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Autocatalytic Biochemical Networks and Their Fundamental Limits

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Autocatalytic Biochemical Networks and Their Fundamental Limits

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I dedicate this thesis to my husband, who has shared this entire amazing journey with me, and my parents for patiently waiting for my graduation. This accomplishment would not have been possible without you.

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Abstract

In the present work, we study autocatalytic pathways which contain reactions that need the use of one of their own productions. These pathways are common in biology; one of the simplest and widely studied autocatalytic pathways is Glycolysis. This pathway produces energy by breaking down Glucose. It is shown that this pathway can be simplified as a network of three biochemical reactions. We first revisit some conditions on the underlying structure of the autocatalytic network, which guarantee the existence of fundamental limits on the output energy of such networks. Then we focus on autocatalytic pathways with several biochemical reactions. Our aim is to characterize the zero-dynamics for a class of autocatalytic networks and then study the fundamental limitations of feedback control laws, using their associated zero-dynamics. For this aim, it is shown that the zero-dynamics of autocatalytic networks play an important role in studying the fundamental limits on performance. Zero-dynamics is defined as the dynamics of a system restricted to the control input and initial conditions such that the output of the system remains zero for all future time instances. We characterize the zero-dynamics for a class of unperturbed autocatalytic networks based on the structure of the original network. It is well-known that by knowing the zero-dynamics of a specific class of systems, one can obtain lower bounds on the best achievable performance (L_2-norm of the output) for the system. For a specific class of autocatalytic networks, we characterize their zero-dynamics in terms of the state-space matrices of the underlying network. This can be utilized to quantify inherent fundamental limits on performance (the level of disturbance attenuation) for this class of network. In general, one should apply numerical algorithms to obtain such fundamental limits. We explain our method using a simple but illustrative example.

Chapter 1

Introduction

A biochemical autocatalytic network (pathway) is a collection of biochemical reactions, such that the network's product is necessary to power its own production. This class of networks are common in biology and engineering; one of the simplest and widely studied autocatalytic pathway is glycolysis, which is conserved from bacteria to human [18, 19, 22, 25, 26]. This pathway produces energy by breaking down glucose. The free energy released in this process is used to form adenosine triphosphate (ATP), which is considered as the cell's energy currency.

There have been several recent studies on models of glycolysis pathways which are examples of autocatalytic networks in biology. We refer to [5–8, 18, 19, 22, 25, 26, 28] and reference in there for more details and discussions. In [19], it is shown that glycolysis pathway can be simplified as a network of three biochemical reactions. For a linearized model of simple two-state model of glycolysis, the authors use Bode's sensitivity integral to explicitly derive equation for hard-tradeoffs between robustness and efficiency. In reference [6], the authors employ a two-state model of Glycolysis pathway to study inherent fundamental limits on the minimum achievable L_2-gain disturbance attenuation and the minimum achievable output energy. Later on in reference [5], these results are generalized for a cyclic model of the glycolysis pathway with several intermediate biochemical reactions. Schwartz et al. show that for the first-order linear systems, optimal disturbance attenuations can be calculated based on the zero-dynamics of the system [2].

In this work, we revisit the minimal model for glycolysis pathway which is presented in [5, 6, 19] and also a higher dimensional model of interconnected pathways [5], to obtain their underlying zero-dynamics in order to use them to obtain fundamental limits on performance. We will only present a simple example

to explain the main idea. Zero-dynamics is defined as the dynamics of a system restricted to the control input and initial conditions such that the output of the system remains zero for all future time instances.

In this thesis, we briefly review fundamental limits on the output energy for a class of autocatalytic networks (e.g., ATP or Energy) when the control effort is free. Then, we discuss about the results in [5, 6] which explains how the smallest achievable L_2 norm of the output relates to structural property of the network. It is well known that the smallest achievable L_2 norm of the output is equal to the least needed amount of control energy to stabilize the unstable part of the underlying zero-dynamics [2]. Next, we investigate the zero-dynamics for a class of autocatalytic networks in presence of disturbances and we review some of the results in the literature that shows such fundamental limits can be related to the general structure of the zero-dynamics of the system. It is shown that for first-order linear systems, optimal disturbance attenuations can be calculated based on the zero-dynamics of the system, such that the hard limit function (L_2 gain from disturbances to output) is zero if and only if disturbance does not affect the unstable mode of the zero-dynamics of the system [1–4, 12–14].

The underlying zero-dynamics of dynamicsl networks plays an important role in emergence of fundamental limits on performance in such networks. Due to such foundational role, we characterize the zero-dynamics for a class of autocatalytic networks based on the structure of the original network. For this aim, we focus on a specific class of autocatalytic networks and calculate state-space matrices of associated zero-dynamics using matrix projections of the original state-space matrices of the network. Then, we review the existing results in the literature that show how one can use the resulting zero-dynamics to characterize limits of performance in such networks. In general, one should employ numerical tools to compute such limits. We show that how an approximate bound can be calculated in terms of design parameters.

The rest of the thesis is organized as follows. Chapter 2 reviews some preliminaries in matrix analysis and biology. Based on [5, 18, 19], a minimal glycolysis model is introduced which will be used through the thesis.

In Chapter 3, we characterize the zero-dynamics for a class of autocatalytic networks based on the state space matrices of the original network. Then we extend our results for a class of autocatalytic networks in presence of disturbances. Finally, in this chapter some necessary and sufficient conditions under which, the autocatalytic network has meaningful fixed points are reviewed.

In Chapter 4, we first consider some characteristics of the underlying structure of the autocatalytic network to discuss a sufficient condition for the existence of fundamental limits on the output energy. Then, we revisit an approach to obtain fundamental limits (lower bounds) on the L_2-gain from disturbance input to regulated output for two classes of nonlinear and linear systems with internal stability [2–4]. Finally, we discuss that by knowing the state-space matrices of zero-dynamics of a linear dynamical network one can calculate the limits of performance numerically. In general, finding closed-form solution for such limits is difficult, if not impossible. Moreover, some numerical examples are provided in Chapter 4.

We end in Chapter 5 with some conclusion remarks as well as discussion of some open questions.

Chapter 2

Preliminaries

The following notations and definitions from reference book [23] will be used throughout the thesis.

2.1 Matrix Analysis

Definition 2.1.1. *A symmetric $n \times n$ real matrix A is said to be positive-semidefinite if $x^T Ax$ is nonnegative for all non-zero vector $x \in \mathbb{R}^n$. Here x^T denotes the transpose of x.*

Definition 2.1.2. *A symmetric $n \times n$ real matrix A is said to be positive definite if $x^T Ax$ is positive for all non-zero vector $x \in \mathbb{R}^n$. Here x^T denotes the transpose of x.*

Definition 2.1.3. *The non-negative orthant consists of all vectors in $\mathbb{R}^n$ whose elements are all non-negative: $\mathbb{R}^n_+ = \{x : x_i \geq 0 \; \forall i = 1, ..., n\}$.*

Definition 2.1.4. *The positive orthant consists of all vectors in $\mathbb{R}^n$ whose elements are all positive: $\mathbb{R}^n_{++} = \{x : x_i > 0 \; \forall i = 1, ..., n\}$.*

Definition 2.1.5. *For any vector $x \in \mathbb{R}^n$, a diagonal $n \times n$ matrix is defined by*

$$\mathbf{diag}(x) = \begin{pmatrix} x_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & x_n \end{pmatrix}. \tag{2.1}$$

Definition 2.1.6. *A matrix is called anti-stable if all its eigenvalues have positive real parts.*

Definition 2.1.7. *The class of Z_n matrices are those matrices whose off-diagonal entries are less than or equal to zero, i.e., a matrix $Z = [z_{ij}]$ in Z_n satisfies $z_{ij} \leq 0$ if $i \neq j$.*

Definition 2.1.8. *M-matrix is a Z-matrix with eigenvalues whose real parts are positive. In other word, matrix A is called an M-matrix if $A \in Z_n$ and A is anti-stable. Whenever A is invertible and A^{-1} is an M-matrix, A is called inverse M-matrix.*

Definition 2.1.9. *Let A be a complex $n \times n$ matrix, with entries a_{ij}. Let $R_i = \sum_{i \neq j} |a_{ij}|$ be the sum of the absolute values of the non-diagonal entries in the $i - th$ row. The closed disc centered at a_{ii} and radius R_i is called the Gershgorin disc and shown by $D(a_{ii}, R_i)$.*

Theorem 2.1.10. Gershgorins Theorem: *Every eigenvalue of $n \times n$ matrix A, lies within at least one of the Gershgorin discs $D(a_{ii}, R_i)$.*

2.2 Biological Preliminaries

A chemical reaction is a process that leads to the transformation of one set of chemical species to another. Chemical reactions are graphically illustrated by using chemical equations, which consist of chemical formulas of the reactants on the left and chemical formulas of the products on the right. $A \xrightarrow{k} B$ denotes a chemical reaction that converts the chemical species A to the chemical species B at rate k. In a more general form, the following chemical equation shows that the collection of a_i copies of chemical reactants x_i, $1 \leq i \leq n$, converts to the collection of b_i copies of chemical produts y_i, $1 \leq j \leq m$ at rate r:

$$a_1 x_1 + \cdots + a_n x_n \xrightarrow{k} b_1 y_1 + \cdots + b_m y_m. \tag{2.2}$$

Here a_i, $1 \leq i \leq n$, and b_i, $1 \leq j \leq m$ are the stoichiometric coefficients of chemical reaction. The reaction rate (rate of reaction) r, for a reactant or product in a particular reaction is defined as how fast or slow a reaction takes place which is defined as:

$$r = -\frac{1}{a_1}\frac{dX_1}{dt} = \cdots = -\frac{1}{a_n}\frac{dX_n}{dt} = \frac{1}{b_1}\frac{dY_1}{dt} = \cdots = \frac{1}{b_m}\frac{dY_m}{dt}, \tag{2.3}$$

where X denotes the concentration of the substance x.

To determine the reaction rate r, we consider the most common kinetics model, mass-action kinetics, which link the rate of a reaction to the concentration of each reactant as follow:

$$r = kX_1^{a_1} \cdots X_n^{a_n}, \tag{2.4}$$

where k is the reaction rate coefficient or rate constant which is given by Arrhenius equation. Arrhenius' equation gives the dependence of the rate constant k of a chemical reaction on the absolute temperature T (in kelvin)

$$k = Ae^{\frac{-E_a}{RT}}, \tag{2.5}$$

where A is the non-negative pre-exponential factor, E_a is the activation energy, and R is the Universal gas constant.

Remark 2.2.1. *According to equation (2.5), the reaction rate coefficient k is always a non-negative number.*

Remark 2.2.2. *For convenience of notation, from now on we will use x to denote the chemical species x as well as its concentration X.*

2.2.1 Dynamical Representation of Biochemical Reactions

For a set of biochemical reactions, the stoichiometry matrix denoted by S, is an $n \times m$ matrix, where m equals to the number of reactions and n is the number of species. Each row corresponds to a species, and each column corresponds to a reaction. The stoichiometry matrix indicates which species and reactions are involved as reactants and products. Reactants are represented in the matrix with their stoichiometric coefficients at the appropriate location with a negative sign; row of species and column of reaction. Products are represented in the matrix with their stoichiometric coefficients with a positive sign; at the appropriate location; row of species and column of reaction. All other locations in the matrix contain a zero. Then for a set of chemical reactions $R_1, R_2, \cdots, R_m$ that involves chemical species $x_1, x_2, \cdots, x_n$, we have

$$\frac{dX}{dt} = Sr, \tag{2.6}$$

where $X \triangleq (X_1, \cdots, X_n)^T$, the vector of the concentrations of the species, and $r = (r_1, \cdots, r_m)^T$ denotes the reaction rate vector, such that the rate of reaction i, $1 \leq i \leq m$ is given by r_i.

Example 2.2.3. *Consider the following autocatalytic network*

$$\begin{aligned} s + \alpha x_3 &\xrightarrow{f_1} x_1 \\ x_1 + \alpha x_4 &\xrightarrow{f_2} x_2 \\ x_2 &\xrightarrow{k_1} (1+\alpha)x_3 \\ x_3 &\xrightarrow{k_2} (1+\alpha)x_4 \\ x_4 &\xrightarrow{k_3} \oslash \end{aligned} \tag{2.7}$$

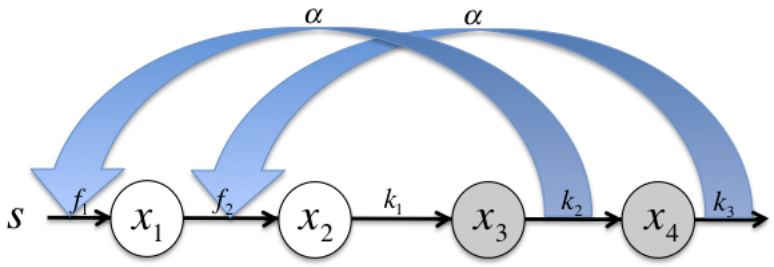


Figure 2.1: Diagram of four-state autocatalytic model of Example 2.2.3

For this set of reactions, the Stoichiometry matrix is given by:

$$S = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 \\ -\alpha & 0 & 1+\alpha & -1 & 0 \\ 0 & -\alpha & 0 & 1+\alpha & -1 \end{pmatrix}. \tag{2.8}$$

The system dynamics can be considered as

$$\dot{x} = S \begin{pmatrix} f_1 \\ f_2 \\ k_1 x_2 \\ k_2 x_3 \\ k_3 x_4 \end{pmatrix}, \tag{2.9}$$

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 \\ -\alpha & 0 & 1+\alpha & -1 & 0 \\ 0 & -\alpha & 0 & 1+\alpha & -1 \end{pmatrix} \begin{pmatrix} f_1 \\ f_2 \\ k_1 x_2 \\ k_2 x_3 \\ k_3 x_4 \end{pmatrix}$$

$$= \begin{pmatrix} f_1 - f_2 \\ f_2 - k_1 x_2 \\ -\alpha f_1 + (1+\alpha) k_1 x_2 - k_2 x_3 \\ -\alpha f_2 + (1+\alpha) k_2 x_3 - k_3 x_4 \end{pmatrix}$$

$$= \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & -k_1 & 0 & 0 \\ 0 & (1+\alpha)k_1 & -k_2 & 0 \\ 0 & 0 & (1+\alpha)k_2 & -k_3 \end{pmatrix} x + \begin{pmatrix} 1 & -1 \\ 0 & 1 \\ -\alpha & 0 \\ 0 & -\alpha \end{pmatrix} \begin{pmatrix} f_1 \\ f_2 \end{pmatrix}.$$

2.2.2 A Minimal Glycolysis Model

Glycolysis is a metabolic pathway that converts glucose $C_6H_{12}O_6$ into pyruvate $CH_3COCOO^- + H^+$. The free energy released in this process is used to form adenosine triphosphate (ATP), which is considered as the cell's energy currency, and NADH (reduced nicotinamide adenine dinucleotide). Glycolysis produces the high-energy compound ATP from glucose. The energy of ATP molecule stores in the bonds between its three phosphate groups. During the glycolysis pathway, two molecules of ATP are consumed in the early steps (hexokinase, phosphofructokinase/PFK) and four ATPs are generated later. ATP is also a regulator for PFK reaction, such that PFK is inhibited by high cellular ATP concentration. Since the

product of glycolysis pathway, ATP, is necessary to catalyze its own production, therefore the glycolysis pathway can be considered as an autocatalytic network [5, 19, 26]. Among different discussed models for glycolysis autocatalysis, we consider the minimal 2-state model from [5, 19, 26]. This minimal system contains three reactions with a single intermediate metabolite reaction as follows

$$s + \alpha y \quad \xrightarrow{f} \quad x_1 \quad \xrightarrow{k_x} \quad (\alpha + \beta)y + x_1', \tag{2.10}$$

$$y \quad \xrightarrow{k_y} \quad \varnothing. \tag{2.11}$$

In the first reaction, s is the source of energy for the pathway, without any dynamics associated and y denotes the product of the pathway (ATP). Regarding the rate of the first reaction, we choose $f(y) = \frac{Vy^\alpha}{1+\gamma y^h}$ which is consistent with experimental data in the case of the glycolysis pathway [17, 20], where $V > 0$ depends on s. Parameter $\alpha > 0$ is the number of y molecules that are invested in the pathway and captures the strength of autocatalysis, while $\gamma, h > 0$ capture the strength of inhibition. Therefore, the function f captures the interplay between the autocatalysis and inhibition. In (2.10), x_1 shows an intermediate metabolites, $\alpha + \beta$ is the total number of y molecules produced and x_1' is one of the by-products of the second biochemical reaction. In (2.11) $\varnothing$ is a null state.

Based on [5], the following 2-state minimal model is associated to the three biochemical reactions (2.10)-(2.11) and it governs the changes in concentrations x_1 and y

$$\dot{x}_1 = -k_x x_1 + \frac{Vy^\alpha}{1+\gamma y^h}, \tag{2.12}$$

$$\dot{y} = -k_y y + (\alpha + \beta)k_x x_1 - \frac{\alpha V y^\alpha}{1+\gamma y^h}. \tag{2.13}$$

for $x_1 \geq 0$ and $y \geq 0$. In [5], by normalizing the concentration such that steady states are $\bar{y} = 1$ and $\bar{x} = \frac{k_y}{\beta k_x}$, and also considering the expression $\frac{1}{1+\gamma y^h}$ as the regulatory feedback control employed by nature, the minimal model (2.12)-(2.13) is reformulated as the following control system

$$\dot{x} = -k_x x + V y^\alpha u, \tag{2.14}$$

$$\dot{y} = -k_y y + (\alpha + \beta)k_x x - \alpha V y^\alpha u. \tag{2.15}$$

We will use this model in Chapters 3 and 4.

Chapter 3

Zero-dynamics of Autocatalytic Networks

Autocatalytic networks are one of the most interesting dynamical networks, in which the systems product is necessary to produce its own production. This class of networks are common in biology and engineering. Glycolysis is one of the most common autocatalytic networks in biology, which conserved from bacteria to humans and has been discussed in section 2.2.2. It is shown that the zero-dynamics plays an important role to obtain the fundamental limits on the performances (e.g., L_2 norm of the output and the level of disturbance attenuation) of the autocatalytic networks [2, 6], which will be discussed in chapter 4. Therefore, in this chapter we characterize the zero-dynamics for a class of autocatalytic networks based on the state space matrices of the original network. Moreover, we revisit the necessary and sufficient conditions under which, the autocatalytic network has meaningful fixed points. Finally, we investigate the zero-dynamics for a class of autocatalytic networks in presence of disturbances, based on its state space matrices.

3.1 Zero-dynamics of LTI Systems

Consider the following minimal linear time invariant system

$$\begin{aligned} \dot{x} &= Ax + Bu, \\ y &= Cx, \end{aligned} \tag{3.1}$$

where

$$A = \begin{pmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ -a_0 & -a_1 & -a_2 & \cdots & -a_{n-1} \end{pmatrix}_{n\times n}, \tag{3.2}$$

$$B = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 0 \\ k \end{pmatrix}_{n\times 1}, \quad C = \begin{pmatrix} b_0 & b_1 & \cdots & b_{n-r-1} & 1 & 0 & \cdots & 0 \end{pmatrix}_{1\times n}.$$

The corresponding transfer function of (3.1) is obtained by

$$G(s) = k\frac{b_0 + b_1 s + \cdots + b_{n-r-1}s^{n-r-1} + s^{n-r}}{a_0 + a_1 s + \cdots + a_{n-1}s^{n-1} + s^n}. \tag{3.3}$$

Note that the relative degree of $G(s)$ is r. Using the state transformation matrix T, this system can be transformed into the **normal form** state-space representation as follow:

$$\begin{cases} \dot{z} = A_z z + B_z y, \\ \dot{\xi}_1 = \xi_2, \\ \quad \vdots \\ \dot{\xi}_{r-1} = \xi_r, \\ \dot{\xi}_r = Wz + V\xi + ku, \\ y = \xi_1, \end{cases}$$

where the state transformation matrix T is given by

$$T = \begin{pmatrix} I_{(n-r)\times(n-r)} & & 0_{r\times r} \\ & -C & \\ & -CA & \\ & \vdots & \\ & -CA^{r-1} & \end{pmatrix}_{n\times n}, \tag{3.4}$$

and

$$z = \begin{pmatrix} z_1 \\ z_2 \\ \vdots \\ z_{n-r} \end{pmatrix} = \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_{n-r} \end{pmatrix}, \tag{3.5}$$

$$\xi = \begin{pmatrix} \xi_1 \\ \xi_2 \\ \vdots \\ \xi_r \end{pmatrix} = \begin{pmatrix} Cx \\ CAx \\ \vdots \\ CA^{r-1}x \end{pmatrix},$$

$$A_z = \begin{pmatrix} 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \\ -b_0 & -b_1 & -b_2 & \cdots & -b_{n-r-1} \end{pmatrix},$$

$$B_z = \begin{pmatrix} 0 \\ \vdots \\ 0 \\ 1 \end{pmatrix}.$$

Zero-dynamics is defined as the dynamics of system (3.1) restricted to the set of control input u and initial conditions x_0 such that $y(t) = 0,\ \forall t \geq 0$. In terms of normal form coordinates, the output is:

$$y(t) = \xi_1(t). \tag{3.6}$$

Therefore, in order to keep $y(t) = 0$ for all t, we must have

$$\dot{\xi}_1 = \dot{\xi}_2 = \cdots = \dot{\xi}_r = 0, \tag{3.7}$$

which leads to $\xi(t) = 0$ for all t. So we conclude that the zero dynamics is a linear system represented by

$$\dot{z} \quad = \quad A_z z + B_z y, \tag{3.8}$$

which is defined on the subspace

$$Z^* \triangleq \{x : CA^i x = 0, i = 0, \cdots, r-1\}. \tag{3.9}$$

Note that eigenvalues of A_z corresponds to the zeros of the system's transfer function $G(s)$.

3.2 Zero-dynamics for Autocatalytic Networks

Consider the following system with $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$:

$$\begin{aligned} \dot{x} &= Ax + Bg(x, u), \\ y &= Cx. \end{aligned} \tag{3.10}$$

Zero-dynamics is defined as the dynamics of system (3.10) restricted to the control input $g(x, u)$ and initial conditions x_0 such that $y(t) = 0,\ \forall t \geq 0$. According to (3.10), $\dot{y}$ is given by

$$\dot{y} \quad = \quad CAx + CBg(x, u). \tag{3.11}$$

Based on the definition for a zero-dynamic system we have $\dot{y} = 0$, therefore

$$g(x, u) = -(CB)^{-1}CAx. \tag{3.12}$$

Now, by substituting (3.12) in (3.10) we get

$$\begin{aligned} \dot{x} &= Ax - B(CB)^{-1}CAx \\ &= (I_{n\times n} - B(CB)^{-1}C)Ax \\ &= PAx, \end{aligned} \tag{3.13}$$

where $P = I_{n\times n} - B(CB)^{-1}C$.

Remark 3.2.1. *Note that matrix P is a projection matrix (i.e.,$P^2 = P$).*

Proof. It is enough to show that

$$\begin{aligned} P^2 &= (I_{n\times n} - B(CB)^{-1}C)(I_{n\times n} - B(CB)^{-1}C) \\ &= I_{n\times n} - B(CB)^{-1}C - B(CB)^{-1}C + B(CB)^{-1}CB(CB)^{-1}C \\ &= I_{n\times n} - B(CB)^{-1}C - B(CB)^{-1}C + B(CB)^{-1}C \\ &= I_{n\times n} - B(CB)^{-1}C \\ &= P. \end{aligned} \tag{3.14}$$

□

In our approach, we define output y as a vector in $\mathbb{R}^m$ which elements are m selective elements of x. These elements are chosen as the system's autocatalysis reactants. Therefore, the full rank matrix C has exactly one 1 in each row and the rest elements are zero. We now define matrix D such that vector $\bar{x} = Dx$ gives us the rest $n - m$ elements of x and $DC^T = 0$. Similar to matrix C, matrix D is full rank with exactly one 1 in each row and the zero as the rest elements. The zero-dynamics state vector, z, is defined as

$$z = (D + MC)x = Dx + My, \tag{3.15}$$

where matrix M need to be chosen appropriately, such that input function does not have any effect on the zero-dynamics.

For this parameters the following equation holds:

$$\begin{pmatrix} C \\ D \end{pmatrix} x = \begin{pmatrix} y \\ \bar{x} \end{pmatrix}, \tag{3.16}$$

$$\begin{aligned} \rightarrow x &= \begin{pmatrix} C^T & D^T \end{pmatrix} \begin{pmatrix} y \\ \bar{x} \end{pmatrix} \\ &= C^T y + D^T \bar{x}. \end{aligned} \tag{3.17}$$

Since $\dot{y} = 0$,

$$\begin{aligned} \dot{z} &= D\dot{x} \\ &= DPAx \\ &= DPAC^T y + DPAD^T \bar{x}. \end{aligned}$$

Therefore, the zero-dynamics of (3.10) can be written as follows

$$\dot{z} = A_z z + B_z y, \tag{3.18}$$

where

$$\begin{cases} A_z = DPAD^T, \\ B_z = DPA(C^T - D^T M). \end{cases} \tag{3.19}$$

Example 3.2.2. *Consider the following autocatalytic network, in which both autocatalysis and regulating control feedbacks applies on the same biochemical reaction.*

$$\begin{aligned} s + \alpha x_2 &\xrightarrow{f_1} x_1 \\ x_1 &\xrightarrow{k_1} (1+\alpha) x_2 \end{aligned}$$

$$
\begin{aligned}
x_2 + \alpha x_4 &\xrightarrow{f_2} x_3 \\
x_3 &\xrightarrow{k_2} (1+\alpha)x_4 \\
x_4 &\xrightarrow{k_3} \oslash
\end{aligned}
$$

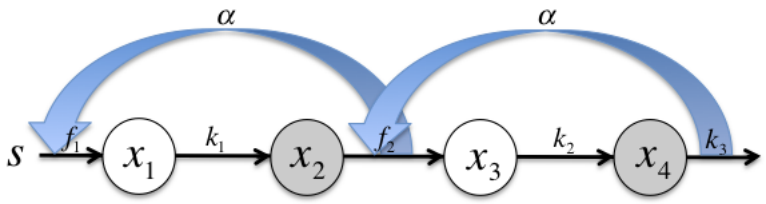


Figure 3.1: Diagram of four-state autocatalytic model of Example 3.2.2

For this set of reactions, the Stoichiometry matrix is given by:

$$
S = \begin{pmatrix}
1 & -1 & 0 & 0 & 0 \\
-\alpha & 1+\alpha & -1 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 \\
0 & 0 & -\alpha & 1+\alpha & -1
\end{pmatrix}.
$$

Dynamic of the system can be considered as

$$
\dot{x} = S \begin{pmatrix} f_1 \\ k_1 x_1 \\ f_2 \\ k_2 x_3 \\ k_3 x_4 \end{pmatrix},
$$

$$
\begin{pmatrix} \dot{x_1} \\ \dot{x_2} \\ \dot{x_3} \\ \dot{x_4} \end{pmatrix} = \begin{pmatrix}
1 & -1 & 0 & 0 & 0 \\
-\alpha & 1+\alpha & -1 & 0 & 0 \\
0 & 0 & 1 & -1 & 0 \\
0 & 0 & -\alpha & 1+\alpha & -1
\end{pmatrix} \begin{pmatrix} f_1 \\ k_1 x_1 \\ f_2 \\ k_2 x_3 \\ k_3 x_4 \end{pmatrix}
$$

$$
\begin{aligned}
&= \begin{pmatrix} f_1 - k_1 x_1 \\ -\alpha f_1 + (1+\alpha) k_1 x_1 - f_2 \\ f_2 - k_2 x_3 \\ -\alpha f_2 + (1+\alpha) k_2 x_3 - k_3 x_4 \end{pmatrix} \\
&= \begin{pmatrix} -k_1 & 0 & 0 & 0 \\ (1+\alpha)k_1 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & 0 \\ 0 & 0 & (1+\alpha)k_2 & -k_3 \end{pmatrix} x + \begin{pmatrix} 1 & 0 \\ -\alpha & -1 \\ 0 & 1 \\ 0 & -\alpha \end{pmatrix} \begin{pmatrix} f_1 \\ f_2 \end{pmatrix}. \qquad (3.20)
\end{aligned}
$$

$$
\begin{aligned}
y &= \begin{pmatrix} x_2 \\ x_4 \end{pmatrix} = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} x, \\
D &= \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}.
\end{aligned}
$$

$$
\begin{aligned}
P &= I - B(CB)^{-1}C = \begin{pmatrix} 1 & \frac{1}{\alpha} & 0 & -\frac{1}{\alpha^2} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & \frac{1}{\alpha} \\ 0 & 0 & 0 & 0 \end{pmatrix}, \\
A_z &= DPAD^T = \begin{pmatrix} \frac{k_1}{\alpha} & -\frac{k_2(1+\alpha)}{\alpha^2} \\ 0 & \frac{k_2}{\alpha} \end{pmatrix}.
\end{aligned}
$$

$$
\begin{cases} \lambda_1 = \frac{k_1}{\alpha} > 0, \\ \lambda_2 = \frac{k_2}{\alpha} > 0. \end{cases} \qquad (3.21)
$$

The zero-dynamics of autocatalytic network (3.20) is unstable.

With following assumptions

$$\begin{cases} k_1 = k_2 = k_3 = k, \\ u_1 = u_2 = 1, \\ x_1 = \frac{1}{k}, \end{cases}$$

by solving $\dot{x} = 0$, fixed points of system (3.20) can be calculated as follow:

$$\begin{cases} x_1 = x_2 = x_3 = x_4 = \frac{1}{k}, \\ u_1 = u_2 = 1. \end{cases} \tag{3.22}$$

3.3 Interconnected Networks of Pathways

In this section, we consider the problem of determining meaningful equilibrium points for an arbitrary interconnection of n autocatalytic pathways with minimal representations as shown in Fig.(3.2). This problem first has been studied in [5]. Now we are going to revisit this problem in more details and extend their results.

The model of each pathway consists of three biochemical reactions as follows

$$\alpha_{i1}y_1 + \cdots + \alpha_{in}y_n \xrightarrow{f_i} x_i \tag{3.23}$$

$$x_i \xrightarrow{k_{x_i}} (\alpha_i + \beta_i)y_i + x_i' \tag{3.24}$$

$$y_i \xrightarrow{k_{y_i}} \varnothing \tag{3.25}$$

where $\alpha_i = \alpha_{1i} + \cdots + \alpha_{ni}$, parameter α_{ij} is the number of y_i molecules that are invested in the pathway j and $\alpha_i + \beta_i$ is the number of y_i molecules produced in pathway i. Since the by-product of a pathway is a necessary reactant in several other pathways, hence perturbation in one pathway will affect the subsequence ones. This interconnection topology appears in various pathways in cell. The interconnection between the pathways can be represented by a directed graph $\mathcal{G}$ with n nodes. Each node of the graph represents a pathway and the directed edge from node i to node j shows that the product of node i is a necessary reactant to produce the output of node j.

Remark 3.3.1. *Note that k_{x_i} and k_{y_i} are the chemical reaction rate constants of (3.24) and (3.25) respectively, which are always a nonnegative constant according to remark 2.2.1.*

We assume that in the interconnected network of pathways, all biochemical reactions occur instantaneously and simultaneously. The corresponding stoichiometry matrix to (3.23)-(3.25) is a $2n \times 3n$ matrix and denoted by S

$$S \triangleq \begin{pmatrix} -I_{n\times n} & \mathbf{0}_{n\times n} & I_{n\times n} \\ \mathbf{diag}\big[(\beta_1+\alpha_1),\ldots,(\beta_n+\alpha_n)\big]_{n\times n} & -I_{n\times n} & -\big[\alpha_{ij}\big]^T_{n\times n} \end{pmatrix}. \tag{3.26}$$

The dynamics of interconnected network of autocatalytic pathways (3.23)-(3.25) is given by

$$\begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = S \begin{pmatrix} \mathbf{diag}(k_x)x \\ \mathbf{diag}(k_y)y \\ f_{(y,u)} \end{pmatrix} = \tilde{S} \begin{pmatrix} x \\ y \\ f_{(y,u)} \end{pmatrix}, \tag{3.27}$$

in which $x = [x_1, x_2, \ldots, x_n]^T$, $k_x = [k_{x_1}, k_{x_2}, \ldots, k_{x_n}]^T$, $y = [y_1, y_2, \ldots, y_n]^T$, $k_y = [k_{y_1}, k_{y_2}, \ldots, k_{y_n}]^T$, $u = [u_1, u_2, \ldots, u_n]^T$, and the modified stoichiometry matrix is defined as follows

$$\tilde{S} \triangleq \begin{pmatrix} A_1 & B_1 & C_1 \\ A_2 & B_2 & C_2 \end{pmatrix}, \tag{3.28}$$

where

$$\begin{cases} A_1 = -\mathbf{diag}(k_x), \\ B_1 = \mathbf{0}_{n\times n}, \\ C_1 = I_{n\times n}, \\ A_2 = \mathbf{diag}\big[(\beta_1+\alpha_1)k_{x_1},\ldots,(\beta_n+\alpha_n)k_{x_n}\big], \\ B_2 = -\mathbf{diag}(k_y), \\ C_2 = -\big[\alpha_{ij}\big]^T, \end{cases} \tag{3.29}$$

and $f_{(y,u)} = [f_1(y,u_1), \cdots, f_n(y,u_n)]^T$, where the reaction rate functions are considered as $f_i(y,u_i) =$

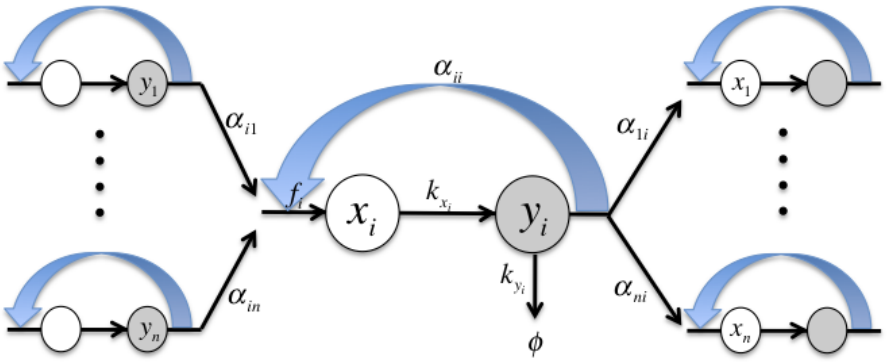


Figure 3.2: An schematic diagram of autocatalytic pathway i defined by (3.23)-(3.25). The variables x_i and y_i denote internal states of the pathway.

$K_i \prod_{j=1}^{n} y_j^{\alpha_{ij}} u_i$. Using $(3.27) - (3.28)$, dynamics of interconnected network of autocatalytic pathways (3.23)-(3.25) can be recast as follows

$$\begin{pmatrix} \dot{x} \\ \dot{y} \end{pmatrix} = \begin{pmatrix} A_1 & \mathbf{0}_{n\times n} & I_{n\times n} \\ A_2 & B_2 & C_2 \end{pmatrix} \begin{pmatrix} x \\ y \\ f_{(y,u)} \end{pmatrix}. \tag{3.30}$$

We should highlight that matrix C_2 is the adjacency matrix of the corresponding underlying weighted structure of the interconnected network of autocatalytic pathways (3.23)-(3.25). Fig. 3.2 illustrates details of the interconnection graph of the entire network in node level. Each autocatalytic pathway is treated as a node in this representation. In order to characterize fundamental tradeoffs of system (3.27), we need to cast the system in a canonical form so that the zero-dynamics of the system appears in the new representation. Let us introduce new set of variables by $z = x + Qy$. We assume that matrix C_2 is invertible. To obtain the zero-dynamics, we consider $f_{(y,u)} = C_2^{-1}(A_2 x - B_2 y)$ which comes from $\dot{y} = 0$. Then we get

$$\dot{x} = (-A_1 + C_1 C_2^{-1} A_2)x + (B_1 - C_1 C_2^{-1} B_2)y, \tag{3.31}$$

$$\dot{z} = (-A_1 + C_1 C_2^{-1} A_2)z + (B_1 - C_1 C_2^{-1} B_2 + A_1 Q - C_1 C_2^{-1} A_2 Q)y. \tag{3.32}$$

By Considering $Q = C_1 C_2^{-1} = C_2^{-1}$, the dynamics of the system with respect to y and z is given by

$$\begin{pmatrix} \dot{z} \\ \dot{y} \end{pmatrix} = \begin{pmatrix} A_0 & B_0 & 0 \\ \bar{A}_2 & \bar{B}_2 & \bar{C}_2 \end{pmatrix} \begin{pmatrix} z \\ y \\ f_{(y,u)} \end{pmatrix}, \tag{3.33}$$

in which

$$A_0 = -A_1 + C_2^{-1} A_2, \tag{3.34}$$

$$B_0 = A_1 C_2^{-1} - C_2^{-1} A_2 C_2^{-1} - C_2^{-1} B_2. \tag{3.35}$$

In Lemmas 3.3.2, 3.3.3 and 3.3.4, we extend the results in [5], to show that under what conditions the autocatalytic network (3.27) has meaningful fixed points. The following lemma presents a relationship between concentrations of biochemical species at meaningful equilibrium points.

Lemma 3.3.2. *Let $\bar{x}$ and $\bar{y}$ be the vectors of concentrations of biochemical species x_i and y_i, $i = 1, \cdots, n$, in the steady-state respectively. According to the dynamics of interconnected network of autocatalytic pathways (3.30), the relation between $\bar{x}$ and $\bar{y}$ is given by*

$$(A_2 - C_2 A_1)\bar{x} \quad = \quad -B_2 \bar{y}. \tag{3.36}$$

Proof. According to (3.30) we have

$$\dot{x} \quad = \quad A_1 x + f_{(y,u)}, \tag{3.37}$$

$$\dot{y} \quad = \quad A_2 x + B_2 y + C_2 f_{(y,u)}. \tag{3.38}$$

In the steady-state we have $\dot{x} = \dot{y} = 0$, therefore $f_{(\bar{y},\bar{u})} = -A_1 \bar{x}$ and we get

$$(A_2 - C_2 A_1)\bar{x} + B_2 \bar{y} = 0. \tag{3.39}$$

□

Since $\bar{x}$ and $\bar{y}$ indicates the concentrations of biochemical species in the autocatalytic network, there-

fore to obtain a meaningful biological equilibrium points we need to have $\bar{x} \geq 0$ and $\bar{y} \geq 0$.

The following lemmas characterize necessary and sufficient conditions under which meaningful equilibria exist. From now on we assume that the equilibrium of interest for the output vector is $\bar{y} \in \mathbb{R}^n_{++}$.

Lemma 3.3.3. *The autocatalytic network (3.30) has a meaningful equilibrium point, i.e., $\bar{x} \in \mathbb{R}^n_+$ and $\bar{y} \in \mathbb{R}^n_{++}$, if and only if*

$$\bar{A}_0 \triangleq C_2 A_0, \tag{3.40}$$

is an M-matrix.

Proof. From the definition of matrices A_1, A_2, C_2, one can easily show that

$$\bar{A}_0 = C_2 A_0 = A_2 - C_2 A_1,$$

therefore $\bar{A}_0 \in Z_n$. Then according to Theorem 2.5.3 of [23], matrix $\bar{A}_0^{-1}$ is nonnegative if and only if $\bar{A}_0$ is anti-stable. In addition, since $k_{y_i} \geq 0$ for $1 \leq i \leq n$, then $B_2 = \mathbf{diag}\big[k_{y_1}, \ldots, k_{y_n}\big]$ is nonnegative and since the equilibrium of interest for the vector of outputs is $\bar{y} \in \mathbb{R}^n_{++}$, therefore

$$\bar{x} \quad = \quad \bar{A}_0^{-1} B_2 \bar{y}, \tag{3.41}$$

is nonnegative if and only if $\bar{A}_0$ is an M-matrix. ■ □

Lemma 3.3.4. *Consider autocatalytic network (3.30). Then matrix $\bar{A}_0$ is an M-matrix if $\beta_i > 0$ for all $i = 1, \cdots, n$.*

Proof. One can show that

$$\bar{A}_0 = [\mathfrak{B} + (\mathfrak{A} - C_2)] diag\big[k_{x_1}, \ldots, k_{x_n}\big] = (\mathfrak{B} + L_{\mathcal{G}}) diag\big[k_{x_1}, \ldots, k_{x_n}\big], \tag{3.42}$$

where $\mathfrak{B} \triangleq \text{diag}[\beta_1, \ldots, \beta_n]$, $\mathfrak{A} \triangleq \text{diag}[\alpha_1, \cdots, \alpha_n]$ and $L_{\mathcal{G}} \triangleq \mathfrak{A} - C_2$ is the Laplacian matrix of the underlying graph $\mathcal{G}$. By Gersgorins Theorem (2.1.10), the real parts of eigenvalues of $L_{\mathcal{G}}$ are nonnegative. Moreover, $\mathfrak{B}$ is a positive definite matrix. Thus, according to Theorem 2.5.4 of [23], $\mathfrak{B} + L_{\mathcal{G}}$ is an M-

matrix and since all $k_{x_i} \geq 0$, it follows that $\bar{A}_0 = (\mathfrak{B} + L_{\mathcal{G}})diag\big[k_{x_1}, \ldots, k_{x_n}\big]$ is an M-matrix as well. ■ □

The results of Lemmas 3.3.2, 3.3.3 and 3.3.4 imply that the autocatalytic network (3.27) has meaningful fixed points, if $\mathfrak{B} > 0$, i.e., the net production of all pathways are positive.

3.4 Zero-dynamics of Autocatalytic Networks in Presence of Disturbances

In this section, we are going to obtain the zero-dynamics for the following system with external disturbances based on its state-space representation

$$\begin{aligned} \dot{x} &= Ax + Bg(x,u) + Q\delta, \\ y &= Cx. \end{aligned} \tag{3.43}$$

Since we are trying to omit the input control in the zero-dynamics, it should be calculated as a function of other matrices in state-space representation. To this end, in the following we use a straightforward conclusion from the definition of the zero-dynamics, $y = 0$ and $\dot{y} = 0$.

$$\dot{y} = CAx + CBg(x,u) + CQ\delta = 0, \tag{3.44}$$

$$g(x,u) = -(CB)^{-1}(CAx + CQ\delta). \tag{3.45}$$

By substitution of (3.45) in (3.43), we obtain

$$\dot{x} = PAx + PQ\delta. \tag{3.46}$$

Here $P = I - B(CB)^{-1}C$. The zero-dynamics state vector, z, is defined as

$$z = (D + MC)x = Dx + My, \tag{3.47}$$

where matrix M need to be chosen appropriately, such that input function does not have any effect on the zero-dynamics. We define a new variable $\bar{x} = Dx$, then the following equation holds:

$$\begin{pmatrix} C \\ D \end{pmatrix} x = \begin{pmatrix} y \\ \bar{x} \end{pmatrix}, \tag{3.48}$$

$$\begin{aligned} x &= \begin{pmatrix} C^T & D^T \end{pmatrix} \begin{pmatrix} y \\ \bar{x} \end{pmatrix} \\ &= C^T y + D^T \bar{x}. \end{aligned} \tag{3.49}$$

Since $\dot{y} = 0$, therefore $\dot{z} = D\dot{x}$. Then (3.46) can be recast as follow:

$$\begin{aligned} \dot{z} &= DPAx + DPQ\delta \\ &= DPAC^T y + DPAD^T \bar{x} + DPQ\delta. \end{aligned}$$

Therefore the zero-dynamics of (3.43) is given by

$$\dot{z} = A_z z + B_z y + Q_z \delta, \tag{3.50}$$

where

$$\begin{cases} A_z = DPAD^T, \\ B_z = DPA(C^T - D^T M), \\ Q_z = DPQ. \end{cases} \tag{3.51}$$

In this chapter, we characterize the zero-dynamics for the class of unperturbed autocatalytic networks, as well as the class of autocatalytic networks in presence of disturbances. In chapter 4, we show that how these associated zero-dynamics help us to obtain the fundamental limits on the performances (e.g., L_2 norm of the output for unperturbed network and the level of disturbance attenuation for perturbed one) of the autocatalytic networks.

Chapter 4

Characterization of fundamental limits

In this chapter, we consider the characteristics of the underlying structure of the autocatalytic network and review a sufficient condition for the existence of fundamental limits on the output energy [5]. Then, we revisit an approach to obtain lower bounds on the L_2-gain from disturbance input to regulated output for two classes of nonlinear and linear systems with internal stability [2–4]. It is shown that for first-order linear systems, optimal disturbance attenuations can be calculated based on the zero-dynamics of the system, such that the hard limit function (L_2 gain from disturbances to output) is zero if and only if disturbance does not affect the unstable mode of the zero-dynamics of the system [2]. Then based on the resulting zero-dynamics in chapter 3 one can calculate the fundamental limits on the performances (e.g., L_2 norm of the output for unperturbed network and the level of disturbance attenuation for perturbed one) of the autocatalytic networks. Finally, a numerical example is provided.

4.1 Fundamental Limits on Output Energy

In this section, we study the characteristics of the underlying structure of the autocatalytic network to discuss a sufficient condition for the existence of fundamental limits. The following theorem in [5] states that under what conditions there is a fundamental limit on the performance of the autocatalytic network (3.23)-(3.25).

Theorem 4.1.1. *Assume that the zero-dynamics of network (3.27) is anti-stable. Then the output energy of the network (3.27) is lower bounded by a constant which only depends on the underlying structure of*

the system, i.e.,

$$\int_0^\infty (y(t;u_0)-\bar{y})^T(y(t;u_0)-\bar{y})\,dt \;\geq\; \bar{z}_0^T P_0 \bar{z}_0, \tag{4.1}$$

where $z_0 = (x(0)-\bar{x}) + Q(y(0)-\bar{y})$, u_0 *is an arbitrary stabilizing feedback control law for system (3.27),* $y(t;u_0)$ *is the output of the system with respect to* u_0*, and* $P_0 > 0$ *is the unique positive definite solution of the following algebraic Riccati equation*

$$A_0^T P_0 \;+\; P_0 A_0 \;=\; P_0 B_0 B_0^T P_0. \tag{4.2}$$

Lemma 4.1.2. *Suppose that in network (3.27) all* k_{x_i} *are equal, then the zero-dynamics of (3.27) is anti-stable (i.e.,* A_0 *is anti-stable).*

Proof. First, assume that all k_{x_i} are nonzero and equal to k_x. Then, using Gershgorin theorem 2.1.10, we obtain that all Gershgorins disks of $A_2^{-1}C_2$ have the real parts less than k_x^{-1}. Therefore, as a consequence, we get that all Gershgorins disks of $C_2^{-1}A_2$ have the real parts greater than k_x. Using 3.29 and $\mathbf{Re}\{\lambda(C_2^{-1}A_2)\} > k_x$, it follows that A_0 is anti-stable. ■ □

We note that the result of Lemma 4.1.2 recovers the result of Lemma 5 in [5]. The following lemma in [5] presents an important relation between the underlying graph of (3.27) and its zero-dynamics.

Lemma 4.1.3. *If the adjacency matrix of underlying graph of (3.27) is an inverse* M*-matrix, then the zero-dynamics of (3.27) is anti-stable. Moreover, the matrix* A_0 *is an* M*-matrix if and only if* C_2 *is an inverse* M*-matrix.*

Keep in mind that all M-matrices are anti-stable, therefor if A_0 is M-matrix then the zero-dynamics is anti-stable. Therefore Lemma 4.1.3 states a sufficient condition to have an anti-stable zero-dynamics.

Remark 4.1.4. *Consider a cascade interconnection of* n *autocatalytic pathways as shown in Fig. 4.1 with* $\beta_i > 0$ *for* $i = 1, \ldots, n$*. Then, according to Lemmas 3.3.3 and 3.3.4, this network has a meaningful fixed point. Moreover, in the case that all reaction rates* k_{x_i}*'s are equal, based on Lemma 4.1.2 and Theorem 4.1.1, it follows that the network has a fundamental limit on the output energy.*

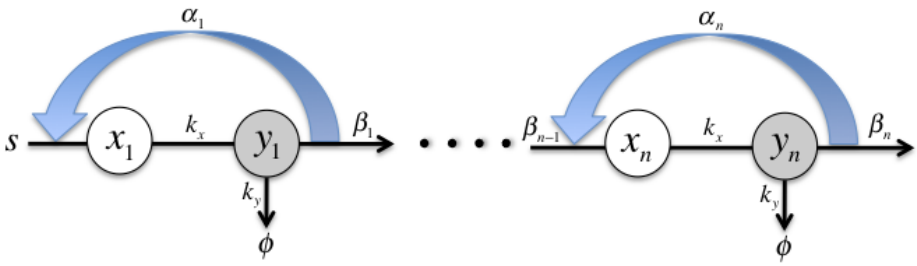


Figure 4.1: Cascade interconnection of autocatalytic pathways.

4.2 Fundamental Limit on L_2-gain Disturbance Attenuation

4.2.1 L_2-gain Disturbance Attenuation Problem

Now, we want to quantify fundamental limits using lower bounds on L_2-gain disturbance attenuation of the following nonlinear system, which is affine in the control and disturbance input:

$$\dot{x} = f(x) + g(x)u + p(x)\delta, \tag{4.3}$$

$$y = h(x). \tag{4.4}$$

Here $x \in \mathbb{R}^n$, $u \in \mathbb{R}$, $\delta \in \mathbb{R}$ and $y \in \mathbb{R}$. In this case, our approach to quantify fundamental limits for the system (4.3)-(4.4), is based on formulating and solving the corresponding regional state feedback L_2-disturbance attenuation problem with stability which consists of determining a control law $u = u(x)$ such that the closed loop system has following properties. First, the zero equilibrium of the system (4.3)-(4.4) with $\delta(t) = 0$, for all $t \geq 0$, is asymptotically stable with region of attraction containing Ω (an open set containing the origin of $\mathbb{R}^n$). Second, for every $\delta \in L_2(0, T)$ such that the trajectories of the system remain in Ω, the L_2-gain of the system (1) from δ to y, is less than or equal to γ, i.e.,

$$\int_0^T |y(t)|^2 dt \leq \gamma^2 \int_0^T |\delta(t)|^2 dt, \tag{4.5}$$

for all $T \geq 0$ and zero initial state. It is well-known that there exists a solution to the static state feedback L_2-disturbance attenuation problem with stability, in some neighborhood of the origin, if there exists a smooth positive definite solution of the Hamilton-Jacobi inequality (see [3], [4]).

More specifically, using the strict feedback form [11], the system can be represented by

$$\begin{cases} \dot{z} &= f_0(z,\xi_1) + q_0(z,\xi_1)\delta, \\ \dot{\xi}_1 &= \xi_2 + p_1(z,\xi_1)\delta, \\ &\vdots \\ \dot{\xi}_{r-1} &= \xi_r + p_{r-1}(z,\xi_1,\xi_2,\ldots,\xi_{r-1})\delta, \\ \dot{\xi}_r &= u + p_r(z,\xi_1,\xi_2,\ldots,\xi_r)\delta, \\ y &= \xi_1, \end{cases} \tag{4.6}$$

where $z \in \mathbb{R}^{n-r}$ and $f_0(0,0) = 0$. Here our fundamental limits problem reduces to the disturbance attenuation problem for the zero dynamics with cost on the control. Because, as shown in [12–14] disturbance attenuation to a given level γ can be achieved for the system (4.6) if there exists a smooth real-valued function $v(z)$, with $v(0)$, a smooth proper real-valued function $V(z) > 0$ such that

$$\frac{\partial V}{\partial z} f_0(z,v(z)) + \frac{1}{2\gamma^2}\Big[\frac{\partial V}{\partial z} p_0(z,v(z))\Big]^2 + v^2(z) < 0. \tag{4.7}$$

The interesting fact is that γ^*, the optimal disturbance attenuation is indeed a hard limit function for system (4.3)-(4.4). This fundamental limit quantifies a fundamental obstruction to performance of the system.

4.2.2 L_2-gain Disturbance Attenuation for LTI Systems

For linear systems, optimal disturbance attenuations can be calculated based on the zero-dynamics of the system. The hard limit function (ideal performance) is zero if and only if the disturbance δ does not affect the unstable mode of the zero-dynamics of the system. the zero-dynamic can be split as an stable and unstable part as follows

$$\begin{aligned} \dot{z}_s &= A_{z_s} z_s + C_{z_s} y + Q_{z_s}\delta, \\ \dot{z}_u &= A_{z_u} z_u + C_{z_u} y + Q_{z_u}\delta, \end{aligned} \tag{4.8}$$

where $\lambda(A_{z_s}) \in \mathbb{C}^-$ and $\lambda(A_{z_u}) \in \mathbb{C}^+$.

Schwartz *et al.* [2] presented a formula to compute the optimal value of γ, which reduces to the following form if the system does not have any zero with zero real part

$$\gamma^* = \left(\lambda_{max}(\mathcal{L}_c^{-1}\mathcal{L}_d)\right)^{\frac{1}{2}}. \tag{4.9}$$

Here the control and disturbance Gramians define as follow

$$\mathcal{L}_c \triangleq \int_0^\infty e^{-A_{z_u}t} C_{z_u} C_{z_u}^T e^{-A_{z_u}^T t} dt, \tag{4.10}$$

$$\mathcal{L}_d \triangleq \int_0^\infty e^{-A_{z_u}t} Q_{z_u} Q_{z_u}^T e^{-A_{z_u}^T t} dt. \tag{4.11}$$

Therefore, from (4.9) we conclude that $\gamma^* = 0$ if and only if the disturbance does not enter the unstable zero dynamics (4.8).

We now study how to calculate the optimal value of γ through an example.

Example 4.2.1. *Consider autocatalytic network described in Example 3.2.2 in presence of disturbance δ_1 on x_2 and δ_2 on x_4.*

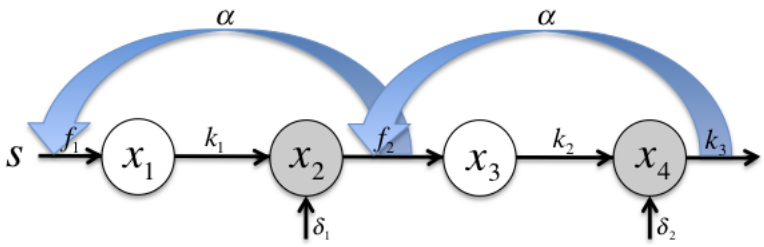


Figure 4.2: Diagram of four-state autocatalytic model of Example 4.2.1

The systems dynamic is given by

$$\begin{cases} \dot{x} &= Ax + Bg(x,u) + Q\delta, \\ y &= Cx, \end{cases} \tag{4.12}$$

where

$$
\begin{aligned}
A &= \begin{pmatrix} -k_1 & 0 & 0 & 0 \\ (1+\alpha)k_1 & 0 & 0 & 0 \\ 0 & 0 & -k_2 & 0 \\ 0 & 0 & (1+\alpha)k_2 & -k_3 \end{pmatrix}, \\
B &= \begin{pmatrix} 1 & 0 \\ -\alpha & -1 \\ 0 & 1 \\ 0 & -\alpha \end{pmatrix}, \\
C &= \begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}, \\
Q &= \begin{pmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{pmatrix}.
\end{aligned}
\tag{4.13}
$$

For autocatalytic network (4.12), the zero-dynamics vector z is defined by

$$
z = \Big[D + \frac{1}{\alpha} \begin{pmatrix} 1 & -\frac{1}{\alpha} \\ 0 & 1 \end{pmatrix} C \Big] x,
$$

$$
\begin{cases}
\dot{z}_1 &= \dot{x}_1 + \frac{1}{\alpha}\dot{x}_2 - \frac{1}{\alpha^2}\dot{x}_4 \\
&= \frac{k_1 x_1}{\alpha} - \frac{(1+\alpha)k_2 x_3}{\alpha^2} + \frac{k_3 x_4}{\alpha^2} + \frac{\delta_1}{\alpha} - \frac{\delta_2}{\alpha^2}, \\
\dot{z}_2 &= \dot{x}_3 + \frac{1}{\alpha}\dot{x}_4 \\
&= \frac{k_2 x_3}{\alpha} - \frac{k_3 x_4}{\alpha} + \frac{\delta_2}{\alpha}.
\end{cases}
$$

By assuming $k_1 = k_2 = k_3 = k$ *and considering*

$$\begin{cases} x_1 &= z_1 - \frac{1}{\alpha}x_2 + \frac{1}{\alpha^2}x_4, \\ x_3 &= z_2 - \frac{1}{\alpha}x_4, \end{cases}$$

we get the following representation:

$$\dot{z} = \frac{k}{\alpha}\begin{pmatrix} 1 & -\frac{(1+\alpha)}{\alpha} \\ 0 & 1 \end{pmatrix} z - \frac{k}{\alpha^2}\begin{pmatrix} 1 & -\frac{2(1+\alpha)}{\alpha} \\ 0 & 1+\alpha \end{pmatrix} y + \frac{1}{\alpha}\begin{pmatrix} 1 & -\frac{1}{\alpha} \\ 0 & 1 \end{pmatrix} \delta. \tag{4.14}$$

Calculated matrices A_z, B_z *and* Q_z *can be also obtained directly from (3.51). To calculate control Gramian from (4.10), first we need* $e^{-A_z t}$

$$e^{-A_z t} = \begin{pmatrix} e^{-\frac{k}{\alpha}t} & \frac{kt(1+\alpha)}{\alpha^2}e^{-\frac{k}{\alpha}t} \\ 0 & e^{-\frac{k}{\alpha}t} \end{pmatrix}.$$

By substitution of $e^{-A_z t}$ *in (4.10),* $\mathcal{L}_c$ *is derived as follow*

$$\mathcal{L}_c = \begin{pmatrix} \frac{k}{4\alpha^5}(\alpha^4 + 4\alpha^2 + 8\alpha + 5) & -\frac{(1+\alpha)k}{4}(-\alpha^3 + 2\alpha^2 + 3\alpha) \\ -\frac{(1+\alpha)k}{4}(-\alpha^3 + 2\alpha^2 + 3\alpha) & \frac{k(1+\alpha)^2}{2\alpha^3} \end{pmatrix}. \tag{4.15}$$

To calculate disturbance Gramian from (4.11), first we need $e^{-A_z^T t}$

$$e^{-A_z^T t} = \begin{pmatrix} e^{-\frac{k}{\alpha}t} & 0 \\ \frac{kt(1+\alpha)}{\alpha^2}e^{-\frac{k}{\alpha}t} & e^{-\frac{k}{\alpha}t} \end{pmatrix}.$$

By substitution of $e^{-A_z^T t}$ *in (4.11),* $\mathcal{L}_d$ *is derived as follow*

$$\mathcal{L}_d = \begin{pmatrix} \frac{3\alpha^2+1}{4k\alpha^3} & \frac{\alpha-1}{4k\alpha^2} \\ \\ \frac{\alpha-1}{4k\alpha^2} & \frac{1}{2k\alpha} \end{pmatrix}. \tag{4.16}$$

From (4.15) and (4.16), the largest eigenvalue of $\mathcal{L}_c^{-1}\mathcal{L}_d$ is obtained by

$$\lambda_{max}(\mathcal{L}_c^{-1}\mathcal{L}_d) = \frac{1}{k^2}\frac{a(\alpha)}{b(\alpha)},$$

where $a(\alpha)$ is a polynomial of degree 11 and $b(\alpha)$ is a polynomial of degree 16. Therefore, by assuming large α from (4.9) γ^* is a polynomial of degree -2.5 with respect to α:

$$\gamma^* \approx \frac{\alpha^{-2.5}}{k}, \quad \textit{as} \quad \alpha \to \infty.$$

To find the relation between γ^*, α and k without solving (4.15) and (4.16), we can simplify these equations as $\alpha \to \infty$:

$$\begin{aligned} \mathcal{L}_c &\approx \begin{pmatrix} \frac{k}{\alpha} & k\alpha^4 \\ k\alpha^4 & \frac{k}{\alpha} \end{pmatrix}, \\ \mathcal{L}_d &\approx \frac{1}{k\alpha}\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}. \end{aligned} \tag{4.17}$$

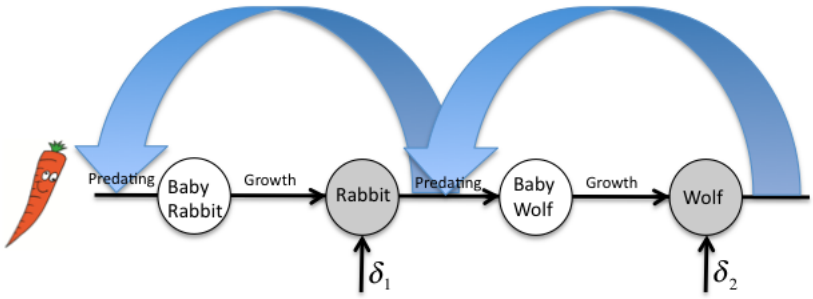
Then, it follows that

$$\begin{aligned} \mathcal{L}_c^{-1}\mathcal{L}_d &\approx \frac{\alpha^5 - 1}{k^2(\alpha^{10}-1)}\begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}, \\ \lambda_{max}(\mathcal{L}_c^{-1}\mathcal{L}_d) &\approx \frac{2(\alpha^5-1)}{k^2(\alpha^{10}-1)} \approx \frac{\alpha^{-5}}{k^2}, \\ \to \gamma^* &\approx \frac{\alpha^{-2.5}}{k}. \end{aligned} \tag{4.18}$$

Remark 4.2.2. *According to (4.18) the optimal disturbance attenuation γ^* is a decreasing function with respect to α. It means that increasing α can result in a better performance. From (4.18), γ^* is also a decreasing function with respect to k, which shows a tradeoff between robustness and efficiency. For a larger k, γ^* is smaller and therefore the glycolysis mechanism is more robust. On the other hand, large k requires either a more efficient or a higher level of enzymes, which decreases the efficiency.*

4.2.3 A motivation Example (rabbit and wolf)

In Example 4.2.1, we considered 4 states which can be interpreted as baby rabbit, rabbit, baby wolf and wolf. In presence of enough nutrition source for bunnies (i.e., carrot), they grow up and become adult rabbits. A disturbance δ_1 is considered on the number of rabbits, which can be a natural death or any other kind of increasing or decreasing in their population. Wolves are nourished by predating rabbits, then they grow up and give birth to another wolf, or they die without any parturition. Similar to rabbits, disturbance δ_2 is considered on the number of wolfs, which can be interpreted as any other kind of increasing or decreasing in their population rather than their natural death.



Chapter 5

Conclusions and Future Directions

This work studies the zero-dynamics for a class of autocatalytic networks, in which the network's product is necessary to power its own production. We review conditions on the underlying structure of the network, which guarantee the existence of fundamental limits on the output energy. As it is discussed in this thesis, the zero-dynamics of the autocatalytic network plays an important role in studying the fundamental limits in autocatalytic networks. We propose a method to characterize the zero-dynamics based on the state-space matrices of the original network, for a class of unperturbed autocatalytic networks as well as a class of autocatalytic networks in presence of disturbances on consumptions of some biochemical species. Then based on the resulting zero-dynamics, we show that one can calculate the fundamental limits on the global performance (e.g., L_2 norm of the output for unperturbed network and the level of disturbance attenuation for perturbed one) of autocatalytic networks.

For the future work, my plan is to explore relationships between combinatorial properties of underlying structure of biochemical reactions and the global performance of the network or explicitly derive the fundamental limits on the performances.

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Biography

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