The zero deficiency theorem*

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Abstract

We prove the zero deficiency theorem in Theorems 4 and 8 below.

1 Chemical reaction networks (CRN's)

Notation When $x, y \in \mathbb{R}^n$, we abuse notation and define the vector xy by taking entrywise products of the vectors x and y. The natural inner product of two vectors x and y in the Euclidean space $\mathbb{R}^n$ is denoted as $< x, y >$.

When $x \in \text{int}(\mathbb{R}^n_+)$, we let $\ln(x)$ denote the n vector obtained from x by taking entrywise natural logarithms. Similarly, for $y \in \mathbb{R}^n$, we let e^y denote the n vector obtained from y by taking entrywise exponentials. If $x \in \mathbb{R}^n_+$ and $a \in \mathbb{Z}^n_+$, then we define

$$x^a := \prod_{i=1}^{n} x_i^{a_i},$$

where we define $0^{a_i} := 1$ if $a_i > 0$ and $x_i^0 := 1$ for all $x_i \geq 0$.

A CRN is given by a set of r reactions between p complexes involving n species. Each complex is a linear combination of the species with non-negative integer coefficients. The concentrations obey:

$$\dot{x} = SER(x), \tag{1}$$

where S is a $n \times p$ matrix in which the jth column contains the stoichiometric coefficients of the species in the jth complex, and E describes the reactions taking place between the complexes. This matrix is a $p \times r$ matrix for which each column corresponds to a unique reaction, and it has exactly one entry equal to $+1$, one entry equal to -1 and the other entries equal to 0. The ith entry of the kth column of E is -1 $(+1)$ if the kth reaction has the ith complex as its reaction (product) complex. Notice in particular that all columns of E add to 0:

$$1^T E = 0.$$

Finally, the vector $R(x)$ is the r vector containing the reaction rates of the various reactions. We assume that this vector has non-negative entries that depend in some sufficiently smooth way on the state vector x, and that if $x \in \text{int}(\mathbb{R}^n_+)$, then $R(x) > 0$. In addition we assume that $R_i(x) = 0$ if $x_j = 0$ for some species j appearing in the reaction complex of reaction i. This is a natural assumption which simply expresses that the reaction does not take place if one of its reactants is missing. As a consequence it is not hard to prove that

Fact 1. $\mathbb{R}^n_+$ is forward invariant for (1).

The proof is omitted but relies on the easily established fact that if $x_i = 0$, then the ith component of the vector field of (1) is non-negative. The geometrical interpretation of this condition is that the vector field does not point away from $\mathbb{R}^n_+$ on its boundary. The result should now be intuitively clear.

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By setting

$$\Gamma = SE,$$

we obtain a second description for the evolution of the species concentrations:

$$\dot{x} = \Gamma R(x) \tag{2}$$

The matrix Γ is usually called the stoichiometric matrix. Perhaps this name should have been reserved for the matrix S. Notice that every column of Γ is the differences of two columns of the matrix S. For some purposes, description (1) is useful, but for others (2) is. Later we will see a third way to represent the ODE for the concentrations.

A second invariance result follows immediately since (2) implies that any solution $x(t)$ must satisfy:

$$x(t) = x(0) + \Gamma \int_0^t R(x(s))ds,$$

hence solutions are restricted to lie on affine subspaces of the form $\{x + \Gamma z \,|\, z \in \mathbb{R}^r\}$, for some given $x \in \mathbb{R}^n$. These are called stoichiometry classes, and positive stoichiometry classes if they contain a positive vector.

Fact 2. Each stoichiometry class is invariant for (2).

2 Complex balanced CRN

It turns out to be useful to first introduce the directed graph whose vertices are the complexes of the CRN, and whose directed edges are the reactions between these complexes. The matrix E is then nothing but what in graph theory is called the incidence matrix of the directed graph. We will use a few more concepts from graph theory. First, we say that a directed graph is strongly connected if there is a directed path from each vertex to each other vertex. (A directed path is a finite, ordered, alternating sequence of vertices and directed edges $v_1, e_1, v_2, e_2, \ldots, e_{k-1}, v_k$ with $k > 1$). A directed cycle is a closed directed path, ie it is a directed path in which the first and final vertices coincide ($v_1 = v_k$). A simple directed cycle is a directed cycle in which all vertices are pairwise distinct, except for the first and last vertex. For each directed graph, there is an associated undirected graph, obtained by dropping the direction of the edges. For such an undirected graph, we can define the notions of an undirected path, cycle and simple cycle in a similar way as we did for their directed cousins.

We can partition the vertices of a directed graph into its components. These are the equivalence classes of the equivalence relation defined by declaring that two vertices are equivalent if there is an undirected path between them. When there is one component, we say that the graph is connected. Otherwise it is said to be disconnected. A stronger notion are the strong components which are the equivalence classes of the equivalence relation defined by declaring that two vertices are equivalent if there is a directed path from the first to the second vertex, and a directed path from the second to the first as well. When every component is a strong component, we say that the directed graph is weakly reversible (the same terminology is also used for the corresponding CRN).

The incidence matrix E has the following algebraic properties.

Lemma 1. *Let the directed graph associated to E have l components. Then*

$$dim(Im(E)) = p - l, \quad dim(Ker(E)) = r - (p - l)$$

Moreover, if the directed graph is weakly reversible, then $Ker(E)$ contains a positive vector.

Proof. First we show that $\dim(\mathrm{Im}(E)) = p - l$. If $l = 1$, we can delete edges to obtain a spanning tree (a spanning tree is an undirected subgraph that contains all vertices, and has one component -hence it is still a connected graph-, with the additional property that if we would remove one additional edge, the resulting graph would be disconnected). At the level of the incidence matrix E, edge removal corresponds to column deletion, resulting in a reduced incidence matrix E_r. Note that a spanning tree has $p - 1$ edges, and thus E_r has $p - 1$ columns. It is not hard to see that these columns are linearly independent and hence E_r has rank $p - 1$. (pf: relabel vertices so that

vertex 1 is the root, then there is a 2nd level of vertices, a third level etc; in this case, the reduced incidence matrix is the sum of an upper triangular matrix and a matrix having entries on the subdiagonal only.) We claim that the original incidence matrix E has the same rank as E_r (the rank of E must obviously be at least equal to the rank of E_r). Indeed, each deleted edge from the directed graph gives rise to an undirected simple cycle when added to the spanning tree. On the level of the matrix E_r, adding this edge means that we add another column which is easily seen to be linearly dependent on the columns of E_r. Thus, the span of the columns of E is the same as the span of E_r, establishing that if $l = 1$, then $\dim(\mathrm{Im}(E)) = \dim(\mathrm{Im}(E_r)) = p - 1$. A similar argument shows the result for $l > 1$. Since E is a p by r matrix the dimension of $\mathrm{Ker}(E)$ must equal $r - \dim(\mathrm{Im}(E)) = r - (p - l)$ (see Appendix), establishing the first part of the lemma.

For the second part, we first assume that the directed graph is strongly connected. We will use a result from graph theory (proved in the Appendix), which states that if a directed graph is strongly connected, then it has a directed cycle that contains all edges. Define the vector d as follows. For all $i = 1, \ldots, r$ we let

$$d_i = \text{ number of times the ith directed edge occurs in the directed cycle.}$$

Then d is clearly a non-negative vector. In fact, it is a positive vector since each edge appears at least once in the directed cycle. We claim that

$$Ed = 0.$$

This is true if $(Ed)_j = 0$ for all $j = 1, \ldots, p$. But each $(Ed)_j$ is equal to the difference of the number of incoming edges into vertex j and the number of outgoing edges of vertex j that appear in the directed cycle. This difference must be zero. Indeed, assume wlog that the directed cycle start at vertex j (if not, then we shift the alternating sequence characterizing the directed cycle so that vertex j becomes the first vertex). Then for every outgoing edge from vertex j, there is a subsequent incoming edge to vertex j in the directed cycle. This establishes the claim in case the graph is strongly connected. If the graph is only weakly reversible, then we can relabel the vertices and edges such that the incidence matrix has the following block structure:

$$E = \begin{pmatrix} E_1 & 0 & \ldots & 0 \\ 0 & E_2 & \ldots & 0 \\ \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & E_l \end{pmatrix}, \tag{3}$$

where $l > 1$ is the number of strong components (which equals the number of components because the directed graph is weakly reversible), and each E_j is the incidence matrix correpsonding to a strongly connected component of the graph. By the previous paragraph we have that there exists for each j, a positive vector d_j such that $E_j d_j = 0$. Define the vector d by stacking the vectors $d_1, d_2, \ldots, d_s$ into a single positive column vector. Then clearly $Ed = 0$, which concludes the proof. □

Definition 1. *A CRN is complex balanced if there is some vector $d > 0$ such that*

$$Ed = 0.$$

Remark 1. This definition requires that there is a positive vector (it is a rate vector, and as such, it can be thought of as a vector of flows), such that the net flow into each complex of the CRN is zero. This is nothing more than a stronger version of Kirchoff's current law. It is stronger since the vector d is required to be positive here, whereas in electrical circuit theory, the vector d could take any value in $\mathbb{R}^n$.

The main result is the following.

Theorem 1. *A CRN is complex balanced iff it is weakly reversible.*

Proof. If. This is immediate from Lemma 1.

Only if. We will show that if the CRN is not weakly reversible, then there is a vector v such that:

$$E^T v \geq 0 \text{ but } \neq 0. \tag{4}$$

From this it is clear that there cannot be a positive vector d such that $Ed = 0$ (for $v^T Ed > 0$ for every positive vector d whenever (4) holds), and therefore the CRN is not complex balanced.

Let us determine the vector v. If the CRN is not weakly reversible, then the complex graph has a component which is not strongly connected. Wlog we assume that there is just one component. Then we can relabel the vertices of the complex graph in such a way that the incidence matrix takes the following form:

$$E = \begin{pmatrix} E_1 & + \\ 0 & E_2 \end{pmatrix},$$

where + denotes a nonzero block-matrix having non-negative entries only. In other words, the vertices of the complex graph have been split into two groups in such a way that there are directed edges from the second group to the first, but not from the first into the second. Since $1^T E = 0$ it follows that $1^T E_1 = 0$ and $1^T E_2 = -b^T$, where $b \geq 0$ but $\neq 0$. Thus,

$$(0 - 1^T)E = (0\ b^T),$$

and hence $v = \begin{pmatrix} 0 \\ -1 \end{pmatrix}$ fits the bill. □

3 Deficiency of a CRN

Clearly,

$$\mathrm{Ker}(E) \subset \mathrm{Ker}(SE), \tag{5}$$

but the reverse inclusion is not necessarily true. A rough measure for the discrepancy in the size of these vector spaces, is the following concept.

Definition 2. *We define the deficiency of a CRN as*

$$\delta := dim(Ker(SE)) - dim(Ker(E))$$

Theorem 2.

$$\delta = 0 \Leftrightarrow Ker(SE) = Ker(E)$$

Proof. This is immediate from (5) and the definition of the deficiency. □

Note that by its very definition, the deficiency is always a non-negative integer, a fact which is not immediately clear from the following characterization of the deficiency which is often taken as its definition.

Theorem 3.

$$\delta = p - l - rank(\Gamma),$$

where l denotes the number of components in the complex graph.

Proof. By definition,

$$\begin{aligned} \delta &= \dim(\mathrm{Ker}(SE)) - \dim(\mathrm{Ker}(E)) \\ &= \dim(\mathrm{Ker}(\Gamma)) - \dim(\mathrm{Ker}(E)) \\ &= (r - \mathrm{rank}(\Gamma)) - (r - \mathrm{rank}(E)) \\ &= \mathrm{rank}(\Gamma) + \mathrm{rank}(E) \\ &= \mathrm{rank}(\Gamma) + (p - l), \end{aligned}$$

where in the last step we used the fact from Lemma 1 that $\mathrm{rank}(E) = p - l$. In the third step we used the standard fact from linear algebra (see Appendix) that if $T : V \to W$ is a linear map between two finite-dimensional vector spaces, then $\dim(\mathrm{Ker}(T)) + \dim(\mathrm{Im}(T)) = \dim(V)$. □

The following result provides us with a necessary condition for the existence of a positive equilibrium of a CRN that has zero deficiency.

Theorem 4. *Suppose that $\delta = 0$.*

If the CRN has a positive equilibrium, or has a positive periodic solution, then the CRN is weakly reversible.

Proof. Let $x^* > 0$ be such that $SER(x^*) = 0$. Since $\delta = 0$, Theorem 2 implies that $ER(x^*) = 0$. Since $x^* > 0$ we have that $R(x^*) > 0$, and thus the CRN is complex balanced. The conclusion now follows from Theorem 1.

Let $x(t) = x(t+T)$ be a positive T-periodic solution for some $T > 0$. Then also $R(x(t)) > 0$ for all t. Hence $R_{\text{ave}} := 1/T \int_0^T R(x(s))ds > 0$ as well. Integrating (1) from 0 to T and dividing by T yields

$$SER_{\text{ave}} = 0,$$

and thus again by Theorem 2 and the assumption that $\delta = 0$, that

$$ER_{\text{ave}} = 0,$$

implying that that CRN is complex balanced. The conclusion follows again from Theorem 1. □

Remark 2. The reaction vector $R(x)$ at such an equilibrium x contains the equilibrium rates (or "flows") of all the reactions in the CRN. The equilibrium flows must thus satisfy Kirchoff's laws, and this explains the terminology of calling the CRN complex balanced.

Remark 3. If $\delta > 0$, then the conclusion of Theorem 4 does not necessarily hold: At a positive steady state x (where $SER(x) = 0$), it is not necessarily the case that $ER(x) = 0$, and thus the rates of the various equilibrium rates (or flows) do not necessarily balance at each complex. In other words, although the CRN could be at equilibrium at the level of the species concentrations (i.e. the concentrations do not change in time), Kirchoff's laws for the flows might be violated at a positive steady state of a CRN with positive deficiency.

Remark 4. One of the surprising aspects of the Zero Deficiency Theorem is that the reverse implication in Theorem 4 holds as well, provided that the reaction rates obey the law of mass action. We will see this in the next section.

We conclude this section with the following property of the deficiency, which will play a role later on.

Lemma 2.

$$\delta = dim\,(Ker(S) \cap Im(E))$$

Proof. Consider the linear map $S|_{\text{Im}(E)}$. By a basic linear algebra fact (Appendix):

$$\dim\left(\text{Im}(E)\right) = \dim\left(\text{Ker}(S|_{\text{Im}(E)})\right) + \dim\left(\text{Im}(S|_{\text{Im}(E)})\right),$$

which is equivalent to:

$$p - l = \dim\left(\text{Ker}(S) \cap \text{Im}(E)\right) + \dim\left(\text{Im}(SE)\right).$$

Since $SE = \Gamma$, the conclusion follows from Theorem 3. □

4 Mass action kinetics

We say that a CRN has mass action kinetics, if the reaction rate vector $R(x)$ has a particular form:

$$R_i(x) = k_i x^{S_l}, \quad i = 1, \ldots, r,$$

where the lth complex is the reactant complex of reaction i, and S_l is the lth column of matrix S, and k_i is a positive constant called the rate constant of reaction i. Thus, the rate of every reaction depends only on the concentrations of the species appearing in the corresponding reaction complex.

For the special case of a CRN with mass action kinetics, we will obtain a third representation for the ODE that describes the evolution of the concentrations. First, we factor $R(x)$ as follows:

$$R(x) = K\Psi(x),$$

where K is a $r \times p$ matrix:

$$K_{ij} = \begin{cases} k_i, \text{ if complex } j \text{ is the reactant complex of reaction } i, \quad i = 1, \ldots, r, \quad j = 1, \ldots, p, \\ 0, \text{ otherwise} \end{cases}$$

Thus each column of K corresponds to a complex, and it contains the reaction rates of those reactions that have that complex as their reaction complex (and zeros everywhere else). The vector $\Psi(x)$ is a p vector whose components are monomials, defined as follows:

$$\Psi_i(x) = \prod_{j=1}^{n} x_j^{S_{ji}}, \quad i = 1, \ldots, p.$$

Consequently, for a CRN with mass action kinetics, we find that (1) can be rewritten as:

$$\dot{x} = SA_k\Psi(x), \tag{6}$$

where

$$A_k := EK$$

is a $p \times p$ matrix. This matrix has non-negative off-diagonal entries and non-positive diagonal entries. If $i \neq j$, then

$$(A_k)_{ij} = \sum_l E_{il}K_{lj} = \begin{cases} 0 \text{ if there is no reaction from complex } j \text{ to complex } i \\ k_{l^*} \text{ if the } l^*\text{th reaction goes from complex } j \text{ to complex } i \end{cases}$$

and

$$(A_k)_{ii} = \sum_l E_{il}K_{li} = -\sum_l K_{li} = -\sum_l k_l,$$

where the last sum runs over all indices l having the property that the lth reaction has the ith complex as its reaction complex (this set of indices could be empty, in which case the sum is zero).

4.1 Existence of a positive steady state

We are trying to find a positive x such that $SER(x) = 0$. Since we are assuming that the deficiency is zero, this is equivalent with solving $ER(x) = 0$ for a positive x by Theorem 2. Clearly, as $R(x)$ is positive for positive x, a necessary condition for solvability of the latter problem, is that the CRN is complex balanced, and thus weakly reversible by Theorem 4, a condition which we assume henceforth.

Since the CRN has mass action kinetics, we are thus trying to solve $SA_k\Psi(x) = 0$ for a positive x. One can show that the zero deficiency condition (ie $\text{Ker}(SE) = \text{Ker}(E)$) is equivalent with saying that $\text{Ker}(SA_k) = \text{Ker}(A_k)$. (pf:clearly $\text{Ker}(A_k) \subset \text{Ker}(SA_k)$; if the inclusion would be a proper inclusion, then there exists z with $SA_kz = 0$ such that $A_kz \neq 0$. Set $y = Kz$, then there is y with $SEy = 0$ but $Ey \neq 0$, contradicting zero deficiency) Thus we only need to solve $A_k\Psi(x) = 0$.

Now comes the amazing fire power of the Perron-Frobenius Theorem! Up to a permutation of the complexes, the matrix A_k can be put in block-diagonal form:

$$A_k = \begin{pmatrix} (A_k)_1 & 0 & 0 & \ldots & 0 \\ 0 & (A_k)_2 & 0 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots & \\ 0 & 0 & \ldots & \ldots & (A_k)_l \end{pmatrix} \tag{7}$$

where each $(A_k)_j$ is an irreducible matrix having non-negative off-diagonal entries. Moreover $1^T(A_k)_j = 0$ for all j, and therefore the principal eigenvalue of each $(A_k)_j$ (which is simple by the P-F Thm) is zero. Thus there exist positive vectors d_j with $(A_k)_jd_j = 0$, and these are the only eigenvectors having non-negative entries (up to multiplication by positive scalars of course).

Solving $A_k\Psi(x) = 0$ for some positive x is therefore equivalent with finding a positive x such that:

$$\Psi(x) = \sum_{i=1}^{l} \lambda_i d_i^e, \text{ for positive } \lambda_i, \quad i = 1, \ldots, l,$$

where the d_i^e are p vectors having entry equal to d_i in the ith block, and zeros elsewhere. Taking logarithms entrywise this is equivalent to solving:

$$S^T \ln(x) = \ln(\sum_{i=1}^{l} \lambda_i d_i^e)$$

for positive λ_i, $i = 1, \ldots, l$. Setting $\lambda_i = \mathrm{e}^{z_i}$ for suitable real z_i, and letting s_i be the non-negative vector obtained from d_i^e by replacing positive entries by 1, and zeros by 0 (thus s_i can be viewed as the support vector corresponding to d_i^e), this is equivalent to solving:

$$S^T \ln(x) = \sum_{i=1}^{l} z_i s_i + \ln(\sum_{i=1}^{l} d_i^e) \tag{8}$$

for some z_i, $i = 1, \ldots, l$.

The following result (it is a pure linear algebra statement!) is crucial.

Lemma 3. *Let a weakly reversible CRN have deficiency δ. Then*

$$dim\left(Im(S^T) + span\{s_i\}\right) = p - \delta$$

Proof. We have from Lemma 2 that

$$\dim\left(\mathrm{Ker}(S) \cap \mathrm{Im}(E)\right) = \delta$$

and thus

$$\begin{aligned} p - \delta &= \dim\left([\mathrm{Ker}(S) \cap \mathrm{Im}(E)]^{\perp}\right) \\ &= \dim\left([\mathrm{Ker}(S)]^{\perp} + [\mathrm{Im}(E)]^{\perp}\right) \\ &= \dim\left(\mathrm{Im}(S^T) + \mathrm{span}\{s_i\}\right) \end{aligned}$$

That $[\mathrm{Im}(E)]^{\perp} = \mathrm{span}\{s_i\}$ follows from the fact that each s_i is clearly contained in $[\mathrm{Im}(E)]^{\perp} = \mathrm{Ker}(E^T)$ (recall that for a weakly reversible CRN, E takes the form (3) and $1^T E_i = 0$ for all $i = 1, \ldots, l$, so that $s_i^T E = 0$ for all $i = 1, \ldots, l$), and since $[\mathrm{Im}(E)]^{\perp}$ and $\mathrm{span}\{s_i\}$ have the same dimension l (for the former, use Lemma 1 and the fact that $\mathrm{Im}(E) \oplus [\mathrm{Im}(E)]^{\perp} = \mathbb{R}^p$; the latter should be clear from the definition of the s_i in the discussion prior to the Lemma). □

Combining (8) and Lemma 3 we have just proved the main result of this subsection.

Theorem 5. *Let the CRN have mass action kinetics, be weakly reversible and have zero deficiency. Then it has a positive steady state x^* with*

$$ER(x^*) = A_k \Psi(x^*) = 0$$

4.2 Characterization of all positive steady states

Let E_+ be the set of positive steady states of a CRN with mass action kinetics:

$$E_+ = \{x \in \mathrm{int}(\mathbb{R}^n_+) | S A_k \Psi(x) = 0\}.$$

Under the assumptions of Theorem 5, we know that $E_+ \neq \emptyset$. In fact, $x^* \in E_+$.

We also define the following set, parametrized by a parameter in the vector space $[\mathrm{Im}(\Gamma)]^{\perp}$:

$$\tilde{E} := \{x \mid x = x^* \, \mathrm{e}^{\mu}, \;\; \mu \in [\mathrm{Im}(\Gamma)]^{\perp}\}. \tag{9}$$

We will prove the following characterization for E_+:

Theorem 6. *Under the conditions of Theorem 5,*

$$E_+ = \tilde{E}.$$

To prove this result, we shall need the following auxiliary result.

Lemma 4. *Let a CRN have l components (not necessarily strong components). Then if $\mu \in [Im(\Gamma)]^{\perp}$, and if the ith and jth complex belong to the same component, then:*

$$< \mu, S_i >=< \mu, S_j >,$$

where S_i denotes the ith column of the matrix S.

Proof. Since $\mu \in [\mathrm{Im}(\Gamma)]^{\perp}$, it follows that:

$$\mu^T \Gamma = \mu^T S E = 0.$$

Recall that every column of E corresponds to a reaction in the CRN and that it has precisely two nonzero entries. One of these is -1 and the other is $+1$, and they occur in position k, respectively l, when the reaction transforms complex k into complex l. Also notice that the column of the matrix SE which corresponds to this reaction contains the difference of the stoichiometry vectors $S_k - S_l$. By assumption, the ith and jth complex belong to the same component, and thus there is a sequence of complexes $C_i, C_{r_1}, C_{r_2}, \ldots, C_{r_q}, C_j$ in which every pair of consecutive complexes is linked by some reaction (the direction of the reaction is irrelevant). Since $\mu^T S E = 0$, it follows that:

$$\mu^T (S_i - S_{r_1}) = \mu^T (S_{r_1} - S_{r_2}) = \cdots = \mu^T (S_{r_q} - S_j) = 0.$$

Adding these expressions yields:

$$\mu^T (S_i - S_j) = 0,$$

which completes the proof. □

Proof. (Proof of Theorem 6). First we show that $\tilde{E} \subset E_+$. Let $\mu \in [\mathrm{Im}(\Gamma)]^{\perp}$, and consider $x = x^* \, \mathrm{e}^{\mu}$. We must show that $A_k \Psi(x) = 0$. Wlog we assume that A_k has the block diagonal form (7), where each block corresponds to a strong component of the CRN, and that $\Psi(x)$ is partitioned correspondingly:

$$\Psi(x) = \begin{pmatrix} (\Psi(x))_1 \\ (\Psi(x))_2 \\ \vdots \\ (\Psi(x))_l \end{pmatrix}$$

It suffices to show that each vector $(A_k)_i \, (\Psi(x))_i = 0$ for $i = 1, \ldots, l$. Pick the ith component of the CRN and assume that it has q complexes $C_{i_1}, \ldots, C_{i_q}$. Then:

$$\begin{aligned} (\Psi(x))_i &= (\Psi(x^* \, \mathrm{e}^{\mu}))_i \\ &= \left((x^* \, \mathrm{e}^{\mu})^{S_{i_1}}, (x^* \, \mathrm{e}^{\mu})^{S_{i_2}}, \ldots, (x^* \, \mathrm{e}^{\mu})^{S_{i_q}} \right)^T \\ &= \left((x^*)^{S_{i_1}} \, \mathrm{e}^{<\mu, S_{i_1}>}, (x^*)^{S_{i_2}} \, \mathrm{e}^{<\mu, S_{i_2}>}, \ldots, (x^*)^{S_{i_q}} \, \mathrm{e}^{<\mu, S_{i_q}>} \right)^T \\ &= \mathrm{e}^{<\mu, S_{i_1}>} \, (\Psi(x^*))_i \end{aligned}$$

where we used the fact that $< \mu, S_{i_1} >=< \mu, S_{i_2} >= \cdots =< \mu, S_{i_q} >$ by Lemma 4. This implies that $(A_k)_i \, (\Psi(x))_i = \mathrm{e}^{<\mu, S_{i_1}>} (A_k)_i \, (\Psi(x^*))_i = 0$, because $x^* \in E_+$. This concludes the proof of the first part.

Next we show that $E_+ \subset \tilde{E}$. This will be proved later in Section 4.4.

□

4.3 Uniqueness of positive steady states in each positive stoichiometry class

Theorem 7. *Let the conditions of Theorem 5 hold, and let P be an arbitrary positive stoichiometry class:*

$$P = \{ z \in \mathbb{R}^n_+ | z = p + Im(\Gamma) | \}$$

for some $p \in int(\mathbb{R}^n_+)$. Then $P \cap E_+$ is a singleton.

Proof. **Step 1.** E_+ intersects each positive stoichiometry class. A result from convex analysis is used for this proof, see Appendix.

We need to show that $P \cap E_+ \neq \emptyset$, i.e.:

$$\exists \mu \in [\mathrm{Im}(\Gamma)]^\perp \ : \ x^* \, \mathrm{e}^\mu - p \in \mathrm{Im}(\Gamma)$$

The idea of the proof is to construct a continuous function on a compact subset of $[\mathrm{Im}(\Gamma)]^\perp$, and to show that the function achieves a minimum at the sought-after point μ.

Consider the function $g : \mathbb{R}^n \to \mathbb{R}$, defined as follows:

$$g(x) :=< x^*, \mathrm{e}^x > - < p, x > .$$

Then its derivative is

$$Dg(x) = x^* \, \mathrm{e}^x - p,$$

and its Hessian is

$$H(x) = \mathrm{diag}(x^* \, \mathrm{e}^x),$$

a positive definite matrix for all $x \in \mathbb{R}^n$, which implies that the function g is convex.

Note that g is radially unbounded, that is, for all $x \neq 0$,

$$\lim_{a \to +\infty} g(ax) = +\infty. \tag{10}$$

Now consider g^r, the restriction of g to $[\mathrm{Im}(\Gamma)]^\perp$. Then g^r is continuous, convex and radially unbounded as well. Consider the following set

$$C = \{x \in [\mathrm{Im}(\Gamma)]^\perp \mid g^r(x) \leq g^r(0)\}.$$

Then C is closed, contains $x = 0$, and is convex (pf: if $x, y \in C$, then for $\lambda \in [0, 1]$, we have that $g^r(\lambda x + (1-\lambda)y) \leq \lambda g^r(x) + (1-\lambda) g^r(y) \leq g^r(0)$). We claim that in fact, C is compact. Indeed, if C were unbounded, then by the result in the Appendix it would contain a half-ray through the origin. Since g^r is radially unbounded, this implies that g^r takes arbitrary large values in C, which contradicts that g^r is bounded by $g^r(0)$ for all points in C.

Thus, g^r achieves a minimum on the set C, and we assume it is achieved at $x = \mu$. By the definition of C we have in fact that g^r achieves its minimum on $[\mathrm{Im}(\Gamma)]^\perp$ at $x = \mu$. It follows that the gradient of g^r, evaluated at $x = \mu$, is zero. As a consequence, the gradient of g, evaluated at $x = \mu$ is perpendicular to $[\mathrm{Im}(\Gamma)]^\perp$, and hence belongs to $\mathrm{Im}(\Gamma)$. More precisely,

$$Dg(\mu) = x^* \, \mathrm{e}^\mu - p \in \mathrm{Im}(\Gamma),$$

which concludes the proof of the first step.

Step 2. The intersection of E_+ with each positive stoichiometry class is unique.

Suppose not, then there is a stoichiometry class containing positive and distinct x_1 and x_2 with

$$x_2 - x_1 = \Gamma y, \text{ for some } y, \text{ and } x_1 = x^* \, \mathrm{e}^{\mu_1}, \ \ x_2 = x^* \, \mathrm{e}^{\mu_2}, \text{ for some } \mu_1 \neq \mu_2 \in [\mathrm{Im}(\Gamma)]^\perp .$$

Then since also $\mu_2 - \mu_1 \in [\mathrm{Im}(\Gamma)]^\perp$,

$$0 =< \Gamma y, \mu_2 - \mu_1 >=< x_2 - x_1, \mu_2 - \mu_1 >=< x^*(\mathrm{e}^{\mu_2} - \mathrm{e}^{\mu_1}), \mu_2 - \mu_1 > .$$

The last expression is positive because x^* is positive, $\mu_1 \neq \mu_2$, and the exponential is a strictly increasing function. We have reached a contradiction. □

4.4 Local asymptotic stability of each positive steady state within its corresponding stoichiometry class

We will show

Theorem 8. *Assume that the conditions of Theorem* 7 *hold, and let* $P \cap E_+ = \{x^*\}$ *so that* x^* *is the unique positive equilibrium in the positive stoichiometry class* P*. Then* x^* *is a locally stable equilibrium of* (6)*. Moreover,* x^* *is locally asymptotically stable with respect to initial conditions in* $P \cap \mathrm{int}(\mathbb{R}^n_+)$.

Proof. We will establish the existence of the following Lyapunov function on $\mathrm{int}(\mathbb{R}^n_+)$:

$$V(x) = \sum_{i=1}^{n} \int_{x_i^*}^{x_i} \ln\left(\frac{y_i}{x_i^*}\right) dy_i,$$

where x^*. Note for future reference that V is continuously differentiable in $\mathrm{int}(\mathbb{R}^n_+)$, and positive definite with respect to x^* (i.e. $V(x) \geq 0$ and $= 0$ iff $x = x^*$), and that

$$\nabla V(x) = \ln\left(\frac{x}{x^*}\right).$$

We claim that $\dot{V}(x) \leq 0$ in $\mathrm{int}(\mathbb{R}^n_+)$, and $= 0$ iff x is a steady state of the CRN. Indeed, along solutions of (1) (or equivalently (2)) with mass action kinetics, there holds that:

$$\begin{aligned}
\dot{V} &= < \dot{x}, \ln\left(\frac{x}{x^*}\right) > \\
&= < \Gamma R(x), \ln\left(\frac{x}{x^*}\right) > \\
&= \sum_{l=1}^{r} < \Gamma_l R_l(x), \ln\left(\frac{x}{x^*}\right) >
\end{aligned}$$

where Γ_l denotes the lth column of the matrix Γ. Assuming that the lth reaction has a reaction and product complex whose stoichiometric vector equals α_l and β_l respectively, it follows that:

$$\begin{aligned}
\dot{V} &= \sum_{l=1}^{r} k_l x^{\alpha_l} < \Gamma_l, \ln\left(\frac{x}{x^*}\right) > \\
&= \sum_{l=1}^{r} k_l (x^*)^{\alpha_l} \, \mathrm{e}^{<\alpha_l, \ln\left(\frac{x}{x^*}\right)>} < \Gamma_l, \ln\left(\frac{x}{x^*}\right) > .
\end{aligned}$$

The reason for rewriting the function S^{α_l} using the exponential functions explicitely, will soon become clear. Then

$$\dot{V} = \sum_{l=1}^{r} k_l (x^*)^{\alpha_l} \, \mathrm{e}^{<\alpha_l, \ln\left(\frac{x}{x^*}\right)>} \left(< \beta_l, \ln\left(\frac{x}{x^*}\right) > - < \alpha_l, \ln\left(\frac{x}{x^*}\right) > \right)$$

Now comes the first key step: By strict convexity of the exponential function, it follows that

$$\dot{V} \leq \sum_{l=1}^{r} k_l (x^*)^{\alpha_l} \left(\mathrm{e}^{<\beta_l, \ln\left(\frac{x}{x^*}\right)>} - \mathrm{e}^{<\alpha_l, \ln\left(\frac{x}{x^*}\right)>} \right),$$

and equality holds if and only if

$$< \beta_l, \ln\left(\frac{x}{x^*}\right) > = < \alpha_l, \ln\left(\frac{x}{x^*}\right) >, \quad \forall l = 1, \ldots, r \tag{11}$$

We will investigate later what it means for a vector x to satisfy these r equations. For now, we continue the calculation of $\dot{V}$:

$$\dot{V} \leq \sum_{l=1}^{r} k_l (x^*)^{\alpha_l} \left(\mathrm{e}^{<\beta_l, \ln\left(\frac{x}{x^*}\right)>} - \mathrm{e}^{<\alpha_l, \ln\left(\frac{x}{x^*}\right)>} \right)$$

Now comes the second key step. Denoting the ith standard basis vector of $\mathbb{R}^p$ by e_i, the latter expression can be rewritten as:

$$\dot{V} \leq \sum_{l=1}^{r} k_l (x^*)^{\alpha_l} < E_l, \sum_{i=1}^{p} \mathrm{e}^{<S_i, \ln\left(\frac{x}{x^*}\right)>} e_i >,$$

where E_l denotes the lth column of the incidence matrix E, and S_i is the ith column of the matrix S. Note that this can be rewritten more compactly as:

$$\dot{V} \leq < ER(x^*), \sum_{i=1}^{p} \mathrm{e}^{<S_i, \ln(\frac{x}{x^*})>} e_i > .$$

Since $ER(x^*) = 0$ (because by assumption x^* is a positive equilibrium, that is $SER(x^*) = 0$, the CRN has deficiency zero, which implies that in fact $ER(x^*) = 0$), it follows that

$$\dot{V} \leq 0.$$

Let us now investigate for which states x there holds that $\dot{V}(x) = 0$. As we have seen this happens if and only if (11) is satisfied. This set of equations can be rewritten more compactly as follows:

$$\ln\left(\frac{x}{x^*}\right) \in [\mathrm{Im}(\Gamma)]^{\perp},$$

or equivalently if $x \in \tilde{E}$, where the set $\tilde{E}$ was defined in (9). On the other hand, we know that $x \in E_+$ implies that $\dot{V}(x) = 0$ (since by definition $\dot{V}(x) = < \Gamma R(x), \nabla V(x) >$), and thus by the above that $x \in \tilde{E}$. In other words, we have shown that $E_+ \subset \tilde{E}$, which provides the proof of the second part of Theorem 6.

Summarizing, we have shown that for all $x \in \mathrm{int}(\mathbb{R}^n_+)$ holds that $\dot{V}(x) \leq 0$, and that $\dot{V}(x) = 0$ if and only if $x \in \tilde{E} = E_+$.

From Lyapunov's stability theorem follows at once that x^* is a stable equilibrium. In fact, a stronger conclusion is possible. If we restrict initial conditions to those *positive* initial conditions in the positive stoichiometry class P that contains x^*, it follows that $\dot{V}(x) < 0$, unless $x = x^*$, since x^* is the unique equilibrium in this set. And thus Lyapunov's stability theorem implies that x^* is locally *asymptotically* stable with respect to initial conditions in $P \cap \mathrm{int}(\mathbb{R}^n_+)$.

□

Remark 5. Recent work on CRN's has focused on the notion of persistence. We say that a CRN is persistent if (1) has the property that

$$\omega(x) \cap \mathrm{bd}(\mathbb{R}^n_+) = \emptyset, \quad \text{for all } x \in \mathrm{int}(\mathbb{R}^n_+),$$

where $\omega(x)$ denotes the omega limit set of x.

If we assume that the CRN is persistent (and bearing in mind that both necessary and sufficient conditions for persistence have been obtained in the literature), then the conclusion of Theorem 8 can be strengthened substantially :

Theorem 9. *Let the assumptions of Theorem* 8 *hold, and assume that the CRN is persistent. Then x^* is globally asumptotically stable with respect to all initial conditions in $P \cap \mathrm{int}(\mathbb{R}^n_+)$.*

Proof. For $x \in P \cap \mathrm{int}(\mathbb{R}^n_+)$, the corresponding omega limit set is contained in $P \cap \mathrm{int}(\mathbb{R}^n_+)$ because the CRN is persistent. But since $\dot{V}(y) \leq 0$ for all $y \in P \cap \mathrm{int}(\mathbb{R}^n_+)$ and $\dot{V}(y) = 0$ iff $y = x^*$, it follows from Lasalle's invariance principle that $\omega(x) = \{x^*\}$. □

Appendix

A Facts from linear algebra

Let V and W be subspaces of a Euclidean space $\mathbb{R}^n$. Then

$$(V \cap W)^{\perp} = V^{\perp} + W^{\perp}.$$

Let $L : X \to Y$ be a linear mapping, where X and Y are subspaces of certain Euclidean spaces. Then

$$\dim(X) = \dim(\mathrm{Ker}(L)) + \dim(\mathrm{Im}(L)),$$

and

$$[\mathrm{Ker}(L)]^{\perp} = \mathrm{Im}(L^T), \text{ and } [\mathrm{Im}(L)]^{\perp} = \mathrm{Ker}(L^T),$$

where L^T is the adjoint of L.

B Facts from graph theory

Lemma 5. *If G is a strongly connected directed graph, then it has a directed cycle (not necessarily simple) containing all edges of the graph.*

Proof. The proof provides an algorithm for the construction of the directed cycle. It will consist of the concatenation of several directed cycles and directed paths.

Wlog we assume that G has more than 1 vertex (otherwise there is nothing to prove).

We start with vertex 1, and consider the set of outgoing directed edges leaving this vertex $\mathcal{E}^1 = \{e_1^1, \ldots, e_k^1\}$, and the corresponding set of target vertices $\mathcal{T}^1 = \{v_1^1, \ldots, v_k^1\}$. For every $i = 1, \ldots, k$, we can construct directed cycles starting at vertex 1, passing via edge e_i^1 to vertex v_i^1, and returning to vertex 1 via some directed path (which exists because G is strongly connected). These k directed cycles are then concatenated into one large directed cycle.

From vertex 1 we pick a directed path to vertex 2. The previous large directed cycle can be connected with this directed path, to form a part of the sought after directed cycle. Now we repeat the construction performed at vertex 1, but at vertex 2: We consider the set of outoing directed edges $\mathcal{E}^2$ leaving vertex 2, and the corresponding set of target vertices $\mathcal{T}^2$, and we construct directed cycles starting and ending at vertex 2 which are all concatenated into a second large directed cycle which is concatenated with the previously described part of the sought after directed cycle.

This procedure can be continued until we reach vertex n. The final part of the directed cycle will be some directed path from vertex n to vertex 1, which leads to the sought after directed cycle. Clearly, it contains all edges of the graph. Indeed, by construction it contains all outgoing edges of the graph, and every edge of the graph is an outgoing edge leaving some vertex.

□

C The Perron-Frobenius Theorem

D A result from convex analysis

Theorem 10. *Let C be a closed convex set in $\mathbb{R}^n$ and $0 \in C$. If C is unbounded, then it contains a half ray through the origin, ie. there is some $y^* \in C$ with $y^* \neq 0$, such that $R_{y^*} := \{ay^* \mid a \geq 0\} \subset C$.*

Proof. Let $x_n \in C$ be a sequence with $|x_n| \to +\infty$ as $n \to +\infty$. Since $0 \in C$, it follows by convexity of C that every segment $[0, x_n]$ is also in C. For all sufficiently large n, this implies that $y_n := x_n/|x_n| \in C$ as well. Since y_n belongs to the unit sphere in $\mathbb{R}^n$, the sequence y_n has a converging subsequence with limit $y^* \neq 0$, and since C is closed, it follows that $y^* \in C$. We claim that R_{y^*} is contained in C. If not, there would be some $\tilde{y} \in R_{y^*}$ with $\tilde{y} \notin C$. Since C is closed, there is an open ball $B_{\tilde{y}}$ of radius $\epsilon > 0$, containing $\tilde{y}$, and such that $B_{\tilde{y}}$ is contained in the complement of C. We return to the converging subsequence y_n in the unit sphere, and consider the corresponding sequence x_n. It follows that for all sufficiently large n, the segments $[0, x_n]$ intersect the ball $B_{\tilde{y}}$. Since these segments $[0, x_n]$ are contained in C, this implies that $B_{\tilde{y}}$ and C intersect, a contradiction. □

E Lyapunov's stability theorem and Lasalle's invariance principle

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