

# A CHARACTERIZATION OF THE LINEAR APPROXIMATION FOR THE NONLINEAR BICOMPARTMENTAL POLYNOMIAL SYSTEM: APPLICATION IN PARAMETERS IDENTIFICATION

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## ABSTRACT

Applying of the linearization method in nonlinear polynomial bicompartmental systems raises a fundamental problem: the linear model obtained is not usually real. The presented work shows by means of the modified distance functional introduced by Y. Cherruault that it is possible to provide a characterization of a real system. A direct application of earlier works allows us to give an approximate identification to the nonlinear system.

**KEYWORDS:** Nonlinear Polynomial, Bicompartmental Systems

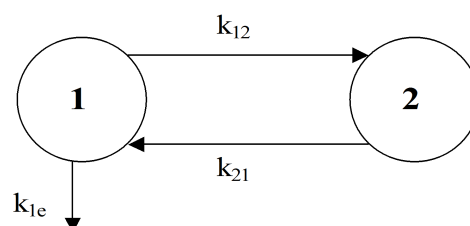
## INTRODUCTION

Compartmental analysis consists of studying the exchange of matter between two or several compartments. This technique of modeling is commonly used into biomathematics. It is also found in other fields as chemistry, physics and even of the economy. It is simple and quickly leads to mathematical relationships. The substance being studied is divided into different "compartments" that we can define mathematically as equivalent classes which are characterized by the physical properties (physical, electrical or chemical states). These exchanges are shown in the figure 1. Hebri and Cherruault have solved the identification problem of the coefficients in the case where the exchange is linear.

It is possible to adapt the method used in [1], which is based on the linearization method to a nonlinear system. This method allows, as in the Michaelis-Menten system, to identify simply the exchange coefficients for a nonlinear polynomial compartmental system. However, it requires that the obtained linear system be the replica of a real physical situation, i.e. the corresponding compartmental matrix should be positive. In general, this condition is not verified as in the polynomial systems which we are interested here. The first aim of this paper is to show how to exploit the measures made on the initial system to characterize a linear model in compliance with Physical reality.

## A GENERAL DESCRIPTION OF THE LINEARIZATION METHOD

Let  $\mathcal{G}_{NL}$  be the nonlinear open bicompartmental system shown in figure 1



**Figure 1**

We will denote by

$$X : [0, +\infty[ \rightarrow \mathbb{R}^2$$

$$t \rightarrow X^T(t) = (x_1(t), x_2(t)),$$

The state function associated with a compartmental system, that is we use  $x_1(t)$  and  $x_2(t)$  for the mass Quantity of a certain substance to be studied, present in compartments 1 and 2 at time  $t$ ., respectively.

Our basic assumptions are the following:

The exchange from compartment  $i$  to compartment  $j$  is governed by a law  $h_i(x_1, x_2)$

The exchange from compartment 1 towards the outside is given by a law  $k_{1e}x_1^\alpha$  ( $\alpha \geq 1$ )

The balance of exchanges ( cf [2] ) leads to the equations

$$\begin{cases} x_1'(t) = -k_{1e}x_1^\alpha(t) - h_1(x_1(t), x_2(t)) + h_2(x_1(t), x_2(t)) \\ x_2'(t) = h_1(x_1(t), x_2(t)) - h_2(x_1(t), x_2(t)) \end{cases}$$

Denote by

$$F : \mathbb{R}^2 \rightarrow \mathbb{R}^2$$

$$F(x_1, x_2) = (f_1(x_1, x_2), f_2(x_1, x_2))$$

The vector function, characterizing this exchange, then:

$$\begin{cases} f_1(x_1, x_2) = -k_{1e}x_1^\alpha - h_1(x_1, x_2) + h_2(x_1, x_2) \\ f_2(x_1, x_2) = h_1(x_1, x_2) - h_2(x_1, x_2) \end{cases}$$

So the nonlinear system  $(S_{NL})$  is governed by the following differential problem with initial condition

$$\begin{cases} X' = F(X) \\ X(0) = (a_1, a_2) \end{cases}$$

Where  $a_1$  and  $a_2$  are the substance quantities which are present in the compartments 1 and 2 at the initial instant.

Applying Taylor's formula, we obtain the following differential system with initial condition that we can consider as an approach of the differential nonlinear system :( 2.1)

$$\begin{cases} Z'(t) = F(a_1, a_2) Z(t) \\ Z(0) = (a_1, a_2) \end{cases}$$

Where  $(DF)_{(a_1, a_2)}$  is the  $F$ -Jacobian matrix. Set

$$\begin{cases} p_{1e} = \alpha_1 e^{\alpha_1} \\ p_{12} = \frac{\partial h_1(a_1, a_2)}{\partial x_1} \\ p_{21} = \frac{\partial h_2(a_1, a_2)}{\partial x_2} \end{cases}$$

$(DF)_{(a_1, a_2)}$  has the form:

$$(DF)_{(a_1, a_2)} = \begin{pmatrix} p_{1e} & p_{12} & p_{21} \\ p_{12} & p_{21} \end{pmatrix}$$

Taking the following assumption

$$\frac{\partial h_1(a_1, a_2)}{\partial x_2} - \frac{\partial h_2(a_1, a_2)}{\partial x_1} \neq 0$$

Which will be explained later; we get

$$\det(DF)_{(a_1, a_2)} = -\alpha a_1^{\alpha-1} k_{1e} \left( \frac{\partial h_1(a_1, a_2)}{\partial x_2} - \frac{\partial h_2(a_1, a_2)}{\partial x_1} \right) \neq 0;$$

We deduce that for any open system, there exists a unique couple  $(\alpha_1, \alpha_2)$  such that

$$F(a_1, a_2) = (DF)_{(a_1, a_2)} \cdot \begin{pmatrix} \alpha_1 \\ \alpha_2 \end{pmatrix}$$

Thus, the differential systems (2.2) becomes

$$\begin{cases} Z'(t) = (DF)_{(a_1, a_2)} \begin{pmatrix} z_1(t) + \alpha_1 - a_1 \\ z_2(t) + \alpha_2 - a_2 \end{pmatrix} \\ Z(0) = (a_1, a_2) \end{cases}$$

By taking the scaling function:

$$Y(t) = \begin{pmatrix} y_1(t) \\ y_2(t) \end{pmatrix} = \begin{pmatrix} z_1(t) + \alpha_1 - a_1 \\ z_2(t) + \alpha_2 - a_2 \end{pmatrix}$$

We may write the differential system (2.5) in the equivalent form:

$$\begin{cases} Y'(t) = (DF)_{(a_1, a_2)} Y(t) \\ Y(0) = (\alpha_1, \alpha_2) \end{cases}$$

The differential  $(DF)_{(a_1, a_2)}$  presents a formal compartmental matrix, so the system (2.7) can be interpreted (or at least formally) as a model governing exchanges in a compartmental linear system (that will be noted as  $(S_{Lin}^{(P)})$ ) (see figure 2)

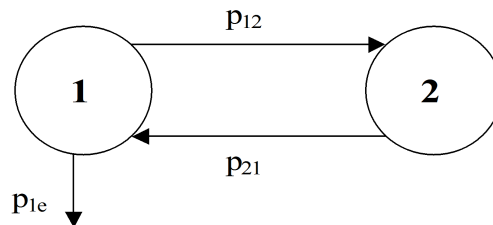


Figure 2

The nonlinear compartmental system  $(S_{NL})$  is then "approached" by this linear model. The problem of the stability has been treated and resolved in [8]

**POSITION OF THE PROBLEM**

Two problems are inferred by this method:

- The associated exchange coefficients to the system are of unknown signs,
- The obtained system is nonhomogeneous and undetermined (an initial condition is unknown).

**Study of the First Problem**

Our aim is to study the identification of the polynomial compartmental system of order  $\alpha + \beta$

These compartmental systems are characterized by the following exchange nonlinear function  $F$

$$F : \mathbb{R}^2 \rightarrow \mathbb{R}^2$$

$$(x_1, x_2) \mapsto F(x_1, x_2) = (f_1(x_1, x_2), f_2(x_1, x_2)),$$

Where

$$\begin{cases} f_1(x_1, x_2) = k_{21} x_2^\alpha x_1^\beta - k_{12} x_1^\alpha x_2^\beta - k_{1e} x_1^\alpha \\ f_2(x_1, x_2) = k_{12} x_1^\alpha x_2^\beta - k_{21} x_2^\alpha x_1^\beta \end{cases}$$

In identification theory, we consider systems, at rest, which we stimulate by the injection of a quantity  $a$  in one compartment. This corresponds to consider the following differential homogeneous system:

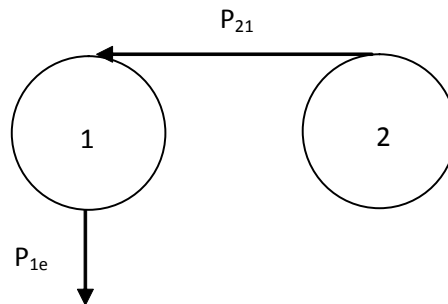
$$\begin{cases} X'(t) = F(X(t)) \\ X(0) = (a, 0) \end{cases}$$

**Preliminary Study**

The differential of  $F$  being

$$(DF)_{(a,0)} = \begin{pmatrix} \alpha k_{1e} a^{\alpha-1} & p_{21} \\ 0 & -p_{21} \end{pmatrix} \text{ with } p_{21} \text{ possibly negative or zero.}$$

The system  $(S_{Lin}^{(p)})$  is then reduced to the form shown in figure 3



**Figure 3**

We are facing two major difficulties:  $p_{12} = 0$

- The main coefficient  $p_{12} = 0$
- And  $p_{21}$  may be negative.

Under these conditions the linear system does not correspond to a real physical situation: there cannot be exchange between compartments 1 and 2 ; consequently it is not identifiable. This modeling does not present any interest. Also the initial condition  $(a, 0)$  seems inappropriate and incompatible with the linearization of the polynomial system. We recommend the following solution: introducing a “temporisation”.

This solution consists in introducing an "adequate" temporization  $t^*$  (if it exists), i.e. “wait a moment “to make it possible for the exchange to settle in the system  $(S_{NL}^{(p)})$  after injection of the quantity  $a$  in the main compartment, then measure this compartment at this moment  $t^*$  . We consider only systems admitting a nonobvious solution  $\Omega_2 \Omega_2 \Omega_2 \Omega_2$  . For  $t > t^*$  the system  $(S_{NL}^{(p)})$  is then governed by the Cauchy problem:

$$\begin{cases} x_1'(t) = k_{21}x_2^\alpha(t)x_1^\beta(t) - k_{12}x_1^\alpha(t)x_2^\beta(t) - k_{1e}x_1^\alpha(t) \\ x_2'(t) = k_{12}x_1^\alpha(t)x_2^\beta(t) - k_{21}x_2^\alpha(t)x_1^\beta(t) \\ x_1(t^*) = a^* \\ x_2(t^*) = b \end{cases}$$

Which we can write in following equivalent vectorial form:

$$\begin{cases} X'(t) = F^T(X^T(t)) \\ X^T(t^*) = (a^*, b) \end{cases}$$

But the compartment 2 is not generally accessible to measurements; then  $b$  is **unknown**. This involves a supplementary difficulty. Thus we are brought to consider differential

$$(DF)_{(a^*, b)} = \begin{pmatrix} \beta k_{21} b^\alpha a_*^{\beta-1} - \alpha k_{12} a_*^{\alpha-1} b^\beta - \alpha k_{1e} a_*^{\alpha-1} & \alpha k_{21} b^{\alpha-1} a_*^\beta - \beta k_{12} a_*^\alpha b^{\beta-1} \\ \alpha k_{12} a_*^{\alpha-1} b^\beta - \beta k_{21} b^\alpha a_*^{\beta-1} & \beta k_{12} a_*^\alpha b^{\beta-1} - \alpha k_{21} b^{\alpha-1} a_*^\beta \end{pmatrix}$$

In the neighborhood of a nonhomogeneous condition  $(a^*, b)$

$$F^T(a^*, b) = (k_{21} b^\alpha a_*^\beta - k_{12} a_*^\alpha b^\beta - k_{1e} a_*^\alpha, k_{12} a_*^\alpha b^\beta - k_{21} b^\alpha a_*^\beta)$$

The exchange coefficients in the system  $(S_{Lin})$  are then given by:

$$\begin{cases} p_{12} = \alpha k_{12} a_*^{\alpha-1} b^\beta - \beta k_{21} b^\alpha a_*^{\beta-1} \\ p_{21} = \alpha k_{21} b^{\alpha-1} a_*^\beta - \beta k_{12} a_*^\alpha b^{\beta-1} \\ p_{1e} = \alpha k_{1e} a_*^{\alpha-1} \end{cases} \tag{3.1}$$

**Problem Analysis and Study**

In the expressions of  $p_{12}$ , and  $p_{21}$ , the exchange coefficients  $k_{12}, k_{21}$ , and the constants  $\alpha, \beta$  characterise the system, consequently they are the constants of the problem. But  $a_*$  and  $b$  depend on the choice of  $t^*$  so the signs of  $p_{12}$  and  $p_{21}$  depend on the choice of  $t^*$ . For the system  $(S_{Lin}^{(P)})$  represents a measurable physical reality; it is necessary to take both  $p_{12}$  and  $p_{21}$  positive.

$$\begin{cases} p_{12} > 0 \\ p_{21} > 0 \end{cases} \Leftrightarrow \begin{cases} \alpha k_{12} a_*^\alpha - \beta k_{21} b^{\alpha-\beta} a_*^\beta > 0 \\ \alpha k_{21} b^{\alpha-\beta} a_*^\beta - \beta k_{12} a_*^\alpha > 0 \end{cases}$$

This raises two questions

- The first one is preliminary: is there a value of  $a_*$  and  $b$  such that  $\begin{cases} p_{12} > 0 \\ p_{21} > 0 \end{cases}$  ?

- The second one is fundamental: knowing that  $a_*$  and  $b$  are connected and depend on  $t^*$ , are there values satisfying the precondition?

The answer to the first question is provided by the following proposition:

**Proposition 3.1:** There are values of  $a_*$  and  $b$  such that

$$\begin{cases} p_{12} > 0 \\ p_{21} > 0 \end{cases}$$

If, and only if,  $\alpha > \beta$

Proof

Knowing that:

$$\begin{cases} p_{12} > 0 \\ p_{21} > 0 \end{cases} \Leftrightarrow \begin{cases} \alpha k_{12} a_*^\alpha - \beta k_{21} b^{\alpha-\beta} a_*^\beta > 0 \\ \alpha k_{21} b^{\alpha-\beta} a_*^\beta - \beta k_{12} a_*^\alpha > 0 \end{cases}$$

Set  $x = k_{12} a_*^\alpha$  and  $y = k_{21} b^{\alpha-\beta} a_*^\beta$  ( $x > 0$  and  $y > 0$ )

$$\begin{cases} p_{12} > 0 \\ p_{21} > 0 \end{cases} \Leftrightarrow \begin{cases} \alpha x - \beta y > 0 \\ \alpha y - \beta x > 0 \end{cases}$$

So, it suffices to remark that : If  $\alpha \leq \beta$  then the solutions set of the system

$$\begin{cases} \alpha x - \beta y > 0 \\ \alpha y - \beta x > 0 \end{cases} \text{ is empty.}$$

If  $\alpha > \beta$  then the solutions set of the system  $\begin{cases} \alpha x - \beta y > 0 \\ \alpha y - \beta x > 0 \end{cases}$  is not empty.

Now, we will show that it is possible to choose time  $t^*$  which is *compatible with a real system* as soon as the eigenvalues, corresponding to the compartmental matrix, are negative. This result is obtained thanks to the minimization of the functional  $J$  introduced by Y. Cherruault [3]

Suppose that the main compartment of the system  $(S_{NL}^{(p)})$  is measured at times  $t_j$   $1 \leq j \leq m$ .

This enables us to bring an answer to our second question by considering one variant  $J_{(i_1, i_p)}$  of the functional  $J$  that we define by

$$J_{(i_1, i_p)}(\beta_1^1, \beta_2^1, \lambda_1, \lambda_2) = \sum_{j=i_1}^{i_p} (x_1(t_j) - (\beta_1^1 e^{\lambda_1 t_j} + \beta_2^1 e^{\lambda_2 t_j}))^2. \text{ where } : 1 \leq i_1 < i_p \leq m$$

**Théorème 3.1:** Assume that the principal compartment of the system  $(S_{NL}^{(P)})$  is measured at times  $t_j$   $1 \leq j \leq m$ .

If there exists a couple  $(i_1^*, i_p^*)$  such that  $MinJ_{(i_1^*, i_p^*)}(\beta_1^1, \beta_2^1, \lambda_1, \lambda_2)$  is reached for

$$\beta_1^{1*}, \beta_2^{1*}, \lambda_1^*, \lambda_2^* ; (MinJ_{(i_1^*, i_p^*)}(\beta_1^1, \beta_2^1, \lambda_1, \lambda_2) = J_{(i_1^*, i_p^*)}(\beta_1^{1*}, \beta_2^{1*}, \lambda_1^*, \lambda_2^*))$$

Such that these values verify

$$\lambda_1^* < 0, \lambda_2^* < 0, \beta_1^{1*} \neq 0, \text{ and } \beta_2^{1*} \neq 0$$

Then the choice  $t^* = t_{i_1^*}$  gives that

$$(DF)_{(a^*, b)} = \begin{pmatrix} -p_{1e} - p_{12} & p_{21} \\ p_{12} & -p_{21} \end{pmatrix}$$

(Where we have set  $a^* = x_1(t^*)$  and  $b = x_2(t^*)$ ), is compartmental i.e.

$$p_{12} > 0 \text{ et } p_{21} > 0$$

**Proof:** Suppose that the couple  $(i_1^*, i_p^*)$  exists. Set  $t^* = t_{i_1^*}$ ,  $x_1(t_{i_1^*}^*) = a^*$  and associate

$$(DF)_{(a^*, b)} = \begin{pmatrix} -p_{1e} - p_{12} & p_{21} \\ p_{12} & -p_{21} \end{pmatrix}, \text{ the compartmental matrix of the linear } (S_{Lin}^{(P)}) \text{ with the initial}$$

$$\text{condition } X^T(t^*) = (a^*, b)$$

We have

$$\det(DF)_{(a^*, b)} = \lambda_1^* \lambda_2^* = p_{1e} p_{21} \text{ and } p_{1e} = \alpha k_{1e}$$

we conclude simply that  $p_{21} > 0$

Hebri and Cherruault have established in [7] that:

$$\left\{ \begin{array}{l} (-\lambda_1^*) < p_{1e} < (-\lambda_2^*) \\ \text{and} \\ \beta_1^{1*} \neq 0 \Rightarrow p_{12} = -\frac{(\lambda_1^* + p_{1e})(\lambda_2^* + p_{1e})}{p_{1e}} \end{array} \right.$$

It follows that:  $p_{12} > 0$ .



## AN APPROXIMATION OF THE SYSTEM IDENTIFICATION $(S_{NL}^{(P)})$

### Identification of the System $(S_{Lin}^{(P)})$

Through the scaling variable  $s = t - t^*$  the system  $(S_{Lin}^{(P)})$  is governed by the differential system with initial condition

$$\begin{cases} Y'(s) = F^T(Y^T(s)) \\ Y^T(0) = (a^*, b) \end{cases}$$

The initial conditions are not completely determined since  $b$  is unknown. We are exactly under identification assumptions of the *nonhomogeneous linear compartmental systems with an unspecified initial condition* cf. [6]

$$\begin{cases} y_1(0) = \frac{a^*}{\alpha} \\ y_2(0) = b \end{cases}$$

The system  $(S_{Lin}^{(P)})$  is then identified as in [6], let us set

$$\begin{cases} v_1^* = p_{1e} \\ v_2^* = p_{12} \\ v_3^* = p_{21} \end{cases} \tag{4.1}$$

And complete the partial measurement matrix  $P_1^* = \begin{pmatrix} \beta_1^{1*} & \beta_1^{2*} \\ \beta_2^{1*} & \beta_2^{2*} \end{pmatrix}$  by

$$\overline{P_1^*} = \begin{pmatrix} \beta_1^{1*} & \beta_1^{2*} \\ \beta_2^{1*} & \beta_2^{2*} \end{pmatrix} \tag{4.2}$$

As in [7]

### One Approximation of the Nonlinear System Identification $(S_{NL}^{(P)})$

The definitions of  $p_{12}$  and  $p_{21}$  (3.1) and the notations (4.1) make it possible to write the following algebraic system (where the unknowns are  $k_{12}$ ,  $k_{21}$  and  $b$ )

$$\begin{cases} \alpha_2 \beta_1^{1*} k_{12} a^{\alpha_1} b^{\alpha_2} - \alpha_2 \beta_1^{2*} k_{21} b^{\alpha_1} a^{\alpha_2} \\ \alpha_3 \beta_2^{1*} k_{21} b^{\alpha_1} a^{\alpha_2} - \alpha_3 \beta_2^{2*} k_{12} a^{\alpha_1} b^{\alpha_2} \end{cases} \tag{4.3}$$

To identify the coefficients  $(k_{12}, k_{21})$  of the nonlinear system  $(S_{NL}^{(P)})$  one must first determine  $b$

Proposition: Let  $\overline{P}_1^* = \begin{pmatrix} \beta_1^{1*} & \beta_1^{2*} \\ \beta_2^{1*} & \beta_2^{2*} \end{pmatrix}$  be the matrix (4.2) corresponding with the system  $(S_{Lin}^{(P)})$ . Assume that

the system is identified as in (4.1), and the functional  $J_{(i,i_p)}$  is minimized

Then the initial condition  $b$  is determined by

$$b^* = \frac{1}{v_3^*} \left( k_{21} b^{\otimes} a^{\otimes} - k_{12} a^{\otimes} b^{\otimes} \right) \tag{4.4}$$

**Proof:** The system (4.3) allows to calculate  $b v_3^* - a_* v_2^*$ , :

$$\begin{aligned} b v_3^* - a_* v_2^* &= \left( k_{21} b^{\otimes} a^{\otimes} - k_{12} a^{\otimes} b^{\otimes} \right) \\ &= \left( k_{21} b^{\otimes} a^{\otimes} - k_{12} a^{\otimes} b^{\otimes} \right) \end{aligned}$$

And as a consequence:  $b = \frac{1}{v_3^*} \left[ (\alpha + \beta) (-\lambda_1^* \beta_1^{2*} - \lambda_2^* \beta_2^{2*}) + a_* v_2^* \right] = b^*$

**Remark:**  $v_3^* \neq 0$  and  $b \neq 0$ , temporization was introduced for this purpose.

**Theorem:** Let  $P_1^* = \begin{pmatrix} \beta_1^{1*} & \beta_1^{2*} \\ \beta_2^{1*} & \beta_2^{2*} \end{pmatrix}$  be the matrix of partial measurements associated with the system  $(S_{Lin}^{(P)})$

identified by the relation (4.1). If

$$\left\{ \begin{aligned} & i) \lambda_1^* \beta_1^{2*} \neq \lambda_2^* \beta_2^{2*} \\ & ii) \lambda_1^* \beta_1^{1*} \neq \lambda_2^* \beta_2^{1*} \\ & \text{and} \\ & iii) \lambda_1^* \beta_1^{1*} \neq \lambda_2^* \beta_2^{1*} \end{aligned} \right.$$

Identifying the nonlinear system  $(S_{NL}^{(P)})$  is approximated by

Then the identification of the nonlinear system  $(S_{NL}^{(P)})$  is identified in a single way, moreover

$$\begin{cases} k_{12} = \frac{\alpha v_2^* a_* - \beta v_3^* b^*}{\alpha v_2^* a_* + \beta v_3^* b^*} \\ k_{21} = \frac{\alpha v_3^* b^* - \beta v_2^* a_*}{\alpha v_3^* b^* + \beta v_2^* a_*} \end{cases}$$

**Proof:** If  $\alpha > \beta$  we can approach the nonlinear compartmental system  $(S_{NL}^{(P)})$  by the real linear model  $(S_{Lin}^{(P)})$

If

$$v_1^* = v_2^* = v_3^* = 0 \text{ and } v_1^* = v_2^* = v_3^* = \frac{3}{4} v_1^* = v_2^* = v_3^*$$

The system  $(S_{Lin}^{(P)})$  is identified (cf [6]) by

$$\begin{cases} v_2^* = \alpha k_{12} a_*^{\alpha-1} b^{\beta} - \beta k_{21} b^{\alpha} a_*^{\beta-1} \\ v_3^* = -\beta k_{12} a_*^{\alpha} b^{\beta-1} + \alpha k_{21} b^{\alpha-1} a_*^{\beta} \end{cases}$$

Knowing that  $b^*$  is determined by relation (4.4), the system (4.3) appears as a linear algebraic system of unknown  $(k_{12}, k_{21})$  whose determinant noted  $D$  is:

$$D = (\alpha^2 - \beta^2)(a_* b^*)^{\alpha+\beta-1}, \quad D \neq 0 \text{ because } \alpha > \beta \text{ and } b^* \neq 0 \tag{4.3}$$

Admits a unique solution  $(k_{12}, k_{21})$  which is

$$\begin{cases} k_{12} = \frac{\alpha v_2^* a_* + \beta v_3^* b^*}{(\alpha^2 - \beta^2) a_*^{\beta} b^{*\alpha}} \\ k_{21} = \frac{\alpha v_3^* b^* + \beta v_2^* a_*}{(\alpha^2 - \beta^2) a_*^{\beta} b^{*\alpha}} \end{cases}$$

The uniqueness of the solution is established by a method similar to that used in the systems of Michaelis-Menten [6].

### CONCLUSIONS

The nature of the polynomial systems involves three problems

- The initial condition  $X(0) = (a, 0)$  cannot be well adapted to the method of linearization. A temporization is essential to be reduced to the framework linear real systems.
- This temporization applies only to the class of the polynomial systems defined for  $\alpha > \beta \in \mathbb{R}$

The condition  $\ominus \star \in$  involves a negative exchange coefficient in the linearized compartmental system, so the linearization method is inappropriate for solving this case which remains open problem.

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