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Application of Maximum Hands-off Control to Cellular Metabolic Oscillation

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Abstract: Biological oscillation is one of the most important biological functions for maintaining homeostasis. In particular, it is known that yeast and *Escherichia coli* maintain homeostasis by oscillating the intracellular metabolite to increase the intracellular energy production in a starvation state where there is no nutrient such as glucose in the external environment. In this paper, we focus on the dynamical model of metabolic oscillations in yeast and report on tracking control from non-oscillation to oscillation using maximum hands-off control, also known as sparse control.

Keywords: Cellular oscillation, Metabolic system, Maximum hands-off control, Sparsity.

1. INTRODUCTION

There are many phenomena in the natural world where a single cell acquires diversity as a group. In particular, collective biological oscillations are a universal phenomenon observed in various life layers such as the heartbeat, somitogenesis, and biological clock. In this research, we discuss the control mechanism of metabolic oscillation from the viewpoint of optimal control. A typical example of biological oscillations that has been known for a long time is the oscillation phenomenon of the glycolysis system (Gustavsson et al., 2015; Jacobsen et al., 1982). Furthermore, Chandra et al. (Chandra et al., 2011) simplified the glycolytic metabolic reaction of yeast and ATP production into two variables. They performed the stability analysis based on the robust control theory for the simplified dynamical metabolic system and identified the parameter region where ATP oscillated. Furthermore, Hancock et al. (Hancock et al., 2017) revealed the homeostatic regulation between intracellular buffering effect and allosteric feedback by expanding the research of (Chandra et al., 2011). On the other hand, the actual cellular system controls the internal state while sensing changes in environmental stimuli. Therefore, it is not enough to identify the parameters of an autonomous system by dynamical system analysis. In addition, since ATP is an intracellular energy currency, controlling the ATP state in a situation where intracellular disturbance is sparsely optimized is important for synthetic biological research (Vecchio et al., 2016). In this study, we report the design of a sparse control input (that is, the eco-input that minimizes disturbance to ATP consumption from the viewpoint of energy metabolism) that changes the ATP state from non-oscillation to oscillation for the Chandra model.

The sparse control is obtained by using a design method called the maximum hands-off control (Nagahara et al., 2016). The problem is formulated as an L^0 optimal control problem with state and control constraints, which is proved in (Nagahara et al., 2016) to be equivalent to L^1 optimal control problem under a mild assumption. Since the L^1 optimal control problem is a convex problem, one can easily obtain the solution by using numerical optimization toolboxes such as CVX (Grant and Boyd, 2013).

2. MAXIMUM HANDS-OFF CONTROL OF METABOLIC OSCILLATION

2.1 Chandra Model

Chandra et al. have proposed the following nonlinear dynamical model that simplifies the glycolytic system in yeast cell [1]:

$$\begin{cases} \dot{x} = \dfrac{2y^a}{1+y^{2h}} - \dfrac{2kx}{1+2y^{2g}}, \\ \dot{y} = -q\dfrac{2y^a}{1+y^{2h}} + (q+1)\dfrac{2kx}{1+2y^{2g}} - (1+\delta) \end{cases} \tag{1}$$

The six metabolic reactions for glycolysis of glucose are defined as the state variable $x(t)$ and the ATP concentration generated by the glycolysis process is defined as the output variable $y(t)$. Allosteric control of the enzyme via ATP is expressed by the Hill equation $f(x) = \frac{f(x)^n}{1+f(x)^n}$, where n is the hill coefficient. The parameters h *and* g indicate the intensity of feedback reaction from ATP to enzyme. The variable δ(t) is a disturbance related to ATP consumption, k is the reaction coefficient of the intermediate, q is the reaction coefficient of autocatalyst, and a is the cooperativity of the enzyme and ATP.

Furthermore, the Chandra model (1) can be transformed into the following linearized system around equilibrium points:

$$\begin{bmatrix}\dot{\Delta x}\\ \dot{\Delta y}\end{bmatrix} = \begin{bmatrix}-k & (a-h)+g\\ (q+1)k & -q(a-h)-(q+1)g\end{bmatrix}\begin{bmatrix}\Delta x\\ \Delta y\end{bmatrix} + \begin{bmatrix}0\\ -1\end{bmatrix}\delta \quad (2)$$

2.2 Maximum Hands-off Control

Here we consider the maximum hands-off control for the linearized system (2). The maximum hands-off control is obtained by solving the following optimal control problem:

$$\min_{\delta}\|\delta\|_0 \quad \text{subject to } \dot{x} = Ax + B\delta$$
$$x(0) = x_0, x(T) = x_T, |\delta(t)| \le \delta_{max}. \quad (3)$$

Firstly, for the linearized model (2), we identify the parameters of the oscillation system assuming that the system is stable. Then, we compute the maximum hands-off control by solving the optimization problem (3) based on L^1 relaxation and time discretization (Nagahara et al., 2016). In detail, we consider the sparse tracking control in which the output of a stable system follows the reference value using the output of the oscillation system as a reference signal by minimizing the tracking error.

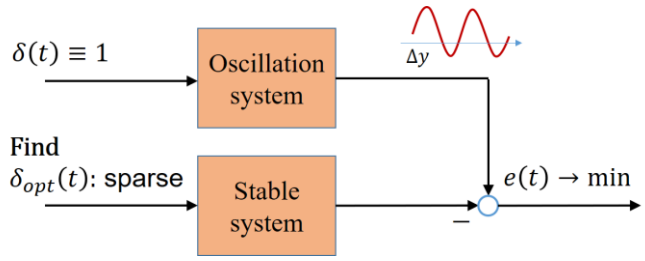

Fig1: Outline of sparse tracking control. The signal $e(t)$ indicates the error between oscillation signal and sparse controlled signal.

3. NUMERICAL RESULTS

The parameters set of the stable system are $[a = 1, k = 3, h = 3, g = 5, q = 1]$. By contrast, the parameters set of the oscillation system are $[a = 1, k = 3, h = 14, g = 5, q = 1]$. The numerical simulation is shown below (Fig.2).

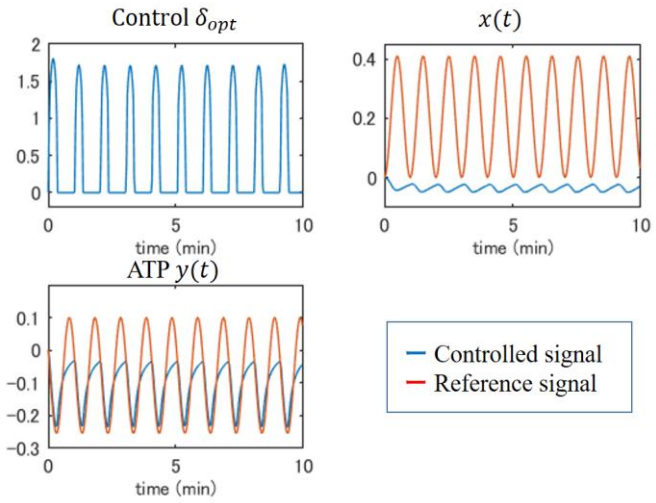

Fig.2: Results of sparse tracking control. The red curve indicates the reference signal (output signal of oscillation system). The blue curve shows the controlled signal (the output signal of the oscillation system). The signal δ(t) is the control input as a disturbance related to ATP consumption, and $x(t)$ is the internal variable of metabolic reaction. The output $y(t)$ is ATP concentration.

The numerical results show that the control input $\delta(t)$ exhibit the impulse-like signal and the ATP output $y(t)$ can follow the oscillation system. By contrast, the internal variable $x(t)$ of glycolysis did not exhibit the oscillation phenomenon.

4. CONCLUSIONS

In this paper, we have focused on the oscillation phenomenon of metabolites in yeast and applied maximum hands-off control to a linearized dynamical model of metabolism to identify sparse control inputs from stable to oscillatory systems. As a future plan, we will examine the comparison with the control input by L^2 control. And moreover, recently, many researches about model-based control of actual intracellular systems with an interdisciplinary approach of optimal control and live-cell measurement have been reported in (Khammash, 2016; Milias-Argeitis et al., 2011, 2016). We also plan to perform experiments and verifications on a real cellular system using the ATP monitoring live-cell imaging system (Imamura et al., 2009).

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