Robust Lyapunov Functions for Reaction Networks: An Uncertain System Framework

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Abstract

We present a framework to transform the problem of finding a Lyapunov function of a Chemical Reaction Network (CRN) in concentration coordinates with arbitrary monotone kinetics into finding a common Lyapunov function for a linear parameter varying system in reaction coordinates. Alternative formulations of the proposed Lyapunov function is presented also. This is applied to reinterpret previous results by the authors on Piecewise Linear in Rates Lyapunov functions, and to establish a link with contraction analysis. Persistence and uniqueness of equilibria are discussed also.

Keywords: Lyapunov stability, Persistence, Contraction Analysis, Linear Parameter Varying Systems, Biochemical Networks.

1 Introduction

Chemical Reaction Networks Theory (CRNs) is a multi-disciplinary area of research connecting engineering, mathematics, physics and systems biology. Despite diverse applications in engineering and science, the recent interest in CRNs is mainly due to the emergence of systems biology.

In the context of systems biology, CRNs are key to understand complex biological systems at the cellular level by explicitly taking into account the sophisticated network of chemical interactions that regulate cell life. This is because all major biochemical networks such as signalling pathways, gene-regulatory networks, and metabolic networks are naturally cast in the framework of CRNs.

A major obstacle in biochemical networks is the very large degree of uncertainty inherent in their modeling as well as the variability or poor knowledge of the parameters involved. Thus, a useful analysis of these networks shall be robust, for instance with respect to arbitrary variations in the values of parameters. In other words, it is desirable to provide nontrivial conclusions based solely on the structural properties of the network. However, it is natural to expect that this is not always possible, since dynamics may be subject to bifurcations which are entirely dependent on parameter values. Fortunately, many results \cite{1, 2, 3, 4} identified wide classes of CRNs in which such analysis is indeed possible, where it has been shown that some major dynamical properties such as stability, persistence, monotonicity, etc can be determined based on structural information only, and regardless of the parameters involved.
Early work [1, 3] studied Lyapunov stability for weakly reversible networks which meet a certain graphical condition known as the zero deficiency property. It was shown that for this class of networks with mass-action kinetics, there exists a unique equilibrium in the interior of each invariant manifold, which is locally asymptotically stable regardless of the constants involved. In addition, the absence of boundary equilibria implies global asymptotic stability [5]. Nevertheless, whether this is true without this additional assumption is still an open problem.

A more recent approach for the stability problem utilized monotonicity [4]. If a derived system from the CRN is shown to be monotone, stability theorems for monotone systems can be used. Piecewise linear Lyapunov functions based methods has been proposed recently [6, 7, 8, 9].

In a previous work [7, 8], the authors proposed a direct approach to the problem, where Piecewise-Linear in Rates (PWLR) Lyapunov functions were introduced. In addition to their simple structure, these functions are robust with respect to kinetic constants, and require mild assumptions on the kinetic rates, mass-action being a special case.

In this paper, we generalize this approach by transforming the problem of finding a Lyapunov function expressed in concentration coordinates for networks with arbitrary monotone kinetics into finding a common Lyapunov function for a linear parameter varying system written in reaction coordinates. Furthermore, several related Lyapunov functions are presented. As a result, we link the PWLR Lyapunov functions introduced in [7] with results known in literature for piecewise linear Lyapunov functions [10, 11, 12]. Furthermore, we show to interpret our results in terms of contraction analysis and variational dynamics. Related results on persistence and uniqueness of equilibria are also presented. Note that some of the results in this paper were published in [13].

This paper is organized as follows. In Section 2, we present the background and assumptions. Section 3 defines what we mean by a Robust Lyapunov function, and introduces the uncertain systems framework. PWLR Lyapunov functions are introduced in Section 4, uniqueness of equilibria and persistence is presented in Section 5. Section 6 discuss the relationship with contraction analysis. The proofs are presented in the Appendix.

**Notation**  Let $A \subset \mathbb{R}^n$ be a set, then $A^\circ, \bar{A}, \partial A, \text{co } A$ denote its interior, closure, boundary, and convex hull, respectively. Let $x \in \mathbb{R}^n$ be a vector, then its $\ell_\infty$-norm is $\|x\|_\infty = \max_{1 \leq i \leq n} |x_i|$. The inequalities $x \geq 0$, $x > 0$, $x \gg 0$ denote elementwise nonnegativity, elementwise nonnegativity with at least one positive element, and elementwise positivity, respectively. $A$ is a signature matrix if $A \in \{-1, 1\}^{n \times n}$ and $A$ is diagonal. Let $A \in \mathbb{R}^{n \times \nu}$, then $\ker(A)$ denotes the kernel or null-space of $A$, while $\text{Im}(A)$ denotes the image space of $A$. $A \in \mathbb{R}^{n \times n}$ is Metzler if all off-diagonal elements are nonnegative. The set of $n \times n$ real symmetric matrices is denoted by $\mathbb{S}^n$. Let $A \in \mathbb{S}^n$, then $A \succeq (\succ) 0$ denotes $A$ being positive semi-definite (definite), respectively. $A \succeq 0$ denotes $A$ being nonnegative. The all-ones vector is denoted by $\mathbf{1}$, where its dimension can be inferred from the context. Let $\{X_i\}_{i=1}^k \subset \mathbb{R}^{n \times m}$, its conic hull denotes the set $\{\sum_{i=1}^k \lambda_i X_i : \lambda_i \in \mathbb{R}_+\}$. Let $V : D \to \mathbb{R}$, then the kernel of $V$ is $\ker(V) = V^{-1}(0)$. $TM$ is the tangent bundle of the differentiable manifold $M$.

**2 Background on Complex Reaction Networks**

We summarize in this section main definitions and notions of CRNs [7, 8].
2.1 Ordinary Differential Equations Formulation

A Complex (or Chemical) Reaction Network (CRN) is defined by a set of species \( S = \{ X_1, \ldots, X_n \} \), and set of reactions \( R = \{ R_1, \ldots, R_\nu \} \). Each reaction is denoted as:

\[
R_j : \sum_{i=1}^n \alpha_{ij} X_i \longrightarrow \sum_{i=1}^n \beta_{ij} X_i, \quad j = 1, \ldots, \nu,
\]

where \( \alpha_{ij}, \beta_{ij} \) are nonnegative integers called stoichiometry coefficients. The expression on the left-hand side is called the reactant complex, while the one on the right-hand side is called the product complex. The forward arrow refers to the idea that the transformation of reactant into product is only occurring in the direction of the arrow. If it occurs in the opposite direction also, the reaction is said to be reversible and its inverse is listed as a separate reaction. The reactant or product complex can be empty, though not simultaneously, which is used to model external inflows and outflows of the CRN.

A nonnegative concentration \( x_i \) is associated to each species \( X_i \). Each chemical reaction \( R_j \) is specified by a rate function \( R_j : \bar{R}^n_+ \rightarrow \bar{R}_+ \) which is assumed to satisfy the following:

**A1.** it is a \( C^1 \) function, i.e. continuously differentiable;

**A2.** \( x_i = 0 \Rightarrow R_j(x) = 0 \), for all \( i \) and \( j \) such that \( \alpha_{ij} > 0 \);

**A3.** it is nondecreasing with respect to its reactants, i.e

\[
\frac{\partial R_j}{\partial x_i}(x) \begin{cases} \geq 0 & : \alpha_{ij} > 0 \\ = 0 & : \alpha_{ij} = 0 \end{cases}.
\]

**A4.** The inequality in (2) holds strictly for all \( x \in \mathbb{R}^n_+ \).

A widely-used expression for the reaction rate function is the Mass-Action which is given by:

\[
R_j(x) = k_j \prod_{i=1}^n x_i^{\alpha_{ij}},
\]

with the convention \( 0^0 = 1 \).

The stoichiometry coefficients are arranged in an \( n \times \nu \) matrix \( A = [\alpha_{ij}], B = [\beta_{ij}] \). They can be subtracted to yield \( \Gamma = [\gamma_1 \ldots \gamma_n]^T \) which is called the stoichiometry matrix, which is defined element-wise as:

\[ [\Gamma]_{ij} = \beta_{ij} - \alpha_{ij}. \]

Therefore, the dynamics of a CRN with \( n \) species and \( \nu \) reactions is described by a system of ordinary differential equations (ODEs) as:

\[
\dot{x}(t) = \Gamma R(x(t)), \quad x_0 := x(0) \in \bar{\mathbb{R}}^n_+ \quad (3)
\]

where \( x(t) \) is the concentration vector evolving in the nonnegative orthant \( \bar{\mathbb{R}}^n_+ \), \( \Gamma \in \mathbb{R}^{n \times \nu} \) is the stoichiometry matrix, \( R(x(t)) \in \bar{\mathbb{R}}^\nu_+ \) is the reaction rates vector.

Note that (3) belongs to the class of nonnegative systems, i.e, \( \bar{\mathbb{R}}^n_+ \) is forward invariant. In addition, the manifold \( \mathcal{C}_{x_0} := (\{x_0\} + \text{Im}(\Gamma)) \cap \bar{\mathbb{R}}^n_+ \) is forward invariant, and it is called the stoichiometric compatibility class associated with \( x_0 \).

Furthermore, the graph is assumed to satisfy:

**AG.** There exists \( v \in \ker \Gamma \) such that \( v \gg 0 \). This condition is necessary for the existence of equilibria in the relative interior of stoichiometric compatibility classes.

The set of reaction rate functions, i.e. kinetics, satisfying A1-A4 for a given \( A, B \) is denoted by \( \mathcal{K}_A \). A CRN family \( \mathcal{N}_{A,B} \) is the triple \( (\mathcal{S}, \mathcal{R}, \mathcal{K}_A) \).
### 2.2 Graphical Representation

A CRN can be represented via a bipartite weighted directed graph given by the quadruple \((V_S, V_R, E, W)\), where \(V_S\) is a set of nodes associated with species, and \(V_R\) is associated with reactions.

The edge set \(E \subset V \times V\) is defined as follows. Whenever a certain reaction \(R_j\) is given by \((i, j)\), then \((X_i, R_j) \in E\) for all \(X_i\)’s such that \(\alpha_{ij} > 0\). That is, \((X_i, R_j) \in E\) if \(\alpha_{ij} > 0\), and we say in this case that \(R_j\) is an output reaction for \(X_i\). Similarly, we draw an edge from \(R_j \in V_R\) to every \(X_i \in V_S\) such that \(\beta_{ij} > 0\). That is, \((R_j, X_i) \in E\) whenever \(\beta_{ij} > 0\), and we say in this case that \(R_j\) is an input reaction for \(X_i\). Note that there are no edges connecting two reactions or two species. The weight function \(W : E \to \mathbb{N}\) assigns to each edge a positive integer as \(W(X_i, R_j) = \alpha_{ij}\), and \(W(R_j, X_i) = \beta_{ij}\). Hence, the stoichiometry matrix \(\Gamma\) becomes the incidence matrix of the graph.

The set of output reactions of \(P\) is denoted by \(\Lambda(P)\). A nonempty set \(P \subset V_S\) is called a siphon if for any choice of \(A, B \in V_S\), \(\Lambda(P) = V_R\). A siphon is a deadlock if \(\Lambda(P) = V_R\). A siphon or a deadlock is said to be critical if it does not contain a set of species corresponding to the support of a conservation law.

### 3 Robust Lyapunov Functions and Linear Inclusions

#### 3.1 Robust Lyapunov Functions

In order for the stability analysis of CRNs to be independent of the specific kinetics, we aim at constructing Lyapunov functions which are dependent only on the graphical structure, and hence are valid for all reaction rate functions that belongs to \(\mathcal{K}_T\). Therefore, we state the following definition:

**Definition 1** (Robust Lyapunov Function). Given \(\tilde{V} : \tilde{\mathbb{R}}^q \to \tilde{\mathbb{R}}_+\) be locally Lipschitz, and let \(W_{R, x_e} : \mathbb{R}^n \to \mathbb{R}^q\) be a \(C^1\) function, where \(x_e\) is an equilibrium. Then, \((\tilde{V}, W_{R, x_e})\) is said to induce a Robust Lyapunov Function (RLF) with respect to the network family \(\mathcal{M}_{A,B}\) if for any choice of \(R \in \mathcal{K}_A, x_e \in \mathbb{R}^n_+\), the function \(V_{R, x_e} = \tilde{V} \circ W_{R, x_e}\) is,

1. **Positive-Definite:** \(V(x) \geq 0\), and \(V(x) = 0\) if and only if \(R(x) \in \ker \Gamma\).
2. **Nonincreasing:** \(\dot{V}(x) \leq 0\) for all \(x \in \mathcal{C}_{x_e}\).

A network for which an RLF exists is termed a Graphically Stable Network (GSN).

**Remark 1.** As will be seen afterwards, the function \(\tilde{V}\) used in the definition of the Lyapunov function (through composition) is invariant with respect to the specific network realization in \(\mathcal{K}_A\), while the function \(W_{R, x_e}\) is allowed to depend on the kinetics of the network. Two main examples of the function \(W_{R, x_e}\) are \(W_{R, x_e}(x) = R(x)\), and \(W_{R, x_e}(x) = x - x_e\), and they will be used afterwards.

As an abuse of notation, we will call the parametrized Lyapunov function \(V_{R, x_e}\) an RLF.

**Remark 2.** The time-derivative in the definition above is the upper right Dini’s derivative:

\[
\dot{V}(x) := \limsup_{h \to 0^+} \frac{V(x + hR(x)) - V(x)}{h},
\]

which is finite for all \(x\) since \(V\) is locally Lipschitz.

Since the RLF defined above is not strict, we need the following definition:
Definition 2. An RLF $V_{R,x,e}$ for $\mathcal{N}_{A,B}$ is said to satisfy the LaSalle’s condition if for any choice $R \in \mathcal{K}_A$ the following statement holds:

If a solution $\varphi(t;x_0)$ of (3) satisfies $\varphi(t;x_0) \in \ker \dot{V} \cap C_{x,e}$, $t \geq 0$, then this implies that $\varphi(t;x_0) \in E_{x_e}$ for all $t \geq 0$, where $E_{x_e} \subset C_{x,e}$ be the set of equilibria for (3).

The following theorem adapts Lyapunov’s second method to our context.

Theorem 1 (Lyapunov’s Second Method). Given (3) with initial condition $x_0 \in \mathbb{R}_+^n$, and let $C_{x_e}$ as the associated stoichiometric compatibility class. Assume there exists an RLF Lyapunov function, and suppose that $x(t)$ is bounded,

1. then the equilibrium set $E_{x_e}$ is Lyapunov stable.

2. If, in addition, $V$ satisfies the LaSalle’s Condition, then $x(t) \to E_{x_e}$ as $t \to \infty$ (i.e., the point to set distance of $x(t)$ to $E_{x_e}$ tends to 0). Furthermore, any isolated equilibrium relative to $C_{x_e}$ is asymptotically stable.

3. If $V$ satisfies the LaSalle’s condition, and all the trajectories are bounded, then: If there exists $x^* \in E_{x_e}$, which is isolated relative to $C_{x_e}$ then it is unique, i.e., $E_{x_e} = \{x^*\}$. Furthermore, it is globally asymptotically stable equilibrium relative to $C_{x_e}$.

Remark 3. Note that the RLF Lyapunov function considered can not be used to establish boundedness, as it may fail to be proper. Therefore, we need to resort to other methods so that the boundedness of solutions can be guaranteed. For instance, if the network is conservative, i.e the exists $w \in \mathbb{R}_+^n$ such that $w^T \Gamma = 0$, which ensures the compactness of $C_{x_e}$.

3.2 Uncertain Systems Framework: Reaction Coordinates

In this subsection, the function $W_{R,x_e}$ is assigned to be $R$, as in the case of PWLR functions. As arbitrary monotone kinetics are allowed in our formulation of the CRN family $\mathcal{N}_{A,B}$, the system (3) with kinetics $\mathcal{K}_A$ can be viewed as an uncertain system. However, this system does not fit directly to the traditional types of uncertainties (e.g parameter uncertainty) known in the literature. In this subsection, we show that shifting the analysis of the system to reaction coordinates enables us to view it as a linear parameter varying (LPV) system where the existence of a common Lyapunov function for the LPV system implies the existence of a robust Lyapunov function for the CRN.

Let $r(t) := R(x(t))$, then we have:

$$\dot{r}(t) = \frac{\partial R}{\partial x}(x(t))\Gamma r(t) = \rho(t)\Gamma r(t),$$  \hspace{1cm} (5)

where $\rho(t) := \frac{\partial R}{\partial x}(x(t))$. We can write $\rho(t)$ as a conic combination of individual partial derivatives as follows:

$$\frac{\partial R}{\partial x}(x(t)) = \rho(t) = \sum_{i,j: \alpha_{ij} > 0} \rho_{ji}(t)E_{ji},$$  \hspace{1cm} (6)

where $[\rho(t)]_{ji} = \rho_{ji}(t)$, and $[E_{ji}]_{j'i'} = 1$ if $(j',i') = (j,i)$ and zero otherwise.

Let $s$ denote the number of elements in the support of $\partial R/\partial x$, and let $\kappa : \{1, ..., s\} \to \{(i,j) : \alpha_{ij} > 0\}$ be an
equivalently as:
functions of
written. Given (3), and let $x$
subsection.
The RLF introduced in the previous subsection was a function of $x - x_e$. This will be carried out in a manner that is dual to what has been done in the previous subsection.
In order to present the dual framework, an alternative representation of the system dynamics can be written. Given (3), and let $x_e$ be an equilibrium. Then, there exists $x''(x)$ such that (3) can written equivalently as:
\[
\dot{x} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e), x(0) \in C_{x_e}
\] (8)
The existence of $x'' := x_e + \varepsilon x(x - x_e)$ for some $\varepsilon x \in [0, 1]$ follows by applying the Mean-Value Theorem to $R(x)$ around $x_e$.
Let $z = x - x_e$, then similar to the previous section, the conic combination (6) can be used to rewrite (8) as:
\[
\dot{z} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e) = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma \ell z = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma \ell^T z,
\] (9)
where $\rho_\ell(t) = \frac{\partial R}{\partial x_\ell}(x''(t))$, and $\Gamma_i$ is the $i$th column of $\Gamma$. Therefore, the systems dynamics has been embedded in the linear differential inclusion with vertices \{$\Gamma_i e_j^T, ... , \Gamma_i e_j^T$\}.
Let $D^T$ be a matrix whose columns are basis vectors of $\ker \Gamma^T$, the following theorem can be stated:
\begin{theorem}[Common Lyapunov Function] Given the system (3). There exists a common Lyapunov function $\hat{V} : \mathbb{R}^n \rightarrow \mathbb{R}_+$ for the set of linear systems \{$\dot{x} = \Gamma^1 r, ... , \dot{x} = \Gamma^s r$\} if it is a Lyapunov function for each of them, and \ker $\hat{V} = \cap_{\ell=1}^{s} \ker \Gamma^\ell$.
\end{theorem}

Hence, we are ready to state the main result whose proof is present in the appendix:
\begin{theorem}[Common Lyapunov Function] Given the system (3). There exists a common Lyapunov function $\hat{V} : \mathbb{R}^n_+ \rightarrow \mathbb{R}_+$ for the set of linear systems \{$\dot{\rho} = \Gamma^\ell r + , ... , \dot{\rho} = \Gamma^s r$\} if it is a Lyapunov function for each of them, and \ker $\hat{V} = \cap_{\ell=1}^{s} \ker \Gamma^\ell$.
\end{theorem}

Remark. Since the zero matrix belongs to the conic hull of \{$\Gamma^1, ... , \Gamma^s$\}, asymptotic stability can’t be established by the mere existence of the common Lyapunov function. A LaSalle’s argument is needed as will be mentioned in the following section.

3.3 Dual Robust Lyapunov Function: Species Coordinates
The RLF introduced in the previous subsection was a function of $R(x)$. We investigate now RLFs that are functions of $x - x_e$. This will be carried out in a manner that is dual to what has been done in the previous subsection.

Then, there exists $x''(x)$ such that (3) can written equivalently as:
\[
\dot{x} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e), x(0) \in C_{x_e}
\] (8)
The existence of $x'' := x_e + \varepsilon x(x - x_e)$ for some $\varepsilon x \in [0, 1]$ follows by applying the Mean-Value Theorem to $R(x)$ around $x_e$.
Let $z = x - x_e$, then similar to the previous section, the conic combination (6) can be used to rewrite (8) as:
\[
\dot{z} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e) = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma \ell z = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma \ell^T z,
\] (9)
where $\rho_\ell(t) = \frac{\partial R}{\partial x_\ell}(x''(t))$, and $\Gamma_i$ is the $i$th column of $\Gamma$. Therefore, the systems dynamics has been embedded in the linear differential inclusion with vertices \{$\Gamma_i e_j^T, ... , \Gamma_i e_j^T$\}.
Let $D^T$ be a matrix whose columns are basis vectors of $\ker \Gamma^T$, the following theorem can be stated:
\begin{theorem}[Common Lyapunov Function] Given the system (3). There exists a common Lyapunov function $\hat{V} : \mathbb{R}^n \rightarrow \mathbb{R}_+$ for the set of linear systems \{\dot{z} = (\Gamma_i e_j^T)z, ... , \dot{z} = (\Gamma_i e_j^T)z\}, with the constraint
For each of them if and only if \((\dot{V}, W_e), W_e = x - x_e\) induces the Robust Lyapunov function parameterized as \(V_e(x) = \dot{V}(x - x_e)\) for the CRN family \(\mathcal{N}_{A,B}\).

**Proof.** Let \(V(x) = \dot{V}(x - x_e)\), then when \(\partial \dot{V}/\partial z\) exists we can write:

\[
\dot{V} = \frac{\partial \dot{V}}{\partial z} z = \sum_{t=1}^{s} \rho_t(t) \Gamma_i e_i^T z = \sum_{t=1}^{s} \rho_t(t) \left( \frac{\partial \dot{V}}{\partial z} \Gamma_i e_i^T z \right).
\]

Since we assumed that \(\dot{V}\) is a common Lyapunov function for the set of linear systems \(\{\dot{z} = (\Gamma_i e_i^T) z\}\) the proof can proceed in both directions in a similar way to the proof of Theorem 2. Note that the constraint \(Dz(0) = 0\) is needed since \(D\dot{x}(t) \equiv 0\) is a constraint imposed by the structure of the original system \(\mathcal{N}\).

### 3.4 Relationship Between the Two Frameworks

We show now that if \(\dot{V}\) can be written as a certain composition, then the Lyapunov function of the form \(\dot{V}(x - x_e)\) can be used, where \(x_e\) is an equilibrium point for \(\mathcal{N}\).

Hence, the following theorem can be stated:

**Theorem 4 (Relationship).** Let \(V_1(x) = \dot{V}(R(x))\) be representing an RLF for the network family \(\mathcal{N}_{A,B}\). If there exists \(\dot{V} : \mathbb{R}_n \to \mathbb{R}_+\) such that for all \(r\):

\[
\dot{V}(r) = \dot{V}(\Gamma r), \quad (10)
\]

then \(V_2(x) = \dot{V}(x - x_e)\) represents an RLF for the network family \(\mathcal{N}_{A,B}\), where \(x_e\) is an equilibrium point for \(\mathcal{N}\).

**Proof.** Condition 1 in Definition 1 is clearly satisfied. It remains to show the second condition. Let \(z = x - x_e\). Then, whenever \(\dot{V}\) is differentiable:

\[
\dot{V}_2(x) = \frac{\partial \dot{V}(x - x_e)}{\partial z} \dot{x} = \frac{\partial \dot{V}(x - x_e)}{\partial z} \Gamma R(x),
\]

Before proceeding, we state two statements that we need: First, from \((10)\), we get \((\partial \dot{V}(r)/\partial r) = (\partial \dot{V}(\Gamma r)/\partial z)\Gamma\). Second, note that \(x - x_e \in \text{Im}(\Gamma)\), hence \(\exists R(x')\) such that \(\Gamma R(x') = x - x_e\), where \(R(x')\) can always be chosen nonnegative by A7. Hence, when \(\dot{V}\) is differentiable, we can use \((8)\) to write:

\[
\dot{V}_2(x) = \frac{\partial \dot{V}(x - x_e)}{\partial r} (\Gamma R(x')) = \frac{\partial \dot{V}(R(x'))}{\partial r} (x - x_e) = \sum_{t=1}^{s} \rho_t(t) \frac{\partial \dot{V}(R(x'))}{\partial r} \Gamma R(x') = \sum_{t=1}^{s} \rho_t(t) [\frac{\partial \dot{V}(R(x'))}{\partial r}] \Gamma^{s} R(x') \leq 0,
\]

where the last inequality follows from \((20)\). Lemma \((18)\) implies that \(\dot{V}_2(x) \leq 0\) for all \(x\).

**Remark 5.** Note that \(V_2\) has a simpler structure than \(V_1\) since it depends on \(x - x_e\). However, it can be noticed in the proof that for a specific choice of \(x_e\), the Lyapunov function \(\dot{V}(x - x_e)\) is nonincreasing only along trajectories that starts in \(\mathcal{E}_{x_e}\).
Remark 6. Note that if we consider the system for \( z = \dot{x} \) where
\[
\dot{z} = \Gamma \frac{\partial R(x)}{\partial x} z, \quad Dz(0) = 0.
\] (11)
then \( \tilde{V}(z) \) is a Lyapunov function for the above system.

**Relationship to the Extent of Reaction Formulation**

Recall that the extent of reaction \([2]\) is defined as:
\[
\xi(t) = \int_0^t R(\dot{x}(\tau))d\tau + \xi(0).
\]
If \( x(t) \in C_{x_e} \), then \( \exists \xi^* \geq 0 \) such that \( x_e - x_0 = \Gamma \xi^* \). We set \( \xi(0) := \xi^* \). Hence, we can write:
\[
\Gamma \xi(t) = x(t) - x_e,
\] (12)
and
\[
\dot{\xi} = R(x_e + \Gamma \xi), \quad \xi(0) := \xi^*,
\] (13)
which is the extent-of-reaction ODE representation of the dynamics of the CRN.

Therefore, we state the following result:

**Corollary 5.** Given \( \Gamma \). Let \( \tilde{V} : \bar{R}_+^n \to \bar{R}_+ \). Assume there exists \( \hat{V} : R_+^n \to R_+^n \) such that for all \( r \),
\[
\tilde{V}(r) = \hat{V}(\Gamma r).
\]
If \( \hat{V} \) is a common Lyapunov function for \( \{ \dot{r} = e_j \gamma_i r, \ldots, \dot{r} = e_j \gamma_i r \} \) where \((i, j, j) = \kappa(\ell)\). Then, \( \tilde{V}(\xi) \) is nonnegative, and nonincreasing along the trajectories of \( \dot{\xi} = R(x_e + \Gamma \xi) \).

**Proof.** The first two statements follow from Theorems 2, 4. We prove now the third statement. Using (10), (12) we get \( \tilde{V}(\xi) = \hat{V}(x - x_e) \). Therefore, the required statement follows from the result that \( \hat{V}(x - x_e) \) is nonincreasing along the trajectories of (3).

**Q.E.D.**

4 Application to PWLR Lyapunov Functions

4.1 Relationship to Previous Results

In the previous papers \([7, 8]\), the concept of Piecewise Linear in Rate (PWLR) Lyapunov functions has been introduced based on a direct analysis of the CRN. Such functions satisfy the conditions of Definition 1, and hence they are Robust Lyapunov functions. In this section, we show that those results can be interpreted in the uncertain systems framework introduced above. This also allows us to provide alternative algorithms for the existence and construction of PWLR functions.

Consider a CRN \([3]\) with a \( \Gamma \in \mathbb{R}^{n \times r} \). Two representation were discussed of the PWLR Lyapunov function. Given a partitioning matrix \( H \in \mathbb{R}^{p \times r} \) such that \( \ker H = \ker \Gamma \). PWLR Lyapunov functions are piecewise linear in rates, i.e. they have the form: \( V(x) = \tilde{V}(R(x)) \), where \( \tilde{V} : \mathbb{R}^r \to \mathbb{R} \) is a continuous PWL function given as
\[
\tilde{V}(r) = |c_k^T r|, \quad r \in \pm \mathcal{W}_k, k = 1, \ldots, m/2,
\] (14)
where the regions \( \mathcal{W}_k = \{ r \in \mathbb{R}^r : \Sigma_k Hr \geq 0 \}, k = 1, \ldots, m \) form a proper conic partition of \( \mathbb{R}^r \), while \( \{ \Sigma_k \}_{k=1}^m \) are signature matrices with the property \( \Sigma_k = -\Sigma_{m+1-k}, k = 1, \ldots, m/2 \). The coefficient vectors of each linear component can be collected in a matrix \( C = [c_1, \ldots, c_m]^T \in \mathbb{R}^4 \times r \). If the function \( \tilde{V} \) is convex,
then we have the following simplified representation of $V$:

$$V(x) = \|CR(x)\|_\infty.$$

This representation reminds of the $\ell_\infty$ Lyapunov functions that were used for linear systems as in \[11\]. In fact, the next theorem establishes the link between the results introduced in \[7, 8\] for checking candidate PWLR functions based on direct analysis and previous work on $\ell_\infty$ Lyapunov functions using the framework introduced in the previous section:

**Proposition 6.** Given $\Gamma$ and $H$. Let $V = \tilde{V} \circ R$ be the candidate continuous nonnegative PWLR with $C = [c_1 \ldots c_m]^T \in \mathbb{R}^{m \times r}$. Then $(\tilde{V}, R)$ induces an RLF if and only if:

1. $\ker C = \ker \Gamma$, and
2. there exists $\{\Lambda^\ell\}_{\ell=1}^s \subset \mathbb{R}^{m_2 \times m_2}$ such that
   $$\Lambda^\ell H = -C \Gamma^\ell,$$
   and $\lambda_k^\ell \Sigma_k > 0$, where $\Lambda^\ell = [\lambda_1^T \ldots \lambda_{m_2/2}^T]^T$.

   If $\tilde{V}$ is convex, then the second condition can be replaced with,

2) there exists $\{\Lambda^\ell\}_{\ell=1}^s \subset \mathbb{R}^{m \times m}$ Metzler matrices such that

   $$\Lambda^\ell \tilde{C} = \tilde{C} \Gamma^\ell,$$
   and $\Lambda^\ell 1 = 0$ for all $\ell = 1, \ldots, s$, where $\tilde{C} = [CT - CT^T]^T$.

**Proof.** The proof can be carried out by performing elementary algebraic manipulations on the results presented as Theorems 4,5 in \[8\]. The details are omitted for brevity.

**Remark 7.** Note that by the symmetries in \[16\], it can be written equivalently:

$$CT^\ell = \tilde{\Lambda}^\ell C,$$

where $\tilde{\Lambda}^\ell$ is an $\frac{m_2}{2} \times \frac{m_2}{2}$ matrix which be defined by subtracting the upper $\frac{m_2}{2} \times \frac{m_2}{2}$ blocks of $\Lambda^\ell$. $\tilde{\Lambda}^\ell$ will satisfy:

$$\max_k \left( \tilde{\lambda}_{kk} + \sum_{j \neq k} |\tilde{\lambda}_{kj}| \right) \leq 0. \tag{18}$$

This is exactly the condition for which $\ell_\infty$-norm Lyapunov functions need to satisfy for a linear system \[10, 15\]. This shows that Theorem \[3\] provides us with the framework to utilize the existing linear stability analysis techniques in the literature to construct robust Lyapunov functions for nonlinear systems such as CRNs. For example, we can verify $\ell_1$ Lyapunov functions of the form $V(x) = \|CR(x)\|_1$ directly by replacing condition \[18\] by

$$\max_k \left( \tilde{\lambda}_{kk} + \sum_{j \neq k} |\tilde{\lambda}_{kj}| \right) \leq 0, \tag{19}$$

instead of converting them to the $\ell_\infty$-norm form.
Before proceeding to the construction algorithm, we need to introduce the concept of a neighbor to a region. Fix $k \in \{1, \ldots, m/2\}$. Consider $H$: for any pair of linearly dependent rows $h_{i_1}^T, h_{i_2}^T$ eliminate $h_{i_2}^T$. Denote the resulting matrix by $\hat{H} \in \mathbb{R}^{p \times r}$, and let $\tilde{\Sigma}_1, \ldots, \tilde{\Sigma}_m$ the corresponding signature matrices. Therefore, the region can be represented as $W_k = \{ r | \tilde{\Sigma}_k \hat{H} r \geq 0 \}$. The distance $d_r$ between two regions $W_k, W_j$ is defined to be the Hamming distance between $\tilde{\Sigma}_k, \tilde{\Sigma}_j$. Hence, the set of neighbors of a region $W_k$ are defined as:

$$N_k = \{ j | d_r(W_j, W_k) = 1, j = 1, \ldots, m \},$$

Equivalently, note that a neighboring region to $W_k$ is one which differs only by the switching of one inequality. Denote the index of the switched inequality by the map $s_k(\ell) : N_k \rightarrow \{1, \ldots, \nu\}$. For simplicity, we use the notation $s_k(\ell) := s_k(\ell)$.

We use Theorem 2 to show that the problem of constructing a PWLR Lyapunov function over a given partition, i.e. a given $H$, can be solved via linear programming. However, instead of encoding the nondecreasingness condition into precomputed sign patterns as in [8], we use here alternative condition which are stated in the following proposition:

**Proposition 7.** Given the system (3) and a partitioning matrix $H \in \mathbb{R}^{p \times r}$. Consider the following linear program:

$$\begin{align*}
\text{Find} & \quad c_k, \xi_k, \zeta_k \in \mathbb{R}^\nu, \Lambda^l \in \mathbb{R}^{m \times m}, \eta_{kj} \in \mathbb{R}, \\
& \quad k = 1, \ldots, \frac{m}{2}, j \in N_k, \ell = 1, \ldots, s, \\
\text{subject to} & \quad c_k^T = \xi_k^T \tilde{\Sigma}_k H, \\
& \quad C \Gamma^l = -\Lambda^l H, \lambda^l_k \tilde{\Sigma}_k \geq 0, \\
& \quad c_k - c_j = \eta_{kj} \sigma_{s_ksj} h_{sj}, \\
& \quad \xi_k \geq 0, 1^T \xi_k > 0, \Lambda^l \geq 0.
\end{align*}$$

Then there exists a PWLR RLF with partitioning matrix $H$ if and only if there exist feasible solution to the above linear program with $\ker C = \ker \Gamma$ satisfied. Furthermore, the PWLR RLF can be made convex by adding the constraints $\eta_{kj} \geq 0$.

**Remark 8.** A natural choice for $H$ is $H = \Gamma$. Refer to Remark 17 in [8].

**Remark 9.** The LaSalle’s condition can be verified via a graphical algorithm described in §III-F in [8].

### 4.2 The Dual PWL Lyapunov Function

In §III-C, it was shown that if there exists $\hat{V}$ such that $\hat{V}(r) = \hat{V}(\Gamma r)$, then there exists a dual RLF for the same network family. In the case of PWLR Lyapunov functions, condition 1 in Proposition 6 implies that this is always possible. Hence, consider a PWLR Lyapunov function defined with a partitioning matrix $H$ as in (14). By Proposition 6 and the assumption that $\ker H = \ker \Gamma$, there exists $G \in \mathbb{R}^{p \times n}, B \in \mathbb{R}^{m \times n}$ such that $H = GT, C = BT$. Similar to $\{W_k\}_{k=1}^m$, we can define the following regions:

$$V_k = \{ z | \Sigma_k G z \geq 0 \}, k = 1, \ldots, m,$$

where it can be seen that $V_k$ has nonempty interior iff $W_k$ has nonempty interior.

Therefore, as the pair $(C, H)$ specify the PWLR function fully, also the pair $(B, G)$ specifies the following
function:
\[ \hat{V}(z) = b_k^T z, \] when \( \Sigma_k Gz \geq 0 \),
where \( B = [b_1, \ldots, b_m]^T \). If \( \tilde{V} \) is convex, then it can be written in the form: \( V_1(x) = \| CR(x) \|_\infty \). Similarly, the convexity of \( \hat{V} \) implies that \( V_2(x) = \| B(x - x_e) \|_\infty \),
where the later is the Lyapunov function used in [16, 19].

Theorem 8. Given (3). Then, if there exists \( G \in \mathbb{R}^{p \times n}, B \in \mathbb{R}^{m \times n} \) such that:

1. \((B\Gamma, G\Gamma)\) defines a PWLR RLF, then \((B, G)\) defines a dual PWL RLF.
2. \((B, G)\) defines a dual PWL RLF, then \((B\Gamma, G\Gamma)\) defines a PWLR RLF.

The proof is presented in the appendix.

Remark 10. Note that since \( D^T(x - x_e) = 0 \) for \( x \in \mathcal{C}_{x_e} \), then \( \| B(x - x_e) \|_\infty \) is a Lyapunov function, then \( \| (B + YD^T)(x - x_e) \|_\infty \) is also for an arbitrary matrix \( Y \). Furthermore, since Theorem 8 showed that the reaction-based and the species-based representations are equivalent; it is easier to check and construct RLFs in the reaction-based formulation.

5 Uniqueness of Equilibria and Persistence

5.1 Robust Non-singularity

It has been shown in [3] that the Jacobian of any network admitting a PWLR RLF is \( P_0 \), which implies that all principal minors are nonnegative. This can be used to show the following result:

Theorem 9 (Robust Nonsingularity). Given (3). Assume that it is a graphically stable network. If for some realization \( R \in \mathcal{X}_A \), there exists an isolated equilibrium \( x_e \) relative to \( \mathcal{C}_{x_e} \), the reduced Jacobian with any realization of the kinetics is non-singular in the interior of \( \mathbb{R}^n_+ \). This implies that any positive equilibrium of this network is isolated relative to its class.

Proof. The proof is based on the result that the negative Jacobian is \( P_0 \) for any choice of \( R \in \mathcal{X}_A \). Using the Cauchy-Binet formula [17], let \( I \subset \{1, \ldots, n\} \) be an arbitrary subset so that \(|I| = k\). The corresponding principle minor can be written as:

\[
\det_I \left( -\Gamma \frac{\partial R}{\partial x} \right) = \sum_{J \subset \{1, \ldots, \nu\}, |J| = k} \det(-\Gamma_{IJ}) \det \left( \frac{\partial R}{\partial x} \right)_{IJ} \prod_{\ell \in \nu \setminus I} \rho_{\ell},
\]

where \( (*) \) refers to the fact that the sum can be expressed as a linear combination of products of \( \rho_1, \ldots, \rho_s \).
We claim that the coefficients \( a_i \) are all nonnegative. To show this, assume for the sake of contradiction that there is some \( a_i \) is negative. If we set all \( \rho \)'s to zero except the ones appearing in \( i \)'th term, then this implies that the corresponding principle minor can be negative; a contradiction.
Now, the theorem can be proven by noting that the reduced Jacobian is non-singular iff the sum of all $k \times k$ principle minors of the negative Jacobian is positive, where $k = \text{rank}(\Gamma)$. Since it was assumed that there exists an isolated positive equilibrium, this implies that the sum of principle minors is positive for some choice of $\rho_1, \ldots, \rho_s$. Since all of the principle minors are nonnegative, then at least one of them is positive. By AK4, that principle minor will stay positive for any choice of positive $\rho_1, \ldots, \rho_s$, i.e. it stays positive over the interior of $\mathbb{R}_+^n$.

5.2 Uniqueness of Equilibria

A main result the links injectivity of a map to the notion of $P$-matrices which is first shown in [18], which states the a map is injective if its Jacobian is a $P$ matrix. This implies that if an equilibrium exists, then it is unique. This notion has been studied extensively for reaction networks, where graphical conditions were provided by Banaji et al. [17], Banaji and Craciun [19].

It has been established in [19, Appendix B] the network can not admit multiple nondegenerate positive equilibria in a single stoichiometric computability class if the Jacobian is $P_0$. Hence, the following theorem follows:

**Theorem 10 (Uniqueness of Positive Equilibria of GSNs).** If $\mathcal{N}_{A, B}$ is GS, then it can not admit multiple nondegenerate positive equilibria in a single stoichiometric computability class. Furthermore, if there exists an isolated positive equilibrium $x_e$ then it is unique relative to $\mathcal{C}_{x_e}$.

**Proof.** Since the negative of the Jacobian is $P_0$, the first statement follow directly from the statement before the theorem.

For the second statement, Theorem 9 implies that the existence of an isolated positive equilibrium $x_e$ ensures that the reduced Jacobian is non-singular on the interior of the orthant. In order to show uniqueness, assume for the sake of contradiction that there exists $y \neq x_e, y \in \mathcal{C}_{x_e}$ such that $\Gamma R(y) = 0$. Then the fundamental theorem of calculus implies,

$$0 = \Gamma R(x_e) - \Gamma R(y) = \Gamma \int_0^1 \frac{\partial R}{\partial x}(tx_e + (1-t)y)(x_e - y)dt = \Gamma \frac{\partial R}{\partial x}(x^*)(x_e - y),$$

where $x^* = t^* x_e + (1-t^*)y$, and $t^* \in (0, 1)$. The existence of $t^*$ is implied by the integral mean-value theorem. Since $x^* \in \mathcal{C}_{x_e}$, then the reduced Jacobian at $x^*$ is non-singular relative to $\text{Im} \Gamma$. Since $x_e - y \in \text{Im} \Gamma$, then $y = x_e$; a contradiction.

**Remark 11.** Note that since the Jacobian is $P_0$, then if arbitrary inflows and outflow were added to every species of a GSN, then the resulting Jacobian will be a $P$ matrix [20]; this is also known as the continuous-flow stirred tank reactor (CFSTR) version of the network. The CFSTR network will be injective. This shows that our framework has a direct relationship to the recent results on injectvity and $P$ matrices of reaction networks [21, 17, 19, 22].

5.3 Persistence

Persistence is a dynamical property that is satisfied if all trajectories that start in the interior of the positive orthant does not approach to the boundary. Angeli et al. [23] showed that if a conservative network does not have critical siphons, then it is persistent. Note that this is a graphical property, and it is independent of the specific realization of the kinetics involved.
In this section, it is shown that this can be established for conservative GSNs under some conditions detailed in the following theorem whose proof is presented in the appendix:

**Theorem 11 (Absence of Types of Critical Siphons).** Given \( \mathcal{N}_{A,B} \). Consider the network family \( \mathcal{N}_{A,B} \). Assume there exists a critical siphon \( P \), and let \( \Lambda(P) \) the set of output reactions of \( P \). Then, \( \mathcal{N}_{A,B} \) is a not GS, i.e., the network does not admit a PWLR Lyapunov function if any of the following conditions is satisfied:

1. If \( P \) is a critical deadlock.
2. If the network is conservative, and if for some realization of the network family there exists an isolated positive equilibrium in the interior of a proper stoichiometric compatibility class,
3. If the network is conservative, and if \( \ker \Gamma \) is one-dimensional.

The third item and the fourth items of the previous theorem can be combined with the main result in [23], and by noting the inclusion of a reverse of a reaction does not create a critical siphon we get the following theorem:

**Theorem 12 (Persistence of A Class of GSNs).** Given \( \mathcal{N}_{A,B} \). Assume the network is conservative. Then the network family \( \mathcal{N}_{A,B} \) is persistent if

1. \( \ker \Gamma \) is one-dimensional, or
2. if by removing the reverse of some reactions the reduced network has a one-dimensional kernal and is GS, or
3. there exists an isolated positive equilibrium in the interior of some proper stoichiometric class for a realization of \( \mathcal{N}_{A,B} \).

6 Relationship to Contraction Analysis

Contraction analysis is an approach which study stability of a trajectory with respect to other trajectories, and not with respect to a given equilibrium point. This area of research is old as the concept of contraction maps is, however, it has sparked growing interest in the control systems community in relationship to the analysis of dynamical systems [24], [25], [26].

One the formulation of interest to us is one which utilizes matrix measures, or logarithmic norms.

**Definition 4 (Logarithmic Norms).** For a given norm \( \| . \|_* \) on \( \mathbb{R}^n \), the associated matrix measure can be define as a following for a matrix \( A \in \mathbb{R}^{n \times n} \):

\[
\mu_*(A) := \limsup_{h \to 0^+} \frac{\|I + hA\|_* - 1}{h}.
\]  

(20)

Note that the same definition applies if was \( \| . \|_* \) a semi-norm.

**Remark 12.** The logarithmic norm can be evaluated for the standard norms, in fact, the following expression can be used for the \( \ell_\infty \) norm:

\[
\mu_\infty(A) = \max_i \left( a_{ii} + \sum_{j \neq i} |a_{ij}| \right).
\]

(21)
Note that this is an identical expression to one appearing in \[18\].

For a dynamical system, negativity of the logarithmic norm can be linked to contraction. This result were stated in different forms and have long history, refer to the tutorial \[26\] for more details. We state the result as the following:

**Theorem 13** (Aminzare and Sontag \[26\]). Consider a dynamical system $\dot{x} = f(x)$ defined on a convex subset of $\mathbb{R}^n$. Let $\|\cdot\|_*$ be a norm on $\mathbb{R}^n$, and assume that

$$\forall x, \mu_* \left( \frac{\partial f}{\partial x} \right) \leq c.$$  

Then, for any two solutions $\varphi(t;x), \varphi(t;y)$ of the dynamical system, the following condition holds:

$$\|\varphi(t;x) - \varphi(t;y)\|_* \leq e^{ct}\|\varphi(0;x) - \varphi(0;y)\|_* .$$  \hspace{1cm} (22)

Note that if $c < 0$, then the solutions of the system will be exponentially contracting. If $c = 0$, then the system will be non-expansive. The choice of the norm plays a crucial role even with respect to diagonal weighings. Russo et al. \[27\] has applied the result above to CRNs by weighting the $\ell_1$-norm with a diagonal matrix.

This motivates the following question: since our convex PWLR Lyapunov functions are semi-norms weighted by a non-square matrix, is it possible to find a link with contraction analysis? The link between the logarithmic norms and norm-based Lyapunov functions has been established before \[15\]. Therefore, it might expected that such a relationship exists with contraction analysis. Indeed, the answer is yes. The following theorem states precisely the relationship between our convex PWLR functions and contraction analysis, while the proof is presented in the appendix:

**Theorem 14** (Relationship to Contraction Analysis). 1. Given the extent of reaction representation of CRNs $\dot{\xi} = R(x_e + \Gamma \xi)$. Assume that there exists convex PWLR function $\tilde{V}(\xi) = \|C\xi\|_\infty$, and let $\mu_C$ be the logarithmic norm associated. Let the associated Jacobian be: $J_1(\xi) := \frac{\partial R}{\partial x} \Gamma$. Then,

$$\forall \xi, \mu_C(J_1(\xi)) \leq 0.$$  

Hence, the system is non-expansive along directions orthogonal to $\ker \Gamma$.

2. Given the ODE $\dot{x} = \Gamma R(x)$. Assume that there exists convex PWLR function $\tilde{V}(\xi) = \|B(x - x_e)\|_\infty$, and let $\mu_B$ be the logarithmic norm associated. Let the associated Jacobian be: $J_2(x) := \Gamma \frac{\partial R}{\partial x}$. Then,

$$\forall x \in \mathcal{C}_{x_e}, \mu_B(J_2(x)) \leq 0.$$  

Hence, the system is non-expansive in each stoichiometric class $\mathcal{C}_{x_e}$.

**6.1 Variational Dynamics and LaSalle Argument for Contraction Analysis**

In a recent work, Forni and Sepulchre \[28\] proposed a Lyapunov framework for contraction analysis using a so called Finsler structure. In order to minimize the background needed, we apply it directly to our context. The Finsler-Lyapunov function for the system \[13\] is $V_F : TR^+_e \to R_+$. If contraction analysis was carried
out with respect to the norm: $\|\cdot\|_*: \xi \mapsto \|C\xi\|_\infty$, then the correspoindring Finsler-Lyapunov function is:

$$V_F(\delta \xi) = \|C\delta \xi\|_\infty.$$  

The Finsler structure is given by the mapping $\delta \xi \mapsto \|C\delta \xi\|_\infty$. Therefore, $V_F$ can considered as a Lyapunov function for the variational system:

$$\dot{\delta \xi} = \frac{\partial R}{\partial x} \Gamma \delta \xi.$$  

The Finsler structure induces a distance function, which is in this case $d_F(x, y) = \|C(x - y)\|_\infty$. Hence, if $V_F$ was strictly decreasing then this implies that this system is incrementally asymptotically stable with respect to the distance function $d_F$; which is equivalent to the result given by Theorem 13. However, if the strict decreasingness is not available, the Finsler-Lyapunov framework for contraction analysis has the advantage of accommodating a LaSalle’s invariance principle that can be used to show strict contraction. In fact, the same algorithm given in §III-F can be used for the Finsler-Lyapunov function. The following theorem states the result:

**Theorem 15 (Strict Contraction).** Given (3). Assume that $V(x) = \|CR(x)\|_\infty$ is a PWLR Lyapunov function that satisfies condition $C5^i$. Then, the trajectories of (13) are exponentially contractive with respect to the norm $\|\cdot\|_*: \xi \mapsto \|C\xi\|_\infty$ in directions orthogonal to $\ker \Gamma$.

**Proof.** As per [28, Theorem 2], we need to show that if a trajectory lives in $\ker \dot{V}_F$, then it is an equilibrium for the variational system above. Since $V_F$ is a piecewise function it can be studied per partition regions as before. Hence let

$$\dot{V}_F(\delta \xi) = c^T \delta \xi = c^T \frac{\partial R}{\partial x} \Gamma \delta \xi.$$  

Note that the expression above is analogous to [8, eq. (25)]. In fact, the arguments of the proof of Proposition 7 in [8] can be replicated to show that $C5^i$ implies that when $\delta \xi(t) \in \ker \dot{V}_F$ for all $t \geq 0$, then $\Gamma \delta \xi(t) \equiv 0$. 

**Appendix: Proofs**

Before proving the results of the paper, we need to state and prove the following Lemma:

**Lemma 16.** Let $\dot{x} := f(x)$, and let $V: \mathbb{R}_{+}^n \rightarrow \mathbb{R}_{+}$ be a locally Lipschitz function such that:

$$\frac{\partial V(x)}{\partial x} f(x) \leq 0,$$

then $V(x) \leq 0$ for all $x$.

**Proof.** Since $V$ is assumed to be locally Lipschitz, Rademacher’s Theorem implies that it is differentiable (i.e., gradient exists) almost everywhere [29]. Recall that for a locally Lipschitz function the Clarke’s gradient at $x$ can be written as $\partial cV(x) := \text{co} \partial V(x)$, where:

$$\partial V(x) := \{p \in \mathbb{R}^n : \exists x \rightarrow x \text{ with } \partial V(x_i)/\partial x \text{ exists, such that } p = \lim_{i \rightarrow \infty} \partial V(x_i)/\partial x\}.$$  

Let $p \in \partial V(x)$ and let $\{x_i\}_{i=1}^\infty$ be the corresponding sequence. By the assumption stated in the lemma, $(\partial V(x_i)/\partial x)f(x_i) \leq 0$, for all $i$. Hence, the definition of $p$ implies that $p^T f(x) \leq 0$. Since $p$ was arbitrary,
the inequality holds for all \( p \in \partial V(x) \).

Now, let \( p \in \partial V(x) \) where \( p = \sum_i \lambda_i p_i \) is a convex combination of any \( p_1, ..., p_{n+1} \in \partial V(x) \). By the inequality above, \( p^T f(x) = \sum_i \lambda_i (p_i^T f(x)) \leq 0 \). Hence, \( p^T f(x) \leq 0 \) for all \( p \in \partial V(x) \).

As in [29], the Clarke’s derivative of \( V \) at \( x \) in the direction of \( f(x) \) can be written as \( D^C_{f(x)} V(x) = \max\{p^T f(x) : p \in \partial V(x)\} \). By the above inequality, we get \( D^C_{f(x)} V(x) \leq 0 \) for all \( x \). Since the Dini’s derivative is upper bounded by the Clarke’s derivative, we finally get:

\[
\dot{V}(x) := \limsup_{h \to 0^+} \frac{V(x + hf(x)) - V(x)}{h} = \limsup_{h \to 0^+} \frac{V(y + hf(x)) - V(y)}{h} =: D^C_{f(x)} V(x) \leq 0,
\]

for all \( x \).

\[\blacksquare\]

**Proof of Theorem 2** We show the existence of the common Lyapunov function implies the existence of the RLF. Nonnegativity of \( V \) follows from the nonnegativity of \( \dot{V} \). Let \((i, j) = (\kappa(\ell), \) recall that \( \Gamma^\ell = e_j \gamma_i^T \), hence \( \ker \dot{V} = \cap_{\ell=1}^{s} \ker \Gamma^\ell = \ker \Gamma \). Therefore, \( R(x) \in \ker \Gamma \) iff \( \Gamma R(x) = 0 \), which establishes the positive-definiteness of \( V \).

We assumed that \( \dot{V} \) has a negative semi-definite time-derivative for every linear system in the considered set. Hence, when \( \dot{V} \) is differentiable, we can write \((\partial \dot{V} / \partial r)^\ell r \leq 0, \ell = 1, ..., s \). Hence, for any \( \rho^1, ..., \rho^s \in \mathbb{R}_+ \):

\[
\sum_{\ell=1}^{s} \rho^\ell \frac{\partial \dot{V}}{\partial \Gamma} \gamma_i^\ell r \leq 0, \text{ when } (\partial V(r)/\partial r) \text{ exists.}
\]  

(23)

Therefore, when \( \dot{V} \) is differentiable:

\[
\dot{V}(x) = \frac{\partial \dot{V}}{\partial \Gamma} \gamma_i^\ell r \Gamma R(x)
\]

(24)

where \( \partial \dot{V}/\partial r := (\partial \dot{V}/\partial r) \bigg|_{r=R(x)} \).

Now, denote \( \rho^\ell = \frac{\partial \Gamma R}{\partial x_i}(x) \), which is nonnegative by A3. This allows us to write:

\[
\dot{V}(x) = \sum_{\ell=1}^{s} \rho^\ell \frac{\partial \dot{V}}{\partial \Gamma} \gamma_i^\ell r \Gamma R(x)
\]

(25)

\[
\dot{V}(x) = \sum_{\ell=1}^{s} \rho^\ell \frac{\partial \dot{V}}{\partial \Gamma} \gamma_i^\ell r \Gamma R(x) \leq 0, \text{ for almost all } x.
\]

(26)

The last inequality follows from (23). Using Lemma 10 \( \dot{V}(x) \leq 0 \) for all \( x \), and for all \( R \in \mathcal{K}_r \).

In order to show the other direction, almost all properties outlined in Definition 3 are clearly satisfied, we just show nonincreasigness. Assume that there exists \( \ell \) such that \( \dot{V} (r) \) is not nonincreasing along the trajectories of \( \dot{r} = \Gamma^\ell r \). Consider the corresponding term in (25). Since \( V(R(x)) \) is a Lyapunov function for any choice of admissible rate reaction function \( R \), choose \( \rho^\ell = \frac{\partial \Gamma R}{\partial x_i} \) to be large enough such that \( \dot{V}(x) \geq 0 \).
for some $x$; a contradiction.

**Proof of Theorem 8**: The first statement follows from Theorem 4. In order to show the second statement, let $V_2(x) = b_k^T(x - x_c)$, for $x - x_c \in V_k$. We will show that $V_1(x) = c_k^T R(x)$, for $R(x) \in \mathcal{W}_k$ is nondecreasing. Without loss of generality, the partition matrix can be written in the form: $G = [I \, G^T]^T$. This representation implies that the sign of $x - x_c$ is determined in every region $V_k$. Now, assume that $x - x_c \in V_k^\circ$, then:

$$
\dot{V}_2(x) = b_k^T \Gamma R(x) = c_k^T R(x) \leq 0 = c_k^T R(x_c), \text{ for all } R \in \mathcal{X}_A.
$$

Let $R_j(x) \in \text{supp } R(x)$, and let $\alpha_{ij} > 0$. Since $R$ is nondecreasing by A3, if $\text{sgn}(x_i - x_{e_i}) \cdot \text{sgn}(c_{kj}) > 0$, there exists $R \in \mathcal{X}_A$ such that $\dot{V}_2(x) \geq 0$. Hence, this implies that the inequality $\text{sgn}(c_{kj}) \cdot \text{sgn}(x_i - x_{e_i}) \leq 0$ holds.

Fix $j$, if there exists $i_1, i_2$ such that $\alpha_{i_1 j}, \alpha_{i_2 j} > 0$ and $\text{sgn}(x_{i_1} - x_{e_{i_1}}) \cdot \text{sgn}(x_{i_2} - x_{e_{i_2}}) < 0$, then $\sigma_{kj} = 0$. Otherwise, $\sigma_{kj} := \text{sgn}(x_i - x_{e_i})$ for some $i$ such that $\alpha_{ij} > 0$.

Hence, in order to have $\dot{V}_2(x) \leq 0$ for all $R \in \mathcal{X}_A$ we need that $\sigma_{kj} \cdot (x_i - x_{e_i}) \geq 0$ whenever $x - x_c \in V_k$, for all $k, j, i$ with $\alpha_{ij} > 0$. By Farkas Lemma 30, this is equivalent to the existence of $\lambda_{kji} \in \mathbb{R}_+^p, \zeta_{kji} \in \mathbb{R}^i$:

$$
\sigma_{kj} e_i^T = \lambda_{kji}^T \Sigma_k G + \zeta_{kji} D,
$$

where $D^T \in \mathbb{R}^r \times n$ is a matrix whose columns are basis vectors for $\ker \Gamma^T$.

If we multiply both sides of (27) by $\Gamma$ from the left, then we get condition C4 in Theorem 4 which necessary and sufficient for $\dot{V}_1(x) = \frac{d}{dt}(c_k^T R(x)) \leq 0$.

**Proof of Theorem 11**: Assume $P$ is a critical siphon for the petri-net associated with $\Gamma$, and let $n_p = |P|$. Let $\Lambda(P)$ be the set of output reactions of $P$, and let $\nu_p = |\Lambda(P)|$.

Before we prove item 1 of Theorem 11, the following lemma is needed.

**Lemma 17.** Consider a network family $\mathcal{N}_{A,B}$. Let $P$ be a set of species that does not contain the support of a conservation law; let its indices be numbered as $\{1, ..., n_p\}$. Then, there exists a nonempty-interior region $\{r|\Sigma_k \Gamma r \geq 0\}$ with a signature matrix $\Sigma_k$ that satisfies $\sigma_{k1} = ... = \sigma_{kn_p} = 1$.

**Proof.** Assume the contrary. This implies that $\bigcap_{i=1}^{n_p} \{R|\gamma_i^T R > 0\} \bigcap \bigcup_{i=n_p+1}^{n} \{R|\sigma_i \gamma_i^T R > 0\} = \emptyset$ for all possible choices of signs $\sigma_i = \pm 1$. However, $\mathbb{R}^r$ can be partitioned into a union of all possible half-spaces of the form $\bigcup_{i=1}^{n_p} \{R|\sigma_i \gamma_i^T R \geq 0\}$. Therefore, this implies that $\bigcap_{i=1}^{n_p} \{R|\gamma_i^T R > 0\} = \emptyset$. By Farkas Lemma, this implies that there exists $\lambda \in \mathbb{R}^r$ satisfying $\lambda > 0$ such that $|\lambda^T 0| \Gamma = 0$. Therefore, $P$ contains the support of the conservation law $|\lambda^T 0|^T$; a contradiction.

Therefore, we can state the proof of the first item:

**Proof of Theorem 11-1.** Without loss of generality, let $\{1, ..., n_p\}$ be the indices of the species in $P$. Using Lemma 17 there exists a nonempty-interior sign region $\mathcal{S}_k, 1 \leq k \leq m_s$ with a signature matrix $\Sigma_k$ that satisfies $\sigma_{k1} = ... = \sigma_{kn_p} = 1$. Since $\Lambda(P) = \mathcal{S}$, this implies $b_{kj} \leq 0$ for all $j = 1, ..., \nu$. However, this is not allowable by Theorem 9 since $\zeta_k^T B_k v \leq 0$ for all $v \in \ker \Gamma \cap \mathbb{R}_+^n$, and for any choice of admissible $\zeta_k$.

In order to proceed, an existence result of equilibria is needed:
Lemma 18. Consider a network family \( \mathcal{N}_{A,B} \). Let \( P \) be a critical siphon, and let \( \Psi_P \) be the associated face. If the network is conservative, then for any proper stoichiometric compatibility \( \mathcal{C} \), there exists an equilibrium \( x_e \) of \( \mathcal{N} \) such that \( x_e \in \Psi_P \cap \mathcal{C} \).

Proof. The set \( \Psi_P \cap \mathcal{C} \) is compact, forward invariant, and convex, since the both sets \( \Psi_P, \mathcal{C} \) are as such. Hence, the statement of the lemma follows directly from the application of the Brouwer’s fixed point theorem on the associated flow. 

We are ready now to prove the second item of Theorem 11.

Proof of Theorem 11-2). By Lemma 18, there exists an equilibrium in \( \Psi_P \). Since it is assumed that there exists an isolated equilibrium in interior, Theorem 10 implies that \( \mathcal{N}_{A,B} \) is not GS.

Before concluding the proof, a simple lemma is stated and proved:

Lemma 19. Let \( x_e \) be an equilibrium of \( \mathcal{N} \). Let \( \tilde{P} \) be a set of species that correspond to \( \{1, \ldots, n\} \setminus \text{supp}(x_e) \). Then, \( \tilde{P} \) is a siphon.

Proof. Assume that \( \tilde{P} \) is not a siphon, then there exists some \( X_i \in \tilde{P} \) and \( R_j \in \mathcal{R} \) such that \( X_i \) is a product of \( R_j \) and \( R_j \neq \Lambda(\tilde{P}) \). At the given equilibrium, all negative terms in the expression of \( \dot{x}_i \) vanish since \( x_{ei} = 0 \). Since \( X_i \) is not a reactant in \( R_j \) this implies \( \beta_{ij} > 0, \alpha_{ij} = 0 \) then \( R_j(x) \) has a strictly positive coefficient which implies \( \dot{x}_i > 0 \); a contradiction.

Hence, we are ready to conclude the proof of Theorem 11

Proof of Theorem 11-3). By Lemma 18 there exists an equilibrium \( x^* \in \Psi_P \) such that \( \Gamma R(x^*) = 0 \). Since dim(\( \ker \Gamma \)) = 1, this implies that \( R(x^*) = tv \) for some \( t \geq 0 \). Consider the case \( t = 0 \). This implies \( R(x^*) = 0 \). Then, \( P \subset \tilde{P} := \{1, \ldots, n\} \setminus \text{supp}(x^*) \). \( \tilde{P} \) is a siphon by Lemma 19 and since \( P \subset \tilde{P} \) it is a critical deadlock. However, by Theorem 11-1), \( \mathcal{N}_{A,B} \) is not GS. If \( t > 0 \), this implies that \( P = \emptyset \); a contradiction.

Proof of Theorem 13 Write the logarithmic norm expression using (20):

\[
\mu_C(J_1(\xi)) = \limsup_{h \to 0^+} \frac{1}{h} \left( \left\| I + h \frac{\partial R}{\partial x} \Gamma \right\|_C - 1 \right)
\]

The expression above includes the induced matrix norm. However, it is not easy to find a explicit expression of the induced matrix norm with respect to non-square weighting. Therefore, the definition of the induced
matrix norm is used as follows:

\[ \left\| I + h \frac{\partial R}{\partial x} \Gamma \xi \right\|_C = \sup_{\|C\xi\|_\infty = 1} \left\| C \left( I + h \frac{\partial R}{\partial x} \Gamma \right) \xi \right\|_\infty \]

\[ \overset{(*)}{=} \sup_{\|C\xi\|_\infty = 1} \left\| C\xi + h \sum_{\ell = 1}^{s} \rho_{\ell}(x)Ce_{\ell}\gamma_{i}^T \xi \right\|_\infty \]

\[ \overset{(**)}{=} \sup_{\|C\xi\|_\infty = 1} \left\| C\xi + h \sum_{\ell = 1}^{s} \rho_{\ell}\hat{\Lambda}^\ell C\xi \right\|_\infty \]

\[ \leq \sup_{\|C\xi\|_\infty = 1} \left\| I + h \sum_{\ell = 1}^{s} \rho_{\ell}\hat{\Lambda}^\ell \right\|_\infty \|C\xi\|_\infty \]

\[ = \left\| I + h \sum_{\ell = 1}^{s} \rho_{\ell}\hat{\Lambda}^\ell \right\|_\infty \]

where \((*)\) is by \([8]\) and \((**)\) is by \([17]\). Therefore, the expression of the logarithmic norm above can be written as:

\[ \mu_C(J_1(\xi)) \leq \mu_\infty \left( \sum_{\ell = 1}^{s} \rho_{\ell}\hat{\Lambda}^\ell \right) \leq \sum_{\ell = 1}^{s} \rho_{\ell}\mu_\infty(\hat{\Lambda}^\ell) = 0, \quad (28) \]

where the inequalities follow by the subadditivity of the logarithmic norm and \([18]\).

Note since \(C\) has nonempty kernel space, then \(\|C\xi\|_\infty\) is a semi-norm. However, Theorem \([13]\) requires a norm. This can be remedied by studying the system in directions orthogonal to ker \(\Gamma\) by defining a transformation of coordinates using a matrix \(T_1 = [\hat{T}_1, v_1, ..., v_{\nu_\gamma - \nu_r}]^T\), where \(\{v_1, ..., v_{\nu_\gamma - \nu_r}\}\) is a basis of ker \(\Gamma\), \(\nu_r = rank(\Gamma)\), and \(\hat{T}_1\) is chosen so that \(T_1\) is invertible. Defining \(\hat{\xi} = T_1\xi\), then the first \(\nu_r\) coordinates of \(\hat{\xi}\) are decoupled from the rest. Hence, inequality \((28)\) can be established similarly for the reduced Jacobian which is the upper right \(\nu_r \times \nu_r\) block of \(T_1J_1(\xi)T_1^{-1}\). The norm in the reduced subspace is \(\|\cdot\|_{\hat{\xi}} : z \mapsto \|\hat{C}z\|_\infty, z \in \mathbb{R}^{\nu_r}\), where \(\hat{C}\) is \(\frac{m}{2} \times \nu_r\) defined as the nonzero columns of \(CT_1^{-1}\). The equations \(Ce_{\ell}\gamma_{i}^T = \hat{\Lambda}^\ell C\) are equivalent to \((CT_1^{-1})(T_1e_{\ell}\gamma_{i}^TT_1^{-1}) = \hat{\Lambda}^\ell(CT_1^{-1})\). Therefore, everything goes through in the reduced space, and the same upper bound is valid.

The same argument can be replicated for to prove the second item in the theorem. This is accomplished by utilizing the alternative representation \([8]\), the rank-one decomposition of the Jacobian \([9]\), and noting that conditions \([17]\) can be written as: \(B\Gamma_{r}e_{\ell}^T = Y_{1}^TB + Y_{\ell}^TD^T\) for some matrices \(Y_1, ..., Y_{\ell}\). The reduced space argument can be carried out also by using a transformation matrix \(T_2 = [\hat{T}_2, D]^T\).

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