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Article *in* IEEE transactions on bio-medical engineering · November 2012

DOI: 10.1109/TBME.2012.2230259 · Source: PubMed

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An Optimization-Based Design Framework for Steering Steady States and Improving Robustness of Glycolysis–Glycogenolysis Pathway

Surajit Panja, *Student Member, IEEE*, Sourav Patra, Anirban Mukherjee*, *Member, IEEE*, Madhumita Basu, Sanghamitra Sengupta, and Pranab K. Dutta, *Member, IEEE*

***Abstract*—A robust synthesis technique is devised for synergism and saturation systems, commonly known as S-systems, for controlling the steady states of the glycolysis–glycogenolysis pathway. The development of the *robust* biochemical network is essential owing to the fragile response to the perturbation of intrinsic and extrinsic parameters of the nominal S-system. The synthesis problem is formulated in a computationally attractive convex optimization framework. The linear matrix inequalities are framed to aim at the minimization of steady-state error, improvement of robustness, and utilization of minimum control input to the biochemical network.**

***Index Terms*—Glycogenolysis, glycolysis, linear matrix inequality (LMI), robustness, S-system.**

I. Introduction

STOICHIOMETRIC modeling and regulation of cellular reaction networks are increasingly popular to guide metabolic engineering of industrially important microorganisms for new and improved product formation. As the principle of biological systems is complex, canonical modeling frameworks with prior biological knowledge are essential to interpret its dynamics and robustness. The metabolism of a typical heterotrophic cell can be portrayed as three interconnected functional blocks: 1) catabolism, 2) anabolism, and 3) macromolecular synthesis and growth. Despite the complexity of these processes in each block, the connections among them involve only a limited number of substances. The catabolic intermediates from glycolysis, the pentose phosphate pathway, and the citric acid cycle serve as raw materials for most of the anabolism and these include four kinds of sugar phosphates (viz. triose-P, tetrose-P, pentose-P, hexose-P), three alpha-keto acids (such as pyruvate, oxaloacetate, and alpha-ketoglutarate), two coenzyme A derivatives (acetyl-CoA and succinyl-CoA), and phosphoenolpyruvate (PEP). This study centers around one of such common set of reactions pertaining to two important metabolic pathways, namely glycolysis and glycogenolysis (GG). The overall goal of GG in a cell is to conserve energy as ATP from the catabolism of carbohydrates and also to maintain the glucose homeostasis [1].

The metabolic control analysis has shown that large changes in metabolic flux may be achieved by introducing minimal disturbance of metabolite concentrations and/or fluxes in other pathways by coordinated changes in the activities of enzymes involved in common mechanisms. Related experimental and theoretical evidence propose that regulatory enzymes, exhibiting allosteric properties, are effective agents for control of metabolic flux [2]–[5]. Another school of opinion is that they have a more significant role in homoeostasis [6].

S-systems are proposed in [1], [7]–[10] as a canonical nonlinear model (in the framework of biochemical systems theory) to represent the dynamics of a large class of genetic regulatory networks and metabolic pathways. The problem of estimating the S-system model parameters, the rate coefficients, and the kinetic orders is addressed in [11]–[14]. At the steady state, this nonlinear model can be analyzed by linear algebraic equations under logarithmic transformation [9], [15]. Many applications require altering the steady state of a given pathway and in order to address this, novel intervention strategies are developed [16]. Altering the production of certain compounds in metabolism is essential for many industrial applications such as cosmetics and food industries. Sometimes, external factors or genetic mutations modify the steady state of the metabolic pathway. Thus, steering the state of the metabolism back to a desired level is often needed. In this regard, the controllability of S-systems is discussed in [15] based on feedback linearization. In [17], Klipp *et al.* proposed an optimization framework in order to get a fast response, considering constraints on the input enzyme concentration. Vera *et al.* proposed a method called the optimization program for drug discovery to detect target enzymes [18]. Voit provided a mathematical framework emphasizing on simplexes with physiological constraints to characterize health and disease states [19]. Lee *et al.* [20] have established two methods to steer steady states—one involves the pseudoinverse to characterize the admissible solution space and the other one is based

Manuscript received June 12, 2012; revised September 25, 2012; November 8, 2012; accepted November 10, 2012. Date of publication November 29, 2012; date of current version January 16, 2013. The work of S. Panja was supported by the Council of Scientific and Industrial Research, India, under Fellowship 09/81(1031)/ 2010/EMR-I. *Asterisk indicates corresponding author.*

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Digital Object Identifier 10.1109/TBME.2012.2230259

on mixed integer programming to tackle physical constraints. In this paper, the goal of the control strategy is to transfer the dependent variables from an initial steady state to the desired final ones by manipulating a selective number of independent variables (enzymes). It is ensured that the achieved steady state remains within a closed vicinity of the target steady state. This steering of the steady state(s) is performed with the minimum possible control input. Additionally, the robustness is guaranteed against a certain class of parameter perturbation. The optimization problem and the design constrains are formulated in an LMI framework leading to a computationally advantageous method implemented in MATLAB environment [21].

The rest of this paper is organized as follows. In Section II, the structure of the S-system model and its linearized steady-state form are discussed. The enzymatic manipulation-based optimization problem is discussed in Section III. Section IV provides the numerically attractive LMI-based synthesis methodology of the biochemical network. Sections III and IV provide the principal contributions of this paper. The S-system model of GG pathway is discussed in Section V. To show the effectiveness of the proposed method, a numerical example is illustrated in Section VI. Finally, the concluding remarks are presented in Section VII.

Notations: Let $\mathbb{R}$, $\mathbb{R}_+$, and $\mathbb{R}^{m\times n}$ denote the set of all real numbers, the set of all positive real numbers and the set of all real matrices with m rows and n columns, respectively. $\mathbb{R}^n$ and $\mathbb{R}^n_+$ represent the set of all column vectors having n real numbers and the set of all column vectors having n positive real numbers, respectively. The vector ${}^n e_i, i$=1, 2, ..., n is an n-length unit normal toward ith direction in $\mathbb{R}^n$. ${}^n e_1, {}^n e_2$, and ${}^n e_n$ can be represented as $[10\ldots0]^T$, $[01\ldots0]^T$ and $[0\,0\ldots1]^T$, respectively. $c(A)$ denotes the condition number of a matrix A.

II. Biochemical Pathways: S-System Model and Steady-State Analysis

The cellular and intracellular metabolic processes are the collection of enzymatic reactions. The primary interest in biochemical systems analysis is to understand (and control) the masterly orchestrated cooperation among many reactions and modulations that govern biochemical and metabolic pathways. There are various models to study the biochemical pathways. Among these, the S-system model [1], [7], referring to the synergism and saturation properties of biochemical networks, is one of the most popular models. The general equation describing temporal changes in a biochemical system is

$$\dot{X}_i = \alpha_i \prod_{j=1}^{n+m} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} X_j^{h_{ij}} \quad i = 1, 2, \ldots, n \qquad (1)$$

where $n > 0, m \geq 0$ and $X_1, X_2, \ldots, X_{n+m} \geq 0$ are the concentrations of metabolites, such as substrates and products of the biochemical pathways. $X_i, i = 1, \ldots, n$ denote n-dependent variables. The independent variables, $X_j, j = n+1, \ldots, n+m$ may act as a catalyst in the metabolic process governed by (1). The rate of change of concentration is the difference between the production and the degradation term. The non-negative rate constants $\alpha_i > 0$ and $\beta_i > 0$ are the production and the degradation rate constants, respectively. Each variable X_j is raised to a power by the kinetic parameters g_{ij} and/or h_{ij}, which are known as kinetic order of the S-systems. At the steady state, (1) becomes linear upon logarithmic transformation. The dependent variables can be expressed in terms of the system parameters and the independent variables [9], [15]. The transformed dependent variables $y_i = \ln(X_i)\ i = 1, 2, \ldots, n$ are collected in a vector $Y_D = [y_1\ y_2 \ldots y_n]^T = \ln(X_D) \in \mathbb{R}^n$. Similarly, the transformed independent variables, $y_i = \ln(X_i)\ \ i = n+1, \ldots, n+m$, are assembled in a vector $Y_I = [y_{n+1} y_{n+2} \ldots y_{n+m}]^T = \ln(X_I) \in \mathbb{R}^m$. The system matrix $A_D \in \mathbb{R}^{n\times n}$ and the interaction matrix $A_I \in \mathbb{R}^{n\times m}$ are formed by the differences $g_{ij} - h_{ij}$ of kinetic orders associated with the dependent and the independent variables. The rate constant vector $b \in \mathbb{R}^n$ is formed with the elements $b_i = \ln(\frac{\beta_i}{\alpha_i}) \in \mathbb{R}, i = 1, 2, \ldots, n$. At the steady state, the influx and efflux of $X_i, i = 1, 2, \ldots, n$ are equal and the concentrations of the dependent variables do not change with time. Material flows through the system but all fluxes are perfectly in a balance. The steady-state model of the biochemical network [7], [9], [15], [22] can be represented by

$$A_D Y_D = b - A_I Y_I \qquad (2)$$

where, $A_D = [a_{ij}] = [g_{ij} - h_{ij}] \in \mathbb{R}^{n\times n}, A_I = [a_{ik}] = [g_{ik} - h_{ik}] \in \mathbb{R}^{n\times m}, \quad i, j = 1, 2, \ldots, n, \quad$ and $\quad k = n+1, n+2, \ldots, n+m$. In order to steer the steady-state value of transformed dependent variable vector Y_D to a desired level Y_D'' the transformed independent variable vector Y_I is tuned. The strategy of optimization needs manipulation of some or all of the independent "control"variables, which are typically the inputs, the enzyme activities, or the magnitudes of transport steps, but could also include factors like temperature or pH. In this paper, an effort has been made to modify the enzyme activities in order to achieve the desired state with minimum steady-state error. The modified S-system model is

$$\dot{\overline{X}}_i = \alpha_i \prod_{j=1}^{n+m} \overline{X}_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} \overline{X}_j^{h_{ij}}, i = 1, 2, \ldots, n \qquad (3)$$

where $n > 0, m \geq 0$ and $\overline{X}_i \in \mathbb{R}_+, i = 1, 2, \ldots, n+m$ are the concentrations in the corresponding biochemical system. The collection of n dependent variables $\overline{X}_i \in \mathbb{R}_+, i = 1, 2, \ldots, n$ is denoted by a set $\mathcal{D}$. At the steady state, $\overline{X}_i = X_i', i = 1, 2, \ldots, n$. Similarly, the collection of m independent variables $\overline{X}_i \in \mathbb{R}, i = n+1, \ldots, n+m$ is denoted by a set $\mathcal{I}$. Some of these m independent variables are chosen as control variables and form another set $\mathcal{M} \subseteq \mathcal{I}$. This can be expressed as $\overline{X}_i = k_{i-n} \cdot X_i, i = n+1, n+2, \ldots, n+m$ where

$$k_{i-n} = \begin{cases} 1 & \text{for} \quad X_i \in \mathcal{I} - \mathcal{M}, \quad n+1 \leq i \leq n+m \\ e^{f_{i-n}} & \text{for} \quad X_i \in \mathcal{M}, \quad n+1 \leq i \leq n+m. \end{cases}$$

Assuming the existence of this new steady state, $Y_D' = [\ln(X_1')\ln(X_2') \ldots \ln(X_n')]^T = \ln(X_D') \in \mathbb{R}^n$, the steady-state model is given by

$$A_D Y_D' = b - A_I (Y_I + f) \qquad (4)$$

where, $f = [f_1 f_2 \ldots f_m]^T \in \mathbb{R}^m$ is the control parameter vector of a given structure based on the characteristics of the

S-system under consideration. Some of the independent variables, $X_i \in \mathcal{M} \subseteq \mathcal{I}, n+1 \leq i \leq n+m$, representing the enzyme activity in (1), are manipulated as $\overline{X}_i = e^{f_{i-n}} \cdot X_i$ [in (3)]. This appears additive in logarithmic scale as in (4). In most of the biochemical systems, the number of control variables m is more than the number of target variables n. The steady-state analysis will lead to infinite number of solutions. Assuming full row rank of A_I, the minimum-norm solution [23] (assuming locally stable target steady state) is given by

$$f_{mn} = {A_I}^T \left(A_I {A_I}^T\right)^{-1} (b - A_D Y'_D) - Y_I. \tag{5}$$

As opposed to this, the number of target variables n may be more than the number of control variables m. Assuming full column rank of A_I, in this case, the steady-state analysis leads to the following least-square error solution [23]:

$$f_{ls} = \left({A_I}^T A_I\right)^{-1} {A_I}^T (b - A_D Y'_D) - Y_I. \tag{6}$$

With the assumption of having a particular structure of f or constraints in the form of lower and upper bound on the elements of f, it is not feasible to simply use (5) and (6) to find out f. Additionally, it is not clear whether these minimum-norm/least-square solutions are the optimal ones having any relevance to the view-point of biochemical engineers or not.

III. Formulating an Optimization Problem

The motivation of this study is to design a control parameter vector f which can steer a present steady state Y_D of a biochemical system (modeled by S-system) to a desired steady-state goal vector $Y''_D = \ln(X''_D)$. Ideally, this system should reach a desired steady-state goal vector (without any steady-state error) by designing the control parameter vector f. $X'_D = [X'_1 X'_2 X'_3]^T$ is the *achieved* steady state which may be close to (if not same) the *desired* steady state $X''_D = [X''_1 X''_2 X''_3]^T$ of the biochemical system. In contrast to attaining the desired steady-state goal vector Y''_D, the system may reach a new steady state Y'_D owing to the presence of other biochemical constraints (like the structure of f). This is written as $Y'_D = A_D^{-1}[b - A_I(Y_I + f)]$. If the biochemical system is unable to reach the desired steady-state vector Y''_D the design requirement is to keep the achieved steady-state vector Y'_D within an open ball of radius δ around the desired steady-state vector Y''_D. Assuming $\delta' > 0$, the design requirement can be expressed as $\frac{\|Y''_D - Y'_D\|}{\|Y''_D\|} < \delta' \in \mathbb{R}_+$. This can be equivalently expressed as $\|Y''_D - Y'_D\| < \delta' \|Y''_D\| = \delta$. The control parameter vector f of a given structure can be chosen by minimizing $\delta \in \mathbb{R}_+$. The minimization of δ guarantees the minimum steady-state error between the desired steady-state vector Y''_D and the achieved steady-state vector Y'_D. Now, the following minimization problem can be introduced:

$$\underset{f}{\text{Minimize}}\ \delta$$
$$\text{Subject to: } \|Y''_D - A_D^{-1}[b - A_I(Y_I + f)]\| < \delta,\ \delta \in \mathbb{R}_+. \tag{7}$$

Defining $k = Y''_D - A_D^{-1}(b - A_I Y_I)$, from the design specification and the desired steady state, this minimization problem can equivalently be written as

$$\underset{f}{\text{Minimize}}\ \delta \text{ Subject to: } \|k + A_D^{-1} A_I f\| < \delta,\ \delta \in \mathbb{R}_+. \tag{8}$$

A. Reframing the Optimization Problem by Incorporating Robustness

The parameters of the S-systems are estimated from the steady-state data and dynamical data. Whatever method is used, the parameter estimation problem is directly tied to the experimental data. These experiments may be simple perturbations or actual time series of measurements on transients. In reality, data points may be scarce and may be a result of experimental error. Additionally, a systematic design of experiment may be difficult due to the scarcity of suitable enzymes and metabolites. At this point, most of the information about the dynamics of a biochemical system is inferred from the experiments *in vitro*. The validity of the estimates of biochemical systems *in vivo* poses a serious question. The *uncertainty* refers to the difference between a model and reality and whatever mechanism is used to express this error will be known as a representation of uncertainty. In this study, the perturbation ΔA_I of the interaction matrix A_I is analyzed as the uncertainty. In presence of ΔA_I, the steady-state equation is given by

$$A_D Y^s_D = b - (A_I + \Delta A_I)(Y_I + f) \tag{9}$$

where $Y^s_D = Y'_D + \Delta Y'_D$ is the perturbed steady state of the biochemical system. The deviation in transformed dependent variable vector $\Delta Y'_D$ can be found by subtracting (4) from (9) and is given by $\Delta Y'_D = -A_D^{-1} \Delta A_I (Y_I + f)$. Consequently, the perturbation sensitivity S_{A_I} is given by

$$S_{A_I} = \frac{\|\Delta Y'_D\|}{\|\Delta A_I\|} \leq \|A_D^{-1}\| \|Y_I + f\| \leq \|A_D^{-1}\| (\|Y_I\| + \|f\|). \tag{10}$$

The upperbound on perturbation sensitivity S_{A_I} is defined as

$$S^b_{A_I} = \|A_D^{-1}\| \|A_D\| \frac{\|Y_I + f\|}{\|A_D\|} = c(A_D) s_b \tag{11}$$

where $s_b = \frac{\|Y_I + f\|}{\|A_D\|}$. The objective of this study is to design a *robust* biochemical network which will reach within an open ball of radius $\delta \in \mathbb{R}_+$ around the desired steady-state goal vector $Y''_D \in \mathbb{R}^n$. The minimization of the perturbation sensitivity S_{A_I} offers improved robustness to the perturbation of interaction matrix A_I. This can be achieved by formulating the objective function $\underset{f}{\text{Minimize}}\ s_1$, subject to: $\|Y_I + f\| < s_1, s_1 \in \mathbb{R}_+$, where s_1 is an optimization parameter. This can be written as

$$\underset{f}{\text{Minimize}}\ s_1^2$$
$$\text{Subject to: } (Y_I + f)^T (Y_I + f) < s_1^2,\ s_1 \in \mathbb{R}_+. \tag{12}$$

In order to transfer the steady state from Y_D to Y'_D, the required control effort $\|f\|$ needs to be minimized. It can be inferred from (10) that this minimum input control scheme offers robustness by minimizing the sensitivity S_{A_I}. This can be achieved via the objective function $\underset{f}{\text{Minimize}}\ s_2$ subject to: $\|f\| < s_2, s_2 \in \mathbb{R}_+$.

This can be equivalently written as

$$\underset{f}{\text{Minimize}}\ s_2^2 \text{ Subject to: } f^T f < s_2^2,\ \ s_2 \in \mathbb{R}_+. \tag{13}$$

Consequently, the minimization of s_1 and s_2, respectively, in (12) and (13), offers minimum control input-oriented robustness to the perturbation of the interaction matrix A_I.

IV. Synthesis of Biochemical System Using LMI Approach

The goal of the intervention strategies is to transfer the target variables from an initial steady state to a desired state by varying the control variables in a robust manner. The following theorem provides a set of sufficient conditions for the existence of a control parameter vector f to achieve the desired steady state with improved robustness.

Theorem 1: Let Y_D be the steady state of the nominal system $A_D Y_D = b - A_I Y_I$ and $k = Y_D'' - A_D^{-1}(b - A_I Y_I)$, where A_D is nonsingular and Y_D'' be the desired steady state. Let s_1, s_2, and δ be three positive scalars. Then, a control parameter vector f keeps the two norm of the steady-state error within the given bound δ with improved robustness if f is a feasible solution of the following optimization problem:

$$\underset{f}{\text{Minimize}} \quad \mathcal{J} = w_1 s_1^2 + w_2 s_2^2$$

Subject to

$$\begin{bmatrix} \delta^2 I & \left(A_D^{-1} A_I f + k\right)^T \\ \left(A_D^{-1} A_I f + k\right) & I \end{bmatrix} > 0 \tag{14}$$

$$\begin{bmatrix} s_1^2 I & (Y_I + f)^T \\ (Y_I + f) & I \end{bmatrix} > 0 \tag{15}$$

$$\begin{bmatrix} s_2^2 I & f^T \\ f & I \end{bmatrix} > 0. \tag{16}$$

where w_1 and w_2 are given, and satisfy the conditions $0 \leq w_1, w_2 \leq 1$ and $w_1 + w_2 = 1$.

Proof: The nominal system is $A_D Y_D = b - A_I Y_I$ and via supposition, A_D is nonsingular. Let Y_D' be the achieved steady state due to f, i.e., $A_D Y_D' = b - A_I (Y_I + f)$. Then, the steady-state error is equal to $\|k + A_D^{-1} A_I f\|$ [see (8)] and $\|k + A_D^{-1} A_I f\| < \delta$ implies that the two norm of the steady-state error is bounded by δ. Now, using the Schur complement lemma [23], (14) can equivalently be written as $\delta^2 I - \left(A_D^{-1} A_I f + k\right)^T \left(A_D^{-1} A_I f + k\right) > 0$ which is equivalent to: $\left(A_D^{-1} A_I f + k\right)^T \left(A_D^{-1} A_I f + k\right) < \delta^2 I \Leftrightarrow \| \left(A_D^{-1} A_I f + k\right) \| < \delta$. Hence, satisfying the condition (14) implies that the two norm of the steady-state error is bounded by δ. Similarly, by using the Schur complement lemma, (15) can be written as $s_1^2 I - (Y_I + f)^T (Y_I + f) > 0$ which is equivalent to: $(Y_I + f)^T (Y_I + f) < s_1^2 I \Leftrightarrow \|Y_I + f\| < s_1$ Now, minimizing s_1 implies the minimization of $\|Y_I + f\|$, which in turn reduces the sensitivity with respect to the perturbations in A_I [see (10)] and hence the robustness is improved. Now using the Schur complement lemma, the following inequality can be equivalently written from (16) as $s_2^2 I - f^T f > 0 \Leftrightarrow f^T f < s_2^2 I \Leftrightarrow \|f\| < s_2$ Note that the minimization of s_2 offers the minimum input control to bring the steady state from its nominal value to the desired one. This completes the proof. ■

V. S-System Model of GG Pathway

The S-system model of glucose-6-phosphate metabolism is considered [7]. GG are central steps of carbohydrate metabolism. They yield common intermediate glucose-6-phosphate. The principal route of glycogen utilization is the glycogenolysis via glycogen phophorolysis to glucose-1-phosphate and the subsequent conversion to glucose-6-phosphate via phosphoglucomutase reaction. Glucose-6-phosphate can subsequently be used for the production of energy or the formation of glucose. The translation task of the biochemical map into a model is the identification of dependent and independent variables, specified as follows [7], [24], [25]:

Dependent variables: X_1-Glucose-1-phosphate (G1P); X_2-Glucose-6-phosphate (G6P); X_3-Fructose-6-phosphate (F6P).

Independent variables: Phosphate $(P_i) \rightarrow X_4 = 10.0$ mM; Glucose $(C_6H_{12}O_6) \rightarrow X_5 = 5.0$ mM; Phosphorylase a $\rightarrow X_6 = 3.0\,\mu$mol/min/gram; Phosphoglucomutase (PGM) $\rightarrow X_7 = 40.0\,\mu$mol/min/gram; Phosphoglucose isomerase (PGI) $\rightarrow X_8 = 136.0\,\mu$mol/min/gram; Phosphofructokinase (PFK) $\rightarrow X_9 = 2.86\,\mu$mol/min/gram; Glucokinase$\rightarrow X_{10} = 4.0\,\mu$mol/min/gram; Glycogen$\rightarrow X_{11} = 50$ mM.

The nominal dynamical equation of the S-system model of the GG pathway is as follows [7]:

$$\begin{aligned}
\dot{X}_1 &= \left(7.7884314\times10^{-2}\right) {X_4}^{0.66} X_6 \\
&\quad - 1.062708258\ {X_1}^{1.53} X_2^{-0.59} X_7, \\
\dot{X}_2 &= \left(5.85012402\times10^{-1}\right) {X_1}^{0.95} X_2^{-0.41} X_5^{0.32} X_7^{0.62} X_{10}^{0.38} \\
&\quad - \left(7.93456\times10^{-4}\right) {X_2}^{3.97} X_3^{-3.06} X_8, \\
\dot{X}_3 &= \left(7.93456\times10^{-4}\right) {X_2}^{3.97} X_3^{-3.06} X_8 \\
&\quad - 1.05880847\ {X_3}^{0.3} X_9.
\end{aligned} \tag{17}$$

Since glycogen is experimentally kept at saturation, small changes in its amount have negligible effect on the phosphorelase a reaction in the synthesis of glucose-6-phosphate. Consequently, the dynamical system (17) is independent of X_{11} [7]. The collection of the dependent and independent variables forms the sets $\mathcal{D} = \{X_1, X_2, X_3\}$ and $\mathcal{I} = \{X_4, X_5, X_6, X_7, X_8, X_9, X_{10}\}$, respectively. The system matrix A_D related to the transformed dependent variable vector Y_D and the interaction matrix A_I associated with the dependent and independent variables are found to be

$$A_D = \begin{bmatrix} -1.53 & 0.59 & 0 \\ 0.95 & -4.38 & 3.06 \\ 0 & 3.97 & -3.36 \end{bmatrix}$$

and

$$A_I = \begin{bmatrix} 0.66 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0.32 & 0 & 0.62 & -1 & 0 & 0.38 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 \end{bmatrix},$$

respectively. The rate constant vector b and the transformed independent variable vector Y_I are computed as $b = [2.613 - 6.603\ 7.196]^T$ and $Y_I = \ln(X_I) = [2.303\ 1.609\ 1.099\ 3.689\ 4.913\ 1.051\ 1.386]^T$, respectively. The steady state of the transformed dependent variable vector is found to be $Y_D = [\text{-}2.7031\ \text{-}0.7657\ \text{-}1.8971]^T$ [7]. As a result, the dependent variable vector at the steady state is $X_D = e^{Y_D} = [0.067\ 0.465\ 0.150]^T$.

VI. Steering Steady States of GG Pathway

A. Steady-State Performance of GG Pathway

In the three-state GG pathway, the control parameter vector f is a solution of the optimization problem, discussed in Theorem 1. It is assumed that phosphorylase a (X_6), phosphoglucomutase (X_7), phosphofructokinase (X_9), and glucokinase (X_{10}) in (17), are treated as the manipulating control variables. The activity and the level of these enzymes can be regulated by the respective substrate, product and cofactors. For example, Phosphorylase a (X_6) is allostreically inhibited by glucose (X_5), G6P (X_2), ATP and pyridoxal pyrophosphate (PLP) as cofactors. On the other hand, X_7 undergoes substrate (X_1) inhibition while X_9 and X_{10} are inhibited by their products (Fructose 1,6-bisphosphate and X_2, respectively) and cofactors (ATP and citrate) [26]–[30]. The collection of these variables forms the set $\mathcal{M} \subseteq \mathcal{I}$ and the structure of the control parameter vector f can be written as follows:

$$\begin{aligned} f &= f_3\left({}^7e_3\right) + f_4\left({}^7e_4\right) + f_6\left({}^7e_6\right) + f_7\left({}^7e_7\right) \\ &= [0\ 0\ f_3\ f_4\ 0\ f_6\ f_7]^T \end{aligned} \tag{18}$$

where $f_i \in \mathbb{R}, i = 3,4,6,7$ are the control variables. In order to transfer the dependent variables $X_D = [X_1 X_2 X_3]^T$ from the nominal state $\left[e^{-2.702} e^{-0.765} e^{-1.896}\right]^T$ to the desired goal (at the steady state) $X_D'' = [X_1'' X_2'' X3'']^T = 0.75 X_D = 0.75\left[e^{-2.702} e^{-0.765} e^{-1.896}\right]^T$, the optimal variables, s_1, s_2, and f, obtained via Theorem 1, are shown in Table I, along with the relative weights w_1 and $w_2 = 1 - w_1$. The results are shown with different values of δ as 0.001, 0.01, and 0.1. The steady-state error $e_{ss}^x \in \mathbb{R}^n$ is given as follows:

$$e_{\text{ss}}^x = X_D'' - X_D' = e^{Y_D''} - e^{Y_D'} = e^{Y_D''} - e^{A_D^{-1}[b - A_I(Y_I + f)]} \tag{19}$$

where Y_D'' and f are the desired steady-state vector and the optimal control parameter vector, respectively. e_{ss}^x is the deviation among the desired goal (at the steady state), $X_D'' \in \mathbb{R}_+^n$, and the achieved steady state, $X_D' \in \mathbb{R}_+^n$ by designing the control parameter vector $f \in \mathbb{R}^m$. A biochemical engineer can choose a value of w_1 and $w_2 = 1 - w_1$ based on the specific requirement. $[w_1 w_2]^T = [01]^T$ will converge to a solution of having large bound s_1 on the perturbation sensitivity with an improved figure of the input effort bound s_2. If $[w_1 w_2]^T$ is chosen as $[10]^T$, the effect of robustness (against the perturbation in A_I) will be achieved at the cost of large bound s_2 on the input effort. The specification of δ needs to be provided based on the allowable steady-state error. A biochemical designer can independently specify the desired steady-state goal X_1'', X_2'', and X_3'' along with the tolerable steady-state error.

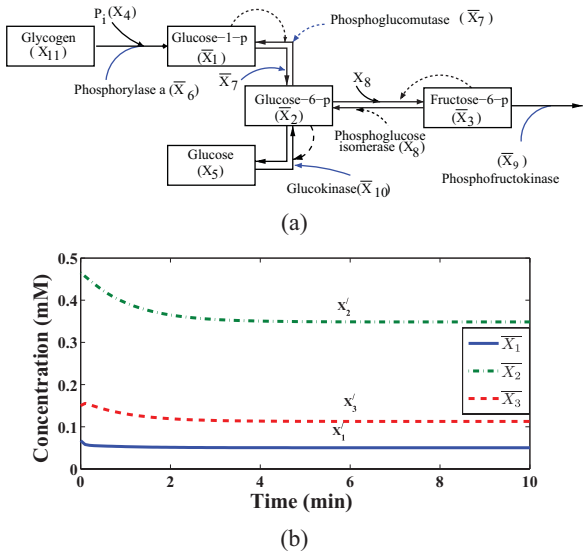

Fig. 1. (a) Biochemical map of the *synthetic* GG pathway described by (20). Blue lines signify synthetic influence. Solid blue lines and dotted blue lines signify the activation and inhibition effect, respectively. (b) Time responses of unpertubed *synthetic* GG pathway described by the dynamic variables $\overline{X}_1$, $\overline{X}_2$, and $\overline{X}_3$ in (20). The respective achieved steady-state values are X_1', X_2', and X_3'.

The S-system model of the *synthetic* 3-state GG pathway (using $f = [0\ 0\ \text{-}0.5855\ \text{-}0.3157\ 0\ \text{-}0.1803\ 0.2216]^T$ from the second row of Table I) is as follows:

$$\begin{aligned} \dot{\overline{X}}_1 &= \left(4.3368118\times10^{-2}\right) X_4^{0.66} X_6 \\ &\quad - 0.775009966\ \overline{X}_1^{1.53} \overline{X}_2^{-0.59} X_7 \\ \dot{\overline{X}}_2 &= \left(5.23274952\times10^{-1}\right) \overline{X}_1^{0.95} \overline{X}_2^{-0.41} X_5^{0.32} X_7^{0.62} X_{10}^{0.38} \\ &\quad - \left(7.93456 \times 10^{-4}\right) \overline{X}_2^{3.97} \overline{X}_3^{-3.06} X_8 \\ \dot{\overline{X}}_3 &= \left(7.93456\times10^{-4}\right) \overline{X}_2^{3.97} \overline{X}_3^{-3.06} X_8 \\ &\quad - 0.884125897\ \overline{X}_3^{0.3} X_9. \end{aligned} \tag{20}$$

The value of w_1 and δ are chosen as 0.5 and 0.001, respectively, to provide equal weight on robustness and control effort along with the stringent criterion on steady-state error. The biochemical map and the time response of $\overline{X}_1$, $\overline{X}_2$, and $\overline{X}_3$ of unperturbed three-state *synthetic* GG pathway are shown in Fig. 1. For a desired steady-state goal of $X_D'' = 0.75\,[0.067\ 0.465\ 0.150]^T = [0.0503\ 0.3488\ 0.1125]^T$, the dependent variables, $\overline{X}_1$, $\overline{X}_2$, and $\overline{X}_3$, attain a steady state of $X_D' = [0.0503\ 0.3485\ 0.1126]^T$ and offer the steady-state error of $2.710E$-04. Fig. 2(a) shows that s_1 is improving (decreasing) with its increasing weight w_1. Similarly, the input effort bound s_2 is also improving (decreasing) with its increasing weight $w_2 = 1 - w_1$. This is observed for $\delta = 0.001, 0.01, 0.1$. The norm of the achieved steady-state error $\|e_{\text{ss}}^x\|$ is found to be of one order less than the prescribed respective bound of δ in all three cases. It remains constant in the range of [0.4,1.0], if the value of δ is chosen as 0.1. Otherwise,

TABLE I
OPTIMAL SOLUTION VARIABLES OF GG PATHWAY, ($X_D'' = 0.75X_D$, $w_2 = 1 - w_1$)

w_1	δ	s_1	s_2	$f = [0 \quad 0 \quad f_3 \quad f_4 \quad 0 \quad f_6 \quad f_7]^T$	$\|e_{ss}^x\|$	s_b
0.00	0.001	458.4377	0.4092	$[0 \quad 0 \quad -0.3059 \quad -0.0350 \quad 0 \quad -0.1703 \quad -0.2089]^T$	2.843E-04	0.9247
0.50	0.001	6.8633	0.7869	$[0 \quad 0 \quad -0.5855 \quad -0.3157 \quad 0 \quad -0.1803 \quad 0.2216]^T$	2.710E-04	0.9135
1.00	0.001	6.8312	103.6807	$[0 \quad 0 \quad -0.8566 \quad -0.5869 \quad 0 \quad -0.1806 \quad 0.6632]^T$	2.867E-04	0.9102
0.00	0.01	812.3232	0.3319	$[0 \quad 0 \quad -0.2650 \quad 0.0100 \quad 0 \quad -0.1236 \quad -0.1565]^T$	0.0028	0.9305
0.50	0.01	6.8169	0.7932	$[0 \quad 0 \quad -0.6222 \quad -0.3585 \quad 0 \quad -0.2236 \quad 0.1706]^T$	0.0027	0.9081
1.00	0.01	6.7882	202.032	$[0 \quad 0 \quad -0.8961 \quad -0.6326 \quad 0 \quad -0.2261 \quad 0.6111]^T$	0.0028	0.9044
0.00	0.1	1602	0.1177	$[0 \quad 0 \quad -0.0916 \quad 0.0565 \quad 0 \quad 0.0423 \quad -0.02150]^T$	0.0113	0.9433
0.50	0.1	6.4510	1.4872	$[0 \quad 0 \quad -0.9867 \quad -0.8087 \quad 0 \quad -0.6507 \quad -0.3320]^T$	0.0267	0.8594
1.00	0.1	6.4086	97.0811	$[0 \quad 0 \quad -1.2938 \quad -1.0972 \quad 0 \quad -0.6858 \quad 0.0821]^T$	0.0278	0.8539

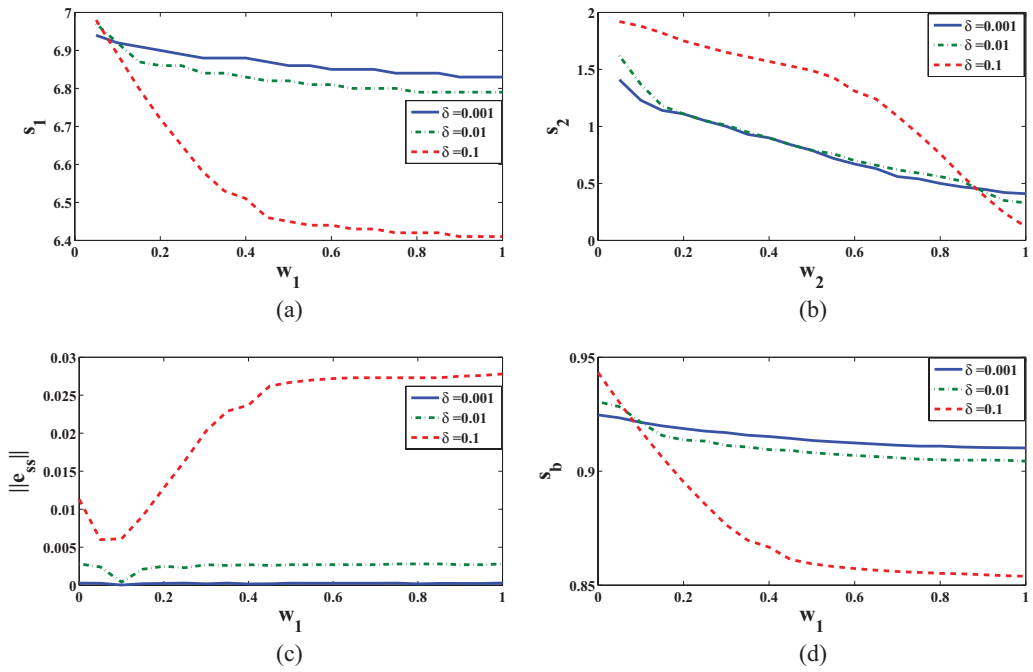

Fig. 2. (a) s_1 versus w_1 with the various values of $\delta = 0.001$ (Blue), $\delta = 0.01$ (Green), and $\delta = 0.1$ (Red). (b) s_2 versus w_2 with the various values of $\delta = 0.001$ (Blue), $\delta = 0.01$ (Green), and $\delta = 0.1$ (Red). (c) $\|e_{ss}\|$ versus w_1 with the various values of $\delta = 0.001$ (Blue), $\delta = 0.01$ (Green) and $\delta = 0.1$ (Red). (d) s_b versus w_1 with the various values of $\delta = 0.001$ (Blue), $\delta = 0.01$ (Green), and $\delta = 0.1$ (Red). The desired steady state is assumed to be $X_D'' = 0.75X_D$.

it is flat throughout the range of $0 \leq w_1 \leq 1.0$. If the value of w_1 is chosen in the range of $0 \leq w_1 \leq 0.2$, the achieved steady-state error, $\|e_{ss}^x\|$, and the required bound on control input s_2 are improved at the enhanced cost of degradation of the robustness in terms of s_1. On the contrary, if $0.8 \leq w_1 \leq 1.0$, the improved figure of robustness s_1 is achieved at the increased cost of control effort s_2. Additionally, it is observed from Fig. 2(a) that with the increasing tolerance δ in the steady-state error (keeping w_1 fixed), the value of s_1 is improving (decreasing). This signifies the enhanced robustness of the biochemical system. The same trend is observed for the δ versus control effort characteristics. Similarly, the norm of steady-state error $\|e_{ss}^x\|$ increases with the specified tolerance δ [see Fig. 2(c)], as expected. As a result, in order to achieve the desired target (goal) state, the biochemical engineer needs to suitably choose the value of δ and w_1 keeping the tradeoff between performance (steady-state error) and robustness in mind demanding minimum control effort.

B. Robustness of Synthetic GG Pathway With Parameter Perturbation

In order to study the robustness of the synthetic GG pathway, the perturbation in the interaction matrix ΔA_I is considered. The upper bound on the perturbation sensitivity S_{A_I} is computed via the perturbation sensitivity bound $S_{A_I}^b = c(A_D)s_b$, where $s_b = \frac{\|Y_I + f\|}{\|A_D\|}$ and $c(A_D) = 46.32$ [see (11)]. s_b is provided in Table I. The perturbation sensitivity bound offers an upper limit to the deviation of the dependent variables for a given norm of perturbation in the interaction matrix of the synthetic GG pathway. If the value of this bound is approaching to zero, the synthetic pathway becomes robust against the perturbation of the interaction matrix. Fig. 2(d) shows the trend of s_b for $X_D'' = 0.75X_D$. For a given bound of the steady-state error δ, s_b shows a decreasing trend (improved robustness) with increasing w_1. This is evident in all the three cases of δ. In a sense,

the value of s_b offers an approximate measure of the robustness of the GG pathway. If w_1 is considered as 0, it is equivalent to the synthesis of a biochemical system without minimizing the perturbation sensitivity, i.e., (12), sacrificing robustness. It is observed that s_b is improved (decreases) with an increasing value of the allowable steady-state error δ (0.001–0.1) throughout the range of $0.1 \leq w_1 \leq 1.0$. A biochemical engineer may choose $0.35 \leq w_1 \leq 0.65$ to meet a tradeoff between the robustness and the control effort. The value of δ may be chosen in the range of 0.01-0.05, depending on the stringent requirement on the steady-state error. One can equivalently specify the value of δ' as an allowable proportional deviation from the desired steady-state goal vector Y_D''. It is worth mentioning that the proposed optimization framework makes a tradeoff among the steady-state error and the robustness in terms of sensitivity minimization. While a larger bound is set for the steady-state error, this design offers a scope to achieve more robustness, sacrificing some performance in the steady-state accuracy.

C. Simulation Details

The optimization problem is solved using the *mincx* solver of LMI Toolbox in MATLAB software with the version 7.8.0.347 (R2009a). All time responses are generated using Power Law Analysis and Simulation (PLAS 1.2.0.120) [31] tool with the *Taylor series* method with a tolerance value of 10^{-12}.

VII. Conclusion

A robust design technique is proposed to steer steady states of biochemical networks. The proposed design formulates a multiobjective optimization framework where a tradeoff between the steady-state error and the robustness is established. An improved robustness can be achieved for a large allowable steady-state error. The robustness is defined in terms of the minimization of the perturbation sensitivity of the interaction matrix only. The proposed framework facilitates to find the reference control input for indirect control of S-system model, shown in [16]. Furthermore, in order to steer steady states, one may also apply the optimal control strategy in finite time horizon, shown in [15]; however, after the elapse of finite time horizon, a little can be inferred about the desired steady states. In this case, the design technique of this paper can be invoked in finding the control parameter vector that can be applied immediately after the finite-time horizon to hold the desired steady states. To this end, additional constraints on the control input vector may be imposed to avoid sudden jump between the value obtained from the finite-time optimal control strategy and that of the present optimization framework. As a future extension, the proposed optimization framework can be explored for synthetic biochemical networks, considering both the control input design and the modification in system structure to accomplish robustness with respect to all parameter variations and to get a fast and accurate steady-state response. Furthermore, considering redundancy in the control input design is another direction of research that can be explored as a future extension of this research.

Acknowledgment

The authors would like to thank Dr. M. Osinuga for proofreading this paper.

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