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The Global Attractor Conjecture in the Chemical Reaction Network Theory

Diploma thesis
of

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abstract. The work of Horn, Jackson and Feinberg laid the foundations of the chemical reaction network theory. The topic of this theory is the relation between the simple structure and the qualitative dynamical features of a chemical reaction network without knowing the specific reaction rates inherent. The focus in the dynamical features lies on the existence, uniqueness and stability of steady states. This thesis surveys the progress made in chemical reaction theory up to its current state and especially the remaining open problems in this field, the global attractor conjecture and the persistence conjecture. The global attractor conjecture, which is the most important open problem in this theory makes the connection between complexed balanced reaction networks and globally asymptotically stable steady states. The attempt of its proof by August and Barahona [6] will be rebutted. However we will present network structure cases, which are the single linkage class networks and the two or three species reaction networks (Anderson [3], Craciun et al. [9]), for which the conjecture holds. Besides we are treating the persistence conjecture and its link to the global attractor conjecture. Furthermore we are presenting necessary conditions for persistency using Petri-net theory, Angeli et al. [4].

1 Introduction

1.1 Motivation

In the 1970s, *Roy Jackson*, *Fritz Horn*, and *Martin Feinberg* laid the foundations for the *chemical reaction network theory*, [17, 10, 13, 14, 11]. The aim of this theory is to relate qualitative dynamical features to the topological structure of the chemical reaction network without the knowledge of any kinetic parameters. The approach is to link chemical reaction network characteristics, like weak reversibility or deficiency, to dynamical properties such as existence of positive steady states, stability properties of these steady states and the non-extinction of species. Background of this theory is the difficulty of analyzing these qualitative dynamical features through the system of differential equations of rather complex chemical reaction networks. This difficulty presents itself in the non-linearity of these differential equations when considering chemical reaction networks with mass-action kinetics, which means that we assume the rate of a reaction to be proportional to the product of the reactant concentrations. As the corresponding system of differential equations to complex reaction networks cannot generally be solved analytically, the dynamical properties, such as existence of unique steady states, stability properties of these steady states and the non-extinction of species, should be tied to the topological structure of the reaction network.

There are many fields of application in biological and medical sciences for chemical reaction network theory since the dynamical systems theory plays an important role in the understanding of biological and physiological processes. Its most well-suited application would be systems biology, where parameter uncertainty is predominant. Systems biology aims at the understanding of cell behavior and function at the level of chemical interactions, and, in particular the characterization of qualitative features of dynamical behavior. However, there exists a very large degree of uncertainty in the models of cellular biochemical networks. As such, chemical reaction network theory could become useful as a tool of verification of the developed models.

A well-known and still unsolved problem in chemical reaction network theory is the *Global Attractor Conjecture* which states that in every complex balanced chemical reaction network every concentration trajectory with positive initial conditions has a unique positive steady state and this steady state is globally attractive respective to its stoichiometric compatibility class. The resolution of the conjecture has important biological and mathematical implications since it would grant a desired level of stability and persistence to a large class of chemical reaction networks. The actual sticking point of the global attractor conjecture is the persistence, in other words the non-extinction of the species inherent in complex balanced chemical reaction networks. As complex balanced reaction networks are also weakly reversible the conjecture would be solved by a proof of the *persistence conjecture*, which states that weakly reversible reaction networks are persistent.

Although the conjectures have not been proven in general, there are special cases of reaction networks which have been proven to obtain global attractors. These cases are the single linkage class networks and the two or three species reaction networks, [3, 1, 9].

The outline of this thesis is as follows: In this section we will continue by setting up the basic vocabulary and notations commonly used in chemical reaction network theory and proceed with an insight into the early results by *M. Feinberg*, *F. Horn* and *R. Jackson*, which are the Deficiency Zero and Deficiency One Theorem. In the second section we will prove that complex balanced steady states are locally asymptotically stable with the help

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of Lyapunov stability theory. In the third section we will delve into the global attractor conjecture and deal with an attempt to prove the persistence conjecture. In the fourth and last section we will mention some special cases for which the global attractor conjecture has been proven. These special cases consist of the case of single linkage class reaction networks and the case of reaction networks containing only two or three different species. Furthermore we will elaborate under which necessary conditions the persistence conjecture will hold by using the Petri net theory.

1.2 Vocabulary and notations

We will use this first section to set the basic vocabulary and notations commonly used in reaction network theory. We will for this rely on the definitions and notations of the lecture notes by M. Feinberg [11].

Let \mathcal{S} denote the set of species in a network. Under the assumption that the number of species is finite, we shall use the symbol N to denote the number of species in a network ($\#\{\mathcal{S}\} = N$). We will write S_j for the j th species, thus, we have $\{S_1, \dots, S_N\} = \mathcal{S}$.

Reactants and products of the different reactions occurring in a network will be called *complexes*. The set of complexes in a network will be denoted by the symbol \mathcal{C} and the number of complexes in the considered network will be denoted by n ($\#\{\mathcal{C}\} = n$).

$V = \mathbb{R}^N$ will be called the *species space*, where we can represent the N species as a standard basis in V by associating S_i with v_i , the i th unit vector. \bar{V}^+ denotes the non-negative orthant of the species space, so that every $x \in \bar{V}^+$ only has non-negative coordinates, $x_i \geq 0$ for all $i \in \{1, \dots, N\}$. V^+ will denote the positive orthant of the species space.

In \bar{V}^+ we can represent the complex y_j , $j \in \{1, \dots, n\}$, as *complex vector* where the entries y_{j1}, \dots, y_{jN} are the stoichiometric coefficients of the respective species S_1, \dots, S_N in the complex: $y_j = (y_{j1}, \dots, y_{jN})^T \in \mathbb{N}^N \subset \bar{V}^+$ for $j \in \{1, \dots, n\}$. Alternatively we can associate the j th complex in the *complex space* $W = \mathbb{R}^n$ with the j th unit vector, $w_j \in W$. If we combine the complex vectors in V in a $(N \times n)$ -matrix Y :

$$Y = \{y_1, \dots, y_n\} : W \longrightarrow V \quad (1)$$

$$w_j \longmapsto y_j,$$

then Y defines a linear transformation of the complex space W into the species space V .

A *reaction diagram* is a graph, in which the vertices are the complexes $y_i \in \mathcal{C}$ and the directed edges represent the reactions between complexes.

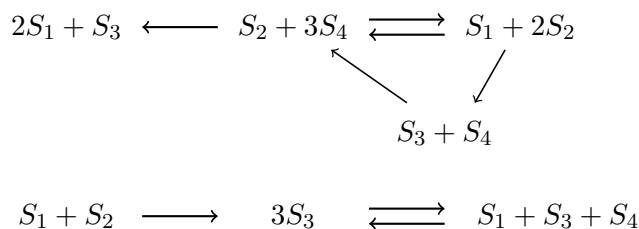


Figure 1: Reaction diagram of a network with $\mathcal{S} = \{S_1, \dots, S_4\}$ and $\mathcal{C} = \{2S_1 + S_3, S_2 + 3S_4, S_1 + 2S_2, S_3 + S_4, S_1 + S_2, 3S_3, S_1 + S_3 + S_4\}$.

For example we have in figure 1 the complex vectors: $y_1 = \{2, 0, 1, 0\}$, $y_2 = \{0, 1, 0, 3\}$, $y_3 = \{1, 2, 0, 0\}$, $y_4 = \{0, 0, 1, 1\}$, $y_5 = \{1, 1, 0, 0\}$, $y_6 = \{0, 0, 3, 0\}$, $y_7 = \{1, 0, 1, 1\}$. So the

matrix Y is:

$$Y = \begin{pmatrix} 2 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 1 & 2 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 3 & 1 \\ 0 & 3 & 0 & 1 & 0 & 0 & 1 \end{pmatrix}$$

It should be clear of the context, if we regard the complexes to be vertices in a graph, vectors in the species space respectively complex space or as simple elements of the set of complexes.

\mathcal{R} will be the set of reactions in a system. If there exists a reaction from complex y_j to complex y_l we say $y_j \rightarrow y_l \in \mathcal{R}$. For a reaction $y_j \rightarrow y_l \in \mathcal{R}$ we will define the corresponding *reaction vector* as $y_l - y_j = (y_{l1} - y_{j1}, \dots, y_{lN} - y_{jN})^T \in V$. If $y_j = \vec{0}$ or $y_l = \vec{0}$ then the reaction represents an input or an output to the system respectively.

The *rank* $s \in \mathbb{N}$ of a chemical reaction network is the number of linearly independent reaction vectors in a network. If we consider a reaction network with N species and r reaction vectors, s can easily be determined by listing the reaction vectors in an $r \times N$ - matrix and counting the non-zero rows left after reducing the matrix to an echelon form. For example, the rank s for the reaction diagram depicted in figure 1 is 4.

We require of a chemical reaction network to satisfy certain properties which are consistent with the chemical approach of a reaction network. A *chemical reaction network* is a triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, where $\mathcal{S} = \{S_i\}_{i=1}^N$ is the set of species, $\mathcal{C} = \{y_j\}_{j=1}^n$ the set of complexes and $\mathcal{R} = \{y_j \rightarrow y_l\}_{j,l}$ is the set of reactions and the network admits the following properties:

- (1) For any $S_i \in \mathcal{S}$, there exists at least one complex $y_j \in \mathcal{C}$ for which $y_{ji} > 0$,
- (2) there is no trivial reaction $y_j \rightarrow y_j \in \mathcal{R}$ for any complex $y_j \in \mathcal{C}$,
- (3) for any $y_j \in \mathcal{C}$ there exists at least one complex $y_l \in \mathcal{C}$ for which $y_j \rightarrow y_l \in \mathcal{R}$ or $y_l \rightarrow y_j \in \mathcal{R}$.

Using the notation of [14], we say that two complexes $y_i, y_j \in \mathcal{C}$ are *directly linked* if either $y_i \rightarrow y_j \in \mathcal{R}$ or $y_j \rightarrow y_i \in \mathcal{R}$, and we write $y_i \leftrightarrow y_j$. Two complexes are *linked* if they satisfy any of the following conditions:

- $y_i = y_j$
- $y_i \leftrightarrow y_j$
- $\exists y_1, \dots, y_m \in \mathcal{C}$ such that $y_i \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow \dots \leftrightarrow y_m \leftrightarrow y_j$

If two complexes y_i, y_j are linked, we write $y_i \sim y_j$. This relation between complexes is an equivalence relation, since it is reflexive, symmetric and transitive. It therefore induces a partition on the set of complexes and the induced equivalence classes will be called *linkage classes*. It should be clear, that the linkage classes are sets of complexes, which are linked to each other, but do not describe which complexes are reactants or products to other complexes. Let ℓ denote the number of linkage classes and $\mathcal{L}_i, i = 1, \dots, \ell$ the linkage classes of a network.

If two networks present the same complexes and the same linkage classes, then the rank of the two networks is also the same. If we consider the complexes as vectors in V and the linkage classes as subspaces of V , which are the span of the complexes they contain, then

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the statement is proven by simple matrix theory in linear algebra.

A complex y_i is said to *ultimately react* to another complex y_j if they satisfy one of the following conditions:

- $y_i \rightarrow y_j$
- $\exists y_1, \dots, y_m \in \mathcal{C}$ such that $y_i \rightarrow y_1 \rightarrow y_2 \rightarrow \dots \rightarrow y_m \rightarrow y_j$.

We then write $y_i \Rightarrow y_j$. This definition slightly differs from the definition given in [14]. *M. Feinberg* and *F. Horn* include the condition $y_i = y_j$ in the definition of 'ultimately reacts to', which is rather confusing since by definition of a chemical reaction network, no complex reacts to itself.

We say that two complexes y_i and y_j are *strongly linked* if $y_i = y_j$ or $y_i \Rightarrow y_j$ and $y_j \Rightarrow y_i$, we denote this equivalence relation by $y_i \approx y_j$. A *strong linkage class* $\mathcal{L}^S \subset \mathcal{C}$ is a set of complexes where each pair of complexes is strongly linked.

A *terminal strong linkage class* is defined as a strong linkage class where no complex of the set reacts to a complex belonging to a different strong linkage class. That is, we say $\mathcal{L}^T \subset \mathcal{C}$ is a terminal strong linkage class if for every complex $y_i \in \mathcal{L}^T$ for which $y_i \rightarrow y_j \in \mathcal{R}$ it follows that $y_j \in \mathcal{L}^T$. We denote the number of terminal strong linkage classes by the symbol t . As there exists in each linkage class at least one terminal strong linkage class, we have $t \geq \ell$. (This is ensured by the convention that every complex is strongly linked to itself.)

If for every reaction $y_j \rightarrow y_l \in \mathcal{R}$ the reverse reaction $y_l \rightarrow y_j$ is also part of the network, then we say the network is *reversible*. We call a network *weakly reversible* if for every complex y_i that ultimately reacts to another complex y_j , $y_i \Rightarrow y_j$, it follows that $y_j \Rightarrow y_i$. In other words, in a weakly reversible reaction network every two complexes that are linked to each other are strongly linked to each other. Any theorem for weakly reversible networks also applies to reversible networks as a special case.

For weakly reversible networks every linkage class is a terminal strong linkage class, since in a linkage class every complex is strongly linked to every other complex in the same linkage class, therefore $t = \ell$.

Remark Note that weak reversibility implies $t = \ell$, but not every network for which the condition $t = \ell$ holds, is weakly reversible.

A chemical reaction network with n complexes and ℓ linkage classes need to contain only $n - \ell$ reactions. Since the rank s of a network is defined as the number of linearly independent reaction vectors, see p. 3, the rank of a network with n complexes and ℓ linkage classes cannot exceed $n - \ell$. Thus, we can say that $n - \ell - s \geq 0$ for any reaction network. We call this non-negative integer the *deficiency* of a chemical reaction network

$$\delta = n - \ell - s \in \mathbb{N}. \quad (2)$$

Since two reaction networks with the same complexes and the same linkage classes also have the same rank, the deficiency for two reaction networks with the same complexes and linkage classes will be the same.

Let s_θ denote the rank and δ_θ denote the deficiency of the θ t linkage class. As before, if we consider the complexes to be vectors in the space V and the linkage classes to be subspaces, we know from linear algebra that the sum of the ranks of the subspaces may not

1.3 Kinetics and the corresponding differential equations of a chemical reaction network

coincide with the rank of the space they span, $s \leq \sum_{\theta \leq \ell} s_\theta$. So it follows from equation (2) that the sum of the deficiencies of the different linkage classes may not coincide with the deficiency of the reaction network, $\delta \geq \sum_{\theta \leq \ell} \delta_\theta$.

1.3 Kinetics and the corresponding differential equations of a chemical reaction network

For $\{S_i\}_{i=1}^N$ species in a chemical reaction network, we denote by $c_1(t), \dots, c_N(t)$ the respective *molar concentrations at time t*. For a chemical reaction network with N species we denote by $c(t) = (c_1(t), \dots, c_N(t))$ the *concentration vector at time t*, or simply the *concentration at time t* of the considered chemical reaction network. By the *support of the concentration vector c* at the time t , we shall mean the set of species with nonzero molar concentration at time t ,

$$\text{supp}(c(t)) = \{S_i | c_i(t) > 0\}.$$

By the *support of the complex y_j* we mean the set of species with nonzero stoichiometric coefficient in the complex y_j : $\text{supp}(y_j) = \{S_i | y_{ji} \neq 0\}$.

In order to formulate differential equations that describe the way in which the concentration vector evolves in time, we need to understand how the instantaneous rate function of the individual reactions in the network depend upon the instantaneous molar concentrations of the different species of the reactor. Considering a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ with N species we define a kinetics to be an assignment to each reaction $y_j \rightarrow y_l$ of a rate function

$$\begin{aligned} \mathcal{K}_{y_j \rightarrow y_l}(\cdot) : \bar{V}^+ &\longrightarrow \mathbb{R}_{\geq 0} \\ c(t) &\longmapsto \mathcal{K}_{y_j \rightarrow y_l}(c(t)) \end{aligned}$$

where $\mathcal{K}_{y_j \rightarrow y_l}(c(t))$ is the rate of the reaction $y_j \rightarrow y_l$ at concentration $c(t)$ at the time t . We require that this function satisfies the following properties:

- (1) $\mathcal{K}_{y_j \rightarrow y_l}(\cdot)$ is continuously differentiable, and
- (2) $\mathcal{K}_{y_j \rightarrow y_l}(c(t)) > 0 \iff \text{supp}(y_j) \subseteq \text{supp}(c(t))$.

A kinetics of a chemical network is called *mass-action* if for each reaction $y_j \rightarrow y_l \in \mathcal{R}$ there exists a positive *rate constant* $k_{j \rightarrow l} \in (0, \infty)$ such that

$$\mathcal{K}_{y_j \rightarrow y_l}(c(t)) \equiv k_{j \rightarrow l} \prod_{i=1}^N (c_i(t))^{y_{ji}}. \quad (3)$$

By presuming mass-action kinetics, we assume that the rate of a reaction is proportional to the product of the reactant concentrations. This is a rough approximation of the idealization that a reaction's occurrence is proportional to the probability of the reactants occupying the same point in space.

To make the notation (3) easier we will write:

$$c(t)^{y_j} = \prod_{i=1}^N (c_i(t))^{y_{ji}}. \quad (4)$$

Note, that if for any species $S_i \in \mathcal{S}$ the concentration at a time t is $c_i(t) = 0$, then $c(t)^{y_j} = 0$. Unless the species S_i is not contained in the complex y_j , for then $c_i^{y_{ji}}(t) = 0^0 = 1$.

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A chemical reaction network together with a kinetics will be called a *reaction system* and denoted by $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$. If the kinetics are of mass-action type, then we will call it *mass-action system* and denote it by $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$, where $k = \{k_{j \rightarrow l}\}_{y_j \rightarrow y_l \in \mathcal{R}}$.

For a reaction system we formulate the corresponding differential equation as follows:

$$\dot{c}(t) = \sum_{\mathcal{R}} \mathcal{K}_{y_j \rightarrow y_l}(c(t))(y_l - y_j), \quad c(t) \in \bar{V}^+. \quad (5)$$

Integrating (5) over t , we obtain

$$c(t) = c(0) + \sum_{y_j \rightarrow y_l \in \mathcal{R}} \left(\int_0^t \mathcal{K}_{y_j \rightarrow y_l}(c(s)) ds \right) (y_l - y_j). \quad (6)$$

Thus, $c(t) - c(0)$ remains in the span $S = \text{span}\{y_l - y_j | y_j \rightarrow y_l \in \mathcal{R}\}$, called the *stoichiometric subspace*. This linear subspace of V is the smallest subspace, that contains all reaction vectors of the network. Note that the dimension of the stoichiometric subspace is evidently the same as the rank of the reaction network. Therefore we denote the dimension of the stoichiometric subspace by the symbol s : $s = \dim S$.

For two concentration vectors $c(t_1), c(t_2)$ at different times, $t_1, t_2 \in [0, \infty)$, to lie on the same trajectory, their difference has to stay in the stoichiometric subspace. We shall denote by $c(t) + S = \{c(t) + r | r \in S\}$ the parallel subspace to the stoichiometric subspace that contains the concentration $c(t)$.

We say that two concentrations c, c' are *stoichiometrically compatible* if they lie on the same trajectory, that is if $c - c' \in S$. In this manner, we can partition the set of all possible concentrations into *stoichiometric compatibility classes*. For a concentration c , the corresponding stoichiometric compatibility class will be $(c + S) \cap \bar{V}^+$. More frequently we will use the *positive stoichiometric compatibility class* $(c + S) \cap V^+$, which only includes positive concentrations.

If the kinetics of the reaction network is of mass-action type, we can formulate the differential equation by using equation (3)

$$\dot{c}(t) = \sum_{\mathcal{R}} k_{j \rightarrow l} c(t)^{y_j} (y_l - y_j). \quad (7)$$

A concentration $\bar{c} \in \bar{V}^+$ for which

$$0 = \sum_{\mathcal{R}} \mathcal{K}_{y_j \rightarrow y_l}(\bar{c})(y_l - y_j) \quad (8)$$

is called a *steady state* of the reaction system under consideration. If the species' concentrations at the steady state are positive $\bar{c} \in V^+$, then we call the concentration a *positive steady state* of the reaction network.

1.4 Deficiency Zero and Deficiency One Theorems

In 1979 M. Feinberg achieved a first result in chemical reaction network theory by proving the deficiency zero theorem and followed up with the deficiency one theorem. To that matter we will lean on one of his papers, [12].

The two theorems stated in this section give rise to a relationship between the structure of a reaction network and the corresponding differential equations. While the kinetics of the

network are of mass-action type, it is of no relevance at which rate the different reactions in the network appear. This means, that no matter what value $k_{j \rightarrow l} \in (0, \infty)$ for every $y_j \rightarrow y_l \in \mathcal{R}$ takes, the statements for the networks of deficiency zero or one hold. The two theorems state that for certain restrictions on the reaction network structure we have a unique positive steady state in each positive compatibility class. Furthermore, for the networks which satisfy the properties of one of the two theorems, there exist no cyclic concentration trajectory.

We say that $c(\cdot)$ is a *cyclic concentration trajectory* if there exists a $T \in (0, \infty)$ so that $c(0) = c(T)$. It follows then that $c(T) - c(0) = \sum_{\mathcal{R}} (\int_0^T \mathcal{K}_{y_j \rightarrow y_l}(c(\tau)) d\tau) (y_l - y_j) = 0$.

Let $\bar{c} \in V^+$ be a positive steady state in a chemical reaction network. We say that this steady state is asymptotically stable in $(c_0 + \mathcal{S}) \cap V^+$ if for every neighborhood \mathcal{O} of \bar{c} in $(c_0 + \mathcal{S}) \cap V^+$, there is a neighborhood \mathcal{O}' of \bar{c} in \mathcal{O} such that every solution $c(t)$ with $c(0) = c_0$ in \mathcal{O}' is defined and remains in \mathcal{O} for all $t > 0$ and $\lim_{t \rightarrow \infty} c(t) = \bar{c}$, [16]. We will need to distinguish under *local* and *global* asymptotical stability. We will say that a steady state is locally asymptotically stable if the steady state is only asymptotically stable respective to a neighborhood in the stoichiometric compatibility class to the steady state. Whereas, we will say that a steady state is globally asymptotically stable if it is asymptotically stable respective to the entire positive stoichiometric compatibility class.

Theorem 1.4.1 (Feinberg [12]). ***Deficiency Zero Theorem** In a weakly reversible network with mass-action kinetics and deficiency zero, every positive stoichiometric compatibility class contains precisely one steady state and this steady state is locally asymptotically stable:*

For all positive initial concentration vector $c_0 \in V^+$ there exists one and only one $\bar{c} \in (c_0 + \mathcal{S}) \cap V^+$ such that:

$$\sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} \bar{c}(t)^{y_j} (y_l - y_j) = 0.$$

Furthermore, there is no nontrivial cyclic concentration trajectory along which all concentrations are positive.

Theorem 1.4.2 (Feinberg [12]). ***Deficiency One Theorem** Consider a chemical reaction network with mass-action kinetics and ℓ linkage classes, which each contain only one terminal strong linkage class ($t = \ell$). If every linkage class has deficiency no greater than one ($\delta_\theta \leq 1$) and the sum of the deficiencies of the linkage classes is equal to the deficiency of the whole reaction network ($\sum \delta_\theta = \delta$), then the corresponding differential equation can admit no more than one steady state in each positive stoichiometric compatibility class. If the network is weakly reversible then the corresponding differential equation admits precisely one steady state in each positive stoichiometric compatibility class.*

Remark In the *Deficiency Zero Theorem*, the weak reversibility property of the networks is essential for the existence and the uniqueness of the positive steady states. Whereas in the *Deficiency One Theorem*, the existence of the positive steady state is guaranteed by the property that deficiency of the network is no greater than one and the sum of the deficiencies of the linkage classes coincides with the deficiency of the network itself. The uniqueness then is an implication of the weak reversibility property. More insight and proofs of the two theorems can be found in [12] and [11].

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Remark These versions of the deficiency theorems are actually the combination of two theorems. The prior deficiency zero theorem states that a weakly reversible chemical reaction system with deficiency zero is *complex balanced*, [10]. Furthermore, a chemical reaction network which follows the conditions of the deficiency one theorem admits only complex balanced steady states, and, hence, the reaction network is complex balanced. For the definition of complex balanced reaction system see page 10. A second theorem stated first in [17] implies the local asymptotic stability of complex balanced steady states.

2 Application of a Lyapunov function

A first major result in chemical reaction network theory by F. Horn, R. Jackson and M. Feinberg, [17, 11], was the proof of local asymptotic stability for steady states in complex balanced chemical reaction networks. To be able to prove this, they used a method commonly applied in ordinary differential equation theory. By finding an appropriate Lyapunov function to every positive steady state of the differential equation for the corresponding complex balanced reaction network, they proved local asymptotic stability of these steady states.

Let us assume that the kinetics for the reaction network considered here are of mass-action type. In this case the corresponding differential equation is defined in (7).

To prove some statements we need a different approach to the differential equation. Therefore we will refer to the approach of J. Gunawardena [15]. Recall the linear map $Y : W \rightarrow V$ transforming the standard basis $\{w_j\}_{j=1,\dots,n} \in W$ into the reaction vectors $\{y_j\}_{j=1,\dots,n} \in V$, defined in equation (1). Let $\psi : V \rightarrow W$ be the nonlinear map, defined by:

$$\psi(c(t)) = \sum_{j=1}^n c(t)^{y_j} w_j$$

Let $x \in W$ and suppose x has a composition based on the standard basis: $x = \sum_{j=1}^n x_j w_j$. For a given kinetics on the network, we define the map $A_\kappa : W \rightarrow W$ by:

$$A_\kappa(x) = \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} x_j (w_l - w_j) \in W', \quad (9)$$

where W' denotes a subset of W and is defined as $W' := \text{span}\{w_j - w_i \mid y_i \rightarrow y_j \in \mathcal{R}\}$.

Remark The span of reaction vectors generated by actual reactions of the network coincides with the span of reaction vectors generated by linked complexes:

$$\text{span}\{w_j - w_i \mid y_i \rightarrow y_j \in \mathcal{R}\} = \text{span}\{w_j - w_i \mid y_i \sim y_j\}.$$

The proof for this can be found in the proof of Proposition 2.0.3.

If $f : V \rightarrow V$ denotes the right hand side of (7), then the following diagram commutes:

$$\begin{array}{ccc} W & \xleftarrow{A_\kappa} & W \\ Y \downarrow & & \uparrow \psi \\ V & \xleftarrow{f} & V \end{array} \quad (10)$$

and we have $f(c) = Y A_\kappa \psi(c)$. We will call f the *species formation rate function* for the mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$.

The set of positive steady states of a network can be formulated as $E = \{c \in V^+ \mid f(c) = 0\}$. There are only two possibilities for the composition $Y A_\kappa \psi$ to be zero in the positive orthant of V . Since for $c \in V^+$ it follows that $\psi(c) \in W^+$, we always have $\psi(c) \neq 0$. If $c \in V^+$ is a positive steady state, we have $A_\kappa \psi(c) = 0$ or $A_\kappa \psi(c) \in \ker Y$.

2 Application of a Lyapunov function

We will call a kinetic system *complex balanced at a concentration* $c \in V^+$ if $A_\kappa \psi(c) = 0$, that is if for every $y_j \in \mathcal{C}$ the following equation holds:

$$\sum_{\{l|y_j \rightarrow y_l \in \mathcal{R}\}} \mathcal{K}_{y_j \rightarrow y_l}(c) c^{y_j} = \sum_{\{l|y_l \rightarrow y_j \in \mathcal{R}\}} \mathcal{K}_{y_l \rightarrow y_j}(c) c^{y_l}. \quad (11)$$

This means that for every complex the rate of creation and the rate of annihilation coincide. We denote the set of all complex balanced steady states of a kinetic system by $C = \{c \in V^+ | A_\kappa \psi(c) = 0\}$. Obviously, $C \subset E$. If for a reaction network $C = E \neq \emptyset$, then the kinetic system will be called *complex balanced*.

Furthermore, we will call a reversible kinetic system *detailed balanced at a concentration* $c \in V^+$, if for every reaction $y_j \leftrightarrow y_l \in \mathcal{R}$ it holds $k_{j \rightarrow l} c^{y_j} = k_{l \rightarrow j} c^{y_l}$. The set of all detailed balanced steady states in a reaction network will be denoted by $D = \{c \in V^+ | \forall y_j, y_l \in \mathcal{C} \text{ with } y_j \leftrightarrow y_l : k_{j \rightarrow l} c^{y_j} = k_{l \rightarrow j} c^{y_l}\}$. Obviously, $D \subset C \subset E$. A kinetic system will be called *detailed balanced* if $D = C = E \neq \emptyset$.

Remark In [15] another definition for the deficiency of a network is used:

$$\delta = \dim(\ker Y \cap \text{Im } A_\kappa) \quad (12)$$

In general, the two definitions (2) and (12) differ in the way that $0 \leq \dim(\ker Y \cap \text{Im } A_\kappa) \leq n - \ell - s$. Though for chemical reaction networks, for which every linkage class contains one and only one terminal strong linkage class, in symbols $t = \ell$, the two definitions coincide, so in this special case we have $\dim(\ker Y \cap \text{Im } A_\kappa) = n - \ell - s$.

Proposition 2.0.3. *If in a reaction network every linkage class contains one and only one terminal strong linkage class, that is if $t = \ell$, then $\dim(\ker Y \cap \text{Im } A_\kappa) = n - \ell - s$.*

Proof. To prove this, we first notice that for every reaction network we have:

$$W' = \text{span}\{w_j - w_i | y_i \rightarrow y_j\} = \text{span}\{w_j - w_i | y_i \sim y_j\} =: W'' \quad (13)$$

If $y_i \rightarrow y_j \in \mathcal{R}$, then $w_j - w_i \in W'$ and because of the definition, it follows $y_i \sim y_j$, therefore $w_j - w_i \in W''$.

On the other hand, if $y_i \sim y_j$, then there exist y_1, \dots, y_k so that $y_i \leftrightarrow y_1 \leftrightarrow \dots \leftrightarrow y_k \leftrightarrow y_j$. Since $w_p - w_{p-1} = -(w_{p-1} - w_p) \in W'$, for every $2 \leq p \leq k$, it follows $w_j - w_i \in W'$. So we have $W' = W''$.

The second observation is that $\dim(\ker Y \cap W'') = \delta$. Let $Y|_{W''} : W'' \rightarrow V$ be the restriction of Y to W'' . Since Y is a linear map we have $\dim W'' = \dim \ker Y|_{W''} + \dim \text{Im } Y|_{W''}$.

- $\dim W'' = n - \ell$

Let $\Gamma_k = \text{span}\{w_j - w_i | y_i, y_j \in \mathcal{L}_k\}$ for $1 \leq k \leq \ell$, then we have $W'' = \Gamma_1 \oplus \Gamma_2 \oplus \dots \oplus \Gamma_\ell$ and $\Gamma_k = \text{span}\{w_{\tau(2)} - w_{\tau(1)}, w_{\tau(3)} - w_{\tau(1)}, \dots, w_{\tau(n_k)} - w_{\tau(1)}\}$ with n_k denoting the number of complexes in the k th linkage class, $\{y_{\tau(1)}, \dots, y_{\tau(n_k)}\} = \mathcal{L}_k$. Since the linkage classes form a partition of the set of complexes the following implication follows:

$$\dim \Gamma_k = n_k - 1, \quad k = 1, \dots, \ell \quad \Rightarrow \quad \dim W'' = \sum_{k=1}^{\ell} (n_k - 1) = n - \ell.$$

- $\dim \text{Im } Y|_{W''} = s$
Since Y is a linear map and (13) it follows:

$$\text{Im } Y|_{W''} = Y(W'') = Y(W') = S = \text{span}\{y_j - y_i \mid y_i \rightarrow y_j \in \mathcal{R}\}.$$

Hence, $\dim \text{Im } Y|_{W''} = s$.

From this it follows now

$$\dim(\ker Y \cap W'') = \dim \ker Y|_{W''} = \dim W'' - \dim Y|_{W''} = n - \ell - s = \delta.$$

It follows from proposition 2.1.1 that $\dim \ker A_\kappa = t$. Since A_κ is a linear map, we have $\dim \text{Im } A_\kappa = \dim W - \dim \ker A_\kappa = n - t$. We can deduce from the definitions of A_κ , (9), and W'' , (13), that $\text{Im } A_\kappa \subset W''$. Since $\dim W'' = n - \ell$ and $\dim \text{Im } A_\kappa = n - t$ it follows

$$t = \ell \quad \iff \quad \dim W'' = \dim \text{Im } A_\kappa \quad \iff \quad W'' = \text{Im } A_\kappa.$$

Hence, we have $t = \ell \iff \dim(\ker Y \cap \text{Im } A_\kappa) = \delta$. □

We want to describe the linear map $A_\kappa : W \rightarrow W$ as a matrix. Therefore we first define a matrix $A \in \mathbb{R}_{\geq 0}^{n \times n}$ by:

$$A = (A_{ij})_{i,j \leq n}, \quad A_{ij} = \begin{cases} k_{i \rightarrow j} & \text{if } y_i \rightarrow y_j \in \mathcal{R}, \\ 0 & \text{otherwise.} \end{cases}$$

The entries of this matrix are the rate constants of the different reactions occurring in the network, where the row index stands for the reactant complex and the column index for the product complex. If there is no reaction occurring between two complexes y_j, y_l the entry $A_{jl} = 0$. Considering the reaction diagram, we can observe that for one vertex, one complex y_j respectively, the rate of formation is $\sum_{\{i \mid y_i \rightarrow y_j\}} x_i A_{ij} - x_j (\sum_{\{l \mid y_j \rightarrow y_l\}} A_{jl})$ on a vector $x \in W$. It follows then:

$$A_\kappa = A^T - \text{diag}(Ae_n) \tag{14}$$

where $e_n \in W$ is the vector with 1 in every entry. The map diag inserts the components of a vector in the main diagonal of a matrix, so that for a vector $b \in \mathbb{R}^n$

$$(\text{diag } b)_{ij} = \begin{cases} b_i & \text{if } i = j, \\ 0 & \text{if } i \neq j. \end{cases}$$

If $c \in V^+$, Y is defined by (1) and c^{y_j} is defined by (4), then c^Y will be defined by $c^Y = (c^{y_1}, \dots, c^{y_n})^T$.

For mass-action kinetics, we can then express the species formation rate function in a matrix form:

$$f(c) = Y A_\kappa c^Y. \tag{15}$$

2.1 Complex balanced network and its dynamical properties

A mass-action system with a complex balanced steady state ensures certain stability properties to the steady states. By getting a closer insight about the kernel of the linear kinetic map A_κ we are going to be able to draw some important conclusions regarding the kinetic properties of the system. These stability properties for complex balanced reaction systems were first proven by M. Feinberg and F. Horn, [14, 11] and later proven in a different form by J. Gunawardena [15], on which this section is also based on.

Recall the definition for the concentration vector (4). We simplify the algebra by contraction of the notations for certain functions. Recall the definition of the $(N \times n)$ -transformation matrix Y , (1), and the composition c^Y . The natural logarithm of a vector $c \in V^+$ will be defined by $\ln c = (\ln c^1, \dots, \ln c^N)^T$ and the ratio c/a of two vectors $c, a \in V^+$ will be defined by

$$\frac{c}{a} = \left(\frac{c^1}{a^1}, \dots, \frac{c^N}{a^N} \right)^T \in V^+$$

By these definitions we can deduce the following relations:

$$\begin{aligned} \ln c^{y_i} &= \ln \left(\prod_{j=1}^N c_j^{y_{ij}} \right) = \sum_{j=1}^N \ln c_j^{y_{ij}} = y_i \cdot \ln c \in \mathbb{R} \\ \ln c^Y &= Y^T \ln c \in V \\ \ln \frac{c}{a} &= \ln c - \ln a \in V \\ \left(\frac{c}{a} \right)^{y_i} &= \prod_{j=1}^N \left(\frac{c_j}{a_j} \right)^{y_{ij}} = \frac{c^{y_i}}{a^{y_i}} \in \mathbb{R} \end{aligned}$$

where \cdot denotes here and in the following the scalar product in \mathbb{R}^N or in \mathbb{R}^n respectively. We start by mentioning a major proposition stated and proven in [14]. The statement will be of importance for the properties of the Lyapunov function and is often referred to as the *master* proposition.

Proposition 2.1.1. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a mass-action system with t terminal strong linkage classes $\{\mathcal{L}_1^T, \dots, \mathcal{L}_t^T\}$ and let $A_\kappa : W \rightarrow W$ be the linear kinetic map. Then $\ker A_\kappa$ has a basis $\{\chi_1, \dots, \chi_t\} \subset \bar{W}^+$ such that*

$$\text{supp } \chi_i = \mathcal{L}_i^T, \quad \forall i \in \{1, \dots, t\}. \quad (16)$$

To prove this proposition we have to get a better insight on $\ker A_\kappa$ and it will require preliminary work. We will prove the proposition by means of a series of lemmas.

We define the absolute value of a vector to be: $|(x_1, \dots, x_n)| = (|x_1|, \dots, |x_n|)$ and for vectors $x, y \in W$ we say $x \leq y$ if, and only if, $x_i \leq y_i$ for $1 \leq i \leq n$ and $x < y$ if $x \leq y$ and for some $i \in \{1, \dots, n\}$, $x_i < y_i$.

Lemma 2.1.2. *If there exist $x \in W$ such that $x \in \ker A_\kappa$ then $|x| \in \ker A_\kappa$.*

Proof. Let $x \in \ker A_\kappa$, then it follows with (14) that $A^T x = \text{diag}(Ae_n)x$. Taking absolute values on both sides and since $|A^T x| \leq A^T |x|$, $|\text{diag}(Ae_n)x| = \text{diag}(Ae_n)|x|$ we have:

$$\begin{aligned} |A^T x| &= |\text{diag}(Ae_n)x| \Rightarrow A^T |x| \geq \text{diag}(Ae_n)|x| \\ &\Rightarrow (A^T - \text{diag}(Ae_n))|x| \geq 0 \end{aligned}$$

2.1 Complex balanced network and its dynamical properties

From $e_n^T(A^T - \text{diag}(Ae_n)) = e_n^T A^T - e_n^T \text{diag}(Ae_n) = (Ae_n)^T - (Ae_n)^T = 0$ it follows:

$$\text{if } (A^T - \text{diag}(Ae_n))x \geq 0 \text{ then } (A^T - \text{diag}(Ae_n))x = 0 \quad (17)$$

for all $x \in W$ since $((A^T - \text{diag}(Ae_n))x)^T e_n = e_n^T (A^T - \text{diag}(Ae_n))x = (e_n^T (A^T - \text{diag}(Ae_n)))x = 0$.

So we have $(A^T - \text{diag}(Ae_n))|x| = 0$ and therefore $|x| \in \ker A_\kappa$. \square

Lemma 2.1.3. *Let $x \in \ker A_\kappa$ and $x \geq 0$. If for some $y_j \in \mathcal{C}$ we have $x_j = 0$ and there exist $y_i \in \mathcal{C}$ such that $y_i \rightarrow y_j \in \mathcal{R}$, then $x_i = 0$.*

Proof. From $A_\kappa(x) = 0$ it follows with equation (14):

$$\sum_{\{i|y_i \rightarrow y_j\}} x_i A_{ij} = x_j \left(\sum_{\{l|y_j \rightarrow y_l\}} A_{jl} \right).$$

Since by hypothesis $x_j = 0$, it follows that $x_j \left(\sum_{\{l|y_j \rightarrow y_l\}} A_{jl} \right) = 0$. Since $A_{ij} > 0$ whenever there exists an elementary reaction $y_i \rightarrow y_j$ it follows then from $\sum_{\{i|y_i \rightarrow y_j\}} x_i A_{ij} = 0$ that $x_i = 0$ whenever there exists a reaction $y_i \rightarrow y_j$. \square

Remark From this lemma it follows immediately, that if $x \in \ker A_\kappa$ and there exists $y_j \in \mathcal{C}$ such that $x_j = 0$ then $x_i = 0$ whenever $y_i \Rightarrow y_j$. It directly implies the next corollary.

Corollary 2.1.4. *Let \mathcal{L}_i^S be a strong linkage class of the mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ and let $x \in \ker A_\kappa$. If $x_j = 0$ for some $y_j \in \mathcal{L}_i^S$, then for all $y_l \in \mathcal{L}_i^S$: $x_l = 0$.*

Remark From this corollary it follows: $\mathcal{L}_i^S \cap \text{supp } x \neq \emptyset \Rightarrow \mathcal{L}_i^S \subset \text{supp } x$.

Lemma 2.1.5. *Let $\mathcal{L}^T = \bigcup_{i=1}^t \mathcal{L}_i^T \subset \mathcal{C}$ be the set of complexes residing in a terminal strong linkage class for a mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$. If $x \in \ker A_\kappa$, then $\text{supp } x \subset \mathcal{L}^T$.*

Proof. Recall that

$$(A_\kappa(x))_j = \sum_{\{i|y_i \rightarrow y_j \in \mathcal{R}\}} k_{i \rightarrow j} x_i - \left(\sum_{\{l|y_j \rightarrow y_l \in \mathcal{R}\}} k_{j \rightarrow l} \right) x_j$$

Since by lemma 2.1.2 we have $|x| \in \ker A_\kappa$ it follows:

$$\begin{aligned} \sum_{\{i|y_i \rightarrow y_j \in \mathcal{R}\}} k_{i \rightarrow j} |x_i| &= \left(\sum_{\{l|y_j \rightarrow y_l \in \mathcal{R}\}} k_{j \rightarrow l} \right) |x_j| \quad \forall y_j \in \mathcal{C} \\ \Rightarrow \sum_{y_j \in \mathcal{L}^T} \sum_{\{i|y_i \rightarrow y_j \in \mathcal{R}\}} k_{i \rightarrow j} |x_i| &= \sum_{y_j \in \mathcal{L}^T} \left(\sum_{\{l|y_j \rightarrow y_l \in \mathcal{R}\}} k_{j \rightarrow l} \right) |x_j| \end{aligned}$$

In fact we can reduce the second left-hand summation to a summation over all i for which $y_i \in \mathcal{L}^T$, for then both sides of the equation will sum over all reactions $y_j \rightarrow y_l$ where $y_j, y_l \in \mathcal{L}^T$. Hence,

$$\sum_{y_j \in \mathcal{L}^T} \sum_{\substack{\{i|y_i \rightarrow y_j \in \mathcal{R}\} \\ y_i \notin \mathcal{L}^T}} k_{i \rightarrow j} |x_i| = 0$$

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This means, that for every $y_i \notin \mathcal{L}^T$ such that $y_i \rightarrow y_j$ and $y_j \in \mathcal{L}^T$ we have $x_i = 0$. With Lemma 2.1.3 (more exactly with its following remark) it follows that for every $y_i \notin \mathcal{L}^T$ such that $y_i \Rightarrow y_j$ for $y_j \in \mathcal{L}^T$ we have $x_i = 0$, hence, for every $y_i \in \mathcal{C} \setminus \mathcal{L}^T$ we have $x_i = 0$, which completes the proof. \square

For a mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ let $\{\mathcal{L}_i^T\}_{i=1, \dots, t}$ be the terminal strong linkage classes. We define:

$$\Gamma_i = \text{span}\{w \in W \mid \text{supp } w = \mathcal{L}_i^T\}, \quad i = 1, \dots, t.$$

Then, by the previous lemma we have: $\ker A_\kappa \subset \Gamma_1 \oplus \dots \oplus \Gamma_t$.

Lemma 2.1.6. *For $i \in \{1, \dots, t\}$ if $x \in \Gamma_i$, then $A_\kappa(x) \in \Gamma_i$.*

Proof. Let \mathcal{R}_i denote the reactions of \mathcal{R} between the complexes of \mathcal{L}_i^T . It then follows with the previous lemma for $x \in \Gamma_i$:

$$A_\kappa(x) = \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} x_j (w_l - w_j) = \sum_{y_j \rightarrow y_l \in \mathcal{R}_i} k_{j \rightarrow l} x_j (w_l - w_j).$$

If $\mathcal{R}_i = \emptyset$, respectively $\#\mathcal{L}_i^T = 1$, then $A_\kappa(x) = 0$ and the proof is complete.

If $\mathcal{R}_i \neq \emptyset$, we have for every $y_j \rightarrow y_l \in \mathcal{R}_i$ that $y_j, y_l \in \mathcal{L}_i^T$ and therefore $w_l - w_j \in \Gamma_i$. Hence, $A_\kappa(x) \in \Gamma_i$. \square

Lemma 2.1.7. *For every $i \in \{1, \dots, t\}$ there exists a $\chi_i \in \Gamma_i$ such that:*

$$\begin{aligned} A_\kappa(\chi_i) &= 0, \\ \forall y_j \in \mathcal{L}_i^T : (\chi_i)_j &> 0, \\ \forall x \in \Gamma_i \text{ with } A_\kappa(x) &= 0 \quad \exists \alpha \in \mathbb{R} \text{ such that } x = \alpha \chi_i. \end{aligned}$$

Proof. We set $A_\kappa^i : \Gamma_i \rightarrow \Gamma_i$ to be the restriction of A_κ on Γ_i :

$$A_\kappa^i(x) = \sum_{y_j \rightarrow y_l \in \mathcal{R}_i} k_{j \rightarrow l} x_j (w_l - w_j).$$

We then have $\dim(\text{Im } A_\kappa^i) \leq \dim \Gamma_i$. For every $y_j \rightarrow y_l \in \mathcal{R}_i$ we have $y_j, y_l \in \mathcal{L}_i^T$ and $(w_j + w_l) \cdot (k_{j \rightarrow l} x_j (w_l - w_j)) = -k_{j \rightarrow l} x_j + k_{j \rightarrow l} x_j = 0$. Hence, $(\sum_{y_j \in \mathcal{L}_i^T} w_j) \cdot A_\kappa^i(x) = 0$ for all $x \in W$ and $\sum_{y_j \in \mathcal{L}_i^T} w_j \in \Gamma_i$, therefore $\dim(\ker A_\kappa^i) = \dim \Gamma_i - \dim \text{Im } A_\kappa^i > 0$. So $\ker A_\kappa^i \neq \emptyset$, that is there exists an $\chi_i \in \ker A_\kappa^i$ and $\emptyset \neq \text{supp } \chi_i \subset \mathcal{L}_i^T$. Corollary 2.1.1 implies $\mathcal{L}_i^T \subset \text{supp } \chi_i$, therefore we conclude $\text{supp } \chi_i = \mathcal{L}_i^T$. So, it follows:

$$(\chi_i)_j \begin{cases} \neq 0 & \text{if } y_j \in \mathcal{L}_i^T \\ = 0 & \text{if } y_j \notin \mathcal{L}_i^T \end{cases}$$

From Lemma 2.1.2 we can assume if $(\chi_i)_j \neq 0$ then $(\chi_i)_j > 0$.

Let $x \in \Gamma_i$ be such that $x \neq \chi_i$ and $A_\kappa(x) = 0$. Let α be chosen such that $x_j - \alpha(\chi_i)_j = 0$ for some $y_j \in \mathcal{L}_i^T$. Evidently $x - \alpha\chi_i \in \ker A_\kappa$, so with the remark to 2.1.3 it follows $x_j - \alpha(\chi_i)_j = 0$ for all $y_j \in \mathcal{L}_i^T$. Since $\text{supp}(x - \alpha\chi_i) \subset \mathcal{L}_i^T$ it follows $x = \alpha\chi_i$. \square

Proof. (Proposition 2.1.1)

We now prove that every $x \in \ker A_\kappa$ can be expressed as a composition of $\{\chi_i\}_{1 \leq i \leq t}$, where every χ_i in the set has the following properties:

- $\chi_i \in \Gamma_i$
- $A_\kappa(\chi_i) = 0$
- $(\chi_i)_j > 0$ if $y_j \in \mathcal{L}_i^T$.

It is clear that the set $\{\chi_i\}_{1 \leq i \leq t}$ is linearly independent. So if we are able to prove this statement, it would mean that this set constitutes a basis for $\ker A_\kappa$.

Let $x \in \ker A_\kappa$. Since $\ker A_\kappa \subset \Gamma_1 \oplus \Gamma_2 \oplus \dots \oplus \Gamma_t$, we have: $x = \bar{x}_1 + \bar{x}_2 + \dots + \bar{x}_t$ with $\bar{x}_i \in \Gamma_i$, $i = 1, \dots, t$. So, $A_\kappa(x) = A_\kappa(\bar{x}_1) + \dots + A_\kappa(\bar{x}_t) = 0$. Lemma 2.1.4 implies that $A_\kappa(\bar{x}_i) \in \Gamma_i$ and since the Γ_i are linearly independent it follows: $A_\kappa(\bar{x}_i) = 0$, $\forall 1 \leq i \leq t$. The last lemma implies that there exists $\{\alpha_i\}_{1 \leq i \leq t}$ such that: $x = \alpha_1 \chi_1 + \alpha_2 \chi_2 + \dots + \alpha_t \chi_t$. By this last argument we have proven proposition 2.1.1. \square

From this proposition we deduce a series of important statements. One of them is the following corollary:

Corollary 2.1.8. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a mass-action system. Then:*

$$\ker A_\kappa \cap W^+ \neq \emptyset \iff \text{the network is weakly reversible.}$$

Proof. For the forward implication, let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a reaction system that is not weakly reversible. Hence, there exists a complex $y_j \in \mathcal{C}$ that is not part of a terminal strong linkage class. By proposition 2.1.1 every element $x \in \ker A_\kappa$ has a decomposition $x = x_1 + \dots + x_t$ such that $\text{supp } x_i = \mathcal{L}_i^T$, $i = 1, \dots, t$. Therefore we have for every element of $x \in \ker A_\kappa$: $x_j = 0$. This implies $\ker A_\kappa \cap W^+ = \emptyset$.

For the reverse implication let the network be weakly reversible. Then every complex is part of a terminal strong linkage class and the sum of the basis vectors of $\ker A_\kappa$ is an element of $\ker A_\kappa \cap W^+$. \square

Corollary 2.1.9. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a mass-action system. If there exists $c^* \in V^+$ such that $A_\kappa \psi(c^*) = 0$, that is, if there exists a positive complex balanced steady state to the system, then the network is weakly reversible.*

Proof. Since $c^* \in V^+$ it follows that $\psi(c^*) = \sum_{i=1}^n (c^*)^{y_i} w_i > 0$. So there exists a positive vector $\psi(c^*) \in W^+$ in the kernel of A_κ . From Corollary 2.1.8 it then follows that the network is weakly reversible. \square

Remark Recall that for a chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ we defined the stoichiometric subspace $S \subset V$ as $S = \text{span}\{y_l - y_j \in V | y_j \rightarrow y_l \in \mathcal{R}\}$. S^\perp is the orthogonal complement to S in V , $S^\perp = \{v \in V | v \cdot u = 0 \text{ for } u \in S\}$. So, we have $V = S \oplus S^\perp$.

A mass-action system will be called *conservative* if S^\perp contains a vector in the nonnegative orthant \bar{V}^+ of the species space. If for example we have in chemical terminology conservation of mass, then the mass-action system is conservative. Conservation of mass is not the only characteristic that leads to a conservative system. Consider the *Michaelis-Menten-Equation* in figure 2 on page 16:

In this example we have conservation of the number of molecules of $S + SE + P$ and the

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Figure 2: Michaelis-Menten-model, where S denotes the substrate, E the enzyme, SE the enzyme-substrate complex and P the product

number of molecules of $E + SE$. Let X_I denote the number of molecules of the species I , then we have $X_S + X_{SE} + X_P = K_1$ and $X_E + X_{SE} = K_2$ where K_1, K_2 are constants. So we have two conservation relations: $(1, 0, 1, 1)^T \in S^\perp$ and $(0, 1, 1, 0)^T \in S^\perp$. If we consider a more general notion of conservation, i.e. conservation of a reactant-product-relation, it is only necessary that S^\perp is nonempty and S^\perp may also contain vectors with negative coefficients. Assume that there is no input or output to the system, then the system must be conservative due to conservation of mass.

Proposition 2.1.10 (Feinberg [11], lecture 4).

$$\forall a, b \in V^+ \quad \exists! \eta \in S^\perp : \quad ae^\eta - b \in S. \quad (18)$$

Proof. Let $a, b \in V^+$, we define $\varphi : V \rightarrow \mathbb{R}$ by

$$\varphi(x) := \sum_{i=1}^N (a_i e^{x_i} - b_i x_i).$$

Through computation we have: $\varphi'(x) = ae^x - b = (a_1 e^{x_1} - b_1, \dots, a_N e^{x_N} - b_N)$, where $e^x = \{e^{x_i}\}_{i=1, \dots, N}$. It so follows that the Hessian $H_\varphi(x)$ of φ at x is given by $z^T H_\varphi(x) z = z^T (\text{diag } ae^x) z$ for all $z \in V$. So we have for every $z \in V$, $z \neq 0$:

$$z^T H_\varphi(x) z = z^T (\text{diag } ae^x) z = \sum_{i=1}^N a_i e^{x_i} z_i^2 > 0.$$

This means H_φ is positive definite. Hence, φ is strictly convex.

For $i \in \{1, \dots, N\}$ we have

$$\lim_{\alpha \rightarrow \infty} (a_i e^{\alpha x_i} - \alpha b_i x_i) = \begin{cases} \infty & \text{if } x_i \neq 0 \\ a_i & \text{if } x_i = 0 \end{cases}$$

It then follows for $x \neq 0$ that

$$\lim_{\alpha \rightarrow \infty} \varphi(\alpha x) = \infty. \quad (19)$$

We now prove the existence of $\eta \in S^\perp$ such that $ae^\eta - b \in S$. Let therefore $\varphi|_{S^\perp} : S^\perp \rightarrow \mathbb{R}$ be the restriction of φ to S^\perp . As φ is continuous and convex, it follows that $\varphi|_{S^\perp}$ is too. Hence, the set $G := \{x \in S^\perp \mid \varphi|_{S^\perp}(x) \leq \varphi|_{S^\perp}(0) = a\}$ is closed and convex. Moreover, G is bounded. Let $i \in \{1, \dots, N\}$ and $\psi_i : S^\perp \rightarrow \mathbb{R}$, $\psi_i(x) = a_i e^{x_i} - b_i x_i$, then there exists some adequate $\gamma_i \in \mathbb{R}$ such that for all i and all $x \in S^\perp$ holds $\varphi(x)_{S^\perp} \geq \psi_i(x) \geq \gamma_i$. Since ψ_i is continuous and convex for all i , we have $\{x \in S^\perp \mid \psi_i(x) \leq a_i\}$ is bounded, hence, $\bigcap_{1 \leq i \leq N} \{x \in S^\perp \mid \psi_i(x) \leq a_i\}$ is bounded. Since $G \subset \bigcap_{1 \leq i \leq N} \{x \in S^\perp \mid \psi_i(x) \leq a_i\}$

2.1 Complex balanced network and its dynamical properties

it follows that G is also bounded. So the set G is closed and bounded, hence, compact. Therefore, there exists a $\eta \in G$ such that:

$$\begin{aligned} & \varphi|_{S^\perp}(\eta) \leq \varphi|_{S^\perp}(x) && \forall x \in G \\ \Rightarrow & \varphi|_{S^\perp}(\eta) \leq \varphi|_{S^\perp}(x) && \forall x \in S^\perp \\ \Rightarrow & 0 = \frac{d}{d\gamma} \varphi|_{S^\perp}(\eta + \gamma x)|_{\gamma=0} = \frac{d}{d\gamma} \varphi(\eta + \gamma x)|_{\gamma=0} = \varphi'(\eta) \cdot x && \forall x \in S^\perp \\ \Rightarrow & ae^\eta - b = \varphi'(\eta) \in S. \end{aligned}$$

At this point we only have to prove uniqueness to complete the proof. Let $\bar{\eta} \in S^\perp$ such that $\bar{\eta} \neq \eta$ and $ae^{\bar{\eta}} - b \in S$. Then it must be such that $a(e^{\bar{\eta}} - e^\eta) \in S$ and with $\bar{\eta} - \eta \in S^\perp$, it follows

$$0 = (\bar{\eta} - \eta) \cdot a(e^{\bar{\eta}} - e^\eta) = \sum_{i=1}^N a_i(\bar{\eta}_i - \eta_i)(e^{\bar{\eta}_i} - e^{\eta_i}).$$

Since $a \in V^+$ this equation can only hold if $\bar{\eta}_i = \eta_i$ for all $i \in \{1, \dots, N\}$. Hence, uniqueness follows. \square

Corollary 2.1.11. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network and let $S \subset V$ be its stoichiometric subspace. For all $c^* \in V^+$ $\{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ meets every positive stoichiometric compatibility class $(c_0 + S) \cap V^+$ in precisely one point.*

Proof. Let $d \in V^+$ and $d \in (d_0 + S) \cap V^+$. First we are going to prove the existence of an element $c \in (d_0 + S) \cap \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ for $d \in V$ been chosen arbitrarily. Proposition 2.1.10 implies the unique existence of a vector $\eta \in S^\perp$ such that $c^*e^\eta - d \in S$. If we define $c := c^*e^\eta$, then $c \in (d_0 + S) \cap V^+$ and $\ln c - \ln c^* = \ln(c^*e^\eta) - \ln c^* = \ln e^\eta = \eta \in S^\perp$. So c satisfies the requirement of the corollary.

To prove uniqueness of c , let $c' \in V^+$ be such that $c' \in (d_0 + S) \cap \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ and $c' \neq c$. Then it follows from $c, c' \in \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ that $\ln c - \ln c' \in S^\perp$. Since $c - c' \in S$ it then follows:

$$0 = (c - c') \cdot (\ln c - \ln c') = \sum_{i=1}^N (c_i - c'_i)(\ln c_i - \ln c'_i).$$

Since $\ln : (0, \infty) \rightarrow \mathbb{R}$ is a strictly increasing function, the last equation can only hold if $c'_i = c_i$ for all $i \in \{1, \dots, N\}$. Thus, uniqueness is proven. \square

Recall the notations $E = \{c \in V^+ \mid f(c) = 0\}$ and $C = \{c \in V^+ \mid A_\kappa \psi(c) = 0\}$ for the set of steady states, respectively complex balanced steady states.

Theorem 2.1.12 (Feinberg [11], lecture 5). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a mass-action system and let S be its stoichiometric subspace and $f = Y A_\kappa \psi$ the species formation rate function. If $c^* \in V^+$ is a complex balanced steady state to the system, then the following statements hold:*

- (1) $\forall c \in V^+, c \notin E : (\ln c - \ln c^*) \cdot f(c) < 0$
- (2) $E = \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$
- (3) $E = C$.

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Proof. (1): We define

$$\begin{aligned}\phi : V^+ &\longrightarrow V \\ c &\longmapsto \ln c - \ln c^*\end{aligned}$$

For every $c \in V^+$ we have $c^y = (c^*)^y e^{y \cdot \phi(c)}$, $\forall y \in \mathcal{C}$. This implies:

$$\begin{aligned}f(c) &= \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} e^{y_j \cdot \phi(c)} (y_l - y_j) \\ \Rightarrow f(c) \cdot (\ln c - \ln c^*) &= \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} e^{y_j \cdot \phi(c)} (y_l \cdot \phi(c) - y_j \cdot \phi(c))\end{aligned}$$

With the argument

$$e^\alpha (\alpha' - \alpha) \begin{cases} < \\ = \end{cases} e^{\alpha'} - e^\alpha \iff \begin{cases} \alpha \neq \alpha' \\ \alpha = \alpha' \end{cases}$$

it follows:

$$f(c) \cdot (\ln c - \ln c^*) \leq \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} (e^{y_l \cdot \phi(c)} - e^{y_j \cdot \phi(c)}) \quad \forall c \in V^+ \quad (20)$$

with equality holding if and only if $\phi(c) \cdot (y_l - y_j) = 0$ for every $y_j \rightarrow y_l \in \mathcal{R}$.

$$\begin{aligned}\Rightarrow f(c) \cdot (\ln c - \ln c^*) &\leq \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} (e^{y_l \cdot \phi(c)} - e^{y_j \cdot \phi(c)}) \\ &= \left(\sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} (w_l - w_j) \right) \sum_{y_i \in \mathcal{C}} e^{y_i \cdot \phi(c)} w_i = 0 \quad (21)\end{aligned}$$

since $\sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} (w_l - w_j) = A_\kappa \psi(c^*) = 0$. With equality holding if and only if $f(c) = 0$.

(2): Let $c \in \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ and $c \neq c^*$, so it follows since $f(c) \in S$ for all $c \in V$ that $f(c) \cdot (\ln c - \ln c^*) = 0$. $\ln : (0, \infty) \rightarrow \mathbb{R}$ is a strictly increasing function, so that for $c \neq c^*$, $\ln c \neq \ln c^*$. It therefore follows that $f(c) = 0$ and consequently $c \in E$.

If $c \in E$, then $f(c) \cdot (\ln c - \ln c^*) = 0$. So it follows from (20) that

$$0 = f(c) \cdot (\ln c - \ln c^*) \leq \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l}(c^*)^{y_j} (e^{y_l \cdot \phi(c)} - e^{y_j \cdot \phi(c)}) \stackrel{(21)}{=} 0.$$

The middle inequality is an equality only if $\phi(c) \cdot (y_l - y_j) = 0$. Since $y_l - y_j \in S$, it follows that $\phi(c) = \ln c - \ln c^* \in S^\perp$. Hence, $c \in \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$.

(3): From the second part we know that $c \in E$ implies $\ln c - \ln c^* \in S^\perp$. So we will now prove that from this last statement follows that $A_\kappa \psi(c) = 0$.

Since $c^* \in V^+$ is a complex balanced steady state, we know from Corollary 2.1.9 that the network is weakly reversible. Hence, every complex resides in a terminal strong linkage class. Furthermore, proposition 2.1.1 implies existence of a basis $\{\chi_1, \dots, \chi_t\} \subset \bar{W}^+$ of $\ker A_\kappa$ such that $\text{supp } \chi_i = \mathcal{L}_i^T$, $i = 1, \dots, t$. It follows:

$$\psi(c^*) = \sum_{i=1}^n (c^*)^{y_i} w_i = \sum_{j=1}^t \left(\sum_{y_i \in \mathcal{L}_j^T} (c^*)^{y_i} w_i \right) = \sum_{j=1}^t \lambda_j \chi_j,$$

2.2 Construction of the Lyapunov function

where $\lambda_1, \dots, \lambda_t \in (0, \infty)$. Since the terminal strong linkage classes are disjoint, it follows that $\sum_{y_i \in \mathcal{L}_j^T} (c^*)^{y_i} w_i = \lambda_j \chi_j$, $j = 1, \dots, t$. Hence, $\{\sum_{y_i \in \mathcal{L}_j^T} (c^*)^{y_i} w_i\}_{j=1, \dots, t}$ also represents a basis of $\ker A_\kappa$.

We have $\ln c - \ln c^* \in S^\perp$, so for every pair of linked complexes $y_j \sim y_l$ it follows from $y_l - y_j \in S$ that $y_j \cdot (\ln c - \ln c^*) = y_l \cdot (\ln c - \ln c^*)$. This implies, that there exist $\theta_1, \dots, \theta_t$ such that $y_j \cdot (\ln c - \ln c^*) = \theta_j$ for all $y_j \in \mathcal{L}_j^T$. So it follows that

$$\begin{aligned} \psi(c) &= \sum_{i=1}^n c^{y_i} w_i = \sum_{i=1}^n (c^*)^{y_i} e^{y_i \cdot (\ln c - \ln c^*)} w_i \\ &= \sum_{j=1}^t \left(\sum_{y_i \in \mathcal{L}_j^T} (c^*)^{y_i} e^{y_i \cdot (\ln c - \ln c^*)} w_i \right) = \sum_{j=1}^t e^{\theta_j} \left(\sum_{y_i \in \mathcal{L}_j^T} (c^*)^{y_i} w_i \right) \\ &\in \ker A_\kappa. \end{aligned}$$

This means $A_\kappa \psi(c) = 0$ and the proof is complete. \square

Remark This theorem tells us that if a mass-action system contains one complex balanced steady state, then every steady state in this system is complex balanced and therefore is a complex balanced mass-action system. With Corollary 2.1.8 it follows then that this system is weakly reversible. On the whole we have the implication:

$\exists c^* \in V^+ : A_\kappa \psi(c^*) = 0 \Rightarrow$ complex balanced system \Rightarrow weakly reversible system.

Corollary 2.1.13. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a complex balanced mass-action system. Then the differential equations admit in each positive stoichiometric compatibility class exactly one steady state.*

Proof. Since from the theorem 2.1.12 we know that the set of positive steady states coincides with the set $\{c \in V^+ \mid \ln c - \ln c^*\}$ for $c^* \in V^+$ a complex balanced steady state, corollary 2.1.11 proves the statement. \square

2.2 Construction of the Lyapunov function

In the previous section we have seen that a complex balanced mass-action system with terminal strong linkage classes $\{\mathcal{L}_i^T\}_{i=1, \dots, t}$ implies:

- $\ker A_\kappa$ has a basis $\{\chi_1, \dots, \chi_t\}$ such that $\text{supp } \chi_i = \mathcal{L}_i^T$, $i = 1, \dots, t$;
- the mass-action system is weakly reversible;
- $\forall c \in V^+ : f(c) \cdot (\ln c - \ln c^*) \leq 0$, where $c^* \in V^+$ is a complex balanced steady state of the system;
- $C = \{c \in V^+ \mid A_\kappa \psi(c) = 0\} = \{c \in V^+ \mid \ln c - \ln c^* \in S^\perp\}$ where $c^* \in V^+$ is a complex balanced steady state and $S \subset V$ is the stoichiometric subspace of the system.

Let the network be complex balanced at a concentration $c^* \in V^+$, we introduce the function $H : \bar{V}^+ \rightarrow \mathbb{R}$ defined in [11] by

$$H(c) := \sum_{j=1}^N \left((\ln(c_j) - \ln(c_j^*) - 1)c_j + c_j^* \right) \quad (22)$$

where $H(0) = c^*$.

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From the definition of H , we can derive the following properties:

(H1) $H(c) > 0$ for all $c \neq c^*$ and $H(c^*) = 0$.

(H2) $\forall c \in V^+ : H(c) = (\ln c - \ln c^* - e_N) \cdot c + c^*$, where e_N is the vector in V with all entries equal to 1. Furthermore H is continuously differentiable on V^+ with

$$H'(c) = \ln c - \ln c^*. \quad (23)$$

(H3) If $0 \leq \lambda < 1, c_1 \in \partial \bar{V}^+, c_2 \in V^+$, then $c_2 + \lambda(c_1 - c_2) \in V^+$ and

$$\lim_{\lambda \rightarrow 1} \left(\frac{d}{d\lambda} H(c_2 + \lambda(c_1 - c_2)) \right) = +\infty \quad (24)$$

(H4) H is continuous on its domain.

(H5) H is strictly convex, that is

$$\forall t \in (0, 1), \forall c_1, c_2 \in \bar{V}^+ \text{ with } c_1 \neq c_2 : H(tc_1 + (1-t)c_2) < tH(c_1) + (1-t)H(c_2).$$

(H6)

$$\lim_{|c| \rightarrow \infty} H(c) = +\infty \text{ where } |c| = \sqrt{c_1^2 + \dots + c_N^2} \quad (25)$$

Proof. (H1) We have $\ln c_j - \ln c_j^* \geq (c_j - c_j^*)/c_j$ for all $j \in \{1, \dots, N\}$. Therefore, it follows:

$$H(c) = \sum_{j=1}^N \left((\ln(c_j) - \ln(c_j^*) - 1)c_j + c_j^* \right) > \sum_{j=1}^N \left(\left(\frac{1}{c_j}(c_j - c_j^*) - 1 \right) c_j + c_j^* \right) = 0$$

for all $c \neq c^*$ and $H(c) = 0$ if and only if $c = c^*$.

(H2) H is a composition of continuously differentiable functions and:

$$\begin{aligned} H'(c) &= \left((\ln c - \ln c^* - 1)c + c^* \right)' = \sum_{j \leq N} \frac{d}{dc_j} \left((\ln c_j - \ln c_j^* - 1)c_j + c_j^* \right) v_j^T \\ &= \sum_{j \leq N} \left(1 + \ln c_j - \ln c_j^* - 1 \right) v_j^T = \ln c - \ln c^*, \end{aligned}$$

where v_j is the j th unit vector in V .

(H3) For $\lambda < 1$ we have $\frac{d}{d\lambda} H(c_2 + \lambda(c_1 - c_2)) = (\ln(c_2 + \lambda(c_1 - c_2)) - \ln(c^*)) \cdot (c_1 - c_2)$, it then follows:

$$\begin{aligned} \lim_{\lambda \rightarrow 1} \left(\frac{d}{d\lambda} H(c_2 + \lambda(c_1 - c_2)) \right) &= \lim_{\lambda \rightarrow 1} (\ln(c_2 + \lambda(c_1 - c_2)) - \ln(c^*)) \cdot (c_1 - c_2) \\ &= \lim_{\lambda \rightarrow 1} (\ln(c_2 - \lambda c_2) \cdot (-c_2)) \\ &= \lim_{\lambda \rightarrow 1} (\ln(c_2 - \lambda c_2)) \cdot (-c_2) = +\infty \end{aligned}$$

The second equality follows with the we can assume $c_1 = 0$, since for every j with $(c_1)_j > 0$ it follows that $(\ln((c_2)_j + \lambda((c_1)_j - (c_2)_j)) - \ln(c^*)_j)((c_1)_j - (c_2)_j)$ is finite.

(H4) H is a composition of continuous functions.

(H5) From (23) it follows that $\forall c \in V^+, \forall a \in V : a^T \mathcal{H}(H(c))a = \sum \frac{a_i^2}{c_i} > 0$, so the Hessian matrix \mathcal{H} of H is positive-definite and therefore H is strictly convex.

(H6) follows directly from the definition of H . □

In [16] the classification of a steady state is defined as follows:

A steady state c^* of a dynamical system is called *stable* if for every neighborhood \mathcal{O} of c^* in V there is a neighborhood \mathcal{O}' of c^* in \mathcal{O} such that every concentration trajectory $c(t)$ with $c_0 = c(0)$ in \mathcal{O}' is defined and remains in \mathcal{O} for all $t > 0$.

A steady state c^* is called *asymptotically stable* if it is stable and $\lim_{t \rightarrow \infty} c(t) = c^*$ holds.

A steady state that is not stable, is called *unstable*.

Considering a chemical reaction network, it is evidently more significant to admit asymptotically stable steady states. If, for example, there are perturbations to the systems, which are likely not only for biological systems, then it is desirable that these deviations are canceled out by the system rather than maintain a slight change of the system.

Theorem 2.2.1 (Hirsch et al. [16] Lyapunov Stability, p.194). *Let c^* be a steady state for $\dot{c} = f(c)$. Let $H : \mathcal{O} \rightarrow \mathbb{R}$ be a differentiable function defined on an open set \mathcal{O} containing c^* . Suppose further that*

(1) $H(c^*) = 0$ and $H(c) > 0$ if $c \neq c^*$;

(2) $\frac{d}{dt}H(c(t)) \leq 0$ for every $c(t) \in \mathcal{O} \setminus \{c^*\}$

Then c^ is stable and H is called a Lyapunov function. Furthermore, if H also satisfies*

(3) $\frac{d}{dt}H(c(t)) < 0$ for every $c(t) \in \mathcal{O} \setminus \{c^*\}$,

then c^ is asymptotically stable and H is called a strict Lyapunov function.*

Corollary 2.2.2. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a complex balanced mass-action system and let $c^* \in (c_0 + \mathcal{S}) \cap V^+$ be a steady state to the system. If we take \mathcal{O} in the previous theorem to be the largest level set of H restricted to the positive stoichiometric compatibility class of c^* that contains c^* , then $H_{c^*} : (c_0 + \mathcal{S}) \cap V^+ \rightarrow \mathbb{R}$ represents the restriction of H to the positive stoichiometric compatibility class, a strict Lyapunov function to the considered positive stoichiometric compatibility class.*

Proof. From the definition of H it follows directly that the function is differentiable and $H(c) > 0$ for every $c \neq c^*$. The second condition

$$\frac{d}{dt}H(c(t)) = H'(c(t)) \cdot \dot{c}(t) = H'(c) \cdot f(c) \leq 0 \quad \forall c \in V^+ \quad (26)$$

with equality holding if and only if $A_\kappa \psi(c) = 0$ follows directly from (23) and the theorem 2.1.12. □

It follows immediately from this corollary that complex balanced steady states are locally asymptotically stable relative to their corresponding positive stoichiometric compatibility class. For a better understanding of the Lyapunov theory and the Lyapunov function we

2 Application of a Lyapunov function

are going to explain how the different properties of a Lyapunov function interact to guarantee stability, respectively, local asymptotic stability of the differential system in question. For a fixed complex balanced steady state c^* we define H_{c^*} to be the restriction of H onto the positive stoichiometric compatibility class containing c^* . Property (H1), (H4) and (H5) imply that for each complex balanced steady state c^* , H_{c^*} admits only one minimum, namely c^* . From property (H2) together with (26) it follows that H_{c^*} is non-increasing along any concentration trajectory residing in the same stoichiometric compatibility class and H' is zero only at c^* , therefore c^* is stable. It follows even that the restricted Lyapunov function is decreasing along any trajectory for $c(t) \neq c^*$, and with the property (H6) that H converges to infinity as the concentration trajectory tends to infinity, it follows that every trajectory is bounded. Hence, with the Lyapunov theory we are able to state that every complex balanced mass-action system implies bounded concentration trajectories and asymptotically stable steady states.

One might now assume that the complex balanced steady states are asymptotically stable respective to the entire stoichiometric compatibility class. However, this is not warranted. The Lyapunov function is not radially unbounded with respect to the stoichiometric compatibility class and consequently we cannot rule out the possibility that trajectories tend toward the boundary of the set. This is the actual sticking point of the global attractor conjecture which we will get into more detail in the next chapter. Additionally we will show how the global attractor conjecture is linked to the *persistence conjecture*.

3 Global Attractor Conjecture

3.1 Open problem of the Global Attractor Conjecture

So far we have seen that in a complex balanced mass-action system there exists only one steady state in each positive stoichiometric compatibility class and in all chemical reaction networks every concentration trajectory remains for all time in the same stoichiometric compatibility class as it initialized. Furthermore complex balanced mass-action systems give rise to locally asymptotically stable steady states relative to the positive stoichiometric compatibility classes. This means that in a complex balanced mass-action system, every trajectory initializing in a close neighborhood of a steady state remains in a close neighborhood in the same stoichiometric compatibility class of the steady state and tends to the steady state. The natural question is now how large a neighborhood we can chose so that the asymptotic stability still holds. As we already noted in the last paragraph the trajectories may also tend to the boundary of the positive orthant of the species space.

Theorem 3.1.1 (Anderson [2]). *Let $c(t)$ be a concentration trajectory with initial concentration $c(0)$. Let c^* be the complex balanced steady state in the open stoichiometric compatibility class $(c(0) + S) \cap V^+$. Let H be the Lyapunov function (22), then either*

$$\liminf_{t \rightarrow \infty} d(c(t), c^*) = 0 \quad \text{or} \quad \liminf_{t \rightarrow \infty} d(c(t), \partial \bar{V}^+) = 0.$$

Proof. Assume that for some $c(t)$, $c^* \in (c(0) + S) \cap V^+$ $c(t) \not\rightarrow c^*$. From property (H2) of V we know that H_{c^*} decreases along trajectories, hence $H_{c^*}(c(t))$ is bounded from above by $H_{c^*}(c(0))$ for all $t \geq 0$ and $c(t)$ is bounded for all $t > 0$. Since we assumed that $c(t) \not\rightarrow c^*$ and c^* is locally asymptotically stable, there exists a $\delta > 0$ such that $\|c(t) - c^*\| > \delta$ for all $t > 0$.

Let $\epsilon > 0$ and let $C_\epsilon = \{c(t) \in (c(0) + S) \cap V^+ \mid d(c(t), \partial \bar{V}^+) \geq \epsilon \text{ and } |c(t) - c^*| \geq \delta\}$. Since the trajectories are bounded and H' , f are continuous functions there exists a $\eta = \eta(\epsilon)$ such that $H'(f(c(t))) = H'(c(t)) \cdot f(c(t)) < -\eta$ for all $c(t) \in C_\epsilon$. So it follows that $H(c(0))/\eta$ is the maximum amount of time that any trajectory can spend in the set C_ϵ , as otherwise $c(t) \rightarrow c^*$. ϵ was chosen arbitrarily, hence, $\liminf_{t \rightarrow \infty} d(c(t), \partial \bar{V}^+) = 0$. \square

Though as for now we cannot prove asymptotic stability for the complete positive stoichiometric compatibility class, the system is asymptotically stable in the neighborhood of the steady state. Hence, we say complex balanced mass-action systems are *locally asymptotically stable*.

Proposition 3.1.2 (La Salle and Lefschetz [18], §13. The Extent of Asymptotic Stability). *Let $H(c)$ be a scalar function with continuous first partial derivatives. Let D_l designate the region where $H(c) < l$. Assume that D_l is bounded and that within D_l :*

- $H(c) > 0$ for $c \neq c^*$,
- $H'(c) < 0$ for $c \neq c^*$.

Then every trajectory $c(t)$ in D_l tends to c^ as $t \rightarrow \infty$.*

For big enough l , the domain D_l includes the boundary of the positive orthant, where the conditions for H to be a strict Lyapunov function do not hold anymore. Without the unboundedness of the Lyapunov function towards the boundary we cannot assume that

3 Global Attractor Conjecture

asymptotic stability holds for the complete positive stoichiometric compatibility class. However it is conjectured since the early 1970s that the the steady states of complex balanced systems are *globally asymptotically stable*, meaning asymptotically stable in the complete positive stoichiometric compatibility class. This conjecture was given the name *global attractor conjecture* by Craciun et al. [8].

Conjecture 1 (Global Attractor Conjecture). *A complex balanced steady state contained in a positive stoichiometric compatibility class is globally asymptotically stable relative to the interior of its positive stoichiometric compatibility class.*

The open problem of the global attractor conjecture is the non-extinction of the species of the network. D. Anderson [2] proved that the conjecture holds if it can be proven that there exist no steady states on the boundary. This brings us to two important definitions in chemical reaction network theory.

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ be a chemical reaction network. We will call a concentration trajectory $c(t)$ *persistent* if

$$\liminf_{t \rightarrow \infty} c_i(t) > 0 \quad \forall i \in \{1, \dots, N\}.$$

We will call the chemical reaction network *persistent* if every concentration trajectory of the network is persistent.

If it can be shown that every complex balanced mass-action system is persistent, then the conjecture will be proven.

The set of ω -limit points for a concentration trajectory $c(t)$ with initial concentration c_0 is defined as

$$w(c(\cdot)) := w(c(\cdot), c_0) = \{z \in \bar{V}^+ \mid \lim_{n \rightarrow \infty} c(t_n) = z \text{ for some sequence } t_n \rightarrow \infty\}. \quad (27)$$

Hence, the other possibility to prove that the species of a complex balanced mass-action system do not become extinct, is to prove that $w(c(\cdot)) \cap \partial \bar{V}^+ = \emptyset$.

In the last years research has been concentrated more on proving the *Persistence conjecture* stated by Feinberg, M. in [12][Remark 6.1.E]:

Conjecture 2 (Persistence Conjecture). *Any weakly reversible mass-action system is persistent.*

There exists a weaker version of the persistence conjecture stated by [3] which requires the concentration trajectories to be bounded so that the mass-action system will be persistent.

Conjecture 3. *Any weakly reversible mass-action system with bounded concentration trajectories is persistent.*

In fact it is still an open problem whether weakly reversible reaction networks only give rise to bounded concentration trajectories.

Conjecture 4. *Any weakly reversible mass-action system has bounded trajectories.*

Hence, the common persistence conjecture can be divided into conjecture 3 and conjecture 4, which together are equivalent to the open problem of the global attractor conjecture. Note that the Global Attractor Conjecture only considers complex balanced reaction networks, whereas the Persistence Conjecture considers a larger class of reaction networks, the weakly reversible reaction networks.

3.2 Bounded solutions of the reaction rate equation for weakly reversible networks

If the persistence conjecture holds, then the global attractor conjecture will be proven too. Since every complex balanced reaction network is also weakly reversible and persistence of the network would mean that every concentration trajectory with positive initial condition does not reach the boundary $\partial\bar{V}^+$, we can conclude with the *Lyapunov theory* that the steady states are globally asymptotically stable.

In the next section we will see an attempt to prove the persistence conjecture.

3.2 Bounded solutions of the reaction rate equation for weakly reversible networks

This section is based on the paper of E. August and M. Barahona, [6]. They claim to have proven that every concentration trajectory in a weakly reversible reaction system with positive initial conditions is bounded from above and below. Thus, the persistence conjecture would be proven. Though we are not entirely convinced about the completeness of the proof, it presents an interesting approach to solving the persistence conjecture. We are going to elaborate the proof of the paper and point out where we suspect the imprecision.

In this section we are considering a weakly reversible reaction system endowed with mass-action kinetics. As for the sections before, let N be the number of species and n the number of complexes in the weakly reversible network. For $\{\mathcal{L}_1, \dots, \mathcal{L}_\ell\}$ the (terminal strong) linkage classes of the reaction system, we have:

$$\forall 1 \leq p, q \leq \ell, p \neq q : \mathcal{L}_p \cap \mathcal{L}_q = \emptyset \quad \text{and} \\ \forall y_i, y_j \in \mathcal{L}_p, y_i \rightarrow y_j \in \mathcal{R}, \exists y_{\tau(1)}, \dots, y_{\tau(k)} \in \mathcal{L}_p : y_j \rightarrow y_{\tau(1)} \rightarrow \dots \rightarrow y_{\tau(k)} \rightarrow y_i.$$

The main graphical tool of this argumentation is to break up the linkage classes into reaction cycles. Since we are considering weakly reversible networks all reactions of the network will appear in at least one reaction cycle.

Example Let us consider the following reaction network with $\mathcal{S} = \{S_1, \dots, S_7, S_8\}$:

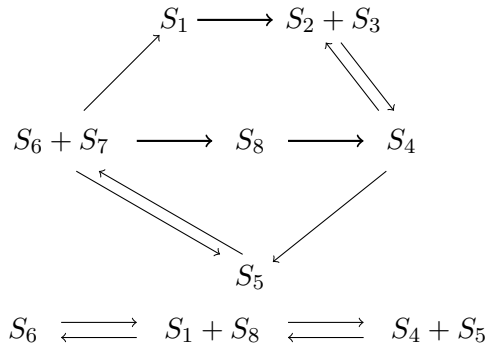


Figure 3: A weakly reversible reaction network

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In this reaction network the reaction cycles are

$$\begin{aligned}
\mathcal{R}_1 &= \{S_1 \rightarrow S_2 + S_3, S_2 + S_3 \rightarrow S_4, S_4 \rightarrow S_5, S_5 \rightarrow S_6 + S_7, S_6 + S_7 \rightarrow S_1\}, \\
\mathcal{R}_2 &= \{S_6 + S_7 \rightarrow S_8, S_8 \rightarrow S_4, S_4 \rightarrow S_5, S_5 \rightarrow S_6 + S_7\}, \\
\mathcal{R}_3 &= \{S_2 + S_3 \rightarrow S_4, S_4 \rightarrow S_2 + S_3\}, \\
\mathcal{R}_4 &= \{S_5 \rightarrow S_6 + S_7, S_6 + S_7 \rightarrow S_5\}, \\
\mathcal{R}_5 &= \{S_6 \rightarrow S_1 + S_8, S_1 + S_8 \rightarrow S_6\}, \\
\mathcal{R}_6 &= \{S_1 + S_8 \rightarrow S_4 + S_5, S_4 + S_5 \rightarrow S_1 + S_8\}, \\
\mathcal{R}_7 &= \{S_6 \rightarrow S_1 + S_8, S_1 + S_8 \rightarrow S_4 + S_5, S_4 + S_5 \rightarrow S_1 + S_8, S_1 + S_8 \rightarrow S_6\}.
\end{aligned}$$

As we can see, some reaction arrows can participate in more than one reaction cycle. We will denote the multiplicity of the reaction $y_j \rightarrow y_l$ in the union of the reaction cycles by β_{jl} . Let us denote the number of reaction cycles in the reaction system by C . So we can rewrite the corresponding differential equation (7) as a summation over these cycles:

$$\dot{c}(t) = \sum_{z=1}^C \sum_{y_j \rightarrow y_l \in \mathcal{R}_z} k_{j \rightarrow l} \frac{1}{\beta_{jl}} c(t)^{y_j} (y_l - y_j), \quad (28)$$

where \mathcal{R}_z denotes the z th reaction cycle of the system. If we consider one reaction cycle, we have: $\sum_{y_j \rightarrow y_l \in \mathcal{R}_z} (y_l - y_j) = 0$. For the stoichiometric coefficients this means that either for every elementary reaction the stoichiometric coefficients of species S_ν are equal, or there exists a complex y_M for which $y_{M\nu} \geq y_{j\nu}$ for all $1 \leq j \leq n$ and $y_{M\nu} > y_{i\nu}$ for some $1 \leq i \leq n$ and there exists a complex y_m for which $y_{m\nu} \leq y_{j\nu}$ for all $1 \leq j \leq n$ and $y_{m\nu} < y_{i\nu}$ for some $1 \leq i \leq n$. It also follows that

$$\sum_{z=1}^C \sum_{y_j \rightarrow y_l \in \mathcal{R}_z} (y_l - y_j) = 0.$$

Lemma 3.2.1. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a weakly reversible mass-action system. If $c_\nu(t_0) > 0$ and $c_{\min}, c_{\max} \in (0, \infty)$ are such that $0 < c_{\min} \leq c_i(t) \leq c_{\max} < \infty$, $\forall i \in \{1, \dots, N\}$, $i \neq \nu$, $\forall t \in [0, \infty)$, then*

$$0 < c_\nu(t) < \infty \text{ for all } t \in [0, \infty).$$

Proof. From the preceding we know that $\sum_{z=1}^C \sum_{\mathcal{R}_z} (y_{j\nu} - y_{i\nu}) = 0$ and therefore either (1) $y_{j\nu} = y_{i\nu}$ for every $y_i \rightarrow y_j \in \mathcal{R}_z$ and for all $1 \leq z \leq C$ or (2) there exists $M \in \{1, 2, \dots, n\}$ such that

- $y_{M\nu} \geq y_{j\nu}$ for all $1 \leq j \leq n$
- $y_{M\nu} > y_{i\nu}$ for some $1 \leq i \leq n$, $i \neq M$.

Case (1) is trivial so we will focus on case (2).

Assume that $c_\nu(t)$ is unbounded from above for $t \rightarrow \infty$. If $c_\nu(t) > \gamma_1 > 1$ for a constant $\gamma_1 \in (1, \infty)$ and for all $t > t'$ then it follows:

- $c_\nu(t)^{y_{M\nu}} \geq c_\nu(t)^{y_{j\nu}}$ for all $1 \leq j \leq n$

3.2 Bounded solutions of the reaction rate equation for weakly reversible networks

- $c_\nu(t)^{y_{M\nu}} > c_\nu(t)^{y_{i\nu}}$ for some $1 \leq i \leq n$, $i \neq M$.

Since $0 < c_{\min} \leq c_i(t) \leq c_{\max} < \infty$ for all $i \neq \nu$ and for all t , we have for any $j \in \{1, 2, \dots, n\}$:

$$0 < \prod_{\substack{i=1 \\ i \neq \nu}}^N (c_{\min})^{y_{ji}} \leq \prod_{\substack{i=1 \\ i \neq \nu}}^N c_i(t)^{y_{ji}} \leq \prod_{\substack{i=1 \\ i \neq \nu}}^N (c_{\max})^{y_{ji}} < \infty$$

Let us consider a reaction cycle \mathcal{R}_z and denote by \mathcal{C}_z the set of complexes participating in the reactions of the cycle. Within this cycle we have a complex $y_M \in \mathcal{C}_z$ for which $c_\nu(t)^{y_{M\nu}} \geq c_\nu(t)^{y_{j\nu}}$ for all complexes y_j in the cycle \mathcal{R}_z and $c_\nu(t)^{y_{M\nu}} > c_\nu(t)^{y_{i\nu}}$ for some complexes $y_i \neq y_M$ in the cycle \mathcal{R}_z . So there exists a constant $\gamma \in (1, \infty)$ such that if $c_\nu > \gamma$ it follows:

$$\begin{aligned} k_{M \rightarrow l} \frac{1}{\beta_{Ml}} \prod_{i=1}^N c_i(t)^{y_{Mi}} |y_{l\nu} - y_{M\nu}| &\geq k_{M \rightarrow l} \frac{1}{\beta_{Ml}} c_\nu(t)^{y_{M\nu}} \prod_{\substack{i=1 \\ i \neq \nu}}^N (c_{\min})^{y_{Mi}} |y_{l\nu} - y_{M\nu}| \\ &> \sum_{\substack{y_j \in \mathcal{C}_z \\ y_{j\nu} < y_{M\nu}}} k_{j \rightarrow k} \frac{1}{\beta_{jk}} c_\nu(t)^{y_{j\nu}} \prod_{\substack{i=1 \\ i \neq \nu}}^N (c_{\max})^{y_{ji}} |y_{k\nu} - y_{j\nu}| \\ &\geq \sum_{\substack{y_j \in \mathcal{C}_z \\ y_{j\nu} < y_{M\nu}}} k_{j \rightarrow k} \frac{1}{\beta_{jk}} \prod_{i=1}^N c_i(t)^{y_{ji}} |y_{k\nu} - y_{j\nu}|, \end{aligned}$$

where $y_M \rightarrow y_l$, $y_j \rightarrow y_k \in \mathcal{R}_z$. This holds too when summing over all reactions where the stoichiometric coefficient for species S_ν is maximal in the reactant complex:

$$\begin{aligned} \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} |y_{j'\nu} - y_{j\nu}| &\geq \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} c_\nu(t)^{y_{j\nu}} \prod_{\substack{r=1 \\ r \neq \nu}}^N (c_{\min})^{y_{jr}} |y_{j'\nu} - y_{j\nu}| \\ &> \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} < y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} c_\nu(t)^{y_{j\nu}} \prod_{\substack{r=1 \\ r \neq \nu}}^N (c_{\max})^{y_{jr}} |y_{j'\nu} - y_{j\nu}| \\ &\geq \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} < y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} |y_{j'\nu} - y_{j\nu}| \end{aligned} \quad (29)$$

For all $j \in \{1, \dots, n\}$ with $y_{j\nu} = y_{M\nu}$ we have for all reactions $y_j \rightarrow y_{j'} \in \mathcal{R}$ that $y_{j'\nu} - y_{j\nu} \leq 0$. So it follows that

$$\sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} |y_{j'\nu} - y_{j\nu}| = - \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} (y_{j'\nu} - y_{j\nu})$$

By subtracting the right hand side of this equation from both sides of the inequality (29),

3 Global Attractor Conjecture

we get:

$$\begin{aligned}
0 &> \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} (y_{j'\nu} - y_{j\nu}) + \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} < y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} |y_{j'\nu} - y_{j\nu}| \\
&\geq \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} = y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} (y_{j'\nu} - y_{j\nu}) + \sum_{\substack{y_j \rightarrow y_{j'} \in \mathcal{R}_z \\ y_{j\nu} < y_{M\nu}}} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} (y_{j'\nu} - y_{j\nu}) \\
&= \sum_{y_j \rightarrow y_{j'} \in \mathcal{R}_z} \frac{k_{j \rightarrow j'}}{\beta_{jj'}} \prod_{r=1}^N c_r(t)^{y_{jr}} (y_{j'\nu} - y_{j\nu})
\end{aligned}$$

For c_ν large enough, that is, there exists $\tilde{\gamma} \in (1, \infty)$ such that for $c_\nu > \tilde{\gamma}$, we have:

$$\dot{c}_\nu(t) = \sum_{z=1}^C \sum_{y_j \rightarrow y_l \in \mathcal{R}_z} k_{j \rightarrow l} \frac{1}{\beta_{jl}} \prod_{i=1}^N c_i(t)^{y_{ji}} (y_{l\nu} - y_{j\nu}) < 0 \quad (30)$$

Thus there exists a $t_1 > t'$ such that $c_\nu(t) < \tilde{\gamma}$ for $t > t_1$.

Let us see the implication when c_ν is not bounded away from zero for $t \rightarrow \infty$. As before we know that since the reaction system is weakly reversible that $\sum_{z=1}^C \sum_{\mathcal{R}_z} (y_{j\nu} - y_{i\nu}) = 0$. Therefore either $y_{j\nu} = y_{i\nu}$ for every $y_i \rightarrow y_j \in \mathcal{R}_z$ and for all $1 \leq z \leq C$ or there exists $m \in \{1, 2, \dots, n\}$ such that

- $y_{m\nu} \leq y_{j\nu}$ for all $1 \leq j \leq n$ and
- $y_{m\nu} < y_{i\nu}$ for some $1 \leq i \leq n$, $i \neq m$.

So we have $\sum_{\mathcal{R}_z} |y_{j\nu} - y_{m\nu}| \geq \sum_{\mathcal{R}_z} (y_{j\nu} - y_{m\nu}) > 0$. If $0 < c_\nu(t) < \gamma' < 1$ for $t > t'$, then

- $(c_\nu(t))^{y_{m\nu}} \geq (c_\nu(t))^{y_{j\nu}}$ for all $1 \leq j \leq n$
- $(c_\nu(t))^{y_{m\nu}} > (c_\nu(t))^{y_{i\nu}}$ for some $1 \leq i \leq n$, $i \neq m$.

Analogously to the above arguments, it then follows that for $c_\nu < 1$ small enough, that is, for some $\tilde{\gamma}' \in (0, 1)$, if $c_\nu \in (0, \gamma')$, then:

$$\dot{c}_\nu(t) = \sum_{z=1}^C \sum_{y_j \rightarrow y_l \in \mathcal{R}_z} k_{j \rightarrow l} \frac{1}{\beta_{jl}} \prod_{i=1}^N c_i(t)^{y_{ji}} (y_{l\nu} - y_{j\nu}) > 0 \quad (31)$$

So there exists a $t_2 > t'$ such that $c_\nu(t) > \tilde{\gamma}'$ for $t > t_2$.

This proves that $0 < \tilde{\gamma}' < c_\nu(t) < \tilde{\gamma} < \infty$ for $t \geq \max\{t_1, t_2\}$. \square

Remark The previous lemma even holds if for some species their concentrations are 0. Let there be a species S_d such that $c_d(0) = 0$ and $\dot{c}_d(t) = 0$ for every $t > 0$. If for every complex $y_j \in \mathcal{C}$ $y_{jd} \neq 0$, then $\prod_{i=1}^N c_i(t)^{y_{ji}} = 0$ for every $1 \leq j \leq n$. Generally we have for all $1 \leq j \leq n$: $\prod_{i=1}^N c_i(t)^{y_{ji}} y_{jd} = 0$, so we can reduce the reaction rate equation for the concentration c_d :

$$\dot{c}_d(t) = \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} \prod_{i=1}^N c_i(t)^{y_{ji}} (y_{ld} - y_{jd}) = \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} \prod_{i=1}^N c_i(t)^{y_{ji}} y_{ld}.$$

3.2 Bounded solutions of the reaction rate equation for weakly reversible networks

Since $\dot{c}_d = 0$, it follows $\prod_{i=1}^N c_i(t)^{y_{ji}} y_{ld} = 0$. This means that the species S_d is not created, so the reactions having as product complexes complexes with S_d contained in their support are inactive. This implies that the reactant complexes of these reactions are absent. Consequently, these reactant complexes are not created, which means that the reactions producing these complexes are inactive. In this manner, by following the reactions backwards through all reaction cycles containing species S_d , it follows that those reaction cycles are inactive. So the reaction rate equation can be reduced to a sum over those reaction cycles that do not contain species S_d . Let $C' < C$ be the number of reaction cycles that do not contain S_d and $\{\mathcal{R}_{\tau(1)}, \dots, \mathcal{R}_{\tau(C')}\}$ the set of reaction cycles not containing species S_d .

Let us assume that species S_ν participates in at least one of the remaining reaction cycles. Otherwise it follows $c_\nu(t_0) > 0$ and $\dot{c}_\nu(t) = 0, \forall t$, so that c_ν remains constant for all time t . So we can reduce the reaction rate equation for the concentration of S_ν to:

$$\dot{c}_\nu(t) = \sum_{z=1}^{C'} \sum_{y_j \rightarrow y_l \in \mathcal{R}_{\tau(z)}} k_{j \rightarrow l} \prod_{i=1}^N c_i(t)^{y_{ji}} (y_{l\nu} - y_{j\nu})$$

Thus, it follows from the previous lemma that if $c_d = 0, 0 < c_{\min} \leq c_j(t) \leq c_{\max} < \infty$ for all $j \neq \nu$ and $j \neq d, t > 0$, then c_ν is also bounded from above and below.

So far we agree with the reasoning. However we suspect an imprecision in the argumentation in the proof of the following step .

Part (III) of the proof of theorem 6 (August and Barahona [6]). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a weakly reversible mass-action system. If $c_\nu(t_0) > 0, c_\mu(t_0) > 0$ and $0 < c_j(t) \leq c_{\max} < \infty, \forall j \in \{1, \dots, n\}, j \neq \nu, j \neq \mu, \forall t \in [0, \infty)$, then $c_\nu(t)$ and $c_\mu(t)$ are also bounded from above and below for all $t \in [0, \infty)$.*

We will follow the proof by E. August and M. Barahona, [6], to the point where we suspect the imprecision. To support our assumption we will give a counterexample and we will propose additional conditions on the concentration trajectories c_ν, c_μ so that the conclusion will probably hold. However, with these additional conditions the initial statement of the lemma and subsequently the main statement, persistence of weakly reversible systems, is unproven.

Since the reaction system is weakly reversible, we have $\sum_{z=1}^C \sum_{\mathcal{R}_z} (y_l - y_j) = 0$. Especially,

$$\left(\sum_{z=1}^C \sum_{\mathcal{R}_z} (y_{l\nu} - y_{j\nu}) = 0 \text{ and } \sum_{z=1}^C \sum_{\mathcal{R}_z} (y_{l\mu} - y_{j\mu}) = 0 \right) \Rightarrow \sum_{z=1}^C \sum_{\mathcal{R}_z} (y_{l\nu} + y_{l\mu} - y_{j\nu} - y_{j\mu}) = 0.$$

So either $y_{l\nu} + y_{l\mu} - y_{j\nu} - y_{j\mu} = 0$ for every reaction in every reaction cycle, from which follows that $c_\nu(t) + c_\mu(t) = \gamma$ for all time $t, \gamma > 0$ a constant, or there exists a complex $y_H \in \mathcal{C}$ for which

- $y_{H\nu} + y_{H\mu} \geq y_{j\nu} + y_{j\mu}$ for all $1 \leq j \leq n$ and
- $y_{H\nu} + y_{H\mu} > y_{i\nu} + y_{i\mu}$ for some $1 \leq i \leq n, i \neq H$.

3 Global Attractor Conjecture

Assume that both c_ν, c_μ are unbounded from above. In August and Barahona [6] it is then implied that:

If $c_\nu(t)c_\mu(t) > \gamma > 1$ for all $t > t_1$, $\gamma \in (1, \infty)$ a constant, then we have:

- $c_\nu(t)^{y_{H\nu}}c_\mu(t)^{y_{H\mu}} \geq c_\nu(t)^{y_{j\nu}}c_\mu(t)^{y_{j\mu}}$ for all $1 \leq j \leq n$ and
- $c_\nu(t)^{y_{H\nu}}c_\mu(t)^{y_{H\mu}} > c_\nu(t)^{y_{i\nu}}c_\mu(t)^{y_{i\mu}}$ for some $1 \leq i \leq n$, $i \neq H$.

With the assistance of *Dr. Bence Mélykúti* we made the observation that these inequalities do not hold in general.

Counterexample Consider a weakly reversible reaction network, where $y_{H\nu} = 5$, $y_{H\mu} = 1$, $y_{j\nu} = 1$, $y_{j\mu} = 3$, then we have $y_{H\nu} + y_{H\mu} > y_{j\nu} + y_{j\mu}$.

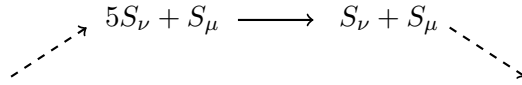


Figure 4: Part of an example of a weakly reversible reaction network holding the assumptions

Assume now that there exists $T > 0$ such that $c_\nu(T)^2 < c_\mu(T)$. It follows that there exists $\gamma \in (1, \infty)$ such that if $c_\mu(T) > \gamma$ then:

$$c_\nu(T)^5 c_\mu(T)^1 < c_\nu(T)^1 c_\mu(T)^3$$

This is in opposition to the statement above.

We can assume that for the boundedness of the concentration trajectories c_μ, c_ν , we need more insight about the relation between the two concentrations. We discern two distinct cases:

(C1) $\liminf_{t \rightarrow \infty} \frac{c_\nu(t)}{c_\mu(t)} > 0$ and $\limsup_{t \rightarrow \infty} \frac{c_\nu(t)}{c_\mu(t)} < \infty$

(C2) otherwise.

By adding property (C1) to the assumptions of the lemma we conjecture the lemma to hold.

Lemma 3.2.2 (Conjecture). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a weakly reversible mass-action system. If*

(1) $c_\nu(t_0) > 0, c_\mu(t_0) > 0,$

(2) $\lim_{t \rightarrow \infty} \frac{c_\nu(t)}{c_\mu(t)} = \delta, 0 < \delta < \infty$ and

(3) $0 < c_j(t) \leq c_{max} < \infty, \quad \forall j \in \{1, \dots, n\}, j \neq \nu, j \neq \mu, \forall t \in [0, \infty),$

then there exist $c_m, c_M \in (0, \infty)$ such that $c_m \leq c_\nu(t), c_\mu(t) \leq c_M$ for all $t \in [0, \infty)$.

As we did mention before, the main statement of the paper August and Barahona [6], Theorem 6, builds on the accuracy of the last step without the additional conditions on the concentration trajectories. Since there are additional conditions needed for the proof the theorem can not be proven on its initial conditions.

3.2 Bounded solutions of the reaction rate equation for weakly reversible networks

Theorem 6.[[6]] *For every weakly reversible reaction system, the concentration trajectories with strictly positive initial conditions are bounded from above and below and remain in their corresponding positive stoichiometric compatibility class.*

$$\forall i \in \{1, \dots, N\}, \forall t \in [0, \infty) : 0 < c_{\min} \leq c_i(t) \leq c_{\max} < \infty$$

The authors claim that the purported theorem can be proven by induction over $\nu \in \{1, \dots, N\}$. Since the details are missing about the induction it is difficult to verify this reasoning.

Even if we assume additionally that for every two distinct species $S_\nu, S_\mu \in \mathcal{S}$ there exists a $\delta_{\nu\mu} > 0$ and a $T > 0$ such that for all $t \geq T$ $c_\nu(t) = \delta_{\nu\mu} c_\mu(t)$, we cannot assume that the system is persistent.

4 Proven cases of the Global Attractor Conjecture

4.1 Single linkage class case

In 2011 *David F. Anderson* proved the global attractor conjecture in the single linkage class case. To do so, he proved that complex balanced mass-action systems with a single linkage class are persistent. In this section we are going to review the most important steps of this proof. For further details we refer to [3].

One of the tools of the proof of this special case is to project the dynamical system of the network onto a reduced network. The later use of this tool is to lay focus on those species which tend to extinction.

The *reduced reaction network* of $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ associated with $U \subseteq \{1, \dots, N\}$ is the reaction network $\{\mathcal{S}_U, \mathcal{C}_U, \mathcal{R}_U\}$ constructed in the following manner:

- (1) $\mathcal{S}_U := \{S_i \in \mathcal{S} \mid i \in U\}$.
- (2) $\mathcal{C}_U := \{y_j|_U \mid y \in \mathcal{C}\}$. The complex y_j is reduced to the complex $y_j|_U$. For the complex vector, this means $y_j|_U := \{y_{j1}, \dots, y_{jM}\} \in \mathbb{R}^M$.
- (3) $\mathcal{R}_U := \{y_j|_U \rightarrow y_k|_U \mid y_j \rightarrow y_k \in \mathcal{R}, y_j|_U \neq y_k|_U\}$.
- (4) If in the reduced network a linkage class contains only one complex, then this complex is deleted from \mathcal{C}_U . Hence, the linkage class is deleted too.

The first property of a typical chemical reaction network is that every species in \mathcal{S} has to participate in at least one of the complexes of the network. For the reduced network though it is possible that some species are *inactive*. That means, there may be a species $S_i \in \mathcal{S}_U$ such that for all $y_j \in \mathcal{C}_U$ we have $S_i \notin \text{supp } y_j$. If for example one species only participates in the complex that after reduction is the single element in a linkage class and, hence, this linkage class, respectively complex, gets deleted by property (4), then the species remains in the set \mathcal{S}_U , but is not a participant of the reduced network. Although we omit the first property of chemical reaction networks, the reduced reaction network follows all the other properties established on page 3.

- (2) there is no trivial reaction $y_j \rightarrow y_j \in \mathcal{R}_U$ for any $y_j \in \mathcal{C}_U$. This follows immediately from (3) of the definition of reduced reaction networks.
- (3) For any $y_j \in \mathcal{C}_U$ there exists a $y_l \in \mathcal{C}_U$ for which $y_j \rightarrow y_l \in \mathcal{R}_U$ or $y_l \rightarrow y_j \in \mathcal{R}_U$. By property (4) of reduced chemical networks this is guaranteed. Furthermore, if there exist $y_i \rightarrow y_j, y_j \rightarrow y_l \in \mathcal{R}$ for which $y_j|_U = y_l|_U$ then it follows by definition $y_i|_U \rightarrow y_l|_U \in \mathcal{R}_U$.

Now we need to provide the kinetics to the reduced network. For that, we project the dynamics of the original system on the elements of U . Let the original chemical reaction system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ be a mass-action system with the general differential equation

$$\dot{c}(t) = f(c(t)) = \sum_{y_j \rightarrow y_l \in \mathcal{R}} k_{j \rightarrow l} c(t)^{y_j} (y_l - y_j) \quad (32)$$

If we want to project this dynamical system onto a subset of the dependent variables, say $U = \{1, \dots, M\} \subset \{1, \dots, N\}$ with $U \neq \emptyset$, we include the concentrations $c_i(t)$ for

$M + 1 \leq i \leq N$ in the kinetics,

$$\hat{k}_{j \rightarrow l}(t) := \sum_{\substack{y_p \rightarrow y_q \in \mathcal{R} \\ y_j|_U = y_p|_U \text{ and } y_l|_U = y_q|_U}} k_{p \rightarrow q}(c(t)|_{U^c})^{y_p|_{U^c}}$$

where $U^c = N \setminus U = \{M + 1, \dots, N\}$ and $c(t)|_{U^c, i} = c_i(t)$ for all $i \in U^c$.

As by then we can consider the dynamical system in \mathbb{R}^M with state concentration vector $c|_U$ with $c|_{U, i}(t) = c_i(t)$ for all $1 \leq i \leq M$. In \mathbb{R}^M we then get differential equations of the form:

$$\dot{c}|_U(t) = \hat{f}(c|_U(t)) := \sum_{y_j \rightarrow y_l \in \mathcal{R}} \hat{k}_{j \rightarrow l}(t) \prod_{i=1}^M c|_{U, i}(t)^{y_j^i} (y_l - y_j)$$

We call this system of differential equations the *projected dynamics* of (32) with respect to U . Note that the original system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ is *autonomous*, which means that the kinetics are not dependent on the time parameter t . However, the kinetics in the reduced system $\{\mathcal{S}_U, \mathcal{C}_U, \mathcal{R}_U, \hat{k}(t)\}$ are functions of time, hence the reduced system is *nonautonomous*.

Note also that in the original and the reduced reaction system the differential equation for each species $S_i \in \mathcal{S}$ with $i \in U$ are the same and there has been made no change to the dynamics of the system.

Proposition 4.1.1. *The number of linkage classes of the reduced reaction network is less than or equal to the number of linkage classes of the original reaction network.*

Proof. By the property (3) of reduced chemical networks the number of reactions may only reduce and if two complexes y_i, y_j were in the same linkage class in the original network, then $y_i|_U, y_j|_U$ are in the same linkage class in the reduced network. With property (4) the number of linkage classes may only reduce. \square

Proposition 4.1.2. *If the original reaction network is weakly reversible, then the reduced reaction network is also weakly reversible.*

Proof. Let y_j, y_l be strongly linked in $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, then there exist $y_{\tau(1)}, \dots, y_{\tau(k)}$ such that $y_j \rightarrow y_{\tau(1)} \rightarrow \dots \rightarrow y_{\tau(k)} \rightarrow y_l$. If $y_{\tau(i)}|_U \neq y_{\tau(i+1)}|_U$ for every $1 \leq i \leq k - 1$ and $y_j|_U \neq y_{\tau(1)}|_U, y_l|_U \neq y_{\tau(k)}|_U$, then $y_j|_U \rightarrow y_{\tau(1)}|_U \rightarrow \dots \rightarrow y_{\tau(k)}|_U \rightarrow y_l|_U$. If there exists $1 \leq i \leq k - 1$ such that $y_{\tau(i)}|_U = y_{\tau(i+1)}|_U$, then it follows by definition that $y_{\tau(i-1)}|_U \rightarrow y_{\tau(i)}|_U \rightarrow y_{\tau(i+2)}|_U$. Hence, $y_j|_U \Rightarrow y_l|_U$. It then also follows that $y_j|_U \approx y_l|_U$. \square

The most important tool in proving the global attractor conjecture in the single linkage class case is partitioning vectors along sequences. The set of complex vectors is partitioned into subsets such that for a given concentration trajectory $c(\cdot)$ the subsets contain complexes y for which $c(t)^y$ grow similarly.

Let $\mathcal{C} \subset \bar{V}^+$ be the set of complex vectors in the species space for a chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$. Moreover let $c(t) \in V^+$ denote a strictly positive trajectory. \mathcal{C} is *partitioned along the sequence $c(t)$* if there exists a partition $\dot{\bigcup}_{i=1}^P T_i = \mathcal{C}$ such that $T_i \neq \emptyset$ and a constant $C > 1$, such that

(1) if $y_j, y_k \in T_i$ for some $i \in \{1, \dots, P\}$, then for all t

$$\frac{1}{C} c(t)^{y_j} \leq c(t)^{y_k} \leq C c(t)^{y_j};$$

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(2) if $y_k \in T_i$ and $y_j \in T_{i+m}$ for some $i \in \{1, \dots, P\}$ and some $m \in \{1, \dots, P - i\}$, then

$$\frac{c(t)^{y_k}}{c(t)^{y_j}} \rightarrow \infty \text{ as } t \rightarrow \infty.$$

We will call the subsets $T_i \subset \mathcal{C}$ *tiers*. Through this definition we get an ordering of the tiers: $T_1 \succ T_2 \succ \dots \succ T_P$, where T_1 contains the complexes for which $c(t)^y$ is increasing the fastest and T_P contains the complexes for which $c(t)^y$ is increasing the slowest.

Lemma 4.1.3. *Let $c(t)$ be a concentration trajectory in the positive orthant V^+ . Then there exists a subsequence $c(t_k)$ along which \mathcal{C} is partitioned.*

Proof. We are only going to sketch the proof of this lemma, for the more detailed proof we refer to [3].

Since there are $n! < \infty$ ways to order the complexes, there exists a reordering of the complex vectors such that the set of time steps t_k for which $c(t_k)^{y_1} \geq c(t_k)^{y_2} \geq \dots \geq c(t_k)^{y_n}$ holds is infinite. By this, we obtain the subsequence and an ordering of the complexes along this subsequence.

To partition the complexes into tiers we analyze the lower limit of the ratio $c(t_k)^{y_i}/c(t_k)^{y_{i+1}}$ for every $i \in \{1, \dots, n - 1\}$ starting with $i = 1$ as k tends to infinity. Whenever the lower limit of the ratio exists, the two complexes belong to the same tier and we can choose a subsequence of time such that $\lim_{t_n \rightarrow \infty} c(t_k)^{y_i}/c(t_k)^{y_{i+1}}$ exists. If the lower limit of the ratio tends to infinity, then we begin another tier and repeat the process of testing for existence of lower limits. In this manner we get the partition of the complexes into tiers.

Let P denote the number of tiers. For every $j \in \{1, \dots, P\}$ and every $y_i, y_{i+1} \in T_j$ we set $C_{j,i} = \lim_{k \rightarrow \infty} c(t_k)^{y_i}/c(t_k)^{y_{i+1}}$. So there exists $K > 1$ such that for every $k \geq K$ it holds $1 \leq c(t_k)^{y_i}/c(t_k)^{y_{i+1}} \leq C_{j,i} + 1$. For each tier we can then set a constant, $C_j = \prod_{\{i | y_i, y_{i+1} \in T_j\}} (C_{j,i} + 1)$ which the ratios of this tier cannot exceed. Taking the maximum of these constants, we get the requested constant C . \square

Let $\{T_i\}_{1 \leq i \leq P}$ denote a partition of \mathcal{C} and let $U \subset \{1, \dots, N\}$ be nonempty. We say that the vector $w \in \bar{V}^+$ is a *nonnegative conservation relation that respects the pair* $(U, \{T_i\}_{1 \leq i \leq P})$ if

(1) $\text{supp } w = U$ and

(2) whenever $y_j, y_l \in T_i$ for some $i \in \{1, \dots, P\}$, we have that $w \cdot (y_j - y_l) = 0$.

If $T_i = \{y_i\}$ for each $i \in \{1, \dots, P\}$ and $P = n$, then any vector w with $\text{supp } w = U$ is a nonnegative conservation relation that respects the pair $(U, \{y_i\})$.

If $P = 1$, which means $\mathcal{C} = T_1$, then the conservation relation describes the conservation of mass which we described in section 2.1.

To prove the next theorem, we are going to need the help of a theorem from linear algebra stated by E. Stiemke.

Lemma 4.1.4 (Stiemke [22]). *For $k = 1, \dots, n$, let $v_k \in \mathbb{R}^m$. Either*

- *there exists $\alpha \in \mathbb{R}^n$ such that for all $j = 1, \dots, m$*

$$\left(\sum_{k=1}^n \alpha_k v_k \right)_j \leq 0$$

and such that there exists at least one $j \in \{1, \dots, m\}$ for which $(\sum_{k=1}^n \alpha_k v_k)_j < 0$, or

- there exists a positive vector $w \in \mathbb{R}_{>0}^m$ such that $w \cdot v_k = 0$ for each $k \in \{1, \dots, n\}$.

Theorem 4.1.5 (Anderson [3]). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network and let $c(t) \in V^+$ denote a concentration trajectory with $c(t) \rightarrow z \in \partial\bar{V}^+$, as $t \rightarrow \infty$. Set $U = \{i \in \{1, \dots, N\} \mid z_i = 0\}$. If \mathcal{C} is partitioned along $c(t)$ with tiers T_i , for $i = 1, \dots, P$, and constant $C > 0$, then there is a nonnegative conservation relation $w \in \bar{V}^+$ that respects the pair $(U, \{T_i\})$.*

Proof. The method used for proving this theorem is proof by contradiction. So we assume that there exists no nonnegative conservation relation that respects the pair $(U, \{T_i\})$. Let us define

$$\mathcal{T}_i := \{y_j - y_l \mid y_j, y_l \in T_i\} \quad \text{and} \quad \mathcal{T}' := \bigcup_{i=1}^P \mathcal{T}_i$$

and let $\mathcal{T}_i|_U, \mathcal{T}|_U$ the respective projections on \mathbb{R}^m . Since we assumed that there exists no nonnegative conservation relation that respects $(U, \{T_i\})$, $\mathcal{T}|_U$ must contain at least one nonzero vector v_k . From the same assumption it follows with Lemma 4.1.4 that there exists $\alpha_k \in \mathbb{R}$ such that $(\sum_{v_k \in \mathcal{T}|_U} \alpha_k v_k)_j \leq 0$ for every $j \in \{1, \dots, m\}$ and that the inequality is strict for at least one j . Let

$$M : \bar{V}^+ \longrightarrow \mathbb{R} \\ x \longmapsto \prod_{u_k \in \mathcal{T}} (x^{u_k})^{\alpha_k/m_k}$$

where m_k denotes the number of vectors $u_k \in \mathcal{T}$ that reduce to the vector $v_k \in \mathcal{T}|_U$. By construction the complexes are partitioned such that there exists a sequence $c(t_k)$ constant $C > 0$ such that $1/C \leq c(t_k)^{u_k} = c(t_k)^{y_l} / c(t_k)^{y_j} \leq C$ for $u_k = y_l - y_j$. Therefore it follows that $M(c(t))$ is uniformly bounded from above and below. Since $c(t) \in V^+$ we have

$$\ln(M(c(t))) = \left(\sum_{u_k \in \mathcal{T}} \frac{\alpha_k}{m_k} u_k \right) \cdot \ln c(t).$$

Dividing the left hand of the equation up into summations over U and U^c , we have that the summation over U^c is bounded from above and below since $c_j(t)$ is bounded for all $j \in U^c$. However, the second summation $(\sum_{u_k \in \mathcal{T}|_U} \alpha_k v_k) \cdot \ln(c|_U(t))$ tends to $+\infty$ as $t \rightarrow \infty$ since $(\sum_{v_k \in \mathcal{T}|_U} \alpha_k v_k)_j < 0$ for at least one j and $c|_U(t) \rightarrow 0$. This is in contradiction with the boundedness of the left hand of the equation, $\ln(M(c(t)))$. By this contradiction then the proof of the theorem follows. \square

A nonautonomous mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ is said to have *bounded kinetics* if there exists a constant $\eta > 0$ such that $\eta < k_{i \rightarrow j}(t) < 1/\eta$ for every reaction $y_i \rightarrow y_j \in \mathcal{R}$ and for all $t \geq 0$.

Let $H : \bar{V}^+ \rightarrow [0, \infty)$ be the Lyapunov function defined in (22) and H_{c^*} the restriction of H to the positive stoichiometric compatibility class containing c^* . For this section c^* in the function H_{c^*} does not need to be a complex balanced steady state.

Lemma 4.1.6. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ be a weakly reversible, nonautonomous mass-action system with bounded kinetics. Suppose $c_0 \in V^+$ is chosen such that the concentration trajectory $c(t)$ with initial condition c_0 remains bounded and $\text{dist}(c(t), \partial\bar{V}^+) \rightarrow 0$ as $t \rightarrow \infty$. Then one or both of the following conditions holds:*

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- (1) $\forall c^* \in V^+, \exists T(c^*) > 0 \forall t > T(c^*) : H'_{c^*}(c(t)) = f(c(t)) \cdot (\ln c(t) - \ln c^*) < 0$.
- (2) $\exists (t_n) \subset [0, \infty), t_n \rightarrow \infty : c(t_n) \rightarrow z \in w(c(\cdot)) \cap \partial \bar{V}^+$ as $t_n \rightarrow \infty$ and
- (i) \mathcal{C} is partitioned along $c(t_n)$ with tiers $\{T_i\}_{i=1}^P$, and constant C , and
 - (ii) T_1 consists of a union of linkage classes

For the proof of this lemma we are referring to Anderson [3].

Lemma 4.1.7. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ be a nonautonomous mass-action system with bounded kinetics and with a single linkage class and let $c(t)$ be a bounded concentration trajectory with initial condition $c_0 \in V^+$. Moreover, let $d(c(t), \partial \bar{V}^+) \rightarrow 0$ as $t \rightarrow \infty$. Then, there exists no subsequence $(t_n) \rightarrow \infty$ such that \mathcal{C} is partitioned along $c(t_n)$ in which T_1 consists of a union of linkage classes.*

Proof. The system consists of only one linkage class, hence, for T_1 to consist of a union of linkage classes it must be the case $T_1 = \mathcal{C}$. As for the proof before we are going to assume the negated statement, that there exists such a sequence $t_n \rightarrow \infty$ so that \mathcal{C} is partitioned along $c(t_n)$ with $T_1 = \mathcal{C}$ and that this statement leads to a contradiction.

Since the concentration trajectory is bounded, there exists a subsequence $c(t_n)$ that has a limit point c . Since the trajectory tends to the boundary of V^+ we can define the nonempty set $U = U(c) = \{i \in \{1, \dots, N\} \mid c_i = 0\}$. \mathcal{C} is partitioned along this sequence as well and with theorem 4.1.5 there exists a nonnegative conservation relation $w \in \bar{V}^+$ that respects the pair (U, T_1) . Hence, $w = \text{supp } U \neq \emptyset$ and it follows $w \cdot c(t_n) \rightarrow 0$ for $n \rightarrow \infty$. On the other hand we have $w \cdot (y_l - y_j) = 0$ for all $y_j \rightarrow y_l \in \mathcal{R}$ since $T_1 = \mathcal{C}$, so with (32) it follows $w \cdot c(t) > 0$ is constant in time t . This contradicts $w \cdot c(t_n) \rightarrow 0$ for $n \rightarrow \infty$, so the lemma is proven. \square

Lemma 4.1.8. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ be a nonautonomous reaction system with bounded mass-action kinetics. Suppose $c_0 \in V^+$ such that for any $c^* \in (c_0 + \mathcal{S}) \cap V^+$ there exists a $T(c^*) > 0$ so that for every $t > T(c^*)$ we have $H'_{c^*}(c(t)) < 0$. Then the ω -limit set of $c(t)$ consists of a single element.*

Proof. Since we assumed that for any $c^* \in (c_0 + \mathcal{S}) \cap V^+$ there exists a $T(c^*) > 0$ so that for every $t > T(c^*)$ we have $H'_{c^*}(c(t)) < 0$, H_{c^*} is bounded. Hence, the trajectory remains bounded which implies that the ω -limit set is nonempty.

Furthermore, for any $c^* \in V^+$ there exists a $h_{c^*} \geq 0$ such that $H_{c^*}(c(t)) \rightarrow h_{c^*}$ as $t \rightarrow \infty$. Let us suppose there exist two distinct elements w_1, w_2 in the ω -limit set. It follows that for every $c^* \in V^+$ $H_{c^*}(w_1) = H_{c^*}(w_2) = h_{c^*}$. Choose arbitrary $c_1^*, c_2^* \in V^+$, then we have:

$$\begin{aligned} 0 &= H_{c_1^*}(w_1) - H_{c_1^*}(w_2) - (H_{c_2^*}(w_1) - H_{c_2^*}(w_2)) \\ &= (w_1 - w_2) \cdot (\ln c_2^* - \ln c_1^*), \end{aligned} \tag{33}$$

where (33) follows from the following computation: For $i \in \{1, \dots, N\}$ we have

$$\begin{aligned} &(w_{1,i}(\ln(w_{1,i}) - \ln(c_{1,i}^*) - 1) + c_{1,i}^*) - (w_{2,i}(\ln(w_{2,i}) - \ln(c_{1,i}^*) - 1) + c_{1,i}^*) \\ &- (w_{1,i}(\ln(w_{1,i}) - \ln(c_{2,i}^*) - 1) + c_{2,i}^*) + (w_{2,i}(\ln(w_{2,i}) - \ln(c_{2,i}^*) - 1) + c_{2,i}^*) \\ &= w_{1,i}(\ln(c_{2,i}^*) - \ln(c_{1,i}^*)) - w_{2,i}(\ln(c_{2,i}^*) - \ln(c_{1,i}^*)). \end{aligned}$$

Since we chose $c_1^*, c_2^* \in V^+$ arbitrarily, it must follow from (33) that $w_1 = w_2$. Hence, there exists only a single point in the ω -limit set. \square

Theorem 4.1.9 (Anderson 3). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ be a complex balanced mass-action system with a single linkage class and $c(t)$ a concentration trajectory with initial concentration $c_0 \in V$ then $w(c(\cdot)) \cap \partial\bar{V}^+ = \emptyset$. Hence, the concentration trajectory is persistent.*

Proof. Let us assume there exists an initial concentration c_0 to a trajectory $c(t)$ such that $w(c(\cdot)) \cap \partial\bar{V}^+ \neq \emptyset$ and define $U := \{i \in \{1, \dots, N\} \mid c_i = 0 \text{ for some } c \in w(c(\cdot))\}$. U is the set of indices for the species whose concentrations tend to zero for some subsequence of the considered concentration trajectory. Additionally we know from section 2.2 that complex balanced mass-action systems imply bounded concentration trajectories. So we have for each $i \in U$:

$$\liminf_{t \rightarrow \infty} c_i(t) = 0 \quad \text{and} \quad \limsup_{t \rightarrow \infty} c_i(t) < \infty.$$

On the other hand, we have for each $j \in U^c$:

$$0 < \liminf_{t \rightarrow \infty} c_j(t) \leq \limsup_{t \rightarrow \infty} c_j(t) < \infty. \quad (34)$$

Let $\{\mathcal{S}_U, \mathcal{C}_U, \mathcal{R}_U, \hat{k}(t)\}$ denote the reduced reaction system of $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ defined at the beginning of this section. Because of (34) and the definition of $\hat{k}(t)$ we know that there exists an $\eta > 0$ such that $\eta < \hat{k}_{i \rightarrow j}(t) < 1/\eta$ for all $t \geq 0$ and all reactions $y_i \rightarrow y_j \in \mathcal{R}_U$. This means, the reduced reaction system has bounded mass-action kinetics.

By proposition 4.1.1 and proposition 4.1.2 the reduced reaction network is weakly reversible and contains only one linkage class.

Without loss of generality let us assume $|\mathcal{S}_U| = N$ and set $\bar{c}(t)$ the concentration trajectory to the reduced system. Because of the definition of the set U the set of ω -limit points of $\bar{c}(t)$ must intersect with $\partial\mathbb{R}_{\geq 0}^N$. Proposition 4.1.1 and lemmas 4.1.6, 4.1.7, 4.1.8 imply then that the ω -limit set of the reduced system must consist of a single point. Hence, this must be the point $0 \in \partial\mathbb{R}_{\geq 0}^N$. Since otherwise there exists an $i \in U$ such that $\liminf_{t \rightarrow \infty} c_i(t) > 0$, which is a contradiction to the definition of U . However it also follows by the three lemmas 4.1.6, 4.1.7, 4.1.8 that for t large enough $H'_{c^*}(\bar{c}(t)) < 0$ for some $c^* \in V^+$, so 0 is a local maximum of the Lyapunov function. Hence, $\bar{c}(t) \not\rightarrow 0$. It follows that $w(c(\cdot)) \cap \partial\bar{V}^+ = \emptyset$. \square

This theorem also holds for a weakly reversible mass-action system with a single linkage class, for which the concentration trajectories follow the conditions:

- the concentration trajectories are bounded, and
- the ω -limit set of the concentration trajectories is either completely contained in the boundary of the positive orthant or completely contained in the interior of the positive orthant.

Note that not the persistence but the global attractor conjecture has been proven since a complex balanced steady state was assumed.

We remark that to prove the persistence conjecture in the single linkage class case, we would have to prove that for every weakly reversible mass-action system the ω -limit set is completely contained in either the boundary or the interior of the positive orthant V^+ , [3].

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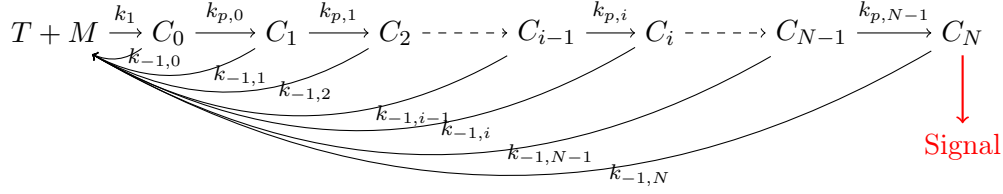


Figure 5: Model for kinetic proofreading in T-cell receptor signal transduction

Example McKeithan model

In 1995 *T.W. McKeithan* proposed a model for kinetic proofreading for T-cell receptor signal transduction, [19]. The aim was that it should describe a possible mechanism explaining the selectivity of T-cell interactions. In this model depicted in figure 5, the process of kinetic proofreading can be described as follows: After binding the ligand peptide-major histocompatibility complex, short peptide-MHC, the T-cell receptor complex undergoes a number of modification, including tyrosine phosphorylation steps before transmitting a signal. The assumption is that recognition signals are determined by the concentrations of the final complex C_N and that this chain of modification is the reason for both increased sensitivity and selectivity of response.

Let T be the T-cell receptors not bound to a ligand and M the peptide-MHC complexes not bound to a receptor. When a peptide-MHC complex binds to a receptor this gives the basic form of the occupied receptor C_0 . This basic form can be modified, for example by tyrosine phosphorylations, at up to N sites. These successive modifications like tyrosine phosphorylations are leading from the initial complex C_0 to the final complex C_N and the corresponding rate constants are denoted by $k_{p,i}$. However, there are also dissociation reactions, where the peptide-MHC complex detaches from the receptor and the receptor is simultaneously completely dephosphorylated. Whether or not a signal is transmitted depends on the reaction rate constants, which are specific for the binding ligands. For nonspecific complexes (self-antigens) the rate of dissociation is sufficiently high that dissociation most always occurs before the nonspecific complex can be activated and generate signals. With this feature the receptor is able to discriminate between a foreign antigen and self-antigens with only moderately lower affinity.

The corresponding system of differential equations are described as follows:

$$\begin{aligned} \dot{c}_T(t) &= -k_1 c_T(t) c_M(t) + \sum_{i=0}^N k_{-1,i} c_{C_i}(t) \\ \dot{c}_M(t) &= \dot{c}_T(t) \\ \dot{c}_{C_0}(t) &= k_1 c_T(t) c_M(t) - (k_{-1,0} + k_{p,0}) c_{C_0}(t) \\ &\vdots \\ \dot{c}_{C_i}(t) &= k_{p,i-1} c_{C_{i-1}}(t) - (k_{-1,i} + k_{p,i}) c_{C_i}(t) \\ &\vdots \\ \dot{c}_{C_N}(t) &= k_{p,N-1} c_{C_{N-1}}(t) - k_{-1,N} c_{C_N}(t) \end{aligned}$$

The total concentrations of T-cell receptors T^* and peptide-MHC complexes M^* (both bound and free) are conserved quantities and can be used to eliminate the variables c_T

4.2 Chemical reaction networks with 2 or 3 species

and c_M from the system if desired.

$$T^* = c_T(t) + \sum_{i=0}^N c_{C_i}(t), \quad M^* = c_M(t) + \sum_{i=0}^N c_{C_i}(t) \quad \text{for all } t > 0.$$

This gives the system for the variables C_i :

$$\begin{aligned} \dot{c}_{C_0}(t) &= k_1 \left(T^* - \sum_{i=0}^N c_{C_i}(t) \right) \left(M^*(t) - \sum_{i=0}^N c_{C_i}(t) \right) - (k_{-1,0} + k_{p,0}) c_{C_0}(t) \\ &\vdots \\ \dot{c}_{C_i}(t) &= k_{p,i-1} c_{C_{i-1}}(t) - (k_{-1,i} + k_{p,i}) c_{C_i}(t) \\ &\vdots \\ \dot{c}_{C_N}(t) &= k_{p,N-1} c_{C_{N-1}}(t) - k_{-1,N} c_{C_N}(t) \end{aligned} \quad (35)$$

E. Sontag was the first to apply the results of chemical reaction network theory to this model, in [21]. Evidently, the model consists of a single linkage class. Furthermore, the deficiency of the model is zero since the number of complexes is $N + 2$ and the dimension of the stoichiometric subspace is $N + 1$ as we can depict from the reduced reaction system (35). Hence, with the deficiency zero theorem we can conclude that the reaction system is complex balanced for every choice of rate constants. The proven global attractor conjecture in the single linkage class case then implies that there is exactly one steady state concentration in each stoichiometric compatibility class and that it is globally asymptotically stable. Especially, there is exactly one steady state concentration for the final complex in each stoichiometric compatibility class. The steady state concentrations depend solemnly on the rate constants and, in particular, on the constants T^* and M^* . This conclusion rules out periodic orbits and chaotic behavior and shows the “determinism” of the process described by T. W. McKeithan.

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A chemical reaction network is called *permanent* if there exists a compact set $\mathcal{P} \subset V^+$ such that every concentration trajectory of the network with positive initial concentration ends up in \mathcal{P} . In other words, if a reaction network is persistent and the concentration trajectories are *uniformly bounded*, that is, there exists a constant $\epsilon > 0$ such that

$$\epsilon < \liminf_{t \rightarrow \infty} c_i(t) \leq \limsup_{t \rightarrow \infty} c_i(t) < 1/\epsilon \quad \text{for all } i \in \{1, \dots, N\},$$

then the reaction network is permanent. So it is clear that from permanence persistence of a reaction system immediately follows. Also, if we can prove that a complex balanced reaction system is permanent, then by the uniqueness of the positive complex balanced steady states in each positive stoichiometric compatibility class it follows the global asymptotic stability of these steady states. Hence, the global attractor conjecture holds.

G. Craciun, F. Nazarov and C. Pantea, [9], were the first to prove permanence of a general class of chemical reaction systems, precisely they proved that *any two-species endotactic κ -variable mass-action system is permanent*. An earlier result by D. Anderson and A. Shiu proved the global attractor conjecture for two-species mass-action systems, [1]. In fact,

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they showed the global attractor conjecture to be true for systems for which the associated positive stoichiometric compatibility classes are two-dimensional, which include the systems with only two species. The main step of that proof is the demonstration that for each co-dimension one face of a stoichiometric compatibility class there must exist a reaction that pushes the concentration trajectory away from that face and that the corresponding reaction rates dominates all others at this point. By face of a stoichiometric compatibility class we mean the topological definition of a face of a polyhedron. In [2] and [8] it already has been proven that vertices of a positive stoichiometric compatibility class cannot be ω -limit points of concentration trajectories with positive initial concentration even if these points are steady states. With this idea of proof, that the boundary is somewhat “repelling” to the concentration trajectories, G. Craciun, F. Nazarov and C. Pantea were able to extend their result to a proof of the global attractor conjecture for three-species mass-action systems, [9].

For the greater part of this section we will consider a two-species reaction network, therefore we have $\mathcal{S} = \{S_1, S_2\}$ and $V = \mathbb{R}^2$. Moreover, we will consider a larger class of reaction systems than the common mass-action systems. The systems under consideration are κ -variable mass-action systems, which means that system is nonautonomous, but it has bounded kinetics. That is, the kinetics is a function $\kappa : (0, \infty) \rightarrow (\eta, 1/\eta)^{\mathcal{R}}$ for some $0 < \eta < 1$, which is piecewise differentiable. The differential equation to the system can then be described as:

$$\dot{c}(t) = \sum_{y_i \rightarrow y_j \in \mathcal{R}} \kappa_{i \rightarrow j}(t) c(t)^{y_i} (y_j - y_i). \quad (36)$$

In addition we will consider endotactic networks, which are a larger class of networks than weakly reversible networks. In order to define endotactic networks, we first have to set some definitions. Let \mathcal{C}_r denote the set of lattice points corresponding to reactant complexes, that is $\mathcal{C}_r(\mathcal{R}) = \{(y_{i1}, y_{i2}) \in \bar{V}^+ \mid \exists y_j \in \mathcal{C} : y_i \rightarrow y_j \in \mathcal{R}\}$.

Consider the plane V and let \mathcal{A} be a set of points and v a vector in the plane. We denote by $\mathcal{O}_v(\mathcal{A})_{\geq 0}$ the minimal closed half-plane which contains \mathcal{A} and the positive direction of v and is bounded by a line perpendicular to v , which we will denote by $\partial\mathcal{O}_v(\mathcal{A})_{\geq 0}$. If $\mathcal{A} = \emptyset$ then $\partial\mathcal{O}_v(\mathcal{A})_{\geq 0} = \emptyset$.

Let $\mathcal{R}^v = \mathcal{R} \setminus \{y_i \rightarrow y_j \mid (y_j - y_i) \cdot v = 0\}$, then we define the v -essential support of a reaction network to be

$$esupp^v(\mathcal{R}) = \partial\mathcal{O}_v(\mathcal{C}_r(\mathcal{R}^v))_{\geq 0}. \quad (37)$$

If $\mathcal{R}^v = \emptyset$, which means that every reaction vector is orthogonal to v , then $esupp^v(\mathcal{R}) = \emptyset$. We will also set:

$$\begin{aligned} esupp^v(\mathcal{R})_- &= \{(y_{j1}, y_{j2}) \in V \mid (y_j - y_i) \cdot v < 0 \text{ for all } y_i \in esupp^v(\mathcal{R})\} \\ esupp^v(\mathcal{R})_+ &= \{(y_{j1}, y_{j2}) \in V \mid (y_j - y_i) \cdot v > 0 \text{ for all } y_i \in esupp^v(\mathcal{R})\}. \end{aligned}$$

A chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is called *endotactic* if for any vector $v \neq 0$ with $\mathcal{R}^v \neq \emptyset$ we have

$$\{y_i \rightarrow y_j \mid y_i \in esupp^v(\mathcal{R}) \text{ and } y_j \in esupp^v(\mathcal{R})_-\} = \emptyset. \quad (38)$$

More visually, we say a chemical reaction network is endotactic if it passes the “parallel sweep test” for any nonzero vector v . This test is made as follows. Sweep the plane V with

a line L , which is orthogonal to v in the positive direction of v and stop when L meets a reactant complex participating in a reaction, whose arrow is not parallel to the line L . If no reaction arrow with reactant complex on the stopped line L points to the swept region, we say the reaction network passed the parallel sweep test for the vector v . Note that for $\mathcal{R}^v = \emptyset$ the line L sweeps the complete plane and never stops. In this case the network also passes the ‘‘parallel sweep test’’ for the vector v . If the network passes the test for every vector v then the network is called endotactic.

For any set of points \mathcal{A} let $\text{conv}(\mathcal{A})$ denote the convex hull of \mathcal{A} . We also set G to be the set of inward normal vectors to the sides of $\text{conv}(\mathcal{C}_r(\mathcal{R}))$. If $\text{conv}(\mathcal{C}_r(\mathcal{R}))$ is a line segment, then both normal vectors are considered as inward. We denote by $\{\pm(1, 0), \pm(0, 1)\}$ the standard base of the cartesian plane V .

Proposition 4.2.1. *A two-species chemical reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is endotactic if and only if (38) holds for any vector $v \in G \cup \{\pm(1, 0), \pm(0, 1)\}$.*

Proof. We only have to prove that if (38) holds for every vector $v \in G \cup \{\pm(1, 0), \pm(0, 1)\}$ then it also holds for every other vector as well. Let therefore w be any unit vector with $w \notin G \cup \{\pm(1, 0), \pm(0, 1)\}$ and let $[y_{\sigma(1)}, \dots, y_{\sigma(k)}], \sigma(k) \leq n$ denote the polygon $\partial \text{conv}(\mathcal{C}_r(\mathcal{R}))$. Let us assume $\{y_{\sigma(j)}\} = \text{esupp}^w(\mathcal{R})$.

First we consider the case where $\text{conv}(\mathcal{C}_r(\mathcal{R}))$ is not contained in a line. We set v_{j-1}, v_j the inward normal unit vectors to $[y_{\sigma(j-1)}y_{\sigma(j)}]$ and $[y_{\sigma(j)}y_{\sigma(j+1)}]$ respectively. Then $y_{\sigma(j)}$ is either contained in exactly one or both of the sets $\text{esupp}^{v_{j-1}}(\mathcal{R}), \text{esupp}^{v_j}(\mathcal{R})$.

- (1) $y_{\sigma(j)} \in \text{esupp}^{v_{j-1}}(\mathcal{R}) \cap \text{esupp}^{v_j}(\mathcal{R})$: Applying (38) to v_{j-1} and v_j implies that the product complex $y_p \in \mathcal{C}$ of any reaction $y_{\sigma(j)} \rightarrow y_p \in \mathcal{R}$ must reside in the closed positive cone generated by $\overrightarrow{y_{\sigma(j)}y_{\sigma(j-1)}}$ and $\overrightarrow{y_{\sigma(j)}y_{\sigma(j+1)}}$. Therefore it follows that $y_p \in \text{esupp}^w(\mathcal{R})_+$ since the generated cone is contained in $\text{esupp}^w(\mathcal{R})_+$.
- (2) $y_{\sigma(j)}$ belongs to only one of the sets, let us assume $y_{\sigma(j)} \in \text{esupp}^{v_{j-1}}(\mathcal{R}) \setminus \text{esupp}^{v_j}(\mathcal{R})$. Every reaction $y_{\sigma(j)} \rightarrow y_p$ are along the line $y_{\sigma(j-1)}y_{\sigma(j)}$ and in direction of $\overrightarrow{y_{\sigma(j)}y_{\sigma(j-1)}}$, this follows by applying (38) to v_j . So we have $y_p \in \text{esupp}^w(\mathcal{R})$.

Let us now assume that $\text{conv}(\mathcal{C}_r(\mathcal{R}))$ is a line segment, set $\text{conv}(\mathcal{C}_r(\mathcal{R})) = [y_{\sigma(1)}y_{\sigma(2)}]$. If we apply (38) to both normal vectors, then we get that all product complexes lie on the line $y_{\sigma(1)}y_{\sigma(2)}$. By applying (38) to the basis vectors $\{\pm(1, 0), \pm(0, 1)\}$, then we have that all product complexes have to be contained in the segment $[y_{\sigma(1)}y_{\sigma(2)}]$.

Consequently (38) holds for every vector. □

Proposition 4.2.2. *Every weakly reversible two-species reaction network is endotactic.*

Proof. Since in a weakly reversible reaction network every complex is a reactant complex, we have $\mathcal{C}_r(\mathcal{R}) = \mathcal{C}$. It follows immediately from the definition that for every vector $v \in V$ all reactions originating in $\text{esupp}^v(\mathcal{R})$ have their product complexes in $\text{esupp}^v(\mathcal{R})_+$. □

In order to prove permanence, it is essential to be able to construct a compact subset of the positive orthant such that the concentration trajectory stays inside this subset for any positive initial concentration. We will have to prove that this compact subset is forward invariant for the concentration trajectories. For this we use Nagumo’s theorem and its application of the *Bouligand tangent cone*. This tool to prove forward invariance will also be used in the Petri net case, which follows afterwards.

For a set $\mathcal{S} \subset \mathbb{R}^N$ we denote

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- $\text{int}\{\mathcal{S}\}$ the interior of the set,
- $\partial\mathcal{S}$ the boundary of \mathcal{S} .

We will say that the set $\mathcal{S} \subset V$ is *forward invariant* for a system $\dot{c}(t) = f(c(t))$ if for every initial condition $c(0) \in \mathcal{S}$ the concentration trajectory $c(t) \in \mathcal{S}$ for $t > 0$.

If $\mathcal{S} \subset V$ is a compact set and $x \in V$ then we define the Bouligand tangent cone as

$$TC_{\mathcal{S}}(x) = \{z \in V \mid \exists k_n \in \mathcal{S}, k_n \rightarrow x \text{ and } \lambda_n \searrow 0 \text{ as } n \rightarrow \infty : \frac{1}{\lambda_n}(k_n - x) \rightarrow z\}. \quad (39)$$

It should be clear that

$$\begin{aligned} x \in \text{int}\{\mathcal{S}\} &\Rightarrow TC_{\mathcal{S}}(x) = \mathbb{R}^N \\ x \notin \mathcal{S} &\Rightarrow TC_{\mathcal{S}}(x) = \emptyset. \end{aligned}$$

This makes clear that the Bouligand tangent cone is only non-trivial for $x \in \partial\mathcal{S}$. Geometrically the Bouligand tangent cone for $x \in \partial\mathcal{S}$ is a cone having center in the origin and which contains all the vectors, like \dot{x} , whose directions point from x inside or are tangent to the set \mathcal{S} .

Theorem 4.2.3 (Nagumo's theorem, Aubin and Cellina [5], Blanchini [7]). *Consider the system $\dot{c}(t) = f(c(t))$ and for initial conditions in a set \mathcal{H} , the system admits a unique trajectory. Moreover, let $\mathcal{S} \subseteq \mathcal{H}$ be a closed convex set. Then, \mathcal{S} is positively invariant for the system if and only if*

$$f(c) \in TC_{\mathcal{S}}(c) \text{ for all } c \in \mathcal{S}. \quad (40)$$

We are not going to prove this theorem, because it would exceed the subject of this thesis. However, the interested reader can look it up in Aubin and Cellina [5].

Property (40) is often referred to as *sub-tangentiality condition* and is only non-trivial for $c \in \partial\mathcal{S}$ since for $c \in \text{int}\{\mathcal{S}\}$ $TC_{\mathcal{S}}$ represents the whole space \mathbb{R}^N . Thus, condition (40) can be replaced by

$$f(c) \in TC_{\mathcal{S}}(c) \text{ for all } c \in \partial\mathcal{S}. \quad (41)$$

In geometric terms, the theorem states that if $c \in \partial\mathcal{S}$ \dot{c} "points inside or is tangent to \mathcal{S} " then the trajectory $c(t)$ remains in \mathcal{S} .

In fact the theorem holds for more general classes of sets which are not necessarily convex. Conversely, the requirement of the uniqueness of the trajectory is fundamental.

An equivalent characterization can be given in terms of the first order normal cone, or simply normal cone which is the polar cone to the Bouligand tangent cone,

$$\mathcal{N}_{\mathcal{S}}(x) = \{p \in V \mid p \cdot (y - x) \leq 0 \text{ for all } y \in \mathcal{S}\}. \quad (42)$$

We can reformulate Nagumo's theorem as follows

Corollary 4.2.4. *\mathcal{S} is forward invariant for the system $\dot{c}(t) = f(c(t))$ if and only if $f(c(t)) \cdot (-n) \geq 0$ for all $n \in \mathcal{N}_{\mathcal{S}}(c(t))$ and all $c(t) \in \partial\mathcal{S}$.*

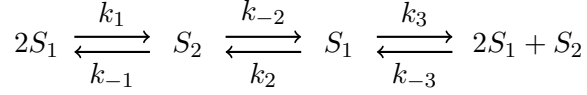


Figure 6: Graph of an example of a reversible reaction network

Construction of a forward invariant polygon The construction of the polygon is based on comparing reactant monomials up to a constant. For $(y_{i1}, y_{i2}) \in \mathcal{C}_r(\mathcal{R})$ we say $c_1(t)^{y_{i1}} c_2(t)^{y_{i2}}$ is the reactant monomial. Since the theoretic construction of this polygon is hard to follow graphically, we start by demonstrating the setup by use of a simple example. Consider a κ -variable reversible reaction network as depicted in figure 6 with $k_i(t) \in (\eta, 1/\eta)$ for all $i \in \{-3, -2, \dots, 3\}$ and all $t \geq 0$.

From the graph of the reaction network we can easily deduce the corresponding differential equation:

$$\begin{aligned} \begin{pmatrix} \dot{c}_1(t) \\ \dot{c}_2(t) \end{pmatrix} &= (k_1(t)c_1(t)^2 - k_{-1}(t)c_2(t)) \begin{pmatrix} -2 \\ 1 \end{pmatrix} + (k_2(t)c_1(t) - k_{-2}(t)c_2(t)) \begin{pmatrix} -1 \\ 1 \end{pmatrix} \\ &+ (k_3(t)c_1(t) - k_{-3}(t)c_1(t)^2 c_2(t)) \begin{pmatrix} 1 \\ 1 \end{pmatrix}. \end{aligned} \quad (43)$$

The aim is now to construct a polygon \mathcal{P} such that if at any time $T \geq 0$ where $c(T) \in \mathcal{P}$ then $\dot{c}(T)$ points inside \mathcal{P} . To do so we want every component of $\dot{c}(T)$ corresponding to a reaction in the network, to point inside the polygon.

Let us analyze the first component of our example (43) $(k_1(t)c_1(t)^2 - k_{-1}(t)c_2(t)) \begin{pmatrix} -2 \\ 1 \end{pmatrix}$, which corresponds to the first reversible reaction $2S_1 \rightleftharpoons S_2$ in Figure 6. This reaction drives the concentration trajectory along $\begin{pmatrix} -2 \\ 1 \end{pmatrix}$ with a rate $(k_1(t)c_1(t)^2 - k_{-1}(t)c_2(t))$. Depending on which side of the curve $c_2 = (k_1(t)/k_{-1}(t))c_1^2$ the concentration trajectory is residing at a time $t > 0$ the trajectory will follow the vector $\begin{pmatrix} -2 \\ 1 \end{pmatrix}$ or $\begin{pmatrix} 2 \\ -1 \end{pmatrix}$. Since $k_1(t)/k_{-1}(t) \in (\eta^2, 1/\eta^2)$ the component of $\dot{c}(t)$ corresponding to this first reaction is in direction $\begin{pmatrix} 2 \\ -1 \end{pmatrix}$ for $c(t) \in \{(c_1, c_2) \in V^+ | c_2 > (1/\eta^2)c_1^2\}$ and in direction $\begin{pmatrix} -2 \\ 1 \end{pmatrix}$ for $c(t) \in \{(c_1, c_2) \in V^+ | c_2 < \eta^2 c_1^2\}$, which is illustrated in point (a) of figure 7 where $\delta = \eta^2$. In the region between the two curves $\Lambda := \{(c_1, c_2) \in V^+ | (1/\delta^2)c_1^2 < c_2 < \delta^2 c_1^2\}$ the concentration trajectory corresponding to the first reaction can follow both directions, hence, $\Lambda \cap \mathcal{P}$ must be parallel to $\begin{pmatrix} -2 \\ 1 \end{pmatrix}$, so that $\dot{c}(t)$ points inside the polygon. Point (b) and (c) of figure 7 illustrate $\dot{c}(t)$ for the two other components of the complete reaction network. We then combine the conditions for the three components of $\dot{c}(t)$ to obtain a forward invariant polygon depicted in point (d) of figure 7.

The polygon needs to be close enough to the axes and large enough to contain $c(0)$ in the interior and to allow for cuts in regions where $c_2 = \delta c_1^m$, $c_2 = (1/\delta)c_1^m$, for $m \in \{1, 2\}$ are ordered with respect to m . In our example we need in the corner of $(0, 0)$ that the edges of the polygon are in a region where $\delta c_1^2 < (1/\delta)c_1^2 < \delta c_1 < (1/\delta)c_1$ and at the opposite corner of the polygon we need $\delta c_1 < (1/\delta)c_1 < \delta c_1^2 < (1/\delta)c_1^2$. We require this arrangement so that the edges do not intersect with more than one Λ -region and additionally it is necessary for the convexity of the polygon.

We now are going to describe the theoretical construction of the polygon. Our aim is to show that at time T with $c(T) \in \mathcal{P}$ there is a complex that is reactant to a reaction that dictates the direction of $\dot{c}(T)$ inside the polygon \mathcal{P} (up to a small enough perturbation)

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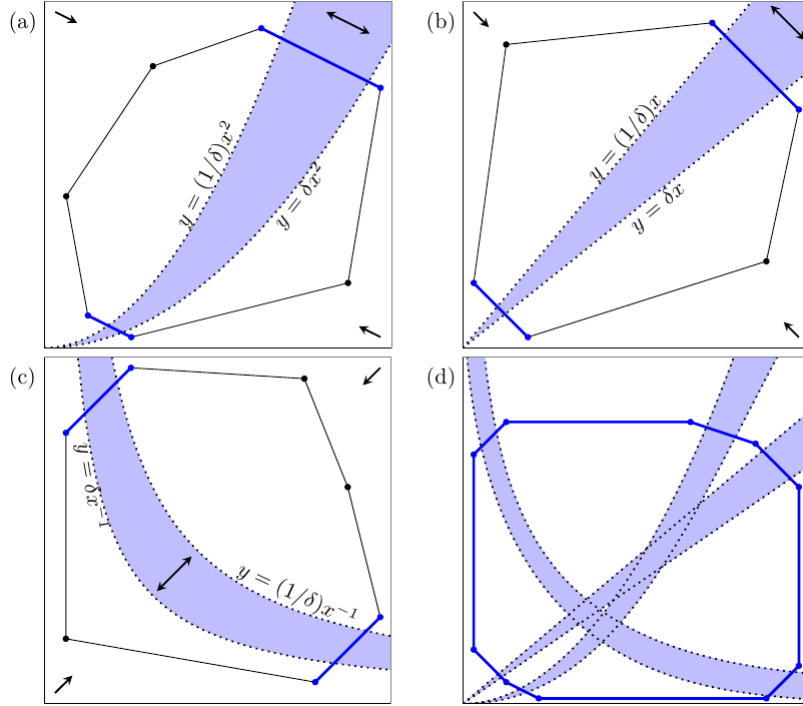


Figure 7: Setup of the invariant polygon \mathcal{P} for an example of a reversible reaction network. Picture taken from [9]

and whose reactant monomial therefore has to be larger than the monomials corresponding to all other reactant complexes. So we need to compare monomials $c(t)^{y_i}$ and $c(t)^{y_j}$ for all pairwise combinations of reactant complexes y_i and y_j . We set:

$$\{r_1, \dots, r_e, s_1, \dots, s_f\} := \left\{ \frac{y_{i1} - y_{j1}}{y_{j2} - y_{i2}} \mid y_i, y_j \in \mathcal{C}_r, y_{i1} \neq y_{j1}, y_{i2} \neq y_{j2} \right\}$$

with $s_1 < \dots < s_f < 0 < r_1 < \dots < r_e$. Then $(1, r_1), \dots, (1, r_e)$ and $(1, s_1), \dots, (1, s_f)$ represent normal vectors of edges in the complete graph with vertices $\mathcal{C}_r(\mathcal{R})$.

Fix $0 < \delta < 1$. The pairwise comparison of reactant complexes y_i and y_j up to a constant leads to $c(t)^{y_i} - \delta c(t)^{y_j} = 0$ and $c(t)^{y_i} - (1/\delta)c(t)^{y_j} = 0$, or $c_2(t) = \delta^{1/(y_{i2}-y_{j2})}c_1(t)^m$ and $c_2(t) = (1/\delta)^{1/(y_{i2}-y_{j2})}c_1(t)^m$, where $m \in \{r_1, \dots, r_e, s_1, \dots, s_f\}$. We set

$$\delta' = \min\{\delta^{1/(y_{j2}-y_{i2})} \mid (y_{i1}, y_{i2}), (y_{j1}, y_{j2}) \in \mathcal{C}_r(\mathcal{R}), y_{i2} \neq y_{j2}\}.$$

Moreover let $r_{i+.5}$ and $s_{j+.5}$ for all $i \in \{1, \dots, e\}$, $j \in \{1, \dots, f\}$ be such that $r_{i-.5} < r_i < r_{i+.5}$ and $s_{j-.5} < s_j < s_{j+.5}$.

Let $0 < \xi < 1$ be small enough and $M > 1$ be large enough so that they have the following properties:

(P1) $c(0) \in (\xi, M)^2$;

(P2) all intersections of the curves

- $c_2 = \delta' c_1^{r_i}$, $c_2 = (1/\delta') c_1^{r_i}$ for $i \in \{1, \dots, e\}$,

4.2 Chemical reaction networks with 2 or 3 species

- $c_2 = \delta' c_1^{s_j}$, $c_2 = (1/\delta') c_1^{s_j}$ for $j \in \{1, \dots, f\}$,
- $c_2 = c_1^{r_i+0.5}$ for $i \in \{1, \dots, e\}$ and
- $c_2 = c_1^{s_j+0.5}$ for $j \in \{1, \dots, f\}$

lie in the square $(\xi, M)^2$;

(P3) $(0, \xi)^2$ and $(M, \infty)^2$ lie below, respectively above all negative-exponent (s_j or $s_{j+0.5}$) curves mentioned in the previous point. On the other hand, $(0, \xi) \times (M, \infty)$ and $(M, \infty) \times (0, \xi)$ lie above, respectively below all positive-exponent curves (r_i or $r_{i+0.5}$) mentioned before;

(P4) All negative-exponent curves intersect the line segments $(0, \xi) \times \{M\}$ and $\{M\} \times (0, \xi)$;

(P5)

$$\begin{aligned} \xi &< \min\{\delta^{1/(y_{j2}-y_{i2})} | (y_{i1}, y_{i2}), (y_{j1}, y_{j2}) \in \mathcal{C}_r(\mathcal{R}), y_{j2} \neq y_{i2}\}, \\ \xi &< \min\{\delta^{1/(y_{j1}-y_{i1})} | (y_{i1}, y_{i2}), (y_{j1}, y_{j2}) \in \mathcal{C}_r(\mathcal{R}), y_{j1} \neq y_{i1}\}, \\ M &> \max\{(1/\delta)^{1/(y_{j2}-y_{i2})} | (y_{i1}, y_{i2}), (y_{j1}, y_{j2}) \in \mathcal{C}_r(\mathcal{R}), y_{j2} \neq y_{i2}\}, \\ M &> \max\{(1/\delta)^{1/(y_{j1}-y_{i1})} | (y_{i1}, y_{i2}), (y_{j1}, y_{j2}) \in \mathcal{C}_r(\mathcal{R}), y_{j1} \neq y_{i1}\}. \end{aligned}$$

We want to construct a polygon $\mathcal{P} = A_1 \dots A_{e+1} B_1 \dots B_{f+1} C_1 \dots C_{e+1} D_1 \dots D_{f+1}$ such that the curves $c_2 = \delta' c_1^m$ and $c_2 = (1/\delta') c_1^m$ for $m \in \{r_1, \dots, r_e, s_1, \dots, s_f\}$ intersect the two sides of \mathcal{P} that are orthogonal to the vector $(1, m)$ for $m \in \{r_1, \dots, r_e, s_1, \dots, s_f\}$ and only these two sides. This will be assured by the properties (P1)-(P5). We construct \mathcal{P} one vertex at the time. For $\alpha > 0$ we begin with $A_1 = (\alpha, \alpha^{s_1})$ and go on counterclockwise. So, every vertex will lie on a curve $c_2 = c_1^{r_i+0.5}$ or $c_2 = c_1^{s_j+0.5}$ and the sides $A_i A_{i+1}$, $C_i C_{i+1}$ are orthogonal to $(1, r_i)$ whereas the sides $B_j B_{j+1}$, $D_j D_{j+1}$ are orthogonal to $(1, s_j)$. In addition, we want the sides $A_{e+1} B_1$, $C_{e+1} D_1$ to be horizontal and $B_{f+1} C_1$ to be vertical. The polygon constructed this way is unique.

Note that $\mathcal{P}(\alpha)$ varies continuously with α and $\text{conv}(\mathcal{P}(\alpha))$ is decreasing in $\alpha \in (0, \alpha_0)$ and $\bigcup_{\alpha=0}^{\alpha_0} \text{conv}(\mathcal{P}(\alpha)) = V^+$.

Lemma 4.2.5. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ a κ -variable mass-action system with $\kappa : (0, \infty) \rightarrow (\eta, 1/\eta)^{\mathcal{R}}$. Furthermore let $y_0 \rightarrow y_p \in \mathcal{R}$ and let v be a vector such that $(y_p - y_0) \cdot v > 0$. Also let $\mathcal{U} \subseteq \mathcal{C}_r(\mathcal{R}) \setminus \{y_0\}$. There exists a constant δ such that if for some $t_0 \geq 0$ we have $c(t_0) \in V^+$ and $c(t_0)^{y_i} < \delta c(t_0)^{y_0}$ for all $y_i \in \mathcal{U}$ then*

$$\left(\kappa_{0 \rightarrow p}(t_0) (y_p - y_0) c(t_0)^{y_0} + \sum_{\substack{y_i \rightarrow y_j \in \mathcal{R} \\ y_i \in \mathcal{U}}} \kappa_{i \rightarrow j}(t_0) (y_j - y_i) c(t_0)^{y_i} \right) \cdot v > 0.$$

Proof. By setting

$$\delta = \frac{\eta^2 (y_p - y_0) \cdot v}{\|v\| \sum_{y_i \rightarrow y_j, y_i \in \mathcal{U}} \|y_j - y_i\|}$$

we get the desired result. □

Theorem 4.2.6 (Craciun et al. 9). *A κ -variable endotactic chemical mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}(t)\}$ with $\mathcal{S} = \{S_1, S_2\}$ is persistent.*

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We are not going to prove the theorem in detail, but we are going to outline the important steps.

Proof. Let $n \in G \cup \{\pm(1, 0), \pm(0, 1)\}$ be a inward normal vector of $\text{conv}(\mathcal{C}_r(\mathcal{R}))$. We denote $y_n \rightarrow y_{n'}$ a fixed reaction such that $y_n \in \text{esupp}^n(\mathcal{R})$ and $y_{n'} \in \text{esupp}^n(\mathcal{R})_+$, which is ensured since the network is endotactic. Furthermore we denote by δ_n the constant corresponding to the reaction $y_n \rightarrow y_{n'}$ defined in lemma 4.2.5, where we set $\mathcal{U} = \mathcal{C}_r(\mathcal{R}) \cap \text{esupp}^n(\mathcal{R})_+$. Then, we set $\delta = \min\{\delta_n | n \in G \cup \{\pm(1, 0), \pm(0, 1)\}\} < 1$. With this constant we are able to construct the convex polygon as described above $\mathcal{P}(\alpha_0) = A_1 \dots A_{e+1} B_1 \dots B_{f+1} C_1 \dots C_{e+1} D_1 \dots D_{f+1}$ which we will denote by \mathcal{P} for simplicity. If we can prove that the polygon is forward invariant for the dynamics (36), so that every concentration trajectory $c(t)$ with $c(0) \in \text{conv}(\mathcal{P})$, then the reaction system is proven persistent.

Since by construction $c(0) \in \text{conv}(\mathcal{P})$ we have to prove $c(t) \in \text{conv}(\mathcal{P})$ for $t > 0$. By using corollary 4.2.4, this amounts to proving that if $c(T) \in \mathcal{P}$ for some $T > 0$, then $\dot{c}(T) \cdot n \geq 0$, where $-n$ is a generator of the normal cone $\mathcal{N}_{\mathcal{P}}(c(T))$ defined in (42). Hence, we have to prove

$$\left(\sum_{y_i \rightarrow y_j \in \mathcal{R}_n} \kappa_{i \rightarrow j}(T)(y_j - y_i)c(T)^{y_i} \right) \cdot n \geq 0 \text{ whenever } c(T) \in \mathcal{P}. \quad (44)$$

If $\mathcal{R}_n = \emptyset$, then the inequality holds. If otherwise, let $y_n \rightarrow y_{n'} \in \mathcal{R}^n$ and $y_n \in \text{esupp}^n(\mathcal{R})$. We separate the summation by isolating the term over $y_n \rightarrow y_{n'}$ and by separating the sums over the reactions where the reactant complex lies in $\text{esupp}^n(\mathcal{R})$ and those where the reactant complex does not lie in this set. For $y_i \rightarrow y_j \in \mathcal{R}_n$ and $y_i \in \text{esupp}^n(\mathcal{R})$ we have $(y_j - y_i) \cdot n \geq 0$ and for the fixed reaction $y_n \rightarrow y_{n'}$ the inequality is strict. It follows, that we only have to prove that

$$\left(\kappa_{n \rightarrow n'}(T)(y_{n'} - y_n)c(T)^{y_n} + \sum_{\substack{y_i \rightarrow y_j \in \mathcal{R}_n \\ y_i \notin \text{esupp}^n(\mathcal{R})}} \kappa_{i \rightarrow j}(T)(y_j - y_i)c(T)^{y_i} \right) \cdot n \geq 0.$$

This follows from lemma 4.2.5 if we set $\mathcal{U} = \mathcal{C}_r(\mathcal{R}) \cap \text{esupp}^n(\mathcal{R})_+$ and if we can prove that $\delta c(T)^{y_n} > c(T)^{y_i}$ for all $y_i \in \mathcal{U}$. This is done by a proof by cases, where the cases are the sides where $c(t)$ may reside on. Through the properties of the constructed convex polygon this can easily be deduced. □

Remark

- (1) Since we have proven that the constructed polygon is forward invariant, we can also imply that every two-species κ -variable endotactic chemical mass-action system has bounded trajectories. Especially conjecture 4 holds for this special case of reaction networks, since every weakly reversible reaction network is also endotactic (Proposition 4.2.2)
- (2) Not only does this theorem prove the persistence conjecture for two-species reaction networks, but it also implies the validity of the global attractor conjecture in this special case of reaction networks. As we have seen in section 3.1 do complex balanced mass-action systems already imply bounded concentration trajectories and more importantly

uniqueness of the positive steady state in each positive stoichiometric compatibility class and, hence, the missing element to a proof of the global attractor conjecture is the persistence of these reaction systems.

Theorem 4.2.7 (Craciun et al. 9). *Any two-species endotactic κ -variable mass-action system is permanent.*

Proof. Let $\alpha_0 > 0$ and $\epsilon > 0$ small, then we construct the polygon $\mathcal{P}(\alpha_0 + \epsilon)$. Recall that by definition we have $\text{conv}(\mathcal{P}(\alpha)) \supset \text{conv}(\mathcal{P}(\alpha'))$ for $\alpha < \alpha' < \alpha_0 + \epsilon$. Our goal is to prove that any concentration trajectory with positive initial concentration $c(0) > 0$ eventually ends up inside the polygon $\mathcal{P}(\alpha_0)$, which means permanence of the system.

Since the union of all polygons constructed upon $0 < \alpha < \alpha_0 + \epsilon$ is a covering of V^+ , there exists $\alpha_1 \in (0, \alpha_0)$ such that $c(0) \in \bigcup_{\alpha \in [\alpha_1, \alpha_0 + \epsilon]} \text{conv}(\mathcal{P}(\alpha))$. We define a function Φ by

$$\begin{aligned} \Phi : \bigcup_{\alpha \in [\alpha_1, \alpha_0 + \epsilon]} \mathcal{P}(\alpha) &\rightarrow [\alpha_1, \alpha_0 + \epsilon] \\ (c_1, c_2) &\mapsto \alpha \text{ if } (c_1, c_2) \in \mathcal{P}(\alpha) \end{aligned}$$

Then the proof will be complete if we can show that $\Phi(c(t)) \geq \alpha_0$ for $t \geq T$ and some $T > 0$.

Let us assume the contrary, that is $\Phi(c(t)) \in [\alpha_1, \alpha_0]$ for all $t > 0$ since $\Phi^{-1}[\alpha_0, \infty) = \text{conv}(\mathcal{P}(\alpha_0))$ and $\Phi^{-1}[\alpha_1, \infty) = \text{conv}(\mathcal{P}(\alpha_1))$ are forward invariant for the system. We can easily see that Φ is differentiable on its domain except at the vertices of a polygon, that is on the curves $c_2 = c_1^p$ where $p \in \{r_{.5}, \dots, r_{e+.5}, s_{.5}, \dots, s_{f+.5}\}$. Let $\bar{c} \in V^+$ be such a point on one of the curves and Φ_1, Φ_2 the smooth curves that represent Φ on either side of this curve in a neighborhood of \bar{c} . To complete the proof, we are going to use some notations and theory of variational analysis by Rockafellar and Wets [20]. A subgradient of a map $f : \mathbb{R}^n \rightarrow \mathbb{R}$ at a point \bar{x} is a vector $v \in \mathbb{R}^n$ if there exists a sequence $x_\mu \rightarrow \bar{x}$, $f(x_\mu) \rightarrow f(\bar{x})$ and a sequence $v_\mu \rightarrow v$ with

$$f(x) \geq f(\bar{x}) + v_\mu \cdot (x - \bar{x}) + o(|x - \bar{x}|) \text{ for } x \in \mathbb{R}^n.$$

We then will write $v \in \partial f(\bar{x})$. With Φ_1 and Φ_2 the subgradient of Φ at \bar{c} can be written as

$$\partial\Phi(\bar{c}) = \{a\nabla\Phi_1(\bar{c}) + (1-a)\nabla\Phi_2(\bar{c}) \mid a \in [0, 1]\}. \quad (45)$$

So Φ is *strictly continuous* at \bar{c} , which means that

$$\limsup_{\substack{c, c' \rightarrow \bar{c} \\ c \neq c'}} \frac{|\Phi(c') - \Phi(c)|}{|c' - c|} < \infty.$$

For single-valued mappings, strict continuity is equivalent to the better known local Lipschitz continuity. Even for points \bar{c} not residing on a curve of the form $c_2 = c_1^p$, the subgradient (45) holds, since for these points $\nabla\Phi(\bar{c}) = \nabla\Phi_1(\bar{c}) = \nabla\Phi_2(\bar{c})$. Also, the composition $\Phi \circ c(t)$ is strictly continuous since the concentration trajectory is a smooth function. By the theorem 10.48 in Rockafellar and Wets [20], an extension of the mean-value theorem, there exists a $\tau_t \in [0, t]$ for all $t > 0$ such that $\Phi(c(t)) - \Phi(c(0)) = s_t t$ for some scalar $s_t \in \partial(\Phi \circ c)(\tau_t)$. By the chain rule for subgradients (Theorem 10.6, Rockafellar and Wets [20]), which connects the subgradient of $\Phi \circ c$ to that of Φ , we have

$$\partial(\Phi \circ c)(t) \subseteq \{v \cdot \dot{c}(t) \mid v \in \partial\Phi(c(t))\}.$$

4 Proven cases of the Global Attractor Conjecture

We can modify lemma 4.2.5 so that for any compact set in V^+ there exists a constant $\zeta > 0$ such that $\nabla\Phi_1(c(t)) \cdot \dot{c}(t) > \zeta$ and $\nabla\Phi_2(c(t)) \cdot \dot{c}(t) > \zeta$ for $c(t)$ in this compact set. It then follows with both formulations of the subgradients $\partial\Phi$ and $\partial(\Phi \circ c)$ that $\inf_t \partial(\Phi \circ c)(t) > \zeta$. From the extension of the mean-value theorem we get $\Phi(c(t)) > \Phi(0) + \zeta t$ for all $t > 0$. This is in contradiction to $\Phi(c(t)) \in [\alpha_1, \alpha_0]$ for all $t \geq 0$. Hence, $\Phi(c(t)) > \alpha_0$ for large enough $t > 0$, which implies that the system is permanent. \square

Theorem 4.2.8 (Craciun et al. [9], Global Attractor Conjecture for three-species networks). *A complex balanced three-species mass-action system $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ has one and only one globally attractive steady state in each stoichiometric compatibility class.*

Proof. We are going to prove the global attractor conjecture in the three-species mass-action system case by proving that there does not exist any ω -limit points on the boundary of the positive orthant $\bar{V}^+ = \mathbb{R}_{\geq 0}^3$. At the end of chapter 2 we deduced that the Lyapunov function implies that concentration trajectories are bounded for complex balanced systems. Furthermore, the concentration trajectories do not pass the neighborhood of the origin. Let $c(t) = (c_1(t), c_2(t), c_3(t))$, then there exists $\epsilon > 0$ such that

$$c_1(t) + c_2(t) + c_3(t) > 3\epsilon \text{ and } c_1(t) < 1/\epsilon, c_2(t) < 1/\epsilon, c_3(t) < 1/\epsilon \text{ for all } t \geq 0.$$

We will construct a compact set $K \subset V^+$ and prove that every trajectory with positive initial concentration, once it has entered K , does not leave K for all time t . For a complex $y_i \in \mathcal{C}$ we set $\pi_{12}(y_i) = (y_{i1}, y_{i2}, 0)$, where π_{12} denotes the projection onto the coordinate plane $v_1 v_2$. So we have

$$\begin{bmatrix} \dot{c}_1(t) \\ \dot{c}_2(t) \end{bmatrix} = \sum_{y_i \rightarrow y_j \in \mathcal{R}} k_{i \rightarrow j} c_3(t)^{y_{i3}} (c_1(t), c_2(t))^{\pi_{12}(y_i)} \pi_{12}(y_j - y_i).$$

In the last section (4.1) we already used this method of projecting the dynamics on a subset of variables and embedded the dynamics of the remaining variables into the kinetics. Let $k_{min} = \min\{k, 1/k \mid k \text{ is a rate constant of some reaction in } \mathcal{R}\}$ and let $s_{max} = \max\{y_{ij} \mid y_i \in \mathcal{C}, S_j \in \mathcal{S}\}$, we set $\eta = k_{min} \epsilon^{s_{max}} < 1$. So we get the following κ -variable mass action system:

$$\begin{bmatrix} \dot{c}_1(t) \\ \dot{c}_2(t) \end{bmatrix} = \sum_{y_i \rightarrow y_j \in \pi_{12}(\mathcal{R})} \kappa_{i \rightarrow j}(t) (c_1(t), c_2(t))^{y_i} (y_j - y_i), \quad (46)$$

where $\kappa(t) \in (\eta, 1/\eta)$ for all $t \geq 0$. As we saw in the last section in proposition 4.1.2 (only there we called it a reduced reaction network), the projection of a weakly reversible network is also weakly reversible. In particular the projection of an endotactic network is also endotactic. Similar to the previous proof, we construct the convex polygon for the projected system. Although we are going to make a slight difference to the original setup. For the previous construction we set the vertices of \mathcal{P} on the curves $c_2 = c_1^{r_{i+.5}}$ and $c_2 = c_1^{s_{j+.5}}$, $i \in \{0, \dots, e\}$, $j \in \{0, \dots, f\}$, which is not necessary for the polygon to be invariant for the system. For the polygon of the projected system, which we will denote by \mathcal{P}_{12} , we want the edge $A_1 D_{f+1}$ to be parallel to the c_2 -axis and to maintain the same distance to this axis as $A_{e+1} B_1$ to the c_1 -axis. Let us set $d > 0$ to denote this distance. We assume furthermore that $[\epsilon, 1/\epsilon]^2$ lies within $[\xi, M]^2$. We construct the polygons for the other projected systems the same way and denote them by \mathcal{P}_{23} and \mathcal{P}_{31} . We set

$$\mathcal{K} = \{(c_1, c_2, c_3) \in [0, 1/\epsilon]^3 \mid (c_1, c_2) \in \text{conv}(\mathcal{P}_{12}), (c_2, c_3) \in \text{conv}(\mathcal{P}_{23}), (c_3, c_1) \in \text{conv}(\mathcal{P}_{31})\}.$$

Evidently this set is compact in V^+ and includes $c(0)$. If we can prove that the concentration trajectory does not leave \mathcal{K} , then the theorem is proven. Suppose at a time T the concentration trajectory reaches the boundary of \mathcal{K} . Using corollary 4.2.4 we only need to prove $n \cdot \dot{c}(T) \geq 0$ for $-n \in \mathcal{N}_{\mathcal{K}}(c(T))$ a generator of the normal cone of \mathcal{K} at $c(T)$.

Let \mathcal{L}_{12} denote the polygonal line $D_{f+1}A_1 \dots A_{e+1}B_1$ of the polygon \mathcal{P}_{12} and $\mathcal{L}_{23}, \mathcal{L}_{31}$ the similar polygonal lines of \mathcal{P}_{23} , respectively \mathcal{P}_{31} . Since $c(t) \in (0, 1/\epsilon)^3$ for all $t > 0$ it follows that

$$c(T) \in [0, 1/\eta]^3 \cap ((\mathcal{L}_{12} \times (0, \infty)) \cup (\mathcal{L}_{23} \times (0, \infty)) \cup (\mathcal{L}_{31} \times (0, \infty))). \quad (47)$$

From $c_1(T) + c_2(T) + c_3(T) > 3\epsilon$ it follows that at least one component of $c(T)$ is larger than ϵ . Let this component be $c_3(T)$, then it follows from (47) that $c(T) \in \mathcal{P}_{12} \times (0, \infty)$ and therefore the third component of n must be zero. So, we have

$$\begin{aligned} n \cdot \dot{c}(T) &\geq 0 \\ \iff \pi_{12}(n) \cdot \left(\sum_{y_i \rightarrow y_j \in \mathcal{R}} k_{i \rightarrow j} c_3(T)^{y_{i3}} (c_1(T), c_2(T))^{\pi_{12}(y_i)} (\pi_{12}(y_j) - \pi_{12}(y_i)) \right) &\geq 0, \end{aligned}$$

where $-\pi_{12}(n)$ is a generator of the normal cone of \mathcal{P}_{12} at $(c_1(T), c_2(T))$. Since we have chosen η such that $k_{i \rightarrow j} c_3(T)^{y_{i3}} \in (\eta, 1/\eta)$ the last inequality holds by earlier argumentation. \square

Example: Thomas mechanism We are going to apply this last result to a substrate-inhibition model, specifically on the *Thomas mechanism*. In all organisms, from bacteria to mammals (except humans), uric acid and oxygen react in the presence of the enzyme uricase to form allantoin and carbonic acid gas. Uricase is harvested from pigs' livers and serves in the clinical diagnostics as an indicator for elevated uric acid concentration in humans, which is the case for the gout disease.

Substrate-inhibition is a type of feedback control. Essentially feedback is when the product of one step in a reaction sequence has an effect on other reaction steps in the sequence. The effect is generally nonlinear and in this case it inhibits reactions. Substrate-inhibition is the inhibition of an enzyme activity by a substrate of the reaction catalyzed by that same enzyme; often, this type of inhibition occurs at elevated substrate levels in which the substrate is binding to a second, non-active site on the enzyme.

Since an enzyme is a biological catalyst it is not consumed during the reaction, hence the concentration of the free enzyme plus the concentration of the combined enzyme is a conservation relation. So there is no change in the total concentration. Moreover the differential equation for the resulting product is uncoupled from the others.

Through experimental research, Thomas D. proposes the following system of differential equations for oxygen, denoted by v and uric acid u in the reaction network described above:

$$\begin{aligned} \frac{du}{dt} &= a - u - T(u, v)uv, \\ \frac{dv}{dt} &= \alpha(b - v) - T(u, v)uv, \end{aligned}$$

where $T(u, v) = \rho(1 + u + Ku^2)^{-1}$ describes the substrate inhibition and a, b, α, ρ are positive constants. Note that, T is continuous and does not vanish on a compact $K \supset [0, a] \times [0, b]$. Hence, for $t \geq t_0$ and for some $\eta > 0$ we have $\eta < T(u(t), v(t)) < 1/\eta$.

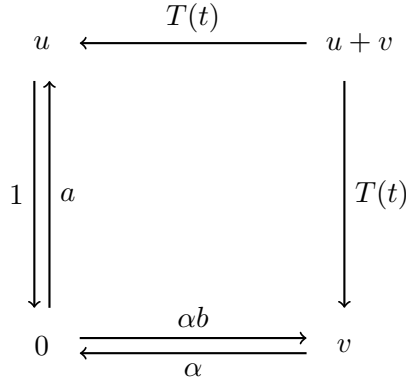


Figure 8: Thomas model

As we can clearly see in Figure 8 the reaction network of the Thomas model is endotactic. So Theorem 4.2.7 implies that the system is permanent. Hence, for this model the reaction system is persistent.

4.3 Persistence in Petri nets

With the concepts and tools of *Petri net theory* D. Angeli, P. De Leenheer and E. D. Sontag provided checkable necessary and sufficient conditions for persistence in chemical reaction networks, [4]. Modeling of reaction networks using Petri net formalism is often used with biochemical applications, in particular in the context of metabolic pathways.

A *species-reaction Petri net*, or SR-net for short, is a graphical description of a chemical reaction network. It consists of two types of nodes, species and reactions, and of weighted edges represented as a quadruple (V_S, V_R, E, W) . The set V_S of nodes represents the different species in the reaction network and the set V_R of nodes represents the reactions of the network under consideration. Let $y_j \rightarrow y_{j'} \in \mathcal{R}$ be a reaction in the reaction network. We will associate to the reaction $y_j \rightarrow y_{j'}$ the node $R_{jj'} \in V_R$. For every species $S_i \in V_S$ contained in the support of the reactant complex y_j , $S_i \in \text{supp } y_j$, we draw a directed edge from species S_i to $R_{jj'}$ and for every species $S_l \in V_S$ contained in the support of the product complex $y_{j'}$, $S_l \in \text{supp } y_{j'}$, we draw a directed edge from $R_{jj'}$ to the species S_l . E represents the set of edges in the SR-net, so we have $(S_i, R_{jj'}), (R_{jj'}, S_l) \in E$. Note that there are no edges drawn between two species or two reaction nodes. W represents a function $W : E \rightarrow \mathbb{N}$, which associates to each edge the stoichiometric coefficient that the respective species takes in the complex of the reaction:

$$W(S_i, R_{jj'}) = y_{ji} \qquad W(R_{jj'}, S_l) = y_{j'l}.$$

Let us define $\tilde{Y} \in \mathbb{Z}^{N \times r}$ the *stoichiometric matrix* with entries $\tilde{Y} = (y_{j'} - y_j)_{y_j \rightarrow y_{j'} \in \mathcal{R}}$. Furthermore we set $\mathcal{K}(c(t)) \in \mathbb{R}^r$ be the column vector with the entries representing the kinetics of the respective reaction at the time t for a concentration $c(t) \in \bar{V}^+$. We are going to enumerate the reactions: for every reaction $y_j \rightarrow y_{j'} \in \mathcal{R}$ we will associate a number $q \in \{1, \dots, r\}$, then we can formulate the vector $\mathcal{K}(c(t))$, $t \geq 0$, as follows

$$\mathcal{K}(c(t)) = (\mathcal{K}_q(c(t)))_{1 \leq q \leq r}$$

With these definitions we can reformulate the reaction rate function as follows:

$$\dot{c}(t) = \tilde{Y} \mathcal{K}(c(t)). \tag{48}$$

For the reaction diagram, let $\mathcal{I} \in \mathbb{Z}^{n \times r}$ be the *incidence matrix*, where the rows represent the complexes and the columns the reactions. That is, for every $q \in \{1, \dots, r\}$ representing each a specific reaction $y_i \rightarrow y_j \in \mathcal{R}$ in the chemical reaction network, we will set $\mathcal{I}_{i,q} = -1, \mathcal{I}_{j,q} = 1$ and all other entries in the q th column are 0. If $Y \in \mathbb{N}_0^{N \times n}$ is the matrix defined in (1), then we have:

$$\tilde{Y} = Y\mathcal{I}. \quad (49)$$

Recall that for a vector $v \in \mathbb{R}^N$ we defined:

- $v \geq 0$ if $v_i \geq 0$ for every $1 \leq i \leq N$ and
- $v > 0$ if $v \geq 0$ and $v \neq 0$.

Additionally, we will write $v \gg 0$ if $v_i > 0$ for every $1 \leq i \leq N$.

A *P-semiflow* is a row vector $v \in \mathbb{R}^N, v > 0$ such that $v\tilde{Y} = 0$. For the system (48) a P-semiflow means, that there exists a non-negative linear first integral v such that $(d/dt)vc(t) = 0$ along all concentration trajectories $c(t)$. We say that a Petri net is *conservative* if there exists a P-semiflow $v \gg 0$.

A conservative SR-net has the same meaning as a conservative mass-action system, which we defined in chapter 2. However here we demand the conserved linear quantity to be strictly positive.

A *T-semiflow* is a column vector $w \in \mathbb{R}^r, w > 0$ such that $\tilde{Y}w = 0$. A Petri net is *consistent* if there exists a T-semiflow $w \gg 0$.

Proposition 4.3.1. *Every weakly reversible reaction network is consistent.*

Proof. From Corollary 2.1.8 it follows from weak reversibility of the reaction network that there exists a $v \gg 0$ such that $\mathcal{I}v = 0$. Since Y is a linear transformation it follows immediately $Y\mathcal{I}v = 0$. With equation (49) we have $\tilde{Y}v = 0$. Hence, the reaction network is consistent. \square

Remark Note that the reverse statement does not hold in general – not every consistent reaction network is weakly reversible.

A set $\Sigma \subset \mathcal{S}$ is called a *siphon* if for every reaction for which there is an element of Σ in the product complex, there is an element of Σ in the reactant complex. We will say a siphon is minimal if it does not contain any other siphons. In the following we will often use the set of concentration vectors with 0 in those entries which correspond to a species in the siphon: $L_\Sigma := \{c \in \bar{V}^+ | c_i = 0 \iff S_i \in \Sigma\}$.

We are now able to state the necessary conditions for persistence of a chemical reaction network.

Theorem 4.3.2. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a conservative and persistent chemical reaction network. Then, the associated Petri net is consistent.*

Proof. Let $c_0 \in V^+$ be any initial concentration. Since the reaction network is conservative, the concentration trajectories with initial concentration c_0 satisfy $vc(t) = vc_0$ for a $v \in V^+$ and therefore are bounded. This implies that the ω -limit set is nonempty and compact. From the persistence of the reaction network it follows that $\omega(c(\cdot)) \cap \partial\bar{V}^+ = \emptyset$, hence, $\mathcal{K}(\bar{c}) \gg 0$ for all $\bar{c} \in \omega(c(\cdot))$. Moreover, it follows from the compactness of the ω -limit set and the continuity of \mathcal{K} that there exists a $w \gg 0$ such that $\mathcal{K}(\bar{c}) \geq w$ for every $\bar{c} \in \omega(c(\cdot))$.

4 Proven cases of the Global Attractor Conjecture

For any $\bar{c} \in \omega(c_0)$ we have $\mathcal{K}(c(t)) \geq w$ for $c(t) \in (\bar{c} + S) \cap V^+$ and all $t \in [0, \infty)$ because of the invariance of the ω -limit set. By taking time averages it then follows:

$$\lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T \tilde{Y} \mathcal{K}(c(t)) dt = \lim_{T \rightarrow \infty} \frac{c(T) - \bar{c}}{T} = 0, \quad (50)$$

where the right-hand equation is a consequence of the bounded concentration trajectories. We also have

$$\frac{1}{T} \int_0^T \mathcal{K}(c(t)) dt \geq w \text{ for all } T > 0.$$

Hence, by taking any subsequence $T_n \rightarrow \infty$, it follows that

$$\lim_{n \rightarrow \infty} \frac{1}{T_n} \int_0^{T_n} \mathcal{K}(c(t)) dt = \bar{w} \geq w.$$

With (50) it follows then that $\tilde{Y} \bar{w} = 0$ with $\bar{w} \geq w \gg 0$. Hence, the network is consistent. \square

Having seen a necessary condition for a persistent reaction network we will now deduce some sufficient conditions to ensure persistence in a reaction network. To prove the main theorem of this section 4.3 we will need some technical tools from differential equation theory, which we will present in the following.

Let $\text{sign}(a) := 1, 0, -1$ if $a > 0, a = 0$, or $a < 0$ respectively be the sign function for real numbers $a \in \mathbb{R}$. We define for a vector $v \in V$ $\text{sign}(v) = (\text{sign}(v_1), \dots, \text{sign}(v_N))^T$.

Lemma 4.3.3. *Let $\mathcal{O} \supset \bar{V}^+$ be an open neighborhood of \bar{V}^+ and f a real-analytic vector field defined on \mathcal{O} . Let us further suppose that \bar{V}^+ is forward invariant for the flow of f . If $c(t)$ is a trajectory following $\dot{c} = f(c)$ and if $c(t)$ is defined on some interval \mathcal{J} then $\text{sign}(c(t))$ is constant on \mathcal{J} .*

The main argumentation of the proof is that the coordinate functions of the vector field f are also real-analytic and forward invariant. For a detailed proof we refer to Angeli et al. [4].

Lemma 4.3.4. *Let $\Omega \in \bar{V}^+$ be a closed set and invariant for (48). If for some set $Z \subset \mathcal{S}$ we have $\Omega \cap L_Z \neq \emptyset$, then $\Omega \cap L_Z$ is also invariant for (48).*

Proof. Let $c_0 \in \Omega \cap L_Z$. Since Ω is invariant, we have $c(t) \in \Omega$ for every concentration trajectory $c(t)$ with initial concentration c_0 and with $t \in \mathcal{J}$, \mathcal{J} open domain of definition of $c(t)$. Hence, $c(t) \in \bar{V}^+$. By the previous lemma it follows that $\text{sign}(c(t))$ is constant for all $t \in \mathcal{J}$ and, hence, $c(t) \in L_Z$. \square

Let $K \subset \bar{V}^+$ be any set. We defined the *Bouligand tangent cone* $TC_K(\zeta)$ at a point $\zeta \in \bar{V}^+$ as follows:

$$TC_K(\zeta) = \{v \in V \mid \exists k_n \in K, k_n \rightarrow \zeta \text{ and } \lambda_n \searrow 0 \text{ as } n \rightarrow \infty : \frac{1}{\lambda_n} (k_n - \zeta) \xrightarrow{n \rightarrow \infty} v\}.$$

Through this notation we can check invariance of closed sets. If K is a closed set in \bar{V}^+ then K is invariant for (48) if and only if $\tilde{Y} \mathcal{K}(\zeta) \in TC_K(\zeta)$ for all $\zeta \in K$ by theorem 4.2.3. However we will also consider the Bouligand tangent cone for the not closed set L_Z for $S \subset \mathcal{S}$ at a point $\zeta \in L_Z$, which can be written as: $TC_{L_Z}(\zeta) = \{v \in V \mid v_i = 0 \forall S_i \in Z\}$. Also we have $\text{cl}[L_Z] = \bigcup_{X \supseteq Z} L_X$ with $X \subset \mathcal{S}$.

Lemma 4.3.5. *Let $Z \subset \mathcal{S}$ with $Z \neq \emptyset$. If there exists $\zeta \in L_Z$ such that $\tilde{Y}\mathcal{K}(\zeta) \in TC_{L_Z}(\zeta)$, then Z is a siphon.*

Proof. For some $\zeta \in L_Z$ we have $\tilde{Y}\mathcal{K}(\zeta) \in TC_{L_Z}(\zeta)$, that is $[\tilde{Y}\mathcal{K}(\zeta)]_i = 0$ for all $S_i \in Z$. Since $\zeta \in L_Z$ it also follows that $\zeta_i = 0$ for all $S_i \in Z$, so every reaction in which S_i is contained in the reactant complex are shut off at ζ . From $[\tilde{Y}\mathcal{K}(\zeta)]_i = 0$ it then also follows that all reactions in which S_i is contained in the product complex are shut off at ζ . Let $y_j \rightarrow y_l \in \mathcal{R}$ be a reaction in the network with $y_{li} \neq 0$, then there exists a species S_k in the reactant complex y_j , $y_{jk} \neq 0$ with $\zeta_k = 0$. Hence, $S_k \in Z$. By repeating this argumentation, it follows easily that Z is a siphon. \square

Lemma 4.3.6. *If for some $Z \subset \mathcal{S}$ there exists a $\bar{c} \in \bar{V}^+$ such that $\omega(\bar{c}) \cap L_Z \neq \emptyset$, then Z is a siphon.*

Proof. $\omega(\bar{c})$ is a closed and invariant set in \bar{V}^+ , so it follows with lemma 4.3.4 that $L_Z \cap \omega(\bar{c})$ is also invariant. Since for all $X \subset \mathcal{S}$ with $L_X \cap \omega(\bar{c}) \neq \emptyset$ $L_X \cap \omega(\bar{c})$ is invariant, the set

$$\text{cl}[L_Z] \cap \omega(\bar{c}) = \bigcup_{X \supseteq Z} (L_X \cap \omega(\bar{c}))$$

is also invariant. By Nagumo's theorem 4.2.3, we know that, for any $\zeta \in \text{cl}[L_Z] \cap \omega(\bar{c})$ we have

$$\tilde{Y}\mathcal{K}(\zeta) \in TC_{\omega(\bar{c}) \cap \text{cl}[L_Z]}(\zeta) \subset TC_{\text{cl}[L_Z]}(\zeta).$$

Especially, for $\zeta \in L_Z \cap \omega(\bar{c})$ we have $\tilde{Y}\mathcal{K}(\zeta) \in TC_{L_Z}(\zeta)$. So it follows with lemma 4.3.5 that Z is a siphon. \square

Lemma 4.3.7. *$Z \neq \emptyset$ is a siphon if and only if $\text{cl}[L_Z]$ is invariant for (48).*

Proof. Let $\text{cl}[L_Z]$ be invariant for (48) and set $\zeta \in L_Z$. It then follows immediately $\tilde{Y}\mathcal{K}(\zeta) \in TC_{\text{cl}[L_Z]}(\zeta)$. Since $\zeta \in L_Z$ we have $TC_{\text{cl}[L_Z]}(\zeta) = TC_{L_Z}(\zeta)$. With lemma 4.3.5 it follows then that Z is a siphon.

Let $Z \subset \mathcal{S}$ be a siphon and let $\zeta \in \text{cl}[L_Z]$. This means that $\zeta_i = 0$ for all $S_i \in Z \cup Z'$, where $Z' \in \mathcal{S}$ and not necessarily nonempty. By Nagumo's theorem 4.2.3 we only need to prove that

$$[\tilde{Y}\mathcal{K}(\zeta)]_i = \begin{cases} = 0 & \text{for all } S_i \in Z \\ \geq 0 & \text{for all } S_i \in Z' \text{ for } Z' \neq \emptyset. \end{cases}$$

By the differential system (48) we have

$$[\tilde{Y}\mathcal{K}(\zeta)]_i = \sum_{\substack{q: y_j \rightarrow y_{j'} \in \mathcal{R} \\ 1 \leq q \leq r}} y_{j'i} \mathcal{K}_q(\zeta) - \sum_{\substack{p: y_j \rightarrow y_{j'} \in \mathcal{R} \\ 1 \leq p \leq r}} y_{ji} \mathcal{K}_p(\zeta) = \sum_{\substack{q: y_j \rightarrow y_{j'} \in \mathcal{R} \\ 1 \leq q \leq r}} y_{j'i} \mathcal{K}_q(\zeta) - 0 \geq 0, \quad (51)$$

where the second sum is 0 because if $y_{ji} > 0$, then S_i is contained in the reactant complex of the p th reaction and, consequently, $\mathcal{K}_p(\zeta) = 0$ since $\zeta_i = 0$. From (51) it already follows that $[\tilde{Y}\mathcal{K}(\zeta)]_i \geq 0$ for $S_i \in Z'$.

Assume that $S_i \in Z$. If $y_{j'i} > 0$ for a term on the right hand of equation (51), then this term is equal to zero since Z is a siphon. Hence, $[\tilde{Y}\mathcal{K}(\zeta)]_i = 0$ for all $S_i \in Z$. \square

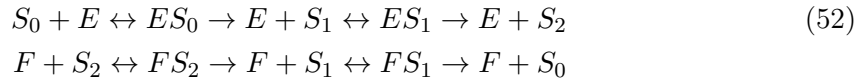
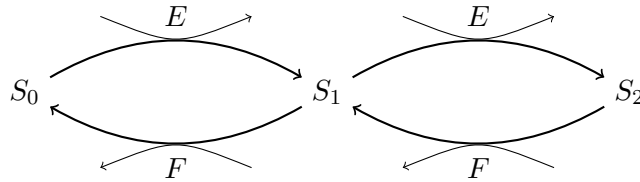
4 Proven cases of the Global Attractor Conjecture

Theorem 4.3.8 (Angeli et al. [4]). *A chemical reaction network that satisfies the following conditions:*

- (1) *the associated Petri net is conservative and*
 - (2) *each siphon contains the support of a P-semiflow*
- is persistent.*

Proof. Let $\bar{c} \in V^+$ and let $\Omega = \omega(\bar{c})$ denote the corresponding ω -limit set. Let us assume that $\Omega \cap \partial \bar{V}^+ \neq \emptyset$, then $\Omega \cap L_Z \neq \emptyset$ for some $\emptyset \neq Z \subset \mathcal{S}$. By lemma 4.3.6 it then follows that Z is a siphon. Because of condition (2) of the theorem there exists $v > 0$ whose support is contained in Z . So there exists a sequence $t_n \rightarrow \infty$ such that $vc(t_n) \rightarrow 0$ for $c(t_n) \in (\bar{c} + S) \cap \bar{V}^+$. This is in contradiction to $vc(t) = v\bar{c}$ for all $t \geq 0$. So, we necessarily have $\Omega \cap \partial \bar{V}^+ = \emptyset$. Hence, the network is persistent. \square

Example A substrate S_0 ultimately reacts to the product S_2 , in a reaction catalyzed by an enzyme E , and, simultaneously, S_2 is transformed back into the substrate S_0 catalyzed by a second enzyme F .



As a concrete example, it may represent one of the mechanisms in the signaling by mitogen-activated protein kinase cascades, short MAPK cascades. MAPK cascades is a chain of proteins communicating a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. This pathway of reactions include phosphorylations of neighboring proteins. These reactions act as an on or off switch. The reaction network depicted in (52) could represent such a phosphorylation reaction in which the enzyme E reversibly adds a phosphate group to a certain specific amino acid in the protein S_0 , resulting in a single-phosphorylated protein S_1 . Afterwards E can then bind to S_1 so as to produce a double-phosphorylated protein S_2 , when a second amino acid site is phosphorylated. A different enzyme F reverses the process. In MAPK cascades, several more steps as in this example are arranged in a cascade, with the protein S_2 serving as an enzyme for the next stage.

It can be verified that the Petri net in figure 9 is *consistent*. To verify this, we order the species and reactions by reading (52) from left to right and from top to bottom (e.g., S_1 is the fourth species and the reaction $ES_0 \rightarrow E + S_1$ is the third reaction). The construction of the matrix \tilde{Y} is then obvious, and it can easily be proven that $\tilde{Y}w = 0$ with $w = (2, 1, 1, 2, 1, 1, 2, 1, 1, 2, 1, 1)^T$.

The network itself, however, is *not weakly reversible*, since neither of the linkage classes of (52) is strongly linked. By computations we can see that there are three minimal siphons:

$$\{E, ES_0, ES_1\}, \{F, FS_1, FS_2\} \text{ and } \{S_0, S_1, S_2, ES_0, ES_1, FS_2, FS_1\}.$$

There are three independent conservation laws:

$$E + ES_0 + ES_1 = \text{constant}_1,$$

$$F + FS_2 + FS_1 = \text{constant}_2 \text{ and}$$

$$S_0 + S_1 + S_2 + ES_0 + ES_1 + FS_2 + FS_1 = \text{constant}_3,$$

whose supports coincide with the tree mentioned siphons. Hence, each one of the minimal siphons contains the support of a P-semiflow. The network is conservative, because the sum of the three mentioned conservation laws is in itself a conservation law. Therefore, by theorem 4.3.8 it can be implied that the network is persistent.

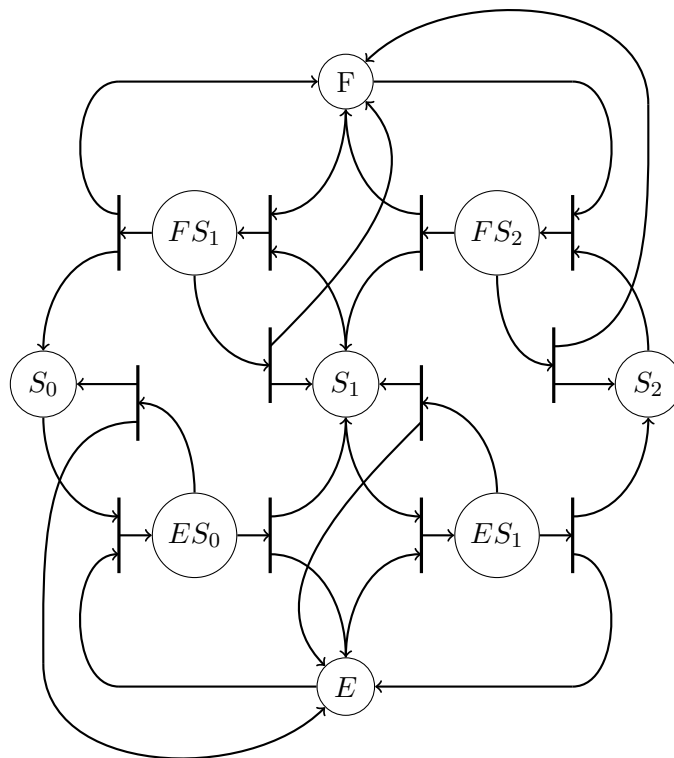


Figure 9: Petri net graph of a two sequential step reaction

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