Configurable Linear Control of Biochemical Systems

Tai-Yin Chiu, Ruei-Yang Huang, Hui-Ju Chiang, Jie-Hong Jiang, François Fages

Configurable Linear Control of Biochemical Systems

Tai-Yin Chiu[1], Ruei-Yang Huang[2], Hui-Ju K. Chiang[2,4], Jie-Hong R. Jiang[2,3], and François Fages[4]
[1]Department of Physics, National Taiwan University, Taipei 10617, Taiwan
[2]Graduate Institute of Electronics Engineering, National Taiwan University, Taipei 10617, Taiwan
[3]Department of Electrical Engineering, National Taiwan University, Taipei 10617, Taiwan
[4]EPI Lifeware, Inria Paris-Rocquencourt, France
{b99202046, b97901166, d01943033, jhjiang}@ntu.edu.tw; Francois.Fages@inria.fr

1. INTRODUCTION

The advancements of synthetic biology make biochemical systems of increasing complexity realizable in living cells. Many computation and control design examples have been demonstrated either *in vivo* or *in vitro*. In principle, any polynomial ordinary differential equation can be approximated by chemical reaction networks [1]. When control systems are of concern, linear control is one of the most widely applied control methods. Any linear control system can be realized with three elementary building blocks: integration, gain, and summation. Realizing linear control with biochemical reactions has been proposed in [2], where reaction rates of the underlying reactions play a key role to achieve the desired building blocks. Essentially the reaction rates have to be matched exactly, and it imposes serious practicality restriction because in reality the reaction rates of available reactions are predetermined and can be limited. In this paper we devise a mechanism to make linear control systems configurable by adding auxiliary species as control knobs. The concentrations of the auxiliary species can be adjusted not only to compensate reaction rate mismatch, but also to reconfigure different control systems out of the same control architecture. Hence implementing linear control systems in biochemistry can be made more practical.

2. METHODS

Following [2], we represent a real variable x by the difference $(x^+ - x^-)$ between the concentrations of two molecular species x^+ and x^-. In the sequel, we shall not distinguish a species and its concentration.

2.1 Integration Block

An integration block takes an input signal $u(t)$ and outputs a signal $y(t) = \alpha \int_0^t u(\tau)\mathrm{d}\tau + y(0)$ for $\alpha \in \mathbb{R}$. The integration block for $\alpha \geq 0$ consists of a pair of catalytic reactions (one with the species of upper signs in superscript and the other with species of lower signs) in (1) and an annihilation reaction in (2).

$$x^\pm + u^\pm \overset{k_1^\pm}{\to} x^\pm + u^\pm + y^\pm \tag{1}$$

$$y^+ + y^- \overset{\eta_{\text{int}}}{\to} \phi \tag{2}$$

Auxiliary species $x^\pm$ and input species $u^\pm$ serve as catalysts in (1). With the definition that $k_1^+ x^+ = k_1^- x^- \equiv \alpha$, the kinetics of y is exactly the integration of u as shown below.

$$\dot{y}^\pm = k_1^\pm x^\pm u^\pm - \eta_{\text{int}}\ y^+ y^-$$
$$y' = \dot{y}^+ - \dot{y}^- = k_1^+ x^+ u^+ - k_1^- x^- u^- = \alpha u$$

Because the concentrations of x^+ and x^- can be controlled but not $k_1^\pm$, in theory it is always possible to design a reaction network to meet any required α. For $\alpha < 0$, the signs in the superscript of y in (1) should be swapped to $\mp$.

2.2 Gain and Weighted Summation Blocks

A weighted summation block takes a number of input signals $u_i(t)$, $i = 1, 2, ..., n$ and outputs a signal $y(t) = \sum_{i=1}^n \alpha_i u_i(t)$ for $\alpha_i \in \mathbb{R}$. A gain block is a special weighted summation block with only one input $u(t)$ and producing output $y(t) = \alpha u(t)$ for $\alpha \in \mathbb{R}$. The gain block with $\alpha \geq 0$ can be realized by two pairs of catalytic reactions of (3) and (4), where $x^\pm$ and $z^\pm$ are auxiliary species, and by an annihilation reaction of (5).

$$x^\pm + u^\pm \overset{k_1^\pm}{\to} x^\pm + u^\pm + y^\pm \tag{3}$$

$$z^\pm + y^\pm \overset{k_2^\pm}{\to} z^\pm \tag{4}$$

$$y^+ + y^- \overset{\eta_{\text{gs}}}{\to} \phi \tag{5}$$

These reactions induce the following equation.

$$\dot{y}^\pm = k_1^\pm x^\pm u^\pm - k_2^\pm z^\pm y^\pm - \eta_{\text{gs}}\ y^+ y^-$$

Let $k_u \equiv k_1^+ x^+ = k_1^- x^-$ and $k_y \equiv k_2^+ z^+ = k_2^- z^-$. The mass action of y becomes

$$y' = k_u(u^+ - u^-) - k_y(y^+ - y^-) = k_u u - k_y y$$

If k_y is large enough compared to $|s| = \omega$, Laplace transform converts the above equation to

$$G = \frac{Y}{U} = \frac{k_u}{s + k_y} \approx \frac{k_u}{k_y} \equiv \alpha \tag{6}$$

That is, with properly chosen k_y, the value of y at equilibrium equals αu, which accomplishes the implementation of the gain block. For $\alpha < 0$, the superscript of y in (3) should be swapped.

The weighted summation block can be implemented with the same reactions as the gain block, except that (3) has to be changed to

$$x_i^\pm + u_i^\pm \overset{k_{1,i}^\pm}{\to} x_i^\pm + u_i^\pm + y^\pm,\ i = 1, 2, ..., n \tag{7}$$

If the scaling factor $\alpha_j < 0$, we simply swap the signs in the superscript of y in the reaction of (7) corresponding to input u_j.

3. CASE STUDY

We perform case study on the mass-spring-damper (MSD) system as shown in Fig. 1 A. The system can be modeled by the equation

$$M\ddot{x} + b\dot{x} + kx = F.$$

With $M = 1$ kg, $b = 10$ N s/m, $k = 20$ N/m, $F = 1$ N, by Laplace transform we derive the transfer function

$$G = \frac{1}{s^2 + 10s + 20} \approx 0.2236\left(\frac{1}{s + 2.764} - \frac{1}{s + 7.236}\right)$$

The transfer function can be implemented with the block diagram shown in Fig. 1 B. The proportional-integral (PI) controller to the MSD system is shown in Fig. 1 C.

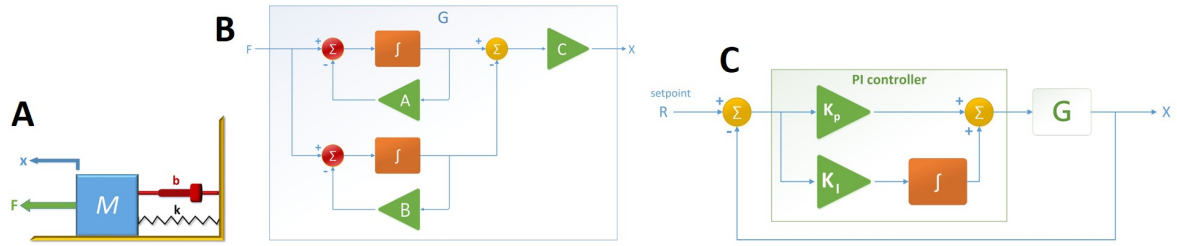
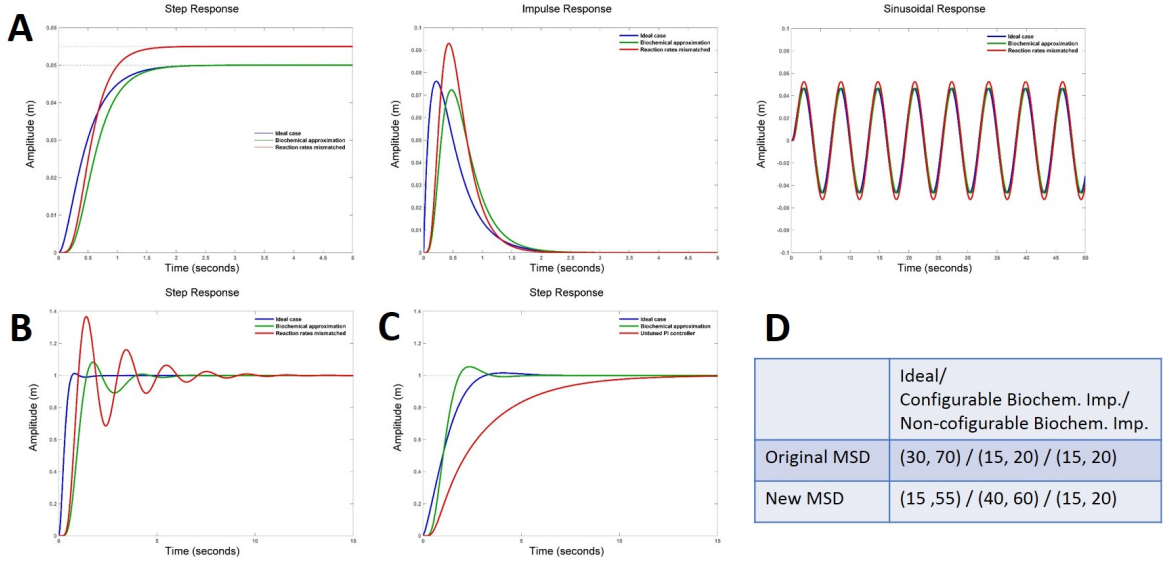


Figure 1: (A) Mass-spring-damper system. (Let $F = 1$ N, $M = 1$ kg, $b = 10$ N s/m, $k = 20$ N/m.) (B) MSD model, where triangular blocks denote gain functions with their corresponding weights, rectangular blocks denote integrators, and circle blocks denote mixers for summation and/or subtraction. (Let $A = 2.764$, $B = 7.236$ and $C = 0.2236$.) (C) PI-controlled MSD model, where G is the plant shown in (B). (Assume the values of K_P and K_I are given in Fig. 2 D.)



	Ideal/ Configurable Biochem. Imp./ Non-cofigurable Biochem. Imp.
Original MSD	(30, 70) / (15, 20) / (15, 20)
New MSD	(15 ,55) / (40, 60) / (15, 20)

Figure 2: The blue, green, and red curves represent the responses in ideal, configurable biochemical implementation, and nonconfigurable biochemical implementation cases, respectively. (A) Step, impulse, and sinusoidal (from left to right) responses of MSD. (B) Step responses of PI-controlled MSD. (Assume 10% rate mismatch in the MSD system.) (C) Step responses of PI-controlled MSD, where the MSD undergos parameter change with $b = 40$ N s/m and $k = 60$ N/m, respectively, which induces gain change of $A = 1.561$, $B = 38.44$ and $C = 0.0271$. (D) The values of (K_P, K_I) in simulation.

The block diagrams are constructed with $k_y = 10$ for all the summation and gain blocks except those summation blocks in red and gain blocks A and B with $k_y = 50$. The values of k_u are set to αk_y where the values of α equal the weights specified in the corresponding gain blocks. Also we assume k_2's have the same values as k_y's and k_1's are in 10% mismatch to k_u's.

Fig. 2 A and B show the responses of the MSD and the PI-controlled MSD systems. As can be seen, our method achieves better approximation to the ideal cases than the prior method [2]. One of the advantages of our method is that we can match the weight k_u/k_y by tuning the concentrations of $x^{\pm}$ and $z^{\pm}$, whereas in the prior method [2] no tuning is possible to avoid the inexact gain k_1/k_2 due to the mismatch of reaction rates k_1 and k_2. (Note that the biochemical implementations have their own optimal K_P and K_I values, shown in Fig. 2 D, to approximate the ideal system.)

Suppose that the spring and damper of the above MSD system are now replaced with new ones for $b = 40$ N s/m and $k = 60$ N/m. Without redesigning the PI-controller, our method can still adapt the PI-controller to the new MSD system whereas prior method has no such capability. Since we can tune the concentrations of $x^{\pm}$ and $z^{\pm}$ in biochemical implementation, it is possible for us to adapt (K_P, K_I) to optimal values $(40, 60)$ for the new PI-controlled MSD system, in contrast to the original $(15, 20)$. Fig. 2 C compares the results with and without such reconfigurability.

4. DISCUSSIONS

The aforementioned linear control systems can possibly be realized using the DNA strand-displacement technique. However the rate constants in the displacement reactions are about six orders of magnitude in 1 M^{-1} s^{-1} [3]. If we require $k_y = k_2^{\pm} z^{\pm}$ in (6) to be 100 M^{-1} s^{-1}, then the concentrations of $z^{\pm}$ will be of five orders of magnitude in nM. Such a high concentration might be impractical. To alleviate this high concentration requirement, one may try to increase the reaction rates. Zhang et al. have constructed and characterized DNA catalytic circuits driven by entropic gains [4]. Based on the entropy effects, a variant, called the tethered entropy driven catalytic circuits, has been introduced [5] to shorten the catalytic cycle and thus increase reaction rates. With these techniques, linear control systems may be effectively realized using DNA displacement reactions.

5. REFERENCES

[1] W. Klonowski. Simplifying principles for chemical and enzyme reaction kinetics. *Biophys. Chem.*, 18(2):73–87, 1983.

[2] K. Oishi and E. Klavins. Biomolecular implementation of linear I/O systems. *IET Syst Biol*, 5(4):252–260, 2011.

[3] D. Y. Zhang and G. Seelig. Dynamic DNA nanotechnology using strand-displacement reactions. *Nature Chem.*, 3(2):103–113, 2011.

[4] D. Y. Zhang, A. J. Turberfield, B. Yurke, and E. Winfree. Engineering entropy-driven reactions and networks catalyzed by DNA. *Science*, 318(5853):1121–1125, 2007.

[5] N. Gopalkrishnan, H. Chandran, S. Garg, and J. Reif. Speeding up DNA circuits using localized hybridization. In *Foundations of Nanoscience Meeting (FNANO)*, 2011.