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Design of *In-silico* Optimal Controller for Adaptive Molecular Network Based on Particle Filter

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Abstract: Cell transmit dynamical signals from extracellular stimulation such as growth factor and hormones to downstream gene expression, controlling various cellular function. In this study, we report the application of optimal control based on particle filter to adaptive molecular network. We have implemented the tracking control of output generated from the adaptive molecular network to sine signal as a reference signal by using the particle filter based optimal controller.

Keywords: Adaptive molecular network, Particle filter, Optimal control, Systems biology.

1. INTRODUCTION

Cell transmit dynamical signals from extracellular stimulation such as growth factor and hormones to downstream gene expression, controlling various cellular function such as cellular decision making (proliferation and differentiation) and metabolism. In conventional systems biology, the research on "understanding of system" has been energetically conducted, such as identification of regulatory network and system analysis using mathematical models (Alon, 2006). By contrast, in system engineering, system identification and analysis are performed for precise and optimal control and design of target dynamic system using predictive mathematical models (Khammash, 2016; Vecchio et al., 2016). Recently, many interdisciplinary researches of model-based control of cellular system have been reported (Milias-Argeitis et al., 2011, 2016; Milias-Argeitis and Khammash, 2015). For example, Milias-Argeitis et al. have reported the design of optimal controller for intracellular system based on optogenetic actuator and sensor and particle filter, which is one of nonlinear system identifications. In this study, we report the tracking control of output generated from adaptive molecular network to reference signal as the application of particle filter based optimal control to adaptive molecular network (Fig1).

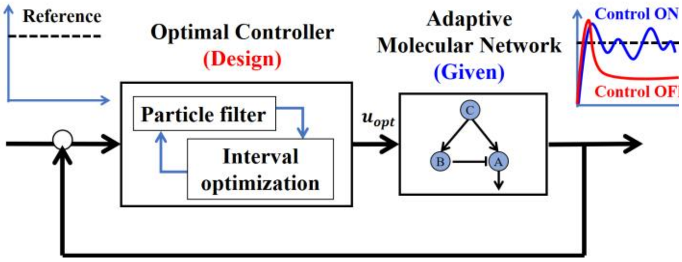

Fig1: Schematic representation of tracking control for adaptive molecular network by using the particle filter based optimal control

2. ADAPTIVE MOLECULAR NETWORK

In this research, we focus on the adaptive molecular network as the control target system. Biological adaptation is used in intracellular signaling networks to maintain cellular homeostasis in the presence of external perturbation. Also, adaptation detects the changes in the input more accurately. We refer the adaptive molecular network to intracellular dynamical system that can exhibit the transient response for external stimuli. Some adaptive molecular networks have been reported (Ferrell, 2016; Ma et al., 2009). In this research, we focus on the incoherent Feed-Forward Loop model (iFFL model) from these previous researches. iFFL model have been reported as the core network structure that regulate the cellular decision making such as cellular proliferation and differentiation (Sasagawa et al., 2005). For example, mathematical description of iFFL model can be defined as

$$\begin{cases} \dfrac{dA}{dt} = k_1 u(1-A) - k_2 AB \\ \dfrac{dB}{dt} = k_3 u \dfrac{1-B}{K_3 + (1-B)} - k_4 B \end{cases} \tag{1}$$

In iFFL model, the input u effects the downstream output in two opposite pathways: One is direct positive effect of the input on output node A. The other is indirect negative effect through the buffering node B which promotes the inactivation of output node A (Fig.2A). We have assumed the mass action law for first rate equation. Unit of variable show the molecular concentration. As the example, simulation result in case of step input is below (Fig.2).

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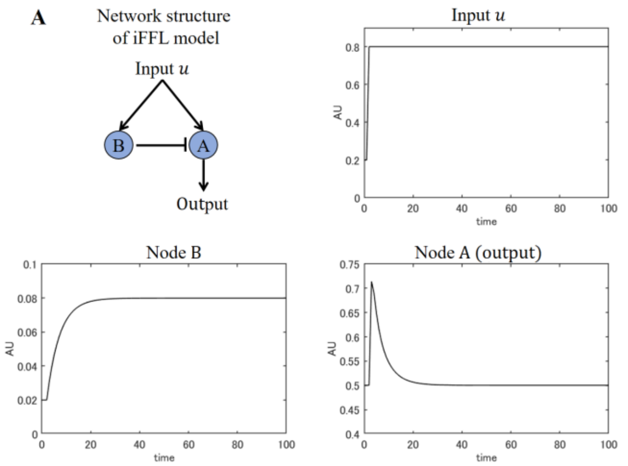

Fig2: Fig **A** indicate schematic structure of iFFL model. Other figures show the numerical simulation of iFFL model in case of following parameters. Parameter set is $[k_1 = 10, k_2 = 100, k_3 = 0.1, K_3 = 0.001, k_4 = 1]$.

3. OPTIMAL CONTROL BASED ON PARTICLE FILTER

3.1 State estimation based on particle filter

In order to estimate the state variable and model parameters, we used the particle filter, which is one of recursive Bayesian estimation (Särkkä, 2013). Filter distributions of state variable and model parameters are defined as

$$p(x_t|y_{1:t}) \approx \frac{1}{N}\sum_{i=1}^{N} \delta(x_t - \hat{x}_t^i) \tag{2}$$

$$p(\theta_t|\theta_{t-1}) \sim N_n(\theta_{t-1}, \Sigma) \approx \frac{1}{N}\sum_{i=1}^{N} \delta(\theta_t - \hat{\theta}_t^i) \tag{3}$$

θ is n-dimensional model parameters. x indicate the state variable. y show measurement data. N is number of particles. $\delta(x)$ indicate the Dirac's delta function. Symbol of hat indicate resampled variable and parameter.

3.2 Interval Optimization

In order to estimate optimal input that tracking to reference signal, we set up the following optimization problem. we adapted the interval optimization, which is optimization method of *model predictive control* to robustly predict the controlled output signal.

Find $u_{opt} = \underset{u}{\operatorname{argmin}} J$ **s.t.**

$$J = \frac{1}{N}\sum_{p=1}^{N} \int_t^{t+H} \left(Y_{ref}(\tau) - Y_p(\tau, u)\right)^2 d\tau \tag{4}$$

Y_{ref} is reference signal. Y_p indicate the predictive signal. u is input signal. H show the control horizon. J indicate the cost function. This optimization can be solved with *MATLAB* optimization toolbox.

4. NUMERICAL RESULTS

As numerical examples, we have performed tracking problem to reference signal with the above iFFL model (Fig1). Model representation that transformed from iFFL model to state variable, and parameter conditions are as follows. $x = [A \quad B]^T$, $y = A$, $\theta = [k_1\, k_2\, k_3\, K_3\, k_4]$, $N = 5000$, $H = 1$.

Result: Tracking to the sine signal

We considered the tracking control to sine signal. Numerical result is below (Fig.3).

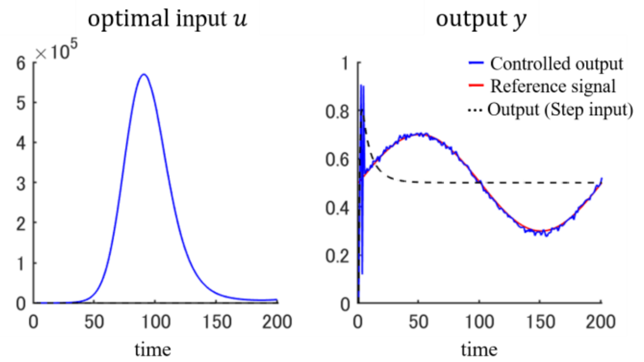

Fig3: Numerical results of tracking control in case of sine signal as reference signal. Left figure indicate the optimal input signal. Right figure shows the output signal.

From above numerical results, tracking to the sine signal showed good performance. On the other hand, optimal control inputs exhibited large variation range over 10^6. Furthermore, we have performed the tracking control to step signal in which steady-state value is higher than stationary value (0.5). Result of step signal indicated good tracking accuracy in early phase, but it showed the instability in late phase (data not shown).

5. CONCLUSIONS

We have implemented the tracking control of output of adaptive molecular network to reference signal by developing the particle filter based optimal controller. As future perspective, first we will consider the magnitude of optimal control input (Fig. 3) and the control mechanism of molecular kinetics. And we will reconstruct the cost function that involve the constraint conditions of input signal so that the optimal input is within the range close to physiological conditions (e.g. around 10^3 range in the case of growth factor). Furthermore, we will compare with other state estimation method (e.g. Extended Kalman Filter). We also applicate to other adaptive molecular networks (e.g. NFBL model: Negative Feed-Back Loop model and quantitative mathematical model).

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