Intervention in Biological Phenomena Modeled by S-Systems: A Model Predictive Control Approach

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Abstract—Recent years have witnessed extensive research activity in modeling genetic regulatory networks (GRNs) as well as in developing therapeutic intervention strategies for such networks. S-systems, which offer a good compromise between accuracy and mathematical flexibility, are a promising framework for modeling the dynamical behavior of GRNs, as well as that of biochemical pathways. In this paper, an intervention strategy is proposed for the S-system model. In this approach, a model predictive control algorithm is developed which guides the target variables to their desired values. The proposed intervention strategy is applied to the glycolytic-glycogenolytic pathway as well as a generic branched pathway and the simulation results presented demonstrate the effectiveness of the proposed scheme.

I. INTRODUCTION

An ambitious goal of genetic regulatory network modeling is to develop therapeutic intervention strategies for shifting the undesirable state of a diseased network towards a more desirable one. To date, different modeling approaches such as Probabilistic Boolean networks (PBNs) [1], S-systems [2]–[6], and Bayesian networks [7], to name a few, have been proposed in the literature to mathematically capture the behavior of genetic regulatory networks. In addition, various intervention approaches [8]–[19] have been developed for biological systems. In [20], the authors studied the controllability of S-systems based on feedback linearization approach. In this paper we develop an intervention strategy applicable to biological systems and phenomena modeled by S-systems. These include genetic regulatory networks and metabolic pathways.

S-systems are proposed in [21] as a canonical nonlinear model to capture the dynamical behavior of a large class of biochemical pathways. They are characterized by a good trade-off between accuracy and mathematical flexibility [22]. In this modeling approach, nonlinear systems are approximated by products of power-law functions which are derived from multivariate linearization in logarithmic coordinates. It has been shown that this type of representation is a valid description of biological processes in a variety of settings.

II. CONTROL OF S-SYSTEMS

Consider the following S-system dynamics

\[ \dot{x}_i = \alpha_i \prod_{j=1}^{N+m} x_j^{g_{ij}} - \beta_i \prod_{j=1}^{N+m} x_j^{h_{ij}}, \quad i = 1, 2, ..., N \tag{1} \]

where \( \alpha_i > 0 \) and \( \beta_i > 0 \) are rate coefficients and \( g_{ij} \) and \( h_{ij} \) are kinetic orders and there exist \( N+m \) variables (genes/metabolites) where the first \( N \) variables are dependent and the remaining \( m \) variables can be manipulated to control the system. In order to control the values (expressions/concentrations) of the dependent variables, we consider an integral control approach where the following \( m \) equations are added to the above S-system

\[ \dot{x}_{i+N} = u_i, \quad i = 1, ..., m. \tag{2} \]

Figure 1 shows the S-system (1) augmented by the integral control. The S-system with integral control ((1) and (2)) can...
be written as follows:

\[ \dot{x} = f(x) + g(x)u \]  
(3)

where \( x = [x_1, \ldots, x_{N+m}]^T \in \mathbb{R}^{N+m}, \quad u = [u_1, \ldots, u_m]^T \in \mathbb{R}^m, \) and

\[
\begin{bmatrix}
    f(x) \\
g(x)
\end{bmatrix}
= 
\begin{bmatrix}
    \alpha_1 \prod_{j=1}^{N+m} x_j^g_{i,j} - \beta_1 \prod_{j=1}^{N+m} x_j^h_{i,j} \\
    \vdots \\
    \alpha_N \prod_{j=1}^{N+m} x_j^g_{N,j} - \beta_N \prod_{j=1}^{N+m} x_j^h_{N,j} \\
    0 \\
    0
\end{bmatrix}
\]  

Using the Euler approximation, we can write the discrete time representation of the equation (3) as

\[ x(k+1) = F(x(k)) + G(x(k))u(k) \]  
(4)

where

\[ F(x(k)) = x(k) + T_s f(x(k)) \]
\[ G(x(k)) = T_s g(x(k)) \]

and \( T_s \) is the sampling time.

**Problem Formulation**

Suppose that the S-system (1) is initially in the steady state condition \( x^{s_0} \). Let us denote by \( \mathcal{X}_i \subset \{1, \ldots, N\} \) the set of indices corresponding to the target variables (genes/metabolites) whose desired final steady state values are specified as \( x^{s_s} \). Then the control problem is to find the control inputs \( u_i, \ i = 1, \ldots, m \) that can guide the target variables from the initial steady state condition \( x^{s_0} \) to the final one \( x^{s_s} \).

**A. Controller Design**

In this section, a control design approach to the S-system control problem is proposed. In this approach, we try to control the target variables (genes/metabolites) corresponding to the indices \( \mathcal{X}_i \) using an MPC approach. In other words the control problem for system (1) reduces to finding a control policy by solving the following optimization problem:

\[
\begin{aligned}
\min_{u(k), \ldots, u(k+T_s-1)} & \sum_{i=0}^{T_s-1} \left( \sum_{j \in \mathcal{X}_i} q_{i,j} (x_j(k+i) - x_j^{s_s})^2 \right) \\
& + \sum_{j=1}^m r_{i+1,j} u_j^2(k+i) + \sum_{j=1}^m w_{i+1,j} \Delta u_j^2(k+i)
\end{aligned}
\]  
(5)

subject to the following constraints

\[
\begin{aligned}
& u_{\text{min},i} \leq u_i \leq u_{\text{max},i}, \quad i = 1, \ldots, m \\
& 0 \leq x_i \leq x_{i,\text{Max}}, \quad i = 1, \ldots, N + m \\
& \Delta u_{i,\text{min}} \leq \Delta u_i \leq \Delta u_{i,\text{max}}, \quad i = 1, \ldots, m \\
& x(k+j+1) = F(x(k+j)) + G(x(k+j))u(k+j) \\
& j = 0, \ldots, T_s - 1
\end{aligned}
\]

where \( T \) is the prediction horizon and \( T_s \) is the sampling time. In the cost function in (5), the weight variable \( q \) penalizes the deviation of the dependent variables from their desired steady-state values, while the weights \( r \) and \( w \) penalize the control input and changes in the control input, respectively. The above optimization problem is solved at each controller sample point and the control input is selected as

\[ u(t) = u^*(k), \quad kT_s \leq t < (k+1)T_s \]

where \( u^*(k) \) is the solution of the above optimization problem. Figure 2 shows a schematic diagram for the MPC control of S-systems.

Due to the fact that the S-systems are inherently nonlinear, the optimization problem (5) is a complex nonlinear one and finding the solution for it is in general difficult. One way to solve (5) is to make it linear via local linearization [25]. In this approach, at any time step, the nonlinear system

\[ x(k+1) = F(x(k)) + G(x(k))u(k) \]

is linearized at the current state, and the local linear model

\[ x(k+1) = Az(k) + Bu(k) \]

is used as the system constraint in the optimization problem. The new local optimization problem can be solved using the quadratic programming approach.

**III. Case Studies**

**A. glycolytic-glycogenolytic**

In this section, we demonstrate the efficacy of the proposed intervention approach developed in this paper by applying it to an S-system that can be used to model a well-studied biological pathway. Consider the following S-system which represents the glycolytic-glycogenolytic pathway, shown in Figure 3 [20], [26]:

\[
\begin{aligned}
\dot{x}_1 &= 0.077883414x_2^{0.66}x_6 - 1.06270825x_2^{1.53}x_7^{0.59} \\
\dot{x}_2 &= 0.585012402x_2^{0.95}x_2^{0.41}x_3^{0.32}x_7^{0.62}x_9^{0.38} \\
&\quad - 0.0007934561x_2^{3.97}x_3^{3.06}x_8 \\
\dot{x}_3 &= 0.0007934561x_2^{3.97}x_3^{3.06}x_8 - 1.05880847x_3^{0.3}x_9
\end{aligned}
\]  
(6)
where $N = 3$, $m = 7$ and the independent variables have the values $x_4 = 10$, $x_5 = 5$, $x_6 = 3$, $x_7 = 40$, $x_8 = 136$, $x_9 = 2.86$, and $x_{10} = 4$. The steady state concentrations can be found as $x_1 = 0.067$, $x_2 = 0.465$ and $x_3 = 0.150$.

1) Scenario # 1: In the first scenario, we try to control $x_1$, $x_2$, and $x_3$ by manipulating $x_4$, $x_5$ and $x_8$, i.e.

$$
\begin{align*}
\dot{x}_4 &= u_1 \\
\dot{x}_5 &= u_2 \\
\dot{x}_8 &= u_3
\end{align*}
$$

(7)

and all other $x_i$’s $i = 6, 7, 9, 10$ are kept fixed. Physically, this corresponds to the problem of using the glucose, inorganic phosphate ion and phosphoglucose isomerase concentrations to control the concentrations of glucose-1-phosphate, glucose-6-phosphate and fructose-6-phosphate. The target values for $x_1$, $x_2$ and $x_3$ are selected as $x_1^{*} = 0.2$, $x_2^{*} = 0.5$ and $x_3^{*} = 0.4$.

We try to apply the MPC control approach for guiding $x_1$, $x_2$ and $x_3$ to their target values. The local linear model is used at any time step for solving the optimization problem (5). The optimization parameters are selected as: $T = 10$ (prediction horizon), $r_{i+1,j} = 0$, $w_{i+1,j} = 0.01$, $i = 0, ..., 9$, $j = 1, 2, 3$ (control input weights), $q_{i+1,j} = 1$, $i = 0, ..., 9$, $j = 1, 2, 3$ (target state weights), $u_{\text{max},i} = 2$, $u_{\text{min},i} = -2$, $i = 1, 2$, $u_{\text{max},3} = 50$, $u_{\text{min},3} = -50$, $\Delta u_{\text{max},i} = 1$, $\Delta u_{\text{min},i} = -1$, $i = 1, 2, 3$, and $T_s = 3$ minutes (sampling time). Figures 4 and 5 show the trajectory response and control input for the S-system (6) controlled by the MPC-based approach whose goal is to make the target states $x_1$, $x_2$ and $x_3$ converge to their desired values.

2) Scenario # 2: In this scenario, we consider the case where the number of control variables is more than the number of target variables. For instance, we seek to control $x_1$, $x_2$ by manipulating $x_4$, $x_5$ and $x_8$ where $x_1^{*} = 0.2$ and $x_2^{*} = 0.5$. Physically, this corresponds to the problem of using the glucose, inorganic phosphate ion and phosphoglucose isomerase concentrations to control the concentrations of glucose-1-phosphate and glucose-6-phosphate. Figures 6 and 7 depict the trajectory response and control input for the system (6) corresponding to scenario # 2, controlled by the MPC approach, where the optimization parameters...
are selected as: $T = 10$ (prediction horizon), $r_{i+1,j} = w_{i+1,j} = 0.01$, $i = 0, ..., 9, j = 1, 2, 3$ (control input weights), $q_{i+1,j} = 1$, $i = 0, ..., 9, j = 1, 2$ (target state weights) and $T_s = 3$ minutes (controller sampling time). As shown in Figure 6, for the above choice of optimization parameters, the steady state value of $x_3$ is 0.178.

B. Branched Pathway

In this section, we demonstrate the efficacy of the proposed intervention approach developed in this paper by applying it to an S-system that can be used to model a generic branched pathway. Consider the following S-system which represent a generic branched pathway with the following typical parameters [2] shown in Figure 8:

$$\begin{align*}
\dot{x}_1 &= 20x_3^{-0.8}x_5^{1.0} - 10x_1^{0.5} \\
\dot{x}_2 &= 8x_1^{0.5} - 3x_2^{0.75} \\
\dot{x}_3 &= 3x_2^{0.75} - 5x_3^{0.5}x_4^{0.2} \\
\dot{x}_4 &= 2x_1^{0.5} - 6x_4^{0.8}
\end{align*}$$  

where $N = 4$, $m = 1$ and the initial condition $x_1(0) = 5.6$, $x_2(0) = 3.1$, $x_3(0) = 2.9$, $x_4(0) = 3.1$, and $x_5(0) = 0.9$. As shown in Figure 8, the production of $x_1$ depends on the independent variable $x_5$ with inhibition effect exerted by $x_3$. Moreover $x_4$ has an activation effect of the depletion of $x_3$. It is assumed that $x_3$ is the target gene/metabolite in this pathway and we try to control the value of $x_3$ by manipulating $x_5$, i.e.

$$\dot{x}_5 = u_1$$

and the target value for $x_3$ is selected as $x_3^* = 5$.

We try to apply the MPC control approach for guiding $x_3$ to its target value. The local linear model is used at any time step for solving the optimization problem (5). The optimization parameters are selected as: $T = 10$ (prediction horizon), $r_{i+1,1} = 0.1$, $w_{i+1,1} = 0.01$, $i = 0, ..., 9$, (control input weights), $q_{i+1,1} = 1$, $i = 0, ..., 9$, (target state weights), $u_{\text{max},1} = 2$, $u_{\text{min},1} = -2$, $\Delta u_{\text{max},1} = 1$, $\Delta u_{\text{min},1} = -1$, and $T_s = 10$ minutes (sampling time). Figures 9 and 10 show the trajectory response and control input for the S-system (8) controlled by the MPC-based approach whose goal is to make the target states $x_3$ converges to its desired value.

IV. Conclusion

In this paper, we have developed an intervention strategy for biological phenomena modeled in the S-system framework. In the proposed approach, a model predictive control algorithm is developed which guides the target variables.
to their desired values. The proposed control algorithm is applied to the glycolytic-glycogenolytic pathway as well as a generic branched pathway and the simulation results look promising. One of the future research directions for this work would be the development of robust control algorithms for biological phenomena modeled by S-systems. Such robust control algorithms are essential to ensure that a control design based on a theoretical model succeeds when applied to the actual biological phenomenon.

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REFERENCES


