SOME CONSEQUENCES OF THERMODYNAMIC FEASIBILITY FOR THE MULTISTABILITY AND INJECTIVITY IN CHEMICAL REACTION NETWORKS

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Abstract. The result of this paper is the elucidation of the consequences for the chemical reaction network theory under the assumption of feasibility with respect to thermodynamic-energetic constraints. Thermodynamic feasible reaction networks limit the amount of "allowed" reaction patterns to the set of loopless reaction fluxes. Combined with the chemical reaction network theory (CRN) reversible and weakly reversible CRN’s are injective. Furthermore, injectivity is reduced to the injectivity of the stoichiometric space into the reactant space.

We can extend the restriction of injectivity to Continuously Flow Stirred Tank Reactors (CFSTR) by considering the difference of inflow and outflow as a reaction.

Key words. Thermodynamic Feasible Flux; Multiple Equilibria; Injectivity; Chemical Reaction Network; Loop-less flux.

MSC. 80A30; 52B40; 37C25;82B30

1. Introduction. Summarizing the results which have been lately obtained in [1] and [2] we derive some obvious consequences. The loop-less and so called thermodynamic feasible fluxes outlined and specified in [1] obey in an almost natural way the injectivity conditions in [2]. There is a long history of achievements analyzing injectivity and multistationarity of chemical reaction networks (CRN’s) ([10], [11], [12], [15], [16]). There have been numerous refinements and generalizations of previous results in ([3], [2], [4], [6], [8], [13], [14]). We would like to insert thermodynamical requirements [1] into CRN’s as recently manifestet in [2] to elucidate their consequences for their stability behaviour.

2. Thermodynamic Considerations. In this section we give some basic explanations for the physical description of chemical reactions as occurring in chemical reaction networks of continuous stirred tank reactors (CSTR). Generally there is a known thermodynamic potential that governs reaction kinetics between complexes. We will consider every reaction as reversible and described by the boltzmann distribution between potentials. Reaction dynamics derived from power law kinetics allow by that assumption flows in both directions (reversible).

We will therefore assume that all reactions are reversible unless we explicitely mention where we can neglect full reversibility.

An example of a reversible reaction for illustration considered here is:

\[
A + B \xrightleftharpoons[\kappa_b]{\kappa_f} C + D .
\] (2.1)

This reaction has a reaction constant for both directions. A reaction constant \( \kappa(T) \) is

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almost universally described as dependent upon activation potential $\Delta E_a$ as in [17], p. 9, 1-25

$$\kappa(T) = \kappa_0 \cdot e^{-\frac{\Delta E_a}{k T}}. \tag{2.2}$$

CSTR nearly operating under constant temperature $T$ have reaction constants that can be assumed to be fixed approximately. On the other side we have to check whether applied theorems withstand validity under perturbations of parameters.

For a theoretical derivation of the formula for the forward and backward reaction constants for power law kinetics see [18]. We denote here the concentrations of the species $\{A, B, C, D\}$ as $\{x_A, x_B, x_C, x_D\}$ in reaction (2.1). Complexes in a reaction are the union of all reactant species and all product species. In the case of reaction (2.1) we have the complexes $C_1 = \{A + B\}$ and $C_2 = \{C + D\}$ with $C = \{C_1, C_2\}$ being the collection of all reactions. Assuming powerlaw kinetics for reaction (2.1) we obtain for the change rate of species $x_A$:

$$\dot{x}_A = \kappa_b x_C x_D - \kappa_f x_A x_B \tag{2.3}$$

Similar relations hold for all other three species.

A more detailed treatment of reaction constants with the example given in eqn. (2.1) is obtained in [18] where we have at the equilibrium steady state the following relation:

$$\frac{\kappa_f(T)}{\kappa_b(T)} = \left(\frac{\mu_{CD}}{\mu_{AB}}\right)^{(3/2)} \left(\frac{x_C x_D}{x_A x_B}\right)_{\text{int}} \exp(-\Delta E_0/k_b T) \tag{2.4}$$

The energy difference

$$\Delta E_0 = E_{0,C_2} - E_{0,C_1}$$

is given by the zero-point energies of the reactant ($E_{0,C_1}$) and product ($E_{0,C_2}$) complex. Here we do neglect the reduced masses $\mu_{CD}$ and $\mu_{AB}$, since we can absorb them into the related reaction constants of the specific reaction.

3. Background material. A chemical reaction as in equation (3.1)

$$R_i : C_1 \rightarrow C_2 \tag{3.1}$$

between two complexes $C_1$ and $C_2$ is defined by the reactant complex $C_1 = \{A, B\}$ and product complex $C_2 = \{C, D\}$ with stoichiometric vectors $y_1 = y_{AB} = (1, 1, 0, 0)$ and $y_2 = y_{CD} = (0, 0, 1, 1)$. Furthermore we have the associated forward and backward reaction constants $\kappa_{C_1 \rightarrow C_2}$ and $\kappa_{C_2 \rightarrow C_1}$. We can also denote the difference stoichiometric vector $[y_2 - y_1] = (-1, -1, 1, 1)$. and by enumerating the species by $x = (x_1, x_2, x_3, x_4) = (x_A, x_B, x_C, x_D)$ we can rewrite equation (2.3) by:

$$\dot{x}_1 = \kappa_{C_2 \rightarrow C_1} x^{y_2} - \kappa_{C_1 \rightarrow C_2} x^{y_1} \tag{3.2}$$

where $x^y = \prod_{i \in [4]} x_i^{(y)_i}$. 

Following the notation given in [3] and [2] for a CRN we can form the stoichiometric difference matrix $A = \{[y_{CD} - y_{AB}], [y_{AB} - y_{CD}]\} \in \mathbb{R}^{4 \times 2}$, the diagonal reaction
constant matrix \( \text{diag}(\kappa) = \text{diag}(\kappa_{C_1 \rightarrow C_2}, \kappa_{C_2 \rightarrow C_1}) \in \mathbb{R}^{2 \times 2} \) and the complex matrix 

\[ B = \{ y_{AB}, y_{CD} \} \in \mathbb{R}^{2 \times 4} \]

and rewrite the change rate of all species \( x \) as:

\[ \dot{x} = A \text{ diag}(\kappa)x^B, \quad (3.3) \]

where \( x^B \in \mathbb{R}^2 \) is calculated for each row-vector in \( B \).

Generally we define for the case of \( n \) species \( x \in \mathbb{R}_+^n \) involved in \( r \) reactions \( \mathcal{R} \) (possibly reversible or not) and corresponding stoichiometric difference matrix \( A \in \mathbb{R}^{n \times r} \) and complex matrix \( B \in \mathbb{R}^{r \times n} \) with associated reaction rates \( \kappa \in \mathbb{R}_+^r \) the generalized polynomial map \( f_\kappa(x) : \mathbb{R}_+^n \rightarrow \mathbb{R}^n \), where we have \( A_\kappa = A \text{ diag}(\kappa) \), by:

\[ \frac{dx}{dt} = f_\kappa(x) = A_\kappa x^B \quad (3.4) \]

In the case of a fully reversible network we have for each reaction the forward \( \kappa_f^i \) and backward \( \kappa_b^i \) reaction constant where \( i \in [r] \) with \( r = 2r' \) reactions in total. We will develop the subject for the fully reversible case even when we can admit less restrictive conditions for the validity of the result.

We will first state the result from [1] here. We will consider \( r \) reactions \( \mathcal{R} \) with positive reaction constants \( \kappa_f^i, j \in [r] \) over \( n \) different species. The number \( p \) of complexes \( y_i \in \mathbb{R}_+^n, \ i \in [p] \) are reduced to these taking place in one of the \( r \) unidirectional reactions. The difference stoichiometry vectors of each reaction \( j \in [r] \) denoted by \( [y - y'](j) \) form the columns of the matrix \( A \). The notation here is the same for a matrix \( A \) representing the internal reaction of a CRN. We exclude here external reactions first and analyse the internal system of reactions. At the end of the text we will insert an external flux representing the inflow of a chemostat reactor (CFSTR).

In order to consider thermodynamic aspects in a flux distribution we have to assign potential differences \( \Delta G \) between the complexes of each reaction of the CRN in form of a vector of potentials for the complexes. The Gibbs potential for example (2.1) is related to equation (2.4) by

\[ \Delta G = y_C G^0_C + y_D G^0_D - y_A G^0_A - y_B G^0_B + RT \ln(K_a) \quad (3.5) \]

over the constant \( R = N_A \cdot k_b \), the activities

\[ K_a = \prod_i x^{[y_2 - y_1]} \]

from equation (2.4) and the zero point Energies \( G^0 \) (see also [3] eqn. (1)). Through that notation we can find a vector \( \gamma \in \mathbb{R}^n \) for the potentials of the individual species depending on their concentrations and stoichiometric coefficient, such that we obtain

\[ \Delta G = \gamma^T A \quad (3.6) \]

as the differential energy between the complexes for the current temperature and species concentrations.

The following classification of fluxes can be traced back to the Gordan theorem of alternatives [1] which we will state here:

**Theorem 1.** (Gordan’s theorem) \( \forall A \in \mathbb{R}^{n \times m} \) exactly one of the following two statements is true:
(a) \( \exists z \in \mathbb{R}^m_+ \setminus \{0\}, \ s.t. \ A z = 0 \)
(b) \( \exists y \in \mathbb{R}^n \ s.t. \ A^T y > 0 \)

In \( \Pi \) a transformation of the Gordan theorem for the case of reversible fluxes of a chemical reaction network is given. A reaction system fully reversible will be called loop-free/thermodynamically feasible (b) or thermodynamically not feasible with loops (a) if the following holds:

**Corollary 3.1.** For all \( \hat{A} \in \mathbb{R}^{n \times r} \) where \( n \) is the number of species and \( r \) the number of (bidirectional/reversible) reactions and every \( \nu \in \mathbb{R}^r \) one of the following cases is true:

(a) \( \exists \hat{z} \in \mathbb{R}^r \setminus \{0\}, \ s.t. \ (\forall i \ \text{sign}(\hat{z}_i) \in \{\text{sign}(\nu_i), 0\}) \land \hat{A} \hat{z} = 0 \)
(b) \( \exists \gamma \in \mathbb{R}^n \ s.t. \ (\forall i \ \text{sign}(A^T \gamma)_i = -\text{sign}(\nu_i) \lor \nu_i = 0) \)

**Proof.** See [1]. \( \square \)

The idea behind that alternative is that we cannot have a flux keeping the concentrations of the species constant when there are differences between the potential of the complexes. The net energy consumption would be zero and the turnover would be non-zero which would be impossible due to the conservation of energy. It is more important to know that there is a potential distribution behind that which does not allow thermodynamically infeasible fluxes. In Corollary 3.1 we were choosing \( \gamma \) instead of \( y \) in order to avoid an overlap with the stoichiometry vector \( y_i \) and also to give the link to the chemical potential introduced in equations (3.5) and (3.6) since \( \gamma^T A \) is equivalent to \( A^T \gamma \). (b) in Corollary 3.1 reflects the fact that the flux \( \nu_i \) is in opposite direction to the increasing potential \( (A^T \gamma)_i \) between complexes.

We can link that relation to our reversible system. We set \( m = 2r \) the number of all unidirectional reaction in a fully reversible chemical reaction network and order the signs of the flux \( \nu \in \mathbb{R}^r \) with \( \text{sign}(\nu_i) = d_i \) for \( i \in [r] \) according to the first \( r \) forward and \( r \) backward fluxes or each reversible reaction where we have \( d_i = -d_{i+r} \) and the total flux results as the sum of the forward and backward flux: \( \nu_i = z_i - z_{i+r} \) for \( z \in \mathbb{R}^m_+ \). We can set up the following result which is an equivalent formulation of loop-free fluxes from Corollary 3.1 for unidirectional fully reversible CRN’s.

**Corollary 3.2.** For all \( A \in \mathbb{R}^{n \times m} \) where \( n \) is the number of species and \( m = 2r \) the number of reactions and every \( \nu \in \mathbb{R}^r \) one of the following cases is true:

(a) \( \exists z \in \mathbb{R}^m_+ \setminus \{0\} \land (\exists j \in [r] \text{ with } z_j \neq z_{j+r}), \ s.t. \ (\forall i \in [r] \ \text{sign}(z_i - z_{i+r}) \in \{\text{sign}(\nu_i), 0\}) \land A z = 0 \)
(b) \( \exists \gamma \in \mathbb{R}^n \ s.t. \ (\forall i \ \text{sign}(A^T \gamma)_i = -\text{sign}(A^T \gamma)_{i+r} = -\text{sign}(\nu_i)) \lor \nu_i = 0 \)

**Proof.** Equivalence between Corollary 3.1 and 3.2 concerning (a) can be seen by doubling the matrix \( A \) for the bidirectional case by setting \( A = (\hat{A}, -\hat{A}) \) and also doubling the vector \( \hat{z} \) by setting \( z_i = \max(\hat{z}_i, 0) \) and \( z_{i+r} = -\min(\hat{z}_i, 0) \) for \( i \in [r] \). The reverse can be done by halving \( A \) to form \( \hat{A} \) and by taking differences \( \hat{z}_i = z_i - z_{i+r} \) for \( i \in [r] \). (b) is equivalent in both Corollaries. \( \square \)

**Remark 3.3.** Corollary 3.2 can be extended to the case where reaction \( R_i, i \in [r] \) are not reversible by choosing \( \nu \in \mathbb{R}^r \) such that the sign of \( \nu_i \) is in accordance with the direction of the reaction \( R_i \).

**Remark 3.4.** The exclusion of the case (a) comes as the assumption that there is no component \( x \) of \( \nu \) that is in the nullspace of \( A \). The process of elimination of
components \( x \in \ker(A) \) implies that \( \nu \) is orthogonal to the nullspace of \( A \):

\[
\nu \perp \ker(A).
\] (3.7)

We can now use that fact from equation (3.7) to derive conditions for possible injectivity according to [2]. Therefore we have to suffer some more notation. The sign \( \sigma(a) \) of a vector \( a \in \mathbb{R}^n \) is given by \( \sigma(a)_i = \text{sign}(a_i) \). Therefore we have \( \sigma(a) \in \{-1, 0, 1\}^n \). For a subspace \( K \subset \mathbb{R}^n \) we get consequently \( \sigma(K) = \{ \sigma(a) | a \in K \} \). Furthermore we define \( \Sigma(K) = \sigma^{-1}(\sigma(K)) \). We can now state the following theorem:

**Theorem 2 ([2]).** Let \( f_\kappa : \mathbb{R}_+^n \to \mathbb{R}^m \) be the generalized polynomial map \( f_\kappa(x) = A_\kappa x B \), where \( A_\kappa \in \mathbb{R}^{n \times r} \), \( B \in \mathbb{R}^{r \times n} \) and reaction rates \( \kappa \in \mathbb{R}_+^r \). Let \( K \subset \mathbb{R}^n \) with \( K^* = K \setminus \{0\} \), the following statements are equivalent:

\[ \text{(inj)} \ f_\kappa \text{ is injective with respect to } K, \text{ for all } \kappa \in \mathbb{R}_+^r \]
\[ \text{(sig)} \ \sigma(\ker(A)) \cap \sigma(B(\Sigma(K^*))) = \emptyset. \]

**Proof.** See [2] Theorem 1.4.

The number of reactions \( r \) in theorem 2 includes both reversible and nonreversible reactions by counting reversible reactions double and irreversible reactions single. For further purposes we need the analysis of the second (sig) property. We know from [2]:

**Lemma 3.5.** Let \( B \in \mathbb{R}^{r \times n} \) and \( K \subset \mathbb{R}^n \) where we set \( K^* = K \setminus \{0\} \). Further let \( \varphi_B : \mathbb{R}_+^n \to \mathbb{R}_+^r \) be the generalized polynomial map \( \varphi_B(x) = x B \), then the following statements are equivalent:

1. \( \varphi_B \) is injective with respect to \( K \).
2. \( \sigma(\ker(B)) \cap \sigma(K^*) = \emptyset \)

**Proof.** See [2] Proposition 2.5.

**4. Injectivity relations for thermodynamic feasible fluxes.** We will now describe the system under consideration. We will use the CRN's as introduced in [3]. By setting

\[
A = SE
\] (4.1)

we have similar to eqn. (4.1) the specific CRN

\[
\frac{dx}{dt} = f_\kappa(x) = SE \text{diag}(\kappa)x B .
\] (4.2)

The columns of \( S \) are the stoichiometry vectors of all \( p \) complexes \( y_j, j \in [p] \) involved in the \( r \) reactions \( \mathcal{R} \). \( E \) is the incidence matrix between the interacting complexes forming the matrix \( A \), which consists of all stoichiometric differences of the reacting complexes \( [y_i - y_i'] \in \mathcal{R}, i \in [r] \). The rows of \( B \) are all reactant complexes of each reaction.

We define \( K = \text{im}(A) \). For \( x, y \in \mathbb{R}^r \) we denote \( \sigma(x) \subseteq \sigma(y) \) if \( \sigma(x)_i \in \{ \sigma(y)_i, 0 \} \), \( \forall i \in [r] \). We now use the relation in eqn. (3.7) to show the following lemma:

**Lemma 4.1.**

\[
\ker(A) \perp \text{diag}(\kappa)x B \iff \ker(A_\kappa) \perp x B ,
\] (4.3)
Proof. \( \text{diag}(\kappa) \) is orderpreserving since we have \( \kappa \in \mathbb{R}_+^n \) s.t. we have an equivalence between \( a \in \ker(A_k) \) with \( \sigma(a) \subseteq \sigma(x^B) \) and \( \text{diag}(\kappa)a = b \in \ker(A) \) with \( \sigma(b) \subseteq \sigma(\text{diag}(\kappa)x^B) = \sigma(\nu) \) through \( \sigma(a) = \sigma(b) \). By the same minimization process as pointed out in Remark 3.4, we obtain equation (4.3).

**Lemma 4.2.** Let \( V, W \subset \mathbb{R}^n \) be two subspaces for which \( v \in V \) and \( w \in W \) implies \( v \perp w \) then \( \sigma(V) \cap \sigma(W^*) = \emptyset \). (The converse does not hold).

**Proof.** Assume there exists \( v \in V \) and \( w \in W \) s.t. \( \sigma(v) = \sigma(w) \neq 0 \) then \( v \cdot w > 0 \) which contradicts \( v \perp w \).

We can now state our main theorem:

**Theorem 3.** For a system as in equation (3.4) where \( n \) is the number of species with concentrations \( x \in \mathbb{R}_+^n \) involved in \( r \) reactions \( \{R_i\}_{i \in [r]} \) and stoichiometric difference matrix \( A \in \mathbb{R}^n \times r \) and complex matrix \( B \in \mathbb{R}^r \times n \) with reaction rates \( \kappa \in \mathbb{R}^n_+ \) and corresponding generalized polynomial map \( f_\kappa(x) : \mathbb{R}_+^n \to \mathbb{R}^n \) with \( A_\kappa = A \cdot \text{diag}(\kappa) \) we get under the condition that there exists a specific \( \kappa^t \in \mathbb{R}^r_+ \) s.t.

\[
\text{diag}(\kappa^t)x^B \perp \ker(A) \tag{4.4}
\]

(c.f. eqn. (3.7)) holds for all \( x \in \mathbb{R}_+^n \) the following sufficient conditions for injectivity in the sense of theorem 2:

\[
\text{span(reaction differences in } A) \subseteq \text{span(reactant complexes in } B). \tag{4.5}
\]

Lemma 4.1 provides more than we need to prove (2) (sig) and is part of the proof of (2) (sig), since we need only the disjoint sign condition. The relation holds for all \( \kappa \in \mathbb{R}^r_+ \).

To see that a loop free flux system implies injectivity we have to show that \( \varphi_B \) is injective with respect to \( K \) and we have to show that the image of \( B \) with respect to \( K \) is perpendicular/sign-disjoint to \( \ker(A) \) (theorem 2 (sig)).

We derive another relation from (3.7) and (4.1) by using the fact that the differential \( \delta \nu \) of the flux \( \nu \) does also satisfy these relations.

\[
\frac{d\varphi_B(x)}{dx} = \text{diag}(x^B)B \text{diag}(x^{-1}) \in \mathbb{R}^r \times n, \ x \in \mathbb{R}_+^n \tag{4.6}
\]

We have

\[
\delta \nu \perp \ker(A) \tag{4.7}
\]

too. Calculating \( \delta \nu \):

\[
\delta \nu = \text{diag}(\kappa)\frac{d\varphi_B(x)}{dx} \frac{dx}{dt} dt = \text{diag}(\kappa) \text{diag}(x^B)B \text{diag}(x^{-1}) \cdot SE \text{diag}(\kappa)x^B \cdot dt \tag{4.8}
\]

Lemma 4.2 together with condition (4.7) and (4.8) shows that (sig) in theorem 2 is satisfied in the case where we set \( \sigma(B(\Sigma(K))^*) = \sigma(B(\Sigma(K)) \setminus \{0\}) \) instead of \( \sigma(B(\Sigma(K^*)) \) for all \( \kappa \). It remains to show that \( \varphi_B \) is injective with respect to \( K \) in order to apply the \( \sigma \)-operator to \( K \) directly.

**Remark 4.3.** Relation (4.5) holds for all \( x \in \mathbb{R}_+^n \). This might be a too restrictive condition for CRN systems. We assume that there exists such a parameter system
such that condition (4.3) is satisfied. In the theorem we also allow κ for which thermodynamic feasibility is not allowed. But we obtain in that case that thermodynamic feasible reaction systems from theorem are contained in the set of injective systems as characterized in theorem.

The basis of $K = \text{im}(SE) = \text{im}(A)$ consists of the stoichiometric differences $[y_i - y'_i] \in \mathcal{R}$. The basis of the rowspace of $B$ consists of all reactant complexes $y'_i$.

According to theorem (sig) and lemma 3.5, 2. we need to show that the columnspace of $SE$ maps injectively on the rowspace of $B$. By the definition of equation (4.5) this shows theorem 3.

\[\text{Lemma 4.4.}\]
For $[y_i - y'_i] \in \mathcal{R}$ with $y_i \neq y'_i$ at least one of the following two cases is true:

a) $y_i \cdot [y_i - y'_i] \neq 0$

b) $y'_i \cdot [y_i - y'_i] \neq 0$

\[\text{Proof.}\] Assume that both are zero then we would have $0 < [y_i - y'_i] \cdot [y_i - y'_i] = 0$. ■

\[\text{Corollary 4.5.}\]
For a system of $r$ reversible reactions with thermodynamic feasible fluxes the corresponding generalized polynomial $f_\kappa(x)$ is injective.

\[\text{Proof.}\] Weak reversibility implies that every reactant and product complex is represented at least once in the rows of $B$. Hence the columnspace of $SE = A$ is contained in the rowspace of $B$. Together with lemma 4.4 we see that $K^\ast$ is mapped injectively into $\text{im}(B)$, which is orthogonal to $\ker A_\kappa$.

\[\text{Corollary 4.6.}\]
For all weakly reversible thermodynamically feasible fluxes the generalized polynomial map $f_\kappa(x)$ is injective.

\[\text{Proof.}\] Deficiency as introduced in [11] is replaced by thermodynamic feasibility as represented in equation (4.5). The injectivity relation is reduced to

\[
\text{span(reactant complexes)} \subseteq \text{span(reactant complexes)}.
\]

5. Continuous flow stirred tank reactors. We can extend the closed system of reactions as developed until now by a continuous external flow as described in the continuous flow stirred tank reactor (CFSTR). We introduce an artificial reaction by the inflow $y^\ast$ as a reactant complex and the resulting outflow $y'^\ast$ as a product complex by setting $\Delta y^\ast = [y^\ast - y'^\ast]$. By that reaction a stoichiometry class is fixed from external imposed conditions. We assume that the interior system given by the closed CRN as described until now has a thermodynamical feasible flux system and especially an interior fixed point and is hence injective by definition. The response to the external flux is equivalent to the fixation of the system to a starting position, which is unique by injectivity of the interior system. By these assumption we obtain
the corollary:

**Corollary 5.1.** A CRN as given under the same assumptions from theorem is injective with respect to a continuous inflow where \( y^*_i \) are the concentrations of the species for the inflow and \( y'^*_i \) are the concentrations in the outflow which is the species concentration in the system. We can write for the response of the internal system:

\[
f_\kappa,(x) = [y^* - y'^*]
\]

(5.1)

\( y^*_i = c_i \) is the number of species \( x_i \) inflow per unit Volume and similar for \( y'^*_i = x_i \). The reaction rate \( \kappa^* = 1 \).

6. **Conclusion.** Including thermodynamic principles into CRN’s leads to a restriction of the available parameter space. Thermodynamic feasible reaction dynamics requires injective generalized polynomial maps for the dynamics of the species concentrations. Reversible and weakly reversible CRN’s imply injectivity. Regarding cell differentiation we can conclude that metabolic networks are regulated by signal transduction and not by triggering intrinsic multistability. Therefore we can assume or predict that multistability is governed by regulatory mechanisms, which are not subjected to powerlaw kinetics and thermodynamic energy potentials.

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**REFERENCES**

[1] E. Noor, N. E. Lewis, and R. Milo, *A proof for loop-law constraints in stoichiometric metabolic networks*, BMC Systems Biology 2012, 6:140.

[2] S. Müller, E. Feliu, G. Regensburger, C. Conradi, A. Shiu, and A. Dickenstein, *Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry*, submitted.

[3] G. Craciun and M. Feinberg, *Multiple equilibria in complex chemical reaction networks: I. the injectivity property*, SIAM J. APPL. MATH., 65 5 (2005), pp. 1526-1546.

[4] D. Angeli, P. De Leenheer, and E. D. Sontag, *A Petri net approach to the study of persistence in chemical reaction networks*, Math. Biosci., 210 (2007), pp. 598–618.

[5] A. Kümmler, S. Panke and M. Heinemann, *Systematic assignment of thermodynamic constraints in metabolic network models*, BMC Bioinformatics, (2006), 7:512.

[6] M. Banaji and G. Craciun, *Graph-theoretic criteria for injectivity and unique equilibria in general chemical reaction systems*, Adv. in Appl. Math., 44 (2010), pp. 168–184.

[7] A. Ben-Israel, *Notes on linear inequalities, 1: The intersection of the nonnegative orthant with complementary orthogonal subspaces*, J. Math. Anal. Appl., 9 (1964), pp. 303–314.

[8] C. Conradi and D. Flockerzi, *Multistationarity in mass action networks with applications to ERK activation*, J. Math. Biol., 65 (2012), pp. 107–156.

[9] M. Feinberg, *Complex reaction balancing in general kinetic systems*, Arch. Ration. Mech. Anal., 49 (1972), pp. 187–194.

[10] ———, *Chemical reaction network structure and the stability of complex isothermal reactors - I. The deficiency zero and deficiency one theorems*, Chem. Eng. Sci., 42 (1987), pp. 2229–2268.

[11] ———, *The existence and uniqueness of steady states for a class of chemical reaction networks*, Arch. Rational Mech. Anal., 14. XII., 132 4 1995, pp 311-370.

[12] F. Horn and R. Jackson, *General mass action kinetics*, Arch. Ration. Mech. Anal., 47 (1972), pp. 81–116.

[13] B. Joshi and A. Shiu, *Atoms of multistationarity in chemical reaction networks*, J. Math. Chem., 51 (2013), pp. 153–178.

[14] A. Shiu and B. Sturmfels, *Siphons in chemical reaction networks*, Bull. Math. Biol., 72 (2010), pp. 1448–1463.
[15] C. Soulé. *Graphic requirements for multistationarity*. Complexus, 1 (2003), pp. 123–133.

[16] R. Thomas. *On the relation between the logical structure of systems and their ability to generate multiple steady states or sustained oscillations*, in Numerical methods in the study of critical phenomena, J. Delia-Dora, J. Demongeot, and B. Lacolle, eds., vol. 9 of Springer Series in Synergetics, Springer series, 1981, pp. 180–193.

[17] J.B. Butt. *Reaction Kinetics and Reactor Design*, Marcel Dekker Inc, 2000.

[18] N.E. Henriksen and F.Y. Hansen. *Theories of molecular reaction dynamics; the microscopic foundation of chemical kinetics*. Oxford U. Press, 2008.