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

N. Meskin, *Member, IEEE,* H. Nounou, *Senior Member, IEEE,* M. Nounou, *Senior Member, IEEE,*
A. Datta, *Fellow Member, IEEE,* and E. R. Dougherty, *Senior Member, IEEE*

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

N. Meskin is with the Electrical Engineering Department, Qatar University, Doha, Qatar (email: nader.meskin@qu.edu.qa).

H. Nounou is with the Electrical and Computer Engineering Program, Texas A&M University at Qatar, Doha, Qatar (email: hazem.nounou@qatar.tamu.edu).

M. Nounou is with the Chemical Engineering Program, Texas A&M University at Qatar, Doha, Qatar (email: mohamed.nounou@qatar.tamu.edu).

A. Datta is with the Department of Electrical and Computer Engineering, Texas A&M University, College Station, TX, 77843, USA (email: datta@ece.tamu.edu).

E. R. Dougherty is with the Department of Electrical and Computer Engineering, Texas A&M University, College Station, TX 77843 USA, and also with the Translational Genomics Research Institute, Phoenix, AZ 85004 USA (email: edward@ece.tamu.edu).
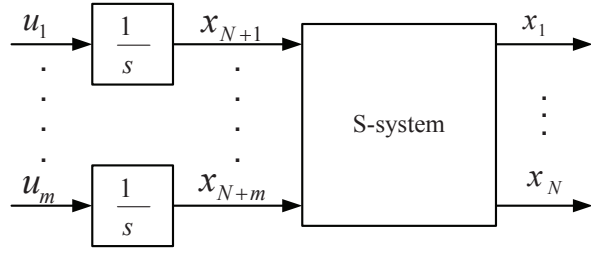
has been shown that this type of representation is a valid description of biological processes in a variety of settings. For a more elaborate discussion of S-systems, the interested reader is referred to [21], [23].

In this paper, an intervention strategy is proposed for biological phenomena modeled by S-systems. The goal of the intervention strategy is to transfer the target variables from an initial steady state level to desired final ones by manipulating the control variables. Towards this goal, the S-system model of biological phenomena is first augmented by integrators. This provides a mechanism for manipulating the control (independent) variables and guaranteeing zero steady state error in accordance with the internal model principle of control theory [24]. Then an MPC-based control intervention is developed to achieve the intervention objective. In the cases where the number of control variables is more than the number of target variables, the choice of the optimization parameters in the MPC approach determines the optimal values of the variables with no pre-specified desired values. The main advantage of MPC-based approach is that it allows the incorporation of input and state constraints in the control design.

The paper is organized as follows. In Section II, the control problem for S-systems is formulated and an MPC based control approach is proposed. In Section III, the glycolytic-glycogenolytic pathway model and generic branched pathway are considered as case studies. Comments and possible future research directions are outlined in Section IV.

II. CONTROL OF S-SYSTEMS

Consider the following S-system dynamics

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

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

$$\dot{x}_{i+N} = u_i, \qquad i = 1, ..., m. \quad (2)$$

Figure 1 shows the S-system (1) augmented by the integral control. The S-system with integral control ((1) and (2)) can

Fig. 1. S-system with integral control architecture.

be written as follows:

$$\dot{x} = f(x) + g(x)u \tag{3}$$

where $x = [x_1, ..., x_{N+m}]^T \in \mathbb{R}^{N+m}$, $u = [u_1, ..., u_m]^T \in \mathbb{R}^m$, and

$$f(x) = \begin{bmatrix} \alpha_1 \prod_{j=1}^{N+m} x_j^{g_{1j}} - \beta_1 \prod_{j=1}^{N+m} x_j^{h_{1j}} \\ \vdots \\ \alpha_N \prod_{j=1}^{N+m} x_j^{g_{Nj}} - \beta_N \prod_{j=1}^{N+m} x_j^{h_{Nj}} \\ 0 \\ \vdots \\ 0 \end{bmatrix} \left.\vphantom{\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}}\right\} m$$

$$g(x) = \begin{bmatrix} 0_{N \times m} \\ I_{m \times m} \end{bmatrix}$$

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

$$x(k+1) = F(x(k)) + G(x(k))u(k) \tag{4}$$

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^{ss^0}. Let us denote by $\mathcal{X}_t \subset \{1, ..., N\}$ the set of indices corresponding to the target variables (genes/metabolites) whose desired final steady state values are specified as x^{ss^d}. Then the control problem is to find the control inputs u_i, $i = 1, ..., m$ that can guide the target variables from the initial steady state condition x^{ss^0} to the final one x^{ss^d}.

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 $\mathcal{X}_t$ 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:

$$\min_{u(k),...,u(k+T-1)} \sum_{i=0}^{T-1} \Big(\sum_{j \in \mathcal{X}_t} q_{i+1,j}(x_j(k+i) - x_j^{ss^d})^2 + \sum_{j=1}^{m} r_{i+1,j} u_j^2(k+i) + \sum_{j=1}^{m} w_{i+1,j} \Delta u_j^2(k+i) \Big) \tag{5}$$

subject to the following constraints

$$u_{min,i} \leq u \leq u_{max,i}, \qquad i = 1, ..., m$$
$$0 \leq x_i \leq x_{i,Max}, \qquad i = 1, ..., N+m$$
$$\Delta u_{i,min} \leq \Delta u_i \leq \Delta u_{i,max}, \qquad i = 1, ..., m$$
$$x(k+j+1) = F(x(k+j)) + G(x(k+j))u(k+j)$$
$$j = 0, ..., T-1$$

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

$$x(k+1) = Ax(k) + Bu(k)$$

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]:

$$\dot{x}_1 = 0.077884314 x_4^{0.66} x_6 - 1.06270825 x_1^{1.53} x_2^{-0.59} x_7$$
$$\dot{x}_2 = 0.585012402 x_1^{0.95} x_2^{-0.41} x_5^{0.32} x_7^{0.62} x_{10}^{0.38}$$
$$\quad - 0.0007934561 x_2^{3.97} x_3^{-3.06} x_8$$
$$\dot{x}_3 = 0.0007934561 x_2^{3.97} x_3^{-3.06} x_8 - 1.05880847 x_3^{0.3} x_9 \tag{6}$$
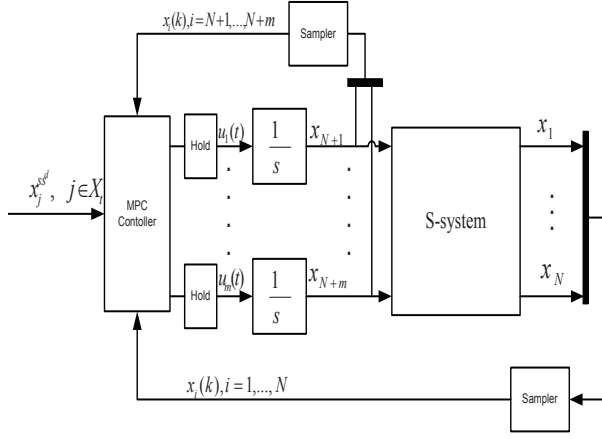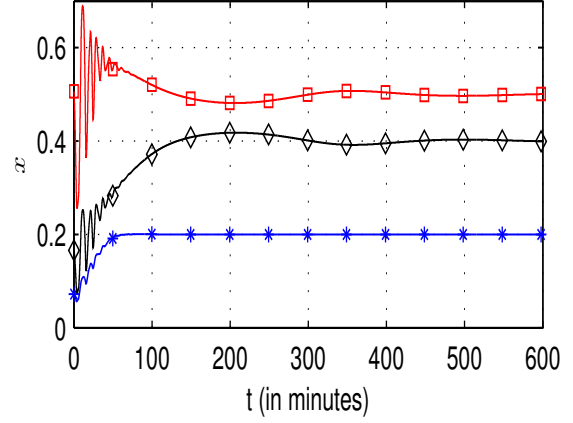
Fig. 2. MPC Control of S-system.

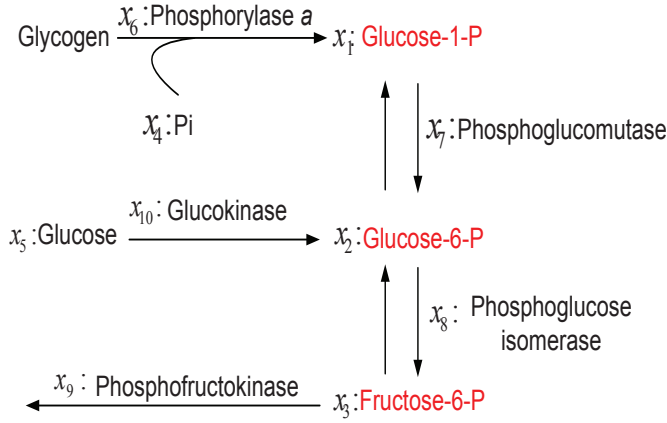Fig. 4. Metabolite concentrations corresponding to scenario # 1 with MPC-based controller.
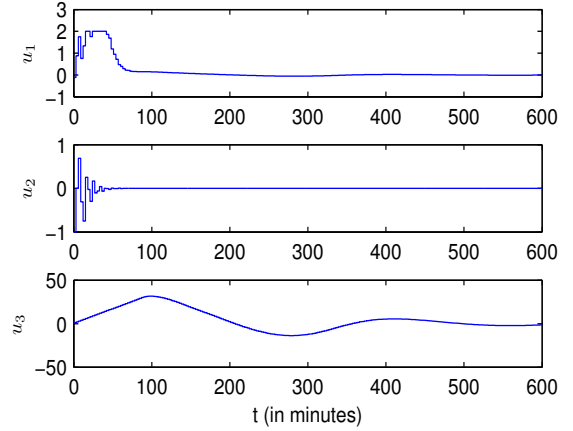

Fig. 3. Glycolytic-glycogenolytic pathway.

Fig. 5. Control input signals u corresponding to scenario # 1 with MPC-based controller.

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.

$$\begin{aligned} \dot{x}_4 &= u_1 \\ \dot{x}_5 &= u_2 \\ \dot{x}_8 &= u_3 \end{aligned} \quad (7)$$

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 $x_1^{ss^d} = 0.2$, $x_2^{ss^d} = 0.5$ and $x_3^{ss^d} = 0.4$.

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), $u_{max,i} = 2$, $u_{min,i} = -2$, $i = 1, 2$, $u_{max,3} = 50$, $u_{min,3} = -50$, $\Delta u_{max,i} = 1$, $\Delta u_{min,i} = -1$, $i = 1, 2, 3$, 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 $x_1^{ss^d} = 0.2$ and $x_2^{ss^d} = 0.5$. 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
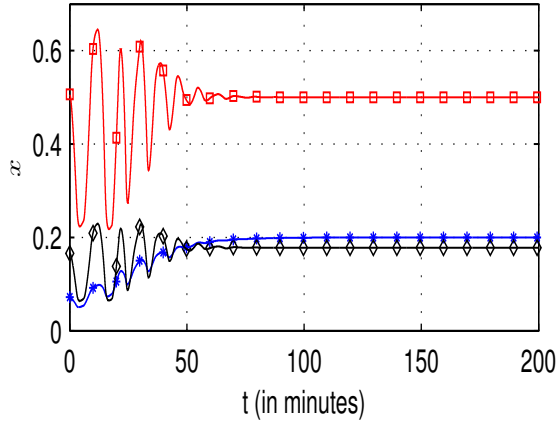
Fig. 6. Metabolite concentrations corresponding to scenario # 2 with MPC-based controller.
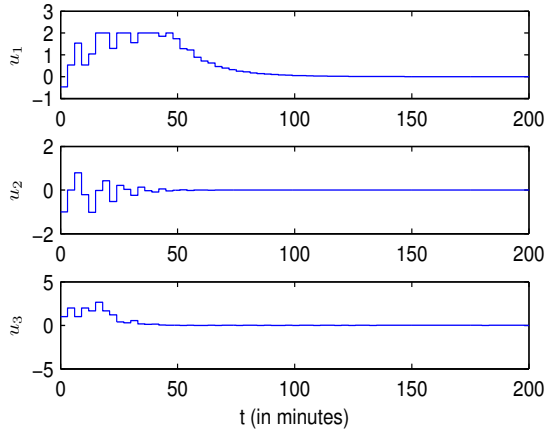

Fig. 7. Control input signals u corresponding to scenario # 2 with MPC-based controller.

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:

$$
\begin{aligned}
\dot{x}_1 &= 20x_3^{-0.8}x_5^1 - 10x_1^{0.5} \\
\dot{x}_2 &= 8x_1^{0.5} - 3x_2^{0.75} \\
\dot{x}_3 &= 3x_2^{0.75} - 5x_3^{0.5}x_4^{0.2} \\
\dot{x}_4 &= 2x_1^{0.5} - 6x_4^{0.8}
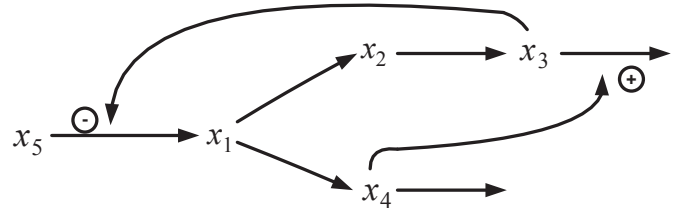\end{aligned}
\tag{8}
$$

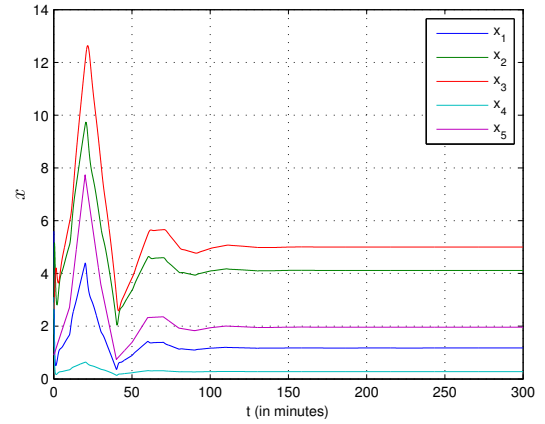Fig. 8. Generic branched pathway with four dependent variables.

Fig. 9. Metabolite concentrations corresponding to the branched pathway with MPC-based controller.

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 $x_3^{ss^d} = 5$.

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), $u_{max,1} = 2$, $u_{min,1} = -2$, $\Delta u_{max,1} = 1$, $\Delta u_{min,1} = -1$, 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
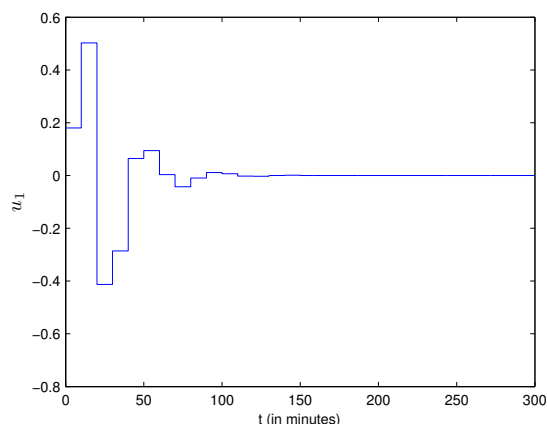
Fig. 10. Control input signal u_1 corresponding to the branched pathway with MPC-based controller.

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.

V. ACKNOWLEDGEMENT

REFERENCES

[1] I. Shmulevich, E. R. Dougherty, and W. Zhang, "From boolean to probabilistic boolean networks as models of genetic regulatory networks," *Proceedings of IEEE*, vol. 90, no. 11, pp. 1778–1792, 2002.
[2] E. O. Voit and J. Almeida, "Decoupling dynamical systems for pathway identification from metabolic profiles," *Bioinformatics*, vol. 20, no. 11, pp. 1670–1681, 2004.
[3] I.-C. Chou, H. Martens, and E. O. Voit, "Parameter estimation in biochemical systems models with alternating regression," *Theoretical Biology and Medical Modelling*, vol. 3, no. 25, 2006.
[4] H. Wang, L. Qian, and E. Dougherty, "Inference of genetic regulatory networks by evolutionary algorithm and H∞ filtering," *IEEE Statistical Signal Processing Workshop*, 2007.
[5] ——, "Steady-state analysis of genetic regulatory networks modeled by nonlinear ordinary differential equations," *IEEE CIBCB*, 2009.
[6] ——, "Inference of gene regulatory networks using S-systems: a unified approach," *IET System Biology*, vol. 4, no. 2, pp. 145–156, 2010.
[7] N. Friedman, M. Linial, I. Nachman, and D. Pe'er, "Using bayesian networks to analyze expression data," *Journal of Computational Biology*, vol. 7, pp. 601–620, 2000.
[8] A. Julius, A. Halasz, M. Sakar, H. Rubin, V. Kumar, and G. Pappas, "Stochastic modeling and control of biological systems: The lactose regulation system of escherichia coli," *IEEE Transactions on Automatic Control*, vol. 53, pp. 51–65, 2008.
[9] B. Faryabi, J. F. Chamberland, G. Vahedi, A. Datta, , and E. R. Dougherty, "Optimal intervention in asynchronous genetic regulatory networks," *IEEE Journal of Selected Topics in Signal Processing*, vol. 2, no. 3, pp. 412–423, 2008.

[10] A. Aswani and C. Tomlin, "Topology based control of biological genetic networks," *47th IEEE Conference on Decision and Control*, pp. 3205–3210, 2008.
[11] A. Motter, N. Gulbahce, E. Almaas, and A.-L. Barabasi, "Predicting synthetic rescues in metabolic networks," *Molecular Systems Biology*, vol. 4, no. 168, 2008.
[12] K. Yang, H. Bai, Q. Ouyang, L. Lai, and C. Tang, "Finding multiple target optimal intervention in disease-related molecular network," *Molecular Systems Biology*, vol. 4, no. 228, 2008.
[13] G. Vahedi, B. Faryabi, J. F. Chamberland, A. Datta, and E. R. Dougherty, "Optimal intervention strategies for cyclic therapeutic methods," *IEEE Transactions of Biomedical Engineering*, vol. 56, no. 2, pp. 281–291, 2009.
[14] B. Faryabi, G. Vahedi, A. Datta, J. F. Chamberland, and E. R. Dougherty, "Recent advances in the external control of Markovian gene regulatory networks," *Current Genomics*, vol. 10, no. 7, pp. 463–477, 2009.
[15] E. R. Daugherty, R. Pal, X. Qian, M. Bittner, and A. Datta, "Stationary and structural control in gene regulatory networks: basic concepts," *International Journal of System Science*, vol. 41, no. 1, pp. 5–16, 2010.
[16] R. K. Layek, R. Pal, A. Datta, and E. R. Dougherty, "Adaptive intervention in probabilistic boolean networks," *Bioinformatics*, vol. 25, no. 16, pp. 2042–2048, 2009.
[17] A. Aswani and C. Tomlin, "Computer-aided drug discovery for pathway and genetic diseases," *49th IEEE Conference on Decision and Control*, pp. 4709–4714, 2010.
[18] M. Chaves and J.-L. Gouz, "Exact control of genetic networks in a qualitative framework: The bistable switch example," *Automatica*, vol. In Press, Corrected Proof, pp. –, 2011.
[19] J. Uhlendorf, S. Bottani, F. Fages, P. Hersen, and G. Batt, "Towards real-time control of gene expression: Controlling the hog signaling cascade," *Pacific Symposium On Biocomputing*, pp. 338–349, 2011.
[20] A. Ervadi-Radhakrishnan and E. O. Voit, "Controllabilty of non-linear biochemical systems," *Mathematical Biosciences*, vol. 196, pp. 99–123, 2005.
[21] E. O. Voit, *Canonical nonlinear modeling : S-system approach to understanding complexity*, 1991.
[22] R. Gentilini, "Toward integration of systems biology formalism: the gene regulatory networks case," *Genome Inform.*, vol. 16, pp. 215–224, 2005.
[23] E. O. Voit, *Computational Analysis of Biochemical System. A practice guide for biochemists and Molecular biologists.* Cambridge University Press, 2002.
[24] B. A. Francis and W. M. Wonham, "The internal model principle of control theory," *Automatica*, vol. 12, no. 5, pp. 457–465, 1976.
[25] J. H. Lee and N. L. Ricker, "Extended Kalman filter based nonlinear model predictive control," *Ind. Eng. Chem. Res.*, vol. 33, no. 6, pp. 1530–1541, 1994.
[26] N. V. Torres, "Modelization and experimental studies on the control of the glycolytic-glucogenolytic pathway in rat liver," *Molecular and Cellular Biochemistry*, vol. 132, no. 2, 1994.