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Feedback Linearization and Optimal Control-based Approach for Steering Steady-States of Nonlinear Biochemical Networks

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***Abstract*—Biochemical networks normally operate in the neighbourhood of its steady-state which may be of multiple in number. It may reach from one steady-state to other within a finite time. In this paper, it is shown how the biochemical network reaches to a desired steady-state within optimal time and energy, with positive control input. Control signals i.e., the independent state variables in the network, are found in two steps. The first step is designed for steering biochemical network to a desired state within a finite time and then, in the second step, the steered state is preserved as a steady-state of the network. In the first step, the synergism and saturation system, commonly known as S-system, is transformed to the linear controllable Brunovsky Canonical form using feedback linearization and then the optimal control theory is used to find optimal control input. In second step, the control inputs are found from steady-state equations for the new steady-state. In this article, it is shown how to select control inputs so that, biochemical network will reach to a desired steady-state applying a feasible control input profile instead of designing a complex feedback path.**

***Index Terms*—Controllability, Feedback linearzation, Hamiltonian function, S-system, Glycolysis, Glycogenolysis.**

I. Introduction

Due to the environmental and genetic changes, growth rate of cells is time-varying. In some biochemical systems, it is required to coordinate the cell growth. Nowadays, due to availability of high throughput data, the biochemical networks can be modelled as a system of ordinary differential equations. Natural biochemical network is robust [1], [2]. The steady-state behaviour of the biochemical network is studied by Chen et al. [3]. The regulation of the transient behaviour is also an important issue in biochemical network. Model predictive control (MPC) algorithm is developed in [4] that directly guides the target variables to their desired values. The controllability of biochemical network is shown in [5]. To choose a combination of control inputs and design it properly for optimally reach to a desired state is a major challenge now. The objective of this article is to selecting control input combination to steer the biochemical system to a new steady-state.

The cellular and intracellular metabolite processes are collection of enzymatic reaction. There are various models to study the biochemical pathways. Among these, the S-system, [3], [6], referring to the synergism and saturation properties of biochemical network, is one of the most popular model. The general equation describing the temporal changes in a biochemical system can be formulated as

$$\dot{x}_i{=}\alpha_i \prod_{j=1}^{n+m} x_j^{g_{ij}} - \beta_i \prod_{j=1}^{n+m} x_j^{h_{ij}}, i{=}1, 2, \cdots, n \qquad (1)$$

where $n{>}0$, $m{\geq}0$ and $x_1,\ x_2, \cdots, x_{n+m}{\geq}0$ are the concentrations of metabolites, such as substrates and products of the biochemical pathways. $x_i, i{=}1, \cdots, n$ denote n dependent variables. The independent variables $x_j, j{=}n{+}1, ..., n{+}m$ may act as 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, $\alpha_i{\geq}0$ and $\beta_i{\geq}0$ are the production and the degradation rate constants respectively. Each variable x_j is raised to the power by kinetic parameters g_{ij} and/or h_{ij}, which are known as kinetic orders of the S-system.

A Feedback linearization technique is described in the following section to linearize the nonlinear biochemical network. The contributions of this paper are (1) finding possible combination of independent variables to acheive a desired steady-state, and (2) steering the biochemical network to a desired steady- state with positive control input.

II. Classical Feedback Linearization

Following two are required to understand classical feedback linearization. Let $\mathbb{R}$ denote the set of all real numbers and $\mathbb{R}^{m\times n}$ be the set of all real matrices with m rows and n columns.

Definition Let $g_1(X)$, $g_2(X)$,..., $g_k(X)$ be k number of n-dimensional vector fields that form a matrix

$$G{=}[g_1(X)\ g_2(X)\ \cdots\ g_k(X)] \qquad (2)$$

If the matrix has rank k at $X{=}X_0$ and the augmented matrix

$$[g_1(X)\ g_2(X)\ ...\ g_k(X)\ \ [\ g_i(X),\ g_j(X)]]$$

has the same rank at $X{=}X_0$ for any arbitrary index pair (i, j) with $1 \leq i,\ j \leq k$, then the vector field set $\{g_1, g_2, ..., g_k\}$ is called involutive [5].

The nonlinear system is converted to linear approximation around an operating point, then the wider control methodology for linear system is applied there. But, this type of control methodology works only in neighbourhood of the equilibrium point. This problem can be mostly overcome by feedback linearization technique. The transformed linear system works in larger operating region. After the classical feedback linearization, the transformed system is in the Brunovsky Canonical form [7] . This type of transformation is possible only for input-affine nonlinear systems. Consider an input-affine nonlinear system

$$\dot{X} = f(X){+}g(X)u{=}f(X){+}\sum_{i=1}^{m} g_i(X)u_i \tag{3}$$

where $X{\in}\mathbb{R}^n$ denotes the state, $u{\in}\mathbb{R}^m$ is the control input, and $f(X), g_1(X), \cdots, g_m(X)$ are smooth vector fields defined on an open subset of $\mathbb{R}^n$. Affine non-linear systems are linearizable if and only if they satisfy certain conditions. Choosing an index number $m{=}n_1 \geq n_2 \geq \cdots \geq n_N$, $\sum_{i=1}^{N} n_i{=}n$, where m and n are the number of inputs and the order of the system respectively, a set of necessary and sufficient conditions for a multi-input system (3) is as follows.

(i) The following n sets of vector fields

$$\begin{aligned}
&D_1{=}\{g_1\}\\
&\cdots\cdots\\
&D_{n_1}{=}\{g_1, g_2, \cdots, g_{n_1}\}\\
&D_{n_1+1}{=}\{D_{n_1}; ad_f g_1\}\\
&\cdots\cdots\\
&D_{n_1+n_2}{=}\{D_{n_1}; ad_f g_1, \cdots, ad_f g_{n_2}\}\\
&\cdots\cdots\\
&D_n{=}\left\{D_{n-n_N}; ad_f^{N-1} g_1, \cdots, ad_f^{N-1} g_{n_N}\right\}
\end{aligned}$$

are involutive near the equilibrium state, x_0 of (3), where $ad_f^k g_i(X)$ is the k^{th} order Lie bracket defined as $ad_f^k g_i(X){=}\left[f(X),\ ad_f^{k-1} g_i(X)\right]$ and $ad_f^0 g_i(X){=}g_i(X)$.

(ii) The matrix D_n is nonsingular at the point x_0 The feedback linerization algorithm is shown step by step in [5]. In next section Glycolysis and Glycogenolysis pathway will be linearized, considering possible combination of control inputs those are satisfying necessary and sufficient conditions for feedback linearization.

III. Example: Glycolysis and Glycogenolysis Pathway

The nominal dynamical equation of the S-system model of the Glycolysis and Glycogenolysis pathway is as follows:

$$\begin{aligned}
\dot{x}_1 &= \left(7.78843 \times 10^{-2}\right) {x_4}^{0.66} x_6 {-} 1.0627082 x_1^{1.53} x_2^{-0.59} x_7,\\
\dot{x}_2 &= \left(5.85012402 \times 10^{-1}\right) {x_1}^{0.95} x_2^{-0.41} x_5^{0.32} x_7^{0.62} x_{10}^{0.38}\\
&\quad - \left(7.93456 \times 10^{-4}\right) {x_2}^{3.97} x_3^{-3.06} x_8,\\
\dot{x}_3 &= \left(7.93456 \times 10^{-4}\right) {x_2}^{3.97} x_3^{-3.06} x_8 {-} 1.05880847\ {x_3}^{0.3} x_9.
\end{aligned} \tag{4}$$

where the dependent variables are x_1, x_2, and x_3. The independent variables have the nominal values $x_4{=}10$, $x_5{=}5$, $x_6{=}3$, $x_7{=}40$, $x_8{=}136$, $x_9{=}2.86$, $x_{10}{=}4$ [6].

A. Selection of Control Input Combination

The independent variables x_6, x_7, x_9 and x_{10} are enzymatic control variables in (4). Among them $[x_6\ x_9]^T$, $[x_6\ x_{10}]^T$ and $[x_6\ x_9\ x_{10}]^T$ are the possible combinations as they are satisfying necessary and sufficient conditions for feedback linearization [5] . To achieve a new steady-state, at least one control variable should be on the right hand side of the each differential equation of (4), at steady-state $\dot{x}_i{=}0$ for $i{=}1,\ 2,\ 3$. $[x_6\ , x_9\ x_{10}]^T$ is only possible combination of control variables to steer the system to a new steady-state.

B. Exact Linearization

It is possible to use three controls upon embeding the system (4) in a four-dimensional space by defining an auxiliary variable, x_{a4} such as the integrall of x_1 , which is given in differential form as $\dot{x}_{a4} = x_1$. Now, for control input $u_1 = x_6$, $u_2 = x_{10}^{0.38}$ and $u_3 = x_9$, the system (4) becomes

$$\dot{X} = f(X) + \sum_{i=1}^{3} g_i(X)u_i, \tag{5}$$

where $f(X) = \begin{bmatrix} -42.5083\ x_1^{1.53} x_2^{-0.59} \\ -0.1079 {x_2}^{3.97} x_3^{-3.06} \\ 0.1079 {x_2}^{3.97} x_3^{-3.06} \\ x_1 \end{bmatrix}$

$g_1(X) = [0.356\ \ 0\ \ 0\ \ 0]^T$,

$g_2(X) = \begin{bmatrix} 0 & 9.6408 {x_1}^{0.95} x_2^{-0.41} & 0 & 0 \end{bmatrix}^T$,

$g_3(X) = \begin{bmatrix} 0 & 0 & -1.058808 x_3^{0.3} & 0 \end{bmatrix}^T$.

With the following linearization steps described in [5], the transformed variables, $z_i, i{=}1, 2, 3, 4$, will be as follows:

$$Z{=}T(X){=}\begin{bmatrix} x_1 \\ x_2 - x_3 \\ x_3 - x_{a4} \\ x_{a4} \end{bmatrix} \tag{6}$$

where, $Z = [z_1\ z_2\ z_3\ z_4]^T$, $X = [x_1\ x_2\ x_3\ x_{a4}]^T$. The $Z{=}T(X)$ is a diffeomorphism transformation. The feedback

control inputs become

$$u_1 = 2.80899(v_1 + 42.5083x_1^{1.53}x_2^{-0.59})$$
$$u_2 = 0.103726x_1^{-0.95}x_2^{0.41}(v_2 + v_3 + 0.1079x_2^{3.97}x_3^{-3.06} + x_1)$$
$$u_3 = -0.944459x_3^{-0.3}(v_3 - 0.1079x_2^{3.97}x_3^{-3.06} + x_1) \quad (7)$$

Then the affine nonlinear control system (5) is converted into a linearized controllable Brunovsky canonical form as follows,

$$\dot{z}_1 = v_1,$$
$$\dot{z}_2 = v_2,$$
$$\dot{z}_3 = v_3,$$
$$\dot{z}_4 = z_1. \quad (8)$$

where z_1, z_2, z_3, and z_4 are transformed states and v_1, v_2 and v_3 are virtual control inputs. The schematic is shown in Fig. 1. Optimal vertual control input is designed in next section to steer one state to another of system (8).

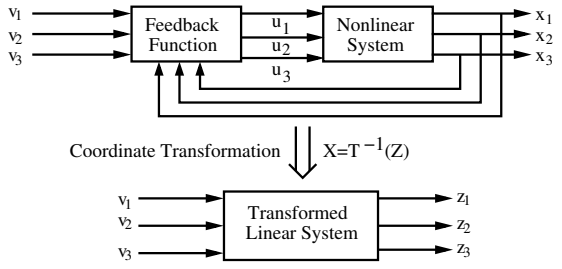


Fig. 1. Schematic diagram of feedback linearization

IV. Determination of Optimal Control Inputs for Steering States

The optimal control inputs v_1 , v_2 and v_3 of the system (4) are found by minimizing the cost function:

$$J = \frac{1}{2}\int_{t_0}^{t_f}(v_1^2 + v_2^2 + v_3^2)\,\mathrm{d}t.$$

The Hamiltonian is defind as [8]

$$H(t, Z, v, \lambda) = \tfrac{1}{2}(v_1^2 + v_2^2 + v_3^2) + \lambda_1(t)v_1(t) + \lambda_2(t)v_2(t) + \lambda_3(t)v_3(t) + \lambda_4(t)z_1(t)$$

where, λ_1, λ_2, λ_3, and λ_4 are the costates of the Hamiltonian system.

Using Pontryagin's minimum principle, the necessary conditions for the optimal control input is

$$(\frac{\partial H}{\partial v_i})_* = 0,\ i{=}1,2,3.$$
$$(\frac{\partial H}{\partial z_j})_* = -\dot{\lambda}_j^*(t),$$
$$(\frac{\partial H}{\partial \lambda_j})_* = \dot{z}_j^*(t),\ j{=}1,2,3,4.$$
$$[H^* + (\frac{\partial S}{\partial t})_*]_{t_f}\delta t_f + [(\frac{\partial S}{\partial Z})_* - \lambda^*(t)]_{t_f}^T\delta Z_f = 0. \quad (9)$$

where * denotes the optimal operating point. S is the final cost, considerd as zero and $\lambda(t) = [\lambda_1(t)\ \lambda_2(t)\ \lambda_3(t)\ \lambda_4(t)]^T$. Z_f is the final state at final time, t_f. For fixed final value and fixed final time problem $\delta Z_f = 0$ and $\delta t_f = 0$.
Solving (9) for fixed final value and fixed time, the optimal states are as follows:

$$z_1^*(t) = c_4\frac{t^2}{2} - c_1 t + c_5$$
$$z_2^*(t) = -c_2 t + c_6$$
$$z_3^*(t) = -c_3 t + c_7$$
$$z_4^*(t) = c_4\frac{t^3}{6} - c_1\frac{t^2}{2} + c_5 t + c_8 \quad (10)$$

The optimal virtual control inputs are

$$v_1^* = c_4 t - c_1$$
$$v_2^* = -c_2$$
$$v_3^* = -c_3. \quad (11)$$

where t is time in minute, $c_i, i{=}1, \cdots, 8$ are constants which can be found from boundary value solution of (10). It is evident from (6), the boundary values of auxiliary state, x_{a4} is required to set the boundary values of Z. The controller profile is sensitive to boundary values of auxiliary state, x_{a4}. The selection of proper boundary value of auxiliary state, x_{a4}, is requered considering the limitations of biological control inputs (x_6, x_9, and x_{10}).

V. Determination of Control Inputs to Achieve a New Steady-State

Using control design methodology in Section IV, the system can be steered to a new state within the finite time, but if it is not a steady-state then the system state will change instantaneously after that, as the linearized system is unstable in nature. This problem can be solved by applying a simple technique. In first step, the system will reach to the desired state using control signal (x_6, x_9 and x_{10} as in section IV) and in the second step these three control signals will be obtained by solving the steady-state equation of (4). This is as follows:

$$0.356x_6 - 42.5083\ x_1^{1.53}x_2^{-0.59} = 0$$
$$9.6408{x_1}^{0.95}x_2^{-0.41}x_{10}^{0.38} - 0.1079{x_2}^{3.97}x_3^{-3.06} = 0$$
$$0.1079{x_2}^{3.97}x_3^{-3.06} - 1.058808x_3^{0.3}x_9 = 0. \quad (12)$$

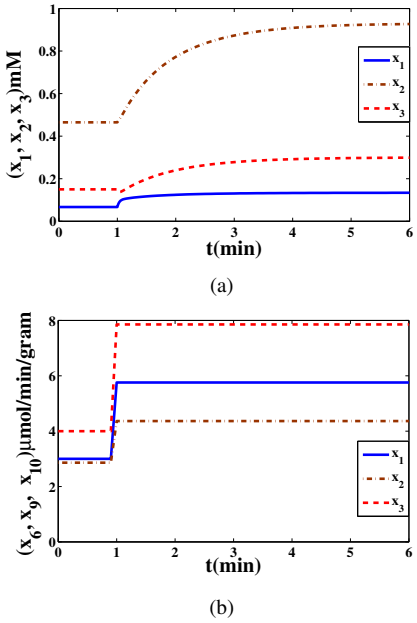
at the desired steady-state $x_1{=}0.134$, $x_2{=}0.93$ and $x_3{=}0.3$.

VI. Results and Discussion

The objective is to determine control signals that steer the system (4) from its initial state, defined by metabolic concentration $\bar{X}(t_0){=}[x_1(t_0)\ x_2(t_0)\ x_3(t_0)]^T$ to a target state $\bar{X}(t_f){=}[x_1(t_f)\ x_2(t_f)\ x_3(t_f)]^T$ in the time interval $[t_0, t_f]$. If the system (4) is initially at nominal steady-state $\bar{X}(t_0){=}[0.067\ 0.465\ 0.150]^T$, the goal is to achieve desired steady-state $\bar{X}(t_f){=}[0.134\ 0.93\ 0.3]^T$ within time $t{=}1\ min$. The system achieves the desired steady-state (as shown in Fig. 2(a)) with the modified value of the control input $x_6{=}5.7556$, $x_9{=}4.3651$, and $x_{10}{=}7.8554$, as shown in Fig. 2(b). If the new constant control input is applied at $t_0{=}1\ min$, the system reaches to steady-state nearly at $t_f{=}6\ min$ as shown in Fig.

2. This procedure has two limitations (1) the system may not reach the desired state within desired time, and (2) the transient state trajectories may not follow the optimum path.

Considering the optimal transient path, fixed time interval, $t_f - t_0 = 1\ min$, , $x_{a4}(t_0)=0$ and $x_{a4}(t_f)=0.1$, the virtual optimal control inputs are $v_1^*=0.006t+0.064$, $v_2^*=0.315$ and $v_3^*=0.05$ as per (9), (10) and (11). Fig. 3(a) shows the optimal trajectories of x_1, x_2, and x_3. Here the initial state is assumed as the nominal steady-state. Fig. 3(b) shows the profile of control input (x_6, x_9, and x_{10}). Initially they have their nominal constant values $x_6=3$, $x_9=2.86$, and $x_{10}=4$ as per (4). At time, $t_0=1\ min$, the control signal is generated by feedback linearization and optimal control approach to steer the steady-states x_1, x_2 and x_3. Then, at time $t_f=2\ min$ the control signals have constant values $x_6=5.7556$, $x_9=4.3651$, and $x_{10}=7.8554$. Thus, the transient time (to reach the desired steady-state from a given initial state) is now under the choice of the biochemical system designer. In this case, it is $t_f - t_0 = 1\ min$.

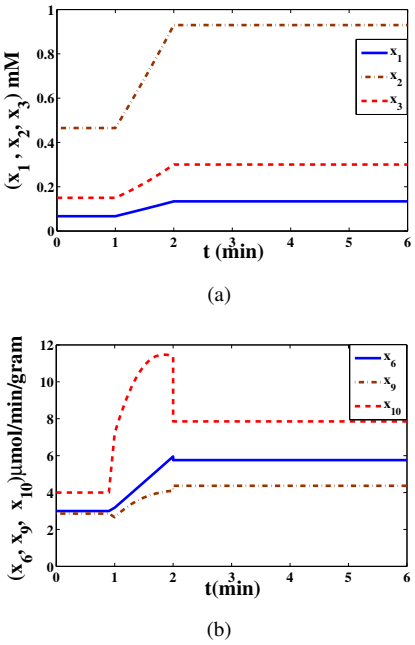


(a)

(b)

Fig. 2. Steering from nominal steady-state to desired steady-state (two times of nominal steady-state) using new constant controller values. (a) Trajectories of states x_1, x_2, and x_3. (b) Profiles of control variables x_6, x_9, and x_{10}.

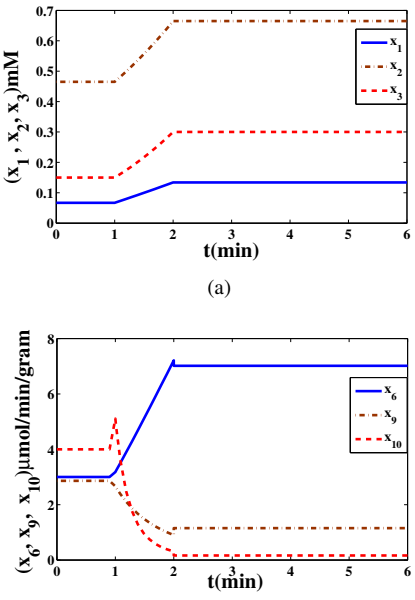
Applying fixed control input continuously for $t \geq 2\ min$, the system remains in this new steady-state. But, still there is a sudden jump in enzyme profile of x_{10} in Fig. 3(b). From (12), it is clear that x_{10} is highly affected by x_2. In order to to reduce this sudden jump in x_{10}, the final value of x_2 should be decreased. Now, Fig. 4(a) shows the optimal trajectories of x_1, x_2, and x_3 and Fig. 4(b) shows the profile of control input (x_6, x_9, and x_{10}) for steering steady-state from nominal steady-state $\bar{X}(t_0)=[0.067\ 0.465\ 0.150]^T$, to $\bar{X}(t_f)=[0.134\ 0.665\ 0.3]^T$ within time $t_f=2\ min$, where $t_0=1\ min$.



(a)

(b)

Fig. 3. Steering from nominal steady-state to desired steady-state (two times of nominal steady-state), within $t = 1\ min$, using feedback linearization and optimal control method. (a) Trajectories of states x_1, x_2, and x_3. (b) Profiles of control variables x_6, x_9, and x_{10}.



(a)

(b)

Fig. 4. Steering from nominal steady-state to desired steady-state ($x_1(t_f)=0.134$, $x_2(t_f)=0.665$, and $x_3(t_f)=0.3$), within $t_f - t_0 = 1\ min$, using feedback linearization and optimal control method. (a) Trajectories of states x_1, x_2, and x_3. (b) Profiles of control variables x_6, x_9, and x_{10}.

VII. Conclusion

In this paper, it is found that the possible control signal profile steers biochemical network from one steady-state to another steady-state. The selection procedure for possible control

inputs combination is discussed in detail. It is proposed that the complex network design can be avoided, considering suitable enzymes as the control input. This preliminary design can be improved by incorporating suitable biological constraints on the seclected control variables.

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