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Hybrid model predictive control of induction of *Escherichia coli*

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***Abstract*— The lactose regulation system of Escherichia coli is known to exhibit a bistable behavior. The stable states correspond to the phenotypical states of the system, *induced* and *uninduced*. Stochastic modeling of the system enables us to reproduce an experimentally observed phenomenon of spontaneous transitions between the induced and uninduced states. The average behavior of a colony of a large number of cells can be accurately described by an abstract model of the system, which is a two state Markov chain.**

In this paper, we consider a control problem that involves regulating the fraction of induction of a colony of Escherichia coli. We use the abstract model to design a feedback controller based on model predictive control strategy. Upon simulation, we show that the model predictive control is superior to other control strategies that we have designed before, in terms of less fluctuation in the control input and less tracking error.

I. Introduction

The advance of genetic sensing and manipulation technology has caused the field of biology to undergo a significant shift in its paradigms. The possibility of manipulating genetic information in living cells has arguably transformed molecular biology and genetics from a largely analytical science into a synthetic science. The possibility of acquiring a vast amount of data (for example, with the availability of genetic microarrays) has helped scientists identify very complex biochemical and genetic networks.

In molecular biology, there are a few organisms that have been designated as model systems [1]. Similarity in the basic principles among many organisms leads biologists to concentrate on several model systems that facilitate easy comparison and sharing of research results. The bacteria *Escherichia coli* are one of the model systems.

The lactose regulation system in *E. coli* [2] is one of the most extensively studied examples of positive feedback in a naturally occurring genetic network. The *lac* operon, which encodes the lactose control system, is often used as a switch to control genes in genetically engineered systems [3], [4]. As illustrated in the upper panel of Figure 1, two of its three component genes encode enzymes (β-galactosidase and permease) which contribute to lactose uptake respectively to the synthesis of allolactose. In turn, allolactose acts as an inducer for the operon itself.

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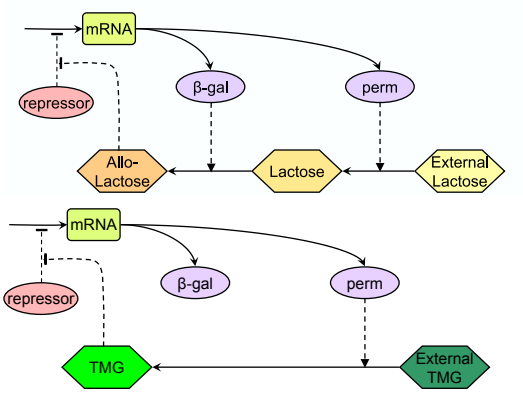

Fig. 1. The lactose network (top) and its modification with the gratuitous inducer TMG (bottom)

The available experimental results, including those used to validate the Yildirim-Mackey model [5], refer to "gratuitous" induction by substances similar to lactose such as *thio-methyl galactosidase* (TMG). Such gratuitous inducers, which are not metabolized by the cell, are often preferred in experimental settings because their presence does not affect the growth rate. From the systems perspective, using TMG instead of lactose also breaks one of the feedback loops in the Yildirim-Mackey model, since β-galactosidase does not act on TMG, and TMG itself can play the inducer role played by allolactose in the full Yildirim-Mackey model, as illustrated in the lower panel of Figure 1.

Multistability is a well known feature of positive autoregulation in genetic networks [6]. The lactose regulation system of *E. coli* is known to be bistable [5]. The two stable states of the dynamics are modulated by the concentration of *inducer* in the environment. Bistability of genetic regulation networks has been exploited in synthetic systems biology, for example in the celebrated design of genetic toggle switch [3].

Feedback control of biological systems is a very active field. In *personalized medicine*, feedback control is used to influence cellular processes. The need for treatment procedures that are widely applicable and give satisfactory clinical results for a variety of individuals with different steady state and dynamic responses requires the use of feedback mechanisms [7]. For every treatment policy there is an inevitable tradeoff between drugs efficacy, organ health and use of therapeutics. This makes optimal control solutions attractive. Souza *et al* [8] and Kirschner *et al* [9] offer an optimal control approach to HIV treatment. Jung *et al* [10] apply optimal control theory to the treatments in a two-strain tuberculosis model. Stengel *et al* [11] demonstrated optimal control solutions to the innate immune response. Another control method, model-based predictive control, is

also advantageous if accurate models are used in controller synthesis. This is so because predictive control provides us an estimate of future behavior. For instance, Parker et al [12] made a review of control algorithms for noninvasive monitoring and regulation in type I diabetic patients and showed that model-based predictive control is an attractive choice for blood glucose concentration regulation. There is a recent attempt to apply external control to neuropharmacology [13]. Finally, we also find applications of control laws to build effective strategies in gene therapies and tissue engineering [14].

In this paper, we study the problem of controlling a colony of *E. coli* by means of global sensing and actuation [15], [16]. In this problem, we assume that we do not have access to the state of individual cells. Rather, we assume that by sensing we can only measure an averaged quantity across the population. Global actuation means we can only manipulate the environment of the whole colony without being able to manipulate the bacteria individually. The control method that we use is hybrid model predictive control [17] based on a piecewise affine model of the colony dynamics. Similar control algorithms have been applied in several other application domains, for example in automotive control systems [18], and related theoretical aspects of stability have been recently studied in [19].

Model predictive control has characteristics that make it an attractive choice for biomedical systems. This is because the controller architecture is particularly well suited to the multivariable nature of these systems, as well as the inherent constraints involved in the related control problems [20].

II. Mathematical model of the lactose regulation system of E. coli

A. ODE model

Yildirim and Mackey [5] proposed a biochemically founded ordinary differential model of the lactose-induced network shown in the upper panel of Figure 1. In our earlier work [15], [16], we adopted the structure of this model and applied it to the TMG-induced network (lower panel of the same figure). The equations of motion for induction by TMG (T) are:

$$\frac{dM}{dt} = \alpha_M \frac{1 + K_1(e^{-\mu\tau_M}T(t-\tau_M))^n}{K + K_1(e^{-\mu\tau_M}T(t-\tau_M))^n} + \Gamma_0 - \tilde{\gamma}_M M, \quad (1a)$$

$$\frac{dB}{dt} = \alpha_B e^{-\mu\tau_B} M(t-\tau_B) - \tilde{\gamma}_B B, \quad (1b)$$

$$\frac{dT}{dt} = \alpha_L P \frac{T_e}{K_{T_e} + T_e} - \beta_L P \frac{T}{K_{L_1} + T} - \tilde{\gamma}_L T, \quad (1c)$$

$$\frac{dP}{dt} = \alpha_P e^{-\mu(\tau_P+\tau_B)} M(t-\tau_P-\tau_B) - \tilde{\gamma}_P P. \quad (1d)$$

The variables M, P, and B signify the concentrations of mRNA, permease, and β-galactosidase in the cell. We take into account time delays due to transcription and translation. Variables without an argument are taken at time t, time delays are indicated by an explicit argument, e.g., $M(t-\tau_B)$ is the value of the variable M delayed with τ_B.

The symbol T_e in equation (1c) signifies the external TMG concentration. If the system is to be viewed as an input-state system, then T_e can be thought of as an input to the system, while the other four concentrations are the state variables.

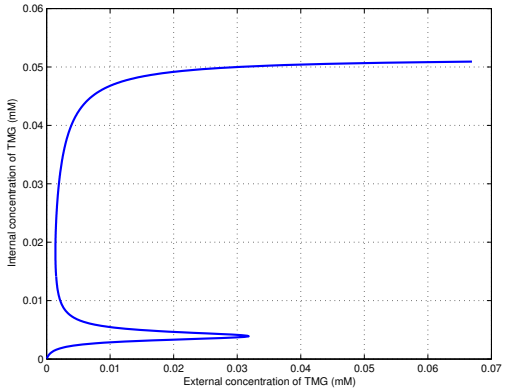

Fig. 2. The equilibria of the system given by (1). The middle range of T_e has three branches of equilibria.

The other symbols in the equation are constant parameters, given by the Table I, together with the following relations

TABLE I
System parameters

	Value	Unit		Value	Unit
μ	$2.26 \cdot 10^{-2}$	min^{-1}	K_{T_e}	$6.5{\cdot}10^{-4}$	mM
γ_M	0.411	min^{-1}	γ_B	$8.33 \cdot 10^{-4}$	min^{-1}
γ_A	0.52	min^{-1}	Γ_0	$1.0 \cdot 10^{-6}$	mM/min
K	7200		α_M	$9.97 \cdot 10^{-4}$	mM/min
τ_B	2.0	min	K_1	$6.3 \cdot 10^{5}$	$(\text{mM})^{-2}$
K_{L_1}	0.36	mM	α_B	$1.66 \cdot 10^{-2}$	min^{-1}
τ_P	0.83	min	β_L	546.32	min^{-1}
τ_M	0.1	min	α_P	10.0	min^{-1}
γ_L	1.52	min^{-1}	γ_P	0.6274	min^{-1}
α_L	81	min^{-1}	n	2	

$$\tilde{\gamma}_M = \gamma_M + \mu, \tilde{\gamma}_B = \gamma_B + \mu, \quad (2)$$

$$\tilde{\gamma}_A = \gamma_A + \mu, \tilde{\gamma}_P = \gamma_P + \mu. \ , \quad (3)$$

where μ is the growth rate. The values of the constants are based on those in [21] but have been modified to give consistent behavior to the TMG model in the limit of a large but finite cell population.

When the value of T_e is maintained between 1.4 - 32 μM, the system has three equilibria. Two of these equilibria are stable, giving rise to bistability of the system. Also, varying the value of T_e causes a hysteresis behavior. See Figure 2 for the illustration.

B. Stochastic hybrid model

The upper and lower stable branches of the equilibria correspond to the so called *induced* and *uninduced* states of the bacteria. Experimental results have shown that in a colony of bacteria, both states coexist with possibly different distributions. Also, the system can spontaneously switch between the two states [22]. These results underline the necessity of expressing stochasticity in the model, if we want to capture these phenomena.

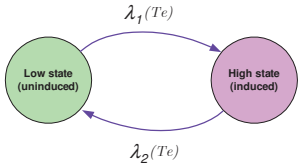

Fig. 3. Two state continuous time Markov chain model.

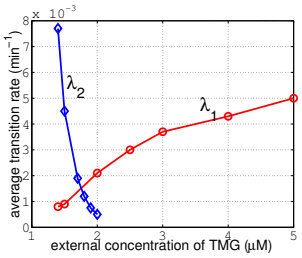

Fig. 4. The relation between the transition rates λ_1 and λ_2 of the Markov chain and T_e.

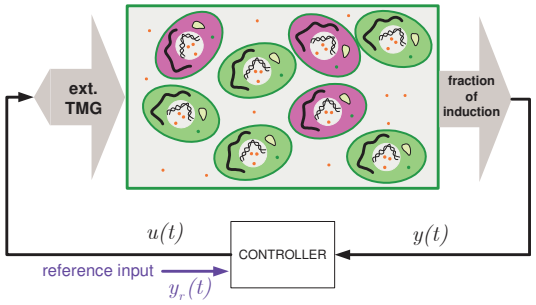

Fig. 5. The control block diagram.

In our earlier work, we expressed the stochasticity of the system by constructing a stochastic hybrid system model of the system [15], [16]. This stochastic hybrid model is based on a modified Gillespie's explicit τ-leaping algorithm [23].

In terms of stochastic differential equations, our hybrid stochastic model can be written as follows.

$$dM_t = d\hat{M}_t - d\tilde{M}_t, \tag{4a}$$
$$dB_t = d\hat{B}_t - d\tilde{B}_t, \tag{4b}$$
$$\frac{dT_t}{dt} = \frac{T_e \alpha_L P_t}{K_{L_e} + T_e} - \frac{\beta_L P_t T_t}{K_{L_1} + T_t} - \tilde{\gamma}_L T_t, \tag{4c}$$
$$\frac{dP_t}{dt} = \alpha_P e^{-\mu(\tau_P+\tau_B)} \frac{M_{(t-\tau_P-\tau_B)}}{C_N} - \tilde{\gamma}_P P_t. \tag{4d}$$

Here the processes $\hat{M}_t$ and $\tilde{M}_t$ are the Poisson processes that are responsible for the creation and breaking up of the messenger RNA molecules, respectively. Similarly, $\hat{B}_t$ and $\tilde{B}_t$ are the Poisson processes that are responsible for the creation and breaking up of the β - galactosidase molecules, respectively. The rates of these processes are state dependent, and are given as follows.

$$\lambda_{\hat{M}}(t) = C_N \left[\alpha_M \frac{1 + K_1 (e^{-\mu\tau_M} T_{(t-\tau_M)})^n}{K + K_1 (e^{-\mu\tau_M} T_{(t-\tau_M)})^n} + \Gamma_0 \right], \tag{5a}$$
$$\lambda_{\tilde{M}}(t) = \tilde{\gamma}_M M_t, \tag{5b}$$
$$\lambda_{\hat{B}}(t) = \alpha_B e^{-\mu\tau_B} M_{(t-\tau_B)}, \tag{5c}$$
$$\lambda_{\tilde{B}}(t) = \tilde{\gamma}_B B_t, \tag{5d}$$

where the conversion constant $C_N = 6.023 \cdot 10^4 \frac{\text{molecules}}{\text{mM}}$.

C. Two state Markov chain model

In our earlier work [15], [16], we also proposed an abstraction for the stochastic hybrid model described in the previous subsection. The fact that the cells can spontaneously switch between the two phenotypical states (induced and uninduced) is captured by modeling the system as a two-state continuous time Markov chain, whose states are `induced` and `uninduced` (see Figure 3). The transition rates between the two states are assumed to be functions of the external TMG concentration (T_e) (see Figure 4).

Given the continuous time Markov chain model as in Figure 3, we can compute the probability distribution of the states as follows. Define $x_{\text{lo}}(t)$ and $x_{\text{hi}}(t)$ as the probability of finding the system at time t in the low and high state respectively. The probability distribution satisfies the following differential equation.

$$\frac{d}{dt} \begin{bmatrix} x_{\text{lo}} \\ x_{\text{hi}} \end{bmatrix} = \begin{bmatrix} -\lambda_1(T_e) & \lambda_2(T_e) \\ \lambda_1(T_e) & -\lambda_2(T_e) \end{bmatrix} \begin{bmatrix} x_{\text{lo}} \\ x_{\text{hi}} \end{bmatrix}. \tag{6}$$

III. Induction control of a colony of E. coli

The architecture of the control system that we discuss in this paper is illustrated in Figure 5. The plant to be controlled in a large colony of *E. coli* bacteria. The controller affects the plant by adjusting of the external concentration of TMG in the environment. Feedback information is read from the plant in the form of a global quantity, which we consider as the *output* of the control system. By this, we mean the controller does not have any information about the individual cells in the colony. Rather, the controller relies on sensing a global quantity, for example, the fraction of induced cells in the population. The control goal is to make the output track a given reference trajectory or attain a desired level.

Control actuation by means of adjusting the external concentration of TMG in the environment can be realized as follows. Increasing the concentration can be done, for example by injecting the enzyme into the plant. There are a number of limitations associated to this method. First, the concentration cannot be made arbitrarily high since it can only be as high as the concentration of the injected enzyme. Second, the concentration cannot evolve arbitrarily fast. Decreasing the external concentration can be done, for example through dilution of the enzyme in the plant.

Sensing activity level of the colony can be done through sensing of certain protein concentrations in the cells. A certain protein called the *gfp* (green fluorescent protein) can be encoded in the *lac* operon. When the genes in the operon are expressed, *gfp* is also produced. Thus, the concentration of *gfp* in the cell can be used as an indicator for the activity of the cell. The protein *gfp* emits green light. Therefore we can use the luminescence of the cells as a way to measure its level of activity. This is actually a standard procedure in synthetic biology [3], [24].

In [15], [16], we have proven that the design of a feedback controller for such a control problem can be cast as the following problem.

Controller design: Given a plant model

$$\frac{d}{dt}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} -\lambda_1(u) & \lambda_2(u) \\ \lambda_1(u) & -\lambda_2(u) \end{bmatrix}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix}, \quad (7a)$$

$$y(t) = x_2(t), \quad (7b)$$

design a controller that reads the output $y(t)$ and outputs the control input $u(t)$, such that the output of the system $y(t)$ tracks a given reference signal $y_r(t)$.

IV. Hybrid Model Predictive Control Solution

In this paper, we propose a model predictive control solution to the above mentioned control problem. The underlying idea is to approximate the plant model (7) by a piecewise linear model that is obtained by assuming that $\lambda_1(u)$ and $\lambda_2(u)$ are piecewise constant functions

$$\lambda_i(u) = \lambda_i^j \text{ if } u_{j-1} \le u < u_j,\ j = 1, \ldots, 6,\ i = 1, 2 \quad (8)$$

where the intervals $[u_{j-1}, u_j)$ and the corresponding values of λ_i^j are given by Table II. The values of λ_1 and λ_2 in the table are determined from the identified rates as in Figure 4.

TABLE II
Transition rates as piecewise constant functions of u.

$u[10^{-3}\text{mM}]$	$\lambda_1(u)[\text{min}^{-1}]$	$\lambda_2(u)[\text{min}^{-1}]$
$[1.4, 1.5)$	$8.68 \cdot 10^{-4}$	$5.91 \cdot 10^{-3}$
$[1.5, 1.6)$	$9.27 \cdot 10^{-4}$	$3.61 \cdot 10^{-3}$
$[1.6, 1.7)$	$1.13 \cdot 10^{-3}$	$2.36 \cdot 10^{-3}$
$[1.7, 1.8)$	$1.39 \cdot 10^{-3}$	$1.54 \cdot 10^{-3}$
$[1.8, 1.9)$	$1.67 \cdot 10^{-3}$	$9.53 \cdot 10^{-4}$
$[1.9, 2.0)$	$1.93 \cdot 10^{-3}$	$5.54 \cdot 10^{-4}$

The control input $u(t)$ is assumed to be a piecewise constant signal that changes value every interval of length T_s. Thus, the idea is to compute and (if necessary) alter the control input value once every sampling interval T_s. The model described by (7), (8) and Table II is then discretized as follows.

$$x\left((n+1)T_s\right) = e^{A(u(nT_s))T_s} x(nT_s), \quad (9a)$$

$$u((n+1)T_s) = u(nT_s) + \Delta_n, \quad (9b)$$

$$y(nT_s) = x_2(nT_s), \quad (9c)$$

for any $n \in \mathbb{Z}_+$. The matrix $A(u(nT_s))$ is given by

$$A(u(nT_s)) = \begin{bmatrix} -\lambda_1(u(nT_s)) & \lambda_2(u(nT_s)) \\ \lambda_1(u(nT_s)) & -\lambda_2(u(nT_s)) \end{bmatrix},$$

where the values of λ_1 and λ_2 are given in Table II. The term Δ_n represents the update of the control input value.

At any time $t = nT_s$, the update of the control input is computed by solving the following receding horizon optimization problem (RCOP) iteratively.

Receding horizon optimization problem (RCOP). Find $\Delta_{n+k}, k \in \{0, \ldots, N-1\}$ that minimize the cost

$$J = \sum_{k=0}^{N-1} |y((n+k)T_s) - y_r((n+k)T_s)| + \gamma\,|\Delta_{n+k}|\,, \quad (10)$$

subject to

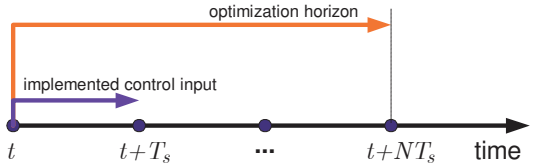

Fig. 6. The receding horizon optimization problem. At any time t, only the first interval of the computer control input is implemented.

- the initial condition $x(nT_s)$
- the system dynamics ((8), (9) and Table II), and
- for $k \in \{0, \ldots, N-1\}$,

$$|\Delta_{n+k}| \le 2 \cdot 10^{-3},$$
$$1.4 \cdot 10^{-3} \le u((n+k)T_s) \le 2 \cdot 10^{-3}.$$

Variable N defines the length of optimization horizon. Although the optimization is solved for N steps, only the control input value of the first interval is actually implemented. At the next step, the RCOP is re-initialized with the actual state as the initial condition. A schematic describing the algorithm is shown in Figure 6.

The cost function J in (10) is designed such that the tracking error $y - y_r$ is minimized. However we also include a term that carries a penalty for Δ. The idea behind this inclusion is to make sure that the update of the control input does not fluctuate too much.

One advantage of using model predictive control over the other control strategies that we have designed in [15], [16] is that we can impose that the control input value does not fluctuate a lot while making sure that the output of the system (the fraction of induction) tracks the reference value. Although at sampling times the control input can be discontinuous, if the sampling interval T_s is large enough, the control can still be realistically implemented.

V. Simulation Results

We simulate the application of the MPC controller on a plant with 5000 cells. We fix the horizon length $N = 2$ and the weight $\gamma = 10$ in the cost function (10). The reference signal is fixed at 0.5. That is, we aim at attaining and maintaining a 50% induction fraction.

The hybrid dynamical system defined by (8), (9) and Table II is modeled in HYSDEL [25] and translated into a mixed logical dynamical system [17] having 3 continuous states, 1 continuous input, 2 continuous outputs, 15 continuous auxiliary variables, 5 binary variables, and 80 mixed-integer linear inequalities.

Figure 7 shows the comparative simulation results of both the abstract model and stochastic hybrid model of the colony of bacteria with 5000 cells for two initial conditions, fully induced and fully uninduced. The sampling time is fixed at $T_s = 10$ min. We can see that the desired fraction of induction of 50% is attained and maintained.

In Figure 7 we can also see that the simulation results using the abstract model and the stochastic hybrid model are close. This demonstrates the effectiveness of using the much simpler abstract model in designing the controller, despite of the application on the stochastic hybrid model.

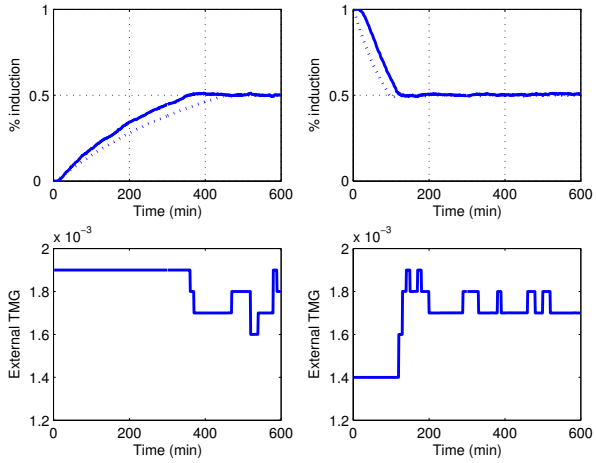

Fig. 7. Simulation results using MPC controller with sampling time $T_s = 10\text{min}$. Top: Fraction of induced cells. The dashed lines are the results obtained from the abstract model. The solid lines are the results from the stochastic model. Bottom: The level of T_e for both simulations (in mM)

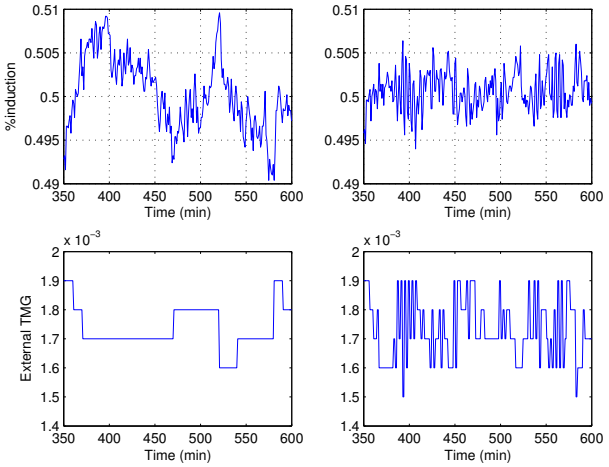

Fig. 9. Simulation results for different T_s values. Top: Fraction of induced cells after 350 minutes. Bottom: The level of T_e for both simulations (in mM) Left: T_s=10min. Right: T_s=2min.

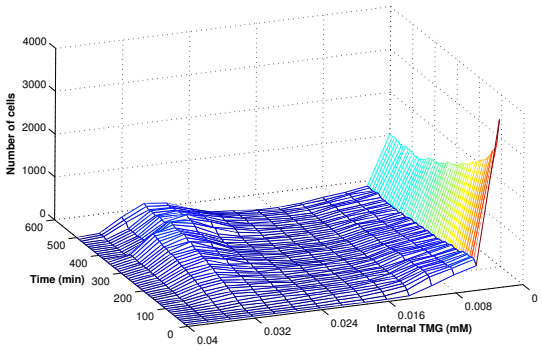

Fig. 8. A dynamic histogram of the distribution of the internal concentration of TMG in the cells when the MPC controller is used

The hybrid MPC controller was designed and simulated through the Hybrid Toolbox for Matlab [26] using the mixed-integer linear programming solver GLPK [27]. The CPU time for controller evaluation is on average 32 ms (280 ms in the worst case) on a 1.2 GHz laptop computer running Matlab 7.3, which is several orders of magnitude smaller than the sampling time $T_s = 10$ min.

Figure 8 shows a dynamic histogram of the internal concentration of TMG in the cells, when the MPC controller is used with fully uninduced initial condition. We can see that at the beginning, the distribution is concentrated at the uninduced state. As time passes, a second cluster, which corresponds to induced cells appears. Note that, after 350 minutes the higher cluster slightly shifts to the right and stabilizes there with small deviations, as it is also demonstrated in the left section of Figure 7.

Intuitively, reducing the sampling time T_s leads to better tracking performance at the cost of (possibly) more fluctuation of the control input and more computation. In real time applications, it might not be possible to change the control input too frequently. Therefore, the choice of sampling time should be a balance between the real world limitations and the steady state performance. We can observe this trade-off in Figure 9. While the steady state tracking error is $\pm 2\%$ for the model with T_s=10min, it is $\pm 1\%$ for the model with T_s=2min.

In a previous work [16], we have implemented three different controllers, namely on-off controller, flow controller and hybrid PI controller on the same model. We showed that hybrid PI controller is superior to the other two strategies with respect to the steady state tracking error. However, as it is shown in Figure 10, the output variation and the steady state tracking error of the MPC controller is smaller than that of the hybrid PI controller. In addition, in MPC controller the external control input follows a much more regular pattern compared to hybrid PI contoller which can also be seen in Figure 10. Unlike hybrid PI controller, in MPC controller scheme, the changes in input occur in a reasonable time scale which is an important issue for possible applications.

The only drawback of MPC control is its computational cost. As it involves a receding horizon optimization problem (RCOP) as described in the previous section. However, we only need to solve the RCOP at every sampling time T_s, which is quite long due to the slow dynamics of the system, and much larger than the CPU time required by a personal computer to solve the mixed-integer programming problem associated with RCOP. With the ever increasing pervasiveness of computation technologies, it is realistic to say that the designed hybrid MPC controller can be implemented in a real application.

VI. Concluding Remarks

In this paper we present a hybrid model predictive control (MPC) based feedback strategy for regulating the induction fraction of a colony of *Escherichia coli*. The model used in the MPC scheme is the abstract model of the system designed to describe the colony scale dynamics [15], [16]. The abstract model, which is a finite state Markov chain (Figure 3), is much simpler than the full stochastic hybrid model of the biochemical dynamics of the lactose regulation system (4).

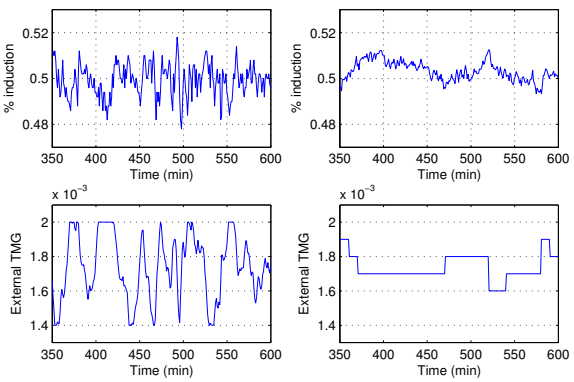

Fig. 10. Comparison of steady state behavior for two different controllers after 350 minutes. Top-left: Fraction of induced cells when the hybrid PI controller is used. Top-right: Fraction of induced cells when the MPC controller is used. Bottom: Corresponding T_e values (in mM)

The hybrid MPC control strategy is based on solving a receding horizon optimization problem, whose cost function is designed to minimize tracking error and fluctuation of the control input signal. Upon simulation, we observe that the abstract model is indeed suitable for control. We also observe the intuitive trade-off between fluctuation of the control input signal and the tracking error when different sampling intervals T_s are used.

One of the attractions for using MPC based strategy, compared to other strategies that we have developed previously [15], [16], is the fact that the control input signal does not have to change in realtime. Since the control input is the concentration level of some enzyme in the environment, less fluctuation generally leads to better and/or easier implementability of the control strategy.

The fact that the computational load of the hybrid MPC based strategy is much higher than those of the other strategies is alleviated by the fact that the slow dynamics of the system lends itself to long sampling interval. Long sampling intervals allows the computation to be solved in a long time, rendering the MPC based strategy feasible.

Many biochemical systems are slow in nature. Many synthetic genetic circuits, such as the well known toggle switch and the repressilator [3], [28] exhibit slow dynamics (in the order of hours). As is the case with the lactose regulation system of *E. coli*, control of such systems might be particularly amenable to MPC based strategies.

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