

# BALANCED CHEMICAL REACTION NETWORKS GOVERNED BY GENERAL KINETICS

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## EXTENDED ABSTRACT

**1. Modelling of balanced chemical reaction networks.** Large-scale chemical reaction networks arise abundantly in systems biology and bio-engineering. The most basic law prescribing the dynamics of the concentrations of the various species is the *law of mass action*, leading to polynomial differential equations for the dynamics of each species. For most of the enzyme-catalyzed reactions that occur in metabolic pathways, another governing law namely, Michaelis-Menten kinetics describes the dynamics of such reactions more appropriately as compared to the law of mass action kinetics. Michaelis-Menten kinetics leads to rational differential equations describing the dynamics of each species. Large-scale chemical reaction networks thus lead to a high-dimensional set of coupled polynomial/rational differential equations, which are usually difficult to analyze.

In order to gain insight into the dynamical properties of complex chemical reaction networks it is important to identify their underlying mathematical structure, and to express their dynamics in the most compact way. The main aim of the paper is to provide a compact mathematical formulation describing the dynamics of chemical reaction networks that accommodates both mass-action as well as Michaelis-Menten kinetics. In line with the recent surge of interest in network dynamics, at least two aspects should be fundamental in such a mathematical formulation: (1) a graph representation, and (2) a specific form of the differential equations.

Consider a chemical reaction network involving  $m$  chemical species (metabolites), among which  $r$  chemical reactions take place. The basic structure underlying the dynamics of the vector  $x \in \mathbb{R}_+^m$  of concentrations  $x_i, i = 1, \dots, m$ , of the chemical species is given by the *balance laws*  $\dot{x} = Sv$ , where  $S$  is an  $m \times r$  matrix, called the *stoichiometric matrix*. The elements of the vector  $v \in \mathbb{R}^r$  are commonly called the (reaction) *fluxes* or *rates*. The stoichiometric matrix  $S$ , which consists of (positive and negative) integer elements, captures the basic conservation laws of the reactions. It already contains useful information about the network dynamics, *independent* of the precise form of the reaction rate  $v(x)$ . Note that the reaction rate depends on the governing law prescribing the dynamics of the reaction network.

The network structure of a chemical reaction network cannot be directly captured by a graph involving the chemical species (since generally there are more than two species involved in a reaction). Instead, we will follow an approach originating in the

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work of Horn & Jackson [4, 3] and Feinberg [1, 2], introducing the space of *complexes*. The set of complexes of a chemical reaction network is simply defined as the union of all the different left- and right-hand sides (substrates and products) of the reactions in the network, where a product complex of one reaction may be the substrate complex of another. The expression of the complexes in terms of the chemical species is formalized by an  $m \times c$  matrix  $Z$ , called here the *complex stoichiometric matrix*, whose  $\rho$ -th column captures the expression of the  $\rho$ -th complex in the  $m$  chemical species.

Since the complexes are left- and right-hand sides of the reactions they can be naturally associated with the vertices of a *directed graph*, with edges corresponding to the reactions. The complexes on the left-hand side of the reactions are called the *substrate* complexes and those on the right-hand side of the reactions are called the *product* complexes. Formally, the reaction  $\sigma \rightleftharpoons \pi$  between the  $\sigma$ -th and the  $\pi$ -th complex defines a directed edge with tail vertex being the  $\sigma$ -th complex and head vertex being the  $\pi$ -th complex. The resulting graph is called the *complex graph*.

Recall, that any directed graph is defined by its *incidence matrix*  $B$ . This is an  $c \times r$  matrix,  $c$  being the number of vertices and  $r$  being the number of edges, with  $(\rho, j)$ -th element equal to  $-1$  if vertex  $\rho$  is the tail vertex of edge  $j$  and  $1$  if vertex  $\rho$  is the head vertex of edge  $j$ , while  $0$  otherwise. Obviously there is a close relation between the matrix  $Z$  and the stoichiometric matrix  $S$ , which is expressed as  $S = ZB$ .

A vector of concentrations  $x^* \in \mathbb{R}_+^m$  is called a *thermodynamic equilibrium* for the dynamics  $\dot{x} = Sv(x)$  if  $v(x^*) = 0$ . A chemical reaction network with dynamics given by  $\dot{x} = Sv(x)$  is called *balanced* if there exists a thermodynamic equilibrium  $x^* \in \mathbb{R}_+^m$ . It can be shown that every reaction of a balanced reaction network is necessarily reversible (see [5, Proposition 3.2] for a proof). Note that if a reaction network has just one reversible reaction, then it is balanced. In this paper, we consider the class of balanced chemical reaction networks.

Let  $Z_{\mathcal{S}_j}$  and  $Z_{\mathcal{P}_j}$  denote the columns of the complex stoichiometric matrix  $Z$  corresponding to the substrate and the product complexes of the  $j$ -th reaction of a balanced chemical reaction network. Define the mapping  $\text{Ln} : \mathbb{R}_+^m \rightarrow \mathbb{R}^m$ ,  $x \mapsto \text{Ln}(x)$ , as the mapping whose  $i$ -th component is given as  $(\text{Ln}(x))_i := \ln(x_i)$ . Let  $k_j^{\text{forw}}$  and  $k_j^{\text{rev}}$  denote the forward and reverse reaction constants of the  $j^{\text{th}}$  reaction of the network. Then the reaction rate of the  $j^{\text{th}}$  reaction of the chemical reaction network between the  $j^{\text{th}}$  substrate  $\mathcal{S}_j$  and the  $j^{\text{th}}$  product  $\mathcal{P}_j$  is given by

$$v_j(x) = d_j(x) \left( k_j^{\text{forw}} \exp(Z_{\mathcal{S}_j}^T \text{Ln}(x)) - k_j^{\text{rev}} \exp(Z_{\mathcal{P}_j}^T \text{Ln}(x)) \right),$$

where for  $j = 1, \dots, r$ ,  $d_j : \mathbb{R}_+^m \rightarrow \mathbb{R}_+$  is a rational function of its argument in case the governing law for the  $j^{\text{th}}$  reaction is Michaelis-Menten-type kinetics and it is equal to  $1$  in case the governing law is mass action kinetics.

As an example, consider the reaction



governed by Michaelis Menten kinetics. For  $i = 1, \dots, 4$ , let  $x_i$  denote the concentration of the species  $X_i$ . Define  $x := [x_1 \ x_2 \ x_3 \ x_4]^T$ . The matrices  $B$ ,  $Z$  and  $S$  for the reaction (1.1) are given by

$$B = \begin{bmatrix} -1 \\ 1 \end{bmatrix} \quad Z = \begin{bmatrix} 1 & 0 \\ 3 & 0 \\ 0 & 1 \\ 0 & 3 \end{bmatrix} \quad S = \begin{bmatrix} -1 \\ -3 \\ 1 \\ 3 \end{bmatrix}$$

Note that  $Z_S$  and  $Z_P$  are given by

$$Z_S = \begin{bmatrix} 1 \\ 3 \\ 0 \\ 0 \end{bmatrix} \quad Z_P = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 3 \end{bmatrix}$$

Let  $K_1, K_2, K_3$  and  $K_4$  denote the ‘‘Michaelis’’ constants of the species  $X_1, X_2, X_3$  and  $X_4$  respectively. Let  $V_f$  and  $V_r$  denote the maximum reaction rates in the forward direction ( $X_1 + 3X_2 \rightarrow X_3 + 3X_4$ ) and the reverse direction ( $X_1 + 3X_2 \leftarrow X_3 + 3X_4$ ) respectively. In this case,  $k^{\text{forw}} = \frac{V_f}{K_1 K_2^3}$  and  $k^{\text{rev}} = \frac{V_r}{K_3 K_4^3}$ . The net rate of the reaction (1.1) is given by

$$v = d(x)(k^{\text{forw}} x_1 x_2^3 - k^{\text{rev}} x_3 x_4^3) = d(x) (k^{\text{forw}} \exp(Z_S^T \text{Ln}(x)) - k^{\text{rev}} \exp(Z_P^T \text{Ln}(x)))$$

where the expression for  $d(x)$  depends on the model used to define the rate of the reaction. One possibility for  $d(x)$  is

$$d(x) = \frac{1}{\left(1 + \frac{x_1}{K_1} + \frac{3x_2}{K_2}\right) \left(1 + \frac{x_3}{K_3} + \frac{3x_4}{K_4}\right)}$$

Define the mapping  $\text{Exp} : \mathbb{R}^m \rightarrow \mathbb{R}_+^m$ ,  $x \mapsto \text{Exp}(x)$ , as the mapping whose  $i$ -th component is given as  $(\text{Exp}(x))_i := \exp(x_i)$ . Let  $x^* \in \mathbb{R}_+^m$  denote a thermodynamic equilibrium, i.e  $v(x^*) = 0$ . Define the *balanced reaction constant* of the  $j^{\text{th}}$  reaction of the network as

$$\kappa_j(x^*) := k_j^{\text{forw}} \exp\left(Z_{S_j}^T \text{Ln}(x^*)\right) = k_j^{\text{rev}} \exp\left(Z_{P_j}^T \text{Ln}(x^*)\right), \quad j = 1, \dots, r$$

Further define

$$D(x) := \text{diag}(d_1(x), d_2(x), \dots, d_r(x)) \quad \mathcal{K}(x^*) := \text{diag}(\kappa_1(x^*), \kappa_2(x^*), \dots, \kappa_r(x^*))$$

Then it can be shown that the dynamics of the balanced chemical reaction network can be written as

$$\dot{x} = -ZBD(x)\mathcal{K}(x^*)B^T \text{Exp}\left(Z^T \text{Ln}\left(\frac{x}{x^*}\right)\right), \quad \mathcal{K}(x^*) > 0 \quad (1.2)$$

**2. Equilibrium and stability.** The compact mathematical formulation (1.2) can be used to prove equilibrium and stability properties of balanced chemical reaction networks. For example, it can be proved that the set of equilibria of a balanced chemical reaction network with governing dynamical equation  $\dot{x} = Sv(x)$  and a given vector of thermodynamical equilibrium concentration  $x^* \in \mathbb{R}_+^m$  is equal to the set  $\mathcal{E} = \{x^{**} \in \mathbb{R}_+^m \mid S^T \text{Ln}(x^{**}) = S^T \text{Ln}(x^*)\}$  (see [5, Theorem 4.1]). It can further be proved that for every  $x_0 \in \mathbb{R}_+^m$ , there exists a unique  $x_1 \in \mathcal{E}$  such that the solution trajectory of (1.2) starting from  $x_0$  converges for  $t \rightarrow \infty$  to  $x_1$ . Hence, there exists a surjective map  $\chi : \mathbb{R}_+^m \rightarrow \mathcal{E}$  that assigns to every initial state its asymptotic thermodynamic equilibrium (see [5, Theorem 4.5]).

**3. Model reduction of balanced chemical reaction networks.** For many purposes one may wish to *reduce* the number of dynamical equations of a complex chemical reaction network in such a way that the behavior of a number of key chemical species is approximated in a satisfactory way. In this paper, we propose a novel

technique for model reduction of complex balanced chemical reaction networks, which is based on *reduction of the complex graph*. Described below is the technique.

Consider a balanced reaction network described in the standard form (1.2)

$$\Sigma : \quad \dot{x} = -ZBD(x)\mathcal{K}(x^*)B^T \text{Exp} \left( Z^T \text{Ln} \left( \frac{x}{x^*} \right) \right)$$

Reduction will be performed by *deleting certain complexes in the complex graph*, resulting in a reduced complex graph. Define  $L(x, x^*) := BD(x)\mathcal{K}(x^*)B^T$ . The matrix  $L$  may be considered as the state-dependent weighted Laplacian matrix of the directed graph of the complex graph corresponding to the network. Let  $\mathcal{V}$  denote the vertex set of the complex graph. Then recall that for any subset of vertices  $\mathcal{V}_r \subset \mathcal{V}$  the Schur complement of  $L$  with respect to the indices corresponding to  $\mathcal{V}_r$  is well-defined, and is the weighted Laplacian matrix  $\hat{L}(x, x^*) = \hat{B}\hat{D}(x)\hat{\mathcal{K}}(x^*)\hat{B}^T$  of another directed graph with incidence matrix  $\hat{B}$  whose vertex set is equal to  $\mathcal{V} - \mathcal{V}_r$ . Leaving out columns corresponding to certain complexes of the complex stoichiometric matrix  $Z$ , one obtains a reduced complex stoichiometric matrix  $\hat{Z}$  (with as many columns as the remaining number of complexes in the complex graph), leading to the reduced reaction network

$$\hat{\Sigma} : \quad \dot{x} = -\hat{Z}\hat{L}(x, x^*)\text{Exp} \left( \hat{Z}^T \text{Ln} \left( \frac{x}{x^*} \right) \right) \quad (3.1)$$

Note that  $\hat{\Sigma}$  is again a *balanced chemical reaction network*, with a reduced number of complexes and with, in general, a different set of reactions (edges of the complex graph). Furthermore, the thermodynamic equilibrium  $x^*$  of the original reaction network  $\Sigma$  is a thermodynamic equilibrium of the reduced network  $\hat{\Sigma}$  as well. It can be proved that the set of equilibria  $\mathcal{E}$  of  $\Sigma$  is a subset of the set of equilibria  $\hat{\mathcal{E}}$  of  $\hat{\Sigma}$ , i.e.  $\mathcal{E} \subset \hat{\mathcal{E}}$  (see [5, Proposition 6.3]).

We have applied our model reduction technique in order to reduce yeast glycolysis model. This model is a balanced chemical reaction network that is governed by Michaelis-Menten kinetics. We have simulated the transient behaviour of the species that were not eliminated during the model reduction procedure. It was found that there is a good agreement between the transient behaviour of the concentration of most of such species in the case of the full network and the reduced network.

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