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## Control of Multi-Affine Systems on Rectangles with Applications to Hybrid Biomolecular Networks

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Given a multi-affine system on an  $N$ -dimensional rectangle, the problem of reaching a particular facet, using multi-affine state feedback is studied. Necessary conditions and sufficient conditions for the existence of a solution are derived in terms of linear inequalities on the input vectors at the vertices of the rectangle, and a method for constructing a multi-affine state feedback solution is presented. The technique is applied to the control of hybrid models of bioregulatory networks.

### Comments

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# Control of Multi-Affine Systems on Rectangles with Applications to Hybrid Biomolecular Networks<sup>1</sup>

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## Abstract

Given a multi-affine system on an  $N$ -dimensional rectangle, the problem of reaching a particular facet, using multi-affine state feedback is studied. Necessary conditions and sufficient conditions for the existence of a solution are derived in terms of linear inequalities on the input vectors at the vertices of the rectangle, and a method for constructing a multi-affine state feedback solution is presented. The technique is applied to the control of hybrid models of bioregulatory networks.

## 1 Introduction

This paper studies multi-affine dynamical systems evolving on rectangles and presents a controller design method for reachability of a facet. This problem is motivated by the control of multi-affine hybrid systems.

A hybrid system is a dynamic system that consists of discrete and continuous components with complex interactions [11]. The safety criticality of many embedded systems has resulted in significant research on computing reachable sets for hybrid systems.

Piece-wise linear hybrid systems have received great attention in the past years. This class of systems consists of automata for which each discrete state is an affine system on a polyhedral set [12]. Specialized tools like HyTech [8], d/dt [4], and CheckMate [3] have been developed for verification of such systems. (CheckMate can also handle low-dimensional nonlinear systems). A particular approach to the reachability problem was developed by van Schuppen in [13], which requires the solution of a facet reachability problem of an affine system on a polyhedral set, given in [5].

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This paper extends the results derived for linear systems in [5, 7] to a class of non-linear dynamical systems. We determine necessary conditions and sufficient conditions for the existence of a multi-affine control such that, independent of the initial state, the trajectory of the closed loop system reaches a particular facet of a rectangle in finite time.

The main motivation for this work are hybrid models of bioregulatory networks, as the one described in [1, 2]. A bioregulatory network is an ensemble of genes, together with their products (mRNA and proteins), and other species affecting the expression of the genes. Traditionally, the level of gene transcription is modeled as a sigmoidal function of the concentration of the regulatory species. However, experimental data on numerous systems in biology suggests that regulation can be modeled as a piecewise constant function. If we consider all the genes in the network with all the corresponding levels of activation, we end up with a switched system with specific dynamics for each mode. The vector fields are multi-affine, because of the rate equations that describe chemical reactions among species. The invariants of the modes are rectangular and the facets correspond to genes being turned on or off. An important question is whether one can drive a genetic system from an arbitrary initial state to a final state so that some genes are turned on while others are not transcribed. To do this, the first problem to be solved is driving a system with multi-affine dynamics within rectangular regions so that some desired facet is hit in finite time. This is exactly the problem we formulate and solve in this work.

## 2 Problem formulation

For  $N \in \mathbb{N}$ , let  $R_N$  denote the  $N$ -dimensional rectangle described by:

$$R_N = \{x = (x_1, \dots, x_N) \in \mathbb{R}^N \mid a_i \leq x_i \leq b_i\}$$

where  $a_i, b_i \in \mathbb{R}$ ,  $a_i < b_i$ ,  $i = 1, \dots, N$ . A multi-affine function  $f : R_N \rightarrow \mathbb{R}^m$  (with  $m \in \mathbb{N}$ ) is a polynomial in the indeterminates  $x_1, \dots, x_N$  with the property that the degree of  $f$  in any of the indeterminates  $x_1, \dots, x_N$  is less than or equal to 1. Stated differently,  $f$  has the form

$$f(x_1, \dots, x_N) = \sum_{i_1, \dots, i_N \in \{0,1\}} c_{i_1, \dots, i_N} x_1^{i_1} \cdots x_N^{i_N}, \quad (1)$$

with  $c_{i_1, \dots, i_N} \in \mathbb{R}^m$  for all  $i_1, \dots, i_N \in \{0, 1\}$  and using the convention that if  $i_k = 0$ , then  $x_k^{i_k} = 1$ .

Consider the following non-linear control system evolving in  $R_N$ :

$$\dot{x} = f(x) + Bu. \quad (2)$$

The drift term  $f : R_N \rightarrow \mathbb{R}^N$  is a multi-affine function,  $B \in \mathbb{R}^{N \times m}$  is a constant matrix whose columns give the directly controllable directions, and the input  $u$  is assumed to take values in a polyhedral set  $U \subset \mathbb{R}^m$  only.

**Problem 1.** Consider the multi-affine system (2) on the rectangle  $R_N$ , and let  $F_j$  be a facet of  $R_N$ , with normal vector  $n_j$  pointing out of  $R_N$ . For any initial state  $x_0 \in R_N$ , we have to find a time instant  $T_0 \geq 0$  and an input function  $u : [0, T_0] \rightarrow U$ , such that

- (i)  $\forall t \in [0, T_0] : x(t) \in R_N$ ,
- (ii)  $x(T_0) \in F_j$ , and  $T_0$  is the smallest time-instant in the interval  $[0, \infty)$  for which the state reaches the exit facet  $F_j$ ,
- (iii)  $n_j^T \dot{x}(T_0) > 0$ , i.e. the velocity vector  $\dot{x}(T_0)$  at the point  $x(T_0) \in F_j$  has a positive component in the direction of  $n_j$ . This implies that in the point  $x(T_0)$ , the velocity vector  $\dot{x}(T_0)$  points out of the rectangle  $R_N$ .

Furthermore, this input function  $u$  should be realized by the application of a continuous feedback law

$$u(t) = k(x(t)), \quad (3)$$

with  $k : R_N \rightarrow U$  a continuous function, that is independent of the initial state  $x_0$ .

For the solution of Problem 1, we are particularly interested in multi-affine feedback laws  $k(x)$ . Note that if the feedback law  $k(x)$  in (3) is multi-affine, the closed-loop system is also multi-affine:

$$\dot{x} = f(x) + Bk(x), \quad x(0) = x_0. \quad (4)$$

To simplify the notation and without restricting the generality, we will solve the problem on the unit cube  $K_N = [0, 1]^N$  rather than on the arbitrary rectangle  $R_N$ . Indeed, by the affine coordinate transformation  $z = S(x) = Ax + b$ , with

$$A = \text{diag} \left\{ \frac{1}{b_1 - a_1}, \dots, \frac{1}{b_N - a_N} \right\} \in \mathbb{R}^{N \times N},$$

$$b = \left[ -\frac{a_1}{b_1 - a_1}, \dots, -\frac{a_N}{b_N - a_N} \right]^T \in \mathbb{R}^N,$$

the problem is translated to the unit cube because  $S$  maps  $R_N$  to  $K_N$  in such a way that vertices are mapped to vertices, edges to edges, facets to facets etc. Moreover, since  $S$  simply consists of a translation and a scaling operation, the system remains multi-affine in the new  $z$ -coordinates. In the rest of the paper, when we refer to Problem 1, we assume that the rectangle  $R_N$  is the unit cube  $K_N$ .

### 3 Multi-affine functions on the unit cube

For any full-dimensional polytope  $P_N$  in  $\mathbb{R}^N$ , a *facet* of  $P_N$  is the intersection of  $P_N$  with one of its supporting hyperplanes. More generally, a *face* of  $P_N$  is the intersection of  $P_N$  with several of its supporting hyperplanes. If the dimension of the intersection is  $n$  (with  $0 \leq n < N$ ) the face is called an  $n$ -*face*.

Let  $(x_1, \dots, x_N) \in [0, 1]^N$  be a point in the unit cube  $K_N$ , and denote the  $2^N$  vertices of  $K_N$  by  $(i_1, \dots, i_N)$ ,  $i_1, \dots, i_N \in \{0, 1\}$ . Let  $m \in \mathbb{N}$  and  $m < N$ . Then every  $N - m$ -dimensional face  $F$  of the unit cube  $K_N = \{(x_1, \dots, x_N) \mid x_i \in [0, 1], (i = 1, \dots, N)\}$ , characterized by  $m$  equations of the form

$$\begin{aligned} x_{i_1} &= 0 \text{ or } x_{i_1} = 1, \\ &\vdots \\ x_{i_m} &= 0 \text{ or } x_{i_m} = 1, \end{aligned}$$

where  $i_1, \dots, i_m \in \{1, \dots, N\}$  and  $i_j \neq i_k$  for  $j \neq k$ , is isomorphic with the  $N - m$  dimensional unit cube  $K_{N-m}$ . If  $f : K_N \rightarrow \mathbb{R}^m$  is a multi-affine function, and  $F$  is an  $N - m$ -dimensional face of  $K_N$ , then the restriction  $f|_F$  of  $f$  to  $F$  is a multi-affine function on the  $N - m$ -dimensional unit cube  $K_{N-m}$ .

**Lemma 1.** Let  $f : K_N \rightarrow \mathbb{R}^m$  be a multi-affine function, and assume that

$$\forall (i_1, \dots, i_N) \in \{0, 1\}^N : f(i_1, \dots, i_N) = 0. \quad (5)$$

Then  $f \equiv 0$ .

**Proposition 1.** Let  $N \in \mathbb{N}$ , and consider  $2^N$  fixed vectors  $v_{i_1, \dots, i_N} \in \mathbb{R}^m$ ,  $((i_1, \dots, i_N) \in \{0, 1\}^N)$ . Then there exists a unique multi-affine function  $f : K_N \rightarrow \mathbb{R}^m$  such that

$$\forall (i_1, \dots, i_N) \in \{0, 1\}^N : f(i_1, \dots, i_N) = v_{i_1, \dots, i_N}, \quad (6)$$

which is given by

$$f(x_1, \dots, x_N) = \sum_{i_1, \dots, i_N \in \{0, 1\}} \prod_{k=1}^N (1 - x_k)^{1 - i_k} x_k^{i_k} v_{i_1, \dots, i_N}. \quad (7)$$

*Proof.* It is obvious that  $f$  defined in (7) is multi-affine. Moreover, for every  $(i_1, \dots, i_N) \in \{0, 1\}^N$ :

$$\prod_{k=1}^N (1 - x_k)^{1 - i_k} x_k^{i_k} =$$

$$\begin{cases} 1 & \text{if } (x_1, \dots, x_N) = (i_1, \dots, i_N), \\ 0 & \text{if } (x_1, \dots, x_N) \in \{0, 1\}^N \setminus \{(i_1, \dots, i_N)\}. \end{cases}$$

So indeed  $f(i_1, \dots, i_N) = v_{i_1, \dots, i_N}$  for all  $(i_1, \dots, i_N) \in \{0, 1\}^N$ .

If  $g : K_N \rightarrow \mathbb{R}^m$  is a multi-affine function satisfying (6), then  $h := f - g$  is multi-affine, and  $h(i_1, \dots, i_N) = 0$  for all  $(i_1, \dots, i_N) \in \{0, 1\}^N$ . By Lemma 1,  $h \equiv 0$ , hence  $f$  defined in (7) is unique.  $\square$

**Proposition 2.** Let  $f : K_N \rightarrow \mathbb{R}^m$  be a multi-affine function, and let  $(\lambda_1, \dots, \lambda_N) \in [0, 1]^N$ . Then  $f(\lambda_1, \dots, \lambda_N)$  is a convex combination of  $\{f(i_1, \dots, i_N) \mid i_1, \dots, i_N \in \{0, 1\}\}$ , i.e.  $f(\lambda_1, \dots, \lambda_N)$  is a convex combination of the values of  $f$  at the vertices of  $K_N$ .

*Proof.* Let  $(\lambda_1, \dots, \lambda_N) \in [0, 1]^N$ . Since  $f$  is a multi-affine function, representation (7) is also valid for  $f$ , with  $v_{i_1, \dots, i_N} = f(i_1, \dots, i_N)$  for all  $(i_1, \dots, i_N) \in \{0, 1\}^N$ . So, in the point  $(\lambda_1, \dots, \lambda_N)$  we have

$$f(\lambda_1, \dots, \lambda_N) = \sum_{i_1, \dots, i_N \in \{0, 1\}} \prod_{k=1}^N (1 - \lambda_k)^{1-i_k} \lambda_k^{i_k} f(i_1, \dots, i_N). \quad (8)$$

Also the identity function  $h \equiv 1$  is multi-affine. In this situation, representation (7) applies with  $v_{i_1, \dots, i_N} = 1$  for  $(i_1, \dots, i_N) \in \{0, 1\}^N$ . So in the point  $(\lambda_1, \dots, \lambda_N)$ :

$$\sum_{i_1, \dots, i_N \in \{0, 1\}} \prod_{k=1}^N (1 - \lambda_k)^{1-i_k} \lambda_k^{i_k} = 1. \quad (9)$$

Combining (8) and (9), it is apparent that (8) represents  $f(\lambda_1, \dots, \lambda_N)$  as a convex combination of the values of  $f$  at the vertices of  $K_N$ .  $\square$

**Corollary 1.** Let  $f : K_N \rightarrow \mathbb{R}^m$  be a multi-affine function. Let  $(\lambda_1, \dots, \lambda_N) \in K_N$ , and let  $F$  be the face of  $K_N$  of lowest dimension of which  $(\lambda_1, \dots, \lambda_N)$  is an element. Then  $f(\lambda_1, \dots, \lambda_N)$  is a convex combination of the values of  $f$  at the vertices of  $F$ .

#### 4 Necessary conditions for feedback control to a facet

**Proposition 3.** Let  $P_N$  be a full-dimensional polytope in  $\mathbb{R}^N$  with vertices  $v_1, \dots, v_M$ , ( $M \geq N + 1$ ). Let  $F_1, \dots, F_K$  denote the facets of  $P_N$ , with normal vectors  $n_1, \dots, n_K$ , respectively, pointing out of the polytope  $P_N$ . For  $i \in \{1, \dots, K\}$ , let  $V_i \subset \{1, \dots, M\}$  be the index set such that  $\{v_j \mid j \in V_i\}$  is the set of vertices of the facet  $F_i$ . Conversely, for every  $j \in \{1, \dots, M\}$ , the set  $W_j \subset \{1, \dots, K\}$  contains the indices of all facets of which  $v_j$  is a vertex. Consider the system

$$\dot{x} = f(x) + G(x) \cdot u, \quad x(0) = x_0, \quad (10)$$

on the polytope  $P_N$ , where  $f : P_N \rightarrow \mathbb{R}^N$  and  $G : P_N \rightarrow \mathbb{R}^{N \times m}$  are assumed to be Lipschitz-continuous functions. If there exists a feedback  $u = k(x)$ , with  $k : P_N \rightarrow U$  a Lipschitz-continuous function, that solves Control Problem 1 with exit facet  $F_1$ , then there exist inputs  $u_1, \dots, u_M \in U$  such that

$$(1) \quad \forall j \in V_1 :$$

- (a)  $n_1^T(f(v_j) + G(v_j)u_j) > 0$ ,
- (b)  $\forall i \in W_j \setminus \{1\} : n_i^T(f(v_j) + G(v_j)u_j) \leq 0$ .

$$(2) \quad \forall j \in \{1, \dots, M\} \setminus V_1 :$$

- (a)  $\forall i \in W_j : n_i^T(f(v_j) + G(v_j)u_j) \leq 0$ ,
- (b)  $\sum_{i \in W_j} n_i^T(f(v_j) + G(v_j)u_j) < 0$ .

**Idea of the proof:** Suppose that the Lipschitz-continuous function  $k : P_N \rightarrow U$  generates a feedback law  $u(t) = k(x(t))$ , that solves Control Problem 1. Then the inputs  $u_j = k(v_j) \in U$ , ( $j = 1, \dots, M$ ), obtained by applying feedback  $k$  to the vertices  $v_1, \dots, v_M$ , satisfy (1) and (2). The proof of this claim is carried out in a similar way as for affine systems (see [6], proof of Proposition 3.1).

The necessary conditions stated in Proposition 3 consist of a set of strict and non-strict linear inequalities on the inputs to the system at the vertices of the polytope  $P_N$ . Since also the input set  $U$  is assumed to be polyhedral, the existence of a solution  $u_1, \dots, u_M \in U$  may be checked, using existing software for polyhedral sets, like e.g. [10, 14]. The computation is further facilitated by the fact that the inequalities for each input are completely decoupled. Note that the formulation in Proposition 3 is more general than needed in this paper; the claim is valid for arbitrary full-dimensional polytopes  $P_N$  and for systems described by Lipschitz-continuous dynamics.

#### 5 Sufficient conditions for feedback control to a facet

In this section, first sufficient conditions for the solvability of Control Problem 1 are stated in terms of the feedback function  $k$ . These conditions have to be satisfied on the polytope  $P_N$  or its facets. For multi-affine systems on the  $N$ -dimensional unit cube, convexity properties are used to transform these conditions into requirements on the inputs to the system at the vertices of the cube  $K_N$ . These conditions turn out to be comparable with the necessary conditions described in Proposition 3.

**Theorem 1.** Let  $P_N$  be a full-dimensional polytope in  $\mathbb{R}^N$  with facets  $F_1, \dots, F_K$ , and let  $n_1, \dots, n_K$  denote the normal vectors of  $F_1, \dots, F_K$ , respectively, pointing out of the polytope  $P_N$ . Consider the system

$$\dot{x} = f(x) + G(x) \cdot u, \quad x(0) = x_0,$$

on the polytope  $P_N$ , with  $f$  and  $G$  Lipschitz-continuous functions. If there exists a Lipschitz function  $k : P_N \rightarrow U$ , such that

- (i)  $\forall x \in P_N : n_1^T(f(x) + G(x) \cdot k(x)) > 0$ ,
- (ii)  $\forall i \in \{2, \dots, K\} \quad \forall x \in F_i : n_i^T(f(x) + G(x) \cdot k(x)) \leq 0$ ,

then the feedback law  $u = k(x)$  solves Control Problem 1 with exit facet  $F_1$ .

*Proof.* If in condition (ii) the inequality is strict, then the proof is straightforward. Since the polytope  $P_N$  is compact, and the function  $x \mapsto n_1^T(f(x) + G(x) \cdot k(x))$  is continuous, condition (i) implies that there exists a  $c > 0$ , such that for all  $x \in P_N$ :  $n_1^T(f(x) + G(x) \cdot k(x)) \geq c$ . So the closed-loop system will move in the direction of  $F_1$  with a strictly positive speed of at least  $c$ , and the polytope  $P_N$  is left in finite time. Condition (ii) with strict inequality indicates that the state of the closed-loop system can not leave  $P_N$  through any of the facets  $F_2, \dots, F_K$ . So the state of the closed-loop system will leave  $P_N$  through  $F_1$  in finite time.

The extension of the proof to the non-strict inequality in (ii) may be carried out in a similar way as for affine systems (see [6]).  $\square$

**Theorem 2.** Let  $K_N$  be the  $N$ -dimensional unit cube in  $\mathbb{R}^N$ , and consider the multi-affine system

$$\dot{x} = f(x) + Bu, \quad x(0) = x_0 \in K_N$$

on  $K_N$ , with  $B \in \mathbb{R}^{N \times m}$ ,  $f : K_N \rightarrow \mathbb{R}^N$  multi-affine, and  $u \in U$ , with  $U \subset \mathbb{R}^m$  a polyhedral set. Each vertex  $(i_1, \dots, i_N) \in \{0, 1\}^N$  of  $K_N$  is also a vertex of the facets  $x_k = i_k$ , ( $k = 1, \dots, N$ ), with normal vectors  $(-1)^{i_k+1} e_k$ , pointing out of  $K_N$ . Let  $F_1 := K_N \cap \{x \in \mathbb{R}^N \mid x_1 = 1\}$  be the exit facet of  $K_N$ . Assume that in every vertex  $(i_1, \dots, i_N) \in \{0, 1\}^N$  there exists an input  $u_{i_1, \dots, i_N}$  such that  $\forall (i_1, \dots, i_N) \in \{0, 1\}^N$ :

- (1)  $e_1^T(f(i_1, \dots, i_N) + Bu_{i_1, \dots, i_N}) > 0$ ,
  - (2)  $\forall k \in \{2, \dots, N\}$ :  
 $(-1)^{i_k+1} e_k^T(f(i_1, \dots, i_N) + Bu_{i_1, \dots, i_N}) \leq 0$ .
- (11)

Let  $k : K_N \rightarrow U$  be the unique multi-affine function satisfying

$$\forall (i_1, \dots, i_N) \in \{0, 1\}^N : k(i_1, \dots, i_N) = u_{i_1, \dots, i_N},$$

that may be constructed using formula (7). Then the continuous multi-affine feedback law  $u = k(x)$  solves Control Problem 1.

*Proof.* The closed-loop dynamics is described by the multi-affine function  $f(x) + Bk(x)$ . According to Proposition 2, for every  $x \in K_N$ ,  $f(x) + Bk(x)$  is a convex combination of  $\{f(i_1, \dots, i_N) + Bk(i_1, \dots, i_N) \mid i_1, \dots, i_N \in \{0, 1\}\}$ . Since by construction  $k(i_1, \dots, i_N) = u_{i_1, \dots, i_N}$ , condition (1) in (11) implies that

$$\forall x \in K_N : e_1^T(f(x) + Bk(x)) > 0,$$

and condition (i) of Theorem 1 is satisfied.

Similarly, if  $F_j$  is a facet of  $K_N$ , different from  $F_1$ , and if  $F_j$  is described by  $x_j = i_j$  for a fixed  $i_j \in \{0, 1\}$ , then Corollary 1 and the definition of  $k$  imply that for every  $x \in F_j$ , the value of  $f(x) + Bk(x)$  is a convex combination of  $\{f(i_1, \dots, i_N) + Bu_{i_1, \dots, i_N} \mid i_1, \dots, i_{j-1}, i_{j+1}, \dots, i_N \in$

$\{0, 1\}\}$ . Hence condition (2) (in combination with condition (1)) of formula (11) implies that

$$\forall x \in F_j : (-1)^{i_j+1} e_j^T(f(x) + Bk(x)) \leq 0,$$

and condition (ii) of Theorem 1 is satisfied.  $\square$

For multi-affine systems on the unit cube the sufficient conditions stated in Theorem 2 differ only slightly from the necessary conditions in Proposition 3: for vertices  $(0, i_2, \dots, i_N)$  of the facet  $x_1 = 0$  the necessary condition

$$\forall i_2, \dots, i_N \in \{0, 1\} :$$

$$e_1^T(f(0, i_2, \dots, i_N) + Bu_{0, i_2, \dots, i_N}) \geq 0,$$

is replaced by the strict inequality

$$\forall i_2, \dots, i_N \in \{0, 1\} :$$

$$e_1^T(f(0, i_2, \dots, i_N) + Bu_{0, i_2, \dots, i_N}) > 0,$$

to obtain a sufficient condition.

Checking the sufficient conditions in formula (11) of Theorem 2 requires the solution of  $2^N$  systems of  $N$  linear inequalities in  $m$  unknowns: for each vertex of  $K_N$ , one system of  $N$  linear inequalities in the unknown  $u \in \mathbb{R}^m$ . If a solution exists, construction of a multi-affine feedback is immediate, using formula (7).

**Remark 1.** Conditions (1) and (2) in formula (11) of Theorem 2 provide polyhedral sets  $U_{i_1, \dots, i_N}$  of controls at the vertices  $(i_1, \dots, i_N)$  that solve Problem 1. If all the sets  $U_{i_1, \dots, i_N}$  are non-empty, then one can choose a representative  $u_{i_1, \dots, i_N}$  from each set and construct the feedback control using formula (7). An interesting special case is when  $\bigcap_{i_1, \dots, i_N \in \{0, 1\}} U_{i_1, \dots, i_N} \neq \emptyset$ . An element  $\bar{u} \in \bigcap_{i_1, \dots, i_N \in \{0, 1\}} U_{i_1, \dots, i_N}$  can be used as a constant (independent of the current state) control that solves Problem 1. Note that this is consistent with (7): if  $u_{i_1, \dots, i_N} = \bar{u}$  in all vertices of a cube, then  $u(x) = \bar{u}$ . This case might be extremely useful for practical situations when the state is not available for feedback.

## 6 Case study: gene transcription control in *Vibrio fischeri*

*Vibrio fischeri* is a marine bacterium that can be found both as free-living organism and as a symbiont of some marine fish and squid. As a free-living organism, *V. fischeri* exists at low densities and appears to be non-luminescent. As a symbiont, the bacteria live at high densities and are, usually, luminescent.

The luminescence in *V. fischeri* is controlled by the transcriptional activation of the *lux* genes [9]. A detailed description and mathematical modeling is given in [2], where

a conventional, highly non-linear, purely continuous model is compared to a lower dimensional, switched system with multi-affine dynamics in each mode.

Under reasonable assumptions, the system of differential equations describing the dynamics of one mode of the simplified hybrid model is three dimensional  $x = [x_1 \ x_2 \ x_3]^T$  with two inputs  $u = [u_1 \ u_2]^T$  in the form given by (2) with

$$f(x) = \begin{bmatrix} k_2 x_2 - k_1 x_1 x_3 \\ k_1 x_1 x_3 - k_2 x_2 \\ k_2 x_2 - k_1 x_1 x_3 - n x_3 \end{bmatrix}, \quad B = \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 0 & n \end{bmatrix}$$

The state variables represent cellular concentrations of different species and the parameters are binding, dissociation and diffusion rates:

$$\begin{aligned} x_1 &= \text{protein LuxR } (ml^{-3}) \\ x_2 &= \text{complex Ai-LuxR } (ml^{-3}) \\ x_3 &= \text{autoinducer Ai } (ml^{-3}) \\ k_1 &= \text{binding rate constant } (30 \ l^3 m^{-1} t^{-1}) \\ k_2 &= \text{dissociation rate constant } (10 \ t^{-1}) \\ n &= \text{diffusion constant } (10 \ t^{-1}) \end{aligned}$$

where  $m$ ,  $l$ , and  $t$  are units for mass, length, and time, respectively. The control variable  $u_1$  could be physically represented by a plasmid producing protein LuxR, while  $u_2$  is an external source of autoinducer. We want to design a multi-affine feedback control so that all states in the rectangle

$$R_3 = \{x = [x_1 \ x_2 \ x_3]^T \in \mathbb{R}^3 \mid 1 \leq x_i \leq 2, \ i = 1, 2, 3\}$$

are driven through the facet  $x_2 = 2$ . In the larger hybrid system, this could correspond to steering the system so that the lux gene is switched on. Also, the controls are supposed to be constrained in the rectangle

$$U = \{20 \leq u_1 \leq 60, \ 1 \leq u_2 \leq 10\}$$

The vector field of the uncontrolled system ( $u = 0$ ) is plotted in Figure 1 (a). We can see that the vector field already has a positive component along  $e_2$ , as desired. On the other hand, the uncontrolled vector field would steer the system out of the rectangle through  $x_1 = 1$  and  $x_3 = 1$ , which is not desired. So, in this problem, we expect the controls to solve the ‘‘stay inside’’ condition.

First, for simplicity, we change the coordinates so that the control problem is reduced to the unit cube  $K_3$ . In this particular case, this consists of translations  $z_i = x_i - 1$ . In the unit cube the dynamics are described by  $\dot{z} = \tilde{f}(z) + Bu$ , where

$$\tilde{f}(z) = \begin{bmatrix} -k_1 + k_2 - k_1 z_1 + k_2 z_2 - k_1 z_3 - k_1 z_1 z_3 \\ k_1 - k_2 + k_1 z_1 - k_2 z_2 + k_1 z_3 + k_1 z_1 z_3 \\ -k_1 + k_2 - n - k_1 z_1 + k_2 z_2 - k_1 z_3 - n z_3 - k_1 z_1 z_3 \end{bmatrix}$$

It is easy to see that

$$e_2^T \dot{z}|_{(i_1, 1, i_3)} > 0, \quad -e_2^T \dot{z}|_{(i_1, 0, i_3)} < 0, \quad i_1, i_3 \in \{0, 1\},$$

mainly because the binding rate  $k_1$  is significantly higher than the dissociation rate  $k_2$ . The two above conditions are equivalent to condition (1) in formula (11) of Theorem 2 and prove that the vector field has a positive component along  $e_2$  everywhere in  $K_3$ , as observed at the beginning of this section.

To make sure that the system does not leave the rectangle through any facet different from  $z_2 = 1$ , we need to design controls. For facet  $z_3 = 1$ , we require  $e_3^T \dot{z}|_{(i_1, i_2, 1)} \leq 0$  which is equivalent to

$$u_2^{001} \leq 7, \quad u_2^{011} \leq 6, \quad u_2^{101} \leq 13, \quad u_2^{111} \leq 12 \quad (12)$$

On the opposite facet  $z_3 = 0$ , the ‘‘stay inside’’ conditions  $-e_3^T \dot{z}|_{(i_1, i_2, 0)} \leq 0$  translate to

$$u_2^{000} \geq 3, \quad u_2^{010} \geq 2, \quad u_2^{100} \geq 6, \quad u_2^{110} \geq 5 \quad (13)$$

For facet  $z_1 = 1$ ,  $e_1^T \dot{z}|_{(1, i_2, i_3)} \leq 0$  is equivalent to

$$u_1^{100} \leq 50, \quad u_1^{101} \leq 110, \quad u_1^{110} \leq 40, \quad u_1^{111} \leq 100 \quad (14)$$

Finally, for  $z_1 = 0$ ,  $-e_1^T \dot{z}|_{(0, i_2, i_3)} \leq 0$  become

$$u_1^{000} \geq 20, \quad u_1^{001} \geq 50, \quad u_1^{010} \geq 10, \quad u_1^{011} \geq 40 \quad (15)$$

According to the above conditions, we can choose the controls at the vertices:

$$\begin{aligned} u_{000} &= \begin{bmatrix} 30 \\ 4 \end{bmatrix}, \quad u_{001} = \begin{bmatrix} 60 \\ 6 \end{bmatrix}, \quad u_{010} = \begin{bmatrix} 20 \\ 3 \end{bmatrix}, \\ u_{011} &= \begin{bmatrix} 50 \\ 5 \end{bmatrix}, \quad u_{100} = \begin{bmatrix} 30 \\ 7 \end{bmatrix}, \quad u_{101} = \begin{bmatrix} 50 \\ 10 \end{bmatrix}, \\ u_{110} &= \begin{bmatrix} 20 \\ 6 \end{bmatrix}, \quad u_{111} = \begin{bmatrix} 40 \\ 10 \end{bmatrix} \end{aligned}$$

Going back to the original coordinates, the multi-affine feedback control is given by  $u(x) = [u_1(x), u_2(x)]^T$  with

$$\begin{aligned} u_1(x) &= -10(x_2 + x_1(-1 + x_3) - 4x_3), \\ u_2(x) &= x_1(3 + x_2(-1 + x_3)) - (-2 + x_2)x_3 \end{aligned} \quad (16)$$

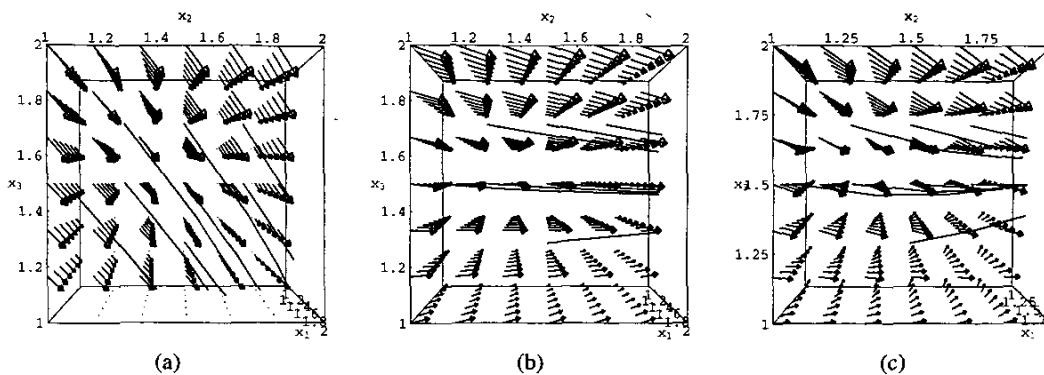
The controlled vector field is plotted in Figure 1 (b).

A careful examination of (12) and (13) shows that a constant  $u_2 = 6$  solves the problem, according to Remark 1. We cannot say the same thing about  $u_1$ , because the intersection of the allowed controls  $u_1$  at the vertices is empty, as it can be noticed from (14) and (15).

The controlled vector field with  $u_1$  as in (16) and  $u_2 = 6$  is given in Figure 1 (c).

## 7 Concluding remarks

For multi-affine systems on the  $N$ -dimensional unit cube, necessary conditions were derived for the existence of a



**Figure 1:** The orientation of the vector field in the rectangle  $1 \leq x_i \leq 2$ ,  $i = 1, 2, 3$  together with some trajectories originating within: (a) the uncontrolled case, (b) the controlled case using (16), and (c) the controlled case with  $u_2 = 6$ .

continuous feedback law, that realizes the control objective of steering the state in finite time to a particular facet of the cube. These conditions consist of linear inequalities on the inputs at the vertices of the cube. For the same control problem also a set of (slightly stronger) sufficient conditions in terms of linear inequalities was obtained, and a method for constructing a continuous multi-affine state feedback law solving the reachability problem under consideration was described. The method can be applied to the control of hybrid models of bioregulatory networks. A case study of gene transcription control for the bacterium *Vibrio fischeri* was presented. Such approaches may lead to novel methods for designing and engineering biological circuits.

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