Control for synchronization of bistable piecewise affine genetic regulatory networks

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Abstract: In this paper, we study the diffusive coupling of a network of identical bistable switch piecewise-affine systems. We propose a control strategy which synchronizes every bistable switch sub-system of the network towards the same steady state.

Keywords: Control of networks, Robust control, Synchronization, Gene networks

1. INTRODUCTION

Piecewise-affine systems are now a frequently used framework for modeling genetic regulatory networks (see, for instance, de Jong (2002); Farcot and Gouzé (2008)). This type of systems has been used to model several distinct dynamical behaviors, such as, multistability (see, for instance, Chaves and Gouzé (2011)) or oscillatory behaviors (see, for instance, Farcot and Gouzé (2009)). Diffusive coupling of identical sub-systems, where each pair of subsystems are coupled by diffusion, and related synchronisation issues have attracted a large interest for years (see Aminzare and Sontag (2014); Scardovi et al. (2010)). In Chaves et al. (2019), the authors have introduced coupling of piecewise affine systems by diffusion and have studied synchronization issues. The systems are coupled by discrete diffusion, that is, the dynamics is the sum of a reaction term corresponding to the individual bistable dynamics and a diffusion term involving symmetric Laplacian matrices, which define a coupling topology, so that the dynamics of the network can be seen as a space discretization of a system of two coupled reaction-diffusion pde's (see, for instance Pouchol et al. (2019); Baccoli et al. (2015) for results about the control of reaction-diffusion equations, Aminzare and Sontag (2016) for synchronisation issues in reaction-diffusion pde's). It has been shown that in the case of the coupling of identical piecewise affine systems, the coupled system may have a much more complex dynamics than the individual one. For instance, the coupling scheme introduces new steady states, that we call in this paper *diffusive steady states*, which may be locally stable (see Chaves et al. (2019)). For biological purposes, these diffusive steady states may be undesirable, so it becomes interesting to find a control strategy that prevents convergence to those states. Controlling coupled piecewise affine systems is a challenging task, and to the best of the authors knowledge, very few results have been developed in this direction. We propose to study a network of two dimensional bistable systems, and consider the problem of stabilizing this network towards its steady states. To take biological constraints into account, we consider qualitative measurements, and propose to use a control which depends only on qualitative knowledge of the state variable, as in Chaves and Gouzé (2011). In this paper, we propose a control method which works for every type of coupling topology, and which is robust w.r.t. the coupling strength. In particular, we prove a result of stabilization of parametric ensembles of systems at steady states (see, for instance, Ryan (2015), or Chittaro and Gauthier (2018), Augier et al. (2018) for results occuring in different frameworks).

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2. SINGLE SYSTEM DYNAMICS AND CONTROL

In this section, we recall some results from Chaves and Gouzé (2011) concerning the control of a single bistable switch system. The two variables represent two proteins which mutually inhibit each other.

2.1 Individual dynamics

Consider first the uncontrolled equation

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + k_1 s^-(x_2, \theta_2) \\ \dot{x}_2 &= -\gamma_2 x_2 + k_2 s^-(x_1, \theta_1), \end{aligned} \tag{1}$$

where for $j \in \{1,2\}$, $x_j \in \mathbb{R}$, and for $\theta \in \mathbb{R}$, $s^-(\cdot, \theta) : \mathbb{R} \to \mathbb{R}$ is such that $s^-(x, \theta) = 0$ if $x > \theta$, and $s^-(x, \theta) = 1$ if $x < \theta$. It is assumed that $s^-(x) \in [0, 1]$ for $x = \theta$. The positive constants $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ correspond, respectively, to the degradation and the production rates of each variable. It is a classical fact (see Chaves and Gouzé (2011)) that the domain $K = [0, \frac{k_1}{\gamma_1}] \times [0, \frac{k_2}{\gamma_2}]$ is forward invariant by the dynamics of Equation (1). From now on we consider only solutions evolving in K.

Define the regular domains

$$B_{00} = \{x = (x_1, x_2) \in \mathbb{R}^2 \mid 0 < x_1 < \theta_1,\ 0 < x_2 < \theta_2\},$$

$$B_{01} = \{x = (x_1, x_2) \in \mathbb{R}^2 \mid 0 < x_1 < \theta_1,\ \theta_2 < x_2 < \frac{k_2}{\gamma_2}\},$$

$$B_{10} = \{x = (x_1, x_2) \in \mathbb{R}^2 \mid \theta_1 < x_1 < \frac{k_1}{\gamma_1},\ 0 < x_2 < \theta_2\},$$

$$B_{11} = \{x = (x_1, x_2) \in \mathbb{R}^2 \mid \theta_1 < x_1 < \frac{k_1}{\gamma_1},\ \theta_2 < x_2 < \frac{k_2}{\gamma_2}\}.$$

For a piecewise affine system defined on $\mathbb{R}^n$ whose dynamics restricted to a regular domain B is a linear dynamical system having an asymptotically stable equilibrium, define the focal point on B as this equilibrium point. Notice that this point may belong to B or not. Each region B_{ij} has a focal point, $\phi_{ij} = (\bar{x}_i, \bar{x}_j)$ corresponding to $\bar{x}_i = \frac{k_i}{\gamma_i} s^-(\bar{x}_j, \theta_j)$. and Equation (1) has two locally asymptotically stable steady states, $\phi_{10} = (\frac{k_1}{\gamma_1}, 0) \in B_{10}$ and $\phi_{01} = (0, \frac{k_2}{\gamma_2}) \in B_{01}$, and an unstable Filippov equilibrium point at (θ_1, θ_2). In addition, there exists a curve, called separatrix, passing through (θ_1, θ_2) and dividing K in two regions (above and below) such that the solutions of Equation (1) reach B_{01} or B_{10}, respectively, in finite time. Moreover, B_{10} (respectively, B_{10}) is included in the bassin of attraction of ϕ_{10} (respectively, ϕ_{01}). We make the following assumptions on the parameters of the system (for more details, see Chaves and Gouzé (2011)):

$$\begin{aligned} &\theta_j < \frac{k_j}{\gamma_j},\ j \in \{1,2\}; \\ &\frac{\theta_2}{\theta_1} > \frac{k_2}{k_1}\frac{\gamma_1}{\gamma_2}; \\ &\frac{\theta_2}{\theta_1} < \frac{k_2}{k_1}. \end{aligned} \tag{H}$$

2.2 Controlling the individual system to ϕ_{01} (respectively, ϕ_{10})

Consider now the controlled equation:

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + u k_1 s^-(x_2, \theta_2) \\ \dot{x}_2 &= -\gamma_2 x_2 + u k_2 s^-(x_1, \theta_1) \end{aligned} \tag{2}$$

The control $u \equiv u(t, x(t))$ is assumed to act on the production rates of each variable. It is assumed to depend only on the domain $(B_{jk})_{j,k\in\{0,1\}}$ to which the solution $x(t)$ of Equation (9) at time t belongs, and u has values in a finite set of the form $\{u_{\min}, 1, u_{\max}\}$, where $u_{\max} \geq 1$ and $u_{\min} \geq 0$. Note that u changes the location of the focal points ϕ_{ij}.

Here we present a control strategy, proposed in (Chaves and Gouzé, 2011, Section 5). The separatrix (S_u), which separates B_{00} into two regions $(S_u)^-$ and $(S_u)^+$ is defined, in the coordinates $(x_1, x_2) \in B_{00}$, for $u \geq 0$, as the curve of equation

$$x_2 = \alpha(x_1, u) = \frac{k_2 u}{\gamma_2} - \left(\frac{k_2 u}{\gamma_2} - \theta_2\right)\left(\frac{\frac{k_1 u}{\gamma_1} - x_1}{\frac{k_1 u}{\gamma_1} - \theta_1}\right)^{\frac{\gamma_2}{\gamma_1}}.$$

One can show that, under Assumption (H), one can choose $u^{01}_{\min}, u^{10}_{\min} < \min_{j\in\{1,2\}}\{\frac{\theta_j \gamma_j}{k_j}\}$, and $u_{\max} \geq 1$ such that $\frac{u^{01}_{\min} k_2}{\gamma_2} > \alpha(u^{01}_{\min}\frac{k_1}{\gamma_1}, u_{\max})$ (that is, $\left(\frac{u^{01}_{\min} k_1}{\gamma_1}, \frac{u^{01}_{\min} k_2}{\gamma_2}\right) \in (S_{u_{\max}})^+$) and $\frac{u^{10}_{\min} k_2}{\gamma_2} < \alpha(u^{10}_{\min}\frac{k_1}{\gamma_1}, u_{\max})$ (that is, $\left(\frac{u^{10}_{\min} k_1}{\gamma_1}, \frac{u^{10}_{\min} k_2}{\gamma_2}\right) \in (S_{u_{\max}})^-$).

Control algorithm:

- First phase: Choose $u \equiv u^{01}_{\min}$ (respectively, $u^{10}_{\min}$) during a time $T > 0$ large enough.
- Second phase: Choose $u \equiv u_{\max}$ until x enters in B_{01} (respectively, B_{10}).
- Third phase: Choose $u \equiv 1$.

During the first phase, every focal point of the system belongs to B_{00}, hence the solution $x(t)$ of Equation (9) converges towards the point $(u_{\min}\frac{k_1}{\gamma_1}, u_{\min}\frac{k_2}{\gamma_2}) \in B_{00}$ when $t \to \infty$. During the second phase, $x(t)$ reaches B_{01} or B_{10} in finite time, depending on the choice of $u \equiv u^{01}_{\min}$ or $u \equiv u^{10}_{\min}$. During the third phase, $x(t)$ converges towards ϕ_{01} or ϕ_{10}.

3. COUPLED SYSTEM

In this section, we consider a network of $N \in \mathbb{N}$ identical systems whose individual dynamics is given by Equation (1), which are coupled by diffusion, as it has been studied in a slightly different setting in Chaves et al. (2019). Then we propose an adaptation of the control algorithm of the individual dynamics presented in Section 2.2 to synchronize the coupled system at the same individual steady state.

3.1 Dynamics of the coupled system

Let $N \in \mathbb{N}$. Define, for $k \in \{1,2\}$, $x_k = (x_{k,j})_{j\in\{1,\ldots,N\}} \in \mathbb{R}^N$, and the N-dimensional vector

$$q(x_k) = {}^t\big(s^-(x_{k,1}, \theta_k), \ldots, s^-(x_{k,N}, \theta_k)\big).$$

Define for every $x = (x_{k,j})_{(k,j)\in\{1,2\}\times\{1,\ldots,N\}} \in \mathbb{R}^{2N}$ the canonical projection $\pi_k(x) = x_k$ for $k \in \{1,2\}$.

Consider the following equation

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1 + L_1)x_1 + k_1 q(x_2) \\ \dot{x}_2 &= -(\Gamma_2 + L_2)x_2 + k_2 q(x_1). \end{aligned} \tag{3}$$

where, $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ satisfy Assumption (H), Γ_j is the N-dimensional diagonal matrix with coefficients γ_j. The matrix L_j is a Laplacian N-dimensional symmetric matrix, that is, its coefficients $(l^j_{kl})_{k,l\in\{1,\ldots,N\}}$ satisfy

$$l^j_{kl} = \begin{cases} \displaystyle\sum_{i=1}^{N} a_{ki},\ l = k \\ -a_{kl},\ l \neq k, \end{cases}$$

where $a_{kl} \geq 0$ for every $k, l \in \{1,\ldots,N\}$.

From now on, assume that for $j \in \{1,2\}$, L_j defines a strongly connected graph. Then it follows that $\Gamma_j + L_j$ is invertible, $-(\Gamma_j + L_j)$ is Hurwitz and $(\Gamma_j + L_j)^{-1}$ is positive.

Define the regular domains of Equation (3) as the cartesian products of the domains $(B_{jk})_{j,k\in\{0,1\}}$ defined in Section 2.1. More precisely, for a sequence $(j_l, k_l)_{l\in\{1,\ldots,N\}}$ such that for every $l \in \{1,\ldots,N\}$, $(j_l, k_l) \in \{0,1\}^2$, we say that $x \in B_{j_1,k_1} \times \cdots \times B_{j_N,k_N}$ if for every $l \in \{1,\ldots,N\}$, $(x_{1,l}, x_{2,l}) \in B_{j_l,k_l}$. One can show that the full domain K^N, where K is defined in Section 2.1, is forward invariant by the dynamics of Equation (3).

For a regular domain B of K^N the focal point corresponding to the domain B is given by

$$\begin{aligned} \bar{x}_1 &= k_1(\Gamma_1 + L_1)^{-1} q(\pi_2(B)) \\ \bar{x}_2 &= k_2(\Gamma_2 + L_2)^{-1} q(\pi_1(B)), \end{aligned} \tag{4}$$

where, by abuse of notations, $q(\pi_j(B))$ is the constant value taken by q in the set $\pi_j(B)$, for every $j \in \{1,2\}$. It follows easily that $(\bar{x}_1, \bar{x}_2)$ is a steady state when $(\bar{x}_1, \bar{x}_2) \in B$, that is

$$\begin{aligned} \bar{x}_1 &= k_1(\Gamma_1 + L_1)^{-1} q(\bar{x}_2) \\ \bar{x}_2 &= k_2(\Gamma_2 + L_2)^{-1} q(\bar{x}_1). \end{aligned} \tag{5}$$

Define $x = \Phi_{10} \in \mathbb{R}^{2N}$ such that for every $k \in \{1, \dots, N\}$, $(x_{1,k}, x_{2,k}) = \phi_{10}$. Define $\Phi_{01} \in \mathbb{R}^{2N}$ similarly. Because of the Laplacian structure of $(L_j)_{j\in\{1,2\}}$, Φ_{10} and Φ_{01}, that we call *synchronized steady-states* are locally stable steady states of Equation (3), which are independent from the coupling L_1 and L_2.

However, as already noticed in Chaves et al. (2019) for a sligthly different class of systems, the dynamics of Equation (3) may converge to other not synchronized steady states, given by Equation (5), that we call *diffusive steady states*.

These diffusive states all belong to K^N. In the following we assume that $||L_1||$ and $||L_2||$ are small enough to guarantee that the diffusive focal points are in the same domains as their respective non-diffusive focal points, that is, for every regular domain B of K^N, the focal point given by (4) with (L_1, L_2) lies in the same domain as the focal point given by (4) with $L_1 = L_2 = 0$.

3.2 Control strategy for the coupled system

This section, where proofs are not given, constitues the main contribution of this paper. We are interested in controlling the dynamics of the coupled system

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1 + L_1)x_1 + uk_1 q(x_2) \\ \dot{x}_2 &= -(\Gamma_2 + L_2)x_2 + uk_2 q(x_1) \end{aligned} \tag{6}$$

towards Φ_{01} or Φ_{10}. The control u is assumed to act on every sub-system of the network and satisfies the same hypothesis as in Section 2.1. For this, we show that the control algorithm exposed in Section 2.2 can be adapted to this case. Let $u_{\min}^{01}, u_{\min}^{10}, u_{\max}$ be chosen as in Section 2.2. For a regular domain B of K^N the focal point of Equation (6) corresponding to the domain B is given by

$$\begin{aligned} \bar{x}_1 &= uk_1(\Gamma_1 + L_1)^{-1} q(\pi_2(B)) \\ \bar{x}_2 &= uk_2(\Gamma_2 + L_2)^{-1} q(\pi_1(B)). \end{aligned} \tag{7}$$

We have the following lemmas.

Lemma 1. Every focal point of Equation (6) with $u \equiv u_{\min}^{01}$ (respectively, $u_{\min}^{01}$) belongs to $B_{00} \times \cdots \times B_{00}$.

Lemma 2. Let $u \geq 0$. Assume that $x_0 \in (S_u)^+ \times \cdots \times (S_u)^+$ (respectively, $x_0 \in (S_u)^- \times \cdots \times (S_u)^-$). Then the solution $x(t)$ of Equation (6) such that $x(0) = x_0$ reaches $B_{01} \times \cdots \times B_{01}$ (respectively, $B_{10} \times \cdots \times B_{10}$) in finite time.

Control algorithm:

First step: synchronization Choose $u \equiv u_{\min}^{01}$ (respectively, $u_{\min}^{01}$). By Lemma 1, every system of the network reaches the domain B_{00} in finite time. We obtain the following.

Theorem 3. The solution x of Equation (6) converges when $t \to \infty$ to the synchronized state $\Phi^* = (\bar{x}_1, \bar{x}_2)$ defined by $\bar{x}_{1,k} = u_{\min}^{01} \frac{k_1}{\gamma_1}$, and $\bar{x}_{2,k} = u_{\min}^{01} \frac{k_2}{\gamma_2}$ (respectively, $\bar{x}_{1,k} = u_{\min}^{10} \frac{k_1}{\gamma_1}$, and $\bar{x}_{2,k} = u_{\min}^{10} \frac{k_2}{\gamma_2}$) for every $k \in \{1, \dots, N\}$.

Fix $\epsilon > 0$ small enough. Lemma 3 allows to consider $T_\epsilon > 0$ such that for every initial condition $x_0 \in K^N$, the solution of Equation (6) such that $x(0) = x_0$ satisfies $||x(T_\epsilon) - \Phi^*|| < \epsilon$, that is, every subsystem of the network can be driven to an arbitrary small neighborhood of $(u_{\min}^{01} \frac{k_1}{\gamma_1}, u_{\min}^{01} \frac{k_2}{\gamma_2})$ (respectively, $(u_{\min}^{10} \frac{k_1}{\gamma_1}, u_{\min}^{10} \frac{k_2}{\gamma_2})$). In particular, one can choose $\epsilon > 0$ small enough to guarantee $x(T_\epsilon) \in (S_{u_{\max}})^+ \times \cdots \times (S_{u_{\max}})^+$ (respectively, $x(T_\epsilon) \in (S_{u_{\max}})^- \times \cdots \times (S_{u_{\max}})^-$).

Second step: Choose $u \equiv u_{\max}$. Using Lemma 2, one can prove the following result.

Theorem 4. Assume that u is defined as in the two steps above. Then the solution $x(t)$ of Equation (6) reaches the regular domain $B_{01} \times \cdots \times B_{01}$ (respectively, $B_{10} \times \cdots \times B_{10}$) in finite time.

Third step: Choose $u \equiv 1$.

Theorem 5. Assume that u is defined as in the three steps above. Then the solution $x(t)$ of Equation (6) converges to Φ_{01} (respectively, Φ_{10}) when $t \to \infty$.

3.3 Robustness

Fix a Laplacian matrix L_j of a strongly connected graph. Consider the system (3), replacing L_j by $\tilde{L}_j$, where $\tilde{L}_j = \alpha_j L_j$, with $\alpha_j \in \mathbb{R}$ is a fixed but unknown parameter in a certain given interval, that is

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1 + \alpha_1 L_1)x_1 + uk_1 q(x_2) \\ \dot{x}_2 &= -(\Gamma_2 + \alpha_2 L_2)x_2 + uk_2 q(x_1). \end{aligned} \tag{8}$$

Up to increasing the time T_ϵ of phase 1 of the control algorithm, by continuity of the flow of Equation (8) w.r.t. $\alpha = (\alpha_1, \alpha_2)$, we obtain a control strategy which is uniform w.r.t. α in every compact subset I of $[0, d_1) \times [0, d_2)$, where $d_1, d_2 > 0$ depend on (L_1, L_2).

We deduce that Equation (8) is ensemble stabilizable at Φ_{10} and Φ_{01}, uniformly w.r.t. $\alpha = (\alpha_1, \alpha_2) \in I$, that is, there exists a control $u : [0, +\infty) \to \{u_{\min}^{10}, 1, u_{\max}\}$ (respectively, $u : [0, +\infty) \to \{u_{\min}^{01}, 1, u_{\max}\}$) independent of α, such that the parametric solution x^α of Equation (8) where, for every $\alpha \in I$, $x^\alpha(0) = x_0 \in K^N$, with x_0 independent of α, is such that $x^\alpha(t)$ converges to Φ_{10} (respectively, Φ_{01}) when $t \to \infty$, uniformly w.r.t. $\alpha \in I$.

4. EXAMPLE: CASE $N = 2$

Consider the following piecewise-affine differential system in $\mathbb{R}^4$,

$$\begin{aligned} \dot{x}_{1,1} &= -\gamma_1 x_{1,1} + k_1 u s^-(x_{2,1}, \theta_2) + a_1(x_{1,2} - x_{1,1}) \\ \dot{x}_{2,1} &= -\gamma_2 x_{2,1} + k_2 u s^-(x_{1,1}, \theta_1) + a_2(x_{1,1} - x_{1,2}) \\ \dot{x}_{1,2} &= -\gamma_1 x_{1,2} + k_1 u s^-(x_{2,2}, \theta_2) + a_1(x_{1,1} - x_{1,2}) \\ \dot{x}_{2,2} &= -\gamma_2 x_{2,2} + k_2 u s^-(x_{1,2}, \theta_1) + a_2(x_{1,2} - x_{1,1}), \end{aligned} \tag{9}$$

where, $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ are positive constants satisfying Assumption (H), and $a_1 \geq 0$ (respectively, $a_2 \geq 0$) are the diffusion couplings on the first variables (respectively, the second variables). We have made simulations of such a system with $(\gamma_1, \gamma_2) = (0.2, 0.8)$, $(k_1, k_2) = (0.5, 1.4)$, $(\theta_1, \theta_2) = (1, 1.2)$, $a_1 = a_2 = 0.05$. For this choice of parameters, the value of $u_{\max}$ can be chosen as $u_{\max} = 1$. One can choose $u_{\min}^{01} = 0.1$, $u_{\min}^{10} = 0.3$, and the time T_ϵ of the second phase of the control strategy is chosen as $T_\epsilon = 20$. Consider the initial conditions: $(x_{1,1}(0), x_{2,1}(0)) = (0.5, 1.3)$, and $(x_{1,2}(0), x_{2,2}(0)) = (0.8, 0.3)$. Figure 1 illustrates the convergence of $x(t)$ towards a diffusive steady state for the uncontrolled system $u \equiv 1$, the dashed line $(S) = (S_{u_{\max}})$ represents the separatrix, as defined in Section 2.1. Figure 2 illustrates the convergence of $x(t)$ towards Φ_{01} for the controlled system. Finally, Figure 3 illustrates the convergence of $x(t)$ towards Φ_{10} for the controlled system. We notice that after the first phase of the control strategy, that is the phase during which the two systems converge towards Φ^*, the two systems (red and green curves) follow very close trajectories.

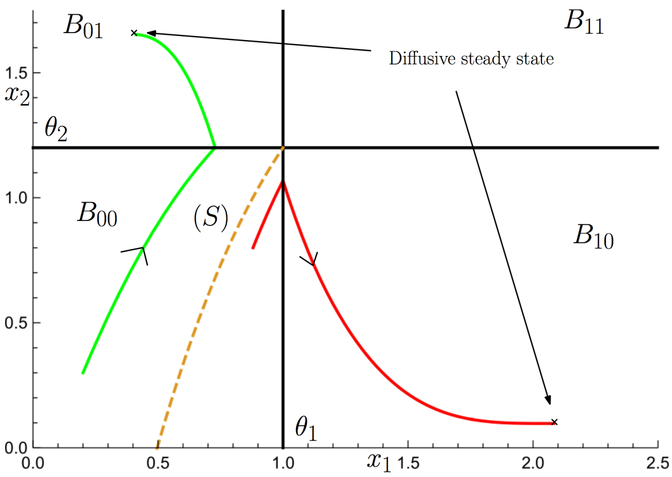

Fig. 1. Convergence towards a diffusive steady state for the uncontrolled system

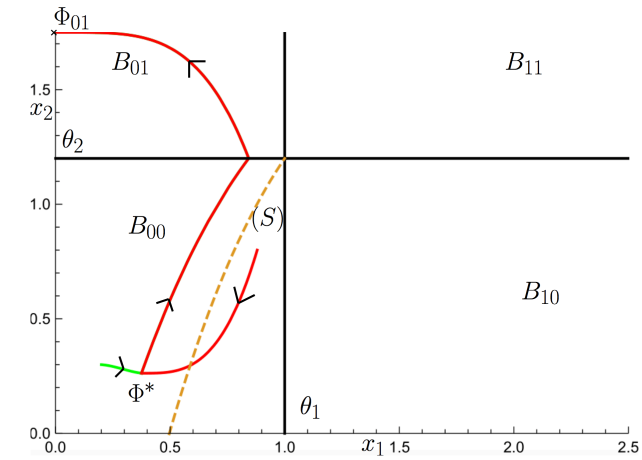

Fig. 2. Convergence towards Φ_{01} for the controlled system

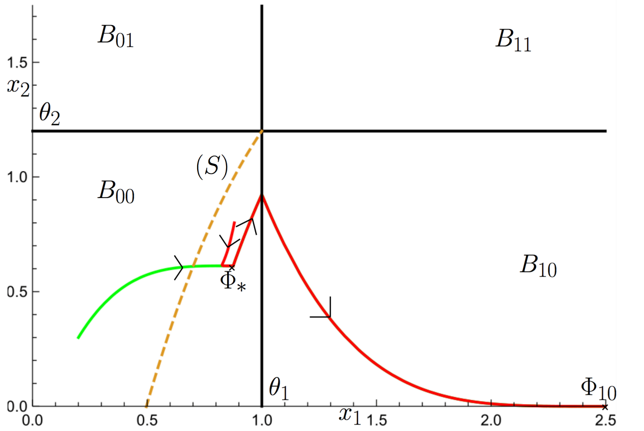

Fig. 3. Convergence towards Φ_{10} for the controlled system

5. CONCLUSION

These results open a new direction in the application of qualitative strategies to the synchronization of coupled identical systems.

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