

Inducing sustained oscillations in mass action kinetic networks of a certain class

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Abstract: Engineering a synthetic oscillator requires an oscillatory model which can be implemented into practice. Some required conditions for a successful practical implementation include the robustness of the oscillation under realistic parameter values and the accessibility to the variables that need to be manipulated. For a particular class of theoretical oscillators derived from mass action kinetic models, oscillations appear provided that some of the concentrations are kept constant at given values. This condition is not trivially accomplished in practice. In this work we provide two different realizations of kinetic networks leading to the desired limit cycle oscillation: a mass action kinetic system with constant inflow and outflow for some of the species, and a stirred tank reactor configuration with some entrapped species where the nonchemical effect of keeping some concentrations constant is achieved by manipulating some accessible variables. The results, together with the robustness of the approach and the conditions for further practical implementation are discussed and illustrated through the well known Brusselator example.

Keywords: biochemical reaction, feedback linearization, nonlinear control systems, oscillators.

1. INTRODUCTION

One recurrent topic in synthetic biology is the design and implementation of biological networks that perform desired oscillations in a predictable manner. We focus on a particular class of theoretical oscillators derived from mass action kinetic models, where sustained oscillations appear provided that the concentration of some of the species involved are kept constant at particular values. A number of reaction networks showing sustained oscillatory behaviour for some ranges of the kinetic parameters have been reported in the literature (Érdi and Tóth, 1989; Nicolis and Nicolis, 1999) where the condition of keeping some concentration constant is considered as a merely theoretical assumption. However, the appearance of sustained oscillations in a real system driven by dynamics of this kind requires this condition to be accomplished experimentally.

In this work, we provide two different realizations leading to the desired oscillatory behaviour. In Section 3 we describe how to obtain a mass action kinetic system (Horn and Jackson, 1972) that in the presence of constant inflow and outflow (or degradation) of some species, will produce the *a priori* defined oscillation. In Section 4, the non-chemical effect of maintaining the concentration of some species constant during a biochemical reaction process is achieved by nonlinear control. We design a linearization-based control law able to keep the key concentrations

constant by manipulating some accessible variables. The results are illustrated through the well known Brusselator network.

2. SYSTEMS UNDER STUDY

Let us consider a mass action kinetic network with m species and r reactions. The evolution of the species concentration vector \mathbf{c} in time is given by:

$$\dot{\mathbf{c}} = \mathcal{N}\mathbf{v} \quad (1)$$

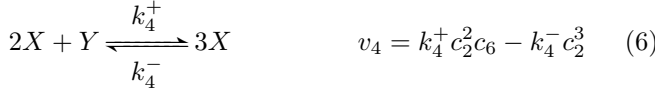
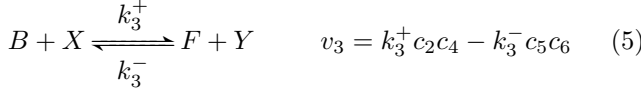
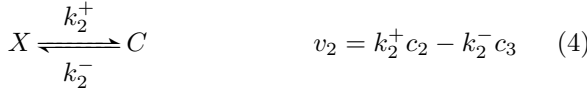
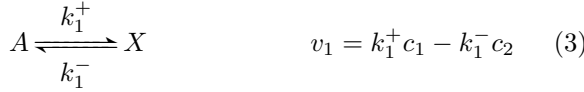
where \mathcal{N} is the $m \times r$ stoichiometric matrix and \mathbf{v} is the vector of reaction rates.

In the systems under study, oscillations appear when the concentration of some species is kept constant. In what follows, we will denote as *key species* the species to be maintained constant to make the system to oscillate. Let p be the number of key species, the dynamics of a system of this kind is described through the literature by a reduced order model of $m - p$ ordinary differential equations:

$$\dot{\mathbf{c}} = \hat{\mathcal{N}}\mathbf{v} \quad (2)$$

where $\hat{\mathcal{N}}$ is the $(m - p) \times r$ matrix containing the rows of the original stoichiometric matrix corresponding to non key species, and \mathbf{v} is the vector containing the reaction rates for the r reactions. The concentrations of the key species in the expression for the reaction rates take the values of given constants.

Example. The well known Brusselator network (Nicolis and Prigogine, 1977) comprises four reversible steps:



According to Nicolis and Nicolis (1999) oscillations appear for some kinetic parameters when the concentrations of the key species A, B, C and F are held constant at particular values denoted by a, b, c and f . For the values in Table 1 the system shows the limit cycle oscillation depicted in Fig. 1. To avoid confusion the concentrations of X and Y are denoted in what follows by x and y . The corresponding reduced order model reads:

$$\begin{aligned} \dot{x} &= k_1^+ a + k_2^- c - (k_3^+ b + k_1^- + k_2^+) x + k_3^- f y \quad \dots \\ &\quad + k_4^+ x^2 y - k_4^- x^3 \\ \dot{y} &= k_3^+ b x - k_3^- f y - k_4^+ x^2 y + k_4^- x^3. \end{aligned} \quad (7)$$

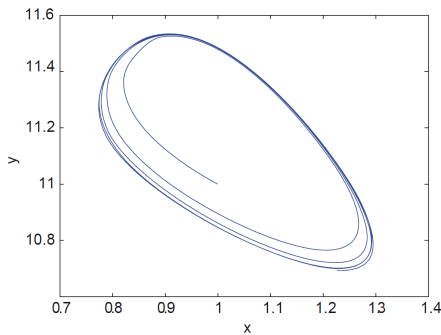


Fig. 1. Brusselator limit cycle for a, b, c, f in Table 1.

Table 1. Key species' values (Brusselator)

k_1^+	k_1^-	k_2^+	k_2^-	k_3^+	k_3^-	k_4^+	k_4^-	a	c	b	f
1	1	1	1	1	1	1	1	1	1	16	0.5

3. MASS ACTION EQUIVALENT REALIZATION

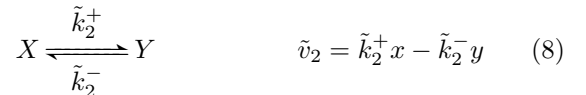
Usually, in order to maintain the concentration of some species constant during a reaction process, one can make them to be in a large excess over the rest. The assumption of constant concentration for species in large excess within the control volume is largely widespread in Chemistry and Chemical Engineering (Missen et al., 1998; Othmer, 2003). Oscillations appearing at constant concentrations of the key species will persist in the real system until the excess of these species vanishes, as it corresponds to a closed system, where the oscillations cannot be sustained

in the long term. Therefore, the reduced order model (2) showing oscillatory behaviour will be only valid for a time period when the excess of the key species persist. It is important to remark here that closed mass action kinetic networks, fulfilling the detailed balance condition, evolve towards a unique and stable equilibrium point (Otero-Muras et al., 2008). Therefore, any mass action kinetic network exhibiting sustained oscillations is necessarily open, where some external forces are maintaining the system far from the thermodynamic equilibrium by means of matter and/or energy exchange through the boundary. This exchange may lead to the unfulfillment of the detailed balance condition and/or of the mass conservation (within the control volume) for any of the atomic species in the network.

Starting from a non mass action oscillatory network of the class introduced in the previous Section, we describe next how to design a mass action kinetic system producing the same sustained oscillation. To this purpose, we construct a network diagram by *stripping away* the key species from the original network such that: i) the key species appearing in a complex¹ together with other non key species are stripped away and their concentration is embedded in the corresponding kinetic constant, ii) if all species in a particular complex have time invariant concentrations, the complex is substituted by the *zero* complex (where all the species' coefficients are zero) representing the environment.

In this way, the oscillatory behaviour can be reproduced by a mass action kinetic system by modifying some kinetic constants (case R.1) and/or adding a constant input/output flow of some non key species (case R.2).

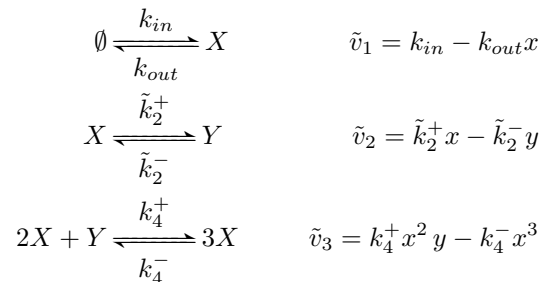
Example. Next, we construct a mass action kinetic network leading to the same dynamics as (7). In first instance, by keeping B and F constant at the values b and f , respectively, the reaction step (5) is transformed into:



with $\tilde{k}_2^+ = b k_3^+$, $\tilde{k}_2^- = f k_3^-$. Keeping A and C constant, the reactions (3) and (4) lead to:



where \emptyset represents the environment and k_{in} , k_{out} are the inflow/production rate and the outflow/degradation rate constant of the species X . An equivalent mass action kinetic network for the Brusselator assuming constant concentrations of the species A, C, B and F reads:



¹ Complexes are the sets of species in both sides of a reaction arrow

and the dynamics, described by:

$$\begin{aligned}\dot{x} &= -\tilde{v}_2 + \tilde{v}_3 + k_{in} - k_{out}x, \\ \dot{y} &= \tilde{v}_2 - \tilde{v}_3,\end{aligned}$$

with $k_{in} = k_1^+ a + k_2^- c$, $k_{out} = k_2^- + k_1^-$ is equivalent to (7).

4. FEEDBACK LINEARIZING CONTROL

In this Section we design a controller that, by keeping the key species concentrations constant at some specific critical values, drives the system to the manifold in the state-space where the desired nonlinear dynamics occurs, in this case, a sustained oscillation. The control approach, inspired by Grogard and Canudas de Wit (2004), includes an input-output linearization by feedback. Before stating the main result, let us introduce the following Proposition. The complete statement and proof can be found in the Appendix, together with a description of the needed notation and geometric properties (*internal dynamics*, *normal form* and *relative degree*).

Proposition 1. Consider the Multi Input Multi Output (MIMO) system

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}) + \mathbf{g}(\mathbf{x})\mathbf{u} \quad \mathbf{u} \in \mathcal{U} \quad (10)$$

$$\mathbf{y} = \mathbf{h}(\mathbf{x}) \quad \mathbf{y} \in \mathcal{Y} \quad (11)$$

with $\mathbf{x} \in \mathbb{R}^m$, $\mathcal{U} = \mathcal{Y} = \mathbb{R}^p$, and vector relative degree $\{r_1, \dots, r_p\}$, globally defined and constant. The feedback:

$$\mathbf{u} = -R^{-1}(\mathbf{x})(\alpha(\mathbf{x}) + \mathbf{w}) \quad (12)$$

with R being the $m \times m$ matrix:

$$R(\mathbf{x}) = \begin{pmatrix} L_{g_1} L_f^{r_1-1} h_1(\mathbf{x}) & \dots & L_{g_p} L_f^{r_1-1} h_1(\mathbf{x}) \\ L_{g_1} L_f^{r_2-1} h_2(\mathbf{x}) & \dots & L_{g_p} L_f^{r_2-1} h_2(\mathbf{x}) \\ \vdots & \ddots & \vdots \\ L_{g_1} L_f^{r_p-1} h_p(\mathbf{x}) & \dots & L_{g_p} L_f^{r_p-1} h_p(\mathbf{x}) \end{pmatrix} \quad (13)$$

and $\alpha(\mathbf{x})$ being:

$$\alpha = \begin{pmatrix} L_f^{(r_1)} h_1(\mathbf{x}) \\ \vdots \\ L_f^{(r_{p-1})} h_{p-1}(\mathbf{x}) \\ L_f^{r_p} h_p(\mathbf{x}) \end{pmatrix} \quad (14)$$

linearizes the MIMO system from the new input \mathbf{w} to the output \mathbf{y} .

Remark 1. The closed loop dynamic system (11) with feedback (12) can be expressed in (\mathbf{z}, \mathbf{y}) coordinates such that²:

$$\begin{cases} \dot{\mathbf{z}} = \mathbf{f}(\mathbf{z}, y_1, \dots, y_1^{(r_1-1)}, \dots, y_p, \dots, y_p^{(r_p-1)}) \\ \begin{cases} y_1^{(1)} = L_f h_1(\mathbf{x}) \\ \vdots \\ y_1^{(r_1)} = w_1 \\ \vdots \\ y_p^{(1)} = L_f h_p(\mathbf{x}) \\ \vdots \\ y_p^{(r_p)} = w_p \end{cases} \end{cases} \quad (15)$$

where $\dot{\mathbf{z}} = \mathbf{f}(\mathbf{z}, y_1, \dots, y_1^{(r_1-1)}, \dots, y_p, \dots, y_p^{(r_p-1)})$ represent the *internal dynamics*.

² Let us remind here the notation $y^{(k)} \equiv dy^k/d^k t$

Now, we are in the position to introduce the control law driving the dynamics to a limit cycle.

Proposition 2. Consider a reaction network with p key species $s_i \in S_{key}$, such that the species formation function $f: \mathbb{R}^m \mapsto \mathbb{R}^m$ corresponding to the inner kinetics

$$f(\mathbf{c}) = \mathcal{N}\mathbf{v}, \quad (16)$$

exhibits sustained oscillations when the concentration of p key species is kept constant at some specific critical values $\tilde{\mathbf{c}} \in \mathbb{R}_{\geq 0}^p$.

Then, the system

$$\begin{aligned}\dot{\mathbf{c}} &= \mathcal{N}\mathbf{v} + \phi(\mathbf{c}_{in}(t) - \mathbf{c}) & \mathbf{c} \in \mathbb{R}_{\geq 0}^m \\ \mathbf{y} &= \mathbf{h}(\mathbf{c})\end{aligned} \quad (17)$$

where $h: \mathbb{R}^m \mapsto \mathbb{R}^p$, with a control law of the form:

$$\mathbf{c}_{in}(t) = \mathbf{c} + \frac{1}{\phi} \mathcal{G}(\mathbf{c})\mathbf{u} \quad (18)$$

and \mathbf{u} given by:

$$\mathbf{u} = - \left[\frac{\partial \mathbf{h}}{\partial \mathbf{c}} \mathcal{G}(\mathbf{c}) \right]^{-1} \frac{\partial \mathbf{h}}{\partial \mathbf{c}} \mathcal{N}\mathbf{v} + \left[\frac{\partial \mathbf{h}}{\partial \mathbf{c}} \mathcal{G}(\mathbf{c}) \right]^{-1} \mathbf{w}, \quad (19)$$

exhibits a limit cycle in the internal dynamics, provided that:

- (i) $\mathbf{w} \in \mathbb{R}^p$ is a external reference input of the form:

$$\mathbf{w} = -K(\mathbf{y} - \tilde{\mathbf{y}}), \quad (20)$$

such that ($\dim \mathbf{y} = \dim \mathbf{u} = p$), $K \in \mathbb{R}^{p \times p}$ is an arbitrary positive definite diagonal matrix and $\tilde{\mathbf{y}} = \tilde{\mathbf{c}}$, with $\tilde{\mathbf{c}}$ containing the critical concentration values.

- (ii) The matrix $\mathcal{G}(\mathbf{c}) \in \mathbb{R}^{m \times p}$ is constructed as follows. Let $\mathcal{G}' \in \mathbb{R}^{m \times m}$ defined as:

$$\mathcal{G}'_{ij}(\mathbf{c}) = \begin{cases} -c_i + 1 & \text{for } i = j, & \text{if } s_i, s_i \in S_{key} \\ -c_i & \text{for } i \neq j, & \text{if } s_i, s_j \in S_{key} \\ 0 & \text{for } j = 1, \dots, p & \text{if } s_i, s_j \notin S_{key}. \end{cases} \quad (21)$$

$$\mathcal{G}(\mathbf{c}) = \mathcal{G}'(\mathbf{c})I_k, \quad (22)$$

with $I_k = \{1, 0\}^{m \times p}$, where the columns $1, \dots, p$ of I_k are the vectors of the euclidean basis corresponding to key species $1, \dots, p$.

Proof Substituting the expression (18) into (17), the system reads:

$$\begin{aligned}\dot{\mathbf{c}} &= \mathcal{N}\mathbf{v} + \mathcal{G}(\mathbf{c})\mathbf{u} & \mathbf{c} \in \mathbb{R}_{\geq 0}^m \\ \mathbf{y} &= \mathbf{h}(\mathbf{c})\end{aligned} \quad (23)$$

where $h: \mathbb{R}^m \mapsto \mathbb{R}^p$ and $\mathcal{G}(\mathbf{c})$ is defined by (21).

Let us compute now the MIMO linearizing law introduced in Proposition (1). The matrix $R(\mathbf{c})$ in (13) reads:

$$R(\mathbf{c}) = \begin{pmatrix} L_{g_1} h_1(\mathbf{c}) & \dots & L_{g_p} h_1(\mathbf{c}) \\ L_{g_1} h_2(\mathbf{c}) & \dots & L_{g_p} h_2(\mathbf{c}) \\ \vdots & \ddots & \vdots \\ L_{g_1} h_p(\mathbf{c}) & \dots & L_{g_p} h_p(\mathbf{c}) \end{pmatrix} \quad (24)$$

where by construction, the relative degree of the system (23) fulfills:

$$r_1 = r_2 = \dots = r_p = 1.$$

The expression for α in (14) becomes:

$$\alpha = \begin{pmatrix} L_f h_1(\mathbf{c}) \\ \vdots \\ L_f h_{p-1}(\mathbf{c}) \\ L_f h_p(\mathbf{c}) \end{pmatrix}. \quad (25)$$

After substituting (24) and (25) in (12), the MIMO linearizing feedback is transformed into (19). According to Proposition 1, this feedback linearizes the MIMO system (23) from the input \mathbf{w} to the output \mathbf{y} . The closed loop system in the (\mathbf{z}, \mathbf{y}) coordinates can be expressed, according to Eq. (2), as:

$$\dot{\mathbf{z}} = f(\mathbf{z}, y_1, y_2, \dots, y_p)$$

$$\begin{cases} \dot{y}_1 = w_1 \\ \dot{y}_2 = w_2 \\ \vdots \\ \dot{y}_p = w_p. \end{cases}$$

Setting the external reference given by (20) in the system above, we arrive to the following expression for the closed loop dynamics, in compact form:

$$\dot{\mathbf{z}} = \zeta(\mathbf{z}, \mathbf{y}) \quad (26)$$

$$\dot{\mathbf{y}} = -K(\mathbf{y} - \tilde{\mathbf{y}}) \quad (27)$$

where (26) is the internal dynamics, and the linear stabilizing feedback (20) drives the system exponentially to the manifold $\tilde{\mathbf{y}}$. The internal dynamics (26), as it was assumed in the main statement, shows a limit cycle oscillation when the concentrations of the key species $s_i \in S_{key}$ are constant and equal to the critical values \tilde{c}_i . Provided that $\tilde{\mathbf{y}} = \tilde{\mathbf{c}}$ in (20), the controller drives the concentrations of the key species to the critical values, and the oscillation will appear for the controlled system in the reduced manifold determined by $c_i = \tilde{c}_i$ for $s_i \in S_{key}$.

The system can be implemented into practice provided that: i) all concentrations can be measured, ii) inflow concentrations of key species can be manipulated as required, iii) the control volume is constant during the process, iv) the non key species are entrapped within the control volume. The feedback linearization technique is known to be sensitive to model error. However, in the systems under study, oscillatory behaviour prevail for ranges of kinetic parameters and key species reference concentrations, hence error within certain margins will be tolerated without losing the desired oscillation.

Example. The Brusselator network is again selected as a proof of concept for the proposed control law. As reported previously, a limit cycle oscillation appears in the Brusselator when A, B, C and F are held constant at the values shown in Table 1. Using the results presented a controller is designed next to drive the dynamics (3-6) to the sustained oscillation shown in Fig. 1. The key species A, B, C and F are chosen to be controlled by their inlet flow rate. The selected output vector is:

$$\mathbf{y} = (c_1 \ c_3 \ c_4 \ c_5)^T.$$

and the closed loop expression is of the form (23) with:

$$\mathcal{N}\mathbf{v} = \begin{pmatrix} -1 & 0 & 0 & 0 \\ 1 & -1 & -1 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix}.$$

The expressions for the reaction rates v_1, v_2, v_3 and v_4 are given by Eqs. (3-6), and $\mathcal{G}(\mathbf{c})$ is constructed following (21):

$$\mathcal{G}(\mathbf{c}) = \begin{pmatrix} -c_1 + 1 & -c_1 & -c_1 & -c_1 \\ 0 & 0 & 0 & 0 \\ -c_3 & -c_3 + 1 & -c_3 & -c_3 \\ -c_4 & -c_4 & -c_4 + 1 & -c_4 \\ -c_5 & -c_5 & -c_5 & -c_5 + 1 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The matrix (13) reads:

$$R(\mathbf{c}) = \begin{pmatrix} -c_1 + 1 & -c_1 & -c_1 & -c_1 \\ -c_3 & -c_3 + 1 & -c_3 & -c_3 \\ -c_4 & -c_4 & -c_4 + 1 & -c_4 \\ -c_5 & -c_5 & -c_5 & -c_5 + 1 \end{pmatrix},$$

and the vector (14) is of the form:

$$\alpha(\mathbf{c}) = \begin{pmatrix} -k_1^+ c_1 + k_1^- c_2 \\ k_2^+ c_2 - k_2^- c_3 \\ -k_3^+ c_2 c_4 + k_3^- c_5 c_6 \\ k_3^+ c_2 c_4 - k_3^- c_5 c_6 \end{pmatrix}.$$

According to Proposition 1, the feedback law (19) linearizes the system from the input \mathbf{w} to the output \mathbf{y} . The input \mathbf{w} is defined by (20), where the constant reference for \mathbf{y} to be tracked by the controller is

$$\tilde{\mathbf{y}} = (1 \ 1 \ 16 \ 0.5)^T$$

and the linear feedback gain K selected to stabilize the linear part of the input-output linearized system is the (4×4) identity matrix. The trajectories of the closed loop system evolve to the manifold where the limit cycle appears, as it is shown in Fig. 2 (a, b). We choose a

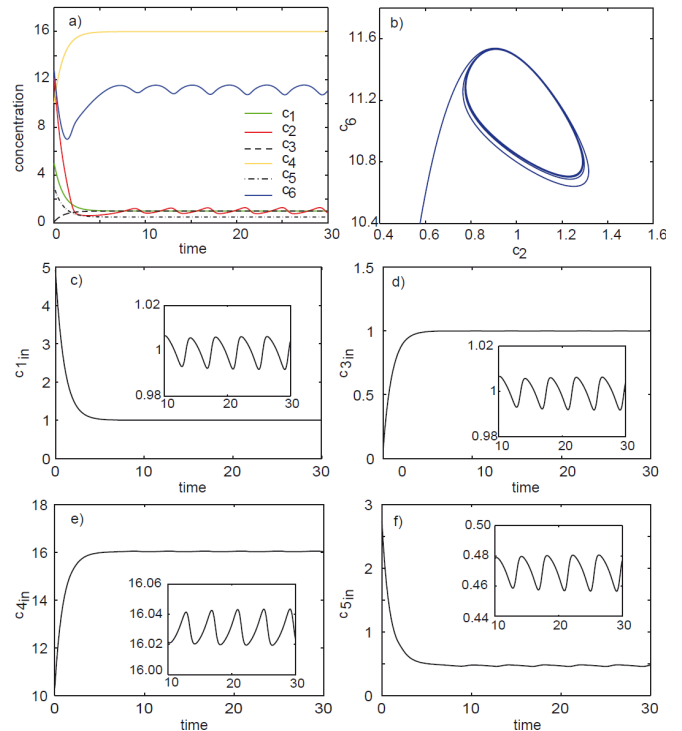


Fig. 2. Closed loop response (a) in the time domain (b) in the c_2 - c_6 phase space. (c), (d), (e), (f) key species' inlet concentrations.

residence time such that (18) is satisfied for positive inlet concentrations. In Fig. 2 (c-f) the inlet concentrations of the key species driving the system to the desired oscillation computed using (18) are depicted. Here it is important to

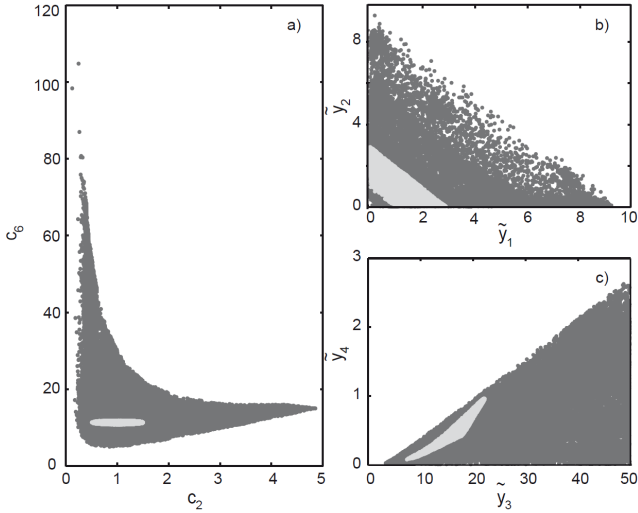


Fig. 3. Viable reference values for a sustained oscillation (b-c), and corresponding locations of the unstable focus (a). In light grey, viable reference values for a sustained oscillation with focus within a circle of radius 0.5 around the nominal value.

note that both the required inlet and outlet concentrations for species X and Y are zero, thus X and Y must be entrapped in the control volume. In order to analyze the capacity of the controller to maintain a given desired behaviour in presence of uncertainty, we explore the space of the reference values, using the algorithm by Zamora-Sillero et al. (2011). In Fig. 3 we depict the values of the reference $\tilde{\mathbf{y}}$ found to preserve a sustained oscillation (blue regions). In light grey, we depict the values of the reference $\tilde{\mathbf{y}}$ found to preserve the oscillation where distance of the unstable focus to the reference value (1, 11) is less or equal than 0.5.

APPENDIX

Concepts and results summarized in this Appendix are closer discussed in (Isidori, 1989; Kravaris, 1990; Grogard and Canudas de Wit, 2004). Let us define a nonlinear system affine in the input and without feedthrough term of the form:

$$\begin{aligned} \dot{\mathbf{x}} &= f(\mathbf{x}) + g(\mathbf{x})\mathbf{u} & \mathbf{u} &\in \mathcal{U} \\ \mathbf{y} &= h(\mathbf{x}) & \mathbf{y} &\in \mathcal{Y} \end{aligned} \quad (28)$$

where $\mathbf{x} \in \mathbb{R}^n$. For a MIMO (Multi Input Multi Output) system with p outputs and m inputs, $\mathcal{U} = \mathbb{R}^m$, $\mathcal{Y} = \mathbb{R}^p$, $g(\mathbf{x})$ is an $n \times m$ matrix:

$$g(\mathbf{x}) = [g_1(\mathbf{x}), \dots, g_m(\mathbf{x})]$$

and $h(\mathbf{x})$ a p -vector.

Basic geometric properties

Let $\lambda(\mathbf{x}) : \mathbb{R}^n \rightarrow \mathbb{R}$. The derivative of λ along f is denoted:

$$L_f \lambda(\mathbf{x}) = \left(\frac{\partial \lambda}{\partial \mathbf{x}} \right)^T f(\mathbf{x}) = \sum_{i=1}^n \frac{\partial \lambda}{\partial x_i} f_i(\mathbf{x}). \quad (29)$$

We also define:

$$L_g L_f h(\mathbf{x}) = \frac{\partial(L_f h)}{\partial \mathbf{x}} g(\mathbf{x}) \quad (30)$$

and

$$L_f^k h(\mathbf{x}) = \frac{\partial(L_f^{k-1} h)}{\partial \mathbf{x}} f(\mathbf{x}). \quad (31)$$

Definition 1. The MIMO system (28) with $\mathcal{U} = \mathcal{Y} = \mathbb{R}^m$ is said to have a (vector) *relative degree* $\{r_1, \dots, r_m\}$ at a point \mathbf{x}^0 if, for all \mathbf{x} in a neighborhood of \mathbf{x}^0 :

- (i) $L_{g_j} L_f^k h_i(\mathbf{x}) = 0$ for all $1 \leq i, j \leq m$ and $k < (r_i - 1)$;
- (ii) the $m \times m$ matrix:

$$R(\mathbf{x}) = \begin{pmatrix} L_{g_1} L_f^{r_1-1} h_1(\mathbf{x}) & \dots & L_{g_m} L_f^{r_1-1} h_1(\mathbf{x}) \\ L_{g_1} L_f^{r_2-1} h_2(\mathbf{x}) & \dots & L_{g_m} L_f^{r_2-1} h_2(\mathbf{x}) \\ \vdots & \ddots & \vdots \\ L_{g_1} L_f^{r_m-1} h_m(\mathbf{x}) & \dots & L_{g_m} L_f^{r_m-1} h_m(\mathbf{x}) \end{pmatrix} \quad (32)$$

is not singular at $\mathbf{x} = \mathbf{x}^0$.

Definition 2. Let us consider a dynamic system of the form (28) in which relative degree is defined. For the sake of simplicity, let us consider the SISO system (28) with $p = m = 1$, and assume that the relative degree r of the system is globally defined and constant. Let us apply a one to one change of coordinates

$$[\boldsymbol{\xi}, \mathbf{z}] = \Phi(\mathbf{x}) \quad (33)$$

being:

$$\boldsymbol{\xi} = [\phi_1(\mathbf{x}), \dots, \phi_r(\mathbf{x})], \quad \mathbf{z} = [\phi_{r+1}(\mathbf{x}), \dots, \phi_n(\mathbf{x})] \quad (34)$$

such that $\phi_i(\mathbf{x}) = L_f^{i-1} h(\mathbf{x})$ for $1 \leq i \leq r$ and $L_g \phi_i(\mathbf{x}) = 0$ for $r+1 \leq i \leq n$, then:

$$\begin{aligned} \xi_1 &= h(\mathbf{x}) \\ \xi_2 &= L_f h(\mathbf{x}) \\ &\vdots \\ \xi_{r-1} &= L_f^{r-2} h(\mathbf{x}) \\ \xi_r &= L_f^{r-1} h(\mathbf{x}) \end{aligned}$$

and therefore:

$$\begin{aligned} \dot{\xi}_1 &= \xi_2 \\ \dot{\xi}_2 &= \xi_3 \\ &\vdots \\ \dot{\xi}_{r-1} &= \xi_r \\ \dot{\xi}_r &= \frac{\partial L_f^{r-1} h(\mathbf{x})}{\partial \mathbf{x}} \dot{\mathbf{x}} = L_f^r h(\mathbf{x}) + L_g L_f^{r-1} h(\mathbf{x}) u = v \end{aligned} \quad (35)$$

Using the condition $L_g \phi_i(\mathbf{x}) = 0$ for $r+1 \leq i \leq n$, subsystem \mathbf{z} takes the form:

$$\dot{\mathbf{z}} = F(\mathbf{z}, \boldsymbol{\xi}). \quad (36)$$

The expression of the dynamic system (28) after the change of coordinates described, constituted by two subsystems of the form (35) and (36) is denoted as *normal form* in the context of nonlinear feedback theory. The subsystem (36) represents the internal dynamics of (28) with respect to the output y .

Input Output linearizing feedback

Proposition 3. Consider the MIMO system (28) with $\mathcal{U} = \mathcal{Y} = \mathbb{R}^m$, and vector relative degree $\{r_1, \dots, r_m\}$, globally defined and constant. The feedback:

$$\mathbf{u} = -R^{-1}(\mathbf{x})(\boldsymbol{\alpha}(\mathbf{x}) + \mathbf{v}) \quad (37)$$

with R defined by (32) and $\alpha(\mathbf{x})$ being:

$$\alpha = \begin{pmatrix} L_f^{(r_1)} h_1(\mathbf{x}) \\ \vdots \\ L_f^{(r_{m-1})} h_{m-1}(\mathbf{x}) \\ L_f^{r_m} h_m(\mathbf{x}) \end{pmatrix} \quad (38)$$

linearizes the MIMO system from the input \mathbf{v} to the output \mathbf{y} . That is, transforms the system into a system whose input-output behaviour is identical to that of a linear system having a transfer function matrix:

$$\frac{Y(s)}{V(s)} = \begin{pmatrix} \frac{1}{s^{r_1}} & 0 & \dots & 0 \\ 0 & \frac{1}{s^{r_2}} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \dots & \frac{1}{s^{r_m}} \end{pmatrix} \quad (39)$$

proof First, let us transform (28) to normal form by means of a change of coordinates of the form:

$$[\xi^1, \dots, \xi^m, \mathbf{z}] = \Phi(\mathbf{x}) \quad (40)$$

where, for $i = 1, \dots, m$

$$\xi^i = [\xi_1^i, \dots, \xi_{r_i}^i] = [\phi_1^i(\mathbf{x}), \dots, \phi_{r_i}^i(\mathbf{x})] \quad (41)$$

and

$$\mathbf{z} = [z_1, \dots, z_{n-r}] = [\phi_{r+1}(\mathbf{x}), \dots, \phi_n(\mathbf{x})] \quad (42)$$

such that, on the one hand:

$$\begin{aligned} \xi_1^i &= h_i(\mathbf{x}) \\ \xi_2^i &= L_f h_i(\mathbf{x}) \\ &\vdots \\ \xi_{r-1}^i &= L_f^{r-2} h_i(\mathbf{x}) \\ \xi_r^i &= L_f^{r-1} h_i(\mathbf{x}) \end{aligned}$$

for $i = 1, \dots, m$ and then:

$$\begin{aligned} \dot{\xi}_1^i &= \xi_2^i \\ \dot{\xi}_2^i &= \xi_3^i \\ &\vdots \\ \dot{\xi}_{r_i-1}^i &= \xi_{r_i}^i \\ \dot{\xi}_{r_i}^i &= L_f^{r_i} h_i(\mathbf{x}) + L_{g_j}^{r_i} L_f^{r_i-1} h_i(\mathbf{x}) \end{aligned} \quad (43)$$

and, on the other hand, $\phi_{r+1}(\mathbf{x}), \dots, \phi_n(\mathbf{x})$ are such that:

$$\dot{\mathbf{z}} = f(\mathbf{z}, \xi^1, \dots, \xi^m). \quad (44)$$

Conditions under which such a change of coordinates can be found are described by Isidori (1989). The feedback (37), known as the *Standard Noninteractive Feedback* (Isidori, 1989), applied to the system described by (43) and (44) yields the following system, characterized, on the one hand, by m sets of equations of the form:

$$\begin{aligned} \dot{\xi}_1^i &= \xi_2^i \\ \dot{\xi}_2^i &= \xi_3^i \\ &\vdots \\ \dot{\xi}_{r_i-1}^i &= \xi_{r_i}^i \\ \dot{\xi}_{r_i}^i &= v_i \end{aligned} \quad (45)$$

plus an additional set of the form (44) constituted by $n-r$ equations. The input-output behaviour of this system coincides with the corresponding to a linear system having the transfer function matrix (39).

Remark 2. Taking in account the following equivalences:

$$\begin{aligned} y_i^1 &= \xi_2^i \\ y_i^2 &= \xi_3^i \\ &\vdots \\ y_i^{(r-1)} &= \xi_r^i \\ y_i^r &= v_i \end{aligned}$$

the system in normal form described by (45) and (44) can be expressed in an equivalent form by:

$$\begin{aligned} \dot{\mathbf{z}} &= f(\mathbf{z}, y_1, \dots, y_1^{(r_1-1)}, \dots, y_m, \dots, y_m^{(r_m-1)}) \\ \begin{cases} y_1^{(1)} = L_f h_1(\mathbf{x}) \\ \vdots \\ y_1^{(r_1)} = v_1 \\ \vdots \\ y_m^{(1)} = L_f h_m(\mathbf{x}) \\ \vdots \\ y_m^{(r_m)} = v_m \end{cases} \end{aligned} \quad (46)$$

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