Biomolecular Implementation of a Quasi Sliding Mode Feedback Controller based on DNA Strand Displacement Reactions

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***Abstract*— A fundamental aim of synthetic biology is to achieve the capability to design and implement robust embedded biomolecular feedback control circuits. An approach to realize this objective is to use abstract *chemical reaction networks* (CRNs) as a programming language for the design of complex circuits and networks. Here, we employ this approach to facilitate the implementation of a class of nonlinear feedback controllers based on sliding mode control theory. We show how a set of two-step irreversible reactions with ultrasensitive response dynamics can provide a biomolecular implementation of a nonlinear *quasi sliding mode* (QSM) controller. We implement our controller in closed-loop with a prototype of a biological pathway and demonstrate that the nonlinear QSM controller outperforms a traditional linear controller by facilitating faster tracking response dynamics without introducing overshoots in the transient response.**

I. INTRODUCTION

Almost all proposed biomedical applications of synthetic biology will require the ability to precisely and robustly control the behaviour of synthetic circuits or devices at a biomolecular level, [1], [2], [3]. A fundamental aim of synthetic biology is thus to achieve the capability to design and implement robust embedded biomolecular feedback control circuits. An appropriate modelling and design framework for tackling this problem is provided by *chemical reaction networks* (CRNs), which represent a convenient and concise way to model chemical and biological processes and provide an effective tool for the analysis of their behaviour, [4]. Previous work on the implementation of feedback controllers within this framework has focussed on the design of linear time-invariant systems only, e.g. the *proportional+integrator* (PI) controllers described in [5], [6], [7]. This approach fails to exploit the inherently nonlinear dynamics of biomolecular circuits, and also requires the use of additional circuitry to overcome the wind-up effects associated with the integrator action. Here, we extend this approach to allow the implementation of a well-known type of nonlinear controller, based on sliding mode control theory, whose strong performance and robustness characteristics have been widely recognised in more traditional control engineering application domains [8], [9], [10]. We show how a set of two-step irreversible reactions with ultrasensitive response dynamics can provide a biomolecular implementation of a nonlinear quasi sliding mode controller. We implement this controller on a prototype closed loop feedback system that consists of three individual modules, a *subtractor, controller* and *process*, each realized by mass action kinetics at a molecular level and interconnected using a modular approach. The performance of the *quasi sliding mode* (QSM) controller is compared with that of a linear PI controller, and is shown to provide faster response dynamics without introducing overshoots in the transient response.

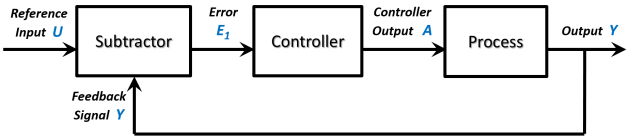

Fig. 1: The closed loop feedback control system

The paper is organised as follows: in section II we describe the methodology used to convert the chemical reactions underlying the desired operation of each module in the control system to its corresponding mathematical model within the CRN framework. In section III we show comparative results on the closed loop performance properties of the proposed nonlinear QSM controller versus a standard linear PI controller. Section IV provides some conclusions.

II. METHODOLOGY

Extending the methodology of [11], we compile CRNs of unimolecular and bimolecular reactions into strand displacement DNA-based chemistry to achieve the desired dynamic behaviour of the biomolecular system under consideration. The implementation of our closed loop feedback system in Fig. 1 consists of three basic modules realized using CRNs. Chemical concentrations in strand displacement reactions can be represented as signals, as shown in Fig. 1. In feedback control theory, signals may take positive or negative values when evolving over time, whereas chemical concentrations can *only take positive values*. To resolve this difficulty, we follow [5] and represent each signal x as a difference in the concentrations of two particular chemical species x^+ and x^- which are referred to as the positive and negative components of the signal x, respectively, so that $x = x^+ - x^-$. Thus, x^+ and x^- takes the positive and negative *absolute values* of the signal x, respectively. Each module in Fig. 1 can be represented using CRNs, and the resulting *ordinary differential equations* (ODEs) are obtained by applying generalised mass-action kinetics, as follows in the next section. Note that in Fig. 1 the subtractor is shown by block rather than the standard circle used in control theory, as we also consider its dynamics.

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A. Quasi Sliding Mode Controller

The activation-deactivation process involved in the DNA strand displacement mechanism is realized by a set of two step irreversible reactions that implement our QSM controller. Here, the output sequence of the first bimolecular reaction initiates another strand displacement. For notational convenience, we denote the chemical species in the CRNs and their respective concentrations in the system of ODEs by the same symbols.

$$I^{\pm} + E_1^{\pm} \underset{d_I}{\overset{a_I}{\rightleftharpoons}} C_1^{\pm} \xrightarrow{k_{u_I}} A^{\pm} + E_1^{\pm} \tag{1a}$$

$$A^{\pm} + E_2^{\pm} \underset{d_2}{\overset{a_2}{\rightleftharpoons}} C_2^{\pm} \xrightarrow{k_{u_2}} I^{\pm} + E_2^{\pm} \tag{1b}$$

The forward reaction (1a) gives product (A), from partially double stranded DNA segment (E_1) and invader (I), which is able to react further and the backward reaction (1b) deactivates product (A), by means of species (E_2). In these two step reactions, the intermediate product formed, complex $(I:E_1)$, is denoted by C_1, and complex $(A:E_2)$ is denoted by C_2. In (1), a_1, a_2 represent the species association rates and d_1, d_2, the dissociation rates. Catalytic rates for activation-deactivation reactions are denoted by k_{u_1} and k_{u_2} respectively.

Applying generalized mass action kinetics to (1) results in a system of differential equations that implements the biomolecular QSM controller. The derivation of the ODEs for these two-step irreversible reactions is summarised as follows:

$$\dot{A}^+ = -a_2 A^+ E_2^+ + k_{u_1} C_1^+ + d_2 C_2^+$$
$$\dot{A}^- = -a_2 A^- E_2^- + k_{u_1} C_1^- + d_2 C_2^-$$

Using the relation in [5] for the above equation set, we arrive at the differential equation for A:

$$\begin{aligned}
\dot{A} = \;& \dot{A}^+ - \dot{A}^- \\
= \;& (-a_2 A^+ E_2^+ + k_{u_1} C_1^+ + d_2 C_2^+) \\
& - (-a_2 A^- E_2^- + k_{u_1} C_1^- + d_2 C_2^-) \\
= \;& -a_2[(A^+ E_2^+) - (A^- E_2^-)] \\
& + k_{u_1}(C_1^+ - C_1^-) + d_2(C_2^+ - C_2^-)
\end{aligned}$$

Assuming, $(A^+E_2^+) = (AE_2)^+$ and $(A^-E_2^-) = (AE_2)^-$

$$\begin{aligned}
&= -a_2[(AE_2)^+ - (AE_2)^-] + k_{u_1} C_1 + d_2 C_2 \\
\Rightarrow \quad \dot{A} = \;& -a_2(AE_2) + k_{u_1} C_1 + d_2 C_2
\end{aligned} \tag{2}$$

Similarly, for $\dot{C}_1$ we write:

$$\dot{C}_1^+ = a_1 I^+ E_1^+ - (d_1 + k_{u_1}) C_1^+$$
$$\dot{C}_1^- = a_1 I^- E_1^- - (d_1 + k_{u_1}) C_1^-$$

and obtain the differential equation for C_1 as:

$$\begin{aligned}
\dot{C}_1 = \;& \dot{C}_1^+ - \dot{C}_1^- \\
= \;& (a_1 I^+ E_1^+ - (d_1 + k_{u_1}) C_1^+) \\
& - (a_1 I^- E_1^- - (d_1 + k_{u_1}) C_1^-) \\
= \;& a_1[(I^+ E_1^+) - (I^- E_1^-)] - (d_1 + k_{u_1})(C_1^+ - C_1^-)
\end{aligned}$$

Assuming, $(I^+E_1^+) = (IE_1)^+$ and $(I^-E_1^-) = (IE_1)^-$

$$\begin{aligned}
&= a_1[(IE_1)^+ - (IE_1)^-] - (d_1 + k_{u_1}) C_1 \\
\Rightarrow \quad \dot{C}_1 = \;& a_1 IE_1 - (d_1 + k_{u_1}) C_1
\end{aligned} \tag{3}$$

Following the same procedure as above to obtain the signal dynamics for C_2, we write:

$$\dot{C}_2^+ = a_2 A^+ E_2^+ - (d_2 + k_{u_2}) C_2^+$$
$$\dot{C}_2^- = a_2 A^- E_2^- - (d_2 + k_{u_2}) C_2^-$$

and the corresponding differential equation for C_2 is:

$$\begin{aligned}
\dot{C}_2 = \;& \dot{C}_2^+ - \dot{C}_2^- \\
= \;& (a_2 A^+ E_2^+ - (d_2 + k_{u_2}) C_2^+) \\
& - (a_2 A^- E_2^- - (d_2 + k_{u_2}) C_2^-) \\
= \;& a_2[(A^+ E_2^+) - (A^- E_2^-)] - (d_2 + k_{u_2})(C_2^+ - C_2^-) \\
= \;& a_2[(AE_2)^+ - (AE_2)^-] - (d_2 + k_{u_2}) C_2 \\
\Rightarrow \quad \dot{C}_2 = \;& a_2 AE_2 - (d_2 + k_{u_2}) C_2
\end{aligned} \tag{4}$$

For the QSM controller defined by (2), (3) and (4), the total substrate concentration of involved species in active, inactive, bound and unbound form is denoted by, S. Here, quantities S and E_2 are constants as their concentration is assumed to be preserved throughout the reaction process and the constraint on S determines I such that, $I = S - A - C_1 - C_2$.

Equations (2), (3) and (4) defining the QSM controller, is an approximation of an ideal sliding mode controller (SMC), [8], [9], [10]. To see this, note that if E_2 goes to zero, the controller approximates a simple switching mechanism so its output, U_c, can be represented by the following formula:

$$U_c(t) = k_{SMC} \cdot sgn(E_c(t)) \tag{5}$$

This kind of controller takes only two values, k_{SMC} and $-k_{SMC}$ (based on the sign of its input signal, the error E_c), and has a discontinuity on the straight line $E_c = 0$, whose equation is called the sliding manifold $\sigma \overset{def}{=} E_c = 0$, where σ is the sliding variable. The control signal U_c, defined by (5), is therefore designed to force the system to move toward the sliding manifold $\sigma = 0$ (the *reaching phase* of SMC) and then maintain this condition (i.e. $\sigma = 0$) for all future time (the *sliding phase* of SMC). In practice, however, implementations of perfect sliding mode controllers cause the system's closed loop response to exhibit a zigzag motion of small amplitude and high frequency, due to imperfections in switching devices and delays [8], [9], [10] (see Fig. 4). This effect, known as *chattering*, is typically avoided by

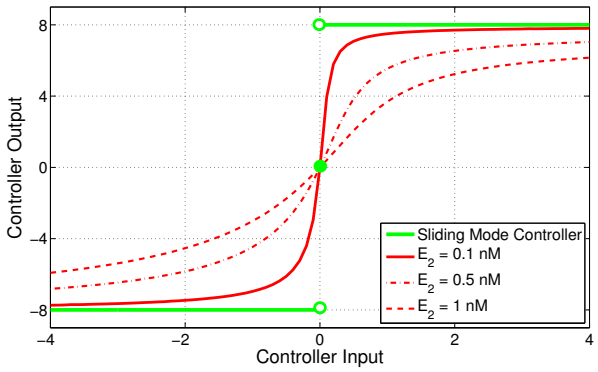

Fig. 2: Input-output characteristics of an ideal sliding mode controller (green) and quasi sliding mode controller (red) as the parameter E_2 is tuned.

using continuous/smooth approximations of the discontinuous SMC. Our controller is an example of such a function, which can be used to approximate the nonlinearity $\text{sgn}(E_c)$, constituting a QSM controller. Since with a QSM controller there is no ideal sliding mode in the closed-loop system, the sliding variable cannot be driven exactly to zero in a finite time, [10]. However, as the response of our controller is made more ultrasensitive (by decreasing E_2), the input-output characteristics of the QSM controller converge to that of the ideal SMC, as shown in Fig. 2.

B. Process to be Controlled

The process to be controlled in the closed loop feedback scheme is a simple first order linear system defined by a set of catalysis, degradation and annihilation reactions as:

$$A^{\pm} \xrightarrow{k_I} A^{\pm} + Y^{\pm} \tag{6a}$$
$$Y^{\pm} \xrightarrow{k_2} \phi \tag{6b}$$
$$Y^{+} + Y^{-} \xrightarrow{\eta} \phi \tag{6c}$$

The signal dynamics resulting from applying mass action kinetics to (6) are:

$$\dot{Y} = k_1 A - k_2 Y \tag{7}$$

where, k_1 and k_2 are catalysis and degradation rates, respectively. Species A concentration is the controller manipulated output that serves as input to the process and Y is the actual output of the closed loop feedback system.

C. Subtractor

Feedback control requires the capability to compare a signal representing the desired value of the process output with the current output of the process. The difference between these two signals thus constitutes an error signal, which acts as an input to the feedback controller. In our framework, the required subtraction operation for two input signals (i.e. two chemical species), U and Y, is performed by four irreversible unimolecular reactions that produce the error signal E_1 which is then input to the controller [5]:

$$U^{\pm} \xrightarrow{k_s} U^{\pm} + E_1^{\pm} \tag{8a}$$
$$Y^{\pm} \xrightarrow{k_s} Y^{\pm} + E_1^{\mp} \tag{8b}$$
$$E_1^{\pm} \xrightarrow{k_s} \phi \tag{8c}$$
$$E_1^{+} + E_1^{-} \xrightarrow{\eta} \phi \tag{8d}$$

The dynamics of the error signal from applying mass action kinetics to (8) are:

$$\dot{E}_1 = k_s(U - Y - E_1) \tag{9}$$

Here, k_s is the catalysis as well as degradation rate and error signal dynamics are dependent on the concentration of all the three species involved.

D. Linear PI Controller

We use a linear PI controller, expressed by a set of seven CRNs, as a baseline to evaluate the closed loop performance of our QSM controller. The chemical reactions and corresponding rates and kinetic constants are based on those given by [5] and references therein [11] and are given by:

$$E_1^{\pm} \xrightarrow{k_I} E_1^{\pm} + Q^{\pm} \tag{10a}$$
$$Q^{+} + Q^{-} \xrightarrow{\eta} \phi \tag{10b}$$

$$\phi \xrightarrow{\gamma\delta_I} A^{\pm} \tag{10c}$$
$$E_1^{\pm} \xrightarrow{\gamma k_P} E_1^{\pm} + A^{\pm} \tag{10d}$$
$$Q^{\pm} \xrightarrow{\gamma} Q^{\pm} + A^{\pm} \tag{10e}$$
$$A^{\pm} \xrightarrow{\gamma(1+\delta_2)} \phi \tag{10f}$$
$$A^{+} + A^{-} \xrightarrow{\eta} \phi \tag{10g}$$

The PI controller is approximated using species E_1, Q and A. Here, E_1 is the input (error signal) and A is the output of the controller. The signal dynamics of the first order linear PI controller are:

$$\dot{Q} = k_I E_1 \tag{11a}$$
$$\dot{A} = \gamma[(k_p E_1 + Q + \delta_1) - (1 + \delta_2)A] \tag{11b}$$

III. RESULTS

We compared the closed loop dynamic response of the linear PI controller and the nonlinear QSM controller for a square wave reference signal U of amplitude 4 nM. The reaction rates and kinetic constants of the QSM controller are set to their nominal values as reported in Table I. $K_1 = \frac{k_1+d_1}{a_1}$ and $K_2 = \frac{k_2+d_2}{a_2}$ are the Michaelis Menten constants. Initial concentrations of the species A, C_1, C_2 are set to zero (A_0, C_{1_0}, $C_{2_0} = 0$ nM). The nominal values of all the kinetic

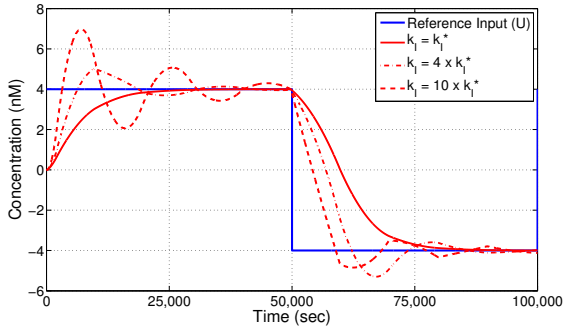

Fig. 3: Large overshoots occur in the closed loop response of the PI controller (red) when k_I is increased to achieve a faster response.

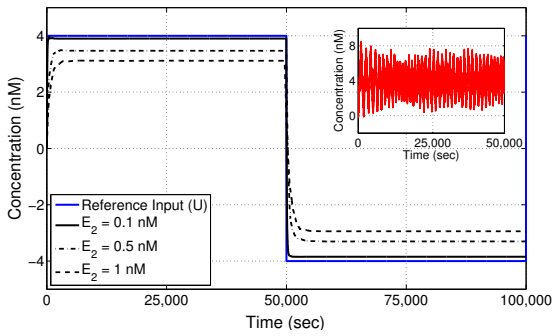

Fig. 4: Effect of tuning E_2 as shown in Fig. 2 on the closed loop response of the QSM controller (black) while the problem of "chattering" in the closed loop response of the implemented SMC (red) is also avoided.

TABLE I: QSM Controller

	Parameters	Nominal Values
S	total substrate conc.	8 nM
E_2	total substrate conc.	0.1 nM
a_1	forward association rate	5000 /nM/s
a_2	forward dissociation rate	5000 /nM/s
k_{u_1}	catalytic reaction rate	17 /s
k_{u_2}	catalytic reaction rate	17 /s
K_1	Michelis Menten constant	8 nM
K_2	Michelis Menten constant	8 nM

TABLE II: PI Controller

	Parameters	Nominal Values
γ	forward reaction rate	0.4×10^{-6} /s
k_I	forward reaction rate	0.4×10^{-6} /s
k_P	kinetic constant	1
δ_1	kinetic constant	0
δ_2	kinetic constant	2

constants for PI controller are enlisted in Table II and initial concentrations of all the species involved in CRNs (10) are set to zero ($E_{1_0},\ Q_0,\ A_0 = 0\ nM$). For the subtractor, k_s is set to nominal value $0.4 \times 10^{-6}\ /s$.

As shown in Fig. 3, the PI controller with nominal value of k_I is able to track the reference signal, however the response time is rather slow (settling time of $25,000\ s$). If the gain of the PI controller is increased (by increasing the values of k_I) to obtain a faster response, significant overshoots are then observed in the closed loop dynamics. Fig. 4 shows the corresponding closed loop response achieved by the QSM controller. The response is now dramatically faster (settling time of 200 s), without the presence of overshoots, and by decreasing the value of E_2, the steady state error can be made as small as desired. The QSM controller also avoids the problem of chattering in the closed loop response exhibited by the ideal SMC (shown in red). Increasing the accuracy of the solution computed by the ODE solver for the closed loop system with the ideal SMC reduces the zigzag motion, but due to the discrete-time nature of the computer simulation the output response continues to exhibit chattering.

IV. CONCLUSIONS

In this paper we construct DNA strand displacement based unimolecular [5] and bimolecular [11] CRNs in order to realize a nonlinear quasi sliding mode feedback controller. When compared with the performance of a traditional linear PI controller, our proposed QSM controller yields dramatically faster responses, without producing overshoots in the tracking response. The presented approach is highly modular, fully exploits the inherently nonlinear nature of biomolecular reaction kinetics, and makes for the first time a direct link between the biological concept of ultrasensitivity and the engineering theory of sliding mode control.

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