



Asymptotic Stability of Delayed Complex Balanced Reaction Networks with Non-Mass Action Kinetics

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Abstract

We consider delayed chemical reaction networks with non-mass action monotone kinetics and show that complex balancing implies that within each positive stoichiometric compatibility class there is a unique positive equilibrium that is locally asymptotically stable relative to its class. The main tools of the proofs are respectively a version of the well-known classical logarithmic Lyapunov function applied to kinetic systems and its generalization to the delayed case as a Lyapunov–Krasovskii functional. Finally, we demonstrate our results through illustrative examples.

Keywords Delayed chemical reaction networks · Complex balancing · Asymptotical stability · Lyapunov–Krasovskii functional

Mathematics Subject Classification 34D20 · 92C45 · 37C75 · 34K20

1 Introduction

Chemical reaction networks (also called CRNs or kinetic systems) are dynamical systems which can be formally represented as a set of (mathematically generalized) chemical reactions assuming certain reaction rates determining the velocity of the transformations of complexes to each other (Feinberg 2019; Chellaboina et al. 2009). The scope of reaction networks reaches far beyond the (bio)chemical application field, since they can be considered as general descriptors of nonlinear dynamics capable of producing complex dynamical phenomena, such as multiple equilibria, nonlinear oscillations, limit cycles, and even chaos (Érdi and Tóth 1989). It is known that majority of compartmental models used, e.g., in population dynamics or epidemiology are

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naturally in kinetic form. Additionally, many other non-chemically motivated models can be algorithmically transformed to reaction network form (Samardzija et al. 1989; Craciun et al. 2019). Therefore, the results of chemical reaction network theory (CRNT) relating network structure and qualitative dynamics can be of general importance in the field of dynamical systems (Angeli 2009).

Stability is a key qualitative property of dynamical models and their equilibria. In Horn and Jackson (1972), the local stability of complex balanced equilibria of kinetic systems was shown using an entropy-like logarithmic Lyapunov function. The most well-known stability-related result in CRNT is probably the Deficiency Zero Theorem which states that weakly reversible deficiency zero CRNs are complex balanced independently of the (positive) values of reaction rate coefficients (Feinberg 1987). According to the Global Attractor Conjecture, the stability of complex balanced networks is actually global within the nonnegative orthant (Craciun 2015; Anderson 2011). The stability of a wide class of CRNs with more general kinetics than mass action was shown in Sontag (2001). These results were further extended in Chaves (2005) for time-varying reaction rates using the notion of input-to-state stability.

The explicit modeling of time delays is often necessary to understand complex dynamical phenomena in nature or technology, and to build models having sufficient level of reliability (Stépán 1989). Various phenomena may justify the inclusion of time delays into dynamical models such as protein expression time in systems biology (Zhu et al. 2024), hatching or maturation time in population dynamics (Ruiz-Herrera 2019), driver reaction times in traffic flow models (Orosz et al. 2009), latent periods in epidemic modeling (Wang et al. 2023), or communication and feedback delays in complex networks (Zhu et al. 2020). The most commonly used approach in the stability analysis of time-delay systems is the construction of appropriate Lyapunov–Krasovskii functionals which is generally a challenging problem (Fridman 2014).

The main motivation for introducing delayed chemical reactions was to focus on the most important species and chemical transformations, and to avoid the detailed description of mechanisms of less interest (Roussel 1996). In delayed reactions, the consumption of reactant species is immediate, while the formation of products is delayed either through discrete or distributed delays. The notion of stoichiometric compatibility classes was generalized for delayed mass action CRNs in Lipták et al. (2018a), and it was proved using a logarithmic Lyapunov–Krasovskii functional that complex balanced networks are at least locally stable for arbitrary finite delays. An analogous result for kinetic systems with distributed delays was given in Lipták et al. (2019). In Komatsu and Nakajima (2019) the authors introduced the notion of stoichiometric compatibility classes for arbitrary delayed CRNs and proved the generalization of well-known persistence results (Angeli et al. 2007, 2011) to the delayed case. In Komatsu and Nakajima (2020) the authors prove a delayed version of the deficiency zero theorem and discuss global asymptotic stability. In Zhang and Gao (2021) the authors provide several sufficient conditions for the persistence of delayed complex balanced CRNs with mass action kinetics, and they improve the practical applicability of these results via semilocking set decomposition in Zhang et al. (2023).

Using the achievements outlined above, the purpose of the present paper is to further extend stability results for delayed complex balanced kinetic systems with general (non-mass action) kinetics. For this, an appropriate Lyapunov–Krasovskii functional

is proposed through which the local asymptotic stability of positive equilibria can be shown.

The structure of the paper is as follows. Section 2 introduces the basic notions related to kinetic systems. In Sect. 3 we study the set of positive equilibria in the context of complex balancing and the quasi-thermodynamic/thermostatic properties for non-mass action kinetics, our first main contribution. The other main contribution can be found in Sect. 4, where the local asymptotic stability of positive complex balanced equilibria is shown. Section 6 contains three computational examples to illustrate the theory. Finally, conclusions of the paper are given in Sect. 7.

2 Preliminaries

Throughout the paper $\mathbb{R}^N, \mathbb{R}_+^N$ and $\overline{\mathbb{R}}_+^N$ denote the N -dimensional space of real, positive and nonnegative column vectors, respectively, and the Euclidean norm is denoted by $|\cdot|$. For $x, y, \in \mathbb{R}_+^N$ the vector exponential x^y is defined as $x^y = \prod_{k=1}^N x_k^{y_k}$ and the inner product $x \cdot y$ is defined as $x \cdot y = \sum_{k=1}^N x_k y_k$. For $x \in \mathbb{R}_+^N$ the vector logarithm $\log(x)$ is defined element-wise. For every $\tau \geq 0$ we denote the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into \mathbb{R}^N , into \mathbb{R}_+^N and into $\overline{\mathbb{R}}_+^N$ by $\mathcal{C}_\tau = C([-\tau, 0], \mathbb{R}^N), \mathcal{C}_{+,\tau}$ and $\overline{\mathcal{C}}_{+,\tau}$, respectively. We equip the spaces $\mathcal{C}_\tau, \mathcal{C}_{+,\tau}$ and $\overline{\mathcal{C}}_{+,\tau}$ with the standard norm $\|\psi\| = \sup_{s \in [-\tau, 0]} |\psi(s)|$, and the open ball around ψ with radius $\epsilon > 0$ is denoted by $\mathcal{B}_\epsilon(\psi)$. The space of continuously differentiable functions on \mathbb{R} is denoted by $C^1(\mathbb{R})$. The dynamics of mass action kinetic systems can be given as

$$\dot{x}(t) = \sum_{k=1}^M \kappa_k x^{y_k}(t)(y_{k'} - y_k), \tag{1}$$

where $x(t) \in \overline{\mathbb{R}}_+^N$ is the state vector representing the concentrations of species (Feinberg 2019). The system consists of M reactions, where each reaction k has a source and product complex with corresponding stoichiometric vectors $y_k, y_{k'} \in \mathbb{N}^N$, respectively, and a positive real reaction rate constant κ_k . The set of stoichiometric vectors is denoted with \mathcal{K} . In some cases we will use the complex matrix Y that has the stoichiometric vectors as columns. The reaction vector of reaction k is defined as $y_{k'} - y_k$. The linear span of the reaction vectors is called the stoichiometric subspace \mathcal{S} of (3), defined as

$$\mathcal{S} = \text{span}\{y_{k'} - y_k | k = 1, 2, \dots, M\}$$

and for $p \in \mathbb{R}_+^N$ the corresponding positive stoichiometric compatibility class \mathcal{S}_p is defined by

$$\mathcal{S}_p = \{x \in \mathbb{R}_+^N | x - p \in \mathcal{S}\}.$$

It is well-known that the positive stoichiometric compatibility classes are positively invariant under (1); that is, we have that $x(t) \in \mathcal{S}_p$ for $t \geq 0$ if $x(0) \in \mathcal{S}_p$.

Stability of systems of the form (1) can be investigated through the entropy-like logarithmic Lyapunov function

$$V(x, \bar{x}) = \sum_{i=1}^N (x_i (\log x_i - \log \bar{x}_i - 1) + \bar{x}_i) = \sum_{i=1}^N \left(x_i \log \frac{x_i}{\bar{x}_i} + \bar{x}_i - x_i \right), \tag{2}$$

where \bar{x} is a positive equilibrium. We aim to generalize certain stability results to include non-mass action cases like the Michaelis–Menten kinetics or general Hill-type kinetics, while still relying on a similar Lyapunov function. In order to do so, we consider kinetic systems of the form

$$\dot{x}(t) = \sum_{k=1}^M \kappa_k \gamma^{y_k}(x(t))(y_{k'} - y_k), \tag{3}$$

where the function $\gamma : \overline{\mathbb{R}}_+^N \mapsto \overline{\mathbb{R}}_+^N$ is defined element-wise by the increasing functions $\gamma_i \in C^1(\mathbb{R})$. This class of systems include a wide variety of interesting and relevant kinetics, while the product structure of $\gamma^{y_k}(x)$ allows us to rely on logarithmic identities in the calculations. In particular, the Michaelis-Menten kinetics can be given by $\gamma_i(s) = \frac{s}{c_i+s}$ for $c_i > 0$, and more general Hill kinetics can be given by $\gamma_i(s) = \frac{s^{n_i}}{c_i+s^{n_i}}$ for $c_i > 0$ and $n_i > 0$.

We impose the following assumptions on the γ_i functions. First of all, if the concentration of any reactant is zero, the reaction should not take place; that is, we assume that $\gamma_i(0) = 0$. A fundamental case for the choice of the γ_i transformations is $\gamma_i(s) = s$, which corresponds to mass action kinetics. For regularity, in particular for the existence of nontrivial equilibria, we usually assume that the γ_i functions further satisfy $\int_0^1 |\log \gamma_i(s)| ds < \infty$ and that $\gamma_i : \overline{\mathbb{R}}_+ \mapsto \overline{\mathbb{R}}_+$ are onto. In this case the inverse of $\gamma_i^{-1}(s)$ is strictly increasing from $\overline{\mathbb{R}}_+$ onto $\overline{\mathbb{R}}_+$, and thus

$$\lim_{x \rightarrow \infty} \left(\int_a^x \gamma_i^{-1}(e^s) ds - bx \right) = \infty \tag{4}$$

holds for any $0 \leq a < \infty$ and any b . While the $\gamma_i(s) = s$ mass action case satisfies the above assumptions, many fundamental examples from biochemistry do not; in particular, the Michaelis-Menten kinetics and the Hill kinetics fail to do so, since they are not onto $\overline{\mathbb{R}}_+$ and they do not meet assumption (4). However, as we will show, a slightly relaxed condition still ensures the existence of nontrivial equilibria. Instead of assuming that the γ_i function are onto $\overline{\mathbb{R}}_+$, we only require that they are onto $[0, \sigma_i)$, where $0 < \sigma_i \leq \infty$ can be finite. Then instead of (4) we will require that

$$\lim_{x \uparrow \log \sigma_i} \left(\int_a^x \gamma_i^{-1}(e^s) ds - bx \right) = \infty \tag{5}$$

holds for any $0 \leq a < \infty$ and any b . For more details we refer to (Sontag 2001, Section IV.B.)

We note that (3) can be rewritten in matrix form as follows. Assume that the number of distinct complexes is L and define κ_{ij} as κ_k if there is a reaction k such that $y_{k'} = y_j$ and $y_k = y_i$, and zero otherwise. Denoting by K the matrix defined element-wise as $[K]_{ij} = \kappa_{ij}$, the system (3) takes the form

$$\dot{x}(t) = Y(K - \text{diag}(1_L^\top K))\Gamma(x) =: Y\tilde{K}\Gamma(x), \tag{6}$$

where $1_L \in \mathbb{R}^L$ denotes a column vector with all of its coordinates equal to one and $\Gamma : \mathbb{R}_+^N \mapsto \mathbb{R}_+^N$ is defined as

$$\Gamma(x) = [\gamma^{y_1}(x) \ \gamma^{y_2}(x) \ \dots \ \gamma^{y_L}(x)].$$

Note, that \tilde{K} is the weighted negative Laplacian of the reaction graph of the system.

We also consider the delayed version of (3), having the form

$$\dot{x}(t) = \sum_{k=1}^M \kappa_k \left(\gamma^{y_k}(x(t - \tau_k))y_{k'} - \gamma^{y_k}(x(t))y_k \right), \tag{7}$$

where $\tau_k \geq 0$ are discrete constant time delays. The solution corresponding to an initial function $\psi \in \bar{\mathcal{C}}_{+, \tau}$ at time $t \geq 0$ is denoted by $x^\psi(t) \in \mathbb{R}_+^N$ or by $x_t^\psi \in \bar{\mathcal{C}}_{+, \tau}$ when we use it as a function. A positive vector $\bar{x} \in \mathbb{R}_+^N$ is called a positive equilibrium of (7) if $x(t) \equiv \bar{x}$ is a solution of (7); that is, the equilibria of (7) and (3) coincide. The Lyapunov–Krasovskii approach for such delayed systems is formally very similar to the Lyapunov approach of ODEs (Fridman 2014; Haddad et al. 2010). Let $\tau = \max_k \tau_k$ and \bar{x} be an equilibrium of (7). If the functional $V : \mathcal{C}_{+, \tau} \rightarrow \mathbb{R}$ is such that $V(\bar{x}) = 0$ and

$$\begin{aligned} V(\psi) &\geq \alpha(|\psi(0) - \bar{x}|), \\ \dot{V}(\psi) &\leq 0, \end{aligned}$$

holds for $\psi \in \mathcal{C}_{+, \tau}$, where $\alpha : \mathbb{R}_+ \mapsto \mathbb{R}_+$ is a continuous and strictly increasing function with $\alpha(0) = 0$, then \bar{x} is Lyapunov stable. If there exists a $\gamma : \mathbb{R}_+ \mapsto \mathbb{R}_+$ is a continuous and strictly increasing function with $\gamma(0) = 0$ such that

$$\dot{V}(\psi) \leq -\gamma(|\psi(0) - \bar{x}|)$$

then the system is locally asymptotically stable. Finally, if $\alpha(s) \rightarrow \infty$ as $s \rightarrow \infty$, then the system is globally asymptotically stable.

3 Quasi-thermodynamic property and complex balancing

In this section, we restate some of the stability results described in Sontag (2001) under milder conditions using the computational approach of Feinberg (2019). Here

we consider nondelayed kinetic systems of the form (3). First, let us recall some definitions. A positive vector $\bar{x} \in \mathbb{R}_+^N$ is called a positive equilibrium of (3) if $x(t) \equiv \bar{x}$ is a solution of (3); that is, the equilibria of (3) satisfy the equation

$$f(\bar{x}) := \sum_{k=1}^M \kappa_k \gamma^{y_k}(\bar{x})(y_{k'} - y_k) = 0,$$

where $f : \mathbb{R}_+^N \mapsto \mathcal{S}$ denotes the species formation rate function of the kinetic system (3). In the classical terminology of Horn and Jackson (1972); Feinberg (2019) a kinetic system is called quasi-thermostatic if there exists a positive vector $\bar{x} \in \mathbb{R}_+^N$ such that the set of positive equilibria is identical to the set

$$\mathcal{E} = \left\{ \tilde{x} \in \mathbb{R}_+^N \mid \log(\tilde{x}) - \log(\bar{x}) \in \mathcal{S}^\perp \right\}.$$

In this case we say that the kinetic system is *quasi-thermostatic* with respect to \bar{x} . Standard arguments show that then the system is quasi-thermostatic with respect to any element of \mathcal{E} . The distribution of positive equilibria of quasi-thermostatic systems can be efficiently characterized, namely, each positive stoichiometric compatibility class contains precisely one positive equilibrium (Horn and Jackson 1972).

Furthermore, a kinetic system is called *quasi-thermodynamic* if there exists an $\bar{x} \in \mathbb{R}_+^N$ such that the system is quasi-thermostatic with respect to \bar{x} , and

$$(\log(x) - \log(\bar{x})) \cdot f(x) \leq 0 \tag{8}$$

holds for $x \in \mathbb{R}_+^N$, with equality holding only if $f(x) = 0$ or, equivalently, if $\log(x) - \log(\bar{x}) \in \mathcal{S}^\perp$. In this case we say that the kinetic system is quasi-thermodynamic with respect to \bar{x} . Similarly to quasi-thermostaticity, a system is quasi-thermodynamic with respect to any element of \mathcal{E} . The main consequence of quasi-thermodynamicity is that the unique positive equilibrium of each positive stoichiometric compatibility class is locally asymptotically stable relative to its class. This arises from the fact that the gradient of the function

$$H(x, \bar{x}) = \sum_{i=1}^N x_i (\log x_i - \log \bar{x}_i - 1)$$

is given by $\log(x) - \log(\bar{x})$ which is a term in Eq. (8). Thus, the function (2) is a Lyapunov function for quasi-thermodynamic kinetic models. The short physical background of this is that H was used to describe the Helmholtz free energy density of the system, and its gradient is the chemical potential function.

As noted in Horn and Jackson (1972), while the above definition is physically associated with mass action kinetics and ideal gas mixtures, it could apply to any kinetic system. In some cases the definitions can be extended without voiding their consequences. In order to do so, following (Sontag 2001), we define for $x \in \mathbb{R}_+^N$ the function

$$\rho(x) = \log(\gamma(x)),$$

where γ is defined as in Eq. (3). A kinetic system of the form (3) is called *quasi-thermostatic in the generalized sense* if there exists an $\bar{x} \in \mathbb{R}_+^N$ such that the set of positive equilibria is identical to the set

$$\mathcal{E} = \left\{ \tilde{x} \in \mathbb{R}_+^N \mid \rho(\tilde{x}) - \rho(\bar{x}) \in \mathcal{S}^\perp \right\}. \tag{9}$$

For brevity, we simply say that the kinetic system is quasi-thermostatic with respect to \bar{x} . Again, similarly to classical quasi-thermostaticity, standard arguments show that then the system is quasi-thermostatic with respect to any element of \mathcal{E} . Furthermore, the distribution of the positive equilibria of quasi-thermostatic kinetic systems across positive stoichiometric compatibility classes can be characterized. We describe that distribution in the following proposition.

Proposition 3.1 *Assume that the kinetic system (3) is quasi-thermostatic. Then, for every $p \in \mathbb{R}_+^N$ the corresponding positive stoichiometric compatibility class \mathcal{S}_p contains precisely one positive equilibrium.*

Proof We first show the existence of a point in $\mathcal{S}_p \cap \mathcal{E}$. Let \bar{x} be an element of \mathcal{E} . By (Feinberg 1995, Proposition B.1) there exists a (unique) vector $\mu \in \mathcal{S}^\perp$ such that

$$\gamma(\bar{x})e^\mu - p \in \mathcal{S}.$$

Let \tilde{x} be defined by

$$\gamma(\tilde{x}) := \gamma(\bar{x})e^\mu.$$

Then $\tilde{x} \in \mathcal{S}_p$ and taking logarithm shows that

$$\rho(\tilde{x}) - \rho(\bar{x}) = \mu \in \mathcal{S}^\perp;$$

that is, we have that $\tilde{x} \in \mathcal{E}$ as well.

In order to show uniqueness, let us assume by contradiction that \tilde{x} and \bar{x} are distinct positive equilibria in \mathcal{S}_p . Then $\tilde{x} - \bar{x} \in \mathcal{S}$ and $\rho(\tilde{x}) - \rho(\bar{x}) \in \mathcal{S}^\perp$, and thus

$$0 = (\rho(\tilde{x}) - \rho(\bar{x})) \cdot (\tilde{x} - \bar{x}) = \sum_{i=1}^N (\log \gamma_i(\tilde{x}_i) - \log \gamma_i(\bar{x}_i)) (\tilde{x}_i - \bar{x}_i).$$

Since the functions γ_i and the logarithm are strictly increasing, the above expression is zero if and only if $\tilde{x} = \bar{x}$. □

Remark 3.2 Note that we implicitly used assumption (5), see (Sontag 2001, Lemma IV.1) and Proposition 4.2 for more details.

A kinetic system of the form (3) is called *quasi-thermodynamic in the generalized sense* if there exists an $\bar{x} \in \mathbb{R}_+^N$ such that the system is quasi-thermostatic with respect to \bar{x} and

$$(\rho(x) - \rho(\bar{x})) \cdot f(x) \leq 0$$

holds for $x \in \mathbb{R}_+^N$, where equality holds only if $f(x) = 0$ or, equivalently, if $\rho(x) - \rho(\bar{x}) \in \mathcal{S}^\perp$. Again, for brevity, we simply say that the kinetic system is quasi-thermodynamic with respect to \bar{x} , however, similarly to quasi-thermostaticity, a system is quasi-thermodynamic with respect to any element of \mathcal{E} .

The following proposition and its proof shows that the underlying function

$$V(x, \bar{x}) = \sum_{i=1}^N \int_{\bar{x}_i}^{x_i} (\log \gamma_i(s) - \log \gamma_i(\bar{x}_i)) ds \tag{10}$$

is a Lyapunov function of the system (3). Note, that (10) reduces to (2) in the mass action case.

Proposition 3.3 *Assume that the kinetic system (3) is quasi-thermodynamic. Then, each positive stoichiometric compatibility class contains precisely one positive equilibrium and that equilibrium is locally asymptotically stable, and there is no nontrivial periodic trajectory along which all species concentrations are positive.*

Proof The fact that each positive stoichiometric compatibility class contains precisely one positive equilibrium follows from quasi-thermostaticity.

Let us consider any positive stoichiometric compatibility class \mathcal{S}_p and denote its unique positive equilibrium by \bar{x} . Then, for any $x \in \mathcal{S}_p$ other than \bar{x} , we have that

$$(\rho(x) - \rho(\bar{x})) \cdot f(x) < 0. \tag{11}$$

It is easy to see that $V(x, \bar{x}) \geq 0$ and equality holds only if $x = \bar{x}$, and that $\nabla V(x, \bar{x}) = \rho(x) - \rho(\bar{x})$. This, combined with (11) show that

$$\nabla V(x, \bar{x}) \cdot f(x) < 0$$

holds for any $x \in \mathcal{S}_p$ other than \bar{x} . Standard arguments show that $V(x, \bar{x})$ is a strict Lyapunov function for \bar{x} on its positive stoichiometric compatibility class \mathcal{S}_p , thus \bar{x} is locally asymptotically stable relative to \mathcal{S}_p .

To show that no nontrivial periodic trajectories can exist along which all species concentrations are positive, assume by contradiction that $x : [0, T] \mapsto \mathbb{R}_+^N$ is such a solution with $x(T) = x(0)$ and denote the unique positive equilibrium of the corresponding positive stoichiometric compatibility class by \bar{x} . Then

$$V(x(T), \bar{x}) - V(x(0), \bar{x}) = \int_0^T \nabla V(x(t), \bar{x}) \cdot f(x(t)) dt < 0,$$

and thus

$$V(x(T), \bar{x}) < V(x(0), \bar{x}),$$

contradicting $x(T) = x(0)$. □

In Sontag (2001) the author considers systems of the form (3) or, equivalently, of the form (6), and assumes that the complex matrix Y is of full rank and none of its rows vanishes, and that \tilde{K} is irreducible (implying that the reaction graph is strongly connected). Then, without using the above terminology, the author shows that such systems are quasi-thermodynamic. We note, that these assumptions imply that if \bar{x} is an equilibrium of (6), then $\tilde{K}\Gamma(\bar{x}) = 0$; that is, the vector $\Gamma(\bar{x})$ is in the kernel of \tilde{K} . Thus, systems that satisfy the above assumptions are complex balanced, defined as follows.

Without any restrictions on Y or assuming that \tilde{K} is irreducible, an equilibrium \bar{x} is called *complex balanced* if $\tilde{K}\Gamma(\bar{x}) = 0$ or, equivalently, if for every complex $\eta \in \mathcal{K}$ we have that

$$\sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) = \sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_{k'}}(\bar{x}),$$

where the sum on the left-hand side is taken over the reactions where η is the source complex and the sum on the right-hand side is taken over the reactions where η is the product complex. Therefore, complex balanced equilibria are also called vertex-balanced in the literature (Müller 2023). We note that this setting is indeed more general than that of Sontag (2001), as for mass action systems complex balancing can occur in weakly reversible systems, not just in strongly connected systems; that is, there can be more than one linkage classes.

First, we show that the existence of a positive complex balanced equilibrium affects every positive equilibrium.

Proposition 3.4 *Assume that the kinetic system (3) admits a positive complex balanced equilibrium. Then every positive equilibrium is complex balanced.*

Proof Let us assume that $\bar{x} \in \mathbb{R}_+^N$ is a positive complex balanced equilibrium and $\tilde{x} \in \mathbb{R}_+^N$ is a positive equilibrium other than \bar{x} . Then $\tilde{x} \in \mathcal{E}$; that is, we have that $\rho(\tilde{x}) - \rho(\bar{x}) \in \mathcal{S}^\perp$. Let us define for $k = 1, 2, \dots, M$ the function $q_k : \mathbb{R}_+^N \mapsto \mathbb{R}$ by

$$q_k(x) = (\rho(x) - \rho(\bar{x})) \cdot y_k.$$

Then, for any complex $\eta \in \mathcal{K}$ we have that

$$\begin{aligned} & \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\tilde{x}) - \sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\tilde{x}) \\ &= \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) e^{q_k(\tilde{x})} - \sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\bar{x}) e^{q_k(\tilde{x})} \\ &= e^{q_\eta(\tilde{x})} \left(\sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) - \sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\bar{x}) \right) = 0, \end{aligned}$$

thus \tilde{x} is indeed complex balanced. □

The above Proposition shows that positive complex balancing is a system property. Thus, a system of the form (3) is called complex balanced if it admits a positive complex balanced equilibrium. Finally, the connection between complex balanced systems and quasi-thermodynamic systems are described in the following proposition.

Proposition 3.5 *Assume that the kinetic system (3) is complex balanced. Then it is quasi-thermodynamic.*

Proof Let us consider the positive complex balanced equilibrium \bar{x} ; that is, the equality

$$\sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) = \sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\bar{x})$$

holds for any complex $\eta \in \mathcal{K}$. Observe that for any $x \in \mathbb{R}_+^N$ we have that

$$\begin{aligned} (\rho(x) - \rho(\bar{x})) \cdot f(x) &= \sum_{k=1}^M \kappa_k \gamma^{y_k}(x) (q_{k'}(x) - q_k(x)) \\ &= \sum_{k=1}^M \kappa_k \gamma^{y_k}(\bar{x}) e^{q_k(x)} (q_{k'}(x) - q_k(x)). \end{aligned}$$

Using the well-known inequality

$$e^a (b - a) \leq e^b - e^a \tag{12}$$

leads to

$$\begin{aligned} (\rho(x) - \rho(\bar{x})) \cdot f(x) &\leq \sum_{k=1}^M \kappa_k \gamma^{y_k}(\bar{x}) (e^{q_{k'}(x)} - e^{q_k(x)}) \\ &= \sum_{\eta \in \mathcal{K}} e^{q_\eta(x)} \left(\sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\bar{x}) - \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) \right) = 0, \end{aligned} \tag{13}$$

where equality holds if and only if $q_k(x) = q_k(\bar{x})$ for each reaction $k = 1, 2, \dots, M$; that is, if and only if $\rho(x) - \rho(\bar{x})$ lies in \mathcal{S}^\perp . In particular, if $f(x) = 0$, then $\rho(x) - \rho(\bar{x})$ lies in \mathcal{S}^\perp . It remains to be shown that if $\rho(x) - \rho(\bar{x})$ lies in \mathcal{S}^\perp , then $f(x) = 0$, as a quasi-thermodynamic system needs to be quasi-thermostatic as well. Rewrite the species formation rate function as

$$\begin{aligned} f(x) &= \sum_{\eta \in \mathcal{K}} \eta \left(\sum_{k:\eta=y_k'} \kappa_k \gamma^{y_k}(x) - \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(x) \right) \\ &= \sum_{\eta \in \mathcal{K}} \eta \left(\sum_{k:\eta=y_k'} \kappa_k \gamma^{y_k}(\bar{x}) e^{q_k(x)} - \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) e^{q_k(x)} \right). \end{aligned}$$

If x is such that $\rho(x) - \rho(\bar{x}) \in \mathcal{S}^\perp$, then $\rho(x) - \rho(\bar{x})$ is orthogonal to every reaction vector, and thus

$$f(x) = \sum_{\eta \in \mathcal{K}} e^{q_\eta(x)} \eta \left(\sum_{k:\eta=y_k'} \kappa_k \gamma^{y_k}(\bar{x}) - \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) \right) = 0;$$

that is, the vector x is an equilibrium. This shows that the set of positive equilibria coincides with the set \mathcal{E} , and thus the system is quasi-thermostatic. This, combined with (13) shows that the system is quasi-thermodynamic as well. \square

4 Stability of delayed kinetic models

In this section, we consider kinetic systems with delayed reactions having the form (7). In order to do so, first, we have to extend the notion of positive stoichiometric compatibility classes to the delayed case. We note, that the following definition and invariance proof was already established in Lipták et al. (2018a) for the case of mass action kinetics and in Komatsu and Nakajima (2019) for the general case. For each $v \in \mathbb{R}^N$ define the functional $c_v : \mathcal{C}_{+,\tau} \mapsto \mathbb{R}$ as

$$c_v(\psi) = v \cdot \left[\psi(0) + \sum_{k=1}^M \left(\kappa_k \int_{-\tau_k}^0 \gamma^{y_k}(\psi(s)) ds \right) y_k \right], \quad \psi \in \mathcal{C}_{+,\tau}.$$

For each $\theta \in \mathcal{C}_{+,\tau}$ the positive stoichiometric compatibility class of (7) corresponding to θ is denoted by \mathcal{D}_θ and is defined by

$$\mathcal{D}_\theta = \left\{ \psi \in \mathcal{C}_{+,\tau} \mid c_v(\psi) = c_v(\theta) \text{ for all } v \in \mathcal{S}^\perp \right\}.$$

Clearly, $\psi \in \mathcal{D}_\theta$ if and only if $\psi \in \mathcal{C}_{+,\tau}$ and

$$\psi(0) - \theta(0) + \sum_{k=1}^M \left(\kappa_k \int_{-\tau_k}^0 (\gamma^{y_k}(\psi(r)) - \gamma^{y_k}(\theta(s))) ds \right) y_k \in \mathcal{S}. \quad (14)$$

This shows that if each delay τ_k is zero, then the delayed positive stoichiometric compatibility classes reduce to the positive compatibility classes of (3).

The following Proposition establishes the invariance property of \mathcal{D}_θ .

Proposition 4.1 *For every $\theta \in \mathcal{C}_{+,\tau}$ the positive stoichiometric compatibility class \mathcal{D}_θ is a closed subset of $\mathcal{C}_{+,\tau}$. Moreover, \mathcal{D}_θ is positively invariant under (7); that is, if $\psi \in \mathcal{D}_\theta$, then $x_t^\psi \in \mathcal{D}_\theta$ for all $t \geq 0$.*

Proof The closedness follows from the continuity of c_v . We will show that for each $v \in \mathcal{S}^\perp$ the functional c_v is constant along the trajectories of (7). To see this, let us assume that x is a solution of (7). Then for $t \geq 0$ we have that

$$\begin{aligned} \frac{d}{dt} c_v(x_t) &= v \cdot \left(\dot{x}(t) + \sum_{k=1}^M \kappa_k (\gamma^{y_k}(x(t)) - \gamma^{y_k}(x(t - \tau_k))) y_k \right) \\ &= v \cdot \left(\sum_{k=1}^M \kappa_k \gamma^{y_k}(x(t - \tau_k)) (y_{k'} - y_k) \right) \\ &= \sum_{k=1}^M \kappa_k \gamma^{y_k}(x(t - \tau_k)) v \cdot (y_{k'} - y_k) = 0, \end{aligned}$$

where the last equality follows from the fact that $v \in \mathcal{S}^\perp$. Thus, if $\psi \in \mathcal{D}_\theta$, then for every $v \in \mathcal{S}^\perp$ and $t \geq 0$ the equalities

$$c_v(x_t^\psi) = c_v(x_0^\psi) = c_v(\psi) = c_v(\theta)$$

hold, showing that $x_t^\psi \in \mathcal{D}_\theta$ as desired. \square

The delayed kinetic system of form (7) is quasi-thermostatic if its nondelayed version, obtained by setting each $\tau_k = 0$, is quasi-thermostatic, since their equilibria coincide. The following proposition is the generalization of Proposition 3.1 for delayed systems.

Proposition 4.2 *Assume that the kinetic system (7) is quasi-thermostatic. Then, for every $\theta \in \mathcal{C}_{+,\tau}$ the corresponding delayed positive stoichiometric compatibility class \mathcal{D}_θ of the system (7) contains precisely one positive equilibrium.*

Proof In the nondelayed case (see Proposition 3.1) existence is shown via (Feinberg 1995, Proposition B.1) without modification. However, in the delayed case we need to adapt certain steps of the proof based on (Komatsu and Nakajima 2020, Theorem 4.4), where the authors prove the statement for delayed mass action systems.

Let us for $\bar{x} \in \mathcal{E}$ define the positive vector $b \in \mathbb{R}_+^N$ by

$$b_i = \theta_i(0) + \sum_{k=1}^M \kappa_k \int_{-\tau_k}^0 \gamma^{y_k}(\theta(s)) ds$$

and the continuously differentiable function $g : \mathbb{R}^N \mapsto \mathbb{R}$ by

$$g(x) = \sum_{i=1}^N \left(\int_0^{x_i} \gamma_i^{-1}(\gamma_i(\bar{x}_i)e^s) ds + \bar{x}_i - b_i x_i \right) + \sum_{k=1}^M \kappa_k \tau_k (\gamma(\bar{x})e^x)^{y_k}.$$

We note that adding \bar{x}_i to the integral is not necessary for the following analysis, but adding it ensures that $g(x)$ reduces precisely to the analogous function in the known proof of this theorem for mass action systems.

The gradient of g is given by

$$\nabla g(x) = \gamma^{-1}(\gamma(\bar{x})e^x) - b + \sum_{k=1}^M \kappa_k \tau_k (\gamma(\bar{x})e^x)^{y_k} y_k$$

and that the Hessian of g is written as

$$H_g(x) = \text{diag} \left(\frac{\gamma(\bar{x})e^x}{\gamma'(\gamma^{-1}(\gamma(\bar{x})e^x))} \right) + \sum_{k=1}^M \kappa_k \tau_k (\gamma(\bar{x})e^x)^{y_k} y_k y_k^\top,$$

where the fraction in the diagonal matrix is defined element-wise. The corresponding quadratic form is positive-definite as the first term is a diagonal matrix with positive entries, and thus is positive-definite, and the second term consists of positive factors and the positive-semidefinite matrix $y_k y_k^\top$. Then the function g is strictly convex everywhere.

From the property (5) of the γ_i functions it follows that for any nonzero vector $x \in \mathbb{R}^N$ we have that

$$\lim_{a \rightarrow \infty} \left(\int_0^{x_i} \gamma_i^{-1}(\gamma_i(\bar{x}_i)e^{as}) ds + \bar{x}_i - a b_i x_i \right) = \begin{cases} \infty, & x_i \neq 0, \\ \bar{x}_i & x_i = 0, \end{cases}$$

and thus

$$\lim_{a \rightarrow \infty} \sum_{i=1}^N \left(\int_0^{x_i} \gamma_i^{-1}(\gamma_i(\bar{x}_i)e^{as}) ds + \bar{x}_i - a b_i x_i \right) \leq \lim_{a \rightarrow \infty} g(ax) = \infty. \tag{15}$$

Let $\bar{g} : \mathcal{S}^\perp \mapsto \mathbb{R}$ be the restriction of g to \mathcal{S}^\perp , which is also continuously differentiable and strictly convex. Define the subset

$$\mathcal{S}^\perp \supset G = \left\{ x \in \mathcal{S}^\perp \mid \bar{g}(x) \leq g(0) \right\}.$$

Clearly G is convex, closed in \mathbb{R}^N , contains the zero vector and contains no half line with endpoint 0 because of (15). Then G is bounded, and thus compact as well, since in a finite-dimensional vector space every unbounded closed convex set containing 0 must contain a half line with endpoint 0 (Stoer and Witzgall 1970, Theorem 3.5.1).

The continuity of \bar{g} and the compactness of G implies that there exists $\mu \in G$ such that

$$\bar{g}(\mu) \leq \bar{g}(x), \quad \forall x \in G.$$

In fact, $\bar{g}(0) < \bar{g}(x)$ for $x \in \mathcal{S}^\perp \setminus G$, and thus

$$\bar{g}(\mu) \leq \bar{g}(x), \quad \forall x \in \mathcal{S}^\perp.$$

Then for $\xi \in \mathcal{S}^\perp$, the equality

$$0 = \frac{d}{dt} \bar{g}(\mu + t\xi) \Big|_{t=0} = \frac{d}{dt} g(\mu + t\xi) \Big|_{t=0} = \nabla g(\mu) \cdot \xi$$

holds; that is, the vector $\nabla g(\mu)$ is in \mathcal{S} , and thus

$$\begin{aligned} & \gamma^{-1}(\gamma(\bar{x})e^\mu) - b + \sum_{k=1}^M \kappa_k \tau_k (\gamma(\bar{x})e^\mu)^{y_k} y_k \\ &= \gamma^{-1}(\gamma(\bar{x})e^\mu) - \theta(0) + \sum_{k=1}^M \left(\kappa_k \int_{-\tau_k}^0 ((\gamma(\bar{x})e^\mu)^{y_k} - \gamma^{y_k}(\theta(s))) ds \right) y_k \in \mathcal{S}. \end{aligned}$$

Let \tilde{x} be defined by

$$\tilde{x} = \gamma^{-1}(\gamma(\bar{x})e^\mu).$$

Then $\tilde{x} \in \mathcal{D}_\theta$ and taking logarithm shows that

$$\rho(\tilde{x}) - \rho(\bar{x}) = \mu \in \mathcal{S}^\perp;$$

that is, we have that $\tilde{x} \in \mathcal{E}$ as well.

To show uniqueness, assume by contradiction that \tilde{x} and \bar{x} are distinct positive equilibria in \mathcal{D}_θ . Then by (14) it follows that

$$\tilde{x} - \bar{x} + \sum_{k=1}^M \left(\kappa_k \int_{-\tau_k}^0 (\gamma^{y_k}(\tilde{x}) - \gamma^{y_k}(\bar{x})) ds \right) y_k \in \mathcal{S}.$$

This, combined with the characterization (9) shows that

$$\begin{aligned} 0 &= (\rho(\tilde{x}) - \rho(\bar{x})) \cdot \left[\tilde{x} - \bar{x} + \sum_{k=1}^M \left(\kappa_k \int_{-\tau_k}^0 (\gamma^{y_k}(\tilde{x}) - \gamma^{y_k}(\bar{x})) ds \right) y_k \right] \\ &= \sum_{i=1}^N (\log \gamma(\tilde{x}_i) - \log \gamma(\bar{x}_i)) (\tilde{x}_i - \bar{x}_i) \\ &\quad + \sum_{k=1}^M \left(\kappa_k \tau_k (\log \gamma^{y_k}(\tilde{x}) - \log \gamma^{y_k}(\bar{x})) (\gamma^{y_k}(\tilde{x}) - \gamma^{y_k}(\bar{x})) \right). \end{aligned}$$

Since the functions γ_i and the logarithm are strictly increasing, the above expression is zero if and only if $\tilde{x} = \bar{x}$. □

As a clear consequence of our nondelayed analysis, a delayed complex balanced system is quasi-thermostatic. To discuss quasi-thermodynamicity we define the candidate Lyapunov–Krasovskii functional, a main contribution of the paper, as

$$\begin{aligned} V(\psi) &:= V(\psi, \bar{x}) = \sum_{i=1}^N \int_{\bar{x}_i}^{\psi_i(0)} (\log \gamma_i(s) - \log \gamma_i(\bar{x}_i)) ds \\ &\quad + \sum_{k=1}^M \kappa_k \int_{-\tau_k}^0 \left(\gamma^{y_k}(\psi(s)) \left(\log \gamma^{y_k}(\psi(s)) - \log \gamma^{y_k}(\bar{x}) - 1 \right) + \gamma^{y_k}(\bar{x}) \right) ds. \end{aligned} \tag{16}$$

A delayed kinetic system of the form (7) is called quasi-thermodynamic if there exists $\bar{x} \in \mathbb{R}_+^N$ such that the system is quasi-thermostatic with respect to \bar{x} , and

$$\dot{V}(x_t, \bar{x}) \leq 0$$

holds along the trajectories x_t for $t \geq 0$, with equality holding only if $f(x) = 0$.

The following theorem is a generalization of Proposition 3.3 for delayed systems.

Theorem 4.3 *Assume that the kinetic system (7) is quasi-thermodynamic. Then, every positive equilibrium of the system is Lyapunov stable relative to its positive stoichiometric compatibility class.*

Proof The fact that each positive stoichiometric compatibility class contains precisely one positive equilibrium follows from quasi-thermostaticity. Using (12) shows that the second term of (16) is nonnegative and zero if only if $x = \bar{x}$, while in Sontag (2001) the author shows the same for the first term. Since the system is quasi-thermodynamic, the functional (16) is a Lyapunov–Krasovskii functional for the system and the proof is finished. □

Note, that in the nondelayed case Proposition 3.3 guaranteed local asymptotic stability and that there are no nontrivial periodic trajectories. In the delayed case the analogous definition only implies Lyapunov stability. However, in our final theorem that generalizes Proposition 3.5 to the delayed case, we can ensure these properties.

Theorem 4.4 *Assume that the delayed kinetic system (7) is complex balanced. Then it is quasi-thermodynamic. Moreover, each equilibrium is locally asymptotically stable relative to its positive stoichiometric compatibility class and there are no nontrivial periodic trajectory along which all species concentrations are positive.*

Proof Let \bar{x} be a complex balanced equilibrium. The gradient of the first term of (16) is $\rho(x) - \rho(\bar{x})$, and thus the Lyapunov–Krasovskii directional derivative along trajectories of (7) is given by

$$\begin{aligned} \dot{V}(x_t) &= \sum_{k=1}^M \kappa_k (\gamma^{y_k}(x(t - \tau_k)) q_{k'}(x(t)) - \gamma^{y_k}(x(t)) q_k(x(t))) \\ &\quad + \sum_{k=1}^M \kappa_k (\gamma^{y_k}(x(t)) q_k(x(t)) - \gamma^{y_k}(x(t - \tau_k)) q_k(x(t - \tau_k))) \\ &\quad + \sum_{k=1}^M \kappa_k (\gamma^{y_k}(x(t - \tau_k)) - \gamma^{y_k}(x(t))) \\ &= \sum_{k=1}^M \kappa_k (\gamma^{y_k}(x(t - \tau_k)) (q_{k'}(x(t)) \\ &\quad - q_k(x(t - \tau_k))) + \gamma^{y_k}(x(t - \tau_k)) - \gamma^{y_k}(x(t))). \end{aligned}$$

Rewrite the above as

$$\begin{aligned} \dot{V}(x_t) &= \sum_{k=1}^M \kappa_k \gamma^{y_k} \\ &\quad \left(\bar{x} (e^{q_k(x(t - \tau_k))} (q_{k'}(x(t)) - q_k(x(t - \tau_k))) + e^{q_k(x(t - \tau_k))} - e^{q_k(x(t))}) \right) \end{aligned}$$

and use inequality (12) to find that

$$\begin{aligned} \dot{V}(x_t) &\leq \sum_{k=1}^M \kappa_k \gamma^{y_k}(\bar{x}) (e^{q_{k'}(x(t))} - e^{q_k(x(t))}) \\ &= \sum_{\eta \in \mathcal{K}} e^{q_\eta(x(t))} \left(\sum_{k:\eta=y_{k'}} \kappa_k \gamma^{y_k}(\bar{x}) - \sum_{k:\eta=y_k} \kappa_k \gamma^{y_k}(\bar{x}) \right) = 0, \end{aligned}$$

as the system is complex balanced, and $\dot{V}(x_t) = 0$ if and only if the equality

$$q_{k'}(x(t)) = q_k(x(t - \tau_k))$$

holds for each reaction $k = 1, 2, \dots, M$. Standard arguments, see (Lipták et al. 2018a, Theorem 3), show that the largest invariant subset of the set

$$\begin{aligned} \mathcal{R} &= \left\{ \psi \in \mathcal{C}_{+, \tau} \mid \dot{V}(\psi) = 0 \right\} \\ &= \left\{ \psi \in \mathcal{C}_{+, \tau} \mid q_k(x^\psi(t)) = q_k(x^\psi(t - \tau_k)), k = 1, 2, \dots, M \right\} \end{aligned}$$

consists of constant functions that are positive complex balanced equilibria.

The fact that there are no nontrivial periodic trajectories along which all species concentrations are positive can be shown similarly as in 3.3, thus we omit the calculation. \square

5 Discussion

In this section some further remarks are discussed about the results shown in Sects. 3 and 4.

5.1 Interpretation of delayed entropy

In the nondelayed case, the Lyapunov function (10) depends only on the concentration configuration of the system and does not include any information about the reactions, such as the reactants, the products or the reaction rate coefficients. Such Lyapunov functions are called *universal*, a term used by Gorban (2019). In the delayed case, the Lyapunov–Krasovskii functional (16) is not universal in this sense, since it explicitly contains the stoichiometric vectors and the rate coefficients. In the entropy (or free energy) interpretation of the Lyapunov function, the history of the trajectories temporarily increase the entropy. As we have shown, this residual entropy can be described by the second term of (16). While it might be possible to define the delayed entropy with less information about the reactions, our Lyapunov–Krasovskii functional is inherently tied to the delayed system. To see this, we can use the chain method to approximate the delayed reactions in (7) with cascades of first-order mass action reactions (Györi 1988; Györi and Turi 1991). The Lyapunov function of the approximating system will then converge uniformly to (16) on compact subsets of $[0, \infty)$. For a more detailed explanation, we refer to Lipták et al. (2018b), where the authors derive this in the mass action case.

5.2 Lyapunov–Krasovskii functional in a different notation

In the literature of CRNs, both system descriptions (3) and (6) are used frequently. In the former case, we sum the right-hand side w.r.t. the reactions, while in the latter case

we sum w.r.t. the complexes. The delayed system (7) can be similarly rewritten as

$$\dot{x}(t) = \sum_{i=1}^L \sum_{j=1}^L \kappa_{ij} [\gamma^{y_i}(x(t - \tau_{ij}))y_j - \gamma^{y_i}(x(t))y_i].$$

Then the Lyapunov–Krasovskii functional takes the form

$$\begin{aligned} V(\psi) := V(\psi, \bar{x}) &= \sum_{i=1}^N \int_{\bar{x}_i}^{\psi_i(0)} (\log \gamma_i(s) - \log \gamma_i(\bar{x}_i)) ds \\ &+ \sum_{i=1}^L \sum_{j=1}^L \kappa_{ij} \int_{-\tau_{ij}}^0 \left(\gamma^{y_i}(\psi(s)) (\log \gamma^{y_i}(\psi(s)) - \log \gamma^{y_i}(\bar{x}) - 1) - \gamma^{y_i}(\bar{x}) \right) ds. \end{aligned}$$

The computation on $\dot{V}(x_t)$ can be repeated with minor notational modifications to obtain

$$\dot{V}(x_t) \leq \sum_{i=1}^L \sum_{j=1}^L \kappa_{ij} \gamma^{y_i}(\bar{x}) (e^{q_j(x(t))} - e^{q_i(x(t))}).$$

The right-hand side is equal to

$$\sum_{j=1}^L e^{q_j(x(t))} \left(\sum_{i=1}^L \kappa_{ij} \gamma^{y_i}(\bar{x}) \right) - \sum_{i=1}^L e^{q_i(x(t))} \left(\sum_{j=1}^L \kappa_{ij} \right) \gamma^{y_i}(\bar{x}) =: Q(x(t)) \tilde{K} \Gamma(\bar{x}).$$

Since \bar{x} is a complex balanced equilibrium, the vector $\Gamma(\bar{x})$ is in the kernel of \tilde{K} ; that is, we have that $\dot{V}(x_t) \leq 0$.

5.3 Connection with semistability

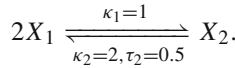
Our results also show that the positive equilibria of a delayed complex balanced CRN are semistable, defined as follows. An equilibrium \bar{x} is called semistable, if it is Lyapunov stable and there exists $\delta > 0$ such that $\psi \in \mathcal{B}_\delta(\bar{x})$ implies that $x^\psi(t)$ converges to a Lyapunov stable equilibrium as $t \rightarrow \infty$. In Lipták et al. (2018a) the authors showed semistability for delayed mass action complex balanced CRNs. We note that the existence of an equilibrium in each positive stoichiometric compatibility class was not known at that time, but it was since proved in Komatsu and Nakajima (2020) for delayed mass action systems and in Proposition 4.2 for the more general case.

6 Examples

In the following examples we illustrate our notations and results.

6.1 Example 1

First, let us consider the delayed kinetic system from (Lipták et al. 2018a) with mass action kinetics. The system consists of a reversible reaction



The corresponding kinetic system takes the form

$$\dot{x}(t) = \kappa_1 \left(x_1^2(t) \begin{bmatrix} 0 \\ 1 \end{bmatrix} - x_1^2(t) \begin{bmatrix} 2 \\ 0 \end{bmatrix} \right) + \kappa_2 \left(x_2(t - \tau_2) \begin{bmatrix} 2 \\ 0 \end{bmatrix} - x_2(t) \begin{bmatrix} 0 \\ 1 \end{bmatrix} \right).$$

The stoichiometric subspace and its orthogonal complement is

$$\mathcal{S} = \text{span} \left\{ \begin{bmatrix} -2 \\ 1 \end{bmatrix} \right\} \quad \mathcal{S}^\perp = \text{span} \left\{ \begin{bmatrix} 1 \\ 2 \end{bmatrix} \right\}.$$

It is easy to verify that $[2 \ 2]^\top$ is a positive complex balanced equilibrium, and thus the positive equilibria are given by

$$\mathcal{E} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} \log x_1 - \log 2 \\ \log x_2 - \log 2 \end{bmatrix} \in \mathcal{S}^\perp \right\}.$$

For any $\bar{x} \in \mathcal{E}$ we consider the set of points

$$\mathcal{X}_{\bar{x}} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} x_1 - \bar{x}_1 \\ (1 + \kappa_2 \tau_2)(x_2 - \bar{x}_2) \end{bmatrix} \in \mathcal{S} \right\}.$$

If we construct constant functions in $\mathcal{C}_{+, \tau}$ from \bar{x} and the elements of $\mathcal{X}_{\bar{x}}$ in the obvious way, then by (14) we have $\mathcal{X}_{\bar{x}} \in \mathcal{D}_{\bar{x}}$.

Let us consider the transformations $\gamma_1(s) = \frac{s^2}{1+s}$ and $\gamma_2(s) = \frac{s^3}{1+s}$; that is, the transformed system takes the form

$$\begin{aligned} \dot{x}(t) = & \kappa_1 \left(\frac{x_1^4(t)}{(1+x_1(t))^2} \begin{bmatrix} 0 \\ 1 \end{bmatrix} - \frac{x_1^4(t)}{(1+x_1(t))^2} \begin{bmatrix} 2 \\ 0 \end{bmatrix} \right) \\ & + \kappa_2 \left(\frac{x_2^3(t - \tau_2)}{1+x_2(t - \tau_2)} \begin{bmatrix} 2 \\ 0 \end{bmatrix} - \frac{x_2^3(t)}{1+x_2(t)} \begin{bmatrix} 0 \\ 1 \end{bmatrix} \right). \end{aligned}$$

Is it easy to verify that $[\frac{\sqrt{5}}{2} + \frac{1}{2} \ 1]^\top$ is a positive complex balanced equilibrium, and thus the positive equilibria are given by

$$\mathcal{E} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} \log \frac{x_1^2}{1+x_1} - \log 1 \\ \log \frac{x_2^3}{1+x_2} - \log \frac{1}{2} \end{bmatrix} \in \mathcal{S}^\perp \right\},$$

and $\mathcal{X}_{\bar{x}}$ is given by

$$\mathcal{X}_{\bar{x}} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} x_1 - \bar{x}_1 \\ x_2 - \bar{x}_2 + \kappa_2 \tau_2 \left(\frac{x_2^3}{1+x_2} - \frac{\bar{x}_2^3}{1+\bar{x}_2} \right) \end{bmatrix} \in \mathcal{S} \right\}.$$

Using the terminology of Komatsu and Nakajima (2019, 2020) it is easy to see that the set $W = \{X_1, X_2\}$ is the only minimal semilocking set (called siphon in the theory of Petri nets). The L_W space consists of functions $w \in \bar{\mathcal{C}}_{+,\tau}$ such that

$$\begin{aligned} w_i(s) &= 0, & X_i &\in W, \\ w_i(s) &\neq 0, & X_i &\notin W \end{aligned}$$

holds for $s \in [-\tau, 0]$. Then (Komatsu and Nakajima 2020, Theorem 5.1) states that the boundary equilibria of the system is contained in

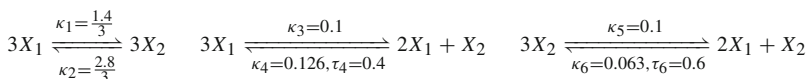
$$\bigcup_{\theta \in \mathcal{C}_{+,\tau}} \bar{\mathcal{D}}_\theta \cap L_W,$$

but the above set consists of only the constant zero function; that is, all nontrivial equilibria are positive and globally asymptotically stable w.r.t. their positive stoichiometric compatibility classes.

In Fig. 1, the positive equilibria, several positive stoichiometric compatibility classes and trajectories of the original mass action system are depicted with red dashed, green dashed and green continuous lines, respectively. The same objects for the transformed system are drawn with black dashed, blue dashed and blue continuous lines, respectively.

6.2 Example 2

Our next example is a delayed version of another complex balanced small reaction network, taken from Szederkényi and Hangos (2011). We consider the set of reversible reactions



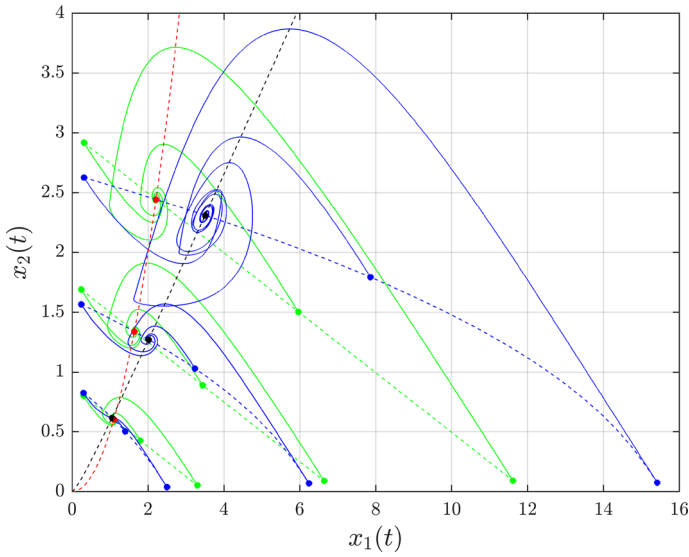


Fig. 1 Phase plot of example 1

with the transformations $\gamma_1(s) = s$ and $\gamma_2(s) = \frac{s^2}{1+s}$. Then the system takes the form

$$\begin{aligned} \dot{x}(t) = & \kappa_1 \left(x_1^3(t) \begin{bmatrix} 0 \\ 3 \end{bmatrix} - x_1^3(t) \begin{bmatrix} 3 \\ 0 \end{bmatrix} \right) + \kappa_2 \left(\frac{x_2^6(t)}{(1+x_2(t))^2} \begin{bmatrix} 3 \\ 0 \end{bmatrix} - \frac{x_2^6(t)}{(1+x_2(t))^2} \begin{bmatrix} 0 \\ 3 \end{bmatrix} \right) \\ & + \kappa_3 \left(x_1^3(t) \begin{bmatrix} 2 \\ 1 \end{bmatrix} - x_1^3(t) \begin{bmatrix} 3 \\ 0 \end{bmatrix} \right) \\ & + \kappa_4 \left(x_1^2(t - \tau_4) \frac{x_2^2(t - \tau_4)}{1+x_2(t - \tau_4)} \begin{bmatrix} 3 \\ 0 \end{bmatrix} - x_1^2(t) \frac{x_2^2(t)}{1+x_2(t)} \begin{bmatrix} 2 \\ 1 \end{bmatrix} \right) \\ & + \kappa_5 \left(\frac{x_2^6(t)}{(1+x_2(t))^2} \begin{bmatrix} 2 \\ 1 \end{bmatrix} - \frac{x_2^6(t)}{(1+x_2(t))^2} \begin{bmatrix} 0 \\ 3 \end{bmatrix} \right) \\ & + \kappa_6 \left(x_1^2(t - \tau_6) \frac{x_2^2(t - \tau_6)}{1+x_2(t - \tau_6)} \begin{bmatrix} 0 \\ 3 \end{bmatrix} - x_1^2(t) \frac{x_2^2(t)}{1+x_2(t)} \begin{bmatrix} 2 \\ 1 \end{bmatrix} \right). \end{aligned}$$

The stoichiometric subspace and its orthogonal complement are

$$S = \text{span} \left\{ \begin{bmatrix} -3 \\ 3 \end{bmatrix} \right\} \quad S^\perp = \text{span} \left\{ \begin{bmatrix} 3 \\ 3 \end{bmatrix} \right\}.$$

It is easy to verify via the Cardano formula that

$$\bar{x} = \left[\begin{array}{c} \sqrt[3]{2} \\ \sqrt[3]{\frac{1}{2} + \sqrt{\frac{23}{108}}} + \sqrt[3]{\frac{1}{2} - \sqrt{\frac{23}{108}}} \end{array} \right]$$

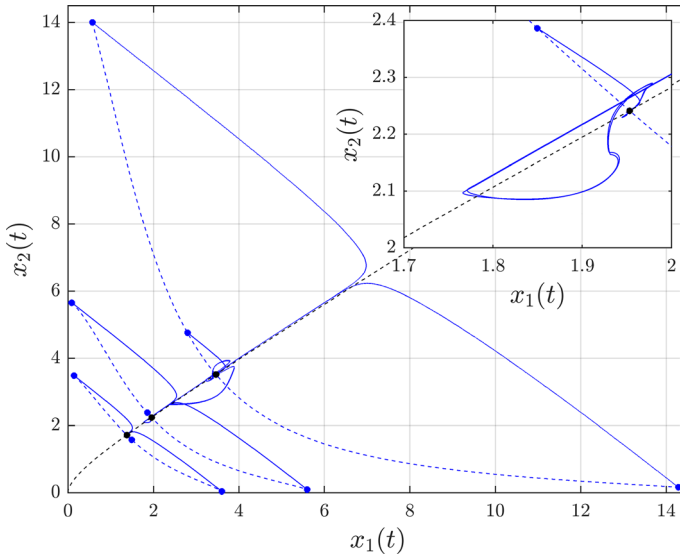


Fig. 2 Phase plot of example 2

is a positive complex balanced equilibrium, and thus the positive equilibria are given by

$$\mathcal{E} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} \log x_1 - \log \bar{x}_1 \\ \log \frac{x_2^2}{1+x_2} - \log \frac{\bar{x}_2^2}{1+\bar{x}_2} \end{bmatrix} \in \mathcal{S}^\perp \right\},$$

and $\mathcal{K}_{\bar{x}}$ is given by

$$\mathcal{K}_{\bar{x}} = \left\{ x \in \mathbb{R}_+^2 \mid \begin{bmatrix} x_1 - \bar{x}_1 + 2(\kappa_4\tau_4 + \kappa_5\tau_5)\left(x_1^2 \frac{x_2^2}{1+x_2} - \bar{x}_1^2 \frac{\bar{x}_2^2}{1+\bar{x}_2}\right) \\ x_2 - \bar{x}_2 + (\kappa_4\tau_4 + \kappa_5\tau_5)\left(x_1^2 \frac{x_2^2}{1+x_2} - \bar{x}_1^2 \frac{\bar{x}_2^2}{1+\bar{x}_2}\right) \end{bmatrix} \in \mathcal{S} \right\}.$$

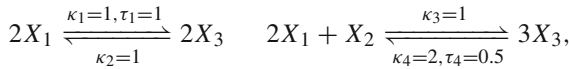
Similarly to the previous example, it can be shown via (Komatsu and Nakajima 2020, Theorem 5.1) that all nontrivial equilibria of the system are positive and globally asymptotically stable w.r.t. their positive stoichiometric compatibility classes.

In Fig. 2, the positive equilibria, several positive stoichiometric compatibility classes and trajectories of system are drawn with black dashed, blue dashed and blue continuous lines, respectively.

6.3 Example 3

Our final example focuses on the Lyapunov–Krasovskii functional. Of course it cannot be visualized in general as it maps an infinite dimensional function space to nonnegative numbers. However, if we restrict the functional to constant history functions as in the previous examples, then we can compare it to the nondelayed Lyapunov function.

In order to do so, we consider the following delayed reversible reactions



with transformations $\gamma_1(s) = s$, $\gamma_2(s) = \frac{s^2}{1+s}$ and $\gamma_3(s) = \frac{s}{1+s}$. Omitting the vector notation, the corresponding delayed differential equation takes the form

$$\begin{aligned} \dot{x}_1(t) &= -2\kappa_1 x_1^2(t) + 2\kappa_2 \left(\frac{x_3(t)}{1+x_3(t)} \right)^2 - 2\kappa_3 x_1^2(t) \frac{x_2^2(t)}{1+x_2(t)} + 2\kappa_4 \left(\frac{x_3(t-\tau_4)}{1+x_3(t-\tau_4)} \right)^3 \\ \dot{x}_2(t) &= \kappa_4 \left(\frac{x_3(t-\tau_4)}{1+x_3(t-\tau_4)} \right)^3 - \kappa_3 x_1^2(t) \frac{x_2^2(t)}{1+x_2(t)} \\ \dot{x}_3(t) &= 2\kappa_1 x_1^2(t-\tau_1) - 2\kappa_2 \left(\frac{x_3(t)}{1+x_3(t)} \right)^2 + 3\kappa_3 x_1^2(t) \frac{x_2^2(t)}{1+x_2(t)} - 3\kappa_4 \left(\frac{x_3(t)}{1+x_3(t)} \right)^3. \end{aligned}$$

It is easy to see that the nondelayed system is conservative as $x_1 + x_2 + x_3$ is a first integral; that is, the nondelayed positive stoichiometric compatibility classes can be characterized as

$$\mathcal{S}_p = \left\{ x \in \mathbb{R}_+^3 \mid x_1 + x_2 + x_3 = p_1 + p_2 + p_3 \right\},$$

where $p \in \mathbb{R}_+^3$ is arbitrary. Then for any fixed $p \in \mathbb{R}_+^3$ we can visualize the Lyapunov function (10) as a two-dimensional function defined on the region

$$\mathcal{D}_p = \left\{ x \in \mathbb{R}_+^2 \mid x_1 + x_2 \leq p_1 + p_2 + p_3 \right\}.$$

The delayed positive stoichiometric compatibility class of the delayed system is more complicated and, in particular, it is not a plane; that is, the delayed system is not conservative in this sense. However, it can be shown similarly to the previous examples that the system is persistent, and thus every delayed positive stoichiometric compatibility class contains precisely one positive equilibrium. Assuming a constant history function constructed from an element of \mathcal{D}_p , we can compute the value of the functional at the initial point of the corresponding trajectory. Figure 3 shows the contour plots of the Lyapunov function and the Lyapunov–Krasovskii functional on \mathcal{D}_p with $p_1 + p_2 + p_3 = 1$.

7 Conclusions

The stability of kinetic systems with time delays and general kinetics was studied in this paper. In preparation for the subsequent analysis, certain stability results of Sontag (2001) were slightly generalized using the notion of quasi-thermodynamicity introduced in Horn and Jackson (1972). Then it was shown for delayed complex balanced reaction networks that each positive stoichiometric compatibility class contains precisely one positive equilibrium that is locally asymptotically stable within their

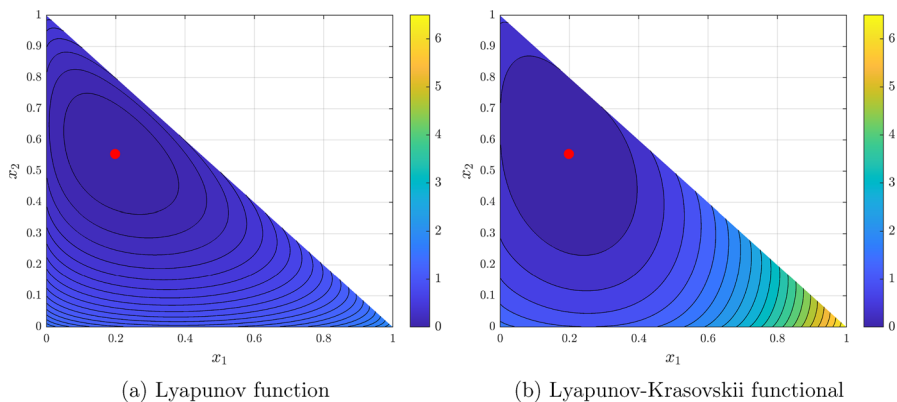


Fig. 3 Level curves of the Lyapunov function of the nondelayed system and the Lyapunov–Krasovskii functional of the delayed system for constant history functions

positive stoichiometric compatibility classes for arbitrary finite time delays. A key result of the paper allowing the stability proof is the construction of an appropriate Lyapunov–Krasovskii functional. Thus, the results proposed in Lipták et al. (2018a) have been generalized for a wide class of delayed non-mass action reaction networks. It was also shown that the global stability of equilibria can be proved as well if the conditions in Komatsu and Nakajima (2019, 2020) are fulfilled. Three illustrative examples were given to visualize the theoretical results. Further work will be focused on the kinetic realization and control of general nonlinear delayed models given in DDE form.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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