21st International Symposium on
Mathematical Theory of Networks and Systems
July 7-11, 2014. Groningen, The Netherlands

Open complex-balanced mass action chemical reaction networks

Shodhan Rao Arjan van der Schaft Bayu Jayawardhana

Abstract— **We consider open chemical reaction networks, i.e. ones with inflows and outflows. We assume that all the inflows to the network are constant and all outflows obey the mass action kinetics rate law. A complex-balanced open reaction network is one that admits a complex-balanced steady state. We show how such a system can be modelled using graph-theoretic principles. It is well known that every steady state of a complex-balanced open reaction network is complex-balanced. Using graph-theoretic principles, we provide a more insightful proof of this fact as compared to the known proof.**

I. Introduction

The foundations for chemical reaction network theory was laid in the 70s by Maria Horn, Roy Jackson and Martin Feinberg [1]–[3], who analyzed chemical reaction networks. For the analysis, they introduced the notion of the graph of complexes which is a graph whose vertices are associated with the complexes, i.e., the left-hand (substrate) and right-hand (product) sides of reactions and the edges with the reactions of the network. Since then a lot of work has been carried out in this area, (for example, see [4]–[9] among others). In the last few years, there has been a lot of interest in the monotonicity [10], [11], graph-theoretic analysis approach [12]–[14], conditions for multiple equilibria [15], persistence and global stability [16]–[18] of closed chemical reaction networks.

In many cases of interest, especially in biochemical reaction networks, there is a continuous interaction with the environment. In many of these biochemical reaction networks, it has been observed that the inflows from the environment are constant and directed towards complexes, and the outflows are from complexes to the environment and these obey the law of mass action kinetics (see for example, the biochemical model in [19]). In some models of biochemical networks, some complexes made of single species are clamped or maintained at constant concentrations (see for example, [19], [20]). If the rate governing law of the reactions involving such complexes is mass action kinetics, then it can be shown that the system can be considered as having constant inflows and outflows obeying the law of mass action kinetics.

In this paper, we consider open reaction networks with constant inflows to and mass action kinetics outflows (as described previously) from certain complexes, assuming that the governing law of the network is mass action kinetics. We first add a virtual complex called the *environment* complex to the graph of complexes corresponding to the network in order to obtain an *extended graph of complexes*. All the constant inflows are directed edges emanating from the environment complex and all the proportional outflows are edges directed towards the environment complex in the extended graph of complexes. This idea of adding an environment complex to model constant inflows and proportional outflows is already known and was discussed in [1] and [21]. Although the main result (Theorem 3.3) of this abstract is the same as [1, Lemma 5B], we provide a more insightful proof using graph-theoretic principles. While in [1], a general framework has been provided which includes both closed and open reaction networks, in this abstract we specifically focus on the modelling of open chemical reactions networks and show clearly the difference with modelling for the case of closed reaction networks.

A *complex balanced* open reaction network is one for which there exists a complex-balanced steady state, i.e., a steady state of species concentrations at which the rate of inflow into any complex including the environment complex is equal to the rate of outflow from it. Fig. 1 shows an example of a complex balanced open reaction network. With reference to Fig. 1, for $i = 0, \ldots, 5$, $\mathcal{C}_i$ denotes the

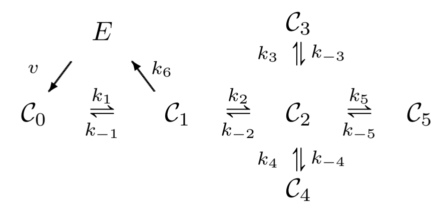

Fig. 1. Example of a complex-balanced open reaction network

complexes, E denotes the environment complex, v denotes a constant inflow rate and the k's represent the reaction coefficients of the reactions of the network.

In this abstract, we show that all the steady states of an open complex balanced reaction network are complex balanced. This is done by first arriving at a compact mathematical formulation for the dynamics of an open complex-balanced reaction network in terms of a known steady state. This formulation is then used to arrive at properties of all the remaining steady states of the network. The approach that we use in this abstract can be considered as an extension of the one used in [14].

Notation: $\mathbb{1}_m$ denotes a vector of dimension m with all entries equal to 1. The mapping $\mathrm{Ln} : \mathbb{R}^m_+ \to \mathbb{R}^m, \quad x \mapsto$

Shodhan Rao is with the Center for Systems Biology, University of Groningen, email: s.rao@umcg.nl. The centre is funded by the Netherlands Organisation for Scientific Research.

Arjan van der Schaft is with the Johann Bernoulli Institute for Mathematics and Computer Science, University of Groningen, e-mail: A.J.van.der.Schaft@rug.nl

Bayu Jayawardhana is with the Research Institute of Technology and Management, University of Groningen, email: b.jayawardhana@rug.nl

$\mathrm{Ln}(x)$, is defined as the mapping whose i-th component is given as $(\mathrm{Ln}(x))_i := \ln(x_i)$. Similarly, the mapping $\mathrm{Exp} : \mathbb{R}^m \to \mathbb{R}^m_+, \quad x \mapsto \mathrm{Exp}(x)$, is the mapping whose i-th component is given as $(\mathrm{Exp}(x))_i := \exp(x_i)$.

II. Complex balanced networks with constant inflows and mass action kinetics outflows

First consider a closed chemical reaction network. Corresponding to the original graph of complexes associated with the network, let m, c and r denote the number of species (metabolites), complexes and reactions respectively. Define as in [14], the complex stoichiometric matrix Z as the $m \times c$ matrix whose α-th column captures the expression of the α-th complex in the m chemical species. Define the incidence matrix D corresponding to the original graph of complexes as the $c \times r$ matrix for which the (α, j)-th element is equal to -1 if vertex α is the tail vertex of edge j and 1 if vertex α is the head vertex of edge j, while 0 otherwise.

The dynamics of the closed reaction network has the form

$$\dot{x} = ZDv(x), \quad x \in \mathbb{R}^m_+, \tag{1}$$

where $v(x) \in \mathbb{R}^r$ is the vector of reaction rates. In case the reaction rates $v(x)$ are given by *mass-action kinetics* then, following [12], [14], the dynamics can be written into the form

$$\dot{x} = -ZL\mathrm{Exp}(Z^T \mathrm{Ln}(x)), \quad x \in \mathbb{R}^m_+.$$

Here L is an $c \times c$ matrix defined on the basis of the reaction coefficients as follows. For $i \neq j$ define L_{ij} as minus the sum of the reaction coefficients of all reactions from the j-the complex to the i-th complex, $i, j = 1, \cdots, c$. Furthermore, define the elements L_{jj} as $L_{jj} = -\sum_{i \neq j} L_{ij}$. By construction L satisfies

$$\mathbb{1}_c^T L = 0.$$

Furthermore, L has non-negative diagonal elements and non-positive off-diagonal elements, and is called a *Laplacian matrix*.

Now we will extend this setting to mass action kinetics chemical reaction networks with *constant inflows* and *proportional outflows*, which means that the dynamical equations (1) of the closed network are extended to

$$\dot{x} = ZDv(x) + ZD_{\mathrm{in}}v_{\mathrm{in}} + ZD_{\mathrm{out}}v_{\mathrm{out}}(x), \quad x \in \mathbb{R}^m_+. \tag{2}$$

Here the matrices D_{in} and D_{out} specify the structure of the inflows and outflows. D_{in} is a matrix whose columns consist of exactly one element equal to $+1$ (at the row corresponding to the complex which has inflow) while the other elements are zero. Similarly, D_{out} is a matrix whose columns consist of exactly one element equal to -1 (at the row corresponding to the complex which has outflow) while the rest are zero. As in the closed network case, $v(x)$ is the vector of (internal) mass action kinetics reaction rates given by $Dv(x) = -L\mathrm{Exp}(Z^T \mathrm{Ln}(x))$. Furthermore, $v_{\mathrm{in}} \in \mathbb{R}^k_+$ is a vector of constant positive inflows with k denoting the number of inflows, while $v_{\mathrm{out}}(x)$ is a vector of proportional outflows, which is also described by mass action kinetics, that is,

$$D_{\mathrm{out}}v_{\mathrm{out}}(x) = -\Delta_{\mathrm{out}}\mathrm{Exp}(Z^T \mathrm{Ln}(x))$$

for a certain diagonal matrix Δ_{out} with nonnegative diagonal elements (given by the mass action kinetics rate constants).

As mentioned in the introduction, we now add an *environment complex* to the graph of complexes. Corresponding to the constant inflows we then add directed edges emanating from the environment complex to the complexes with inflows. Likewise corresponding to the proportional outflows, we add edges directed towards the environment complex starting from the complexes with proportional outflows. We call the resulting graph, the *extended graph of complexes* associated with the open network.

The complex stoichiometric matrix (Z_e) corresponding to the extended graph of complexes is defined as

$$Z_e = \begin{bmatrix} Z & 0_m \end{bmatrix}.$$

The last column of Z_e corresponds to the expression of the environment complex in terms of the species of the network, and it is quite logical to fill it up with zeros. Let D_e denote the incidence matrix corresponding to the extended graph of complexes. Partition D_e as

$$D_e = \begin{bmatrix} B \\ B_E \end{bmatrix},$$

where B_E is a row vector corresponding to the environment complex. This row vector has entries -1 corresponding to the inflow reactions, +1 corresponding to the outflow reactions and zeros corresponding to the remaining internal reactions of the system. Notice that the matrix B can be partitioned as

$$B = \begin{bmatrix} D & D_{\mathrm{in}} & D_{\mathrm{out}} \end{bmatrix}. \tag{3}$$

Now define the c-dimensional column vector L_{in} as $L_{\mathrm{in}} := -D_{\mathrm{in}}v_{\mathrm{in}}$ and furthermore, let L_{out} be the c-dimensional row vector whose i-th element is equal to minus the i-th diagonal element of Δ_{out}. Then extend the $c \times c$ Laplacian matrix L of the graph of (ordinary) complexes to an $(c+1) \times (c+1)$ Laplacian matrix L_e of the extended graph of complexes as follows

$$L_e := \begin{bmatrix} L + \Delta_{\mathrm{out}} & L_{\mathrm{in}} \\ L_{\mathrm{out}} & \delta_{\mathrm{in}} \end{bmatrix},$$

where δ_{in} is the non-negative number equal to minus the sum of the elements of L_{in}. Note that by construction L_e has non-negative diagonal elements, non-positive off-diagonal elements, while its columns sums are all zero.

It follows that the dynamics (2) of the mass action reaction network with constant inflows and proportional outflows can be rewritten as

$$\dot{x} = Z_e D_e v_e(x) = -Z_e L_e \mathrm{Exp}(Z_e^T \mathrm{Ln}(x)), \quad x \in \mathbb{R}^m_+, \tag{4}$$

where

$$v_e(x) := \begin{bmatrix} v(x) \\ v_{\mathrm{in}} \\ v_{\mathrm{out}}(x) \end{bmatrix}.$$

Since the last column of Z_e is the zero vector, (4) reduces to

$$\begin{aligned}\dot{x} &= -\begin{bmatrix} Z & 0 \end{bmatrix} L_e \begin{bmatrix} \mathrm{Exp}(Z^T \mathrm{Ln}(x)) \\ 1 \end{bmatrix} \\ &= -Z[(L+\Delta_{\text{out}})\mathrm{Exp}(Z^T \mathrm{Ln}(x)) + L_{\text{in}}]\end{aligned}.$$

Example 2.1: As a simple linear example (with complexes consisting of single species) consider a reaction network with $Z = I_2$, $x \in \mathbb{R}^2_+$ consisting of one reversible reaction with positive reaction constants k_+, k_-, where there is a constant inflow k_{in} towards the first species X_1 (with concentration x_1) and proportional outflow $k_{\text{out}} x_2$ out of species X_2 (with concentration x_2).

$$\xrightarrow{k_{\text{in}}} X_1 \underset{k_-}{\overset{k_+}{\rightleftharpoons}} X_2 \xrightarrow{k_{\text{out}}}$$

The Laplacian matrix of the internal reversible reaction (split into a forward and reverse reaction) is

$$L = \begin{bmatrix} k_+ & -k_- \\ -k_+ & k_- \end{bmatrix}.$$

Together with the environment complex this corresponds to the Laplacian of the extended graph of complexes

$$L_e = \begin{bmatrix} k_+ & -k_- & -k_{\text{in}} \\ -k_+ & k_- + k_{\text{out}} & 0 \\ 0 & -k_{\text{out}} & k_{\text{in}} \end{bmatrix}$$

and the following dynamics of the reaction network with inflow and proportional outflow

$$\dot{x} = -\begin{bmatrix} k_+ & -k_- \\ -k_+ & k_- \end{bmatrix} x + \begin{bmatrix} k_{\text{in}} \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ k_{\text{out}} x_2 \end{bmatrix}.$$

III. Complex balanced open reaction networks

In this section, we extend the notion of complex balancedness to the case of open reaction networks, and derive an important property of such a network. We follow the method of formulation of the dynamics of complex balanced closed chemical reaction networks using a known equilibrium that was introduced in [14] and show that this method can be extended for the case of open reaction networks. We begin with the following definition.

Definition 3.1: An $x^* \in \mathbb{R}^m_+$ is called a *steady-state* for the mass action kinetics reaction network with constant inflows and proportional outflows (2) if

$$Z[Dv(x^*) + D_{\text{in}} v_{\text{in}} + D_{\text{out}} v_{\text{out}}(x^*)] = 0$$

and a *complex-balanced* steady-state if

$$Dv(x^*) + D_{\text{in}} v_{\text{in}} + D_{\text{out}} v_{\text{out}}(x^*) = 0.$$

Furthermore, we call the reaction network with constant inflows and proportional outflows (2) *complex-balanced* if there exists a complex-balanced steady-state $x^* \in \mathbb{R}^m_+$.

The condition for a complex-balanced steady-state x^* can be succinctly written as $Bv_e(x^*) = 0$. We have the following crucial observation.

Proposition 3.2: x^* is a complex-balanced steady-state, i.e., $Bv_e(x^*) = 0$, if and only if $D_e v_e(x^*) = 0$.

Proof: D is the incidence matrix of the extended graph of complexes. Hence $\mathbb{1}^T D_e = 0$, and thus the last row of D_e is dependent on the first c rows, that is, B. Hence $v_e(x^*) \in \ker D_e$ if and only if $v_e(x^*) \in \ker B$. ■

If the network with constant inflows and proportional outflows has a complex-balanced steady state x^* then, similarly to the developments before for a closed complex-balanced reaction network in [14], we define the diagonal matrix

$$\begin{aligned}\mathcal{K}_e(x^*) &:= \mathrm{diag}\left(\exp(Z_i^T \mathrm{Ln}(x^*))\right)_{i=1,\cdots,c+1} \\ &= \begin{bmatrix} \mathrm{diag}\left(\exp(Z_i^T \mathrm{Ln}(x^*))\right)_{i=1,\cdots,c} & 0 \\ 0 & 1 \end{bmatrix}, \\ &=: \begin{bmatrix} \mathcal{K}(x^*) & 0 \\ 0 & 1 \end{bmatrix}\end{aligned}$$

where Z_i denotes the i^{th} column of Z. Rewrite

$$\begin{aligned}D_e v_e(x) &= -\mathcal{L}_e(x^*)\mathrm{Exp}\begin{bmatrix} Z^T \mathrm{Ln}(\frac{x}{x^*}) \\ 0 \end{bmatrix} \\ &= -\mathcal{L}_e(x^*)\begin{bmatrix} \mathrm{Exp}\left(Z^T \mathrm{Ln}(\frac{x}{x^*})\right) \\ 1 \end{bmatrix},\end{aligned} \tag{5}$$

where

$$\mathcal{L}_e(x^*) := L_e \mathcal{K}_e(x^*) = \begin{bmatrix} (L+\Delta_{\text{out}})\mathcal{K}(x^*) & L_{\text{in}} \\ L_{\text{out}}\mathcal{K}(x^*) & \delta_{\text{in}} \end{bmatrix}. \tag{6}$$

Note that $\begin{bmatrix} \mathrm{Exp}\left(Z^T \mathrm{Ln}(\frac{x^*}{x^*})\right) \\ 1 \end{bmatrix} = \mathbb{1}_{c+1}$. Hence, the existence of a complex-balanced steady state x^* implies by Proposition 3.2 that

$$\mathcal{L}_e(x^*)\mathbb{1}_{c+1} = 0.$$

Note that $\mathcal{L}_e(x^*)$ has both row sums and column sums equal to zero and has all diagonal elements positive and all off-diagonal elements negative.

We now state and prove the main result of the abstract.

Theorem 3.3: Every steady state of a complex balanced open reaction network is complex balanced.

Proof: The proof of this theorem relies on the following lemma

Lemma 3.4: Define $\mathcal{L}_e(x^*)$ as in equation (6). Then

$$\gamma_e^T \mathcal{L}_e(x^*)\mathrm{Exp}(\gamma_e) \geqslant 0$$

for all $\gamma_e \in \mathbb{R}^{c+1}$. Moreover $\gamma_e^T \mathcal{L}_e(x^*)\mathrm{Exp}(\gamma_e) = 0$ if and only if $D_e^T \gamma = 0$. Furthermore, if γ_e has last component zero, i.e., is of the form

$$\gamma_e = \begin{bmatrix} \gamma \\ 0 \end{bmatrix} \tag{7}$$

then equality holds if and only if $B^T\gamma = 0$, or equivalently

$$D^T\gamma = 0, D_{\text{in}}^T\gamma = 0, D_{\text{out}}^T\gamma = 0 \tag{8}$$

Proof: Performing the same computation as in [14, Lemma 4.2], we obtain

$$\gamma_e^T \mathcal{L}_e(x^*)\mathrm{Exp}(\gamma_e) \geqslant (\mathcal{L}_e(x^*)\mathbb{1})^T \mathrm{Exp}(\gamma_e) = 0,$$

with equality if and only if $D_e^T\gamma_e = 0$. Clearly, if γ_e is given as in (7) then $D_e^T\gamma_e = 0$ if and only if $B^T\gamma = 0$. ■

Now consider a given open reaction network with a complex-balanced steady state x^*. Assume that x^{**} is another steady state of the network. Then

$$Z_e \mathcal{L}_e(x^*) \mathrm{Exp}\left(Z_e^T \mathrm{Ln}\left(\frac{x^{**}}{x^*} \right) \right) = 0. \tag{9}$$

We prove in the following that x^{**} is complex balanced. Define $\gamma_e(x^{**}) := Z_e^T \mathrm{Ln}(x^{**}/x^*)$. Premultiplying equation (9) with $\mathrm{Ln}(x^{**}/x^*)^T$, we get

$$\gamma_e(x^{**})^T \mathcal{L}_e(x^*) \mathrm{Exp}\big(\gamma_e(x^{**})\big) = 0.$$

From Lemma 3.4, it follows that $D_e^T \gamma_e(x^{**}) = D_e^T Z_e^T \mathrm{Ln}(x^{**}/x^*) = 0$. Since the last column of Z_e is the zero vector, we get

$$B^T Z^T \mathrm{Ln}\left(\frac{x^{**}}{x^*} \right) = 0. \tag{10}$$

We prove that x^{**} is complex balanced. $B^T \gamma(x^{**}) = 0$ is equivalent to (8). In particular, $D_{\mathrm{in}} \gamma(x^{**}) = 0$ and $D_{\mathrm{out}} \gamma(x^{**}) = 0$, and thus the components of $\gamma(x^{**})$ corresponding to the complexes directly linked to the environment complex are zero. Since $B^T \gamma(x^{**}) = 0$, it follows that the components of $\gamma(x^{**})$ corresponding to each of the remaining connected components of the extended graph are equal. Since $\mathcal{L}_e(x^*)$ can be partitioned as $\mathcal{L}_e(x^*) = \mathrm{diag}_{i=1}^{\ell}(\mathcal{L}_{e,i}(x^*))$ with ℓ denoting the number of connected components of the extended graph, and $\mathcal{L}_{e,i}(x^*)$ denoting the weighted Laplacian corresponding to the i^{th} connected component and since $\mathcal{L}_{e,i}(x^*)\mathbb{1} = 0$,

$$\mathcal{L}_e(x^*) \mathrm{Exp}\big(\gamma(x^{**})\big) = 0,$$

i.e., x^{**} is complex balanced. ■

IV. Conclusion

In this abstract, we have extended a key result of our previous paper [14] for the case of open reaction networks, i.e., reaction networks with constant inflows and mass action kinetics outflows. In [14], a compact mathematical formulation in terms of a known fixed point was obtained for closed complex-balanced chemical reaction networks. This formulation helped us in obtaining elegant proofs for well known properties of equilibria of closed complex-balanced chemical reaction networks. In this abstract, we showed that introduction of an environment complex in the graph of complexes of the network helps us in extending the approach of [14] for open complex-balanced reaction networks. We have also shown the difference between the modelling of open and closed chemical reaction networks and the changes in the Laplacian matrix corresponding to the graph of complexes due to addition of constant inflows and mass action kinetics outflows. As future work, we wish to see the effectiveness of the model reduction method introduced in [14] for the case of open reaction networks.

References

[1] F. Horn and R. Jackson, "General mass action kinetics", *Arch. Rational Mech. Anal.*, 47, pp. 81–116, 1972.
[2] F.J.M. Horn, "Necessary and sufficient conditions for complex balancing in chemical kinetics", *Arch. Rational Mech. Anal.*, 49, pp. 172–186, 1972.
[3] M. Feinberg, "Complex balancing in chemical kinetics", *Arch. Rational Mech. Anal.*, 49, pp. 187–194, 1972.
[4] J.F. Oster, A.S. Perelson, A. Katchalsky, "Network dynamics: dynamic modeling of biophysical systems", *Quarterly Reviews of Biophysics*, 6(1), pp. 1-134, 1973.
[5] J.F. Oster, A.S. Perelson, "Chemical reaction dynamics, Part I: Geometrical structure", *Archive for Rational Mechanics and Analysis*, 55, pp. 230-273, 1974.
[6] J.F. Oster, A.S. Perelson, "Chemical reaction networks", IEEE Circuits Syst. Mag, 21(6), pp. 709–721, 1974.
[7] M. Feinberg, "Chemical reaction network structure and the stability of complex isothermal reactors -I. The deficiency zero and deficiency one theorems", *Chemical Engineering Science*, 43(10), pp. 2229–2268, 1987.
[8] M. Feinberg, "The existence and uniqueness of steady states for a class of chemical reaction networks", *Arch. Rational Mech. Anal.*, 132, pp. 311–370, 1995.
[9] M. Feinberg, "Necessary and sufficient conditions for detailed balancing in mass action systems of arbitrary complexity", *Chemical Engineering Science*, 44(9), pp. 1819–1827, 1989.
[10] P. De Leenheer, D. Angeli and E.D. Sontag, "Monotone Chemical Reaction Networks", *Journal of Mathematical Chemistry*, 41(3), pp. 295–314, 2006.
[11] D. Angeli, P. De Leenheer, E.D. Sontag, "Graph-theoretic characterizations of monotonicity of chemical networks in reaction coordinates", *J. Math. Biol.*, 61, pp. 581–616, 2010.
[12] E.D. Sontag, "Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction", *IEEE Trans. Autom. Control*, 46(7), pp. 1028–1047, 2001.
[13] A.J. van der Schaft, S. Rao and B. Jayawardhana, "On the Mathematical Structure of Balanced Chemical Reaction Networks Governed by Mass Action Kinetics", *SIAM J. Appl. Math.*, 73 (2), pp. 953-973, 2013.
[14] S. Rao, A.J. van der Schaft and B. Jayawardhana, "A graph-theoretical approach for the analysis and model reduction of complex-balanced chemical reaction networks", *J. Math. Chem.*, 51 (9), pp. 2401-2422, 2013.
[15] G. Craciun, M. Feinberg, "Multiple equilibria in complex chemical reaction networks: I. the injectivity property", *SIAM J. Appl. Math.*, 65(5), pp. 1526–1546, 2006.
[16] D. Siegel and D. MacLean, "Global stability of complex balanced mechanisms", *Journal of Mathematical Chemistry*, 27, pp. 89–110, 2000.
[17] D.F. Anderson, "A proof of the global attractor conjecture in the single linkage class case", *SIAM J. Appl. Math.*, 71(4), pp. 1487–1508, 2011.
[18] D. Angeli, P. De Leenheer, E.D. Sontag, "Persistence results for chemical reaction networks with time-dependent kinetics and no global conservation laws", *SIAM J. Appl. Math.*, 71, pp. 128–146, 2011.
[19] K. van Eunen, J.A.L Kiewiet, H.V. Westerhoff and B.M. Bakker, "Testing Biochemistry Revisited: How In Vivo Metabolism Can Be Understood from In Vitro Enzyme Kinetics". *PLoS Comput Biol*, 8(4):e1002483, 2012.
[20] K van Eunen, S.M. Simons, A. Gerding, A. Bleeker, G. den Besten, C.M. Touw, S.M. Houten, B.K. Groen, K. Krab, D.J. Reijngoud, B.M. Bakker, "Biochemical competition makes fatty-acid β-oxidation vulnerable to substrate overload", *PLoS Comput Biol*, 9(8):e1003186, 2013.
[21] M. Feinberg, F.J.M. Horn, "Dynamics of open chemical systems and the algebraic structure of the underlying reaction network", *Chem. Eng. Sc.*, 29, pp. 775–787, 1974.
[22] A. Dickenstein and M.P. Millán, "How far is complex balancing from detailed balancing", *Bull. Math. Biol.*, 73, pp. 811–828, 2011.