A Genetic Optimizer Module for Synthetic Biology ⋆

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Abstract: Living organisms must fine-tune a vast array of complex processes for optimal performance, including metabolism, respiration, and growth. Performance decisions are intertwined due to a limited availability of resources, and involve a large collection of unknown trade-offs. Although synthetic biology enables us to control gene expression, we currently lack an ability to automatically tune expression to an optimal level online, to maximize/minimize a user-defined performance metric (e.g., biomass production or growth rate) in a way that is responsive to changing environmental conditions. To attain such tuning, we present an optimizer module that can be constructed from standard genetic parts. Our feedback control module is inspired by classical gradient-based numerical methods, but conforms to unique biological constraints such as non-negative concentration signals. Importantly, we show that the performance of our optimizer module is robust to parameter variations in an unknown and time-varying plant and objective function, as well as to disturbances that affect the optimizer itself.

Keywords: Optimization; timescale separation; stability analysis; synthetic biology; modularity

1. INTRODUCTION

Synthetic biology currently lacks rationally-engineered cell-based genetic control systems that are capable of dynamically adjusting the activity profile of gene networks to optimize their performance. Example performance metrics include simple maximization of biomass production or growth rate, or a more complex optimal allocation of resources between growth and toxin production to outcompete an invader species (Ahmad et al., 2019). On-line optimization is especially challenging due to the uncertain and context-dependent nature of genetic circuit design.

To tackle this challenge, we present a genetic feedback control system that can successfully optimize the performance of an unknown time-varying process with an unknown time-varying objective function, while adhering to biological constraints like non-negative concentration signals. Our optimizer module is inspired by gradient-based optimization methods, and is comprised of three steps: a delay of state and output signals to overcome a lack of innate memory, a detection of the change in these signals, and the use of this information to generate control inputs.

This paper is organized as follows. First, we introduce the mathematical model and the biological constraints. We then provide a brief overview of our proposed optimizer module. Finally, we illustrate robust optimizer module performance to parameter variations, concluding that our module is well-suited to typically uncertain cellular contexts.

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2. MATHEMATICAL MODEL AND PROBLEM FORMULATION

2.1 System of Interest and Optimizer

Consider the system $\dot{x} = f(x, u, t)$ with $y = F(x, t)$, where $x, y \in \mathbb{R}$, $u \in \mathbb{R}^2$. We assume that $F(x, t) = 0$ only at the unique optimum $x^*(t)$. We consider scalar dynamics with $f(x, u, t) = u_1(t)\alpha(t) - u_2(t)\gamma(t)x(t)$, where dynamics due to context and disturbances are captured by the time-varying production rate $\alpha(t)$ and degradation rate $\gamma(t)$.

For the above system, we seek a feedback optimizer of the form $\dot{z} = g(z, x, y)$, with $u_i = h_i(z)$ for $i = 1, 2$, such that the closed-loop system has x approaching x^* as $t \to \infty$. Importantly, as the production/degradation rate constants must be non-negative, the optimizer must satisfy $u_1, u_2 \geq 0$.

2.2 Limitations

In the absence of biological constraints, one solution for the optimizer would be a gradient-based system with a choice of $u_i(t) = -(-1)^i \lambda_i \nabla_x F(x, t)$, where $\nabla_x F(x, t)$ denotes the gradient of $F(x, t)$, and $\lambda_1, \lambda_2 > 0$ for maximization, and $\lambda_1, \lambda_2 < 0$ for minimization. In a biological context, there are two problems with this approach:

(i) we do not have access to $\nabla_x F(x, t)$ and to $-\nabla_x F(x, t)$;
(ii) $u_1(t)$ and $u_2(t)$ cannot physically realize negative values.

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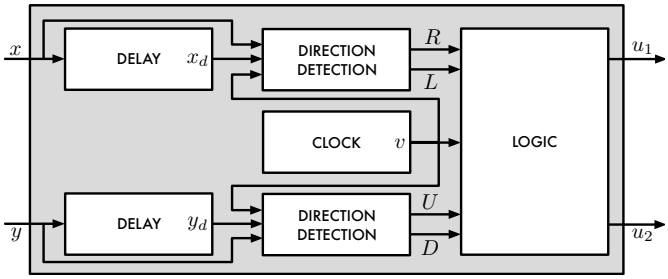

Fig. 1. The proposed optimizer comprises three steps.

3. RESULTS

To overcome these issues, define $\Delta x(t) = x(t) - x(t-\tau)$, $\Delta y(t) = y(t) - y(t-\tau)$, and $I(t) = \Delta x(t)\Delta y(t)$. With this, the control law

$$u_1(t) = \begin{cases} \lambda_1 & I(t) > 0, \\ 0 & I(t) < 0, \end{cases} \qquad u_2(t) = \begin{cases} 0 & I(t) > 0, \\ \lambda_2 & I(t) < 0, \end{cases} \tag{1}$$

ensures not only that the closed-loop dynamics approach the optimal value x^* where $F(x,t)$ is maximized (for minimization, the above u_1 and u_2 conditions can be swapped), but also that x stays close to x^* after convergence.

To realize (1), our optimizer relies on three steps (Fig. 1): (i) a delay of $x(t)$ and $y(t)$; (ii) a comparison of these signals and their delayed versions; and (iii) logic to obtain the indicator I. Next, we introduce modules that realize these functions using standard genetic parts.

(i) Signal Delay With the dynamics $\epsilon_1 \dot{x}_d = x - x_d$ and $\epsilon_1 \dot{y}_d = y - y_d$, the signals x_d and y_d track x and y, respectively, with a time delay that increases with ϵ_1.

(ii) Direction Detection Consider a periodic signal $v(t)$ that switches between two values of 0 and 1, for instance, the normalized output of an activator-repressor clock (Guantes and Poyatos, 2006). We introduce the dynamics

$$\begin{aligned} \epsilon_2 \dot{L} &= v\,(x_d - L) + (1-v)\left(\tfrac{\beta}{1+R^2} - L\right), \\ \epsilon_2 \dot{R} &= v\,(x - R) + (1-v)\left(\tfrac{\beta}{1+L^2} - R\right), \end{aligned} \tag{2}$$

and note that when $v = 1$, we have $L \to x_d$ and $R \to x$ as $t \to \infty$. Conversely, when $v = 0$, the dynamics in (2) become that of the standard toggle switch (Gardner et al., 2000), so that when $\beta \gg 2$, we have two stable equilibria that are approximately β and 0, independent of the initial conditions ($L \approx x_d$, $R \approx x$). Therefore, the initial conditions only determine which stable state we converge to: if L is greater than R (i.e., $x_d > x$) at the end of the first phase (when $v = 1$), then in the second phase (when $v = 0$) we have $L \to \beta$ and $R \to 0$, and vice versa. Hence, L and R denote moving Left or Right, respectively, along the x-axis in the (x,y)-plane. A similar consideration of (2) for D and U denotes moving Down or Up, respectively, along the y-axis in the (x,y)-plane.

(iii) Logic Finally, we use standard AND and OR gates to combine the direction signals L, R, D, and U. To this end, we introduce $H(a) = a^n/(1+a^n)$ and $g(s_1,s_2) = H(s_1/K)H(s_2/K)$ with $K > 0$. With this, the dynamics

$$\epsilon_3 \dot{A}_1 = \lambda_0 g(R,U) - A_1, \qquad \epsilon_3 \dot{B}_1 = \lambda_0 g(L,D) - B_1,$$
$$\epsilon_3 \dot{A}_2 = \lambda_0 g(R,D) - A_2, \qquad \epsilon_3 \dot{B}_2 = \lambda_0 g(L,U) - B_2,$$

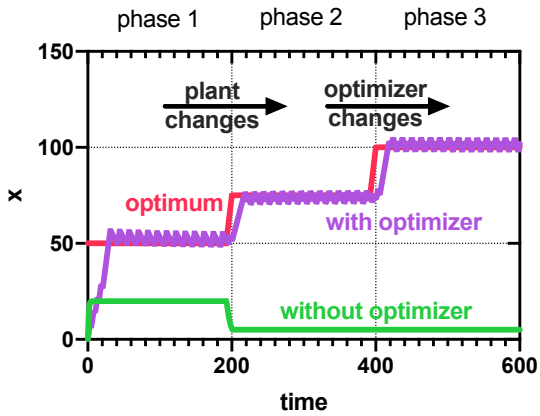

Fig. 2. Without the optimizer, the plant behaves independently of the value of y, whereas with the optimizer, the state x tracks the optimum x^*. Throughout the simulation, $\beta = 100$, $K = \beta/2$, $\sigma = 10$, $\epsilon_1 = 1$, $\epsilon_2 = \epsilon_3 = 0.01$, $n = 2$, $\lambda_0 = 1$, and in the three phases $\alpha = (20, 10, 10)$, $\gamma = (1, 2, 2)$, $\mu = (50, 75, 100)$, $\lambda_1 = (0.5, 0.25, 0.75)$, $\lambda_2 = (0.05, 0.05, 0.025)$.

yield that $A_1 \to \lambda_0$ when R and U are ON, and zero otherwise, and similarly for the other signals. This, together with $\epsilon_3 \dot{u}_i = (1-v)\left[\lambda_i \left(H\left(A_i\right) + H\left(B_i\right)\right) - u_i\right]$ for $i = 1, 2$ yields (1), the control law for maximizing $F(x,t)$. For minimizing $F(x,t)$, we swap U and D above.

4. SIMULATION RESULTS

Consider the objective function $F(x,t) = \exp[(x - \mu(t))^2/(2\sigma^2(t))]$. Without the optimizer, the plant converges to α/γ as $t \to \infty$, which is far from the optimal state $x^* = \mu$ (Fig. 2). Conversely, our optimizer displays robust performance, even in the presence of considerable parameter variations (of the plant, the objective function, and even the optimizer) and noise (Fig. 2).

5. CONCLUSION

Here, we outlined an optimizer module for a wide array of synthetic biology applications. Our developed optimizer module is inspired by gradient-based optimization methods, but it can be constructed using standard and readily-available genetic parts. Our optimizer performs robustly despite substantial parameter uncertainty and noise.

REFERENCES

Ahmad, S., Wang, B., Walker, M.D., Tran, H.K.R., Stogios, P.J., Savchenko, A., Grant, R.A., McArthur, A.G., Laub, M.T., and Whitney, J.C. (2019). An interbacterial toxin inhibits target cell growth by synthesizing (p)ppApp. *Nature*, 1–5. doi:10.1038/s41586-019-1735-9.

Gardner, T.S., Cantor, C.R., and Collins, J.J. (2000). Construction of a genetic toggle switch in Escherichia coli. *Nature*, 403(6767), 339–342.

Guantes, R. and Poyatos, J.F. (2006). Dynamical principles of two-component genetic oscillators. *PLOS Computational Biology*, 2(3), 1–10. doi: 10.1371/journal.pcbi.0020030. .

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