NEW APPROACH TO THE STABILITY AND CONTROL OF REACTION NETWORKS

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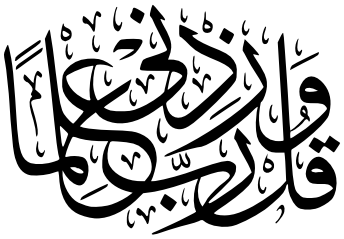
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"*O my Lord, increase me in knowledge*"

Q:XX.114

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Abstract

A new system-theoretic approach for studying the stability and control of chemical reaction networks (CRNs) is proposed, and analyzed. This has direct application to biological applications where biochemical networks suffer from high uncertainty in the kinetic parameters and exact structure of the rate functions. The proposed approach tackles this issue by presenting "structural" results, i.e. results that extract important qualitative information from the structure alone regardless of the specific form of the kinetics which can be arbitrary monotone kinetics, including Mass-Action.

The proposed method is based on introducing a class of Lyapunov functions that we call *Piecewise Linear in Rates (PWLR) Lyapunov functions*. Several algorithms are proposed for the construction of these functions. Subject to mild technical conditions, the existence of these functions can be used to ensure powerful dynamical and algebraic conditions such as Lyapunov stability, asymptotic stability, global asymptotic stability, persistence, uniqueness of equilibria and exponential contraction. This shows that this class of networks is well-behaved and excludes complicated behaviour such as multi-stability, limit cycles and chaos.

The class of PWLR functions is then shown to be a subset of larger class of Robust Lyapunov functions (RLFs), which can be interpreted by shifting the analysis to reaction coordinates. In the new coordinates, the problem transforms into finding a common Lyapunov function for a linear parameter varying system. Consequently, dual forms of the PWLR Lyapunov functions are presented, and the interpretation in terms of the varia-

tional dynamics and contraction analysis are given. An other class of Piecewise Quadratic in Rates Lyapunov function is also introduced. Relationship with consensus dynamics are also pointed out.

Control laws for the stabilization of the proposed class of networks are provided, and the concept of control Lyapunov function is briefly discussed. Finally, the proposed framework is shown to be widely applicable to biochemical networks.

Contents

Contents **11**

List of Figures **15**

Acronyms **17**

Notation **19**

1 Introduction **21**

1.1 Motivation 21

1.2 Contribution 23

2 Preliminaries and Literature Review **29**

2.1 Chemical Reaction Networks 29

2.1.1 Algebraic Description 30

2.1.2 Graphical Description 35

2.1.3 Dynamic Description 37

2.1.4 Equilibria 39

2.1.5 Illustrative Example 41

2.2 Stability of Reaction Networks: A Review 43

2.2.1 Boltzmann's H-Theorem and Detailed-Balance 44

2.2.2 Linear and Compartmental Reaction Networks 46

2.2.3 Horn-Jackson-Feinberg Theory of Complex-Balance 47
2.2.4 Monotonicity-Based Approaches 48
2.2.5 Miscellaneous Stability Results 49
2.3 Persistence of Reaction Networks 50
2.3.1 Persistence and Siphons 51

3 Piecewise Linear in Rates Lyapunov Functions 53
3.1 Stability of Reaction Networks 53
3.1.1 Stability Relative to An Invariant Manifold 53
3.1.2 Motivating Example 56
3.2 Piecewise Linear in Rates Functions 58
3.2.1 Formal Definition 59
3.3 PWLR Lyapunov Functions and Stability 62
3.3.1 Generalized Derivatives 62
3.3.2 Definition of a PWLR Lyapunov Function 64
3.4 Checking Candidate PWLR functions 67
3.4.1 Geometry of the Partition Regions 67
3.4.2 Candidate Continuous PWLR Lyapunov Functions 70
3.4.3 Checking candidate convex PWLR functions 73
3.5 The LaSalle's Condition 74

4 Properties of Graphically Stable Networks 77
4.1 Existence of Convex PWLR Functions 77
4.1.1 Set-Based Representation of the PWLR function 78
4.1.2 The Result 79
4.2 Constraints on Admissible Sign Patterns 79
4.2.1 A Necessary Condition 81
4.3 Injectivity of Graphically Stable Networks 82

4.3.1 Jacobians of GSNs are P_0 82
4.3.2 Uniqueness of Equilibria of Graphically Stable Networks 85
4.4 Siphons and Persistence of Graphically Stable Networks 86
4.4.1 Statement of Results 86
4.4.2 Proof of Theorem 4.6 88

5 Construction of PWLR Lyapunov Functions 91
5.1 Construction of PWLR Lyapunov function over a given partition 91
5.1.1 Special Cases 94
5.1.2 Extension to Networks Without Interior Equilibria 94
5.2 Iterative Algorithm for Convex PWLR functions 96
5.3 Constructions Based on Graphical Conditions 98
5.3.1 Relationship to Consensus Dynamics 102

6 Uncertain System Framework 105
6.1 Robust Lyapunov Functions and Differential Linear Inclusions 105
6.1.1 Robust Lyapunov Functions 106
6.1.2 Uncertain Systems Framework: Reaction Coordinates 107
6.1.3 Dual Robust Lyapunov Function: Species Coordinates 111
6.1.4 Relationship Between the Two Frameworks 113
6.2 Application to PWLR Lyapunov Functions 115
6.2.1 Relationship to Previous Results 115
6.2.2 The Dual PWL Lyapunov Function 119
6.2.3 Robust Non-singularity and Exponential Stability 121
6.3 Contraction Analysis 125
6.3.1 Variational Dynamics and LaSalle Argument for Contraction Analysis 129
6.4 Piecewise Quadratic in Rates Lyapunov Functions 130

7 Control of GSNs and Control Lyapunov Functions 135

7.1 Stabilization of an Equilibrium of A GSN 136
7.1.1 State-Feedback Stabilization With Respect to Stoichiometry Class . 136
7.2 PWLR Control Lyapunov Functions 139
7.2.1 Controller Design: A Brief Discussion 141

8 Examples and Applications **143**
8.1 Illustrative Examples 143
8.1.1 Application of PWLR Construction Methods 143
8.1.2 Stabilization of A Selected Equilibrium 148
8.1.3 Counterexamples 148
8.1.4 Exponentially Contractive Network 150
8.2 Comparison with Horn-Jackson-Feinberg Stability Theory 152
8.3 Biochemical Examples 153
8.3.1 Basic Biochemical Motifs 154
8.3.2 Basic Enzymatic Networks 156
8.3.3 Gene Transcription and Translation Reactions 159
8.3.4 Cascades of Futile Cycles 161
8.3.5 Other Covalent Modification Networks 164
8.3.6 T-Cell Kinetic Proofreading: McKeithan's Network 167
8.3.7 ERK Signalling Pathway with RKIP Regulation 168
8.3.8 An Open Example: A Signal Transduction Network 169

9 Conclusions and Future Directions **173**
9.1 Conclusions 173
9.2 Future Directions 176

Bibliography **179**

List of Figures

1.1 Bipartite graph representation of the network example. 25

2.1 Illustration of the Petri-net compact notation for reversible reactions 36

2.2 Simplified futile cycle. 42

3.1 Analysis of the sign of $\dot{V}$ in the region $\mathcal{W}$ for the futile cycle. (a) The sign next to each reaction denotes the sign of the corresponding coefficient in (3.3). (b) Signs of the time-derivatives of species concentrations as implied by the inequalities defining $\mathcal{W}$ (3.2) and the resulting signs of the rates of change of the reactions rates. Note that for each reaction the sign of the rate of change is opposite to the sign of its coefficient. 57

8.1 Bipartite graph representation of the example CRN (1.1). 144

8.2 Lyapunov function level sets and phase portrait with (a) Mass-Action Kinetics, (b) 2^{nd}-order Hill kinetics. 147

8.3 Sample 200 trajectories for the stabilization with Mass-Action kinetics with $x(0) \in [0, 12]^4$, uniformly distributed. 149

8.4 Basic Biochemical Examples 154

8.5 Basic Enzymatic Reactions 157

8.6 Translation and Transcription 159

8.7 Trajectories of the futile cycle cascade with Michaelis-Menten kinetics in the stoichiometric class corresponding to the conserved moieties 10,11,12,13,14. . . 164
8.8 Several Types of Cascades of Futile Cycles. 165
8.9 Covalent Modification Networks 167
8.10 McKeithan's network. 168
8.11 ERK Signalling Pathway With RKIP Regulation 170
8.12 Signal Transconduction Pathway 170

Acronyms

CICS	Converging-Input Converging-State
CRN	Chemical Reaction Network
GAS	Globally Asymptotically Stable
GS	Graphically Stable
GSN	Graphically Stable Network
LDI	Linear Differential Inclusion
LMI	Linear Matrix Inequality
LP	Linear Program
ODE	Ordinary Differential Equation
PWL	Piecewise Linear
PWLR	Piecewise Linear in Rates
PWQ	Piecewise Quadratic
PWQR	Piecewise Quadratic in Rates
RLF	Robust Lyapunov Function
SDP	Semi-Definite Program
w.l.o.g	without loss of generality

Notation

Let n be a positive integer, $a_1, .., a_n, h \in \mathbb{R}$, $x, v \in \mathbb{R}^n, y \in \mathbb{R}$, A be an $n \times n$ matrix, $U \subset \mathbb{R}^n, V : U \to \mathbb{R}$, W be some arbitrary set, M be a differentiable manifold, and let $\{h_k\}_{k=1}^{\infty} \subset \mathbb{R}$ be an infinite sequence, then:

Sets, Functions, Topology, and Analysis

$\mathbb{R}^n_+$	set of n-tuples of positive real numbers,
$\bar{\mathbb{R}}^n_+$	set of n-tuples of nonnegative real numbers,
$\mathbb{N}$	set of natural numbers {1,2,3,..},
$\vee$	logical disjunction,
$\lvert W \rvert$	the cardinality of W,
$U^{n \times m}$	matrices of dimension $n \times m$ with entries that belong to U,
U°	interior of the set U,
$\bar{U}$	closure of the set U,
∂U	boundary of the set U,
$\operatorname{co} U$	convex hull of the set U,
$T_x U$	tangent cone to U at $x \in U$,
$T_x^{(B)} U$	tangent cone to U at $x \in U$ in the sense of Boulingand,
$\boldsymbol{T}M$	tangent bundle of the differentiable manifold M
$\ker(V)$	the inverse image of zero, i.e. $V^{-1}(0)$,
$\log y$	the natural logarithm of y,
$\omega(x)$	omega limit set of x,

$o(h)$	some function $g(h)$ which satisfies $\lim_{h\to\infty} h/g(h) = 0$,
$D_v^+V(x)$	the upper Dini's derivative of V at x in the direction of v (see (3.7)),
$D_v^CV(x)$	the Clarke's derivative of V at x in the direction of v (see (3.8)),
$h_k \searrow 0$	h_n is strictly decreasing and $h_k \to 0$.

Linear Algebra

$\|x\|_\infty$	ℓ_∞-norm of x defined as $\|x\|_\infty = \max_{1\le i\le n} \|x_i\|$,
$\|x\|_1$	ℓ_1-norm of x defined as $\|x\|_1 = \sum_{i=1}^n \|x_i\|$,
$\text{supp}(x)$	the support of x which is $\text{supp}(x) = \{i \in \{1,..,n\} \| x_i \neq 0\}$,
$x \geq 0$	elementwise nonnegativity,
$x > 0$	elementwise nonnegativity with at least one positive element,
$x \gg 0$	elementwise positivity,
$[A]_{ij}$	the element at the $(i,j)^{\text{th}}$ position,
$A \geq 0$	the symmetric matrix A is positive semi-definite,
$A > 0$	the symmetric matrix A is positive-definite,
$\ker(A)$	kernel or null-space of A,
$\text{Im}(A)$	the image space of A,
$\text{adj}(A)$	the adjoint of A,
$\text{diag}[a_1,..,a_n]$	diagonal matrix A with $[A]_{ii} = a_i$.
O_n	zero matrix of dimension $n \times n$,
I	the identity matrix, where its dimension can be inferred from the context,
$\mathbf{1}$	all-ones vector, where its dimension can be inferred from the context,

Reaction Networks

M_j	the set of indices of reactants of a reaction $\mathbf{R}_j$ (see §2.1.4),
$\mathcal{I}$	the set of inflows of a certain network (see §2.1.4),
$\Lambda(P)$	the set of output reactions of a set of species P (see §2.1.4) ,
$\mathscr{A}(\mathbf{R}_j)$	The set of ancestors of a reaction $\mathbf{R}_j$ (see §2.1.4),

Chapter 1

Introduction

1.1 Motivation

Dynamical System theory is the universal language for modeling and analyzing quantifiable phenomena that undergo evolution in time. This theory offers powerful tools especially for the class of systems that evolve according to a linear mapping in time. However, almost all models of phenomena arising in nature are inherently *nonlinear*. Theoretical tools for handling nonlinear systems are less powerful and are highly limited by the class of systems considered. On the other hand, this difficulty has made the theory of nonlinear systems more diverse and interesting.

An example of *nonlinear systems* is the dynamic of *Chemical Reaction Networks* (CRNs), since the reaction rates are generally nonlinear function of the reactants. However, systems arising from CRNs have distinguishing features that make them deserve dedicated study. First, the dynamics of CRNs describe the evolution of the concentration of chemical species, which are naturally nonnegative. Therefore, the state space of nonlinear systems arising from CRNs evolve over the nonnegative orthant $\bar{\mathbb{R}}^n_+$, hence they belong to the class of *nonnegative systems*. Second, CRNs admit graphical representations which imply certain structural constraints on the model. It also implies that the CRN model has two

underlying models: the structural and the kinetic. Furthermore, since CRNs involve the transformation of species to others, conservation of mass implies a certain factorization for the resulting equations; this is discussed further in Chapter 2.

Despite diverse applications in engineering and science, the recent interest in CRNs stems from the fact that it is the main modeling language in the emerging field of *molecular systems biology*. This new field of research was formed after many scientists arrived to the conclusion that a deeper understanding of living organisms is only possible by abandoning the reductionist paradigm and taking a more holistic and system oriented approach [18, 58]. This was further motivated by the recent advances in data collection and measurement approaches that have facilitated the application of mathematical and system-oriented techniques to biological systems. *Control and System theory* is at the heart of this new field, since basic living systems can be modeled as dynamical systems incorporating basic dynamic processes, feedback control loops, and signal processing. In this respect, one of the main goals is to understand the cell behavior and function at the level of chemical interactions and, in particular, the characterization of qualitative features of dynamical behavior (stability, periodic orbits, chaos, etc.) resulting from such interactions.

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 overall regulate cell life. This is because all major biochemical networks such as signal transconduction networks, gene-regulatory networks, and metabolic pathways are naturally cast in the framework of CRNs. Therefore, a wide interest in the area of CRNs has been witnessed in the control community in the last decade [22, 89, 31, 9].

However, a major obstacle in biochemical network models is the very large degree of uncertainty inherent in their modeling as well as the variability or poor knowledge of the parameters involved. This is known as the data-rich/data-poor paradox [91]. This means that there exists a large amount of graphical network knowledge pertaining to *qualitative* description of reaction network structure but the *quantitative* knowledge required to con-

struct full mathematical models are very little in comparison. This is due to the fact that biological methods for measurements and data collection are highly noisy. Thus, it has been recognized [18] that the desired analysis for these networks shall be *parameter-free* or *robust* with respect to arbitrary variations in the values of the parameters and, if possible, the exact formula of reaction rate functions. In other words, it is desirable to provide nontrivial conclusions based solely on the qualitative 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. This has been well-known to be challenging; Leon Glass and Stuart Kauffman [50] in 1973 complained: "so far it has proved impossible to develop general techniques which may be applied to find the asymptotic behavior of complex chemical systems".

1.2 Contribution

Major stability results in the literature (as will be reviewed in Chapter 2) are based on using thermodynamic energy functions as Lyapunov functions for studying the stability of the network. Moreover, these cover only a small percentage of networks which are observed to be stable in practice. The theory that we introduce for the stability of reaction network system starts a new line of research in this area which is distinct from previous work. Unlike previous approaches, our approach is truly system-theoretic and elementary in the sense that it have been conceived and implemented based on the graphical analysis directly without the need intuitions derived from thermodynamics and statistical mechanics.

In this dissertation, we follow a qualitative approach. In order to illustrate the meaning of robust analysis that we described above, we consider the CRN which is depicted in Figure

1.1, and is described by:

$$\begin{aligned} X_1 &\longrightarrow X_2 + X_3, \\ 2X_2 &\longrightarrow X_4, \\ X_3 + X_4 &\longrightarrow X_1 + X_2. \end{aligned} \tag{1.1}$$

The corresponding ODE system is:

$$\dot{x} = \begin{bmatrix} -1 & 0 & 1 \\ 1 & -2 & 1 \\ 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} R_1(x_1) \\ R_2(x_2) \\ R_3(x_3, x_4) \end{bmatrix}, \tag{1.2}$$

$x \in \mathbb{R}^4$, and R_1, R_2, R_3 are the reaction rate functions, where the species appearing in the argument correspond to the reactants.

Despite its simplicity, the stability of the network above can not be established via previous results in the literature even for the Mass-Action case[1]. However, consider the following:

$$V(x) = \max\{|R_1(x) - R_2(x)|, |R_2(x) - R_3(x)|, |R_3(x) - R_1(x)|\}. \tag{1.3}$$

It can be verified that V is decreasing along all trajectories for *any choice* of monotone reaction rate functions, where exact conditions are to be detailed in §2.1.1. Using this, asymptotic stability of the equilibrium set can be established. In fact, in this case global asymptotic stability can be shown.

In this work, we consider the problem of stability of CRNs by invoking Lyapunov functions of the form (1.3), which we call *Piecewise Linear in Rates (PWLR) Lyapunov*

[1]Results in the literature are discussed in details in Chapter 2.2, while this specific example is revisited in §8.1.1

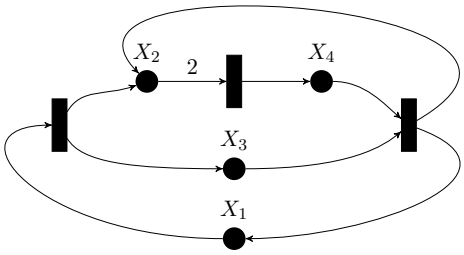


Figure 1.1: Bipartite graph representation of the network example.

functions. If the required function exists for a given network structure, it is termed a "Graphically Stable Network" (GSN). For such networks, there exists a PWLR Lyapunov function for each CRN that consist of a network of that graphical structure coupled with any arbitrary monotone kinetics. As is discussed throughout the thesis, this implies that this class of network can not produce "interesting" behaviour like multistability, limit cycles, chaos, etc. Its behaviour is mostly limited to trajectories converging to a unique equilibrium per stoichiometric class.

Publications and Statement of Contributions

Many of the results of this dissertation have been published in a journal article [1], conference papers [2, 3, 4], and a manuscript posted currently in arXiv [5].
The contributions per chapter is summarized below, where the mapping of contributed is results to publications is indicated in the superscripts.

Chapter 3

1. A new approach for studying the stability of nonlinear networks in general and CRNs in particular is provided by introducing the concept of PWLR function and GSNs via few motivating examples.[1],[3]
2. Exact conditions are provided for checking candidate PWLR functions.[1],[3]
3. Exact conditions are provided for checking candidate convex PWLR functions.[1],[3]

4. A graphical algorithm is provided for verifying the LaSalle condition.[1],[3]

Chapter 4

5. Convex PWLR Lyapunov functions are shown to exist once a continuous counterpart exists.[1]
6. Characterizations of PWLR Lyapunov functions using precomputed signed patterns is introduced.[1],[3]
7. The Jacobian matrix of GSNs is shown to be a P_0 matrix.[1]
8. GSNs are shown not to admit multiple nondegenerate positive equilibria.[1] Furthermore, if there exists isolated positive equilibria, they are shown to be unique.
9. GSNs are shown to be unable to exhibit critical deadlocks.[1] Critical siphons are excluded subject to widely applicable conditions.[5]
10. Persistence of $\mathscr{P}$ networks is established for wide classes of conservative networks.[5]

Chapter 5

11. Linear Programming algorithms are provided for constructing PWLR functions over any given partition.[1],[3]
12. An iterative algorithm is provided for constructing convex PWLR functions.[1],[3]
13. Explicit formulae are provided for PWLR Lyapunov functions for networks satisfying easily-checkable graphical conditions.[1],[2],[3]
14. A link is established between consensus algorithms and the stability of reaction networks, and this is used to propose consensus algorithms for a class of nonlinear systems.[1],[3]

Chapter 6

15. Generic analysis tools for CRNs are provided by shifting the analysis to reaction coordinates, and the concept of robust Lyapunov function is proposed as common Lyapunov function for a set of linear systems.[4],[5]

16. Robust Lyapunov functions are shown to exist in two dual formulation: as functions of reaction rates, and species concentrations.[4],[5]
17. Interpretation of the results in the coordinates of extent of reactions.[4],[5]
18. The class of PWLR Lyapunov functions is shown to be a special case of the class of robust Lyapunov functions, and hence alternative algorithms are provided based on this interpretation.[4],[5]
19. Exponential stability for GSN is presented, and robust non-singularity is shown to follow directly from the existence of at least one isolated positive equilibrium.[5]
20. The relationship between the proposed results and contraction analysis is established, and the associated Finsler-Lyapunov function is given.[5]
21. The concept of piecewise quadratic Lyapunov functions is proposed, and LMI-based construction algorithm are proposed over given partition.[4]

Chapter 7

22. A stabilization method for equilibria of GSNs is presented.
23. The concept of control PWLR Lyapunov function is introduced.

Chapter 8

24. Many examples of biochemical networks are shown to be amenable to the analysis methods introduced in this dissertation.

Chapter 2

Preliminaries and Literature Review

In this chapter we review technical background and literature.

2.1 Chemical Reaction Networks

A chemical reaction is a process in which a number of reacting molecules collide to form a product molecule. Hence, chemical reactions occur at the atomic level. However, since reactions occur usually as large collection of collisions, CRN theory is concerned with dynamical models that are based on a *macroscopic* view of reactions, rather than a microscopic view.

There are several models for CRN dynamics [41]. As collisions between molecules occur randomly in time between a discrete number of molecules, the most natural dynamic model is a *stochastic* model in which the state space is discrete, and time is continuous. The simplest and most commonly used stochastic model is the continuous-time Markov chain model [8]. However, Kurtz [61] showed that the infinite volume limit for the Markov chain model gives rise to an ODE model, therefore deterministic models are more commonly used with very large number of molecules. In this dissertation, we are concerned with *deterministic* models only.

2.1.1 Algebraic Description

Algebraic descriptions of CRNs have varying degrees of details. Some of them account for the atomic structure of molecules as the one proposed by Aris [16]; a detail that we will not need. In this work, we follow closely the standard mathematical formalism expounded in [53, 43, 32, 41, 9].

A reaction network consists of *species* and *reactions*. A set of species $\mathscr{S} = \{X_1, .., X_n\}$ consists of all reactant and product molecules in the network, while the set of reactions $\mathscr{R} = \{\mathbf{R}_1, ..., \mathbf{R}_\nu\}$ describes how reactants transforms into products. Both sets are assumed to be finite.

A reaction network has two mathematical elements: the *stoichiometry* and the *kinetics*. Stoichiometry describes the relative number of molecules of reactants and products between sides of each reaction, while kinetics is concerned with the relations that govern the velocity of transformation of reactants into products. We explain both below.

Stoichiometry: Mathematically, each reaction is an ordered pair of formal sums of species, i.e., $\mathbf{R}_j := (\sum_{i=1}^n \alpha_{ij} X_i, \sum_{i=1}^n \beta_{ij} X_i)$. Customarily, it is written as follows:

$$\mathbf{R}_j : \quad \sum_{i=1}^{n} \alpha_{ij} X_i \longrightarrow \sum_{i=1}^{n} \beta_{ij} X_i, \;\; j = 1, .., \nu, \tag{2.1}$$

where α_{ij}, β_{ij} are nonnegative integers called *stoichiometry coefficients*. Species that appear on the left-hand side are called *reactants*, and the expression on the left-hand side is called the *reactant complex*. Similarly, species that appear on the right-hand side are called *products*, and the expression appearing in the right-hand side is called the *product complex*. All complexes can be included in a set $\mathscr{C} = \{C_1, ..., C_{n_c}\}$. Each complex can be thought to be a vector that belongs to an n-dimensional Euclidean vector space of which the unit vectors correspond to species.

The forward arrow refers to the idea that the transformation of reactants into products is only occurring in the direction of the arrow and in a single step. This means that the

formation of products from reactants is direct with no intermediate reactions; such reactions are called *elementary reactions* [41]. Note that this does not mean necessarily that the reaction is elementary at the mechanistic level, it might consist of a series of reactions which are modelled as a single elementary reaction (e.g, singular perturbation of enzymatic reactions). However, this is a detail that belongs to the modeling step. For us, all reactions are considered to be elementary.

If the transformation is occurring also in the opposite direction, the reaction is said to be *reversible* and its reverse is listed as a separate reaction. For convenience, the reverse reaction of $\mathbf{R}_j$ is denoted as $\mathbf{R}_{-j}$. For brevity, the notation $C_1 \rightleftharpoons C_2$ denotes the pair of reactions $C_1 \to C_2, C_2 \to C_1$. The set of reactions $\mathscr{R}$ is said to be *reversible*, if for every $\mathbf{R}_j \in \mathscr{R}$, $\mathbf{R}_{-j} \in \mathscr{R}$ also.

The reactant or product complex are allowed to be empty, though not simultaneously. The empty complex is denoted by 0. Reactions in which 0 appears as a reactant are called *inflows*, and are called *outflows* if 0 appears as a product. A reaction network which has neither outflows nor inflows is called *closed*, and is called *open* otherwise.

An *autocatalytic reaction* is a reaction in which there exists a species which appears on both sides of the reaction simultaneously, i.e., $\mathbf{R}_j$ is autocatalytic if there exists X_i such that $\alpha_{ij}\beta_{ij} > 0$. If all reactions are non-autocatalytic, the network is termed *non-autocatalytic*.

The stoichiometric details of a network can be encoded by arranging the stoichiometric coefficients in an augmented matrix $n \times 2\nu$ as:

$$\tilde{\Gamma} = [A|B], \text{where } [A]_{ij} = \alpha_{ij}, [B]_{ij} = \beta_{ij}. \tag{2.2}$$

The two matrices can be subtracted to yield an $n \times \nu$ matrix $\Gamma = [\gamma_1^T \; ..\gamma_n^T]^T$ called the *stoichiometry matrix*, which is defined as $\Gamma = B - A$, or element-wise as:

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

If we remove the redundant columns of $\tilde{\Gamma}$, this yields an $n \times n_c$ matrix Γ_c, where each column correspond to a certain *complex*. It can be easily verified that there exists a matrix $Y \in \{0, \pm 1\}^{n_c \times \nu}$ such that the stoichiometry matrix admits the following factorization:

$$\Gamma = \Gamma_c Y. \tag{2.3}$$

The matrix Y is interpreted graphically in §2.1.2.

The stoichiometry of the network is assumed, unless otherwise stated, to satisfy the following assumption throughout the thesis.

AS1 There exists $v \in \ker \Gamma$ such that $v \gg 0$. This condition is necessary for the existence of positive equilibria as discussed in §2.1.3.

Remark 2.1: AS1 is not essential for our methods, however, imposing it simplifies many of the results. §5.1.2 and Remark 5.4 discuss how to modify some of the results without AS1.

Remark 2.2: Our published works [1, 2, 3, 4] have included a second assumption which is that the network is non-autocatalytic. However, most of the results hold without it.

Kinetics: Assume we have an isothermal well-stirred fixed-volume chemical reactor; this implies that the species are distributed uniformly in the reactor. Also, the temperature is assumed to be constant which implies that the kinetics are time-invariant.
In order to study kinetics, a nonnegative number x_i is associated to each species X_i to denote its *concentration*. Assume that the chemical reaction $\mathbf{R}_j$ takes place continuously in time. A *reaction rate* or velocity function $R_j : \bar{\mathbb{R}}_+^n \to \bar{\mathbb{R}}_+$ is assigned to each reaction.

Considering a microscopic setup and the associated statistical thermodynamics considerations, the reaction happens when the reactant molecules collide simultaneously. Therefore, it is natural to assume that the reaction rate is proportional to the product of concentrations of reactant species. This is the basis of the widely-used *Mass-Action* kinetics.

This intuition has been backed with empirical evidence, and can be derived from the first law of thermodynamics in ideal cases [60]. The reaction rate functions can be represented by:

$$R_j(x) = k_j \prod_{i=1}^{n} x_i^{\alpha_{ij}}, \tag{2.4}$$

with the convention $0^0 = 1$, where $k_j, j = 1, .., m$ are positive constants known as the reaction constants. These constants can be dependent on the temperature, species concentration and other uncertain parameters.

Mass-action kinetics are mostly used in chemical engineering. However, other models are also used in biology. Reactions in the cell happen in different time-scales, therefore it is customary to approximate a series of reaction by single reaction with a modified reaction-rate function. The most famous of these alternative models is the *Michaelis-Menten kinetics* which is derived from Mass-Action kinetics by singular perturbation of enzymatic reactions [54]. The reaction rate function can be written generally as:

$$R_j(x) = k_j \prod_{i=1}^{n} \left(\frac{x_i}{a_{ij} + x_i} \right)^{\alpha_{ij}}, \tag{2.5}$$

where $a_{ij}, i = 1, .., n, j = 1, .., \nu$ are positive constants. A generalization of Michaelis-Menten kinetics is known as *Hill kinetics* and is given by the formula:

$$R_j(x) = k_j \prod_{i=1}^{n} \left(\frac{x_i^{b_{ij}}}{a_{ij} + x_i^{b_{ij}}} \right)^{\alpha_{ij}}. \tag{2.6}$$

The results that are presented in this thesis are applicable for any monotone kinetics where the exact assumptions are detailed below. Although there exist special biochemical models in which monotonicity does not apply [84], this assumption conforms to the mostly used and popular reaction rate models including Mass-Action, Michaelis-Menten, and Hill kinetics, mentioned above. Furthermore, monotonic dependence of the reaction rate on the concentration of its reactants captures the basic intuition about the nature of a reac-

tion since, as the concentration of reactants increases, the likelihood of collision between molecules increases, and hence the rate of the reaction.

Therefore, we assume throughout the thesis that the each reaction rate function $R_j(x), j = 1, .., \nu$ satisfy the following assumptions.

AK1 R is a $\mathscr{C}^1$ function, i.e. continuously differentiable;

AK2 $x_i = 0 \Rightarrow R_j(x) = 0$, for all i and j such that $\alpha_{ij} > 0$; this captures the basic requirement that a reaction stops if any of its reactants vanishes.

AK3 it is nondecreasing with respect to its reactants, i.e

$$\frac{\partial R_j}{\partial x_i}(x) \begin{cases} \geq 0 & : \alpha_{ij} > 0 \\ = 0 & : \alpha_{ij} = 0 \end{cases} . \tag{2.7}$$

AK4 The inequality in (2.7) holds strictly for all $x \in \mathbb{R}^n_+$.

Remark 2.3: In principle, AK3 can be replaced with a sign-definiteness condition instead of a positivity condition. This accommodates reaction rates which are *decreasing* with respect to their reactants. Such reactants are said to be *inhibitory* with respect to the corresponding reaction. This can model the effect of repressers in a gene-regulatory network.

Remark 2.4: Conditions AK1-AK4 can be interpreted as prescribing a zero sign-pattern for the Jacobian matrix $\frac{\partial R}{\partial x}$. This sign pattern is given by the sign pattern of matrix of reactants A defined in (2.2), and if the network is non-autocatalytic then the sign pattern can be recovered from Γ directly by replacing positive entries with zeros and negative entries with ones. Also, it can be read from the graph as a transposed species-to-reaction adjacency matrix. §2.1.5 explains these interpretations for an example.

For every matrix J^* that satisfies the prescribed zero sign-pattern, there exists a reaction

rate function R that satisfies the assumptions AK1-AK4 and an x^* such that $J^* = \frac{\partial R}{\partial x}(x^*)$. In other words, any matrix satisfying that sign pattern can be interpreted as a Jacobian.

Since our results apply to networks having the same stoichiometry with any monotone kinetics satisfying the assumptions above, the following definition is given.

Definition 2.1. *Given $(\mathscr{S}, \mathscr{R})$, and let Γ be the induced stoichiometry matrix as above:*

- *A **reaction network** is the triple $(\mathscr{S}, \mathscr{R}, R)$.*
- *The set of **admissible kinetics** with respect to A is denoted by $\mathscr{K}_A$ and is given by:*

$$\mathscr{K}_A := \{R : \bar{\mathbb{R}}^n_+ \to \bar{\mathbb{R}}^\nu_+ | R_1, .., R_\nu \text{ satisfies AK1-AK4}\}. \tag{2.8}$$

- *A **network family** is the triple $(\mathscr{S}, \mathscr{R}, \mathscr{K}_A)$ and is denoted by $\mathscr{N}_{A,B}$. A reaction network which is a member of $\mathscr{N}_{A,B}$ is called a **realization** of $\mathscr{N}_{A,B}$.*

2.1.2 Graphical Description

CRNs admit graphical representations naturally, and hence many models have been proposed. Graphs that include species as vertices include directed set-graphs [32], directed bipartite multigraphs [95], the (undirected) species-reaction graph [36], weighted directed bipartite graphs (Petri-nets) [11], and the directed species-reaction graph [19]; the first three of these representation are very similar. Different graph representations associate species to edges (similar to electric circuits) [74], and some use the terminology of bond graphs [76]. Horn [52] and Feinberg [43] have proposed using graphs in which the complexes are the vertices. In this dissertation, the Petri-net representation is used and is reviewed below. Also, the complex graph representation is reviewed in order to compare it with our results.

Petri-net Representation: Although Petri-nets are mostly known for modeling distributed computing and discrete-event systems, they have been introduced originally for



(a) Two Irreversible Reactions (b) Equivalent Reversible Reaction

Figure 2.1: Illustration of the Petri-net compact notation for reversible reactions

representing chemical reactions [77]. Formally, a Petri-net is a weighted directed bipartite graph given by the quadruple $(\mathscr{S}, \mathscr{R}, \mathbf{E}, \mathbf{W})$, where $\mathscr{S}$ is the set of species corresponding to the first set of vertices, while the set of reactions $\mathscr{R}$ correspond to the second set of vertices[1,2]. The set of all vertices is denoted by $\mathbf{V} = \mathscr{S} \cup \mathscr{R}$.

The edge set $\mathbf{E} \subset \mathbf{V} \times \mathbf{V}$ is defined as follows. We draw an edge from $X_i \in \mathscr{S}$ to $\mathbf{R}_j \in \mathscr{R}$ for all X_i's such that $\alpha_{ij} > 0$. That is, $(X_i, \mathbf{R}_j) \in \mathbf{E}$ iff $\alpha_{ij} > 0$, and we say in this case that $\mathbf{R}_j$ is an *output reaction* for X_i. Similarly, we draw an edge from $\mathbf{R}_j \in \mathscr{R}$ to every $X_i \in \mathscr{S}$ such that $\beta_{ij} > 0$. That is, $(\mathbf{R}_j, X_i) \in \mathbf{E}$ whenever $\beta_{ij} > 0$, and we say in this case that $\mathbf{R}_j$ is an *input reaction* for X_i. Notice that there can not be edges connecting two reactions or two species.

Finally, $\mathbf{W} : \mathbf{E} \to \mathbb{N}$ is the weight function which associates to each edge a positive integer as $\mathbf{W}(X_i, \mathbf{R}_j) = \alpha_{ij}$, and $\mathbf{W}(\mathbf{R}_j, X_i) = \beta_{ij}$. Hence, the stoichiometry matrix Γ becomes the *incidence matrix*[3] of the graph. Figure 1.1 depicts such a representation.

For reversible reactions, a simplified notation is used where the two reactions are combined in one, and bidirectional arrows are used as in Figure 2.1.

[1]Species and reactions correspond to places and transitions in the Petri-net literature.

[2]Recall that in §2.1.1 we have mentioned that species can be thought as unit vectors in a Euclidean vector space, and reactions as ordered pairs of weighted sums of species, however, this algebraic structure is irrelevant here. From a graph-theoretic view, the sets $\mathscr{S}, \mathscr{R}$ are just sets of vertices. We have opted to keep the notation for simplification.

[3]Referring to Γ as an incidence matrix is according to the standard usage in the Petri-net literature [71], and it should not be interpreted as an incidence matrix for the network as a weighted directed graph. Nevertheless, it can be interpreted in the later sense if we model the network as a directed graph with generalized edges, i.e., each edge is an ordered pair of multisets of vertices.

We state other definitions that are needed later. A reaction $\mathbf{R}_{j_2}$ is called an *ancestor* of $\mathbf{R}_{j_1}$ if there exists a directed sequence of edges $(\mathbf{R}_{j_2}, X_{k_1})$, $(X_{k_1}, \mathbf{R}_{k_1}), .., (X_{k_n}, \mathbf{R}_{j_1})$ connecting them. The set of ancestors of $\mathbf{R}_j$ is denoted $\mathscr{A}(\mathbf{R}_j)$. Denote the set of *reactants* of $\mathbf{R}_j$ by $M_j = \{X_i | (X_i, \mathbf{R}_j) \in \mathbf{E}, 1 \leq i \leq n\}$, and let the set of *inflows* be $\mathcal{I} = \{\mathbf{R}_j | M_j = \varnothing, 1 \leq j \leq \nu\}$.

A conservation law d is referred to as *P-semiflow* in Petri-net literature terminology, while a positive vector in the kernel of Γ is referred to as a T-semiflow.

Remark 2.5: Graphical representations of a CRN can be recovered directly from the stoichiometry regardless of the kinetics. Hence, the information needed to perform a "robust" or "kinetics-independent" analysis of the kind we are proposing can be recovered completely from the Petri-net graph.

Complex Graph Representation: The Complex graph (C-graph) is a directed graph with vertices being the complexes, and edges given by reactions. It plays a central role in the stability theory developed by Horn [52], Feinberg [43]. Formally, the C-graph is given by a pair $(\mathscr{C}, \mathscr{R})$[4]. Therefore, an edge (C_i, C_j) belongs to the C-graph if and only if $C_i \to C_j$ is a reaction of the network. The incidence matrix of the C-graph is Y which was defined in (2.3).

A C-graph is called *weakly reversible* if for every directed path from C_i to C_j there exists a directed path from C_j to C_i.

2.1.3 Dynamic Description

Formulation of chemical reaction dynamics in terms of dynamical system theory were proposed and analyzed in the early 1960's for mono-molecular (linear) systems by Wei and Prater [98]. Axiomatic treatments were attempted with general kinetics by Wei [97], Mass-

[4]Recall that any $\mathbf{R}_j \in \mathscr{R}$ can be written as $\mathbf{R}_j = (\sum_{i=1}^n \alpha_{ij} X_i, \sum_{i=1}^n \beta_{ij} X_i) = (C_i, C_j)$. Hence, $\mathscr{R}$ is interpreted as a set of ordered pairs of complexes for the C-graph, but it is interpreted as a set of vertices for the Petri-net representation.

action kinetics by Horn and Jackson [53], but none were universally adopted. Oster and Perelson [73] proposed dynamical models that emphasize the thermodynamic underpinning of a reversible reaction network by associating chemical potentials to species and nonlinear passive resistive relationships to reactions; the equations of motion can be derived thereafter. However, this framework is not suited to our analysis since our subsequent results apply to irreversible networks with arbitrary monotone kinetics, and can be stated with respect to concentration dynamics directly. We follow the commonly used ODE models for CRNs [53, 32, 43, 41].

Let $\mathscr{S}, \mathscr{R}, R$ be given as in the previous section. The dynamics of a CRN with n species and ν reactions are described by a system of ordinary differential equations (ODEs) as:

$$\dot{x} = \Gamma R(x),\ x(0) \in \bar{\mathbb{R}}^n_+ \tag{2.9}$$

where x is the concentration vector evolving in the nonnegative orthant $\bar{\mathbb{R}}^n_+$, $\Gamma \in \mathbb{R}^{n\times\nu}$ is the stoichiometry matrix, $R(x(t)) = [R_1(x(t)), R_2(x(t)), ..., R_\nu(x(t))]^T \in \bar{\mathbb{R}}^\nu_+$ is the reaction rates vector. A solution of (2.9) initialized as $x(0)$ is denoted $\varphi(t; x(0))$.
Equation (2.9) above can be interpreted intuitively as follows. For every concentration x_i, the corresponding row in (2.9) is the weighted sum of reaction rates in which X_i appears as a reactant subtracted from the weighted sum of reaction rates in which X_i appears as a product; the weights are specified by the stoichiometry coefficients.

The nonnegative orthant $\bar{\mathbb{R}}^n_+$ can be shown to be forward invariant, hence the system represented by (2.9) belongs to the class of *nonnegative systems*. In addition, the manifold $\mathscr{C}_{x_\circ} := (\{x_\circ\} + \mathrm{Im}(\Gamma)) \cap \bar{\mathbb{R}}^n_+$ is forward invariant, and it is called *the stoichiometric compatibility class* associated with $x_\circ$.
A left null vector $d \in \mathbb{R}^n, d^T\Gamma = 0$ with $d > 0$ is said to be a *conservation law*. If there exists a conservation law $d \gg 0$, the network is said to be *conservative* since the quantity $d^T x(t)$ remains constant for all $t \geq 0$. A stoichiometric class $\mathscr{C}_{x_\circ}$ is said to be *proper* if $d^T x_\circ > 0$ for all conservations laws.

The dynamics of a CRN can be stated with respect to another variable called *the extent of a reaction* $\xi(t)$ [32, 10], which satisfies $R(x(t)) = \dot{\xi}(t)$. Hence, it can be defined as:

$$\xi(t) := \xi(0) + \int_0^t R(x(\tau))d\tau. \tag{2.10}$$

Assume $\xi(0) \in \ker \Gamma$, multiplying both sides by Γ, the concentration vector can be written as:

$$x(t) = x_\circ + \Gamma\xi(t), \tag{2.11}$$

the dynamics for the CRN can be written alternatively as:

$$\dot{\xi}(t) := R(x_\circ + \Gamma\xi(t)), \xi(0) = 0. \tag{2.12}$$

The significance of the notion of the extent of reaction is clarified in Chapter 6.

2.1.4 Equilibria

Since the stability theory that we develop is with respect to equilibria, notions of equilibria and main existence and uniqueness theorems are reviewed.

Notions of Equilibria: A point x_e is said to an *equilibrium* of (2.9) if $\Gamma R(x_e) = 0$. It is called an *interior equilibrium* if it is strictly positive, i.e., $x_e \in \mathbb{R}^n_+$. Otherwise, it is called a *boundary equilibrium.*

An equilibrium x_e is *nondegenerate* if the Jacobian evaluated at x_e relative to $\mathscr{C}_{x_e}$ is nonsingular. More precisely, considering shifting coordinates using a transformation matrix:

$$T = \begin{bmatrix} T_1 \\ D^T \end{bmatrix}, \tag{2.13}$$

where D^T has full row rank and $D^T\Gamma = 0$, and T_1 is any matrix such that T is nonsingular. Then, the Jacobian in the new coordinates can be written as:

$$T\Gamma\frac{\partial R}{\partial x}T^{-1} = \begin{bmatrix} J_1 & J_2 \\ 0 & 0 \end{bmatrix}. \tag{2.14}$$

Therefore, x_e is nondegenerate iff J_1 evaluated at x_e is nonsingular. J_1 is called the *reduced Jacobian*.

For a reversible network, the reaction rate function can always be written as $R(x) = [R_+(x)^T, R_-(x)^T]^T$, where $R_-(x)$ includes rate functions that correspond to the inverse reactions of the reactions that correspond to $R_+(x)$. If an equilibrium x_e satisfies $R_+(x_e) = R_-(x_e)$, then the system (2.9) is said to be at a *detailed-balance*, and x_e is called a *thermodynamic equilibrium*. For Mass-action kinetics, this implies that all equilibria are detailed-balanced, and hence the network is called a *detailed-balanced network*.

Recall the factorization (2.3). Let $\phi_c(x) = YR(x)$ be the *complex formation function*. If x_e satisfies $\phi_c(x_e) = 0$, then x_e is called a *complex-balanced equilibrium*. For Mass-action kinetics, this implies that all equilibria are complex-balanced, and hence the network is called a *complex-balanced network*. Let $E = \{x|\Gamma R(x) = 0\}$ and $E_c = \{x|\phi_c(x) = YR(x) = 0\}$ be the sets of equilibria and complex-balanced equilibria, respectively. Clearly, $E_c \subset E$. Consider the case $\ker\Gamma = \ker Y$. If $x_e \in E$, then $R(x_e) \in \ker\Gamma$ implies $R(x_e) \in \ker Y$. Hence, $E_c = E$. Hence, a geometric condition constrains all equilibria to be complex-balanced *regardless of the exact form of R*. This motivates the introduction of the graphic notion of *deficiency* defined as

$$\delta = \dim(\ker\Gamma) - \dim(\ker Y). \tag{2.15}$$

Using graph theoretic arguments, it can be shown that $\delta = n - \ell - \text{rank}(\Gamma)$, where ℓ is the number of connected components, also known as linkage classes, in the C-graph. If $\delta = 0$,

then the network is said to have *zero deficiency*, and all its equilibria are complex-balanced.

Existence and Uniqueness of Equilibria: Since multi-stable CRNs can model biochemical switches, a significant portion of the literature has focused on characterizing the ability of a CRN to have multiple equilibria in each class. For example, the deficiency zero theorem [43] states that if a network is weakly reversible and has deficiency zero (refer to §2.1.4) then there is a unique positive equilibrium in every stoichiometric compatibility class. The deficiency one theorem [44] provides linear programming conditions for the uniqueness of equilibria of a subclass of deficiency one networks. A recent direction of research has concentrated of providing graphical conditions for the injectivity of the map associated with the CRN, and hence uniqueness of equilibria for mass-action kinetics [35], and general kinetics [20, 19, 87].

2.1.5 Illustrative Example

A common motif in systems biology is the phosphorylation-dephosphorylation cycle, which is also known as a futile cycle, or activation-inactivation cycle. An inactive protein X is transformed into an intermediate state, then to an active state Y in a reaction catalyzed by an enzyme E_1. The active state Y is then deactivated by a second enzyme E_2. This can be modeled by the following reaction network:

$$X + E \xrightarrow{R_1} EX \xrightarrow{R_2} Y + E,$$
$$Y + F \xrightarrow{R_3} FY \xrightarrow{R_4} X + F,$$

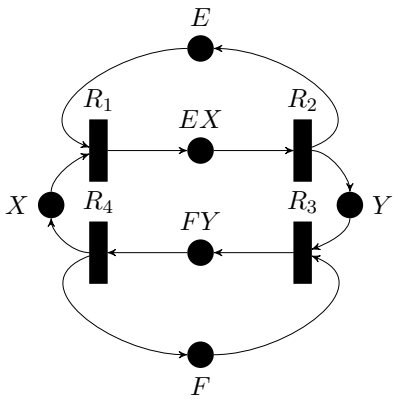


Figure 2.2: Simplified futile cycle.

where the ODE expression can be written as:

$$\dot{x} = \begin{bmatrix} -1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \\ -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 \end{bmatrix} \begin{bmatrix} R_1(x_1, x_5) \\ R_2(x_3) \\ R_3(x_2, x_6) \\ R_4(x_4) \end{bmatrix} \tag{2.16}$$

where $x_1, .., x_6$ correspond to X, Y, EX, FY, E, F.

The Petri-net representation is given in Figure 2.2, and it can be noted that Γ can be read from the graph as the incidence matrix.

Recall Remark 2.4, then conditions AK1-AK4 imply that the Jacobian of R has the following zero sign-pattern:

$$\frac{\partial R}{\partial x} = \begin{bmatrix} + & 0 & 0 & 0 & + & 0 \\ 0 & 0 & + & 0 & 0 & 0 \\ 0 & + & 0 & 0 & 0 & + \\ 0 & 0 & 0 & + & 0 & 0 \end{bmatrix}. \tag{2.17}$$

The sign-pattern can be interpreted as a transposed (bipartite) species-to-reaction *adjacency matrix* for the Petri-net.

2.2 Stability of Reaction Networks: A Review

One of the central questions in the study of the behaviour of a dynamical system is the problem of stability of equilibrium points, which is important in its own and in its consequences. In the context of biochemical networks, a stable equilibrium is an example of a *phenotype*, i.e., an observable outcome of the network. If the equilibrium is globally asymptotically stable over wide range of parameter variations then this implies that the biochemical network has a unique and robustly-observable phenotype. Furthermore, establishing global stability precludes other interesting behaviour that the network may potentially exhibit. Examples of these behaviours include switching between multiple locally stable equilibria which is known as *multi-stability* or multi-stationarity, sustained oscillations which are known as *limit cycles*, and the existence of strange attractors which are known as *chaos*.

Convergence of the trajectories of chemical networks had been widely observed for a large class of networks with diverse parameters and kinetics to the extent that Wei [97] in 1962 postulated that all chemical systems need to satisfy an "axiom of convergence" and that there shall exist an appropriate Lyapunov function. He suggested the use of Gibb's free energy. However, despite the special structure of CRNs, they are still able to exhibit the behaviours outlined above such as limit-cycles and chaos [41]. Nevertheless, global stability is still a very common phenomenon in reaction networks, which requires an explanation. There are wide variety of results in the literature establishing stability for many classes of networks, however, they only cover a small subset of CRNs which are in practice observed to be stable. Furthermore, major results utilizes Lyapunov functions that have thermodynamic interpretation as energy-like functions.

In this section these results are reviewed: we focus on stability results that have some

robustness properties such as having a degree of independence on the parameters involved.

2.2.1 Boltzmann's H-Theorem and Detailed-Balance

The problem of stability of reaction networks has its earliest roots in the statistical mechanics literature in the 19^{th} century. For closed reaction networks, the principle of *microscopic reversibility* states that any molecular reaction and its reverse have the same rate at equilibrium [92]. Therefore, all equilibria are detailed-balanced. Note that the law of mass-action is assumed also. For networks satisfying this principle, Ludwig Boltzmann in 1872 defined a quantity called H which indicates the deviance of the system from its equilibrium. He showed that H tends to decrease to a minimum which correspond to the equilibrium distribution from any initial condition. This result "may be regarded as among the greatest achievements of physical science", as the renowned physicist Richard Tolman [92] described it.

In order to interpret this result in our framework consider the reversible network (2.9) with Mass-Action Kinetics (2.4). Let $R_+(x)$ and $R_-(x)$ be the rates corresponding to the forward and reverse reactions, respectively. For arbitrary kinetic constants, there might exist an equilibrium x_e for which $R_+(x_e) \neq R_-(x_e)$, thus violating the principle of microscopic reversibility. Hence, the so called "Wegscheider's condition" was introduced in [85] to describe algebraic relationships that the kinetics constants $\{k_j\}_{j=1}^{\nu}$ need to obey.

To summarize, for any family of reversible Mass-Action networks, the subset of networks which satisfy Wegscheider's conditions are shown to be asymptotically stable. For a given equilibrium $x_e = [x_{e,1}, ..., x_{e,n}]^T$, the Lyapunov function

$$V(x) = \sum_{i=1}^{n} \int_{x_{e,i}}^{x_i} (\log \tilde{x}_i - \log x_{e,i})\, d\tilde{x} = \sum_{i=1}^{n} x_i \log(x_i/x_{e,i}) - x_i + x_{e,i} \tag{2.18}$$

can be used.

Despite the fact that microscopic reversibility is a well-known principle in statistical

mechanics, Horn and Jackson [53] noted that it is "less firmly rooted" in the laws of thermodynamics and there are "particular examples of kinetic systems which are fully consistent with classical thermodynamics, but do not satisfy the principle of detailed balancing".

Passivity and Thermodynamic Interpretation of the Lyapunov function

The Lyapunov function (2.18) has a thermodynamic interpretation: we need to introduce some notation to state it properly. Consider a closed spatially homogeneous chemical reactor at constant temperature and pressure. Thermodynamically, a chemical reaction occurs because of the difference of the *chemical potential* of both sides of the reaction [73]. Consider a reaction network: $C_j^{'} \rightleftharpoons C_j^{''}, j = 1, .., \nu$. For each complex $C_j^{'} = \sum_i \alpha_{ij} X_i$, a *chemical affinity* is associated. This can be written as: $\zeta_j^{'} = \sum_i \alpha_{ij} \mu_i$, where μ_i is the chemical potential associated to X_i and $\zeta_j^{''}$ is defined similarly. The chemical potential is a function of the corresponding concentration x_i, and is specified physically as the gradient of the Gibb's energy function $\mu(x) = \nabla G(x)$. The standard expression for the chemical potential is

$$\mu_i(x_i) = \mu_{i,\circ} + RT \log x_i, \tag{2.19}$$

where R is the ideal gas constant, and T is the constant temperature of the system.

The reaction advances based on (2.11) which writes the concentration in terms of the extent of reaction. In order to model the whole dynamics, the right hand side of (2.11) needs to be written in terms of x. This is accomplished via a map Λ that relates chemical potentials and the extent of reaction as follows: $\Lambda : (\zeta^{'}, \zeta^{''}) \mapsto \dot{\xi}$. Note that $R_j - R_{-j} = \dot{\xi}_j$. Using the logarithmic expression for the chemical potential, Λ can be written for Mass-Action kinetics as $R_j - R_{-j} = \dot{\xi}_j = k_j \left(e^{\zeta_j^{''}/(RT)} - e^{\zeta_j^{'}/(RT)} \right)$.

Using the introduced notation, note that the Lyapunov function (2.18) is simply a

normalized expression for the chemical energy stored in all the species, which is,

$$V(x) = \sum_{i=1}^{n} \int_{x_{e,i}}^{x_i} \mu_i(\tilde{x}_i)\ d\tilde{x},$$

where $\mu_{i,\circ} = RT \log x_{e,i}$. Furthermore, taking the time-derivative of the above expression yields:

$$\dot{V}(x) = -[\log(x_1), .., \log(x_n)]\Gamma_r R_r(x) = -[\zeta'^T, \zeta''^T]\Lambda(\zeta', \zeta'') \leq 0.$$

Hence, the output variable $\Lambda(\zeta', \zeta'')$ is *passive* with respect to input variable $[\zeta'^T, \zeta''^T]$. Full details are available in [73].

2.2.2 Linear and Compartmental Reaction Networks

A basic definition of a linear network is a network in which the stoichiometry and the kinetics implies that (2.9) reduces to a linear system $\dot{x} = \Gamma K x$, where K is a matrix of kinetics constants. Wei and Prater [98] studied monomolecular networks of the form $X_i \to X_j$ with Mass-Action kinetics, and they suggest the use of Gibb's energy function G as a Lyapunov function (similarly to the last subsection). Nevertheless, an alternative analysis can be carried out easily within the modern framework of linear stability theory using eigenvalue analysis or quadratic Lyapunov functions.

A generalized concept of a linear network considers studying monomolecular reactions, but it allows monotonic nonlinear reaction rates. Therefore, a monomolecular network is a network in which $R(x)$ is a vector of *single-valued* functions only. This class of networks has been studied using the notion of compartmental systems [55]. A matrix is compartmental if it is a diagonally-dominant Metzler matrix[5]. A reaction network is *compartmental* if its Jacobian matrix is compartmental for all time. Maeda et al. [65] studied a compartmental

[5] An $n \times n$-matrix J is Metzler if all off-diagonal elements are nonnegative. A Metzler matrix J is diagonally dominant if $\mathbf{1}^T J \leq 0$.

network with constant outflows and inflows of the form:

$$\dot{x}_i = \sum_{i \neq j} R_{ij}(x_j) - \sum_{i \neq j} R_{ji}(x_i) + u_i - R_i(x_i), i, j = 1, .., n, i \neq j,$$

where $R_{ij}, R_i, i, j = 1, .., n, i \neq j$, are monotonically increasing functions that vanish at the origin, and $u_i, i = 1, .., n$, are constant inflows. In the context of reaction networks, the above ODE can be interpreted as (2.9) for the network:

$$X_i \underset{R_{ij}}{\overset{R_{ji}}{\rightleftharpoons}} X_j, X_i \underset{u_i}{\overset{R_i}{\rightleftharpoons}} 0, i, j = 1, .., n.$$

The Lyapunov function used is:

$$V(x) = \|\dot{x}\|_1.$$

Note that V is piecewise linear in term of the reaction rates, this is revisited in §5.1.1.

2.2.3 Horn-Jackson-Feinberg Theory of Complex-Balance

There have been several attempts to generalize Boltzmann's H-theorem to a wider class of networks. Shear [86] claimed that the Lyapunov function (2.18) works for general reaction networks. However, he was shown to be wrong, and Horn and Jackson [53] have shown that (2.18) is a Lyapunov function for a class that they defined and called *complex-balanced networks*, i.e the class of networks that has at least one complex-balanced equilibrium as defined in §2.1.4. Therefore, it has been shown that for a complex-balanced network there exists a unique equilibrium in the interior of each stoichiometric compatibility class, and that equilibrium is locally asymptotically stable.

Similar to Wegscheider's conditions for detailed balance, there exist algebraic conditions that prescribe relationships that the kinetic constants need to obey for the network to be complex-balanced. However, Feinberg [42] showed that if a network is weakly reversible and has zero deficiency, then all equilibria are complex-balanced for any choice of the kinetic

constants. Henceforth, graphical properties of the C graph where linked to algebraic and dynamic properties of the corresponding system [43]. This result is remarkable since asymptotic stability has been established independently of the constants involved.

Horn and Jackson [53] initially claimed global stability. However, the uniqueness of an equilibrium in the interior of each stoichiometric class does not exclude the possibility of having equilibria on the boundary of the positive orthant. Sontag [89] showed that if there are no equilibria on the boundary of the class, then global asymptotic stability of the interior equilibrium holds. Global stability have been shown also in the single linkage class case [7]. However, global asymptotic stability of complex-balanced networks remained open in general, which is called the *global attractor conjecture* [37].

Since all linear networks which admit positive equilibria are weakly reversible and have deficiency zero, Horn-Jackson-Feinberg Theory encompasses both earlier theories of detailed-balanced networks and linear networks and preserves the thermodynamic interpretation by using the chemical energy as a Lyapunov function. Thus it remains the main theory for the stability of reaction networks with Mass-Action kinetics, and there exists considerable amount of literature in this area.

In the case of zero-deficiency networks, the incidence matrices of the Petri-net and the C-graph has the same row space. Hence, the C-graph can emphasize important properties that are concealed in the Petri-net. However, this advantage is lost for higher deficiencies. Therefore, deficiency-based theories have not been able to produce any stability results for other than zero deficiency networks. Furthermore, the class of zero deficiency networks is a relatively a small class of application-relevant networks which are observed to be stable over wide range of kinetics. Also, the theory is only valid with Mass-Action kinetics.

2.2.4 Monotonicity-Based Approaches

Monotonicity is a dynamical property that allows to deduce nontrivial statements regarding dynamical properties of the system including the global convergence of trajectories. A

dynamical system is said to be monotone with respect to a partial order if its time flow operator preserves that order. More specifically, if $x_1(0) \leq x_2(0)$, then $\varphi(t, x_1(0)) \leq \varphi(t, x_2(0))$ for all t. The partial order can be taken with respect to any proper cone; the nonnegative orthant for example.

Monotonicity with respect to the nonnegative orthant is called *cooperativity*. If the Jacobian is Metzler, then the system is cooperative. Angeli and Sontag [10] showed that the cooperativity of a specific network known as the futile cycle can be established by shifting the analysis to the extent-of-reaction coordinates. Thereafter, Angeli et al. [14] provided graphical conditions for verifying cooperativity in the extent-of-reaction coordinates. If persistence is also established (see the next section) and AS1 is satisfied, then global stability follows. However, one of the graphical conditions constrains the species to be connected to at most two vertices in the Petri-net, which is a highly constraining assumption.

2.2.5 Miscellaneous Stability Results

Many authors have studied the stability of CRNs from different perspectives. Vol'pert and Hudjaev [95] have studied global asymptotic reactions for tree reactions, and reversible reactions with detailed balance.

Another early approach was pursued by Clarke [32] where the CRN was decomposed into what he called "extreme subnetworks", and stability for the linearized system was shown for complex-balanced and tree CRNs.

A recent approach by Angeli et al. [13] considered representing the ODE as a state-dependent linear differential equation, and then used results for linear differential inclusions to establish stability for sufficiently small inflows.

Blanchini and Franco [27] proposed using the Lyapunov function $V(x) = \|x - x_e\|_1$ for some specific biochemical networks, but no general theory have been proposed. Recently, Blanchini and Giordano [28] generalized the use of these Lyapunov functions to more

general settings. This proposed function is related to the dual formulation of our Lyapunov function, and it will be discussed in §6.2.2.

2.3 Persistence of Reaction Networks

An important dynamical property in the context of systems that evolve over a manifold with a boundary is the property of *persistence*. Informally this means that if the trajectory is initialized in the interior of the manifold, then it will not approach the boundary asymptotically. This has been initially studied in the field of population dynamics [49, 96]. In that context, persistence is synonymous with survival, this means that if every species is present initially, then no species will extinct asymptotically, i.e. all species *survive*.

In the context of reaction networks, Feinberg [43] proposed *the persistence conjecture* which states that if the trajectories are bounded for a weakly reversible mass-action network, then they do not approach the boundary. However, the first major result in this regard was presented by Angeli et al. [12, 11] who gave a graphical condition to establish the persistence of a conservative network with any kinetics that satisfies AK1-AK4. This has been extended to networks with no conservation laws in [15].

Persistence is a powerful dynamical property since it precludes the possibility of convergence to the boundary of the positive orthant. This implies that the state space can be treated essentially to be without a boundary. Thus the dynamics of a persistent nonnegative system are essentially the same as standard system that evolves over $\mathbb{R}^n$; this is since $\mathbb{R}^n_+$ is diffeomorphic to $\mathbb{R}^n$. This in turn has strong implications on stability of the system. For example, if a complex-balanced network is persistent, then equilibria are globally asymptotically stable. Hence, the global attractor conjecture introduced in the last section is affirmed for a persistent system.

Since some of our results depend on the theory developed in Angeli et al. [11, 12, 15], we review it below.

2.3.1 Persistence and Siphons

Consider the ODE (2.9). Let $\varphi(t; x_\circ)$ be a trajectory initialized at $x_\circ$. The following definition is stated next.

Definition 2.2 (Persistence)**.** *A solution $\varphi(t; x_\circ)$ of (2.9) is said to be **persistent** if*

$$\liminf_{t\to\infty} \varphi(t; x_\circ) \gg 0.$$

A network given by (2.9) is said to be persistent if all solutions with $x_\circ \in \mathbb{R}^n_+$ are persistent. A network family $\mathscr{N}_{A,B}$ is said to be persistent if it is persistent for all its realizations.

Note that persistence can only be violated asymptotically. In other words, a trajectory can not enter the boundary of the positive orthant in finite time. Also, if a solution travels in the boundary, it can not get out. This is stated rigorously in the following lemma.

Lemma 2.1. *[12] Let $\varphi(t)$ be any solution of (2.9), and let $J \subset \mathbb{R}$ be an open interval. Then, $sgn\,\varphi(t)$ is constant on J.*

An important graphical notion for Petri-nets that has direct implication on the issue of persistence is the notion of a *siphon*. A siphon [71, 11] is a set of species that if absent at the beginning of the reaction remain absent for all time. Hence, we state the following definition.

Definition 2.3 (Siphon)**.** *Let $P \subset \mathscr{S}$ be a nonempty set of species. Then P is said to be a **siphon** if each input reaction associated to P is also an output reaction associated to P. Denote the set of output reactions of P by $\Lambda(P) \subset \mathscr{R}$, then a siphon is a **deadlock** if $\Lambda(P) = \mathscr{R}$.*

In order to analyze the network when species in P are initialized to zero, we denote the face associated to P by Ψ_P. It is given by:

$$\Psi_P = \{x \in \mathbb{R}^n_+ | X_i \in P \Rightarrow x_i = 0\}.$$

The following Lemma gives a useful characterization for the forward invariance of faces associated to siphons.

Lemma 2.2. *[12] Let $P \subset \mathscr{S}$ be nonempty. Then P is a siphon if and only if Ψ_P is forward invariant for the system* (2.9).

To study persistence meaningfully trajectories should have the potential ability to travel from the interior to the boundary. This means that the interior (with respect to the relative topology) of stoichiometric compatibility class should not be empty, i.e. $\mathscr{C}_{x_0}^{\circ} \neq \emptyset$. However, if the set P contains the support of a conservation law, then initializing it to zeros means that the whole stoichiometric compatibility class is a subset of $\partial\mathbb{R}^n_+$. This motivates the following definition.

Definition 2.4 (Critical Siphon)**.** *A siphon or a deadlock is said to be* ***critical*** *if it does not contain a set of species that corresponds to the support of a conservation law.*

The absence of critical siphons guarantees persistence, as the following theorem states.

Theorem 2.1 ([12, 15])**.** *Given* (2.9)*. Consider the network family $\mathscr{N}_{A,B}$ with admissible kinetics. If the associated Petri-net has no critical siphons then any bounded trajectory for a realization of $\mathscr{N}_{A,B}$ is persistent*[6]*. If a network family is also conservative, then it is persistent.*

The theorem above is an example of a dynamical property that can be guaranteed by a graphical property of the network, regardless of its kinetics.

[6] In the terminology of [15], this is called bounded-persistence.

Chapter 3

Piecewise Linear in Rates Lyapunov Functions

In this section, we propose a Lyapunov function that we call a "Piecewise Linear in Rates Lyapunov function", and discuss the stability properties it induces for the associated reaction network.

3.1 Stability of Reaction Networks

3.1.1 Stability Relative to An Invariant Manifold

Explicit analytical solutions of nonlinear differential equations are mostly unavailable, which mandates a qualitative approach to study their behaviour. Stability is one of the basic qualitative features of a system that is of interest. Informally, consider trajectories starting close to an equilibrium point. If all of them remain close to it for all future time, then the equilibrium point is said to be *Lyapunov stable*. If, in addition, all these trajectories converge to the equilibrium point asymptotically, then the equilibrium point is said to be *asymptotically stable*.

Conventional stability theory [51] examines stability with respect to an isolated equilibrium point, usually placed at the origin. However, for reaction networks, there is usually a *continuum* of equilibria. This means that asymptotic stability or Lyapunov stability are not achieved in the sense presented above. Nevertheless, since the state space of reaction networks is usually divided into stoichiometric compatibility classes which are forward invariant (see §2.1.3), statements regarding stability can be stated relative to the stoichiometric class; some authors refer to this as semi-stability [31].

Since it is possible that there is a continuum of equilibria even in each $\mathscr{C}_{x_e}$, we need to define the meaning of the distance between a point and a set, and the meaning of the neighborhood of a set.

Definition 3.1 (Distance and Neighborhood)**.** *Let $E = \{x_e | \Gamma R(x_e) = 0\}$ be the set of equilibria, and let $E_{x_e} = E \cap \mathscr{C}_{x_e}$ be the set of equilibria in $\mathscr{C}_{x_e}$ for some $x_e \in E$. Let $\|.\|$ be any norm defined on $\mathbb{R}^n$.*

- *The distance d of a point $x_\circ$ to the set E_{x_e} is defined as:*

$$d(x_\circ, E_{x_e}) := \inf_{\omega \in E_{x_e}} \|x_\circ - \omega\|.$$

  *Note that "*inf*" can be replaced by "*min*" since E_{x_e} is a closed set.*

- *A set $N_{E_{x_e}}$ is a neighborhood of E_{x_e} relative to $\mathscr{C}_{x_e}$ if it is a neighborhood relative to $\mathscr{C}_{x_e}$ for every $x \in E_{x_e}$.*

We are ready now to state formal definition of stability relative to a stoichiometric class.

Definition 3.2 (Stability Relative to An Invariant Manifold)**.** *Consider the system* (2.9).

- *An **equilibrium** $x_e \in E$ is **Lyapunov stable** if for every $\varepsilon > 0$ there exists $\delta_\varepsilon > 0$ such that $\|x_\circ - x_e\| < \delta_\varepsilon$ and $x_\circ \in \mathscr{C}_{x_e}$ implies that $\|\varphi(t; x_\circ) - x_e\| < \varepsilon$ for all t.*

  *A Lyapunov stable x_e is said to be **asymptotically stable** if there exists a relative neighborhood $N_{x_e} \subset \mathscr{C}_{x_e}$ of x_e such that $\lim_{t\to\infty} \varphi(t; x_\circ) = x_e$ for every $x_\circ \in N_{x_e}$.*

x_e *is said to be* ***globally asymptotically stable*** *if* $N_{x_e} = \mathscr{C}_{x_e}$.

- *The* ***equilibrium set*** E_{x_e} *is* ***Lyapunov stable*** *if for every* $\varepsilon > 0$ *there exists* $\delta_\varepsilon > 0$ *such that* $d(x_\circ, E_{x_e}) < \delta_\varepsilon$ *and* $x_\circ \in \mathscr{C}_{x_e}$ *implies that* $d(\varphi(t; x_\circ), E_{x_e}) < \varepsilon$ *for all* t.

  A Lyapunov stable E_{x_e} *is said to be* ***asymptotically stable*** *if there exists a relative neighborhood* $N_{E_{x_e}} \subset \mathscr{C}_{x_e}$ *of* E_{x_e} *such that* $\lim_{t\to\infty} \varphi(t; x_\circ) \in E_{x_e}$ *for every* $x_\circ \in N_{E_{x_e}}$.

  E_{x_e} *is said to be* ***globally asymptotically stable*** *if* $N_{E_{x_e}} = \mathscr{C}_{x_e}$.

- *The* ***basin of attraction*** *of an asymptotically stable set* E_{x_e} *is the largest relative neighborhood* $N_{E_{x_e}}$ *that can be chosen in the definition above.*

The central problem is verifying the stability of given equilibrium without solving the differential equation analytically. For linear systems this is easily solved by examining the eigenvalues of the system matrix, however, the situation is harder for nonlinear systems. The most popular approach to tackle this issue is via the use of a function V that acts like an energy of the system; this function is called a *Lyapunov function*. Intuitively, it must be nonnegative and have a global minimum at the equilibrium. If it is possible to show that this virtual energy decreases in time along the system trajectories meaning that $dV/dt < 0$, then it is possible to show stability. Converse Lyapunov theorems guarantee that such functions exist: if the equilibrium is stable, then there exists a Lyapunov function [51]. However, proofs of these results are non-constructive since they make use of the solutions of the ODE.

Generally, the task of finding a Lyapunov function is hard. The first hint usually arises from studying the underlying physics of the problem, and indeed, this is a major approach for tackling the stability of reaction networks as we have seen in §2.2. However, after decades of research in this direction, no new major results are produced. The approach proposed is this dissertation is elementary in the sense that it is not based on thermodynamics' background, and it has been motivated by examining the manner in which the

sign of the time-derivative of the reaction rate depends on the sign of the time-derivative of the states; this can be observed easily by examining the Petri-net of the network as the next subsection explains. This is explained in the next subsection.

3.1.2 Motivating Example

Recall the futile cycle presented in §2.1.5 and depicted in Figure 2.2. An intuitive way to analyze the network is to consider the main loop in Figure 2.2 and study the sum of absolute reaction differences along the loop. This can be loosely paralleled to considering reactions as potentials, and noting that the difference of "potentials" causes the concentration of species to change. If this sum decreases along the trajectories of (2.9) then the network is stable. Hence, consider the following function:

$$\begin{aligned} V(x) &= |R_1(x) - R_2(x)| + |R_2(x) - R_3(x)| + |R_3(x) - R_4(x)| + |R_4(x) - R_1(x)| \\ &= |\dot{x}_3| + |\dot{x}_2| + |\dot{x}_4| + |\dot{x}_1|, \end{aligned} \tag{3.1}$$

which is a piecewise linear in rates (PWLR) function. The function can be analyzed region-wise. Consider for instance the region

$$\mathcal{W} = \{R(x) : R_1(x) \geq R_2(x), R_3(x) \geq R_2(x), R_3(x) \geq R_4(x), R_1(x) \geq R_4(x)\}. \tag{3.2}$$

The function (3.1) can be written over $\mathcal{W}$ as:

$$\tfrac{1}{2}V(x) = R_1(x) - R_4(x) + R_3(x) - R_2(x) \tag{3.3}$$

Note that in the given region, the sign of $\dot{x}$ is determined by the inequalities (3.2) and they can be read from the graph as Figure 3.1 illustrates. Consider the species EX for example. Since $R_1(x) \geq R_2(x)$, then this implies that $\dot{x}_3 \geq 0$. Similarly $\dot{x}_1, \dot{x}_2, \dot{x}_5, \dot{x}_6 \geq 0$ and $\dot{x}_4 \geq 0$. By noting that these signs are matched to the coefficients of $R(x)$ in (3.3)

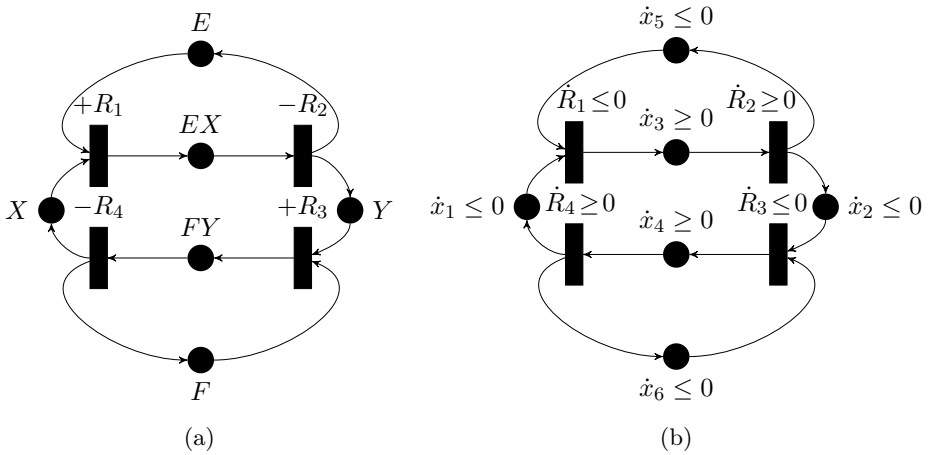


Figure 3.1: Analysis of the sign of $\dot{V}$ in the region $\mathcal{W}$ for the futile cycle. (a) The sign next to each reaction denotes the sign of the corresponding coefficient in (3.3). (b) Signs of the time-derivatives of species concentrations as implied by the inequalities defining $\mathcal{W}$ (3.2) and the resulting signs of the rates of change of the reactions rates. Note that for each reaction the sign of the rate of change is opposite to the sign of its coefficient.

and that each reaction depends monotonically on its reactants it can be seen that V is decreasing in this region. Algebraically, we can write the following inequality in $\mathcal{W}^\circ$:

$$\tfrac{1}{2}\dot{V}(x) = \frac{\partial R_1}{\partial x_5}\overset{-}{\dot{x}_5} + \frac{\partial R_1}{\partial x_1}\overset{-}{\dot{x}_1} - \frac{\partial R_4}{\partial x_4}\overset{+}{\dot{x}_4} \quad + \frac{\partial R_3}{\partial x_2}\overset{-}{\dot{x}_2} + \frac{\partial R_3}{\partial x_6}\overset{-}{\dot{x}_6} - \frac{\partial R_3}{\partial x_3}\overset{+}{\dot{x}_3} \leq 0,$$

where the sign of the rate of change of each concentration is indicate above it.
Therefore, $\operatorname{sgn}\dot{V}$ can be determined conclusively *without knowing the kinetics*. This can be repeated for all regions to conclude that V is decreasing along the trajectories of (2.17) for any *admissible* R.

The lesson that can be taken from this example is that a robust analysis of reaction networks can be carried out in the *reaction coordinates*. In addition, this analysis can be carried out by the utilization of PWLR functions that are defined in such manner that the sign pattern of $\dot{x}$ can be determined in each region by region inequalities, the signs of the coefficients of $R(x)$ are matched to the sign pattern, and the function can be patched continuously over the regions.

The remaining of the chapter presents a systematic generalization of this approach. We consider the problem of stability of CRNs by proposing the use of Lyapunov functions of the form above, which we call *Piecewise Linear in Rates (PWLR) Lyapunov functions*. Not only they have simple structure, these functions are robust with respect to arbitrary positive kinetic constants and require mild assumptions on the reaction kinetics. Mass-Action kinetics is just a special case of the admissible kinetics.

3.2 Piecewise Linear in Rates Functions

The concept of utilizing convex piecewise linear functions as Lyapunov functions to establish stability is not new. For instance, it has been used for special nonlinear systems by Rosenbrock [80], Mitra and So [67]. Willems [99] proposed using them for diagonally-dominant linear systems. Molchanov and Pyatnitskiy [69], and Blanchini [26] have shown that they can replace quadratic Lyapunov functions in the context of uncertain linear systems. Moreau [70] used a max-min function for consensus dynamics.

In the context of reaction networks those functions received little attention (see §2.2). Maeda et al. [65] have used a piecewise linear function in term of the time derivative of the states for monomolecular reaction networks, and Blanchini and Franco [27] proposed piecewise linear Lyapunov functions for some specific networks.

In this chapter we extend systematically this approach to classes of nonlinear systems which have a graphical structure. But, instead of using a Lyapunov function which is piecewise linear in terms of states, we identify nodes which are represented by nonlinear functions, and construct Lyapunov functions which are piecewise linear in terms of the node functions. This approach is used for reaction networks where node functions are reaction rates.

3.2.1 Formal Definition

Although we name our proposed class of functions "piecewise linear in rates functions", the set of functions which are described by the definitions below is a proper subset of the former. Therefore, we need to define precisely the class of functions that we are going to consider.

Since the proposed functions are piecewise linear in the rates, they are defined as a composition of a piecewise linear function and the reaction rate function, i.e., $V = \tilde{V} \circ R$. Since R is specified by the network, we aim mainly to study and construct $\tilde{V}$.

Consider a continuous Piecewise Linear (PWL) function $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ which is defined over a polyhedral conic partition of $\mathbb{R}^\nu$. Each region in the partition is a polyhedral cone which is constructed by intersecting half-spaces defined by vectors $h_1, .., h_p$. The vectors are collected as *rows* in a matrix $H \in \mathbb{R}^{p\times\nu}$. The matrix is assumed to have no zero rows, and also we assume the existence of $\mu \in \ker H$ with $\mu \gg 0$. The reason for this assumption is clarified in Remark 3.1.

In order to describe each partition properly, the following matrices are defined. Let $\Sigma_1, ..., \Sigma_{2^p}$ be the set of $p \times p$ signature matrices, i.e. all possible $\{\pm 1\}$-diagonal matrices of size $p \times p$. Define cones $\mathcal{W}_1, ..., \mathcal{W}_{2^p}$ as:

$$\mathcal{W}_k = \{r \in \mathbb{R}^\nu : \Sigma_k H r \geq 0\}. \tag{3.4}$$

Each cone $\mathcal{W}_k$ can be seen as the intersection of half-spaces given by the inequalities $\sigma_{ki} h_i^T r \geq 0, i = 1, .., p$, where $H = [h_1^T \ ... \ h_p^T]^T$, $\Sigma_k = \text{diag}[\sigma_{k1}...\sigma_{kp}]$. Note that these cones are not pointed as all of them contain $\ker H$ which we have assumed to be nontrivial.

As some of the intersections may have empty interiors, i.e., conflicting inequalities, we reorder the cones' indices such that the first m cones are the nonempty-interior cones, i.e. $\mathcal{W}_k^\circ \neq \varnothing$ iff $k \in \{1, .., m\}$. Note that $m \leq 2^p$, where the equality is achieved iff no left null vector of H exists. Otherwise, the value of m depends on the number of left null vectors

and their supports.

The partition regions as defined above have simplifying properties that can be utilized to ensures the well-posedness of our subsequent definitions. Hence, the following proposition can be stated.

Proposition 3.1 (Properties of the Partition)**.** *Let H, and $\{\mathcal{W}_k\}_{k=1}^m$ be defined as above, then the following holds:*

1. ***Partitioning:*** *We have $\mathbb{R}^\nu = \bigcup_{k=1}^m \mathcal{W}_k$, $\bigcap_{k=1}^m \mathcal{W}_k = \ker H$, and $\mathcal{W}_k \cap \mathcal{W}_j = \partial W_k \cap \partial \mathcal{W}_j$, for all $j, k = 1, .., m$.*

2. ***Positivity:*** *All the cones intersect the positive orthant nontrivially, i.e., $\mathcal{W}_k^\circ \cap \mathbb{R}_+^\nu \neq \varnothing, k = 1, ..., m$. Hence, $\mathbb{R}_+^\nu = \bigcup_{k=1}^m (\mathcal{W}_k \cap \mathbb{R}_+^\nu)$ is a partition to non-empty-interior cones.*

3. ***Symmetry:*** *For each $1 \leq k_1 \leq m$, there exists $1 \leq k_2 \leq m$ such that $\Sigma_{k_1} = -\Sigma_{k_2}$. Hence, m is always even and we can reorder the cones so that $\mathcal{W}_k = -\mathcal{W}_{m-k+1}, k = 1, .., m/2$.*

Proof. a) By construction, we have $\mathbb{R}^\nu = \bigcup_{k=1}^{2^p} \mathcal{W}_k$. To prove the claim it is sufficient to show that if $\mathcal{W}_k^\circ = \varnothing$, then $\exists j \in \{1, .., m\}$ such that $\mathcal{W}_k \subset \mathcal{W}_j$. By definition, $\mathcal{W}_k = \bigcap_{i=1}^p \{r | \sigma_{ki} h_i^T r \geq 0\}$. We construct the set $\mathcal{W}_j$ as follows. Let $\mathcal{W}_j^{(1)} = \{r | \sigma_{k1} h_1^T r \geq 0\}$ which has nonempty interior. Let $i > 1$, we set $\mathcal{W}_j^{(i)} = \mathcal{W}_j^{(i-1)} \cap \{r | \sigma_{ki} h_i^T r \geq 0\}$ if it has nonempty interior. Otherwise, $\mathcal{W}_j^{(i-1)} \cap \{r | \sigma_{ki} h_i^T r \geq 0\} = \mathcal{W}_j^{(i-1)} \cap \{r | \sigma_{ki} h_i^T r = 0\} \subseteq \mathcal{W}_j^{(i-1)} \cap \{r | \sigma_{ki} h_i^T r \leq 0\} := \mathcal{W}_j^{(i)}$ and the latter has nonempty interior. Therefore, $\mathcal{W}_j = \mathcal{W}_j^{(p)}$ has nonempty interior and includes $\mathcal{W}_k$. Furthermore, it is evident from the definitions that $\bigcap_{k=1}^m \mathcal{W}_k = \ker H$, $\mathcal{W}_j \cap \mathcal{W}_k = \partial \mathcal{W}_k \cap \partial \mathcal{W}_j$, $j \neq k \in \{1, .., 2^p\}$.

b) Let $r^* \in \mathcal{W}_k^\circ$ and let $\mu \in \ker H, \mu \gg 0$. Then there exists $t > 0$ sufficiently large such that $(r^* + t\mu) \in \mathbb{R}_+^\nu$. Furthermore, $H(r^* + t\mu) = Hr^*$, hence $(r^* + t\mu) \in \mathcal{W}_k^\circ$.

c) Assume that $r^* \in \mathcal{W}_k^\circ$, then $-r^* \in -\mathcal{W}_k^\circ$, which implies that the latter is nonempty and there exists $j \in \{1, .., m\}$ such that $\mathcal{W}_j = -\mathcal{W}_k$. □

After defining the partition and establishing some of its properties, we are ready to define a Piecewise Linear in Rates function formally.

Definition 3.3 (PWLR Function)**.** *Let H be such that* $\ker H = \ker \Gamma$*, and* $\{\mathcal{W}_k\}_{k=1}^m$ *be defined as above, and assume that* $C = [c_1^T \; .. \; c_{m/2}^T]^T \in \mathbb{R}^{m/2\times\nu}$ *be the* coefficients matrix*. Then,* $V : \mathbb{R}^n \to \mathbb{R}$ *is said to be a Piecewise Linear in Rates (PWLR) function if it admits the representation* $V(x) = \tilde{V}(R(x))$*, where* $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ *is a continuous PWL function given as*

$$\tilde{V}(r) = |c_k^T r|, \; r \in \mathcal{W}_k \cap -\mathcal{W}_k, k = 1, .., m/2. \tag{3.5}$$

Remark 3.1: The assumptions imposed on $\ker H$ are useful to simplify some theorems and algorithms. This is later justified in Theorem 4.1 where it is shown that the existence of a Lyapunov function induced by a generic PWLR continuous function, i.e without assumptions on H, implies the existence of a corresponding convex PWL function. The H associated with this convex function satisfies the outlined conditions automatically.

Note that by definition, if $\tilde{V}(r) = c_k^T r$, then the function is defined over the region $\mathcal{W}_k$, and if $\tilde{V}(r) = -c_k^T r$, then the corresponding region is $\mathcal{W}_{-k} := \mathcal{W}_{m-k+1} = -\mathcal{W}_k$.

Within the class of PWLR functions, the subclass of *convex* PWLR functions admits a simpler representation, where the adjective "convex" is refers to $\tilde{V}$, not $V = \tilde{V} \circ R$.

Definition 3.4 (Convex PWLR Functions)**.** *Let* $C = [c_1^T \; .. \; c_{m/2}^T]^T \in \mathbb{R}^{m/2\times\nu}$ *be given such that there exists* $v \in \ker C$ *with* $v \gg 0$*. Then,* $V : \mathbb{R}^n \to \mathbb{R}$ *is said to be a convex PWLR function if it admits the representation* $V(x) = \tilde{V}(R(x))$*, where* $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ *is a convex PWL given by*

$$\tilde{V}(r) = \max_{1\le k\le m/2} |c_k^T r| = \|Cr\|_\infty. \tag{3.6}$$

Remark 3.2: The matrices H and C are crucial in the construction of the Lyapunov function. Methods for choosing them are introduced in Chapter 5.

Remark 3.3: It can be shown that any convex PWL function which satisfies (3.5) can be represented using (3.6) [24]. Therefore for a convex PWLR function represented by (3.5),

it can be simply written as (3.6).

Furthermore, given a function represented by (3.6), the partition regions $\{\tilde{\mathcal{W}}_k\}_{k=1}^{m}$ and the matrix H can be determined as follows: Let $\{c_k - c_j | j, k = 1, .., m, j \neq k\}$ be a set of vectors. Eliminate a vector from every linearly dependent pair, and eliminate zero vectors. Collect the remaining vectors as rows in a matrix and call it H. Let $\{\tilde{\mathcal{W}}_k\}_{k=1}^{\tilde{m}}$ be defined as above. Note that these regions do not necessarily coincide with the **active regions** for each coefficient vector c_k defined as:

$$\mathcal{W}_k := \{r \in \mathbb{R}^r | (c_k - c_j)^T r \geq 0, (c_k + c_j)^T r \geq 0, j = 1, .., \tfrac{m}{2}, j \neq k\}, k = 1, .., \tfrac{m}{2}.$$

Nevertheless, for every $\tilde{\mathcal{W}}_k$, there exists $\mathcal{W}_j$ such that $\tilde{\mathcal{W}}_k \subset \mathcal{W}_j$. This determines the coefficient vector which is active in each region $\tilde{\mathcal{W}}_k$.

3.3 PWLR Lyapunov Functions and Stability

The main theme of this chapter is to introduce a new class of Lyapunov functions for CRNs (2.9) which are piecewise linear in terms of the reaction rates (PWLR). Therefore, the functions introduced in Definitions 3.3 and 3.4 are candidate Lyapunov functions.

3.3.1 Generalized Derivatives

The basic property of a Lyapunov function is that it need to be non-increasing along the system's trajectories, and this is usually translated into a negativity requirement for the time-derivative. However, since PWLR functions are non-differentiable on regions' boundaries, a generalized derivative need to be considered. It has been known in the early stability literature (see Hahn [51], Yoshizawa [100]) that standard Lyapunov theorems can be generalized without difficulty with locally Lipschitz[1] Lyapunov functions and Dini derivatives.

[1] A function $V : \bar{\mathbb{R}}_+^n \to R$ is locally Lipschitz if for every x there exists a neighborhood N_x such that there exists $K > 0$ with $\|f(x_1) - f(x_2)\| \leq K\|x_1 - x_2\|$ for any $x_1, x_2 \in N_x$.

The upper Dini's derivative for V in the direction of a function $f(x)$ is defined as:

$$D^+_{f(x)}V(x) := \limsup_{h\to 0^+} \frac{V(x+hf(x)) - V(x)}{h}. \tag{3.7}$$

For a locally Lipschitz function, the above quantity is always finite.

An alternative definition of derivative, which is more restrictive but has more convenient calculus, is the *Clarke's derivative*, which is defined as [33]:

$$D^C_f V(x(t)) := \limsup_{\substack{h\to 0^+ \\ y\to x}} \frac{V(y+hf(x)) - V(y)}{h}. \tag{3.8}$$

Note that $D^+_f(x)V(x) \leq D^C_f V(x(t))$.

We are ready to provide an expression for the derivative of V along $f(x) = \Gamma R(x)$.

Lemma 3.1. *Consider* (2.9)*, and let* $V = \tilde{V} \circ R$ *be a PWLR function defined as in Definition 3.4. Then,*

$$D^+_{\Gamma R(x)}V(x) \overset{(\star)}{\leq} D^C_{\Gamma R(x)}V(x) = \max_{k\in K_x} c_k^T \dot{R}(x) =: \dot{V}(x), \tag{3.9}$$

where $\dot{R}(x) := \frac{\partial R(x)}{\partial x}\Gamma R(x)$*, and* $K_x = \{k : c_k^T R(x) = V(x), 1 \leq k \leq m\}$*,* $c_k = -c_{m+1-k}, k = 1, .., \frac{m}{2}$*. The equality in the inequality* $(\star)$ *above is achieved if* $\tilde{V}$ *is convex.*

Proof. Write the expression for the Dini's derivative as follows:

$$\begin{aligned} D^+_{\Gamma R(x)}V(x) &:= \limsup_{h\to 0^+} \frac{V(x+h\Gamma R(x)) - V(x)}{h} = \limsup_{h\to 0^+} \frac{\tilde{V}(R(x+h\Gamma R(x))) - \tilde{V}(R(x))}{h} \\ &= \limsup_{h\to 0^+} \frac{\tilde{V}(R(x)+h\dot{R}(x)) - \tilde{V}(R(x))}{h}, \end{aligned}$$

where the last equality is achieved by writing the Taylor expansion. Note the above expression is the derivative of $\tilde{V}$ in the direction of $\dot{R}(x)$. If $R(x)$ belongs to the interior of a region, then the limit evaluates simply to $c_k^T \dot{R}(x)$. If $R(x)$ belongs to the boundary of

a region and since the Clarke's derivative takes the supremum over all directions, then the Clarke's derivative is equal to the maximum of $c_k^T \dot{R}(x)$ over $k \in K_x$. In other words,

$$D^+_{\Gamma R(x)} V(x) \overset{(\star)}{\leq} \limsup_{\substack{h \to 0^+ \\ r \to R(x)}} \frac{\tilde{V}(r + h\dot{R}(x)) - \tilde{V}(r)}{h} = \max_{k \in K_x} c_k^T \dot{R}(x).$$

Danskin's Theorem [33] can be in invoked to show that $(*)$ is an equality if $\tilde{V}$ is convex. □

Remark 3.4: The use of the Clarke's derivative can be avoided to establish the inequality above. However, we have chosen to use it since Clarke's calculus is used further in later chapters.

3.3.2 Definition of a PWLR Lyapunov Function

As it has been mentioned in Chapter 1, the approach undertaken in this work is a graphical-approach, i.e., it is independent of the specific form of kinetics. Thus, we require $\tilde{V} \circ R$ to be a Lyapunov function for every choice of $R \in \mathscr{K}_A$. This is stated formally in the following definition.

Definition 3.5 (PWLR Lyapunov Function)**.** *Given* (2.9) *with initial condition* $x_\circ := x(0) \in \bar{\mathbb{R}}^n_+$. *Let* $V : \bar{\mathbb{R}}^n_+ \to \bar{\mathbb{R}}_+$ *be given as:* $V(x) = \tilde{V}(R(x))$, *where* $\tilde{V}$ *is the associated PWL function. Then* V *is said to be a* ***PWLR Lyapunov Function*** *if for each* $R \in \mathscr{K}_A$, *the function* $V = \tilde{V} \circ R$ *is:*

1. ***Positive-Definite****:* $V(x) \geq 0$ *for all* x, *and* $V(x) = 0$ *if and only if* $R(x) \in \ker \Gamma$.

2. ***Nonincreasing****:* $\dot{V}(x) \leq 0$ *for all* x, *where* $\dot{V}$ *is defined in* (3.9).

The set of networks for which there exists a PWLR Lyapunov function is called ***Graphically Stable Networks*** *(GSNs)*[2].

[2]The adjective "graphical" has been used instead of "structural" since "structural stability" has another meaning in the context of dynamical systems which refers to robustness against $\mathscr{C}^1$ perturbations.

Note that the inequality for $\dot{V}$ in the definition above is not strict. Hence, in order to be able to claim asymptotic stability, a LaSalle's condition need to be defined.

Definition 3.6 (LaSalle's Condition)**.** *A PWLR Lyapunov function is said to satisfy* ***the LaSalle's condition*** *if for any choice of $R \in \mathscr{K}_A$ the following statement holds:*
If a solution $\varphi(t; x_\circ)$ of (2.9) satisfies $\varphi(t; x_\circ) \in \ker \dot{V} \cap \mathscr{C}_{x_e}$, $t \geq 0$, then this implies that $\varphi(t; x_\circ) \in E_{x_\circ}$ for all $t \geq 0$, where $E_{x_\circ} \subset \mathscr{C}_{x_\circ}$ be the set of equilibria for (2.9).

The following theorem adapts Lyapunov's second method [100] to our context, and state the stability properties induced by the existence of a PWLR Lyapunov function.

Theorem 3.2 (Lyapunov's Second Method)**.** *Given (2.9) with initial condition $x_\circ \in \mathbb{R}^n_+$, and let $\mathscr{C}_{x_\circ}$ be the associated stoichiometric compatibility class. Assume there exists a PWLR Lyapunov function, and suppose that $\varphi(t; x_\circ)$ is bounded,*

1. *then the equilibrium set $E_{x_\circ}$ is Lyapunov stable.*
2. *If, in addition, V satisfies the LaSalle's condition, then $\varphi(t; x_\circ) \to E_{x_\circ}$ as $t \to \infty$ (meaning that $d(\varphi(t; x_\circ), E_{x_\circ}) \to 0$). Furthermore, any isolated equilibrium relative to $\mathscr{C}_{x_\circ}$ is asymptotically stable.*

Proof. Denote $x = \varphi(t; x_\circ)$, and for simplicity let $\varphi(t) = \varphi(t; x_\circ)$. Take the Dini derivative along solutions of (2.9) to get

$$\begin{aligned} D^+V(\varphi(t)) &:= \limsup_{h\to 0^+} \frac{V(\varphi(t+h)) - V(\varphi(t))}{h} = \limsup_{h\to 0^+} \frac{\tilde{V}(R(\varphi(t+h))) - \tilde{V}(R(\varphi(t))}{h} \\ &\overset{(\star)}{=} \limsup_{h\to 0^+} \frac{\tilde{V}(R(x) + h\dot{R}(x))) - \tilde{V}(R(x))}{h} \\ &\leq \max_{k\in K_x} c_k^T \dot{R}(x) = \dot{V}(x) \leq 0. \end{aligned}$$

The equality $(\star)$ follows from application of Taylor's expansion with respect to t using $R(\varphi(t+h)) = R(\varphi(t)) + h\frac{\partial R}{\partial \varphi(t)}\dot{\varphi}(t) + o(h) = R(x) + h\dot{R}(x) + o(h)$ and considering that $\tilde{V}$ is a locally Lipschitz function. The last inequality follows from Lemma 3.1.

Therefore, the claims of Theorem 3.2 follow from the Lyapunov Second's Method and Krasovskii-LaSalle's principle for the stability of equilibrium points and sets [100] since, by assumption, the solution $x(t)$ is bounded, so the ω-limit set $\omega(x(0))$ is non-empty and compact, hence a subset of $\ker \dot{V}$. □

Remark 3.5: For a given stoichiometry matrices A, B, the existence of a PWLR Lyapunov function establishes the stability of all of equilibria for any system within the network family $\mathscr{N}_{A,B}$. Therefore, the Lyapunov function is robust with respect to all kinetic details of the network, and depends only on its graphical structure. It might seem that it is difficult for such function to exist, however, we describe construction algorithms that are valid for wide classes of networks.

Remark 3.6: Note that the PWLR Lyapunov function considered can not be used to establish boundedness, as it may fail to be proper (see §8.1.3). Therefore, we need to resort to other methods to guarantee boundedness a priori. For instance, if the network is conservative, i.e the exists $w \gg 0$ such that $w^T\Gamma = 0$, the stoichiometric compatibility class $\mathscr{C}_{x_\circ}$ is compact and all trajectories are bounded.

Remark 3.7: The LaSalle's condition in Theorem 3.2 can be verified via a graphical algorithm to be described in §3.5.

If the boundedness of all solutions in a certain stoichiometric class is known a priori, then Theorem 3.2 can be strengthened to the following.

Theorem 3.3 (Global Asymptotic Stability)**.** *Consider a GSN that satisfies the LaSalle condition for some PWLR Lyapunov function. Assume that all the trajectories are bounded. If there exists $x^* \in E_{x_\circ}$, which is isolated relative to $\mathscr{C}_{x_\circ}$ then it is unique, i.e., $E_{x_\circ} = \{x^*\}$. Furthermore, it is a globally asymptotically stable equilibrium relative to $\mathscr{C}_{x_\circ}$.*

Proof. Since $x^\star$ is isolated, then it is asymptotically stable as well as $E_{x_\circ}\backslash\{x^\star\}$. Let $\mathcal{B}_{x^*}$ be its basin of attraction, and let $\mathcal{B}_c$ be the basin of attraction of $E_{x_\circ}\backslash\{x^\star\}$. The standard arguments [51] can be replicated to show that $\mathcal{B}_{x^*}$ and $E_{x_\circ}\backslash\{x^\star\}$ are open relative to $\mathscr{C}_{x_\circ}$.

However, as all trajectories starting in $\mathscr{C}^{\circ}_{x_\circ}$ converge to the equilibrium set, this implies that $\mathscr{C}_{x_\circ} = \mathcal{B}_{x^*} \cup \mathcal{B}_c$. Hence, the connected open set $\mathscr{C}_{x_0} \cap \mathbb{R}^n_+$ is a union of two disjoint open sets; a contradiction. Therefore, $E_{x_\circ} = \{x^*\}$ and $\mathcal{B}_{x^*} = \mathscr{C}^{\circ}_{x_\circ}$. □

Remark 3.8: If stoichiometry classes are compact and contain only isolated equilibria, then the claims of the above theorem can be proven alternatively using Poincarè-Hopf Theorem [59] which states that the sum of indices of equilibria equal the Euler characteristic of $\mathscr{C}_{x_\circ}$. A compact stoichiometric class is an intersection of a set hyperplanes with the cone of the positive orthant, which results in a polyhedron. The Euler characteristic of any polyhedron equals 1. Furthermore, the index of an isolated asymptotically stable equilibrium equals one [59, p. 340]. Hence, this imply that there can not be more than one isolated asymptotically stable equilibrium in any compact stoichiometric compatibility class.

Remark 3.9: Theorem 3.3 implies that the existence of two or more isolated equilibria, even if the interior's equilibrium is unique, excludes the possibility of the existence of a PWLR Lyapunov function which satisfies the LaSalle's condition. This is to be contrasted with deficiency-zero theorem [45] where boundary equilibria can be accommodated. This remark is revisited in §4.3.

3.4 Checking Candidate PWLR functions

The first problem we shall tackle is that of checking whether a given PWLR function is a Lyapunov function for a network family $\mathscr{N}_{A,B}$ given by $\Gamma \in \mathbb{R}^{n\times\nu}$. This provides conditions that a PWLR function must satisfy.

3.4.1 Geometry of the Partition Regions

In order to state the conditions properly, two properties of the geometry of the partition regions introduced need to be stated. We claim that for proving the continuity of V it is

enough to test it between *neighbors*, which we define next.

Fix $k \in \{1, .., m/2\}$. Consider H, and 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 $\tilde{H} \in \mathbb{R}^{\tilde{p} \times \nu}$, and let $\tilde{\Sigma}_1, .., \tilde{\Sigma}_m$ be the corresponding signature matrices. Note that (3.4) can be written equivalently as $\mathcal{W}_k = \{r | \tilde{\Sigma}_k \tilde{H} r \geq 0\}$. The *distance* d_r between two regions $\mathcal{W}_k, \mathcal{W}_j$ is defined to be the *Hamming distance* between $\tilde{\Sigma}_k$ and $\tilde{\Sigma}_j$, i.e. it is equal to the number of entries in which the two matrices differ. Hence, the set of neighbors of a region $\mathcal{W}_k$, and the set of neighbor pairs are defined as:

$$\mathcal{N}_k = \{j | d_r(\mathcal{W}_j, \mathcal{W}_k) = 1, j = 1, .., m\},$$
$$\mathcal{N} = \{(j,k) | d_r(\mathcal{W}_j, \mathcal{W}_k) = 1, 1 \leq j, k \leq m\}$$

Equivalently, a neighboring region to $\mathcal{W}_k$ is one which differs only by the switching of one inequality. Denote the index of the switched inequality by the map $s_k(.) : \mathcal{N}_k \to \{1, .., p\}$. For simplicity, we use the notation $s_{k\ell} := s_k(\ell)$.

An important property for the distance function is that for any pair of non-neighboring region, there exists a third region which lies between them in the sense which is stated precisely in the following lemma.

Lemma 3.2. *Let $\tilde{H}$, and $\{\mathcal{W}_k\}_{k=1}^m$ be as above. Assume that $d_r(\mathcal{W}_k, \mathcal{W}_j) = N > 1$, then $\exists \mathcal{W}_\ell, 1 \leq \ell \leq m, \ell \neq k, j$ such that $d_r(\mathcal{W}_k, \mathcal{W}_\ell) + d_r(\mathcal{W}_\ell, \mathcal{W}_j) = N$.*

Proof. We use mathematical induction. Assume that $\tilde{N} = 2$. We can represent $\mathcal{W}_j, \mathcal{W}_k$, w.l.o.g, by the matrices $H_k = [\hat{H}^T \, h_{t_1} \, h_{t_2}]^T, H_j = [\hat{H}^T \, -h_{t_1} \, -h_{t_2}]^T$. For the sake of contradiction, assume there does not exist $\mathcal{W}_\ell$ satisfying the claim. This implies that the regions represented by the matrices $[\hat{H}^T \, h_{t_1} \, -h_{t_2}]^T, [\hat{H}^T \, -h_{t_1} \, h_{t_2}]^T$ have empty interiors. By Farkas Lemma [79], there exists $\xi_1, \xi_2 \in \bar{\mathbb{R}}_+^{\tilde{p}-2}, \xi_{1t_1}, \xi_{2t_2} \in \bar{\mathbb{R}}_+$ with: $h_{t_1}^T = \xi_1^T \hat{H} + \xi_{1t_1} h_{t_2}^T = -(\xi_2^T \hat{H} - \xi_{2t_2} h_{t_2}^T)$. Hence, $(\xi_1 + \xi_2)^T \hat{H} = (\xi_{1t_1} - \xi_{2t_2}) h_2^T$. If $\xi_{1t_1} \neq \xi_{2t_2}$, then either $[\hat{H} \, -h_{t_2}]^T$ or $[\hat{H} \, h_{t_2}]^T$ correspond to a region with empty interior, which is

not true. Thus, $\xi_{1t_1} = \xi_{2t_2}$, which implies $(\xi_1 + \xi_2)^T \hat{H} = 0$. Since $\mathcal{W}_j^\circ, \mathcal{W}_k^\circ \neq \varnothing$, then $\xi_1 = \xi_2 = 0$. Thus, we get $h_{t_1} = \xi_{1t_1} h_{t_2}$, which contradicts our assumption that $\tilde{H}$ does not have linearly dependent row pairs. Therefore, the statement is true for $N = 2$.
Assume now that the statement is true for $\tilde{N} = N-1$, and let $\tilde{N} = N$. We can represent $\mathcal{W}_j$ and $\mathcal{W}_k$, w.l.o.g, by the matrices $H_k = [(\hat{\Sigma}_k \hat{H})^T \, h_{t_1} \, .. \, h_{t_N}]^T, H_j = [(\hat{\Sigma}_k \hat{H})^T \, .. \, -h_{t_1} \, -h_{t_N}]^T$. Let $\mathcal{W}_k^-, \mathcal{W}_j^-$ be the regions corresponding to the matrices $H_k^- = [(\hat{\Sigma}_k \hat{H})^T \, h_{t_1} \, .. \, h_{t_{N-1}}]^T, H_j^- = [(\hat{\Sigma}_k \hat{H})^T \, .. \, -h_{t_1} \, -h_{t_{N-1}}]^T$. By the induction hypothesis, $\exists \mathcal{W}_\ell^-$ satisfying the claim. Moreover, either $\mathcal{W}_\ell^- \cap \{r | h_N r \geq 0\}$,$\mathcal{W}_\ell^- \cap \{r | h_N r \leq 0\}$ or both have a nonempty interior. Let $\mathcal{W}_\ell$ be a nonempty one. Thus, $\mathcal{W}_\ell$ satisfies the claim. □

Before proceeding, the notion of a conic basis needs to be defined. A conic basis for $\mathcal{W}_k$ is a set of vectors $\{v_1, .., v_s\} \subset \mathcal{W}_k$ such that:

1. it is *conically independent*, this means that there does not exist $a = [a_1, .., a_s]^T, a > 0$ such that $\sum_{i=1}^s a_i v_i = 0$.

2. it has a *full conic span*, that is for any $v \in \mathcal{W}_k$, $\exists a = [a_1, .., a_s]^T, a \geq 0$ such that $v = \sum_{i=1}^s a_i v_i$.

A second property that for every region $\mathcal{W}_k$, a conic basis can be found via the notion of neighboring regions as the following lemma states.

Lemma 3.3. *Let H, and $\{\mathcal{W}\}_{k=1}^m$ be as above. Denote $o_k = |\mathcal{N}_k|$. Then a conic basis of $\mathcal{W}_k$ is given by the set $\{\sigma_{ks_{k\ell_1}} h_{s_{k\ell_1}}, ..., \sigma_{ks_{k\ell_{o_k}}} h_{s_{k\ell_{o_k}}}\}$.*

Proof. In order to show conic independence, let $\sigma_s h_s$ with $s \in s_k^{-1}(\mathcal{N}_k)$, hence $\sigma_s h_s$ is a row of $\Sigma_k H$. $\sigma_s h_s$ is conically independent of the rest of rows of $\Sigma_k H$, and to show this assume the contrary. Then the region where $\sigma_s h_s$ is replaced with $-\sigma_s h_s$ has empty interior which implies it is not a neighboring region; a contradiction.
It remains to be shown that the rows of $\Sigma_k H$ belong to the conic span of the given set. Assume, w.l.o.g, that $\Sigma_k H = [\hat{H}^T \, h_{t_1} \, h_{t_2}]^T$, where h_{t_1}, h_{t_2} are not conically independent,

and we need to show that they belong to the conic span of the rows of $\hat{H}$. Then by Farkas Lemma $\exists \xi_1, \xi_2 \in \bar{\mathbb{R}}_+^{p-2}, \xi_{1t_1}, \xi_{2t_2} \in \bar{\mathbb{R}}_+$ with: $h_{t_1}^T = \xi_1^T \hat{H} + \xi_{1t_1} h_{t_2}, h_{t_2}^T = \xi_2^T \hat{H} + \xi_{2t_2} h_{t_1}^T$. By substitution, we get $(1 - \xi_{1t_1}\xi_{2t_2}) h_{t_2}^T = (\xi_2 + \xi_{2t_2}\xi_1)^T \hat{H}$. If $1 - \xi_{1t_1}\xi_{2t_2} \leq 0$, then this contradicts the fact that $\mathcal{W}_k$ has nonempty interior. Therefore, the only possibility is $1 - \xi_{1t_1}\xi_{2t_2} > 0$, which proves the claim for two vectors. In general, this procedure can be applied to eliminate all conically dependent rows. □

3.4.2 Candidate Continuous PWLR Lyapunov Functions

In this subsection, we are given a candidate V which is represented by the pair $C \in \mathbb{R}^{m/2 \times \nu}, H \in \mathbb{R}^{p \times \nu}$ as in (3.5).

Let $c_k^T = [c_{k1} \,..\, c_{k\nu}]$, and let $J_k = \text{supp}(c_k) \subset \{1, .., \nu\}$ be the set of indices of reactions appearing in c_k. Define the set of indices of reactants of J_k as follows

$$I_k = \{1 \leq i \leq n | \exists j \in J_k \,\text{such that}\, (X_i, \mathbf{R}_j) \in E\}. \tag{3.10}$$

Also, for all $i \in I_k$, define $J_{ki} = \{j \in J_k | (X_i, \mathbf{R}_j) \in E\}$, which is the set of reactions in J_k that has X_i as a reactant.

We are now ready to state the following theorem.

Theorem 3.4. *Let $A, B \in \mathbb{R}^{n \times \nu}$, and $C \in \mathbb{R}^{m/2 \times \nu}$ be given. Let $\tilde{V}$ be given by (3.5). Then $V(x) = \tilde{V}(R(x))$ is a PWLR Lyapunov function for the network family $\mathscr{N}_{A,B}$ if and only if the following conditions hold.*

C1. Nonnegativity: *For all $1 \leq k \leq m/2$, there exists $\xi_k \in \mathbb{R}^p$ with $\xi_k > 0$ such that $c_k^T = \xi_k^T \Sigma_k H$.*

C2. Positive-Definiteness: $\ker C = \ker \Gamma$.

C3. Continuity: *For all* $(k,j) \in \mathcal{N}$, $\exists \eta_{kj} \in \mathbb{R}$ *such that*

$$c_k - c_j = \eta_{kj} h_{s_{kj}}. \tag{3.11}$$

C4. Nonincreasingness: *The following holds simultaneously.*

a) For all $k = 1,..,m/2$, $i \in I_k$, $sgn(c_{kj_1})\, sgn(c_{kj_2}) \geq 0$ *for every* $j_1, j_2 \in J_{ki}$. *Denote* $\nu_{ki} = sgn(c_{kj}), j \in J_{ki}$.

b) there exists $\lambda^{(ki)} \in \mathbb{R}^p$, *with* $\lambda^{(ki)} \geq 0$ *such that*

$$-\nu_{ki}\gamma_i^T = {\lambda^{(ki)}}^T \Sigma_k H, \tag{3.12}$$

where $c_k := -c_{m+1-k}$ *for* $j = 1 + m/2,..,m$. *Furthermore, if* (3.12) *is satisfied, we choose* $\lambda^{(ki)}$ *so that* $\operatorname{supp}(\lambda^{(ki)}) \subset s_k(\mathcal{N}_k)$.

Moreover, $\tilde{V}$ *is convex if and only if the* η_{kj}*'s can be chosen so that* $\eta_{kj}\sigma_{ks_{kj}} \geq 0$.

Proof. We show that each condition is equivalent to a required property for the Lyapunov function:

C1: Nonnegativity: The inequality $V(x) \geq 0$ holds if and only if $c_k^T r \geq 0$ whenever $\Sigma_k H r \geq 0, r \geq 0$. By Farkas Lemma [79], this is equivalent to the existence of $\xi_k, e_k \in \mathbb{R}^\nu, [\xi_k^T, e_k^T] > 0, k = 1,..,m/2$ so that $c_k = \xi_k^T \Sigma_k H + e_k^T$. We show that $e_k = 0$. Note that by symmetry we have $-c_k = c_{-k} = -\xi_{-k}^T \Sigma_k H + e_{-k}^T$ with $[\xi_{-k}^T, e_{-k}^T] > 0$. Since there exists $v \in \ker \Gamma = \ker H$ with $v \gg 0$, we have $c_k^T v = e_k^T v \geq 0$, and $c_k^T v = -e_{-k}^T v \leq 0$. This implies $e_k = 0$.

C2: Positive-Definiteness: Let $R(x) \in \ker C$ be arbitrary, we see that $V(x) = 0$ and therefore, by definition of PWLR Lyapunov function, $R(x) \in \ker \Gamma$. Thus, $\ker C \subset \ker \Gamma$. To show the converse statement, note that C1 implies that $\ker H \subset \ker C$. However, we have assumed that $\ker H = \ker \Gamma$ and we have shown that $\ker C \subset \ker \Gamma$. Hence,

$\ker C = \ker \Gamma$. Hence, the statement "$V(x) = 0$ iff x is an equilibrium" is equivalent to $\ker C = \ker \Gamma$.

C3: Continuity: Suppose $\tilde{V}$ is continuous, and let $(k, j) \in \mathcal{N}$, i.e. $\mathcal{W}_k$ and $\mathcal{W}_j$ are neighboring regions. Then $c_k^T r = c_j^T r$ whenever $r \in \partial\mathcal{W}_k \cap \partial\mathcal{W}_j = \{r | h_{s_{kj}}^T r = 0\}$. Hence, $(c_k - c_j) \in \mathrm{Im}(h_{s_{kj}})$, which implies (3.11).

Assume now that the converse is true. We need to show that $c_k^T r = c_j^T r$ whenever $r \in \partial\mathcal{W}_k \cap \partial\mathcal{W}_j$. The statement is true when $d_r(\mathcal{W}_k, \mathcal{W}_j) = 1$ by (3.11). Thus, we show it when $d_r(\mathcal{W}_k, \mathcal{W}_j) > 1$. We can write $\partial\mathcal{W}_k \cap \partial\mathcal{W}_\ell = \{r | [h_{t_1}^T .. h_{t_N}^T] r \geq 0\}$. By Lemma 3.2, it can be seen that for any $\mathcal{W}_{k_1}$ and $\mathcal{W}_{k_N}$ with $d(\mathcal{W}_{k_1}, \mathcal{W}_{k_N}) = N$ there exists a sequence of regions $\mathcal{W}_{k_2}, .., \mathcal{W}_{k_{N-1}}$ so that $d_r(\mathcal{W}_{k_\ell}, \mathcal{W}_{k_{\ell+1}}) = 1$ and $s_{k_\ell}(k_{\ell+1}) = h_{t_\ell}$. Hence:

$$c_{k_N} - c_{k_1} = \sum_{\ell=1}^{N} (c_{k_{\ell+1}} - c_{k_\ell}) = \sum_{\ell=1}^{N} \eta_{k_{\ell+1} k_\ell} h_{t_\ell},$$

which implies $(c_{k_N} - c_{k_1})^T r = 0$ when $r \in \partial\mathcal{W}_{k_1} \cap \partial W_{k_N}$.

C4: Nonincreasingness: We prove the nonpositivity of sign of the time-derivative in the interior of partition regions. The nonpositivity on the boundaries follows from Lemma 3.1. Hence, assume $R(x) \in \mathcal{W}_k^\circ$, we can write:

$$\begin{aligned} \dot{V}(x) = c_k^T \dot{R}(x) &= c_k^T \frac{\partial R}{\partial x}(x) \Gamma R(x) \\ &= \sum_{i \in I_k} \sum_{j \in J_{ki}} c_{kj} \frac{\partial R_j}{\partial x_i} \dot{x}_i \leq 0. \end{aligned} \tag{3.13}$$

We claim that this is equivalent to the statement "$c_{kj} \dot{x}_i \leq 0$ whenever $R(x) \in \mathcal{W}_k$, for all $j \in J_{ki}, i \in I_k, k = 1, .., m/2$". Since the sufficiency is clear, we just show necessity: assume that there exists $j^* \in J_{ki}, i^* \in I_k, 1 \leq k^* \leq m/2$ so that $c_{k^* j^*} \dot{x}_i^* \geq 0$. Then, we can choose $(\partial R_{j^*} / \partial x_{i^*})(x)$ large enough so that the corresponding system in the network family $\mathscr{N}_{A,B}$ has $\dot{V}(x) \geq 0$.

Now we show equivalence with conditions a)-b). Considering the statement above and

since R is monotone, this entails that $\operatorname{sgn}(c_{kj_1})\operatorname{sgn}(c_{kj_2}) \geq 0$ for every $j_1, j_2 \in J_{ki}$, which shows condition a). Thus, we define $\nu_{ki} = \operatorname{sgn}(c_{kj^*}), j^* \in J_{ki}$. To show b), by Farkas Lemma, the condition is equivalent to the existence of $\lambda^{(ki)} \in \bar{\mathbb{R}}^n_+$, $i \in I_k, k = 1, .., m/2$ so that (3.12) holds.

It remains to show that we can choose the coefficients so that $\operatorname{supp}(\lambda^{(ki)}) \subset s_k(\mathcal{N}_k)$. This follows directly from Lemma 3.3.

□

Remark 3.10: Note that C2 amounts to linear system solving, while C1,C3-C4 are equivalent to linear programming feasibility problems.

Remark 3.11: An equivalent characterization of C4 is stated in Theorem 4.2.

3.4.3 Checking candidate convex PWLR functions

The conditions in the previous subsection are simplified in the case of convex PWLR functions, as it can be noted that C1, C3 are automatically satisfied. Consider V with $\tilde{V}$ given by (3.6) with $\Gamma \in \mathbb{R}^{n\times\nu}$, and $C \in \mathbb{R}^{m/2\times\nu}$ given.

Theorem 3.5. *Let $A, B \in \mathbb{R}^{n\times\nu}$, and $C \in \mathbb{R}^{m/2\times\nu}$ be given. Then $V(x) = \|CR(x)\|_\infty$ is a PWLR Lyapunov function for the network family $\mathcal{N}_{A,B}$ if and only if the following two conditions hold.*

C2′. Positive-Definiteness: $\ker C = \ker \Gamma$.

C4′. Nonincreasingness: *The following holds simultaneously.*

a) For all $k = 1, .., m/2$, $i \in I_k$. We require $sgn(c_{kj_1})\, sgn(c_{kj_2}) \geq 0$ for every $j_1, j_2 \in J_{ki}$. Denote $\nu_{ki} = sgn(c_{kj}), j \in J_{ki}$.

b) there exists $\lambda^{(ki)} \in \mathbb{R}^m$, with $\lambda^{(ki)} \geq 0$ such that

$$-\nu_{ki}\gamma_i^T = \sum_{\ell=1,\ell\neq k}^{m} \lambda_\ell^{(ki)}(c_k - c_\ell)^T, \tag{3.14}$$

where $c_k := -c_{m+1-k}$ *for* $j = 1 + m/2, .., m$. *Furthermore, if* (3.12) *is satisfied, we choose* $\lambda^{(ki)}$ *with minimal support.*

Proof. The converse direction of C2′ can be shown directly since if $c_k^T R = 0$, and convexity implies that $c_k^T R = 0, k = 1, .., m$. Hence $\ker \Gamma \subset \ker C$. C4′ can be shown via a similar argument to the previous proof. □

3.5 The LaSalle's Condition

In this section we provide graphical algorithms for checking the LaSalle's condition stated in Theorem 3.2. Assume that a PWLR Lyapunov function exists. We use the same notation used in the previous two sections. Consider (3.12) with $\lambda^{(ki)}$ chosen so that $\text{supp}(\lambda^{(ki)}) \subset s_k(\mathcal{N}_k)$. Let $L_{ki} = s_k^{-1}(\text{supp}(\lambda^{(ki)}))$, which is nonempty since the LHS in (3.12) is nonzero. Let $L_k = \bigcup_{i \in I_k} L_{ki}$, $I_k^{(0)} := I_k$, and $L_k^{(0)} := L_k$. Define iteratively the nested sets:

$$I_k^{(i)} = \bigcup_{\ell \in L_k^{(i-1)}} I_\ell, \text{ and } L_k^{(i)} = \bigcup_{\ell \in L_k^{(i-1)}} L_\ell.$$

The iteration terminates when $L_k^{(i^*)} = L_k^{(i^*+1)}$. The iteration can not continue indefinitely since for any i $L_k^{(i)} \subset \{1, .., m\}$ which is finite. Denote $\bar{I}_k := I_k^{(i^*)}$. Using this notation, we state the following condition which we call the LaSalle's interior condition:

C5i. For all $k \in \{1, .., m\}$, $\bar{I}_k = \{1, .., n\}$ holds.

In a nutshell the iterative process can be explained as follows: for every k, our aim is to show that $\dot{x} = 0$ follows from the equality $c_k^T \dot{R}(x) = 0$. Starting from the last equality, we get that the time derivative of species in I_k vanish. Using (3.11) and (3.12), this implies that $c_\ell^T \dot{R}(x) = 0$ for all $\ell \in L_k$. Using this procedure iteratively, we can expand the set of re reactants of which their derivative needs to vanish. If the final set $\bar{I}_k$ is the whole set of species then this ensures that $\dot{x} = \Gamma R(x) = 0$.

If the function $\tilde{V}$ is also convex, then the LaSalle's interior condition can be relaxed to:

C5′i. For all k, $c_k \in \mathrm{Im}(\Gamma_{\bar{I}_k}^T)$, where $\Gamma_{\bar{I}_k} = [\gamma_{i_1}^T .. \gamma_{i_{o_k}}^T]^T, \bar{I}_k = \{i_1, .., i_{o_k}\}$ for some o_k.

Remark 3.12: If the condition required by C5′i is satisfied before the iterative process ends, then there is no need to continue it.

Remark 3.13: As will be shown in the proof of Proposition 3.6, conditions C5i and C5′i guarantee the LaSalle condition only provided $\tilde{x}(0) \in \mathbb{R}_+^n$, which explains the adding the adjective "interior" to the name of the condition. The LaSalle's interior condition alone can only establish the asymptotic stability of isolated equilibria in the relative interior of $\mathscr{C}_{x_0}$. In this case, Theorem 3.3 does not hold, since solutions could in principle approach the boundary. However, if the persistence of the network can be verified a priori, for example by the absence of critical siphons as was discussed in §2.3.1, then the LaSalle's interior condition is sufficient to establish the result of Theorem 3.3.

In order to strengthen the LaSalle's interior condition so that it applies to the boundary of stoichiometric compatibility classes, we use the notion of *critical siphons* defined in §2.1.2. Using Lemma 2.2, a face Ψ of a stoichiometric compatibility class is invariant if and only if there exists a siphon P such that $\Psi = \{x \in \mathscr{C}_{x_\circ} | X_i \in P \Rightarrow x_i = 0\}$. Since invariant faces arising from noncritical siphons correspond to independent stoichiometric compatibility classes, we consider only critical siphons. Let $\mathscr{N}_{A,B}$ be a given network, and P_ℓ be a critical siphon. We define the corresponding *critical subnetwork* $\mathscr{N}_{A_\ell,B_\ell}$ as a network with $\mathbf{V}_{R_\ell} = \mathbf{V}_R \backslash \Lambda(P_\ell)$, and $x_i(0) = 0$ for $X_i \in P_\ell$. Furthermore, critical subnetworks of $\mathscr{N}_{A_\ell,B_\ell}$ are considered to be critical subnetworks of $\mathscr{N}_{A,B}$.
We are now ready to state the LaSalle's condition.

Theorem 3.6 (LaSalle's Condition)**.** *Let $\mathscr{N}_{A,B}$ be a network with a given PWLR Lyapunov function V. The network satisfies the LaSalle condition stated in Definition 3.6 if the following condition holds.*

C5. *The condition C5i (or C′5i if $\tilde{V}$ is convex) is satisfied for $\mathscr{N}_{A,B}$ and all its critical subnetworks.*

Proof. Let $\tilde{x}(t)$, where $t \in$ a maximally defined interval, denote any solution of (2.9) which is contained in $\ker(\dot{V}(x))$. Consider first the case when $\tilde{x}(0) \in \mathbb{R}^+_n$. Let $\mathcal{T}_k = \{t > 0 : c_k^T R(\tilde{x}(t)) = V(\tilde{x}(t))\}$, $k = 1, .., m$, then $\mathcal{T}_k$ are closed relative to some maximally defined interval in which the solution $\tilde{x}$ exists, and $\bigcup_k \mathcal{T}_k = (0, \tau_{x_\circ})$. The existence of an open set $\mathcal{T}$ and $k^\star$ such that $V(\tilde{x}(t)) = c_{k^\star}^T R(\tilde{x}(t))$ for all $t \in \mathcal{T}$ follows by the Baire Category Theorem [81] . By C4, $c_{k^\star}^T \dot{R}(\tilde{x}(t)) = 0$ identically for $t \in \mathcal{T}$ implies $\dot{R}_j(\tilde{x}(t)) = 0$, for all $t \in \mathcal{T}$ and $j \in J_{k^\star}$. Then, by A4, we have $\dot{\tilde{x}}_i(t) = 0$ identically for $t \in \mathcal{T}$ and all $i \in I_{k^\star}$. Using (3.12), $h_i^T R(\tilde{x}(t)) = 0$ for $t \in \mathcal{T}$ and all $i \in \mathrm{supp}(\lambda^{(k^\star i)})$. By (3.11), $c_j^T R(\tilde{x}(t)) = c_{k^\star}^T R(\tilde{x}(t))$ and $\tilde{x}(t) \in \mathcal{W}_j$ for all $j \in L_{k^\star i}$ and all $t \in \mathcal{T}$. Hence, $c_j^T \dot{R}(\tilde{x}(t)) = 0, j \in L_{k^\star}$. Iterating this procedure, we get $c_j^T \dot{R}(\tilde{x}(t)) = 0$ for all $j \in L_k^{(i^\star)}$ and accordingly, $\dot{\tilde{x}}_i(t) = 0$ for all $i \in \bar{I}_{k^\star} = \{1, .., n\}$. Hence $\tilde{x}(t)$ is a constant solution and belongs to the set of equilibria.

An additional comment is needed for C5′i. If $c_k \in \mathrm{Im}(\Gamma_{\bar{I}_k}^T)$, then $c_k^T R(\tilde{x}(t)) = 0$. By convexity, this implies that $V(\tilde{x}(t)) = 0$, and hence $\tilde{x}(t) \in E$.

Assume now that $\tilde{x}(0)$ belongs to a non-invariant face of $\mathscr{C}_{x_\circ}$, then $\tilde{x}(t) \in \mathbb{R}^n_+$ for $t > 0$ and hence the argument of the previous case still applies. Finally, if $\tilde{x}(0)$ belongs to a closed invariant face Ψ_P we may regard the solution $\tilde{x}(t)$ as a solution of the subnetwork obtained by deleting all species that are zeroed in Ψ_P and removing all their associated output reactions.

Then, with a recursive argument, three cases arise, either $\tilde{x}(0)$ belongs to the interior of the stoichiometry class associated to the subnetwork, or it belongs to one of its non-invariant face or it belongs to an invariant face. Since we assumed that C5i applies to each critical subnetwork and in turn subnetworks of subnetworks are regarded as subnetworks themselves, we can continue this recursive procedure to show that $\tilde{x}(t) \in E_{x_\circ}$ for any initial condition $\tilde{x}(0) \in \mathscr{C}_{x_\circ}$. □

Chapter 4

Properties of Graphically Stable Networks

As it is difficult to characterize exactly GSNs, i.e. the class of CRNs which admit a PWLR Lyapunov function, it is desirable to derive conditions which are necessary for a network to be graphically stable. In this chapter several strong remarkable properties of this class of networks is established.

4.1 Existence of Convex PWLR Functions

It has been noted in the previous chapter that convex PWLR Lyapunov functions are easier to check and have stronger properties, therefore it is natural to ask whether the use of nonconvex counterparts is less conservative. In the case of linear systems, it is known that the existence of a nonconvex Lyapunov function implies existence of a convex counterpart [26]. Despite the nonlinear nature of our problem, the next theorem shows that a similar result holds in our context. To this end, we need to derive alternative representation and characterizations of the conditions which were given in the last chapter.

4.1.1 Set-Based Representation of the PWLR function

Let $V(x) = \tilde{V}(R(x))$ be a PWLR function, and denote its polyhedral level set by $G = \{r \in \mathbb{R}^\nu | \tilde{V}(r) \leq 1\}$. By homogeneity and nonnegativity of $\tilde{V}$ we can write

$$\tilde{V}(r) = \inf_{r \in cG} c. \tag{4.1}$$

Note that $\tilde{V}$ would be a Minkowski functional if G were convex. As the level set G characterizes $\tilde{V}$ fully, we want to express C4 for the set G. To that end, we use the notion of *tangent cone*, which we define as follows for a polyhedral set G induced by a PWL function $\tilde{V}$ at a point r: $T_r G := \bigcap_{k \in K_r} \{z \in \mathbb{R}^\nu | c_k^T z \leq 0\}$, where $K_r = \{k \in \{1, .., m\} | r \in \mathcal{W}_k\}$. In fact, our definition of $T_r G$ coincides with *Clarke's Tangent Cone* [33]. We state now the following Lemma.

Lemma 4.1. *Given a polyhedral set $G \subset \mathbb{R}^\nu$. Let $\tilde{V}$ be given by* (4.1)*. Then, $\tilde{V}(R(x))$ satisfies C4 if and only if $\frac{\partial R}{\partial x} \Gamma r \in T_r G$ for all $R \in \mathscr{K}_A$.*

Proof. Note that the condition $\frac{\partial R}{\partial x} \Gamma r \in T_r r$ is equivalent to the requirement that $c_k^T \frac{\partial R}{\partial x} \Gamma r \leq 0$ for all $k \in K_r$ and all admissible $\partial R / \partial x$, i.e., Jacobian matrices satisfying the zero sign-pattern explained in Remark 2.4. This is equivalent to C4 as can be noted from the proof of Theorem 3.4 and (3.13). □

Consider a possibly nonconvex PWLR function V, and let G be defined as above. We need the following lemma to proceed.

Lemma 4.2. *Let $r_1, r_2 \in G, \alpha \in [0, 1]$. Denote $r = \alpha r_1 + (1 - \alpha) r_2 \in co(G)$. Then, $T_{r_1} G \oplus T_{r_2} G \subset T_r\, co(G)$, where $\oplus$ denotes the conic addition of sets.*

Proof. Let $z_1 \in T_{r_1} G$, $z_2 \in T_{r_2} G$, and $h_n \searrow 0$. By the definition of Clarke's tangent cone [33], there exists $z_{1n} \to z_1, z_{2n} \to z_2$ such that $r_1 + h_n z_{1n}, r_2 + h_n z_{2n} \in G$. Let $z = \alpha z_1 + (1 - \alpha) z_2$, and $z_n = \alpha z_{1n} + (1 - \alpha) z_{2n} \to z$. Then, we have $r + h_n z_n \in \mathrm{co}(G)$.

Let $r_n = r + h_n z_n \to r$. Thus, $\frac{1}{h_n}(r_n - r) \to z$. Hence, $z \in T_r^{(B)} \operatorname{co}(G)$, where B denotes the Bouligand's tangent cone [33]. However, as the two cones are identical for convex sets, then $z \in T_r \operatorname{co}(G)$. The argument can be applied to any nonnegative combination with appropriate scaling of h_{1n}, h_{2n}. □

4.1.2 The Result

The main existence result can be stated as follows.

Theorem 4.1. *Let* Γ *and* (2.9) *be given, with the corresponding kinetics* $\mathscr{K}_A$*. If there exists a continuous PWLR Lyapunov function then there exists a convex counterpart of the form* (3.6)*.*

Proof. Let G be defined as in the last subsection. Let $r \in \operatorname{co}(G)$. Hence, there exist r_1, r_2 and $\alpha \in [0,1]$ such that $r = \alpha r_1 + (1-\alpha) r_2$. Therefore, we can write:

$$\tfrac{\partial R}{\partial x}\Gamma r = \alpha \tfrac{\partial R}{\partial x}\Gamma r_1 + (1-\alpha)\tfrac{\partial R}{\partial x}\Gamma r_2, \tag{4.2}$$

for all admissible $\partial R/\partial x$. By Lemma 4.1, $\frac{\partial R}{\partial x}\Gamma r_1 \in T_{r_1} G$, $\frac{\partial R}{\partial x}\Gamma r_2 \in T_{r_2} G$ for all admissible $\partial R/\partial x$. Therefore, Lemma 4.2 implies that $\frac{\partial R}{\partial x}\Gamma r \in T_r \operatorname{co}(G)$ for all admissible $\partial R/\partial x$. Therefore, $V(x) = \inf_{R(x) \in r \operatorname{co}(G)} r$ is a convex PWLR function. □

Remark 4.1: The restrictions imposed on the kernel of H in Definition 3.4 are not needed to prove Theorem 4.1.

4.2 Constraints on Admissible Sign Patterns

In this section we show that there is a set of sign constraints that every PWLR Lyapunov function needs to satisfy. These constraints allow to devise algorithms to construct PWLR Lyapunov functions. Furthermore, these conditions can be checked a priori to decide whether a certain network belongs to the set of GSNs, or otherwise.

Recall from Definition 3.5 that the Lyapunov function needs to be decreasing along the system trajectories for all $R \in \mathscr{K}_A$. Furthermore, it was previously noted in the proof of Theorem 3.4, the nonpositivity of every term in the expansion of $\dot{V}$ (3.13) is needed, and the sign of the derivative depends on the sign of $\dot{x}$. Hence, we partition $\mathbb{R}^\nu$ into *sign regions* within which $\dot{x}$ has a constant term-wise sign. By Assumption AS1, we can define sign regions in an analogous way to §2.1, where we set $H = \Gamma$. Thus, we may write

$$\mathcal{S}_k = \{r \in \mathbb{R}^\nu : \Sigma_k \Gamma r \geq 0\},\ k = 1, .., m. \tag{4.3}$$

Note that the signature matrix Σ_k specifies the sign of $\dot{x}$ in the region $\mathcal{S}_k$.

As a result, any linear-in-rates component $c_k^T R(x)$ operating on $\mathcal{S}_k$ must satisfy the term-wise sign constraint noted in (3.13). To encode this, we need further notation. Define the diagonal matrices $B_k = \text{diag}[b_{k1} \ldots b_{k\nu}]$, $k = 1, .., m_s/2$, where:

$$b_{kj} = \begin{cases} \infty, & \text{if } M_j = \varnothing \\ 0, & \text{if } \exists i_1, i_2 \in M_j \text{ such that } \sigma_{ki_1}\sigma_{ki_2} < 0, \\ -\sigma_{ji^*}, & \text{otherwise, for any } i^* \in M_j. \end{cases} \tag{4.4}$$

Assume now that the PWLR function has been defined on some partition $\{\hat{\mathcal{W}}_k\}_{k=1}^{m_h}$. If we intersect the two partitions $\{\hat{\mathcal{W}}_k\}_{k=1}^{m_h}$ and $\{\mathcal{S}_k\}_{k=1}^{m_s}$. Then the linear function defined in each region in the new partition is inherited from $\{\hat{\mathcal{W}}_k\}$. The matrix generating the new partition can be written as $H = [\Gamma^T \hat{H}^T]^T$. Therefore, we may consider, w.l.o.g, partitions $\{\mathcal{W}_k\}_{k=1}^{m}$ induced by matrices of the form $H = [\Gamma^T \hat{H}^T]^T$, with corresponding sign matrices $\Sigma_k = \text{diag}[\Sigma_k^{(s)}\ \Sigma_k^{(h)}]$. Note that we can consider $\{\mathcal{W}_k\}_{k=1}^{m}$ as a refined partition of $\{\mathcal{S}_k\}_{k=1}^{m_s}$, hence the map $q(.) : k \mapsto \ell$ if $\mathcal{W}_k \subset \mathcal{S}_\ell$ can be defined, and the notation $q(k) = q_k$ is used.

The following theorem can be stated.

Theorem 4.2 (Sign Condition)**.** *Given a PWLR function V defined by* (3.5)*. The function satisfies C4 if and only if the coefficient vectors $c_k, k = 1, ..., m$ satisfy for $\ell \in \{1, .., n\} \backslash \mathcal{I}$,*

the following equality and inequality constraints:

$$\begin{cases} c_{kj} = 0 & \text{if } b_{q_kj} = 0 \\ c_{kj} b_{q_kj} \geq 0 & \text{if } 0 < |b_{q_kj}| < \infty \end{cases} \tag{4.5}$$

Proof. Consider the expression of $\dot{V}$ in the region $\mathcal{W}_k$, which is:

$$\dot{V}(x) = \sum_{i \in I_k} \sum_{j \in J_k} c_{kj} \frac{\partial R_j}{\partial x_i} \dot{x}_i.$$

By the construction explained above, the signs of $\dot{x}_1, .., \dot{x}_n$ are constant in $\mathcal{W}_k$. If $b_{q_kj} = 0$, then this implies that $\mathbf{R}_j$ has two reactants $\dot{x}_{i_1}, \dot{x}_{i_n}$ each with different sign. Therefore, setting $c_{kj} = 0$ is sufficient. It is also necessary since if $c_{kj} \neq 0$ we can choose $(\partial R_j / \partial x_{i_1})$ and $(\partial R_j / \partial x_{i_2})$ to yield a term that has a positive sign in the expansion above, and it can be made large enough to dominate the others.

If $b_{q_kj} > 0$, then this implies that $\dot{x}_i < 0$ for all $i \in J_{ki}$. setting $c_{kj} \geq 0$ is sufficient. It is also necessary because if there exists i such that $x_i > 0$, then the corresponding partial derivative can be chosen large enough to render $\dot{V}$ positive. A similar argument can used for the case $b_{q_kj} < 0$. □

4.2.1 A Necessary Condition

Recall that condition C2 in Theorem 3.4 implies that any PWLR Lyapunov function would satisfy $\ker C = \ker \Gamma$. Furthermore, $\ker \Gamma$ contains a positive vector by assumption AS1. Combining these facts with the sign characterization above gives any easily-checkable necessary condition to preclude that a given network is GS. Informally, for each sign pattern vector b_k it is necessary that there exists some vector c_k that has the same sign-pattern and that it is orthogonal to $\ker \Gamma$. This is stated in the following theorem.

Theorem 4.3. *Given stoichiometry matrices A, B. Consider the network family $\mathcal{N}_{A,B}$, with $\{B_k\}_{k=1}^m$ defined as above, and let U be a matrix the columns of which form a basis*

for $\ker\Gamma$. *If* $\mathscr{N}_{A,B}$ *admits a PWLR Lyapunov function, then there exists* $0 \neq \zeta_k \in \mathbb{R}^\nu, k = 1,..,m/2$ *such that* $\zeta_k^T B_k U = 0$, *with* $\zeta_{kj} \geq 0, j \in \{1,..,\nu\}\backslash\mathcal{I}$.

Proof. Assume that there exists a pair $C \in \mathbb{R}^{m_h/2\times\nu}, H \in \mathbb{R}^{p\times\nu}$ such that $\tilde{V}$ in (3.5) is a PWLR Lyapunov function, and let $\{B_k\}_{k=1}^m$ be as defined in Theorem. Since $\{\mathcal{S}_\ell\}_{\ell=1}^{m_s}$ is a partition, then $\forall k \in \{1,..,m\}, \exists \ell \in \{1,..,m_s\}$ such that $\mathcal{W}_k^\circ \cap \mathcal{S}_{q_k}^\circ \neq \varnothing$. As in the proof of Theorem 3.4, C4 is equivalent to requiring $c_{kj}\dot{x}_i \leq 0$, whenever $R(x) \in \mathcal{W}_k$, for all $j \in J_{ki}, i \in I_k, =_{\tau}1,..,m$. Hence, $c_{kj} = |c_{kj}|b_{q_kj}, j \in \{1,..,\nu\}\backslash\mathcal{I}$. Therefore, $\exists\zeta_k \in \mathbb{R}^\nu$ such that $c_k = \zeta_k^T B_{q_k}$, with $\zeta_k \neq 0, \zeta_{kj} \geq 0, j \in \{1,..,\nu\}\backslash\mathcal{I}$. Furthermore, since $\ker C = \ker\Gamma$, then $\zeta_k^T B_{q_k} U = 0$. □

4.3 Injectivity of Graphically Stable Networks

4.3.1 Jacobians of GSNs are P_0

We have shown in Theorem 3.3 that GS networks with bounded trajectories and satisfying the LaSalle's condition can not have multiple isolated stoichiometrically compatible equilibria. In this subsection we present a result along these lines by showing that the Jacobian matrix of GSNs satisfies a property that has strong implications on uniqueness of equilibria and the injectivity of the map $F(x) = \Gamma R(x)$.

In order to introduce the relevant result we need to define some notation.

Definition 4.1. *Let* $J \in \mathbb{R}^{n\times n}$. J *is said to be a* P *matrix if all its principal minors are positive, and is said to be* P_0 *if all its principal minors are nonnegative.*

Note that the class of P matrices encompasses M-matrices as a subclass.

The following characterization of P_0 matrices is central to our next result, therefore it is stated first.

Lemma 4.3 ([25], p. 149)**.** *A matrix* $J \in \mathbb{R}^{n\times n}$ *is* P_0 *if and only if for every signature matrix* $\Sigma_k, k = 1,...,2^n$, *there exists* $\xi_k > 0$ *such that* $\xi_k^T \Sigma_k J \Sigma_k \geq 0$.

We are ready to state and prove the main result.

Theorem 4.4. *Given a stoichiometry matrices A, B. If $\mathscr{N}_{A,B}$ is GS, then the Jacobian $-\Gamma\frac{\partial R}{\partial x}(x)$ is a P_0 matrix for all x, and for all $R \in \mathscr{K}_A$.*

Proof. Consider the ODE (2.9). Assume that there exists a PWLR Lyapunov function. As explained in the previous section, the PWL function $\tilde{V}$ can be considered to be defined over a partition generated by a matrix of the form $\hat{H} = [\Gamma^T\, H^T]^T$, with $\{\mathcal{W}_k\}_{k=1}^m$.
Fix $k \in \{1, .., m\}$, and let c_k be the corresponding coefficient vector. By C1, we have $c_k^T = \xi_k^T \Sigma_k \hat{H} = \xi^T \operatorname{diag}(\Sigma_k^{(s)}, \Sigma_k^{(h)})[\Gamma^T\, H^T]^T$ with $\xi_k > 0$. By (3.13), the following hold over $\mathcal{W}_k$:

$$\xi_k^T \Sigma_k \hat{H} \frac{\partial R}{\partial x}(x)\dot{x} = \xi_k^T \Sigma_k [\Gamma^T\, H^T]^T \frac{\partial R}{\partial x}(x)\dot{x} \leq 0.$$

The pivotal step is to convert the scalar inequality above to a vector inequality using an observation similar to that in the proof of condition C4 of Theorem 3.4. Recall that $R(x) \in \mathcal{W}_k$ implies that $\dot{x} \in \mathcal{S}_{q_k}$. In other words, the sign pattern of $\dot{x}$ is fixed and identical to $\Sigma_k^{(s)}$. Hence we can decompose the LHS of the above equation over i to get

$$\forall R \in \mathscr{K}_A, \sum_{i=1}^{n} (\xi_k^T \Sigma_k \hat{H}) \frac{\partial R}{\partial x_i}\dot{x}_i \leq 0 \;\text{ iff }\; \forall R \in \mathscr{K}_A, \xi_k^T \Sigma_k \hat{H} \frac{\partial R}{\partial x_i}\sigma_{ki} \leq 0, i = 1, .., n.$$

Since if the second inequality above fails for some i^*, then we can choose $\frac{\partial R}{\partial x_{i^*}}$ sufficiently large so that the first inequality fails. Note that $\frac{\partial R}{\partial x_{i^*}}$ can not be identically zero since every species participate in at least one reaction by AS1.
Now, the n inequalities above can be arranged to get the vector inequality:

$$\left[\xi_k^T \Sigma_k \hat{H} \frac{\partial R}{\partial x_1}\sigma_{k1}, \ldots, \xi_k^T \Sigma_k \hat{H} \frac{\partial R}{\partial x_n}\sigma_{kn}\right] \leq 0.$$

Hence, the following holds over the region $\mathcal{W}_k$ for all x:

$$\xi_k^T \Sigma_k \begin{bmatrix} \Gamma \\ H \end{bmatrix} \frac{\partial R}{\partial x}(x) \Sigma_k^{(s)} = \xi_k^T \begin{bmatrix} \Sigma_k^{(s)} & 0 \\ 0 & \Sigma_k^{(h)} \end{bmatrix} \overbrace{\begin{bmatrix} \Gamma \frac{\partial R}{\partial x}(x) & 0 \\ H \frac{\partial R}{\partial x}(x) & 0 \end{bmatrix}}^{J} \begin{bmatrix} \Sigma_k^{(s)} & 0 \\ 0 & \Sigma_k^{(h)} \end{bmatrix} \leq 0. \tag{4.6}$$

Now, consider the case $k \in \{m+1, .., 2^p\}$. By definition, $\mathcal{W}_k^\circ = \varnothing$. By Farkas Lemma, there exist $t \in \{1, .., p\}, \xi_k > 0$ with $\xi_{kt} = 1$ such that $\sigma_{kt} h_t = -\sum_{i \neq t} \xi_{ki} \sigma_{ki} h_i$. Therefore, $\xi_k^T \Sigma_k [\Gamma^T H^T]^T = 0$. Hence, the inequality (4.6) is satisfied with equality sign. Therefore, we have shown that for all signature matrices $\{\Sigma_k\}_{k=1}^{2^p}$, there exists $\xi_k > 0$ such that $-\xi_k^T \Sigma_k J \Sigma_k \geq 0$. Using Lemma 4.3, $-J$ is a P_0 matrix for all x. In particular, this implies that $-\Gamma \frac{\partial R}{\partial x}(x)$ is P_0 for all x. □

Remark 4.2: It is known that algorithms for checking that a given matrix is P are exponential in time [25], while the conditions provided in the previous section can be casted as a linear program.

Remark 4.3: As can be noted from the proofs, the necessary condition given by Theorem 4.4 is a consequence of the existence of a function V that satisfies C1, C2, C4, i.e. it does not assume continuity. On the other hand, Theorem 4.3 only assumes that V exists satisfying conditions C2 and C4. For instance, consider the network:

$$B \longrightarrow A \longrightarrow 2B, \ B + C \longrightarrow 0 \longrightarrow C.$$

Then there exists a discontinuous V that satisfies C2 and C4, but the Jacobian is not P_0 for any $R \in \mathscr{K}_\Gamma$.

Remark 4.4: Examining the proof above, it can be noted that the satisfaction of C1, C2 and C4 for $H = \Gamma$ is equivalent to the statement "$\forall k \in \{1, .., 2^n\}, \exists \xi_k > 0$ such that $\forall R \in \mathscr{K}_A, \xi_k^T \Sigma_k \Gamma \frac{\partial R}{\partial x} \Sigma_k \leq 0$". This is a sort of a "robust" P_0 condition, since a single vector ξ_k "works" for all $R \in \mathscr{K}_A$. However, one need to be careful, since, in principle, the Jacobian might be P_0 for all $R \in \mathscr{K}_A$ while ξ_k is dependent on the specific realization of

R.

4.3.2 Uniqueness of Equilibria of Graphically Stable Networks

The main result that links injectivity of a map to the notion of P-matrices was first shown by Gale and Nikaido [48]. It 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. [20], Banaji and Craciun [19]. However, since most Jacobians that we might consider are singular, the notion of a P_0 matrix is more relevant to us. A useful result that we utilize is given by the following lemma.

Lemma 4.4 ([19], Appendix B)**.** *Consider* (2.9)*, and let J be the Jacobian of $\Gamma R(x)$. If J or $-J$ is P_0 the network can not admit multiple nondegenerate positive equilibria in a single stoichiometric computability class.*

Hence, the following theorem follows.

Theorem 4.5 (Uniqueness of Positive Equilibria of Graphically Stable Network)**.** *If $\mathscr{N}_{A,B}$ 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 $\mathscr{C}_{x_e}$.

Proof. The first statement follows directly from Theorem 4.4 and Lemma 4.4. For the second statement, we show in Theorem 6.9 that the existence of an isolated positive equilibrium x_e ensures that the reduced Jacobian (see §2.1.4) is non-singular on the interior of the orthant. In order to show uniqueness, assume for the sake of contradiction that there exists $y \neq x_e, y \in \mathscr{C}_{x_e}$ 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 x^* is implied by the integral mean-value theorem. Since $x^* \in \mathscr{C}^\circ_{x_e}$, then the reduced Jacobian at x^* is non-singular relative to $\operatorname{Im}\Gamma$. Since $x_e - y \in \operatorname{Im}\Gamma$, then $y = x_e$: a contradiction. □

Remark 4.5: In comparison to Theorem 3.3, note that no assumption on the boundedness or the satisfaction of the LaSalle's condition is needed.

Remark 4.6: Note that since the Jacobian is P_0, then if arbitrary inflows and outflow were added to every species of a GSN the resulting Jacobian would be a P matrix [25]; this is also known as the continuous-flow stirred tank reactor (CFSTR) version of the network. The CFSTR network is injective. This shows that our framework has a direct relationship to the recent results on injectivity (Craciun and Feinberg [35]), P matrices for reaction networks (Banaji et al. [20], Banaji and Craciun [19]) and concordance (Shinar and Feinberg [87]).

4.4 Siphons and Persistence of Graphically Stable Networks

4.4.1 Statement of Results

Recall that the concept of persistence has been introduced in §2.3, where it has been stated that if a conservative network does not have critical siphons, then it is persistent. If the network is not conservative, then the absence of critical siphons implies that bounded trajectories are persistent. Note that this is a graphical property, and it is independent of the specific realization of the kinetics involved.

All examples of GSNs that have been considered are free of critical siphons. It might be wondered if this can be generalized to establish this property for all GSNs. In this

section, we answer this question affirmatively under specific conditions. We believe that this is true in general, but the proof is elusive till now.

Theorem 4.6 (Absence of Types of Critical Siphons)**.** *Given* (2.9)*. Consider the network family $\mathscr{N}_{A,B}$. Assume there exists a critical siphon P, and let $\Lambda(P)$ be the set of output reactions of P. Then, $\mathscr{N}_{A,B}$ is a not GS, i.e., the network does not admit a PWLR Lyapunov function if any of the following conditions is satisfied.*

1. *P is a critical deadlock.*

2. *the network is conservative and for some realization of the network family there exists a point in the interior of a proper stoichiometric compatibility class on which the reduced Jacobian is nonsingular,*

3. *the network is conservative and* $\ker \Gamma$ *is one-dimensional.*

The following theorem follows immediately from Theorem 2.1 and Theorem 4.6.

Theorem 4.7 (Persistence of A Class of GSNs)**.** *Given* (2.9)*. Assume the network is conservative. Then the network family $\mathscr{N}_{A,B}$ is persistent if*

1. $\ker \Gamma$ *is one-dimensional,* ***or***

2. *by removing the reverse of some reactions the reduced network has a one-dimensional kernel and is GS,* ***or***

3. *there exists an isolated positive equilibrium in the interior of some proper stoichiometric class for a realization of $\mathscr{N}_{A,B}$.*

The second item in Theorem 4.7 follows by the fact that the inclusion of a reverse of a reaction does not create a critical siphon.

Remark 4.7: For the class of networks that Theorem 4.7 is applicable, the LaSalle's interior condition is sufficient to ensure the LaSalle's condition.

Remark 4.8: For the case of conservative networks Theorem 3.3 can be compared to Theorem 4.7. The first assumes the satisfaction of a LaSalle's condition to ensure global stability and hence persistence. While for the second the mere existence of an isolated positive equilibrium can be used to ensure persistence without the need of checking the LaSalle's condition.

We state also the following conjecture which we did not find any counter-example to so far.

Conjecture 1 (Persistence of GSNs)**.** *Given* Γ*. If the associated Petri-net has at least one critical siphon, then* $\mathscr{N}_{A,B}$ *is not GS. Hence, if the network family* $\mathscr{N}_{A,B}$ *is GS then it is bounded-persistent. If the network family is also conservative, then it is persistent.*

The rest of this section contains the proof of Theorem 4.6.

4.4.2 Proof of Theorem 4.6

Assume P is a critical siphon for the Petri-net associated with Γ, 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 4.6, the following lemma is needed.

Lemma 4.5. *Consider a network family* $\mathscr{N}_{A,B}$*. 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* Σ_k *that satisfies* $\sigma_{k1} = ... = \sigma_{kn_p} = 1$*.*

Proof. Assume the contrary. This implies that $\cap_{i=1}^{n_p}\{r|\gamma_i^T r > 0\} \bigcap \cap_{i=n_p+1}^{n}\{r|\sigma_i\gamma_i^T r > 0\} = \emptyset$ 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 $\cap_{i=n_p+1}^{n}\{r|\sigma_i\gamma_i^T r \geq 0\}$. Therefore, this implies that $\cap_{i=1}^{n_p}\{r|\gamma_i^T r > 0\} = \emptyset$. By Farkas Lemma, this implies that there exists $\lambda \in \mathbb{R}^t$ 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 give the proof of the first item:

Proof of Theorem 4.6-1). Without loss of generality, let $\{1, ..., n_p\}$ be the indices of the species in P. Using Lemma 4.5, there exists a nonempty-interior sign region $\mathcal{S}_k, 1 \leq k \leq m_s$ with a signature matrix Σ_k that satisfies $\sigma_{k1} = ... = \sigma_{kn_p} = 1$. Since $\Lambda(P) = \mathscr{R}$, this implies $b_{kj} \leq 0$ for all $j = 1, .., \nu$. However, this is not allowed by Theorem 4.3 since $\zeta_k^T B_k v \leq 0$ for all $v \in \ker \Gamma \cap \bar{\mathbb{R}}_+^n$ and for any choice of admissible ζ_k. □

In order to proceed, an existence result of equilibria is needed.

Lemma 4.6. *Consider a network family $\mathscr{N}_{A,B}$. Let P be a critical siphon and let Ψ_P be the associated face. If the network is conservative, then for any proper stoichiometric compatibility $\mathscr{C}$, there exists an equilibrium x_e of (2.9) such that $x_e \in \Psi_P \cap \mathscr{C}$.*

Proof. The set $\Psi_P \cap \mathscr{C}$ is compact, forward invariant, and convex, since both sets $\Psi_P, \mathscr{C}$ are such. Hence, the statement of the lemma follows directly from the application of Brouwer's fixed point theorem [81] on the associated flow. □

We are ready now to prove the second item of Theorem 4.6.

Proof of Theorem 4.6-2). By Lemma 4.6 there exists an equilibrium in Ψ_P. Since it is assumed that there exists an isolated equilibrium in the interior, Theorem 4.5 implies that $\mathscr{N}_{A,B}$ is not GS. □

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

Lemma 4.7. *Let x_e be an equilibrium of (2.9). Let $\tilde{P}$ be a set of species that correspond to $\{1, .., n\} \backslash \operatorname{supp}(x_e)$. 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 $\mathbf{R}_j \in \mathscr{R}$ such that X_i is a product of $\mathbf{R}_j$ and $\mathbf{R}_j \neq \Lambda(\tilde{P})$. 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 $\mathbf{R}_j$ 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 4.6.

Proof of Theorem 4.6-3). By Lemma 4.6, 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, $P \subset \tilde{P} := \{1, .., n\} \setminus \operatorname{supp}(x^*)$. $\tilde{P}$ is a siphon by Lemma 4.7, and since $P \subset \tilde{P}$ it is a critical deadlock. However, by Theorem 4.6-1) $\mathscr{N}_{A,B}$ is not GS. If $t > 0$, this implies that $P = \emptyset$; a contradiction. □

Remark 4.9: The proof constructed a critical deadlock based on a critical siphon in the context of a conservative network. However, this is not valid in general for non-conservative networks. For example, consider

$$B \longrightarrow A \longrightarrow 2B, B + C \longrightarrow 0 \longrightarrow C.$$

This network has a unique positive kernel vector, and $\{A, B\}$ is a critical siphon, however, there is no critical deadlock. Nevertheless, it can be verified that it is not GS since the Jacobian is not P_0 for any $R \in \mathscr{K}_A$.

Chapter 5

Construction of PWLR Lyapunov Functions

The properties that have been established in the previous chapters for Lyapunov functions remain without application if we do not have the means to find such functions. The characterizations provided in §3.4 of PWLR functions can not be used directly for design. In fact, it is known that constructing convex PWL Lyapunov functions even in the case of systems evolving according to linear equations is not an easy task, and no simple necessary and sufficient conditions are available [78]. In this section we propose several constructions of PWLR Lyapunov functions. Thus, we propose methods to find (H, C) using the representation (3.5), and C using the convex representation (3.6). The main difficulty, however, is that (3.11), (3.12), (3.14) are bilinear in the variables.

5.1 Construction of PWLR Lyapunov function over a given partition

Assume that the partition generator H is fixed, hence $\{\mathcal{W}_k\}_{k=1}^m$ is determined. Then, conditions C1,C3 are linear in C. Furthermore, the inclusion $\ker C \subset \ker \Gamma$ is implied by

C1. The constraint (3.12), however, is nonconvex. Nevertheless, it can be written as linear constraint using the formalism introduced in §4.2.

Recall the sign regions $\{\mathcal{S}_k\}_{k=1}^{m_s}$ defined in §4.3. It has been shown that if an initial partition generator matrix $\hat{H}$ is given with region $\{\hat{\mathcal{W}}_k\}_{k=1}^{m_h}$, then the function V can be alternatively written over a possible refined partition $\{\mathcal{W}_k\}_{k=1}^{m}$ with a generator matrix of the for the form $H = [\Gamma^T \hat{H}^T]^T$, with corresponding sign matrices $\Sigma_k = \text{diag}[\Sigma_k^{(s)}\ \Sigma_k^{(h)}]$. Hence, $\{\mathcal{W}_k\}_{k=1}^{m}$ is a refined partition of $\{\mathcal{S}_k\}_{k=1}^{m_s}$, which means that for all $k \in \{1,..,m\}$ there exists some $\ell \in \{1,..,m_s\}$ such that $\mathcal{W}_k \subset \mathcal{S}_\ell$. As in §4.3, assume that the index map $q(.) : k \mapsto \ell$ is defined. Hence, for $\ell \in \{1,..,m_s\}$, we can write:

$$\mathcal{S}_\ell = \bigcup_{k \in q^{-1}(\ell)} \mathcal{W}_k, \ell = 1,..,m_s.$$

Using this formalism, the following theorem can be stated.

Theorem 5.1. *Consider the system* (2.9)*, with* $H = [\Gamma^T \hat{H}^T]^T$*,* $\{\Sigma_k\}_{k=1}^{m}$*,*$\{B_k\}_{k=1}^{m_s}$*,* q_k *given as above. Consider the following linear programming feasibility problem:*

$$\begin{aligned}
&\textit{Find} && c_k, \xi_k, \zeta_k \in \mathbb{R}^\nu, \eta_{kj} \in \mathbb{R}, k = 1,..,\tfrac{m}{2}; j \in \mathcal{N}_k,\\
&\textit{subject to} && c_k^T = \xi_k^T \Sigma_k H,\\
&&& c_k^T = \zeta_k^T B_{q_k},\\
&&& c_k - c_j = \eta_{kj} \sigma_{k s_{kj}} h_{s_{kj}},\\
&&& \xi_k \geq 0, \mathbf{1}^T \xi_k > 0,\\
&&& \zeta_{kj} \geq 0, j \in \{1,..,\nu\} \backslash \mathcal{I}.
\end{aligned}$$

Then there exists a PWLR Lyapunov function with partitioning matrix H *if and only if there exist feasible solution to the above linear program with C2 satisfied. Furthermore, the PWLR function can be made convex by adding the constraints* $\eta_{kj} \geq 0$*.*

Proof. Note that C1,C3 are represented by the first and third constraints in the linear

program. It remains to be shown that C4 is equivalent to the second constraint. This follows from Theorem 4.2. □

Remark 5.1: If a solution exists to the above linear program then it is necessarily non-unique, since any scalar multiple is a valid solution. An objective function can be added also to minimize or maximize some quantity of interest.

Remark 5.2: The linear program requires the pre-computation of several matrices which are the indices of non-empty-interior regions, the sign pattern matrices $\{B_k\}$, and the set of neighbours $\mathcal{N}$. The last two are computationally light, while the first might appear to be computationally heavy since a brute force algorithm requires solving the following set of linear program feasibility problems:

$$\Sigma_k H r > 0, r > 0, \ k = 1, .., 2^p.$$

However, the computational task can be reduced substantially by noting that the k^{th} linear program is infeasible iff there exists a left null vector of H with the same sign pattern as Σ_k. Therefore, an alternative algorithm requires computing all possible sign patterns of left null vectors of Γ.

Remark 5.3: The continuity constraint above is checked between neighboring region only, which reduces the number of constraints, however, it requires the pre-computation of the set $\mathcal{N}$. An alternative set of constraints is written using orthogonality relations as follows:

$$(c_j - c_k)^T v_\ell = 0, \ell = 1, .., dim(ker H), j = 1, .., \tfrac{m}{2}, k = j + 1, .., m$$

where $\{v_1, ..., v_\ell\}$ is any basis of $\ker H$. Note that convexity can not be enforced using this type of constraints.

5.1.1 Special Cases

Note that since $\ker H = \ker \Gamma$, then $\exists Y \in \mathbb{R}$ such that $H = [I, Y^T]^T\Gamma$. Hence, the Lyapunov function can be written as:

$$\begin{aligned} V(x) = c_k^T R(x) = \xi_k^T \Sigma_k H R(x) = \xi_k^T \Sigma_k \begin{bmatrix} I \\ Y \end{bmatrix} \Gamma R(x) \\ = \left\| \operatorname{diag}\left(\xi_k^{(s)}\right) \dot{x} \right\|_1 + \left\| \operatorname{diag}\left(\xi_k^{(h)}\right) Y \dot{x} \right\|_1, R(x) \in \mathcal{W}_k. \end{aligned}$$

A natural candidate for the partition matrix is $H = \Gamma$. Hence, we get a weighted ℓ_1 norm as follows

$$V(x) = c_k^T R(x) = \xi_k^T \Sigma_k \Gamma R(x) = \| \operatorname{diag}(\xi_k)\dot{x}\|_1, R(x) \in \mathcal{S}_k.$$

If we have additional constraint that for all k, $\xi_k = \mathbf{1}$, then the Lyapunov function considered by Maeda et al. [65], i.e.

$$V(x) = \|\dot{x}\|_1, \tag{5.1}$$

can be recovered as a special case. Therefore, the linear program can be used to find out if the 1-norm of the derivative or one of its diagonal multiple is a Lyapunov function for a certain network.

However, there are classes of networks for which $H = \Gamma$ does not induce a PWLR Lyapunov function, while there exists a partitioning matrix $\hat{H}$ which does. Understanding when this happens is a challenging open question.

5.1.2 Extension to Networks Without Interior Equilibria

Recall that Assumption AS1 requires the existence of a positive vector in $\ker \Gamma$ which is a necessary condition for the existence of equilibria in the interior of stoichiometric classes. This assumption simplifies the geometry of the partition regions, as have been detailed in the previous chapter. Nevertheless, the techniques can be extended without difficulty for

the construction of PWLR Lyapunov functions for generic CRNs that do not satisfy AS1. However, the symmetry of the partition as in Proposition 3.1, and of the PWL function as in (3.5) can not be assumed. Furthermore, recall that the positivity inequality, i.e. $r \geq 0$, in the expression of the regions (3.4) has not been enforced since all regions intersect the positive orthant non-trivially as Proposition 3.1 have shown. However, this is no longer correct in the general case. Consider a matrix H, with $\ker H = \ker \Gamma$. The regions are defined as:

$$\mathcal{W}_k = \{r \in \mathbb{R}^{nu} : \Sigma_k H r \geq 0, r \geq 0\},$$

where $k = 1, .., 2^p$. As before, let m be the number of non-empty interior regions. Then, the regions are ordered such that the first m regions are the non-empty interior ones. The sign constraints given by (4.5) can be defined analogously. Therefore, the following theorem can be stated for networks that do not necessarily satisfy AS1.

Theorem 5.2. *Consider the system* (2.9)*, with* $H = [\Gamma^T \hat{H}^T]^T$*,* $\{\Sigma_k\}_{k=1}^m$*,*$\{B_k\}_{k=1}^{m_s}$*,* q_k *given as before. Consider the following linear program:*

$$\begin{aligned}
&\textit{Find} && c_k, \xi_k, \zeta_k \in \mathbb{R}^\nu, \eta_{kj} \in \mathbb{R}, k = 1, ..m; j = k+1, .., m,\\
&\textit{subject to} && c_k^T = \xi_k^T \Sigma_k H,\\
&&& c_k^T = \zeta_k^T B_{q_k},\\
&&& (c_k - c_j)^T v_\ell = 0,\\
&&& \xi_k \geq 0, \mathbf{1}^T \xi_k > 0,\\
&&& \zeta_{kj} \geq 0, j \in \{1, .., \nu\} \backslash \mathcal{I}, \ell = 1, .., dim(ker H).
\end{aligned}$$

Then there exists a PWLR Lyapunov function with partitioning matrix H *if and only if there exists a feasible solution to the above linear program with C2 satisfied.*

5.2 Iterative Algorithm for Convex PWLR functions

The algorithm presented in the previous section works for continuous and convex functions defined on some chosen partition. In this section, we present an iterative algorithm for constructing convex PWLR Lyapunov functions which utilizes the fact that the active linear component for a convex PWLR function has the maximum value among the other linear components. Therefore, the idea is to start with an initial PWLR function, and aim for restricting the active region of each linear function $c_k^T R(x(t))$ to the region on which it is nonincreasing on it, i.e $c_k^T \dot{R}(x(t)) \leq 0$. This is accomplished by adding extra linear components that ensures this.

Let $C_0 = [c_1 \ ... \ c_{m_0}]^T \in \mathbb{R}^{m_0 \times \nu}$, with the associated PWLR function. Define the *active region* of a vector c_k, $k = 1, .., m_0$, as:

$$\mathcal{W}_0(c_k) := \{r \in \mathbb{R}^\nu : c_k^T r \geq c_j^T r, -m_0 \leq k \leq m_0, k \neq 0\},$$

where $c_{-k} = -c_k$. Conisder (2.9). We define the *permissible region* of a linear component c_k to be the region for which it is nonincreasing.

$$\begin{aligned} \mathcal{P}(c_k) &:= \{r \in \mathbb{R}^\nu : \nu_{ki} \gamma_i^T r \leq 0, i \in I_k\} \\ &\subset \{\tilde{r} \in \mathbb{R}^\nu : \tilde{r} = R(x), c_k^T \tfrac{\partial R}{\partial x}(x) \Gamma R(x) \leq 0\}, \end{aligned} \tag{5.2}$$

where $\nu_{ki} = \text{sgn}(c_{ki})$. Note that in general, $\mathcal{W}_0(c_k) \not\subset \mathcal{P}(c_k)$. Therefore, the iterative procedure defines a new PWL function with matrix C_1 so that $\mathcal{W}_1(c_k) \subset \mathcal{P}(c_k)$. To achieve this, new rows are added to C_0. The new rows can be chosen to be of the form

$$c_{m_0+i} := c_k + \nu_{ki} \gamma_i, i \in I_k. \tag{5.3}$$

Thus, $C_1' := [C_0^T \ c_{m_0+1} \ ... \ c_{m_0+n}]^T$. Finally, C_1 is defined by eliminating linearly dependent pairs of rows from C_1'.

Hence, Algorithm 1 can be described as:

1. Given $C_0 = [c_1 \ ... \ c_{m_0}]^T \in \mathbb{R}^{m_0/2\times\nu}$, $k = 1, .., m_0/2$, and $\ker\Gamma \subset \ker C_0$. Set $k = 1$.

2. Define $C_k^{'} := [C_{k-1}^T \ c_{m_k+1} \ ... \ c_{m_k+n}]^T$, where $c_{m_k+i} := c_k + \nu_{ki}\gamma_i, i \in I_k, c_{m_k+i} := c_k, i \notin I_k$.

3. Define C_k as $C_k^{'}$ with zero rows or linearly dependent pairs of rows eliminated.

4. If $C_k = C_{k-1}$ or $k > N$, stop.

5. Set $k := k + 1$, and go to step 2,

where N is the maximum number of iterations allowed.
If Algorithm 1 terminates then we state the following.

Theorem 5.3. *Consider* (2.9). *If Algorithm 1 terminates after a finite number of iterations and if C2′ is satisfied, then the resulting function is a PWLR Lyapunov function for the network family* $\mathscr{N}_{A,B}$.

Proof. We need to show that C satisfies C4′. It is sufficient to show that $\mathcal{W}_1(c_k) \subset \mathcal{P}(c_k)$, note that $r \in \mathcal{W}_1(c_k)$ implies $(c_k + \nu_{ki}\gamma_i)^T r \leq c_k^T r$, for $i = 1, ..., n$. This in turn implies $\nu_{ki}\gamma_i^T r \leq 0, i = 1, .., n$. Hence, $r \in \mathcal{P}(c_k)$. Therefore, by iterating this procedure through the rows of C_m we get $\mathcal{W}_k(c_k) \subset ... \subset \mathcal{W}_1(c_k) \subset \mathcal{P}(c_k)$. If the algorithm terminates after a finite number of iterations then a nonincreasing convex PWL function is constructed. Furthermore, to ensure that $\ker C \subset \ker\Gamma$ we assume that $\ker\Gamma \subset \ker C_0$. □

Remark 5.4: Theorem 5.3 does not need to assume that AS1 is satisfied, however, when it is not, then the PWLR function can not generally be written in the ∞-norm form as in (3.6). Nevertheless, it can still be represented in the max-form as:

$$V(x) = \max_{k\in\{1,..,m\}} c_k^T R(x).$$

However, if symmetry is not achieved, then positive-definiteness is not automatic and need to be verified.

Remark 5.5: The formula (5.3) is not the unique way for constructing new vectors. Indeed, one can replace the inequality $\nu_{ki}\gamma_i \leq 0$ with any system of inequalities covering the same region. For instance, the region defined by the inequality $R_1 - 2R_2 + R_3 \leq 0$ is a subset of the region defined by the pair $R_1 - R_2 \leq 0, -R_2 + R_3 \leq 0$. Therefore, the **standard setting** of Algorithm 1 means using (5.3) with $C = \Gamma$.

5.3 Constructions Based on Graphical Conditions

The algorithms which have been presented in the previous section do not give a clear insight on the relationship between the graphical structure of the network and the Lyapunov function. In this section we show that it is possible to construct PWLR Lyapunov functions for CRNs with certain graphical structures. We state the following result which enjoys having easy-to-check graphical condition.

Theorem 5.4. *Consider a* ***non-autocatalytic*** *network family $\mathscr{N}_{A,B}$. Suppose the following properties are satisfied.*

1. $\dim(\ker \Gamma) = 1$,
2. $\forall X_i \in \mathbf{V}_S$ *there exists a unique output reaction, i.e every row in* Γ *has a unique negative element.*

Then

1. *the following is a PWLR function for the network family $\mathscr{N}_{A,B}$:*

$$V(x) = \max_{1\leq j\leq \nu} \frac{1}{v_j} R_j(x) - \min_{1\leq j\leq \nu} \frac{1}{v_j} R_j(x), \tag{5.4}$$

where $v = [v_1 \dots v_\nu]^T \in \ker(\Gamma), v \gg 0$.

2. *LaSalle's interior condition holds if* $\mathscr{A}(\mathbf{R}_j) \cap \mathscr{A}(\mathbf{R}_\ell) \neq \varnothing$, *for all* $1 \leq j, \ell \leq \nu$.

If the network is conservative, then in addition to the above,

3. *there are no critical siphons, hence the network family is persistent, i.e,* $\omega(x_0) \cap \partial\mathbb{R}^n_+ = \emptyset$ *for all* $x_\circ$.

4. *The LaSalle's condition is automatically satisfied, hence if there exists an isolated equilibrium it is a unique globally asymptotically stable equilibrium with respect to* $\mathscr{C}_{x_\circ}$.

Proof. The PWLR function is convex by construction, where $C \in \mathbb{R}^{\frac{\nu}{2}(\nu-1)\times\nu}$. We can write $CR(x) = [c^T_{q+s}R(x)]^{q-1,\nu}_{s,q=1} = [\frac{1}{v_q}R_q(x) - \frac{1}{v_s}R_s(x)]^{q-1,\nu}_{s,q=1}$. Note that $\tilde{V}(R(x)) = c^T_{q+s}R(x)$ is equivalent to $\max_{1\leq k\leq\nu}\frac{1}{v_k}R_k(x) = R_q(x)$ and $\min_{1\leq k\leq\nu}\frac{1}{v_k}R_k(x) = R_s(x)$.
Using the first assumption, we have $\ker\Gamma = \ker C$, and hence C2′ is satisfied.
We show C4′ using a direct approach. By assumption 2 we can perform the computation:

$$\begin{aligned}\dot{R}_q(x) &= \frac{1}{v_q}\frac{\partial R_q}{\partial x}\Gamma R(x) \\ &= \frac{1}{v_q}\sum_{i:\alpha_{iq}>0}\frac{\partial R_q}{\partial x_i}\left(-\alpha_{iq}R_q(x) + \sum_{j\neq q}\beta_{ij}R_j(x)\right),\end{aligned} \tag{5.5}$$

$$\begin{aligned}\dot{R}_s(x) &= \frac{1}{v_s}\frac{\partial R_s}{\partial x}\Gamma R(x) \\ &= \frac{1}{v_s}\sum_{i:\alpha_{is}>0}\frac{\partial R_s}{\partial x_i}\left(-\alpha_{is}R_s(x) + \sum_{j\neq s}\beta_{ij}R_j(x)\right).\end{aligned}$$

Since $v \in \ker\Gamma$, then $-\alpha_{iq} = \sum_{j\neq q}\frac{v_q}{v_j}\beta_{ij}$. Hence,

$$-\alpha_{iq}R_q(x) + \sum_{j\neq q}\beta_{ij}R_i(x) \leq -\sum_{j\neq q}\frac{v_q}{v_j}\beta_{ji}R_q(x) + \sum_{j\neq q}\beta_{ji}\frac{v_q}{v_j}R_q(x) = 0.$$

By a similar argument for the second term and by (2.7), we get $\dot{R}_q(x) \leq 0$ and $\dot{R}_s(x) \geq 0$ and as a consequence $\dot{V}(x) = \max_{k \in K_x} c_k^T \dot{R}(x) \leq 0$. Hence, V is a PWLR Lyapunov function.

We show the LaSalle's interior condition. Let $\tilde{x}(t) \subset \ker \dot{V}(x)$. Using the same argument in the proof of Theorem 3.6, there exists $q^\star$ and $s^\star$ and an open subset of $\mathbb{R}$, $\mathcal{T}$, such that $V(x) = \frac{1}{v_{q^\star}} R_{q^\star}(\tilde{x}(t)) - \frac{1}{v_{s^\star}} R_{j^\star}(\tilde{x}(t))$ for all $t \in \mathcal{T}$. However, as both terms are nonincreasing, we have $\dot{R}_{q^\star}(\tilde{x}(t)) = \dot{R}_{s^\star}(\tilde{x}(t)) = 0$. By (5.5) and assumption AS4 we get $\dot{\tilde{x}}_i(t) = 0$ for all i such that $\alpha_{iq^\star} > 0$, $\alpha_{is^\star} > 0$ and all $t \in \mathcal{T}$. Therefore, $\alpha_{iq^\star} R_{q^\star}(\tilde{x}) = \sum_{j \neq q^\star} \beta_{ij} R_j(\tilde{x})$, and since $\frac{1}{v_j} R_j(\tilde{x}(t)) \leq \frac{1}{v_{q^\star}} R_{q^\star}(\tilde{x}(t))$, then $\frac{1}{v_{q^\star}} R_j(\tilde{x}(t)) = R_{q^\star}(\tilde{x}(t))$ for all j such that there is i with $\beta_{ij} > 0$, $\alpha_{iq^\star} > 0$ and all $t \in \mathcal{T}$. A similar argument can be carried out for $R_s(\tilde{x}(t))$. By induction, it follows that $\frac{1}{v_{q^\star}} R_j(\tilde{x}(t)) = R_t(\tilde{x}(t))$ if $\mathbf{R}_j \in \mathscr{A}(\mathbf{R}_{q^\star})$ for $t \in \mathcal{T}$. Similarly, $\frac{1}{v_{q^\star}} R_\ell(\tilde{x}(t)) = R_s(\tilde{x}(t))$ if $\mathbf{R}_\ell \in \mathscr{A}(\mathbf{R}_{s^\star})$. Since $\mathscr{A}(\mathbf{R}_{q^\star}) \cap \mathscr{A}(\mathbf{R}_{s^\star}) \neq \phi$, we get $R_{q^\star}(\tilde{x}(t)) = R_{s^\star}(\tilde{x}(t))$ for all $t \in \mathcal{T}$ and since $\mathcal{T}$ is an open set this implies that $\tilde{x}(t) \in \ker \Gamma$.

Assume the network is conservative. The persistence of the network follows from Theorem 4.7 since the kernel is one-dimensional. Since there exists a conservation law, the common ancestor condition is satisfied. Hence, the LaSalle's condition is satisfied. If there exists an isolated equilibrium, uniqueness and global stability follows from Theorem 3.3. □

Remark 5.6: Both graphical assumptions are necessary. For instance, consider the following network which has a one-dimensional kernel, but does not satisfy the second condition:

$$A \longrightarrow B, A \longrightarrow C, B + C \longrightarrow 2A.$$

The max-min function is not a Lyapunov function. In fact this network violates the necessary condition presented in Theorem 4.3 and hence does not admit any PWLR Lyapunov function.

The following network satisfies the second assumption, but it has a two dimensional kernel,

$$0 \longrightarrow A, 0 \longrightarrow B, 2A \longrightarrow B, 2B \longrightarrow A,$$

then the max-min function is not a PWLR function. Note, however, that this function satisfies C4′, hence it is nonincreasing. But it does not vanish on a proper subset of $\ker \Gamma$. In fact, C4′ is satisfied for any network satisfying the second graphical assumption with the max-min PWLR function.

Theorem 5.4 can be extended to allow the addition of the reverse of certain reactions. Note that adding the reverse of an irreversible reaction increases the dimension of the kernel of Γ so that the original result does not normally apply.

Theorem 5.5. *Consider the network $\mathscr{N}_{A,B}$ with the associated graph $(\mathbf{V}_S, \mathbf{V}_R, \mathbf{E}, \mathbf{W})$ that satisfies the conditions of Theorem 5.4. Let $\mathbf{V}_{R'} \subset \mathbf{V}_R$ be the set of reactions $\mathbf{R}_j$ such that if $(\mathbf{R}_j, S_i) \in E$ and $(\mathbf{R}_k, S_i) \in E$ then $j = k$. Equivalently, $\mathbf{R}_j \in \mathbf{V}_{R'}$ if it is the only input reaction for all of its product species. Let $(\mathscr{S}, \tilde{\mathscr{R}})$ be the CRN constructed by adding reverse reactions for reactions belonging to $\mathbf{V}_{R'}$, and let $\tilde{\Gamma}$ be the new stoichiometry matrix. Then, the claims of the previous theorem are satisfied for $\mathscr{N}_{\tilde{\Gamma}}$ with the following function:*

$$V(x) = \max_{1 \le j \le \nu} \frac{1}{v_j}(R_j(x) - \chi_j R_{-j}(x)) - \min_{1 \le j \le \nu} \frac{1}{v_j}(R_j(x) - \chi_j R_{-j}(x)), \tag{5.6}$$

where $\chi_j = 1$ if $\mathbf{R}_j \in \tilde{\mathscr{R}} \backslash \mathscr{R}$, and $\chi_j = 0$ otherwise.

Proof. Without loss of generality, assume $\mathbf{V}_{R'} = \mathbf{V}_R$. As in the proof of Theorem 5.4, we can write $CR(x) = [c_{q+s}^T R(x)]_{s,q=1}^{q-1,\nu} = [\frac{1}{v_q}(R_q(x) - R_{-q}(x)) - \frac{1}{v_s}(R_s(x) - R_{-s}(x))]_{s,q=1}^{q-1,\nu}$. For

simplicity, denote $\tilde{R}_q = R_q - R_{-q}$, $\tilde{R}_s = R_s - R_{-s}$. Hence,

$$\dot{\tilde{R}}_q(x) = \frac{1}{v_{q^\star}} \sum_{i:\alpha_{iq^\star}>0} \frac{\partial R_{q^\star}}{\partial x_i} \left(-\alpha_{iq^\star}(R_{q^\star}(x) - R_{-q^\star}(x)) + \sum_{\ell \neq q^\star} \beta_{i\ell}(R_\ell(x) - R_{-\ell}(x)) \right) - \frac{1}{v_{q^\star}} \sum_{i:\beta_{iq^\star}>0} \frac{\partial R_{-q^\star}}{\partial x_i} \left(-\beta_{iq^\star}(R_{-q^\star}(x) - R_{q^\star}(x)) + \sum_{\ell \neq q^\star} \alpha_{i\ell}(R_{-\ell}(x) - R_\ell(x)) \right), \tag{5.7}$$

and an analogous expression can be written for $\dot{\tilde{R}}_s(x)$. Having a single negative coefficient in every bracket follows from the additional assumption in the statement of the theorem. Therefore, using a similar argument to the one in the proof of Theorem 5.4 it can be seen that $\dot{\tilde{R}}_q(x) \leq 0$, and $\dot{\tilde{R}}_q(x) \geq 0$. Hence, $\dot{V}(x(t)) \leq 0$.

A similar argument to the one in the proof of Theorem 5.4 can be carried out to show the LaSalle's Interior condition. The absence of critical siphons follows from Theorem 5.4 and that critical siphons are not created by adding reverse reactions. □

5.3.1 Relationship to Consensus Dynamics

Consider a closed, i.e. without inflows or outflows, CRN for which there is a unique reactant for every reaction, and a unique output reaction for every species. In such a network, the bipartite graph representing the network can be replaced with a digraph $G = (\mathbf{V}, \mathbf{E}, \mathbf{W})$ representing the species, reactions and weights respectively. The stoichiometry matrix Γ is the negative transpose of the *Laplacian* of the digraph. Hence,the CRN can be described by the ODE:

$$\dot{x} = -L^T R(x). \tag{5.8}$$

If the graph is strongly connected, then $\mathbf{1}$ is a conservation law, i.e, $\mathbf{1}^T L^T = 0$. Using Perron-Frobenius theory [25], $\ker L^T$ is spanned by a unique vector $v \gg 0$.

In order to state this using our previous notation. Let L^+ and L^- be matrices defined

elementwise as: $[L^+]_{ij} := -\max\{[L^T]_{ij}, 0\}$ and $[L^-]_{ij} := \min\{[L^T]_{ij}, 0\}$. Hence, (5.4) is a Lyapunov function for the network family $\mathscr{N}_{L^+,L^-}$ by Theorem 5.4. Note that this is very similar to the consensus algorithm proposed in [72] where they consider algorithm of the form: $\dot{x} = -Lx$. Indeed, we can derive from Theorem 5.5 the following result for consensus algorithms.

Corollary 5.6. *Consider a network of n integrator agents with a strongly connected digraph $G = (\mathbf{V}, \mathbf{E}, \mathbf{W})$, and let $L = [\ell_{ij}]$ be the associated Laplacian. Define the set $\mathbf{V}' \subset \mathbf{V}$ as $\mathbf{V}' := \{j \in \mathbf{V} : \exists k, j' \in \mathbf{V}$ with $k \neq j \neq j'$ such that $(j,k), (j',k) \in \mathbf{E}\}$. Consider applying the following consensus algorithm:*

$$\dot{x} = -LF(x), \tag{5.9}$$

where $F = [F_1, .., F_n]^T$ is any function such that there exists $F^+, F^- \in \mathscr{K}_{L^-}$ such that $F = F^+ - F^-$ and $F_j^- \equiv 0$ for $j \in \mathbf{V}'$. Then, F-consensus is asymptotically reached for all initial states, i.e, $\lim_{t\to\infty} F(x_1(t)) = .. = \lim_{t\to\infty} F(x_n(t)) < \infty$.

Remark 5.7: A mix-min type Lyapunov function (5.4) has been already used for linear consensus algorithms [70]. Therefore, Corollary 5.6 generalize the results of [70, 72] to nonlinear consensus algorithms. It is worth noting that the dynamics of a detailed balanced network has also been linked with consensus dynamics [93, §4.4].

Chapter 6

Uncertain System Framework

In this chapter the previous results are interpreted in the framework of linear parameter varying uncertain systems, where the PWLR Lyapunov function constructed before are shown to induce a common Lyapunov function for a finite-set of rank-one linear systems.

This allows to introduce dual formulations of the PWLR Lyapunov functions, observe links with contraction theory, and introduce Piecewise Quadratic in Rates (PWQR) Lyapunov functions for CRNs.

6.1 Robust Lyapunov Functions and Differential Linear Inclusions

As mentioned in previous chapters it is highly desirable to be able to develop analysis tools for the dynamics of CRNs that are independent of the particular choice of kinetics within $\mathscr{K}_A$. The PWLR Lyapunov functions that have been introduced before satisfy this requirement. Furthermore, it can be noted that the Lyapunov function can be written as a composition $V = \tilde{V} \circ R$, where $\tilde{V}$ is the piecewise linear function and R is the reaction rate function. The remarkable feature of this factorization is that $\tilde{V}$ remains invariant with respect to the kinetics; it can be computed solely based on the stoichiometry matrix of the

network. In this chapter we investigate whether this class of Lyapunov functions forms a subclass of an appropriately defined class of *Robust Lyapunov functions*. It is shown that this is indeed possible.

6.1.1 Robust Lyapunov Functions

Informally, a robust Lyapunov function is a function that can be determined solely based on the graphical structure, and hence is decreasing for all reaction rate functions that belongs to $\mathscr{K}_A$. Therefore, we state the following definition which can be considered a generalization of Definition 3.3.

Definition 6.1 (Robust Lyapunov Function)**.** *Given* (2.9). *Let* $\tilde{V} : \bar{\mathbb{R}}^q \to \bar{\mathbb{R}}_+$ *be locally Lipschitz, and let* $W_{R,x_e} : \mathbb{R}^n \to \mathbb{R}^q$ *be a* $\mathscr{C}^1$ *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* $\mathscr{N}_{A,B}$ *if for any choice of* $R \in \mathscr{K}_A, x_e \in \bar{\mathbb{R}}^n_+$*, 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* $x \in \mathscr{C}_{x_e}$.

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

Remark 6.1: As will be seen later, the function $\tilde{V}$ used in the definition of the Lyapunov function (through composition) is invariant with respect to the specific network realization in $\mathscr{K}_A$, 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 $W_{R,x_e}(x) = x - x_e$.
As an abuse of notation, we call the parameterized Lyapunov function V_{R,x_e} an RLF.

Since the RLF defined above is not strict, we need the following definition which is identical to Definition 6.2.

Definition 6.2 (The LaSalle's Condition)**.** *An RLF V_{R,x_e} for $\mathscr{N}_{A,B}$ is said to satisfy* ***the LaSalle's condition*** *if for any choice $R \in \mathscr{K}_A$ the following statement holds.*
If a solution $\varphi(t;x_\circ)$ of (2.9) satisfies $\varphi(t;x_\circ) \in \ker \dot{V} \cap \mathscr{C}_{x_e}$, $t \geq 0$, then this implies that $\varphi(t;x_\circ) \in E_{x_\circ}$ for all $t \geq 0$, where $E_{x_\circ} \subset \mathscr{C}_{x_\circ}$ is the set of equilibria for (2.9).

Therefore, Theorem 3.2 and Theorem3.3 can also be stated for RLFs as follows.

Theorem 6.1 (Lyapunov's Second Method)**.** *Given (2.9) with initial condition $x_\circ \in \mathbb{R}^n_+$, and let $\mathscr{C}_{x_\circ}$ 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 $E_{x_\circ}$ is Lyapunov stable.*
2. *If, in addition, V satisfies the LaSalle's Condition, then $x(t) \to E_{x_\circ}$ as $t \to \infty$ (i.e., the point to set distance of $x(t)$ to $E_{x_\circ}$ tends to 0). Furthermore, any isolated equilibrium relative to $\mathscr{C}_{x_\circ}$ is asymptotically stable.*
3. *If V satisfies the LaSalle's condition, and all the trajectories are bounded, then: if there exists $x^* \in E_{x_\circ}$, which is isolated relative to $\mathscr{C}_{x_\circ}$ then it is unique, i.e., $E_{x_\circ} = \{x^*\}$. Furthermore, it is globally asymptotically stable equilibrium relative to $\mathscr{C}_{x_\circ}$.*

Remark 6.2: Remarks 3.6 and 3.7 regarding boundedness and LaSalle's condition applies here also.

6.1.2 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 $\mathscr{N}_{A,B}$, the system (2.9) with kinetics $\mathscr{K}_A$ can be viewed as an uncertain system. However, this system is not in the form of the traditional types of parameter uncertainties known in the literature. In this subsection, we show that shifting the analysis of the system to reaction coordinates enables 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:

$$\dot{r}(t) = \frac{\partial R}{\partial x}(x(t))\Gamma r(t) = \rho(t)\Gamma r(t), \tag{6.1}$$

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:

$$\frac{\partial R}{\partial x}(x(t)) = \rho(t) = \sum_{i,j:\alpha_{ij}>0} \rho_{ji}(t)E_{ji}, \tag{6.2}$$

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 indexing map. Then, we can write (6.1) as:

$$\dot{r} = \sum_{i,j:\alpha_{ij}>0} \rho_{ji}(t)E_{ji}\Gamma r = \sum_{\ell=1}^{s} \rho_\ell(t)\Gamma^\ell r, \tag{6.3}$$

where $\Gamma^\ell = e_j\gamma_i^T$, $\rho_\ell(t) = \rho_{ji}(t)$, with $(i, j) = \kappa(\ell)$, and $\{e_j\}_{j=1}^{\nu}$ denotes the canonical basis of $\mathbb{R}^\nu$. Hence, equation (6.3) represents a linear parameter-varying system which has s nonnegative time-varying parameters $\{\rho_1(t), .., \rho_s(t)\}$ and the system matrix belongs to the conic hull of the set of rank-one matrices $\{\Gamma^1, ..., \Gamma^s\}$.

Hence, we have the following definition.

Definition 6.3 (Common Lyapunov Function)**.** *A function $\tilde{V} : \bar{\mathbb{R}}_+^\nu \to \bar{\mathbb{R}}_+$ is said to be a Lyapunov function for the linear system $\dot{r} = \Gamma^\ell r$ if it is locally Lipschitz, nonnegative, has a negative semi-definite time-derivative along the trajectories of the linear system, and $\ker \tilde{V} \subset \ker \Gamma^\ell$. Furthermore, $\tilde{V}$ is said to be a **common Lyapunov function** for the set of linear systems $\{\dot{r} = \Gamma^1 r, ..., \dot{r} = \Gamma^s r\}$ if it is a Lyapunov function for each of them, and $\ker \tilde{V} = \bigcap_{\ell=1}^{s} \ker \Gamma^\ell$.*

Hence, we are ready to state the main result.

Theorem 6.2 (Common Lyapunov Function)**.** *Given the system* (2.9)*. There exists a common Lyapunov function* $\tilde{V} : \bar{\mathbb{R}}_+^\nu \to \bar{\mathbb{R}}_+$ *for the set of linear systems* $\{\dot{r} = \Gamma^1 r, ..., \dot{r} = \Gamma^s r\}$ *if and only if* $(\tilde{V}, R)$ *induces the Robust Lyapunov function parameterized as* $V_R(x) = \tilde{V}(R(x))$ *for the CRN family* $\mathscr{N}_{A,B}$*.*

Before proving the result, the following lemma is needed.

Lemma 6.1 (Nonpositivity of the Lie Derivative of a Locally Lipschitz Function)**.** *Let* $\dot{x} := f(x)$*, and let* $V : \bar{\mathbb{R}}_+^n \to \bar{\mathbb{R}}_+$ *be a locally Lipschitz function such that:*

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

then $\dot{V}(x) \leq 0$ *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 [33]. Recall that for a locally Lipschitz function the *Clarke's gradient* at x can be written as $\partial_C V(x) := \operatorname{co} \partial V(x)$, where:

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

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 $p \in \partial_C V(x)$ 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 $p \in \bar{\partial} V(x)$.

As in [33], the Clarke's derivative of V at x in the direction of $f(x)$ can be written as $D^C_{f(x)} V(x) = \max\{p^T f(x) : p \in \partial_C V(x)\}$. 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:

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

for all x. □

Proof of Theorem 6.2. We show that the existence of the common Lyapunov function implies the existence of the RLF. Nonnegativity of V follows from the nonnegativity of $\tilde{V}$. Let $(i,j) = \kappa(\ell)$, recall that $\Gamma^\ell = e_j\gamma_i^T$, hence $\ker\tilde{V} = \bigcap_{\ell=1}^s \ker\Gamma^\ell = \ker\Gamma$. Therefore, $R(x) \in \ker V$ iff $\Gamma R(x) = 0$, which establishes the positive-definiteness of V.

We have assumed that $\tilde{V}$ has a negative semi-definite time-derivative for every linear system in the considered set. Hence, when $\tilde{V}$ is differentiable, we can write $(\partial\tilde{V}/\partial r)\Gamma^\ell r \leq 0$, $\ell = 1, ..., s$. Hence, for any $\rho_1, ..., \rho_s \in \bar{\mathbb{R}}_+$:

$$\sum_{\ell=1}^s \rho_\ell \frac{\partial\tilde{V}}{\partial r}\Gamma^\ell r \leq 0, \text{when } (\partial V(r)/\partial r) \text{ exists.} \tag{6.4}$$

Therefore, when $\tilde{V}$ is differentiable:

$$\dot{V}(x) = \frac{\partial\tilde{V}}{\partial R}\frac{\partial R}{\partial x}(x)\Gamma R(x) = \frac{\partial\tilde{V}}{\partial R}\left(\sum_{i,j:\alpha_{ij}>0} \frac{\partial R_j}{\partial x_i}(x)E_{ji}\right)\Gamma R(x), \tag{6.5}$$

where $\partial\tilde{V}/\partial R := (\partial\tilde{V}/\partial r)\Big|_{r=R(x)}$.
Now, denote $\rho_\ell = \frac{\partial R_j}{\partial x_i}(x)$, which is nonnegative by A3. This allows to write:

$$\dot{V}(x) = \sum_{\ell=1}^s \rho_\ell \frac{\partial\tilde{V}}{\partial R}E_{ji}\Gamma R(x) \tag{6.6}$$

$$= \sum_{\ell=1}^s \rho_\ell \frac{\partial\tilde{V}}{\partial R}\Gamma^\ell R(x) \leq 0, \text{ for almost all } x. \tag{6.7}$$

The last inequality follows from (6.4). Using Lemma 6.1, $\dot{V}(x) \leq 0$ for all x, and for all $R \in \mathscr{K}_A$.

In order to show the other direction, almost all properties outlined in Definition 6.3 are clearly satisfied, we just show nonincreasingness. Assume that there exists ℓ such that $\tilde{V}(r)$ is not nonincreasing along the trajectories of $\dot{r} = \Gamma^{\ell} r$. Consider the corresponding term in (6.6). Since $V(R(x))$ is a Lyapunov function for any choice of admissible rate reaction function R, choose $\rho_\ell = \frac{\partial R_j}{\partial x_i}$ to be large enough such that $\dot{V}(x) \geq 0$ for some x; a contradiction. □

Remark 6.3: Since the zero matrix belongs to the conic hull of $\{\Gamma^1, ..., \Gamma^s\}$, asymptotic stability can not be established by the mere existence of the common Lyapunov function. A LaSalle's argument is needed.

Remark 6.4: Although the dynamics of concentrations (2.9) or the dynamics of the extent of reaction (2.12) define positive systems, the differential linear inclusion that can be defined from (6.1) is not a positive differential inclusion. More precisely, this means that it is not necessarily true that all the matrices that belong to conic hull $\{\Gamma^1, ..., \Gamma^s\}$ are Metzler.

6.1.3 Dual Robust Lyapunov Function: Species Coordinates

The RLF introduced in the previous subsection is a function of $R(x)$. We investigate now RLFs that are functions of $x - x_e$. This is 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 ODE (2.9) is needed, and can be expressed by applying the Mean-Value theorem to the reaction rate function as the following Lemma states.

Lemma 6.2 (Alternative Representation)**.** *Given* (2.9)*, and let* x_e *be an equilibrium. Then, for any* $x_\circ \in \mathscr{C}_{x_e}$*, there exists* $x''(x)$ *such that* (2.9) *can be written equivalently*

as:

$$\dot{x} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e), , x(0) = x_\circ. \tag{6.8}$$

Proof. The claim follows by the Mean-Value Theorem [33] (or Taylor's theorem) which implies that there exists $\varepsilon_x \in [0, 1]$ such that $R(x) = R(x_e) + \frac{\partial R(x'')}{\partial x}(x - x_e)$, where $x'' := x_e + \varepsilon_x(x - x_e)$. □

Remark 6.5: It might seem that (6.8) is a linear system approximation based on linearization. However, it is not an approximation, but an exact expression. Furthermore, it is not a linearization since $\partial R/\partial x(x'')$ is a nonlinear function of x. Nevertheless, it can be described as a state-dependent linearization.

Let $z = x - x_e$, then similar to the previous section, the conic combination (6.2) can be used to rewrite (6.8) as:

$$\dot{z} = \Gamma \frac{\partial R}{\partial x}(x'')(x - x_e) = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma E^\ell z = \sum_{\ell=1}^{s} \rho_\ell(t) \Gamma_{i_\ell} e_{j_\ell}^T z, \tag{6.9}$$

where $\rho_\ell(t) = \frac{\partial R_{j_\ell}}{\partial x_{i_\ell}}(x''(x(t))$, and Γ_i is the i^{th} column of Γ. Therefore, the system dynamics has been embedded in the linear differential inclusion with vertices $\{\Gamma_{i_1} e_{j_1}^T, ..., \Gamma_{i_s} e_{j_s}^T\}$.

Let D^T be a matrix with columns that are the basis vectors of $\ker \Gamma^T$. The following theorem can be stated.

Theorem 6.3 (Common Lyapunov Function)**.** *Given the system* (2.9)*. There exists a common Lyapunov function $\hat{V} : \mathbb{R}^n \to \bar{\mathbb{R}}_+$ for the set of linear systems $\{\dot{z} = (\Gamma_{i_1} e_{j_1}^T)z, ..., \dot{z} = (\Gamma_{i_s} e_{j_s}^T)z\}$, with the constraint $D^T z(0) = 0$ for each of them if and only if $(\tilde{V}, W_{x_e}), W_{x_e} = x - x_e$ induces the Robust Lyapunov function parameterized as $V_{x_e}(x) = \hat{V}(x - x_e)$ for the CRN family $\mathscr{N}_{A,B}$.*

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

$$\dot{V} = \frac{\partial \hat{V}}{\partial z}\dot{z} = \frac{\partial \hat{V}}{\partial z}\sum_{\ell=1}^{s}\rho_\ell(t)\Gamma_{i_\ell}e_{j_\ell}^T z = \sum_{\ell=1}^{s}\rho_\ell(t)\left(\frac{\partial \hat{V}}{\partial z}\Gamma_{i_\ell}e_{j_\ell}^T z\right).$$

Since we have assumed that $\hat{V}$ is a common Lyapunov function for the set of linear systems $\{\dot{z} = (\Gamma_{i_1}e_{j_1}^T)z, ..., \dot{z} = (\Gamma_{i_s}e_{j_s}^T)z\}$ the proof can proceed in both directions in a similar way to the proof of Theorem 6.2. 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 (2.9) □

6.1.4 Relationship Between the Two Frameworks

We show now that if $\tilde{V}$ satisfy an assumption, then the Lyapunov function of the form $\hat{V}(x - x_e)$ can be used, where x_e is an equilibrium point for (2.9).

Hence, the following theorem can be stated.

Theorem 6.4 (Relationship)**.** *Let $V_1(x) = \tilde{V}(R(x))$ be representing an RLF for the network family $\mathscr{N}_{A,B}$. If there exists $\hat{V} : \mathbb{R}_n \to \bar{\mathbb{R}}_+$ such that for all r:*

$$\tilde{V}(r) = \hat{V}(\Gamma r), \tag{6.10}$$

then $V_2(x) = \hat{V}(x - x_e)$ represents an RLF for the network family $\mathscr{N}_{A,B}$, where x_e is an equilibrium point for (2.9)*.*

Proof. Condition 1 in Definition 6.1 is clearly satisfied. It remains to show the second condition. Let $z = x - x_e$. Then, whenever $\hat{V}$ is differentiable:

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

Before proceeding, we prove two statements: First, from (6.10), we get $(\partial\tilde{V}(r)/\partial r) = (\partial\hat{V}(\Gamma r)/\partial z)\Gamma$. Second, note that $x - x_e \in \mathrm{Im}(\Gamma)$, hence $\exists R(x')$ such that $\Gamma R(x') = x - x_e$,

where $R(x')$ can always be chosen nonnegative by AS1. Hence, when $\hat{V}$ is differentiable, we can use (6.8) to write:

$$\begin{aligned}\dot{V}_2(x) &= \frac{\partial \hat{V}(x-x_e)}{\partial r}\Gamma\frac{\partial R(x'')}{\partial x}(x-x_e)\\ &= \frac{\partial \tilde{V}(R(x'))}{\partial r}\frac{\partial R(x'')}{\partial x}\Gamma R(x')\\ &= \sum_{\ell=1}^{s}\rho_\ell\frac{\partial \tilde{V}(R(x'))}{\partial r}\Gamma^\ell R(x') \leq 0,\end{aligned}$$

where the last inequality follows from (6.7). Lemma 6.1 implies that $\dot{V}_2(x) \leq 0$ for all x. □

Remark 6.6: V_2 has a simpler structure that V_1 since it depends on $x - x_e$. However, it can be noted in the proof that for a specific choice of x_e, the Lyapunov function $\hat{V}(x-x_e)$ is nonincreasing only along trajectories that starts in $\mathscr{C}_{x_e}$.

Remark 6.7: If we consider the system for $z = \dot{x}$ where

$$\dot{z} = \Gamma\frac{\partial R(x)}{\partial x}z, Dz(0) = 0, \tag{6.11}$$

then $\hat{V}(z)$ is a Lyapunov function for the above system.

Relationship to the Extent of Reaction Formulation

Recall the extent of reaction that was introduced in Chapter 2, and is defined as: $\xi(t) = \int_0^t R(x(\tau))d\tau + \xi(0)$. If $x(t) \in \mathscr{C}_{x_e}$, then $\exists \xi^* \geq 0$ such that $x_e - x_\circ = \Gamma\xi^*$. We set $\xi(0) := \xi^*$. Hence, we can write:

$$\Gamma\xi(t) = x(t) - x_e,$$

and

$$\dot{\xi} = R(x_e + \Gamma\xi), \xi(0) := \xi^*, \tag{6.12}$$

which is the extent-of-reaction ODE representation of the dynamics of the CRN.

Therefore, we state the following result.

Corollary 6.5. *Given* Γ. *Let* $\tilde{V} : \bar{\mathbb{R}}_+^\nu \to \bar{\mathbb{R}}_+$. *Assume there exists* $\hat{V} : \mathbb{R}_+^n \to \bar{\mathbb{R}}_+$ *such that for all* r, $\tilde{V}(r) = \hat{V}(\Gamma r)$. *If* $\tilde{V}$ *is a common Lyapunov function for* $\{\dot{r} = e_{j_1}\gamma_{i_1}^T r, ..., \dot{r} = e_{j_s}\gamma_{i_s}^T r\}$ *where* $(i_\ell, j_\ell) = \kappa(\ell)$ *then* $\tilde{V}(\xi)$ *is nonnegative, and nonincreasing along the trajectories of* $\dot{\xi} = R(x_e + \Gamma\xi)$ *for any* $R \in \mathscr{K}_A$.

Proof. The first two statements follow from Theorems 6.2 and 6.4. We prove now the third statement. Using (6.10), (2.10) 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 (2.9).

□

6.2 Application to PWLR Lyapunov Functions

6.2.1 Relationship to Previous Results

In the previous chapters 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 6.1, 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 to provide alternative algorithms for the existence and construction of PWLR functions.

Consider a CRN (2.9) with a $\Gamma \in \mathbb{R}^{n\times r}$. Two representation of the PWLR Lyapunov function have been discussed. 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 $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ is a continuous PWL function given as

$$\tilde{V}(r) = |c_k^T r|,\ r \in \pm\mathcal{W}_k, k = 1, .., m/2,$$

where the regions $\mathcal{W}_k = \{r \in \mathbb{R}^\nu : \Sigma_k H r \geq 0\}, k = 1, .., m$ form a proper conic partition of $\mathbb{R}^\nu$, while $\{\Sigma_k\}_{k=1}^m$ are signature matrices with the property $\Sigma_k = -\Sigma_{m+1-k}, k = 1, .., m/2$. The coefficient vectors of each linear component can be collected in a matrix $C = [c_1, .., c_{\frac{m}{2}}]^T \in \mathbb{R}^{\frac{m}{2} \times r}$. 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 ℓ_∞-norm Lyapunov functions that have been used for linear systems in [78]. In fact, the next theorem establishes the link between the results introduced in §5.1 for checking candidate PWLR functions based on direct analysis and previous work on ℓ_∞ Lyapunov functions using the framework introduced in the previous section.

Proposition 6.6. *Given Γ and H. Let $V = \tilde{V} \circ R$ be a candidate continuous nonnegative PWLR with $C = [c_1 \ ... \ c_{\frac{m}{2}}]^T \in \mathbb{R}^{\frac{m}{2} \times r}$. Then $(\tilde{V}, R)$ induces an RLF if and only if:*

1. $\ker C = \ker \Gamma$, *and*

2. *there exists $\{\Lambda^\ell\}_{\ell=1}^s \subset \mathbb{R}^{\frac{m}{2} \times \frac{m}{2}}$ such that*

$$\Lambda^\ell H = -C\Gamma^\ell, \tag{6.13}$$

and $\lambda_k^\ell \Sigma_k > 0$, where $\Lambda^\ell = [{\lambda_1^\ell}^T ... {\lambda_{m/2}^\ell}^T]^T$.

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

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

$$\Lambda^\ell \tilde{C} = \tilde{C}\Gamma^\ell, \tag{6.14}$$

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

Proof. The proof can be carried out by performing algebraic manipulations on the results presented in Theorems 3.4 and 3.5. The function has been assumed continuous and non-negative. It remains to show that C4 is equivalent to (6.14). Considering (6.14) by row, it can be written as the following for $k \in \{1, .., \frac{m}{2}\}$:

$$\lambda_k^{\ell T} H = -c_{kj}\alpha_{ij}\gamma_i^T,$$

where $(i, j) = \kappa(\ell)$. c_{kj} can be replaced with $\text{sgn}(c_{kj})$ and α_{ij} can be replaced with 1 if we are considering only $i \in I_k, j \in J_{ki}$. Therefore, equivalence with (3.12) is established.

For the convex PWL function, we can write (3.12) as follows with replacing $\text{sgn}(c_{kj})$ by c_{kj}, and inserting α_{ij}:

$$-c_{kj}\alpha_{ij}\gamma_i^T = \left(\sum_{j=1,j\neq k}^{m} \lambda_{kj}^{\ell}\right) c_k^T - \sum_{j=1,j\neq k}^{m} \lambda_{kj}^{\ell} c_j^T.$$

Let $\lambda_{kk} = \sum_{j=1,j\neq k}^{m} \lambda_{kj}^{\ell}$, then

$$c_k^T e_j \gamma_i^T = \sum_{j=1,j\neq k}^{m} \lambda_{kj}^{\ell} c_j^T - \lambda_{kk}^{\ell} c_k^T,$$

which enforces Λ^ℓ to be Metzler and $\Lambda^\ell \mathbf{1} = 0$ as above. □

Remark 6.8: The symmetries in (6.14) imply that it can be written equivalently:

$$C\Gamma^\ell = \tilde{\Lambda}^\ell C, \tag{6.15}$$

where $\tilde{\Lambda}^\ell$ is an $\frac{m}{2} \times \frac{m}{2}$ matrix which is defined by subtracting the upper $\frac{m}{2} \times \frac{m}{2}$ blocks of Λ^ℓ from each other. $\tilde{\Lambda}^\ell$ satisfies:

$$\max_k \left(\tilde{\lambda}_{kk}^{(\ell)} + \sum_{j\neq k} |\tilde{\lambda}_{kj}^{(\ell)}|\right) \leq 0. \tag{6.16}$$

This is exactly the condition that ℓ_∞-norm Lyapunov functions need to satisfy for a linear system [68, 57]. This shows that Theorem 6.2 provides 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 ℓ_1 Lyapunov functions of the form $V(x) = \|CR(x)\|_1$ directly by replacing condition (6.16) by

$$\max_k \left(\tilde{\lambda}_{kk} + \sum_{j \neq k} |\tilde{\lambda}_{jk}| \right) \leq 0, \tag{6.17}$$

instead of converting them to the ℓ_∞-norm form.

We use Theorem 6.2 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 the previous chapter, we use here alternative condition which are stated in the following proposition.

Proposition 6.7. *Given the system* (2.9) *and a partitioning matrix* $H \in \mathbb{R}^{p \times r}$. *Consider the linear program:*

$$\begin{aligned}
\textit{Find} \quad & c_k, \xi_k, \zeta_k \in \mathbb{R}^\nu, \Lambda^\ell \in \mathbb{R}^{m \times m}, \eta_{kj} \in \mathbb{R}, \\
& k = 1, .., \tfrac{m}{2}; j \in \mathcal{N}_k, \ell = 1, .., s, \\
\textit{subject to} \quad & c_k^T = \xi_k^T \Sigma_k H, \\
& C\Gamma^\ell = -\Lambda^\ell H, \lambda_k^\ell \Sigma_k \geq 0, \\
& c_k - c_j = \eta_{kj} \sigma_{k s_{kj}} h_{s_{kj}}, \\
& \xi_k \geq 0, \mathbf{1}^T \xi_k > 0, \Lambda^\ell \geq 0.
\end{aligned}$$

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

Remark 6.9: The LaSalle's condition can be verified via a graphical algorithm described before.

6.2.2 The Dual PWL Lyapunov Function

In the previous section it has been shown that if there exists $\hat{V}$ such that $\tilde{V}(r) = \hat{V}(\Gamma r)$, then there exists a dual RLF for the same network family. In the case of PWLR Lyapunov functions condition 1 in Proposition 6.6 implies that this is always possible. Hence, consider a PWLR Lyapunov function defined with a partitioning matrix H as in (3.5). By Proposition 6.6 and the assumption that $\ker H = \ker \Gamma$, there exists $G \in \mathbb{R}^{p\times n}$ and $B \in \mathbb{R}^{\frac{m}{2}\times n}$ such that $H = G\Gamma$ and $C = B\Gamma$. Similar to $\{\mathcal{W}\}_{k=1}^{m}$, we can define the regions:

$$\mathcal{V}_k = \{z | \Sigma_k G z \geq 0\}, k = 1, .., m,$$

where it can be seen that $\mathcal{V}_k$ has nonempty interior iff $\mathcal{W}_k$ has nonempty interior.
Therefore, as the pair (C, H) specify the PWLR function fully, also the pair (B, G) specifies the function:

$$\hat{V}(z) = b_k^T z, \text{ when } \Sigma_k G z \geq 0,$$

where $B = [b_1, ..., b_{\frac{m}{2}}]^T$. 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 [27, 28][1].

Theorem 6.4 established that if $\tilde{V}(R(x))$ is an RLF, then $\hat{V}(x - x_e)$ is an RLF also. The following theorem shows that converse holds also for PWLR RLFs, however, it is worth

[1]Results presented in [28] have been published after we have submitted our papers. In fact, we became aware of it by a reviewer of our paper [4]. Despite the similarity with our dual PWL formulation, the vast majority of the results presented in this dissertation are novel.

recalling from Remark 6.6 that $\tilde{V}(R(x))$ is nonincreasing for all initials conditions, while $\hat{V}(x - x_e)$ is nonincreasing only on $\mathscr{C}_{x_e}$.

Theorem 6.8. *Given* (2.9). *Then, if there exists* $G \in \mathbb{R}^{p\times n}$ *and* $B \in \mathbb{R}^{\frac{m}{2}\times n}$ *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.*

Proof. The first statement follows from Theorem 6.4. In order to show the second statement, let $V_2(x) = b_k^T(x - x_e)$, for $x - x_e \in \mathcal{V}_k$. We 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: $G = [I\ \hat{G}^T]^T$. This representation implies that the sign of $x - x_e$ is determined in every region $\mathcal{V}_k$. Now, assume that $x - x_e \in \mathcal{V}_k^\circ$, then:

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

Let $R_j(x) \in \operatorname{supp} R(x)$, and let $\alpha_{ij} > 0$. Since R is nondecreasing by A3, if $\operatorname{sgn}(x_i - x_{e_i}) \operatorname{sgn}(c_{kj}) > 0$, there exists $R \in \mathscr{K}_A$ such that $\dot{V}_2(x) \geq 0$. Hence, this implies that the inequality $\operatorname{sgn}(c_{kj}) \operatorname{sgn}(x_i - x_{e_i}) \leq 0$ holds. Fix j, if there exists i_1, i_2 such that $\alpha_{i_1 j}, \alpha_{i_2 j} > 0$ and $\operatorname{sgn}(x_{i_1} - x_{e_{i_1}}) \operatorname{sgn}(x_{i_2} - x_{e_{i_2}}) < 0$, then $\sigma_{kj} := 0$. Otherwise, $\sigma_{kj} := \operatorname{sgn}(x_i - x_{e_i})$ for some i such that $\alpha_{ij} > 0$.

Hence, in order to have $\dot{V}_2(x) \leq 0$ for all $R \in \mathscr{K}_A$ we need that $\sigma_{kj}(x_i - x_{e_i}) \geq 0$ whenever $x - x_e \in \mathcal{V}_k$, for all k, j, i with $\alpha_{ij} > 0$. By Farkas Lemma [79], this is equivalent to the existence of $\lambda_{kji} \in \bar{\mathbb{R}}_+^p, \zeta_{kji} \in \mathbb{R}^\iota$ such that

$$\sigma_{kj} e_i^T = \lambda_{kji}^T \Sigma_k G + \zeta_{kji}^T D, \tag{6.18}$$

where $D^T \in \mathbb{R}^{\iota\times n}$ is a matrix of the basis vectors for $\ker \Gamma^T$.

If we multiply both sides of (6.18) by Γ from the left, then we get condition C4 in Theorem 3.4 which is necessary and sufficient for $\dot{V}_1(x) = \frac{d}{dt}(c_k^T R(x)) \leq 0$. □

Remark 6.10: Since $D^T(x - x_e) = 0$ for $x \in \mathscr{C}_{x_e}$, then if $\|B(x - x_e)\|_\infty$ is an RLF, then $\|(B + YD^T)(x - x_e)\|_\infty$ is also an RLF for an arbitrary matrix Y. Furthermore, since Theorem 6.8 has shown that the reaction-based and the species-based representations are equivalent; it is easier to check and construct RLFs in the reaction-based formulation.

6.2.3 Robust Non-singularity and Exponential Stability

Using the notation defined previously in this chapter the following result can be proven.

Theorem 6.9 (Robust Nonsingularity)**.** *Given* (2.9)*. Assume that it is a graphically stable network. If for some realization $R \in \mathscr{K}_A$ there exists a point in the interior of a proper stoichiometric class such that the reduced Jacobian is non-singular at it, then the reduced Jacobian is non-singular with any realization of the kinetics is in the interior of $\mathbb{R}^n_+$. This implies that any positive equilibrium of this network is isolated relative to its class.*

Proof. We mainly use the result of Theorem 4.4 which implies that the negative Jacobian is P_0 for any choice of $R \in \mathscr{K}_A$. Using the Cauchy-Binet formula [20], let $I \subset \{1, .., n\}$ be an arbitrary subset so that $|I| = k$. The corresponding principal minor can be written as:

$$\det{}_I\left(-\Gamma\frac{\partial R}{\partial x}\right) = \sum_{J\subset\{1,..,\nu\},|J|=k} \det(-\Gamma_{IJ}) \det\left(\frac{\partial R}{\partial x}\right)_{IJ} \overset{(*)}{=} \sum_\iota a_\iota \prod_{\ell\in L_\iota\subset\{1,..,s\}} \rho_\ell,$$

where $(*)$ refers to the fact that the sum can be expressed as a linear combination of products of $\rho_1, ..., \rho_s$. We claim that the coefficients a_ι are all nonnegative. To show this, assume for the sake of contradiction that there is some a_{ι_*} negative. If we set all ρ's to zero except the ones appearing in the ι_*^{th} term, then this implies that the corresponding principal 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 $k\times k$ principal minors of the negative Jacobian is positive, where $k = \text{rank}(\Gamma)$. Since it is assumed that there exists a point for which the reduced Jacobian is non-singular, this implies that the sum of principal minors is positive for some choice of $\rho_1, .., \rho_s$. Since

all of the principal minors are nonnegative, then at least one of them is positive. By AK4, that principal minor stays positive for any choice of positive $\rho_1, .., \rho_s$, i.e. it stays positive over the interior of $\mathbb{R}^n_+$. □

Exponential Stability and an Alternative Proof

We have shown that the existence of a PWLR Lyapunov function implies that it is a common Lyapunov function for a set of linear systems. This implies that if there exists a PWLR function induced by $\tilde{V}$ then it is a Lyapunov function for the variational system $\dot{\delta\xi} = \frac{\partial R}{\partial x}(x)\Gamma\delta\xi$ for any fixed x. In fact, one of the properties of piecewise linear Lyapunov function is that the asymptotic stability of an equilibrium implies exponential stability.

Theorem 6.10 (Exponential Stability)**.** *Given* (2.9) *that admits a PWLR function. If a positive equilibrium x_e is isolated relative to $\mathscr{C}_{x_e}$, then it is exponentially asymptotically stable.*

Proof. Since, as remarked above, the piecewise linear Lyapunov function is a common Lyapunov function for the variational system, a result by Blanchini and Miani [29, Theorem 4.46] implies that the Jacobian of (2.9) can not admit purely imaginary eigenvalues. Since an isolated equilibrium has a non-singular Jacobian evaluated at it, and excluding the possibility of imaginary eigenvalues, this implies that the equilibrium is exponentially asymptotically stable. □

Remark 6.11: Recall Remark 3.8. If the stoichiometry classes are compact and contain only isolated equilibria, then the uniqueness of equilibria claim of Theorem 3.3 can be verified without the use of a LaSalle's condition, since Theorem 6.10 shows all isolated equilibria are, at least, locally exponentially stable. Poincarè-Hopf Theorem can be used thereafter. Note that this also has been shown by Theorem 4.5.

Remark 6.12: For a conservative network the existence of an isolated equilibrium implies that it is unique (Theorem 4.5), it is locally asymptotically stable (Theorem 6.10), the level

sets of the Lyapunov function are always invariant (Theorem 3.2), the network is persistent (Theorem 4.7), and the state space is compact. However, global asymptotic stability (GAS) can not be claimed directly without a LaSalle argument. It is potentially possible that the equilibrium is not GAS; for instance, there can be a limit cycle living in the boundary of the basin of attraction that attracts the outside trajectories. Despite the fact that this seems unlikely, it can not be precluded completely without a proof. Therefore, the graphical algorithm for verifying the LaSalle's argument §3.5 is still needed to claim GAS.

Since asymptotic stability in our case becomes synonymous with non-singularity, an alternative proof of Theorem 6.9 can be given. The alternative proof has been included in the dissertation since it has been already written when the simpler proof above has been conceived. Therefore, *we have decided to keep it.*

Robust non-singularity have been analyzed with extreme point methods over boxes by Barmish [21], and more recently Blanchini and Giordano [28] applied those results by providing an algorithm for checking it for reaction networks. The following proof takes this a step further by showing that robust non-singularity follows directly from the existence of at least one positive isolated equilibrium. The full proof is provided to make the dissertation self-contained.

Alternative Proof of Theorem 6.9. Recall the rank-one decomposition of the Jacobian (6.9). Let T be a transformation matrix T given by (2.13), and consider the Jacobian in the transformed coordinates as:

$$J = T\Gamma\frac{\partial R}{\partial x}T^{-1} = \sum_{\ell=1}^{s}\rho_\ell T\Gamma_j e_i^T T^{-1}$$

Similar to (2.14), the reduced Jacobian can be taken as the upper left nonzero block of the Jacobian, can be written similarly as a sum of rank-one matrices:

$$J_1 = \sum_{\ell=1}^{s}\rho_\ell u_\ell v_\ell^T,$$

where $u_\ell v_\ell^T$ is the rank-one factorization of the upper left block of the rank-one matrix $T\Gamma_j e_i^T T^{-1}$.

Assume that there exists an isolated positive equilibrium. Hence, for some $\rho_1^*, ..., \rho_s^* > 0$, J_1 is non-singular. Our claim is: J_1 *is non-singular for all positive* $\rho_1, ..., \rho_s$.

Let $\rho = [\rho_1, ..., \rho_s]^T$, the problem can be transformed to the context of determinants, where we need to show that

$$g(\rho) = \det(-J_1) = \det\left(-\sum_{\ell=1}^{s} \rho_\ell u_\ell v_\ell^T\right) > 0,$$

for all $\rho \gg 0$. Since a common Lyapunov function exists, this implies that the Jacobian is Hurwitz[2] for all *nonnegative* ρ. Hence, $g(\rho) \geq 0$ for all $\rho \geq 0$.

Since J_1 is decomposed into a sum of rank-one matrices, the function g is multi-affine in $\rho_1, ..., \rho_s$. This follows by the rank-one update formula as follows:

$$g(\rho) = \det\left(-\rho_1 u_1 v_1^T - \sum_{\ell=2}^{s} \rho_\ell u_\ell v_\ell^T\right) = \det\left(-\sum_{\ell=2}^{s} \rho_\ell u_\ell v_\ell^T\right) - \rho_1 v_1^T \operatorname{adj}\left(-\sum_{\ell=2}^{s} \rho_\ell u_\ell v_\ell^T\right) u_1,$$

which is affine in ρ_1. The same argument can be repeated for $\rho_2, ..., \rho_s$.

Since the function g is homogeneous the claim can be proven if we show that g is positive over the interior of the box $[0, \rho_1^*] \times ... \times [0, \rho_s^*]$. We have a nonnegative multi-affine function defined over a box, therefore it achieves its maxima and minima over the extreme points [21]. For the sake of contradiction, assume that there exists a point $\hat{\rho}$ in the interior of the box such that $g(\hat{\rho}) = 0$. Fix $\hat{\rho}_2, ..., \hat{\rho}_s$, then $g(\rho_1, \hat{\rho}_2, .., \hat{\rho}_s)$ is a nonnegative linear function defined over $[0, \rho_1^*]$ which vanishes over a point in the interior of the interval. Therefore, this function is identically zero. In particular, $g(\rho_1^*, \hat{\rho}_2, ..., \hat{\rho}_s) = 0$. This argument can be repeated for the rest of the indices to show that $g(\rho_1^*, \rho_2^*, ..., \rho_s^*) = 0$; a contradiction. □

[2] A matrix is Hurwitz if all its eigenvalues are in the closed left half plane.

6.3 Contraction Analysis

Contraction analysis is an approach which studies stability of a trajectory with respect to other trajectories, and not with respect to a given equilibrium point. This can be made analogous to investigating the convergence of an infinite sequence in the sense of Cauchy, rather than analyzing it with respect to a given limit 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 [63], [75], [6].

The are several formulations for contraction analysis. We are going to present the formulation that utilizes matrix measures, or logarithmic norms.

Definition 6.4 (Logarithmic Norms)**.** *For a given norm $\|.\|_*$ on $\mathbb{R}^n$, the associated matrix measure (or logarithmic norm) can be defined as follows for a matrix $A \in \mathbb{R}^{n\times n}$:*

$$\mu_*(A) := \limsup_{h\to 0^+} \frac{\|I + hA\|_* - 1}{h}. \tag{6.19}$$

Note that the same definition applies if $\|.\|_*$ is a semi-norm.

Remark 6.13: The logarithmic norm can be evaluated for the standard norms, in fact, the following expression can be used for the ℓ_∞ norm:

$$\mu_\infty(A) = \max_i \left(a_{ii} + \sum_{j\neq i} |a_{ij}| \right). \tag{6.20}$$

Note that this is an identical expression to one appearing in (6.16).

Remark 6.14: Matrix measures can be defined using convex Lyapunov functions in general [94], however, we limit ourselves to norms.

For a dynamical system, negativity of the logarithmic norm can be linked to contraction. This result has been stated in different forms, refer to the tutorial [6] for more details. We state the result as follows.

Theorem 6.11 (Aminzare and Sontag [6]). *Consider a dynamical system $\dot{x} = f(x)$ defined on a convex subset of $\mathbb{R}^n$. Let $\|.\|_*$ 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:

$$\|\varphi(t;x) - \varphi(t;y\|_* \leq e^{ct} \|\varphi(0;x) - \varphi(0;y)\|_*. \tag{6.21}$$

Note that if $c < 0$ the solutions of the system are exponentially contracting. If $c = 0$, then the system is non-expansive. The choice of the norm plays a crucial rule even with respect to diagonal weighings. Russo et al. [82] have applied the result above to CRNs by weighting the ℓ_1-norm with a diagonal matrix.

This motivates the following conjecture: since our convex PWLR Lyapunov functions are norms weighted by a non-square matrix, it there is a potential link with contraction analysis. The link between the logarithmic norms and norm-based Lyapunov functions has been established before [57]. Therefore, it might be 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.

Theorem 6.12 (Relationship to Contraction Analysis).

1. *Given the extent of reaction representation of CRNs $\dot{\xi} = R(x_e + \Gamma\xi)$. Assume that there exists a convex PWLR function $\tilde{V}(\xi) = \|C\xi\|_\infty$, and let μ_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* μ_B *be the logarithmic norm associated. Let the associated Jacobian be:* $J_2(x) := \Gamma \frac{\partial R}{\partial x}$. *Then,*

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

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

Proof. Write the logarithmic norm expression using (6.19):

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

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:

$$\begin{aligned}
\left\| I + h \frac{\partial R}{\partial x} \Gamma \xi \right\|_C &= \sup_{\|C\xi\|_\infty = 1} \left\| C \left(I + h \frac{\partial R}{\partial x} \Gamma \right) \xi \right\|_\infty \\
&\overset{(\star)}{=} \sup_{\|C\xi\|_\infty = 1} \left\| C\xi + h \sum_{\ell=1}^{s} \rho_\ell(x) C e_j \gamma_i^T \xi \right\|_\infty \\
&\overset{(\clubsuit)}{=} \sup_{\|C\xi\|_\infty = 1} \left\| C\xi + h \sum_{\ell=1}^{s} \rho_\ell \tilde{\Lambda}^\ell C\xi \right\|_\infty \\
&\leq \sup_{\|C\xi\|_\infty = 1} \left\| I + h \sum_{\ell=1}^{s} \rho_\ell \tilde{\Lambda}^\ell \right\|_\infty \|C\xi\|_\infty \\
&= \left\| I + h \sum_{\ell=1}^{s} \rho_\ell \tilde{\Lambda}^\ell \right\|_\infty,
\end{aligned}$$

where $(\star)$ is by (6.2) and $(\clubsuit)$ is by (6.15). Therefore, the expression of the logarithmic norm above can be written as:

$$\mu_C(J_1(\xi)) \leq \mu_\infty \left(\sum_{\ell=1}^{s} \rho_\ell \tilde{\Lambda}^\ell \right) \leq \sum_{\ell=1}^{s} \rho_\ell \mu_\infty(\tilde{\Lambda}^\ell) = 0, \tag{6.22}$$

where the inequalities follow by the subadditivity of the logarithmic norm and (6.16).

Note since C has nonempty kernel space, then $\|C\xi\|_\infty$ is a semi-norm. However, Theorem 6.11 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 $T_1 = [\hat{T}_1, v_1, .., v_{\nu-\nu_r}]^T$, where $\{v_1, .., v_{\nu-\nu_r}\}$ is a basis of $\ker\Gamma$, $\nu_r = rank(\Gamma)$, and $\hat{T}_1$ is chosen so that T_1 is invertible. Defining $\hat{\xi} = T\xi$, then the first ν_r coordinates of $\hat{\xi}$ are decoupled from the rest. Hence, inequality (6.22) can be established similarly for the reduced Jacobian which is the upper right $\nu_r \times \nu_r$ block of $T_1 J_1(\xi) T_1^{-1}$. The norm in the reduced subspace is $\|.\|_{\hat{C}} : z \mapsto \|\hat{C}z\|_\infty, z \in \mathbb{R}^\nu$, where $\hat{C}$ is $\frac{m}{2} \times \nu_r$ defined as the nonzero columns of CT_1^{-1}. The equations $Ce_j\gamma_i^T = \tilde{\Lambda}^\ell C$ are equivalent to $(CT_1^{-1})(T_1 e_j \gamma_i^T T_1^{-1}) = \tilde{\Lambda}^\ell (CT_1^{-1})$. Therefore, everything goes through in the reduced space, and the same upper bound is valid.

The same argument can be replicated to prove the second item in the theorem. This is accomplished by utilizing the alternative representation (6.8), the rank-one decomposition of the Jacobian (6.9), and noting that conditions (6.15) can be written as: $B\Gamma_i e_j^T = \tilde{\Lambda}^\ell B + Y^\ell D^T$ for some matrices $Y^1, .., Y^\ell$. The reduced space argument can be carried out also by using a transformation matrix $T_2 = [\hat{T}_2, D]^T$. □

Remark 6.15: The upper bound $\mu_\infty\left(\sum_{\ell=1}^s \rho_\ell \tilde{\Lambda}^\ell\right)$ can be identical to zero especially if $\frac{m}{2} \geq n$. Therefore, an analogous concept to a LaSalle argument need to be introduced. However, in a special case strict negativity can be establish as the next theorem shows.

Theorem 6.13. *Given* (2.9). *If there exists a PWLR Lyapunov function of the form* $V(x) = \|\Theta\dot{x}\|_\infty = \|\Theta\Gamma R(x)\|_\infty$, *and* $\Theta = diag[\theta_1, ..., \theta_n]$ *is a nonzero nonnegative diagonal matrix, then* (2.9) *is exponentially contractive in* $\mathscr{C}^\circ_{x_e}$.

Proof. Remember that $\rho_1, .., \rho_s$ correspond to the nonzero entries of $\partial R/\partial x$ which are strictly positive in $\mathbb{R}^n_+$ by AK3, hence the proof can be accomplished by showing that $\mu_\infty\left(\sum_{\ell=1}^s \rho_\ell \tilde{\Lambda}^\ell\right) < 0$ for any positive $\rho_1, .., \rho_s$.. To show that, it is sufficient to show that

for each $k \in \{1, .., \frac{m}{2}\}$, there exists $\ell \in \{1, ..s\}$ such that $\lambda^{\ell}_{kk} + \sum_{j \neq k} |\lambda^{\ell}_{kj}| < 0$.
Since E might have zero rows, the function can be written (by reordering species if necessary) as $V(x) = \|[\Theta_d, O]\dot{x}\|_\infty$, where Θ_d is an $n_d \times n_d$ positive diagonal matrix for some $n_d \leq n$. Hence, the coefficient vectors are $c_k = \gamma_i, k = i, 1 \leq i \leq n_d$. By AS1, c_k is orthogonal to a positive vector, and hence must have a strictly negative element, say γ_{ij}. Hence, this implies that X_i is a reactant of $\mathbf{R}_j$, and $\partial R_j / \partial x_i$ is nonzero. Let $\ell = \kappa^{-1}(i, j)$. Therefore, recalling the proof of Proposition 6.6 and (3.14), it can be seen it is possible to choose λ^{ℓ}_k as follows: $\lambda^{\ell}_{kk} = -\theta_{kk}$ and $\lambda^{\ell}_{kj} = 0, k \neq j$. Hence, $\lambda^{\ell}_{kk} + \sum_{j \neq k} |\lambda^{\ell}_{kj}| = -\theta_{kk} < 0$. □

Remark 6.16: The dual PWL function is $V_2(x) = \|\Theta(x - x_e)\|_\infty$.

6.3.1 Variational Dynamics and LaSalle Argument for Contraction Analysis

In a recent work, Forni and Sepulchre [46] have 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 (6.12) is $V_F : \boldsymbol{T}\bar{\mathbf{R}}^{\nu}_{+} \to \bar{\mathbf{R}}_{+}$. If contraction analysis was carried out with respect to the norm: $\|.\|_* : \xi \mapsto \|C\xi\|_\infty$, then the corresponding Finsler-Lyapunov function would be

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

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

$$\dot{\delta\xi} = \frac{\partial R}{\partial x} \Gamma \delta\, \xi. \tag{6.23}$$

The Finsler structure induces a distance function, which is, in this case, $d_F(x, y) = \|C(x - y)\|_\infty$. Hence, if V_F were strictly decreasing then this would imply that this system were

incrementally asymptotically stable with respect to the distance function [46], which is equivalent to the result given by Theorem 6.11. However, if 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 defined in §3.5 can be used for the Finsler-Lyapunov function. The following theorem states the result.

Theorem 6.14 (Strict Contraction)**.** *Given* (2.9)*. Assume that* $V(x) = \|CR(x)\|_\infty$ *is a PWLR Lyapunov function that satisfies condition C5′i. Then the trajectories of* (6.12) *are exponentially contractive with respect to the norm* $\|.\|_* : \xi \mapsto \|C\xi\|_\infty$ *in directions orthogonal to* $\ker\Gamma$.

Proof. As per [46, 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 (6.23). Since V_F is a piecewise function it can be studied per partition regions as before. Hence let $V_F(\delta\xi) = c_k^T\delta\xi$ when $\delta\xi \in \mathcal{W}_k$. Then,

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

Note that the expression above is analogous to (3.13), where $\operatorname{sgn}(\Gamma\delta\xi)$ can be made constant in each partition region. In fact, the arguments of the proof of Theorem 3.6 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 $\Gamma\delta\xi(t) \equiv 0$. □

Remark 6.17: C5′i is sufficient since $\boldsymbol{T}\bar{\mathbf{R}}_+^\nu$ has no boundary.

6.4 Piecewise Quadratic in Rates Lyapunov Functions

The most widely used class of Lyapunov functions in the literature is the class of quadratic functions. However, as it has been known that this class of functions is insufficient for uncertain systems stability analysis, convex piecewise linear [69, 26] and convex piece-

wise quadratic [69] counterparts have been proposed. More recently, piecewise quadratic Lyapuonv functions have been used for piecewise affine and hybrid systems [56]. In this section we use Theorem 6.2 to cast a semi-definite program (SDP) for constructing Piecewise Quadratic in Rates (PWQR) Lyapunov function over a given polyhedral conic partition defined as in the previous section. Furthermore, we show that the existence of a PWLR Lyapunov function implies automatically that our PWQR SDP is feasible over the same partition. Thus, the class of PWQR Lyapunov functions is potentially more general than the PWLR functions over a fixed partition.

However, a major disadvantage of PWQR Lyapunov functions defined on polyhedral partitions is the absence of tight tools for checking positive definiteness such as the Farkas Lemma. The corresponding concept here is the concept of *copositive matrices*. A matrix $A \in \mathbb{R}^{n\times n}$ is said to be *copositive* if $x^T Ax \geq 0$ for all $x \geq 0$. The class of optimization problems that involves copositive constraints is termed *copositive programming*. Although copositive programs are convex, solving them generally is shown to be NP-hard [40]. Therefore, several semi-definite relaxations of copositive constraints have been proposed [40]. A simple relaxation method (an S-procedure type) relies on the observation that the class of copositive matrices encompasses the classes of positive semi-definite matrices, and nonnegative matrices. Therefore, copositive constraints can be relaxed to a sum of a nonnegative and semi-definite matrices. This relaxation is exact only for $n \leq 4$, i.e there exists copositive matrices with $n > 4$ that can not be written as a sum of positive semi-definite and nonnegative matrices [40].

We are now ready to define PWQR functions over a conic polyhederal partition.

Definition 6.5. *Let H be given. A function V is a PWQR function if it has the representation $V = \tilde{V} \circ R$, where $\tilde{V} : \bar{\mathbb{R}}^{\nu}_{+} \to \bar{\mathbb{R}}_{+}$ is a continuous nonnegative PWQ function which*

has the form:

$$\tilde{V}(r) = r^T P_k r + 2c_k^T r = \begin{bmatrix} r \\ 1 \end{bmatrix}^T \begin{bmatrix} P_k & c_k^T \\ c_k & 0 \end{bmatrix} \begin{bmatrix} r \\ 1 \end{bmatrix}, \text{ if } r \in \mathcal{W}_k, \tag{6.24}$$

for some matrices $\{P_k\}_{k=1}^m \subset \mathbb{R}^{\nu\times\nu}, \{c_k\}_{k=1}^m \subset \mathbb{R}^\nu$, *with* $P_k = P_{m+1-k}, c_k = -c_{m+1-k}$, *for* $k = 1, .., \frac{m}{2}$.

In order to construct such functions we need to ensure that V and $-\dot{V}$ are nonnegative over the interior of the partition regions. This amounts to add a nonnegativity constraint of a quadratic form over a polyhedral region. Hence, our problem is essentially a copositive programming problem, which we relax to semi-definite programming as in the following theorem.

Theorem 6.15. *Given the system* (2.9) *and a partitioning matrix* $H \in \mathbb{R}^{p\times r}$. *Consider the semi-definite program:*

$$\begin{aligned} \textit{Find} \quad & P_k \in \mathbb{S}^r, c_k \in \mathbb{R}^\nu, A_k^1, A_k^2, B_{k\ell}^1, B_{k\ell}^2 \in \mathbb{S}^p, \xi_k, \zeta_k \in \mathbb{R}^p, \\ & \lambda_{kj} \in \mathbb{R}^r, \eta_{kj} \in \mathbb{R}, k = 1, .., \tfrac{m}{2}, \ell = 1, .., s, j \in \mathcal{N}_k \end{aligned}$$

subject to

$$\begin{bmatrix} P_k & c_k^T \\ c_k & 0 \end{bmatrix} \geq \begin{bmatrix} (\Sigma_k H)^T (A_k^1 + A_k^2)(\Sigma_k H) & \xi_k^T \Sigma_k H \\ (\xi_k^T \Sigma_k H)^T & 0 \end{bmatrix}, \tag{6.25}$$

$$\begin{bmatrix} \Gamma^{\ell T} P_k + P_k \Gamma^\ell + & \\ (\Sigma_k H)^T (B_{k\ell}^1 + B_{k\ell}^2)(\Sigma_k H) & c_k^T \Gamma^\ell + \zeta_k \Sigma_k H \\ (c_k^T \Gamma^\ell + \zeta_k \Sigma_k H)^T & 0 \end{bmatrix} \leq 0, \tag{6.26}$$

$$P_k - P_j = \lambda_{kj} h_{s_{kj}}^T + h_{s_{kj}} \lambda_{kj}^T, c_k - c_j = \eta_{kj} h_{s_{kj}}, \tag{6.27}$$

$$P_k U = 0, c_k^T U = 0, \tag{6.28}$$

$$A_k^1, B_{k\ell}^1 \succeq 0, A_k^2, B_{k\ell}^2 \geq 0, \xi_k \geq 0, \zeta_{kj} \geq 0.$$

If the SDP is feasibleand $\tilde{V}$ (6.24) *satisfies* $\ker \tilde{V} = \ker \Gamma$*, then* $V = \tilde{V} \circ R$ *is a Robust Lyapunov function for the network family* $\mathscr{N}_{A,B}$*.*

Proof. We show that $\tilde{V}$ is a common Lyapunov function for $\{\dot{r} = \Gamma^1 r, ..., \dot{r} = \Gamma^s r\}$ as in Definition 6.3.

In order to show nonnegativity, inequality (6.25) implies that:

$$r^T P_k r + 2c_k^T r \geq (\Sigma_k H r)^T (A_k^1 + A_k^2) \Sigma_k H r + 2c_k^T (\Sigma_k H) r,$$

and since $A_k^1 + A_k^2$ is copositive this implies that $\tilde{V}(r) \geq 0$ when $r \in \pm W_k, k = 1, .., \frac{m}{2}$, which establishes nonnegativity. Positive-definiteness follows from (6.28) and the assumption in the statement of the theorem.

For continuity, Lemma 3.2 implies that it is sufficient to establish it between neighboring regions. Therefore, assume $j \in \mathcal{N}_k$, and let $h_{s_{kj}}^T r = 0$ be the intersection hypersurface, then (6.27) implies that $r^T P_k r + 2c_k^T r = r^T P_j r + 2c_j^T r$ when $r \in \mathcal{W}_k \cap \mathcal{W}_j$. The other direction holds also by writing $P_k - P_j$ over the decomposition $\mathbb{R}^\nu = \text{span}\{h_{s_{kj}}\} \oplus \text{span}\{h_{s_{kj}}\}^\perp$. Continuity of $\tilde{V}$ implies also that $\tilde{V}$ is locally Lipschitz.

In order to show negative semi-definite derivative, consider the ℓ^{th} system, and let $r \in \mathcal{W}_k^\circ$, then:

$$\dot{\tilde{V}}_\ell(r) = r^T (\Gamma^\ell P_k + P_k \Gamma^\ell) r + 2c_k^T \Gamma^\ell r.$$

Note that (6.26) implies that $\dot{\tilde{V}}_\ell(r)) \leq 0$ when $r \in \mathcal{W}_k$. As it is true for all k, then $\dot{\tilde{V}}_\ell(r)) \leq 0$ for all $\ell = 1, ..s$, and all r such that $\partial \tilde{V}(r)/\partial r$ exists. By Lemma 6.1, this implies that $\dot{\tilde{V}}_\ell(r) \leq 0$ for $\ell = 1, .., s$. □

Remark 6.18: The linear term in (6.24) can be set to zero, which simplifies that SDP in Theorem 6.15. In this case, if compared with the linear program for constructing PWLR Lyapunov functions on a given partition as in Proposition 6.7, we note that Theorem 6.15 gives sufficient conditions only due to the relaxation of copositive constraints to semi-definite counterparts. Nevertheless, it can be seen easily that whenever a PWLR Lyapunov function exists over a particular partition, then the SDP is feasible. Therefore, the class of feasible solutions to the SDP in Theorem 6.15 is potentially larger than the PWLR counterparts. This can be stated as follows.

Corollary 6.16. *Given Γ. If there exists a PWLR Lyapunov function $V(x)$ with a partition matrix H, then the SDP problem in Theorem 6.15 is feasible. In particular, $P_k = c_k c_k^T, k = 1, .., m$ is a feasible solution.*

Proof. Assume that $C \in \mathbb{R}^{\frac{m}{2} \times r}$ is given such that $V_L = \tilde{V}_L \circ R$ is a PWLR Lyapunov function, where $\tilde{V}_L$ is defined as in (3.5). Let $V_Q = \tilde{V}_Q \circ R$ with

$$\tilde{V}_Q(r) = r^T P_k r = r^T c_k c_k^T r, r \in \mathcal{W}_k, k = 1, .., m.$$

The constraints (6.27),(6.28) are clearly satisfied. The inequality (6.25) is satisfied with $A_k^1 = A_k^2 = 0$, $k = 1, .., \frac{m}{2}$. It remains to show that (6.26) is satisfied.

Fix $\ell \in \{1, .., s\}$, $k \in \{1, .., \frac{m}{2}\}$. Then

$$-\dot{\tilde{V}}_\ell = -r^T(\Gamma^\ell P_k + P_k \Gamma^\ell) r = -r^T(\Gamma^\ell c_k^T c_k + c_k c_k^T \Gamma^\ell) r.$$

Since it is assumed that $\tilde{V}_L$ is PWLR RLF, there exists $\lambda_k^\ell, \xi_k \geq 0$ such that $c_k^T = \xi_k^T \Sigma_k H$, $c_k^T \Gamma^\ell = \lambda_k^\ell \Sigma_k H$. Therefore:

$$-\dot{\tilde{V}}_\ell = (\Sigma_k H r)^T (\lambda_k^\ell \xi_k + \xi_k {\lambda_k^\ell}^T)(\Sigma_k H r).$$

Hence, (6.26) is satisfied with $B_{k\ell}^1 = \lambda_k^\ell \xi_k + \xi_k {\lambda_k^\ell}^T, B_{k\ell}^2 = 0$. □

Chapter 7

Control of GSNs and Control Lyapunov Functions

This is a brief excursion into the realm of the control of CRN. Control of nonlinear systems usually is concerned by the stabilization of an isolated equilibrium which is placed at the origin. However, reaction networks have usually a continuum of equilibrium. The analogous problem to classical nonlinear control is the stabilization of an equilibrium within its stoichiometric class. Moreover, it can be required to stabilize an equilibrium globally in $\mathbb{R}^n_+$. Furthermore, the creation of a stable equilibrium can be another objective.

In the context of biological networks, control can be implemented in the classical way by collecting measurements, computing feedback control laws *in-silico* (i.e, by a computer) [23], and then using inflows/outflows to implement them. Alternatively, control can be done *in-vivo* by adding certain reactions and species to the network to stabilize the whole network [30]. The methods that we discuss in this chapter suites the first approach.

This chapter is not meant to be a thorough treatment of the topic of reaction network control. Instead, it is meant to be an extension of the results of previous chapters. Therefore, the controllers designed in this chapter use state feedback only.

7.1 Stabilization of an Equilibrium of A GSN

We have observed that equilibria of GSNs are stable with respect to their stoichiometry class. In this section we discuss the problem of global stabilization of a chosen equilibrium.

7.1.1 State-Feedback Stabilization With Respect to Stoichiometry Class

Since the class of networks we are considering is already stable one idea is to design the input so that the resulting trajectory converges to the stoichiometry class of the required equilibrium, and then the stable dynamics of the system guarantee convergence using the converging-input converging-state approach [90]. Therefore, the network has two Lyapunov functions: one for stability, and another for stoichiometry class stabilization. This kind of invariant-manifold approach was proposed by De Leenheer and Aeyels [38]. In this section, we present results along similar lines.

Since a stoichiometry class is given by conservation laws, the control law is simply based on minimizing the distance of the trajectory to the desired stoichiometry class. Given (2.9), assume that there exists a nonnegative basis $\{d_1, ..., d_m\}$ of $\ker \Gamma^T$. Then, the desired stoichiometry class is encoded by positive constants $\{M_1, .., M_m\}$. For the class of GSNs, isolated equilibria are unique in the interior by Theorem 4.5; therefore given the desired x_e, the positive constants can be calculated as $M_k = d_k^T x_e, k = 1, .., m$.

Consider the controlled system as:

$$\dot{x} = \Gamma R(x) + Bu. \tag{7.1}$$

We assume the number of control inputs is equal to the number of conservation laws; therefore $u \in \mathbb{R}^m$. Since the control input can be negative; conditions need to be imposed so that the positive orthant stays invariant. Let $B = [b_1, .., b_m]$, then we assume that: $d_\ell^T b_k \geq 0$ for all k, ℓ. Furthermore, assume that $d_k^T b_k > 0, k = 1, .., m$. We assume also

that

$$d_k^T b_k > \sum_{k \neq \ell} |d_k^T b_\ell|, \tag{7.2}$$

for reasons to be clarified below. Note that this condition guarantees that the matrix $D^T B$ is nonsingular which can be proven directly by Gershgorin circle theorem [21]. A simple special case of vectors satisfying the last condition is to choose B so that $d_k^T b_\ell = \delta_{k\ell}$ where $\delta_{.,.}$ is Kronecker's delta. Such a choice is always possible since the basis $\{d_1, .., d_m\}$ can be found with no nested supports.

Consider the following piecewise linear Lyapunov function:

$$V(x) = \sum_{k=1}^{m} |M_k - d_k^T x| = \sum_{k=1}^{m} |d_k^T (x_e - x)|, \tag{7.3}$$

where x_e is the unique equilibrium in the interior of the stoichiometry class associated with $M_1, ..., M_m$. Choose the control inputs as:

$$u_k(x) = a_k(M_k - d_k^T x) = a_k d_k^T (x_e - x), \tag{7.4}$$

where a_k are positive scalar gains. With out loss of generality, we let $a_k = 1, k = 1, ..m$. Then the derivative of V along (7.1) can be computed in the interior of partition regions as follows

$$\dot{V}(x) = -\sum_{k=1}^{m} \sigma_k(x) d_k^T B u = -\sum_{k=1}^{m} \sum_{\ell=1}^{m} \sigma_k(x) d_k^T b_\ell (M_\ell - d_\ell^T x) = -\sum_{\ell=1}^{m} \sigma_\ell(x) c_\ell(x) (M_\ell - d_\ell^T x),$$

where $\sigma_k(x) := \operatorname{sgn}(M_k - d_k^T x)$, and $c_\ell = d_\ell^T b_\ell + \sum_{k \neq \ell} \sigma_k \sigma_\ell d_k^T b_\ell$. Note that σ_k is nonzero in the interior of partition regions. By assumption (7.2) $c_\ell > 0$. Therefore,

$$\dot{V}(x) = -\sum_{\ell=1}^{m} c_\ell (M_\ell - d_\ell^T x) \operatorname{sgn}(M_\ell - d_\ell^T x) \leq 0, \tag{7.5}$$

and it is zero only if the trajectory belongs to the desired stoichiometry class. The negativ-

ity of the derivative can be extended to the boundaries of the partition regions using Dini's derivatives in a similar manner to the previous chapters. Since V is radially unbounded, Lyapunov's second method implies that $\lim_{t\to\infty} d_k^T x(t) = M_k, k = 1, .., m$.

However, we have not finished yet. If the desired stoichiometric constants $M_1, .., M_m$ are considerably larger than their counterparts corresponding to the stoichiometry class of the initial condition, then the trajectories stay positive. However, this is not true in general. The control input might violate the forward invariance of $\mathbb{R}^n_+$. This can be remedied by modifying the control inputs to the following:

$$\begin{aligned} u_k(x) &= a_k \begin{cases} M_k - d_k^T x & : M_k \geq d_k^T x \\ (M_k - d_k^T x) \prod_{i \in \text{supp}(b_k)} x_i & : M_k < d_k^T x \end{cases} \\ &= a_k \begin{cases} d_k^T (x_e - x) & : M_k \geq d_k^T x \\ d_k^T (x_e - x) \prod_{i \in \text{supp}(b_k)} x_i & : M_k < d_k^T x \end{cases}, \end{aligned} \tag{7.6}$$

where x_e is the unique equilibrium in the interior of the stoichiometry class associated with $M_1, ..., M_m$. Note that the functions $u_k(x)$ are locally Lipschitz. It can be verified that this choice of u_k satisfies

$$(R(x) + Bu(x))|_{x_i=0} \geq 0, \text{ for all } i = 1, .., n.$$

Hence, the positive orthant stays invariant for the controlled system (7.1). The expression (7.5) is modified by nonnegative factors of the form $\prod_{i\in\text{supp}(b_k)} x_i$. Hence, $\dot{V}(x) \leq 0$. However, examining the set $\dot{V}(x) = 0$, we have noted that it might vanish on the boundary. This can be avoided if the system was *persistent*. Indeed, this is the case for a conservative uncontrolled system; this is since we are concerned with stabilizing isolated asymptotically stable equilibrium where Theorem 3.3 and Theorem 4.7 imply that the network is persistent.

Therefore, the system with the control input (7.6) satisfies

$$\lim_{t\to\infty} d_k^T x(t) = M_k, k = 1, .., m.$$

This implies that $\lim_{t\to\infty} u_k(x(t)) = 0, k = 1, .., m$. Therefore, the isolated equilibrium is asymptotically stable and the external input is decaying to zero, a converging-input-converging-state (CICS) argument [90] can be used to imply that the equilibrium in that stoichiometry class is globally asymptotically stable.

Therefore, we state the following theorem.

Theorem 7.1 (Stabilization)**.** *Given* (7.1) *which is conservative, and B satisfies the conditions listed above. Assume that the uncontrolled system admits a PWLR Lyapunov function. Assume that x_e is a positive isolated equilibrium in $\mathscr{C}_{x_e}$ and it satisfies the LaSalle's condition for the uncontrolled system. Then if the input $u(x)$ is chosen by* (7.6) *with any positive gains $a_1, .., a_m$, x_e is globally asymptotically stable in $\mathbb{R}^n_+$.*

Remark 7.1: Although our approach has been motivated by [38] and has apparent similarities to it, the Lyapunov function used, the assumptions on B and the control input formulae are different.

Remark 7.2: Note that this stabilization procedure is **robust** in the sense that it does not require any knowledge of the model of the kinetics of the network apart from satisfying the mild assumptions AK1-AK4. It needs either an equilibrium or a set of desired conserved masses constants. Therefore, global stabilization by state-feedback is possible based on graphical knowledge only and without the need of modeling the kinetics.

7.2 PWLR Control Lyapunov Functions

In this section the use of PWLR Lyapunov function techniques for the stabilization of an equilibrium of an arbitrary CRN is discussed. Therefore, PWLR functions are candidate

Lyapunov functions. Control Lyapunov functions have been introduced by Artstein [17]. For input affine systems, simpler conditions are possible; Sontag [88] showed that for a system of the form $\dot{x} = f(x) + B(x)u(x)$, a function $V(x)$ can act as a control Lyapunov function if $\frac{\partial V}{\partial x}B(x) = 0$, implies that $\frac{\partial V}{\partial x}f(x) \leq 0$. The control law can be chosen to be continuous at zero if V satisfies the *small control property* (consult [88]).

Consider a PWLR Lyapunov function defined over a partition region $\{\mathcal{W}_k\}_{k=1}^m$ and given by:

$$V(x) = c_k^T R(x),\ R(x) \in \mathcal{W}_k.$$

Consider a controlled CRN given by (7.1). For simplification, consider that *each input affect one state only.* Therefore, $B = \text{diag}[b_1, ..., b_n]$, where $b_1, .., b_n$ are nonnegative scalars. The actual number of inputs is equal to the number of nonzero entries, however, we have used this notation for convenience.

Computing the derivative of V along the trajectories of (7.1) when $R(x) \in \mathcal{W}_k$, we get:

$$\dot{V} = \sum_{i=1}^{n} c_k^T \frac{\partial R}{\partial x_i}(\dot{x}_i + b_i u_i) = \sum_{i=1}^{n} \varphi_{ki}(x)(\dot{x}_i + b_i u_i),$$

where $\varphi_{ki}(x) = c_k^T \frac{\partial R}{\partial x_i}$. If all $b_1, .., b_n$ were positive, then we would have a full control case, which means the ability to fully manipulate each state. Therefore, to get a proper control problem, the number of inputs is strictly smaller than the number of states.

Recall that sign pattern characterization of PWLR Lyapunov function discussed in Theorem 4.2. The sign pattern vectors have been computed in the so called sign regions so that they are compatible with the signs of reactants of a reaction $\mathbf{R}_j$ that appears in the support of c_k. By the above type of feedback, it can be noted that if b_i is positive, then the effect of $\dot{x}_i$ can be ignored when computing the sign pattern vectors. In other words, the species X_i can be excluded from the reactants of $\mathbf{R}_j$ while computing the sign pattern constraint. This can be stated precisely in the following definition and theorem.

Definition 7.1 (Robust Control Lyapunov Function)**.** *Let* (7.1) *be given with B specified*

as above. Then, a locally Lipschitz function $V : \bar{\mathbb{R}}^n_+ \to \bar{\mathbb{R}}_+$ *is said to be a* ***robust control Lyapunov function*** *if it is nonnegative, vanishes on* $\{x|\Gamma R(x) = 0\}$*, and satisfies the implication:* $(\partial V/\partial x)B = 0$ *implies that* $(\partial V/\partial x)\Gamma R(x) \leq 0$ *for all* $R \in \mathscr{K}_A$.

Therefore, we have the following theorem, which is a parallel of Theorem 4.2.

Theorem 7.2. *Given* (7.1)*, and associated positive-definite continuous PWLR function* V *defined by* (3.5)*. The function is a control PWLR Lyapunov function if the coefficient vectors* $c_k, k = 1, ..., m$ *satisfy for* $\ell \in \{1, .., n\}\backslash\mathcal{I}$*, the following equality and inequality constraints*

$$\begin{cases} c_{kj} = 0 & \text{if } \tau_{q_k j} = 0 \\ c_{kj}\tau_{q_k j} \geq 0 & \text{if } 0 < |\tau_{q_k j}| < \infty \end{cases} \tag{7.7}$$

where

$$\tau_{kj} = \begin{cases} \infty, & \text{if} \tilde{M}_j = \varnothing \\ 0, & \text{if } \exists i_1, i_2 \in \tilde{M}_j \text{ such that } \sigma_{ki_1}\sigma_{ki_2} < 0, \\ -\sigma_{ji^*}, & \text{otherwise, for any } i^* \in \tilde{M}_j, \end{cases} \tag{7.8}$$

and $\tilde{M}_j = M_j \ \{i|b_i > 0\}$.

Remark 7.3: Since the cardinality of the set M_j has reduced, the set of networks that can admit a control PWLR is strictly larger than the set of networks that admit a PWLR function.

Remark 7.4: Construction of PWLR control Lyapunov functions can be accomplished on given partition regions in a similar manner to Theorem 8.1.1.

7.2.1 Controller Design: A Brief Discussion

The existence of the PWLR control Lyapunov function above does not specify the method of construction of controller. Since our function is non-differentiable, then universal time-invariant constructions such as [88] do not work. Standard constructions, for example by Freeman and Kokotovic [47], give rise to discontinuous closed-loop system. Hence,

rigorous analysis of the resulting system needs tools from the theory of discontinuous systems. Studying the questions posed in this subsection are matters for future research.

Chapter 8

Examples and Applications

The results presented till now might have been highly abstract, therefore this chapter includes examples to illustrate, compare, and show applications of the results of this dissertation.

8.1 Illustrative Examples

8.1.1 Application of PWLR Construction Methods

Consider the network (1.1),(1.2) introduced in the introduction, which is given by:

$$X_1 \longrightarrow X_2 + X_3,$$
$$2X_2 \longrightarrow X_4,$$
$$X_3 + X_4 \longrightarrow X_1 + X_2.$$

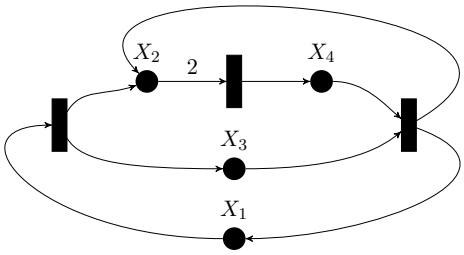


Figure 8.1: Bipartite graph representation of the example CRN (1.1).

The corresponding ODE system is:

$$\dot{x} = \begin{bmatrix} -1 & 0 & 1 \\ 1 & -2 & 1 \\ 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} R_1(x_1) \\ R_2(x_2) \\ R_3(x_3, x_4) \end{bmatrix},$$

The graphical representation is depicted in Figure 8.1

As indicated before, this network does not satisfy the conditions of [45] as it has deficiency 1, and violates the conditions of [65, 14]. Hence, its stability can not be established by methods in the literature.

The network has two conservation laws. Thus, the stoichiometric class is a two dimensional polytope of the form $\mathscr{C}_{x_\circ} = \{x \in \mathbb{R}^4 | x_1 + x_3 = M_1, x_1 + x_2 + 2x_4 = M_2, 0 \leq x_1 \leq M_1, 0 \leq x_1 + x_2 \leq M_2\}$, where $M_1 = x_{\circ 1} + x_{\circ 3}, M_2 = x_{\circ 1} + x_{\circ 2} + 2x_{\circ 4}$ are the conserved quantities.

In order to apply Theorem 5.1, choose $H = \Gamma$. Then, there are six non-empty-interior partition regions of the reaction space $\mathbb{R}^3$, which are:

$$\mathcal{W}_1 = \{r | -h_1^T r \leq 0, -h_2^T r \leq 0, h_3^T r \leq 0, h_4^T r \leq 0\},$$
$$\mathcal{W}_2 = \{r | -h_1^T r \leq 0, h_2^T r \leq 0, h_3^T r \leq 0, -h_4^T r \leq 0\},$$

$$\mathcal{W}_3 = \{r| - h_1^T r \leq 0, h_2^T r \leq 0, h_3^T r \leq 0, h_4^T r \leq 0\},$$
$$\mathcal{W}_4 = -\mathcal{W}_3, \mathcal{W}_5 = -\mathcal{W}_2, \mathcal{W}_6 = -\mathcal{W}_1,$$

where $h_1 = [-1, 0, 1]^T, h_2 = [1, –2, 1]^T, h_3 = [1, 0, -1]^T, h_4 = [0, 1, –1]^T$.
We need to find the coefficients $c_1, .., c_6$, where $c_4 = -c_3, c_5 = -c_2, c_6 = -c_1$. Although we have twelve neighbouring pairs, only three constraints are needed, because of the symmetries involved, which are $c_3 - c_1 = \eta_{31} h_2, c_3 - c_2 = \eta_{32} h_4, c_2 + c_1 = -\eta_{21} h_1$. The sign-constraints vectors are $b_1 = [1, 1, –1]^T, b_2 = [1, –1, 0]^T, b_3 = [1, –1, –1]^T, b_4 = -b_3, b_5 = -b_2, b_6 = -b_1$. Hence, the linear program can be solved and one of its solutions is $V(x) = \tilde{V}(R(x))$, where $\tilde{V}$ is:

$$\tilde{V}(r) = \max\{|r_1 + 3r_2 - 4r_3|, 3|r_1 - r_2|, |3r_1 - r_2 - 2r_3|\}.$$

Alternatively, applying Algorithm 1 with the standard setting yields a PWLR Lyapunov function given by:

$$\tilde{V}(r) = \max\{|r_1 - r_3|,|r_1 - 2r_2 + r_3|,2|r_2 - r_3|,2|r_2 - r_1|\}. \tag{8.1}$$

Finally, Theorem 5.4 gives

$$\tilde{V}(r) = \max\{|r_1 - r_2|, |r_1 - r_3|, |r_2 - r_3|\}.$$

Therefore, our three constructions are successful and have produced three different functions. It can be verified that the LaSalle's condition is fulfilled. Since the network is conservative and injective relative to the stoichiometric class [20] there exists a unique equilibrium in each stoichiometric compatibility class. Therefore, Corollary 3.3 implies that the unique equilibrium is globally asymptotically stable. In order to illustrate the dynamics, we consider the stoichiometric class corresponding to $M_1 = 8, M_2 = 7$. Figure 8.2 depicts

the level sets of the Lyapunov function (1.3) and the phase portraits with Mass-Action kinetics and 2$^{\text{nd}}$-order Hill kinetics which are given by: $R(x) = [k_1x_1^2/(1+x_1^2), k_2x_2^4/(1+x_2^2)^2, k_3x_3^2x_4^2/((1+x_3^2)(1+x_4^2))]^T$ where the rate constants are $k = [1, 0.5, 0.25]$.

Verifying the LaSalle Condition

Note that since the network above satisfies the conditions of Theorem 5.4, then in order to demonstrate an application of the LaSalle's condition, the graphical condition of overlapping ancestors can be observed directly.

Nevertheless, we are going to establish the LaSalle's condition C5$'$ for (8.1). Consider $V(x) = c_1^T(x) = R_1(x) - R_3(x)$. Then, $I_k = \{1, 3, 4\}$. Hence $\dot{x}_1 = \dot{x}_3 = \dot{x}_4 = 0$. Therefore, $c_k \in \text{Im}([\gamma_1, \gamma_2, \gamma_4])$, and hence $\dot{x} = 0$. Indeed, for the rest of coefficient vectors the LaSalle's condition can be verified easily in the first step without the need compute the sets L_k described in §3.5.

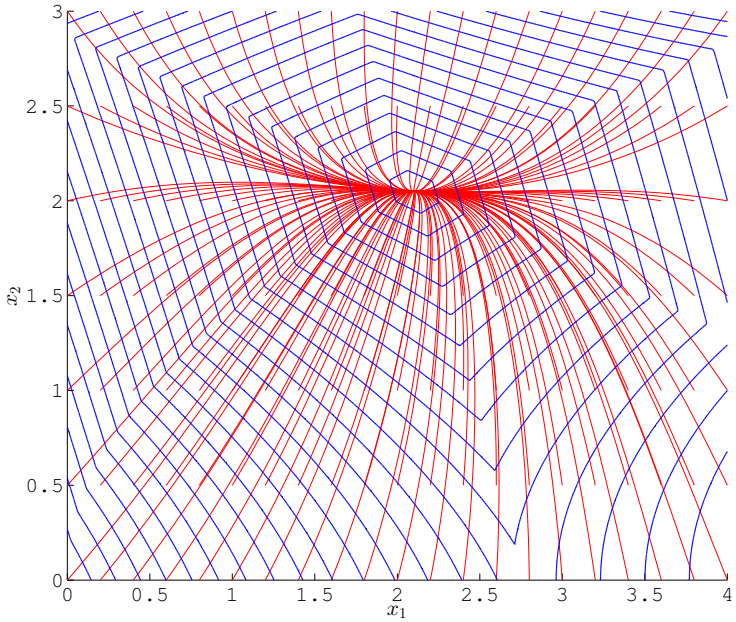
Dual PWL Lyapunov Functions, and PWQR Lyapunov Function

If we apply Proposition 6.7, Theorem 6.4, and Theorem 6.15 we get the following matrices:

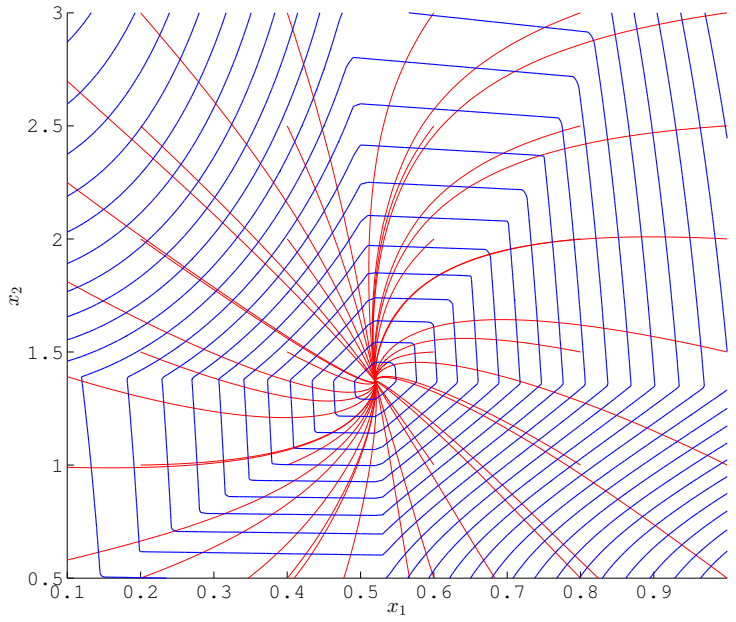
$$C = \begin{bmatrix} 3 & 10 & -13 \\ 10 & -10 & 0 \\ 10 & -4 & -6 \end{bmatrix}, B = \begin{bmatrix} 3 & 0 & -10 & 0 \\ 10 & 0 & 10 & 0 \\ 10 & 0 & 4 & 0 \end{bmatrix}$$

$$P_1 = \begin{bmatrix} -1 & 2 & -1 \\ 2 & 0 & -2 \\ -1 & -2 & 3 \end{bmatrix}, P_2 = \begin{bmatrix} 2 & -2 & 0 \\ -2 & 2 & 0 \\ 0 & 0 & 0 \end{bmatrix}, P_3 = \begin{bmatrix} 2 & 0 & -2 \\ 0 & -4 & 4 \\ -2 & 4 & -2 \end{bmatrix},$$

such that $V(x) = \|CR(x)\|_\infty$, $V(x) = \|B(x - x_e)\|_\infty$, and $V(x) = R^T(x)P_kR(x)$ for $R(x) \in \pm\mathcal{W}_k, k = 1, .., 3$, are RLFs for network family $\mathscr{K}_A$.



(a)



(b)

Figure 8.2: Lyapunov function level sets and phase portrait with (a) Mass-Action Kinetics, (b) 2^{nd}-order Hill kinetics.

8.1.2 Stabilization of A Selected Equilibrium

We demonstrate an application of the technique discussed in §7.1.1 on the stabilization of a selected equilibrium. Let the controlled network with Mass-Action kinetics be given as:

$$\dot{x} = \begin{bmatrix} -1 & 0 & 1 \\ 1 & -2 & 1 \\ 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} k_1 x_1 \\ k_2 x_2^2 \\ k_3 x_3 x_4 \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} u(x).$$

We simulate the control-law (7.6) in the cases of Mass-Action with the target equilibrium $x_e = [1.381528438692838, 2.035765411706354, 2.618492159821783, 0.791354102631111]^T$ and control gains $a_1 = a_2 = 15$. The corresponding stoichiometry class positive constants are $M_1 = 4, M_2 = 5$. Figure 8.3 depicts two-hundreds sample trajectories starting at random points in the hypercube $[0, 12]^4$ with kinetic constant $k_1 = 3, k_2 = 1, k_3 = 2$.

8.1.3 Counterexamples

Relationship of The LaSalle Condition to C1-C4

C5′i does not follow from C2′ and C4′. For example consider the following CRN

$$X_1 + X_2 \xrightarrow{R_1} 0 \xrightarrow{R_2} X_1, 0 \xrightarrow{R_3} X_2, \tag{8.2}$$

then

$$V(x) = |R_1(x) - R_2(x)| + |R_3(x) - R_2(x)| + |R_1(x) - R_2(x)|$$

satisfies C2′ and C4′, but not C5′. It can be shown that there does not exist any C satisfying the three conditions simultaneously, nor any pair (H, C) satisfying C1-5.

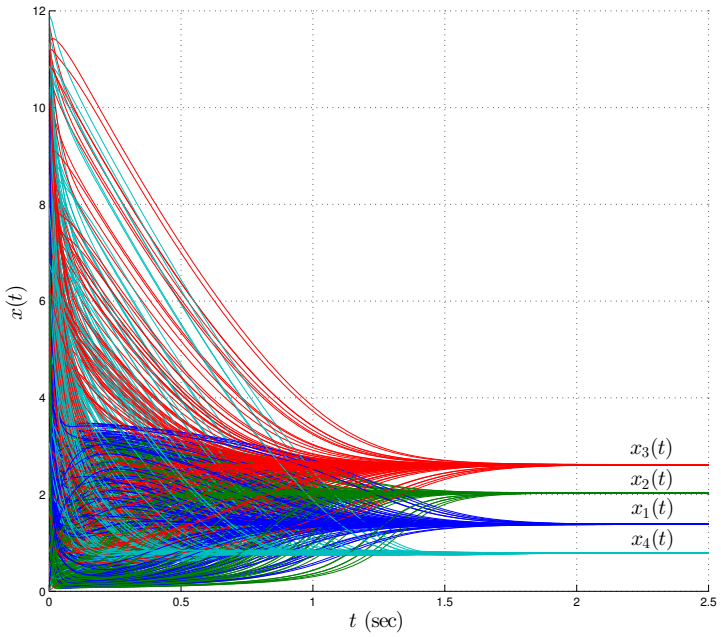


Figure 8.3: Sample 200 trajectories for the stabilization with Mass-Action kinetics with $x(0) \in [0, 12]^4$, uniformly distributed.

PWLR Functions and Boundedness

The following CRN illustrates the fact that the mere existence of the PWLR Lyapunov function does not guarantee the boundedness of the trajectories:

$$X_3 \xrightarrow{k_1} X_1,\ 0 \xrightarrow{k_2} X_2, X_1 + X_2 \xrightarrow{k_3} X_3,$$

The three constructions presented yield a Lyapunov function, in particular (5.4) is a valid one. However, consider the network with Mass-Action Kinetics, and let $A = x_1(0) + x_3(0)$ be the parameter corresponding to the stoichiometric compatibility class. If $A > \frac{k_2}{k_3}$, then the system trajectories are bounded and the unique equilibrium $\left(\frac{k_2 k_3}{k_3 A - k_2}, A - \frac{k_2}{k_3}, \frac{k_2}{k_3}\right)$ is globally asymptotically stable by Theorem 3.2. However, when $A \leq \frac{k_2}{k_3}$, there are no equilibria in the nonnegative orthant, solutions are unbounded and approach the boundary.

Comparison Between the Three Construction Methods

We show that the methods proposed by Theorems 5.1, 5.3 are non-overlapping, i.e., there exist GSNs such that the Lyapunov function can be constructed by only one of the two methods. However, it has been observed that Theorem 5.3 with standard settings is applicable for all examples considered for networks satisfying Theorems 5.4, 5.5.
Consider the following network:

$$X_1 \xrightarrow{k_1} X_2,\ X_5 \xrightarrow{k_4} X_4,\ X_2 + X_4 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_1 + X_5$$

The linear program in Theorem 5.1 with $H = \Gamma$ is infeasible, however, Theorem 3.4 and Theorem 5.4 give rise to the PWLR function (5.4) with $v = \mathbf{1}$. Close examination indicates a partitioning matrix $\hat{H} = [1\,0\,0\ -1]$ renders the linear program feasible.
On the other hand, consider the following network:

$$2X_1 + 3X_3 \xrightarrow{k_1} 0 \xrightarrow{k_3} 3X_1 + X_2 + 2X_3,\ X_1 + X_2 \xrightarrow{k_2} X_3$$

Theorem 5.4 does not apply. Algorithm 1 with standard setting does not terminate. However, Theorem 5.1 with $H = \Gamma$ gives the following convex PWLR Lyapunov function:

$$V(x) = \max\{|6R_1(x) + R_2(x) - 7R_3(x)|, |3R_2(x) - 3R_3(x)|, |6R_1(x) - 6R_3(x)|\}.$$

8.1.4 Exponentially Contractive Network

Consider the following network:

$$Y \xrightarrow{R_1} X, \quad X + E \xrightarrow{R_3} EX \xrightarrow{R_2} Y + E$$

The corresponding equation of motion is given as:

$$\dot{x} = \begin{bmatrix} -1 & 1 & 0 \\ 0 & -1 & 1 \\ 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} R(x_1) \\ R(x_2) \\ R(x_3, x_4) \end{bmatrix},$$

where the species have been ordered as Y, EX, X, E. Then, using Theorem 5.4, it admits the following PWLR Lyapunov function:

$$V(x) = \left\| \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \\ -1 & 0 & 1 \end{bmatrix} R(x) \right\|_\infty = \left\| \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} \dot{x} \right\|_\infty,$$

Therefore, Theorem 6.11 is applicable, and we deduce that the network is exponential contractive in each stoichiometric class without resort to a LaSalle's argument.
Indeed, computing the matrices $\Lambda_1, ..., \Lambda_4$ we get:

$$\tilde{\Lambda}_1 = \begin{bmatrix} -1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 1 & -1 \end{bmatrix}, \tilde{\Lambda}_2 = \begin{bmatrix} -1 & 0 & 1 \\ 0 & -1 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \tilde{\Lambda}_3 = \begin{bmatrix} 0 & 0 & 0 \\ -1 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix}, \tilde{\Lambda}_4 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & -1 & 0 \\ 1 & 0 & -1 \end{bmatrix},$$

where the indices correspond to $\kappa(1) = (1,1), \kappa(2) = (2,2), \kappa(3) = (3,3), \kappa(4) = (3,4)$. Hence, the upper bound on the weighted logarithmic norm of the Jacobian (6.22) can be computed as:

$$\mu_\infty \left(\sum_\ell \rho_\ell \Lambda_\ell \right) = \max \left\{ -\frac{\partial R_1}{\partial x_1}, -\frac{\partial R_2}{\partial x_2} - \frac{\partial R_3}{\partial x_4}, -\frac{\partial R_3}{\partial x_3} \right\} < 0,$$

where the inequality is valid in the interior of the positive orthant. Nevertheless, since the kernel space is one-dimensional, the network is persistent.

However, this bound on the logarithmic norm of the Jacobian is not tight. Computing

μ_C explicitly relative to the stoichiometric class in the species coordinates, or relative to directions orthogonal to $\ker \Gamma$ in the extent of reactions coordinates, we get the following formula for the reduced Jacobian

$$\mu_C(J_T) = \max\left\{-\frac{\partial R_1}{\partial x_1}, -\frac{\partial R_2}{\partial x_2} - \frac{\partial R_3}{\partial x_4}, -\frac{\partial R_3}{\partial x_3} - \frac{\partial R_3}{\partial x_4}\right\} < \mu_\infty\left(\sum_\ell \rho_\ell \Lambda_\ell\right) < 0,$$

where J_T is the reduced Jacobian after the shift of coordinates. Therefore, the network is exponentially contractive in each stoichiometric class, and this shows the existence of at least of one equilibrium trajectory that all trajectories contracts into.

8.2 Comparison with Horn-Jackson-Feinberg Stability Theory

As already observed in the literature review, the most famous theory of the stability of reaction networks in the literature is Horn-Jackson-Feinberg theory. They show the stability of complex-balanced equilibria. Furthermore, if a network is a weakly-reversible deficiency zero then all equilibria are complex-balanced, and it is stable for all choices of kinetics constants with Mass-Action kinetics. A natural question arises: what is the relation between the results that we have presented and the former theory of stability? In this section, we show that the answer is: no clear relationship exists.

Weakly Reversible Zero Deficiency Network Which is not GS

Consider the following network presented by Feinberg [45]:

$$X_1 \leftrightharpoons 2X_2,\ X_1 + X_3 \leftrightharpoons X_3 \longrightarrow X_2 + X_5 \longrightarrow X_1 + X_3$$

The network violates both necessary conditions given by Theorems 4.4 and 4.3, therefore it does not admit a PWLR Lyapunov function. Indeed, the network has two equilibria

in each stoichiometric class: one in the interior and one on the boundary. However, the deficiency-zero theorem [45] can be applied with Mass-Action kinetics to show that the interior equilibrium is asymptotically stable despite the existence of boundary equilibria, a situation which is not allowed by Theorem 4.5.

A GS Network With Arbitrary Deficiency

We gave an example of a zero deficiency network which is not GS. Now, consider the following CRN for a given integer $n \geq 1$:

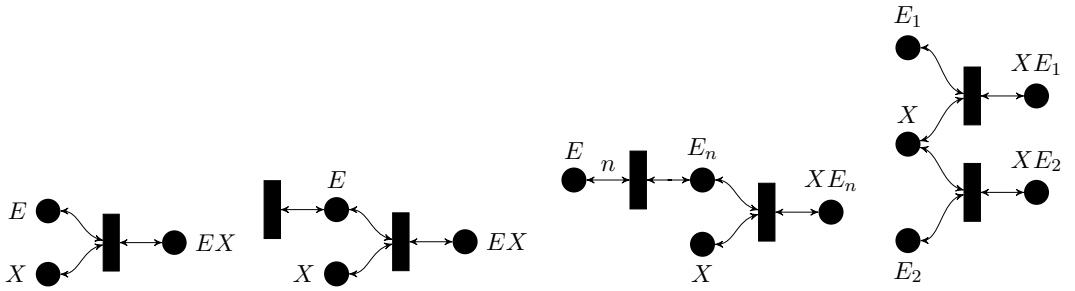
$$\begin{aligned}
&X_1 + E_1 \longrightarrow E_1X_1 \longrightarrow X_2 + E_1,\ X_2 \longrightarrow X_1\\
&X_2 + E_2 \longrightarrow E_2X_2 \longrightarrow X_3 + E_2,\ X_3 \longrightarrow X_2\\
&\vdots\\
&X_n + E_n \longrightarrow E_nX_n \longrightarrow X_{n+1} + E_n, X_{n+1} \longrightarrow X_n,
\end{aligned}$$

which has deficiency n. For every n, a PWLR Lyapunov function is given by $V(x) = \|D\dot{x}\|_1$ where $D = \text{diag}[I_{2n+1}, O_n]$, with species ordered as $X_1, .., E_1X_1, .., E_1, .., E_n$. This shows that there is no simple relationship between our results and the notion of deficiency.

8.3 Biochemical Examples

Within the class of structurally persistent, i.e. critical-siphon-free, CRNs which have a P_0 Jacobian matrix, our proposed algorithms were reasonably successful. In almost all of the examples, either a PWLR function is constructed, or a necessary condition is violated meaning that an RLF does not exist. Nevertheless, there are networks which do not violate any necessary condition, and our algorithms does not succeed in constructing a Lyapunov function.

Note that the biochemical examples provided in this section are easily collected from standard references without extensive search.



(a) Simple Binding (b) Simple Binding With Enzyme Inflow-Outflow (c) Cooperative Binding (d) Competitive Binding

Figure 8.4: Basic Biochemical Examples

8.3.1 Basic Biochemical Motifs

In this subsection, several simple biochemical networks are presented. We consider motifs given by Del Vecchio and Murray [39]. These networks are fairly simple and all of them can be analyzed using the deficiency zero theory in the case of Mass-Action kinetics. However, they are presented here to show that the properties that our theory requires are obeyed by the basic biochemical motifs, which establishes its applicability and generality.

Simple Binding Reaction

Figure 8.4-a) represents a simple reversible binding reaction:

$$X + E \rightleftharpoons EX$$

The corresponding PWLR Lyapunov function can be found easily using Theorem 5.4 and is given by:

$$V(x) = |R_1(x) - R_2(x)|.$$

The LaSalle's condition is satisfied also.

In general any reversible reaction:

$$\sum_{i=1}^{n} \alpha_i X_i \rightleftharpoons \sum_{i=1}^{n} \beta_i X_i,$$

admits the same Lyapunov function.

Simple Binding With Enzyme Inflow-Outflow

Figure 8.4-b) represents the following binding reaction with enzyme inflow-outflow:

$$X + E \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} EX,\ 0 \underset{R_{-2}}{\overset{R_2}{\rightleftharpoons}} E,$$

The corresponding PWLR Lyapunov function found using Theorem 5.5 can be written as:

$$V(x) = \max\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), 0\} - \min\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), 0\}.$$

The LaSalle's condition is satisfied also. The underlying networks for which Theorem 5.5 was applied is $0 \to E, 0 \to X, X + E \to XE, XE \to 0$.

Cooperative Binding Reaction

The following reaction represents the situation where n enzyme molecules E need to bind to each other to react to X, which is given in Figure 8.4-c). The case $n = 2$ is called dimerization:

$$nE \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} E_n,\ E_n + X \underset{R_{-2}}{\overset{R_2}{\rightleftharpoons}} XE_n$$

The corresponding PWLR Lyapunov function can be found using Theorem 5.5 and is given by:

$$V(x) = \max\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), 0\} - \min\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), 0\}.$$

The underlying networks for which Theorem 5.5 was applied is $0 \to E, 0 \to X, E \to E_n, E_n + X \to XE_n, XE_n \to 0$.

Competitive Binding Reaction

The following reaction describes the situation when two molecules E_1, E_2 compete to bind with X, which is given in Figure 8.4-d):

$$E_1 + X \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} XE_1,\ X + E_2 \underset{R_{-2}}{\overset{R_2}{\rightleftharpoons}} XE_2$$

The LaSalle's condition is satisfied also. The corresponding PWLR Lyapunov function can be found using Theorem 5.5 and is given by:

$$V(x) = \max\{R_1(x) - R_{-1}(x), R_{-2}(x) - R_2(x), 0\} - \min\{R_1(x) - R_{-1}(x), R_{-2}(x) - R_2(x), 0\}.$$

The underlying networks for which Theorem 5.5 was applied is $0 \to E_1, E_1 + X \to XE_1 \to XE_1 \to 0, 0 \to XE_2 \to X + E_2, E_2 \to 0$.

8.3.2 Basic Enzymatic Networks

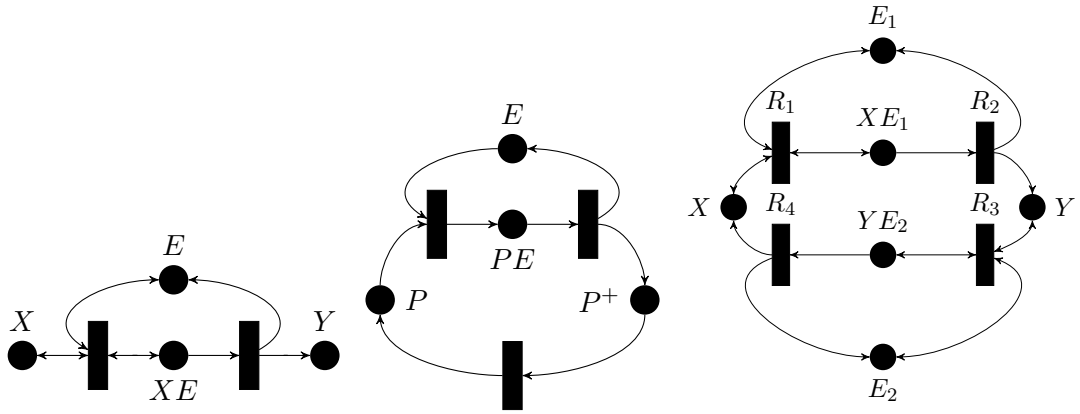
Basic Enzymatic Reactions

Figure 8.5-a) represents the basic enzymatic reaction where an enzyme E binds to a substrate X to produce a protein P as follows [54, 39]:

$$X + E \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} ES \xrightarrow{R_2} E + P.$$

Note that the network does not have full-support kernel vector and thus does not satisfy AS1. Nevertheless, Remark 5.4 tells us that Theorem 5.3 can be used. The resulting Lyapunov function is:

$$V(x) = \max\{|R_1 - R_{-1}|, R_2\}.$$



(a) Basic Enzymatic Reaction (b) Activation of A Protein (c) Enzymatic Futile Cycle

Figure 8.5: Basic Enzymatic Reactions

Note that although this network is deficiency zero, but it is not weakly reversible. This implies that equilibria belong to the boundary, and deficiency-zero theory does not offer any information regarding stability in that case.

Enzymatic Activation of A Protein

Figure 8.5-c) describes the activation a protein P by an enzyme E, and then the activated protein decays back to its inactive state [54]:

$$P + E \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} PE \xrightarrow{R_2} E + P^+, \; P^+ \xrightarrow{R_3} P.$$

This network has already been analyzed in §8.1.4, and the following Lyapunov function has been found:

$$V(x) = \max\{|R_1(x) - R_{-1}(x) - R_2(x)|, |R_1(x) - R_{-1}(x) - R_3(x)|, |R_2(x) - R_3(x)|\}.$$

The LaSalle's condition is satisfied also. The network is conservative and has a unique kernel vector, therefore Theorem 4.7 implies that the network is persistent. Theorem 4.5, implies that there are no multiple non-degenerate equilibria. If there exists an equilibrium

then it is unique and globally asymptotically stable. Indeed, Theorem 6.13 implies that it is exponential contractive and hence there exists a unique GAS equilibrium in each stoichiometric class.

This network has deficiency one, the classical deficiency-based theory [45] excludes the existence of multiple equilibria. No information regarding stability can be inferred in that context. Furthermore, the decay reaction R_3 models a singular perturbed dephosphorylation which has a Michaelis-Menten kinetics. This violates a basic assumption of deficiency-based theories.

Enzymatic Futile Cycle

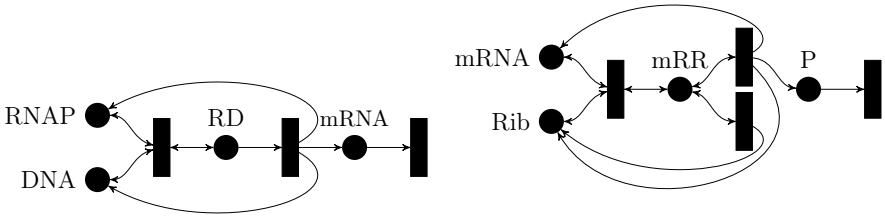
A simplified version of the enzymatic futile cycle has already been used as a motivating example in §3.1.2. The following describes a more complete model [83]:

$$X + E_1 \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} XE_1 \xrightarrow{R_2} Y + E_1,$$
$$Y + E_2 \underset{R_{-3}}{\overset{R_3}{\rightleftharpoons}} YE_2 \xrightarrow{R_4} X + E_2.$$

For instance, X represents the base substrate, E_1 is called a kinase which adds a phosphate group to X to produce Y. This process is called *phosphorylation*. The *dephosphorylation* reaction is achieved by a phosphatase E_2 that removes the phosphate group from Y to produce X.

Theorem 5.5 can be used to find the PWLR Lyapunov function:

$$\begin{aligned} V(x) = &\max\{R_1(x) - R_{-1}(x), R_3(x) - R_{-3}(x), R_2(x), R_4(x)\} \\ &- \min\{R_1(x) - R_{-1}(x), R_3(x) - R_{-3}(x), R_2(x), R_4(x)\}. \end{aligned}$$



(a) Simplified Transcription Process (b) Simplified Leaky Translation Process

Figure 8.6: Translation and Transcription

Alternatively, Theorems 5.1 and5.3 yields this Lyapunov function:

$$V(x) = |R_1(x) - R_{-1}(x) - R_2(x)| + |R_2(x) - R_4(x)| \\ + |R_3(x) - R_{-3}(x) - R_4(x)| + |R_1(x) - R_{-1}(x) - R_4(x)|.$$

The LaSalle's condition is satisfied also.

Since the deficiency of the network is one, stability can not be inferred from deficiency-based approaches. However, monotonicity-based approach works in this case [14].

8.3.3 Gene Transcription and Translation Reactions

Simplified Transcription Reaction

Figure 8.6-a) shows the transcription network which describes the production of mRNA from DNA using the RNA polymerase [39]:

$$\text{RNAP} + \text{DNA} \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} \text{RD} \xrightarrow{R_2} \text{RNAP} + \text{DNA} + \text{mRNA}, \ \text{mRNA} \xrightarrow{R_3} 0.$$

Applying Theorem 5.5 or Theorem 5.3, the following PWLR Lyapunov function can be found:

$$V(x) = \max\{R_1(x) - R_{-1}(x), R_2(x), R_3(x)\} - \min\{R_1(x) - R_{-1}(x), R_2(x), R_3(x)\}.$$

The LaSalle's condition is satisfied also. Alternatively, Theorem 5.1 can be used, and the Lyapunov function found can be written as:

$$V(x) = \| \operatorname{diag}([1,1,1,3]^T)\dot{x}\|_1,$$

where the species are ordered as RNAP, DNA, RD, P.
Note this network has deficiency one, hence no information regarding stability can be inferred. Furthermore, the procedure proposed by Blanchini and Giordano [28] has been reported not to work if the network is considered as whole.

Simplified Translation Reaction With A Leak

Figure 8.6-b) shows the translation network which describes the production of a protein from the translation of mRNA using the Ribosome [39]. However, the leaking of the Ribosome-mRNA complex to a ribosome is also modelled:

$$\mathrm{Rib} + \mathrm{mRNA} \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} \mathrm{mRR} \xrightarrow{R_2} \mathrm{mRNA} + \mathrm{P} + \mathrm{Ribo},\ \mathrm{mRR} \xrightarrow{R_4} \mathrm{Rib},\ \mathrm{P} \xrightarrow{R_4} 0.$$

Note that the kernel space of the stoichiometry matrix is spanned by $[1,1,0,0,1]^T$ and $[1,0,1,0,0]^T$. Hence, AS1 is not satisfied and all equilibria belong to the boundary. Note also, that the dynamic of other species are independent of the dynamics of P. Hence, the network can be consider as a cascade of $\mathrm{Rib} + \mathrm{mRNA} \rightleftharpoons \mathrm{mRR} \longrightarrow \mathrm{mRNA} + \mathrm{Ribo}, \mathrm{mRR} \longrightarrow \mathrm{Rib}$ and $0 \longrightarrow P \longrightarrow 0$. Applying Theorem 5.1 or Theorem 5.3 for the first network we get the Lyapunov function:

$$V_1(x) = \max\{R_4(x), R_1(x) - R_2(x) - R_3(x) - R_4(x), -R_1(x) + R_2(x) + R_3(x)\}.$$

The LaSalle's condition can also verified to establish that $\dot{V}(x) = 0$ implies $\dot{x} = 0$.

Note that it is convex, but lacks symmetry, and can not be written using the ℓ_∞

notation. Nevertheless, it can be verified that it is nonnegative and vanishes exactly on the equilibrium set. The second network can be analyzed using this Lyapunov function:

$$V_2(x) = |R_3(x) - R_4(x)|.$$

Overall stability can be established using a CICS argument [90].

Interestingly, the Algorithm proposed by Theorem 5.3 does not terminate if the network is considered as whole, nevertheless, a Lyapunov function can be found using Theorem 5.1 with a partitioning matrix $\hat{H} = [-1, 2, 1, 1, -1]^T$. However, the resulting Lyapunov function vanishes on a set slightly larger than the equilibrium set, which requires more analysis. Therefore, we have opted for the cascade approach.

8.3.4 Cascades of Futile Cycles

The futile cycle or the phosphorylation-dephosphorylation cycle [83] has been analyzed in a previous section. This kind of cycle appears frequently in biochemical networks, and can be interconnected in several ways. We discuss some here.

Multiple Futile Cycles With Distinct Enzymes

Consider a cascade of n futile cycle as shown in Figure 8.8-a). The associated graph for the case $n = 2$ is depicted in Figure 8.8, and the reaction network is given as:

$$X_0 + E_0 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_0X_0 \xrightarrow{k_2} X_1 + E_0,$$
$$X_1 + F_0 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} F_0X_1 \xrightarrow{k_4} X_0 + F_0,$$
$$X_1 + E_1 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} E_1X_1 \xrightarrow{k_6} X_2 + E_1,$$
$$X_2 + F_1 \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} F_1X_2 \xrightarrow{k_8} X_1 + F_1.$$

The network is conservative with five conservation laws, hence the stoichiometric space is a 6-dimensional compact polyhedron.

Both Theorems 5.1, 5.3 are applicable. For example, a valid PWLR Lyapunov function constructed by Theorem 5.1 can be represented as:

$$V(x) = \| \operatorname{diag}(\xi)\dot{x}\|_1,$$

where $\xi = [2\,2\,2\,1\,1\,1\,1\,1\,1\,1\,1]$ and species are ordered as $X_0, X_1, X_2, \ldots, F_1X_2$. The can not have more than a single isolated equilibrium state in the interior of each stoichiometric class. Furthermore, it has deficiency 2, hence the zero-deficiency theorem does not apply. Also, the results of Angeli et al. [14] can not be applied since X_1 is adjacent to more than two reactions. However, Theorem 3.2 implies that a Lyapunov function exists and that the positive equilibrium is globally asymptotically stable. Figure 8.7 depicts sample trajectories illustrating stability and uniqueness of the equilibrium with Michaelis-Menten kinetics of the form: $R_j(x) = k_j \prod_i (x_i/(a_{ij} + x_i))^{\alpha_{ij}}$, with $a_{ij} = 1$, and kinetic constants k=[1,2,3,4,5,6,7,8,9,10,11,12] and 180 initial conditions distributed in the stoichiometry class with the conserved quantities fixed to 10,11,12,13,14. The unique equilibrium is $x_e \approx [8.9984, 0.3255, 0.2099, 0.1972, 0.0898, 0.1036, 0.0757, 10.8028, 11.9102, 12.8964, 13.9242]^T$. The n-cascade can be analyzed similarly with the Lyapunov function given by $V(x) = \| \operatorname{diag}(\xi)\dot{x}\|_1$ with $\xi = [2, 2, ..., 2, 1, 1, ..., 1]^T$ with the ordering as $X_0, ..., X_n, E_0, E_1, ..., F_{n-1}X_n$.

Multiple Futile Cycles With Processive Mechanism

Figure 8.8-b) depicts a multiple-site futile cycle with a processive mechanism [34]. The reaction network can be written as:

$$X_0 + E \rightleftharpoons EX_0 \rightleftharpoons EX_1 \rightleftharpoons \ldots \rightleftharpoons EX_n \longrightarrow X_n + E,$$
$$X_n + F \rightleftharpoons FX_n \rightleftharpoons \ldots \rightleftharpoons EX_1 \rightleftharpoons EX_0 \longrightarrow X_0 + F,$$

It can be noticed that for every n, the network satisfies the graphical conditions of Theorem 5.3. Therefore, the Lyapunov function can be written as follows:

$$V(x) = \max_{k \neq j} \left(R_k(x) - R_{-k}(x) + R_{-j}(x) - R_j(x) \right),$$

where $R_{-k}(x) :\equiv 0$ if $\mathbf{R}_k$ is irreversible.

The LaSalle's argument can be verified. Hence, multiple degenerate equilibria are precluded. Since the network is conservative, it is persistent. This shows that any positive equilibrium is GAS. This result can be used as an alternative method to discard the above network above as a viable model for the first stage in the MAPK cascade [34]; since the later has been observed experimentally to accommodate multiple non-degenerate equilibria.

Double Futile Cycles With a Distributive Mechanism

Figure 8.8-c) describes a double futile cycle with a distributive mechanism [34], which is described by the following set of reactions:

$$\begin{aligned}
X_0 + E &\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EX_0 \xrightarrow{k_2} X_1 + E, \\
X_1 + F &\underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} FX_1 \xrightarrow{k_4} X_0 + F, \\
X_1 + E &\underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} EX_1 \xrightarrow{k_6} X_2 + E, \\
X_2 + F &\underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} FX_2 \xrightarrow{k_8} X_1 + F,
\end{aligned}$$

It can be verified that the negative of the Jacobian of the network above has always strictly negative principle minor; for instance the minor corresponding to $X_0, X_1, X_2, E, FX_1, EX_1$ is negative for any choice of the kinetics. Therefore, Theorem 4.4 implies that it *can not* admit a PWLR Lyapunov function. Indeed, the above network is known to admit multiple nondegenerate equilibria some of which are unstable.

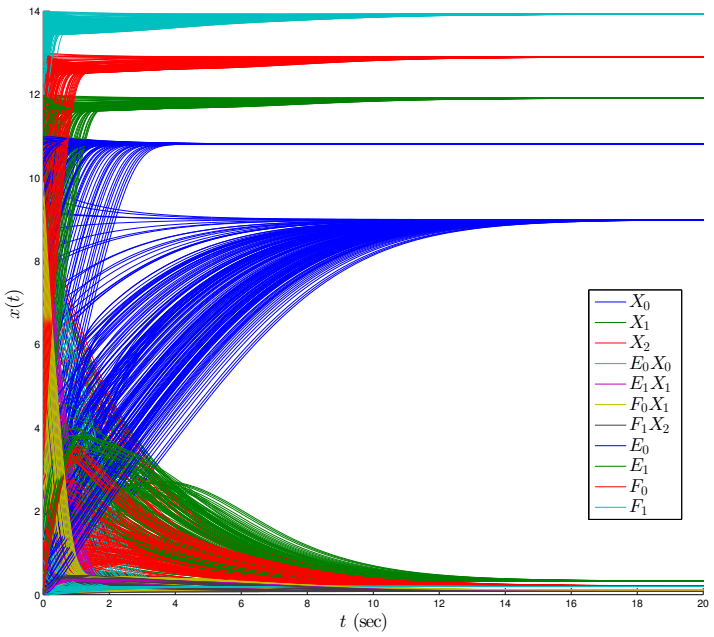


Figure 8.7: Trajectories of the futile cycle cascade with Michaelis-Menten kinetics in the stoichiometric class corresponding to the conserved moieties 10,11,12,13,14.

8.3.5 Other Covalent Modification Networks

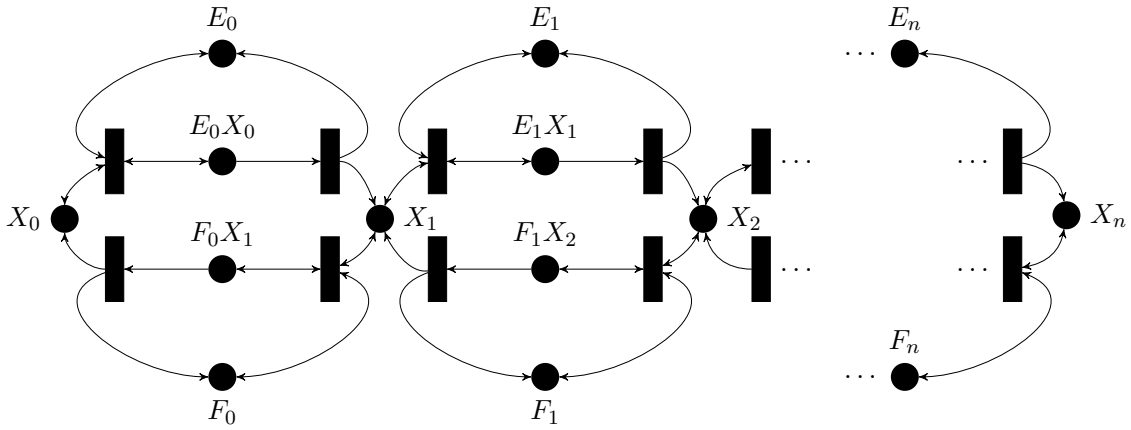
In this subsection, we present other examples of metabolic networks.

Phosphotransfer Network

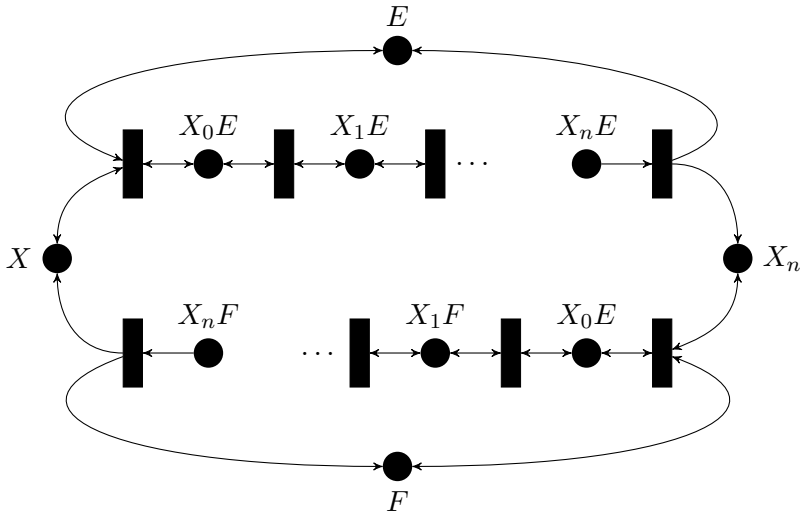
Del Vecchio and Murray [39] present an example of a covalent modification network in which two molecules exchange the phosphate group. This is depicted in Figure 8.9-a). The network can be described by the following set of reactions:

$$Z^+ + X \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} C \underset{R_{-2}}{\overset{R_2}{\rightleftharpoons}} X^+ + Z$$
$$Z \xrightarrow{R_3} Z^+, \; X^+ \xrightarrow{R_4} X,$$

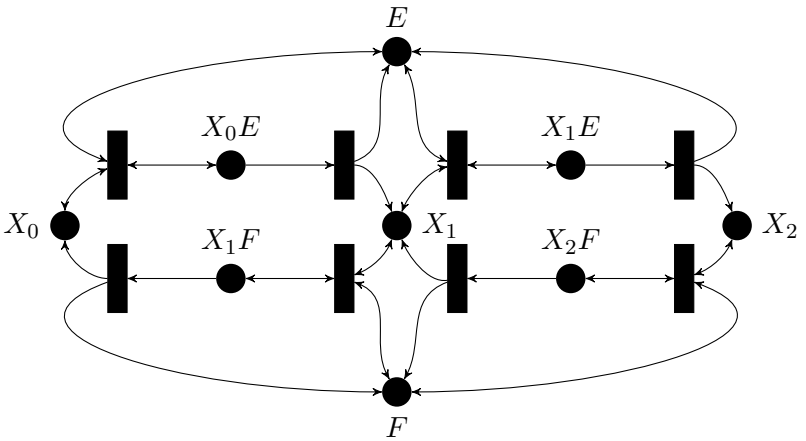
where the "+" superscript refers to a phosphorylated substrate.



(a) Cascade of Multiple Futile Cycles with distinct enzymes



(b) Multiple Futile Cycle with a processive mechanism



(c) Double Futile Cycle with a distributive mechanism

Figure 8.8: Several Types of Cascades of Futile Cycles.

It can be noticed that Theorem 5.5 is applicable, and it admits the following PWLR Lyapunov function:

$$\begin{aligned} V(x) = &\max\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), R_3(x), R_4(x)\} \\ &- \min\{R_1(x) - R_{-1}(x), R_2(x) - R_{-2}(x), R_3(x), R_4(x)\}, \end{aligned}$$

where the LaSalle's argument can be verified to work.

Detailed Phosphorylation Network

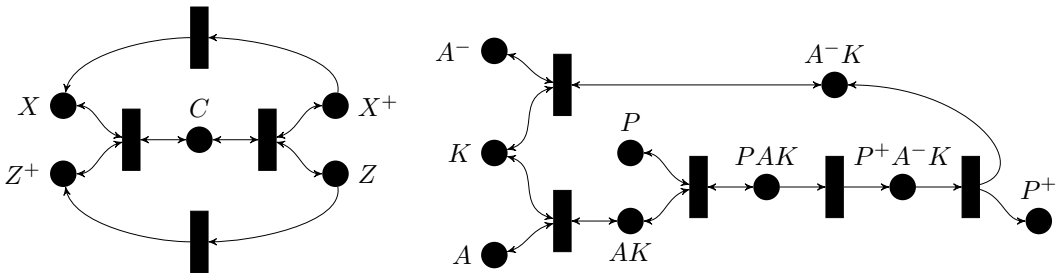
Madhani [64] present this biochemical example of adding a phosphate group to a protein using a kinase. The reaction network is depicted in Figure 8.9-b), which can be written as:

$$\begin{aligned} K + A &\underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} AK \\ P + AK &\underset{R_{-2}}{\overset{R_2}{\rightleftharpoons}} PAK \\ PAK &\xrightarrow{R_3} P^+A^-K \xrightarrow{R_4} P^+ + A^-K \\ A^-K &\underset{R_{-5}}{\overset{R_5}{\rightleftharpoons}} K + A^-, \end{aligned}$$

where K is the kinase, A is the adenosine triphosphate (ATP), A^- is the Adenosine diphosphate (ADP), and P^+ is the phosphorylated protein. Note this network has no full-support kernel vector; reactions R_3, R_4 are not supported, which implies that species PAK, P^+A^-K vanish at any equilibrium point.

Applying Theorem 5.3, one can get the following PWLR Lyapunov function:

$$V(x) = \max\{|R_1(x) - R_{-1}(x)|, |R_2(x) - R_{-2}(x)|, R_3(x), R_4(x), |R_5(x) - R_{-5}(x)|\}.$$



(a) Phosphotransfer Network (b) Detailed Phosphorylation Network

Figure 8.9: Covalent Modification Networks

8.3.6 T-Cell Kinetic Proofreading: McKeithan's Network

Mckeithan [66] proposed a model of a ligand which is peptide-major histocompatibility complex M binding to a T-cell receptor; the receptor-ligand complex undergoes several reactions to reach the final complex C_N. The chain of reactions increases sensitivity and hence it is called a kinetic proofreading process. Figure 8.10 depicts the reaction network, which is given by the following set of reactions:

$$T + M \rightleftharpoons C_0 \longrightarrow C_1 \longrightarrow ... \longrightarrow C_N$$
$$C_1 \longrightarrow T + M, C_2 \longrightarrow T + M, ..., C_N \longrightarrow T + M$$

Applying Theorem 5.1, it can be shown that for any $N \geq 1$, the network admit the following PWLR Lyapunov function:

$$V_N(x) = \| \operatorname{diag}([1, 1, 2, 2, .., 2]^T)\dot{x}\|_1,$$

where the species are ordered as $T, M, C_0, C_1, ..., C_N$. Note that this network does not meet the graphical requirements of Theorem 5.5.

The LaSalle's condition can be verified. The network is conservative, and it is free of critical siphons; hence it is persistent. Any positive equilibrium is unique and GAS.
The monotone-systems approach proposed by Angeli et al. [14] is not applicable here since

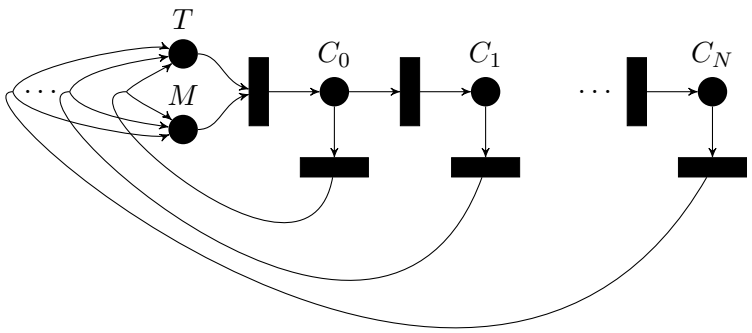


Figure 8.10: McKeithan's network.

the species T and M are adjacent to more than two reactions. Nevertheless, Sontag [89] showed that this network is weakly reversible and zero-deficiency; therefore any positive equilibrium is unique relative to the interior and is locally asymptotically stable. In order to infer global stability, it was needed to compute the equilibria explicitly to preclude the possibility of having a boundary equilibrium stoichiometrically compatible with a positive equilibrium. In comparison, our approach is more powerful, since the former approach is limited to Mass-Action kinetics, and could not infer global stability directly.

8.3.7 ERK Signalling Pathway with RKIP Regulation

Figure 8.11 depicts the network describing the effect the so called Raf Kinase Inhibitor Protein (RKIP) on the Extracellular Regulated Kinase (ERK) signalling pathway as per the model given by Kwang-Hyun et al. [62]. It can be described using the network:

$$
\begin{aligned}
K^+ + M &\underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} K^+M \xrightarrow{R_2} K + M \\
E + P &\underset{R_{-3}}{\overset{R_3}{\rightleftharpoons}} EP \xrightarrow{R_4} E^+ + M \\
K + R &\underset{R_{-5}}{\overset{R_5}{\rightleftharpoons}} KR \\
KR + E^+ &\underset{R_{-6}}{\overset{R_6}{\rightleftharpoons}} KRE^+ \xrightarrow{R_7} R + E + K^+,
\end{aligned}
$$

where K is the RKIP, E is the ERK Kinase, P is the RKIP phosphatase, and M is the phosphorylated MAPK/ERK Kinase, and the plus superscript means that the molecule is phosphorylated.

It can be verified that the requirements of Theorem 5.5 are satisfied, and hence the following is a PWLR Lyapunov function:

$$V(x) = \max_{k \neq j} \; |R_k(x) - R_{-k}(x) + R_{-j}(x) - R_j(x)| \,,$$

where $R_{-k}(x) :\equiv 0$ if $\mathbf{R}_k$ is irreversible. The LaSalle's argument can be verified. Furthermore, since the network is conservative, by Theorem 5.5 the network is persistent.

Note that this network is of deficiency one, hence stability can not be inferred. Nevertheless, monotonicity-based analysis can be applied [14]. Note, however, that our analysis has the advantage of showing persistence directly; rather than requiring to check it a priori. Also, it has the advantage of having an explicit expression for the Lyapunov function.

8.3.8 An Open Example: A Signal Transduction Network

For all the networks discussed so far, we have been successful in constructing a PWLR Lyapunov function, or a necessary condition has been violated. In this final subsection: we present an interesting example, which is depicted in Figure 8.12-a). It describes the basic signal transduction reaction: a ligand binds to a receptor, and ligand-receptor complex acts as enzyme activating a protein P. This is described by the following network:

$$\begin{aligned} R + L &\rightleftharpoons RL \\ RL + P &\rightleftharpoons RLP \longrightarrow P^+ + RL \\ P^+ &\longrightarrow P. \end{aligned}$$

This network has a P_0 Jacobian for all admissible kinetics, and it satisfies that necessary condition given by Theorem 4.3. It also shows a stable behaviour for many simulations

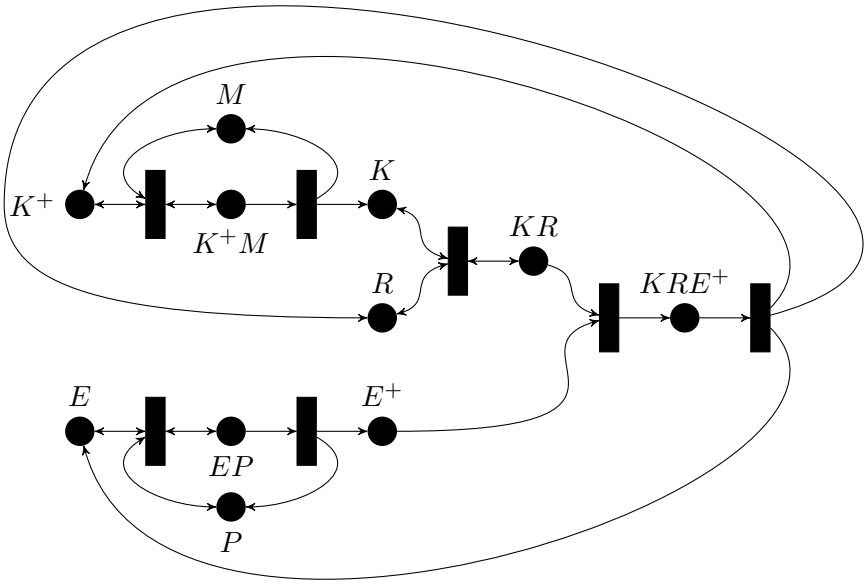
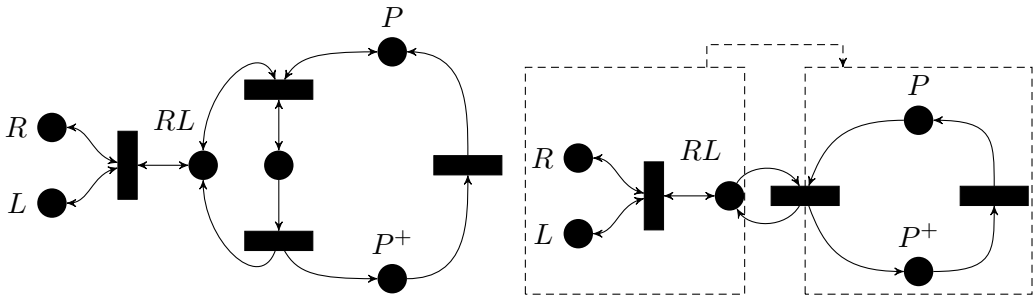


Figure 8.11: ERK Signalling Pathway With RKIP Regulation



(a) Non-Autocatalytic Activation

(b) Autocatalytic Activation: Decomposition to a series cascade

Figure 8.12: Signal Transconduction Pathway

with various kinetic models. However, we have not been successful in constructing any PWLR Lyapunov function. This remains an *open problem.*

Autocatalytic Model

The intermediate species RLP is usually short-lived, a simplified model employing autocatalysis can be written [54]:

$$R + L \underset{R_{-1}}{\overset{R_1}{\rightleftharpoons}} RL$$
$$RL + P \xrightarrow{R_2} P^+ + RL$$
$$P^+ \xrightarrow{R_3} P,$$

which is shown also in Figure 8.12-b). The species RL participates in the second reaction in an autocatalytic manner, which leaves its dynamics uncoupled from the dynamics of P, P^+, hence the system can be decomposed into a cascade as Figure 8.12-b) shows. Therefore, the network $R + L \rightleftharpoons RL$ can be analyzed via the Lyapunov function:

$$V_1(x) = |R_1(x) - R_{-1}(x)|,$$

Let x_3, x_4, x_5 denote the concentrations of RL, P, P^+, respectively. Then, the dynamic of P, P^+ can be written as:

$$\dot{x}_4 = -R_2(x_3, x_4) + R_3(x_4)$$
$$\dot{x}_5 = R_2(x_3, x_4) - R_3(x_4).$$

Assuming that x_3 converges to x_3^*, then $\tilde{R}_3(x_4) = R_3(x_3^*, x_4)$ is a reaction rate function that satisfies our assumptions AK1-AK4. Hence, the following Lyapunov function can be

used for the second system for a fixed x_3^*:

$$V_2(x) = |R_2(x) - R_3(x)|.$$

Then, a CICS argument can be used to infer stability.

If the model was to be considered as a whole, then our algorithms fail to produce a convex PWLR function, however, this continuous PWLR function can be found using the linear program in Theorem 5.1 with a partitioning matrix $\hat{H} = [-1, 1, -1, 1]^T$. It can be written as $V(x) = \tilde{V}(r)$, where

$$\tilde{V}(r) = \begin{cases} |r_1 - r_{-1}| & : (r_1 \geq r_{-1}, r_2 \geq r_3) \vee (r_1 \leq r_{-1}, r_2 \leq r_3), \\ |r_1 - r_{-1} - \frac{1}{2}(r_2 - r_3)| & : (r_1 \geq r_{-1}, r_2 \leq r_3, r_1 + r_2 \geq r_{-1} + r_3) \\ & \quad \vee (r_1 \leq r_{-1}, r_2 \geq r_3, r_1 + r_2 \leq r_{-1} + r_3), \\ \frac{3}{2}|(r_1 - r_{-1})| & : (r_1 \geq r_{-1}, r_2 \leq r_3, r_1 + r_2 \leq r_{-1} + r_3) \\ & \quad \vee (r_1 \leq r_{-1}, r_2 \geq r_3, r_1 + r_2 \geq r_{-1} + r_3), \end{cases}$$

This function is continuous and nonincreasing. However, in the first region for example, it *fails* to meet the LaSalle's condition. Therefore, further analysis is needed. For instance, since $R_1(x_1, x_2), R_{-1}(x_3)$ are decoupled from the rest of species and are convergent as above, the trajectory leaves the interior of all regions. Since this is resemblant to cascade system argument above, we opted for the cascade argument.

Chapter 9

Conclusions and Future Directions

9.1 Conclusions

In this dissertation new theoretical techniques have been developed for a "robust" and "kinetics-free" analysis of ordinary differential equation models of reaction networks. The *main motivation* is the analysis of models that appear in molecular systems biology. This robust approach handles directly a central dilemma in modern systems biology which is that the *quantitative* knowledge required to construct full mathematical models is very little and uncertain in comparison to the availability of detailed graphical network knowledge pertaining to *qualitative* description of the network.

The *main output* of my research is the characterization of the asymptotic behaviour of a wide class of chemical reaction networks based on *graphical information* only and regardless of kinetics or parameters. This new class has been called the class of *Graphically Stable Networks* (GSNs). Many examples of GSNs are not amenable to robust analysis of the dynamics using available methods in the literature.

Unlike previous approaches in the literature which rely on thermodynamic energy functions, our approach is system-theoretic in the sense that it has been conceived and implemented using classical system theory tools and regardless of the thermodynamic interpre-

tation of the network. The proposed method uses the well-established technique in system theory, which is the construction of a Lyapunov function. However, there is no general theory for the construction of Lyapunov functions. Furthermore, the Lyapunov functions that we seek shall be valid regardless of the particular choice of kinetics. Therefore, the task of constructing these functions is highly challenging and system-specific. Nevertheless, we have introduced the class of *Robust Lyapunov Functions* and the subclass of *Piecewise Linear in Rates Lyapunov functions*, and it has been shown to be widely applicable to biochemical networks.

If the required function exists for a given network structure, then any network of that graphical structure coupled with any arbitrary monotone kinetics possesses many powerful dynamical properties. Main properties can be summarized informally has follows:

- The Jacobian is P_0 (Theorem 4.4), and multiple non-degenerate equilibria can not be admitted (Theorem 4.5).

In addition, if the trajectories are bounded, then

- the equilibrium set is Lyapunov stable (Theorem 3.2).
- if a LaSalle's graphical condition is verified, the equilibrium set is asymptotically stable (Theorem 3.6),
- the trajectories are non-expansive (Theorem 6.11). If a LaSalle's graphical condition is verified then the network is exponentially contractive in stoichiometry classes (Theorem 6.14).

If in addition, there exists an isolated positive equilibrium relative to some class, then

- this equilibrium is locally exponentially stable (Theorem 6.10)
- this equilibrium is unique relative to its class (Theorem 4.5),

- the reduced Jacobian is non-singular relative to the interior of the orthant (Theorem 6.9),
- if the graphical LaSalle's condition is verified, the this equilibrium is *globally asymptotically stable* (Theorem 3.3).

If in addition, the network is conservative, then,

- there does not exists any critical siphon, and hence the network is persistent (Theorem 4.7).
- Any equilibrium can be globally stabilized via a kinetics-independent state-feedback (Theorem 7.1).

A full characterization of GSNs in terms of either finding the Lyapunov function or proving that it is non-existent is unavailable. It has been shown that this difficulty parallels the well-known difficulty of constructing Lyapunov functions of linear differential inclusions. Nevertheless, several necessary conditions have been given (refer to Theorems 4.3, 4.4, 4.5, 4.6, and 6.9). Violation of one of these conditions prove that the network is not a GSN.

On the other hand, effective methods for the construction of these functions have been provided which includes three main methods: linear programming-based method, an iterative method, and a graphical condition. For most examples of networks that we have considered, either a necessary condition was violated, or a Lyapunov function is successfully constructed. Nevertheless, there are some examples which are open (refer to §8.3.8).

Links with uncertain systems and robust analysis methods have been established. It has been shown that the class of GS networks have a hidden linear structure. If a common Lyapunov function exists for a set of linear systems, then the nonlinear system is stable. Furthermore, it has been shown that for a given PWLR Lyapunov function several dual Lyapunov functions exist in by a shift of coordinates.

9.2 Future Directions

In this journey, several problems remain open and to be investigated. We mention *nine* below.

First, the problem of the absence of critical siphons for graphically stable networks has not been resolved fully. We conjecture that it follows directly from the mere existence of the PWLR Lyapunov function (see Conjecture 1).

Second, the problem of constructing a PWLR Lyapunov function by finding a partitioning matrix for a network is widely open. The examples in which a partitioning matrix has been found rely on ad-hoc ways. (see §5.1.1).

Third, Theorems 5.1 and 5.3 provide algorithms for the construction of PWLR Lyapunov function that does not link clearly with the properties of the graph of network as does Theorem 5.4. More graphical characterizations are needed. For instance, it can be conjectured from Remark 5.6 that any network that satisfies the second graphical condition of Theorem 5.4 admit a positive-definite PWLR Lyapunov function.

Fourth, all examples for which Theorems 5.4, 5.5 apply, were also amenable to the analysis by Theorem 5.3. It is interesting to have the general statement proven.

Fifth, it is known that the existence piecewise quadratic Lyapunov functions is equivalent to the existence of piecewise linear Lyapunov functions for the stability of linear inclusions [69]. However, if the partition region was fixed, is it possible to find a PWQR Lyapunov function when no PWLR function exists?

Sixth, Control PWLR Lyapunov functions were just defined. A major task is to design controllers based on them.

Seventh, it has been observed that all examples for which the monotonicity-based approach of Angeli et al. [14] was applicable satisfy the conditions of Theorems 5.4,5.5. Investigation of the relationship of our theory with monotonicity-based approaches is interesting.

Eighth, it has been observed in examples presented in §8.2 and §8.3.4 that the Lyapunov

function has some modular properties for certain cascades of networks. Investigation of effects of interconnections of $\mathscr{P}$ networks is valuable.

Ninth, the example presented in §8.3.8 is interesting both theoretically and practically. Therefore, a conclusive analysis is required.

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