Analysis and control of nonnegative polynomial systems

Nemnegatív polinomiális rendszerek analízise és irányítása

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Abstract

The analysis and feedback control of nonlinear systems have been continuously developing in recent decades, because of their practical importance and challenging theoretical nature. Kinetic systems are able to produce all the important qualitative phenomena present in nonlinear systems, so they form a dynamically rich-enough sub-class. It is well-known that the utilization of the physical and/or structural specialities of different nonlinear system classes greatly helps in obtaining theoretically well-grounded, powerful and practically still feasible analysis and control methods.

The realization theory of kinetic systems makes a connection between the structural properties and dynamical behaviour (e.g. complex balancedness, weak reversibility and deficiency). This makes it possible to develop efficient methods for their dynamical analysis. The greatest difficulty of the realization based system analysis is that a system model may have more than one realization.

In this thesis, an optimization-based approach is presented for the computation of kinetic realizations with zero deficiency. The problem is traced back to the solution of an appropriately constructed mixed integer linear programming problem. Furthermore, it is shown that weakly reversible deficiency zero realizations can be determined in polynomial time using standard linear programming.

Feedback design methods are also proposed in this thesis for nonnegative polynomial systems with linear input structure. These methods are based on the optimization based realization computation methods, because the key dynamical properties of the closed loop can be easily prescribed with optimization constraints. The proposed methods are extended to nonnegative polynomial systems with parametric uncertainty, too.

Finally, a class of delayed kinetic systems derived from mass action type reaction network models is introduced. The time delayed positive stoichiometric compatibility classes and the notion of complex balanced time delayed kinetic systems are defined. The semistability of the equilibrium solutions for complex balanced systems with arbitrary time delays is proved.

Zusammenfassung

Die Analyse und Feedback-Kontrolle der nichtlinearen Systeme hat sich in den letzten Jahrzehnten kontinuierlich aufgrund ihrer praktischen Bedeutung und der theoretischen Forderungen entwickelt. Die kinetische Systeme bilden eine breite, aber gut charakterisierbare Klasse der nichtlinearen Systeme und sie sind fähig, die wichtigste nichtlinierare Ereignisse zu beschreiben. Es ist aber auch bekannt, dass physische und/oder strukturelle Eigenschaften verschiedener nichtlinearen Systemklassen sind verwendbar zur Analyse des Systems und der Planung der Rückkoplung.

Die Realisationstheorie kinetischer Systeme stellt einen Zusammenhang zwischen den strukturellen Eigenschaften und dem dynamischen Verhalten her (z. B. komplex-ausgeglichene, schwache Reversibilität und Defizienz). Die Realisationstheorie ermöglicht eine dynamische Analyse durch effizienten Methoden. Die größte Schwierigkeit der realisierungsbasierten Systemanalyse besteht darin, dass ein Systemmodell über mehr als eine Realisierung verfügen kann.

In dieser Arbeit wird ein optimierungsbasierter Ansatz zur Berechnung von kinetischen Realisierungen mit Defizienz Null vorgestellt. Das Problem wird auf die Lösung eines entsprechend konstruierten gemischten ganzzahligen linearen Programmierproblems zurückgeführt. Weiterhin wird gezeigt, dass schwach reversible Defizienz-Null-Realisierungen in polynomieller Zeit unter Verwendung von linearer Standardprogrammierung bestimmt werden können.

In dieser Arbeit werden auch Rückkopplung-Design-Methoden für nichtnegative Polynomsysteme mit linearer Eingangsstruktur vorgeschlagen. Diese Methoden basieren auf den optimierungsbasierten Realisierungsberechnungsmethoden, da die dynamischen Schlüsseleigenschaften der geschlossenen Schleife leicht mit Optimierungsbeschränkungen verordnet werden können. Die vorgeschlagenen Methoden werden auch auf nichtnegative Polynomsysteme mit parametrischer Unsicherheit erweitert.

Abschließend wird eine Klasse von retardierten kinetischen Systemen vorgestellt, die von Reaktionsnetzmodellen des Massenaktionstyps abgeleitet sind. Die retardierten positiven stöchiometrischen Verträglichkeitsklassen und die Vorstellung von komplex-ausgeglichen retardierten kinetischen Systemen sind definiert. Die Semistabilität der Gleichgewichtslösungen für komplex-ausgeglichen Systeme mit beliebigen Zeitverzögerungen wurde nachgewiesen.

Összefoglalás

A nemlineáris rendszerek analízise és irányítása az elmúlt évtizedekben folyamatosan fejlődött, köszönhetően gyakorlati hasznosságának és az elméleti kihívásoknak. A kinetikai rendszerek a nemlineáris rendszerek egy tág, de jól karakterizált struktúrájú osztályát alkotják, és képesek a legfontosabb nemlineáris jelenségek leírására. Ugyanakkor jól ismert, hogy egy-egy rendszerosztály fizikai és/vagy strukturális tulajdonságai jól alkalmazhatóak a rendszer analízisére és irányítás tervezésére.

A kinetikus rendszerek realizáció alapú analízise kapcsolatot teremt a strukturális és a dinamikus tulajdonságok közt, ilyen speciális tulajdonságok a komplex egyensúly, gyengén reverzibilitás és a deficiencia. A realizáció alapú analízis lehetőséget teremt a rendszer dinamikus analízisére hatékony módszereken keresztül. A módszerek nehézsége, hogy egy rendszer modell több realizációval is rendelkezhet.

A dolgozatban optimalizáción alapuló kinetikus realizáció keresési módszerek kerülnek bemutatásra. Az első módszer a nullás deficienciájú realizáció keresés problémáját oldja meg kevert egészértékű lineáris programozás segítségével. A második módszer a gyengén reverzibilis nullás deficienciájú realizációk számítására alkalmas. Ez a probléma lineáris programozás segítségével került megfogalmazásra, ami polinom időben megoldható.

Továbbá a dolgozatban állapot visszacsatolás tervezési módszereket adunk lineáris bemenettel rendelkező nemnegatív polinomiális rendszerekhez. A visszacsatolás tervezése optimalizációs keretbe illeszthető, így a zárt rendszer legfontosabb dinamikus tulajdonságai könnyen előírható optimalizációs feltételek segítségével. A bemutatott módszer kiterjesztésre kerül parametrikusan bizonytalan rendszerekre is.

Végül bevezetésre kerül az időbeli késleltetéssel rendelkező kinetikus rendszerek osztálya. A pozitív sztöchiometrikus kompatibilitási osztályok és a komplex egyensúly tulajdonság kiterjesztésre kerül időbeli késleltetett esetre. A komplex egyensúlyi ponttal rendelkező kinetikus rendszereknek szemistabilitása bizonyításra kerül az időben késleltetett esetre.

Contents

Chapter 1

Introduction

The analysis and feedback control of nonlinear systems have been continuously developing in recent decades, because of their practical importance and challenging theoretical nature [38]. Within the class of smooth nonlinear systems, polynomial systems form a well-studied class that enable us to apply computationally efficient methods for their dynamic analysis and control [74], and at the same time, have practically important applications in the field of process, mechanical, or (bio)chemical etc. control. Within this class, nonnegative polynomial systems play an important role in the applications, where the value of the variables is nonnegative by nature (e.g. concentrations, pressures, number of items in a set etc.). It is important to note that any bounded operation domain of a general non-positive system can be easily shifted into the nonnegative orthant.

1.1 Background and motivation

Because of the challenges in dynamic analysis and control of nonlinear systems and the significance of kinetic systems as a special class allowing the development of efficient methods, the work reported in this thesis is built upon results from a range of interdisciplinary areas including systems and control theory, optimization and differential equations briefly outlined in the following paragraphs. These areas form the background of the results achieved.

Polynomial kinetic systems The class of kinetic systems was proved to be a useful representation of smooth nonnegative system models not only in biochemistry, but also in other areas like population or disease dynamics, process systems, and even transportation networks [24, 33, 57]. A network-based description is often advantageous to describe key properties of potentially large, complex systems with many components [56, 45]. Kinetic systems are naturally equipped with a network (i.e. directed graph) structure called the reaction graph, which is the abstraction of a set of chemical reactions, where the chemical complexes and reactions can be represented by vertices and directed edges, respectively.

The detailed balance property of a thermodynamic system, defined originally by Boltzmann

in the 19th century, means that at equilibrium, each elementary reaction step is equilibriated by the corresponding reverse reaction. A more general condition is complex balance, which requires that the signed sum of incoming and outgoing reaction rates at equilibrium is zero for each complex in a kinetic system [36, 28, 23]. It is worth remarking that complex balance does not depend on a particular equilibrium (if there exist multiple equilibria in a system), but it is a property of a chemical reaction network itself [37]. For a historical review of the notions of detailed and complex balance, see [31]. Generally, complex balance is related to both the structure and the parameters of kinetic systems. First, complex balance implies that each component of the reaction graph is strongly connected (i.e. the reaction network is weakly reversible) [37]. It is also important that deficiency zero weakly reversible reaction networks are complex balanced for any positive values of the reaction rate coefficients [27, 26]. However, complex balance becomes a parameter-dependent property when the deficiency of the network is higher than zero.

The main significance of complex balance in systems and control theory stands in its stability implications [51]. According to the Global Attractor Conjecture, complex balanced kinetic systems are globally stable in the positive orthant with a logarithmic Lyapunov function that does not depend on the model parameters. The conjecture was proved for several special cases such as one linkage class networks [14], and a possible proof for the general problem has recently appeared in [20].

In (bio)chemical applications, the system parameters (typically the reaction rate coefficients) are uncertain, and often only their order of magnitude is known. Therefore, one of the main aims of the theory of kinetic systems is to give conditions on the qualitative behaviour of kinetic models using mainly the stoichiometry and graph structure of reaction networks [37, 27]. In [27] and [26], the authors introduce the study of the dynamics of kinetic systems as a function of a parameter known as the deficiency, which is a nonnegative integer not depending on the rate coefficients. A classical result of kinetic systems with clear significance in nonlinear systems theory is the Deficiency Zero Theorem that establishes a robust stability property for deficiency zero reaction networks consisting of strongly connected reaction graph components [51].

It has been known for a long time, however, that the reaction network representation of a kinetic dynamics is generally not unique, i.e. reaction networks with different structures and/or different sets of chemical complexes may represent the same dynamics. This phenomenon is called macro-equivalence [37], confoundability [22] or dynamical equivalence [53], where the possible kinetic systems corresponding to the same dynamics are called realizations of a kinetic ODE model. The notion of linear conjugacy extends dynamical equivalence by allowing a positive diagonal linear transformation between the states of linearly conjugate realizations [39]. It is known, too, that important model properties such as deficiency, strong connectivity (also called weak reversibility), complex or detailed balance are realization dependent. Therefore, finding dynamically equivalent or linearly conjugate kinetic

systems with certain required properties is an interesting and important problem for proving qualitative properties of the model. It was shown that several sub-problems of this class can be successfully solved in the framework of linear and mixed integer linear programming (see, e.g. [53, 54, 40, 1]).

Feedback control The field of feedback controller design for nonlinear systems is an intensively studied area since the required control goals and performance often cannot be achieved using linear approaches, especially in the case of biologically motivated system models. It is well-known that the utilization of the physical and/or structural specialities of different nonlinear system classes greatly helps in obtaining theoretically well-grounded, powerful and practically still feasible control methods. We have sound methods of nonlinear feedback design for smooth input-affine systems [38], flat systems [65], Hamiltonian or port-Hamiltonian systems [19, 47], or that for Euler-Lagrange systems [44]. Utilizing the engineering insight into the physics and chemistry of the system, the thermodynamic passivity approach [66] as a special control approach has been proposed for nonlinear process systems that is based on controlling its inventories [67]. Further improvements of the physically motivated nonlinear controller design have been achieved by using passivity [68], control Lyapunov [69] and Hamiltonian approaches [70, 60, 46, 71] to nonlinear process systems.

Time delay systems It is known that important dynamical phenomena occurring in nature or in technological systems can often be explained in a satisfactory way by using explicit time-delays in the equations [34, 33].

In general, differential equations with time delay can produce much more complicated dynamics than ordinary differential equations. For example, a time delay may cause a stable equilibrium to become unstable, even if the dynamics is linear. Therefore, sophisticated methods are needed for stability analysis. One possible technique is based on the Lyapunov-Krasovskii functional which is an extension of the classical Lyapunov function [34].

Based on the results summarized in this section, the motivation of my work was to combine the above mentioned powerful but not related results to develop new methods and tools in analysis and control of nonnegative polynomial systems.

1.2 The aims of this work

Inspired by the above mentioned results in kinetic systems, feedback control and time delay systems, the aim of this work has been to develop computationally feasible methods for stability analysis and feedback controller design of nonnegative polynomial systems, where kinetic systems also belong. In particular, the following actual aims have been set for the work:

(i) to develop new and efficient methods for computing kinetic realizations with zero deficiency and combine them with algorithms for computing weakly reversible realizations,

(ii) to develop new and computationally effective methods for designing stabilizing feedback controllers for nonnegative polynomial systems,

(iii) to extend the classical stability result of kinetic system to the time delayed case.

1.3 The structure of this work

The known basic notions and tools of nonnegative and kinetic systems that are used in this thesis are briefly reviewed in Chapter 2. Then, new optimization based methods that enable to compute kinetic realizations with zero deficiency are described in Chapter 3. Thereafter in Chapter 4 we propose convex optimization based feedback design methods to stabilize nonnegative polynomial systems. New stability results of the kinetic systems with time delay are presented in Chapter 5. The main results of this thesis are summarized in Chapter 6. The notations and acronyms are in the Appendix.

Chapter 2

Theoretical background

This chapter is devoted to the notions and tools applied in the theory of *nonnegative polynomial systems*. The main emphasis is put on the most important subclass of nonnegative polynomial systems, being the mass action kinetic systems. The notations used in this chapter are mainly based on [27] and on [32].

2.1 Nonnegative polynomial systems

Let us consider a polynomial autonomous nonlinear system that can be described in the form

$$\dot{x}(t) = f(x(t)) = M \cdot \varphi(x(t)), \tag{2.1}$$

where $x(t) \in \mathbb{R}^n$ is the state variable, $M \in \mathbb{R}^{n \times l}$. The monomial mapping $\varphi : \mathbb{R}^n \mapsto \mathbb{R}^l$ is defined by

$$\varphi_i(x) = \prod_{j=1}^{n} x_j^{Q_{ji}}, \quad i = 1, \ldots, l, \tag{2.2}$$

where $Q \in \overline{\mathbb{Z}}_+^{n \times l}$.

The polynomial system (2.1) is called nonnegative if the nonnegative orthant is positively invariant, i.e if $x(0) \in \overline{\mathbb{R}}_+^n$ then $x(t) \in \overline{\mathbb{R}}_+^n$ for all $t > 0$.

The mapping f is *essentially nonnegative* if $f_i(x) \geq 0$ for all $i = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}_+^n$ such that $x_i = 0$. The polynomial system (2.1) is nonnegative if and only if f is essentially nonnegative [33].

2.2 Kinetic systems, their dynamics and structure

We follow the notation of [27]. A kinetic system consists of species, complexes and reactions between the complexes. The set of species is denoted by $\mathcal{X} = \{X_1, X_2, \ldots, X_n\}$. The set of complex generators is denoted by $\mathcal{K} \subset \overline{\mathbb{Z}}_+^n$ and has m elements. The complexes are

defined by the linear nonegative integer combination of the species, i.e $C_i = \sum_{j=1}[y_i]_j X_j$ where $y_i \in \mathcal{K}$ for $i = 1, \ldots, m$. Since a complex generator uniquely identifies a complex, we often refer to a complex with its complex generator. The set of reactions is denoted by $\mathcal{R} \subset \mathcal{K} \times \mathcal{K} \times \mathbb{R}_+$ and has r elements. Then, the kth reaction is defined as follows

$$C_k \xrightarrow{\kappa_k} C'_k, \tag{2.3}$$

where C_k and C'_k are the source and product complexes of the kth reaction, respectively and they are generated by their complex generators $y_k, y'_k \in \mathcal{K}$. The positive number $\kappa_k > 0$ is the reaction rate constant of the kth reaction. Each reaction can be described by the triplet $(y_k, y'_k, \kappa_k) \in \mathcal{R}$.

The time evolution of a kinetic system can be described by an ordinary differential equation where the state variables $x(t) \in \overline{\mathbb{R}}^n_+$ are the concentrations of the species. The ODEs are defined as follows

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left(x(t)\right)^{y_k} \left[y'_k - y_k\right], \qquad t \geq 0, \tag{2.4}$$

where $x(t) \in \overline{\mathbb{R}}^n_+$ is the state vector.

Simple example of an elementary reaction In this simple example, we describe the synthesis of water using a kinetic system model. The synthesis of water consists of one elementary reaction

$$2H_2 + O_2 \longrightarrow 2H_2O, \tag{2.5}$$

where H_2, O_2 and H_2O denote hydrogen, oxygen and water molecule with the corresponding species X_1, X_2 and X_3, respectively. We have 2 complexes C_1 and C_2 with their complex generator vectors $y_1 = \begin{bmatrix} 2 & 1 & 0 \end{bmatrix}^T$ and $y_2 = \begin{bmatrix} 0 & 0 & 2 \end{bmatrix}^T$, respectively. The kinetic system has only one reaction

$$C_1 \xrightarrow{\kappa} C_2, \tag{2.6}$$

and the corresponding ODEs are

$$\dot{x}(t) = \kappa x_1^2(t) x_2(t) \left(\begin{bmatrix} 0 \\ 0 \\ 2 \end{bmatrix} - \begin{bmatrix} 2 \\ 1 \\ 0 \end{bmatrix} \right), \tag{2.7}$$

where x_i denotes the concentration of the specie X_i for $i = 1, 2, 3$.

The reaction graph The structure of the kinetic system (2.4) is well characterized by a weighted directed graph, called the *reaction graph*. The weighted directed graph (or reaction graph) of kinetic systems is $G = (V, E)$, where $V = \{v_1, v_2, \ldots, v_m\}$ and $E \subseteq V \times V$ denote the set of vertices and directed edges, respectively. The vertex v_i corresponds to the ith complex C_i. In the reaction graph each reaction (y_k, y'_k, κ_k) is represented by a directed edge $e_k = (v_k, v'_k) \in E$ (also denoted by $v_k \mapsto v'_k$) where $v_k, v'_k \in V$ and the positive weight of the edge is $w(e_k) = \kappa_k$.

The reaction graph can be described by its adjacency matrix $A \in \mathbb{R}^{m\times m}$ such that its element $A_{i,j}$ is the weight of the edge when there is an edge from v_i to v_j, and zero when there is no edge. The Kirchhoff matrix $A_k \in \mathbb{R}^{m\times m}$ is a Metzler matrix with zero column sums, i.e. $[A_k]_{i,j} \geq 0$ for all $i \neq j$ and $\mathbf{1}^T A_k = \mathbf{0}$. When a reaction network is given by its adjacency matrix A, then its Kirchhoff matrix can be constructed such that

$$A_k = A^T - \operatorname{diag}(\mathbf{1}^T A^T). \tag{2.8}$$

In addition to the adjacency and Kirchhoff matrices of the system, one can characterize the reaction graph using its incidence matrix $D \in \{-1, 0, 1\}^{m\times r}$ where r is the number of reactions. Each reaction in the kinetic system is represented by the appropriate column of D as follows. Let the ℓ-th reaction in the kinetic system be $v_j \mapsto v_i$ for $1 \leq \ell \leq r$. Then the ℓ-th column vector of D is characterized as: $D_{i\ell} = 1$, $D_{j\ell} = -1$, and $D_{k\ell} = 0$ for $k = 1, \ldots, m$, $k \neq i, j$.

Realizability of polynomial systems A polynomial system (2.1) has a kinetic realization, if a suitable kinetic system can be constructed for it. The problem of kinetic realizability of polynomial ODE models was first examined and solved in [35] where it was shown, that the necessary and sufficient condition for kinetic realizability of a polynomial vector field is that all coordinates functions of f in (2.1) must have the form

$$f_i(x) = -x_i g_i(x) + h_i(x), \ i = 1, \ldots, n, \tag{2.9}$$

where g_i and h_i are polynomials with nonnegative coefficients. It is easy to prove that kinetic systems are nonnegative [33].

Another form of the ODE (2.4) In this thesis, we will use another equivalent representation of the differential equation (2.4) for computation purpose:

$$\dot{x}(t) = Y \cdot A_k \cdot \psi(x(t)), \tag{2.10}$$

where $Y \in \overline{\mathbb{Z}}_+^{n\times m}$ is the complex composition matrix, $\psi : \mathbb{R}^n \to \mathbb{R}^m$, $\psi_k(x) = x^{Y_{\cdot,k}}$ for all $k = 1, \ldots, m$ and $Y_{\cdot,k}$ denotes the kth column of the matrix Y. The matrix $A_k \in \mathbb{R}^{m\times m}$ is the Kirchhoff matrix of reaction network. Finally, the pair of matrices (Y, A_k) is called

the realization of the kinetic system. Note that the realization (Y, A_k) may not be unique. More details about it will be described later in Section 2.6.

2.3 Stoichiometric subspace and compatibility classes

The stoichiometric subspace is defined as

$$\mathcal{S} = \text{span}\left(\{y_k - y'_k \mid \text{ for all } k = 1, \ldots, r\}\right) = \text{im}(S), \tag{2.11}$$

where S denotes the stoichiometric matrix and it is defined as $S = YD$. The *rank* (or *dimension*) of a reaction network denoted by s is the dimension of the stoichiometric subspace.

The stoichiometric compatibility classes of a chemical reaction network are the following affine spaces

$$\mathcal{S}_p = (p + \mathcal{S}) \cap \overline{\mathbb{R}}^n_+, \tag{2.12}$$

where the elements of p are nonnegative. These classes are positively invariant sets of the dynamical system (2.4), i.e if $x(0) \in \mathcal{S}_p$ then $x(t) \in \mathcal{S}_p$ for all $t \geq 0$.

2.4 Weak reversibility, complex balance and deficiency

Important dynamic properties of a kinetic system depend on some of the structural properties of the reaction graph, most notably on its connectivity and its strong components.

A kinetic system is called *weakly reversible* if whenever there exists a directed path from v_i to v_j in its reaction graph, then there exists a directed path from v_j to v_i, too. In graph theoretic terms, this means that all components of the reaction graph are strongly connected components. A kinetic system is called *reversible*, if for each reaction $v_i \mapsto v_j$ there exists another (reverse) reaction $v_j \mapsto v_i$. It is well-known from the literature (see Theorem 3.1 of [30] and Proposition 4.1 of [27]) that a kinetic system is weakly reversible if and only if there is a strictly (elementwise) positive vector $p \in \mathbb{R}^m_+$ in the kernel of A_k, i.e. $A_k \cdot p = \mathbf{0}$.

The notion of complex balance originally comes from the study of the thermodynamic compatibility of reaction networks. An equilibrium point $\overline{x} \in \mathbb{R}^n_+$ of the system (2.4) is called *complex balanced* if for every $\eta \in \mathcal{K}$,

$$\sum_{k:\eta=y_k} \kappa_k(\overline{x})^{y_k} = \sum_{k:\eta=y'_k} \kappa_k(\overline{x})^{y_k}, \tag{2.13}$$

where the sum on the left is over all reactions for which η is the source complex and the sum on the right is over all reactions for which η is the product complex. An equivalent

condition is

$$A_k \cdot \psi(\overline{x}) = \mathbf{0}. \tag{2.14}$$

It is well-known [48] that if (2.4) has a positive complex balanced equilibrium $\overline{x}$, then any other positive equilibrium is complex balanced and the set of all positive equilibria $\mathcal{E}$ can be characterized by

$$\mathcal{E} = \{\tilde{x} \in \mathbb{R}^n_+ \mid \mathrm{Ln}(\tilde{x}) - \mathrm{Ln}(\overline{x}) \in \mathcal{S}^{\perp}\}. \tag{2.15}$$

It is an important result from the literature that complex balance implies weak reversibility, since the kernel condition of weak reversibility is fulfilled [36].

A simple example illustrating the notion of complex balanced equilibrium Let us consider the kinetic system defined by the following four reactions

$$2X_1 \xrightarrow{\kappa_1} X_2;\ X_2 \xrightarrow{\kappa_2} 2X_1;\ X_2 \xrightarrow{\kappa_3} X_3;\ X_3 \xrightarrow{\kappa_4} 2X_1. \tag{2.16}$$

The corresponding differential equations are

$$\begin{aligned} \dot{x}_1(t) &= -2\kappa_1 x_1^2(t) + 2\kappa_2 x_2(t) + 2\kappa_4 x_3(t), \\ \dot{x}_2(t) &= \kappa_1 x_1^2(t) - \kappa_2 x_2(t) - \kappa_3 x_2(t), \\ \dot{x}_3(t) &= \kappa_3 x_2(t) - \kappa_4 x_3(t). \end{aligned} \tag{2.17}$$

The system (2.17) has an equilibrium at

$$\overline{x} = \begin{bmatrix} 1 & \dfrac{\kappa_1}{\kappa_2 + \kappa_3} & \dfrac{\kappa_1 \kappa_3}{\kappa_4(\kappa_2 + \kappa_3)} \end{bmatrix}^T. \tag{2.18}$$

The equilibrium point (2.18) fulfils the condition of complex balance which in this case has the form

$$\begin{aligned} \kappa_1 \overline{x}_1^2 &= \kappa_4 \overline{x}_3, \\ \kappa_2 \overline{x}_2 + \kappa_3 \overline{x}_2 &= \kappa_1 \overline{x}_1^2, \\ \kappa_4 \overline{x}_3 &= \kappa_3 \overline{x}_2. \end{aligned} \tag{2.19}$$

Therefore, the equilibrium point (2.18) is complex balanced.

Deficiency δ is a fundamental property of a reaction network and it is defined as [26]:

$$\delta = m - l - s, \tag{2.20}$$

where m is the number of complexes (vertices) in the reaction graph, l is the number of linkage classes (graph components) and s is the rank of the reaction network. Another

equivalent definition of deficiency [15] is

$$\delta = \dim(\ker(Y) \cap \mathrm{im}(D)), \tag{2.21}$$

where Y is the complex composition matrix and D is the incidence matrix of the reaction network. It is easy to see from (2.20) and (2.21) that deficiency depends only on the complex composition matrix and the network structure (i.e. on the unweighted reaction graph), but not on the values of the reaction rate coefficients. The deficiency is a very useful measure for studying the dynamical properties of reaction networks and for establishing parameter-independent (at least) local stability conditions.

It is important to remark that weak reversibility, complex balance and deficiency are all realization-dependent properties and are not the inherent properties of the kinetic differential equations [40, 1]. This structural non-uniqueness will be utilized for realization computation in Chapter 3 and for feedback design in Chapter 4.

2.5 Qualitative dynamical properties of kinetic systems

A central problem of the kinetic systems is the relation between the network structure/ parametrization and the qualitative properties of the dynamics. From the numerous results and conjectures in the field, we only mention those that are directly related to this thesis.

According to the *Global Attractor Conjecture*, for any complex balanced kinetic system its equilibrium point $\overline{x}$ is a global attractor in the positive stoichiometric compatibility class $\mathcal{S}_{\overline{x}}$ [21]. Important special cases were proven in [14] and [63]. Moreover, the possible general proof of the conjecture has recently appeared in [20].

A fundamental result of the kinetic systems is the *Deficiency Zero Theorem* (Theorem 6.1.1 in [26]) that states the following

(i) If the network is not weakly reversible then, for arbitrary kinetics (not necessarily mass action), the differential equations for the corresponding reaction system cannot admit a positive steady state.

(ii) If the network is not weakly reversible then, for arbitrary kinetics (not necessarily mass action), the differential equations for the corresponding reaction system cannot admit a cyclic composition trajectory along which all species concentrations are positive.

(iii) If the network is weakly reversible then, for mass action kinetics (but regardless of the positive values the rate constants take), the differential equations for the corresponding reaction system have the following properties: There exists within each positive stoichiometric compatibility class precisely one steady state; that steady state is asymptotically stable; and there is no nontrivial cyclic composition trajectory along which all species concentrations are positive.

Part (iii) is proved by a known logarithmic Lyapunov function that is also independent of the rate coefficients and it has the form

$$V(x) = \sum_{i=1}^{n} (x_i(\ln(x_i) - \ln(\overline{x}_i) - 1) + \overline{x}_i), \tag{2.22}$$

where $\overline{x}$ is an equilibrium point. To connect the complex balance and the deficiency zero weak reversibility condition, we also recall from [36] and [28] that a mass action reaction network is complex balanced for any positive choice of rate constants if and only if it is weakly reversible and has a deficiency of zero.

2.6 Dynamically equivalent and linearly conjugate realizations

It is a known result of kinetic systems that a reaction graph corresponding to a given set of kinetic ODEs is generally not unique [22, 53]. Moreover, the kinetic realizability of a polynomial dynamical system is not coordinate-independent and it is preserved only up to the reordering and positive rescaling of the state variables [25].

Based on the above, a kinetic realization (Y, A'_k) is called *dynamically equivalent* to a kinetic system of the form (2.1) if A'_k is an $m \times m$ Kirchhoff matrix, and $Y \in \overline{\mathbb{Z}}_+^{n\times m}$ such that

$$M \cdot \varphi(x) = Y \cdot A'_k \cdot \psi(x), \quad \forall x \in \overline{\mathbb{R}}_+^n. \tag{2.23}$$

We note that the vector functions φ and ψ are not necessary identical, since the monomials corresponding to product complexes without any outgoing reaction do not appear in the kinetic differential equations.

Therefore, the concept of *linear conjugacy* was introduced in [39] that allows a positive diagonal transformation between the solutions of two kinetic systems. For our purposes, it is useful to introduce linear conjugacy in a slightly different way than it was described in [39]. For this, let us perform a state transformation on the kinetic model (2.1) as follows:

$$z(t) = T \cdot x(t), \tag{2.24}$$

where $T = \mathrm{diag}(c)$ with $c \in \mathbb{R}_+^n$. Then the differential equations of the transformed model are given by

$$\dot{z}(t) = T \cdot M \cdot \varphi(T^{-1}z(t)) = T \cdot M \cdot \mathrm{diag}(\varphi(c))^{-1} \cdot \varphi(z(t)). \tag{2.25}$$

Based on the above calculation, a kinetic realization (Y, A'_k) is called *linearly conjugate to a kinetic polynomial system* of the form (2.1) if there exists an $n \times n$ positive definite

diagonal matrix $T = \mathrm{diag}(c)$ with $c \in \mathbb{R}^n_+$ such that

$$T \cdot M \cdot \mathrm{diag}(\varphi(c))^{-1} \cdot \varphi(z) = Y \cdot A'_k \cdot \psi(z),\ \forall z \in \overline{\mathbb{R}}^n_+, \tag{2.26}$$

where $Y \in \overline{\mathbb{Z}}^{n\times m}_+$ and $\psi_j(x) = x^{Y_{\cdot,j}}$ for $j = 1, \ldots, m$. The matrix A'_k is an $m \times m$ Kirchhoff matrix. When we assume that $\psi(x) = \varphi(x)$ for all $x \in \mathbb{R}^n$ and using the notation $A_k = A'_k \cdot \mathrm{diag}(\psi(c))$, we can rewrite (2.26) as follows

$$Y \cdot A_k = T \cdot M, \tag{2.27}$$

where A_k is a Kirchhoff matrix, too, obtained by scaling the columns of A'_k by positive scalars. Therefore, A_k encodes the same reaction graph structure as A'_k. This implies that the weak reversibility and zero deficiency properties of the kinetic realizations (Y, A_k) and (Y, A'_k) are equivalent. It is also clear that Eq. (2.27) is a linear constraint with respect to A_k and the diagonal elements of T. Therefore, instead of A'_k, we will use the scaled matrix A_k for representing and computing linearly conjugate realizations.

2.7 Computing linearly conjugate realization using optimization

In this section, we are going to present how one can solve the problem of computing linearly conjugate realizations with optimization methods. For this we choose the problem of computing of the sparse and dense realizations [53]. Sparse realizations have minimum number of edges and a dense realization has maximum number of edges.

Let us consider the polynomial system (2.1). In the realization computation problem the matrix M and $\varphi(x)$ are given. The goal is to compute a realization (Y, A'_k) with the desired properties (e.g. weak reversibility, zero deficiency) and a diagonal transformation T.

Our optimization based methods assume that the monomials vector $\varphi(x)$ contains all the necessary monomials for the realization computation problem, so $\varphi(x) = \psi(x)$ for all $x \in \mathbb{R}^n$ and $\psi(x)$ is generated by the fixed complex composition matrix Y. *Note that the using of different complex sets results different realizations. Moreover, it is possible that the system* (2.1) *does not have realization with one set of complexes but it has a realization with another set of complexes. The canonical method [35] always constructs a realization for the system* (2.1) *when the condition* (2.9) *is fulfilled. Therefore, it can be used for generating a suitable initial set of complexes but no exact method exists for determining the set of complexes to a given problem.*

In the optimization problems we will use a fixed complex composition matrix Y to the linearly conjugate constraint (2.27) that remains linear as a consequence of it. We are going to use decision variables A_k to represent the Kirchhoff matrix of the realization and $T = \mathrm{diag}([c_1 \ldots c_n])$ to represent the diagonal transformation. First, we have to guarantee

the linear conjugacy as follows

$$\begin{aligned} &\mathrm{diag}([c_1 \dots c_n]) \cdot M = Y \cdot A_k, \\ &c_i > 0, \quad i = 1, \dots, m, \end{aligned} \tag{2.28}$$

where M contains the coefficients of the monomials in the polynomial ODE (2.1) that are given real numbers. *Note that the LP framework does not handle strict inequalities. Therefore, the constraints $c_i > 0$ can be replaced with $c_i \geq \epsilon$ for all $i = 1, \dots, n$ where ϵ is a small positive number.* Constraints of the Kirchhoff property are the following:

$$\begin{aligned} &\mathbf{1}^T A_k = 0, \\ &[A_k]_{i,j} \geq 0, \quad i, j = 1, \dots, m, \ i \neq j. \end{aligned} \tag{2.29}$$

We can introduce a binary matrix variable $\Theta \in \{0,1\}^{m \times m}$ such that $\Theta_{i,j}$ is 0 when $[A_k]_{i,j} = 0$ otherwise $\Theta_{i,j}$ is 1. This property can be given by linear inequalities as follows

$$\epsilon \cdot \Theta_{i,j} \leq [A_k]_{i,j} \leq U \cdot \Theta_{i,j}, \tag{2.30}$$

where ϵ is a small positive constant and U is the upper bound of values $[A_k]_{i,j}$. To reach the maximal (minimal) number of edges we have to maximize (minimize) the following objective function:

$$\sum_{i,j} \Theta_{i,j}. \tag{2.31}$$

The constraints (2.28)-(2.30) together with the objective function in (2.31) form a standard mixed integer linear programming (MILP) problem. Note, that the maximization of (2.31) corresponds to determining a dense realization, while minimization finds the sparse realization [53]. Finally, the Kirchhoff matrix of the linearly conjugate realization A'_k can be computed as $A'_k = A_k \cdot \mathrm{diag}(\psi(c))^{-1}$.

A simple example illustrating the notions of kinetic systems and their realizations Let us consider the following differential equation system in the form

$$\begin{aligned} \dot{x}_1(t) &= -5x_1(t) \\ \dot{x}_2(t) &= 5x_1(t) - x_2(t) + x_3(t) \\ \dot{x}_3(t) &= x_2(t) - x_3(t) - x_1(t)x_2(t)x_3^2(t) + 3x_1(t)x_2(t)x_3(t), \end{aligned} \tag{2.32}$$

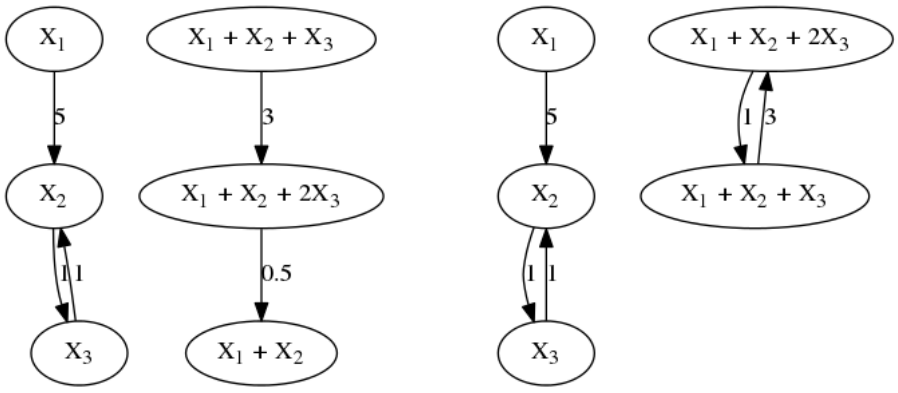
where $x_i(t)$ are the state variables for $i = 1, 2, 3$. The system (2.32) has (at least) two different dynamically equivalent realizations. The first one is

$$\dot{x} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 & 1 \\ 0 & 0 & 1 & 1 & 2 & 0 \end{bmatrix}}_{Y^{(1)}} \underbrace{\begin{bmatrix} -5 & 0 & 0 & 0 & 0 & 0 \\ 5 & -1 & 1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & -3 & 0 & 0 \\ 0 & 0 & 0 & 3 & -0.5 & 0 \\ 0 & 0 & 0 & 0 & 0.5 & 0 \end{bmatrix}}_{A_k^{(1)}} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_1x_2x_3 \\ x_1x_2x_3^2 \\ x_1x_2 \end{bmatrix}}_{\psi^{(1)}(x)}. \tag{2.33}$$

The second one is

$$\dot{x} = \underbrace{\begin{bmatrix} 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 2 \end{bmatrix}}_{Y^{(2)}} \underbrace{\begin{bmatrix} -5 & 0 & 0 & 0 & 0 \\ 5 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & -3 & 1 \\ 0 & 0 & 0 & 3 & -1 \end{bmatrix}}_{A_k^{(2)}} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_1x_2x_3 \\ x_1x_2x_3^2 \end{bmatrix}}_{\psi^{(2)}(x)}. \tag{2.34}$$

The realizations $(Y^{(1)}, A_k^{(1)})$ and $(Y^{(2)}, A_k^{(2)})$ have different complex sets and reaction network structures. The Fig. 2.1. depicts these two realizations, respectively.



(a) Realization $(Y^{(1)}, A_k^{(1)})$ (b) Realization $(Y^{(2)}, A_k^{(2)})$

Figure 2.1. Two different dynamically equivalent realizations of (2.32). Figures use of the notations of Section 2.2.

2.8 State feedback control of polynomial systems

Controllers are (possibly dynamical) external systems connected to the one to be controlled (the original or open-loop system) that are designed to achieve a control aim (or control goal) related to the dynamical behaviour of the original system by manipulating through its inputs (see e.g. [38]). The closed-loop system is a composite system consisting of the original system and its controller.

If the controller uses the state of the original system to compute its input, then a state feedback controller is considered. State feedback controllers are widely applied in control theory, because of their efficiency in both achieving stability of the closed-loop system (stabilizing controllers) and ensuring suitable control performance (for example disturbance rejection).

For the purpose of formulating the stabilizing state feedback controller design problem for nonnegative polynomial systems, one needs to consider the input-affine version of Eq. (2.1) as follows

$$\dot{x}_p(t) = f_p(x_p(t)) + g_p(x_p(t))u_p(t), \tag{2.35}$$

where $x_p(t) \in \mathbb{R}^{n_p}$ is the state variable, $u_p(t) \in \mathbb{R}^{r_p}$ is the input variable, $f_p : \mathbb{R}^{n_p} \mapsto \mathbb{R}^{n_p}$ and $g_p : \mathbb{R}^{n_p} \mapsto \mathbb{R}^{n_p \times r_p}$ are polynomial mappings. We are looking for a dynamic polynomial feedback controller in the form

$$\dot{x}_c(t) = f_c(x_p(t), x_c(t)), \quad u_p(t) = k(x_p(t), x_c(t)), \tag{2.36}$$

where $x_c(t) \in \mathbb{R}^{n_c}$ is the state of the controller, $f_c : \mathbb{R}^{n_p+n_c} \mapsto \mathbb{R}^{n_c}$ and $k : \mathbb{R}^{n_p+n_c} \mapsto \mathbb{R}^{r_p}$ are polynomial mappings. Then, the closed loop system has the form

$$\begin{bmatrix} \dot{x}_p(t) \\ \dot{x}_c(t) \end{bmatrix} = f(x_p(t), x_c(t)) = \begin{bmatrix} f_p(x_p(t)) + g_p(x_p(t))k(x_p(t), x_c(t)) \\ f_c(x_p(t), x_c(t)) \end{bmatrix}. \tag{2.37}$$

The closed loop system is polynomial, and it is nonnegative if and only if the mapping f is essentially nonnegative. The goal of the feedback control is transforming the open loop system into a closed loop system which has desired properties (e.g stability, performance, etc.).

Chapter 3

Computing zero deficiency realizations of kinetic systems

As it has been already discussed in Chapter 2, important model properties such as deficiency, strong connectivity (also called weak reversibility), complex or detailed balancedness are realization dependent but they have strong implications on the qualitative dynamic properties of the kinetic system. Therefore, finding dynamically equivalent or linearly conjugate kinetic system structures with certain required properties is an interesting and important problem for proving qualitative properties of the model.

It was shown earlier that several sub-problems of finding realizations with prescribed properties can be successfully solved in the framework of linear and mixed integer linear programming (see, e.g. [53, 54]). In [40] a MILP-based procedure was proposed for finding weakly reversible linearly conjugate realizations of kinetic systems with minimal deficiency. The algorithm was based on the result that for weakly reversible realizations, maximizing the number of reaction graph components minimizes the deficiency. This method uses integer variables for the partitioning of complexes between linkage classes. However, it is known that MILP problems are generally NP-hard and therefore it is often computationally problematic to solve large problems containing integer variables. Moreover, for general non-weakly reversible kinetic system structures, the basic principle of [40] can not be applied. Therefore, the approach of this chapter is chosen to be different, and the aim is to examine and use the special algebraic consequences of zero deficiency to give a general algorithm for computing such realizations of kinetic systems.

The structure of this chapter is the following. Section 3.1 contains the main result of this chapter that is an optimization based method for the computation of deficiency zero linearly conjugate kinetic realizations. In Section 3.2 two illustrative examples are shown, while Section 3.3 summarizes the contribution of this chapter.

3.1 Computing linearly conjugate zero deficiency realizations

In this section, two new optimization problems are introduced to compute realizations with zero deficiency. The first one works in the general case and it can be solved as an MILP problem. The second one finds weakly reversible zero deficiency realizations, and it can be traced back to an LP problem.

The basic setup for the computations in both cases will follow the problem formulation in Section 2.7. The known parameters are the coefficient matrix M of the ODE (2.1) and the used complex (monomial) set represented by the matrix Y. The decision variables to be computed are the scaled Kirchhoff matrix A_k of the linearly conjugate realization and the diagonal elements of the transformation matrix T. Additional auxiliary constants and decision variables (defined later) will also be used to solve the optimization problems.

3.1.1 Alternative conditions for zero deficiency

In this subsection, equivalent forms of the zero deficiency condition will be given that can directly be used in the framework of optimization.

The next theorem can be found as Lemma 5.8 in [27].

Theorem 1. *Let Y and D be the complex composition matrix and the reaction graph incidence matrix of a kinetic system, respectively. Then*
$\dim(\ker(Y) \cap \operatorname{im}(D)) = 0$ *if and only if*

$$\mathbb{R}^m = \operatorname{im}(Y^T) + \ker(D^T). \tag{3.1}$$

The next theorem was originally published as Corollary 4.11 in [27].

Theorem 2. *Let (Y, A_k) represent a kinetic system of deficiency zero. Then* $\ker(A_k) = \ker(Y \cdot A_k)$.

The following lemma is the immediate consequence of Corollary 4.6 in [27].

Lemma 1. *If A_k is weakly reversible then* $\operatorname{im}(D) = \operatorname{im}(A_k)$.

Using the above results, we can state the following theorem.

Theorem 3. *Let (Y, A_k) represent a weakly reversible kinetic system. Then (Y, A_k) has zero deficiency if and only if*

$$\ker(A_k) = \ker(Y \cdot A_k). \tag{3.2}$$

Proof. $\Rightarrow$ Let us suppose that (Y, A_k) is a weakly reversible kinetic system with zero deficiency. Then, by Lemma 1 we have that $\operatorname{im}(D) = \operatorname{im}(A_k)$. Substituting A_k into (2.21), we obtain that $\ker(Y) \cap \operatorname{im}(A_k) = \mathbf{0}$, from which it follows that $\ker(A_k) = \ker(Y \cdot A_k)$.

$\Leftarrow$ Now, let us assume that A_k is weakly reversible and $\ker(A_k) = \ker(Y \cdot A_k)$. The latter implies that

$$\ker(Y) \cap \mathrm{im}(A_k) = \mathbf{0}. \tag{3.3}$$

Due to weak reversibility, we can apply Lemma 1 and substitute $\mathrm{im}(D)$ for $\mathrm{im}(A_k)$ in (3.3). From this, we obtain that $\ker(Y) \cap \mathrm{im}(D) = \mathbf{0}$ that is equivalent to zero deficiency according to Eq. (2.21). $\square$

3.1.2 Computing linearly conjugate realizations with zero deficiency in the general (not necessarily weakly reversible) case

In order to put the zero deficiency property into the linear programming framework, we are going to reformulate Eq. (3.1) to the form of linear inequalities.

Eq. (3.1) is fulfilled if and only if there exist vectors $y^{(\ell)} \in \mathrm{im}(Y^T)$ and $\eta^{(\ell)} \in \ker(D^T)$, such that an arbitrary basis $\{\tilde{y}^{(\ell)}\}$ of $\ker(Y)$ can be constructed as

$$\tilde{y}^{(\ell)} = \eta^{(\ell)} + y^{(\ell)}\ ,\ \ell = 1, \ldots, m - \mathrm{rank}(Y). \tag{3.4}$$

Let us use the notation $W = \mathrm{im}(Y^T) + \ker(D^T)$. Clearly, if (3.1) holds then $\ker(Y) \subset W$, and therefore any basis of $\ker(Y)$ can be constructed according to Eq. (3.4). Assume now that an arbitrary basis of $\ker(Y)$ can be written as in Eq. (3.4). Then $\ker(Y) \subset W$. Since by construction $\mathrm{im}(Y^T) \subset W$, and $\mathrm{im}(Y^T)$ is the orthogonal complement of $\ker(Y)$, we obtain that $\mathbb{R}^m = \mathrm{im}(Y^T) + \ker(Y) \subseteq W$. Recall that $W \subseteq \mathbb{R}^m$, therefore $W = \mathbb{R}^m$.

Since the matrix Y is a priori given and constant, we can easily determine a basis $\{\tilde{y}^{(\ell)}\}$ of $\ker(Y)$. We can also generate an arbitrary element of $\mathrm{im}(Y^T)$ with the linear combination of the column vectors of Y^T as follows:

$$y^{(\ell)} = Y^T \cdot \alpha^{(\ell)}, \tag{3.5}$$

where $\alpha^{(\ell)} \in \mathbb{R}^n$.

Clearly, a vector $\eta^{(\ell)}$ is in the kernel of the matrix D^T if and only if

$$D^T \cdot \eta^{(\ell)} = \mathbf{0}. \tag{3.6}$$

Since D depends on A_k (i.e. it depends on the reaction graph of the realization), (3.6) is nonlinear in the optimization variables. Therefore, we will use the special structure of the matrix D to convert Eq. (3.6) to an equivalent form which can be inserted into MILP framework. Using the structure of the incidence matrix D, we can state the following theorem.

Theorem 4. *Eq.* (3.6) *can be equivalently represented by the following logical expression:*

$$[A_k]_{i,j} > 0 \implies \eta_i^{(\ell)} = \eta_j^{(\ell)},\ i, j = 1, \ldots, m. \tag{3.7}$$

Proof. $\Rightarrow$ Assume that $D^T \cdot \eta^{(\ell)} = \mathbf{0}$. Let us take the row v of D^T that corresponds to the directed edge $C_j \to C_i$ of the reaction graph. Then $v_i = 1$, $v_j = -1$ and $v_k = 0$ for $k \neq i, j$. Obviously, $v \cdot \eta^{(\ell)} = \eta_i^{(\ell)} - \eta_j^{(\ell)}$ which implies (since $\eta^{(\ell)}$ is in the kernel of D^T) that $\eta_j^{(\ell)} = \eta_i^{(\ell)}$. We repeat this for each directed edge of the reaction graph and the corresponding row of D^T. Then, clearly $[A_k]_{i,j} > 0$ implies $\eta_i^{(\ell)} = \eta_j^{(\ell)}$ using the properties of the Kirchhoff matrix A_k.
$\Leftarrow$ Assume that (3.7) is true. Take any (i, j) for which $[A_k]_{i,j} > 0$. According to (3.7) we have that $\eta_i^{(\ell)} = \eta_j^{(\ell)}$. Let us denote the row vector of D^T corresponding to the directed edge $C_j \to C_i$ by v. Then $v \cdot \eta^{(\ell)} = 0$. Repeating this for each directed edge of the reaction graph, we get that $D^T \cdot \eta^{(\ell)} = \mathbf{0}$. □

It is well-known that logical expressions can be expressed with linear inequalities and integer variables (see, e.g. [16]). For this purpose we introduce a binary matrix $\Theta \in \{0, 1\}^{m \times m}$ such that

$$[A_k]_{i,j} > 0 \implies \Theta_{i,j} = 1, \ \forall i, j = 1, \ldots, m. \tag{3.8}$$

The relation (3.8) can be expressed using the following equivalent linear inequalities:

$$[A_k]_{i,j} \leq U_1 \cdot \Theta_{i,j}, \ \forall i, j = 1, \ldots, m. \tag{3.9}$$

where $U_1 \in \mathbb{R}_+$ is the upper bound for $[A_k]_{i,j}$.

To ensure (3.7), we add the following logical expression in addition to (3.8)

$$\Theta_{i,j} = 1 \implies \eta_i^{(\ell)} = \eta_j^{(\ell)}. \tag{3.10}$$

Similarly to the above, (3.10) can also be described with linear inequalities that are the following:

$$| \ \eta_i^{(\ell)} - \eta_j^{(\ell)} \ | \leq 2 \cdot U_2(1 - \Theta_{i,j}), \tag{3.11}$$

where $U_2 \in \mathbb{R}_+$ is the upper bound of $| \ \eta_i^{(\ell)} \ |$.

Using the calculations described in Subsection 2.6, the sign and column-conservation properties of Kirchhoff matrices, and Eqs. (3.4), (3.5), (3.9), and (3.11), we can summarize the linear constraints for computing deficiency zero linearly conjugate realizations as follows.

$$
\begin{cases}
\mathrm{diag}([c_1 \ \dots \ c_n]^T) \cdot M = Y \cdot A_k \\
c_i > 0, \quad i = 1, \dots, n \\
\mathbf{1}^T \cdot A_k = \mathbf{0}^T \\
[A_k]_{i,j} \geq 0 \quad i, j = 1, \dots, m, \ i \neq j, \\
\tilde{y}^{(\ell)} = \eta^{(\ell)} + Y^T \cdot \alpha^{(\ell)}, \quad \ell = 1, \dots, m - \mathrm{rank}(Y) \\
[A_k]_{i,j} \leq U_1 \cdot \Theta_{i,j} \quad i, j = 1, \dots, m \\
\mid \eta_i^{(\ell)} - \eta_j^{(\ell)} \mid \leq 2 \cdot U_2(1 - \Theta_{i,j}) \quad i, j = 1, \dots, m, \quad \ell = 1, \dots, m - \mathrm{rank}(Y).
\end{cases} \tag{3.12}
$$

The known constants in (3.12) are M, Y, $\tilde{y}^{(\ell)}$ for $\ell = 1, \dots, m - \mathrm{rank}(Y)$, U_1 and U_2. The continuous decision variables are the off-diagonal elements of A_k, c_i for $i = 1, \dots, n$ (with $T = \mathrm{diag}([c_1 \ \dots \ c_n]^T)$), $\alpha^{(\ell)}$, and $\eta_i^{(\ell)}$ for $\ell = 1, \dots, m - \mathrm{rank}(Y)$ and $i = 1, \dots, m$. Additionally, $\Theta_{i,j}$ for $i, j = 1, \dots, m$ are the binary decision variables. The bound U_1 can be chosen as an arbitrary positive real number (e.g. it can be set to 1), because the matrices T and A_k can be scaled by any positive scalar in Eq. (2.27). If the constraint set (3.12) is reported to be infeasible by the applied solver, it is recommended to increase U_2 as long as the numerical tolerance of the solver permits, to maximize the feasibility domain.

The constraint set (3.12) is linear in the unknowns, therefore feasible solutions (if exist) can be found in the framework of mixed integer linear programming (MILP). Since the original problem to be solved can be traced back to the feasibility of the constraint set (3.12), the linear objective function f_{obj} can be chosen freely. Therefore, it can be used to ensure additional properties of the computed realizations. A simple choice can be the minimization of the L^1-norm of the off-diagonal elements of A_k, i.e.

$$
f_{obj} = \sum [A_k]_{i,j}, \ \text{for } i, j = 1, \dots, m, \ i \neq j. \tag{3.13}
$$

So-called dense or sparse solutions containing the maximal or minimal number of directed edges in the realization, respectively, can also be computed as it is described in e.g. [53] by modifying (3.8) to

$$
[A_k]_{i,j} > 0 \Longleftrightarrow \Theta_{i,j} = 1, \ \forall i, j = 1, \dots, m,
$$

and using the objective function $f_{obj} = \pm \sum_{i,j=1}^{m} \Theta_{i,j}$. But note that in this case, the constraint set (3.12) changes and becomes more complicated. We remark that the number of complexes of a kinetic realization can also be minimized using the MILP method described in [55] which can be considered as a kind of model reduction. This result is related to [64], where the number of complexes of a complex-balanced kinetic system is reduced while maintaining the complex balance property and keeping a strong relation between the equilibria of the original and the reduced system.

Example illustrating the condition (3.4) Let us consider a kinetic system given by the following realization

$$Y = \begin{bmatrix} 1 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 \end{bmatrix}, \quad A_k = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & -2 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \end{bmatrix}. \tag{3.14}$$

When A_k is fixed, we can define $\tilde{y}^{(\ell)}$ and $\eta^{(\ell)}$ as follows

$$\tilde{y}^{(1)} = \begin{bmatrix} -1 \\ 0 \\ -1 \\ 1 \\ 0 \end{bmatrix}, \quad \tilde{y}^{(2)} = \begin{bmatrix} -1 \\ -1 \\ 0 \\ 0 \\ 1 \end{bmatrix}, \quad \eta^{(1)} = \begin{bmatrix} a \\ a \\ b \\ b \\ b \end{bmatrix}, \quad \eta^{(2)} = \begin{bmatrix} c \\ c \\ d \\ d \\ d \end{bmatrix}, \tag{3.15}$$

where a, b, c, d are reals. Then, the realization (3.14) has zero deficiency if and only if condition (3.4) is fulfilled. In this example, the condition has the form

$$\begin{bmatrix} -1 \\ 0 \\ -1 \\ 1 \\ 0 \end{bmatrix} = \begin{bmatrix} a \\ a \\ b \\ b \\ b \end{bmatrix} + \alpha_1^{(1)} \begin{bmatrix} 1 \\ 0 \\ 0 \\ 1 \\ 1 \end{bmatrix} + \alpha_2^{(1)} \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \end{bmatrix} + \alpha_3^{(1)} \begin{bmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{bmatrix}, \tag{3.16}$$

and

$$\begin{bmatrix} -1 \\ -1 \\ 0 \\ 0 \\ 1 \end{bmatrix} = \begin{bmatrix} c \\ c \\ d \\ d \\ d \end{bmatrix} + \alpha_1^{(2)} \begin{bmatrix} 1 \\ 0 \\ 0 \\ 1 \\ 1 \end{bmatrix} + \alpha_2^{(2)} \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \end{bmatrix} + \alpha_3^{(2)} \begin{bmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 0 \end{bmatrix}. \tag{3.17}$$

The equations (3.16)-(3.17) have the solutions $a = -3$, $b = -5$, $\alpha_1^{(1)} = 2$, $\alpha_2^{(1)} = 3$, $\alpha_3^{(1)} = 4$ and $c = -1$, $d = 1$, $\alpha_1^{(2)} = 0$, $\alpha_2^{(2)} = 0$, $\alpha_3^{(2)} = -1$. Therefore, the realization (3.14) has zero deficiency.

3.1.3 Computing linearly conjugate weakly reversible realizations with zero deficiency

In this subsection, we are going to apply Theorems 2 and 3 to compute linearly conjugate weakly reversible realizations with zero deficiency as an LP problem. Let us now recall that a necessary and sufficient condition of weak reversibility is the existence of a strictly positive vector in $\ker(A_k)$. It is easy to see that $\ker(M) = \ker(T \cdot M)$ due to the invertibility of the transformation matrix T. If there is no strictly positive vector in $\ker(M)$ then it is trivial that there cannot be a positive vector in $\ker(A_k)$ since $T \cdot M = Y \cdot A_k$. Therefore, as a first step of the computation, we have to check that

$$\exists p \in \mathbb{R}^m_+ \text{ such that } M \cdot p = \mathbf{0} \tag{3.18}$$

is fulfilled.

If (3.18) holds, then we compute an arbitrary basis of $\ker(M)$ denoted by $\{\eta^{(i)}\}$, for $i = 1, \ldots, m - \text{rank}(M)$. Then, according to Theorem 3, there exists a weakly reversible zero deficiency linearly conjugate realization if and only if the constraint set

$$\begin{cases} \text{diag}([c_1 \ \ldots \ c_n]^T) \cdot M = Y \cdot A_k \\ c_i > 0, \quad i = 1, \ldots, n \\ \mathbf{1} \cdot A_k = \mathbf{0} \\ [A_k]_{i,j} \geq 0 \quad i, j = 1, \ldots, m, \ i \neq j, \\ A_k \cdot \eta^{(i)} = \mathbf{0}, \ i = 1, \ldots, m - \text{rank}(M) \end{cases} \tag{3.19}$$

is feasible. The known constants are M, Y and $\eta^{(i)}$ for $i = 1, \ldots, m - \text{rank}(M)$. The decision variables are the off-diagonal elements of A_k and the elements of the vector c. The constraint set (3.19) is clearly linear and it contains only continuous variables, therefore its feasibility can be decided in polynomial time using linear programming. The objective function f_{obj} to be minimized can be chosen as an arbitrary linear function of the decision variables here as well. A practical choice for f_{obj} can be the same as in (3.13) here, too.

If (3.18) holds, but the constraint set (3.19) is infeasible, then, according to Theorem 2, there is no deficiency zero linearly conjugate realization of the kinetic system (2.1) with the complex set given by Y.

The solutions for both (3.12) and (3.19) are parametrically not unique because of the possible scaling of Eq. (2.27) already mentioned in Subsection 3.1.2. By the *structural uniqueness* of a kinetic realization, we mean the uniqueness of its unweighted reaction graph. Matrix A_k of a feasible solution to either (3.12) or (3.19) is simply called a *feasible* A_k. The kinetic realization corresponding to a feasible $A_k^{(0)}$ is structurally unique if and only if there is no feasible $A_k^{(1)}$ that is structurally not equal to $A_k^{(0)}$. This can easily be checked through e.g. a series of optimization steps by adding extra linear constraints to (3.12) or (3.19).

3.2 Examples

In this section, two examples will be provided as case studies for the proposed methods. The algorithms were implemented in MATLAB [59] using the YALMIP modelling language [41]. The freely available GLPK package [58] was used to solve the emerging LP and MILP problems. It can be shown for both examples that there is no dynamically equivalent kinetic realization for the given dynamics with the complexes defined by matrix Y, but there exists a linearly conjugate deficiency zero realization.

3.2.1 Searching for a dynamically equivalent realization with zero deficiency

This example illustrates the general MILP approach described in Subsection 3.1.2. Let us consider a kinetic system of the form (2.1) characterized by the following complex composition matrix Y and the coefficient matrix M:

$$Y = \begin{bmatrix} 0 & 0 & 1 & 0 & 1 \\ 2 & 0 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 & 0 \end{bmatrix}, \quad M = \begin{bmatrix} 0 & 0 & -1 & 4 & -1 \\ -2 & 2 & 0.25 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 \end{bmatrix}.$$

The differential equations defined by M and Y are given by

$$\begin{aligned} \dot{x}_1(t) &= -x_1(t) + 4x_2(t) - x_1(t)x_2(t) \\ \dot{x}_2(t) &= -2x_2^2(t) + 2x_3(t) + 0.25x_1(t) \\ \dot{x}_3(t) &= x_2^2(t) - x_3(t). \end{aligned} \tag{3.20}$$

Now, by using the proposed method for the general (non-weakly-reversible) case we are able to determine a realization (Y, A'_k) which has zero deficiency and it is linearly conjugate to the kinetic system (Y, M) with $c_1 = 0.25, c_2 = 1, c_3 = 1$. The resulting kinetic system is given by (Y, A'_k), where the non-zero off-diagonal elements of the matrix A'_k are the following: $[A'_k]_{2,1} = 1$, $[A'_k]_{1,2} = 1$, $[A'_k]_{4,3} = 1$, $[A'_k]_{5,4} = 1$, $[A'_k]_{4,5} = 1$. The bounds were selected as $U_1 = U_2 = 10$. The non-weakly-reversible reaction graph of the obtained kinetic system is shown in Fig. 3.1. Thus, it follows from the Deficiency Zero Theorem that the corresponding kinetic system (3.20) has no positive steady states.

3.2.2 Computation of a weakly reversible deficiency zero structure

This example illustrates the LP approach described in Subsection 3.1.3 and clearly shows that the additional transformation parameters introduced by linear conjugacy might be necessary to find the desired kinetic structure. The starting kinetic system is given by the

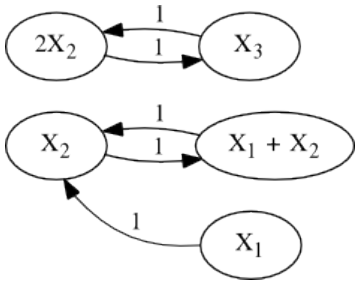


Figure 3.1. Reaction graph of the obtained realization in Subsection 3.2.1

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matrices Y and M as follows:

$$Y = \begin{bmatrix} 0 & 1 & 2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 2 & 0 \\ 0 & 0 & 0 & 1 & 0 & 2 \end{bmatrix}, \quad M = \begin{bmatrix} 1 & -1 & -1 & 1 & 0 & 0 \\ 0 & 2 & 0 & -2 & -2 & 2 \\ 0 & 1 & 0 & -1 & 1 & -1 \end{bmatrix}. \tag{3.21}$$

This representation is equivalent to the following differential equations

$$\begin{aligned} \dot{x}_1(t) &= 1 - x_1(t) - x_1^2(t) + x_2(t)x_3(t) \\ \dot{x}_2(t) &= 2x_1(t) - 2x_2(t)x_3(t) - 2x_2^2(t) + 2x_3^2(t) \\ \dot{x}_3(t) &= x_1(t) - x_2(t)x_3(t) + x_2^2(t) - x_3^2(t). \end{aligned} \tag{3.22}$$

A suitable basis of $\ker(M)$ is the following

$$\eta^{(1)} = \begin{bmatrix} 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \eta^{(2)} = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \quad \eta^{(3)} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 1 \end{bmatrix}. \tag{3.23}$$

It is easy to see that there exists a positive vector in $\ker(M)$, e.g. $p = \mathbf{1}$, so we can apply the LP method presented in Subsection 3.1.3. If we try to find a weakly reversible dynamically equivalent deficiency zero realization, we find that the constraints (3.19) are infeasible with $c_1 = c_2 = c_3 = 1$. However, we can find a weakly reversible realization which is linearly conjugate to the original system (3.21) with the transformation $T = \mathrm{diag}(2, 1, 2)$ that has zero deficiency. This kinetic realization is given by (Y, A'_k) where the Kirchhoff matrix A'_k has the following non-zero off-diagonal entries: $[A'_k]_{3,1} = 1$, $[A'_k]_{4,2} = 1$, $[A'_k]_{1,3} = 0.25$, $[A'_k]_{2,4} = 1$, $[A'_k]_{6,5} = 1$ and $[A'_k]_{5,6} = 0.25$. One can see the reversible reaction graph of this network in Fig. 3.2. Therefore, we obtain from the Deficiency Zero Theorem that the kinetic system (3.22) has precisely one locally asymptotically stable strictly positive

equilibrium point in each stoichiometric compatibility class.

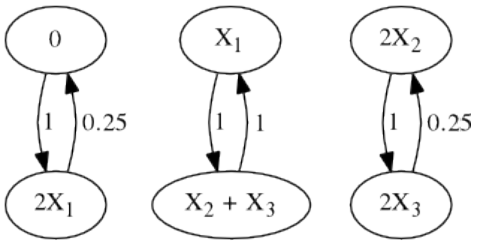


Figure 3.2. Reaction graph of the obtained realization in Subsection 3.2.2. This realization is weakly reversible and has zero deficiency.

3.3 Summary

Optimization-based methods were presented in this chapter for the computation of zero deficiency realizations of kinetic polynomial systems. Previously known algebraic conditions for zero deficiency and weak reversibility were re-formulated to be able to directly include them into the linear optimization framework. It was shown that with a given complex set, weakly reversible deficiency zero linearly conjugate realizations can be found in polynomial time using pure linear programming. It also follows from the computational approach that the existence of deficiency zero weakly reversible linearly conjugate realizations can be decided efficiently even for large kinetic systems. The general non-weakly-reversible deficiency zero case remained a MILP problem in the applied optimization framework.

The developed approach was illustrated through two computational examples, where it could be shown that linearly conjugate realizations indeed represent a wider system class than dynamically equivalent ones in the sense of possible structures.

Chapter 4

Kinetic feedback design for nonnegative polynomial systems

The control design of nonnegative polynomial systems has become an intensively studied topic recently (see e.g. [72]), that is explained by the great practical importance and wide expressive power of such systems [73, 74, 42, 75, 76].

The general purpose of our work in this area is to specialize the results of Section 2.8 to develop a design method for polynomial feedback controllers to nonnegative polynomial systems in order to achieve a kinetic closed loop system with given advantageous structural properties. The aim of this chapter is to propose a systematic approach for the convex optimization-based state feedback computation for nonnegative polynomial systems to achieve asymptotic stability utilizing the complex balanced property of the closed loop system.

The structure of this chapter is the following. In Section 4.1, the open loop system with parametric uncertainty is considered. In Section 4.2, the feedback law is formulated and in Section 4.3 a necessary set of the feedback monomials are determined in special cases. The feedback computation methods are based on convex optimization and the basic constraints are presented in Section 4.4. The design method of the feedback in the uncertain case is in Section 4.6. Constraints of the unique complex balanced equilibrium and the performance criteria are presented in Section 4.5. The proposed methods are demonstrated by a process system example and numerical examples in Section 4.7. Finally, the results of this chapter are summarized in Section 4.8.

4.1 Open loop model form

We assume for the feedback design that the equations of the open loop polynomial system with linear input structure are given as

$$\dot{x}_p(t) = M_p \cdot \psi_p(x_p(t)) + B_p \cdot u_p(t), \tag{4.1}$$

where $x_p(t) \in \overline{\mathbb{R}}_+^{n_p}$ is the plant state vector, $u_p(t) \in \mathbb{R}^{r_p}$ is the input and $\psi_p \in \mathbb{R}^{n_p} \to \mathbb{R}^{m_p}$ contains the monomials of the open-loop system generated by the matrix $Y_p \in \overline{\mathbb{Z}}_+^{n_p \times m_p}$. The coefficient and input matrices are $M_p \in \mathbb{R}^{n_p \times m_p}$ and $B_p \in \mathbb{R}^{n_p \times r_p}$, respectively.

Application for process systems It was shown in [2] that the open loop model (4.1) is able to describe an open process system originating from component molar balances when the inlet concentrations are used as manipulable inputs and the volume is stabilized to a steady-state value.

4.1.1 Parametric uncertainty in the open loop model

In this case, we assume that the coefficient matrix M_p is not known exactly, but it is an element of the polytopic set

$$\mathcal{M} = \{\sum_{i=1}^{L} \alpha_i M_p^{(i)} \;\; | \;\; (\forall i : \alpha_i \geq 0) \;\wedge\; \sum_{i=1}^{L} \alpha_i = 1\}, \tag{4.2}$$

where $M_p^{(i)} \in \mathbb{R}^{n_p \times m_p}$ for $i = 1 \ldots, L$ are the vertex points.

A simple example of the uncertainty described by Eq. (4.2) is the class of models, where the elements of M_p are assumed to belong to predefined intervals [61]. These intervals may easily come from parameter estimation as a result of uncertainty (covariance) analysis of the estimate, since model (4.1) is linear in the parameter matrix M_p. On the other hand, if the open-loop model (4.1) is a reaction network, and some uncertain reaction rate coefficients (i.e. the elements of matrix A_k) are modelled as intervals, we also obtain a polytopic model of the form (4.2) for matrix M_p.

4.2 The state feedback law

We assume a polynomial dynamic feedback of the form

$$u_p(t) = K \cdot \psi(x(t)), \tag{4.3}$$

where $x(t) = [x_p(t)^T \;\; x_c(t)^T]^T$ is the overall state vector with the *state of the controller* $x_c(t) \in \mathbb{R}^{n_c}$. The overall monomial vector is $\psi(x) = [\psi_p(x_p)^T \;\; \psi_c(x_p, x_c)^T]^T$ with $\psi_c : \mathbb{R}^{n_p+n_c} \to \mathbb{R}^{m_c}$ containing *possible additional monomials* for the feedback generated by the

matrix $Y_c \in \overline{Z}_+^{(n_p+n_c)\times m_c}$. In that case, the generator matrix of the overall monomial vector $Y \in \overline{\mathbb{Z}}_+^{(n_p+n_c)\times(m_p+m_c)}$ has the form

$$Y = \begin{bmatrix} Y_p & Y_{cp} \\ 0 & Y_{cc} \end{bmatrix}, \tag{4.4}$$

where $Y_c = \begin{bmatrix} Y_{cp}^T & Y_{cc}^T \end{bmatrix}^T$. The matrix $K \in \mathbb{R}^{r_p\times(m_p+m_c)}$ is a *constant feedback gain* to be computed. The state equations of the controller are

$$\dot{x}_c(t) = M_c \cdot \psi(x(t)). \tag{4.5}$$

Then, we can partition K and M_c into two blocks as $K = [K_p \; K_c]$ and $M_c = [M_{cp} \; M_{cc}]$ where $K_p \in \mathbb{R}^{r_p\times m_p}$, $K_c \in \mathbb{R}^{r_p\times m_c}$, $M_{cp} \in \mathbb{R}^{n_c\times m_p}$ and $M_{cc} \in \mathbb{R}^{n_c\times m_c}$. In that case the equations of the closed loop system are given by

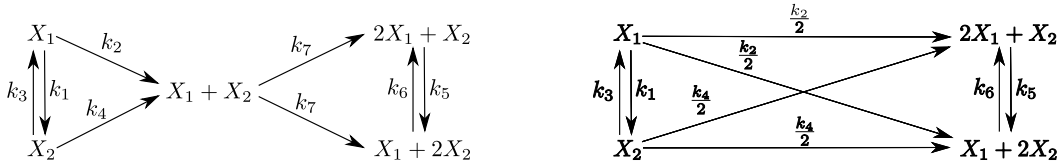
$$\dot{x}(t) = \begin{bmatrix} M_p + B_pK_p & B_pK_c \\ M_{cp} & M_{cc} \end{bmatrix} \cdot \begin{bmatrix} \psi_p(x_p(t)) \\ \psi_c(x_p(t), x_c(t)) \end{bmatrix} = M(K, M_c) \cdot \psi(x(t)), \tag{4.6}$$

where the closed loop coefficient matrix M has an affine dependence on K and M_c. *The aim of the feedback is choosing a suitable feedback gain K and feedback dynamics M_c such that the closed loop system* (4.6) *defines a kinetic system with prescribed properties (e.g. complex balance).* It is clear from Section 2.2 that this is possible if $M(K, M_c)$ can be factorized as $M(K, M_c) = Y \cdot A_k$ where $A_k \in \mathbb{R}^{(m_p+m_c)\times(m_p+m_c)}$ is a valid Kirchhoff matrix. In the following, let $n = n_p + n_c$ and $m = m_p + m_c$.

4.3 The effect of feedback structure on the closed loop dynamics

The results in this section show that involving new monomials (complexes) into the feedback law in (4.3) does not improve the solvability of the feedback problem from the point of view of weak reversibility, deficiency or complex balance. In the following, by *additional complexes*, we mean complexes corresponding to the monomials of ψ_c in (4.6). Therefore, a *closed loop system without additional complexes* means a controlled system of the form (4.6), where $K_c = \mathbf{0}$ and $M_c = \mathbf{0}$. Note that this is a technical solution in order to keep the dimension of the state vector and the Kirchhoff matrix of the closed loop system constant in the calculations. In this case, the complexes corresponding to ψ_c are naturally isolated in the reaction graph.

Lemma 2. *Consider the open loop system* (4.1) *and the feedback law* (4.3)*. Assume that there exists a closed loop system with feedback parameters K, M_c, and it has a realization (Y, A_k) where the jth complex C_j is an additional complex such that $[A_k]_{j,j} \neq 0$ (i.e. it is*



(a) Realization A_k (b) Realization A'_k

Figure 4.1. Realizations of the open loop system (4.8) with different feedbacks $u_p(t)$ and $u'_p(t)$. The realizations 4.1a and 4.1b correspond to the feedbacks $u_p(t)$ and $u'_p(t)$, respectively.

a source complex in at least one reaction). Then, there exist other feedback parameters K' and M'_c such that the corresponding closed loop system has a realization (Y, A'_k), where A'_k is given by

$$[A'_k]_{\cdot,i} = [A_k]_{\cdot,i} + \frac{[A_k]_{j,i}}{-[A_k]_{j,j}}[A_k]_{\cdot,j}, \quad \forall i. \tag{4.7}$$

Remark 1 It can be seen from (4.7) that the jth complex is isolated in the realization (Y, A'_k), since $[A'_k]_{j,i} = 0$ and $[A'_k]_{i,j} = 0$ for all i.

Remark 2 Before the proof, we illustrate the idea behind it by a simple example. Let us consider the following open loop system with a single input

$$\begin{aligned}
\dot{x}_{p_1}(t) &= k_3 x_{p_2}(t) - k_1 x_{p_1}(t) + k_4 x_{p_2}(t) - k_5 x_{p_1}(t)^2 x_{p_2}(t) + k_6 x_{p_1} x_{p_2}(t)^2 + u_p(t) \\
\dot{x}_{p_2}(t) &= k_1 x_{p_1}(t) + k_2 x_{p_1}(t) - k_3 x_{p_2}(t) + k_5 x_{p_1}(t)^2 x_{p_2}(t) - k_6 x_{p_1} x_{p_2}(t)^2 + u_p(t),
\end{aligned} \tag{4.8}$$

where x_{p_1}, x_{p_2} are the states, $k_1, k_2, \ldots, k_6$ are real parameters and $u_p(t)$ is the input. Let the additional monomial in the feedback be $\psi_c(x_p, x_c) = x_{p_1} x_{p_2}$. Then, we can give a feedback as follows

$$u_p(t) = k_7 x_{p_1}(t) x_{p_2}(t), \tag{4.9}$$

where k_7 is a real parameter. With this feedback (4.9) the closed loop system has a realization A_k such that the additional complex $X_1 + X_2$ has outgoing edges in the reaction graph. Furthermore, we can construct a feedback $u'_p(t)$ such that the corresponding realization A'_k fulfils (4.7). The constructed feedback has the form

$$u'_p(t) = 0.5 k_2 x_{p_1}(t) + 0.5 k_4 x_{p_2}(t). \tag{4.10}$$

The Fig. 4.1 compares the corresponding realizations A_k and A'_k.

Proof. It can be seen from (4.7) that the matrix A'_k is Kirchhoff, because the sum of its columns is zero and the off-diagonal elements are positive due to $[A'_k]_{j,i} = 0$ for all i.

First, we can write (4.7) in the following compact form

$$A'_k = A_k + \frac{1}{-[A_k]_{j,j}}[A_k]_{\cdot,j} \cdot [A_k]_{j,\cdot}. \tag{4.11}$$

Then, we can construct the feedback gain K' as

$$K' = K + \frac{1}{-[A_k]_{j,j}}K_{\cdot,j} \cdot [A_k]_{j,\cdot} \tag{4.12}$$

and the matrix M'_c as

$$M'_c = M_c + \frac{1}{-[A_k]_{j,j}}[M_c]_{\cdot,j} \cdot [A_k]_{j,\cdot}. \tag{4.13}$$

Then, the matrix M' is given by

$$M'(K', M'_c) = M(K, M_c) + \frac{1}{-[A_k]_{j,j}} \begin{bmatrix} B_p K \\ M_c \end{bmatrix}_{\cdot,j} [A_k]_{j,\cdot} \tag{4.14}$$

which can be written as

$$M'(K', M'_c) = Y \cdot A_k + \frac{1}{-[A_k]_{j,j}} Y \cdot [A_k]_{\cdot,j} \cdot [A_k]_{j,\cdot} = Y \cdot A'_k. \tag{4.15}$$

Therefore, $M'(K', M'_c)$ has the realization A'_k. □

Lemma 3. *Let A_k and A'_k be Kirchhoff matrices where the matrix A'_k is constructed by* (4.7). *Then* $\ker(A_k) \subseteq \ker(A'_k)$.

Proof. Let us take an element p of $\ker(A_k)$, then

$$p_j = \sum_{i \neq j} p_i \frac{[A_k]_{j,i}}{-[A_k]_{j,j}}. \tag{4.16}$$

Let us consider the product $A'_k \cdot p$:

$$\sum_{i=1}^{m} p_i [A'_k]_{\cdot,i} = \sum_{i \neq j} p_i [A_k]_{\cdot,i} + \sum_{i \neq j} p_i \frac{[A_k]_{j,i}}{-[A_k]_{j,j}} [A_k]_{\cdot,j}. \tag{4.17}$$

We can now substitute (4.16) into (4.17) to obtain

$$\sum_{i=1}^{m} p_i [A'_k]_{\cdot,i} = \sum_{i \neq j} p_i [A_k]_{\cdot,i} + p_j [A_k]_{\cdot,j} = 0 \tag{4.18}$$

that means $p \in \ker(A'_k)$. □

Theorem 5. *Consider the open loop system* (4.1) *and the feedback law* (4.3). *Then the*

following statements apply.

(a) If there exists a weakly reversible closed loop system (4.6) *with additional complexes, then there exists another weakly reversible closed loop system without additional complexes.*

(b) Suppose there exists a weakly reversible closed loop system (4.6) *with additional complexes and deficiency δ. Then there exists another weakly reversible closed loop system without additional complexes, and it has deficiency δ' such that $\delta' \leq \delta$.*

(c) Suppose there exists a complex balanced closed loop system (4.6) *with additional complexes and equilibrium points in the set $\mathcal{E}$. Then there exists another complex balanced closed loop system without additional complexes and it has equilibrium points $\mathcal{E}'$ such that $\mathcal{E} \subseteq \mathcal{E}'$.*

Proof. The proofs of the above statements are the following.

(a) If there exists a closed loop system with a weakly reversible realization (Y, A_k), then there exists another one with realization (Y, A'_k) where the additional complexes are isolated (Lemma 2) and $\ker(A_k) \subseteq \ker(A'_k)$ (Lemma 3.). A Kirchhoff matrix is weakly reversible if and only if there exists a positive vector in its kernel. Therefore, matrix A'_k is weakly reversible, too.

(b) If there exists a closed loop system with a weakly reversible realization (Y, A_k), then there exists another one with realization (Y, A'_k) where the additional complexes are isolated (Lemma 2). Let us denote the corresponding incidence matrices by D and D'. The columns of matrix D' are linear combinations of the columns of matrix D by construction. Therefore, $\mathrm{im}(D') \subseteq \mathrm{im}(D)$. By the definition of deficiency $\delta = \dim(\ker(Y) \cap \mathrm{im}(D))$ and $\delta' = \dim(\ker(Y) \cap \mathrm{im}(D'))$. So $\delta' \leq \delta$.

(c) If there exists a closed loop system with a weakly reversible realization (Y, A_k), then there exists another one with realization (Y, A'_k) where the additional complexes are isolated (Lemma 2) and $\ker(A_k) \subseteq \ker(A'_k)$ (Lemma 3.). According to the assumption, (Y, A_k) is complex balanced, therefore the set of equilibrium points of (4.6) can be described as $\mathcal{E} = \{x \mid A_k \cdot \psi(x) = \mathbf{0}\}$. Since, $\ker(A_k) \subseteq \ker(A'_k)$, then A'_k is complex balanced and $\mathcal{E} \subseteq \mathcal{E}'$.

□

The kinetic feedback structure The theoretical results described in this section can be summarized in the following simple statements to determine the structure of the kinetic feedback, if one wants to achieve complex balanced closed loop kinetic system, or a weakly reversible zero deficiency closed loop kinetic system.

1. It is not necessary to apply dynamic feedback to achieve complex balance or weak reversibility with zero deficiency for the closed loop system.

2. *It is sufficient to use only the monomials of the open loop system* (4.1) *in the monomial function* $\psi(x)$ *of the static feedback* (4.3).

However, increasing the degrees of freedom of the control design with additional state variables, monomials and the corresponding extra parameters using the general form (4.6) might be advantageous to achieve additional goals, such as improving the time-domain performance of the closed loop system.

4.4 The feedback design problem

Based on the structure of the open loop system and that of the polynomial feedback described before in Section 4.2, let us consider

- a polynomial system with linear constant parameter input-affine structure as the open loop system (4.1) with its parameter matrices (M_p, B_p, Y_p),
- and a polynomial feedback law (4.5) where the design parameters are K, M_c and Y_c.

The aim of the feedback is to set a region in the state space, where $\overline{x} \in \mathbb{R}^n_+$ is a (at least) locally asymptotically stable equilibrium point of the closed loop system. This will be achieved by computing a feedback with the parameters K and M_c such as the closed loop system has a complex balanced realization with a *given* equilibrium point $\overline{x}$.

The feedback design problem is solved by using different convex optimization frameworks such that linear programming (LP) and semidefinite programming (SDP). In the following, the basic set of constraints of the problem is presented.

4.4.1 The basic constraints

The first constraint is used to guarantee that the solution will be a kinetic realization of the closed loop system. It is in the form

$$M(K, M_c) = Y \cdot A_k, \tag{4.19}$$

where $A_k \in \mathbb{R}^{m\times m}$, $K \in \mathbb{R}^{r\times m}$ and $M_c \in \mathbb{R}^{n_c\times m}$ are decision variables of the problem and the overall complex composition matrix $Y \in \overline{\mathbb{Z}}^{n\times m}$ is given. Note that the matrix $M(K, M_c)$ depends on K and M_c affinely, so the constraint (4.19) is linear in the decision variables. The Kirchhoff property is required for matrix A_k, so the following constraints are included as well:

$$\mathbf{1}^T \cdot A_k = \mathbf{0}^T \tag{4.20}$$

$$[A_k]_{i,j} \geq 0 \quad i, j = 1, \ldots, m, \ i \neq j. \tag{4.21}$$

The resulting system (Y, A_k) should be complex balanced, which is ensured by the following constraint:

$$A_k \cdot \psi(\overline{x}) = \mathbf{0}, \tag{4.22}$$

that is a linear constraint in A_k, because the positive equilibrium point $\overline{x}$ is given before the optimization.

The basic constraints (4.19)-(4.22) are linear, so the basic design problem can be solved as a linear programming problem with an arbitrary linear objective function. The computed feedback (at least) locally stabilizes the equilibrium point $\overline{x}$ of the closed loop system in the region of the state space $\mathcal{S}_{\overline{x}} = (\overline{x} + \mathcal{S}) \cap \overline{\mathbb{R}}^n_+$, where $\mathcal{S}$ is the stoichiometric subspace of the closed loop system.

Note that we can neglect the additional monomials and the dynamic extension of the feedback law as a result of Section 4.3 in this simple design problem.

4.5 The design problem in the case of parametric uncertainty

In this section, the above feedback computation method will be extended by handling parametric uncertainty. The uncertainty is modelled by the polytopic set given in Eq. (4.2).

Lemma 4. *Let $\overline{x}$ be a joint complex balanced equilibrium point of the realizations $(Y, A_k^{(1)})$ and $(Y, A_k^{(2)})$. Then $\overline{x}$ is a complex balanced equilibrium point of the realization $(Y, A_k^{(3)})$ where $A_k^{(3)}$ is any convex combination of the matrices $A_k^{(1)}$ and $A_k^{(2)}$.*

Proof. It is clear that $A_k^{(3)}$ is a Kirchhoff matrix. Then we have to show that $A_k^{(3)} \cdot \psi(\overline{x}) = \mathbf{0}$ is fulfilled:

$$A_k^{(3)} \cdot \psi(\overline{x}) = (\lambda A_k^{(1)} + (1-\lambda) A_k^{(2)}) \cdot \psi(\overline{x}) = \mathbf{0}. \tag{4.23}$$

for any $\lambda \in [0, 1]$. □

The above convexity result shows that it is enough to compute a complex balanced realization $(Y, A_k^{(h)})$ with the joint equilibrium point $\overline{x}$ in each vertex $M_p^{(h)}$ ($h = 1, ..., L$ where L is the number of vertices of the convex set) with the same feedback parameters K and M_c. This gives the following *constraints*

$$\begin{cases} M^{(h)}(K, M_c) = Y \cdot A_k^{(h)} \\ \mathbf{1}^T \cdot A_k^{(h)} = \mathbf{0}^T \\ [A_k^{(h)}]_{i,j} \geq 0 \quad i, j = 1, \ldots, m, \ i \neq j \\ A_k^{(h)} \cdot \psi(\overline{x}) = \mathbf{0} \end{cases}, \tag{4.24}$$

where the closed loop coefficient matrix $M^{(h)}(K, M_c)$ corresponds to the case when $M_p = M_p^{(h)}$ and $h = 1, \ldots, L$. The feedback parameters K and M_c can be computed (if they exist) in an LP framework using the linear constraints (4.24) and an arbitrary linear objective function. The resulting feedback stabilizes the equilibrium point $\overline{x}$ of *all possible closed loop systems* in the region $\mathcal{S}_{\overline{x}} = (\overline{x} + \mathcal{S}) \cap \overline{\mathbb{R}}_+^n$, where $\mathcal{S}$ is the stoichiometric subspace of the closed loop system.

Note that in this simple design problem we can neglect the additional monomials and the dynamic extension of the feedback law as a result of Section 4.3.

4.6 Satisfying performance criterion and uniqueness of equilibrium

In this section, additional properties and possibilities of the basic feedback design problem (which is presented in Section 4.4) will be described.

4.6.1 Uniqueness of the complex balanced equilibrium

First, let us consider the following results about characterizing the stoichiometric subspace by a semidefinite matrix. The direct consequence of this result is the uniqueness of the complex balanced equilibrium point.

Lemma 5. *Let us consider a complex balanced kinetic system (Y, A_k) with its positive equilibrium point $\overline{x}$. Then the matrix $Y(A_k diag(\overline{x}) + diag(\overline{x})A_k^T)Y^T$ is negative-semidefinite and satisfies*

$$\mathrm{im}(Y(A_k diag(\overline{x}) + diag(\overline{x})A_k^T)Y^T) = \mathcal{S}. \tag{4.25}$$

Proof. The matrix $-(A_k \mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)$ is a balanced and symmetric Laplacian matrix which is positive-semidefinite ([80]). Therefore, the matrix $Y(A_k \mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T$ is negative-semidefinite. Then Eq. (4.25) is a direct consequence of the Theorem 4.3.3 in the paper [62]. □

The following theorem is a direct consequence of Lemma 5. It gives a negative-definite condition of the full dimensional stoichiometric subspace in the complex balanced case.

Theorem 6. *Let us consider a complex balanced kinetic system (Y, A_k) with its positive equilibrium point $\overline{x}$. Then, $\mathcal{S} = \mathbb{R}^n$ if and only if*

$$Y(A_k diag(\overline{x}) + diag(\overline{x})A_k^T)Y^T < 0. \tag{4.26}$$

Proof. $\Rightarrow$ If $\mathrm{im}(\mathrm{im}(Y(A_k \mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T)) = \mathbb{R}^n$, then $Y(A_k \mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T$ is invertible. Therefore, $Y(A_k \mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T$ is negative-definite.

$\Leftarrow$ If $Y(A_k\mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T$ is negative-definite, then it is invertible. Therefore, $\mathrm{im}(Y(A_k\mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T) = \mathbb{R}^n$. □

Choosing the monomials of the feedback In this special full dimensional stoichiometric subspace case, the results of Section 4.3 are not valid anymore. Therefore, we have to have a strategy to determine the new monomials of the feedback $\psi_c(x)$. In the case of $\mathcal{S} = \mathbb{R}^n$, a *necessary condition* is

$$\mathbb{R}^n = \mathrm{span}\left(\{Y_{\cdot,i} - Y_{\cdot,j} \mid \forall i \neq j\}\right), \tag{4.27}$$

where $Y_{\cdot,i}$ is the ith column of the common complex composition matrix Y which contains Y_p and Y_c. When Eq. (4.27) is not fulfilled, then there does not exist a closed loop system which satisfies the condition $\mathcal{S} = \mathbb{R}^n$ but the introduction of suitable new complexes (i.e. new columns of Y_c) are needed.

It is important to note that the choice of the new monomials is generally not unique, and it has an impact on the achievable control performance. Therefore, the selection of the new monomials is an important degrees of freedom of the proposed feedback design method.

Semidefinite constraint of the uniqueness of the equilibrium We can guarantee the uniqueness of the desired equilibrium point $\overline{x}$ with setting the stoichiometric subspace $\mathcal{S} = \mathbb{R}^n$. This can be formulated as a semidefinite constraint (see Theorem 6.)

$$Y(A_k\mathrm{diag}(\overline{x}) + \mathrm{diag}(\overline{x})A_k^T)Y^T < 0. \tag{4.28}$$

4.6.2 Additional performance condition

Since the constraint set is formulated in a way that all the solutions are guaranteed to be complex balanced with $\mathcal{S} = \mathbb{R}^n$, we can be sure that all eigenvalues of the closed loop system have negative real parts. Hence, a suitable performance of the feedback design can be achieved by minimizing the largest eigenvalue of the linearised closed loop system

$$\min\left\{\mathrm{Re}(\lambda_{\max}(YA_k\mathrm{diag}(\overline{x})Y^T\mathrm{diag}(\overline{x})^{-1}))\right\}, \tag{4.29}$$

where $\lambda_{\max}$ denotes the eigenvalue of its argument with the largest real part.

In the general case, the problem (4.29) is a non-smooth optimization problem. Therefore, we consider the relaxed version (proposed in the paper [17]) of the above objective (4.29):

$$\min\left\{\lambda_{\max}(YA_k\mathrm{diag}(\overline{x})Y^T\mathrm{diag}(\overline{x})^{-1} + \mathrm{diag}(\overline{x})^{-1}Y\mathrm{diag}(\overline{x})A_k^TY^T)\right\}. \tag{4.30}$$

This objective contains a symmetric matrix in the argument, therefore its eigenvalues are negative real numbers.

Using the above relaxed objective a semidefinite programming problem can be formulated for the feedback design as follows:

$$\min -t \tag{4.31}$$

subject to

$$YA_k\mathrm{diag}(\overline{x})Y^T\mathrm{diag}(\overline{x})^{-1} + \mathrm{diag}(\overline{x})^{-1}Y\mathrm{diag}(\overline{x})A_k^TY^T + tI \leq 0, \tag{4.32}$$

where t is a variable of the optimization. Choosing larger t values leads to solutions with smaller $\lambda_{\max}$ values and hence to closed loop systems with faster local convergence.

By putting together the constraints described in (4.19)-(4.22), (4.28), (4.32) and considering (4.31) as the objective function, the semidefinite optimization problem can be constructed. The decision variables of the optimization are the Kirchhoff matrix A_k, the set of feedback parameters K and M_c and the auxiliary variable t.

Note that the formulated optimization problem may not be feasible. In this case we can try to choose additional monomials in the polynomial feedback to make the problem feasible.

4.7 Case studies

In this section, we present the applicability of the proposed design technique on three different examples. The first one is a simple process example where the basics control design method is used. The second one demonstrates the robust design method which is an LP problem. The third one shows the case when the closed loop system has to have only one positive equilibrium point with the presented performance criteria. The algorithms were implemented in [79] using the YALMIP modelling language [78]. The solver reported in [77] was used to solve the LP and the SDP problems.

4.7.1 A process control example

Let us consider an open process system in which the chemical reactions

$$2X_1 + X_3 \mapsto X_1 + X_2 \quad , \quad X_1 + X_2 \mapsto X_1 + 2X_3 \quad , \quad X_1 + 2X_3 \mapsto X_1 + X_2$$
$$X_1 + 2X_2 \mapsto X_1 + X_2 \quad , \quad X_1 + 2X_2 \mapsto X_1 + 2X_3$$

take place under isothermal conditions, where all the reaction rate constants are equal to one. Let us choose the inlet concentrations of the species X_1 and X_2 as input variables and assume constant volume in the open chemical reaction network.

Then the open loop system model is in the following form

$$\dot{x}_p(t) = \underbrace{\begin{bmatrix} -1 & 0 & 0 & 0 & -1 & 0 & 0 \\ 1 & -1 & -3 & 1 & 0 & -1 & 0 \\ -1 & 2 & 2 & -2 & 0 & 0 & -1 \end{bmatrix}}_{M_p} \cdot \underbrace{\begin{bmatrix} x_{p_1}^2(t)x_{p_3}(t) \\ x_{p_1}(t)x_{p_2}(t) \\ x_{p_1}(t)x_{p_2}^2(t) \\ x_{p_1}(t)x_{p_3}^2(t) \\ x_{p_1}(t) \\ x_{p_2}(t) \\ x_{p_3}(t) \end{bmatrix}}_{\psi_p(x_p(t))} + \underbrace{\begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}}_{B_p} u_p(t). \quad (4.33)$$

We are looking for the nonnegative feedback gain K which transforms the system into a complex balanced one with the desired equilibrium point $\overline{x} = [1\ 1\ 1]^T$.

The computed feedback gain is

$$K = \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix}, \quad (4.34)$$

and the corresponding feedback is

$$u_{p_1}(t) = x_{p_1}(t) + x_{p_3}(t) \quad (4.35)$$

$$u_{p_2}(t) = x_{p_1}^2(t)x_{p_3}(t) + x_{p_2}(t) + x_{p_3}(t). \quad (4.36)$$

The above equation (4.36) ensures the nonnegativity of the input variables, that are the inlet concentrations of X_1 and X_2.

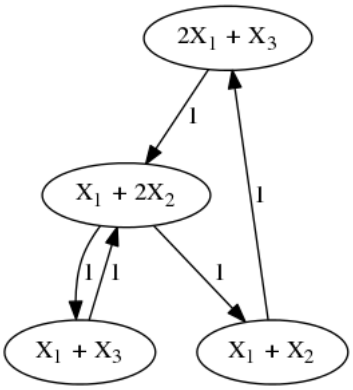


Figure 4.2. Complex balanced realization of the closed loop process example (of Subsection 4.7.1).

The closed loop system has a complex balanced realization which is depicted in Fig. 4.2. The dimension of the stoichiometric subspace of the closed loop system is 3, so it has only one positive equilibrium point $\overline{x} = [1\ 1\ 1]^T$ which is locally asymptotically stable.

Fig. 4.3. shows the time domain simulation under different initial conditions. The solutions asymptotically converge to the desired equilibrium.

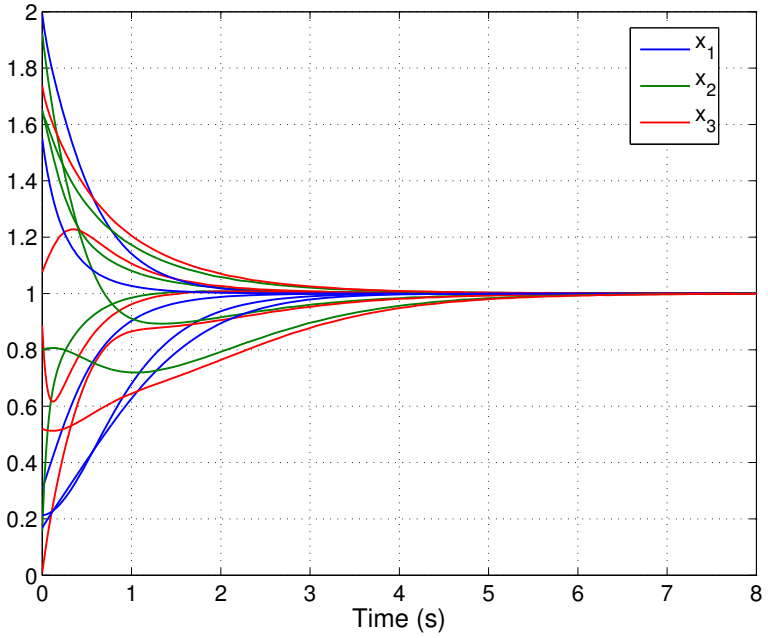


Figure 4.3. Time domain simulation of closed loop system (of Subsection 4.7.1) with five different initial values. The blue, green, and red lines show the state variables x_{p_1}, x_{p_2} and x_{p_3}, respectively.

4.7.2 Robust, complex balanced closed loop

In this numerical example, the robust design case is considered, when the uncertain coefficient matrix of a polynomial system is characterized as the convex combination constant matrices of appropriate dimensions. Let the open loop system be given as

$$\dot{x}_p(t) = M_p \underbrace{\begin{bmatrix} x_{p_1}(t)x_{p_2}(t) \\ x_{p_2}(t)x_{p_3}(t) \\ x_{p_1}(t) \end{bmatrix}}_{\psi_p(x_p(t))} + \underbrace{\begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}}_{B_p} u_p(t), \tag{4.37}$$

where M_p is the arbitrary convex combination of the following three matrices

$$M_p^{(1)} = \begin{bmatrix} -1 & 1 & 0 \\ 2 & 1 & 2 \\ 1 & -1 & 0 \end{bmatrix}, \quad M_p^{(2)} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 1 & 3 \\ 0 & 0 & 0 \end{bmatrix}, \quad M_p^{(3)} = \begin{bmatrix} 0 & 1 & -1 \\ 2 & 0 & 3 \\ 0 & -1 & 1 \end{bmatrix}.$$

Let the desired equilibrium point be chosen as $\overline{x} = [1\ 1\ 1]^T$. Then, we are looking for a feedback law with the gain K that transforms the systems characterized by the matrices

$M_p^{(i)}$ into a complex balanced kinetic system with the given equilibrium point.

By solving the feedback design LP optimization problem using the linear constraints (4.24), we obtain the following feedback

$$u_p(t) = -2x_{p_1}(t)x_{p_2}(t) - x_{p_2}(t)x_{p_3}(t) - 2x_{p_1}(t). \tag{4.38}$$

Fig. 4.4. depicts the complex balanced realization of the closed loop system when the parameters of the system are $M_p = 0.6M_p^{(1)} + 0.2M_p^{(2)} + 0.2M_p^{(3)}$. The stoichiometric subspace considering these parameters is the following

$$\mathcal{S} = \text{span}\left(\begin{bmatrix} -1 \\ 0 \\ 1 \end{bmatrix}, \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \right). \tag{4.39}$$

Thus, the equilibrium point $\overline{x}$ will be asymptotically stable in the region $\mathcal{S}_{\overline{x}} = (\overline{x} + \mathcal{S}) \cap \overline{\mathbb{R}}_+^n$. Therefore, if the initial value is chosen from the set $\mathcal{S}$, then the corresponding solution will converge to the desired equilibrium point $\overline{x}$. Fig. 4.5 shows the time domain behaviour of the closed loop system with randomly sampled parameters from the convex set $\mathcal{M}$.

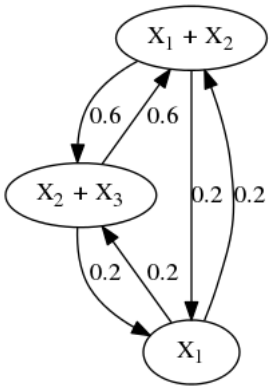


Figure 4.4. Complex balanced realization of the closed loop system (of Subsection 4.7.2) in the case $M_p = 0.6M_p^{(1)} + 0.2M_p^{(2)} + 0.2M_p^{(3)}$.

4.7.3 Example with performance tuning

In this subsection, the proposed design method for achieving additional performance criteria is demonstrated by a computational example. Two different choices of new monomials in the feedback are also given to illustrate the effect of this choice on the closed loop dynamic behaviour.

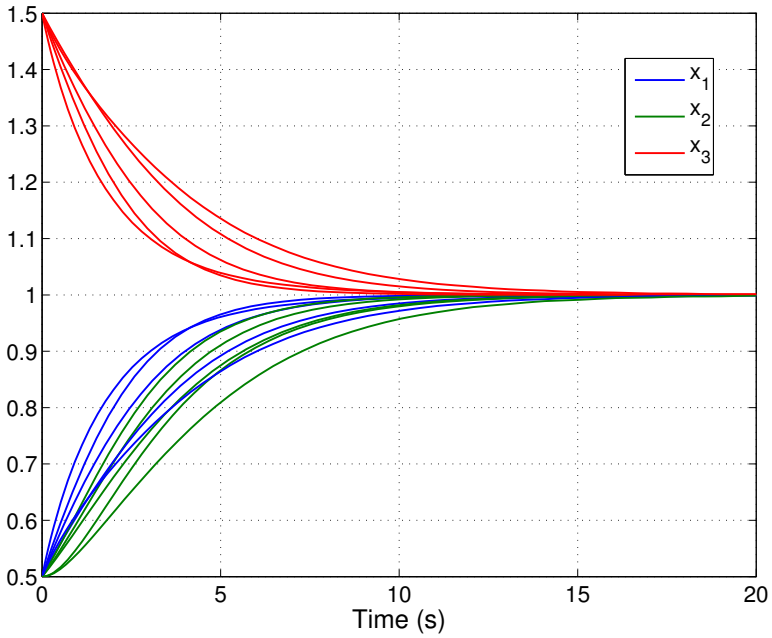


Figure 4.5. Time domain simulation of the closed loop system (of Subsection 4.7.2) with randomly sampled parameters from the convex set $\mathcal{M}$. The simulations are started from the initial value $x_0 = [0.5\ 0.5\ 1.5]$. The blue, green, and red lines show the state variables x_{p_1}, x_{p_2} and x_{p_3}, respectively.

Let the open loop system be given as

$$\dot{x}_p(t) = \underbrace{\begin{bmatrix} 5 & -5 & -3 \\ 4 & 3 & -5 \\ -1 & 0 & 2 \end{bmatrix}}_{M_p} \underbrace{\begin{bmatrix} x_{p_1}(t)x_{p_2}(t)x_{p_3}(t) \\ x_{p_1}^2(t)x_{p_2}(t) \\ x_{p_1}(t)x_{p_2}^2(t) \end{bmatrix}}_{\psi_p(x_p(t))} + \underbrace{\begin{bmatrix} 1 \\ 1 \\ 0 \end{bmatrix}}_{B_p} u_p(t). \tag{4.40}$$

The open loop model without the input is unstable and does not have any complex balanced realization. Let the desired equilibrium point be chosen as $\overline{x} = [1\ 2\ 4]^T$. It is easy to see that condition (4.27) is not fulfilled. Therefore, we have to choose new monomials to be able to achieve $\mathcal{S} = \mathbb{R}^n$.

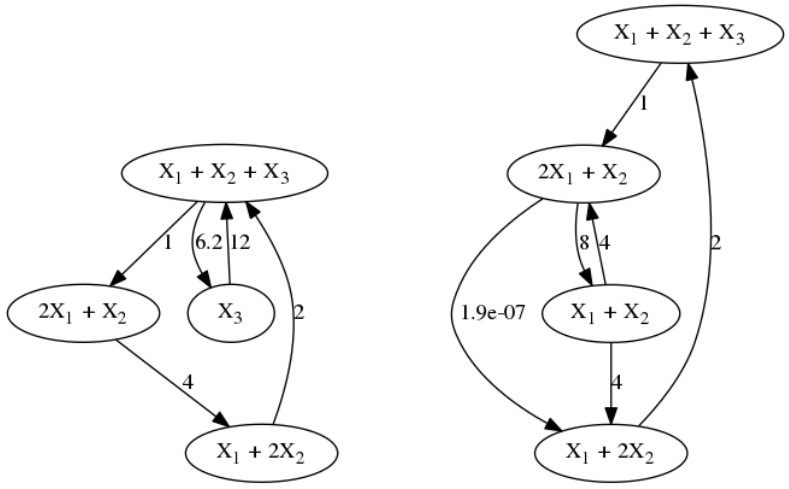
Now, let us apply the feedback design method which is proposed in Section 4.6. The optimization problem is described by (4.19)-(4.22), (4.28), (4.32) and the objective function is (4.31). The problem is solved in two different cases where the additional monomials are $\psi_c^{(1)}(x_p) = x_{p_3}$ and $\psi_c^{(2)}(x_p) = x_{p_1}x_{p_2}$. The computed feedback gains are the followings:

$$K^{(1)} = \begin{bmatrix} -10.1912 & 1.0000 & 3.0000 & 12.3824 \end{bmatrix}, \tag{4.41}$$

and

$$K^{(2)} = \begin{bmatrix} -4.0000 & -3.0000 & 3.0000 & 4.0000 \end{bmatrix}. \tag{4.42}$$

The closed loop systems are complex balanced with the equilibrium point $\overline{x}$. The complex balanced realizations of the two closed loop systems are depicted in Fig. 4.6.



(a) The realization $(Y^{(1)}, A_k^{(1)})$ (b) The realization $(Y^{(2)}, A_k^{(2)})$

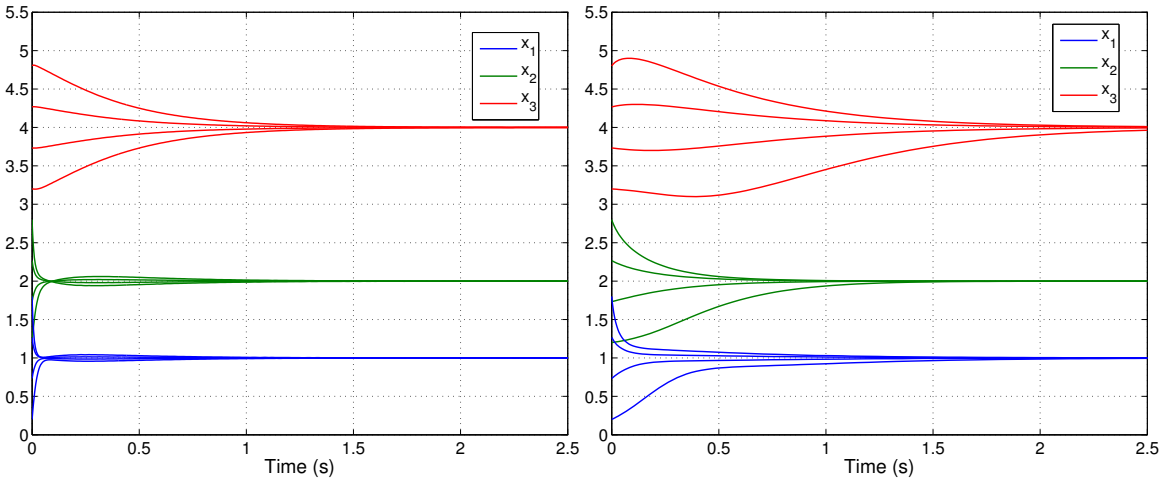
Figure 4.6. The complex balanced realizations of the two closed loop systems (of Subsection 4.7.3). The first realization (a) corresponds to the closed loop with the feedback gain $K^{(1)}$ and additional monomials $\psi_c^{(1)}(x_p)$. The second one (b) corresponds to the closed loop with the feedback gain $K^{(2)}$ and additional monomials $\psi_c^{(2)}(x_p)$.

The locally linearised models have the eigenvalues $\lambda^{(1)} = \{-2.8562, -7.0820, -78.3564\}$ and $\lambda^{(2)} = \{-2, -4, -16\}$, respectively. The main difference is the achieved performance in terms of the largest closed loop eigenvalue. In the second case, the largest closed loop eigenvalue $\lambda_{\max}^{(2)} = -2$ is larger than in the first case $\lambda_{\max}^{(1)} = -2.8562$. This results a slower local convergence of the design with $\psi_c^{(2)}$. Fig. 4.7 shows the time domain simulations of the two closed loop systems with four different initial values. It is seen that the resulted closed loop dynamics are indeed rather different.

Note that the choice of the monomial $\psi_c(x_p) = x_{p_1} x_{p_3}$ results in an infeasible problem.

4.8 Summary

A novel approach is proposed in this chapter to asymptotically stabilize polynomial systems with linear constant parameter input terms around a positive equilibrium point. The stabilization is achieved by constructing a polynomial state feedback that results in a closed loop system that has a kinetic realization which is complex balanced with a given equilibrium.



(a) (b)

Figure 4.7. Time domain simulations of the two closed loop systems (of Subsection 4.7.3). The first simulation (a) uses the feedback gain $K^{(1)}$ and additional monomials $\psi_c^{(1)}(x_p)$. The second one (b) uses the feedback gain $K^{(2)}$ and additional monomials $\psi_c^{(2)}(x_p)$. The simulations are started from 4 different initial values. The blue, green, and red lines show the state variables x_{p_1}, x_{p_2} and x_{p_3}, respectively.

Based on the theory of kinetic systems and the phenomenon of dynamical equivalence, a complex balanced realization is aimed at by computing the feedback gain of a polynomial feedback using convex optimization. First, the sufficient feedback structure is determined by proving that it is enough to apply a static feedback with constant gains containing only the monomials of the open loop polynomial system in the simplest case.

The case of requiring a closed loop system with complex balanced kinetic realization having a prescribed equilibrium point results in a linear optimization problem that is solvable in the LP framework. The robust version of the problem, when a convex set of polynomial systems is given over which an asymptotically stabilizing controller is searched for, is also solvable with an LP solver.

The simple feedback design problem is extended with a semidefinite constraint which guaranties the uniqueness of the equilibrium point. In that case, minimizing the objective function also minimizes the eigenvalue having the largest real part of the state matrix of the linearised closed loop system, that enables to adjust the performance of the closed loop system by finding the fastest local convergence to the specified equilibrium point.

The proposed methods and tools are illustrated with a process example and with two simple numerical examples.

Chapter 5

Semistability of complex balanced kinetic systems with arbitrary time delays

Time-delays are often present in natural and technological processes, and the detailed mathematical treatment of such delays is sometimes necessary to model and understand important observed dynamical phenomena [52, 29]. An excellent summary of the fundamental results on nonnegative and compartmental systems with time-delay can be found in Chapter 3 of [33], where simple algebraic necessary and sufficient conditions are given for the asymptotic stability of delayed linear compartmental systems. Among other results, the semistability of an important special class of nonlinear compartmental systems for arbitrary time-delays was shown in [18].

Motivated by the above results, the purpose of this chapter is to introduce the complex balance condition for kinetic systems with delayed reactions, and to study the stability properties of such systems using logarithmic Lyapunov-Krasovskii functionals and LaSalle's invariance principle.

The structure of this chapter is the following. In Section 5.1 and Section 5.2, the time delayed kinetic system and the time delayed stoichiometry compatibility classes are introduced, respectively. Section 5.3 contains the main result of this chapter that is the semistability of the complex balanced kinetic systems with time delay. In Section 5.4 an illustrative example is shown, while Section 5.5 summarizes the contribution of this chapter.

5.1 Kinetic systems with time delays

In this section, mass-action kinetic systems with time delays are introduced and it is shown that they generate a nonnegative semiflow.

For this purpose the mass-action kinetic system with time delays [43] will be considered

in the form

$$\dot{x}(t) = \sum_{k=1}^{r} \kappa_k \left[(x(t-\tau_k))^{y_k} \, y_k' - (x(t))^{y_k} \, y_k \right], \qquad t \geq 0, \tag{5.1}$$

where $\tau_k \geq 0$, $k = 1, \ldots, r$ are the time delays. In the special case $\tau_k = 0$, $k = 1, \ldots, r$, Eq. (5.1) reduces to the ordinary mass action law kinetic system (2.4). Solutions of (5.1) are generated by initial data $x(t) = \theta(t)$ for $-\tau \leq t \leq 0$, where $\tau = \max_{1 \leq k \leq r} \tau_k$ is the maximum delay and $\theta \in \overline{\mathcal{C}}_+$ is a nonnegative continuous initial function. Throughout the chapter, the solution of (5.1) with initial function $\theta \in \overline{\mathcal{C}}_+$ will be denoted by $x = x^\theta$. Note that the solutions of delay differential equations are usually interpreted in $\mathcal{C}$. For every $t \geq 0$, $x_t \in \mathcal{C}$ is defined by $x_t(s) = x(t+s)$ for $-\tau \leq s \leq 0$.

In the following theorem, we show that the semiflow $x^\theta(t)$ for $t \geq 0$ generated by the time delay kinetic system (5.1) is nonnegative.

Theorem 7. *For every initial function $\theta \in \overline{\mathcal{C}}_+$, the solution x^θ of (5.1) is nonnegative, i.e. $x_t^\theta \in \overline{\mathcal{C}}_+$ for all $t \geq 0$.*

Proof. Eq. (5.1) can be written in the form

$$\dot{x}(t) = F(x_t),$$

where $F : \overline{\mathcal{C}}_+ \to \mathbb{R}^n$ is given by

$$F(\phi) = \sum_{k=1}^{r} \kappa_k \left[(\phi(-\tau_k))^{y_k} \, y_k' - (\phi(0))^{y_k} \, y_k \right], \qquad \phi \in \overline{\mathcal{C}}_+.$$

It follows from the definition of the vector exponential that if $\phi \in \overline{\mathcal{C}}_+$ and $\phi_i(0) = 0$ for some $i \in \{1, \ldots, n\}$, then

$$F_i(\phi) = \sum_{k=1}^{r} \kappa_k (\phi(-\tau_k))^{y_k} \, (y_k')_i \geq 0.$$

Here ϕ_i and F_i denote the i-th coordinate function of ϕ and F, respectively. The conclusion follows from Theorem 2.1 in Chap. 5 of [50]. Alternatively, we can use the generalization of Proposition 3.1 of [33] to equations with multiple delays. □

5.2 Stoichiometric compatibility classes for delayed kinetic systems

Recall [27] that the stoichiometric subspace $\mathcal{S}$ for the ordinary mass-action kinetic system (2.4) is defined by

$$\mathcal{S} = \operatorname{span} \{ y_k' - y_k \mid k = 1, \ldots, r \}, \tag{5.2}$$

and for each $p \in \overline{\mathbb{R}}^n_+$ the corresponding positive stoichiometric compatibility class $\mathcal{S}_p$ is given by

$$\mathcal{S}_p = \left\{ x \in \overline{\mathbb{R}}^n_+ \;\mid\; x - p \in \mathcal{S} \right\}. \tag{5.3}$$

The positive stoichiometric compatibility classes $\mathcal{S}_p$ are positively invariant under the mass-action kinetic system (2.4), i.e. $x(0) \in \mathcal{S}_p$ implies $x(t) \in \mathcal{S}_p$ for all $t \geq 0$ [27].

In this section, we will extend the definition of the positive stoichiometric compatibility classes to the time delayed kinetic system (5.1) and we will prove their invariance property.

For each $v \in \mathbb{R}^n$, define the functional $c_v : \overline{\mathcal{C}}_+ \to \mathbb{R}$ by

$$c_v(\psi) = v^T \left[\psi(0) + \sum_{k=1}^{r} \left(\kappa_k \int_{-\tau_k}^{0} (\psi(s))^{y_k} \, ds \right) y_k \right], \qquad \psi \in \overline{\mathcal{C}}_+. \tag{5.4}$$

Let $\mathcal{S}^\perp$ denote the orthogonal complement of the stoichiometric subspace $\mathcal{S}$ given by $\mathcal{S}^\perp = \{ v \in \mathbb{R}^n \mid v^T y = 0 \text{ for all } y \in \mathcal{S} \}$. Now we can formulate the definition of the positive stoichiometric compatibility classes for the delayed kinetic system (5.1). For each $\theta \in \overline{\mathcal{C}}_+$, the *positive stoichiometric compatibility class of* (5.1) *corresponding to* θ is denoted by $\mathcal{D}_\theta$ and is defined by

$$\mathcal{D}_\theta = \{ \psi \in \overline{\mathcal{C}}_+ \mid c_v(\psi) = c_v(\theta) \quad \text{for all } v \in \mathcal{S}^\perp \}. \tag{5.5}$$

It is easily seen that $\psi \in \mathcal{D}_\theta$ if and only if $\psi \in \overline{\mathcal{C}}_+$ and

$$\psi(0) - \theta(0) + \sum_{k=1}^{r} \left(\kappa_k \int_{-\tau_k}^{0} [(\psi(s))^{y_k} - (\theta(s))^{y_k}] \, ds \right) y_k \in \mathcal{S}. \tag{5.6}$$

Therefore, if we ignore the delays in (5.1), i.e. $\tau_k = 0$ for $k = 1, \ldots, r$, then the above delayed positive stoichiometric compatibility classes coincide with the positive stoichiometric compatibility classes of the ordinary kinetic system (2.4).

In the next theorem, we establish the invariance property of the above delayed positive stoichiometric compatibility classes.

Theorem 8. *For every $\theta \in \overline{\mathcal{C}}_+$, the positive stoichiometric compatibility class $\mathcal{D}_\theta$ is a closed subset of $\overline{\mathcal{C}}_+$. Moreover, $\mathcal{D}_\theta$ is positively invariant under Eq.* (5.1)*, i.e. if $\psi \in \mathcal{D}_\theta$, then $x_t^\psi \in \mathcal{D}_\theta$ for all $t \geq 0$.*

Proof. Let $\theta \in \overline{\mathcal{C}}_+$. The closedness of $\mathcal{D}_\theta$ is a simple consequence of the continuity of functionals c_v, $v \in \mathcal{S}^\perp$. We will show that for every $v \in \mathcal{S}^\perp$ the functional c_v defined by (5.4) is constant along the solutions of Eq. (5.1). Indeed, if x is a solution of (5.1), then we

have for $t \geq 0$,

$$\begin{aligned}\frac{d}{dt}(c_v(x_t)) &= v^T \sum_{k=1}^{r} \kappa_k \left(x(t-\tau_k)\right)^{y_k} \left(y'_k - y_k\right) \\ &= \sum_{k=1}^{r} \kappa_k \left(x(t-\tau_k)\right)^{y_k} v^T (y'_k - y_k) = 0,\end{aligned}$$

the last equality being a consequence of the definition of $\mathcal{S}^{\perp}$. From this, we find that if $\psi \in \mathcal{D}_\theta$, then for every $v \in \mathcal{S}^{\perp}$ and $t \geq 0$,

$$c_v(x_t^{\psi}) = c_v(x_0^{\psi}) = c_v(\psi) = c_v(\theta)$$

and hence $x_t^{\psi} \in \mathcal{D}_\theta$. This shows that $\mathcal{D}_\theta$ is invariant under Eq. (5.1). □

5.3 Semistability of delayed complex balanced kinetic systems

Before we formulate our main stability criterion, we recall some definitions.

By a *positive equilibrium* of (2.4) or (5.1), we mean a positive vector $\overline{x} \in \mathbb{R}^n_+$ such that $x(t) \equiv \overline{x}$ is a solution of (2.4) and (5.1), respectively. Note that Eqs. (2.4) and (5.1) share the same equilibria satisfying the algebraic equation

$$\sum_{k=1}^{r} \kappa_k (\overline{x})^{y_k} \left[y'_k - y_k\right] = 0. \tag{5.7}$$

Recall that, a positive equilibrium $\overline{x}$ is called *complex balanced* if for every $\eta \in \mathcal{K}$,

$$\sum_{k:\eta=y_k} \kappa_k (\overline{x})^{y_k} = \sum_{k:\eta=y'_k} \kappa_k (\overline{x})^{y_k}, \tag{5.8}$$

where the sum on the left is over all reactions for which η is the source complex and the sum on the right is over all reactions for which η is the product complex. Finally, an ordinary or delayed kinetic system is called *complex balanced* if it has a positive complex balanced equilibrium.

It is well-known [48] that if Eq. (2.4) and hence (5.1) have a positive complex balanced equilibrium $\overline{x}$, then any other positive equilibrium is complex balanced and the set of all positive equilibria $\mathcal{E}$ can be characterized by

$$\mathcal{E} = \{\tilde{x} \in \mathbb{R}^n_+ \mid \mathrm{Ln}(\tilde{x}) - \mathrm{Ln}(\overline{x}) \in \mathcal{S}^{\perp}\}. \tag{5.9}$$

Now we formulate the main result of this chapter about the semistability of positive equilibria of delayed complex balanced systems in the sense of the following definition. A positive

equilibrium $\overline{x}$ of Eq. (5.1) is called *semistable* if it is Lyapunov stable and there exists $\delta > 0$ such that if $\theta \in \hat{\mathcal{B}}_\delta(\overline{x})$, then $x^\theta(t)$ converges to a Lyapunov stable equilibrium of (5.1) as $t \to \infty$. As usual, $\hat{\mathcal{B}}_\delta(\overline{x}) = \{\, \psi \in \mathcal{C} \mid \|\psi - \overline{x}\| \leq \delta \,\}$.

Theorem 9. *Every positive complex balanced equilibrium of the delayed kinetic system* (5.1) *is semistable.*

As a preparation for the proof of Theorem 9, we establish an auxiliary result about the uniqueness of positive equilibria in the positive stoichiometric compatibility classes of complex balanced systems.

Theorem 10. *Suppose that the delayed kinetic system* (5.1) *is complex balanced. Then for every $\theta \in \overline{\mathcal{C}}_+$ the corresponding delayed stoichiometric class $\mathcal{D}_\theta$ contains at most one positive equilibrium.*

Proof. Let $\theta \in \overline{\mathcal{C}}_+$. Suppose that $\tilde{x}$ and $\overline{x}$ are positive equilibria belonging to $\mathcal{D}_\theta$. From the characterization (5.6) of $\mathcal{D}_\theta$, we find that

$$\tilde{x} - \overline{x} + \sum_{k=1}^{r} \left(\kappa_k \int_{-\tau_k}^{0} [\tilde{x}^{y_k} - \overline{x}^{y_k}]\, ds \right) y_k \in \mathcal{S}.$$

This, together with (5.9), yields

$$\begin{aligned} 0 &= (\mathrm{Ln}(\tilde{x}) - \mathrm{Ln}(\overline{x}))^T \left[\tilde{x} - \overline{x} + \sum_{k=1}^{r} \left(\kappa_k \int_{-\tau_k}^{0} [\tilde{x}^{y_k} - \overline{x}^{y_k}]\, ds \right) y_k \right] \\ &= \sum_{i=1}^{n} (\ln(\tilde{x}_i) - \ln(\overline{x}_i))\, (\tilde{x}_i - \overline{x}_i) + \sum_{k=1}^{r} \kappa_k \tau_k\, (\ln(\tilde{x}^{y_k}) - \ln(\overline{x}^{y_k}))\, (\tilde{x}^{y_k} - \overline{x}^{y_k})\,. \end{aligned}$$

Since $(\ln(a) - \ln(b))(a - b) \geq 0$ whenever $a,\, b > 0$ with equality if and only if $a = b$, this is possible only if $\tilde{x}_i = \overline{x}_i$ for all $i = 1, \ldots, n$. □

Now we are in a position to give a proof of Theorem 9. It will be based on the Lyapunov-Krasovskii method and LaSalle's invariance principle [33], [34], [49], [13].

Proof of Theorem 9. We will use the following two inequalities. For every $a, b \in \mathbb{R}$,

$$e^a(b - a) \leq e^b - e^a, \tag{5.10}$$

with equality if and only if $a = b$. For every $b > 0$ there exists $c > 0$ such that for all $x > 0$,

$$x\big[\ln(x) - \ln(b) - 1\big] + b \geq c \ln\big[\, 1 + (x - b)^2 \,\big] \geq 0. \tag{5.11}$$

Inequality (5.10) is not new. It is a simple consequence of the mean value theorem applied to the exponential function. Inequality (5.11) is less obvious. Its proof is given in Appendix C.

Consider the candidate Lyapunov–Krasovskii functional $V : \mathcal{C}_+ \to \overline{\mathbb{R}}_+$ defined by

$$\begin{aligned} V(\psi) = &\sum_{i=1}^{n} (\psi_i(0)(\ln(\psi_i(0)) - \ln(\overline{x}_i) - 1) + \overline{x}_i) \\ &+ \sum_{k=1}^{r} \kappa_k \int_{-\tau_k}^{0} \{(\psi(s))^{y_k} [\ln((\psi(s))^{y_k}) - \ln(\overline{x}^{y_k}) - 1] + \overline{x}^{y_k}\} \, ds \end{aligned} \tag{5.12}$$

for $\psi \in \mathcal{C}_+$. Clearly, $V(\overline{x}) = 0$. We will show that there exists a continuous strictly increasing function $\alpha : [0, \infty) \to [0, \infty)$ with $\alpha(0) = 0$ such that

$$V(\psi) \geq \alpha(|\psi(0) - \overline{x}|), \qquad \psi \in \mathcal{C}_+, \tag{5.13}$$

where $|\cdot|$ is the Euclidean norm in $\mathbb{R}^n$. By virtue of (5.11), the second sum in (5.12) is nonnegative and the first sum in (5.12) can be estimated from below using the first inequality in (5.11). Thus, (5.11) implies the existence of positive constants c_i, $1 \leq i \leq n$, such that for all $\psi \in \mathcal{C}_+$,

$$\begin{aligned} V(\psi) &\geq \sum_{i=1}^{n} c_i \ln \left[1 + (\psi_i(0) - \overline{x}_i)^2\right] \geq \gamma \sum_{i=1}^{n} \ln \left[1 + (\psi_i(0) - \overline{x}_i)^2\right] \\ &= \gamma \ln \prod_{i=1}^{n} \left[1 + (\psi_i(0) - \overline{x}_i)^2\right] \geq \gamma \ln \left(1 + \sum_{i=1}^{n} (\psi_i(0) - \overline{x}_i)^2\right) \\ &= \gamma \ln \left(1 + |\psi(0) - \overline{x}|^2\right), \end{aligned}$$

where $\gamma = \min_{1 \leq i \leq n} c_i$. Thus, (5.13) holds with

$$\alpha(r) = \gamma \ln(1 + r^2), \qquad r \geq 0.$$

Next, it follows that the Lyapunov-Krasovskii directional derivative along trajectories of the

system (5.1) is given by

$$\begin{aligned}
\dot{V}(x_t) &= \sum_{k=1}^{r} \kappa_k \operatorname{Ln}\left(\frac{x(t)}{\overline{x}}\right)^T \left[(x(t-\tau_k))^{y_k}\, y_k' - (x(t))^{y_k}\, y_k\right] \\
&+ \sum_{k=1}^{r} \kappa_k \left(x(t)\right)^{y_k} \left(\ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k}\right) - 1\right) \\
&- \sum_{k=1}^{r} \kappa_k \left(x(t-\tau_k)\right)^{y_k} \left(\ln\left(\left\{\frac{x(t-\tau_k)}{\overline{x}}\right\}^{y_k}\right) - 1\right) \\
&= \sum_{k=1}^{r} \kappa_k \left[(x(t-\tau_k))^{y_k} \ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k'}\right) - (x(t))^{y_k} \ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k}\right)\right] \\
&+ \sum_{k=1}^{r} \kappa_k \left[(x(t))^{y_k} \ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k}\right) - (x(t-\tau_k))^{y_k} \ln\left(\left\{\frac{x(t-\tau_k)}{\overline{x}}\right\}^{y_k}\right)\right] \\
&+ \sum_{k=1}^{r} \kappa_k \left[(x(t-\tau_k))^{y_k} - (x(t))^{y_k}\right] \\
&= \sum_{k=1}^{r} \kappa_k\, \overline{x}^{y_k} \left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k} \left[\ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k'}\right) - \ln\left(\left\{\frac{x(t-\tau_k)}{\overline{x}}\right\}^{y_k}\right)\right] \\
&+ \sum_{k=1}^{r} \kappa_k\, \overline{x}^{y_k} \left[\left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k} - \left(\frac{x(t)}{\overline{x}}\right)^{y_k}\right].
\end{aligned}$$

By virtue of (5.10), we have for each $k = 1, \ldots, r$,

$$\begin{aligned}
&\left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k} \left[\ln\left(\left\{\frac{x(t)}{\overline{x}}\right\}^{y_k'}\right) - \ln\left(\left\{\frac{x(t-\tau_k)}{\overline{x}}\right\}^{y_k}\right)\right] \\
&\leq \left(\frac{x(t)}{\overline{x}}\right)^{y_k'} - \left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k}
\end{aligned}$$

with equality if and only if for each $k = 1, \ldots, r$,

$$\left(\frac{x(t)}{\overline{x}}\right)^{y_k'} = \left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k}.$$

From this, we find that

$$\begin{aligned}
\dot{V}(x_t) &\leq \sum_{k=1}^{r} \kappa_k\, \overline{x}^{y_k} \left[\left(\frac{x(t)}{\overline{x}}\right)^{y_k'} - \left(\frac{x(t)}{\overline{x}}\right)^{y_k}\right] \\
&= \sum_{\eta \in \mathcal{K}} \left(\frac{x(t)}{\overline{x}}\right)^{\eta} \left[\sum_{k:\eta = y_k'} \kappa_k \overline{x}^{y_k} - \sum_{k:\eta = y_k} \kappa_k \overline{x}^{y_k}\right] = 0,
\end{aligned}$$

where the last equality follows from the complex balanced property (5.8). This implies that the complex balanced equilibrium $\overline{x}$ of (5.1) is Lyapunov stable.

Choose ϵ such that $0 < \epsilon < \min_{1 \leq i \leq n} \overline{x}_i$ so that $\hat{\mathcal{B}}_\epsilon(\overline{x}) \subset \mathcal{C}_+$. The Lyapunov stability of

the equilibrium $\overline{x}$ implies the existence of $\delta > 0$ such that if $\theta \in \hat{\mathcal{B}}_\delta(\overline{x})$, then $x_t^\theta \in \hat{\mathcal{B}}_\epsilon(\overline{x})$ for all $t \geq 0$. We will show that for every $\theta \in \hat{\mathcal{B}}_\delta(\overline{x})$ the solution $x^\theta(t)$ converges to a Lyapunov stable equilibrium of (5.1). Let

$$\mathcal{R} = \{\, \psi \in \hat{\mathcal{B}}_\epsilon(\overline{x}) \mid \dot{V}(\psi) = 0 \,\}.$$

From the previous calculations, we find that

$$\mathcal{R} = \left\{ \psi \in \hat{\mathcal{B}}_\epsilon(\overline{x}) \mid \left(\frac{\psi(0)}{\overline{x}}\right)^{y_k'} = \left(\frac{\psi(-\tau_k)}{\overline{x}}\right)^{y_k} \quad \text{for } k = 1, \ldots, r \right\}.$$

Let $\mathcal{M}$ be the largest set in $\mathcal{R}$ which is invariant under Eq. (5.1). We will show that every element of $\mathcal{M}$ is a positive equilibrium of (5.1). Let $\psi \in \mathcal{M}$ and write $x = x^\psi$ for brevity. Rewrite Eq. (5.1) in the form

$$\dot{x}(t) = \sum_{\eta \in \mathcal{K}} \left[\sum_{k:\eta = y_k'} \kappa_k \overline{x}^{y_k} \left(\frac{x(t-\tau_k)}{\overline{x}}\right)^{y_k} - \sum_{k:\eta = y_k} \kappa_k \overline{x}^{y_k} \left(\frac{x(t)}{\overline{x}}\right)^{y_k} \right] \eta.$$

Since $\mathcal{M} \subset \mathcal{R}$ is invariant, we have that $x_t \in \mathcal{R}$ for all $t \geq 0$ and hence

$$\dot{x}(t) = \sum_{\eta \in \mathcal{K}} \left(\frac{x(t)}{\overline{x}}\right)^{y_k} \left[\sum_{k:\eta = y_k'} \kappa_k \overline{x}^{y_k} - \sum_{k:\eta = y_k} \kappa_k \overline{x}^{y_k} \right] \eta = 0$$

for $t \geq 0$, where the last equality is a consequence of the complex balanced property (5.8). Thus, $x = x^\psi$ is a constant solution of (5.8) and hence $\psi \equiv \tilde{x}$ is a positive equilibrium. Now suppose that $\theta \in \hat{\mathcal{B}}_\delta(\overline{x})$. As noted before, $x_t^\theta \in \hat{\mathcal{B}}_\epsilon(\overline{x})$ for all $t \geq 0$. By the application of LaSalle's invariance principle [49], we conclude that $\omega(\theta) \subset \mathcal{M}$, where

$$\omega(\theta) = \left\{ \phi \in \mathcal{C} \mid \text{there exists } t_n \to \infty \text{ such that } x_{t_n}^\theta \to \phi \right\} \tag{5.14}$$

is the omega limit set. On the other hand, since $\theta \in \mathcal{D}_\theta$ and according to Theorem 8 the stoichiometric compatibility class $\mathcal{D}_\theta$ is closed and invariant, it follows that $\omega(\theta) \subset \mathcal{D}_\theta$. Thus, $\omega(\theta) \subset \mathcal{M} \cap \mathcal{D}_\theta$. As shown before, every element of $\mathcal{M}$ is a positive equilibrium of (5.1), while Theorem 10 implies that $\mathcal{D}_\theta$ contains at most one positive equilibrium. Hence $\omega(\theta) = \{\tilde{x}\}$ for some $\tilde{x} \in \mathcal{E}$ and $x^\theta(t) \to \tilde{x}$ as $t \to \infty$. The Lyapunov stability of the positive equilibrium $\tilde{x}$ follows from the first part of the proof. □

Remark. In the previous proof we have shown that for every positive initial function θ from a neighbourhood of the positive complex balanced equilibrium $\overline{x}$ of (5.1) the stoichiometric compatibility class $\mathcal{D}_\theta$ contains exactly one positive equilibrium. A simple modification of the above proof can be used to show that if system (5.1) is complex balanced then $\mathcal{D}_\theta$ contains exactly one positive equilibrium whenever the closure of the forward orbit $\mathcal{O}_\theta^+ = \{\, x_t^\theta \mid t \geq 0 \,\}$

remains in $\mathcal{C}_+$. This last condition certainly holds if the solution x^θ is persistent in the sense that $\liminf_{t\to\infty} x_i^\theta(t) > 0$ for each $i = 1, \ldots, n$.

Let $\overline{x}$ be a positive complex balanced equilibrium of Eq. (5.1). Theorem 10 implies that $\overline{x}$ is the only positive equilibrium in its positive stoichiometric compatibility class $\mathcal{D}_{\overline{x}}$. This, together with Theorem 9 yields the following analogue of a known result for ordinary kinetic systems.

Theorem 11. *Every positive complex balanced equilibrium $\overline{x}$ of the delayed kinetic system* (5.1) *is locally asymptotically stable relative to its positive stoichiometric compatibility class $\mathcal{D}_{\overline{x}}$.*

5.4 Example

In this section, we will illustrate our results and notations on a simple example. The studied system is intentionally low dimensional in order to be able to simply illustrate the relations and differences between non-delayed and delayed kinetic systems.

Let the time delayed complex balanced kinetic system be given by a reversible reaction $2X_1 \leftrightarrows X_2$ containing one undelayed and a delayed reaction as follows

$$2X_1 \xrightarrow{\kappa_1=1} X_2, \quad X_2 \xrightarrow{\kappa_2=2,\tau_2} 2X_1.$$

Then, the corresponding time-delay differential equation is

$$\begin{aligned}\dot{x}(t) = 1 &\left((x_1(t))^2 \begin{bmatrix} 0 \\ 1 \end{bmatrix} - (x_1(t))^2 \begin{bmatrix} 2 \\ 0 \end{bmatrix} \right) \\ &+ 2 \left(x_2(t-\tau_2) \begin{bmatrix} 2 \\ 0 \end{bmatrix} - x_2(t) \begin{bmatrix} 0 \\ 1 \end{bmatrix} \right),\end{aligned} \tag{5.15}$$

where $x = [x_1, x_2]^T \in \overline{\mathbb{R}}^2_+$ are the states and τ_2 is the time delay of the second reaction. It is easily verified that $[2,2]^T$ is a positive complex balanced equilibrium of (5.15). The stoichiometric subspace is

$$\mathcal{S} = \operatorname{span}\left\{ [-2,1]^T \right\} \qquad \text{and} \qquad \mathcal{S}^\perp = \operatorname{span}\left\{ [1,2]^T \right\}.$$

The dimension of S is one, therefore Eq. (5.15) has infinitely many positive equilibria given by the set

$$\mathcal{E} = \left\{ \overline{x} \in \mathbb{R}^2_+ \;\middle|\; \begin{bmatrix} \ln(\overline{x}_1) - \ln(2) \\ \ln(\overline{x}_2) - \ln(2) \end{bmatrix} \in \mathcal{S}^\perp \right\}. \tag{5.16}$$

For $\overline{x} \in \mathcal{E}$, consider the set $\mathcal{X}_{\overline{x}}$ of those positive constant functions which belong to $\mathcal{D}_{\overline{x}}$:

$$\mathcal{X}_{\overline{x}} = \left\{ \eta \in \mathbb{R}^2_+ \;\middle|\; \begin{bmatrix} \eta_1 - \overline{x}_1 \\ (1+2\tau_2)(\eta_2 - \overline{x}_2) \end{bmatrix} \in \mathcal{S} \right\}. \tag{5.17}$$

According to Theorem 11, if $\theta \equiv \eta \in \mathcal{X}_{\overline{x}}$ is close to the equilibrium $\overline{x} \in \mathcal{E}$, then $x^\theta(t) \to \overline{x}$ as $t \to \infty$.

Fig. 5.1 shows the phase portrait of the system (5.15) with $\tau_2 = 0.5$ and with different constant initial conditions. The initial conditions are chosen such that the corresponding solutions converge to three different equilibria. Fig. 5.2 shows the time domain behaviour of the system (5.15) when there are different time delays, but the initial conditions are the same.

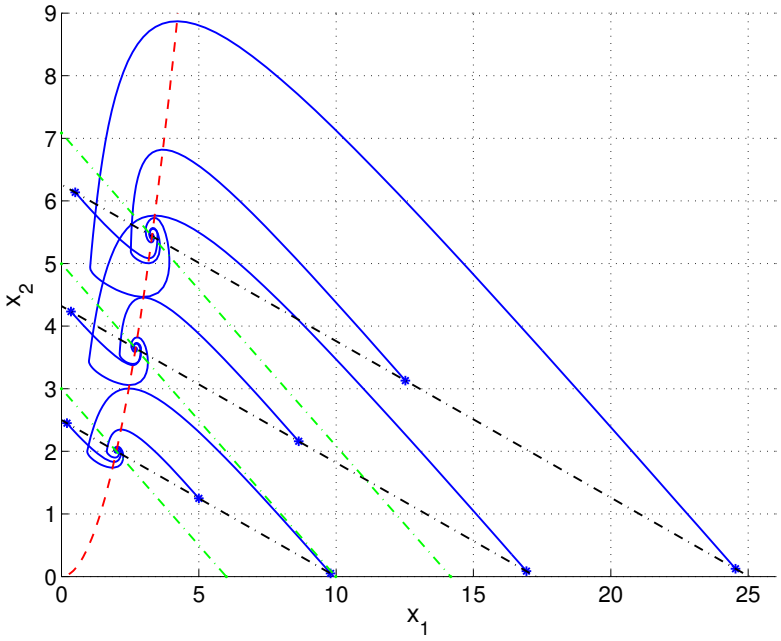


Figure 5.1. The phase portrait of the system (5.15) with $\tau_2 = 0.5$. The red dash curve shows the equilibrium set $\mathcal{E}$ of the network. The black dash-dot lines show the set of points for which the corresponding constant initial functions result in the same equilibrium point. The green dashed lines show three stoichiometric compatibility classes of the non-delayed network having the same structure and reaction rate coefficients as the delayed one. The blue curves show the solution trajectories of (5.15) with different constant initial functions.

5.5 Summary

In this chapter, a class of delayed kinetic systems is introduced, where different constant time-delays can be assigned to the individual reactions of the network. The complex balance property is defined for this system in a straightforward way. It is shown that the equilibrium

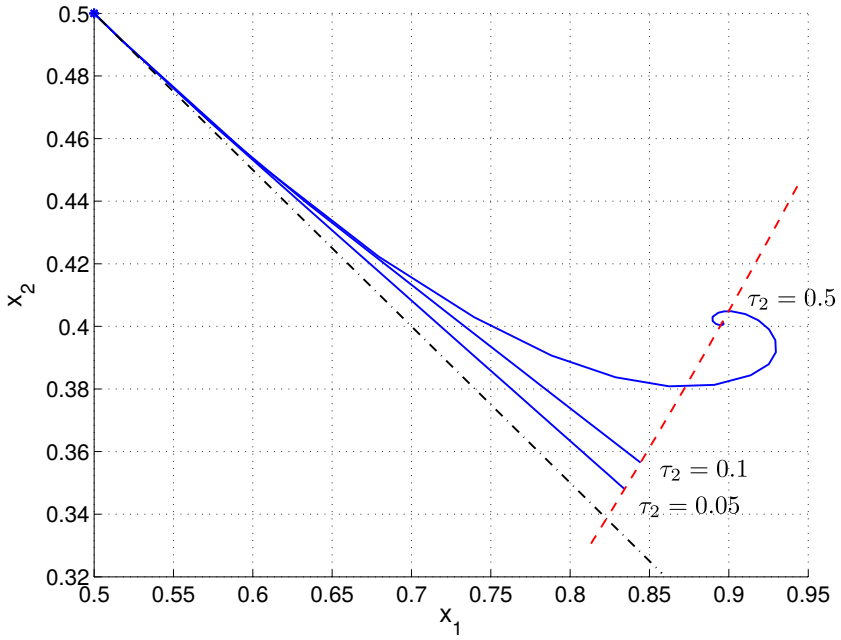


Figure 5.2. The phase portrait of the system (5.15) with different time delays $\tau_2 = \{0.05, 0.1, 0.5\}$ and with the same constant initial function defined by $\eta = [0.5\ 0.5]^T$. The red dashed line shows the equilibrium set $\mathcal{E}$ of the network. The black dash-dot line shows the positive stoichiometric compatibility class of the undelayed system having the same structure and reaction rate coefficients as the delayed one. The blue curves show the solution trajectories of (5.15) with different time delays.

solutions of complex balanced kinetic systems can directly be obtained from the equilibria of the corresponding non-delayed kinetic system. Therefore, the complex balance property of a delayed network can be checked in the same way as in the non-delayed model. The notion of stoichiometric compatibility classes is extended to delayed networks. It is shown that in contrary to the classical mass action case, these classes are no longer linear manifolds in the state space. The uniqueness of equilibrium solutions within a time delayed positive stoichiometric compatibility class is proven for delayed complex balanced models. By introducing a logarithmic Lyapunov-Krasovskii functional and using LaSalle's invariance principle, the semistability of equilibrium solutions in complex balanced systems with arbitrary time delays is also proved. As a consequence, a positive complex balanced equilibrium is always locally asymptotically stable relative to its positive stoichiometric compatibility class. The obtained results further underline the significance of the complex balance principle in the theory of dynamical systems.

Chapter 6

Conclusions

In this chapter, we conclude this thesis with a summary of the main contributions and give suggestions for possible future research.

6.1 New scientific contributions (thesis points)

In this section, the new scientific contributions are summarized.

Thesis I.
I have proposed an optimization-based approach to compute deficiency zero reaction network structures that are linearly conjugate to a given kinetic dynamics assuming that the set of complexes is known. The problem is traced back to the solution of an appropriately constructed mixed integer linear programming problem. Furthermore, I have shown that weakly reversible deficiency zero realizations can be determined in polynomial time using standard linear programming.

The corresponding publication is [1], details are in Chapter 3.

Thesis II.
I have proposed computationally efficient methods to construct polynomial feedback controllers for the stabilization of nonnegative polynomial systems with linear input structure around a positive equilibrium point. Using the theory of kinetic systems, a complex balanced closed loop realization is achieved by computing the parameters of a polynomial feedback using convex optimization.

(i) I have shown that the feedback resulting in a complex balanced closed loop system having a prescribed equilibrium point can be computed using linear programming.

(ii) I have given a linear programming-based solution for the robust version of the problem, when a convex set of polynomial systems is given over which a stabilizing controller is searched for.

(iii) I have shown that introducing new monomials in the feedback does not improve the solvability of the feedback design problem if one only wants to achieve a complex balanced kinetic closed loop, or a weakly reversible zero deficiency kinetic closed loop.

(iv) I have proposed a semidefinite constraint which guarantees the uniqueness of the equilibrium point. The feedback law was computed using semidefinite programming where the objective function is used to adjust the performance of the closed-loop system by minimizing the eigenvalue of the linearised closed-loop system with the largest real part.

The corresponding publications are [2, 11, 8, 6, 7], details are in Chapter 4.

Thesis III.
I have introduced and analysed a general class of delayed kinetic system models obtained from mass action models by assigning constant time delays to the individual reactions. I have defined the time delayed positive stoichiometric compatibility classes and the complex balancedness in the case of time delay. I have proved the uniqueness of equilibrium solutions within the time delayed positive stoichiometric compatibility classes. It was proved that the equilibrium solutions for complex balanced systems with arbitrary constant time delays are semistable. As a consequence, I have shown that every positive complex balanced equilibrium solution is locally asymptotically stable relative to its positive stoichiometric compatibility class.

The corresponding publications are [3, 5] details are in Chapter 5.

6.2 Suggestions for future research

In this section, the possible future research directions are indicated.

- In Chapter 4, we have shown that involving new monomials into the feedback does not improve the solvability of the problems in some basic cases. When we introduce additional constraints or performance criteria, then the success of the design depends on the additionally introduced monomials. This situation would raise the problem of new monomial selection as a possible research direction.

- We have proved only the local stability in Chapter 5. In the light of [14] and [20], it is an interesting question whether the asymptotic stability of a delayed complex balanced system is global relative to its positive stoichiometric class.

- A crucial part of the feedback design is considering the time delay. Therefore, utilizing our time delayed stability results (Chapter 5) in our feedback design method is a promising future direction of this work.

The Author's Publications

[1] **Gy. Lipták**, G. Szederkényi, and K. M. Hangos, "Computing zero deficiency realizations of kinetic systems," *Systems and Control Letters*, vol. 81, pp. 24–30, 2015. IF: 2.55.

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Appendix

A. Acronyms

The acronyms used in this thesis are listed below.

Notation	Meaning
CRN	Chemical Reaction Network
LP	Linear Programming
MILP	Mixed Integer Linear Programming
ODE	Ordinary Differential Equation
SDP	Semidefinite Programming

B. Notation

The notations used in this thesis are listed below.

Symbols

$\mathbb{Z}$	integer numbers
$\overline{\mathbb{Z}}_+$	nonnegative integer numbers
$\overline{\mathbb{Z}}_+{}^n$	n-dimensional space of nonegative integer column vectors
$\mathbb{R}$	real numbers
$\mathbb{R}_+$	positive real numbers
$\overline{\mathbb{R}}_+$	nonnegative real numbers
$\mathbb{R}^n$	n-dimensional space of real column vectors
$\mathbb{R}^n_+$	set of (element-wise) positive vectors in $\mathbb{R}^n$
$\overline{\mathbb{R}}^n_+$	set of (element-wise) nonnegative vectors in $\mathbb{R}^n$
$\mathbf{0}$	null vector, null matrix
$\mathbf{1}$	column vector of ones
$\mathbb{R}^{n\times m}$	set of $n \times m$ real matrices
$\mathrm{diag}(v)$	$n \times n$ diagonal matrix whose ith diagonal element is v_i
$\mathrm{im}(A)$	range space of the matrix A
$\ker(A)$	null space of the matrix A
$\mathrm{rank}(A)$	rank of the matrix A
$A_{i,j}$ or $[A]_{i,j}$	the (i,j)th element of the matrix A (indexing order: row, column)
$A_{\cdot,j}$ or $[A]_{\cdot,j}$	jth column of a matrix A
$A_{i,\cdot}$ or $[A]_{i,\cdot}$	ith row of a matrix A
A^T	transpose of the matrix A
$\dim(V)$	dimension of the vector space V
$V^\perp$	orthogonal complement of the vector space V
$U + V$	sum of the vector spaces U and V
$\frac{x}{y}$	n-dimensional real column vector whose ith element is $\frac{x_i}{y_i}$
x^y	the vector exponential $x^y = \prod_{i=1}^n x_i^{y_i}$
$\mathrm{Ln}(x)$	the element-wise logarithmic mapping defined by $[\mathrm{Ln}(x)]_i = \ln(x_i)$
$\mathcal{C}(X, Y)$	the set of continuous functions mapping from X to Y
$\mathcal{C}$	the set of continuous functions mapping from $[-\tau, 0]$ to $\mathbb{R}^n$
$\mathcal{C}_+$	the set of continuous functions mapping from $[-\tau, 0]$ to $\mathbb{R}^n_+$
$\overline{\mathcal{C}}_+$	the set of continuous functions mapping from $[-\tau, 0]$ to $\overline{\mathbb{R}}^n_+$
$\|\psi\|$	the maximum norm $\|\psi\| = \sup_{-\tau\le s\le 0} \|\psi(s)\|$ for $\psi \in \mathcal{C}$
$\dot{x} = \frac{dx}{dt}$	time derivative of x
$x_t(s)$	the segment function defined by $x_t(s) = x(t + s)$, where $x \in \mathcal{C}$
$\Longrightarrow$	implies relation between logical expressions
$\Longleftrightarrow$	equivalence relation between logical expressions

C. Proof of the inequality (5.11)

We give a proof of inequality (5.11). Let $b > 0$ be fixed. For $x > 0$, define

$$f(x) = x\,[\,\ln(x) - \ln(b) - 1] + b$$

and

$$g(x) = \ln\bigl[1 + (x-b)^2\bigr].$$

Since $f'(x) = \ln(x) - \ln(b)$ for $x > 0$, $f' < 0$ on $(0, b)$ and $f' > 0$ on (b, ∞). This implies that f has a strict minimum at $x = b$. Hence $f(x) > f(b) = 0$ for $x \in (0, b) \cup (b, \infty)$. Clearly, the same inequality holds for g. A repeated application of l'Hospital's rule yields

$$\lim_{x \to b} \frac{f(x)}{g(x)} = \frac{1}{2b}.$$

Therefore the function $h : (0, \infty) \to \mathbb{R}$ defined by

$$h(x) = \begin{cases} \dfrac{f(x)}{g(x)} & \text{for } x \in (0, b) \cup (b, \infty) \\ \dfrac{1}{2b} & \text{for } x = b \end{cases}$$

is positive and continuous. Since $x \ln(x) \to 0$ as $x \to 0+$, h can be extended continuously to the interval $[0, \infty)$ by

$$h(0) = \lim_{x \to 0+} h(x) = \frac{b}{\ln(1 + b^2)}.$$

Since $\lim_{x \to \infty} h(x) = \infty$, there exists $T > 0$ such that $h(x) > h(0)$ for all $x > T$. The continuity of h implies the existence of $c = \min_{0 \le x \le T} h(x)$. Since $h(x) > h(0) \ge c > 0$ for $x > T$, we have that $h(x) \ge c$ for all $x \ge 0$ which implies the desired inequality (5.11).