The computation of stability boundaries in state space for a class of biochemical engineering systems

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Abstract

The stability of a class of biochemical processes defined by a set of \( m \) biochemical reactions involving \( n \) components is analysed. The processes operate in a continuous mode and possess at least two stable equilibrium states: the normal operating point and a biological wash out state. Using a canonical state representation of the process dynamics the geometric structure of the operating point's stability boundary is characterized. Numerical algorithms are developed to evaluate this boundary and to visualize its extent in state space. The proposed technique is illustrated with a representative engineering example.

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1. Introduction

This paper considers a class of biochemical reaction systems governed by a set of \( m \) reactions involving \( n \) components, with \( n > m \). The process is assumed to operate in a continuous mode, in which reactants are continuously fed to the system while an effluent stream is continuously withdrawn from it, such that the reactor volume remains constant. The dynamics of such systems can be encoded into a reaction network described by a characteristic matrix of constant yield coefficients [2,3]. The rank of this matrix is called the rank of the reaction network [5].

The system dynamics constitute a \( n \)th order, highly nonlinear system of ordinary differential equations. Due to the presence of reaction rate functions displaying various types of process inhibition effects, the system usually possesses at least two stable equilibrium points, one of which corresponds to the normal operating point of the process and the other one to a wash out state, where all or almost all biological activity in the reactor vessel has disappeared. In addition, there exist one or more than one unstable equilibria.

For the analysis and design of biochemical engineering systems, it is essential to be able to decide from which initial states the process will converge to normal operation and which initial states will lead the system to a wash out condition. Below, this problem is discussed for a class of biochemical reaction systems where the rank of the characteristic matrix coincides with the number of biochemical reactions \( m \). It is shown that the system equations can be cast in a canonical form consisting of a linear time invariant system dynamically coupled with a nonlinear system of order \( m \). This specific

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canonical representation is exploited to characterize the geometric structure of the operating point’s stability boundary and to develop numerical algorithms to estimate this boundary. Furthermore, algorithms are designed that allow to visualize the extent of the stability regions by computing intersections of the stability boundary with well-selected planes in state space. The proposed technique is illustrated with a representative engineering example.

For the system under consideration the reactor dynamics can generally be written in the form
\[
\dot{\xi} = Cr(\xi) - D\xi + F - Q,
\]
where $\xi$, of dimension $n$, is the vector of concentrations of the various components participating to the process, such as populations of microorganisms, enzymes, external substrates fed to the reactor, products of reactions possibly acting as substrates of other reactions, etc. It constitutes the state vector of the system.

$F = \text{col}(F_i; i = 1 \ldots n)$ and $Q = \text{col}(Q_i; i = 1 \ldots n)$ represent the vectors of supply rates, respectively rates of removal in gaseous form of the components. They satisfy
\[
F_i \geq 0; \quad Q_i \geq 0; \quad i = 1 \ldots n.
\]

$D$, a positive scalar, is the specific volumetric outflow rate or dilution rate. This paper is focused on uncontrolled reactors, where $F$ and $D$ are constants. It is assumed that $Q$ is constant and that
\[
F_i - Q_i \geq 0; \quad i = 1 \ldots n.
\]

$r(\xi) = \text{col}(r_i(\xi); i = 1 \ldots m)$ is the reaction rate function. Let $r(\xi) \in C^1$ (continuous with continuous partial derivatives w.r.t. the components of $\xi$). This condition ensures the existence and the uniqueness of the solutions of (1) for given initial conditions. It is assumed that for all values of the composition vector $\xi$,
\[
r_i(\xi) \geq 0; \quad i = 1 \ldots m.
\]
Furthermore, if in the reaction with index $j$ the component $\xi_i$ is consumed, then
\[
r_j(\xi) = 0 \quad \text{for} \quad \xi_i = 0
\]
$C \in \mathbb{R}^{m \times m}$ is the matrix of yield coefficients. Its entries $c_{ij}$ can be positive, negative or zero depending on whether the $i$th component is produced, consumed or nonparticipating in the $j$th reaction. If rank $C = m$, we can assume without loss of generality that
\[
C = \begin{bmatrix} C_a \\ C_b \end{bmatrix},
\]
where $C_a \in \mathbb{R}^{m \times m}$ is nonsingular.

It is easy to show [2,9] that under fairly weak and physically plausible conditions and in accordance with their physical meaning, the state variables of the system (1) cannot become negative and remain upper bounded for increasing time. Along the system’s solutions the following holds:
\[
\xi_i(0) \geq 0; \quad i = 1 \ldots n \implies 0 \leq \xi_i(t) \leq \xi_{i\text{max}} < +\infty; \quad \forall t \geq 0; \quad i = 1 \ldots n.
\]

More specifically [9], there exists a bounded set
\[
S_\xi \triangleq \{ \xi; \quad \mu^T \xi \leq \alpha; \quad \xi_i \geq 0; \quad i = 1 \ldots n \},
\]
where $\mu \in \mathbb{R}^n; \quad \mu_i > 0; \quad i = 1 \ldots n$ such that, for $\alpha > 0$ and sufficiently large,
\[
\xi(0) \in S_\xi \implies \xi(t) \in S_\xi \quad \forall t \geq 0.
\]

A system such as (1), whose state variables only assume nonnegative values, is called a positive system. Its state space is defined as
\[
\mathbb{R}^{+n} \triangleq \{ \xi \in \mathbb{R}^n; \quad \xi_i \geq 0; \quad i = 1 \ldots n \}.
\]
Finally, using (6) the system (1) can be brought in a canonical form by the state transformation
\[ x_a \triangleq \xi, \quad x_b \triangleq A_0 \xi + \xi_b, \quad \xi, \xi_b \in \mathbb{R}^{n-m}, \]
where \( \xi \triangleq \text{col}(\xi_a, \xi_b), x \triangleq \text{col}(x_a, x_b) \) and \( A_0 = -C_b C_a^{-1} \).

The canonical representation reads
\[ \dot{x}_a = D(w_a - x_a) + C_a \rho(x), \]
\[ \dot{x}_b = D(w_b - x_b), \]
where \( w_a \in \mathbb{R}^m \) and \( w_b \in \mathbb{R}^{n-m} \) are constants and
\[ \rho(x) = r(\xi)|_{\xi_a=x_a; \xi_b=x_b-A_0 x_a}. \]

Let \( X \) be the state space of (10), (11), i.e. \( X \) is the image of \( \mathbb{R}^{+n} \) under the state transformation \( \xi \to x \).

2. Convergence

In this section conditions are established which ensure that, as \( t \to +\infty \), every solution of the system (10), (11) converges to an equilibrium point. Let
\[ V_1(x_b) \triangleq \frac{1}{2} a(x_b - w_b)'(x_b - w_b); \quad a > 0 \]
be a candidate Lyapunov function for (10), (11). Along its solutions
\[ \dot{V}_1(x_b) = -a D(x_b - w_b)'(x_b - w_b) \]
\[ = -a D \dot{x}_b \dot{x}_b \leq 0; \quad \forall x \in X \]
\[ = 0 \iff \dot{x}_b = 0 \iff x_b = w_b. \]

Hence, invoking the boundedness of solutions we have from basic Lyapunov theory [6]:

**Lemma 1.** As \( t \to +\infty \) every solution of (10), (11) converges to the set \( A \triangleq \{ x \in X; \ x_b = w_b \} \).

Convergence to \( A \) means that the solutions \( x(t) \) satisfy
\[ \min_{y \in A} |x(t) - y| \to 0 \quad \text{for} \quad t \to +\infty. \]

\( A \) is an invariant set for (10), (11). The dynamics on \( A \) read:
\[ \dot{x}_a = D(w_a - x_a) + C_a \rho_0(x_a), \]
where \( \rho_0(x_a) \triangleq \rho(x)|_{x_b=w_b} \). Lyapunov functions for the system (17) can only be obtained for specific types of processes, which constitute the subject of the present research. The following two cases are considered:

1. Assume \( \rho(x) \) has the form
\[ \rho(x) = \text{col}[f_i(b_i' x_a, x_b); \ i = 1 \ldots m]. \]

Then
\[ \rho_0(x_a) = \text{col}[\rho_i(b_i' x_a); \ i = 1 \ldots m], \]
where \( \rho_i(b_i' x_a) \triangleq f_i(b_i' x_a, w_b). \) Define
\[ W_2(x_a) \triangleq \int_{0}^{B' x_a} \rho_0'(\theta) P d\theta, \]
where \(B \triangleq [b_1 \ldots b_m] \in \mathbb{R}^{m \times m}, \ P \triangleq \text{diag}[p_i; i = 1 \ldots m]\) and \(\theta \in \mathbb{R}^m \). (20) is a shorthand notation for

\[
W_2(x_a) = \sum_{i=1}^{m} \int_0^{b_i/x_a} p_i(\theta_i)p_i \ d\theta_i. \tag{21}
\]

Now

\[
\dot{W}_2(x_a) = \rho_0'(x_a)PB'\dot{x}_a = \dot{x}_a'BPC_a^{-1}[\dot{x}_a - D(w_a - x_a)]. \tag{22}
\]

Assume that \(P\) can be chosen such that \(BPC_a^{-1}\) is symmetric, which holds if and only if

\[C_a'BP < 0\]  

(26) requires that \(P\) is nonsingular. Hence, we have:

**Lemma 2.** Suppose a diagonal nonsingular \(P \in \mathbb{R}^{m \times m}\) can be found such that

\[C_a'BP = (C_a'BP)' < 0.\]  

Then, as \(t \to +\infty\), every solution of the system (17), (19) converges to an equilibrium point.

Note that for systems of rank one, \(\rho_0(x_a)\) always has the form (19), with \(m = 1, B = 1\) and (27) can always be satisfied since \(C_a'BP\) is scalar.

(2) Assume \(C_a\) is diagonal and \(\rho(x)\) has the form

\[\rho(x) = F(x)K'x,\]  

(28)

where \(F(x) = \text{diag}[f_i(x_i, x_b); \ i = 1 \ldots m], 0 \leq F(x) \leq F_{\text{max}} \triangleq \text{diag}[f_{\text{max}}] \) for all \(x \in X\) and \(K \in \mathbb{R}^{n \times m}\). Let \(K = \text{col}[K_1, K_2]\) where \(K_1 \in \mathbb{R}^{m \times m}\). Then (17) can be written as

\[F_0^{-1}(x_a)\dot{x}_a = -\psi_0(x_a) + C_aK_1x_a,\]  

(29)

where \(F_0(x_a) = \text{diag}[f_i(x_i, w_b); \ i = 1 \ldots m]\) and

\[
\psi_0(x_a) = DF_0^{-1}(x_a)(x_a - w_a) - C_aK_2w_b = \text{col}[\psi_i(x_i); \ i = 1 \ldots m].
\]

Define

\[
W_2(x_a) \triangleq \int_0^{x_a} \psi_0'(\theta)P \ d\theta, \tag{30}
\]
where again $P = \text{diag}\{p_i; \ i = 1 \ldots m\}$ and $\theta \in \mathbb{R}^m$. Now
\begin{align*}
\dot{W}_2(x_a) &= \psi_0(x_a) P \dot{x}_a \\
&= -\dot{x}_a^T PF_0^{-1}(x_a) \dot{x}_a + \dot{x}_a^T PC_a K_1' x_a. \\
\end{align*}
Assume $P$ can be chosen such that $PC_a K_1'$ is symmetric. (32)

Let
\begin{align*}
V_2(x_a) &= W_2(x_a) - \frac{1}{2} x_a^T PC_a K_1' x_a. \\
\end{align*}
Then by (31),
\begin{align*}
\dot{V}_2(x_a) &= -\dot{x}_a^T PF_0^{-1}(x_a) \dot{x}_a \\
&\leq 0; \ \forall x \in X \\
&= 0 \iff \dot{x}_a = 0
\end{align*}
if $P > 0$. Hence, we have:

**Lemma 3.** Suppose a diagonal $P > 0$ can be found such that (32) holds. Then, as $t \to +\infty$, every solution of the system (17), (28) converges to an equilibrium point.

The following theorems result from combining Lemma 1 with Lemmas 2 and 3:

**Theorem 4.** If the conditions (18), (27) are satisfied then, as $t \to +\infty$, every solution of the system (10), (11) converges to an equilibrium point.

**Proof.** A proof of Theorem 4 can be obtained using
\begin{align*}
V(x) &\equiv V_1(x_b) + V_2(x_a)
\end{align*}
as a candidate Lyapunov function. From (13), (24) we have
\begin{align*}
\dot{V}(x) &= -\frac{a}{D} \dot{x}_b \dot{x}_b + \dot{x}_a^T BP \rho_0(x_a) + D \dot{x}_a^T BPC_a^{-1} w_a - D \dot{x}_a^T BPC_a^{-1} x_a.
\end{align*}
But
\begin{align*}
\rho(x) &= \rho_0(x_a) + \rho_d(x)(x_b - w_b) = \rho_0(x_a) + \frac{1}{D} \rho_d(x) \dot{x}_b,
\end{align*}
where
\begin{align*}
\rho_d(x) &\equiv \left[ \frac{\partial \rho(x)}{\partial x_{m+1}} \cdots \frac{\partial \rho(x)}{\partial x_n} \right] \in \mathbb{R}^{m \times (n-m)}
\end{align*}
and where each component of (37) must be evaluated at some point $\tilde{x}_{ij} \in X$, $i = 1 \ldots m$, $j = 1 \ldots n - m$, because of the mean value theorem. Eliminating $\rho_0(x_a)$ between (35) and (36) and using (10) produces
\begin{align*}
\dot{V}(x) &= -\frac{a}{D} \dot{x}_b \dot{x}_b + \dot{x}_a^T BPC_a^{-1} \dot{x}_a - \dot{x}_a^T B \frac{1}{D} \rho_d(x) \dot{x}_b.
\end{align*}
Let $S_x$ be the image of $S_\xi$ under the state transformation $\xi \to x$. Since $r(\xi) \in C^1$, $\|\rho_d(x)\|$ remains bounded for all $x \in S_x$. It follows that for $a > 0$ and sufficiently large:
\begin{align*}
\dot{V}(x) &\leq 0; \ \forall x \in S_x \\
&= 0 \iff \dot{x} = 0; \ x \in S_x.
\end{align*}
Because of (8) where $S_\xi \to \mathbb{R}^+^{n}$ for $x \to +\infty$ this proves Theorem 4. □
In a similar way, write (10), (28) as

\[ F^{-1}(x) \dot{x}_a = -\psi(x) + C_a K_1' x_a, \]

where

\[ \psi(x) = DF^{-1}(x)(x_a - w_a) - C_a K_2' x_b \]

and where it is assumed that \( \psi(x) \in C^1 \) for \( x \in X \), hence \( \|\psi_d(x)\| \) is bounded for all \( x \in S_x \). Then we have:

**Theorem 5.** If the conditions (28), (32) are satisfied then, as \( t \to +\infty \), every solution of the system (10), (11) converges to an equilibrium point.

**Proof.** We omit here the proof. \( \square \)

Obviously every solution of (10), (11) converges to an arbitrarily close neighbourhood \( G \triangleq \{ x; |x_b - w_b| < \varepsilon \} \) of the set \( A \) in finite time, and subsequently remains in \( G \) for all future times. Therefore, it is sufficient that \( V(x) \) is a Lyapunov function in the set \( G \). This simplifies the computation of the minimum value for the parameter \( a \), which will be needed in Section 3. Indeed, (38) can be written as

\[ -\dot{V}(x) = \left[ \dot{x}_a - C_a \rho_d(x) \frac{1}{2D} \dot{x}_b \right] (-BPC_a^{-1}) \left[ \dot{x}_a - C_a \rho_d(x) \frac{1}{2D} \dot{x}_b \right] \]

\[ + \dot{x}_b \left[ \frac{a}{D} I_{n-m} + \frac{1}{4D^2} \rho_d'(x) C_a' BP \rho_d(x) \right] \dot{x}_b. \]

Hence if \( \rho(x) \) has the form (18) we must take

\[ a I_{n-m} > \max \left\{ \frac{1}{4D} \rho_d'(x)(-C_a' BP) \rho_d(x) \mid x_b = w_b \right\}. \]  

(39)

Similarly it can be verified that if \( \rho(x) \) has the form (28) then we must take

\[ a I_{n-m} > \max \left\{ \frac{1}{4D} \psi_d'(x) F_{\max} P \psi_d(x) \mid x_b = w_b \right\}. \]  

(40)

3. The computation of stability boundaries

In addition to a stable operating point, a biochemical reactor often possesses additional equilibrium states which can be stable or unstable. For example, in cases where substrate inhibition occurs, not only there may be an unstable equilibrium point, but the reactor may also possess a stable wash out state, where microbial activity has completely or nearly completely disappeared [3]. In such cases the operating point, say \( x = \hat{x}_i \), is surrounded in state space by a region of attraction \( \Omega(\hat{x}_i) \), which is a proper subset of \( X \). The boundary set \( \partial \Omega(\hat{x}_i) \), which is invariant, is called the system’s stability boundary. It has been established that, as time increases, all solutions of the system (10), (11) remain bounded and that, for certain types of reaction rate functions \( \rho(x) \), a global Lyapunov function can be found such that

\[ \dot{V}(x) \leq 0; \quad \forall x \in X \]

\[ = 0 \iff \dot{x} = 0. \]

These properties imply that:

(A1) Every solution on the stability boundary \( \partial \Omega(\hat{x}_i) \) converges to an equilibrium state.

In this section we assume three additional properties, of a generic nature, which allow us to characterize the geometric structure of the boundary \( \partial \Omega(\hat{x}_i) \) and to compute it numerically:

(A2) The system’s equilibrium points \( \hat{x}_k, k = 1, 2, \ldots \) are hyperbolic, i.e. their Jacobian matrix \( J(\hat{x}_k) \) has no eigenvalues on the imaginary axis.
(A3) For every pair of equilibrium points \( \hat{x}_j \) and \( \hat{x}_k \) on \( \partial \Omega(\hat{x}_i) \), the stable manifold \( W^s(\hat{x}_k) \) and the unstable manifold \( W^u(\hat{x}_j) \) satisfy the transversality condition.

(A4) The quasi-stability boundary \( \partial \Omega(\hat{x}_i) \) coincides with the true stability boundary \( \partial \Omega(\hat{x}_i) \).

A detailed discussion of these concepts can be found in the stability theory literature, e.g. [4,7,10,11]. Under the conditions above the following holds:

**Theorem 6 (Chiang et al. [4]).** The equilibrium states \( \hat{x}_j \neq \hat{x}_i \) satisfy

\[
\hat{x}_j \in \partial \Omega(\hat{x}_i) \iff W^u(\hat{x}_j) \cap \Omega(\hat{x}_i) \neq \emptyset.
\]

**Theorem 7 (Zaborszky et al. [11]).**

\[
\partial \Omega(\hat{x}_i) = \bigcup_{\hat{x}_k \in \Psi} W^s(\hat{x}_k),
\]

where

\[
\Psi \triangleq \{ \hat{x}_k; \text{ index } \hat{x}_k = 1; \hat{x}_k \in \partial \Omega(\hat{x}_i) \}.
\]

The index of \( \hat{x}_k \) is the number of characteristic values of \( J(\hat{x}_k) \) with positive real part.

(42) displays that estimating the stability boundary essentially consists of the identification of the index one equilibria on the stability boundary and the (approximate) computation of their stable manifolds. For the first step, Theorem 6 can be used. Subsequently, for each \( \hat{x}_k \in \Psi \), an estimate of \( W^s(\hat{x}_k) \) must be computed such that \( W^s(\hat{x}_k)_{\text{est}} \subset \Omega(\hat{x}_i) \) and \( W^s(\hat{x}_k)_{\text{est}} \to W^s(\hat{x}_k) \) as some algorithmic parameter \( \varepsilon \to 0 \). In this way an estimated stability boundary can be obtained, in principle of any desired accuracy, lying inside \( \Omega(\hat{x}_i) \). This estimate \( \partial \Omega(\hat{x}_i)_{\text{est}} \) surrounds an estimated stability region \( \Omega(\hat{x}_i)_{\text{est}} \subset \Omega(\hat{x}_i) \). For this problem we use a trajectory reversing algorithm [7]. We proceed as follows:

1. To decide whether an index one equilibrium point \( \hat{x}_k \in \Psi \), the unique eigenvalue \( \lambda_1 > 0 \) of \( J(\hat{x}_k) \) and its corresponding eigenvector \( e_1 \) are determined. According to Theorem 6, \( \hat{x}_k \in \Psi \) if and only if for a sufficiently small \( |\varepsilon e_1| \), either \( x_{01} \triangleq \hat{x}_k + \varepsilon e_1 \in \Omega(\hat{x}_i) \) or \( x_{02} \triangleq \hat{x}_k - \varepsilon e_1 \in \Omega(\hat{x}_i) \). Choose \( e_1 \) such that for a small \( \varepsilon > 0 \):

\[
x_{01} \in \Omega(\hat{x}_i).
\]

Then \( x_{02} \notin \Omega(\hat{x}_i) \) because of assumption A4. (44) can be checked by numerical integration of the system’s state equations from the initial states \( x_{0i}; \ i = 1, 2 \).

2. To estimate \( W^s(\hat{x}_k) \) an anchor set \( \gamma \) of initial states for backward integration of the system (10), (11) is constructed. To this end, the quadratic approximation of the level set \( \{ x \in X; \ V(x) = V(\hat{x}_k) \} \) in the neighbourhood of \( \hat{x}_k \) is computed:

\[
\delta S = \{ z \in \mathbb{R}^n; \ z' R z = 0 \},
\]

where \( z \triangleq x - \hat{x}_k \) and

\[
R = R' = \frac{1}{2} \left. \frac{\partial^2 V(x)}{\partial x^2} \right|_{x=\hat{x}_k}.
\]

It is readily verified that

\[
R = \frac{1}{2} \left[ \left. \frac{\partial^2 V_2(x_a)}{\partial x_{a}^2} \right|_{x=\hat{x}_k} \right] a I_{n-m},
\]

where for \( V_2(x_a) \) given by (24),

\[
\frac{\partial^2 V_2(x_a)}{\partial x_{a}^2} = \text{diag} \left\{ \frac{\partial^2 \rho_i}{\partial x_{i}}; \ i = 1 \ldots m \right\} - DBPC^{-1}_a.
\]
and for $V_2(x_a)$ given by (33),
\[
\frac{\partial^2 V(x_a)}{\partial x_a^2} = \text{diag}\left\{ p_i \frac{\partial \psi_i}{\partial x_i}; \quad i = 1 \ldots m \right\} - PC_i K_i'.
\]

Using the fact that index $\hat{s}_k = 1$ and applying the inertia theorem, it can be shown that $R$ has exactly one eigenvalue $\mu_1 < 0$ and $(n - 1)$ eigenvalues $\mu_i > 0; \quad i = 2 \ldots n$ [7]. Let
\[
U = \begin{bmatrix} U_1 & \ldots & U_{n-m} \end{bmatrix}; \quad U_1 = [u_1 \ldots u_m] \in \mathbb{R}^{m \times m}
\]

be the real orthogonal matrix of eigenvectors of $R$, such that $U'RU = \text{diag}[\mu_i; \quad i = 1 \ldots n]$ and let $z = U y$. Now the anchor set $\gamma$ is given by
\[
\gamma = \delta S \cap \{ \gamma_1 = \epsilon u_1' e_1 \}
\]
\[
= \left\{ y \in \mathbb{R}^n; \quad y_1 = \epsilon u_1' e_1; \quad \sum_{i=2}^n \mu_i y_i^2 = -\mu_1 y_1^2 \right\}
\]
\[
= \left\{ z \in \mathbb{R}^m; \quad u_1' z_a = \epsilon u_1' e_1; \quad \sum_{i=2}^m \mu_i (u_i' z_a)^2 + \frac{a}{2} \epsilon u_1' \sum_{i=2}^n \mu_i y_i^2 = -\mu_1 (\epsilon u_1' e_1)^2 \right\},
\]  

(46)

where $z = \text{col}(z_a, z_b); \quad z_a \in \mathbb{R}^n; \quad z_b \in \mathbb{R}^{m-n}$. In $z$-space, (10), (11) take the form
\[
\dot{z}_a = \xi(z_a, z_b) \triangleq \{ D(w_a - x_a) + C_a p(x) \}_{x = \hat{x}_a + z},
\]
(47)
\[
\dot{z}_b = -D z_b.
\]
(48)

$W_s(\hat{x}_k)_{\text{est}}$ is formed by solving (47), (48) in reverse time, starting from initial points on (46). Since (48) can be integrated analytically, the procedure requires the numerical integration of a set of $m$ ordinary differential equations.

4. Visualization

To visualize the extent of the region of attraction of $\hat{x}_1$ in state space, a simple technique consists in computing the intersections in $z_a$-space of $\partial \Omega(\hat{x}_1)_{\text{est}}$ with a set $H \triangleq \{ z \in \mathbb{R}^n; \quad z_b = \eta \}$ for constant vectors $\eta = \text{col}(\eta_1 \ldots \eta_{m-n})$.

Suppose a trajectory of (47), (48) computed in reverse time $\tau = -t$ and starting at $\tau = 0$ in a point of (46), reaches the set $H$ at time $\tau = \tau_f$. Then
\[
z_b(\tau) = \exp(D\tau)z_b(0); \quad z_b(0) = \exp(-D\tau_f)\eta.
\]

Thus, to find the intersections, solve the equations
\[
\frac{dz_a}{d\tau} = -\xi[z_a, e^{D(t-\tau_f)\eta}]
\]
for the initial values $z_a(0)$ on
\[
\left\{ z_a \in \mathbb{R}^n; \quad u_1' z_a = \epsilon u_1' e_1; \quad \sum_{i=2}^m \mu_i (u_i' z_a)^2 + \frac{a}{2} e^{-2D\tau_f \eta^2} = -\mu_1 (\epsilon u_1' e_1)^2 \right\}
\]

and for all $\tau_f$ in the interval $\tau_f_{\text{min}} \leq \tau_f < +\infty$ with
\[
\frac{a}{2} e^{-2D\tau_f \eta^2} = -\mu_1 (\epsilon u_1' e_1)^2.
\]

The points $z_a(\tau_f), \quad \tau_f_{\text{min}} \leq \tau_f < +\infty$, yield the desired intersection line.

For $m = 2$ and 3, which constitute the most common cases, the intersections are curves or surfaces in, respectively, a two-dimensional or a three-dimensional $z_a$-space.
5. Example

We consider a simple model of a fermentation process of the form (1), with \( n = 4 \) and \( m = 1 \). \( \xi_1, \xi_2, \xi_3 \) and \( \xi_4 \), respectively, represent biomass, substrate and products concentrations. Let \( C = [c_1 \ c_2 \ c_3 \ c_4]' \), \( c_1 > 0, c_2 < 0, c_3 > 0 \) and \( c_4 > 0 \), \( F = [0 \ F_2 \ 0 \ 0]' \), \( F_2 > 0 \), \( Q = 0 \) and \( r(\xi) \) a reaction rate function of the form:

\[
r(\xi) = \mu_m \frac{\xi_2}{K_p + \frac{\xi_2^2}{K_i}} \cdot \frac{P_1}{P_1 + \frac{\xi_3}{K_1}} \cdot \frac{P_2}{P_2 + \xi_4} \cdot \xi_1,
\]

where \( \mu_m > 0, K_p > 0, K_i > 0, P_1 > 0, P_2 > 0 \).

The corresponding canonical representation (10), (11) has three equilibrium points. The first equilibrium state \( \hat{x}_1 = [0 \ w_2 \ 0 \ 0]' \), \( w_2 = F_2/D \), represents a situation of complete wash out. The additional two equilibria are an unstable index one equilibrium point \( \hat{x}_2 \) and a locally asymptotically stable equilibrium point \( \hat{x}_3 \), the reactor’s normal operating state. The numerical values of the model parameters are: \( c = [1 \ 1.2 \ 0.5 \ 0.2]' \), \( \mu_m = 4.1 \text{ h}^{-1} \), \( K_p = 2000 \text{ g l}^{-1} \), \( K_i = 5 \text{ g l}^{-1} \), \( D = 0.05 \text{ h}^{-1} \), \( F_2 = 25 \text{ g h}^{-1} \text{l}^{-1} \), \( P_1 = 220 \text{ g l}^{-1} \), \( P_2 = 1000 \text{ g l}^{-1} \). The equilibrium points are

\[
\hat{\xi}_1 = \begin{bmatrix} 0 \\ 500 \\ 0 \\ 0 \end{bmatrix}, \quad \hat{\xi}_2 = \begin{bmatrix} 262.65 \\ 184.83 \\ 131.32 \\ 52.53 \end{bmatrix}, \quad \hat{\xi}_3 = \begin{bmatrix} 353.17 \\ 76.2 \\ 176.59 \\ 70.63 \end{bmatrix}.
\]

In \( z \)-space they are given by

\[
\hat{z}_1 = \begin{bmatrix} 0 \\ -262.65 \\ 0 \\ 0 \end{bmatrix}, \quad \hat{z}_2 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \hat{z}_3 = \begin{bmatrix} 90.53 \\ 0 \\ 0 \\ 0 \end{bmatrix}.
\]

Fig. 1. The phase portrait of the system in the \( z_1 \text{-} z_2 \)-plane
Recalling that (1) is a positive system, several physical boundary conditions must be fulfilled in \( z \)-space:

\[
\begin{align*}
    z_1 + 262.65 &\geq 0, \\
    z_2 - 1.2z_1 + 184.83 &\geq 0, \\
    z_3 + 0.5z_1 + 131.32 &\geq 0, \\
    z_4 + 0.2z_1 + 52.53 &\geq 0.
\end{align*}
\]  

(52)

**Fig. 1** illustrates the phase portrait of the system in the \( z_1-z_2 \)-plane (\( z_3 \equiv 0, z_4 \equiv 0 \)) together with the equilibrium points of the system. Every trajectory converges to one of the equilibria. The stability boundary separating the regions of attraction of \( \hat{z}_1 \) and \( \hat{z}_3 \) is \( W^s(\hat{z}_2) \). An estimate of the stability boundary \( W^s(\hat{z}_2)_{est} \subset \Omega(\hat{z}_3) \) is obtained by applying the trajectory reversing technique.
The proposed visualization technique is used to display the estimated stability boundary in a two-dimensional plane, namely in the $z_1-z_2$-plane. To this end, various intersections of $\partial \Omega(\hat{z}_3)_{\text{est}}$ with planes $\{z_3 = \eta_3, z_4 = \eta_4\}$ have been calculated and the obtained intersections have been graphically represented in Figs. 2 and 3.

6. Conclusion

Numerical algorithms have been formulated to estimate and to visualize stability regions for certain types of biochemical reaction systems. The proposed method has several advantages: Estimated stability regions are obtained, which are arbitrarily close approximations of the exact stability regions. The estimated stability boundaries are composed of one or more surfaces which, for a parameter $\varepsilon \to 0$, tend to the stable manifolds of the index one equilibrium states on this boundary. They are obtained by backward numerical integration of the system’s state equations, where iterative trial and error schemes to find initial states for these integrations are avoided.

The main disadvantage of the technique is that it only applies to system models which, in addition to certain generic properties, possess a suitable global Lyapunov function. Such a Lyapunov function can only be found for systems of rank one and for certain special classes of higher rank systems. Rank one systems are widely encountered in practice: microbial growth [2], activated sludge wastewater treatment [8], etc. An example of higher order system for which a Lyapunov function can be found is the anaerobic digestion process [1].

If a global Lyapunov function is not available, extensive additional numerical work may be required to establish the geometric structure of the stability boundary and to find suitable anchor sets for trajectory reversion, lying inside the stability region to be estimated. These problems constitute subjects for further research.

References