Dynamic System Properties of Biochemical Reaction Systems

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Preface

I had been working on this master thesis in Amsterdam between September 2007 and May 2008. The thesis is submitted to both the Institute of Mathematics at Eötvös Loránd University in Budapest and the Department of Mathematics at VU University Amsterdam in Amsterdam.

I would like to thank Jan H. van Schuppen for the fruitful discussions we made during the time I had been working on the master project. It has been a pleasure to work with him.

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Chapter 1

Introduction

The functioning of a cell is driven by biochemical processes. For their detailed study, we model the individual chemical reactions and integrate them into a reaction network. There is a difference between ordinary chemistry, anorganic chemistry, and biochemical chemistry, organic chemistry. In biochemistry the reactions are catalyzed by enzymes which are very large molecules on which small molecules are assembled into larger ones. This makes biochemistry different from ordinary chemistry.

Mathematical models of biochemical reaction networks have been investigated for many decades. Nowadays, as the genome is known, there is a reinforced interest into mathematical models of the biochemical reactions of the cell. The attention has been focused mainly on the dynamic system properties of a biochemical reaction system such as investigating the set of equilibria, the stability properties of equilibrium points, and periodic trajectories. Accordingly, control theory of biochemical reaction networks is also gaining interest. This introductory text is based on [12].

The objective of this thesis is to provide an introduction to the basic known facts about the theory of biochemical reaction systems. In most cases, detailed proofs are presented. These proofs often use a different approach than it is common in the literature. We also extend some of the results.

After a short chapter on notations, the model of a biochemical reaction system is introduced in Chapter 3. This model consist of a biochemical reaction network and of a kinetics on it. We shall consider a continuous-time model in which the state of the system will be the instantaneous concentrations of the chemical species included in the model. The evolution of the species concentrations in time is governed by an ordinary differential equation. As we shall see, the model also includes a directed graph. Several dynamic system properties are direct consequences of certain properties of that graph. Therefore basic concepts of graph theory such as the incidence matrix and circulations are useful to introduce. Hence, Chapter 4 will serve as a detailed summary on the needed notions of graph theory. It is more convenient to discuss properties of biochemical reaction systems by using the terminology of graph theory.

As we shall see, an integer number can be associated to each reaction network. This number is called the deficiency of the network. As it will turn out, the deficiency has an important role in the dynamic behaviour of a reaction system. For instance, in case of a special kind of kinetics, if the deficiency is zero then the set of equilibria has a nice structure.

Namely, each positive stoichiometric class contains exactly one interior equilibrium point. Moreover, in this case, asymptotic stability of equilibrium points relative to stoichiometric classes can also be proven. It turns out that the existence and uniqueness of interior equilibrium points in positive stoichiometric classes can be extended to a considerable wider class of systems. At the same time, the stability property does not remain valid. Chapter 5 therefore deals with the notion of deficiency. We present three definitions for the deficiency of a reaction network and we show that those three notions coincide. It is depending on the situation which definition of these three is the most convenient to use.

One can be interested in the long term behaviour of a biochemical reaction system. Chapter 6 summarizes the basic known facts about it. From Section 6.1 till Section 6.3 we deal with forward invariant sets for the differential equation that governs the evolution of the system in time. In Section 6.4 and Section 6.5 we examine the set of equilibria for that differential equation. The latter section contains a construction of a new system from the original one. The connection between these two systems allows us to reduce questions about the set of boundary equilibria to the investigation of the set of interior equilibria. Then we investigate stability properties of equilibrium points and also convergence of solutions of the above mentioned differential equation in Section 6.6. We conclude Chapter 6 by a short section on periodic solutions.

Chapter 7 serves as a brief summary on the contributions of this thesis to the theory of biochemical reaction systems. We also mention possible directions of further research.

Chapter 2

Notations

In this chapter we introduce notations, which are then used throughout the thesis.

Denote by $\mathbb{Z}$ the set of integers. Let $p, q \in \mathbb{Z}$. Define the set $\overline{p,q}$ by

$$\overline{p,q} = \{k \in \mathbb{Z} \mid p \leq k \leq q\}.$$

Denote by $\mathbb{R}$ the set of the real numbers. We refer to $\mathbb{R}_+ = \{x \in \mathbb{R} \mid x > 0\}$ as the set of *positive real numbers* and to $\mathbb{R}_{\geq 0} = \{x \in \mathbb{R} \mid x \geq 0\}$ as the set of *nonnegative real numbers*.

Let n be a positive integer. Then the functional $\langle \cdot, \cdot \rangle : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}$ is the scalar product defined by

$$\langle x, y \rangle = \sum_{s=1}^{n} x_s y_s \quad \text{for} \quad x, y \in \mathbb{R}^n.$$

Orthogonality in this thesis is always understood with respect to this scalar product. Let $|x| = \sqrt{\langle x, x \rangle}$ for $x \in \mathbb{R}^n$. Define the positive orthant $\mathbb{R}^n_+$ and the nonnegative orthant $\mathbb{R}^n_{\geq 0}$ by

$$\begin{aligned} \mathbb{R}^n_+ &= \{x \in \mathbb{R}^n \mid x_s \in \mathbb{R}_+ \text{ for all } s \in \overline{1,n}\} \text{ and} \\ \mathbb{R}^n_{\geq 0} &= \{x \in \mathbb{R}^n \mid x_s \in \mathbb{R}_{\geq 0} \text{ for all } s \in \overline{1,n}\}. \end{aligned}$$

Note that if the topology on $\mathbb{R}^n$ is defined by the above scalar product then $\mathbb{R}^n_{\geq 0}$ is closed and its interior is $\mathbb{R}^n_+$. Denote by $\mathbb{R}^n_0$ the boundary of $\mathbb{R}^n_{\geq 0}$. Note that

$$\mathbb{R}^n_0 = \mathbb{R}^n_{\geq 0} \backslash \mathbb{R}^n_+ = \{x \in \mathbb{R}^n_{\geq 0} \mid \text{there exists } s \in \overline{1,n} \text{ such that } x_s = 0\}.$$

Clearly, $\mathbb{R}^n_{\geq 0}$ is the disjoint union of $\mathbb{R}^n_+$ and $\mathbb{R}^n_0$.

Define the *distance* between $x \in \mathbb{R}^n$ and $H \subseteq \mathbb{R}^n$ by

$$\operatorname{dist}(x, H) = \inf\{|x - h| \mid h \in H\}.$$

If A is any matrix then $A_{i,\cdot}$, $A_{\cdot,j}$, and $A_{i,j}$ denote the ith row, the jth column, and the (i,j)th element of A, respectively.

The function $\operatorname{sgn} : \mathbb{R} \to \{-1, 0, 1\}$ is the sign function ($\operatorname{sgn}(x) = 1$ for $x > 0$, $\operatorname{sgn}(x) = -1$ for $x < 0$, and $\operatorname{sgn}(0) = 0$).

The empty sum is always defined to be zero.

Chapter 3

Biochemical reaction systems

In this chapter we introduce the concept of a biochemical reaction system. Properties of such systems are then investigated in the subsequent chapters.

3.1 Purposes of the modelling of a biochemical reaction system

This section is based on [12]. A mathematical model of the dynamic behaviour of the chemical species in a cell is needed. The purposes of the model are to evaluate the behaviour of the chemical reaction network; to determine the dynamic system properties of networks such as the existence of an equilibrium point, the uniqueness or the multiplicity of equilibrium points, local or global asymptotic stability of equilibrium points, periodic trajectories; and to analyse control of such networks for rational drug design or for biotechnology. The subject of this thesis is to investigate these properties, except the control theoretical aspects, which are not discussed here.

The exposition of Section 3.2 and Section 3.3 is based on the formalism developed by M. Feinberg, F.J.M. Horn, and R. Jackson [5, 6, 7] and follows quite closely the paper of M. Feinberg, [5].

3.2 Biochemical reaction networks

Before we introduce *biochemical reaction networks*, we need to introduce several related notions and terminology.

Consider *chemical species* also referred to as chemical substances of chemical compounds. We shall refer to chemical species as *species*. Let $\mathcal{A}$ be a nonempty finite set of species. Let $n = |\mathcal{A}|$. Denote the elements of $\mathcal{A}$ by the symbols $A_1, \ldots, A_n$.

We shall use the notations $\mathcal{A} = \{A_1, \ldots, A_n\}$ and $\overline{1,n} = \{1, \ldots, n\}$ interchangeably. Accordingly, the notation $s \in \mathcal{A}$ is also used, where $s \in \overline{1,n}$.

A *chemical complex* or *complex* consists of species. More precisely, one can specify a complex by associating nonnegative integer numbers to each species. Those numbers are then called the *stoichiometric coefficients*. In other words, a complex can be specified by an n-tuple $(p_1, \ldots, p_n)$, where p_s is a nonnegative integer for all $s \in \overline{1,n}$. One can then refer to a complex as $p_1A_1 + \cdots + p_nA_n$. However, we do not display those species in this

notation, for which the stoichiometric coefficient is zero. For example, if $n = 3$ then the complex associated to the triple $(3, 2, 0)$ is $3A_1 + 2A_2$. The complex associated to $(0, \ldots, 0)$ is called the *zero complex*. One can refer to the zero complex by the symbol 0. The practical utility of allowing the zero complex in the model is described in [5]. The set of complexes is denoted by $\mathcal{C}$, which is assumed to be a nonempty finite set. Denote by c the number of complexes. The complexes are denoted by the symbols $C_1, \ldots, C_c$. One can use the notation $C_i = p_1A_1 + \cdots + p_nA_n$ $(i \in \overline{1, c})$. In this case we shall say that the stoichiometric coefficient of the species A_s in complex C_i is p_s $(s \in \overline{1, n})$.

We shall use the notations $\mathcal{C} = \{C_1, \ldots, C_c\}$ and $\overline{1, c} = \{1, \ldots, c\}$ interchangeably. Accordingly, the notation $i \in \mathcal{C}$ is also used, where $i \in \overline{1, c}$.

We assume that if i and j are distinct elements of the set $\overline{1, c}$ then there exists $s \in \overline{1, n}$ such that the stoichiometric coefficient of species A_s in C_i and in C_j are not the same. Roughly speaking, it means that complexes are listed only once.

To define reaction networks, another object is needed. An ordered pair of complexes is called a *reaction*. If (C_i, C_j) is a reaction for some $i, j \in \overline{1, c}$ then we say that complex C_i reacts to become C_j. In this case, C_i and C_j are called the *reactant* and the *product* of the reaction (C_i, C_j), respectively. The set of reactions is denoted by $\mathcal{R}$ and assumed to be nonempty. The number of reactions is denoted by m. We also assume that if $i \in \overline{1, c}$ then $(C_i, C_i) \notin \mathcal{R}$. So

$$\emptyset \neq \mathcal{R} \subseteq (\mathcal{C} \times \mathcal{C}) \backslash \{(C_i, C_i) \in \mathcal{C} \times \mathcal{C} \mid i \in \overline{1, c}\}.$$

We also assume that for every $C_i \in \mathcal{C}$ there exists $C_j \in \mathcal{C}$ such that at least one of the ordered pairs (C_i, C_j) and (C_j, C_i) is an element of $\mathcal{R}$. This means that if a complex is not involved in any of the reactions then that complex is not part of the model.

We often write (i, j) instead of (C_i, C_j).

We are now in the position to define what we mean by a biochemical reaction network.

Definition 3.2.1 A *biochemical reaction network* is a triple $(\mathcal{A}, \mathcal{C}, \mathcal{R})$ of three nonempty finite sets, where $\mathcal{A}$ is the set of species, $\mathcal{C}$ is the set of complexes, and $\mathcal{R}$ is the set of reactions as described above.

By *reaction network* and *network* we always mean biochemical reaction network.

An example for reaction network follows.

Example 3.2.2 Let the set of species be $\mathcal{A} = \{A_1, \ldots, A_8\}$. Let the set of complexes be $\mathcal{C} = \{C_1, \ldots, C_7\}$, where

$$C_1 = A_1 + A_2, \quad C_2 = A_3, \quad C_3 = A_4 + A_5, \quad C_4 = A_6,$$

$$C_5 = 2A_1, \quad C_6 = A_2 + A_7, \quad \text{and} \quad C_7 = A_8.$$

For instance, the notation $C_6 = A_2 + A_7$ means that the stoichiometric coefficient of both species A_2 and A_7 in complex C_6 is 1. The stoichiometric coefficients of other species in complex C_6 are zero. As another instance, the stoichiometric coefficient of species A_1 in complex C_5 is 2, while stoichiometric coefficient in complex C_5 is 0 for the other species. Let the set of reactions be

$$\mathcal{R} = \left\{ \begin{array}{c} (C_1, C_2), (C_2, C_1), (C_2, C_3), (C_3, C_4), (C_4, C_3), \\ (C_5, C_6), (C_6, C_7), (C_7, C_6), (C_7, C_5) \end{array} \right\}. \tag{3.1}$$

Note that $n = 8, c = 7$, and $m = 9$ in this example. □

Reaction networks can be visualized using *reaction schemes*. One can represent complexes in a figure and indicate reactions by arrows. As an example, the reaction scheme of the reaction network in Example 3.2.2 is displayed in Figure 3.1.

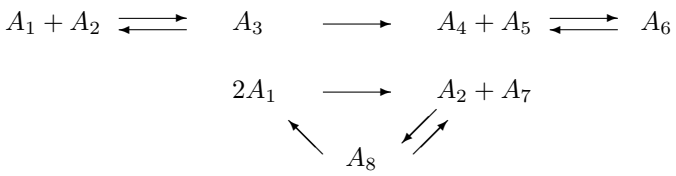


Figure 3.1: Scheme of the reaction network in Example 3.2.2

A convenient way to specify the set of complexes is to provide an $n \times c$ matrix whose entries are nonnegative integers. Denote this matrix by B. The matrix $B \in \mathbb{R}^{n\times c}$ is called the *matrix of complexes*. Using the introduced terminology, $B_{s,i}$ is then the stoichiometric coefficient of species A_s in complex C_i ($s \in \overline{1,n}, i \in \overline{1,c}$). The fact that complexes are listed only once can be expressed in terms of the B matrix by requiring that if $i, j \in \overline{1,c}$ and $i \neq j$ then $B_{\cdot,i} \neq B_{\cdot,j}$. We remark that if the zero complex is involved in the network then one of the columns of B has only zero entries.

The matrix of complexes for Example 3.2.2 is

$$B = \begin{bmatrix} 1 & 0 & 0 & 0 & 2 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \in \mathbb{R}^{8\times 7}.$$

Sometimes the assumption that no row of B vanishes is made for convenience [10]. This would mean that if a certain species is not involved in any of the complexes then that species is not considered to be part of the model. However, we do not make this assumption in this thesis.

The notations and terminology introduced in this section are used throughout the thesis.

3.3 Biochemical reaction systems

The notion of biochemical reaction networks was defined in the previous section. However, it was not discussed how exactly the complexes become other complexes. In other words, the dynamic evolution was not yet investigated.

Consider a biochemical reaction network $(\mathcal{A}, \mathcal{C}, \mathcal{R})$. Let us represent by the vector $x \in \mathbb{R}^n_{\geq 0}$ the *concentrations* of the species in a biochemical reaction network. The sth coordinate of x, x_s, represents the concentration of the species A_s ($s \in \overline{1,n}$). A continuous-time model will be considered, where the species concentrations are changing in accordance with a

differential equation. We are interested in the evolution of the species concentrations in time. A vector $x \in \mathbb{R}^n$ denotes then the *state* of the biochemical reaction system. Accordingly, the linear space $\mathbb{R}^n$ is called the *state space* of the biochemical reaction system. Note however that we are always interested in nonnegative states, because the coordinates of the vector x are representing species concentrations. The notion of a biochemical reaction system is defined below.

It will be useful to introduce the following notation. Let $x \in \mathbb{R}^n$. Denote by $\operatorname{supp}(x)$ the set

$$\operatorname{supp}(x) = \{s \in \overline{1,n} \mid x_s \neq 0\}.$$

Recall that $B \in \mathbb{R}^{n \times c}$ is the matrix of complexes.

Definition 3.3.1 Let $(\mathcal{A}, \mathcal{C}, \mathcal{R})$ be a biochemical reaction network. Let $(i,j) \in \mathcal{R}$. A locally Lipschitz continuous function $R_{(i,j)} : \mathbb{R}^n \to \mathbb{R}$ is called a *rate function* of the reaction (i,j) if the properties

$$R_{(i,j)}(x) \geq 0 \text{ and} \tag{3.2}$$

$$R_{(i,j)}(x) > 0 \text{ if and only if } \operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x) \tag{3.3}$$

hold for all $x \in \mathbb{R}^n_{\geq 0}$. The value $R_{(i,j)}(x)$ of $R_{(i,j)}$ at $x \in \mathbb{R}^n_{\geq 0}$ is called the *reaction rate* of reaction (i,j) at x.

An example of a rate function is the following. Let $(i,j) \in \mathcal{R}$. Define the function $R_{(i,j)} : \mathbb{R}^n \to \mathbb{R}$ by

$$R_{(i,j)}(x) = \kappa_{(i,j)} |x_1|^{B_{1,i}} |x_2|^{B_{2,i}} \cdots |x_n|^{B_{n,i}} = \kappa_{(i,j)} \prod_{s=1}^{n} |x_s|^{B_{s,i}} \tag{3.4}$$

for $x \in \mathbb{R}^n$, where $\kappa_{(i,j)} > 0$. The positive number $\kappa_{(i,j)}$ is called the *rate constant* of the reaction (i,j). The power z^0 is considered to be 1 for all $z \geq 0$. One can easily check that the above defined function is indeed a rate function in the sense of Definition 3.3.1. The local Lipschitz continuity is guaranteed by the fact that the entries of B are nonnegative integers.

We are now in the position to introduce the notion of a biochemical reaction system. Recall that m denotes the number of reactions.

Definition 3.3.2 Let $(\mathcal{A}, \mathcal{C}, \mathcal{R})$ be a biochemical reaction network. Let $R : \mathbb{R}^n \to \mathbb{R}^m$ be any function. Assume that the coordinate functions of R are indexed by the set of reactions. The quadruple $(\mathcal{A}, \mathcal{C}, \mathcal{R}, R)$ is called a *biochemical reaction system* if $R_{(i,j)} : \mathbb{R}^n \to \mathbb{R}$ is a rate function of the reaction (i,j) in the sense of Definition 3.3.1 for all $(i,j) \in \mathcal{R}$.

By *reaction system* and *system* we always mean a biochemical reaction system.

A reaction systems is called a *mass action system* if the coordinates of R are defined by (3.4).

We introduce now the differential equation that governs the evolution of species concentrations in time, in other words we introduce the kinetics of a biochemical reaction system. We remark at this point that if one understands a differential equation automatically to be a scalar one then the precise terminology in our case would be to speak about *system of*

differential equations. However, we shall use the term *differential equation* even when it is not a scalar one, but a system of scalar differential equations.

Consider a reaction system $(\mathcal{A}, \mathcal{C}, \mathcal{R}, R)$. Recall that $B \in \mathbb{R}^{n\times c}$ is the matrix of complexes. We shall consider a model in which the species concentrations are evolving in accordance with the autonomous differential equation

$$\dot{x} = f(x) = \sum_{(i,j)\in\mathcal{R}} R_{(i,j)}(x)(B_{\cdot,j} - B_{\cdot,i}) \tag{3.5}$$

with state space $\mathbb{R}^n$. Note that $f : \mathbb{R}^n \to \mathbb{R}^n$ in (3.5) is locally Lipschitz continuous. This is guaranteed by the fact that a rate function is assumed to be locally Lipschitz continuous. Hence, for all $t_0 \in \mathbb{R}$ and for all $\xi \in \mathbb{R}^n$ there exists a maximal open interval $J(t_0, \xi) \subseteq \mathbb{R}$ containing t_0 and there exists a unique differentiable function $\phi(\cdot; t_0, \xi) : J(t_0, \xi) \to \mathbb{R}^n$, which satisfies

$$\dot{\phi}(\cdot; t_0, \xi) = f(\phi(\cdot; t_0, \xi)), \quad \phi(t_0; t_0, \xi) = \xi.$$

Because (3.5) is autonomous, one can assume without loss of generality that the initial time t_0 is 0. Hence, let $t_0 = 0$ from now on. Denote by $J(\xi)$ the interval $J(0, \xi)$. For the sake of convenience, denote by $J_+(\xi)$ and by $J_{\geq 0}(\xi)$ the intervals $J(\xi) \cap \mathbb{R}_+$ and $J(\xi) \cap \mathbb{R}_{\geq 0}$, respectively. Similarly, let us denote by $\phi(\cdot; \xi)$ the function $\phi(\cdot; 0, \xi)$.

As the introduced differential equation describes the evolution of species concentrations, we are always interested in solutions with initial value in the nonnegative orthant. We shall show in Section 6.1 that no solution starting from $\xi \in \mathbb{R}^n_{\geq 0}$ can leave the nonnegative orthant. This means that the mathematical model of a biochemical reaction system satisfies the qualitative property that no species concentration can become negative.

We now give a short explanation on the assumptions imposed on the rate functions. Let $(i, j) \in \mathcal{R}$. The local Lipschitz continuity is made to guarantee the existence and uniqueness of the solution of (3.5) for every initial value. Further conditions are imposed on the restriction of the rate function $R_{(i,j)}$ to the nonnegative orthant $\mathbb{R}^n_{\geq 0}$. The function $R_{(i,j)}|_{\mathbb{R}^n_{\geq 0}}$ describes how the instantaneous occurrence of reaction (i, j) depends on the instantaneous concentrations. This explains why the values are assumed to be nonnegative. Condition (3.3) expresses that the occurrence of reaction (i, j) is positive if and only if all the ingredient species of the reactant complex C_i are actually present in the system (i.e. their concentrations are positive). Conditions (3.2) and (3.3) are the ones that are imposed on the rate functions in [5]. It is stated in [5] that for particular purposes one should consider a different class of rate functions. Rather, these conditions are regarded as the natural ones that are likely to be respected by a wide variety of kinetic models.

We provide now further explanation on the differential equation (3.5). Let $s \in \overline{1, n}$. Consider the sth equation in (3.5):

$$\dot{x}_s = f_s(x) = \sum_{(i,j)\in\mathcal{R}} R_{(i,j)}(x)(B_{s,j} - B_{s,i}), \tag{3.6}$$

for $x \in \mathbb{R}^n$. The subindex of f indicates the corresponding coordinate function. Thus $\dot{x}_s$ equals to the weighted sum of the reaction rates at x over the set of reactions. The weight for $(i, j) \in \mathcal{R}$ is the difference between the stoichiometric coefficients of A_s in the product complex C_j and in the reactant complex C_i. Suppose now that $R_{(i,j)}(x) > 0$ for some $x \in \mathbb{R}^n_{\geq 0}$. Then the sign of $R_{(i,j)}(x)(B_{s,j} - B_{s,i})$ equals to the sign of $B_{s,j} - B_{s,i}$. Therefore

the concentration of the species A_s in that individual reaction increases, decreases, or does not change, respectively to the sign of $B_{s,j} - B_{s,i}$.

Another form of (3.5) is useful to introduce. Recall that m denotes the number of elements of the set of reactions $\mathcal{R}$ and the coordinate functions of the function $R : \mathbb{R}^n \to \mathbb{R}^m$ are indexed by the reactions. Let $q : \mathcal{R} \to \overline{1,m}$ be a bijection. Define $S \in \mathbb{R}^{n\times m}$ by

$$S_{\cdot,k} = B_{\cdot,j} - B_{\cdot,i}$$

for $k \in \overline{1,m}$, where $q(i,j) = k$. The matrix S is called the *stoichiometric matrix*. Denote the range of S by $\mathcal{S}$. The linear space $\mathcal{S}$ is called the *stoichiometric subspace*. If we label the reactions in Example 3.2.2 according to (3.1) then the stoichiometric matrix $S \in \mathbb{R}^{8\times 9}$ in that example is

$$S = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & -2 & 0 & 0 & 2 \\ -1 & 1 & 0 & 0 & 0 & 1 & -1 & 1 & 0 \\ 1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & -1 \end{bmatrix}.$$

One can now easily see that (3.5) can be written equivalently in the form

$$\dot{x} = S \cdot R(x). \tag{3.7}$$

We remark that (3.7) allows us to reduce the dimension of the state space of the reaction system. Assume that the s^*th row of S is a linear combination of the other rows of S for some $s^* \in \overline{1,n}$:

$$S_{s^*,\cdot} = \sum_{s\in\overline{1,n}\setminus\{s^*\}} \alpha_s S_{s,\cdot},$$

where $\alpha_s \in \mathbb{R}$ for $s \in \overline{1,n}\setminus\{s^*\}$. Let $\xi \in \mathbb{R}^n$ be the initial value of (3.7). Then

$$\dot{x}_{s^*} = \sum_{s\in\overline{1,n}\setminus\{s^*\}} \alpha_s \dot{x}_s$$

and hence there exists $d \in \mathbb{R}$ such that

$$\phi_{s^*}(t;\xi) - \sum_{s\in\overline{1,n}\setminus\{s^*\}} \alpha_s \phi_s(t;\xi) = d$$

for all $t \in J(\xi)$, where the subindex of ϕ indicates the corresponding coordinate function. The constant d equals to

$$\phi_{s^*}(0;\xi) - \sum_{s\in\overline{1,n}\setminus\{s^*\}} \alpha_s \phi_s(0;\xi) = \xi_{s^*} - \sum_{s\in\overline{1,n}\setminus\{s^*\}} \alpha_s \xi_s.$$

After one has the constant d, it is possible to write for $s \in \overline{1,n}\setminus\{s^*\}$

$$\dot{x}_s = f_s\left(x_1, \ldots, x_{s^*-1}, \left(d + \sum_{\overline{s}\in\overline{1,n}\setminus\{s^*\}} \alpha_{\overline{s}} x_{\overline{s}}\right), x_{s^*+1}, \ldots, x_n\right).$$

A new differential equation with state space $\mathbb{R}^{n-1}$ can thus be obtained. Clearly, if one has established certain dynamic system properties of the new differential equation then direct consequences for the original system can also be derived. Using this procedure successively, one can reduce the dimension of the state space of the system to rank S. However, we will not consider this reduction in this thesis, we shall examine the differential equation in its original form.

We conclude this section by introducing another equivalent form of (3.5) in case of mass action systems. This form is then not used later in this thesis, but it is worth to mention that one can also investigate dynamic system properties using this new form. This way is followed in [10].

Recall that the rate functions are defined by (3.4) in case of a mass action system. Note that for mass action systems the rate functions $R_{(i,j_1)}$ and $R_{(i,j_2)}$ differ only in the constants $\kappa_{(i,j_1)}$ and $\kappa_{(i,j_2)}$ ($(i,j_1),(i,j_2) \in \mathcal{R}$). In other words, if two reactions have the same reactant complex then the rate functions corresponding to those reactions satisfy the equality

$$\frac{1}{\kappa_{(i,j_1)}} R_{(i,j_1)} = \frac{1}{\kappa_{(i,j_2)}} R_{(i,j_2)}.$$

Define the diagonal matrix $\widetilde{G} \in \mathbb{R}^{c \times c}$ by

$$\widetilde{G}_{i,i} = \sum_{\substack{(i',j') \in \mathcal{R} \\ i'=i}} \kappa_{(i',j')}$$

for $i \in \overline{1,c}$. Define $G \in \mathbb{R}^{c \times c}$ by

$$G_{i,j} = \begin{cases} \kappa_{(j,i)}, & \text{if } (j,i) \in \mathcal{R}, \\ 0, & \text{if } (j,i) \notin \mathcal{R} \end{cases}$$

for $i,j \in \overline{1,c}$. Define the function $\Theta_B : \mathbb{R}^n \to \mathbb{R}^c_{\geq 0}$ by

$$\Theta_B(x) = \begin{bmatrix} \prod_{s=1}^n |x_s|^{B_{s,1}} \\ \vdots \\ \prod_{s=1}^n |x_s|^{B_{s,c}} \end{bmatrix}$$

for $x \in \mathbb{R}^n$. It is easy to see that in case of mass action systems, $S \cdot R(x) = B \cdot (G - \widetilde{G}) \cdot \Theta_B(x)$. Hence, one can reformulate (3.5) as

$$\dot{x} = B \cdot (G - \widetilde{G}) \cdot \Theta_B(x). \tag{3.8}$$

Let $i,j \in \overline{1,c}$ such that $i \neq j$. Then $(G - \widetilde{G})_{i,j} \neq 0$ if and only if $(j,i) \in \mathcal{R}$. We remark that one can define irreducibility of a square matrix in several equivalent ways. It turns out that $G - \widetilde{G}$ is irreducible if and only if the directed graph $(\mathcal{C}, \mathcal{R})$ is strongly connected. Directed graphs and related notions are discussed in Chapter 4. However, we do not discuss in more detail irreducibility, because we will not use (3.8) later.

Chapter 4

Preliminaries on graphs

In Chapter 3 the notion of biochemical reaction network is introduced. It is natural to associate a directed graph to a biochemical reaction network. First we introduce the notion of a directed graph and explain how can one relate a directed graph to a biochemical reaction network. This graph will be called the *graph of complexes*.

In this chapter we introduce some well known concepts of graph theory. General reference for these concepts is [9]. The terminology and results of this chapter are then applied to the graph of complexes in the subsequent chapters.

4.1 Directed graphs

In this section we introduce the notion of directed graphs and also related notions to it. All the definitions in this section are well known, they are collected here for the sake of completeness. The definitions however are adjusted to the situation we have in case of biochemical reaction networks. For instance, we do not consider infinite graphs.

Let V be a nonempty finite set with c elements. Let A be a nonempty family of ordered pairs from V. Then the ordered pair $D = (V, A)$ is called a *directed graph*, or *digraph*. The set V is called the set of *vertices* of D and the family A is called the family of *arcs* of D. The term *family* is used to indicate that the same pair of vertices may occur several times in A. A pair occurring more than once is called a *multiple arc*. An arc of the form (i, i) is called a *loop* ($i \in V$). A directed graph is said to be *simple* if A does not contain any loop or multiple arc.

In this thesis the term *graph* always refers to a directed graph.

Recall that the nonempty finite set $\mathcal{C}$ denotes the set of complexes of a biochemical reaction network. Recall also that $\mathcal{R}$ denotes the set of reactions. The ordered pair $(\mathcal{C}, \mathcal{R})$ is a directed graph in the sense of the above definition. This graph is called the *graph of complexes*. Note that $(\mathcal{C}, \mathcal{R})$ is a simple directed graph. The terminology and results of this chapter are applied to the graph of complexes. Hence, a directed graph in this chapter is automatically understood to be a simple one. In case of simple graphs, one does not have to use the term *family*. We shall always call A to be the *set* of arcs.

Let (V, A) be a directed graph. Let $(i, j) \in A$. Then $i \in V$ is called the *tail* of the arc (i, j) and $j \in V$ is called the *head* of the arc (i, j).

Directed graphs are often visualized in figures. One can represent vertices by points and

indicate arcs by arrows. The arrows are pointing from the tail of the arc to the head of the arc. For reaction networks, these figures are called reaction schemes. For instance, the graph of complexes for Example 3.2.2 is displayed in Figure 3.1.

In terms of graphs, that each complex of a reaction network is involved in at least one reaction of the biochemical reaction network means that for all vertices there exists an arc for which that vertex is the head or the tail. We also assume from now on that all the considered graphs have this property.

Further terminology follows.

Definition 4.1.1 Let $D = (V, A)$ be a directed graph. Let $l \geq 0$, $i_0, i_1, \ldots, i_l \in V$, and $a_1, \ldots, a_l \in A$. Then $P = (i_0, a_1, i_1, \ldots, a_l, i_l)$ is called a *directed walk* between i_0 and i_l if $a_k = (i_{k-1}, i_k)$ for all $k \in \overline{1,l}$. A directed walk between i_0 and i_l is called a *directed path* if $i_0, i_1, \ldots, i_l$ are all distinct. A directed walk between i_0 and i_l is called a *directed circuit* if $i_0 = i_l$, $l \geq 1$, and $i_1, \ldots, i_l$ are all distinct.

Definition 4.1.2 Let $D = (V, A)$ be a directed graph. Let $l \geq 0$, $i_0, i_1, \ldots, i_l \in V$, and $a_1, \ldots, a_l \in A$. Then $P = (i_0, a_1, i_1, \ldots, a_l, i_l)$ is called an *undirected walk* between i_0 and i_l if $a_k = (i_{k-1}, i_k)$ or $a_k = (i_k, i_{k-1})$ for all $k \in \overline{1,l}$. The arcs a_k with $a_k = (i_{k-1}, i_k)$ are called the *forward arcs* of P and the arcs a_k with $a_k = (i_k, i_{k-1})$ are called the *backward arcs* of P ($k \in \overline{1,l}$). An undirected walk between i_0 and i_l is called an *undirected path* if $i_0, i_1, \ldots, i_l$ are all distinct. An undirected walk between i_0 and i_l is called an *undirected circuit* if $i_0 = i_l$, $l \geq 1$, and $i_1, \ldots, i_l$ are all distinct.

Definition 4.1.3 Let $D = (V, A)$ be a directed graph. The directed graph $D' = (V', A')$ is called a *subgraph* of D if $V' \subseteq V$ and $A' \subseteq A$. If $V' = V$ then D' is called a *spanning subgraph* of D.

Definition 4.1.4 Let $D = (V, A)$ be a directed graph. Then D is called *connected* if for all $i, j \in V$ there exists an undirected path between i and j. The directed graph D is called *strongly connected* if for all $i, j \in V$ there exists a directed path between i and j. A maximal connected subgraph of D is called a *connected component*, or just a *component*, of D.

The term maximal in the above definition is taken with respect to taking subgraphs.

We remark that sometimes the terms *weakly connected* and *weakly connected component* are used instead of *connected* and *connected component*, respectively. However, we avoid these terms, because in Chapter 6 we introduce the notion of a *weakly reversible* reaction network, which is defined in [5]. As we shall see, it would be misleading to use the terms weakly connected and weakly connected component when speaking about biochemical reaction networks.

It shall turn out later that the directed graphs, which have the property that all of its components are strongly connected are especially interesting in the study of biochemical reaction systems.

Definition 4.1.5 A directed graph is called a *directed forest* if there is no undirected circuit in it. A connected directed forest is called a *directed tree*.

4.2 The incidence matrix

The aim of this section is to introduce the notion of incidence matrix of a directed graph. The main results of this section are two proposition about the rank and the range of an incidence matrix. These propositions are then applied in Chapter 5.

Even though the content of this section is well known, we present also the proofs of the statements, because the reader of this thesis may not be familiar with graph theory.

Let us start with the definition of the incidence matrix. Let $D = (V, A)$ be a directed graph. Consider V to be the set $\overline{1, c}$ for some positive integer c. Denote by m the number of elements of A. Let $q : A \to \overline{1, m}$ be a bijection.

Definition 4.2.1 Let us define the *incidence matrix* $I \in \mathbb{R}^{c \times m}$ of the directed graph $D = (V, A)$ by

$$I_{i,k} = \begin{cases} -1, & \text{if } q^{-1}(k) = (i, j) \text{ for some } j \in V, \\ +1, & \text{if } q^{-1}(k) = (j, i) \text{ for some } j \in V, \\ 0, & \text{otherwise,} \end{cases}$$

where $i \in \overline{1, c}$ and $k \in \overline{1, m}$.

The following proposition contains the main observation that will be applied in the proposition that establishes the rank of the incidence matrix.

Proposition 4.2.2 Let I be the incidence matrix of the directed graph $D = (V, A)$. Then the columns of I are linearly dependent if and only if the graph contains an undirected circuit.

Proof Suppose that the graph contains an undirected circuit. Consider a linear combination of the columns of the incidence matrix corresponding to this undirected circuit, where the coefficients are 1 and -1 depending on whether the arc is a forward or a backward one of that undirected circuit. Clearly, the result is the zero vector in $\mathbb{R}^c$, hence, the columns of I are linearly dependent.

To show the converse direction, assume that the columns of I are linearly dependent. Let us choose a nonempty linearly dependent subset of the columns (i.e. a subset of the arcs) such that all its nonempty proper subsets consists of linearly independent vectors. Consider a nontrivial linear combination of the chosen vectors, which results the zero vector. By the above property, all the coefficients are nonzero. Consider the vertices, which are tails or heads of at least one chosen arc. Then there exist at least two of chosen arcs for which these vertices are heads or tails (by the nonzero coefficients). One can then easily construct an undirected circuit. □

Denote by ℓ the number of connected components of D.

Proposition 4.2.3 Let I be the incidence matrix of the directed graph $D = (V, A)$. Then $\operatorname{rank} I = c - \ell$.

Proof Pick any linearly independent subset of the columns of the incidence matrix such that adding any other column to that subset yields in a set of linearly dependent vectors. The rank of the incidence matrix equals to the cardinality of such a set. By Proposition

4.2.2, we get linearly independent columns of the incidence matrix exactly when we choose columns for which the corresponding subgraph of (V, A) does not contain any undirected circuit (i.e. it is a directed forest). Thus, to choose maximal number of linearly independent columns is exactly to choose a directed forest, which is maximal among the directed trees, which are spanning subgraphs of D. Clearly, the number of vertices and the number of connected components of this chosen directed tree are the same as in D. This concludes the proof, because the number of arcs in a directed forest equals to the number of vertices minus the number of connected components. □

Due to the above proposition, $\operatorname{rank} I = c - \ell$. It is also possible to completely determine the range of I. There is a natural way of enumerating the vertices and arcs. Let us assume that $D = (V, A)$ has ℓ connected components: $D_1 = (V_1, A_1), D_2 = (V_2, A_2), \ldots, D_\ell = (V_\ell, A_\ell)$. Then V is the disjoint union of the sets $V_1, V_2, \ldots, V_\ell$ and A is the disjoint union of the sets $A_1, A_2, \ldots, A_\ell$. Let $c_r = |V_r|$ and $m_r = |A_r|$ $(r \in \overline{1,\ell})$. Let us enumerate the vertices and arcs according to these partitions and let us denote by $I^r \in \mathbb{R}^{c_r \times m_r}$ the incidence matrix of $D_r = (V_r, A_r)$ $(r \in \overline{1,\ell})$. Then the incidence matrix I has the following block diagonal form:

$$I = \begin{bmatrix} I^1 & 0 & \cdots & 0 \\ 0 & I^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & I^\ell \end{bmatrix} \in \mathbb{R}^{(\sum c_r)\times(\sum m_r)}.$$

We also write the incidence matrix I in the following form:

$$I = [I_1, I_2, \ldots, I_\ell],$$

where $I_r \in \mathbb{R}^{c \times m_r}$ $(r \in \overline{1,\ell})$.

It can be seen from these forms of the incidence matrix that

$$\operatorname{ran} I = \operatorname{ran} I_1 \oplus \operatorname{ran} I_2 \oplus \cdots \oplus \operatorname{ran} I_\ell,$$

where ran denotes the range of a matrix and the symbol $\oplus$ denotes direct sum. One can see from these observations that it is enough to determine the range of the incidence matrix for a connected graph. If $D_r = (V_r, A_r)$ is connected then $\operatorname{rank} I^r = c_r - 1$ due to Proposition 4.2.3 $(r \in \overline{1,\ell})$. The sum of the rows of the incidence matrix I^r is the zero vector in $\mathbb{R}^{m_r}$, because all the columns contains an entry 1, an entry -1, and the other entries are zeros. This means that $\operatorname{ran} I^r$ is a linear subspace of the linear space $\{v \in \mathbb{R}^{c_r} : v_1 + v_2 + \cdots + v_{c_r} = 0\}$ $(r \in \overline{1,\ell})$. But the dimensions of these two linear spaces are equal, thus these linear spaces must be equal. Thus, we have proven the following proposition:

Proposition 4.2.4 The range of the incidence matrix I is

$$\{v \in \mathbb{R}^c \mid v_{N_r+1} + v_{N_r+2} + \cdots + v_{N_r+c_r} = 0 \text{ for all } r \in \overline{1,\ell}\},$$

where $N_r = \sum_{i=1}^{r-1} c_i$ $(r \in \overline{1,\ell})$.

4.3 Circulations

In this section we introduce the notion of a circulation on a directed graph. As it turns out in the subsequent chapters, this is a useful tool for examining some dynamic system properties

of biochemical reaction systems. The notion of a circulation is standard in graph theory (see e.g. [9]).

Let $D = (V, A)$ be a directed graph and $T \subseteq V$. Let us define the sets $A_\delta(T)$ and $A_\varrho(T)$ by

$$\begin{aligned} A_\delta(T) &= \{(i,j) \in A \mid i \in T, j \in V\backslash T\} \text{ and} \\ A_\varrho(T) &= \{(i,j) \in A \mid i \in V\backslash T, j \in T\}. \end{aligned}$$

In words, an arc in $A_\delta(T)$ has its tail in T and its head in $V\backslash T$. Similarly, an arc in $A_\varrho(T)$ has its tail in $V\backslash T$ and its head in V. Clearly, $A_\delta(T) = A_\varrho(V\backslash T)$ and $A_\varrho(T) = A_\delta(V\backslash T)$. Let $y : A \to \mathbb{R}$ be a function. Using the above notations, define $\delta_y(T)$ and $\varrho_y(T)$ by

$$\begin{aligned} \delta_y(T) &= \sum_{(i,j)\in A_\delta(T)} y(i,j) \text{ and} \\ \varrho_y(T) &= \sum_{(i,j)\in A_\varrho(T)} y(i,j). \end{aligned}$$

Clearly, $\delta_y(T) = \varrho_y(V\backslash T)$ and $\varrho_y(T) = \delta_y(V\backslash T)$.

The symbol δ will have a different meaning in the subsequent chapters. This will not cause ambiguity, because notations of this section that are containing the symbol δ are not used in those chapters.

Definition 4.3.1 Let $D = (V, A)$ be a directed graph. A function $y : A \to \mathbb{R}$ is called a *circulation* if $\delta_y(\{i\}) = \varrho_y(\{i\})$ for all $i \in V$.

The requirement in the definition is called the *conservation rule*. Clearly, we have an equivalent definition for circulation if we require that $\delta_y(T) = \varrho_y(T)$ for all $T \subseteq V$. An example of a circulation can be found in Figure 4.1.

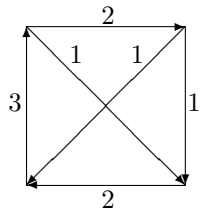


Figure 4.1: Example of a circulation

An important observation is the following proposition. Recall that I denotes the incidence matrix of $D = (V, A)$ and $q : A \to \overline{1, m}$ is a bijection.

Proposition 4.3.2 Let $D = (V, A)$ be a directed graph. Let $y : A \to \mathbb{R}$ be any function. Let us define the vector $\underline{y} \in \mathbb{R}^m$ by $\underline{y}_k = y(q^{-1}(k))$ for $k \in \overline{1, m}$. Then y is a circulation if and only if $\underline{y} \in \ker I$.

Proof The statement is clear from the definitions of the incidence matrix and of a circulation. □

As we shall see in the subsequent chapters, when examining equilibrium points of biochemical reaction systems, $\ker I$ is of interest. Hence, the above observation about the connection between the kernel of the incidence matrix and circulations on a directed graph

allows us to use tools of graph theory when investigating the set of equilibria for a biochemical reaction system. For this purpose, we work out statements about circulations.

For biochemical reaction systems, the elements of $\ker I$ for which all entries are positive are the most interesting. Let us call a circulation to be a *positive circulation* if $y(i,j) > 0$ for all $(i,j) \in A$. Clearly, if y is defined by $y(i,j) = 0$ for $(i,j) \in A$ then y is a circulation. Call this circulation the *zero circulation*. Any other circulation than the zero circulation is called *nonzero circulation*.

Theorem 4.3.3 Let $D = (V, A)$ be a directed graph. Then there exists a positive circulation on D if and only if all the components of D are strongly connected.

Proof Assume that there exists a positive circulation $y : A \to \mathbb{R}_+$ on D. Let $D' = (V', A')$ be a connected component of D, which is not strongly connected. Then there exist $\emptyset \neq T \subseteq V'$ such that $A_\delta(T) = \emptyset$ and $A_\varrho(T) \neq \emptyset$. Then, by the positivity of y, $0 = \delta_y(T) = \varrho_y(T) > 0$, contradiction. Hence, all the components of D must be strongly connected.

Assume now that all of the components of D are strongly connected. We shall show a construction of a positive circulation y. If $P = (i_0, a_1, i_1, \ldots, a_l, i_l)$ is a directed circuit then let us define $y_P : A \to \mathbb{R}$ by

$$y_P(i,j) = \begin{cases} 1, & \text{if } (i,j) = a_k \text{ for some } k \in \overline{1,l}, \\ 0, & \text{otherwise} \end{cases}$$

for $(i,j) \in A$. Clearly, y_P is a circulation. Since $\ker I$ is a linear space, linear combination of circulations is a circulation due to Proposition 4.3.2. We assumed that all the components of D are strongly connected. This means that for each $(i,j) \in A$ there exists a directed circuit through (i,j). Choose a set of directed circuits such that each $(i,j) \in A$ is covered by at least one of the chosen directed circuits. For each directed circuit we define a circulation as it was shown for P. Sum these circulations and the resulting circulation is clearly a positive circulation. □

The preceding theorem tells us what property of a graph is equivalent to the existence of a positive circulation on it. Another question is also arising when biochemical reaction systems are examined. Which property of a graph can guarantee that there exists a positive circulation y for which $y(i,j_1) = y(i,j_2)$ holds for all $(i,j_1),(i,j_2) \in A$? In words, if two arcs have common tail then the value of y on those arcs must be equal. It turns out that if a positive circulation exists then a positive circulation with the above property also exists. We shall show that this claim holds, moreover, a little more is also true.

Let us start with a well known proposition of linear algebra.

Proposition 4.3.4 If $u, v \in \mathbb{R}^m_+$ are linearly independent vectors then the linear subspace of $\mathbb{R}^m$ generated by u and v contains vectors with both positive and negative coordinates.

Proof Let us define the function $g : \mathbb{R} \to \mathbb{R}^m$ by $g(\lambda) = v - \lambda u$ for $\lambda \in \mathbb{R}$. Let $\lambda_1 = \min\{\frac{v_k}{u_k} \mid k \in \overline{1,m}\}$ and $\lambda_2 = \max\{\frac{v_k}{u_k} \mid k \in \overline{1,m}\}$. The imposed requirements on u and v ensure that $0 < \lambda_1 < \lambda_2 < \infty$. For any $\lambda \in (\lambda_1, \lambda_2)$, $g(\lambda)$ is in the linear subspace generated by u and v, and has both positive and negative coordinates. □

It is not known to the author of this thesis whether the implication of Theorem 4.3.5 is known or not.

Let $y : A \to \mathbb{R}$ be any function. If $\alpha \in \mathbb{R}$ then define $\alpha y : A \to \mathbb{R}$ by $(\alpha y)(i,j) = \alpha \cdot y(i,j)$ for $(i,j) \in A$.

Theorem 4.3.5 Let us assume that $D = (V, A)$ is a strongly connected graph. Let $\kappa : A \to \mathbb{R}_+$ be a given function. Then there exists a positive circulation $y : A \to \mathbb{R}$ such that

$$\frac{y(i,j_1)}{\kappa(i,j_1)} = \frac{y(i,j_2)}{\kappa(i,j_2)} \tag{4.1}$$

for all $(i,j_1),(i,j_2) \in A$. Moreover, if $y : A \to \mathbb{R}$ is such a circulation then the set

$$\{\alpha y : A \to \mathbb{R} \mid \alpha \in \mathbb{R}_+\}$$

gives all the circulations with the above property.

Proof Note that $A \neq \emptyset$ and the strong connectivity of D implies that for all $i \in V$ there exists $a \in A$ for which i is the tail of a. Let us fix $i \in V$. Assume that there are t_i different arcs in A with tail i: $(i,j_1),\ldots,(i,j_{t_i}) \in A$. Due to the first sentence of this proof, $t_i \geq 1$. Then there are $t_i - 1$ homogeneous linear requirements of the form

$$\frac{y(i,j_1)}{\kappa(i,j_1)} = \frac{y(i,j_k)}{\kappa(i,j_k)} \tag{4.2}$$

for $k \in \overline{2,t_i}$. It means that we have $\sum_{i\in V}(t_i - 1) = (\sum_{i\in V} t_i) - c = m - c$ homogeneous linear equations. We also have c linear equations for a circulation from the incidence matrix (see Proposition 4.3.2). So altogether we have $(m-c)+c = m$ homogeneous linear equations for the m values of a circulation. But these conditions are linearly dependent, because the sum of the rows of the incidence matrix is the zero vector in $\mathbb{R}^m$. It means that there exists a nonzero circulation which satisfies condition (4.1).

The next step is to show that a positive circulation with the above property also exists. Let $y : A \to \mathbb{R}$ be a nonzero circulation which satisfies condition (4.1). Recall that the values of κ are positive. This implies that the value of y on arcs with common tail have the same sign: $\operatorname{sgn}(y(i,j_1)) = \operatorname{sgn}(y(i,j_2))$ $((i,j_1),(i,j_2) \in A)$. Let us define the sets V_-, V_0, and V_+ by

$$\begin{aligned} V_- &= \{i \in V \mid y(i,j) < 0 \text{ for arcs with tail } i\}, \\ V_0 &= \{i \in V \mid y(i,j) = 0 \text{ for arcs with tail } i\}, \quad \text{and} \\ V_+ &= \{i \in V \mid y(i,j) > 0 \text{ for arcs with tail } i\}. \end{aligned}$$

Clearly, V is the disjoint union of V_-, V_0, and V_+. Suppose that $V_- \neq \emptyset$ and $V_0 \cup V_+ \neq \emptyset$. The digraph $D = (V, A)$ is assumed to be strongly connected, hence $A_\delta(V_-) = A_\varrho(V_0 \cup V_+) \neq \emptyset$ and $A_\varrho(V_-) = A_\delta(V_0 \cup V_+) \neq \emptyset$. Then $0 > \delta_y(V_-) = \varrho_y(V_-) = \delta_y(V_0 \cup V_+) \geq 0$, contradiction. (Note that the conservation rule was used for the set V_-.) This means that either $V_- = \emptyset$ or $V_0 \cup V_+ = \emptyset$. If $V_0 \cup V_+ = \emptyset$ then $V_- = V$ and $-y$ satisfies all the conditions in the statement of the theorem and we are done. If $V_- = \emptyset$ then $V = V_0 \cup V_+$. The set V_+ cannot be the empty set, because y is assumed to be nonzero. If $V_0 \neq \emptyset$ then $A_\delta(V_0) = A_\varrho(V_+) \neq \emptyset$ and $A_\varrho(V_0) = A_\delta(V_+) \neq \emptyset$. Then $0 = \delta_y(V_0) = \varrho_y(V_0) = \delta_y(V_+) > 0$, contradiction. (Note that the conservation rule was used for the set V_0.) This means that $V_0 = \emptyset$ and $V_+ = V$. Hence, y is a positive circulation.

It is clear from the previous paragraph that if a nonzero circulation y satisfies condition (4.1) then either y or $-y$ is positive.

Pick now any positive circulation y that satisfies condition (4.1). Clearly, αy ($\alpha \in \mathbb{R}_+$) also satisfies all the conditions in the statement of the theorem. Moreover, if we leave the positivity requirement then circulations satisfying condition (4.1) constitute a linear space. It remains to show that all the positive circulations satisfying condition (4.1) are positive multiples of y. Suppose by contradiction that there exist two positive circulations y_1 and y_2 that satisfy condition (4.1). Suppose that $\underline{y_1}$ and $\underline{y_2}$ are linearly independent. Then $\underline{y_1}$ and $\underline{y_2}$ satisfy the conditions of Proposition 4.3.4. This means that there exists a circulation which has both positive and negative values and satisfies conditions (4.1). But this is not possible, as we saw it in the previous paragraph of this proof. This concludes the proof. □

A similar statement to the above theorem also holds when the graph has more than one component and each of the components is strongly connected. Recall that ℓ denotes the number of connected components of $D = (V, A)$. Let us denote by $A_r \subseteq A$ the set of arcs in the rth connected component ($r \in \overline{1, \ell}$). Clearly, A is the disjoint union of the sets $A_1, A_2, \ldots, A_\ell$. If $y : A \to \mathbb{R}$ is a circulation and $r \in \overline{1, \ell}$ then let us define the circulation $y_r : A \to \mathbb{R}$ by

$$y_r(i,j) = \begin{cases} y(i,j), & \text{if } (i,j) \in A_r, \\ 0, & \text{if } (i,j) \in A \backslash A_r. \end{cases}$$

Clearly, y_r is indeed a circulation on $D = (V, A)$. The following theorem is an immediate consequence of Theorem 4.3.5.

Theorem 4.3.6 Let us assume that all components of the graph $D = (V, A)$ are strongly connected. Let $\kappa : A \to \mathbb{R}_+$ be a given function. Then there exists a positive circulation $y : A \to \mathbb{R}$ such that

$$\frac{y(i,j_1)}{\kappa(i,j_1)} = \frac{y(i,j_2)}{\kappa(i,j_2)}$$

for all $(i, j_1), (i, j_2) \in A$. Moreover, if $y : A \to \mathbb{R}$ is such a circulation then the set

$$\left\{ \sum_{r=1}^{\ell} \alpha_r y_r : A \to \mathbb{R} \;\middle|\; \alpha_r \in \mathbb{R}_+ \text{ for all } r \in \overline{1, \ell} \right\}$$

gives all the circulations with the above property.

We conclude this section by a remark. Suppose that all the components of $D = (V, A)$ are strongly connected and the function $\kappa : A \to \mathbb{R}_+$ in Theorem 4.3.6 is defined by $\kappa(i, j) = 1$ for $(i, j) \in A$. Then the conclusion is that there exists a positive circulation $y : A \to \mathbb{R}$ on D such that the values of y are equal on arcs with common tail.

Chapter 5

Deficiency

In this chapter we introduce the notion of *deficiency*. It turns out that this notion plays an important role in the dynamic behaviour of biochemical reaction systems.

5.1 Introduction

Biochemical reaction systems are defined in Chapter 3. Let $(\mathcal{A}, \mathcal{C}, \mathcal{R}, R)$ be a reaction system. Recall that n denotes the number of species, c denotes the number of complexes, and m denotes the number of reactions in the underlying biochemical reaction network. Recall also the definition of the $n \times m$ stoichiometric matrix S. We repeat (3.7), the differential equation, which governs the evolution of the system:

$$\dot{x} = S \cdot R(x). \tag{5.1}$$

Having in hand the notion of the incidence matrix, the differential equation (5.1) can be written in a new form. Namely, the stoichiometric matrix S can be written as a product of two matrices. Recall that $B \in \mathbb{R}^{n \times c}$ is the matrix of complexes. Denote by I the incidence matrix of the directed graph $(\mathcal{C}, \mathcal{R})$. Then $I \in \mathbb{R}^{c \times m}$.

Proposition 5.1.1 The stoichiometric matrix is the product of the matrix of complexes and the incidence matrix of the graph of complexes: $S = B \cdot I$.

Proof Recall that $q : \mathcal{R} \to \overline{1, m}$ is a bijection. If $q(i, j) = k$ then the kth column of I contains an entry -1 in its ith row and an entry 1 in its jth row. The other entries in the kth column are zeros. This means that the kth column of the product $B \cdot I$ is $B_{\cdot,j} - B_{\cdot,i}$. The definition of S is the same. □

By Proposition 5.1.1, the differential equation (5.1) can be written in the form

$$\dot{x} = B \cdot I \cdot R(x). \tag{5.2}$$

One can expect that certain properties of the matrices S, B, and I have crucial role in the behaviour of the system. The notion of deficiency relates an integer number to a reaction network via these matrices. Note that these matrices are determined by the underlying reaction network of a reaction system. In other words, they are not depending on the precise nature of the rate functions. In Chapter 6, assumption on the deficiency of the underlying reaction network is often imposed.

5.2 Linkage classes

Before introducing the notion of deficiency, we define the linkage classes of a biochemical reaction network.

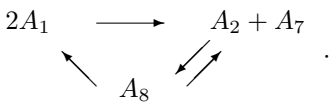
Let $(\mathcal{C}, \mathcal{R})$ be the graph of complexes. Denote by ℓ the number of connected components of $(\mathcal{C}, \mathcal{R})$. Let the connected components be $(\mathcal{C}_1, \mathcal{R}_1), \ldots, (\mathcal{C}_\ell, \mathcal{R}_\ell)$. The sets $\mathcal{C}_1, \ldots, \mathcal{C}_\ell$ are called the *linkage classes* of a reaction network [5]. Using this terminology, the linkage classes for Example 3.2.2 are the sets

$$\{A_1 + A_2, A_3, A_4 + A_5, A_6\} \text{ and } \{2A_1, A_2 + A_7, A_8\}.$$

However, the author of this thesis proposes to call the components of $(\mathcal{C}, \mathcal{R})$ to be the linkage classes of a reaction network. This seems to be more convenient, because then one can speak about reactions in a certain linkage class. It also allows us to speak about graph theoretic properties of a linkage class, for instance, one can say that a certain linkage class is strongly connected. Applying this new terminology, the linkage classes in Example 3.2.2 are the connected graphs

$$A_1 + A_2 \rightleftarrows A_3 \longrightarrow A_4 + A_5 \rightleftarrows A_6$$

and



Throughout this thesis, we shall use the proposed new terminology.

Denote by ℓ the number of linkage classes. In Example 3.2.2, $\ell = 2$.

Assume that the linkage classes are labeled by the elements of the set $\overline{1, \ell}$. Let $r \in \overline{1, \ell}$. Then it is natural to introduce quantities for the rth linkage class. As it was already done before, denote by $\mathcal{C}_r$ and by $\mathcal{R}_r$ the set of complexes and the set of reactions in the rth linkage class, respectively. Using these notations, the linkage classes of a reaction network are the directed graphs $(\mathcal{C}_1, \mathcal{R}_1), \ldots, (\mathcal{C}_\ell, \mathcal{R}_\ell)$. Denote by c_r and m_r the number of complexes and the number of reactions in the rth linkage class, respectively. Other notions, for instance the stoichiometric matrix of a linkage class, are also useful to introduce, but this is done at the moment when we first need them.

5.3 Deficiency of a reaction network

In this section we define the notion of *deficiency* for a reaction network. Alternative definitions are also discussed.

Recall that ℓ denotes the number of linkage classes of a biochemical reaction network. The following definition is due to M. Feinberg [5].

Definition 5.3.1 Define the *deficiency* of a reaction network as $c - \ell - \operatorname{rank} S$. Usual notation for the deficiency is the symbol δ.

In Definition 5.3.1, using the notations introduced in Chapter 3, one can replace $\operatorname{rank} S$ by $\dim \mathcal{S}$. The deficiency of the reaction network in Example 3.2.2 can be calculated easily. In that example, $\operatorname{rank} S = 5$ and therefore $\delta = 7 - 2 - 5 = 0$.

We emphasise that the deficiency is defined for a reaction network. Naturally, one can speak about the deficiency of a reaction system. Namely, it is the deficiency of its reaction network. The deficiency of a reaction system is therefore not depending on the kinetics of the system. The following proposition implies that the deficiency of a network is not depending on how the reactions connect complexes inside a linkage class. In other words, one can determine the deficiency of a network just by knowing how the set of complexes $\mathcal{C}$ is partitioned according to the connected components of the graph of complexes $(\mathcal{C}, \mathcal{R})$.

Recall that $B \in \mathbb{R}^{n \times c}$ denotes the matrix of complexes and $\mathcal{S}$ denotes the range of the stoichiometric matrix $S \in \mathbb{R}^{n \times m}$.

Proposition 5.3.2 Let

$$\mathcal{S}' = \operatorname{span}\{B_{\cdot,j} - B_{\cdot,i} \in \mathbb{R}^n \mid i, j \in \mathcal{C}_r \text{ with } r \in \overline{1,\ell}\}. \tag{5.3}$$

Then $\mathcal{S} = \mathcal{S}'$.

Proof Since the set of spanning vectors of $\mathcal{S}$ is a subset of the set of spanning vectors of $\mathcal{S}'$, $\mathcal{S} \subseteq \mathcal{S}'$.

Observe that the stoichiometric subspace $\mathcal{S}$ can also be defined by

$$\mathcal{S} = \operatorname{span}\{B_{\cdot,j} - B_{\cdot,i} \in \mathbb{R}^n \mid (i,j) \in \mathcal{R} \text{ or } (j,i) \in \mathcal{R}\}.$$

Pick any $i, j \in \mathcal{C}_r$ with $r \in \overline{1,\ell}$ such that $i \neq j$. Since C_i and C_j are from the same component of the graph of complexes $(\mathcal{C}, \mathcal{R})$, there exists an undirected path $(i, a_1, i_1, \ldots, a_{l-1}, i_{l-1}, a_l, j)$ between i and j for some $l \geq 1$. Using the notations $i_0 = i$ and $i_l = j$, due to the above made observation,

$$B_{\cdot,i_q} - B_{\cdot,i_{q-1}} \in \mathcal{S} \text{ for all } q \in \overline{1,l}.$$

The observation

$$B_{\cdot,j} - B_{\cdot,i} = \sum_{q=1}^{l} (B_{\cdot,i_q} - B_{\cdot,i_{q-1}})$$

implies that $B_{\cdot,j} - B_{\cdot,i} \in \mathcal{S}$. This shows that $\mathcal{S} \supseteq \mathcal{S}'$. □

The deficiency of a reaction network is an integer number. Due to the following proposition, the deficiency is always nonnegative.

Proposition 5.3.3 The deficiency of a reaction network is always nonnegative.

Proof We have to show that $\dim \mathcal{S} \leq c - \ell$.

Fix any $i_r \in \mathcal{C}_r$ for all $r \in \overline{1,\ell}$. Define the linear subspace $\mathcal{S}''$ of $\mathbb{R}^n$ by

$$\mathcal{S}'' = \operatorname{span}\{B_{\cdot,j} - B_{\cdot,i_r} \in \mathbb{R}^n \mid j \in \mathcal{C}_r \backslash \{i_r\} \text{ with } r \in \overline{1,\ell}\}.$$

We claim that $\mathcal{S}' = \mathcal{S}''$, where $\mathcal{S}'$ is defined by (5.3). Clearly, the inclusion $\mathcal{S}' \supseteq \mathcal{S}''$ holds. To show the converse inclusion, fix any $r \in \overline{1,\ell}$. Pick any $i, j \in \mathcal{C}_r$ such that $i \neq j$. Then

$$B_{\cdot,j} - B_{\cdot,i} = (B_{\cdot,j} - B_{\cdot,i_r}) - (B_{\cdot,i} - B_{\cdot,i_r}).$$

This shows that $\mathcal{S}' \subseteq \mathcal{S}''$.

Proposition 5.3.2 then implies that $\dim \mathcal{S} = \dim \mathcal{S}''$. From the definition of $\dim \mathcal{S}''$ it is clear that

$$\dim \mathcal{S}'' \leq \sum_{r=1}^{\ell} (c_r - 1) = c - \ell,$$

where c_r denotes the number of complexes in the rth linkage class ($r \in \overline{1,\ell}$). This concludes the proof. □

An alternative definition of deficiency is sometimes used [1]. Namely, the deficiency of a reaction network is defined by

$$\delta = \dim \ker S - \dim \ker I. \tag{5.4}$$

Before we prove that the two notions coincide, we recall a theorem of linear algebra.

Theorem 5.3.4 Let U and V be finite dimensional vector spaces and let $A : U \to V$ be a linear map. Then $\dim U = \dim \ker A + \operatorname{rank} A$.

Proposition 5.3.5 The equality $c - \ell - \operatorname{rank} S = \dim \ker S - \dim \ker I$ holds for all reaction networks.

Proof By Theorem 5.3.4 and Proposition 4.2.3,

$$\dim \ker S - \dim \ker I = (m - \operatorname{rank} S) - (m - \operatorname{rank} I) =$$

$$= \operatorname{rank} I - \operatorname{rank} S = c - \ell - \operatorname{rank} S.$$

□

We remark that Proposition 5.3.3 is an immediate consequence of Proposition 5.3.5 and Proposition 5.1.1, because $S = B \cdot I$ and hence the kernel of I is a linear subspace of the kernel of S.

As a matter of fact, we propose a third alternative definition for the deficiency. That this third alternative definition is equivalent to Definition 5.3.1 can be found in [4] as a side remark. This alternative definition was discovered by the author of this thesis prior to reading that paper.

Recall that m_r denotes the number of reactions in the rth linkage class ($r \in \overline{1,\ell}$). The matrix B can be written in the block form

$$B = [B_1, B_2, \ldots, B_\ell],$$

where $B_r \in \mathbb{R}^{n \times m_r}$ and the columns of B_r correspond to the complexes in the rth linkage class ($r \in \overline{1,\ell}$). Define the block matrix $\widehat{B} \in \mathbb{R}^{(n+\ell)\times c}$ by

$$\widehat{B} = \begin{bmatrix} B_1 & B_2 & \cdots & B_\ell \\ 1 \cdots 1 & 0 \cdots 0 & \cdots & 0 \cdots 0 \\ 0 \cdots 0 & 1 \cdots 1 & \cdots & 0 \cdots 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 \cdots 0 & 0 \cdots 0 & \cdots & 1 \cdots 1 \end{bmatrix}.$$

The third alternative definition of the deficiency of a reaction network is

$$\delta = \dim\ker \widehat{B}. \tag{5.5}$$

The following proposition shows that the third alternative definition is equivalent to the previous ones.

Proposition 5.3.6 The equality $\dim\ker S - \dim\ker I = \dim\ker \widehat{B}$ holds for all reaction network.

Proof Let $e_1, \dots, e_{t_1}$ be a basis of $\ker I$ and $e_1, \dots, e_{t_1}, e_{t_1+1}, \dots, e_{t_2}$ be a basis of $\ker S$. (If $t_1 = t_2$ then $\dim\ker S - \dim\ker I \leq \dim\ker \widehat{B}$ obviously holds. Hence, we can assume that $t_1 < t_2$.) Denote by U the linear subspace of $\mathbb{R}^m$, which is spanned by $e_{t_1+1}, \dots, e_{t_2}$. Then $Ie_{t_1+1}, \dots, Ie_{t_2}$ is an independent system of $t_2 - t_1$ vectors in $\operatorname{ran} I$. We claim that $Ie_{t_1+1}, \dots, Ie_{t_2}$ are elements of $\ker \widehat{B}$. Indeed, $S = B \cdot I$ implies that $B \cdot Ie_q = Se_q = 0$ for all $q \in \overline{t_1+1, t_2}$. Due to Proposition 4.2.4, every element in the range of the incidence matrix has the property that the sum of its coordinates corresponding to the same component of the graph is zero. Therefore $Ie_{t_1+1}, \dots, Ie_{t_2} \in \ker \widehat{B}$. So $\dim\ker S - \dim\ker I = t_2 - t_1 \leq \dim\ker \widehat{B}$.

It remains to show that $\dim\ker S - \dim\ker I \geq \dim\ker \widehat{B}$. Let us choose a basis $f_1, \dots, f_{t_3}$ in $\ker \widehat{B}$. (If $t_3 = 0$ then the statement trivially holds. Hence, we can assume that $t_3 > 0$.) Due to Proposition 4.2.4, $f_1, \dots, f_{t_3}$ are in the range of I. If $I|_U$ is considered as the restriction of the map I to the linear space U then $I|_U$ is a linear bijection. Hence, $(I|_U)^{-1}f_1, \dots, (I|_U)^{-1}f_{t_3}$ are independent elements in U. (Note that $t_3 > 0$ therefore implies that $t_1 < t_2$.) So $\dim\ker \widehat{B} = t_3 \leq t_2 - t_1 \leq \dim\ker S - \dim\ker I$. □

We summarize the contents of Proposition 5.3.5 and Proposition 5.3.6 in the following theorem:

Theorem 5.3.7 The deficiency of a reaction network is

$$\delta = c - \ell - \operatorname{rank} S = \dim\ker S - \dim\ker I = \dim\ker \widehat{B}.$$

We remark that the nonnegativity of the deficiency is an immediate consequence of the fact that the deficiency of a reaction network equals to $\dim\ker \widehat{B}$.

We also remark that the previously mentioned fact that the deficiency of a reaction network is not depending on how the reactions connect complexes inside a linkage class can be seen directly from (5.5). This is due to the fact that the matrix $\widehat{B}$ does not depend on how reactions connect complexes inside connected components of $(\mathcal{C}, \mathcal{R})$.

It is worth to mention what is the meaning of the $\widehat{B}$ matrix in the language of reaction networks. Let us introduce ℓ extra species $A_{n+1}, \dots, A_{n+\ell}$. In the rth linkage class, add to each complex the new species A_{n+r} ($r \in \overline{1, \ell}$). Then the matrix of the complexes for the resulting new reaction network is $\widehat{B}$.

5.4 Deficiency of a linkage class

After one has defined the deficiency of a reaction network, the notion of *deficiency of a linkage class* is quite natural. In this section, we introduce this notion and we also provide several propositions, which are then used in Chapter 6.

When a linkage class of a network is under consideration, it can happen that there exists $s \in \overline{1,n}$ such that the species A_s is not appearing in any of the complexes of that linkage class. However, we continue to regard the network as a network with n species.

Consider a reaction network. Recall that m_r denotes the number of reactions in the rth linkage class ($r \in \overline{1,\ell}$). Clearly, $\sum_{r=1}^{\ell} m_r = m$. Let us assume that the arcs of the graph of complexes $(\mathcal{C}, \mathcal{R})$ are labeled in such a way that the stoichiometric matrix can be written in the block form

$$S = [S_1, S_2, \ldots, S_\ell],$$

where $S_r \in \mathbb{R}^{n \times m_r}$ and the columns of S_r are corresponding to reactions inside the rth linkage class ($r \in \overline{1,\ell}$). Recall also that c_r denotes the number of complexes in the rth linkage class ($r \in \overline{1,\ell}$).

Definition 5.4.1 Let $r \in \overline{1,\ell}$. Define the *deficiency of the rth linkage class* of a reaction network as $c_r - 1 - \operatorname{rank} S_r$. Usual notation for the deficiency of the rth linkage class is the symbol δ_r.

For instance, if the upper linkage class in Figure 3.1 is considered to be the first one and the lower one to be the second one in Example 3.2.2 then $c_1 = 4, c_2 = 3$,

$$S_1 = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 1 & -1 & 1 \\ 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad \text{and} \quad S_2 = \begin{bmatrix} -2 & 0 & 0 & 2 \\ 1 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix}.$$

One can then calculate that $\operatorname{rank} S_1 = 3$ and $\operatorname{rank} S_2 = 2$. Hence, $\delta_1 = 4 - 1 - 3 = 0$ and $\delta_2 = 3 - 1 - 2 = 0$.

The following proposition is an immediate consequence of Proposition 5.3.2 and Proposition 5.3.3, because one can consider a linkage class to be a reaction network with one linkage class. Note that the assumption that no row of B vanishes was not made. Hence, one can regard a linkage class as a reaction network with the same set of species as the original network has, even if there exists species, which appears in the complexes of the original network, but does not appear in the complexes of that linkage class.

Proposition 5.4.2 Let $r \in \overline{1,\ell}$. Let $\mathcal{S}_r = \operatorname{ran} S_r$ and

$$\mathcal{S}'_r = \operatorname{span}\{B_{\cdot,j} - B_{\cdot,i} \in \mathbb{R}^n \mid i, j \in \mathcal{C}_r\}.$$

Then $\mathcal{S}_r = \mathcal{S}'_r$ and $\delta_r \geq 0$.

Let us call for later reference $\mathcal{S}_r$ in the above proposition the *stoichiometric subspace of the rth linkage class*.

Naturally, alternative definitions for the deficiency of a linkage class can also be introduced. Recall from Section 4.2 that the incidence matrix I can be written in the block

form

$$I = [I_1, \dots, I_\ell],$$

where $I_r \in \mathbb{R}^{c \times m_r}$ and the columns of I_r are corresponding to the arcs in the rth connected component of $(\mathcal{C}, \mathcal{R})$. Similarly, let

$$\widehat{B} = [\widehat{B}_1, \dots, \widehat{B}_\ell],$$

where $\widehat{B}_r \in \mathbb{R}^{(n+\ell) \times c_r}$ and the columns of $\widehat{B}_r$ are corresponding to the complexes in the rth linkage class.

Theorem 5.4.3 Let $r \in \overline{1, \ell}$. Then

$$\delta_r = c_r - 1 - \operatorname{rank} S_r = \dim \ker S_r - \dim \ker I_r = \dim \ker \widehat{B}_r.$$

Proof Let $r \in \overline{1, \ell}$. The kernel of I_r and the kernel of the incidence matrix of the graph $(\mathcal{C}_r, \mathcal{R}_r)$ are clearly the same. Similarly, the kernel of $\widehat{B}_r$ and the kernel of the matrix

$$\begin{bmatrix} B_r \\ 1 \cdots 1 \end{bmatrix} \in \mathbb{R}^{(n+1) \times c_r}$$

are the same. Hence, application of Theorem 5.3.7 for the network, which consists of the rth linkage class yields the result. □

The following proposition shows a relation between the deficiency of a reaction network and the deficiencies of its linkage classes.

Proposition 5.4.4 The sum of the deficiencies of the linkage classes is less than or equal to the deficiency of the whole network:

$$\delta_1 + \delta_2 + \cdots + \delta_\ell \leq \delta.$$

Furthermore, $\delta_1 + \delta_2 + \cdots + \delta_\ell = \delta$ if and only if the stoichiometric subspace is the direct sum of the stoichiometric subspaces of the linkage classes.

Proof Recall that $S = [S_1, S_2, \dots, S_\ell]$ and hence $\operatorname{rank} S \leq \sum_{r=1}^{\ell} \operatorname{rank} S_r$. Using Definition 5.3.1 and Definition 5.4.1, the first statement of the proposition follows:

$$\sum_{r=1}^{\ell} \delta_r = \sum_{r=1}^{\ell} (c_r - 1 - \operatorname{rank} S_r) = \left(\sum_{r=1}^{\ell} c_r \right) - \left(\sum_{r=1}^{\ell} 1 \right) - \left(\sum_{r=1}^{\ell} \operatorname{rank} S_r \right) =$$

$$= c - \ell - \left(\sum_{r=1}^{\ell} \operatorname{rank} S_r \right) \leq c - \ell - \operatorname{rank} S = \delta.$$

It is also apparent from the above estimation that equality between δ and $\sum_{r=1}^{\ell} \delta_r$ holds if and only if $\operatorname{rank} S = \sum_{r=1}^{\ell} \operatorname{rank} S_r$. The latter is equivalent to the fact that the stoichiometric subspace is the direct sum of the stoichiometric subspaces of the linkage classes. □

We remark that the above proposition can also be proven by using the second alternative definitions and the fact that

$$\operatorname{ran} I = \operatorname{ran} I_1 \oplus \cdots \oplus \operatorname{ran} I_\ell.$$

The following estimation gives the alternative proof.

$$\sum_{r=1}^{\ell}\delta_r=\sum_{r=1}^{\ell}(\dim\ker S_r-\dim\ker I_r)=\sum_{r=1}^{\ell}((m_r-\operatorname{rank}S_r)-(m_r-\operatorname{rank}I_r))=$$

$$=-\left(\sum_{r=1}^{\ell}\operatorname{rank}S_r\right)+\operatorname{rank}I\leq-\operatorname{rank}S+\operatorname{rank}I=$$

$$=-(m-\dim\ker S)+(m-\dim\ker I)=\delta.$$

The following estimation shows how the first part of Proposition 5.4.4 can be proven by using the third alternative definitions.

$$\sum_{r=1}^{\ell}\delta_r=\sum_{r=1}^{\ell}\dim\ker\widehat{B}_r=\sum_{r=1}^{\ell}(c_r-\operatorname{rank}\widehat{B}_r)=\left(\sum_{r=1}^{\ell}c_r\right)-\left(\sum_{r=1}^{\ell}\operatorname{rank}\widehat{B}_r\right)=$$

$$=c-\left(\sum_{r=1}^{\ell}\operatorname{rank}\widehat{B}_r\right)\leq c-\operatorname{rank}\widehat{B}=\dim\ker\widehat{B}=\delta.$$

The above estimation also shows that an equivalent condition to $\delta_1+\delta_2+\cdots+\delta_\ell=\delta$ can also be formulated in terms of the $\widehat{B}$ matrix. We summarize this and an earlier result in the following proposition.

Proposition 5.4.5 Denote by $\widehat{\mathcal{B}}$ the linear space $\operatorname{ran}\widehat{B}$. Similarly, denote by $\widehat{\mathcal{B}}_r$ the linear space $\operatorname{ran}\widehat{B}_r$ for $r\in\overline{1,\ell}$. Then the following are equivalent.

(i) $\delta=\delta_1+\cdots+\delta_\ell$,

(ii) $\mathcal{S}=\mathcal{S}_1\oplus\cdots\oplus\mathcal{S}_\ell$,

(iii) $\widehat{\mathcal{B}}=\widehat{\mathcal{B}}_1\oplus\cdots\oplus\widehat{\mathcal{B}}_\ell$.

The following proposition shows that deficiency zero networks have the property that the stoichiometric subspace is the direct sum of the stoichiometric subspaces of the linkage classes.

Proposition 5.4.6 Assume that $\delta=0$. Then $\delta=\delta_1+\cdots+\delta_\ell$.

Proof The nonnegativity of the deficiencies of the linkage classes and the inequality part of Proposition 5.4.4 implies that $\delta_r=0$ for all $r\in\overline{1,\ell}$. Hence, the result of this proposition follows. □

We conclude this section by providing a simple proposition, which is then used in Chapter 6. Recall that the function $f:\mathbb{R}^n\to\mathbb{R}^n$ denotes the right hand side of the differential equation (3.5). Let $r\in\overline{1,\ell}$. Define the function $f^r:\mathbb{R}^n\to\mathbb{R}^n$ by

$$f^r(x)=\sum_{(i,j)\in\mathcal{R}_r}R_{(i,j)}(x)(B_{\cdot,j}-B_{\cdot,i}) \tag{5.6}$$

for $x\in\mathbb{R}^n$. Clearly, $f(x)=f^1(x)+\cdots+f^\ell(x)$ for all $x\in\mathbb{R}^n$.

Proposition 5.4.7 Assume that $\delta=\delta_1+\cdots+\delta_\ell$. Let $x\in\mathbb{R}^n$. Then $f(x)=0$ implies that $f^r(x)=0$ for all $r\in\overline{1,\ell}$.

Proof Clearly, $f(x)\in\mathcal{S}$ and $f^r(x)\in\mathcal{S}_r$ for all $x\in\mathbb{R}^n$ and for all $r\in\overline{1,\ell}$. Proposition 5.4.5 implies the result. □

Chapter 6

Dynamic system properties of biochemical reaction systems

In this chapter we investigate dynamic system properties of biochemical reaction systems. First we show that the positive and the nonnegative orthants are forward invariant sets for (3.5). Then we introduce the notion of stoichiometric classes, which are also forward invariant sets for (3.5). In Section 6.3 we introduce the notion of a siphon. This will be useful in understanding the long term behaviour of the solutions of (3.5). Section 6.4 and Section 6.5 deals with the set of equilibria (3.5). Stability properties of equilibrium points are investigated in Section 6.6. Finally, in Section 6.7 we show that in some special cases the existence of periodic orbits is excluded.

6.1 Forward invariance of the positive and the nonnegative orthants

Let $(\mathcal{A}, \mathcal{C}, \mathcal{R}, R)$ be a biochemical reaction system. Recall that the differential equation that governs the evolution of species concentrations in time for a biochemical reaction system has the form

$$\dot{x} = f(x) = \sum_{(i,j)\in\mathcal{R}} R_{(i,j)}(x)(B_{\cdot,j} - B_{\cdot,i}), \tag{6.1}$$

where $B \in \mathbb{R}^{n\times c}$ is the matrix of complexes and the state space is $\mathbb{R}^n$.

In this section we show that the positive and nonnegative orthants are forward invariant for (6.1). This means that the mathematical model of a biochemical reaction system satisfies the qualitative property that no species concentration can become negative. This section is based on [10] with the difference that we consider here the rate functions as specified in Section 3.3, which is more general than the ones in [10]. This extension can be done without any new idea.

Definition 6.1.1 Let $K \subseteq \mathbb{R}^n$. The set K is said to be *forward invariant* for (6.1) if $\phi(t;\xi) \in K$ for all $\xi \in K$ and for all $t \in J_+(\xi)$.

Recall that $f_s : \mathbb{R}^n \to \mathbb{R}$ is the sth coordinate function of f ($s \in \overline{1,n}$). Let $s \in \overline{1,n}$. Then

$$f_s(x) = \sum_{(i,j)\in\mathcal{R}} R_{(i,j)}(x)(B_{s,j} - B_{s,i}).$$

Define the functions $\beta_s^+ : \mathbb{R}^n \to \mathbb{R}$ and $\beta_s^0 : \mathbb{R}^n \to \mathbb{R}$ by

$$\begin{aligned} \beta_s^+(x) &= \sum_{\substack{(i,j)\in\mathcal{R} \\ B_{s,i}>0}} R_{(i,j)}(x)(B_{s,j} - B_{s,i}), \\ \beta_s^0(x) &= \sum_{\substack{(i,j)\in\mathcal{R} \\ B_{s,i}=0}} R_{(i,j)}(x)B_{s,j}. \end{aligned}$$

Clearly, $f_s = \beta_s^+ + \beta_s^0$.

Recall from Chapter 2 the definition of the sign function $\operatorname{sgn} : \mathbb{R} \to \{-1, 0, 1\}$.

Proposition 6.1.2 Suppose that $x_s = 0$ for some $s \in \overline{1,n}$ and $x \in \mathbb{R}^n_{\geq 0}$. Then $\beta_s^+(x) = 0$ and $f_s(x) = \beta_s^0(x) \geq 0$. Moreover, $\operatorname{sgn}(f_s(x))$ depends only on $\operatorname{supp}(x)$.

Proof Let x be as in the statement. Assume that $B_{s,i} > 0$ for some $i \in \overline{1,c}$. Then $s \in \operatorname{supp}(B_{\cdot,i})$ and $s \notin \operatorname{supp}(x)$. Due to (3.3), this implies that $R_{(i,j)}(x) = 0$. Hence, $\beta_s^+(x) = 0$. This also shows that $f_s(x) = \beta_s^0(x)$.

Since all the summands in the defining sum of β_s^0 are nonnegative, it follows that $\beta_s^0(x) \geq 0$.

Obviously, $f_s(x) > 0$ if and only if there exists a positive summand in the defining sum of β_s^0. Due to (3.3), for all $(i,j) \in \mathcal{R}$, $\operatorname{sgn}(R_{(i,j)}(x))$ is determined by $\operatorname{supp}(x)$. This implies the desired result. □

The key observation for proving the forward invariance of the positive orthant for (6.1) is Proposition 6.1.4. We follow the line of [10] to prove that proposition. First we recall a comparison theorem. A proof of it can be found for example in [13].

Theorem 6.1.3 Let $G : \mathbb{R}^2 \to \mathbb{R}$ be locally Lipschitz continuous in its second variable. Let $I \subseteq \mathbb{R}$ be an open interval and let $u, v : I \to \mathbb{R}$ be differentiable functions. Let $[a,b] \subseteq I$ be a compact interval. Assume that $u(a) \leq v(a)$ and that $\dot{u}(t) - G(t,u(t)) \leq \dot{v}(t) - G(t,v(t))$ for all $t \in [a,b]$. Then $u(t) \leq v(t)$ for all $t \in [a,b]$.

Proposition 6.1.4 Let $\xi \in \mathbb{R}^n_{\geq 0}$ and let $s \in \overline{1,n}$ such that $\xi_s > 0$. Let $t^* \in J_+(\xi)$. Assume that $\phi(t;\xi) \in \mathbb{R}^n_{\geq 0}$ for all $t \in [0,t^*]$. Then $\phi_s(t^*;\xi) > 0$.

Proof Let us define the function $F : \mathbb{R}^2 \to \mathbb{R}$ by

$$F(t,y) = \begin{cases} f_s(\phi_1(t;\xi), \ldots, \phi_{s-1}(t;\xi), y, \phi_{s+1}(t;\xi), \ldots, \phi_n(t;\xi)), & \text{if } 0 \leq t \leq t^*, \\ F(0,y), & \text{if } t < 0, \\ F(t^*,y), & \text{if } t^* < t \end{cases}$$

for $(t,y) \in \mathbb{R}^2$. Note that F is locally Lipschitz continuous. Note also that $F(t,0) \geq 0$ for all $t \in \mathbb{R}$, because, by Proposition 6.1.2, $f_s(x) = \beta_s^0(x) \geq 0$ whenever $x \in \mathbb{R}^n_{\geq 0}$ and $x_s = 0$. Consider the scalar initial value problem

$$\dot{y} = F(t,y), \quad y(0) = \xi_s.$$

It can be seen that the unique solution of this initial value problem equals to $\phi_s(\cdot;\xi)$ in $[0,t^*]$. We prove that this solution does not vanish at t^*.

Let us define the function $G:\mathbb{R}^2\to\mathbb{R}$ by $G(t,p)=F(t,p)-F(t,0)$ for $(t,p)\in\mathbb{R}^2$. Introduce another scalar initial value problem

$$\dot{z}=G(t,z),\quad z(0)=\xi_s.$$

Note that G is locally Lipschitz continuous and $0\in\mathbb{R}$ is an equilibrium point ($0=G(t,0)$ for all $t\in\mathbb{R}$). Denote by z the solution of this initial value problem. As solutions cannot intersect each other, $z(t)>0$ for all t in its domain of definition. Moreover, we have that $G(t,z)\leq F(t,z)$ for all $(t,z)\in\mathbb{R}^2$. Theorem 6.1.3 implies that $z(t)\leq\phi_s(t;\xi)$ for all $t\geq 0$ in the common domain of definition of z and $\phi_s(\cdot;\xi)$. Since $\phi_s(t^*;\xi)$ is well defined, z remains bounded on $[0,t^*]$, and thus is defined as well at t^*. So, $\phi_s(t^*;\xi)\geq z(t^*)>0$. □

Note that in the above proposition it was assumed that the examined solution of the differential equation lies in $\mathbb{R}^n_{\geq 0}$ on a compact interval $[0,t^*]$.

We are now in the position to prove the forward invariance of the positive orthant.

Proposition 6.1.5 The positive orthant $\mathbb{R}^n_+$ is a forward invariant set for (6.1).

Proof Let $\xi\in\mathbb{R}^n_+$. A solution can leave the positive orthant only if there exists $t\in J_+(\xi)$ such that $\phi(t;\xi)\in\mathbb{R}^n_0$. Assume that this happens. Let $t^*=\min\{t\in J_+(\xi)\mid\phi(t;\xi)\in\mathbb{R}^n_0\}$. Then $t^*\in J_+(\xi)$. By the minimality of t^*, $\phi(t;\xi)\in\mathbb{R}^n_{\geq 0}$ for all $t\in[0,t^*]$. By the definition of t^*, there exists $s\in\overline{1,n}$ such that $\phi_s(t^*;\xi)=0$, which contradicts Proposition 6.1.4. □

One can prove that the closure of a forward invariant set is also forward invariant by using the continuous dependence of the solution on the initial value. The proof of the following theorem can be found for example in [8].

Theorem 6.1.6 Let $g:D\to\mathbb{R}^n$ be locally Lipschitz continuous, where $D\subseteq\mathbb{R}^n$ is an open connected set. Consider the differential equation $\dot{x}=g(x)$. Let $\xi\in D$ and assume that $J(\xi)\supseteq[0,t^*]$ for some $t^*>0$. Let $\varepsilon>0$. Then there exists $\eta>0$ such that $|\zeta-\xi|<\eta$ and $\zeta\in D$ implies that $J(\zeta)\supseteq[0,t^*]$ and $|\phi(t;\zeta)-\phi(t;\xi)|<\varepsilon$ for all $t\in[0,t^*]$.

Proposition 6.1.7 Let $g:D\to\mathbb{R}^n$ be locally Lipschitz continuous, where $D\subseteq\mathbb{R}^n$ is an open connected set. Let $K\subseteq D$ be forward invariant for $\dot{x}=g(x)$. Then the intersection of D and the closure $\mathrm{cl}(K)$ of K is forward invariant as well.

Proof If K is closed then the statement trivially holds. Assume that K is not closed and pick any $\xi\in(\mathrm{cl}(K)\cap D)\backslash K$. Suppose by contradiction that there exists $t^*\in J_+(\xi)$ such that $\phi(t^*;\xi)\notin\mathrm{cl}(K)$. (Clearly, $\phi(t;\xi)\in D$ for all $t\in J(\xi)$.) Let $\varepsilon=\mathrm{dist}(\phi(t^*;\xi),\mathrm{cl}(K))$. (See Chapter 2 for the definition of dist.) Note that $\varepsilon>0$. Due to Theorem 6.1.6, there exists $\eta>0$ such that $|\zeta-\xi|<\eta$ and $\zeta\in D$ implies that $J(\zeta)\supseteq[0,t^*]$ and $|\phi(t;\zeta)-\phi(t;\xi)|<\varepsilon$ for all $t\in[0,t^*]$. Clearly, there exists $\zeta\in K$ such that $|\zeta-\xi|<\eta$. Since K is forward invariant, $\phi(t^*;\zeta)\in K$, which implies that $|\phi(t^*;\zeta)-\phi(t^*;\xi)|\geq\varepsilon$, contradiction. □

The forward invariance of the nonnegative orthant is therefore an immediate consequence of the forward invariance of the positive orthant.

Proposition 6.1.8 The nonnegative orthant $\mathbb{R}^n_{\geq 0}$ is a forward invariant set for (3.5).

Combining Proposition 6.1.4 and Proposition 6.1.8 yields the following proposition.

Proposition 6.1.9 Let $\xi \in \mathbb{R}^n_{\geq 0}$ and let $s \in \overline{1,n}$ such that $\xi_s > 0$. Then $\phi_s(t;\xi) > 0$ for all $t \in J_+(\xi)$.

Proposition 6.1.9 expresses that the mathematical model of a biochemical reaction network has the property that no positive species concentration can become zero in finite time.

6.2 Stoichiometric classes

In this section we introduce the notion of *stoichiometric classes*. The importance of these objects is given by the facts that they provide a partition of $\mathbb{R}^n_{\geq 0}$ and that they are forward invariant sets for the differential equation (6.1).

Recall that $S \in \mathbb{R}^{n\times m}$ and $\mathcal{S} \subseteq \mathbb{R}^n$ denote the stoichiometric matrix and its range, respectively. If $p \in \mathbb{R}^n$ then denote by $p+\mathcal{S}$ the parallel of $\mathcal{S}$, which contains p, i.e. $p+\mathcal{S} = \{p+v \in \mathbb{R}^n \mid v \in \mathcal{S}\}$.

Definition 6.2.1 Let $p \in \mathbb{R}^n_{\geq 0}$. The set $\mathcal{P} = (p+\mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ is called a *stoichiometric class*. A stoichiometric class $\mathcal{P}$ is called *positive*, if $\mathcal{P} \cap \mathbb{R}^n_+ \neq \emptyset$.

The above definition coincides with the one in [10]. Note however that a slightly different definition for positive stoichiometric classes is given in [5].

Let $\xi \in \mathcal{P} = (p+\mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ for some $p \in \mathbb{R}^n_{\geq 0}$. By the preceding section, $\phi(t;\xi) \in \mathbb{R}^n_{\geq 0}$ for all $t \in J_+(\xi)$. Let $t^* \in J_+(\xi)$. Integrating (6.1) along $\phi(\cdot;\xi)$ yields

$$\phi(t^*;\xi) - \xi = \sum_{(i,j)\in\mathcal{R}} \int_0^{t^*} R_{(i,j)}(\phi(\tau;\xi))\mathrm{d}\tau(B_{\cdot,j} - B_{\cdot,i}). \tag{6.2}$$

Formula (6.2) shows that $\phi(t^*;\xi) - \xi \in \mathcal{S}$, or equivalently, $\phi(t^*;\xi) \in \xi + \mathcal{S}$, because the right hand side of (6.2) is a linear combination of the spanning vectors of $\mathcal{S}$. In other words, if a solution of (6.1) starts in the stoichiometric class $\mathcal{P}$ then $\phi(t;\xi) \in \mathcal{P}$ for all $t \in J_+(\xi)$. This yields the following proposition:

Proposition 6.2.2 Any stoichiometric class is forward invariant for (6.1).

Proposition 6.1.5 and Proposition 6.2.2 together yield the following proposition:

Proposition 6.2.3 Let $\mathcal{P}$ be a positive stoichiometric class. Then the set $\mathcal{P} \cap \mathbb{R}^n_+$ is forward invariant for (6.1).

Note that either all or none of the stoichiometric classes are bounded. If they are bounded then no solution of (6.1) can explode in finite time. In other words, for all initial values $\xi \in \mathbb{R}^n_{\geq 0}$ the inclusion $J(\xi) \supseteq \mathbb{R}_{\geq 0}$ holds. This will follow immediately from Theorem 6.6.13 in Section 6.6.

6.3 Forward invariant sets on the boundary of the nonnegative orthant

In this section we deal with forward invariant sets for (6.1) on the boundary of the nonnegative orthant.

Let $H \subseteq \overline{1,n}$. Denote by H^c the set $\overline{1,n} \backslash H$. Define the set F_H by

$$F_H = \{x \in \mathbb{R}^n_{\geq 0} \mid x_s = 0 \text{ if and only if } s \in H\}.$$

For later use we mention that the closure of F_H is

$$\mathrm{cl}(F_H) = \{x \in \mathbb{R}^n_{\geq 0} \mid x_s = 0 \text{ if } s \in H\}.$$

Let $x \in \mathbb{R}^n_{\geq 0}$. Then the statements

$$x \in F_H \text{ if and only if } \mathrm{supp}(x) = H^c$$

and

$$x \in \mathrm{cl}(F_H) \text{ if and only if } \mathrm{supp}(x) \subseteq H^c.$$

trivially hold.

Note that $F_\emptyset = \mathbb{R}^n_+$ and $\mathrm{cl}(F_\emptyset) = \mathbb{R}^n_{\geq 0}$. The forward invariance of the positive and the nonnegative orthants is proven in Section 6.1. The sets F_H and $\mathrm{cl}(F_H)$ are lying on the boundary of the positive orthant if and only if $H \neq \emptyset$. We shall derive equivalent conditions to the forward invariance of the sets F_H and $\mathrm{cl}(F_H)$ in terms of the set of reactions $\mathcal{R}$ and the B matrix. As it will turn out, the forward invariance of these sets is independent of the precise nature of the rate functions.

We now provide a simple equivalent condition to the forward invariance of the set F_H.

Proposition 6.3.1 Let $\emptyset \neq H \subseteq \overline{1,n}$. Then F_H is forward invariant for (6.1) if and only if $f_s(x) = 0$ for all $s \in H$ and for all $x \in F_H$.

Proof As earlier, denote by $\phi(\cdot;\xi) : J(\xi) \to \mathbb{R}^n$ the unique solution of the differential equation $\dot{x} = f(x)$, which satisfies $\phi(0;\xi) = \xi$ for $\xi \in \mathbb{R}^n$.

Suppose that F_H is forward invariant. Let $\xi \in F_H$. Then $\phi_s(t;\xi) = 0$ for all $s \in H$ and for all $t \in J_{\geq 0}(\xi)$. Hence, $0 = \dot{\phi}_s(t;\xi) = f_s(\phi(t;\xi))$ for all $s \in H$ and for all $t \in J_{\geq 0}(\xi)$. In particular, $0 = f_s(\phi(0;\xi)) = f_s(\xi)$ for all $s \in H$. Since $\xi \in F_H$ was arbitrary, the only if part of the proposition is proven.

Suppose now that $f_s(x) = 0$ for all $s \in H$ and for all $x \in F_H$. If $H = \overline{1,n}$ then $f_s(0) = 0$ for all $s \in \overline{1,n}$. Hence, the unique solution starting from $0 \in \mathbb{R}^n$ is clearly the identically zero function. This shows that $F_{\overline{1,n}}$ is forward invariant.

Assume for the rest of this proof that $\emptyset \neq H \subsetneq \overline{1,n}$. Let $\xi \in F_H$. Let $\overline{n} = |H^c|$. In what follows the coordinates of vectors in $\mathbb{R}^{\overline{n}}$ are indexed by the elements of the set H^c. Denote by K the linear space

$$K = \{x \in \mathbb{R}^n \mid x_s = 0 \text{ if } s \in H\}.$$

Define the function $P : K \to \mathbb{R}^{\overline{n}}$ by $(Px)_s = x_s$ for $s \in H^c$ and for $x \in K$. Clearly, $P|_{F_H}$ is a bijection between F_H and $\mathbb{R}^{\overline{n}}_+$. Define the differential equation $\dot{\overline{x}} = g(\overline{x})$ on $\mathbb{R}^{\overline{n}}_+$

by the function $g(\overline{x}) = Pf(P^{-1}\overline{x})$ for $\overline{x} \in \mathbb{R}^{\overline{n}}_+$. Note that $f(F_H) \subseteq K$ by assumption and hence $g : \mathbb{R}^{\overline{n}}_+ \to \mathbb{R}^{\overline{n}}$ is well defined. Clearly, g inherits the local Lipschitz continuity from f, provided by the fact that P is a linear homeomorphism.

Denote by $\varphi(\cdot;\overline{\xi}) : \overline{J}(\overline{\xi}) \to \mathbb{R}^{\overline{n}}_+$ the unique solution of the new differential equation, which satisfies $\varphi(0;\overline{\xi}) = \overline{\xi}$ for $\overline{\xi} \in \mathbb{R}^{\overline{n}}_+$. We claim that $\phi(t;\xi) = P^{-1}\varphi(t;P\xi)$ for all $\xi \in F_H$ and for all $t \in \overline{J}(P\xi)$. To verify this claim, define $y : \overline{J}(P\xi) \to \mathbb{R}^n$ by $y(t) = P^{-1}\varphi(t;P\xi)$ for $t \in \overline{J}(P\xi)$. It is enough to check that $\dot{y}(t) = f(y(t))$ for all $t \in \overline{J}(P\xi)$ and $y(0) = \xi$ (because of the uniqueness of the solution). Clearly, $y(0) = P^{-1}P\xi = \xi$. Moreover,

$$\dot{y}(t) = P^{-1}\dot{\varphi}(t;P\xi) = P^{-1}g(\varphi(t;P\xi)) = P^{-1}Pf(P^{-1}\varphi(t;P\xi)) = f(y(t))$$

for all $t \in \overline{J}(P\xi)$. The claim is verified. Hence, $\overline{J}(P\xi) \subseteq J(\xi)$. Moreover, $\phi(t;\xi) \in F_H$ for all $t \in \overline{J}(P\xi)$, because $\varphi(t;P\xi) \in \mathbb{R}^{\overline{n}}_+$ for all $t \in \overline{J}(P\xi)$ and $P^{-1}\overline{x} \in F_H$ for all $\overline{x} \in \mathbb{R}^{\overline{n}}_+$.

Moreover, we claim that $\overline{J}_{\geq 0}(P\xi) = J_{\geq 0}(\xi)$. Suppose by contradiction that $\overline{J}(P\xi) \subsetneq J(\xi)$. Let $t^* = \sup \overline{J}(P\xi)$. Then $\phi(t^*;\xi) \in \mathrm{cl}(F_H)$ and

$$\lim_{t \to t^* - 0} P^{-1}\varphi(t;P\xi) = \phi(t^*;\xi).$$

Hence, t^* cannot be a finite explosion time for $\varphi(\cdot;P\xi)$. It follows that

$$\lim_{t \to t^* - 0} \varphi(t;P\xi) \in \mathbb{R}^{\overline{n}}_0.$$

Consequently, $\phi(t^*;\xi) \in \mathrm{cl}(F_H) \backslash F_H$. This is a contradiction, because we know from Section 6.1 that no positive species concentration can become zero in finite time. This proves that $\overline{J}_{\geq 0}(P\xi) = J_{\geq 0}(\xi)$.

It follows now that F_H is forward invariant for $\dot{x} = f(x)$. □

We formulate an equivalent condition to $f_s(x) = 0$ for all $s \in H$ and for all $x \in F_H$.

Proposition 6.3.2 Let $\emptyset \neq H \subseteq \overline{1,n}$, $x \in F_H$, and $s \in H$. Then $f_s(x) = 0$ if and only if for all $(i,j) \in \mathcal{R}$, $B_{s,i} = 0$ and $B_{s,j} > 0$ implies that $\mathrm{supp}(B_{\cdot,i}) \nsubseteq H^c$.

Proof Due to Proposition 6.1.2, $f_s(x) = \beta^0_s(x)$. The sum in the definition of β^0_s contains only nonnegative terms. The sum is zero if and only if all the summands are zero. This means that $f_s(x) = 0$ if and only if for all $(i,j) \in \mathcal{R}$, $B_{s,i} = 0$ and $B_{s,j} > 0$ implies that $R_{(i,j)}(x) = 0$. By condition (3.3), $R_{(i,j)}(x) = 0$ if and only if $\mathrm{supp}(B_{\cdot,i}) \nsubseteq \mathrm{supp}(x)$. Due to the discussion at the beginning of this section, $x \in F_H$ if and only if $\mathrm{supp}(x) = H^c$. This concludes the proof. □

Let $x \in F_H$ for some $\emptyset \neq H \subseteq \overline{1,n}$. Biologically, $x_s = 0$ means that species A_s is not present in the system. That $B_{s,i} = 0$ and $B_{s,j} > 0$ for some $(C_i, C_j) \in \mathcal{R}$ means that the reactant complex C_i of reaction (C_i, C_j) does not contain species A_s, while the product complex C_j contains it. Hence, reaction (C_i, C_j) provides a chance to the formation of species A_s. However, $\mathrm{supp}(B_{\cdot,i}) \nsubseteq H^c$ expresses that reaction (C_i, C_j) does not take place, because there exists a constituent species of the reactant complex, which is (similarly to A_s) not present in the system.

In the rest of this section we introduce the notion of *siphon* in the same way as it is done in [2]. As it will turn out, the notion of a siphon provides another characterization of the forward invariance of the sets F_H for $\emptyset \neq H \subseteq \overline{1,n}$.

We associate to the set of reactions and the matrix of complexes a *bipartite digraph*. By bipartite graph we mean that the set of vertices can be partitioned into two sets such that there are no arcs, which connect vertices of the same element of the partition. Recall that $\mathcal{A}$ denotes the set of species $\{A_1, \ldots, A_n\} = \overline{1,n}$.

Definition 6.3.3 Define the set $\mathcal{E} \subseteq (\mathcal{A} \cup \mathcal{R}) \times (\mathcal{A} \cup \mathcal{R})$ by

$$\mathcal{E} = \{(s,(i,j)) \in \mathcal{A} \times \mathcal{R} \mid B_{s,i} > 0\} \cup \{((i,j),s) \in \mathcal{R} \times \mathcal{A} \mid B_{s,j} > 0\}.$$

The bipartite digraph $(\mathcal{A} \cup \mathcal{R}, \mathcal{E})$ is called the *species-reaction graph*.

Note that the digraph $(\mathcal{A} \cup \mathcal{R}, \mathcal{E})$ is indeed bipartite, because there are no arcs between species, and similarly, there are no arcs between reactions. In notation, $\mathcal{E} \cap (\mathcal{A} \times \mathcal{A}) = \emptyset$ and $\mathcal{E} \cap (\mathcal{R} \times \mathcal{R}) = \emptyset$.

Definition 6.3.4 The reaction $(i,j) \in \mathcal{R}$ is called an *input reaction* for species $s \in \mathcal{A}$ if $((i,j),s) \in \mathcal{E}$. The reaction $(i,j) \in \mathcal{R}$ is called an *output reaction* for species $s \in \mathcal{A}$ if $(s,(i,j)) \in \mathcal{E}$.

We now introduce notations, which help in formulating the definition of a siphon in a compact form. Let $\emptyset \neq H \subseteq \overline{1,n}$. Define the set of input reactions associated to H and the set of output reactions associated to H by

$$\mathcal{R}_H^{\mathcal{I}} = \{(i,j) \in \mathcal{R} \mid \text{there exists } s \in H \text{ such that } ((i,j),s) \in \mathcal{E}\} =$$

$$= \{(i,j) \in \mathcal{R} \mid \text{there exists } s \in H \text{ such that } B_{s,j} > 0\}$$

and

$$\mathcal{R}_H^{\mathcal{O}} = \{(i,j) \in \mathcal{R} \mid \text{there exists } s \in H \text{ such that } (s,(i,j)) \in \mathcal{E}\} =$$

$$= \{(i,j) \in \mathcal{R} \mid \text{there exists } s \in H \text{ such that } B_{s,i} > 0\},$$

respectively.

Definition 6.3.5 A set $\emptyset \neq H \subseteq \overline{1,n}$ is called a *siphon* if each input reaction associated to H is also an output reaction associated to H (i.e. $\mathcal{R}_H^{\mathcal{I}} \subseteq \mathcal{R}_H^{\mathcal{O}}$).

In words, a set $\emptyset \neq H \subseteq \overline{1,n}$ is a siphon if the following holds: if $(C_i, C_j) \in \mathcal{R}$ is a reaction such that there exists a species A_s, which is a constituent part of the product complex C_j for some $s \in H$ then there exists a species $s' \in H$, which is a constituent part of the reactant complex C_i.

Note that $\emptyset \neq H \subseteq \overline{1,n}$ is a siphon if and only if none of the input reactions associated to H takes place at concentrations $\xi \in F_H$.

Example 6.3.6 Let $n = 4$ and $c = 4$. We consider the complexes

$$C_1 = A_1 + 3A_2, \quad C_2 = 2A_3, \quad C_3 = 4A_1 + A_4, \quad \text{and} \quad C_4 = A_3.$$

Then

$$B = \begin{bmatrix} 1 & 0 & 4 & 0 \\ 3 & 0 & 0 & 0 \\ 0 & 2 & 0 & 1 \\ 0 & 0 & 1 & 0 \end{bmatrix}.$$

Let $\mathcal{R} = \{(C_1, C_2), (C_2, C_1), (C_3, C_4)\}$ be the set of the reactions. The scheme of the defined reaction network is displayed in Figure 6.1. The species-reaction graph associated to the reaction network is displayed in Figure 6.2. The siphons of this example are the sets

$$\{A_4\}, \{A_1, A_3\}, \{A_1, A_2, A_3\}, \{A_1, A_3, A_4\}, \{A_2, A_3, A_4\}, \quad \text{and} \quad \{A_1, A_2, A_3, A_4\}.$$

$$A_1 + 3A_2 \rightleftharpoons 2A_3$$

$$4A_1 + A_4 \longrightarrow A_3$$

Figure 6.1: Scheme of the reaction network in Example 6.3.6

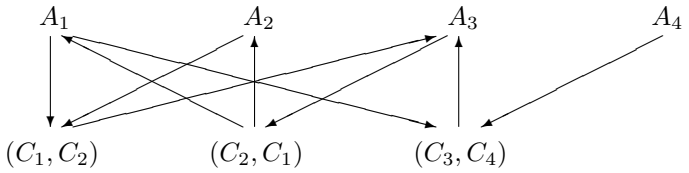


Figure 6.2: The digraph $(\mathcal{A} \cup \mathcal{R}, \mathcal{E})$ associated to the reaction network in Example 6.3.6

□

The notion of a siphon is very closely related to the previously examined forward invariant sets. The statement that (i) and (iii) in Theorem 6.3.7 are equivalent can be found in [2]. The proof presented there makes use of the so called Bouligand contingent cones. We present here another proof and also several other equivalent statements. The major part of the work was done in the proof of Proposition 6.3.1.

Theorem 6.3.7 Let $\emptyset \neq H \subseteq \overline{1,n}$. Denote by H^c the set $\overline{1,n} \backslash H$. Then the following are equivalent.

(i) H is a siphon,

(ii) F_H is forward invariant,

(iii) $\mathrm{cl}(F_H)$ is forward invariant,

(iv) $f_s(x) = 0$ for all $s \in H$ and for all $x \in F_H$,

(v) $f_s(x) = 0$ for all $s \in H$ and for all $x \in \mathrm{cl}(F_H)$,

(vi) there exists $x \in F_H$ such that $f_s(x) = 0$ for all $s \in H$,

(vii) for all $s \in H$ and for all $(i, j) \in \mathcal{R}$, $B_{s,i} = 0$ and $B_{s,j} > 0$ implies that $\mathrm{supp}(B_{\cdot,i}) \nsubseteq H^c$.

Proof As $F_H \subseteq \mathrm{cl}(F_H)$, (v) immediately implies (iv). Continuity of f guarantees that (iv) implies (v).

Equivalence of (iv) and (vii) is the content of Proposition 6.3.2.

Statement (iv) trivially implies (vi). Due to Proposition 6.3.2, (vi) implies (vii).

The equivalence of (iv),(v),(vi), and (vii) is now proven.

If F_H is forward invariant then $\mathrm{cl}(F_H)$ is forward invariant as well, because of Proposition 6.1.7. Hence, (ii) implies (iii).

Suppose that (iii) holds. Then (ii) is satisfied as well. Indeed, the forward invariance of F_H consists of two things. That positive coordinates cannot become zero is guaranteed by Proposition 6.1.9. That zero coordinates corresponding to H cannot become positive is provided by the forward invariance of $\mathrm{cl}(F_H)$.

The statements in (ii) and (iv) are equivalent by Proposition 6.3.1.

The equivalence of (ii),(iii),(iv),(v),(vi), and (vii) is now proven.

As concluding step, we show that (vii) is equivalent to $\mathcal{R}_H^{\mathcal{I}} \subseteq \mathcal{R}_H^{\mathcal{O}}$. Suppose first that (vii) holds. Pick any $(i,j) \in \mathcal{R}_H^{\mathcal{I}}$. Let $s \in H$ such that $B_{s,j} > 0$. If $B_{s,i} > 0$ then $(i,j) \in \mathcal{R}_H^{\mathcal{O}}$. If $B_{s,i} = 0$ then (vii) implies that there exists $s' \in H$ such that $B_{s',i} > 0$. Hence, again, $(i,j) \in \mathcal{R}_H^{\mathcal{O}}$.

Suppose now that $\mathcal{R}_H^{\mathcal{I}} \subseteq \mathcal{R}_H^{\mathcal{O}}$ holds. Let $s \in H$ and $(i,j) \in \mathcal{R}$ such that $B_{s,i} = 0$ and $B_{s,j} > 0$. Then $(i,j) \in \mathcal{R}_H^{\mathcal{I}}$. By the assumption, $(i,j) \in \mathcal{R}_H^{\mathcal{O}}$. Hence, there exists $s' \in H$ such that $B_{s',i} > 0$. Hence, $s' \in \mathrm{supp}(B_{\cdot,i})$ and $s' \notin H^c$. □

Recall that $F_\emptyset = \mathbb{R}^n_+$ and $\mathrm{cl}(F_\emptyset) = \mathbb{R}^n_{\geq 0}$. We remark that it is possible to allow $H = \emptyset$ in the definition of a siphon. In this case, $\mathcal{R}_H^{\mathcal{I}} = \mathcal{R}_H^{\mathcal{O}} = \emptyset$. Hence, $\emptyset$ is always a siphon. Recall from Section 6.1 that $F_\emptyset$ and $\mathrm{cl}(F_\emptyset)$ are always forward invariant sets for (6.1). Note also that the statements (iv),(v),(vi), and (vii) in Theorem 6.3.7 are true for $H = \emptyset$. Therefore Theorem 6.3.7 holds true if we allow $H = \emptyset$ in the definition of a siphon. The following paragraph provides explanation for the name siphon. The text is borrowed from [2].

Removing all the species of a siphon from the network (or equivalently, setting their initial concentrations equal to zero) will prevent those species from being present at all future times. Hence, those species literally lock a part of the network and shut off all the reactions that therein involved. In particular, once emptied a siphon will never be full again.

As we saw in the preceding theorem, $\emptyset \neq H \subseteq \overline{1,n}$ is a siphon if and only if F_H is forward invariant. In other words, that H is a siphon means that if species corresponding to H are not present in the system (i.e. each of those has zero concentration) then those species will never be present in the future.

That the positive orthant $\mathbb{R}^n_+$ is forward invariant means that a trajectory cannot leave $\mathbb{R}^n_+$. In other words, $\mathrm{supp}(\phi(t;\xi)) = \overline{1,n}$ for all $\xi \in \mathbb{R}^n_+$ and for all $t \in J_+(\xi)$. We are also interested in how trajectories, which start on the boundary of the nonnegative orthant evolve in time. The following proposition expresses that a trajectory starting from the boundary immediately enters a forward invariant set F_H.

Proposition 6.3.8 Let $\emptyset \neq H \subseteq \overline{1,n}$. Let $\xi \in F_H$. Then there exists $H' \subseteq H$ such that $\phi(t;\xi) \in F_{H'}$ for all $t \in J_+(\xi)$. Moreover, $F_{H'}$ is forward invariant.

Proof First we remark that one cannot replace the forward invariance of $F_{H'}$ in the statement by the expression H' is a siphon. This is due to the fact that H' may be empty.

Keep in mind that positive species concentrations cannot become zero in finite time. Hence, $\operatorname{supp}(\phi(t;\xi)) \supseteq H^c$ for all $t \in J_{\geq 0}(\xi)$. Define t_s^* for $s \in \overline{1,n}$ by

$$t_s^* = \min\big\{ \inf\{t \in J_{\geq 0}(\xi) \mid \phi_s(t;\xi) > 0\}, \sup J(\xi)\big\},$$

where $\inf \emptyset = \infty$ and $\min\{a, \infty\} = a$ for all $a \in \mathbb{R}_{\geq 0} \cup \{\infty\}$. Then $t_s^* \geq 0$ for all $s \in \overline{1,n}$ with the convention $\infty > 0$. Define the set $H' \subseteq \overline{1,n}$ by

$$H' = \{s \in \overline{1,n} \mid t_s^* > 0\}.$$

Then $H' \subseteq H$. Indeed, $s \in H'$ implies that $t_s^* > 0$ and $\phi_s(t;\xi) = 0$ for all $t \in [0, t_s^*)$. In particular, $\phi_s(0;\xi) = \xi_s = 0$ and hence $s \in H$.

It suffices to show that $t_s^* = \sup J(\xi)$ for all $s \in H'$. Suppose by contradiction that there exists $s \in H'$ such that $t_s^* < \sup J(\xi)$. Let

$$t^* = \min\{t_s^* \mid s \in H' \text{ and } t_s^* < \sup J(\xi)\}.$$

Then $t^* > 0$ and $\operatorname{supp}(\phi(t;\xi)) = (H')^c$ for all $t \in (0, t^*)$. It will be shown that $F_{H'}$ is forward invariant and this provides a contradiction.

Due to Theorem 6.3.7, it suffices to show that there exists $x \in F_{H'}$ such that $f_s(x) = 0$ for all $s \in H'$. Since $\phi_s(t;\xi) = 0$ for all $t \in (0, t^*)$ and for all $s \in H'$,

$$0 = \dot{\phi}_s(t;\xi) = f_s(\phi(t;\xi))$$

for all $t \in (0, t^*)$ and for all $s \in H'$. Pick any $t_0 \in (0, t^*)$ and let $x = \phi(t_0;\xi)$. Then $x \in F_{H'}$ and $f_s(x) = 0$ for all $s \in H'$. Hence, $t^* = \sup J(\xi)$.

We have established that there exists $H' \subseteq H$ such that $\phi(t;\xi) \in F_{H'}$ for all $t \in J_+(\xi)$. That $F_{H'}$ is forward invariant can be proven by following the above ideas with the only exception that t^* should be defined to be $\sup J(\xi)$. □

The following proposition states that the set H' depends only on $\operatorname{supp}(\xi)$. In other words, the set H' is the same for all $\xi \in F_H$.

Proposition 6.3.9 The set H' in the above proposition is determined by H (meaning that H' is the same for all $\xi \in F_H$).

Proof The proof we present here is constructive. It can be considered as an algorithm. The set H is the input and the set H' is the output of the algorithm. Denote the set H by H_0.

Recall Proposition 6.1.2. Let $x \in F_G$ for some $G \subseteq \overline{1,n}$. Then either $f_s(x) = 0$ for all $s \in G$ and for all $x \in F_G$ or $f_s(x) > 0$ for all $s \in G$ and for all $x \in F_G$.

If F_{H_0} is forward invariant then clearly $H' = H_0$.

If F_{H_0} is not forward invariant then let $H_1 = \{s \in H_0 \mid f_s(x) = 0 \text{ for all } x \in F_{H_0}\}$. Then $H_1 \subsetneq H_0$. Indeed, if H_1 would be equal to H_0 then F_{H_0} would be forward invariant. Clearly, $\operatorname{supp}(\phi(t;\xi)) \supseteq H_1^c$ for all $t \in J_+(\xi)$. Hence, $H' \subseteq H_1$.

If F_{H_1} is forward invariant then $\operatorname{cl}(F_{H_1})$ is forward invariant as well. Clearly $H' = H_1$ in this case.

If F_{H_1} is not forward invariant then let $H_2 = \{s \in H_1 \mid f_s(x) = 0 \text{ for all } x \in F_{H_1}\}$. Then $H_2 \subsetneq H_1$. Indeed, if H_2 would be equal to H_1 then F_{H_1} would be forward invariant.

We claim that $\mathrm{supp}(\phi(t;\xi)) \supseteq H_2^c$ for all $t \in J_+(\xi)$. Suppose by contradiction that there exists $s \in H_1 \backslash H_2$ such that $\phi_s(t;\xi) = 0$ for all $t \in J_+(\xi)$. Then $s \in H'$ and $f_s(x) > 0$ for all $x \in F_{H_1}$ (by Proposition 6.1.2, $\mathrm{sgn}(f_s(x))$ depends only on $\mathrm{supp}(x)$). This implies that $f_s(\phi(t;\xi)) > 0$ for all $t \in J_+(\xi)$, because $f_s(x) = \beta_s^+(x)$ and the defining sum of β_s^+ contain positive summands, because it already contains a positive summand for $x \in F_{H_1}$. Contradiction. Hence, $H' \subseteq H_2$.

If F_{H_2} is forward invariant then $\mathrm{cl}(F_{H_2})$ is forward invariant as well. Clearly $H' = H_2$ in this case.

If F_{H_2} is not forward invariant then one can continue this procedure by defining H_3.

Since H is a finite set, there exists $i \geq 0$ such that $H_0 \supsetneq H_1 \supsetneq \cdots \supsetneq H_i = H_{i+1}$. It is clear that $H' = H_i$. Since H is a finite set, the above described procedure will terminate after finitely many steps. □

We repeat the algorithm for constructing H' in Algorithm 6.3.10. The correctness of this algorithm is clear from the above proof. It is also clear that the algorithm terminates after finitely many steps.

Algorithm 6.3.10 Input is H and output is H'.

(1) Let $H_0 := H$ and $k := 0$.

(2) If F_{H_k} is forward invariant then let $H' := H_k$ and STOP. If F_{H_k} is not forward invariant then GOTO (3).

(3) Let $H_{k+1} := \{s \in H_k \mid f_s(x) = 0 \text{ for all } x \in F_{H_k}\}$ and $k := k + 1$. GOTO (2).

Due to Proposition 6.1.2, it is enough to determine the sign of $f_s(x)$ in the calculation of the set H_{k+1} for only one fixed $x \in F_{H_k}$ and for all $s \in H_k$. Checking the forward invariance of F_{H_k} can also be done easily by Theorem 6.3.7.

6.4 Interior equilibria

In this section we examine the set of equilibria for (6.1). We provide some simple statements for general kinetics. After that we deal with results for networks with mass action kinetics.

We are interested in the behaviour of the solutions of (6.1) with initial condition in the nonnegative orthant. Hence, we are interested in those equilibrium points of (6.1), which lie in $\mathbb{R}^n_{\geq 0}$.

Definition 6.4.1 Consider the differential equation (6.1). Let us define the set of equilibria E, the set of interior equilibria E_+, and the set of boundary equilibria E_0 by

$$\begin{aligned} E &= \{x \in \mathbb{R}^n_{\geq 0} \mid f(x) = 0\}, \\ E_+ &= \{x \in \mathbb{R}^n_{+} \mid f(x) = 0\}, \quad \text{and} \\ E_0 &= \{x \in \mathbb{R}^n_{0} \mid f(x) = 0\}. \end{aligned}$$

Clearly, E is the disjoint union of E_+ and E_0. The elements of E are called *equilibrium points*, the elements of E_+ are called *positive* or *interior equilibrium points* and the elements of E_0 are called *boundary equilibrium points*.

In this section we investigate mainly the set of interior equilibria. Section 6.5 deals with the set of boundary equilibria. As we shall see in the next section, in certain cases it is possible to reduce the investigation of the set of boundary equilibria to examining the set of interior equilibria for a system, which is derived from the original one.

Recall that δ denotes the deficiency of a reaction network, I denotes the incidence matrix of the digraph $(\mathcal{C}, \mathcal{R})$, and the coordinates of the function $R : \mathbb{R}^n \to \mathbb{R}^m$ are the rate functions. Recall also that S is the stoichiometric matrix and that $S = B \cdot I$, where B is the matrix of complexes.

Proposition 6.4.2 Consider a reaction system. Assume that $\delta = 0$ and let $x \in \mathbb{R}^n_{\geq 0}$. Then $x \in E$ if and only if $R(x) \in \ker I$.

Proof Due to (3.7), $x \in E$ if and only if $R(x) \in \ker S$. Recall that $\delta = \dim \ker S - \dim \ker I$. If $\delta = 0$ then we obtain that $\ker S = \ker I$. Hence, $x \in E$ if and only of $R(x) \in \ker I$. □

The above proposition shows the importance of examining the kernel of the incidence matrix, or equivalently, introducing the notion of a circulation. Also in the case when the deficiency of a network is not zero, part of the equilibrium points comes from the kernel of the incidence matrix. But in this case, other equilibrium points may also occur, because $\ker I$ is strictly smaller than $\ker S$.

Definition 6.4.3 If all the components of the graph of complexes $(\mathcal{C}, \mathcal{R})$ are strongly connected then we say that the reaction network is *weakly reversible*.

Note that the weak reversibility property is a property of a reaction network. By the weak reversibility property of a reaction system we mean the weak reversibility of the underlying reaction network. The following theorem expresses that a deficiency zero network must be weakly reversible for being able to admit interior equilibrium point.

Theorem 6.4.4 If $\delta = 0$ and $E_+ \neq \emptyset$ then the underlying reaction network is weakly reversible.

Proof Suppose that $x \in E_+$. Then $\mathrm{supp}(x) = \overline{1, n}$, thus condition $\mathrm{supp}(B_{\cdot,i}) \subseteq \mathrm{supp}(x)$ is satisfied for all $i \in \mathcal{C}$. Hence, by (3.3), $R(x) \in \mathbb{R}^m_+$. The deficiency is zero by assumption, thus due to Proposition 6.4.2, $R(x) \in \ker I$. This means that there exists a positive circulation on $(\mathcal{C}, \mathcal{R})$. This concludes the proof, because due to Theorem 4.3.3, this implies that all the components of $(\mathcal{C}, \mathcal{R})$ are strongly connected. □

In the rest of this section we deal with mass action systems. Due to the following theorem, for deficiency zero mass action systems, the converse statement of Theorem 6.4.4 also holds.

Theorem 6.4.5 Consider a mass action system with $\delta = 0$. Then $E_+ \neq \emptyset$ if and only if the underlying reaction network is weakly reversible.

Proof The only if part follows from Theorem 6.4.4.

To prove the converse statement, let us assume that the underlying reaction network is weakly reversible. The deficiency was assumed to be zero, hence an equilibrium point

can only come from the kernel of the incidence matrix. Let $x \in \mathbb{R}^n_+$. Define the function $y : \mathcal{R} \to \mathbb{R}_+$ by

$$y(i,j) = \kappa_{(i,j)} \prod_{s=1}^{n} x_s^{B_{s,i}} \tag{6.3}$$

for $(i,j) \in \mathcal{R}$. We have to show that there exists $x \in \mathbb{R}^n_+$ such that (6.3) defines a circulation on $(\mathcal{C}, \mathcal{R})$. Note that the defined $y(i,j)$ is indeed positive for all $(i,j) \in \mathcal{R}$. Observe also that if $(i,j_1), (i,j_2) \in \mathcal{R}$ then

$$\frac{y(i,j_1)}{\kappa_{(i,j_1)}} = \frac{y(i,j_2)}{\kappa_{(i,j_2)}}. \tag{6.4}$$

Positive circulations that satisfy (6.4) are examined in Theorem 4.3.6. Consider a positive circulation $y^* : \mathcal{R} \to \mathbb{R}_+$, which satisfies condition (6.4). Pick any $r \in \overline{1,\ell}$. Clearly, using the same notation as in Theorem 4.3.6, the existence of an interior equilibrium point is equivalent to the existence of $\alpha \in \mathbb{R}^\ell_+$ and $x \in \mathbb{R}^n_+$ such that

$$\sum_{r=1}^{\ell} \alpha_r y_r^*(i,j) = \kappa_{(i,j)} \prod_{s=1}^{n} x_s^{B_{s,i}} \tag{6.5}$$

for all $(i,j) \in \mathcal{R}$. Note that if $(i,j_1), (i,j_2) \in \mathcal{R}$ with common tail then equation (6.5) are the same for these two arcs, because y^* satisfies (6.4). (The unknowns in (6.5) are x and α.) Hence, we can eliminate part of the equations, keeping only one for all $i \in \overline{1,c}$. To be precise, let $p : \mathcal{C} \to \mathcal{R}$ be an injection such that the tail of $p(i)$ is i for all $i \in \mathcal{C}$. Note that by the weakly reversibility and by the assumption that each complex is involved in at least one reaction, such injection exists. Define $\underline{y}^* \in \mathbb{R}^c_+$ by $\underline{y}^*_i = y^*(p(i))/\kappa_{p(i)}$. Recall that c_r denotes the number of complexes in the rth linkage class ($r \in \overline{1,\ell}$). Denote by $\underline{y}^{*r} \in \mathbb{R}^{c_r}_+$ the vector, which coordinates are the coordinates of $\underline{y}^*$ corresponding to the rth linkage class ($r \in \overline{1,\ell}$).

If d is a positive integer then define $\log^d : \mathbb{R}^d_+ \to \mathbb{R}^d$ by

$$[v_1, \ldots, v_d]^T \mapsto [\log(v_1), \ldots, \log(v_d)]^T,$$

where $\log : \mathbb{R}_+ \to \mathbb{R}$ is the natural logarithm function.

Assuming that the columns of B are ordered accordingly to the vectors $\underline{y}^{*r}$ and taking logarithm, (6.5) reduces to

$$\begin{bmatrix} \log^{c_1}(\alpha_1 \underline{y}^{*1}) \\ \vdots \\ \log^{c_\ell}(\alpha_\ell \underline{y}^{*\ell}) \end{bmatrix} = B^T \cdot \log^n(x).$$

Using that $\log(ab) = \log(a) + \log(b)$ for all $a, b \in \mathbb{R}_+$, one can write the above equation in the form

$$\log^c(\underline{y}^*) = \begin{bmatrix} \log^{c_1}(\underline{y}^{*1}) \\ \vdots \\ \log^{c_\ell}(\underline{y}^{*\ell}) \end{bmatrix} = \widehat{B}^T \cdot \begin{bmatrix} \log^n(x) \\ -\log^\ell(\alpha) \end{bmatrix},$$

where $\widehat{B} \in \mathbb{R}^{(n+\ell)\times c}$ is the matrix defined in Section 5.3. Due to Theorem 5.3.7, the deficiency equals to $\dim \ker \widehat{B}$. As $\delta = 0$ by assumption, $\widehat{B}^T$ has full range.

This concludes the proof, because it means that there exist vectors $v^1 \in \mathbb{R}^n$ and $v^2 \in \mathbb{R}^\ell$ such that

$$\log^c(\underline{y}^*) = \widehat{B}^T \cdot \begin{bmatrix} v^1 \\ v^2 \end{bmatrix}. \tag{6.6}$$

Define x_s to be $e^{v^1_s}$ for $s \in \overline{1,n}$ and α_r to be $e^{-v^2_r}$ for $r \in \overline{1,\ell}$. The defined x and α satisfy all desired conditions. □

We remark that the determination of y^* in the above proof is equivalent to finding any positive element of the kernel of an $m \times m$ matrix. After one has y^*, it is possible to solve the linear equation (6.6). Determination of the set of interior equilibria is then straightforward.

The above proof showed that for deficiency zero mass action systems, the weakly reversibility property is equivalent to the existence of an interior steady state. As a matter of fact, we can say more. Recall that $\mathcal{S}$ denotes the stoichiometric subspace.

Proposition 6.4.6 Consider a weakly reversible mass action system with $\delta = 0$. Let $x^1, x^2 \in E_+$. Then $\log^n(x^2) - \log^n(x^1) \in \mathcal{S}^\perp$.

Proof Due to the proof of Theorem 6.4.5, there exist $\alpha^1, \alpha^2 \in \mathbb{R}^\ell_+$ such that

$$\widehat{B}^T \cdot \begin{bmatrix} \log^n(x^1) \\ -\log^\ell(\alpha^1) \end{bmatrix} = \widehat{B}^T \cdot \begin{bmatrix} \log^n(x^2) \\ -\log^\ell(\alpha^2) \end{bmatrix}.$$

One can write out this equation in coordinates. If $i \in \overline{1,c}$ and the complex C_i is in the rth linkage class for some $r \in \overline{1,\ell}$ then the ith equation has the form

$$\log(\alpha^2_r) - \log(\alpha^1_r) = \langle B_{\cdot,i}, \log^n(x^2) - \log^n(x^1) \rangle.$$

If $(i,j) \in \mathcal{R}$ then complex C_i and complex C_j are in the same linkage class. This implies that

$$\langle B_{\cdot,j} - B_{\cdot,i}, \log^n(x^2) - \log^n(x^1) \rangle = 0$$

for all $(i,j) \in \mathcal{R}$. Recall that the stoichiometric subspace $\mathcal{S}$ is spanned by the set $\{B_{\cdot,j} - B_{\cdot,i} \in \mathbb{R}^n \mid (i,j) \in \mathcal{R}\}$. This concludes the proof. □

The above results remain true for a considerable wider class of systems. Recall that δ_r denotes the deficiency of the rth linkage class ($r \in \overline{1,\ell}$). The proof of the following theorem can be found in [6].

Theorem 6.4.7 Consider a weakly reversible mass action system for which $\delta_r \leq 1$ for all $r \in \overline{1,\ell}$ and $\delta = \delta_1 + \cdots + \delta_\ell$. Then $E_+ \neq \emptyset$. Moreover, if $x^* \in E_+$ then

$$E_+ \subseteq \{x \in \mathbb{R}^n_+ \mid \log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp\}. \tag{6.7}$$

Recall that we have shown in Section 5.4 that the property $\delta = \delta_1 + \ldots + \delta_\ell$ holds for all deficiency zero network. Hence, Theorem 6.4.5 and Proposition 6.4.6 provide the proof of a special case of Theorem 6.4.7.

The following proposition shows that the converse inclusion in (6.7) holds for a wide class of systems, including systems in Theorem 6.4.7.

Proposition 6.4.8 Consider a mass action system, which satisfies $\delta = \delta_1 + \cdots + \delta_\ell$. Assume that $E_+ \neq \emptyset$. Fix any $x^* \in E_+$. Then

$$E_+ \supseteq \{x \in \mathbb{R}^n_+ \mid \log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp\}.$$

Proof Pick any $x \in \mathbb{R}^n_+$ such that $\log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp$. Let $i \in \overline{1,c}$. Let us define the function $\pi_i : \mathbb{R}^n_{\geq 0} \times \mathbb{R}^n_+ \to \mathbb{R}_{\geq 0}$ by

$$\pi_i(x,y) = \prod_{s=1}^{n} \left(\frac{x_s}{y_s}\right)^{B_{s,i}} \tag{6.8}$$

for $(x,y) \in \mathbb{R}^n_{\geq 0} \times \mathbb{R}^n_+$. Fix any $x^* \in E_+$ and any $x \in \mathbb{R}^n_+$ such that $\log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp$. Let $(i,j) \in \mathcal{R}$. Then

$$\langle B_{\cdot,j} - B_{\cdot,i}, \log^n(x) - \log^n(x^*)\rangle = 0.$$

The latter can be written equivalently as

$$\pi_i(x,x^*) = \pi_j(x,x^*).$$

Recall that $\mathcal{R}_r$ denotes the set of reactions and $\mathcal{C}_r$ the set of complexes in the rth linkage class ($r \in \overline{1,\ell}$). The above equality implies that $\pi_i(x,x^*) = \pi_j(x,x^*)$ for all $i,j \in \mathcal{C}_r$ ($r \in \overline{1,\ell}$). For fixed x and x^* denote this common value by π^r. Recall also the definition of the function $f^r : \mathbb{R}^n \to \mathbb{R}^n$. Straightforward calculation shows that $x \in E_+$:

$$f(x) = \sum_{r=1}^{\ell} f^r(x) = \sum_{r=1}^{\ell} \left(\sum_{(i,j)\in\mathcal{R}_r} \kappa_{(i,j)} \prod_{s=1}^{n} x_s^{B_{s,i}} (B_{\cdot,j} - B_{\cdot,i}) \right) =$$

$$= \sum_{r=1}^{\ell} \left(\sum_{(i,j)\in\mathcal{R}_r} \kappa_{(i,j)} \left(\prod_{s=1}^{n} (x_s^*)^{B_{s,i}} \right) \pi_i(x,x^*)(B_{\cdot,j} - B_{\cdot,i}) \right) = \sum_{r=1}^{\ell} \pi^r f^r(x^*).$$

Due to $x^* \in E_+$, $f(x^*) = 0$. Hence, Proposition 5.4.7, $f^r(x^*) = 0$ for all $r \in \overline{1,\ell}$. This concludes the proof. □

The following theorem is an immediate consequence of Theorem 6.4.7 and Proposition 6.4.8.

Theorem 6.4.9 Consider a weakly reversible mass action system for which $\delta_r \leq 1$ for all $r \in \overline{1,\ell}$ and $\delta = \delta_1 + \cdots + \delta_\ell$. Fix any $x^* \in E_+$. Then

$$E_+ = \{x \in \mathbb{R}^n_+ \mid \log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp\}.$$

The above theorem allows us to provide a differential geometric statement about E_+. Recall that $\delta = c - \ell - \operatorname{rank} S$. Since $0 < \operatorname{rank} S \leq n$, $0 \leq n - (c - \ell - \delta) < n$. The following proposition can be found in [10] in a slightly different form.

Proposition 6.4.10 Consider a system as in Theorem 6.4.9. Then E_+ is C^∞-diffeomorphic to $\mathbb{R}^{n-(c-\ell-\delta)}$. Hence, E_+ is a C^∞ submanifold of $\mathbb{R}^n$ of dimension $n-(c-\ell-\delta)$. Moreover, E_+ is connected.

Proof Fix any $x^* \in E_+$. Define the map $\Theta : \mathbb{R}^n \to \mathbb{R}^n_+$ by $y \mapsto [x_1^* e^{y_1}, \ldots, x_n^* e^{y_n}]^T$. Then Θ is a C^∞-diffeomorphism. Since $\dim \mathcal{S} = c - \ell - \delta$, $\dim \mathcal{S}^\perp = n - (c - \ell - \delta)$. We claim that $\Theta(\mathcal{S}^\perp) = E_+$. Note that $x \in \Theta(\mathcal{S}^\perp)$ if and only if there exists a $y \in \mathcal{S}^\perp$ such that $\log^n(x^*) + y = \log^n(x)$, that is, if and only if $\log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp$. By Theorem 6.4.9, the latter is equivalent to $x \in E_+$. The claim is verified. The connectedness of E_+ follows from the fact that continuous image of a connected set is connected. □

The proof of the following lemma is borrowed from [10].

Lemma 6.4.11 Let $\mathcal{S}$ be the stoichiometric subspace and $\mathcal{P} = (p + \mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ a positive stoichiometric class for some $p \in \mathbb{R}^n_+$. Then, for each $x^* \in \mathbb{R}^n_+$ there exists a unique $x \in \mathbb{R}^n_+$ such that $x \in \mathcal{P} \cap \mathbb{R}^n_+$ and $\log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp$.

Proof Let $x^* \in \mathbb{R}^n_+$. For $s \in \overline{1,n}$, define function $L_s : \mathbb{R} \to \mathbb{R}$ by

$$L_s(y) = x_s^* e^y - p_s y$$

for $y \in \mathbb{R}$. Then $\lim_{y\to\infty} L_s(y) = \infty$ and $\lim_{y\to-\infty} L_s(y) = \infty$, hence L_s is proper, that is, $\{y \in \mathbb{R} \mid L_s(y) \leq v\}$ is compact for each $v \in \mathbb{R}$. Define the function $Q : \mathbb{R}^n \to \mathbb{R}$ by

$$Q(y) = \sum_{s=1}^{n} L_s(y_s).$$

Note that Q is continuously differentiable. The function Q inherits the proper property from the functions L_s ($s \in \overline{1,n}$):

$$\{y \in \mathbb{R}^n \mid Q(y) \leq w\} \subseteq \bigtimes_{s=1}^{n} \{y_s \in \mathbb{R} \mid L_s(y_s) \leq w - (n-1)M\},$$

where $M \in \mathbb{R}$ is any common lower bound for the functions L_s ($s \in \overline{1,n}$). Restricted to $\mathcal{S}^\perp$, Q is still proper, so it attains a minimum at some point $y^* \in \mathcal{S}^\perp$. The transposed of the gradient of Q at point $y^* \in \mathbb{R}^n$ must be orthogonal to $\mathcal{S}^\perp$:

$$((\mathrm{grad}Q)(y^*))^T = [x_1^* e^{y_1^*} - p_1, \ldots, x_n^* e^{y_n^*} - p_n]^T = [x_1^* e^{y_1^*}, \ldots, x_n^* e^{y_n^*}]^T - p \in (\mathcal{S}^\perp)^\perp = \mathcal{S}.$$

Pick $x \in \mathbb{R}^n_+$ such that $\log^n(x) = y^* + \log^n(x^*)$. Note that $\log^n : \mathbb{R}^n_+ \to \mathbb{R}^n$ is a bijection, hence such x indeed exists. Then $\log^n(x) - \log^n(x^*) = y^* \in \mathcal{S}^\perp$ and the formula for the gradient of Q at point y^* shows that $x - p \in \mathcal{S}$. In other words, $x \in \mathcal{P} \cap \mathbb{R}^n_+$.

It remains to show the uniqueness part of the statement. Suppose that $x^1, x^2 \in \mathbb{R}^n_+$ are such that $x^1 - p \in \mathcal{S}$, $x^2 - p \in \mathcal{S}$, $\log^n(x^1) - \log^n(x^*) \in \mathcal{S}^\perp$, and $\log^n(x^2) - \log^n(x^*) \in \mathcal{S}^\perp$. This implies that $x^1 - x^2 \in \mathcal{S}$ and $\log^n(x^1) - \log^n(x^2) \in \mathcal{S}^\perp$. Since $\log : \mathbb{R}_+ \to \mathbb{R}$ is strictly increasing, $(a-b)(\log(a) - \log(b)) > 0$ for any $a, b \in \mathbb{R}_+$ distinct numbers. Thus

$$\sum_{s=1}^{n} (x_s^1 - x_s^2)(\log(x_s^1) - \log(x_s^2)) = (x^1 - x^2)^T (\log^n(x^1) - \log^n(x^2)) = 0$$

implies that $x_s^1 = x_s^2$ for all $s \in \overline{1,n}$. □

We are now in the position to formulate a theorem, which states that for certain reaction systems there exists a unique interior equilibrium point in each positive stoichiometric class.

Theorem 6.4.12 Consider a system as in Theorem 6.4.9. Then $|\mathcal{P} \cap E_+| = 1$ for all positive stoichiometric class $\mathcal{P}$.

Proof Fix any $x^* \in E_+$. Due to Theorem 6.4.9, the set of positive equilibria is $\{x \in \mathbb{R}^n_+ \mid \log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp\}$. Lemma 6.4.11 then implies that $|\mathcal{P} \cap E_+| = 1$. □

The following two examples illustrate the above theorem. The examples will be revisited in Section 6.6. The examples are borrowed from [10].

Example 6.4.13 Consider the simple example for a reaction network in Figure 6.3.

$$C_1 = A_1 + A_2 \qquad \rightleftarrows \qquad C_2 = 2A_1 + A_2$$

Figure 6.3: Scheme of the reaction network of Example 6.4.13

Using the introduced notations,

$$\mathcal{C} = \{C_1, C_2\}, \quad \mathcal{R} = \{(1,2),(2,1)\}, \quad c = 2, \quad m = 2, \quad \ell = 1, \quad n = 2,$$

$$B = \begin{bmatrix} 1 & 2 \\ 1 & 1 \end{bmatrix}, \quad I = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}, \quad S = B \cdot I = \begin{bmatrix} 1 & -1 \\ 0 & 0 \end{bmatrix},$$

$$\operatorname{rank} S = 1, \quad \delta = 2 - 1 - 1 = 0.$$

Endow the network with mass action kinetics, with rate constants $\kappa_{(1,2)} = 1$ and $\kappa_{(2,1)} = 1$. Then the differential equation for the system is

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = x_1 x_2 \begin{bmatrix} 1 \\ 0 \end{bmatrix} + x_1^2 x_2 \begin{bmatrix} -1 \\ 0 \end{bmatrix} = \begin{bmatrix} (1 - x_1) x_1 x_2 \\ 0 \end{bmatrix}.$$

Thus

$$E_0 = \{[x_1, x_2]^T \in \mathbb{R}^2_0 \mid x_1 x_2 = 0\} \quad \text{and} \quad E_+ = \{[x_1, x_2]^T \in \mathbb{R}^2_+ \mid x_1 = 1\}.$$

The stoichiometric subspace $\mathcal{S}$ is generated by the vector $[1, 0]^T$. Hence, the positive stoichiometric classes are the sets

$$\mathcal{P}_z = \{[x_1, x_2]^T \in \mathbb{R}^2_{\geq 0} \mid x_2 = z\}$$

for $z \in \mathbb{R}_+$. Each positive stoichiometric class contains exactly one interior equilibrium point. The sets E_0, E_+, and $\mathcal{P}_z$ are depicted in Figure 6.4. The unique interior equilibrium point in $\mathcal{P}_z$, $[1, z]^T$, is denoted by x^* in the figure.

□

Example 6.4.14 Consider the simple example for a reaction network in Figure 6.5.

Using the introduced notations,

$$\mathcal{C} = \{C_1, C_2\}, \quad \mathcal{R} = \{(1,2),(2,1)\}, \quad c = 2, \quad m = 2, \quad \ell = 1, \quad n = 2,$$

$$B = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \quad I = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}, \quad S = B \cdot I = \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix},$$

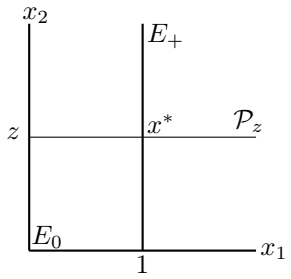


Figure 6.4: The sets E_0, E_+, and $\mathcal{P}_z$ for Example 6.4.13

$$C_1 = A_1 \qquad \rightleftharpoons \qquad C_2 = A_2$$

Figure 6.5: Scheme of the reaction network of Example 6.4.14

$$\operatorname{rank} S = 1, \quad \delta = 2 - 1 - 1 = 0.$$

Endow the network with mass action kinetics, with rate constants $\kappa_{(1,2)} = 1$ and $\kappa_{(2,1)} = 1$. Then the differential equation for the system s:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = x_1 \begin{bmatrix} -1 \\ 1 \end{bmatrix} + x_2 \begin{bmatrix} 1 \\ -1 \end{bmatrix} = \begin{bmatrix} x_2 - x_1 \\ x_1 - x_2 \end{bmatrix}.$$

Thus

$$E_0 = \{[0,0]^T\}, \quad \text{and} \quad E_+ = \{[x_1, x_2]^T \in \mathbb{R}^2_+ \mid x_1 = x_2\}.$$

The stoichiometric subspace $\mathcal{S}$ is generated by the vector $[1,-1]^T$. Hence, the positive stoichiometric classes are the sets

$$\mathcal{P}_z = \{[x_1, x_2]^T \in \mathbb{R}^2_{\geq 0} \mid x_2 = -x_1 + z\}$$

for $z \in \mathbb{R}_+$. Each positive stoichiometric class contains exactly one interior equilibrium point. The sets E_+ and $\mathcal{P}_z$ are depicted in Figure 6.6. The unique interior equilibrium point in $\mathcal{P}_z$, $[z/2, z/2]^T$, is denoted by x^* in the figure.

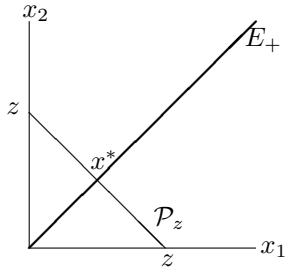


Figure 6.6: The sets E_+ and $\mathcal{P}_z$ for Example 6.4.14

□

We remark that an example in [7] can be found, where a weakly reversible mass action system with $\ell = 1$ and $\delta = 2$ admits exactly three positive equilibrium points in each positive stoichiometric class.

We conclude this section by providing a compact characterization of the set of equilibria for weakly reversible mass action systems with $\delta = 0$. The result is then used in Section 6.6. The introduced characterization is due to E.D. Sontag [10].

Fix any $i \in \overline{1,c}$. Let us define the function $q_i : \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}$ by

$$q_i(x,y) = \langle B_{\cdot,i}, \log^n(x) - \log^n(y) \rangle. \tag{6.9}$$

Define the function $\Phi : \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}_{\geq 0}$ by

$$\Phi(x,y) = \sum_{(i,j)\in\mathcal{R}} (q_j(x,y) - q_i(x,y))^2.$$

It is clear from the definition of Φ that it is indeed nonnegative.

Proposition 6.4.15 Consider a system as in Theorem 6.4.9. Let $x^* \in E_+$ and $x \in \mathbb{R}^n_+$. Then $x \in E_+$ if and only if $\Phi(x, x^*) = 0$.

Proof Clearly, $\Phi(x, x^*) = 0$ if and only if $\log^n(x) - \log^n(x^*) \in \mathcal{S}^\perp$. Theorem 6.4.9 then implies the desired result. □

We remark that the above definition of the function Φ is slightly different than in [10].

6.5 Boundary equilibria

We introduce a construction in this section, which allows us to reduce the investigation of the set of boundary equilibria to the examination of the set of interior equilibria of another system.

We start by a proposition, which expresses that if $(i,j) \in \mathcal{R}$ and all the constituting species of complex C_i are present in the system then each of the constituting species in complex C_j is either present as well or not present, but biochemically being produced.

Proposition 6.5.1 Assume that $(i,j) \in \mathcal{R}$. Pick any $x \in \mathbb{R}^n_{\geq 0}$ such that $\operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x)$. Then $\operatorname{supp}(B_{\cdot,j}) \subseteq \operatorname{supp}(x) \cup \{s \in \overline{1,n} \mid f_s(x) > 0\}$.

Proof Suppose that there exists $s \in \overline{1,n}$ for which $B_{s,j} > 0$ and $x_s = 0$. We have to prove that $f_s(x) > 0$. Proposition 6.1.2 implies that in this case $f_s(x) = \beta^0_s(x)$, where $\beta^0_s(x)$ is a sum of nonnegative summands. It suffices to show that there exists a summand in $\beta^0_s(x)$, which is positive. By the assumption of the proposition, $B_{s,i} = 0$ if $x_s = 0$. By condition (3.3), $R_{(i,j)}(x) > 0$ and hence $R_{(i,j)}(x)B_{s,j} > 0$. □

The following proposition is an immediate consequence of Proposition 6.5.1.

Proposition 6.5.2 Let $H \subseteq \overline{1,n}$ be such that F_H is forward invariant. Let $x \in F_H$ and $(i,j) \in \mathcal{R}$. Then $\operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x)$ implies that $\operatorname{supp}(B_{\cdot,j}) \subseteq \operatorname{supp}(x)$.

Proof If $H = \emptyset$ then the statement is trivial. If $H \neq \emptyset$ then Theorem 6.3.7 implies that $f_s(x) = 0$ for all $s \in H$. It means that $\{s \in \overline{1,n} \mid f_s(x) > 0\} \subseteq \operatorname{supp}(x)$. Finally, Proposition 6.5.1 yields the result. □

Repeated application of Proposition 6.5.2 yields the following result.

Proposition 6.5.3 Let $H \subseteq \overline{1,n}$ be such that F_H is forward invariant. Let $x \in F_H$ and $(\mathcal{C}, \mathcal{R})$ be the graph of complexes. Then, if there exists a directed path between $i \in \mathcal{C}$ and $j \in \mathcal{C}$ then $\operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x)$ implies that $\operatorname{supp}(B_{\cdot,j}) \subseteq \operatorname{supp}(x)$. In particular, if $(\mathcal{C}', \mathcal{R}')$ is a strongly connected subgraph of $(\mathcal{C}, \mathcal{R})$ then either $\operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x)$ for all $i \in \mathcal{C}'$ or $\operatorname{supp}(B_{\cdot,i}) \nsubseteq \operatorname{supp}(x)$ for all $i \in \mathcal{C}'$.

The following proposition shows that boundary equilibrium point can occur in F_H only if F_H is forward invariant. Recall that $\mathcal{C}_r$ denotes the set of complexes in the rth linkage class ($r \in \overline{1,\ell}$).

Proposition 6.5.4 Let $\emptyset \neq H \subseteq \overline{1,n}$. Assume that $F_H \cap E_0 \neq \emptyset$. Then H is a siphon.

Proof Pick any $\xi \in F_H \cap E_0$. Then $f(\xi) = 0$. In particular, $f_s(\xi) = 0$ for all $s \in H$. Due to Theorem 6.3.7, H is a siphon. □

The following proposition shows that in a special case the set of boundary equilibria has a simple structure.

Proposition 6.5.5 Assume that no row of B vanishes and $(\mathcal{C}, \mathcal{R})$ is strongly connected. Let $\emptyset \neq H \subseteq \overline{1,n}$. Then either $F_H \cap E_0 = F_H$ or $F_H \cap E_0 = \emptyset$.

Proof Let $\xi \in F_H \cap E_0$. Then H is a siphon by Proposition 6.5.4. By Proposition 6.5.3, either $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}$ or $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$ for all $i \in \mathcal{C}$. As $H^c \subsetneq \overline{1,n}$ and no row of B vanishes, the latter is not possible. Hence, $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}$. This implies that $R_{(i,j)}(x) = 0$ for all $x \in F_H$ and for all $(i,j) \in \mathcal{R}$. Hence, $x \in E$ for all $x \in F_H$. □

If $H = \overline{1,n}$ and F_H is a siphon then clearly $0 \in E_0$.

We introduce now a construction that associates a new reaction system to a reaction system and a siphon. The advantage of this association will be clear. Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Denote by K the linear space

$$K = \{x \in \mathbb{R}^n \mid x_s = 0 \text{ if } s \in H\}. \tag{6.10}$$

Define the linear homeomorphism $P : K \to \mathbb{R}^{\overline{n}}$ by $(Px)_s = x_s$ for $s \in H^c$ and for $x \in K$, where $\overline{n} = |H^c|$. (The coordinates of vectors in $\mathbb{R}^{\overline{n}}$ are indexed by the elements of H^c.) From now on, if H is a siphon then K and P always denotes the above defined objects.

Construction 6.5.6 Let $(\mathcal{A}, \mathcal{C}, \mathcal{R}, R)$ be a biochemical reaction system. Assume that $\emptyset \neq H \subsetneq \overline{1,n}$ is a siphon. Denote by H^c the set $\overline{1,n} \backslash H$. Quantities corresponding to the new system will be indicated by upper bars. The complexes and species occurring in the new system inherits their indices from the original system. Define the set of species for the new system by

$$\overline{\mathcal{A}} = \{A_s \in \mathcal{A} \mid s \in H^c\}.$$

Define the set of reactions by

$$\overline{\mathcal{R}} = \{(i,j) \in \mathcal{R} \mid \operatorname{supp}(B_{\cdot,i}) \subseteq H^c\}.$$

Note that if $\overline{\mathcal{R}} = \emptyset$ then all the reaction rates in the original system are zero at all $x \in F_H$. Hence, $F_H \cap E_0 = F_H$. Continue the construction only if $\overline{\mathcal{R}} \neq \emptyset$.

Define the set of complexes for the new system by

$$\overline{\mathcal{C}} = \{i \in \overline{1,c} \mid \text{there exists } (j_1, j_2) \in \overline{\mathcal{R}} \text{ such that } j_1 = i \text{ or } j_2 = i\}.$$

Note that if $\overline{\mathcal{R}} \neq \emptyset$ then $\overline{\mathcal{C}} \neq \emptyset$.

Denote by $\overline{n}$ and $\overline{c}$ the number of species and the number of complexes in the new system. Define the matrix of complexes $\overline{B} \in \mathbb{R}^{\overline{n} \times \overline{c}}$ for the new system by $\overline{B}_{s,i} = B_{s,i}$ for $s \in H^c$ and for $i \in \overline{\mathcal{C}}$.

It remains to define the kinetics of the new system. Denote by $\overline{x}$ the new state variable. Define the rate functions of the new system by $\overline{R}_{(i,j)}(\overline{x}) = R_{(i,j)}(P^{-1}\overline{x})$ for $(i,j) \in \overline{\mathcal{R}}$ and $\overline{x} \in \mathbb{R}^{\overline{n}}$. Define $\overline{f}(\overline{x}) : \mathbb{R}^{\overline{n}} \to \mathbb{R}^{\overline{n}}$ by

$$\overline{f}(\overline{x}) = \sum_{(i,j) \in \overline{\mathcal{R}}} \overline{R}_{(i,j)}(\overline{x})(\overline{B}_{\cdot,j} - \overline{B}_{\cdot,i})$$

for $\overline{x} \in \mathbb{R}^{\overline{n}}$. The differential equation that governs the evolution of the new system is then $\dot{\overline{x}} = \overline{f}(\overline{x})$. □

From now on if an object with upper bar appears then we always implicitly assume that a siphon is given and that object with upper bar corresponds to the new system in Construction 6.5.6.

Proposition 6.5.7 Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. Let $i \in \overline{\mathcal{C}}$. Then $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$.

Proof Let $i \in \overline{\mathcal{C}}$. If there exists $j \in \overline{\mathcal{C}}$ such that $(i,j) \in \overline{\mathcal{R}}$ then clearly $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$.

If there exists $j \in \overline{\mathcal{C}}$ such that $(j,i) \in \overline{\mathcal{R}}$ then $\operatorname{supp}(B_{\cdot,j}) \subseteq H^c$. By Proposition 6.5.2, $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$. □

Note that Proposition 6.5.7 implies that $\overline{f}(\overline{x}) = Pf(P^{-1}\overline{x})$ for all $\overline{x} \in \mathbb{R}^{\overline{n}}_+$.

Note also that $\overline{f}$ inherits the local Lipschitz continuity from f. Let us denote by $\overline{\phi}(\cdot, \overline{\xi}) : \overline{J}(\overline{\xi}) \to \mathbb{R}^{\overline{n}}$ the solution of the new differential equation $\dot{\overline{x}} = \overline{f}(\overline{x})$ with initial value $\overline{\xi} \in \mathbb{R}^{\overline{n}}$. The following proposition shows that the dynamics of the original system and the new system are essentially the same.

Proposition 6.5.8 Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. Let $\xi \in F_H$. Then $\overline{J}(P\xi) \subseteq J(\xi)$, $\overline{J}_{\geq 0}(P\xi) = J_{\geq 0}(\xi)$ and $P^{-1}\overline{\phi}(t; P\xi) = \phi(t; \xi)$ for all $t \in \overline{J}(P\xi)$.

Proof Define $y : \overline{J}(P\xi) \to \mathbb{R}^{\overline{n}}$ by $y(t) = P^{-1}\overline{\phi}(t; P\xi)$ for $t \in \overline{J}(P\xi)$. Then $y(0) = P^{-1}\overline{\phi}(0; P\xi) = P^{-1}P\xi = \xi$ and

$$\dot{y}(t) = P^{-1}\dot{\overline{\phi}}(t; P\xi) = P^{-1}\overline{f}(\phi(t; P\xi)) = P^{-1}Pf(P^{-1}\overline{\phi}(t; P\xi)) = f(y(t))$$

for $t \in \overline{J}(P\xi)$. Uniqueness of the solution of the initial value problem $\dot{x} = f(x), x(0) = \xi$ implies that $\overline{J}(P\xi) \subseteq J(\xi)$ and $P^{-1}\overline{\phi}(t; P\xi) = \phi(t; \xi)$ for all $t \in \overline{J}(P\xi)$.

It remains to show that $\overline{J}_{\geq 0}(P\xi) = J_{\geq 0}(\xi)$. Suppose by contradiction that $\overline{J}_{\geq 0}(P\xi) \supsetneq J_{\geq 0}(\xi)$. Let $t^* = \sup \overline{J}_{\geq 0}(P\xi)$. Then t^* cannot be a finite explosion time for $\overline{\phi}(\cdot; P\xi)$, because in this case it would be a finite explosion time for $\phi(\cdot; \xi)$ as well. Hence, the solution of the new differential equation must approach the boundary of $\mathbb{R}^{\overline{n}}_+$. But this is not possible, because then $\phi(t^*; \xi)$ would be in $\operatorname{cl}(F_H) \backslash F_H$, which contradicts the forward invariance of F_H. □

Denote by $\overline{E}_+$ the set of interior equilibria for the new system.

Proposition 6.5.9 Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. Then

$$E_0 \cap F_H = \{x \in F_H \mid Px \in \overline{E}_+\}.$$

Proof The result is an immediate consequence of Proposition 6.5.8. □

The advantage of introducing the new system is that the set $E_0 \cap F_H$ can be examined by investigating the set of interior equilibria $\overline{E}_+$ for the new system. Hence, investigating the set of boundary equilibria can be reduced to the investigation of the set of interior equilibria for the associated new system. We shall show that this technique can be used for instance to establish propositions about the set of boundary equilibria for systems in Theorem 6.4.9.

Let us introduce the following notations for further reference. Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. Let

$$\overline{\mathcal{S}} = \operatorname{span}\{\overline{B}_{\cdot,j} - \overline{B}_{\cdot,i} \in \mathbb{R}^{\overline{n}} \mid (i,j) \in \overline{\mathcal{R}}\}.$$

Due to Proposition 6.5.7,

$$P^{-1}\overline{\mathcal{S}} = \operatorname{span}\{B_{\cdot,j} - B_{\cdot,i} \in \mathbb{R}^n \mid (i,j) \in \overline{\mathcal{R}}\}$$

holds.

The following two propositions express that the new system inherits certain properties of the original system.

Proposition 6.5.10 Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. If the original network is weakly reversible then the new network is weakly reversible as well. Moreover, the linkage classes of the new system are linkage classes of the original system.

Proof Assume that $i \in \overline{\mathcal{C}}$ and $r \in \overline{1,\ell}$ are such that $i \in \mathcal{C}_r$. Then $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$ by Proposition 6.5.7. By Proposition 6.5.3, $\operatorname{supp}(B_{\cdot,j}) \subseteq H^c$ for all $j \in \mathcal{C}_r$. Hence, $\mathcal{R}_r \subseteq \overline{\mathcal{R}}$. In other words, all the reactions in the rth linkage class are reactions in the new network as well. □

Assume now that the original system is weakly reversible. Note that due to the above proposition, the new network essentially consists of certain linkage classes of the original network. Define the set G by

$$G = \{r \in \overline{1,\ell} \mid \operatorname{supp}(B_{\cdot,i}) \subseteq H^c \text{ for all } i \in \mathcal{C}_r\}.$$

Note that $G = \emptyset$ if and only if $\overline{\mathcal{R}} = \emptyset$. Denote by $\overline{\delta}$ and by $\overline{\delta}_r$ the deficiency of the new network and deficiency of the rth linkage class of the new network ($r \in G$), respectively.

Proposition 6.5.11 Consider a weakly reversible reaction network. Let $\emptyset \neq H \subseteq \overline{1,n}$ be a siphon. Assume that $\overline{\mathcal{R}} \neq \emptyset$. Then $\overline{\delta}_r = \delta_r$ for all $r \in G$. Moreover, if $\delta = \sum_{r=1}^{\ell} \delta_r$ then $\overline{\delta} = \sum_{r \in G} \overline{\delta}_r$.

Proof To prove the first statement it suffices to show that $\dim\ker \widehat{\overline{B}}_r = \dim\ker \widehat{B}_r$ for all $r \in G$. By Proposition 6.5.7, $B_{s,i} = 0$ for all $s \in H$ and for all $i \in \overline{\mathcal{C}}$. This implies that $\widehat{\overline{B}}_r$ can be obtained from $\widehat{B}_r$ by deleting identically zero rows ($r \in G$). Namely, one should delete the rows with indices in $H \cup \{n + r \mid r \in \overline{1,\ell} \backslash G\}$. This means that $\ker \widehat{\overline{B}}_r = \ker \widehat{B}_r$ for all $r \in G$.

Assume now that $\delta = \sum_{r=1}^{\ell} \delta_r$. As we saw in Section 5.4, this is equivalent to

$$\operatorname{ran} \widehat{B} = \operatorname{ran} \widehat{B}_1 \oplus \cdots \oplus \operatorname{ran} \widehat{B}_\ell.$$

As $\widehat{\overline{B}}_r$ can be obtained from $\widehat{B}_r$ by deleting identically zero rows, it follows that

$$\operatorname{ran} \widehat{\overline{B}} = \bigoplus_{r \in G} \operatorname{ran} \widehat{\overline{B}}_r.$$

This concludes the proof. □

We are now in the position to establish a theorem about the set of boundary equilibria for certain systems. Note that for a mass action system the defined kinetics for the new system in Construction 6.5.6 is the mass action kinetics corresponding to the new system.

Theorem 6.5.12 Consider a mass action system. Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Assume that $\mathcal{R} \neq \emptyset$. Assume that the constructed new system satisfies the conditions of Theorem 6.4.9. Then $F_H \cap E_0 \neq \emptyset$. Moreover, $|(F_H \cap E_0) \cap (p + P^{-1}\overline{\mathcal{S}})| = 1$ for all $p \in F_H$.

Proof The stoichiometric subspace of the associated new system is $\overline{\mathcal{S}}$. Pick any $\overline{p} \in \mathbb{R}^{\overline{n}}_+$. By Theorem 6.4.12, $|(\overline{p} + \overline{\mathcal{S}}) \cap \overline{E}_+| = 1$. This observation and Proposition 6.5.9 yields the result. □

The preceding theorem applies for systems in Theorem 6.4.9 in case $\mathcal{R} \neq \emptyset$. This is ensured by Proposition 6.5.10 and Proposition 6.5.11.

Proposition 6.5.13 Consider a mass action system. Let $\emptyset \neq H \subseteq \overline{1,n}$ be a siphon. Assume that $\mathcal{R} \neq \emptyset$. Assume that the constructed new system satisfies the conditions of Theorem 6.4.9. Then $F_H \cap E_0$ is a C^∞ submanifold of $\mathbb{R}^n$ of dimension $\overline{n} - (\overline{c} - \overline{\ell} - \overline{\delta})$, where $\overline{\ell}$ is the number of linkage classes in the new system.

Proof Due to Proposition 6.4.10, $\overline{E}_+$ is a C^∞ submanifold of $\mathbb{R}^{\overline{n}}$ of dimension $\overline{n} - (\overline{c} - \overline{\ell} - \overline{\delta})$. Proposition 6.5.9 then implies the desired result. □

Proposition 6.5.14 Consider a system as in Theorem 6.4.9. Then the set of equilibria E is the disjoint union of finitely many C^∞ submanifolds of $\mathbb{R}^n$.

Proof Let $\mathcal{H} = \{H \in 2^{\overline{1,n}} \backslash \{\emptyset\} \mid H \text{ is a siphon}\}$, where $2^{\overline{1,n}}$ denotes the powerset of $\overline{1,n}$. By Proposition 6.5.4,

$$E = E_+ \cup \left(\bigcup_{H \in \mathcal{H}} (F_H \cap E_0) \right).$$

If $\mathcal{R} = \emptyset$ for some $\emptyset \neq H \subsetneq \overline{1,n}$ siphon then $F_H \cap E_0 = F_H$, which is clearly a C^∞ submanifold of $\mathbb{R}^n$. If $\overline{1,n}$ is a siphon then $E_0 \cap F_{\overline{1,n}} = \{0\}$, which is a C^∞ submanifold of $\mathbb{R}^n$ of dimension 0. These remarks, Proposition 6.4.10, and Proposition 6.5.13 then imply the desired result. □

We provide now a useful proposition. Let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Let $\overline{n} = |H^c|$. Let the function $Q : \mathbb{R}^n \to \mathbb{R}^n$ be the orthogonal projection to K, where K is defined by (6.10).

Proposition 6.5.15 Consider a weakly reversible mass action system, which satisfies $\delta = \sum_{r=1}^{\ell} \delta_r$. Assume that $x \in E$ and let $\emptyset \neq H \subsetneq \overline{1,n}$ be a siphon. Then $Qx \in E_0$.

Proof By Proposition 5.4.7, $f^r(x) = 0$ for all $r \in \overline{1,\ell}$. By Proposition 6.5.3, either $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$ for all $i \in \mathcal{C}_r$ or $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}_r$ $(r \in \overline{1,\ell})$.

Let $r \in \overline{1,\ell}$ such that $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}_r$. Then $f^r(Qx) = 0$, because all the rate functions corresponding to the rth linkage class have zero value at Qx.

Let $r \in \overline{1,\ell}$ such that $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$ for all $i \in \mathcal{C}_r$. Then $R_{(i,j)}(x) = R_{(i,j)}(Qx)$ for all $(i,j) \in \mathcal{R}_r$, because $B_{s,i} = 0$ for all $s \in H$ and for all $i \in \mathcal{C}_r$ and hence the power $x_s^{B_{s,i}}$ does not depend on $x_s \in \mathbb{R}_{\geq 0}$. Hence, $0 = f^r(x) = f^r(Qx)$.

Thus, we have obtained that $f^r(Qx) = 0$ for all $r \in \overline{1,\ell}$. Clearly, $Qx \in E_0$. □

We conclude this section by a compact characterization of the set of equilibria for systems in Theorem 6.4.9. The proposition presented here can be found in [3] for the special case of deficiency zero networks and with only one linkage class. The relaxation of the condition on the deficiency does not cause any difficulty. However, the multiple linkage class case is a bit more difficult than the case of one linkage class. It turns out that the result remains true for the multiple linkage class case. We remark however that we do not consider the more general rate functions of [3].

Let $i \in \overline{1,c}$. Let $\pi_i : \mathbb{R}^n_{\geq 0} \times \mathbb{R}^n_+ \to \mathbb{R}_{\geq 0}$ as in (6.8). Define the function $\Psi : \mathbb{R}^n_{\geq 0} \times \mathbb{R}^n_+ \to \mathbb{R}_{\geq 0}$ by

$$\Psi(x,y) = \sum_{(i,j)\in\mathcal{R}} (e^{\pi_j(x,y)} - e^{\pi_i(x,y)})^2.$$

Proposition 6.5.16 Consider a system as in Theorem 6.4.9. Let $x^* \in E_+$ and $x \in \mathbb{R}^n_{\geq 0}$. Then $x \in E$ if and only if $\Psi(x,x^*) = 0$.

Proof Clearly, $\Psi(x,x^*) = 0$ is equivalent to $\pi_i(x,x^*) = \pi_j(x,x^*)$ for all $(i,j) \in \mathcal{R}$. The latter is equivalent to $\pi_i(x,x^*) = \pi_j(x,x^*)$ for all $i,j \in \mathcal{C}_r$ and for all $r \in \overline{1,\ell}$.

Suppose that $\pi_i(x,x^*) = \pi_j(x,x^*)$ for all $i,j \in \mathcal{C}_r$ and for all $r \in \overline{1,\ell}$. The same calculation as at the end of the proof of Proposition 6.4.8 shows that $x \in E$.

To show the converse statement, let $x \in E$. If $x \in E_+$ then $q_i(x,x^*) = q_j(x,x^*)$ for all $(i,j) \in \mathcal{R}$, by Proposition 6.4.15 (recall (6.9)). This implies that $\pi_i(x,x^*) = \pi_j(x,x^*)$ for all $(i,j) \in \mathcal{R}$.

Assume now that $x \in E_0 \cap F_H$ for some $\emptyset \neq H \subseteq \overline{1,n}$. Due to Proposition 6.5.4, H is a siphon. If $H = \overline{1,n}$ then $x = 0$. Fix any $r \in \overline{1,\ell}$. In this case, due to Proposition 6.5.3 either $\operatorname{supp}(B_{\cdot,i}) = \emptyset$ for all $i \in \mathcal{C}_r$ or $\operatorname{supp}(B_{\cdot,i}) \neq \emptyset$ for all $i \in \mathcal{C}_r$. The first case is not possible, because the zero complex cannot constitute a linkage class itself. In the latter case, clearly $\pi_i(0,x^*) = 0$ for all $i \in \mathcal{C}_r$.

Assume for the rest of this proof that $\emptyset \neq H \subsetneq \overline{1,n}$. Construct a new system as described in Construction 6.5.6. If $\overline{\mathcal{R}} = \emptyset$ then $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}$ and hence $\pi_i(x,x^*) = 0$ for all $i \in \mathcal{C}$. Assume for the rest of this proof that $\overline{\mathcal{R}} \neq \emptyset$.

Due to Proposition 6.5.9 and Proposition 6.5.15, both PQx and PQx^* are interior equilibrium points of the new system. Hence, using the already proven part of this proposition for the new system,

$$\prod_{s\in H^c} \left(\frac{x_s}{x_s^*}\right)^{B_{s,i}} = \prod_{s\in H^c} \left(\frac{x_s}{x_s^*}\right)^{B_{s,j}} \tag{6.11}$$

for all $(i,j) \in \overline{\mathcal{R}}$. Note that the facts that $(PQx)_s = x_s$ and $(PQx^*)_s = x_s^*$ for all $s \in H^c$ and $B_{s,i} = \overline{B}_{s,i}$ for all $s \in H^c$ and for all $i \in \overline{\mathcal{C}}$ were used.

Fix any $r \in \overline{1,\ell}$. Due to Proposition 6.5.3, either $\operatorname{supp}(B_{\cdot,i}) \subseteq H^c$ for all $i \in \mathcal{C}_r$ or $\operatorname{supp}(B_{\cdot,i}) \nsubseteq H^c$ for all $i \in \mathcal{C}_r$.

If $\operatorname{supp}(B_{\cdot,i}) \nsubseteq \operatorname{supp}(x) = H^c$ for all $i \in \mathcal{C}_r$ then $\pi_i(x,x^*) = 0$ for all $i \in \mathcal{C}_r$.

Assume that $\operatorname{supp}(B_{\cdot,i}) \subseteq \operatorname{supp}(x) = H^c$ for all $i \in \mathcal{C}_r$. Then

$$\prod_{s \in H^c} \left(\frac{x_s}{x_s^*}\right)^{B_{s,i}} = \prod_{s=1}^{n} \left(\frac{x_s}{x_s^*}\right)^{B_{s,i}}$$

for all $i \in \mathcal{C}_r$. Equality (6.11) then implies the result. □

6.6 Stability

In this section we prove stability properties of weakly reversible deficiency zero mass action systems. Hence, throughout this section, we assume that such a system is given. The presented ideas basically follow the line of [10] with minor changes. We restrict our attention to mass action kinetics and do not consider here the more general rate function that can be found in [10]. However, we examine the multiple linkage class case, while only the case $\ell = 1$ is discussed in detail in [10]. We also investigate stability of boundary equilibrium points. See [11] for a correction to [10].

We start by recalling some well known notions from the theory of ordinary differential equations. Let D be a connected open subset of $\mathbb{R}^n$. Let $g : D \to \mathbb{R}^n$ be continuously differentiable and $\xi \in D$. Consider the autonomous differential equation (6.12) with initial value (6.13):

$$\dot{x} = g(x), \tag{6.12}$$

$$x(0) = \xi. \tag{6.13}$$

The initial value problem (6.12)-(6.13) has a unique solution on a maximal open interval denoted by $J(\xi)$. Denote this solution by $\phi(\cdot;\xi) : J(\xi) \to \mathbb{R}^n$. Let $J_+(\xi) = J(\xi) \cap \mathbb{R}_+$ and $J_{\geq 0}(\xi) = J(\xi) \cap \mathbb{R}_{\geq 0}$.

Definition 6.6.1 Let $p \in D$. If $g(p) = 0$ then p is said to be an *equilibrium point* of (6.12).

Denote the open ball in $\mathbb{R}^n$ of radius $\eta > 0$ with centre $p \in \mathbb{R}^n$ by $B_\eta(p)$.

Definition 6.6.2 An equilibrium point $p \in D$ is said to be *stable* if for all $\varepsilon > 0$ there exists $\eta > 0$ such that $q \in D \cap B_\eta(p)$ implies that $|\phi(t;q) - p| < \varepsilon$ for all $t \geq 0$.

Definition 6.6.3 An equilibrium point $p \in D$ is said to be *asymptotically stable* if it is stable and there exists $\eta > 0$ such that $\lim_{t\to\infty} |\phi(t;q) - p| = 0$ whenever $q \in D \cap B_\eta(p)$.

The open connected set D equals to $\mathbb{R}^n$ in the case of a reaction system and we are interested in equilibrium points in the nonnegative orthant. Theorem 6.4.12 states that each positive stoichiometric class contains exactly one interior equilibrium point. As it was discussed in Section 6.2, the stoichiometric classes are forward invariant sets for (6.1). The stoichiometric classes are lying in $(\operatorname{rank} S)$-dimensional affine subspaces. If $\operatorname{rank} S < n$ then

asymptotic stability of an interior equilibrium point is excluded by the forward invariance of stoichiometric classes. Hence, in the case of biochemical reaction systems, it is necessary to introduce stability notions relative to forward invariant sets.

Definition 6.6.4 Let $\mathcal{F} \subseteq \mathbb{R}^n_{\geq 0}$ be a forward invariant set for (6.1) and $p \in \mathcal{F}$ an equilibrium point. Then p is said to be *stable relative to* $\mathcal{F}$ if for all $\varepsilon > 0$ there exists $\eta > 0$ such that $q \in \mathcal{F} \cap B_\eta(p)$ implies that $|\phi(t;q) - p| < \varepsilon$ for all $t \geq 0$.

Definition 6.6.5 Let $\mathcal{F} \subseteq \mathbb{R}^n_{\geq 0}$ be a forward invariant set for (3.52) and $p \in \mathcal{F}$ an equilibrium point. Then p is said to be *asymptotically stable relative to* $\mathcal{F}$ if it is stable relative to $\mathcal{F}$ and there exists $\eta > 0$ such that $q \in \mathcal{F} \cap B_\eta(p)$ implies that $\lim_{t\to\infty} |\phi(t;q) - p| = 0$.

In addition, we define global asymptotic stability of an equilibrium point relative to a forward invariant set $\mathcal{F}$.

Definition 6.6.6 Let $\mathcal{F} \subseteq \mathbb{R}^n_{\geq 0}$ be a forward invariant set for (6.1) and $p \in \mathcal{F}$ an equilibrium point. Then p is said to be *globally asymptotically stable relative to* $\mathcal{F}$, if it is stable relative to $\mathcal{F}$ and $\lim_{t\to\infty} |\phi(t;q) - p| = 0$ whenever $q \in \mathcal{F}$.

We need several lemmas before stating the main results about the new notion of stability relative to a stoichiometric class.

Lemma 6.6.7 Define the function $\gamma : \mathbb{R} \to \mathbb{R}$ by $\gamma(h) = 1 + h - e^h + \frac{h^2}{h^2+4}$. Then $\gamma(h) \leq 0$ for all $h \in \mathbb{R}$.

Proof For $h \geq 0$ the statement is clear from the Taylor series of the exponential function.

Clearly, $1 + h + \frac{h^2}{h^2+4} \leq 0$ for all $h \leq -2$. Hence, the statement holds for $h \leq -2$.

It remains to show that $\gamma(h) \leq 0$ for all $-2 < h < 0$. It is well known that $1+h+\frac{h^2}{2}+\frac{h^3}{6} \leq e^h$ for all $h \in \mathbb{R}$. It suffices to show that $\frac{h^2}{h^2+4} \leq \frac{h^2}{2} + \frac{h^3}{6}$ for all $-2 < h < 0$. The latter can be checked easily. □

From now on we consider the differential equation (6.1), which corresponds to a weakly reversible mass action system, which has deficiency zero. Recall from the end of Section 6.4 the definition of the functions $q_i : \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}$ for $i \in \overline{1,c}$ and of the function $\Phi : \mathbb{R}^n_+ \times \mathbb{R}^n_+ \to \mathbb{R}_{\geq 0}$.

Lemma 6.6.8 Consider a weakly reversible mass action system with zero deficiency. Let $x^* \in E_+$. Then there exists a continuous function $a : \mathbb{R}^n_+ \to \mathbb{R}_+$ such that

$$\langle \log^n(x) - \log^n(x^*), f(x) \rangle \leq -\frac{a(x)\Phi(x,x^*)}{4 + \Phi(x,x^*)} \text{ for all } x \in \mathbb{R}^n_+.$$

Proof Define the function $a : \mathbb{R}^n_+ \to \mathbb{R}_+$ by

$$a(x) = \min \left\{ \kappa_{(i,j)} \prod_{s=1}^{n} x_s^{B_{s,i}} \;\middle|\; (i,j) \in \mathcal{R} \right\} \quad \text{for} \quad x \in \mathbb{R}^n_+.$$

Note that a is continuous.

Let $x \in \mathbb{R}^n_+$. By assumption, the underlying network has zero deficiency and x^* is assumed to be an equilibrium point. Hence, Proposition 6.4.2 implies that $I \cdot R(x^*) = 0$. Multiplying this equality from the left by the row vector $[e^{q_1(x,x^*)}, \ldots, e^{q_c(x,x^*)}]$ yields that

$$\sum_{(i,j)\in\mathcal{R}} \kappa_{(i,j)} \left(\prod_{s=1}^{n} x_s^{B_{s,i}} \right) (e^{q_j(x,x^*)-q_i(x,x^*)} - 1) = 0. \tag{6.14}$$

Using Lemma 6.6.7 with $h = q_j(x, x^*) - q_i(x, x^*)$ yields

$$\langle \log^n(x) - \log^n(x^*), f(x) \rangle = \sum_{(i,j)\in\mathcal{R}} \kappa_{(i,j)} \left(\prod_{s=1}^{n} x_s^{B_{s,i}} \right) (q_j(x, x^*) - q_i(x, x^*)) =$$

$$= \sum_{(i,j)\in\mathcal{R}} \kappa_{(i,j)} \left(\prod_{s=1}^{n} x_s^{B_{s,i}} \right) (q_j(x, x^*) - q_i(x, x^*) - e^{q_j(x,x^*)-q_i(x,x^*)} + 1) \leq$$

$$\leq - \sum_{(i,j)\in\mathcal{R}} \kappa_{(i,j)} \left(\prod_{s=1}^{n} x_s^{B_{s,i}} \right) \frac{(q_j(x, x^*) - q_i(x, x^*))^2}{4 + (q_j(x, x^*) - q_i(x, x^*))^2} \leq$$

$$\leq - \sum_{(i,j)\in\mathcal{R}} a(x) \frac{(q_j(x, x^*) - q_i(x, x^*))^2}{4 + \Phi(x, x^*)} =$$

$$= -\frac{a(x)\Phi(x, x^*)}{4 + \Phi(x, x^*)}.$$

□

Fix any $y \in \mathbb{R}_+$. Let us define the function $v_y : \mathbb{R}_{\geq 0} \to \mathbb{R}$ by

$$v_y(z) = \int_y^z \log(\tau) - \log(y) \mathrm{d}\tau \quad \text{for} \quad z \in \mathbb{R}_{\geq 0}.$$

Then v_y is continuous on $\mathbb{R}_{\geq 0}$ and continuously differentiable on $\mathbb{R}_+$. Moreover, $v_y'(z) = \log(z) - \log(y)$, which strictly increases and is onto $\mathbb{R}$ on $\mathbb{R}_+$, hence v_y is strictly convex, strictly decreases for $z \in [0, y]$, has a unique global minimum at y, and strictly increases to ∞ for $z \in [y, \infty)$. These properties imply that the set $\{z \in \mathbb{R}_{\geq 0} \mid v_y(z) \leq q\}$ is compact for all $q \in \mathbb{R}$. Note also that $v_y(z) \geq 0$ for all $z \in \mathbb{R}_{\geq 0}$ and $v_y(z) = 0$ if and only if $z = y$.

Let $x^* \in E_+$. Define the function $V_{x^*} : \mathbb{R}^n_{\geq 0} \to \mathbb{R}$ by

$$V_{x^*}(x) = \sum_{s=1}^{n} v_{x_s^*}(x_s) = \sum_{s=1}^{n} \int_{x_s^*}^{x_s} \log(\tau) - \log(x_s^*) \mathrm{d}\tau. \tag{6.15}$$

The following lemma summarizes important properties of V_{x^*}.

Lemma 6.6.9 Define V_{x^*} by (6.15). Then

(i) $V_{x^*}(x) > V_{x^*}(x^*) = 0$ for all $x \in \mathbb{R}^n_{\geq 0} \backslash \{x^*\}$,

(ii) V_{x^*} is continuously differentiable on $\mathbb{R}^n_+$,

(iii) $(\mathrm{grad} V_{x^*})(x) = (\log^n(x) - \log^n(x^*))^T$ for all $x \in \mathbb{R}^n_+$,

(iv) $\{x \in \mathbb{R}^n_{\geq 0} \mid V_{x^*}(x) \leq q\}$ is compact for all $q \in \mathbb{R}$.

Proof All these properties follow directly from the discussion made for the function $v_y : \mathbb{R}_{\geq 0} \to \mathbb{R}$. □

Proposition 6.6.10 Consider a weakly reversible mass action system with zero deficiency. Let $\xi \in \mathbb{R}^n_{\geq 0} \backslash E$ such that $\phi(t;\xi) \in \mathbb{R}^n_+$ for all $t \in J_+(\xi)$. Let $x^* \in E_+$. Then $V_{x^*}(\phi(\cdot;\xi)) : J(\xi) \to \mathbb{R}$ is strictly decreasing on $J_+(\xi)$.

Proof Since no solution can reach an equilibrium point in finite time, $\phi(t;\xi) \in \mathbb{R}^n_+ \backslash E_+$ for all $t \in J_+(\xi)$. Then

$$\frac{d}{dt}(V_{x^*}(\phi(t;\xi))) = \langle \log^n(\phi(t;\xi)) - \log^n(x^*), f(\phi(t;\xi))\rangle \leq -\frac{a(\phi(t;\xi))\Phi(\phi(t;\xi), x^*)}{4 + \Phi(\phi(t;\xi), x^*)}$$

for all $t \in J_+(\xi)$. In the latter expression, the values of a are positive. The denominator is positive as well. Moreover, $\Phi(\phi(t;\xi), x^*) > 0$ for all $t \in J_+(\xi)$, because of Proposition 6.4.15. This concludes the proof, because it means that $V_{x^*}(\phi(\cdot;\xi))$ has negative derivative on $J_+(\xi)$. □

The implication of the above proposition remains true if we omit the condition that in the future the solution is evolving in the interior of the nonnegative orthant.

Proposition 6.6.11 Consider a weakly reversible mass action system with zero deficiency. Let $\xi \in \mathbb{R}^n_{\geq 0} \backslash E$. Let $x^* \in E_+$. Then $V_{x^*}(\phi(\cdot;\xi)) : J(\xi) \to \mathbb{R}$ is strictly decreasing on $J_+(\xi)$.

Proof Due to Proposition 6.3.8 there exists $H \subseteq \overline{1,n} \backslash \mathrm{supp}(\xi)$ such that F_H is forward invariant and $\phi(t;\xi) \in F_H$ for all $t \in J_+(\xi)$. If $H = \emptyset$ then Proposition 6.6.10 can be applied directly.

If $H = \overline{1,n}$ then $\xi = 0$ and $\xi \in E$, which was excluded.

Suppose for the rest of this proof that $\emptyset \neq H \subsetneq \overline{1,n}$. Then H is a siphon. Denote by H^c the set $\overline{1,n} \backslash H$. Let $x \in F_H$. Then

$$V_{x^*}(x) = \sum_{s \in H^c} \int_{x^*_s}^{x_s} \log(\tau) - \log(x^*_s) \mathrm{d}\tau + \sum_{s \in H} \int_{x^*_s}^{0} \log(\tau) - \log(x^*_s) \mathrm{d}\tau.$$

The second addend in the above formula is not depending on $x \in F_H$. Hence, it suffices to show that

$$t \mapsto \sum_{s \in H^c} \int_{x^*_s}^{\phi_s(t;\xi)} \log(\tau) - \log(x^*_s) \mathrm{d}\tau$$

is strictly decreasing on $J_+(\xi)$.

Let us construct a new system as described in Construction 6.5.6. Recall the definition of K, P, and Q from Section 6.5. If $\overline{\mathcal{R}} = \emptyset$ then $\xi \in E$, which is not possible. If $\overline{\mathcal{R}} \neq \emptyset$ then $PQx^* \in \overline{E}_+$ by Proposition 6.5.15 and Proposition 6.5.9. Observe that for the function $\overline{V}_{PQx^*} : \mathbb{R}^{\overline{n}}_{\geq 0} \to \mathbb{R}$, which is associated to the new system,

$$\overline{V}_{PQx^*}(\overline{\phi}(t; PQ\xi)) = \sum_{s \in H^c} \int_{(PQx^*)_s}^{\overline{\phi}_s(t;PQ\xi)} \log(\tau) - \log((PQx^*)_s) \mathrm{d}\tau =$$

$$= \sum_{s \in H^c} \int_{x_s^*}^{\phi_s(t;\xi)} \log(\tau) - \log(x_s^*) \mathrm{d}\tau$$

For all $t \in J_+(PQ\xi) = J_+(\xi)$. Since $\overline{\phi}_s(t;\overline{\xi}) \in \mathbb{R}_+^{\overline{n}} \backslash \overline{E}_+$ for all $t \in J_+(PQ\xi) = J_+(\xi)$, application of Proposition 6.6.10 to the new system implies the desired result. □

We recall one more notion from the theory of ordinary differential equations. Consider the initial value problem (6.12)-(6.13).

Definition 6.6.12 If $J(\xi) \supseteq \mathbb{R}_{\geq 0}$ and there exists a sequence $(t_N)_{N=1}^{\infty} \subseteq J(\xi)$ with

$$\lim_{N \to \infty} t_N = \infty \quad \text{and} \quad \lim_{N \to \infty} \phi(t_N; \xi) = q$$

for some $q \in \mathbb{R}^n$ then q is said to be an *ω-limit point* of ξ. The set of ω-limit points of ξ is called the *ω-limit set* of ξ and is denoted by $\omega(\xi)$.

Recall the definition of dist from Chapter 2. The following theorem is well known. The proof of it can be found for example in [13].

Theorem 6.6.13 Let $\phi(\cdot;\xi) : J(\xi) \to \mathbb{R}^n$ be the solution of the initial value problem (6.12)-(6.13) for some $\xi \in D$. Assume that $\phi(t;\xi) \in K$ for all $t \in J_+(\xi)$, where $K \subseteq \mathbb{R}^n$ is a compact set. Then $J(\xi) \supseteq \mathbb{R}_{\geq 0}$, the ω-limit set $\omega(\xi)$ is nonempty, compact, connected, and forward invariant. Moreover,

$$\lim_{t \to \infty} \mathrm{dist}(\phi(t;\xi), \omega(\xi)) = 0.$$

Theorem 6.6.14 Consider a weakly reversible mass action system with zero deficiency. Let $\xi \in \mathbb{R}_{\geq 0}^n$. Then $J(\xi) \supseteq \mathbb{R}_{\geq 0}$.

Proof If $\xi \in E$ then $J(\xi) \supseteq \mathbb{R}_{\geq 0}$ obviously holds.

If $\xi \in \mathbb{R}_{\geq 0}^n \backslash E$ then $V_{x^*}(\phi(\cdot;\xi))$ is strictly decreasing on $J_+(\xi)$ by Proposition 6.6.11. This fact together with Lemma 6.6.9 implies that there exists a compact set $K \subseteq \mathbb{R}^n$ such that $\phi(t;\xi) \in K$ for all $t \in J_+(\xi)$. Theorem 6.6.13 implies that $J(\xi) \supseteq \mathbb{R}_{\geq 0}$. □

We remark at this point that if the stoichiometric classes of a reaction system are compact then, by Theorem 6.6.13, any solution is defined for all $t \geq 0$. This holds for all reaction systems.

The following theorem is the basis of the stability results.

Theorem 6.6.15 Consider a weakly reversible mass action system with zero deficiency. Let $\mathcal{P} = (p + \mathcal{S}) \cap \mathbb{R}_{\geq 0}^n$ be a positive stoichiometric class for some $p \in \mathbb{R}_+^n$. Let $\xi \in \mathcal{P}$. Let x^* be the unique interior equilibrium point in $\mathcal{P}$. Then either $\omega(\xi) = \{x^*\}$ or $\omega(\xi) \subseteq E_0 \cap \mathcal{P}$.

Proof If $\xi \in E$ then the statement clearly holds.

Let $\xi \in \mathcal{P} \backslash E$. Let $V_{x^*} : \mathbb{R}_{\geq 0}^n \to \mathbb{R}$ as before. By Theorem 6.6.14, $J(\xi) \supseteq \mathbb{R}_{\geq 0}$. Hence, the ω-limit set $\omega(\xi)$ is defined. Due to the argument made in the proof of Theorem 6.6.14, there exists a compact set $K \subseteq \mathbb{R}^n$ such that $\phi(t;\xi) \in K$ for all $t \geq 0$. Due to Theorem 6.6.13, $\omega(\xi)$ is nonempty and forward invariant. As $\mathcal{P}$ is closed and forward invariant, it is clear that $\omega(\xi) \subseteq \mathcal{P}$.

Pick any $\zeta \in \omega(\xi)$. We show that $\zeta \in \{x^*\} \cup (E_0 \cap \mathcal{P})$. Connectedness of $\omega(\xi)$ then implies the result.

Suppose by contradiction that $\zeta \notin \{x^*\} \cup (E_0 \cap \mathcal{P})$. Consider the function $\phi(\cdot, \zeta) : J(\zeta) \to \mathbb{R}^n$. As $\zeta \in \mathbb{R}^n_{\geq 0} \backslash E$, by Proposition 6.6.11, $V_{x^*}(\phi(\cdot, \zeta)) : J(\zeta) \to \mathbb{R}$ is strictly decreasing on $J_+(\zeta)$. This is a contradiction, because the forward invariant set $\omega(\zeta)$ is a subset of $\{x \in \mathbb{R}^n_{\geq 0} \mid V_{x^*}(x) = v\}$ for some $v \in \mathbb{R}$, because of the fact that the value of V_{x^*} cannot increase along trajectories. □

The following theorem is a direct consequence of Theorem 6.6.13 and Theorem 6.6.15.

Theorem 6.6.16 Consider a weakly reversible mass action system with zero deficiency. Let $\mathcal{P} = (p + \mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ be a positive stoichiometric class for some $p \in \mathbb{R}^n_+$. Let $\xi \in \mathcal{P}$. Let x^* be the unique interior equilibrium point in $\mathcal{P}$. Then

$$\lim_{t \to \infty} \operatorname{dist}(\phi(t; \xi), E \cap \mathcal{P}) = 0.$$

Theorem 6.6.17 Consider a weakly reversible mass action system with zero deficiency. Let $\mathcal{P} = (p + \mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ be a positive stoichiometric class for some $p \in \mathbb{R}^n_+$. Let x^* be the unique interior equilibrium point in $\mathcal{P}$. Then x^* is stable. Moreover, x^* is asymptotically stable relative to $\mathcal{P}$.

Proof Let $\varepsilon > 0$. It can be assumed that $\varepsilon < \min\{x^*_s \mid s \in \overline{1, n}\}$. Let $V_{x^*} : \mathbb{R}^n_{\geq 0} \to \mathbb{R}$ as before. Let $\alpha = \min\{V_{x^*}(x) \mid \varepsilon = |x - x^*|\}$. Clearly, $\alpha > V_{x^*}(x^*)$. Let $\eta > 0$ such that $|x - x^*| < \eta$ implies that $V_{x^*}(x) < \alpha$. This η satisfies the requirement in the definition of a stable equilibrium point.

Clearly, stability of x^* relative to $\mathcal{P}$ follows from its stability.

It remains to show that x^* is asymptotically stable relative to $\mathcal{P}$. Let $0 < \eta' < \min\{x^*_s \mid s \in \overline{1, n}\}$. Let $\alpha = \min\{V_{x^*}(x) \mid \eta' = |x - x^*|\}$. Let $\eta > 0$ such that $|x - x^*| < \eta$ implies that $V_{x^*}(x) < \alpha$. We show that the ω-limit set $\omega(\xi)$ is $\{x^*\}$ for all $\xi \in B_\eta(x^*) \cap \mathcal{P}$. This will imply that x^* is asymptotically stable relative to $\mathcal{P}$.

Let $y \in \mathbb{R}^n_{\geq 0}$. Assume that $y_{s'} = 0$ for some $s' \in \overline{1, n}$. Then

$$V_{x^*}(y) = \sum_{s=1}^{n} \int_{x^*_s}^{y_s} \log(\tau) - \log(x^*_s) \mathrm{d}\tau \geq$$

$$\geq \int_{x^*_{s'}}^{0} \log(\tau) - \log(x^*_{s'}) \mathrm{d}\tau > \int_{x^*_{s'}}^{x^*_{s'} - \eta'} \log(\tau) - \log(x^*_{s'}) \mathrm{d}\tau \geq \alpha > V_{x^*}(\xi)$$

for all $\xi \in B_\eta(x^*)$. As V_{x^*} cannot increase along the solution starting from ξ, $\omega(\xi)$ is a subset of $\{x \in \mathbb{R}^n_{\geq 0} \mid V_{x^*}(x) = v\}$ for some $v \leq V_{x^*}(\xi)$. Hence, $\omega(\xi) \cap \mathbb{R}^n_0 = \emptyset$. By Theorem 6.6.15, $\omega(\xi) = \{x^*\}$. Theorem 6.6.13 then implies the result. □

Theorem 6.6.18 Consider a weakly reversible mass action system with zero deficiency. Let $\mathcal{P} = (p + \mathcal{S}) \cap \mathbb{R}^n_{\geq 0}$ be a positive stoichiometric class for some $p \in \mathbb{R}^n_+$. Let x^* be the unique interior equilibrium point in $\mathcal{P}$. Then x^* is globally asymptotically stable relative to $\mathcal{P}$ if and only if $\mathcal{P} \cap E_0 = \emptyset$.

Proof Theorem 6.6.17 implies that x^* is stable relative to $\mathcal{P}$. By Theorem 6.6.15, if $\mathcal{P} \cap E_0 = \emptyset$ then $\omega(\xi) = \{x^*\}$ for all $\xi \in \mathcal{P}$. This implies global asymptotic stability relative to $\mathcal{P}$.

If $\xi \in \mathcal{P} \cap E_0 \neq \emptyset$ then $\phi(t;\xi) = \xi$ for all $t \geq 0$. Hence, x^* is not globally asymptotically stable relative to $\mathcal{P}$. □

Let $\xi \in \mathcal{P}$ for some positive stoichiometric class $\mathcal{P}$ in Example 6.4.13. Theorem 6.6.16 can be applied for this example to show that the solution starting from ξ approaches $\mathcal{P} \cap E$. It can also be seen in that example if $\xi \notin E_0$ then the solution starting from ξ converges to the unique interior equilibrium point in the stoichiometric class of ξ.

Let $\xi \in \mathbb{R}^2_{\geq 0} \backslash \{[0,0]^T\}$ in Example 6.4.14. Theorem 6.6.18 implies that $\lim_{t\to\infty} \phi(t;\xi)$ exists and is the unique interior equilibrium point in the stoichiometric class of ξ.

We conclude this section by providing a theorem about asymptotic stability of boundary equilibrium points.

Theorem 6.6.19 Consider a weakly reversible mass action system with zero deficiency. Let $x^* \in E_0 \backslash \{0\}$. Let $H = \overline{1,n} \backslash \mathrm{supp}(x)$. (Then $\emptyset \neq H \subsetneq \overline{1,n}$ and H is a siphon by Proposition 6.5.4.) Suppose that $\overline{\mathcal{R}} \neq \emptyset$ in Construction 6.5.6. Then x^* is asymptotically stable relative to $(x^* + P^{-1}\overline{\mathcal{S}}) \cap \mathrm{cl}(F_H)$.

Proof Application of Theorem 6.6.17 for the new system in Construction 6.5.6 yields the result. □

6.7 Periodic solutions

In the case of biochemical reaction systems we are always interested in trajectories starting in the nonnegative orthant. Hence, we define nontrivial periodic orbits for nonnegative initial values.

Definition 6.7.1 Let $\xi \in \mathbb{R}^n_{\geq 0}$. A solution of the differential equation (6.1) starting from ξ is called a *nontrivial periodic solution* if $J(\xi) = \mathbb{R}$, there exists $T > 0$ such that $\phi(t;\xi) = \phi(t+T;\xi)$ for all $t \in \mathbb{R}$, and $\phi(\cdot;\xi) : \mathbb{R} \to \mathbb{R}^n$ is not constant.

The following two theorems show that for certain reaction systems the existence of nontrivial periodic solutions is excluded.

Theorem 6.7.2 Consider a deficiency zero reaction network, which is not weakly reversible. Then there is no periodic solution, which lies entirely in $\mathbb{R}^n_+$.

Proof The proof is similar to the proof of Theorem 6.4.4. Suppose by contradiction that $\xi \in \mathbb{R}^n_+$ is such that $J(\xi) = \mathbb{R}$ and $\phi(\cdot;\xi) : \mathbb{R} \to \mathbb{R}^n$ is a nontrivial periodic solution. Let $T > 0$ such that $\phi(0;\xi) = \phi(T;\xi)$. Then, by the forward invariance of the positive orthant, $\phi(t;\xi) \in \mathbb{R}^n_+$ for all $t \in [0,T]$. Hence, $\mathrm{supp}(\phi(t;\xi)) = \overline{1,n}$ for all $t \in [0,T]$. By condition (3.3), this means that $R_{(i,j)}(\phi(t;\xi)) > 0$ for all $(i,j) \in \mathcal{R}$ and for all $t \in [0,T]$. Hence, $\int_0^T R_{(i,j)}(\phi(\tau;\xi))\mathrm{d}\tau > 0$ for all $(i,j) \in \mathcal{R}$. Since $\phi(T;\xi) = \phi(0;\xi)$, formula (6.2) implies that

$$0 = B \cdot I \cdot \int_0^T R(\phi(\tau;\xi))d\tau,$$

where B is the matrix of complexes, I is the incidence matrix of the graph of complexes $(\mathcal{C}, \mathcal{R})$, and the integral is taken coordinate-wise. Since the deficiency is zero, the above equation implies that $0 = I \cdot \int_0^T R(\phi(\tau; \xi))d\tau$. This means that there exists a positive circulation on the graph of complexes $(\mathcal{C}, \mathcal{R})$. However, due to Theorem 4.3.3, this implies that the reaction network is weakly reversible. Contradiction. □

We remark that Proposition 6.3.8 implies that a nontrivial periodic solution starting from $\xi \in \mathbb{R}^n_{\geq 0}$ can occur only if F_H is forward invariant, where $H = \overline{1, n} \backslash \text{supp}(\xi)$.

Theorem 6.7.3 Consider a weakly reversible mass action system with zero deficiency. Then there is no nontrivial periodic orbit.

Proof The result follows directly from Proposition 6.6.11. □

Chapter 7

Concluding remarks

This thesis explored and developed fundamentals of the theory of biochemical reaction systems. We followed a graph theoretic approach. In Chapter 5 we provided details about the deficiency, including three equivalent definitions for the deficiency. We also discussed the notion of deficiency of linkage classes. We examined the notion of a siphon in more details in Chapter 6. This is helpful in understanding the behaviour of a reaction system. It turned out that the investigation of a siphon provides advantages in the analysis of the boundary equilibria and also in the stability investigations. The author of this thesis plans to provide a new proof for Theorem 6.4.7 using similar ideas as in Theorem 6.4.5.

Theorem 6.4.7 establishes the structure of the set of interior equilibria for weakly reversible mass action systems for which $\delta_r \leq 1$ for all $r \in \overline{1,\ell}$ and $\delta = \delta_1 + \cdots + \delta_\ell$. Further directions of research may include the analysis of reaction systems which are not satisfying these assumptions. The structure of the set of equilibria is of importance. Stability properties of equilibrium points could also be interesting. As periodic phenomena are pervasive in nature, the examination of nontrivial periodic orbits of reaction systems seems to be a key direction.

The examination of the reaction control system

$$\begin{aligned} \dot{x}(t) &= f(t, x(t), u(t)) = \sum_{(i,j)\in\mathcal{R}} R_{(i,j)}(x(t)) u_{(i,j)}(t)(B_{\cdot,j} - B_{\cdot,i}) \\ y(t) &= h(t, x(t), u(t)) \end{aligned}$$

is gaining interest. Here, $u_{(i,j)}(t)$ represents enzyme concentration at time t corresponding to reaction (C_i, C_j). Questions that naturally arise are concerning reachability, controllability, observability, reconstructability, and stabilizability. Answering questions about realization, identification, optimal control, and system reduction of reaction control systems could also be of interest. The answers for the mentioned questions could have importance in biotechnology.

Bibliography

[1] D. Angeli. Lecture at a workshop. Personal Communication in Groningen, November 2007.

[2] D. Angeli, P. de Leenheer, and E.D. Sontag. A petri net approach to the study of persistence in chemical reaction networks. *Mathematical Biosciences*, 210:598–618, 2007.

[3] M. Chaves. *Observer design for a class of nonlinear systems, with applications to biochemical networks.* PhD thesis, Rutgers University, New Brunswick, NJ, 2003.

[4] G. Craciun, A. Dickenstein, A. Shiu, and B. Sturmfels. Toric dynamical systems. Technical Report 0708.3431v2[math.DS], 2007.

[5] M. Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors - I. The deficiency zero and the deficiency one theorems. *Chemical Engineering Science*, 42:2229–2268, 1987.

[6] M. Feinberg. The existence and uniqueness of steady states for a class of chemical reaction networks. *Arch. Rational Mech. Anal.*, 132:311–370, 1995.

[7] F.J.M. Horn and R. Jackson. General mass action kinetics. *Arch. Rational Mech. Anal.*, 47:81–116, 1972.

[8] H.K. Khalil. *Nonlinear systems (3rd Ed.).* Prentice Hall, Upper Saddle River, NJ, 2002.

[9] A. Schrijver. *Combinatorial opitmization - Polyhedra and efficiency.* Number 24 in Algorithms and combinatorics. Springer, Berlin, 2003.

[10] E.D. Sontag. Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction. *IEEE Trans. Automatic Control*, 46(7):1028–1047, 2001.

[11] E.D. Sontag. Correction to: " Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction". *IEEE Trans. Automatic Control*, 47(4):705, 2002.

[12] J.H. van Schuppen. Biochemical reaction systems. Personal communication in Amsterdam, February 2008.

[13] W. Walter. *Ordinary differential equations.* Number 182 in Graduate Texts in Mathematics. Springer, Berlin, 1998.