Summary of the Ph.D. Thesis

On the Positive Steady States of Deficiency-One Mass Action Systems

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1 Introduction

The foundations of Chemical Reaction Network Theory (CRNT) was developed by Feinberg, Horn, and Jackson in the 1970's [20, 21, 24, 25, 26, 27, 28, 29, 30, 31]. The aim of the theory is to investigate the qualitative properties of the mathematical models of chemical and biological systems. The most studied model is the so-called *mass action system*, which is a continuous-time continuous-state deterministic model, where the state of the system is the concentrations of the chemical species involved (examples of chemical species are H_2, O_2, and H_2O), and the state varies in time in accordance with an autonomous ordinary differential equation (ODE). The main objects of the model are the directed graph $(\mathcal{C}, \mathcal{R})$, called the *graph of complexes* (the elements of $\mathcal{C}$ are certain linear combinations of the species and the element of $\mathcal{R}$ are the reactions, e.g. once the reaction $2H_2 + O_2 \to 2H_2O$ takes place in the model, we have $2H_2 + O_2, 2H_2O \in \mathcal{C}$ and $(2H_2 + O_2, 2H_2O) \in \mathcal{R}$) and the *rate coefficients* (a positive number appearing in the ODE as a multiplier is assigned to each reaction). Despite the several parameters in the model, there are powerful results concerning the qualitative behaviour of these systems.

In the past decade, a renewed attention has been paid to the understanding of biological phenomena such as multistability or periodic behaviour. Recent works were focusing on the persistence, the boundedness of the trajectories, and global stability of mass action systems [1, 2, 3, 4, 5, 6, 14, 32, 34]. Also, much effort has been dedicated to addressing the question of (ruling out) multiple equilibria [7, 8, 15, 16, 17]. The paper [18] investigates both the existence and the uniqueness of positive steady states.

In the thesis (which is based on the author's publications [9], [10], [11], and [12]), we revisit and improve the *deficiency-oriented* theory developed by Feinberg, Horn, and Jackson. The deficiency, denoted by δ, is a nonnegative integer associated to the *reaction network* under consideration. The classical Deficiency-Zero- and Deficiency-One Theorems answer questions about the existence, uniqueness, and stability properties of the steady states. The main purpose of the thesis is to investigate the existence of steady states of such deficiency-one mass action systems that do not satisfy the assumptions of the Deficiency-One Theorem.

In the thesis, Chapters 1, 2, and 3 serve as preliminaries for Chapters 4, 5, and 6. The main results of the author are presented in the last three. Chapters 4, 5, and 6 are based on [9, 10], [12], and [11], respectively.

In the next section of this summary, we provide a brief introduction on the notions and notations that are necessary to the formulations of our main results (which are presented in the remaining three sections of this summary).

2 Mass action systems

A *chemical reaction network* (*reaction network* or *network* for short) is a triple $(\mathcal{X}, \mathcal{C}, \mathcal{R})$ of three nonempty finite sets, where

- $\mathcal{X} = \{X_1, \ldots, X_n\}$ is the *set of species*,
- $\mathcal{C} = \{C_1, \ldots, C_c\}$ is the *set of complexes*, and
- $\mathcal{R} \subseteq \{(C_i, C_j) \in \mathcal{C} \times \mathcal{C} \mid i, j \in \{1, \ldots, c\}, i \neq j\}$ is the *set of reactions.*

A *mass action system* is a quadruple $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$, where $(\mathcal{X}, \mathcal{C}, \mathcal{R})$ is a reaction network and $\kappa : \mathcal{R} \to \mathbb{R}_+$ is the assigned *rate coefficient function.* We consider a continuous-time continuous-state deterministic model, where the state of the system represents the *concentrations* of the species and the time-evolution of the state is described by the ordinary differential equation

$$\dot{x}(\tau) = B \cdot I_\kappa \cdot \Theta(x(\tau))$$

with state space $\mathbb{R}^n_{\geq 0}$, where $B \in \mathbb{R}^{n \times c}$ is the *matrix of complexes*, $I_\kappa \in \mathbb{R}^{c \times c}$ is the *Laplacian* of the labelled directed graph $(\mathcal{C}, \mathcal{R}, \kappa)$, and $\Theta : \mathbb{R}^n_{\geq 0} \to \mathbb{R}^c_{\geq 0}$ is defined by

$$\Theta(x) = \begin{bmatrix} \prod_{s=1}^n x_s^{B_{s1}} \\ \vdots \\ \prod_{s=1}^n x_s^{B_{sc}} \end{bmatrix} \quad (x \in \mathbb{R}^n_{\geq 0}).$$

The main object we are interested in in the thesis is the *set of positive steady states* of a mass action system, denoted by E^κ_+. Let us define E^κ_+ by

$$E^\kappa_+ = \{x \in \mathbb{R}^n_+ \mid B \cdot I_\kappa \cdot \Theta(x) = 0\}.$$

Denote by ℓ the number of weak components of the directed graph $(\mathcal{C}, \mathcal{R})$. The weak components of $(\mathcal{C}, \mathcal{R})$ are called *linkage classes* in CRNT. In case all the linkage classes of $(\mathcal{C}, \mathcal{R})$ are strongly connected, the network is called *weakly reversible* in CRNT. Denote by t the number of absorbing strong components of the directed graph $(\mathcal{C}, \mathcal{R})$. Since each weak component contains at least one absorbing strong component, we have $\ell \leq t$. Though we do not always restrict ourselves in the thesis to the case $\ell = t$, our main results are about such networks.

The *stoichiometric matrix* of a reaction network is $S = B \cdot I \in \mathbb{R}^{n \times m}$, where $I \in \mathbb{R}^{c \times m}$ is the *incidence matrix* of the directed graph $(\mathcal{C}, \mathcal{R})$. The *positive stoichiometric classes* of a reaction network are the (not necessarily bounded) sets $(q + \operatorname{ran} S) \cap \mathbb{R}^n_{\geq 0}$ with $q \in \mathbb{R}^n_+$.

The *deficiency*, denoted by δ, of a reaction network is $\delta = c - \ell - \operatorname{rank} S$. In words, the deficiency is the number of complexes minus the number of linkage classes minus the rank of the stoichiometric matrix. Though it is not so obvious at first glance, the deficiency is nonnegative.

3 Generalisation of the Deficiency-One Theorem

The classical *Deficiency-One Theorem* (due to Feinberg [20, 22, 23]) states the following in the single linkage class case. (The multiple linkage classes case of the theorem is a consequence of the single linkage class case, a non CRNT-specific lemma, and such a CRNT-specific result, which has nothing to do with the fact that the deficiency is small.)

Theorem 1 (Deficiency-One Theorem, single linkage class case) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be a mass action system for which $\ell = t = 1$ and $\delta \leq 1$ hold. Then*

(a) if $\delta = 0$ then $E_+^\kappa \neq \emptyset$ if and only if $(\mathcal{C}, \mathcal{R})$ is strongly connected,

(b) if $\delta = 1$ and $(\mathcal{C}, \mathcal{R})$ is strongly connected then $E_+^\kappa \neq \emptyset$,

(c) if $E_+^\kappa \neq \emptyset$ and $x^* \in E_+^\kappa$ then $E_+^\kappa = \{x \in \mathbb{R}_+^n \mid \log(x) - \log(x^*) \in (\operatorname{ran} S)^\perp\}$, and

(d) if $E_+^\kappa \neq \emptyset$ then $|E_+^\kappa \cap \mathcal{P}| = 1$ for each positive stoichiometric class $\mathcal{P}$.

Thus, if $\delta = 1$, $\ell = t = 1$, $(\mathcal{C}, \mathcal{R})$ is *not* strongly connected, and $E_+^\kappa \neq \emptyset$ then there exists a unique positive steady state in each positive stoichiometric class. However, the theorem gives no information about the non-emptiness of the set of positive steady states of mass action systems with $\delta = 1$, $\ell = t = 1$, and $(\mathcal{C}, \mathcal{R})$ being *non* strongly connected. Our main contribution to the Deficiency-One Theorem is that we provide an equivalent condition to the non-emptiness of E_+^κ for such systems. To formulate that, we need some further notations.

Denote by $\mathcal{C}'$ the set of those complexes, which are in the absorbing strong components of $(\mathcal{C}, \mathcal{R})$ (we do not make any assumption on ℓ and t in this paragraph). Let $\mathcal{C}'' = \mathcal{C} \backslash \mathcal{C}'$. Let $c' = |\mathcal{C}'|$ and $c'' = |\mathcal{C}''|$. Consider $I_\kappa \in \mathbb{R}^{c \times c}$, $\Theta : \mathbb{R}_{\geq 0}^n \to \mathbb{R}_{\geq 0}^c$, and a vector $v \in \mathbb{R}^c$ in the block forms

$$
\begin{aligned}
I_\kappa &= \begin{bmatrix} I_\kappa' & * \\ 0 & I_\kappa'' \end{bmatrix} \in \mathbb{R}^{(c'+c'') \times (c'+c'')}, \\
\Theta &= \begin{bmatrix} \Theta' \\ \Theta'' \end{bmatrix} : \mathbb{R}_{\geq 0}^n \to \mathbb{R}_{\geq 0}^{c'+c''}, \text{ and} \\
v &= \begin{bmatrix} v' \\ v'' \end{bmatrix} \in \mathbb{R}^{c'+c''},
\end{aligned}
$$

where $I_\kappa' \in \mathbb{R}^{c' \times c'}$, $\Theta' : \mathbb{R}_{\geq 0}^n \to \mathbb{R}_{\geq 0}^{c'}$, and $v' \in \mathbb{R}^{c'}$ correspond to the complexes in $\mathcal{C}'$ and $I_\kappa'' \in \mathbb{R}^{c'' \times c''}$, $\Theta'' : \mathbb{R}_{\geq 0}^n \to \mathbb{R}_{\geq 0}^{c''}$, and $v'' \in \mathbb{R}^{c''}$ correspond to the complexes in $\mathcal{C}''$. It is well-known that I_κ'' is invertible (provided that $\mathcal{C}'' \neq \emptyset$).

For any finite set X, $X_0 \subseteq X$, and function $g : X \to \mathbb{R}$ we define $g(X_0)$ by

$$
g(X_0) = \sum_{x \in X_0} g(x). \tag{1}
$$

We now provide a condition that every non weakly reversible mass action systems with nonempty set of positive steady states must trivially satisfy.

Proposition 2 (necessary condition to $E_+^\kappa \neq \emptyset$) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be a mass action system, which is not weakly reversible (i.e., $\mathcal{C}'' \neq \emptyset$). Assume that $E_+^\kappa \neq \emptyset$. Then*

$$
\textit{there exists a } v \in \ker B \cap \operatorname{ran} I_\kappa \textit{ such that } (I_\kappa'')^{-1} v'' \in \mathbb{R}_+^{c''}.
$$

Moreover, if $v \in \operatorname{ran} I_\kappa$ is such that $(I_\kappa'')^{-1} v'' \in \mathbb{R}_+^{c''}$ then $v(\mathcal{C}'') < 0$ holds, where $v(\mathcal{C}'')$ is understood in accordance with (1).

The next theorem, which is the main result of Chapter 4 and also of [9] and [10], states that the necessary condition for the non-emptiness of E_+^κ in Proposition 2 is also sufficient if $\delta = 1$, $\ell = t = 1$, and $(\mathcal{C}, \mathcal{R})$ is *not* strongly connected.

Theorem 3 (see [9, 10]) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be such a mass action system that satisfies $\delta = 1$, $\ell = t = 1$, and $(\mathcal{C}, \mathcal{R})$ is* not *strongly connected. Let $0 \neq h \in \ker B \cap \operatorname{ran} I_\kappa$ be such that $h(\mathcal{C}'') \leq 0$. Then*

(a) if $h(\mathcal{C}'') = 0$ then $E_+^\kappa = \emptyset$ and

(b) if $h(\mathcal{C}'') < 0$ then $E_+^\kappa \neq \emptyset$ if and only if $(I_\kappa'')^{-1} h'' \in \mathbb{R}_+^{c''}$ (i.e., all the coordinates of $(I_\kappa'')^{-1} h''$ are positive).

We remark that if $\ell = t = 1$ then $\operatorname{ran} I_\kappa$ does not depend on κ and $\delta = \dim(\ker B \cap \operatorname{ran} I_\kappa)$. Thus, if $\ell = t = 1$ and $\delta = 1$ hold and $0 \neq h \in \ker B \cap \operatorname{ran} I_\kappa$ is such that $h(\mathcal{C}'') < 0$ then h is determined up to a positive scalar multiplier. However, this positive scalar multiplier does not affect the condition $(I_\kappa'')^{-1} h'' \in \mathbb{R}_+^{c''}$.

The main tool we use in the course of the proof of Theorem 3 is the following lemma (see [9, 10, 12]). The concept we use to prove Lemma 4 is the so-called excess function on directed graphs.

Lemma 4 (properties of a power function) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be a mass action system with $\ell = t = 1$. Suppose that $\overline{y} \in \mathbb{R}_{\geq 0}^c$, $y^* \in \mathbb{R}_{\geq 0}^c$, and $h \in \mathbb{R}^c \backslash \{0\}$ be such that $I_\kappa \overline{y} = 0$, $I_\kappa y^* = h$,*

$$\begin{aligned}
&\text{for all } j \in \mathcal{C} \text{ we have } j \in \mathcal{C}' \text{ if and only if } \overline{y}_j > 0,\\
&\text{for all } j \in \mathcal{C} \backslash \mathcal{C}' \text{ we have } y_j^* > 0, \text{ and}\\
&\text{there exists } j \in \mathcal{C}' \text{ such that } y_j^* = 0.
\end{aligned}$$

Let us define $\beta^* \in \mathbb{R}$ and $p : (\beta^*, \infty) \to \mathbb{R}_+$ by

$$\begin{aligned}
\beta^* &= \max \left\{ -\frac{\overline{y}_i}{y_i^*} \;\middle|\; i \in \mathcal{C} \text{ and } y_i^* > 0 \right\} \text{ and}\\
p(\beta) &= \prod_{i \in \mathcal{C}} (\beta y_i^* + \overline{y}_i)^{h_i} \quad (\beta \in (\beta^*, \infty)),
\end{aligned}$$

respectively. Then

(a) $\lim_{\beta \to \beta^* + 0} p(\beta) = \infty$,

(b) $\lim_{\beta \to \infty} p(\beta) = 0$,

(c) the derivative of p is negative on (β^*, ∞), and

(d) $p : (\beta^*, \infty) \to \mathbb{R}_+$ is a bijection.

4 Existence of the positive steady states of weakly reversible deficiency-one mass action systems

Since the linkage classes of a reaction network are reaction networks themselves, we can speak of the deficiencies of the linkage classes. Denoting by $\delta^1, \dots, \delta^\ell$ the deficiencies of the linkage classes, respectively, one trivially obtains the inequality $\delta \geq \delta^1 + \cdots + \delta^\ell$. The following theorem by Feinberg is the weakly reversible case of the Deficiency-One Theorem [20, 22, 23].

Theorem 5 (Deficiency-One Theorem, weakly reversible case) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be a mass action system, which satisfies*

(i) $\delta^r \leq 1$ *for all* $r \in \{1, \dots, \ell\}$,

(ii) $\delta = \delta^1 + \cdots + \delta^\ell$, *and*

(iii) $(\mathcal{X}, \mathcal{C}, \mathcal{R})$ *is weakly reversible.*

Then $|E_+^\kappa \cap \mathcal{P}| = 1$ *for each positive stoichiometric class* $\mathcal{P}$.

Thus, if $\delta^1 = \cdots = \delta^\ell = 0$ and $\delta = 1$ then Theorem 5 gives no information directly. This motivates the next theorem, which is the main result of Chapter 5 (and also the main result of [12]).

Theorem 6 (see [12]) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R}, \kappa)$ be a mass action system and denote by δ the deficiency of the underlying reaction network $(\mathcal{X}, \mathcal{C}, \mathcal{R})$. Assume that $(\mathcal{X}, \mathcal{C}, \mathcal{R})$ is weakly reversible and $\delta = 1$. Then each positive stoichiometric class contains a positive steady state (i.e., $E_+^\kappa \cap \mathcal{P} \neq \emptyset$ for each positive stoichiometric class $\mathcal{P}$).*

We emphasise that both the weak reversibility and the fact that the deficiency equals to 1 are properties of the underlying reaction network of a mass action system. Hence, the sufficient condition that guarantees the existence of a positive steady state in each positive stoichiometric class is a property of the underlying reaction network only (i.e., it is not dependent on the precise nature of the kinetics as long as the dynamics follows the mass action law). Qualitative properties that are not dependent on the precise values of the rate coefficients of the mass action system in question could be useful in practice, because these values are often unknown.

We remark that the yet unpublished work [19] by Deng, Feinberg, Jones, and Nachman claims that a generalisation of Theorem 6 also holds. Namely, the authors of that manuscript claim that the same implication holds without any assumption on the deficiency of the underlying reaction network. They assume only the weak reversibility of the network, and they claim that this is sufficient to prove the existence of a positive steady state in each positive stoichiometric class. Their proof technique is significantly different from the one presented in Chapter 5. The proof by Deng et al. owes more to geometric ideas while this work uses more strictly algebraic methods. Most of the intermediate results in [19] rely heavily on the weak reversibility of the network, while in our proof of Theorem 6 the weak reversibility of the network becomes crucial only in the concluding steps of the proof. Rather, we take advantage of the fact that the deficiency of the network is assumed to be one. Thus, the results in Chapter 5 might also contribute to the theory of those deficiency-one mass action systems that are *not* weakly reversible, but significant additional ideas are needed for that.

It can be seen by the analysis of a simple example that uniqueness of the positive steady states does not hold generally in Theorem 6. This raises the natural question of whether we can still prove the finiteness of positive steady states inside the positive stoichiometric classes. Actually, in [19] it is claimed that for weakly reversible mass action systems each positive stoichiometric class contains finitely many positive steady states. However, the concise explanation there relies on a property of analytic functions. Nevertheless, the zero set of a multivariate real analytic function can be much more intricate than the zero set of a univariate real analytic function. It suffices to mention the example $\mathbb{R}^2 \ni (x, y) \mapsto (x^2+y^2-1, x^2+y^2-1) \in \mathbb{R}^2$. Though the zero set of this non-identically zero real analytic function is compact in $\mathbb{R}^2$, it is not finite. We sketch in Chapter 5 of the thesis how one can prove the finiteness of the positive steady states for weakly reversible deficiency-one mass action systems with $\ell \leq 2$. Unfortunately, we cannot directly transfer the argument for the case $\ell \geq 3$.

Among several other tools, the following multidimensional version of the Bolzano Theorem (which is a corollary of the Brouwer Fixed Point Theorem) is the key to prove Theorem 6.

Theorem 7 (The Bolzano Theorem in $\mathbb{R}^n$) *Let $f : [0, 1]^n \to \mathbb{R}^n$ be a continuous function. Assume that for all x on the boundary of $[0, 1]^n$ and for all $i \in \{1, \ldots, n\}$ we have*

$$f_i(x) \geq 0 \text{ if } x_i = 0 \text{ and}$$
$$f_i(x) \leq 0 \text{ if } x_i = 1.$$

Then there exists an $x^* \in [0, 1]^n$ such that $f(x^*) = 0 \in \mathbb{R}^n$.

5 The dependence of the existence of the positive steady states on the rate coefficients for deficiency-one mass action systems

By the Deficiency-Zero Theorem, if the reaction network satisfies $\ell = t = 1$ and $\delta = 0$ then the non-emptiness of E_+^κ does not depend on κ. Also, by the Deficiency-One Theorem, if the reaction network satisfies $\ell = t = 1$ and $\delta = 1$, and moreover $(\mathcal{C}, \mathcal{R})$ is strongly connected then, again, the non-emptiness of E_+^κ does not depend on κ. However, by Theorem 3, we have a different situation for mass action systems for which the underlying reaction network satisfies $\ell = t = 1$ and $\delta = 1$, but $(\mathcal{C}, \mathcal{R})$ is *not* strongly connected. For these mass action systems, the non-emptiness of E_+^κ *may* depend on κ. We used the word "may", because three different kind of phenomena can occur when rate coefficients are assigned to a single linkage class deficiency-one reaction network that is not weakly reversible:

- $E_+^\kappa \neq \emptyset$ for all κ (i.e., for all κ all the coordinates of $(I_\kappa'')^{-1}h''$ are positive),

- $E_+^\kappa = \emptyset$ for all κ (i.e., for all κ there exists a non-positive coordinate of $(I''_\kappa)^{-1}h''$), and
- the non-emptiness of E_+^κ depends on κ (i.e., there exists a κ such that all the coordinates of $(I''_\kappa)^{-1}h''$ are positive and there also exists a κ such that there exists a non-positive coordinate of $(I''_\kappa)^{-1}h''$).

The aim of Chapter 6 is to provide characterisations of the above cases. Namely, we formulate equivalent conditions to the statements

$$\text{“there exists a } \kappa : \mathcal{R} \to \mathbb{R}_+ \text{ such that } E_+^\kappa \neq \emptyset\text{” and} \tag{2}$$

$$\text{“for all } \kappa : \mathcal{R} \to \mathbb{R}_+ \text{ we have } E_+^\kappa \neq \emptyset\text{”.} \tag{3}$$

First, we examine the above questions under the extra assumption that $(\mathcal{C}, \mathcal{R})$ is a “chain”. Then, as a generalisation, we assume only that $(\mathcal{C}, \mathcal{R})$ is “tree-like”. As a matter of fact, we obtain a recursive formula for the coordinates of $(I''_\kappa)^{-1}h''$ (the matrix I''_κ has some special properties in the “chain” and “tree-like” cases, which makes it possible to handle the computation of its inverse). Based on the obtained recursive formula, we deduce equivalent conditions both for (2) and (3). Next, we provide equivalent conditions to (2) and (3) in general. I.e., we assume only that $(\mathcal{C}, \mathcal{R})$ satisfies $\ell = t = 1$, but is *not* strongly connected. In this summary, we present only the general case results of the thesis.

If $\ell = t = 1$ and $\delta = 1$ hold then the linear subspace $\ker B \cap \operatorname{ran} I_\kappa$ is one-dimensional and does not depend on κ. For systems that are moreover *not* weakly reversible, let us fix $h \in \mathbb{R}^c$ such that

$$0 \neq h \in \ker B \cap \operatorname{ran} I_\kappa \text{ and } h(\mathcal{C}'') \leq 0, \tag{4}$$

where the notation $h(\mathcal{C}'')$ is understood in accordance with (1). It is important to note that h does not depend on κ.

The following theorem provides an equivalent condition to (2), see [11].

Theorem 8 (see [11]) *Let $(\mathcal{X}, \mathcal{C}, \mathcal{R})$ be a reaction network for which $\ell = t = 1$ and $\delta = 1$. Assume that $(\mathcal{C}, \mathcal{R})$ is* not *strongly connected and let $h \in \mathbb{R}^c$ be as in (4). Then there exists a $\kappa : \mathcal{R} \to \mathbb{R}_+$ such that $E_+^\kappa \neq \emptyset$ if and only if*

$$h(\widetilde{\mathcal{C}}) < 0 \text{ for all } \emptyset \neq \widetilde{\mathcal{C}} \subsetneq \mathcal{C} \text{ with } \varrho^{\text{in}}(\widetilde{\mathcal{C}}) = \emptyset,$$

where $\varrho^{\text{in}}(\widetilde{\mathcal{C}})$ denotes the set of arcs that enter the vertex set $\widetilde{\mathcal{C}}$.

The proof of Theorem 8 is based on the following corollary of Hoffman's Circulation Theorem.

Theorem 9 (existence of a positive h-transshipment) *Let (V, A) be a weakly connected directed graph and let $h : V \to \mathbb{R}$ be a function with $h(V) = 0$. Then there exists an h-transshipment $z : A \to \mathbb{R}_+$ if and only if*

$$h(U) < 0 \text{ for all } \emptyset \neq U \subsetneq V \text{ with } \varrho^{\text{in}}(U) = \emptyset.$$

By Theorem 3, the important object is $(I''_\kappa)^{-1}h''$, thus it does not restrict the generality if we contract the absorbing strong component of $(\mathcal{C},\mathcal{R})$ into one vertex. So assume throughout this section that $\mathcal{C}'$ is a singleton. Also, in order to ease the notation, we identify the set $\mathcal{C}'$ with the sole element in that set. As a preparation for the formulation of the main result of Chapter 6 and [11], we define the sets $U(i)$, $\mathcal{C}''(j)$, $U(\mathcal{C}''(j))$, and $W(j)$ for $i,j \in \mathcal{C}''$ by

- $U(i) = \{k \in \mathcal{C}'' \mid \text{all directed paths from } k \text{ to } \mathcal{C}' \text{ traverse } i\}$,
- $\mathcal{C}''(j)$ denotes the vertex set of that strong component of $(\mathcal{C},\mathcal{R})$ which contains j,
- $U(\mathcal{C}''(j)) = \{k \in \mathcal{C}'' \mid \text{all directed paths from } k \text{ to } \mathcal{C}' \text{ traverse } \mathcal{C}''(j)\}$, and
- $W(j) = \left\{ k \in \mathcal{C}'' \;\middle|\; \begin{array}{l} \text{there exist a directed path from } k \text{ to } j \text{ and a directed path} \\ \text{from } k \text{ to } \mathcal{C}' \text{ such that their only common vertex is } k \end{array} \right\}$,

respectively. Also, let $\mathcal{J} \subseteq \mathcal{C}''$ be such that $\mathcal{J}$ contains precisely one element of each non-absorbing strong component of $(\mathcal{C},\mathcal{R})$ and for all $j \in \mathcal{J}$ we have $\varrho^{\text{out}}(\{j\}) \cap \varrho^{\text{out}}(\mathcal{C}''(j)) \neq \emptyset$, where $\varrho^{\text{out}}(U)$ denotes the set of arcs that leave the vertex set U.

Theorem 10 (see [11]) *Let $(\mathcal{X},\mathcal{C},\mathcal{R})$ be a reaction network for which $\ell = t = 1$ and $\delta = 1$. Assume that $(\mathcal{C},\mathcal{R})$ is* not *strongly connected and let $h \in \mathbb{R}^c$ be as in (4). For $i,j \in \mathcal{C}''$ let $U(i)$, $W(j)$, $\mathcal{C}''(j)$, $U(\mathcal{C}''(j))$, and $\mathcal{J}$ be as above. Then for all $\kappa : \mathcal{R} \to \mathbb{R}_+$ we have $E_+^\kappa \neq \emptyset$ if and only if*

$$\begin{cases} \textit{for all } i \in \mathcal{C}'' \textit{ we have } h(U(i)) \leq 0 \textit{ and} \\ \textit{for all } j \in \mathcal{J} \textit{ with } W(j) \subseteq \mathcal{C}''(j), \textit{ we have } h(U(\mathcal{C}''(j))) < 0. \end{cases}$$

We arrive to Theorem 10 through several intermediate steps. The starting point of these steps is a formula for the entries of the inverse of I''_κ via the following version of the Matrix-Tree Theorem.

Theorem 11 (Matrix-Tree Theorem) *Let $Z = (z_{ij})_{i,j=1}^c \in \mathbb{R}^{c\times c}$ be a matrix that satisfy*

$$\sum_{j=1}^{c} z_{ij} = 0 \textit{ for all } i \in \{1,\ldots,c\}.$$

Fix $Q \subseteq \{1,\ldots,c\}$ and $i,j \in \{1,\ldots,c\}\backslash Q$. Then

$$d_{Q\cup\{j\},Q\cup\{i\}}(Z) = (-1)^{i+j}(-1)^{c-|Q|-1} \sum_{\widetilde{A} \in \mathcal{T}^{ij}_{D(Z)}(Q\cup\{j\})} z_{\widetilde{A}},$$

where

- *$D(Z)$ is a directed graph with vertex set $V(Z) = \{1,\ldots,c\}$ and arc set $A(Z) = \{(i,j) \in V(Z)\times V(Z) \mid z_{ij} \neq 0\}$,*
- *$d_{Q\cup\{j\},Q\cup\{i\}}(Z)$ is the determinant of that matrix, which is obtained from Z by deleting the rows with index in $Q\cup\{j\}$ and the columns with index in $Q\cup\{i\}$,*

- $\mathcal{T}^{ij}_{D(Z)}(Q \cup \{j\})$ *consists of those inbranchings in* $D(Z)$ *with root set* $Q \cup \{j\}$ *in which there exists a directed path from* i *to* j*, and*

- *the symbol* $z_{\widetilde{A}}$ *is a shorthand notation for the product* $\prod_{a \in \widetilde{A}} z_a$.

This version of the Matrix-Tree Theorem appears in [33, Appendix] as a tool for proving the Markov Chain Tree Theorem. This is a slight generalisation of Tutte's result (see [35, Theorem 3.6]), while it is a special case of the All Minors Matrix Tree Theorem (see [13]). The previous applications of the Matrix-Tree Theorem in CRNT used Tutte's version, while we need a slightly more general variation. We also provide a direct and elementary proof of the Matrix-Tree Theorem, which was worked out by György Michaletzky and the author of the thesis.

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