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Shaping pulses to control bistable systems: Analysis, computation and counterexamples[☆]

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ABSTRACT

In this paper we study how to shape temporal pulses to switch a bistable system between its stable steady states. Our motivation for pulse-based control comes from applications in synthetic biology, where it is generally difficult to implement real-time feedback control systems due to technical limitations in sensors and actuators. We show that for monotone bistable systems, the estimation of the set of all pulses that switch the system reduces to the computation of one non-increasing curve. We provide an efficient algorithm to compute this curve and illustrate the results with a genetic bistable system commonly used in synthetic biology. We also extend these results to models with parametric uncertainty and provide a number of examples and counterexamples that demonstrate the power and limitations of the current theory. In order to show the full potential of the framework, we consider the problem of inducing oscillations in a monotone biochemical system using a combination of temporal pulses and event-based control. Our results provide an insight into the dynamics of bistable systems under external inputs and open up numerous directions for future investigation.

1. Introduction

In this paper we investigate how to switch a bistable system between its two stable steady states using external input signals. Our main motivation for this problem comes from synthetic biology, which aims to engineer and control biological functions in living cells (Brophy & Voigt, 2014). Most of current research in synthetic biology focuses on building biomolecular circuits inside cells through genetic engineering. Such circuits can control cellular functions and implement new ones, including cellular logic gates, cell-to-cell communication and light-responsive behaviours. These systems have enormous potential in diverse applications such as metabolic engineering, bioremediation, and even the energy sector (Purnick & Weiss, 2009).

Several recent works (Menolascina, Di Bernardo, & Di Bernardo, 2011; Milias-Argeitis et al., 2011; Uhlendorf et al., 2012) have showcased how cells can be controlled externally via computer-based feedback and actuators such as chemical inducers or light stimuli (Levskaya, Weiner, Lim, & Voigt, 2009; Mettetal, Muzzey, Gomez-Uribe, & van Oudenaarden, 2008). An important challenge in these approaches is the need for real-time measurements, which tend to be costly and difficult to implement with current technologies. In addition, because of technical limitations and the inherent nonlinearity of biochemical interactions, actuators are severely constrained in the type of input signals they can produce. As a consequence, the input signals generated by traditional feedback controllers (e.g. PID or model predictive control) may be hard to implement without a significant decrease in control performance.

In this paper we show how to switch a bistable system without the need for output measurements. We propose an open-loop

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control strategy based on a temporal pulse of suitable magnitude μ and duration τ:

$$u(t) = \mu h(t,\tau), \quad h(t,\tau) = \begin{cases} 1 & 0 \le t \le \tau, \\ 0 & t > \tau. \end{cases} \tag{1}$$

Our goal is to characterise the set of all pairs (μ, τ) that can switch the system between the stable steady states and the set of all pairs (μ, τ) that cannot. We call these sets *the switching sets* and a boundary between these sets the *switching separatrix*. The pairs (μ, τ) close to the switching separatrix are especially important in synthetic biology applications, as a large μ or a large τ can trigger toxic effects that slow down cell growth or cause cell death.

In a previous paper (Sootla, Oyarzún, Angeli, & Stan, 2015), we showed that for monotone systems the switching separatrix is a monotone curve. This result was therein extended to a class of non-monotone systems whose vector fields can be bounded by vector fields of monotone systems. This idea ultimately leads to robustness guarantees under parametric uncertainty. These results are in the spirit of Gennat and Tibken (2008); Ramdani, Meslem, and Candau (2009, 2010), where the authors considered the problem of computing reachability sets of a monotone system. Some parallels can be also drawn with Chisci and Falugi (2006); Meyer, Girard, and Witrant (2013), where feedback controllers for monotone systems were proposed.

Contributions. In the present paper we provide the first complete proof of our preliminary results in Sootla, Oyarzún, Angeli, and Stan (2015) and extend them in several directions. We formulate necessary and sufficient conditions for the existence of the monotone switching separatrix for non-monotone systems. Although it is generally hard to use this result to establish monotonicity of the switching separatrix, we use it to prove the converse. For example, we show that for a bistable Lorenz system the switching separatrix is not monotone. We then generalise the main result of Sootla et al. (2015) by providing conditions for the switching separatrix to be a graph of a function. We also discuss the relation between bifurcations and the mechanism of pulse-based switching, which provides additional insights into the switching problem. We use this intuition to show and then explain the failure of pulse-based control on an HIV viral load control problem (Adams, Banks, Kwon, & Tran, 2004). We proceed by providing a numerical algorithm to compute the switching separatrices for monotone systems. The algorithm can be efficiently distributed among several computational units and does not explicitly use the vector field of the model. We evaluate the computational tools and the theory on the bistable LacI–TetR system, which is commonly referred to as a *genetic toggle switch* (Gardner, Cantor, & Collins, 2000).

We complement our theoretical findings with several observations that illustrate limitations of the current theory and highlight the need for deeper investigations of bistable systems. For example, we show that for a toxin–antitoxin system (Cataudella, Sneppen, Gerdes, & Mitarai, 2013), the switching separatrix appears to be monotone, even though the system does not appear to be monotone. Finally, in order to demonstrate the full potential of pulse-based control, we consider the problem of inducing an oscillatory behaviour in a generalised repressilator system (Strelkowa & Barahona, 2010).

Organisation. In Section 2 we cover the basics of monotone systems theory, formulate the problem in Section 2.1, and provide an intuition into the mechanism of pulse-based switching for monotone systems in Section 2.2. We also provide some motivational examples for the development of our theoretical results, which we present in Section 3. In Section 4 we derive the computational algorithm and evaluate it on the LacI–TetR system. In Section 5, we provide examples, counterexamples and an application of inducing oscillations in a generalised repressilator system. The proofs are found in the Appendix.

Notation. Let $\|\cdot\|_2$ stand for the Euclidean norm in $\mathbb{R}^n$, Y^* stand for a topological dual to Y, $X \setminus Y$ stand for the relative complement of X in Y, $\mathrm{int}(Y)$ stand for the interior of the set Y, and $\mathrm{cl}(Y)$ for its closure.

2. Preliminaries

Consider a single input control system

$$\dot{x} = f(x,u), \quad x(0) = x_0, \tag{2}$$

where $f : \mathcal{D} \times \mathcal{U} \to \mathbb{R}^n$, $u : \mathbb{R}_{\ge 0} \to \mathcal{U}$, $\mathcal{D} \subset \mathbb{R}^n$, $\mathcal{U} \subset \mathbb{R}$ and $u(\cdot)$ belongs to the space $\mathcal{U}_\infty$ of Lebesgue measurable functions with values from $\mathcal{U}$. We say that the system is *unforced*, if $u = 0$. We define *the flow* map $\phi_f : \mathbb{R} \times \mathcal{D} \times \mathcal{U}_\infty \to \mathbb{R}^n$, where $\phi_f(t, x_0, u)$ is a solution to the system (2) with an initial condition x_0 and a control signal u. We consider the control signals in the shape of *a pulse*, that is signals defined in (1) with nonnegative μ and τ.

In order to avoid confusion, we reserve the notation $f(x,u)$ for the vector field of non-monotone systems, while systems

$$\dot{x} = g(x,u), \qquad x(0) = x_0, \tag{3}$$

$$\dot{x} = r(x,u), \qquad x(0) = x_0, \tag{4}$$

denote so-called *monotone systems* throughout the paper. In short, monotone systems preserve a partial order relation in initial conditions and input signals. A relation $\succeq_x$ is called a *partial order* if it is reflexive ($x \succeq_x x$), transitive ($x \succeq_x y$, $y \succeq_x z$ implies $x \succeq_x z$), and antisymmetric ($x \succeq_x y$, $y \succeq_x x$ implies $x = y$). We define a partial order through a cone $K \subset \mathbb{R}^n$ as follows: $x \succeq_x y$ if and only if $x - y \in K$. We write $x \not\succeq_x y$, if the relation $x \succeq_x y$ does not hold; $x \succ_x y$, if $x \succeq_x y$ and $x \ne y$; and $x \gg_x y$, if $x - y \in \mathrm{int}(K)$. Similarly we define a partial order on the space of signals $u \in \mathcal{U}_\infty$: $u \succeq_u v$, if $u(t) - v(t) \in K$ for all $t \ge 0$. We write $u \succ_u v$, if $u \succeq_u v$ and $u(t) \ne v(t)$ for all $t \ge 0$. Finally, a set M is called *p-convex* if for all x, y in M such that $x \succeq_x y$, and all $\lambda \in (0,1)$ we have that $\lambda x + (1-\lambda) y \in M$.

Definition 1. The system (3) is called *monotone* on $\mathcal{D}_M \times \mathcal{U}_\infty$ with respect to the partial orders $\succeq_x$, $\succeq_u$, if for all $x, y \in \mathcal{D}_M$ and $u, v \in \mathcal{U}_\infty$ such that $x \succeq_x y$ and $u \succeq_u v$, we have $\phi_g(t, x, u) \succeq_x \phi_g(t, y, v)$ for all $t \ge 0$. If additionally, $x \succ_x y$, or $u \succ_x v$ implies that $\phi_g(t,x,u) \gg_x \phi_g(t,y,v)$ for all $t > 0$, then the system is called *strongly monotone*.

In general, it is hard to verify monotonicity of a system with respect to an order other than an order induced by an orthant (e.g., positive orthant $\mathbb{R}^n_{\ge 0}$). Hence throughout the paper, by a monotone system we actually mean *a monotone system with respect to a partial order induced by an orthant*. A certificate for monotonicity with respect to an orthant is referred to as Kamke–Müller conditions (Angeli & Sontag, 2003).

Proposition 2 (*Angeli & Sontag, 2003*)**.** *Consider the system (3), where g is differentiable in x and u and let the sets $\mathcal{D}_M$, $\mathcal{U}$ be p-convex. Let the partial orders $\succeq_x$, $\succeq_u$ be induced by $P_x\mathbb{R}^n_{\ge 0}$, $P_u\mathbb{R}^m_{\ge 0}$, respectively, where $P_x = \mathrm{diag}((-1)^{\varepsilon_1}, \ldots, (-1)^{\varepsilon_n})$, $P_u = \mathrm{diag}((-1)^{\delta_1}, \ldots, (-1)^{\delta_m})$ for some ε_i, δ_i in $\{0,1\}$. Then*

$$(-1)^{\varepsilon_i + \varepsilon_j} \frac{\partial g_i}{\partial x_j} \ge 0, \quad \forall\, i \ne j, \quad (x,u) \in \mathrm{cl}(\mathcal{D}_M) \times \mathcal{U}$$

$$(-1)^{\varepsilon_i + \delta_j} \frac{\partial g_i}{\partial u_j} \ge 0, \quad \forall\, i, j, \quad (x,u) \in \mathcal{D}_M \times \mathcal{U}$$

if and only if the system (3) is monotone on $\mathcal{D}_M \times \mathcal{U}_\infty$ with respect to $\succeq_x$, $\succeq_u$.

If we consider the orthants $\mathbb{R}^n_{\ge 0}$, $\mathbb{R}^m_{\ge 0}$, then the conditions above are equivalent to checking if for all $x \preceq_x y$ such that $x_i = y_i$ for some i, and all $u \preceq_u v$ we have $g_i(x,u) \le g_i(y,v)$.