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Modelling of General Biotechnological Processes*

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ABSTRACT

A general biotechnological process is modelled by a finite dimensional ordinary differential equation. The stoichiometry is only modelled qualitatively. It is shown that the usual biochemically motivated assumptions are not sufficient to guarantee boundedness of the solution. To overcome this, the concept of non-cyclic biotechnological processes is introduced. Loosely speaking it means that the process does not contain any "reaction loop". The assumption of non-cyclicity replaces the common assumption of Conservation of Mass. An algorithm is presented so that after finitely many steps it is decided whether a process is non-cyclic or cyclic. Non-cyclicity is also characterised in terms of an echelon matrix derived from the stoichiometric matrix via permutations of columns and rows.

Keywords: biochemical processes, bioreactors, non-cyclic processes, reaction models.

NOMENCLATURE

\mathbb{R}_+ the set of non-negative real numbers

\mathbb{R}_+^* the set of positive real numbers

1 INTRODUCTION

In this paper we model certain biotechnological processes, such as chemical, biochemical and microbiological processes in batch, fed-batch or continuous stirred tank reactors. If the process is completely mixed and the medium is

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homogeneous in the reactor, then it can be modelled by a set of ordinary differential equations

$$\dot{\xi}_i(t) = \sum_{j=1}^M k_{ij} \varphi_j(\xi(t)) - D(t) \xi_i(t) - q_i(t) + F_i(t), \quad i = 1, \dots, N. \quad (1)$$

Here M is the number of reactions of the process and

$\xi_i(\cdot) : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ are the concentrations of the different components,

$\varphi_j(\cdot) : \mathbb{R}_+^N \rightarrow \mathbb{R}_+$ is the reaction rate of the j -th reaction,

$D(\cdot) : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is the dilution rate,

$F_i(\cdot) : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ are the feed rates of the different components,

$q_i(\cdot) : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ are the gaseous outflow rates of the different components,

$k_{ij} \in \mathbb{R}$ are the so-called stoichiometric (or yield) coefficients. This model is derived from the mass balance dynamics of each component in the reactor where the term $\sum k_{ij} \varphi_j(\xi)$ models the reaction kinetics, and the term $-D\xi_i - q_i + F_i$ models the exchange with the environment.

Notice that if $D(\cdot) \equiv 0$ and $F(\cdot) \equiv 0$, then we have a batch reactor, i.e. no inflow and no outflow; if $D(\cdot) \equiv 0$, then (1) describes a fed-batch reactor, i.e. no outflow; and generally (1) models a continuous stirred tank reactor.

To simplify the notation we may rewrite (1) as

$$\dot{\xi} = K\varphi(\xi) - D\xi - Q\xi + F, \quad (2)$$

where $\varphi(\xi) := (\varphi_1(\xi), \dots, \varphi_M(\xi))^T$, $Q := \text{diag}\{q_1, \dots, q_N\}$, $F := (F_1, \dots, F_N)^T$ and $k = (k_{ij}) = [K_1, \dots, K_M]$ denotes the stoichiometric matrix.

We stress that, although the matrix K is called stoichiometric matrix, we do not require that it represents an *exact* stoichiometric relationship between the components, it represents a qualitative relationship. Components that do not play an important role in the process, such as by-products of a reaction or substrates which are not limiting, have been omitted. The advantage of this description is that the model might be of much smaller dimension. This approach is quite common; see for instance Bastin and Dochain [2]. However, the reaction scheme may not follow the law of conservation of mass. This is different to many traditional approaches, such as for example the well-known contribution on chemical reacting systems by Gavalas [6]. See in particular Section 1.1, where he introduces systems which can be described by an ordinary differential equation of the form (2). Although Gavalas does not explicitly say so (see Section 1.1 and also the sentence after equation (1.8.11)), the Principle of Mass Conservation implies the existence of a positive vector

$$\gamma \in (\mathbb{R}_+^*)^M \text{ so that } \gamma^T K_j = 0 \text{ for all } j = 1, \dots, M. \quad (3)$$

Intuitively, this property means that the concentration remains bounded and is in fact crucial in proving it.

Instead of conservation of mass, we introduce the new notion of non-cyclic processes. It therefore has to be proved that (2) still exhibits practical relevant features, such as existence and uniqueness, positivity and boundedness of the solution. Roughly speaking, Cyclic means that the process contains a reaction loop, i.e. there exists a subset of reactions S , so that every substrate ξ_i involved in a reaction $j \in S$ is also an autocatalyst or a product of one of the reactions $j \in S$. One of the crucial consequences of non-cyclic processes, which is proved at the end of the present paper, is the existence of a positive vector

$$\gamma \in (\mathbb{R}_+^*)^N \quad \text{so that} \quad \gamma^T K_j \leq 0 \quad \text{for all } j = 1, \dots, M. \quad (4)$$

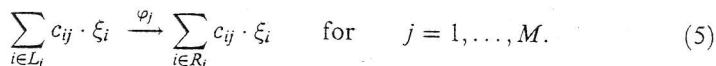
Note that the condition (4) is only slightly less restrictive than (4). However it is sufficient to guarantee boundedness of the trajectories.

Bastin and Dochain [2] refer to (1) as the "general dynamical model" of biological reactors. Modifications and generalisations of (1) have been considered in Gavalas [6], Moser [10] and various authors in Rehm and Reed (eds.) [11]. For control theoretic applications, models of this type were used by [7,3,12,1] to name but a few.

The paper is organised as follows. In Section 2 we describe the model and its assumptions in detail. Existence and uniqueness, invariance of the positive orthant and boundedness of the solution is proved in Section 3. Finally, in Section 4 the concept of non-cyclic processes is introduced. We present an algorithm which checks in finitely many steps whether a biotechnological process is cyclic or non-cyclic. Furthermore, non-cyclicity is characterised in terms of an echelon form of the stoichiometric matrix and a corollary of that is that non-cyclic process do have bounded trajectories.

2 THE GENERAL DYNAMICAL MODEL

Loosely speaking, we study biotechnological processes where N concentrations ξ_1, \dots, ξ_N in the liquid phase of the reactor are related via M reactions $\varphi_1, \dots, \varphi_M$. More precisely such a process is commonly specified by the reaction scheme for each reaction



Here

$L_j \subseteq \{1, \dots, N\}$, $L_j \neq \emptyset$, is the set of indices of the components ξ_i which are the *reactants* of the j th reaction,

$R_j \subseteq \{1, \dots, N\}$, $R_j \neq \emptyset$, is the set of indices of the components ξ_i which are the *reaction products* of the j th reaction.

The quantities of each component involved in the reaction are specified by the nonnegative *stoichiometric coefficients* c_{ij} , sometimes also called *yield coefficients*. The rate of consumption of the reactants, which is equal to the rate of formation of the reaction products, is called the *reaction rate* and denoted by φ_j .

To specify the process in more detail, we introduce the following notation for each reaction $j = 1, \dots, M$:

$$Cat_j := L_j \cap R_j,$$

i.e. the set of the indices of those components, called *catalysts*, which are involved in the j th reaction, but maintained by the reaction;

$$Sub_j := L_j \setminus (L_j \cap R_j) \neq \emptyset,$$

i.e. the set of those components, called *substrates*, that are consumed by the j th reaction;

$$Prod_j \subseteq R_j \setminus (L_j \cap R_j) \neq \emptyset,$$

is the set of the indices of those components, called *products*, that are produced by the j th reaction;

$$Aut_j := R_j \setminus ((L_j \cap R_j) \cup Prod_j),$$

i.e. the set of the indices of those components, called *autocatalysts*, that are accumulated by the j th reaction;

$$Rest_j := \{1, \dots, N\} \setminus (L_j \cup R_j),$$

i.e. the set of the process components that do not take part in the j th reaction. Notice that, for all $j = 1, \dots, M$,

$$Aut_j \cup Prod_j = R_j \setminus (R_j \cap L_j),$$

and $\{1, \dots, N\}$ can be represented as the disjoint union:

$$\{1, \dots, N\} = Cat_j \cup Sub_j \cup Aut_j \cup Prod_j \cup Rest_j.$$

Another helpful specification is the distinction between an external substrate of the process, i.e. a component that is added from the outside to the reactor and only consumed in the reactor, and an internal substrate, i.e., a component that

is produced by some reaction of the process and consumed by another. Formally we define

ξ_j is called an
external substrate if, and only if, $i \in \left(\bigcup_{j=1}^N \text{Sub}_j \right) \setminus \left(\bigcup_{j=1}^N (\text{Aut}_j \cup \text{Prod}_j) \right)$,

ξ_j is called an
internal substrate if, and only if, $i \in \left(\bigcup_{j=1}^N \text{Sub}_j \right) \cap \left(\bigcup_{j=1}^N (\text{Aut}_j \cup \text{Prod}_j) \right)$.

We assume that the dynamics of the process (5) can be described by the ordinary differential equation:

$$\dot{\xi}(t) = K \cdot \varphi(\xi(t)) - D(t) \cdot \xi(t) - Q\xi(t) + F(t), \quad \xi(0) \in (\mathbb{R}_+^*)^N, \quad (6)$$

where

$$\begin{aligned} \xi(t) &= (\xi_1(t), \dots, \xi_N(t))^T \in \mathbb{R}_+^N \text{ are the concentrations,} \\ \varphi(\xi) &= (\varphi_1(\xi), \dots, \varphi_M(\xi))^T \in \mathbb{R}_+^M, \quad \varphi_j: \mathbb{R}_+^N \rightarrow \mathbb{R}_+ \text{ is the reaction rate} \\ &\text{of the } j\text{th reaction,} \\ F(t) &= (F_1(t), \dots, F_N(t))^T \in \mathbb{R}_+^N, \quad F_i(\cdot): \mathbb{R}_+ \rightarrow [0, \bar{F}_i] \text{ is the feed rate} \\ &\text{of the } i\text{th component, and } \bar{F}_i \geq 0, \\ Q &= \text{diag}\{q_1, \dots, q_N\} \in \mathbb{R}^{N \times N}, \quad q_1, \dots, q_N \geq 0, \text{ is the matrix of} \\ &\text{gaseous outflow rates,} \\ D(\cdot): \mathbb{R}_+ &\longrightarrow [\underline{D}, \bar{D}] \text{ is the dilution rate, } 0 \leq \underline{D} \leq \bar{D}, \\ K &= (k_{ij}) = [K_1, \dots, K_M] \in \mathbb{R}^{N \times M} \text{ is the matrix of the stoichiometric} \\ &\text{coefficients.} \end{aligned}$$

The function φ is supposed to be locally Lipschitz continuous and F and D are assumed to be locally integrable. The entries of K relate the reactions as follows:

$$\begin{aligned} k_{ij} &= c_{ij} > 0 \quad \text{if, and only if, } i \in R_j \setminus (L_j \cap R_j), \\ k_{ij} &= 0 \quad \text{if, and only if, } i \in R_j \cap L_j \text{ or } i \notin R_j \cup L_j, \\ k_{ij} &= -c_{ij} < 0 \quad \text{if, and only if, } i \in L_j \setminus (L_j \cap R_j). \end{aligned} \quad (7)$$

Notice that all of the entries of K are determined by (7) since $\{1, \dots, N\}$ is the disjoint union of the sets $R_j \setminus (L_j \cap R_j)$, $L_j \setminus (L_j \cap R_j)$, $R_j \cap L_j$ and $\{1, \dots, N\} \setminus (R_j \cup L_j)$.

We already stressed and explained in the Introduction that, although the matrix K is called stoichiometric matrix, we do not require that it represents an exact stoichiometric relationship between the components, it represents a qualitative relationship.

Remark 1 It is easy to see, and useful in the following, that the catalysts, substrates and products can be characterized as follows:

$$\begin{aligned} \text{Cat}_j &= \{i \in L_j \cup R_j \mid k_{ij} = 0\}, \\ \text{Sub}_j &= \{i \in \{1, \dots, N\} \mid k_{ij} < 0\}, \\ \text{Aut}_j \cup \text{Prod}_j &= \{i \in \{1, \dots, N\} \mid k_{ij} > 0\}. \end{aligned}$$

For notational convenience we also define the following sets:

$$\begin{aligned} R_{\text{Cat}_i} &:= \{j \in \{1, \dots, M\} \mid k_{ij} = 0, i \in L_j \cup R_j\}, \text{ i.e. the set of numbers of} \\ &\text{the reactions that involve } \xi_i \text{ as a catalyst,} \\ R_{\text{Sub}_i} &:= \{j \in \{1, \dots, M\} \mid k_{ij} < 0\}, \text{ i.e. the set of the numbers of the reac-} \\ &\text{tions that involve } \xi_i \text{ as a substrate,} \\ R_{\text{Aut}_i} &:= \{j \in \{1, \dots, M\} \mid k_{ij} > 0, i \in \text{Aut}_j\}, \text{ i.e. the set of numbers of} \\ &\text{the reactions that involve } \xi_i \text{ as an autocatalyst,} \\ R_{\text{Prod}_i} &:= \{j \in \{1, \dots, M\} \mid k_{ij} > 0, i \in \text{Prod}_j\}, \text{ i.e. the set of numbers of} \\ &\text{the reactions that involve } \xi_i \text{ as a product.} \end{aligned}$$

Notice that

$$R_{\text{Aut}_i} \cup R_{\text{Prod}_i} = \{j \in \{1, \dots, M\} \mid k_{ij} > 0\}.$$

Note that if $k_{i_0 j_0} = 0$ for some $i_0 \in \{1, \dots, N\}$ and some $j_0 \in \{1, \dots, M\}$, then without further knowledge of the process details we cannot decide whether $i_0 \in \text{Cat}_{j_0}$ or $i_0 \in \text{Rest}_{j_0}$.

Similarly, if $k_{i_0 j_0} > 0$ for some $i_0 \in \{1, \dots, N\}$ and some $j_0 \in \{1, \dots, M\}$, we do not know whether $i_0 \in \text{Aut}_{j_0}$ or $i_0 \in \text{Prod}_{j_0}$.

Remark 2 In order to distinguish between a reaction which involves an autocatalyst and others which do not, we use in (5) either \rightarrow respectively \leftarrow and write

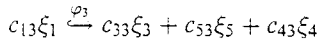
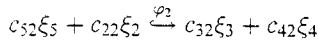
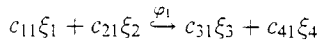
$$\sum_{i \in \text{Sub}_j \cup \text{Cat}_j} c_{ij} \cdot \xi_i \xrightarrow{\varphi_j} \sum_{k \in \text{Prod}_j \cup \text{Cat}_j} c_{kj} \cdot \xi_k, \quad \text{if } \text{Aut}_j = \emptyset$$

and

$$\sum_{i \in \text{Sub}_j \cup \text{Cat}_j} c_{ij} \cdot \xi_i \xleftarrow{\varphi_j} \sum_{k \in \text{Prod}_j \cup \text{Cat}_j \cup \text{Aut}_j} c_{kj} \cdot \xi_k, \quad \text{if } \text{Aut}_j \neq \emptyset.$$

The following example illustrates how a biochemical process presented by (5) is associated with the differential equation (6).

Example 3 The mechanism of yeast growth on glucose with ethanol production is described by the following set of microbiological reactions, see Sonnleitner and Käppli [13].



where ξ_1, \dots, ξ_5 denote the glucose, dissolved oxygen, yeast, dissolved carbon dioxide and the ethanol concentration, respectively.

It is immediate that

$$L_1 = \{1, 2\}, \quad R_1 = \{3, 4\}$$

$$L_2 = \{2, 5\}, \quad R_2 = \{3, 4\}$$

$$L_3 = \{1\}, \quad R_3 = \{3, 4, 5\},$$

and hence

$$Cat_j = L_j \cap R_j = \emptyset \quad \text{for } j = 1, 2, 3,$$

$$Sub_1 = \{1, 2\}, \quad k_{11} = -c_{11}, \quad k_{21} = -c_{21}.$$

$$Prod_1 \cup Aut_1 = \{3, 4\}, \quad k_{31} = c_{31}, \quad k_{41} = c_{41}.$$

$$Sub_2 = \{2, 5\}, \quad k_{22} = -c_{22}, \quad k_{52} = -c_{52}.$$

$$Prod_2 \cup Aut_2 = \{3, 4\}, \quad k_{32} = c_{32}, \quad k_{42} = c_{42}.$$

$$Sub_3 = \{1\}, \quad k_{13} = -c_{13}.$$

$$Prod_3 \cup Aut_3 = \{3, 4, 5\}, \quad k_{33} = c_{33}, \quad k_{43} = c_{43}, \quad k_{53} = c_{53}.$$

Therefore, the mathematical model (6) of the yeast growth process is

$$\begin{pmatrix} \dot{\xi}_1(t) \\ \dot{\xi}_2(t) \\ \dot{\xi}_3(t) \\ \dot{\xi}_4(t) \\ \dot{\xi}_5(t) \end{pmatrix} = K \begin{pmatrix} \varphi_1(\xi(t)) \\ \varphi_2(\xi(t)) \\ \varphi_3(\xi(t)) \end{pmatrix} - D(t) \begin{pmatrix} \xi_1(t) \\ \xi_2(t) \\ \xi_3(t) \\ \xi_4(t) \\ \xi_5(t) \end{pmatrix} - \begin{pmatrix} 0 \\ 0 \\ 0 \\ q_4\xi_4(t) \\ 0 \end{pmatrix} + \begin{pmatrix} F_1(t) \\ F_2(t) \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

where

$$K = (k_{ij}) = \begin{bmatrix} -c_{11} & 0 & -c_{13} \\ -c_{21} & -c_{22} & 0 \\ c_{31} & c_{32} & c_{43} \\ c_{41} & c_{42} & c_{43} \\ 0 & -c_{52} & c_{53} \end{bmatrix}.$$

To be able to prove that the concentrations in Example 3 remain positive and bounded, we need further assumptions on the growth rates. More generally, we assume that the process (6) satisfies the following.

(A1) For $j = 1, \dots, M$ the reaction rates are of the form

$$\varphi_j(\cdot) : \mathbb{R}_+^N \longrightarrow \mathbb{R}_+, \quad \xi \mapsto \varphi_j(\xi) = \alpha_j(\xi) \left(\prod_{k \in Aut_j \cup L_j} \xi_k \right),$$

and the growth rates

$$\alpha_j(\cdot) : \mathbb{R}_+^N \longrightarrow (\underline{\alpha}_j, \bar{\alpha}_j], \quad 0 \leq \underline{\alpha}_j \leq \bar{\alpha}_j,$$

are continuous functions.

(A2) If the lower bound of the dilution rate $D(\cdot)$ is zero, i.e. $\underline{D} = 0$, then the feed rate is proportional to the dilution rate

$$F(\cdot) \equiv D(\cdot) \xi^{in}(\cdot),$$

where, for all $j = 1, \dots, M$, the components of the inflow rate satisfy for some $\bar{\xi}_1^{in}, \dots, \bar{\xi}_N^{in} \geq 0$,

$$\xi_j^{in}(\cdot) : \mathbb{R}_+ \longrightarrow [0, \bar{\xi}_j^{in}].$$

Remark 4 Assumption (A1) corresponds to the physical fact that a reaction rate is always nonnegative and that a reaction can only take place if all its reactants are present in the reactor, which means that as soon as the concentration of one reactant becomes zero the reaction rate is zero.

If the concentrations of the reactants are also bounded from above – which will be shown in Section 3 under additional assumptions – then the chosen reaction rates φ_j agree with the conventional reaction rates. For a comprehensive list see e.g. the Appendix in [2]. The reaction rate φ is often assumed to be proportional to the microbial growth rate μ . Consider for instance the models of Monod or Haldane, where the function μ is used to explain the dependency of

φ on the substrate concentrations. The relationship between $\alpha(\xi)$ and $\mu(\xi)$ is then

$$\begin{aligned} \text{Monod: } \alpha_j(\xi) &= \prod_{i \in \text{Sub}_j} \left(\frac{\tilde{\mu}_i}{K_i + \xi_i} \right) & \text{and } \mu_j(\xi) &= \alpha_j(\xi) \cdot \prod_{i \in \text{Sub}_j} \xi_i, \\ \text{Haldane: } \alpha_j(\xi) &= \prod_{i \in \text{Sub}_j} \left(\frac{\tilde{\mu}_i}{K_i + \xi_i + \frac{\xi_i^2}{K_i}} \right) & \text{and } \mu_j(\xi) &= \alpha_j(\xi) \cdot \prod_{i \in \text{Sub}_j} \xi_i. \end{aligned}$$

Since $\text{Aut}_j \cup L_j = \text{Sub}_j \cup \text{Cat}_j \cup \text{Aut}_j$, the reaction rate φ in (A1) can be written as

$$\varphi_j(\xi) = \mu_j(\xi) \left(\prod_{k \in \text{Aut}_j \cup \text{Cat}_j} \xi_k \right).$$

Assumption (A2) means that if $D(\cdot)$ is not bounded away from zero, then one requires instead that $F(\cdot) \equiv D(\cdot)\xi^{in}(\cdot)$. This means that all the substances that are added from the exterior to the reactor are fed with the influent water stream and ξ_i^{in} is the concentration of the substance ξ_i in the influent water stream.

There might be substances ξ_i which are soluble in the liquid phase and gasifiable at atmospheric pressure. In model (6), where the gaseous outflow is given by the proportion $Q\xi$, the saturation concentration between the liquid and the gas phase is assumed to be "very high".

Remark 5 It is a common assumption of various authors, see e.g. [6], that $N > M$ and $\text{rk } K = M$. This means that the number of components involved in the process exceeds the number of reactions, which usually is the case since one reaction involves more than one component. Furthermore it is often desirable to describe composition changes by the smallest possible number of reactions. If $\text{rk } K = M$, then the reactions are called independent, see e.g. [6], Definition 1.1.1. If K does not have full column rank, then there are certain strategies to pick a set of "key reactions", see e.g. Section I.2 in [10]. However, in our setup there is no need to assume any of these assumptions.

3 INVARIANCE OF THE POSITIVE ORTHANT AND BOUNDEDNESS OF THE SOLUTION

In this section we show existence and uniqueness of the solution of (6) on a maximal interval of existence $[0, \omega)$, where ω might be finite. (A1) does not guar-

antee that finite escape time does not occur, this will be ensured by an extra assumption later on.

Proposition 6 *If the general dynamical model (6) satisfies (A1), then there exists a unique solution $\xi(\cdot) : [0, \omega) \rightarrow \mathbb{R}^N$ on its maximal interval of existence $[0, \omega)$, for some $\omega \in (0, \infty]$. Furthermore, the positive orthant is invariant under the flow, i.e.*

$$\text{if } \xi(0) \in (\mathbb{R}_+^*)^N, \text{ then } \xi(t) \in (\mathbb{R}_+^*)^N \text{ for all } t \in [0, \omega). \quad (8)$$

Proof: Existence and uniqueness of a solution $\xi(\cdot) : [0, \omega) \rightarrow \mathbb{R}^N$ of (6) on a maximal interval of existence follow from the theory of ordinary differential equations, see e.g. Coddington and Levinson [4].

Seeking a contradiction to the invariance of the positive orthant under the flow, suppose there exist some $i \in \{1, \dots, N\}$ and $t_0 \in (0, \omega)$ such that

$$\xi_i(t_0) = 0 \quad \text{and} \quad \xi_k(t) > 0 \quad \text{for all } t < t_0, k \in \{1, \dots, N\}. \quad (9)$$

The i th coordinate of (6) satisfies, for all $t \in [0, t_0]$,

$$\dot{\xi}_i(t) = \sum_{j=1}^M k_{ij} \varphi_j(\xi(t)) - D(t) \cdot \xi_i(t) - \beta_i \cdot \xi_i(t) + F_i(t),$$

and since by Remark 1 $k_{ij} \geq 0$ for $j \notin R_{Sub_i}$ and $F_i(t) \geq 0$ for all $t \geq 0$, it follows that

$$\dot{\xi}_i(t) \geq - \sum_{j \in R_{Sub_i}} |k_{ij}| \varphi_j(\xi(t)) - D(t) \cdot \xi_i(t) - \beta_i \cdot \xi_i(t).$$

Now Assumption (A1) yields

$$\dot{\xi}_i(t) \geq - \sum_{j \in R_{Sub_i}} |k_{ij}| \alpha_j(\xi(t)) \left(\prod_{k \in (\mathcal{A}ut_j \cup \mathcal{L}_j) \setminus \{i\}} \xi_k(t) \right) \xi_i(t) - [D(t) + \beta_i] \xi_i(t),$$

and defining

$$\psi_i(t) := - \left[\sum_{j \in R_{Sub_i}} |k_{ij}| \alpha_j(\xi(t)) \left(\prod_{k \in (\mathcal{A}ut_j \cup \mathcal{L}_j) \setminus \{i\}} \xi_k(t) \right) + D(t) + \beta_i \right]$$

leads to

$$\dot{\xi}_i(t) \geq \psi_i(t)\xi_i(t).$$

Now integration yields, see Lemma 19,

$$\xi_i(t) \geq e^{\int_0^t \psi_i(\tau) d\tau} \xi_i(0) \quad \text{as long as } t \in [0, t_0],$$

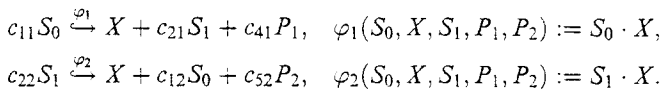
and hence

$$\xi_i(t_0) \geq e^{\int_0^{t_0} \psi_i(\tau) d\tau} \xi_i(0).$$

Since $\xi_i(0) > 0$, this contradicts the assumption $\xi_i(t_0) = 0$ in (9). Therefore a component cannot leave the positive orthant and the state variables stay positive on their maximal interval of existence.

The assumptions (A1)–(A2) are however not sufficient to guarantee existence of the solution on the whole of $[0, \infty)$, finite escape time might occur. This is demonstrated in the following example.

Example 7 Consider the following reaction scheme¹



The corresponding process (6) of the reaction scheme is

$$\begin{aligned} \dot{S}_0(t) &= k_{11}S_0(t)X(t) + k_{12}S_1(t)X(t) - D(t)S_0(t) + D(t)S^{in} \\ \dot{S}_1(t) &= k_{21}S_0(t)X(t) + k_{22}S_1(t)X(t) - D(t)S_1(t) \\ \dot{X}(t) &= [S_0(t) + S_1(t)]X(t) - D(t)X(t) \\ \dot{P}_1(t) &= k_{41}X(t)S_0(t) - D(t)P_1(t) \\ \dot{P}_2(t) &= k_{52}X(t)S_1(t) - D(t)P_2(t). \end{aligned}$$

Setting yields $k_{11} = -c_{11} = 0.5, k_{21} = c_{21} = 1.5, k_{12} = c_{12} = 1.5, k_{22} = -c_{22} = -0.5$

¹This example may be chemically absurd, but it is a general biotechnological process satisfying (A1)–(A2).

$$K = \begin{pmatrix} -0.5 & 1.5 \\ 1.5 & -0.5 \\ 1 & 1 \\ k_{41} & 0 \\ 0 & k_{52} \end{pmatrix}.$$

And since c_{41} and c_{52} are associated with products, we conclude $k_{41} > 0$ and $k_{52} > 0$. Furthermore assume that the initial values of the different state variables are all positive and the dilution rate is a positive constant $D(\cdot) \equiv D > 0$.

Differentiation of the new variable

$$Z(t) = S_0(t) + S_1(t) - X(t)$$

yields

$$\dot{Z}(t) = -DZ(t) + DS^{in}$$

and hence

$$Z(t) = S^{in} + e^{-Dt}(Z_0 - S^{in}).$$

Now $X(\cdot)$ satisfies

$$\begin{aligned} \dot{X}(t) &= X(t)(Z(t) + X(t)) - DX(t) \\ &= X^2(t) + (Z(t) - D)X(t) \\ &\geq (Z(t) - D)X(t), \end{aligned}$$

and hence, by Lemma 19 and substitution of Z , we obtain

$$X(t) \geq e^{\int_0^t Z(s) - D \, ds} X_0 \geq e^{\int_0^t S^{in} + (Z_0 - S^{in})e^{-Ds} - D \, ds} X_0.$$

If we choose $D < S^{in} < Z_0$, then

$$X(t) \geq e^{[S^{in} - D]t} X_0$$

and hence $\lim_{t \rightarrow \infty} X(t) = \infty$. Therefore the concentration of the bacteria is unbounded.

If $D(t) = 1 - \cos t$, so that the alternative in (A2) is satisfied, then a similar calculation proves unboundedness of $X(\cdot)$ in case of $Z_0 > S^{in} > 1$.

Example 7 shows that the assumptions (A1)–(A2) do not guarantee a bounded solution. Since k_{41} and k_{52} are positive, it is easy to see that there does not exist

a vector $\gamma \in \mathbb{R}^3$ with positive components such that $\langle \gamma, K_j \rangle \leq 0$ for $j = 1, 2$. Therefore, condition (4) is not satisfied for this example. This motivates a further assumption which replaces the more restrictive assumption (3) on exact stoichiometric coefficients.

(A3) There exists some $\gamma \in (\mathbb{R}_+^*)^N$ such that

$$\langle \gamma, K_j \rangle \leq 0 \quad \text{for all } j = 1, \dots, M.$$

We are now in a position to prove boundedness of the solution. The main result of Section 4 will be the definition and characterisation of the concept of non-cyclic processes which will be shown to be sufficient for (A3).

Theorem 8 *Suppose the general reactor model (6) satisfies (A1)–(A3), and let $\bar{F} := (\bar{F}_1, \dots, \bar{F}_N)^T$ denote the upper bound for the feed rates, $\bar{\xi}^{in} := (\bar{\xi}_1^{in}, \dots, \bar{\xi}_N^{in})^T$ the upper bound in (A2). Then the following holds.*

- (i) *The initial value problem (6) has a unique solution $\xi(\cdot) : \mathbb{R}_+^* \rightarrow (\mathbb{R}_+^*)^N$ defined on the whole of the half axis $[0, \infty)$ and stays within the positive orthant.*
- (ii) *If $\underline{D} > 0$, then the solution is bounded from above as follows*

$$\langle \gamma, \xi(t) \rangle \leq \max \left\{ \langle \gamma, \xi(0) \rangle, \frac{\langle \gamma, \bar{F} \rangle}{\underline{D}} \right\} \text{ and } \limsup_{t \rightarrow \infty} \langle \gamma, \xi(t) \rangle \leq \frac{\langle \gamma, \bar{F} \rangle}{\underline{D}}.$$

- (iii) *If $\underline{D} = 0$ (which by (A2) yields that $F(\cdot) \equiv D(\cdot)\xi^{in}(\cdot)$), then the solution is bounded from above as follows*

$$\langle \gamma, \xi(t) \rangle \leq \max \left\{ \langle \gamma, \xi(0) \rangle, \langle \gamma, \bar{\xi}^{in} \rangle \right\} \text{ and } \limsup_{t \rightarrow \infty} \langle \gamma, \xi(t) \rangle \leq \langle \gamma, \bar{\xi}^{in} \rangle.$$

Proof: By Proposition 6 we only have to show that the first inequalities in (ii) and (iii) hold true on $[0, \omega)$, the maximal interval of existence. Then boundedness of $\xi(\cdot)$ on $[0, \omega)$ yields $\omega = \infty$, and hence (i) follows.

Multiplying (6) from the left with γ^T yields, for almost all $t \in [0, \omega)$,

$$\gamma^T \dot{\xi}(t) = \gamma^T K \varphi(\xi(t)) - \gamma^T D(t) \xi(t) - \gamma^T \begin{bmatrix} \beta_1 & & 0 \\ & \ddots & \\ 0 & & \beta_N \end{bmatrix} \xi(t) + \gamma^T F(t)$$

and hence, for

$$\Phi(t) := \langle \gamma, \xi(t) \rangle,$$

we obtain

$$\dot{\Phi}(t) = \sum_{j=1}^M \langle \gamma, K_j \rangle \varphi_j(\xi(t)) - D(t)\Phi(t) - \gamma^T \begin{bmatrix} \beta_1 & & 0 \\ & \ddots & \\ 0 & & \beta_N \end{bmatrix} \xi(t) + \langle \gamma, F(t) \rangle.$$

This yields, by assumption (A3) and positivity of $\xi(t)$, for all $t \in [0, \omega)$

$$\dot{\Phi}(t) \leq -D(t) \cdot \Phi(t) + \langle \gamma, F(t) \rangle.$$

If $\underline{D} > 0$, then an application of Lemma 19 and boundedness of $F(\cdot)$ yields, for all $t \in [0, \omega)$,

$$\Phi(t) \leq \max \left\{ \Phi(0), \frac{\langle \gamma, \bar{F} \rangle}{\underline{D}} \right\}.$$

Hence $\xi(\cdot)$ is bounded on $[0, \omega)$ and a repeated application of Lemma 19 proves the second inequality in (ii).

If $F(\cdot) \equiv D(\cdot)\xi^{in}(\cdot)$, then we apply Lemma 19 to conclude

$$\frac{d}{dt} [\Phi(t) - \gamma^T \xi^{in}] = \dot{\Phi}(t) \leq -D(t) [\Phi(t) - \gamma^T \xi^{in}]$$

and the statements in (iii) follow. This completes the proof.

Remark 9

(a): Note that in Example 7 the matrix K does not satisfy (A3).

(b): If assumption (A3) in Theorem 8 is weakened to hold only for some non-negative (but not necessarily positive) $\gamma \in \mathbb{R}_+^N$, then we can only show boundedness for those concentrations ξ_i for which $\gamma_i > 0$.

(c): If the general dynamical model (6) consists of only one reaction, i.e. $M = 1$, then (A3) is satisfied. To see this notice that $L_j \setminus (L_j \cap R_j)$ and $R_j \setminus (L_j \cap R_j)$ are both nonempty, and hence there exist some $i_1 \neq i_2$ so that $k_{i_1 j} > 0$ and $k_{i_2 j} < 0$, whence every column of K has at least one positive and one negative coefficient. Thus, if $K = K_1$ consists of one column only, we may define

$$\gamma_i := \begin{cases} 1 & \text{if } k_{i1} < 0 \\ \bar{\gamma} & \text{if } k_{i1} > 0 \end{cases} \quad \text{with } \bar{\gamma} := \frac{-\sum_{k_{i1} < 0} k_{i1}}{\sum_{k_{i1} > 0} k_{i1}} > 0,$$

and check that in this case $\langle \gamma, K_1 \rangle = 0$.

4 NON-CYCLIC PROCESSES

We now arrive at the main contribution of this paper, that is the concept of *non-cyclic* processes, its characterization and its consequences such as it is a sufficient condition for the crucial assumption (A3). Cyclicity of (6) means that the process contains a reaction loop, i.e. there exists a subset of reactions S , so that every substrate ξ_i involved in a reaction $j \in S$ is also an autocatalyst or a product of one of the reactions $j \in S$. Or in other words, (6) is non-cyclic respectively does not contain a reaction loop if, and only if, for each subset S there exists a substrate ξ_i of some reaction $j_0 \in S$ such that ξ_i is neither an autocatalyst nor a product of one of the reactions $j \in S$. This concept is more formally defined as follows.

Definition 10 *The biotechnological process (6) is said to be cyclic if, and only if, there exists a nonempty subset $S \subseteq \{1, \dots, M\}$, such that*

$$\bigcup_{j \in S} \text{Sub}_j \subseteq \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j). \quad (10)$$

For instance the biotechnological process in Example 7 is cyclic, since for $S = \{1, 2\}$ all the substrates appear also as products.

Rephrasing this definition will be useful in the following.

Remark 11 Consider a biotechnological process (6). Then the following conditions are equivalent

- (i) (6) is *cyclic*,
- (ii) there exists some $S \subseteq \{1, \dots, M\}$, $S \neq \emptyset$, such that

$$i \in \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j) \quad \text{for all } (i, j) \in \text{Sub}_j \times S. \quad (11)$$

and so are also the conditions

- (i') (6) is *non-cyclic*,
- (ii') for each $S \subseteq \{1, \dots, M\}$,

$$\bigcup_{j \in S} \text{Sub}_j \not\subseteq \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j), \quad (12)$$

- (iii') for each $S \subseteq \{1, \dots, M\}$, there exists a pair

$$(i, j_0) \in \text{Sub}_{j_0} \times S \quad \text{such that} \quad i \notin \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j). \quad (13)$$

The characterization of non-cyclicity is based on a constructive procedure which checks whether (10) is satisfied or not. This is comprised in the following pseudo-algorithm.

Algorithm 12 Consider the biotechnological process (6) with specified $M, N, Sub_j, Aut_j, Prod_j$ for $j = 1, \dots, M$.

```

SET    $S_1 := \{1, \dots, M\}$ ;
       $\mathcal{N} := \{1, \dots, N\}$ ;
FOR    $l = 1, \dots, M$ 
DO     IF       $l > 1$  and there exists  $j_l \in S_l$  such that
               $i_{l-1} \in Sub_{j_l}$ 
              SET  $i_l := i_{l-1}$ ;
              GOTO 10 ;
      ELSE IF  there exists  $(i_l, j_l) \in \mathcal{N} \times S_l$  such that
               $i_l \in Sub_{j_l}$  and  $i_l \notin \bigcup_{j \in S_l} (Aut_j \cup Prod_j)$ 
              GOTO 10 ;
      ELSE    PRINT "cyclic"; STOP;
10.      $S_{l+1} := S_l \setminus \{j_l\}$ ;
      END
END
PRINT  "non - cyclic"
END.
```

Remark 13 Instead of using subsets of substances, such as S_l, Sub_{j_l} , etc., it follows from Remark 1 that Algorithm 12 can equally be formulated for the stoichiometric matrix $K = (k_{ij}) \in \mathbb{R}^{N \times M}$ by replacing

$i_{l-1} \in Sub_{j_l}$ in condition IF by $k_{i_{l-1}j_l} < 0$ and

$i_l \in Sub_{j_l}$ and $i_l \notin \bigcup_{j \in S_l} (Aut_j \cup Prod_j)$ in condition ELSE IF by $k_{i_l j} < 0$ and $k_{i_l j} \leq 0$ for all $j \in S_l \setminus \{j_l\}$

Proposition 14 The Algorithm 12 terminates after finitely many steps with "non-cyclic" if, and only if, the process (6) is non-cyclic; it terminates with "cyclic" if, and only if, the process (6) is cyclic.

Proof. (a): We prove that printing "non-cyclic" yields that () is non-cyclic.

This is proved in two steps.

(a₁): It is proved that if Algorithm 12 prints "non-cyclic", then for each $l \in \{1, \dots, M\}$ there exists a pair of indices $(i_l, j_l) \in \{1, \dots, N\} \times S_l$ such that

$$i_l \in \text{Sub}_{j_l} \quad \text{and} \quad i_l \notin \bigcup_{j \in S_l} (\text{Aut}_j \cup \text{Prod}_j). \quad (14)$$

Proceed by induction on l . By assumption either the condition IF or the condition ELSE IF is satisfied. For $l = 1$ IF is excluded, and hence ELSE IF holds and there exists a pair $(i_1, j_1) \in \{1, \dots, N\} \times S_1$ satisfying (14).

Now suppose that $(i_1, j_1), \dots, (i_{l-1}, j_{l-1}) \in \{1, \dots, N\} \times S_{l-1}$ satisfy (14). If IF is true, then there exists $j_l \in S_l$ such that $i_{l-1} \in \text{Sub}_{j_l}$. Since $i_{l-1} \notin \bigcup_{j \in S_{l-1}} (\text{Aut}_j \cup \text{Prod}_j)$ and $S_l \subset S_{l-1}$ it follows that $i_{l-1} \notin \bigcup_{j \in S_l} (\text{Aut}_j \cup \text{Prod}_j)$.

Setting $i_l := i_{l-1}$ yields the pair (i_l, j_l) which satisfies (14).

If ELSE IF is satisfied, it is immediate that $(i_l, j_l) \in \{1, \dots, N\} \times S_l$ satisfies (14).

(a₂): It is proved that if Algorithm prints "non-cyclic", then (iii') in Remark 11 is satisfied.

Let $S \subseteq \{1, \dots, M\}$ be arbitrary but nonempty, set $r = \text{card}S$, and use the notation

$$S = \{j_1, \dots, j_r\}, \quad \text{where} \quad l_1 \leq \dots \leq l_r.$$

Since (i_l, j_l) satisfies (14) and $S_{j_l} = \{j_1, \dots, j_M\}$, it follows that $S \subseteq S_{j_l}$. Therefore (iii') in Remark 11 holds. This proves (a₂) and (a) follows from Remark 11.

(b): We prove that non-cyclicity of (6) yields printing "non-cyclic".

If (6) is non-cyclic, then by (13) for each l there exists a pair (i_l, j_l) such that

$$(i_l, j_l) \in \text{Sub}_{j_l} \times S_l \quad \text{and} \quad i_l \notin \bigcup_{j \in S_l} (\text{Aut}_j \cup \text{Prod}_j). \quad (15)$$

This means ELSE IF is satisfied for all $l = 1, \dots, M$ and the algorithm finally terminates with printing "non-cyclic".

(c): We prove that if Algorithm prints "cyclic", then (6) is cyclic.

If Algorithm prints "cyclic" in the l th loop, then ELSE IF does not hold true and hence (11) is satisfied for $S = S_l$. Now the statement follows from Remark 11.

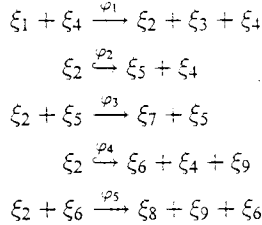
(d): We prove that cyclicity of (6) yields printing "cyclic".

Suppose Algorithm 12 prints "non-cyclic". Then by (a) the process is non-cyclic which contradicts the assumption.

This completes the proof.

The following example illustrates a non-cyclic process.

Example 15 This production of strains for yogurt manufacturing described in [3] is represented by the following reaction scheme²



with ξ_1 representing lactose, ξ_2 glucose, ξ_3 galactose, ξ_4 lactase, ξ_5 lactobacillus bulgarius, ξ_6 streptococcus thermophilus, ξ_7 D-lactate, ξ_8 L-lactate and ξ_9 carbon dioxide. Following Algorithm 12, we choose $i_1 = 1$ and $l_1 = 1$, because $1 \in Sub_1$ and $\xi_1 \notin Aut_j \cup Prod_j$ for $j \in \{2, 3, 4, 5\}$.

Since 1 does not appear in the reactions 2-5, $2 \notin Aut_j \cup Prod_j$ for $j \in \{3, 4, 5\}$ and $2 \in Sub_2$, we choose $i_2 = 2$ and $l_2 = 2$.

For i_3 we choose again $i_3 = i_2 = 2$ and $l_3 = 3$, because $2 \in Sub_3$ and $2 \notin Aut_j \cup Prod_j$ for $j \in \{4, 5\}$.

Finally $i_4 = i_5 = 2$ and $l_4 = 4$, $l_5 = 5$. Now the algorithm stops (after $M = 5$ steps) and hence this process is non-cyclic.

We are now in a position to prove the main result of this paper. It is the characterization of the concept of non-cyclicity in terms of the stoichiometric matrix K in (6).

Theorem 16 *The biotechnological process (6) is non-cyclic if, and only if, there exist permutation matrices $L \in \mathbb{R}^{N \times N}$ and $R \in \mathbb{R}^{M \times M}$ and there exist, for some $r \in \{1, \dots, M\}$, $1 = q_1 < q_2 < \dots < q_{r-1} < q_r \leq M$, such that*

$$LKR = \tilde{K} = (\tilde{k}_{lm})$$

satisfies

$$\begin{aligned} \tilde{k}_{lm} &< 0 \quad \text{for} \quad m = q_l, \dots, q_{l+1} - 1 \quad \text{and} \quad l = 1, \dots, r \\ \tilde{k}_{lm} &= 0 \quad \text{for} \quad m = q_{l+1}, \dots, M \quad \text{and} \quad l = 1, \dots, r - 1, \end{aligned} \quad (16)$$

where $q_{r+1} - 1 := M$.

²For simplicity the stoichiometric coefficients are neglected.

Let $r \leq M$ be the number of different indices i_l and define successively

$$\begin{aligned} \tilde{i}_1 &:= i_1 \\ \tilde{i}_l &:= i_{q_l}, \quad \text{where } q_l = \min\{k \mid i_k \notin \{\tilde{i}_1, \dots, \tilde{i}_{l-1}\}\} \quad \text{for } l = 2, \dots, r. \end{aligned}$$

where, for notational convenience, $q_1 := 1$, $(q_{r+1} - 1) := M$ and $i_{q_{r+1}} > i_M$.

Since by construction we have, for $l = 1, \dots, r$, that $i_{q_{l-1}} < i_l = i_{q_l} = \dots = i_{q_{l+1}-1} < i_{q_{l+1}}$, the sets

$$J_l := \{j_{q_l}, \dots, j_{q_{l+1}-1}\} \quad \text{for } l = 1, \dots, r$$

are disjoint and $\{1, \dots, M\} = \bigcup_{l=1}^r J_l$.

By (18) we have, for $l = 1, \dots, r$,

$$\begin{aligned} k_{i_l j_{q_l}} &= k_{i_{q_l} j_{q_l}} < 0 \\ &\vdots \\ k_{i_l j_{q_{l+1}-1}} &= k_{i_{(q_{l+1}-1)j_{(q_{l+1}-1)}}} < 0 \end{aligned} \tag{19}$$

and, for $l = 1, \dots, r - 1$,

$$k_{i_l j} = k_{i_{(q_{l+1}-1)j}} \leq 0 \quad \text{for all } j \in \{j_{q_{l+1}}, \dots, j_M\} = \bigcup_{r \geq m > l} J_m. \tag{20}$$

Since the i_l s are chosen according to Algorithm 12, we conclude that

$$\tilde{i}_l \notin \left(\bigcup_{j \in \{j_{q_{l+1}}, \dots, j_M\}} \text{Sub}_j \right),$$

which is equivalent to $\tilde{i}_l \notin \text{Sub}_j$ for all $j \in J_m$, $r \geq m > l$, and a repeated application of Remark 1 yields, for all $j \in J_m$, $r \geq m > l$, that $k_{i_l j} \geq 0$.

Therefore, by (19) and (20) we conclude that

$$\begin{aligned} k_{i_l j} &< 0 \quad \text{for } j \in J_l \\ k_{i_l j} &= 0 \quad \text{for } j \in J_m, \quad r \geq m > l. \end{aligned} \tag{21}$$

We are now in a position to determine the permutation matrices.

Let $R \in \mathbb{R}^{M \times M}$ be the permutation matrix of

$$\begin{pmatrix} 1, & \dots, & M \\ j_1, & \dots, & j_M \end{pmatrix}.$$

Then $\bar{K} = (\bar{k}_{lm}) := K \cdot R$ satisfies, for all $l = 1, \dots, N$,

$$\bar{k}_{lm} = k_{lj_m}, \quad m = 1, \dots, M. \quad (22)$$

Let $L \in \mathbb{R}^{N \times N}$ be the permutation matrix of

$$\begin{pmatrix} 1 & , & \dots & , & r & , & r+1 & , & \dots & , & N \\ \bar{i}_1 & , & \dots & , & \bar{i}_r & , & f_{r+1} & , & \dots & , & f_N \end{pmatrix},$$

where (f_{r+1}, \dots, f_N) is some permutation of $\{1, \dots, N\} \setminus \{\bar{i}_1, \dots, \bar{i}_r\}$.

Now $\bar{K} = (\bar{k}_{lm}) := L \cdot \bar{K}$ satisfies, for all $m = 1, \dots, M$,

$$\bar{k}_{lm} = \begin{cases} \bar{k}_{\bar{i}_l m} & , & l = 1, \dots, r \\ \bar{k}_{f_l m} & , & l = r+1, \dots, N. \end{cases}$$

which by (22) yields, for $m = 1, \dots, M$,

$$\bar{k}_{lm} = \begin{cases} \bar{k}_{\bar{i}_l m} = k_{\bar{i}_l j_m} & , & l = 1, \dots, r \\ \bar{k}_{f_l m} = k_{f_l j_m} & , & l = r+1, \dots, N. \end{cases} \quad (23)$$

Therefore (21) and (23) yield

$$\bar{k}_{lm} < 0 \quad \text{for } m = q_l, \dots, (q_{l+1} - 1) \quad \text{and } l = 1, \dots, r$$

$$\bar{k}_{lm} = 0 \quad \text{for } m = q_{l+1}, \dots, M \quad \text{and } l = 1, \dots, r-1,$$

which by (16) leads to the echelon form (17). This proves necessity.

To prove sufficiency assume that $\bar{K} := LKR$ has the form (17) for some permutation matrices $L \in \mathbb{R}^{N \times N}$ and $R \in \mathbb{R}^{M \times M}$.

Let $L \in \mathbb{R}^{N \times N}$ describe the permutation σ

$$\begin{pmatrix} 1 & , & \dots & , & N \\ \sigma(1) & , & \dots & , & \sigma(N) \end{pmatrix}$$

and $R \in \mathbb{R}^{M \times M}$ the permutation π

$$\begin{pmatrix} 1 & , & \dots & , & M \\ \pi(1) & , & \dots & , & \pi(M) \end{pmatrix}.$$

Then the coefficients of $\tilde{K} = (\tilde{k}_{ij})$ and of $K = (k_{ij})$ are related as

$$\tilde{k}_{lm} = k_{\sigma(l)\pi(m)} \quad \text{for } l = 1, \dots, N \quad \text{and } m = 1, \dots, M. \quad (24)$$

Since \tilde{K} has the form (17), there exist r numbers $q_1, \dots, q_r \in \{1, \dots, M\}$ such that (16) is satisfied. Setting $J_l := \{q_l, \dots, q_{l+1} - 1\}^3$ for $l = 1, \dots, r$, yields the

disjoint subsets $\bigcup_{j=1}^r J_l = \{1, \dots, M\}$.

Now let $S \subseteq \{1, \dots, M\}$, $S \neq \emptyset$, be arbitrary and choose $\bar{j} \in S$ such that $\pi^{-1}(\bar{j}) = \min\{\pi^{-1}(j) \mid j \in S\}$. Then there exists $\bar{l} \in \{1, \dots, r\}$ such that $\pi^{-1}(\bar{j}) \in J_{\bar{l}}$.

In order to apply (13), we show that

$$\sigma(\bar{l}) \in \text{Sub}_{\bar{j}} \quad \text{and} \quad \sigma(\bar{l}) \notin \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j). \quad (25)$$

From (16) it follows that $\tilde{k}_{\bar{l}\pi^{-1}(\bar{j})} < 0$ and (24) yields $k_{\sigma(\bar{l})\bar{j}} < 0$, which by Remark 1 means that $\sigma(\bar{l}) \in \text{Sub}_{\bar{j}}$. This means the first condition in (25) is satisfied. Since $\pi^{-1}(\bar{j}) \leq \pi^{-1}(j)$, for all $j \in S$, we obtain

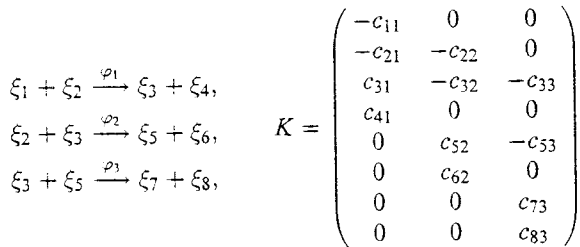
$$\tilde{k}_{\bar{l}\pi^{-1}(j)} \leq 0 \quad \text{for all } j \in S,$$

which by (24) yields $k_{\sigma(\bar{l})j} \leq 0$, for all $j \in S$ and this means, again by Remark 1, that $\sigma(\bar{l}) \notin \bigcup_{j \in S} (\text{Aut}_j \cup \text{Prod}_j)$. This proves the second condition in (25) and hence

(13) is satisfied, whence the process is non-cyclic.

In Example 17 we show that the form (17) is not unique. This completes the proof of the theorem.

Example 17 Consider the reaction scheme and the corresponding stoichiometric matrix



³Put, for notational simplicity, $q_{r+1} - 1 := M$.

Algorithm 12 leaves some freedom how to choose the pairs (i_k, j_k) , $k = 1, 2, 3$. Three possibilities are as follows.

- Let $(i_1, j_1) = (1, 1)$, $(i_2, j_2) = (2, 2)$ and $(i_3, j_3) = (3, 3)$, and hence

$$\tilde{K} = \begin{pmatrix} -c_{11} & 0 & 0 \\ -c_{21} & -c_{22} & 0 \\ c_{31} & -c_{32} & -c_{33} \\ c_{41} & 0 & 0 \\ 0 & c_{52} & -c_{53} \\ 0 & c_{62} & 0 \\ 0 & 0 & c_{73} \\ 0 & 0 & c_{83} \end{pmatrix}.$$

- Let $(i_1, j_1) = (2, 1)$, $(i_2, j_2) = (2, 2)$ and $(i_3, j_3) = (3, 3)$, and hence

$$\tilde{K} = \begin{pmatrix} -c_{21} & -c_{22} & 0 \\ c_{31} & -c_{32} & -c_{33} \\ -c_{11} & 0 & 0 \\ c_{41} & 0 & 0 \\ 0 & c_{52} & -c_{53} \\ 0 & c_{62} & 0 \\ 0 & 0 & c_{73} \\ 0 & 0 & c_{83} \end{pmatrix}.$$

Alternatively we may also choose $i_3 = 5$.

- Another choice is $(i_1, j_1) = (1, 1)$, $(i_2, j_2) = (3, 2)$ and $(i_3, j_3) = (3, 3)$, which yields

$$\tilde{K} = \begin{pmatrix} -c_{11} & 0 & 0 \\ c_{31} & -c_{32} & -c_{33} \\ -c_{21} & -c_{22} & 0 \\ c_{41} & 0 & 0 \\ 0 & c_{52} & -c_{53} \\ 0 & c_{62} & 0 \\ 0 & 0 & c_{73} \\ 0 & 0 & c_{83} \end{pmatrix}.$$

In every case we obtain a matrix \tilde{K} that has the form (17) and we conclude that the process is non-cyclic.

An immediate consequence of the form (17) is the existence of a positive vector $\gamma \in (\mathbb{R}_+^*)^N$ such that $\gamma^T \tilde{K}_j \leq 0$ for each column $\tilde{K}_1, \dots, \tilde{K}_M$ of \tilde{K} . This

immediately yields the following corollary which is crucial to ensure boundedness of the trajectory of the biotechnological process.

Corollary 18 *Theorem 8 remains valid if assumption (A3) is replaced by the assumption that (6) is non-cyclic.*

1 CONCLUSIONS

General reactor models are frequently used in the engineering literature to study the dynamical behaviour and control of biotechnological processes. However, if the stoichiometric matrix is not exact, and this is always the case when components that do not play an important role in the process have been omitted to achieve a lower dimensional model, then these models are not described sufficiently accurate so that it is not clear whether they exhibit dynamical properties which are expected, for example boundedness of the trajectories. To overcome this problem, we introduced the concept of non-cyclic biotechnological processes. This is a restriction on the stoichiometric matrix, however, as far as we are aware, most papers on control of biotechnological processes satisfy this condition. We presented an algorithm which decides in finitely many steps whether a process is non-cyclic or cyclic. This algorithm is also essential when characterising non-cyclic processes in terms of permutations of columns and rows of the stoichiometric matrix K into an echelon form. The main consequence from this form is that non-cyclic processes exhibit bounded trajectories. These dynamical properties can be used to achieve adaptive setpoint control in non-cyclic processes. Preliminary results on this can be found in Ilchmann et al. [8].

APPENDIX

In the following we present some modifications of the Bellman-Gronwall Lemma which are tailored for our needs.

Lemma 19 *Let $\omega \in (0, \infty]$. Suppose $\alpha(\cdot), f(\cdot) : [0, \omega) \rightarrow \mathbb{R}$ are locally integrable functions and $V(\cdot) : [0, \omega) \rightarrow \mathbb{R}_+$ is absolutely continuous. If*

$$\dot{V}(t) \leq -\alpha(t) V(t) + f(t), \quad \text{for almost all } t \in [0, \omega), \quad (26)$$

then $V(t)$ satisfies the following:

- (i) *For all $t \in [t_0, \omega)$ and $t_0 \geq 0$,*

$$V(t) \leq e^{-\int_{t_0}^t \alpha(\tau) d\tau} V(t_0) + \int_{t_0}^t e^{-\int_s^t \alpha(\tau) d\tau} f(s) ds. \quad (27)$$

(ii) If $\alpha(\cdot)$ and $f(\cdot)$ satisfy, for some numbers $\underline{\alpha}, \bar{f}$,

$$0 < \underline{\alpha} = \operatorname{ess\,inf}_{t \in [0, \omega)} \alpha(t) \quad \text{and} \quad \operatorname{ess\,sup}_{t \in [0, \omega)} f(t) \leq \bar{f},$$

then, for all $t \in [t_0, \omega)$ and $t_0 \geq 0$,

$$V(t) \leq \left[V(t_0) - \frac{\bar{f}}{\underline{\alpha}} \right] e^{-\underline{\alpha}(t-t_0)} + \frac{\bar{f}}{\underline{\alpha}} \leq \max \left\{ V(t_0), \frac{\bar{f}}{\underline{\alpha}} \right\}. \quad (28)$$

If $\omega = \infty$, then

$$\limsup_{t \rightarrow \infty} V(t) \leq \frac{\bar{f}}{\underline{\alpha}}. \quad (29)$$

(iii) Suppose instead of (26) we have, for almost all $t \in [0, \omega)$,

$$\dot{V}(t) \geq -\alpha(t) \cdot V(t) + f(t), \quad (30)$$

then, for all $t \in [t_0, \omega)$ and $t_0 \geq 0$,

$$V(t) \geq e^{-\int_{t_0}^t \alpha(\tau) d\tau} V(t_0) + \int_{t_0}^t e^{-\int_s^t \alpha(\tau) d\tau} f(s) ds, \quad (31)$$

and if

$$0 < \bar{\alpha} = \operatorname{ess\,sup}_{t \in [0, \omega)} \alpha(t) \quad \text{and} \quad f_0 \leq \operatorname{ess\,inf}_{t \in [0, \omega)} f(t),$$

then, for all $t \in [t_0, \omega)$ and $t_0 \geq 0$,

$$V(t) \geq \left[V(t_0) - \frac{f_0}{\bar{\alpha}} \right] e^{-\bar{\alpha}(t-t_0)} + \frac{f_0}{\bar{\alpha}} \geq \min \left\{ V(t_0), \frac{f_0}{\bar{\alpha}} \right\}. \quad (32)$$

If $\omega = \infty$, then

$$\liminf_{t \rightarrow \infty} V(t) \geq \frac{f_0}{\alpha}. \quad (33)$$

Proof:

- (i) This part of the proof is a straightforward generalization of the proof of Lemma 3.2.4 in Ioannou and Sun [9], where they consider constant α, f and $\omega = \infty$ instead. Let

$$w(t) := \dot{V}(t) + \alpha(t)V(t) - f(t)$$

and apply Variation-of-Parameters to

$$\dot{V}(t) = -\alpha(t)V(t) + f(t) + w(t)$$

so that, for all $t \in [t_0, \omega)$ and $t_0 \geq 0$,

$$V(t) = e^{-\int_{t_0}^t \alpha(\tau) d\tau} V(t_0) + \int_{t_0}^t e^{-\int_s^t \alpha(\tau) d\tau} [f(s) + w(s)] ds,$$

and since $w(t) \leq 0$, (27) follows.

- (ii) Applying the bounds in (ii) to (27) yields

$$V(t) \leq e^{-\alpha(t-t_0)} V(t_0) + \int_{t_0}^t e^{-\alpha(t-s)} \bar{f} ds$$

and evaluating the integral leads to the first equation in (28).

Now if $V(t_0) < \bar{f}/\underline{\alpha}$, then $V(t) \leq \bar{f}/\underline{\alpha}$; and if $V(t_0) \geq \bar{f}/\underline{\alpha}$, then $V(t) \leq V(t_0)$. This proves the second inequality in (28).

(29) is an immediate observation from (28).

- (iii) The statements in (iii) are proved similarly and the proof is omitted for brevity.

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