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Zero-Retroactivity Subtraction Module for Embedded Feedback Control of Chemical Reaction Networks

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Abstract: The control of biochemical processes is a major goal in systems and synthetic biology. Current approaches are based on ad-hoc designs, whereas a general and modular framework would be highly desirable, in order to exploit the well-assessed methods of control theory. A well-known problem when dealing with complex biosystems is represented by the retroactivity effect, which can significantly modify the dynamics of interconnected subsystem, with respect to the behavior they exhibit when disconnected from each other. In the present work an implementation of a zero-retroactivity Chemical Reaction Network Subtractor (CRNS) is proposed and its effectiveness is investigated through singular perturbation analysis. The proposed CRNS represents a first step towards the development of a modular framework for the design of CRN-based embedded feedback control systems.

Keywords: Chemical reaction networks, retroactivity, Systems biology, synthetic biology.

1. INTRODUCTION

The development of a general control theory for biomolecular processes would require the realization of a set of basic molecular circuits that can be assembled in a modular way. A common approach for designing and analyzing a complex system is to decompose it into smaller modules, whose functions are well isolated by those of the neighboring modules. This approach has been employed for long time in engineering disciplines, such as electrical engineering and computer science and, more recently, it has been proposed also for the analysis of bio-molecular systems. Guaranteeing that the properties of individual components do not change upon interconnection is the central characteristic on the basis of modularity. Unfortunately, in biological systems modularity is generally compromised by *retroactivity*, which plays a role similar to impedance in electrical circuits, and consists in the effect of the reciprocal interactions arising from the interconnection of two modules (Del Vecchio et al. (2008); Del Vecchio (2013, 2015)).

From a design point of view, the retroactivity must be taken into account when engineering bio-molecular circuits and that suitable insulation mechanisms should be designed in order to buffer connected components from each other (Del Vecchio (2013)). Some solutions to attenuate retroactivity, based on high-gain feedback and time scale separation, are now available (Jayanthi and Del Vecchio (2011); Mishra et al. (2014)).Designs of insulation devices have been proposed in literature with the aim of attenuating retroactivity effects (Del Vecchio et al. (2008); Del Vecchio and Sontag (2009); Del Vecchio (2015)). The need for understanding the extent of modularity and attenuating the retroactivity in bio-molecular systems has become particularly pressing when designing synthetic circuits. Towards the realisation of modular embedded feedback controllers in synthetic biological systems, the availability of a well-characterised subtraction module is a key step. In the classical one-degree-of-freedom control scheme, a subtraction module is required to compare the desired set-point with the actual output of the process to be controlled. The realization of an embedded subtractor module remains, to the best of our knowledge, an open issue, as also discussed in Dolan et al. (2012). Oishi and Klavins (2011) have also addressed this problem in, though their approach requires some conditions not easy to meet in practice, whereas Chen et al. (2014) have shown that CRNs can be used to compute continuous piecewise linear functions. Cosentino et al. (2016) have investigated the general properties of a minimal CRN-based molecular subtractor and proposed some realization structures. A preliminar study of the retroactivity of these alternative structures has been conducted in Bilotta et al. (2015).

The present work proposes a zero-retroactivity CRN-based subtraction module, which can be used as a basic component for designing feedback controllers for biochemical reaction networks. It is assumed that the CRNS takes as first input the set-point flux and as second input the output flux of the controller process. In this case, it is important to minimize the retroactivity of the subtractor on the second input, in order to avoid undesired influence

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on the dynamics of the controlled output species. Otherwise, the subtractor would consume the output species of the controlled process, thus affecting the capability of the control system to track the desired set-point.

The paper is organized as follows: in Section 2 we discuss the general properties required from a subtraction block and translate these into two minimal CRN-based subtraction modules. Moreover, the concept of retroactivity and a general modeling scheme for the connection of bio-molecular systems are briefly recalled. In Section 3 a singular perturbation analysis of the two interconnected subtractors is carried out upon interconnection with an upstream and a downstream module. Some illustrative numerical examples are given in Section 4. Finally, Section 5, provides some concluding remarks.

2. PRELIMINARIES

2.1 Minimal properties of a molecular subtractor

Let consider a reactor, containing a generic CRN $\mathcal{C}$ comprising n species. Assume it is possible to inject from outside the reactor only species A and B, and denote with $u_A(t)$ and $u_B(t)$ the number of molecules per unit volume injected per unit time, and with $y_C(t)$ the corresponding number of molecules per unit volume of a species C produced by the CRN in the same time interval. To fix ideas, assume that $u_A(t) > u_B(t) > 0$. Furthermore, denote by

$u_A^{\mathbf{notC}}$**:** the number of molecules of A per unit volume that the CRN *irreversibly* converts into species other than C (including the null species, i.e. degradation of A) over a unit time interval;

$u_A^{\mathbf{C}}$**:** the number of molecules of A per unit volume that the CRN *irreversibly* converts into molecules of C over the same time interval (through any number of intermediate reactions).

Proposition 1. (Cosentino et al. (2016)) Assume that all the reactions in the CRN $\mathcal{C}$ exhibit unitary stoichiometric coefficients, that the input fluxes $u_{\rm A}$, $u_{\rm B}$ are constant and that the following conditions are satisfied

$$u_A^{\rm notC} = u_{\rm B}, \tag{1a}$$

$$u_A^{\rm C} = u_{\rm A} - u_{\rm A}^{\rm notC}\,. \tag{1b}$$

$$u_{\rm A} = 0 \Rightarrow \lim_{t\to\infty} y_{\rm C}(t) = 0\,. \tag{1c}$$

Then, the output flux y_C tends asymptotically to the difference of the input fluxes, $u_{\rm A} - u_{\rm B}$.

Proof Conditions (1a)-(1b) yield $u_{\rm A}^{\rm C} = u_{\rm A} - u_{\rm B}$. Condition (1c) implies that C is a product of either A or a species produced from A, through an arbitrary number of intermediate reactions, and cannot be produced from other sources in the absence of A. Since the reactions have unitary stoichiometric coefficients and the conversion of A to C is irreversible, $y_{\rm C}(t)$ will tend asymptotically to $u_{\rm A}^{\rm C}$. Note that there is an infinite number of CRNs that satisfy conditions (1), since the conversion of A into other molecules (either C or non-C) can occur through any sequence of reactions, involving any number of species.

In order to achieve a minimal realization, only CRNs comprising just the three molecular species associated to the interconnection fluxes are considered. Under this constraints, a possible realization of the CRNS, satisfying conditions (1) is

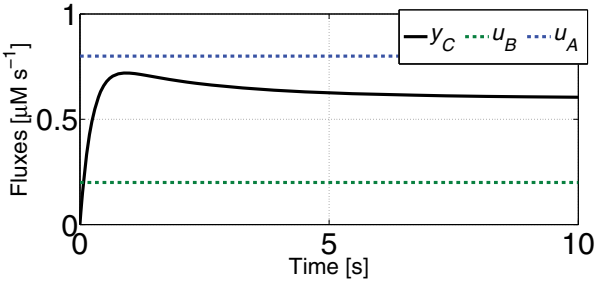

Fig. 1. Response of the isolated CRN subtraction module: The first input flux (species A) is $u_A = 0.8$ μM s^{-1}, the second input flux (species B) is $u_B = 0.2$ μM s^{-1}. The kinetic parameters in CRN (3) are set to $k_1 = 4$s^{-1} and $k_2 = 3$ (μM s)$^{-1}$ therefore the output flux (solid line) of species C represents the difference between the two input fluxes (dashed lines).

$$\varnothing \xrightarrow{u_A} \mathrm{A} \xrightarrow{k_1} \mathrm{C} \tag{2a}$$

$$\varnothing \xrightarrow{u_B} \mathrm{B} \tag{2b}$$

$$\mathrm{A} + \mathrm{B} \xrightarrow{k_2} \circledast\,, \tag{2c}$$

where $y_C = k_1 a$, the symbol "$\circledast$" means that the product of reaction (2c) can be any complex of species different from A, B and C (including the null species $\varnothing$ in the case of degradation), since it does not affect the behavior of the CRN.

2.2 Two possible CRN-based subtraction modules

To realize the subtraction operation between the fluxes of two species, A and B, the CRN-based module we propose to employ is the following CRN.

$$\begin{aligned} \varnothing &\xrightarrow{u_A} \mathrm{A} \xrightarrow{k_1} \mathrm{C} \\ \varnothing &\xrightarrow{u_B} \mathrm{B} \\ \mathrm{A} + \mathrm{B} &\xrightarrow{k_2} \mathrm{W}\,. \end{aligned} \tag{3}$$

The dynamical system describing the behavior of CRN (3) is given by the two input-single output system

$$\dot{a} = u_A - k_1\, a - k_2\, a\, b \tag{4a}$$

$$\dot{b} = u_B - k_2\, a\, b \tag{4b}$$

$$\dot{w} = k_2\, a\, b \tag{4c}$$

$$y_C = \dot{c} = k_1\, a\,, \tag{4d}$$

where italic lowercase letters, a, b, c, and w are used to denote the concentration of species A, B, C and W, respectively.

For each molecule of B that enters the CRN (3), exactly one molecule of A is converted into species W. The molecules of A that are not degraded or converted to W, are turned into molecules of C. In this way, the output flux of species y_C tends asymptotically to the difference of the two inputs fluxes u_A and u_B, see Fig. 1.

Alternatively, let us consider another CRN, which involves a species B that can exist in two forms (e.g., a protein in