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Robust Polytopic Analysis of the Feedback-control of Glycolysis in Yeasts via some System Norms

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Abstract— **In this paper we consider a well studied model of Glycolysis in yeast cells, leading from Glucose to the end product Ethanol, via a minimal nine steps mechanism. We first linearize each step in the pathway around a given set point and we then assemble the (originally nonlinear) system as a linear system subject to various polytopic uncertainties. We study the effect of the negative feedback-loop that is internally exerted on the system. We then probe the sensitivity of the system to variations in certain variables in order to asses the possible optimality of the system in the H_2, H_∞ and the $L_2 - L_\infty$, $L_\infty - L_\infty$ senses.**

I. INTRODUCTION

The issue of robustness of biochemical pathways with respect to changes in the concentration and the rate constants of the enzymes and the substrates involved, has been studied by the seminal work of [1],[2] (see also the references therein) since the late 60's. The work [1] is included within the framework of BST (Biochemical System Theory). Another theoretical approach for studying the dynamics of biochemical pathways is the MCA (Metabolic Control Analysis) which was formulated in the mid 70's (see [3] for a comprehensive study). In the last decade a great deal of research has been conducted by many groups within the framework of "System Biology" (see [4] and the references therein).

The main difficulty in studying biochemical pathways, even relatively simple ones, is that these systems are highly nonlinear and therefore any linearization procedure does not capture the full scope of essentially important qualities such as saturation, cooperativity, etc. In this respect, the Glycolytic pathway is a natural candidate to feedback control theory analysis, being a major metabolic pathway in almost all forms of organic life.

The Glycolytic pathway has been studied extensively in several organisms both in vitro and in vivo ([5], see also [6] and the references therein). The kinetics and regulation of the enzymes involved in the pathway were studied by many research groups due to its central role in human metabolism [5]. In Figure 1,2 we bring a simple model of the Glycolytic pathway in yeasts [6]. This model was originally proposed in order to account for the possible oscillatory aspect of the pathway, as was experimentally measured. The model is composed of nine steps and it was shown to mimic successfully the measured oscillations. In this study we concentrated on the non-oscillatory behavior of the model which was also shown to yield similar results to those obtained experimentally. The non-oscillatory behavior follows a small change in one of the rate constant of the original oscillatory system.

In [7], [8], a new approach has been introduced to the study of biochemical systems, whereby the resulting systems are amenable to various tools of linear feedback-control theory. This approach starts with a simple Taylor expansion of each block of a given pathway around a pre-chosen set point. Next, the resulting linearized system is assembled as a linear one with polytopic uncertainties, [7]. Thus, one is able to better account for the nonlinearity of the system by tuning the uncertainty interval of the obtained polytope. In [8], it was shown that the optimality of the feedback loops constituting the **Threonin** Synthesis system is amenable to the H_∞ control theory measure of optimality.

In the present study we apply some of the tools we developed in [7], [8] to explore the possible optimality of the Glycolytic pathway as a feedback-control system - this time via three additional system norms. This is done in Section II. Our aim is to "track" the adequate system norm that better describes the system sensitivity to parameter uncertainties which may be caused by varying enzyme concentrations, uncertain kinetic rate constants, varying temperature, pH environment, etc.

In Section III, following the linearization of each block of the pathway, we look at the complete linearized pathway and extract the feedback gains involved in the system. We then apply, in Section V, four optimality tests to explore the sensitivity of the system to uncertainties in the kinetic rate constants of the enzymes involved. Our results clearly show that the sensitivity of the system, in the face of relatively large uncertainties, depends on the system norm that is chosen and that, probably, the H_∞ and the peak to peak norms better represent the system sensitivity in the biochemical realm.

II. OPTIMAL CONTROL OF BIOCHEMICAL SYSTEMS VIA SOME SYSTEM NORMS

In order to asses the performance of the pathway under study, we apply four optimality measures which include the H_2, H_∞ (the induced L_2 norm) and the $L_2 - L_\infty$ (energy to peak) and $L_\infty - L_\infty$ (peak to peak, L_1) system norms. We repeat here, for the sake of clarity, the major tools with which we probe the optimality of the system, in the face of

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parameters uncertainties, via the H_∞ optimal criterion [8]. We then bring three propositions that deal with the other system norms used in our study.

A. H_∞ Optimal control

This measure relates to the attenuation level of an arbitrary (energy bounded) disturbance in the system.

In this context, we consider the following H_∞ performance index:

$$J = \int_0^\infty (x^T(Q + C^T K^T RKC)x - \gamma^2 w^T w)dt, \qquad (1)$$

applied to a dynamic system described by the following state-space model.

$$\dot{x} = \tilde{A}x + B_1 w, \; \tilde{A} = A + B_2 KC, \qquad x(0) = 0. \qquad (2)$$

The latter model describes a closed-loop system with a static output-feedback gain matrix K. It will be shown below that nature indeed applies such a feedback in the given Glycolytic pathway.

In our case, the vector x represents the concentrations of the various metabolites in the pathway, the matrix C is a two row matrix and B_2 is composed of two columns. The matrices Q and R in (1) represent the different weighting we put on the metabolic concentration and the control effort. Choosing $Q = qI_n$, where q is a scalar in the interval $[0 \quad 0.001]$ (if not otherwise stated), and $R = I_9$, the corresponding H_∞ -norm of the pathway is calculated for the known K.

For the above choice of Q and R, the H_∞ -norm from the disturbance input w to the system output is obtained by seeking a positive definite matrix P that satisfies the following Linear Matrix Inequality (LMI) for a minimum value of $0 < \gamma$.

$$\begin{bmatrix} \Upsilon + \Upsilon^T + qI_n + C^T K^T RKC & PB_1 \\ * & -\gamma^2 I \end{bmatrix} < 0, \qquad (3)$$

where $\Upsilon = P(A + B_2 KC)$.

It is readily seen that the latter LMI always has a solution, in the case where the system with the given static output-feedback is stable, for large enough γ if the pair (A, C) is observable (we simply obtain then a Lyapunov inequality).

The LMI of (3) refers to the nominal case where the various enzyme concentrations are known constants. In the uncertain case, which stems either from the above 'virtual uncertainty' that better fits the nonlinear nature of the problem, or from actual uncertainty in the enzymes' kinetic constants and concentrations, the matrix P is sought such that the following LMIs are satisfied for the minimum γ.

$$\begin{bmatrix} \tilde{\Upsilon}_j + \tilde{\Upsilon}_j^T + qI + C^T K^T KC & PB_{1j} \\ * & -\gamma^2 I \end{bmatrix} < 0, \quad j = 1, .., L. \qquad (4)$$

In these LMIs the index j refers to the j-th vertex of the uncertainty polytope (all together we have L vertices) and $\tilde{\Upsilon}_j = P(A_j + B_2 KC)$. In our case the uncertain parameters appear in the matrices A and B_1 and for simplicity we seek a single $0 < P$ (the quadratic solution) which satisfies all the L LMIs for the minimum value of γ. The latter solution may be conservative and some non quadratic solutions are suggested in the literature that reduce the entailed conservatism.

B. H_2 Optimal control

The following result gives a sufficient condition for the H_2-norm of the system (2) to be finite [9]:

Proposition 1: Consider (2) where $\tilde{A}$ is Hurwitz. If there exists $P > 0$, and Z such that

$$\begin{bmatrix} P\tilde{A} + \tilde{A}^T P & PB_1 \\ * & -\gamma I \end{bmatrix} < 0, \; \begin{bmatrix} P & C^T \\ * & Z \end{bmatrix} > 0, \text{trace(Z)} < \gamma, \qquad (5)$$

then the H_2 norm of the system is finite.

C. Energy to peak ($L_2 - L_\infty$) Optimal control

The following result gives a sufficient condition for an upper-bound γ of the energy to peak gain of the system (2) [9]:

Proposition 2: Consider (2) where $\tilde{A}$ is Hurwitz. If there exists $P > 0$ such that

$$\begin{bmatrix} P\tilde{A} + \tilde{A}^T P & PB_1 \\ * & -I \end{bmatrix} < 0, \; \begin{bmatrix} P & C^T \\ * & \gamma I \end{bmatrix} > 0, \qquad (6)$$

then the $L_2 - L_\infty$ norm of the system is smaller than γ.

D. Peak to peak ($L_\infty - L_\infty$) Optimal control

The following result gives a sufficient condition for an upper-bound γ of the peak to peak gain of the system (2) [9]:

Proposition 3: Consider (2) where $\tilde{A}$ is Hurwitz. If there exists $P > 0$, $\lambda > 0$ and $\mu > 0$ such that

$$\begin{bmatrix} P\tilde{A} + \tilde{A}^T P + \lambda P & PB_1 \\ * & -\mu I \end{bmatrix} < 0, \; \begin{bmatrix} \lambda P & 0 & C^T \\ * & (\gamma - \mu)I & 0 \\ * & * & \gamma I \end{bmatrix} > 0, \qquad (7)$$

then the peak to peak (or L_∞) induced norm of the system is smaller than γ.

We note that similarly to the uncertain polytopic case of the H_∞ system norm, the uncertain cases for the other systems norms are treated as in (4).

III. THE LINEARIZED MINIMAL MODEL OF YEAST GLYCOLYTIC PATHWAY

In [6] a minimal model description of the Yeast Glycolytic pathway is developed. There, the nonlinear system rate equations are:

$$\begin{aligned} \dot{S}_1 &= J_0 - v_1, \\ \dot{S}_2 &= v_2 - v_1, \\ \dot{S}_3 &= 2v_2 - v_3 - v_8, \\ \dot{S}_4 &= v_3 - v_4, \\ \dot{S}_5 &= v_4 - v_5, \\ \dot{S}_6 &= v_5 - v_6 - J, \\ \dot{S}_6^{ex} &= \phi J - v_9, \\ \dot{A}_3 &= -2v_1 + v_3 + v_4 - v_7, \\ \dot{N}_2 &= v_3 - v_6 - v_8, \end{aligned} \qquad (8)$$

with the following system velocities:

$$
\begin{aligned}
J_0 &= \text{constant},\\
v_1 &= k_1 S_1 A_3 f(A_3),\\
v_2 &= k_2 S_2,\\
v_4 &= k_4 S_4 (A - A_3),\\
v_5 &= k_5 S_5,\\
v_6 &= k_6 S_6 N_2,\\
v_7 &= k_7 S_3,\\
v_8 &= k_8 S_3 N_2,\\
v_9 &= k_9 S_6^{ex},
\end{aligned}
\tag{9}
$$

where the kinetic constants of the system are given in the following table:

Parameter	Value
J_0	$50\ mM\ min^{-1}$
k_1	$550.0\ mM^{-1}\ min^{-1}$
K_i	$1.0\ mM$
k_2	$9.8\ min^{-1}$
k_{GAPDH+}	$323.8\ mM^{-1}\ min^{-1}$
k_{GAPDH-}	$57823.1\ mM^{-1}\ min^{-1}$
k_{PGK+}	$76411.1\ mM^{-1}\ min^{-1}$
k_{PGK-}	$23.7\ mM^{-1}\ min^{-1}$
k_4	$80.0\ mM^{-1}\ min^{-1}$
k_5	$9.7\ min^{-1}$
k_6	$2000.0\ mM^{-1}\ min^{-1}$
k_7	$28.0\ min^{-1}$
k_8	$85.7\ mM^{-1}\ min^{-1}$
κ	$375.0\ min^{-1}$
ϕ	0.1
A	$4\ mM$
N	$1.0\ mM$
n	4

Table 1: Values of the enzymatic kinetic rate constants and additional parameters of the 9 variable model of Yeast Glycolysis taken from [6].

Following linearization of each of the rate equations of (8) we are able to assemble the complete linearized pathway, where the feedback loop around the first step of the system is explicitly exerted in the system via its dependence on ATP. We obtain the following state space realization for the linearized pathway:

$$
\tfrac{d}{dt}\bar{P} = A\bar{P} + B\delta_{-1}(t), \quad \bar{P} = col\{\bar{P}_1, ..., \bar{P}_9\} \tag{10}
$$

where $\overline{A}$ denotes the deviation of some metabolite A from its initial value (for example, $\overline{Glucose} = Glucose(t=0) - Glucose(t)$), δ_{-1} denotes a unity step function and where:

$$
\begin{aligned}
\bar{P}_1 &= \overline{Glucose}\\
\bar{P}_2 &= \overline{Fructose - 1,6\ biphosphate}\\
\bar{P}_3 &= \overline{Triophosphates\ pool}\\
\bar{P}_4 &= \overline{3 - Phosphoglycerate}\\
\bar{P}_5 &= \overline{Pyruvate}\\
\bar{P}_6 &= \overline{acetaldehyde\ in\ the\ cell;}\\
\bar{P}_7 &= \overline{extracellular; acetaldehyde}\\
\bar{P}_8 &= \overline{ATP}\\
\bar{P}_9 &= \overline{NADH}
\end{aligned}
,
$$

where

$$
A = \begin{bmatrix}
\alpha_1 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_2 & 0\\
-\alpha_1 & \beta_1 & 0 & 0 & 0 & 0 & 0 & -\alpha_2 & 0\\
0 & -2\beta_1 & \chi_1 & \chi_2 & 0 & 0 & 0 & \chi_3 & \chi_4\\
0 & 0 & \gamma_1 & \gamma_2 & 0 & 0 & 0 & \gamma_3 & \gamma_4\\
0 & 0 & 0 & \delta_1 & \delta_2 & 0 & 0 & \delta_3 & 0\\
0 & 0 & 0 & 0 & -\delta_2 & \epsilon_1 & \epsilon_2 & 0 & \epsilon_3\\
0 & 0 & 0 & 0 & 0 & \varphi_1 & \varphi_2 & 0 & 0\\
2\alpha_1 & 0 & \gamma_1 & \gamma_2 & 0 & 0 & 0 & \eta_1 & \gamma_4\\
0 & 0 & -\chi_1 & -\chi_2 & 0 & \iota_1 & 0 & -\chi_3 & \iota_2
\end{bmatrix},
\tag{11}
$$

$$
B = \begin{bmatrix}
J_0 - V_{1,0}\\
V_{1,0} - V_{2,0}\\
2V_{2,0} - V_{3,0} - V_{8,0}\\
V_{3,0} - V_{4,0}\\
V_{4,0} - V_{5,0}\\
V_{5,0} - V_{6,0} - J\\
\varphi J - V_{9,0}\\
-2V_{2,0} + V_{3,0} + V_{4,0} - V_{7,0}\\
V_{3,0} - V_{6,0} - V_{8,0}
\end{bmatrix},
$$

where the various entries (i.e., $\alpha_1, \alpha_2,\ ...\ \iota_1..$) in (11) were obtained by the linearization (omitted here due to space limitations) and $V_{i,0}$ denotes the given initial velocity of the rate equation of metabolite i of the system based on the initial values of the system metabolites given in Table 2 in the sequel.

Adding a disturbance w in the concentration of the metabolites, it is readily seen that the model of (10) can be represented by the following static output feedback model.

$$\frac{d}{dt}\bar{P} = (\tilde{A} + B_2KC)\bar{P} + B\delta_{-1}(t) + B_1w(t), \qquad \text{(12a-e)}$$

where

$$\tilde{A} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -2\beta_1 & \chi_1 & \chi_2 & 0 & 0 & 0 & \chi_3 & \chi_4 \\ 0 & 0 & \gamma_1 & \gamma_2 & 0 & 0 & 0 & \gamma_3 & \gamma_4 \\ 0 & 0 & 0 & \delta_1 & \delta_2 & 0 & 0 & \delta_3 & 0 \\ 0 & 0 & 0 & 0 & -\delta_2 & \epsilon_1 & \epsilon_2 & 0 & \epsilon_3 \\ 0 & 0 & 0 & 0 & 0 & \varphi_1 & \varphi_2 & 0 & 0 \\ 0 & 0 & \gamma_1 & \gamma_5 & 0 & 0 & 0 & \eta_1 & \gamma_4 \\ 0 & 0 & -\chi_5 & -\chi_2 & 0 & \iota_1 & 0 & -\chi_3 & \iota_2 \end{bmatrix}$$

$$B_2 = \begin{bmatrix} 1 & 1 \\ -1 & -1 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 4 & 0 \\ 0 & 0 \end{bmatrix}, C^T = \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}, K = \begin{bmatrix} 0.5\alpha_1 & 0 \\ 0.5\alpha_1 & \alpha_2 \end{bmatrix},$$

The model of (12) reveals a feedback loop which is exerted on the first step of the pathway via ATP. In order to asses the effect of this loop, we consider the above step disturbance at the entry to the Glycolysis system. In fact, a disturbance signal can be applied to any of the system metabolites.

IV. THE RESEARCH PROCEDURE

We first linearize the system around the steady state-level values given in [6] and obtain the system coefficients (i.e., $\alpha_1, ..\beta_1, \gamma_1 ...\delta_1$ and so on). We thus derive also the control gain K of (12e). Applying simulations of the response of the linearized system and comparing the results with those obtained for the original nonlinear system shows that the approximation by the linear model is very good. We then apply the optimality measures of Section II. That is, we seek, for a given interval, say $q \in [0 \;\; 0.001]$ and $R = I_9$, a minimal value for γ for the cases of H_∞, $L_2 - L_\infty$ and $L_\infty - L_\infty$ system norms and an upper-bound for the H_2 norm. We apply these measure to probe the closed-loop system sensitivity to uncertainties in several enzymes of the pathway. For each uncertain kinetic rate constant of an enzyme, a set of two LMIs should be solved, each corresponds to edge point of the uncertainty interval. An uncertainty of ±40% in k_2 (which leads from S_1 to S_2 in Figure 1), for example, is taken as an interval of $[0.6V_{k_2} \;\; 1.4V_{k_2}]$ where its nominal value is given in Table 1 [6].

V. NUMERICAL RESULTS

We have probed the system behavior by looking at its time domain dynamics and by considering its optimal behavior for different set points. Nearly identical results were obtained for all the cases examined. In this section we bring various results which correspond to the initial concentration given in Table 2 and for 90% disturbance, namely of magnitude of 90% of its initial concentration of the Glucose flux. In all the tests we obtain the system of (12) with the following matrices

$$\tilde{A} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.1633 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0.3267 & -3.3037 & 0.1266 & 0 & 0 & 0 & 0.1984 & 2.4558 \\ 0 & 0 & 2.7181 & -2.5399 & 0 & 0 & 0 & 0.6816 & -3.2413 \\ 0 & 0 & 0 & 2.4133 & -0.1617 & 0 & 0 & -0.8800 & 0 \\ 0 & 0 & 0 & 0 & 0.1617 & -19.9167 & 6.2500 & 0 & -2.6667 \\ 0 & 0 & 0 & 0 & 0 & 0.6250 & -1.9583 & 0 & 0 \\ 0 & 0 & 2.7181 & 2.2867 & 0 & 0 & 0 & -3.3397 & -3.2413 \\ 0 & 0 & 2.1325 & -0.1266 & 0 & -13.6667 & 0 & -0.1984 & -6.6936 \end{bmatrix}, \qquad (13)$$

where B_2 and C are given in (12c,d) and where the gain matrix is $K = \begin{bmatrix} -7.8175 & 0 \\ -7.8175 & -0.8973 \end{bmatrix}$. The initial values of the system metabolites are given in Table 2.

metabolite	steady-state concentration (mM)
S_1	1.09
S_2	5.10
S_3	0.55
S_4	0.66
S_5	8.31
S_6	0.08
S_6^{ex}	0.02
A_3	2.19
N_2	0.41

Table 2: Initial values of the Glycolytic metabolites.

Applying a disturbance at the entry of Glucose, we obtain the following disturbance matrix:

$$B_1^T = \begin{bmatrix} 2.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

We start by taking $Q = qI_9$, where q is a positive scalar in the feasibility interval [0 0.001] and a control effort weight of $R = I_9$. For the nominal system we obtain an H_∞ minimum disturbance attenuation level of $\gamma = 5.69$. Similarly we obtain for the $L_2 - L_\infty$ and $L_\infty - L_\infty$ minimal values of $\gamma = 4.75$ and $\gamma = 13.76$, respectively. The obtained upper-bound of the H_2 norm is 5.33. Next, we keep the same nominal gain matrix of $K = \begin{bmatrix} -7.8175 & 0 \\ -7.8175 & -0.8973 \end{bmatrix}$ and introduce various uncertainty levels in several of the enzymes kinetic constants: $k_1,\ k_2,\ k_5,\ k_6$ and k_7. In Tables 3,4, we bring the results of the various tests.

Case	Uncer. Par.	H_2	H_∞	L_2-L_∞	$L_\infty-L_\infty$
0	nominal	5.33	5.69	4.75	13.76
1	$(k_1 \pm 10\%)$	5.60	8.22	4.75	17.16
2	$(k_1 \pm 25\%)$	8.0	45.29	6.45	63.6
3	$(k_1 \pm 80\%)$	n.f	n.f	n.f	n.f
4	$(k_5 \pm 50\%)$	5.43	6.21	4.73	17.12
5	$(k_5 \pm 80\%)$	5.64	7.39	4.74	27.66
6	$(k_6 \pm 50\%)$	5.35	5.81	4.73	13.89
7	$(k_6 \pm 80\%)$	5.35	5.81	4.73	13.89
8	$(k_7 \pm 25\%)$	5.48	7.08	4.74	15.49
9	$(k_7 \pm 50\%)$	5.74	9.61	4.75	18.98
10	$(k_7 \pm 80\%)$	6.51	18.36	4.87	31.04
11	$(J_0 \pm 25\%)$	5.33	5.69	4.75	13.76
12	$(J_0 \pm 80\%)$	5.33	5.69	4.75	13.76

Table 3: Optimal analysis results for various uncertainties in the system kinetic constants. Shown are the minimal attenuation levels of γ for the feasibility interval of $q \in [0\ 0.001]$ for the $H_\infty,\ L_2 - L_\infty$ and the $L_\infty - L_\infty$ system norms, and for the upper bound on the H_2 norm. In all these tests the same feedback gain and initial values are kept constants. Uncer. Par. stands for uncertain parameter and n.f for non feasible.

In Table 3, for each row (test) we keep the same feedback controller K and the same system kinetic constants, save those indicated in the table. Thus for case 1 in Table 3, only k_1 was changed in the interval $[0.9k_1\ \ 1.1k_1]$. The results were obtained for the feasibility interval of $q \in [0\ \ 0.001]$ and the given values of Tables 1 and 2, where in each test the response of the linearized system was compared to the one of the original non linearized system. Only cases where the two responses were identical within a tolerance 5% were considered. Case 0 in the table brings the various attenuation levels for the nominal case (i.e without uncertainties). It is shown that in all the cases relating to the various uncertainties (Cases 1-12), the H_2 norm is insensitive to the system parameter uncertainties. The same behavior is also observed for the $L_2 - L_\infty$ measure. On the other hand, the H_∞ and the peak to peak ($L_\infty - L_\infty$) attenuation levels were sensitive to some of the system uncertainties even for mild changes (see for example Cases 1-3 and 8-10). We note that some of the system kinetic rate constants were actually estimated based on relevant kinetic data that are found in the literature [6]. A 50% uncertainty in an estimated kinetic constant of an enzyme is usually considered to be a good approximation. Note that in some cases the uncertainty in the value of an enzymatic kinetic constant may amounts to several folds [10], [5]. It is interesting to try to track the **adequate system norm** which is suitable for probing the sensitivity of the system. In biochemical systems, which are the backbone of life, metabolism is confined within cells and within various compartments in the cells (for example: the nucleus and other internal organelles). Metabolic pathways are always intertwined via the energy sources (i.e ATP and similar molecules) and their redox capacity. The prevalent case is that some metabolite that ”belongs” to a certain pathway (say Glycolysis) is also an intermediate in other pathways. The inflow of such a metabolite from one pathway to a second one affects the transient and steady state- behaviors of both pathways, therefore the peak to peak norm may be - probably in some of the cases - a proper norm to probe the robustness of the given feedback system. It is also possible that the H_∞ optimal criteria may be suitable for sensitivity probing of the system as was shown in the case of Threonin Synthesis system in [8].

Case	Uncer. Par.	L_2-L_∞	H_∞	$L_\infty-L_\infty$
0	nominal	4.75	5.69	13.76
1	$(k_2, k_6) \pm 25\%$	4.74	6.88	15.59
2	$(k_2, k_6) \pm 50\%$	4.75	8.89	20.24
3	$(k_2, k_6) \pm 80\%$	$n.f$	n.f	n.f
4	$(k_2, k_7) \pm 25\%$	4.75	8.37	17.91
5	$(k_2, k_7) \pm 50\%$	4.90	14.79	29.92
6	$(k_2, k_7) \pm 80\%$	$n.f$	n.f	n.f
7	$(k_5, k_7) \pm 25\%$	4.74	7.36	16.74
8	$(k_5, k_7) \pm 50\%$	4.77	10.65	23.52
9	$(k_5, k_7) \pm 80\%$	5.86	24.56	57.04

Table 4: Optimal analysis results for various uncertainties in deferent pairs of the system kinetic constants. Shown are the minimal attenuation levels of γ for the feasibility interval of $q \in [0\ 0.001]$ for the $H_\infty,\ L_2 - L_\infty$ and the $L_\infty - L_\infty$ system norms. In all these tests the same feedback gain and initial steady state values are kept constants. Uncer. Par. stands for uncertain parameter and n.f for non feasible.

In order to further probe the latter behaviors of the system norms, we applied the procedure leading to Table 3, to pairs of kinetic constants which were chosen according to their biochemical role. Again, in Table 4 the same picture emerges as in Table 3 (note that the H_2 test is missing having the same tendency as the $L_2 - L_\infty$). Note that in cases 3, 6, the linearized system behavior deviated from the nonlinear one, therefore these cases were ruled out. Similar results to those reported in Tables 3, 4 were obtained for different values of the control effort R and feasibility interval of q.

VI. CONCLUSIONS

In this work we apply control theory tools to asses the sensitivity of the yeast Glycolytic pathway as presented via the minimal model of [6], in the $H_2,\ L_2 - L_\infty,\ L_\infty - L_\infty$ and the H_∞-norm senses, to various enzymatic kinetic rate constants uncertainties of the system, given a disturbance in the system input Glucose. The H_2 norm test is also applied and was shown to largely agree with the $L_2 - L_\infty$ results.

Following a simple Taylor expansion of the system kinetics, we obtain a linear model for the system from which we derive the nominal controller gain matrix. We then apply the various optimality tests to various uncertainties in the system. The numerical results that were obtained clearly suggest that the nominal controlled system (i.e with the nominal controller) is sensitive to the various enzyme kinetic constants uncertainties that were examined, judging via the H_∞ and the $L_\infty - L_\infty$ norms . It was also shown that the sensitivity of the system to kinetic uncertainties is not similar for all the enzymatic kinetic constants that were tested.

The main finding of this study points at the issue of the adequate input-output relation in the system that better represents the sensitivity of the system to parameter uncertainties. It is interesting that both the H_∞ and the $L_\infty - L_\infty$ system norms have similar tendencies. It may be that the system "seeks" a worst disturbance attenuation while "engaging" in the peak to peak input-output relation. Clearly, the results achieved in this study indicate the need for a further research of additional important issues such as the relative significance of the various negative loops that were missing in the minimal model of [6].

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