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Design of an embedded inverse-feedforward biomolecular tracking controller for enzymatic reaction processes

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ABSTRACT

Feedback control is widely used in chemical engineering to improve the performance and robustness of chemical processes. Feedback controllers require a 'subtractor' that is able to compute the error between the process output and the reference signal. In the case of embedded biomolecular control circuits, subtractors designed using standard chemical reaction network theory can only realise one-sided subtraction, rendering standard controller design approaches inadequate. Here, we show how a biomolecular controller that allows tracking of required changes in the outputs of enzymatic reaction processes can be designed and implemented within the framework of chemical reaction network theory. The controller architecture employs an inversion-based feedforward controller that compensates for the limitations of the one-sided subtractor that generates the error signals for a feedback controller. The proposed approach requires significantly fewer chemical reactions to implement than alternative designs, and should have wide applicability throughout the fields of synthetic biology and biological engineering.

1. Introduction

A major challenge in synthetic biology is to develop practically implementable design methods for the synthesis of feedback controllers that achieve reference tracking, i.e. force the output of a biomolecular process of interest to track desired changes in its concentration over time (Hsiao et al., 2015). The design of feedback controllers to control biochemical processes has received significant attention in the literature (see. e.g. Henson, 2003; Baldea et al., 2013), and the construction of synthetic control circuits has become a major focus of research in the new field of synthetic biology. Ideally, such circuits should be made up of well-defined modules consisting only of molecular reactions, in order to allow the realisation of embedded biomolecular control systems (Cosentino et al., 2016). A promising approach to facilitating the design of such circuits is provided by nucleic acid-based chemistry, wherein the design of biomolecular circuits can be done using abstract chemical reaction network (CRN) theory (e.g. Soloveichik et al., 2010), and then translated to deoxyribonucleic acid (DNA) using strand displacement reactions for implementations (Chen et al., 2013). A CRN is a collection of chemical reactions written in the form

$$\underbrace{X+Y+\ldots}_{\text{Reactants}} \xrightarrow{\gamma} \underbrace{A+B+\ldots}_{\text{Products}} \tag{1}$$

where γ is the reaction rate, the left-hand-side (LHS) of the reaction consists of reactants and the right-hand-side (RHS) of the reaction consists of products. Most of the chemical reactions considered in this paper are either unimolecular (i.e. one reactant on the LHS of (1)) or bimolecular (i.e. two reactants on the LHS of (1)). According to standard CRN theory (see e.g. Feinberg, 1986, 1988) a CRN with n species and m reactions can be represented by an ordinary differential equation (ODE) following generalised mass-action kinetic in the form of

$$\frac{dx}{dt} = Pf(x)$$

where $x \in \mathbb{R}^n_{\geq 0}$ is the species concentration, $f(x) \in \mathbb{R}^m$ is a function describing the reaction rates of the CRN, $P \in \mathbb{R}^{n\times m}$ is the *stoichiometric* matrix that describe the dynamics of the species concentrations following their associated reaction rates, $\mathbb{R}_{\geq 0}$ is the non-negative real number set, $\mathbb{R}$ is the real number set, and n and m are positive integers.

Abbreviations: CRN, chemical reaction network; DNA, deoxyribonucleic acid; LHS, left-hand-side; RHS, right-hand-side; ODE, ordinary differential equation; PI, proportional-integral; FF, feedforward; IMC, internal model control; DSD, DNA strand displacement.

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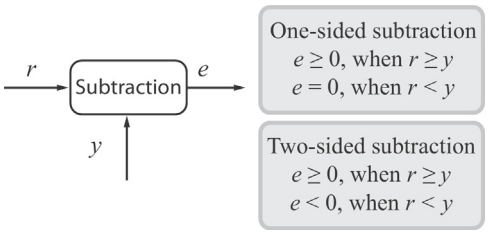

Fig. 1. Subtraction operator.

In any reference tracking feedback system, it is imperative that an appropriate error signal can be computed such that the designed controller can take relevant control action to drive the process output towards the intended state. While such a requirement is trivial to satisfy in standard control theory, it is not in the context of CRN theory. This is because a two-sided subtractor (Fig. 1), which is an operator that is able to compute the difference between two input signals regardless of their relative magnitude, is yet to be realised using standard CRN's. For accurate reference tracking, the error e should be able to take both positive ($r>y$) and negative ($r<y$) values. Thus, the aforementioned constraint is a serious impediment to the design of functional biomolecular feedback control systems that will inevitably lead to poor quality reference tracking and potentially even instability.

To the best of the authors' knowledge, almost all previous designs for biomolecular subtractors using CRNs have resulted in only one-sided subtraction. We note that there is a literature on the design of half-subtractors or full-subtractors using digital logic gates realised using CRNs (see e.g. Xu et al., 2013; Lin et al., 2015), however, as our focus is on the design of analog biomolecular circuitry, we exclude this work from our discussion.

The subtraction operator used in our paper is based on the design presented in Buisman et al. (2009), which can be realised using a set of four chemical reactions (see Page 6 of Buisman et al. (2009)). The authors analysed the Jacobian matrix of the ODE associated with the subtraction operator and found that when the resulting subtraction is zero, the fixed point does not exist. Additionally, when the resulting subtraction is negative, the overall system diverges, as the fixed point is unstable. In view of this, the subtraction outputs a positive value when the magnitude of the first component is greater than the second component and zero when the condition is reversed. We further illustrate this point in Section 2.2 of our paper. Some other relevant results on biomolecular subtraction can be found in Salehi et al. (2016) and Song et al. (2016). The design considered in the former used the subtraction operator to realise a biomolecular computation of a Berstein polynomial and their subtraction is equivalent to the design of Buisman et al. (2009). The latter paper proposed frameworks to build operators using DNA strand displacement, and explicitly mentioned that their subtraction operator is one-sided. In Harris et al. (2015), the authors designed a feedback controller for gene expression regulation, which requires the use of a subtraction, but do not propose a detailed biomolecular implementation of the subtraction operator.

An alternative approach to the design of biomolecular subtraction operators can be found in Cosentino et al. (2013, 2016) and Bilotta et al. (2015, 2016). In this work, the authors developed subtractors that are used to compute the difference between two molecular fluxes, rather than two molecular concentrations. By satisfying certain conditions, and assuming all the reactions involve unitary stoichiometric coefficients with input fluxes constant, the output flux is shown to converge to the difference between the two input fluxes in an asymptotic manner. While the chemical reactions required to realise the subtraction operator in this framework are slightly different to the ones proposed in Buisman et al. (2009), the final ODE representation is exactly the same, and thus also yields a one-sided subtraction.

The only available partial solution to the problem mentioned above is to adopt the design framework proposed in Oishi and Klavins (2011). In this framework, each signal in the biomolecular circuit is implemented as the difference in the concentration of two chemical species. In this way, a two-sided subtraction operator can then be realised. As we show in the following section, however, this approach at least doubles the total number of chemical reactions required to implement the entire feedback circuit. This increase in the number of chemical reactions is highly undesirable as it presents a major challenge for wet lab implementation, and strongly limits the scalability of the design. Moreover, large numbers of chemical reactions potentially increases the probability of unwanted crosstalk interactions. For instance, a circuit whose implementation requires n molecular species will increase the potential bimolecular crosstalk interactions by n^2. This has prompted researchers to look into ways to reduce crosstalk, such as requiring a certain number of mismatches for any two distinct recognition domains (see e.g. Qian and Winfree, 2011). Nonetheless, obtaining large numbers of well-behaved sequences with long domains is extremely difficult to achieve in practice.

In this paper, using the available framework for realising one-sided biomolecular subtraction using CRNs (see e.g. Buisman et al., 2009), we propose a design strategy that uses a model-inversion feedforward controller (see e.g. Devasia, 2002; Franklin and Powell, 2014) to circumvent the limitations of the feedback controller when using a one-sided subtraction operator. In addition, our controller design strategy also aims to utilise the minimal number of chemical reactions, to allow for a more scalable and feasible wet lab implementation.

2. Materials and methods

2.1. One-sided subtraction operator

To the best of authors' knowledge, all current existing designs for biomolecular subtraction operators that utilise standard CRN theory can only implement one-sided subtraction. A comprehensive list of mathematical operators that can be implemented using CRN's, which includes the one-sided subtraction and its detailed analyses can be found in Buisman et al. (2009). Following the design of Buisman et al. (2009), the subtraction operator can be realised using the following abstract chemical reactions:

$$\begin{aligned} x_{i,1} &\xrightarrow{\gamma} x_{i,1} + x_o, \quad x_{itd} + x_o \xrightarrow{\gamma} \emptyset \\ x_{i,2} &\xrightarrow{\gamma} x_{i,2} + x_{itd}, \quad x_o \xrightarrow{\gamma} \emptyset \end{aligned} \tag{2}$$

where $x_{i,1}$ and $x_{i,2}$ are the two inputs, x_o is the resulting output, x_{itd} is the intermediate states and γ is the reaction rate. Note that this one-sided subtraction operator is realised using *four* abstract chemical reactions. Using generalised mass-action kinetics (see e.g. Feinberg, 1986), these abstract chemical reactions can be represented by ODE's, where the corresponding ODE's for (2) are given by

$$\begin{aligned} \frac{dx_o}{dt} &= \gamma(x_{i,1} - x_o x_{itd} - x_o) \\ \frac{dx_{itd}}{dt} &= \gamma(x_{i,2} - x_o x_{itd}) \end{aligned} \tag{3}$$

At steady state, $x_{i,2} = x_o x_{itd}$, leading to $x_o = x_{i,1} - x_{i,2}$. By analysing the Jacobian matrix of the ODE's relating to this subtraction operator, it has been shown in Buisman et al. (2009) that when the subtraction of two components results in either zero or a negative value, the fixed point does not exist or the system converges to