

Monotonicity and convergence in chemical reaction networks

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Abstract—In this note we discuss monotonicity and convergence to equilibria of certain classes -to be specified below- of chemical reaction networks. The results do not assume any particular form for the kinetics of the reactions (such as mass action kinetics) and only rely on stoichiometric constraints. They imply in particular that the Zero Deficiency Theorem -which does assume mass action kinetics- remains valid for a more general class of networks. This suggests a robustness property of this classical result.

I. INTRODUCTION

The study of the qualitative behavior of chemical reaction networks is an area of growing interest, especially in light of the recent challenges posed by molecular and systems biology. One of the goals is the understanding of cell functions at the molecular level. This could lead to new scenarios both in terms of drug design and of therapeutical treatments. It is needless to say that this is a formidable task which may or may not be achievable. Nevertheless, it is apparent that the complexity and high dimensionality of the chemical reaction networks typically found in this context calls for systematic tools to deal with such questions as: What is the functionality of a specific “pathway” or what is its qualitative behavior (for instance in Input-Output terms)? How robust (or insensitive) is the network to parameter changes and/or environmental fluctuations?

One of the classical conceptual tools in dynamical systems theory, which was introduced to deal with questions concerning asymptotic dynamics and their robustness to parameter variations, is the notion of monotone systems [3]. These systems preserve in forward in time, some ordering defined on the state space.

Despite the fact that chemical and biological systems (for instance, eco-systems models) were among the most recurrent sources of examples for the rich literature devoted to the subject, a clear connection between chemical reaction networks and the theory of monotone dynamical systems is still missing. The purpose of this paper is to point out a class of networks whose dynamics can be understood in the light of this theory.

Part of this work was done while D. Angeli was visiting the Department of Mathematics of the University of Florida.

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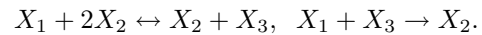
Fig. 1. Graph of complexes for Example 1.

Notation: The set of non-negative n -tuples is denoted by \mathbb{R}_+^n , the set of positive n -tuples by $\text{int}(\mathbb{R}_+^n)$ and we define $\text{bd}(\mathbb{R}_+^n) := \mathbb{R}_+^n \setminus \text{int}(\mathbb{R}_+^n)$.

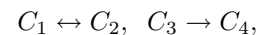
II. CHEMICAL REACTION NETWORKS

Chemical reaction networks can be described by a list of m chemical reactions involving n species.

Example 1:



In the above there are $n = 3$ species X_i and $m = 3$ reactions. Reaction 1 produces one molecule of X_2 and one molecule of X_3 given one molecule of X_1 and two molecules of X_2 . Reaction 2 is the backward reaction of reaction 1, and reaction 3 produces one molecule of X_2 from one molecule of X_1 and one molecule of X_3 . In a network we can always distinguish p ($\leq 2m$) distinct complexes. In Example 1 there are $p = 4$ complexes, namely $C_1 = X_1 + 2X_2$, $C_2 = X_2 + X_3$, $C_3 = X_1 + X_3$ and $C_4 = X_2$. Using complexes instead of species, we can equally well represent the reaction network as follows:



and interpret the reactions as occurring between single complexes, going from the (complex of) reactants to the (complex of) products. This is illustrated in Figure 1.

To every complex C_j , we associate an n -dimensional complex vector c_j whose components are the stoichiometric coefficients of all the species of the network as they appear in the given complex. In Example 1 we have

$$c_1 = \begin{pmatrix} 1 \\ 2 \\ 0 \end{pmatrix}, \quad c_2 = \begin{pmatrix} 0 \\ 1 \\ 1 \end{pmatrix}, \quad c_3 = \begin{pmatrix} 1 \\ 0 \\ 1 \end{pmatrix}, \quad c_4 = \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}.$$

A network is *strongly connected* (*connected*) if given any pair of distinct complexes C_r and C_s , there is a collection of complexes $\{C_{j_1}, \dots, C_{j_l}\}$ ($l > 1$) such that $C_{j_1} = C_r$, $C_{j_l} = C_s$ and such that there is a reaction $C_{j_k} \rightarrow C_{j_{k+1}}$ (a reaction $C_{j_k} \rightarrow C_{j_{k+1}}$, or a reaction $C_{j_{k+1}} \rightarrow C_{j_k}$) between every pair of consecutive complexes C_{j_k} and $C_{j_{k+1}}$ in the

collection, where $k = 1, \dots, l - 1$. The network in Example 1 is not connected, hence certainly not strongly connected.

A collection of l distinct complexes $\{C_{j_1}, \dots, C_{j_l}\}$ ($l > 1$) in a network is called a *loop* if there are l distinct reactions, such that there is either a reaction $C_{j_k} \rightarrow C_{j_{k+1}}$ or a reaction $C_{j_{k+1}} \rightarrow C_{j_k}$ between every pair of consecutive complexes C_{j_k} and $C_{j_{k+1}}$ where $k = 1, \dots, l$ (we agree that $C_{j_{l+1}} \equiv C_{j_1}$). In Example 1, $\{C_1, C_2\}$ is a loop. In fact, it is the only loop in the network. More generally, every reversible reaction gives rise to a loop.

Finally, we associate to every reaction j , a *reaction vector* S_j which is defined as the difference of the complex vector of products and the complex vector of the reactants of the reaction. In Example 1,

$$S_1 = c_2 - c_1 = \begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix}, S_2 = c_1 - c_2 = \begin{pmatrix} 1 \\ 1 \\ -1 \end{pmatrix} = -S_1,$$

$$S_3 = c_4 - c_3 = \begin{pmatrix} -1 \\ 1 \\ -1 \end{pmatrix}.$$

The *stoichiometric matrix* S associated to a chemical reaction network is defined as the $n \times m$ matrix whose j -th column is S_j , the stoichiometric reaction vector associated to reaction j . In Example 1,

$$S = \begin{pmatrix} -1 & 1 & -1 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \end{pmatrix}$$

Later on, we will find it necessary to consider the linear space generated by the columns of S . In this context, the following is useful.

Fact 1: *Let a network contain a loop $\{C_{j_1}, \dots, C_{j_l}\}$. Then the columns of the stoichiometric matrix of the network obtained by deleting one reaction between two consecutive complexes in the loop, generate the same linear space as the columns of the stoichiometric matrix of the original network. In particular, the rank of both stoichiometric matrices is the same.*

Indeed, the linear space generated by the columns of the stoichiometric matrix that correspond to reaction vectors of the reactions in the loop is $\text{span}(L)$ where $L = \{c_{j_2} - c_{j_1}, \dots, c_{j_l} - c_{j_{l-1}}, c_{j_1} - c_{j_l}\}$. Assuming that either reaction $C_{j_l} \rightarrow C_{j_1}$ or reaction $C_{j_1} \rightarrow C_{j_l}$ is deleted (a possible relabeling of complexes shows that the assumption that we are deleting a reaction between the final and first complex means no loss of generality), the linear space generated by the remaining reaction vectors from the original loop is $\text{span}(L^c)$, where $L^c = L \setminus \{c_{j_1} - c_{j_l}\}$. The claim now follows from the observation that $c_{j_1} - c_{j_l}$ is a linear combination of the vectors in L^c .

So far, we have not discussed the dynamics of the chemical reactions. Let us do this now. The vector containing the concentrations of the n species is denoted by x . It will be assumed that the *reaction rate* of reaction j is a non-negative C^1 function of x , denoted by $R_j : \mathbb{R}_+^n \rightarrow \mathbb{R}_+$. In fact, we

assume that reaction rates of all reactions in the network only depend on the concentrations of their reactants. Moreover, we assume that when one of the reactants is missing, the rate is zero and that when all the reactants are present, the rate is positive and strictly increasing in all the concentrations of the reactants. Formally,

Assumption 1:

For all j , the function $R_j : \mathbb{R}_+^n \rightarrow \mathbb{R}_+$ is C^1 ,

- 1) $R_j(x) = 0$ if $x_k = 0$, where x_k is a reactant of reaction j ,
- 2) $R_j(x) > 0$ if $x_l > 0$ for all reactants x_l of reaction j ,
- 3) $\partial R_j / \partial x_k(x) > 0$ if x_k is a reactant of reaction j and if x is such that $x_l > 0$ for all reactants x_l of reaction j , and
- 4) $\partial R_j / \partial x_l \equiv 0$, when x_l is not a reactant of reaction j .

A familiar example occurs when the reaction rates obey the law of *mass action kinetics*. In this case, reaction rates are given by $R_j(x) = \kappa_j \prod_k x_k^{\alpha_k}$. Here, the product consists of factors of powers of concentrations of the reactants of reaction j . The power α_k is the stoichiometric coefficient of reactant X_k in reaction j , and κ_j is some positive constant.

Denoting the *reaction rate vector* whose j -th coordinate is $R_j(x)$ by $R(x)$, we have that the concentrations of the species obey the following ODE:

$$\dot{x} = SR(x). \quad (1)$$

It can be proved that our assumptions imply that if $x(0) \in \mathbb{R}_+^n$, then the corresponding solution $x(t) \in \mathbb{R}_+^n$ for all $t > 0$ for which this solution is defined (essentially because if $x_k(0) = 0$, then $\dot{x}_k(0) \geq 0$). Also, this solution remains in the affine subspace of \mathbb{R}^n , given by

$$\{x(0)\} + \text{span}(S),$$

where $\text{span}(S)$ denotes the linear space generated by the column vectors of the matrix S . This follows from the observation that the vector field of system (1) is a linear combination of the constant columns of S . In general, for every $c \in \mathbb{R}_+^n$ there holds that the set

$$\mathcal{C} = (\{c\} + \text{span}(S)) \cap \mathbb{R}_+^n$$

is forward invariant for system (1). We call such a set a *class* of system (1). If a class of system (1) has nonempty intersection with $\text{int}(\mathbb{R}_+^n)$, we call it a *positive class* and denote it by \mathcal{C}_p . We define the *dimension* of a positive class as the dimension of the vector space $\text{span}(S)$.

Returning to Example 1 one last time, assuming mass action kinetics with all $\kappa_j = 1$, we obtain for the dynamics of the concentrations of the species that

$$\begin{aligned} \dot{x}_1 &= -x_1x_2^2 + x_2x_3 - x_1x_3 \\ \dot{x}_2 &= -x_1x_2^2 + x_2x_3 + x_1x_3 \\ \dot{x}_3 &= x_1x_2^2 - x_2x_3 - x_1x_3 \end{aligned}$$

The classes of this system are the nonempty intersections of \mathbb{R}_+^3 and parallel translates of the (here, planar) linear space

$$\text{span} \left(\begin{pmatrix} -1 \\ -1 \\ 1 \end{pmatrix}, \begin{pmatrix} -1 \\ 1 \\ -1 \end{pmatrix} \right).$$

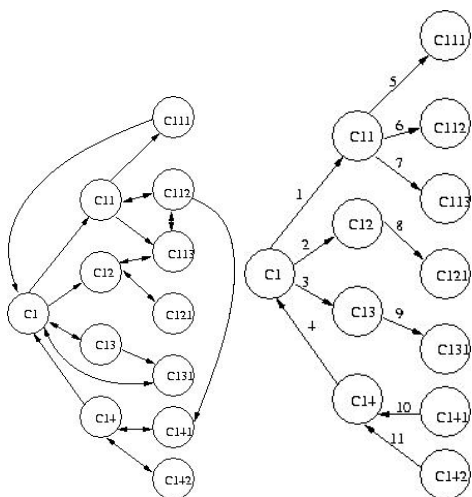


Fig. 2. Network and an associated tree

Notice that these sets are unbounded.

One assumption for the networks that we wish to consider is the following.

Assumption 2:

The chemical reaction network is strongly connected.

This implies that our networks can be depicted as in the left panel of Figure 2. We will now construct a simpler reaction network from the given one by removing reactions. The resulting network is a *tree*, that is, a connected network without loops, illustrated in the right panel of Figure 2. Given an arbitrary graph, there are different ways to obtain a tree (by removing a finite number of edges), and in general the resulting tree is not unique. Any choice will do for what follows. If we assume that the remaining reactions proceed with the same rates as before the deletion, then the ODE for the concentrations of the species in the resulting tree network is easily obtained from system (1) by deleting those columns of S that correspond to the reactions that were deleted, and also by deleting the corresponding entries in the reaction vector $R(x)$. Denoting this reduced matrix and vector by S_r and $R_r(x)$ respectively, we obtain

$$\dot{x} = S_r R_r(x). \quad (2)$$

Denoting the null space of a matrix M by $\ker(M)$, it follows immediately from Fact 1 that

Fact 2: $\text{span}(S) = \text{span}(S_r)$ and $\ker(S^T) = \ker(S_r^T)$.

Fact 2 implies that the (positive) classes of system (1) and (2) are the same.

The main feature of the class of networks we will study is the following:

Assumption 3:

Every chemical species appears in precisely one complex.

In many realistic chemical networks, this assumption does not hold (Assumptions 1 and 2 are less problematic in this respect.).

This assumption in conjunction with Fact 2 enables us to compute the rank of S , and hence the dimension of the positive classes of system (1).

Lemma 1.

Under assumptions 2 and 3, the rank of the stoichiometric matrix S is $p - 1$, and there is some vector $v \in \text{int}(\mathbb{R}_+^n)$ such that $S^T v = 0$.

Proof: We start with relabeling the species according to a natural order suggested by Figure 2: The species in complex C_1 will be the first, followed by those in complex C_{12} (by assumption 3, any given species cannot belong to both complexes). Those are followed by the species in complex C_{13} , etc. Still referring to Figure 2, in assigning new labels, we are traversing the tree from west to east and from north to south. The same rule is used to relabel the reactions.

Let us now consider the matrix S_r . Assumption 3 implies that S_r is generated by the columns of the following matrix:

$$\begin{pmatrix} -c_1 & -c_1 & \dots & -c_1 & 0 & \dots & 0 & \dots \\ c_{11} & 0 & \dots & 0 & -c_{11} & \dots & -c_{11} & \dots \\ 0 & c_{12} & \dots & \vdots & \vdots & \dots & \vdots & \dots \\ \vdots & \vdots & \ddots & \vdots & \vdots & \dots & \vdots & \dots \\ 0 & \vdots & \dots & c_{1n_1} & 0 & \dots & 0 & \dots \\ \vdots & \vdots & \dots & \vdots & c_{111} & \dots & 0 & \dots \\ \vdots & \vdots & \dots & \vdots & \vdots & \ddots & \vdots & \dots \\ \vdots & \vdots & \dots & \vdots & \vdots & \dots & c_{11n_{11}} & \dots \\ \vdots & \vdots & \dots & \vdots & \vdots & \dots & \vdots & \dots \end{pmatrix} \quad (3)$$

where $c_1, c_{11}, c_{12}, \dots$ are vectors with positive entries that equal the stoichiometric coefficients of the relabeled species in the respective complexes $C_1, C_{11}, C_{12}, \dots$.

It is now evident that the rank of S_r is $p - 1$ (= the number of columns in the above matrix, since these are clearly linearly independent) and by Fact 2 this is also the rank of S .

Moreover, denoting by $n_{C_1}, n_{C_{11}}, n_{C_{12}}, \dots$ the number of species in the complexes indicated by the indices, we have that the vector

$$v = \left(\frac{1}{n_{C_1} c_1^T} \frac{1}{n_{C_{11}} c_{11}^T} \dots \frac{1}{n_{C_{1n_1}} c_{1n_1}^T} \frac{1}{n_{C_{111}} c_{111}^T} \dots \frac{1}{n_{C_{11n_{11}}} c_{11n_{11}}^T} \dots \right)^T$$

where the fractions of vectors are understood component-wise, is obviously in $\ker(S_r^T)$ and by Fact 2 also in $\ker(S^T)$. This concludes the proof. ■

III. STATEMENT OF THE MAIN RESULT

Our main result is the following.

Theorem 1.

Under assumptions 1, 2 and 3, every positive class \mathcal{C}_p of system (1) contains a unique equilibrium. This equilibrium belongs to $\text{int}(\mathbb{R}_+^n)$, and it attracts every solution of system

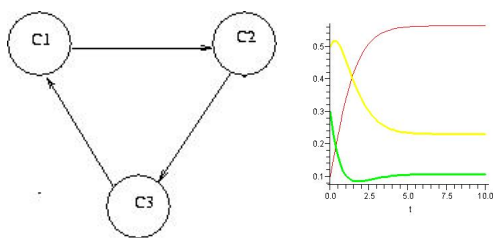
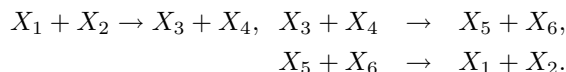


Fig. 3. Graph of complexes for Example 2, and $x_1(t)$, $x_3(t)$ and $x_5(t)$.

(1) which starts in $C_p \cap \text{int}(\mathbb{R}_+^n)$.

Example 2: Consider



There are $n = 6$ chemical species, $m = 3$ reactions, and $p = 3$ complexes $C_1 := X_1 + X_2$, $C_2 := X_3 + X_4$ and $C_3 := X_5 + X_6$. The graph of complexes, depicted in the left panel of Figure 3 is obviously strongly connected. Clearly, assumption 3 is satisfied. Choosing reaction rates $r_1(x) = x_1x_2/(1+x_1)(1+x_2)$, $r_2(x) = 2x_3x_4/(0.5+x_3)(0.3+x_4)$ and $r_3(x) = x_5x_6/(0.2+x_5)(0.9+x_6)$ shows that assumption 1 is satisfied and thus Theorem 1 holds. In the right panel of Figure 3 we plot the odd components of the solution $x(t)$ having initial condition $x_i(0) = 0.i$ for $i = 1, \dots, 6$.

Our main result should be compared to the so-called Zero Deficiency Theorem, see [2], [4] for statements and preliminary proofs, [5] for a retraction of a global stability proof, and [8] for a global stability proof.

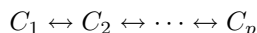
Recall that the deficiency of a chemical reaction network is defined as

$$d = p - l - r$$

where p is the number of complexes, l is the number of linkage classes (this is the number of connected components of the graph of complexes, see [2]) and r is the rank of the stoichiometric matrix S .

From assumption 2 follows that $l = 1$ in our networks and then Lemma 1 implies that their deficiency is $p-1-(p-1) \equiv 0$. Thus the Zero Deficiency Theorem is applicable to our networks. The conclusion of that Theorem is the same as the conclusion of Theorem 1, *provided that mass action kinetics are assumed*. Assumption 1 relaxes this considerably, but on the other hand the structure of the networks we allow is limited by assumption 3.

Theorem 1 also generalizes the results from [1], where the reaction networks were restricted to chains:



in which the distinct complexes don't share any species.

IV. PROOF OF THEOREM 1

We begin with a lemma.

Lemma 2.

Under assumptions 1, 2 and 3, no positive class of system (1) contains equilibria belonging to $\text{bd}(\mathbb{R}_+^n)$.

Proof: Let us argue by contradiction and assume that some positive class C_p of system (1), does have an equilibrium $x^* \in \text{bd}(\mathbb{R}_+^n)$. We first claim that this equilibrium must be such that in *every complex* of the network, there is *at least one species* having zero concentration at x^* . To see this, pick i such that $x_i^* = 0$ (this is always possible because $x^* \in \text{bd}(\mathbb{R}_+^n)$), and consider the i -th equilibrium equation corresponding to system (1), $0 = [SR(x^*)]_i$. This equation takes the form:

$$0 = \alpha_i \left(\sum_j R_j(x^*) - \sum_k R_k(x^*) \right),$$

where α_i is the stoichiometric coefficient of species X_i in the unique complex to which this species belongs (this complex is unique by assumption 3). The sum indexed by j , respectively k , runs over those reactions in which X_i is a reaction product, respectively reactant. Notice that both sets of indices j and k are nonempty by assumption 2. Since $x_i^* = 0$, it follows from assumption 1 (part 1)), that

$$-\sum_k R_k(x^*) = 0,$$

and therefore, since all reaction rates are non-negative, we find that for all reactions j having X_i as a reaction product,

$$R_j(x^*) = 0.$$

Then assumption 1 (parts 1), 2) and 4)) implies that all the complexes of reactants of these reactions, must have at least one species whose concentration at x^* , is zero. This yields a nonempty set of indices l , all different from i , such that $x_l^* = 0$ and we can repeat the argument for the corresponding l -th equilibrium equations that we just performed for the i -th equilibrium equation. By repeating this process a finite number of times, and invoking assumption 2, it follows that in *every complex* of the network, we can find a species whose concentration is zero at x^* . This concludes the proof of our claim.

The positive class C_p can now be written as

$$\{x^*\} + \text{span}(S),$$

or equivalently by Fact 2 and (the proof of) Lemma 1, as

$$\{x^*\} + \text{span}(M),$$

where M is the matrix (3). Since C_p is a positive class, there is some $x \in \text{int}(\mathbb{R}_+^n)$ which belongs to C_p . Therefore, there are scalars γ_i such that

$$x = x^* + \sum_i \gamma_i \text{col}_i(M), \quad (4)$$

where $\text{col}_i(M)$ denotes the i -th column of M . Assume for simplicity that M has only the first $n_1 + n_{11}$ columns in (3) (if M has more columns, the argument is similar).

Then among the scalars γ_i corresponding to the first n_1 columns of M , there must be *at least one negative* scalar. To see this, suppose this were not true and consider the species in complex C_1 (see Figure 2) whose concentration at x^* is zero. Note that such a species exists by the claim we proved above. Then it is clear from (4) that the concentration of that same species in x cannot be positive, contradicting that $x \in \text{int}(\mathbb{R}_+^n)$.

Let $\gamma_j < 0$ be such a scalar for some $j \in \{1, \dots, n_1\}$. In case $j \neq 1$, we can find a species in complex C_{1j} such that it has zero concentration at x^* , by the claim above. But then (4) implies that this species has a *negative* concentration at x , which is nonsense. In case $j = 1$, there must be *at least one negative scalar* γ_j corresponding to the last n_{11} columns of M (same argument as we used before to prove existence of a negative scalar corresponding to the first n_1 columns). This in turn will –as before– lead to a species whose concentration at x is negative, which is nonsense as well. ■

We have the following conservation law.

Lemma 3.

Let assumptions 1, 2 and 3 hold for system (1) and suppose that some complex C of the network contains distinct species X_i and X_j having stoichiometric coefficients α_i , respectively α_j . Then for an arbitrary solution $x(t)$ of system (1), we have that for all $t \geq 0$,

$$x_j(t)/\alpha_j = x_i(t)/\alpha_i + k_{ij} \quad (5)$$

where $k_{ij} = x_j(0)/\alpha_j - x_i(0)/\alpha_i$.

Moreover, this constant is the same for all solutions in the same class.

Proof: By assumption 3, the first claim is immediate from the fact that $v_{ij} \in \ker(S^T)$, where v_{ij} is the n -dimensional vector having precisely two nonzero entries, namely $1/\alpha_i$ and $-1/\alpha_j$ as the i -th, respectively j -th entry. To prove the second claim, notice that if $x(t)$ and $y(t)$ are solutions of system (1), then

$$\dot{x}(t) - \dot{y}(t) = S(R(x(t)) - R(y(t))),$$

hence

$$x(t) - y(t) = x(0) - y(0) + S \int_0^t R(x(s)) - R(y(s)) ds.$$

Now if $x(t)$ and $y(t)$ belong to the same class of system (1), then $x(0) - y(0) \in \text{span}(S)$ and thus

$$x(t) - y(t) = S \left(w + \int_0^t R(x(s)) - R(y(s)) ds \right),$$

for some vector w . The second claim now follows from the first. ■

Sketch of the proof of Theorem 1.

Consider a positive class \mathcal{C}_p of system (1). Obviously, \mathcal{C}_p is convex since it is the intersection of the two convex sets \mathbb{R}_+^n and an affine subspace $\{c\} + \text{span}(S)$ of \mathbb{R}^n . By Lemma 1, \mathcal{C}_p is compact and thus an application of Brouwer’s fixed point Theorem, yields the existence of an equilibrium in \mathcal{C}_p

which by Lemma 2 cannot belong to $\text{bd}(\mathbb{R}_+^n)$. We will later see that such an equilibrium is unique in \mathcal{C}_p .

Now fix a solution $x(t)$ of system (1) which starts in $x(0) \in \mathcal{C}_p \cap \text{int}(\mathbb{R}_+^n)$. To this solution, we will associate a new system.

More precisely, we will consider the dynamics of the vector variable $z(t)$ which is obtained from $x(t)$ as follows. First we select in every complex C_i of the network a *single species* X_{j_i} and thus obtain p distinct (by assumption 3) species, one from each complex. We define the vector $z(t)$ as the vector consisting of the concentrations of the vector $x(t)$ corresponding to the selected species. Then one can verify that $z(t)$ satisfies the following ODE, defined on \mathbb{R}_+^p ,

$$\dot{z} = \tilde{S}r(z), \quad (6)$$

where \tilde{S} is the $p \times m$ matrix obtained from S by deleting those rows of S that correspond to species of the original network which were not selected. The vector $r(z)$ is obtained from the vector $R(x)$ by setting $x_i = z_i$ if X_i was a selected species, and by setting $x_j = \alpha_j(z_i/\alpha_i + k_{ij})$ if X_j was not a selected species. In the latter assignment, X_i is the selected species that belongs to the same complex as X_j and k_{ij} is the constant from (5). By assumption 1, it follows that each component of the vector $r(y)$ is nonnegative and depends on a single component of the vector y . As such, this function is C^1 with a positive derivative whenever this derivative is evaluated in a positive value.

Notice that if $y(t)$ is another solution of (1) which starts in the same positive class as $x(t)$, namely in some $y(0) \in \mathcal{C}_p \cap \text{int}(\mathbb{R}_+^n)$, then we can construct a second -in principle, different- system (6), associated to $y(t)$. However, if in this construction, we select the same species from each complex as we selected in constructing the system (6) associated to $x(t)$, then both systems (6) will be the same, since the parameters k_{ij} associated to $x(t)$ and $y(t)$ are the same by Lemma 3. We will always assume that this is the case.

Although we really are only interested in the behavior of one particular solution of system (6), namely the solution $z(t)$, we will study this system as a whole, defined on \mathbb{R}_+^p . Let us -without proof- summarize the main properties of system (6).

- 1) For every $c \in \mathbb{R}_+^p$, holds that $\mathbb{R}_+^p \cap (\{c\} + \text{span}(\tilde{S}))$ is forward invariant. We will also refer to these sets as classes of system (6). And if they have a nonempty intersection with $\text{int}(\mathbb{R}_+^p)$, then we will call them positive classes.
- 2) System (6) is cooperative and irreducible (see Appendix for definitions) in $\text{int}(\mathbb{R}_+^p)$.
- 3) The rank of \tilde{S} is $p - 1$ and thus the positive classes of system (6) are $(p - 1)$ -dimensional. Moreover, every positive class of system (6) is convex and compact and hence contains an equilibrium, yet no positive class contains an equilibrium on $\text{bd}(\mathbb{R}_+^p)$.
- 4) System (6) has a linear first integral with positive gradient, and the level sets of the first integral coincide with the classes of system (6) (see Appendix for

definitions).

- 5) Let $x(t)$ and $y(t)$ be two solutions of system (1) in the same positive class C_p and assume that $x(0), y(0) \in \text{int}(\mathbb{R}_+^n)$. Let $z(t)$ and $z^*(t)$ be the vector functions associated to $x(t)$, respectively $y(t)$, which satisfy equation (6). Then $z(t)$ and $z^*(t)$ belong to the same positive class of system (6), and hence to the same level set of the first integral of system (6).

Item 2 enables us to apply the Theorem from the Appendix to the restriction of system (6) to $\text{int}(\mathbb{R}_+^p)$. Obviously this restricted system also has a linear first integral whose level sets are the intersections of $\text{int}(\mathbb{R}_+^p)$ with the positive classes of system (6). By item 3 and 4, such level sets contain at least one equilibrium. The Theorem from the Appendix shows that this equilibrium is in fact unique in each level set and attracts all solutions starting in the level set.

In particular, this implies that the two solutions $z(t), z^*(t) \rightarrow q$ as $t \rightarrow \infty$, where q is the unique equilibrium of system (6) contained in the level set associated to the solutions $z(t)$ and $z^*(t)$ (recall that by item 5, these solutions remain in the same level set).

Consequently, $x(t), y(t) \rightarrow e$ as $t \rightarrow \infty$, where e is an equilibrium of system (1) in the positive class C_p . Moreover, e is the unique equilibrium in this class, and this concludes the proof of the Theorem.

V. CONCLUSIONS

We identified a class of chemical reaction networks that give rise to systems whose solutions converge to equilibria. This class is characterized by topological conditions (assumptions 2 and 3) on the graph of complexes, and by the qualitative condition that the reaction rates should be monotonically increasing (assumption 1). The latter shows that some of the results such as the Zero Deficiency Theorem [2], [4] which require reaction rates to be of mass action type, are actually robust with respect to suitable perturbations in the reaction rates, as long as these perturbations result in monotonically increasing reaction rates. On the other hand, the topological requirement expressed in assumption 3 is a rather severe one from the point of view of applications (this is much less of an issue for assumption 2). It would therefore be interesting to see whether or not it can be relaxed.

VI. APPENDIX

We will state an adaptation of a result by Mierczynski (Theorem 10 from [7]), see also [6] for related work.

Recall that a system $\dot{x} = f(x)$ with $x \in X$ for some open $X \subset \mathbb{R}^n$ and some C^1 vector field f , is called *cooperative* if in every point $x \in X$, the Jacobian matrix $\partial f / \partial x$ has non-negative off-diagonal entries. If the Jacobian matrix is an irreducible matrix in every $x \in X$, then we call the system *irreducible* (a matrix M is irreducible if its digraph -which is obtained by drawing an edge from node j to i iff $M_{ij} \neq 0$ -, is strongly connected; that is, given any pair (i, j) , there is a path from i to j following the directed edges of the digraph). A *first integral* H for system $\dot{x} = f(x)$ is a C^1 function whose value remains constant along all solutions

of the system. And a *level set* of a first integral H is every nonempty set of the form $\{x \in X \mid H(x) = c\}$, where c is a given constant.

Mierczynski's result is the following.

Theorem

Let $\dot{x} = f(x)$, $x \in \text{int}(\mathbb{R}_+^n)$, be cooperative and irreducible. Assume that this system has a first integral H with positive gradient and that it is forward complete (that is, all solutions are defined on $[0, +\infty)$). Fix a level set L for H . Then either

- There is exactly one equilibrium in L and all solutions in L converge to L , or
- There is no equilibrium in L and the omega limit set $\omega(x)$ of every point $x \in L$, is empty.

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