Characterization of Hard Limits on Performance of Autocatalytic Pathways*

Milad Siami†, Nader Motee† and Gentian Buzi‡

Abstract— **In this paper, we develop some basic principles to study autocatalytic networks and exploit their structural properties in order to characterize their existing hard limits and essential tradeoffs. In a dynamical system with autocatalytic structure, the system's output is necessary to catalyze its own production. We consider a simplified model of glycolysis as our motivating example. We study the hard limits of the ideal performance of such pathways. First, for a simple two-state model of glycolysis we explicitly derive the hard limit on the minimum L_2-gain disturbance attenuation and the hard limit of its minimum output energy. Then, we generalize our results to higher dimensional model of autocatalytic pathways. Finally, we show that how these resulting hard limits lead to some fundamental tradeoffs between transient and steady-state behavior of the network and its net production.**

I. Introduction

The class of dynamical networks with autocatalytic structures can be found in most of the planet's cells from bacteria to human, engineered, and economic systems [1]. In an interconnected control system with autocatalytic structure, the system's product (output) is necessary to power and catalyze its own production. The destabilizing effects of such "positive" autocatalytic feedback can be countered by negative regulatory feedback. There have been some recent interest to study models of glycolysis pathway which is an example of an autocatalytic dynamical network in biology that generates adenosine triphospate (ATP) which is the cell's energy currency and is consumed by different mechanisms in the cell [1], [2]. Other examples of autocatalytic networks include engineered power grids whose machinery are maintained using their own energy product as well as financial systems which operate based on generating monetary profits by investing money in the market. Recent results show that there can be severe theoretical hard limits on the resulting performance and robustness in autocatalytic dynamical networks. It is shown that the consequence of such tradeoffs stems from the autocatalytic structure of the system [1], [2].

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. Typical examples of such complex networks include metabolic pathways [4], vehicular platoons [5]–[9], arrays of micro-mirrors [10], micro-cantilevers [11], and smart power grids. These systems are diverse in their detailed physical behavior, however, they share an important common feature that all of them consist of an interconnection of a large number of systems. There have been some progress in characterization of fundamental limitations of feedback in this class of systems. For example, only to name a few, reference [12] gives conditions for string instability in an array of linear time-invariant autonomous vehicles with communication constraints, [13] provides a lower bound on the achievable quality of disturbance rejection using a decentralized controller for stable discrete time linear systems with time delays, [14] studies the performance of spatially invariant plants interconnected through a static network.

Most of the above cited research on fundamental limitations of feedback in interconnected dynamical systems have been focused on networks with linear time-invariant dynamics. The main motivation of this paper stems from a recent work presented in [1] which shows 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. In this paper, our approach to characterize hard limits is essentially different in the sense that it uses higher dimensional nonlinear models of the pathway. We interpret fundamental limitations of feedback by using hard limits (lower bounds) on L_2-gain disturbance attenuation of the system [15]–[17], and L_2-norm of the output of the system [2], [18].

In this paper, our goal is to build upon our previous results [2], [3] and develop methods to characterize hard limits on performance of autocatalytic pathways. First, we study the properties of such pathways through a two-state model, which obtained by lumping all the intermediate reactions into a single intermediate reaction (Fig. 1. A). Then, we generalize our results to autocatalytic pathways, which are composed of a chain of enzymatically catalyzed intermediate reactions (Fig. 1. B). We show that due to the existence of autocatalysis in the system (which is necessary for survival of the pathway), a fundamental tradeoff between fragility and net product of the pathway emerges. Also, we show that as the number of intermediate reactions grows, the price for performance increases.

*This work is supported by research funding from the National Science Foundation through Grant ECCS-1202517.

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II. Characterization of hard limits

In this paper, we use two different methods to quantify hard limits for a stabilizable and detectable system of the following form,

$$\begin{aligned} \dot{x} &= f(x) + g(x)u + p(x)\delta, \quad x \in \mathbb{R}^n, \quad u \in \mathbb{R}^m, && (1) \\ y &= h(x), && (2) \end{aligned}$$

where $x \in \mathbb{R}^n$ is the state, $u(t) \in \mathbb{R}$ the control input, and $\delta \in \mathbb{R}$ the exogenous disturbance input of the system. We quantify hard limits (in the form of lower bounds) on measures of robustness and performance by considering L_2-gain disturbance attenuation and L_2-norm of the output of the system.

A. Hard limits on disturbance attenuation

In order to quantify lower bounds on the best achievable robustness measure for (1)-(2), we need to solve the corresponding regional state feedback L_2-gain disturbance attenuation problem with guaranteed stability. This problem consists of determining a control law $u = u(x)$ such that the closed-loop system has the following properties. First, the zero equilibrium of the system (1)-(2) with $\delta(t) = 0$, for all $t \geq 0$, is asymptotically stable with region of attraction containing Ω (an open set containing the origin in $\mathbb{R}^n$). 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)-(2) from δ to y, is less than or equal to γ, i.e., $\int_0^T |y(t)|^2 dt \leq \gamma^2 \int_0^T |\delta(t)|^2 dt$, 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-gain disturbance attenuation problem with stability, in some neighborhood of the origin, if there exists a smooth positive definite solution of the corresponding Hamilton-Jacobi inequality (see [16], [17] for more details).

B. Hard limits on output energy

We characterize fundamental limitations of feedback for system (1)-(2) with initial condition $x(0) = x_0$ and zero external disturbances (i.e., $\delta(t) = 0$) by considering the corresponding cheap optimal control problem. This case consists of finding a stabilizing state feedback control which minimizes the functional

$$J_\epsilon(x_0; u) \; = \; \frac{1}{2} \int_0^\infty \; [\; y^T y \; + \; \epsilon^2 u^T u \;] \; dt, \qquad (3)$$

when ϵ is a small positive number. As $\epsilon \to 0$, the optimal value $J_\epsilon^*(x_0)$ tends to $J_0^*(x_0)$, the ideal performance of the system. It is well-known (e.g., see [22], 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 the ideal performance is indeed a hard limit on performance of system (1)-(2). It is known that the ideal performance is the optimal value of the minimum energy problem for the zero-dynamics of the system (see [18] for more details). The ideal performance (hard limit function) is zero if and only if the system has an asymptotically stable zero-dynamics subsystem.

III. Minimal Autocatalytic Pathway Model

We consider autocatalysis mechanism in a 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 [4], [19]. This pattern of product inhibition is common in metabolic pathways. We refer to [1] for a detailed discussion.

Experimental observations in Saccharomyces cerevisiae suggest that there are two synchronized pools of oscillating metabolites [20]. 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 [21], and indeed, such simplified models qualitatively reproduce the experimental behavior [4], [19]. We consider a minimal system with three reactions (Fig. 1. A) [1], for which we can identify specific mechanisms both necessary and sufficient for oscillations,

$$\begin{aligned} \dot{x} &= \frac{2y^a}{1+y^{2h}} - \frac{2kx}{1+y^{2g}}, && (4) \\ \dot{y} &= -q\frac{2y^a}{1+y^{2h}} + (q+1)\frac{2kx}{1+y^{2g}} - (1+\delta), && (5) \end{aligned}$$

for $x \geq 0$ and $y \geq 0$. In the first reaction in (Fig. 1. A), PFK consumes q molecules of y (ATP) with allosteric inhibition by ATP. In this case, we lump the intermediate metabolites into one variable, x (see Fig. 1. A). In the second reaction, pyruvate kinase (PK) produces $q+1$ molecules of y for a net (normalized) production of one unit, which is consumed in a final reaction modeling the cell's use of ATP. In the final reaction the effect of disturbance δ in ATP demand is considered.

In order to make several comparisons possible, we normalize all concentrations such that unperturbed ($\delta = 0$) equilibrium point of the systems becomes

$$y^* = 1 \qquad \text{and} \qquad x^* = \frac{1}{k}. \qquad (6)$$

In glycolysis model (4)-(5), expression $\frac{2}{1+y^{2h}}$ 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 pathway

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} 1 \\ -q \end{bmatrix} y^a u + \begin{bmatrix} -1 \\ q+1 \end{bmatrix} \frac{2kx}{1+y^{2g}} - \begin{bmatrix} 0 \\ 1+\delta \end{bmatrix}, \qquad (7)$$

where u is the control input. Our primary motivation behind development and analysis of such control system models for metabolic pathways is to rigorously prove that the tradeoffs

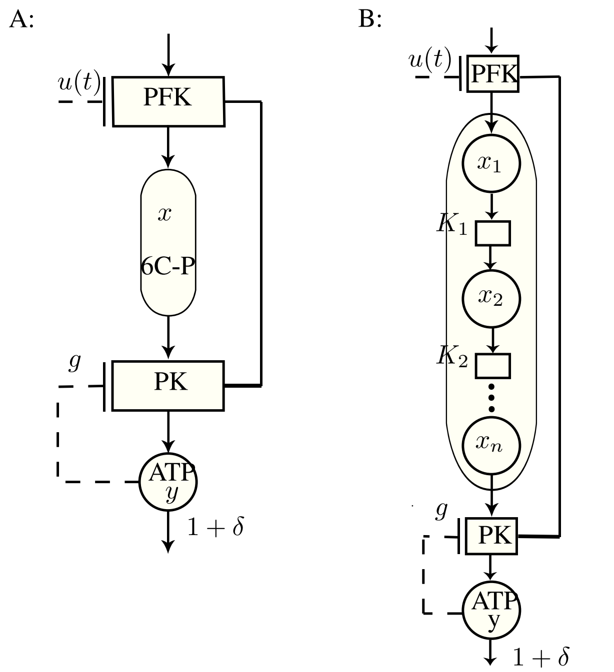

Fig. 1: (**A**) Diagram of two-state glycolysis model. (**B**) Diagram of glycolysis model with intermediate reactions. q ATP molecules, along with constant glucose input, produce a pool of intermediate metabolites, which then produces $q+1$ ATP molecules.

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.

A. *Hard limit on disturbance attenuation*

The simplest robust performance requirement for (7) is that the concentration of y (ATP) remains nearly constant when there is a small constant disturbance in ATP consumption δ (see [1], [2]). But even temporary ATP depletion can result in cell death. Therefore, we are interested in a more complete picture of the transient response to external disturbances.

We show that there exists a hard limit on the best achievable disturbance attenuation, γ^*, for system (7) such that the problem of disturbance attenuation with internal stability is solvable for all $\gamma > \gamma^*$ and not for $\gamma < \gamma^*$,

$$\int_0^T (y(t)-y^*)^2 dt \;\leq\; \gamma^2 \int_0^T \delta^2(t) dt, \tag{8}$$

for all $T \geq 0$ and all $\delta \in L_2(0,T)$ and $y(0) = y^*$. The interesting observation is that the optimal disturbance attenuation γ^* is indeed a hard limit function on robustness of system (1)-(2). It is known that for linear systems, optimal disturbance attenuations can be calculated based on the zero-dynamics subsystem of the system [18]. The hard limit function is zero if and only if the disturbance δ does not influence the unstable part of the zero-dynamics of the system (as defined in [15] for nonlinear systems).

Theorem 1: There exists a hard limit on the best achievable disturbance attenuation, γ^*, for system (7) such that the regional state feedback L_2-gain disturbance attenuation problem with guaranteed stability is solvable for all $\gamma > \gamma^*$, but is not solvable for all $\gamma < \gamma^*$. Moreover, the hard limit function can be written as

$$\gamma^* \geq H(q,k,g) = \frac{q}{k+gq}. \tag{9}$$

Proof: First, by introducing a new variable $z = x + \frac{1}{q}y$, we can cast the system (7) in the following form

$$\begin{aligned} \dot{y} &= -\frac{q+1}{q}\frac{2ky}{1+y^{2g}} + \\ &\quad (q+1)\frac{2kz}{1+y^{2g}} - qy^a u - (1+\delta), \end{aligned} \tag{10}$$

$$\dot{z} = \frac{1}{q}\frac{2kz}{1+y^{2g}} - \frac{1}{q^2}\frac{2ky}{1+y^{2g}} - \frac{1}{q}(1+\delta). \tag{11}$$

The subsystem (11) represents the zero-dynamics of (7). Then, we rewrite (11) in the following form

$$\dot{\bar{z}} = \frac{k}{q}\bar{z} - \frac{gq+k}{q^2}\bar{y} - \frac{1}{q}\delta + \bar{f}(\bar{z},\bar{y}), \tag{12}$$

where $\bar{z} = z - z^* = z - (x^* + \frac{1}{q}y^*)$, $\bar{y} = y - y^*$, $\bar{f}(0,0) = 0$ and $\|\frac{\partial \bar{f}(\bar{z},\bar{y})}{\partial(\bar{z},\bar{y})}\| \leq c|(\bar{z},\bar{y})|$, near the origin in $\mathbb{R}^3$ for a positive number $c \in \mathbb{R}$. Now, according to Proposition. 6 of [17], we know that if the system (11) has L_2-gain less than γ, then the linearized system (13) has L_2-gain less than γ.

Hence, for obtaining the lower bound for the best achievable L_2-gain disturbance attenuation, we just consider the linearized system (13)

$$\dot{\bar{z}} = \frac{k}{q}\bar{z} - \frac{gq+k}{q^2}\bar{y} - \frac{1}{q}\delta. \tag{13}$$

For system (13), the optimal value of γ is given by (see [15], [23] for more details)

$$\gamma_L^* = \frac{q}{k+gq}. \tag{14}$$

Thus, we can conclude that $\gamma^* \geq \gamma_L^* = H(q,k,g) = \frac{q}{k+gq}$. ■

Remark 1: Theorem 1 illustrates a tradeoff between robustness and efficiency (as measured by complexity and metabolic overhead). From (9) the glycolysis mechanism is more robust efficient if k and g are large. On the other hand, large k requires either a more efficient or a higher level of enzymes, and large g requires a more complex allosterically controlled PK enzyme; both would increase the cells metabolic load. Note that, the obtained hard limit in Theorem 1 is increasing function with respect to q. It means that increasing q (more energy investment for the same return) can result in worse performance. It is important to note that these results are consistent with results in [1], where a linearized model with a different performance measure is used.

B. *Hard limit on output energy*

In this subsection, we show that there exists a hard limit on the best achievable ideal performance (output energy) of system (7). One can see that some minimum output energy (i.e., ATP) is required to stabilize the unstable zero-dynamics (11). This output energy represents the energetic cost of the cell to stabilize it to its steady-state. In the following theorem, we show that the minimum output energy is lower bounded by a constant which is only a function of the parameters and initial conditions of the glycolysis model. This hard limit is independent of the feedback control strategy used to stabilize the system.

Theorem 2: Suppose that the equilibrium of interest is given by (6) and $u^* = 1$. Then, there is a hard limit on the performance measure of the unperturbed ($\delta = 0$) system (7) in the following sense

$$\int_0^\infty \ (y(t;u_0) - \bar{y})^2 \ dt \ \geq \ \frac{q^3}{k} \ z_0^2 + J(z_0, q, g), \quad (15)$$

where $z_0 = (x(0) - x^*) + \frac{1}{q}(y(0) - y^*)$, u_0 is an arbitrary stabilizing feedback control law for system (7), and $J(0, q, g) = J(z, q, 0) = 0$ and $|J(z, q, g)| \leq c|z|^3$ on an open set Ω around the origin in $\mathbb{R}$.

Proof: By introduction of a new variable $z = x + \frac{1}{q}y$, we rewrite (7) is the canonical form (10)-(11). The linearization of (10)-(11) is given by

$$A_0 = \begin{bmatrix} -k & a+g \\ (q+1)k & -qa - g(q+1) \end{bmatrix}, B_0 = \begin{bmatrix} 1 \\ -q \end{bmatrix}.$$

We denote by $\pi(y, z; \epsilon)$ the solution of the HJB PDE corresponding to the cheap optimal control problem to (7). We apply the power series method [25], [26] by first expanding $\pi(y, z; \epsilon)$ in series as follows

$$\pi(y, z; \epsilon) = \pi^{[2]}(y, z; \epsilon) + \pi^{[3]}(y, z; \epsilon) + \dots \quad (16)$$

in which kth order term in the Taylor series expansion of $\pi(y, z; \epsilon)$ is denoted by $\pi^{[k]}(y, z; \epsilon)$. Then (16) is plug into the corresponding HJB equation of the optimal cheap control problem. The first term in the series is

$$\pi^{[2]}(y, z; \epsilon) = \begin{bmatrix} y - y^* & z - z^* \end{bmatrix} P(\epsilon) \begin{bmatrix} y - y^* \\ z - z^* \end{bmatrix},$$

where $P(\epsilon)$ is the solution of algebraic Riccati equation to the cheap control problem for the linearized model (A_0, B_0). It can be shown that $P(\epsilon)$ can be decomposed in the form of a series in ϵ (see [24] for more details)

$$P(\epsilon) = \begin{bmatrix} \epsilon P_1 & \epsilon P_2 \\ \epsilon P_2 & P_0 + \epsilon P_3 \end{bmatrix} + \mathcal{O}(\epsilon^2).$$

Since the pole of the zero-dynamics of the linearized model is located at the $\frac{k}{q}$, we can verify that $P_0 = \frac{q^3}{k}$. Therefore, it follows that $\pi^{[2]}(y, z; \epsilon) = \frac{q^3}{k} z_0^2 + \mathcal{O}(\epsilon)$.

Due to space limitations, we eliminate the details of the proof and only explain the key steps. One can obtain governing partial differential equations for the higher-order terms $\pi^{[k]}(y, z; \epsilon)$ for $k \geq 3$ by equating the coefficients of terms with the same order. It can be shown that $\pi^{[k]}(y, z) = \pi_0^{[k]}(z) + \epsilon \pi_1^{[k]}(y, z) + \mathcal{O}(\epsilon)$ for all $k \geq 3$. Then, by constructing approximation of the optimal control feedback by using computed Taylor series terms, one can prove that $\pi(y, z; \epsilon) \to \frac{q^3}{k} z_0^2 +$ (higher order terms in z_0) as $\epsilon \to 0$. Thus, the ideal performance cost value is $\frac{q^3}{k} z_0^2 + J(z_0)$. ■

Remark 2: Based on Theorems 1 and 2, a fundamental tradeoff between fragility and net production of the pathway emerges as follows: increasing q (number of ATP molecules invested in the pathway), increases fragility of the network to small disturbances (based on Theorem 1) and it can result in undesirable transient behavior (based on Theorem 2). 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.

Remark 3: In the case where we have $g = 0$ i.e., without ATP feedback on PF, Theorem 2 reduces to the result given in [2] which provides a hard limit on the best achievable ideal performance of the system (7) without ATP feedback on PK.

IV. Autocatalytic pathways with multiple intermediate metabolite reactions

In this section, we consider autocatalytic pathways with multiple intermediate metabolite reactions as shown in Fig. 1. B. In Section III, we studied the property of such pathways with a two-state model (7), which is obtained by lumping all the intermediate reactions into a single intermediate reaction (see Fig. 1. A). Our notations are similar to those of the two-state pathway model (4)-(5). Therefore, we can derive a control system model for the autocatalytic pathway with multiple intermediate metabolite reactions as follows

$$\begin{aligned} \dot{x}_1 &= y^a u - K_1 x_1, \\ \dot{x}_2 &= K_1 x_1 - K_2 x_2, \\ &\dots \\ \dot{x}_n &= K_{n-1} x_{n-1} - \frac{2K_n x_n}{1 + y^{2g}}, \\ \dot{y} &= (q+1) \frac{2K_n x_n}{1 + y^{2g}} - q y^a u - (1 + \delta), \end{aligned} \quad (17)$$

for $x_i \geq 0$ and $y \geq 0$. In order to simplify our analysis, we assume that $K_1 = \cdots = K_n = K$. We normalize all concentrations such that unperturbed steady states are

$$y^* = 1, \quad x_i = \frac{1}{K} \quad 1 \leq i \leq n. \quad (18)$$

A. Hard limit on disturbance attenuation

We extend our results in Theorem 1 to higher dimensional model of autocatalytic pathways. In the following theorem, we show that there exists a hard limit on the best achievable disturbance attenuation of system (17).

Theorem 3: There exists a hard limit on the best achievable disturbance attenuation, γ^*, for system (17) such that the problem of disturbance attenuation with internal stability is solvable for all $\gamma > \gamma^*$, but is not solvable for all $\gamma < \gamma^*$, i.e.,

$$\int_0^T (y(t;u_0) - \bar{y})^2 dt \ \leq \ \gamma^2 \int_0^T \delta^2(t) dt.$$

Moreover, the hard limit function is given by

$$\gamma^* \geq H(q, K, g, n) \quad (19)$$

where

$$H(q,K,g,n) = \frac{1}{g(q+1)\big(1-(\frac{q}{q+1})^{\frac{1}{n}}\big)+K\big((\frac{q+1}{q})^{\frac{1}{n}}-1\big)}.$$

Proof: Due to space limitations, we eliminate the proof. ■

Remark 4: Theorem 3 illustrates a tradeoff between robustness and efficiency (as measured by complexity and metabolic overhead). It follows from (19), the glycolysis mechanism is more robust efficient if K and g are large. On the other hand, large K requires either a more efficient or a higher level of enzymes, and large g requires a more complex allosterically controlled PK enzyme; both would increase the cells metabolic load.

Remark 5: It can be easily shown that $H(q,K,g,n) \in \mathcal{O}(n)$, and it is approximated by

$$H(q,K,g,n) \approx -\frac{n}{\big(\ln(\frac{q}{q+1})\big)\big(g(q+1)+K\big)}. \tag{20}$$

This means that as the number of intermediate reactions n grows, the price paid for robustness, $H(q,K,g,n)$, increases linearly with n (see Fig. 4).

B. Hard limit on output energy

In this subsection, we show that there exists a hard limit on the best achievable ideal performance (output energy) of system (17).

Theorem 4: Suppose that the equilibrium of interest is given by (18) and $u^* = 1$. Then, there is a hard limit on the performance measure of the unperturbed ($\delta = 0$) system in the following sense

$$\int_0^\infty \left(y(t;u_0)-\bar{y}\right)^2\,dt \tag{21}$$
$$\geq \frac{\lambda k\big(v^{\mathrm{T}}\,(z(0)-z^*)\big)^2}{\big(v^{\mathrm{T}}B\big)^2} + J(z(0),q,g),$$

where u_0 is an arbitrary stabilizing feedback control law for system (17), $J(z^*,q,g) = J(z,q,0) = 0$ and $|J(z,q,g)| \leq c|z-z^*|^3$ where z is close enough to z^*.

Proof: The proof of this theorem is adjusted from [18], [17] and Theorem 3. ■

Remark 6: In the case where $n = 1$, i.e., with only one intermediate reaction, the results of Theorems 4 and 3 reduce to the results of Theorems 2 and 1, respectively.

V. Illustrative Numerical Examples

In this section, we present numerical examples to demonstrate the utility of the obtained hard limits.

Example 1: Consider the system (4)-(5) where $a = 1$, $g = 2$, $q = 2$ and $k = 5$. For $1 < h < 6.5$, we can easily show that the system (4)-(5) is stable [1]. Hence we can define the L_2-gain disturbance attenuation for (4)-(5) as follows

$$\gamma^2 = \sup_{t>0} \frac{\int_0^t y^2(\tau)d\tau}{\int_0^t \delta^2(\tau)\tau}. \tag{22}$$

The simplest robust performance requirement for (4)-(5) is that the concentration of y (ATP) remains nearly constant

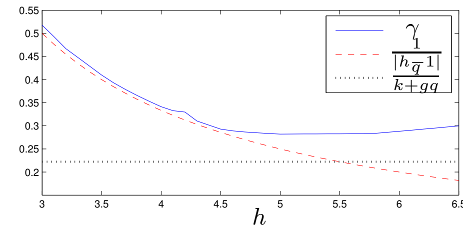

Fig. 2: The solid line shows the L_2-gain disturbance attenuation of (4)-(5) versus h. The dashed line shows the stable steady-state error, and the dotted line demonstrates the hard limit on the best achievable disturbance attenuation. This hard limit is independent of the feedback control strategy used to stabilize the system.

when there is a small constant disturbance in ATP consumption δ. But even temporary ATP depletion can result in cell death. Therefore, the transient response to disturbance plays an important role. In [1], the steady-state error for linearized system is computed by $\frac{1}{|h-a|}$ (dashed red line in Fig. 2). Therefore, by increasing h the steady-state error becomes better. One tradeoff is that large h requires complex enzymes, which are more costly for the cell to produce. A more interesting tradeoff arises because of the transient response to disturbance. Fig. 2 illustrates the effect of h on the transient response to step changes in disturbance. As one can see in Fig. 2 (solid blue line), by increasing h, the L_2-gain disturbance attenuation of (4)-(5) decreases (i.e., proposed robustness performance becomes better). After some critical threshold, although the stable steady-state error becomes better by increasing h, but the robustness performance γ does not become better due to the transient response to disturbance. The dotted line in Fig. 2 shows the hard limit on the best achievable disturbance attenuation obtained form (9). This hard limit is independent of the feedback control strategy used to stabilize the system (Hence, it is independent of h).

Example 2: Consider the autocatalytic pathway (17) where $u = \frac{2}{1+y^{2h}}$ (the regulatory feedback control employed by nature), $g = q = 2$, $K = 5$, $a = 1$ and $\delta(t) = 0.1(1+\sin(8t))$. Now, for each integer $1 \leq n \leq 4$, we calculate the optimal L_2-gain disturbance attenuation (by finding the proper h). In Fig. 3, the optimal L_2-gain disturbance attenuation of the autocatalytic pathways versus the number of intermediate reactions are depicted. As one can see in Fig. 3, as the number of intermediate reactions grows, the price for performance increases. The dashed line shows the obtained hard limit based on Theorem 3. Note that, due to the form of regulatory feedback control which employed by nature, there is a small gap between obtained hard limit in Theorem 3 and the L_2-gain disturbance attenuation of the original model (the distance between the small circles and the dashed line in Fig. 3). Furthermore, Fig. 4 shows that we can approximate $\gamma_L^* = H(q,K,g,n)$ precisely (for any large or small n) by using the proposed linear function in Remark 5. As mentioned earlier, the price

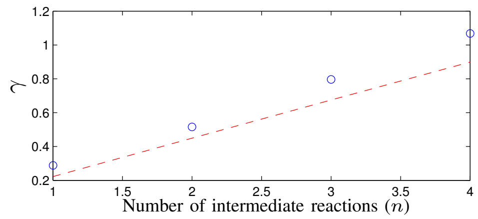

Fig. 3: The small circles (∘) demonstrate the L_2-gain disturbance attenuation of autocatalytic pathways (17), where $u = \frac{2}{1+y^{2h}}$ (the regulatory feedback control employed by nature), versus the number of intermediate reactions. The dashed line shows the obtained hard limit based on Theorem 3.

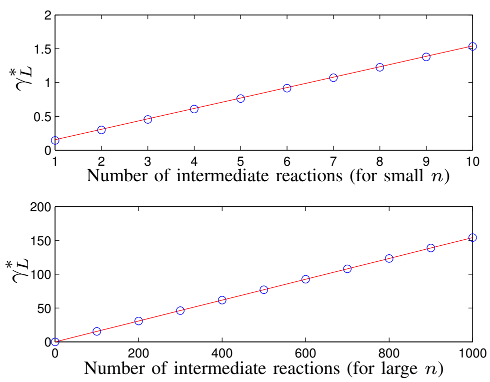

Fig. 4: The small circles (∘) show the obtained hard limit based on Theorem 3 and the solid line shows the linear approximation of that hard limit based on Remark 5.

paid for robustness, $H(q, K, g, n)$, increases linearly with the number of intermediate reactions n.

VI. Conclusion

By using blending ideas from biology and nonlinear control theory, our objective is to develop a methodology to characterize fundamental limits on robustness and performance measures in dynamical networks with autocatalytic structures. We study the hard limits of the ideal performance of a glycolysis model. It is shown that glycolysis model can be used as a basis for such study. Then, we explicitly derive hard limits on the performance of the autocatalytic pathways with intermediate reactions which are characterize as L_2-norm of the output and L_2-gain of disturbance attenuation.

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