On Existence of Hard Limits in Autocatalytic Networks and Their Fundamental Tradeoffs

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Abstract: In this paper, we derive sufficient and necessary conditions for existence of hard limits in interconnected networks of autocatalytic pathways. The existing hard limits are characterized as a lower bound on a performance measure (L^2-norm of an output signal). We show that underlying digraph of the network plays an important role in emergence of such hard limits.

Keywords: Autocatalytic pathways, interconnected dynamical systems, hard limits, fundamental tradeoffs, zero-dynamics, graph theory.

1. INTRODUCTION

One of the fundamental challenges in analysis and synthesis of interconnected networks of dynamical systems is to exploit structural properties of the underlying networks and characterize their existing hard limits and fundamental tradeoffs. In this paper, we consider an important class of interconnected networks of dynamical systems, so called autocatalytic networks. As critical as this class of dynamical networks are to our lives and diverse sectors of our society, we have little rigorous knowledge when it comes to understanding their structure, dynamics and holistic behaviors. We aim to develop underpinning design principles to synthesize hard-limit-free interconnected dynamical networks. This will enable us to build robust-by-design interconnected dynamical networks.

The issue of hard limits and fundamental limitations in control system design lies at the very core of feedback theory since it reveals what is achievable, and conversely what is not achievable, for instance see Seron et al. (1997); Doyle et al. (1992). The recent interest in understanding fundamental limitations of feedback in complex interconnected dynamical networks from biological systems and physics to engineering and economics has created a paradigm shift in the way systems are analyzed, designed, and built. For example, only to name a few, Middleton and Braslavsky (2010) gives conditions for string instability in an array of linear time-invariant autonomous vehicles with communication constraints, Vinay (2007) provides a lower bound on the achievable quality of disturbance rejection using a decentralized controller for stable discrete time linear systems with time delays, Padmasola and Elia (2006) studies the performance of spatially invariant plants interconnected through a static network, and Bamieh et al. (2012) characterizes a fundamental limitation in distributed consensus and vehicular formation control problems and show that in low spatial dimensions, local feedback is unable to regulate large-scale disturbances, but it can in higher spatial dimensions.

Most of the above cited research on fundamental limitations of feedback in interconnected dynamical systems has been focused on networks with linear time-invariant subsystems. The motivation of this research comes from a recent work presented in Chandra et al. (2011) where it is shown that glycolysis oscillation can be an indirect effect of fundamental tradeoffs in this system. The results of this work is based on a linearized model of a two-state model of glycolysis pathway and tradeoffs are stated using Bode's results. Our network models are built upon models presented in Chandra et al. (2011). However, our proposed approach to characterize hard limits in autocatalytic networks is different in spirit from that of Chandra et al. (2011) and uses higher dimensional nonlinear models of the pathways. We interpret fundamental limitations of feedback by using hard limits (lower bounds) on L^2-norm of the output of the system (see Motee et al. (2010); Seron et al. (1999) for more details). Our approach opens up new ways to define general autocatalytic dynamical network models.

We discuss minimal autocatalytic pathway models in Section 3 and show that such minimal autocatalytic models capture essential features of a general autocatalytic feedback, i.e., existence of autocatalytic feedback may impose severe tradeoffs between fragility and net production of the network. For such minimal models, we characterize existing hard limits and their corresponding fundamental tradeoffs. In Section 5, we propose models for interconnected networks of autocatalytic pathways where arbitrary number of autocatalytic pathways can form an interconnected dynamical network with an arbitrary interconnection topology. In Section 6, several sufficient and necessary conditions have been derived for existence of hard limits in a given interconnected network of autocatalytic pathways. More importantly, it is shown that hard limits emerge if the underlying digraph of the network exhibits some specific structural properties.

In this paper, we provide first steps towards development of a mathematical methodology to characterize hard limits in interconnected networks of nonlinear dynamical systems. Tools that are commonly used in optimization as well as in systems and control theory can provide a good foundation for moving toward such an integrated theory. We illustrate the ways in which these ideas have been used to provide a fresh perspective on problems in biology and demonstrate how this new approach allows new progress towards long-standing problems in biology and engineering.

2. NOTATIONS AND PRELIMINARY DEFINITIONS

The following notations and definitions will be used throughout the paper. For a given $n \times n$ matrix A, we denote its eigenvalues by $\lambda_i(A)$ and its singular values by $\sigma_i(A)$ for all $i = 1, \ldots, n$ and sort its singular values in descending order as $\sigma_1(A) \geq \sigma_2(A) \geq \cdots \geq \sigma_n(A)$. We write $A \geq B$ (respectively, $A > B$) if all entries of the matrix $A - B$ are nonnegative (respectively, positive). A matrix is called anti-stable if all its eigenvalues have positive real parts. 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 $z_{ij} \leq 0 \quad \text{if} \quad i \neq j$. A 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.

3. MINIMAL AUTOCATALYTIC PATHWAY MODEL

The first step is development of a biologically motivated minimal model of autocatalytic dynamical networks that exhibits fundamental tradeoffs caused by autocatalysis. Analysis of robustness and efficiency tradeoffs for such canonical model provides a deep understanding of structural properties of autocatalytic networks as well as illustrates theoretical underpinning principles to design efficient and robust networks of dynamical systems.

We consider autocatalysis is glycolysis pathway. The central role of glycolysis is to consume glucose and produce adenosine triphosphate (ATP), the cell's energy currency. Similar to many other engineered systems whose machinery runs on its own energy product, the glycolysis reaction is autocatalytic. The ATP molecule contains three phosphate groups and energy is stored in the bonds between these phosphate groups. Two molecules of ATP are consumed in the early steps (hexokinase, phosphofructokinase/PFK) and four ATPs are generated as pyruvate is produced. PFK is also regulated such that it is activated when the adenosine monophosphate (AMP)/ATP ratio is low; hence it is inhibited by high cellular ATP concentration. This pattern of product inhibition is common in metabolic pathways.

Experimental observations in Saccharomyces cerevisiae suggest that there are two synchronized pools of oscillating metabolites. Metabolites upstream and downstream of phosphofructokinase (PFK) have 180 degrees phase difference, suggesting that a two-dimensional model incorporating PFK dynamics might capture some aspects of system dynamics Betz and Chance (1965), and indeed, such simplified models qualitatively reproduce the experimental behavior Goldbete (1996); Sel'kov (1975). We consider a minimal system with three reactions with a single intermediate metabolite reaction (1)-(2), for which we can identify specific mechanisms both necessary and sufficient for oscillations,

$$s + \alpha y \xrightarrow{f} x_1 \xrightarrow{k_x} (\alpha + \beta)y + x_1' \tag{1}$$

$$y \xrightarrow{k_y} \varnothing \tag{2}$$

In the first reaction, s is some precursor and source of energy for the pathway with no dynamics associated, y denotes the product of the pathway (ATP), x_1 is intermediate metabolites, x_1' is one of the by-products of the second biochemical reaction, $\varnothing$ is a null state, α is the number of y molecules that are invested in the pathway, and $\alpha+\beta$ is the number of y molecules produced. $A \xrightarrow{k} B$ denotes a chemical reaction that converts the chemical species A to the chemical species B at rate k. We choose $f(y) = \frac{Vy^q}{1+\gamma y^h}$, which is consistent with biological intuition and experimental data in the case of the glycolysis pathway (see Banuelos et al. (1977); Dano et al. (2006) for more details), where $V > 0$ depends on s, parameter $q > 0$ captures the strength of autocatalysis, and $\gamma, h > 0$ capture the strength of inhibition. The function f is not monotone and captures the interplay between the autocatalysis and inhibition. A set of ordinary differential equations that govern the changes in concentrations x_1 and y can be written as

$$\dot{x}_1 = -k_x x_1 + \frac{Vy^q}{1+\gamma y^h} \tag{3}$$

$$\dot{y} = -k_y y + (\alpha + \beta)k_x x_1 - \frac{\alpha V y^q}{1+\gamma y^h}, \tag{4}$$

for $x_1 \geq 0$ and $y \geq 0$. To highlight fundamental tradeoffs due to autocatalytic structure of the system, we normalize the concentration such that steady states are $\bar{y} = 1$ and $\bar{x} = \frac{k_y}{\beta k_x}$.

Depending on values of parameters q and h, the system can have another equilibirum point which is unstable when $(\bar{x}, \bar{y})$ is stable. In glycolysis model (3)-(4), expression $\frac{1}{1+\gamma y^h}$ can be interpreted as the regulatory feedback control employed by nature which captures inhibition of the catalyzing enzyme. Hence, we can derive a control system model for glycolysis as follows

$$\dot{x} = -k_x x + V y^q u \tag{5}$$

$$\dot{y} = -k_y y + (\alpha + \beta)k_x x - \alpha V y^q u, \tag{6}$$

where u is the control input. Our primary motivation behind developing and analyzing such control system models for metabolic pathways is to rigorously prove that the tradeoffs in such models are truly unavoidable and independent of control mechanisms (linear or nonlinear) used to regulate such pathways. The following results assert that essential tradeoffs depend only on autocatalytic structure of the network.

In Motee et al. (2010), it is shown that there exists a hard limit on the best achievable ideal performance of system (5)-(6) which is characterized as the following inequality

$$\int_0^\infty (y(t; u_0) - \bar{y})^2 dt \;\geq\; H(x(0), y(0); \alpha, \beta), \tag{7}$$

in which $y(t;u_0)$ is the output of the system with respect to a stabilizing control input u_0 and

$$H(x(0),y(0);\alpha,\beta)=\frac{\alpha^3\beta k_x}{(\alpha k_y+\beta k_x)^2}\ \Big(z(0)-z^*\Big)^2, \quad (8)$$

and $z(0)=x(0)+\frac{1}{\alpha}\ y(0)$ and $\bar{z}=\bar{x}+\frac{1}{\alpha}\ \bar{y}$. Now, we can define rate of profit ρ as the ratio of β (net production of ATP molecules) to α (number of ATP molecules invested in the pathway), i.e., $\rho=\frac{\beta}{\alpha}$. The hard limit function (8) can be rewritten as

$$H(x(0),y(0);\beta,\rho)=\frac{\beta^2 k_x}{\rho(k_y+\rho k_x)^2}\ \Big(z(0)-z^*\Big)^2 \quad (9)$$

A fundamental tradeoff between fragility and net production of the pathway emerges here. When we keep the rate of profit ρ fixed, a fundamental tradeoff between net production of ATP molecules and transient behavior of the system emerges as follows: increasing β can result in undesirable transient behavior (e.g., large–magnitude oscillation in the output of the system) and can increase fragility of the network to small disturbances. For instance, if the level of ATP drops below some threshold, there will not be sufficient supply of ATP for different pathways in the cell and that can result to cell death.

The minimal autocatalytic model (5)-(6) captures fundamental features of a general autocatalytic feedback, i.e., existence of autocatalytic feedback may impose severe tradeoffs between fragility and net production of the network. In this paper, we consider an arbitrary interconnection of several autocatalytic pathways with minimal representations as shown in Fig. 1.

In this model, the by-product of a pathways serves as an external input for several other pathways. Hence, oscillations in one pathway will affect the subsequence ones. This interconnection topology appears in various pathways in cell as well as engineered (e.g., an interconnected network of microgrids) and financial networks. Our objective is to study under what conditions (in terms of system parameters) tradeoffs in one pathway will affect the rest of the network and result in severe situations. This model serves as a perfect deterministic setup to study effects of hard limits in various real-world networks such as power grids, economic, and financial networks. For instance, if one pathway gets greedy to earn more profit, whether that will make other pathways more fragile to external disturbances.

4. CHARACTERIZATION OF HARD LIMITS

Our approach to quantify hard limits for a stabilizable and detectable system

$$\dot{x}=f(x)+g(x)\ u, \qquad x\in\mathbb{R}^n, \qquad u\in\mathbb{R}^m \quad (10)$$

$$y=h(x) \quad (11)$$

with initial condition $x(0)=x_0$, is based on formulating and solving the corresponding cheap optimal control problem which consists of finding a stabilizing state feedback control which minimizes the functional

$$J_\epsilon(x_0;u)\ =\ \frac{1}{2}\ \int_0^\infty\ \left(y^Ty\ +\ \epsilon^2u^Tu\right)\ dt \quad (12)$$

when $\epsilon>0$ is small. As $\epsilon\to 0$, the optimal value $J^*_\epsilon(x_0)$ tends to $J^*_0(x_0)$, the ideal performance. It is well-known (e.g., see Sepulchre et al. (1997), page 91) that this problem has a solution if there exists a positive semidefinite optimal value function which satisfies the corresponding Hamilton–Jacobi-Bellman equation (HJBE). The interesting fact is that $J^*_0(x_0)$ the ideal performance is indeed a hard limit function for system (10)-(11). It is known that the ideal performance is the optimal value of the minimum energy problem for the zero-dynamics subsystem of the system Seron et al. (1999). The ideal performance (hard limit function) is zero if and only if the system has an asymptotically stable zero-dynamics subsystem Seron et al. (1999).

5. INTERCONNECTED NETWORKS OF PATHWAYS

We consider an interconnection of n autocatalytic pathways. The model of each pathway consists of three biochemical reactions shown as follows

$$\alpha_{i1}y_1+\cdots+\alpha_{in}y_n\xrightarrow{f_i}x_i\xrightarrow{k_{x_i}}(\alpha_i+\beta_i)y_i+x_i' \quad (13)$$

$$y_i\xrightarrow{k_{y_i}}\varnothing \quad (14)$$

where $\alpha_i=\alpha_{1i}+\cdots+\alpha_{ni}$. In this model, 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. For simplicity of notations, we use notation x to denote the chemical species x as well as its concentration.

Assumption 1. In the interconnected network of pathways, all biochemical reactions occur instantaneously and simultaneously.

The corresponding stoichiometry matrix to (13)-(14) is a $2n\times 3n$ matrix and denoted by S. 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 value at the appropriate location; row of species and column of reaction. Reactants appear as negative values. Products are represented in the matrix with their stoichiometric value at the appropriate location; row of species and column of reaction. Products appear as positive values. All other locations in the matrix contain a zero. The dynamics of interconnected network of autocatalytic pathways (13)-(14) is given by

$$\begin{bmatrix}\dot{x}\\ \dot{y}\end{bmatrix}=S\begin{bmatrix}x\\ y\\ f_{y,u}\end{bmatrix} \quad (15)$$

in which $x=[x_1,x_2,\ldots,x_n]^T$, $y=[y_1,y_2,\ldots,y_n]^T$, $u=[u_1,u_2,\ldots,u_n]^T$, $f_{y,u}=[f_1(y,u_1),\cdots,f_n(y,u_n)]^T$, and

$$S:=\begin{bmatrix}-A_1 & B_1 & C_1\\ A_2 & -B_2 & -C_2\end{bmatrix} \quad (16)$$

where

$$A_1=\mathbf{diag}\big[k_{x_1},\ldots,k_{x_n}\big],\ B_1=\mathbf{0}_{n\times n},\ C_1=I_{n\times n}, \quad (17)$$

$$A_2=\mathbf{diag}\big[(\beta_1+\alpha_1)k_{x_1},\ldots,(\beta_n+\alpha_n)k_{x_n}\big], \quad (18)$$

$$B_2=\mathbf{diag}\big[k_{y_1},\ldots,k_{y_n}\big],\ C_2=\big[\alpha_{ij}\big]^T, \quad (19)$$

and the reaction rate functions are assumed to be $f_i(y,u_i)=K_i\prod_{j=1}^n y_j^{\alpha_{ij}}u_i$. We should highlight that matrix C_2 is the adjacency matrix of the corresponding underlying weighted digraph $\mathcal{G}$ of the interconnected network of

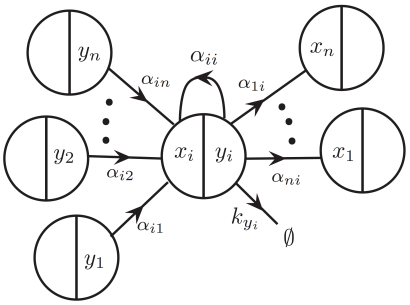

Fig. 1. An schematic diagram of autocatalytic pathway i defined by (13)-(14). The variables x_i and y_i denote internal states of the pathway.

autocatalytic pathways (13)-(14). Fig. 1 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 (15), 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. Then, the dynamics of the system with respect to y and z is given by

$$\begin{bmatrix} \dot{z} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} A_0 & B_0 & 0 \\ \bar{A}_2 & \bar{B}_2 & \bar{C}_2 \end{bmatrix} \begin{bmatrix} z \\ y \\ f_{y,u} \end{bmatrix} \tag{20}$$

in which

$$A_0 = -A_1 + QA_2, \tag{21}$$

$$B_0 = A_1 Q - QA_2 Q - QB_2. \tag{22}$$

where $Q = C_2^{-1}$. Suppose that the equilibrium of interest for the vector of outputs is $\bar{y} \in \mathbb{R}^n_{++}$ (i.e., belongs to the strictly positive orthant of $\mathbb{R}^n$). Then, the equilibrium of interest for the remaining state and input variables are given by

$$(A_2 - C_2 A_1)\bar{x} \;=\; B_2 \bar{y}, \tag{23}$$

$$\bar{u}_i = \frac{k_{x_i} \bar{x}_i}{K_i \prod_{j=1}^n \bar{y}_j^{\alpha_{ij}}}. \tag{24}$$

We define matrix $\bar{A}_0 := A_2 - C_2 A_1$. The following lemmas characterize necessary and sufficient conditions under which meaningful equilibria exist, i.e., $\bar{x} \geq 0$ and $\bar{y} > 0$ for all $k_{y_i} \geq 0$.

Lemma 2. $\bar{x} \geq 0$ for all $k_{y_i} \geq 0$ if and only if $\bar{A}_0$ is an M-matrix.

Proof. From the definition of matrices A_1, A_2, C_2, it is straightforward to verify that $\bar{A}_0 \in Z_n$. It follows that matrix $\bar{A}_0^{-1}$ is nonnegative if and only if $\bar{A}_0$ is anti-stable (see page 115 of Horn and Johnson (1994)). ■

Lemma 3. The matrix $\bar{A}_0$ is an M-matrix if $\mathfrak{B} := \text{diag}[\beta_1, \ldots, \beta_n] > 0$.

Proof. Consider the following equation.

$$\bar{A}_0 = \mathfrak{B} + (\mathfrak{A} - C_2) = \mathfrak{B} + L, \tag{25}$$

where $\mathfrak{A} := \text{diag}[\alpha_1, \cdots, \alpha_n]$ and $L := \mathfrak{A} - C_2$. By Gersgorins theorem, the real part of each nonzero eigenvalue of L is positive. Thus, L is a singular M-matrix. Moreover, $\mathfrak{B}$ is a positive definite matrix. Thus, according to Theorem. 2.5.4 of Horn and Johnson (1994), $\bar{A}_0 = \mathfrak{B} + L$ is an M-matrix. ■

The result of Lemma 3 implies that if $\mathfrak{B} > 0$, i.e., the net production of all pathways are nonzero, then system (15) has meaningful fixed points for all $k_{y_i} \geq 0$. The following theorem states that under what conditions there are hard limits on performance of interconnected network of autocatalytic pathways (13)-(14).

Theorem 4. Suppose that A_0 is anti-stable and the equilibrium of interest is given by (23)-(24). Then, L^2-norm of the output of the system (15) for all $k_y \geq 0$ is lower bounded by a constant which only depends on the underlying structure of the system, i.e.,

$$\int_0^\infty (y(t;u_0) - \bar{y})^T (y(t;u_0) - \bar{y})\; dt \;\geq\; \bar{z}_0^T P_0 \bar{z}_0, \tag{26}$$

where $z_0 = (x(0) - \bar{x}) + Q(y(0) - \bar{y})$, u_0 is an arbitrary stabilizing feedback control law for system (15), $y(t;u_0)$ 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

$$A_0^{\mathrm{T}} P_0 \;+\; P_0 A_0 \;=\; P_0 B_0 B_0^T P_0. \tag{27}$$

Proof. The proof can be easily adjusted from the main theorem of Seron et al. (1999). ■

6. EXISTENCE OF HARD LIMITS

In this section, we will state necessary and sufficient conditions for the existence of hard limits in terms of characteristics of the underlying digraph $\mathcal{G}$ of the interconnected network.

Lemma 5. Suppose that all k_{x_i} are nonzero and equal. Then, A_0 is anti-stable if

$$\sum_{j=1}^n \alpha_{ij} \;-\; \sum_{j=1}^n \alpha_{ji} \;<\; \beta_i. \tag{28}$$

Proof. First, assume that all k_{x_i} are nonzero and equal to k_x. Then, from (28) and Gersgorins theorem, we obtain that $\mathbf{Re}\{\lambda(A_2^{-1}C_2)\} < k_x^{-1}$. As a consequence, we have that $\mathbf{Re}\{\lambda(C_2^{-1}A_2)\} > k_x$. Now, by using (17), (18), (21) and $\mathbf{Re}\{\lambda(C_2^{-1}A_2)\} > k_x$, it follows that A_0 is anti-stable. ■

We recall that all M-matrices are anti-stable. In the following lemma, we relate the structure of the underlying digraph $\mathcal{G}$ of the network to structural properties of A_0.

Lemma 6. The matrix A_0 is an M-matrix if and only if C_2 is an inverse M-matrix.

Proof. ($\Leftarrow$) First, we assume that C_2 is an inverse M-matrix. Then, by using (21) and the fact that C_2 is an inverse M-matrix, we obtain that $A_0 \in Z_n$. Now, from (21) and definition of $\bar{A}_0$ we get that $A_0 = C_2^{-1}\bar{A}_0$. Note that, C_2^{-1} and $\bar{A}_0$ are M-matrix and $A_0 \in Z_n$. Hence, A_0 is an M-matrix (see page 127 of Horn and Johnson (1994) for more details).

($\Rightarrow$) According to (21) we have

$$C_2^{-1} = (A_0 + A_1)A_2^{-1}. \tag{29}$$

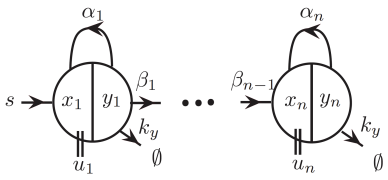

Fig. 2. Cascade interconnection of autocatalytic pathways.

A_0 is an M-matrix and A_1 is a positive diagonal matrix. Thus, matrix $A_0 + A_1$ is an M-matrix. Also, the matrix A_2^{-1} is a positive diagonal matrix. Therefore, it follows that matrix C_2^{-1} is an M-matrix (see page 127 of Horn and Johnson (1994) for more details. ■

Remark 7. Consider a cascade interconnection of n autocatalytic pathways as shown in Fig. 2. First, by using lemma 3, we get that $\bar{A}_0$ is an M-matrix. Thus, according to Lemma 2, this system has meaningful fixed points for all $k_{y_i} \geq 0$. Then, by using Lemma 5, we get that the corresponding matrix A_0 of this interconnection topology is anti-stable. Thus, based on Theorem 4 there exist a hard limits on performance of this interconnected network.

7. CONCLUSION

The results of this paper show that there is a close relationship between the existence of hard limits and the structural properties of the underlying digraph of an interconnected network of dynamical systems.

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