^*) = (S_0^*, 0, 0, \tau_{\text{cr}}^*).$$

For values of the residence time slightly larger than the value at the transcritical bifurcation the substrate concentration along the no-washout branch can be approximated by applying a Taylor series expansion. We obtain

$$S^* \approx S_0^* - \frac{[(1 - k_d^*) S_0^* - k_d^{*2}]}{\beta [1 + S_0^* \gamma (1 + S_0^*)]} \cdot (\tau^* - \tau_{cr}^*) + O(\tau^* - \tau_{cr}^*)^2.$$

3.4 Small dimensionless product inhibition constant approximations

In the limiting case when the inhibition coefficient is small ($\gamma \ll 1$), which corresponds to a large cut-off concentration (P_m), we obtain a series solution along the no-washout branch by assuming that

$$S^* \approx a_0 + a_1 \gamma + O(\gamma)^2.$$

This gives

$$S^* \approx \frac{\beta + k_d^* \tau^*}{(1 - k_d^*) \tau^* - \beta} + \frac{\tau^* (\beta + k_d^* \tau^*) \{(\beta + k_d^* \tau^*) + [\beta + (k_d^* - 1) \tau^*] S_0^*\}}{[\beta - (1 - k_d^*) \tau^*]^3} \cdot \gamma + O(\gamma^2). \quad (22)$$

This indicates the extent to which product inhibition, when the product inhibition is small, increases the substrate concentration inside the reactor.

At large residence times equation (22) further simplifies to give, to order $\frac{1}{\tau^*}$ and γ ,

$$\begin{aligned} S^* &\approx \frac{k_d^*}{1 - k_d^*} + \frac{[(1 - k_d^*) S_0^* - k_d^{*2}] k_d^*}{(1 - k_d^*)^3} \cdot \gamma - \frac{\left\{ - (1 - k_d^*)^2 + [k_d^{*2} + 2k_d^* + (k_d^{*2} - 1) S_0^*] \gamma \right\}}{(1 - k_d^*)^4} \cdot \frac{\beta}{\tau^*}, \\ X^* &\approx \frac{1}{k_d^*} \left\{ S_0^* - \frac{k_d^*}{1 - k_d^*} + \frac{[k_d^* - (1 - k_d^*) S_0^*] k_d^* \gamma}{(1 - k_d^*)^3} \right\} \cdot \frac{1}{\tau^*}, \\ P^* &\approx S_0^* - \frac{k_d^*}{1 - k_d^*} - \frac{[(1 - k_d^*) S_0^* - k_d^{*2}] k_d^*}{(1 - k_d^*)^3} \cdot \gamma + \frac{\left\{ - (1 - k_d^*)^2 + [k_d^{*2} + 2k_d^* + (k_d^{*2} - 1) S_0^*] \gamma \right\}}{(1 - k_d^*)^4} \cdot \frac{\beta}{\tau^*}, \end{aligned} \quad (23)$$

This shows the decrease in product concentration at high residence times due to small inhibition. In the following we define the limiting product concentration at infinite residence time by $P_{\tau^*=\infty}^*$. In the case of no-product inhibition, $\gamma = 0$, and infinite residence time we have

$$P^*(\tau^* = \infty, \gamma = 0) = S_0^* - \frac{k_d^*}{1 + k_d^*}.$$

This reflects the fact that when a biological process is controlled by Monod kinetics there is a limiting concentration, $S^* = \frac{k_d^*}{1 + k_d^*}$, below which the substrate concentration can not be reduced [18]. As the product inhibition constant increases from zero the value for $P^*(\tau^* = \infty, \gamma)$ decreases. We have

$$\frac{P^*(\tau^* = \infty, \gamma \ll 1)}{P^*(\tau^* = \infty, \gamma = 0)} = 1 - \frac{k_d^*}{(1 - k_d^*)^2} \cdot \gamma.$$

Thus the proportional reduction in product concentration at high residence times, compared to a system without product inhibition, is independent of the substrate concentration in the feed.

3.5 Large residence time approximations

At large residence times we have, for arbitrary values of the inhibition constant, the approximations

$$\begin{aligned} S^* &\approx \frac{A}{2} + \frac{1}{2}\sqrt{A^2 + 4k_d^*\gamma^{-1}} + \frac{\beta}{2\gamma} \left[1 + \frac{S_0^* + 2 - (1 - k_d^*)\gamma^{-1}}{\sqrt{A^2 + 4k_d^*\gamma^{-1}}} \right] \cdot \frac{1}{\tau^*} + O\left(\frac{1}{\tau^{*2}}\right), \\ X^* &\approx \frac{1}{2k_d^*} \left[S_0^* + (1 - k_d^*)\gamma^{-1} - \sqrt{A^2 + 4k_d^*\gamma^{-1}} \right] \cdot \frac{1}{\tau^*} + O\left(\frac{1}{\tau^{*2}}\right), \\ P^* &\approx S_0^* - \frac{A}{2} - \frac{1}{2}\sqrt{A^2 + 4k_d^*\gamma^{-1}} - \frac{\beta}{2\gamma} \left[1 + \frac{S_0^* + 2 - (1 - k_d^*)\gamma^{-1}}{\sqrt{A^2 + 4k_d^*\gamma^{-1}}} \right] \cdot \frac{1}{\tau^*} + O\left(\frac{1}{\tau^{*2}}\right), \\ A &= S_0^* - (1 - k_d^*)\gamma^{-1}. \end{aligned}$$

In the limit that the product inhibition concentration is large ($\gamma \gg 1$), corresponding to a small cut-off concentration (P_m), these formulae simplify to

$$\begin{aligned} S^* &\approx S_0^* - \frac{1}{S_0^*} [(1 - k_d^*) S_0^* - k_d^*] \cdot \frac{1}{\gamma} + \beta \left(1 + \frac{1}{S_0^*} \right) \cdot \frac{1}{\gamma\tau^*}, \\ X^* &\approx \frac{1}{k_d^* S_0^*} [(1 - k_d^*) S_0^* - k_d^*] \cdot \frac{1}{\gamma\tau^*}, \\ P^* &\approx \frac{1}{S_0^*} [(1 - k_d^*) S_0^* - k_d^*] \cdot \frac{1}{\gamma} - \beta \left(1 + \frac{1}{S_0^*} \right) \cdot \frac{1}{\gamma\tau^*}. \end{aligned}$$

For large values of the product inhibition constant we have

$$\frac{P^* (\tau^* = \infty, \gamma \gg 1)}{P^* (\tau^* = \infty, \gamma = 0)} = \frac{1 - k_d^*}{S_0^*} \cdot \frac{1}{\gamma}.$$

4 Discussion

In this section we compare the results obtained with the linear inhibition term

$$\mu(P) = \left(1 - \frac{P}{P_m} \right) \mathcal{H}(P_m - P),$$

with those obtained in our earlier papers [7, 8] which used the algebraic inhibition term

$$\mu(P) = \frac{1}{1 + \frac{P}{K_p}},$$

and the exponential inhibition term

$$\mu(P) = \exp \left[-\frac{P}{K_p} \right],$$

respectively.

In section 3.1 the steady-state solution branches were identified for the linear inhibition model. Along the no-washout solution branch the steady-state value for the cell-mass and product concentrations are parameterised by the value of the steady-state substrate concentration (\hat{S}^*), as shown in equation (14). These parameterised values are identical for linear decay, exponential decay and for algebraic decay. In all three models there is only

one solution along the no-washout branch for which the substrate concentration is positive ($S^* \hat{>} 0$). The value for the residence time at the transcritical bifurcation (τ_{cr}^*) occurs is identical in all models. In all three models the substrate concentration is a decreasing function of the residence time along the no-washout solution branch (provided that $\tau^* > \tau_{cr}^*$). Consequently in all three models the product concentration is an increasing function of the residence time along the no-washout solution branch. (provided that $\tau^* > \tau_{cr}^*$).

In section 3.2 the stability of the steady-state solutions is investigated. The condition for the washout branch to be locally/globally stable are the same in all three models. Similarly, the condition for the no-washout branch to be locally stable is the same in all three models.

In section 3.3 an approximate solution is obtained for the substrate concentration for values of the residence time slightly higher than the critical value ($\tau^* - \tau_{cr}^* \ll 1$). This expression was not calculated for the algebraic inhibition model [7]. The expressions for exponential and linear inhibition can be written in the general form

$$S^* \approx S_0^* - \frac{[(1 - k_d^*) S_0^* - k_d^*]^2}{\beta [1 + S_0^* \gamma (1 + S_0^*)]} \cdot \mathcal{C}_i (\tau^* - \tau_{cr}^*) + O(\tau^* - \tau_{cr}^*)^2.$$

where for linear inhibition we have

$$\mathcal{L}_{\text{linear}} = 1,$$

and for exponential inhibition we have

$$\mathcal{L}_{\text{exp}} = \frac{S_0^*}{(1 + S_0^*) (1 - \beta) k_d^* + \beta S_0^*}.$$

For a flow reactor without recycle ($\beta = 1$) we have

$$\mathcal{L}_{\text{linear}} = \mathcal{L}_{\text{exp}} = 1$$

Thus for a flow reactor there is no difference in the asymptotic behaviour of the linear and exponential inhibition models for values of the residence time slightly larger than criticality. This conclusion is not true for reactor configurations which have $0 < \beta < 1$.

In section 3.4 asymptotic formula are obtained for the limiting case of small dimensionless inhibition constant ($\gamma \ll 1$). For the algebraic inhibition asymptotic results were obtained for the case $\beta = 1$. For exponential inhibition asymptotic results were obtained for $0 < \beta < 1$. Where they can be compared, all results agree. Thus when inhibition is sufficiently small ($\gamma \ll 1$) the models are indistinguishable.

In section 3.5 we obtained asymptotic results for the limiting case of large residence time ($\tau^* \gg 1$). These results are valid for arbitrary values of the inhibition constant (γ). Similar results were obtained for the case of algebraic inhibition in [7]. (Long residence time asymptotics for arbitrary positive values of the inhibition constant can not be obtained for the exponential inhibition model [8]). These results are identical in the limit of small inhibition constant ($\gamma \ll 1$). However for the cases of intermediate and large inhibition constant they differ. Thus large residence time experiments provide a mechanism to distinguish between models provided that the inhibition constant is not small.

In the literature no advice is given regarding which inhibition model might be better suited for a particular environment. In practice, the inhibition model that is selected is the one which most accurately fits the experimental data. It is hoped that the comments in this section will aid the selection of inhibition model for experiments carried out in a flow reactor.

5 Conclusion

In this paper we have investigated a reactor model for the interaction between a microorganism and a rate-controlling substrate. The biochemical model used the Monod expression for the specific growth rate, modulated by non-competitive product inhibition, and included a microorganism decay coefficient. Product inhibition was modelled by a term that decreased linearly with product concentration. A generalised reactor model was considered which includes the standard model for a well-stirred reactor without recycle, an idealised membrane reactor, a fixed-bed biological process with biomass detachment and a perfusion bioreactor incorporating a cell bleed as special cases.

Although the combination of linear product inhibition with Monod kinetics is often mentioned in textbooks, the performance of a well-stirred bioreactor with this biokinetic scheme and microorganism death has not been reported in the literature. A scaling of the equations reveals that the key dimensionless parameter which controls the degree of inhibition is the quotient

$$\frac{\alpha_s}{\alpha_p} \cdot \frac{K_s}{P_m}.$$

The steady-state solutions of the model were found and their stability determined as a function of the residence time. Asymptotic solutions were found in the limit of small and large values of the inhibition constant. We compared our results against those obtained earlier for algebraic [7] and exponential [8] inhibition models. Provided that the inhibition constant is not small knowledge of the steady-state solutions and their asymptotic limits can be used to discriminate between the three inhibition models from experimental data

A Symbols used

F	Flowrate through the bioreactor.	$(\text{dm}^3 \text{ hr}^{-1})$
\mathcal{G}	Singularity equation.	$(-)$
\mathcal{H}	Heaviside function.	$(-)$
J	Jacobian matrix.	$(-)$
K_p	The noncompetitive product inhibition constant.	(g dm^{-3})
K_s	Monod constant.	(g dm^{-3})
P	Product concentration within the bioreactor.	(g dm^{-3})
P^*	Dimensionless product concentration.	$(-)$
	$P^* = \alpha_p P / (\alpha_s K_s)$	

P_m	Product concentration at which growth stops.	(g dm^{-3})
P_0	Product concentration in the feed.	(g dm^{-3})
P_0^*	Dimensionless product concentration in the feed. $P_0^* = \alpha_p P_0 / (\alpha_s K_s)$	$(—)$
S	Substrate concentration within the bioreactor.	(g dm^{-3})
S^*	Dimensionless substrate concentration. $S^* = S / K_s$	$(—)$
\hat{S}^*	The dimensionless substrate concentration along the no-washout solution branch.	$(—)$
S_0	Substrate concentration in the feed.	(g dm^{-3})
S_0^*	Dimensionless substrate concentration in the feed. $S_0^* = S_0 / K_s$	$(—)$
V	Volume of the bioreactor.	(dm^3)
X	Concentration of microorganisms within the bioreactor.	(g dm^{-3})
X^*	Dimensionless microorganism concentration. $X^* = X / (\alpha K_s)$	$(—)$
X_0	Concentration of microorganisms in the feed.	(g dm^{-3})
X_0^*	Dimensionless microorganism concentration in the feed. $X_0^* = X_0 / (\alpha K_s)$	$(—)$
k_d	Decay coefficient, representing a combination of endogenous respiration, predation, and cell death followed by subsequent lysis [20].	(hr^{-1})
k_d^*	Dimensionless decay coefficient. $k_d^* = k_d / \mu_m$	$(—)$
t	Time.	(hr^{-1})
t^*	Dimensionless time. $t^* = \mu_m t$	$(—)$
α_p	Product yield factor, the ratio of the weight of product produced to the weight of substrate consumed.	$(—)$
α_s	Substrate yield factor, the ratio of the weight of product produced to the weight of substrate consumed.	$(—)$
β	Reactor parameter model.	$(—)$
γ	Dimensionless product inhibition constant. $\gamma = (\alpha_s / \alpha_p) \cdot (K_s / P_m)$	$(—)$
$\mu(S, P)$	General specific growth rate model including noncompetitive product inhibition.	(hr^{-1})
$\mu(P)$	Noncompetitive product inhibition law.	$(—)$
$\mu(S)$	Specific growth rate model.	(hr^{-1})
μ_m	Maximum specific growth rate in the absence of product inhibition.	(hr^{-1})

τ	residence time.	(hr)
τ^*	Dimensionless residence time.	(—)
	$\tau^* = V\mu_m/F$	
τ_{cr}^*	The value of the dimensionless residence time at the transcritical bifurcation.	(—)

B Attracting Region

In this appendix we show that a solution starting at any physically meaningful initial condition, i.e. the initial coordinates are all strictly non-negative, outside the invariant region eventually enters the invariant region, i.e. the invariant region is attracting.

Suppose that the initial coordinate $S^*(0)$ is outside the invariant region, i.e. $S^*(0) > S_0^*$. Then

$$\begin{aligned}\frac{dS^*}{dt^*} &= \frac{1}{\tau^*} (S_0^* - S^*) - \frac{S^*X^*}{1+S^*} \cdot (1 - \gamma P^*) \mathcal{H}(1 - \gamma P^*), \\ &\leq \frac{1}{\tau^*} (S_0^* - S^*), \\ &< 0.\end{aligned}$$

This inequality holds for any value of the substrate concentration with $S^* > S_0^*$. Thus the substrate concentration must decrease until $S^*(t^*) = S_0^*$, i.e. the substrate component has entered the invariant region.

Suppose that the initial coordinate $P^*(0)$ is outside the invariant region, i.e. $P^*(0) > \gamma^{-1}$. Then

$$\begin{aligned}\frac{dP^*}{dt^*} &= -\frac{1}{\tau^*} P^* + \frac{S^*X^*}{1+S^*} \cdot (1 - \gamma P^*) \mathcal{H}(1 - \gamma P^*), \\ &= -\frac{1}{\tau^*} P^*, \\ &< 0.\end{aligned}$$

This inequality holds for any value of the product concentration with $P^* > \gamma^{-1}$. Thus the product concentration must decrease until $P^*(t^*) < \gamma^{-1}$, i.e. the product component has entered the invariant region.

Thus any physically meaningful initial concentration outside the invariant region eventually enters the invariant region.

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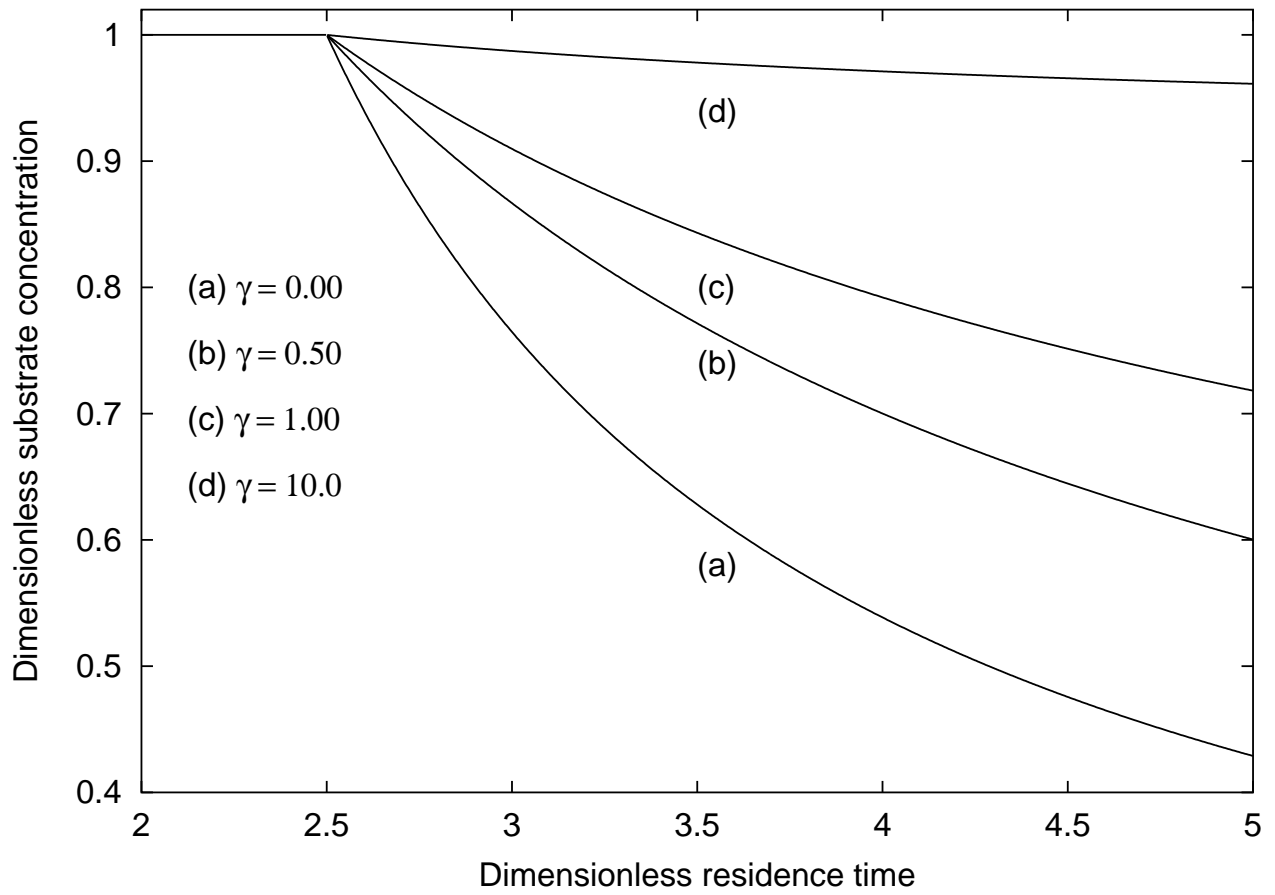


Figure 1: Steady-state diagrams showing the variation of dimensionless substrate concentration (S^*) as a function of the dimensionless residence time (τ^*) in a well-stirred bioreactor. Parameter values: dimensionless death rate, $k_d^* = 0.1$; dimensionless feed concentration, $S_0^* = 1$; reactor parameter, $\beta = 1$. The value of the dimensionless maximum product concentration (P_m^*) is as given.

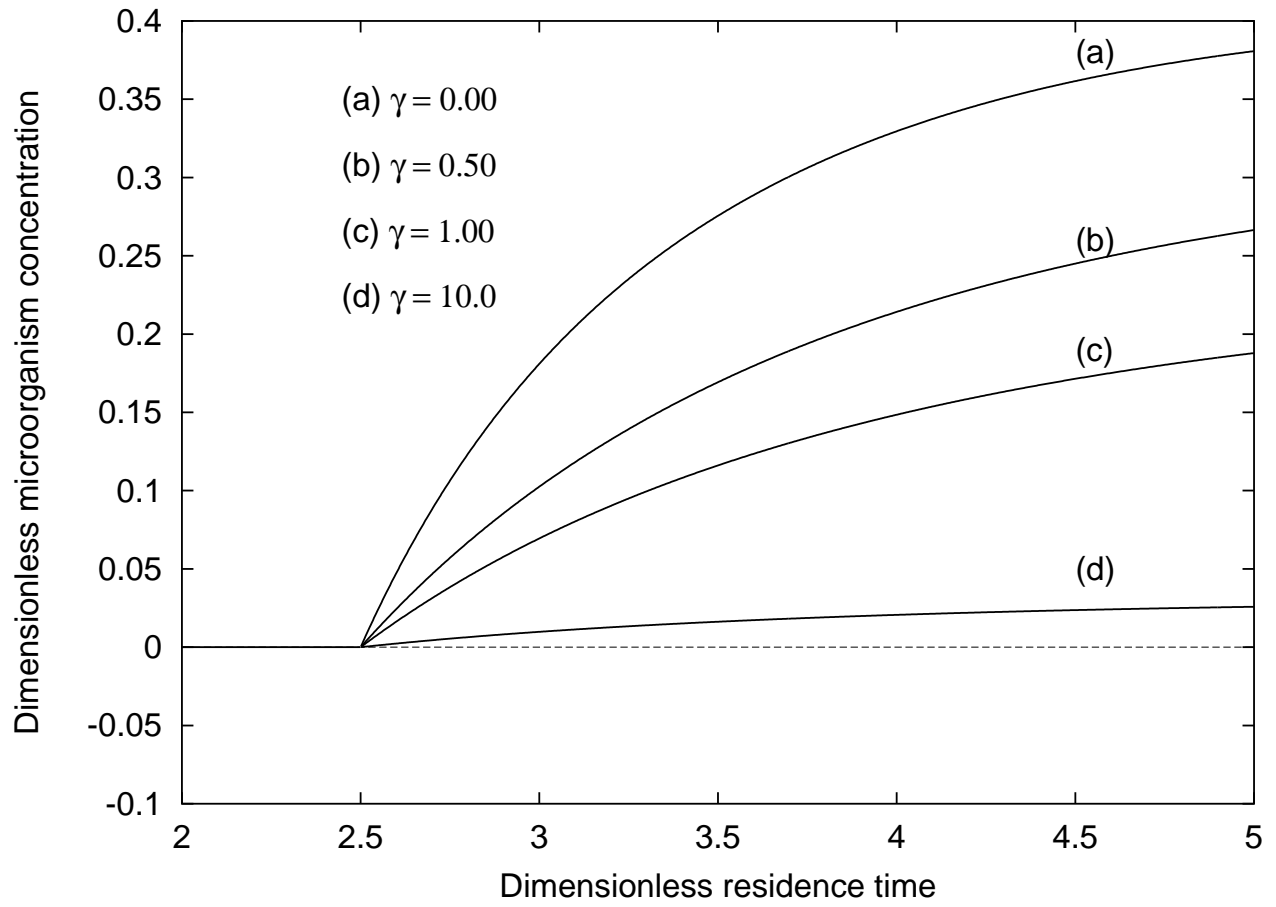


Figure 2: Steady-state diagrams showing the variation of dimensionless cell mass concentration as a function of the dimensionless residence time (τ^*) in a well-stirred bioreactor. Parameter values as given in figure 1.

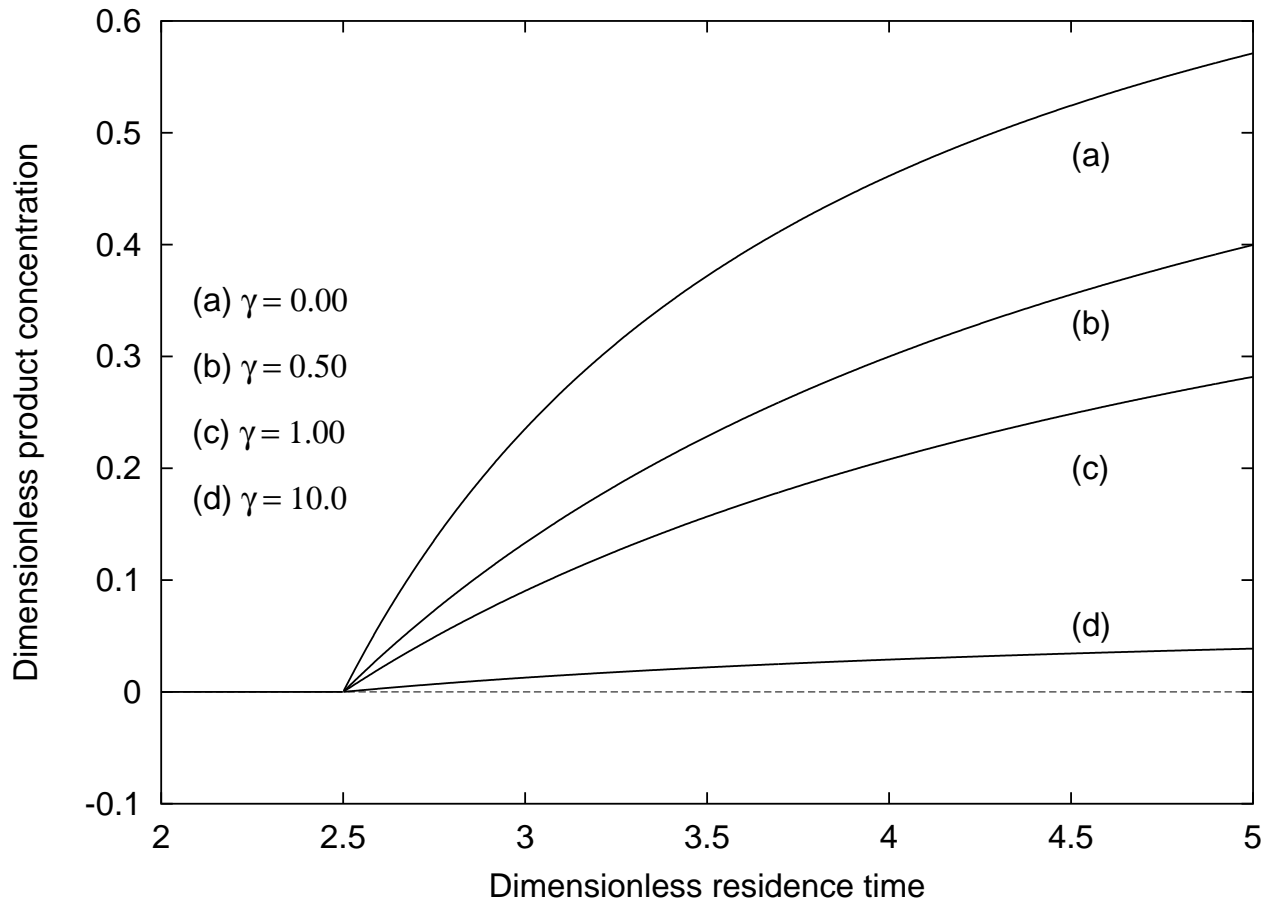


Figure 3: Steady-state diagrams showing the variation of dimensionless product concentration (P^*) as a function of the dimensionless residence time (τ^*) in a well-stirred bioreactor. Parameter values as given in figure 1.