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► **To cite this version:**

Agustín Gabriel Yabo, Mohab Safey El Din, Jean-Baptiste Caillau, Jean-Luc Gouzé. Stability analysis of a bacterial growth model through computer algebra. 2022. hal-03671432v1

HAL Id: hal-03671432

<https://hal.science/hal-03671432v1>

Preprint submitted on 18 May 2022 (v1), last revised 20 Oct 2023 (v3)

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Stability analysis of a bacterial growth model through computer algebra

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ABSTRACT. We describe microbial growth and production of value-added chemical compounds in a continuous bioreactor through a dynamical system and we study the local stability of the equilibrium of interest by means of the classical Routh-Hurwitz criterion. The mathematical model considers various biological and structural parameters related to the bioprocess (concentration of substrate inflow, constants of the microchemical reactions, steady-state mass fractions of intracellular proteins, etc.) and thus, the stability condition is given in terms of these parameters. This boils down to deciding the consistency of a system of polynomial inequalities over the reals, which is challenging to solve from an analytical perspective, and out of reach even for traditional computational software designed to solve such problems. We show how to adapt classical techniques for solving polynomial systems to cope with this problem within a few minutes by leveraging its structural properties, thus completing the stability analysis of our model. The paper is accompanied by a Maple worksheet available online.

1. Introduction

1.1. Biological context

The dynamical system analyzed in this paper is based on previous works [31, 28, 26], and it represents a simplified version of a bioprocess used in scientific research and in the chemical and pharmaceutical industries for the production of value-added chemical compounds. The model is two-fold. On one side, it considers a bacterial model representing the main cellular functions involved in growth and chemical production: metabolism and production of proteins [8, 33, 27, 32]. On the other hand, it models a continuous bioprocess, a production scheme occurring in a bioreactor that allows steady-state operation for long periods of time, avoiding shutdown for cleaning and maintenance [5]. Thus, through a multi-scale modelling approach, the biological model aims to capture intracellular reactions, extracellular processes, and the interplay between them [29, 30].

The principle behind continuous processing is that the bacterial culture is supplied a continuous flow of fresh medium rich in nutrients, while waste products and microbial cells are removed

at the same volumetric flow rate. This creates a constant volume inside the bioreactor and—provided the appropriate operating conditions—a steady-state production regime. The outflow of compounds of interest excreted by bacteria is linear in the volumetric flow, and so the process yield can be improved through this operation parameter. However, if too large, it can lead to *washout*: a undesired condition in which there is no more bacteria in the bioreactor. This usually occurs when the rate of growth of the bacterial culture is not able to "catch-up" with the rate of dilution of the bioreactor. Hence, understanding the asymptotic behavior of the system becomes crucial in successfully operating continuous bioreactors [14].

Additionally, biological models are known to be subject to non-negligible parametric uncertainty [25]. This occurs not only due to the inherent complexity of microorganisms, but also to their genetic variability: generation after generation, bacteria face genetic modifications that can progressively deviate the mathematical model from the real system [9]. Online parameter estimation can compensate for these issues [7], but the operation parameters should be adjusted accordingly. In this context, computing the stability of the equilibria in terms of the internal parameters represents an important advantage.

1.2. Reduction to polynomial system solving

In the analyzed dynamical system, the existence of the equilibrium of interest is described by a series of *strict* inequalities in terms of the system parameters; and its local stability is given by the well-known Routh-Hurwitz stability criterion [6], which yields an additional inequality. Deciding—through an algorithmic procedure—the consistency over the real numbers of polynomial systems with real coefficients is a central problem in the area of *effective real algebraic geometry*. Such systems define *basic semi-algebraic sets*. There are two families of algorithms for tackling such a decision problem. The very first one goes back to Hilbert’s 17-th problem which asks whether a non-negative multivariate polynomial with real coefficients can always been written as a sum of squares of polynomials with real coefficients. Artin [1] showed that non-negative polynomials with real coefficients are actually sums of squares of rational fractions with real coefficients. A central result of real algebra is the *Positivstellensatz* [12, 22] which exhibits the pattern of a certificate of emptiness for a basic semi-algebraic set. Computing such certificates is proved to be hard. A more popular approach to certify non-negativity is based on reductions to semi-definite programming through the moment method and the so-called Lasserre hierarchy (see e.g. [16, 13]). These approaches are convenient to assess that some polynomial (or a family of polynomials) are non-negative while in our setting we have strict inequalities. Besides the certificates which are returned are approximate ones since the resulting semi-definite programs are solved numerically. Lifting them to *exact* certificates is also far from easy [18], especially in our setting (which involve strict inequalities over an unbounded domain).

We then focus on another family of algorithms which are “root finding” methods that can handle systems involving strict inequalities. These procedures will compute points in the solution set of the polynomial system under consideration whenever there exist. When the solution set is empty, they just return an empty list (hence, without a witness of emptiness). To ensure exactness, these algorithms make use of computer algebra methods which manipulate symbolically the input polynomials with an exact arithmetic. Within this framework, there are two families of algorithms. The very first one, initiated by Collins [4], computes a partition of the semi-algebraic set defined by the input into pieces which are homeomorphic to $]0, 1[^i$, for i ranging from 0 to the dimension of the ambient space, and which are arranged cylindrically through repeated projections on coordinate subspaces. The computational cost of this approach is doubly exponential in the dimension of the ambient space and polynomial in the number of input polynomials and their maximum degree. A more modern approach, introduced in [10] and refined in [2] allows one to compute sample points per connected components of basic semi-algebraic sets in time which is *singly* exponential in the number of variables and polynomial in the number of input

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polynomials and their maximum degree. We refer the reader to [3] for the foundations of such approaches and to [20] for more modern algorithms based on the critical point method and to the Maple package RAGLIB [19] which implements them. The two main functions which are provided by Maple package RAGLIB are `HasRealSolutions` and `PointsPerComponents`. Both take as input polynomial systems of equations and strict inequalities with coefficients in \mathbb{Q} . They respectively decide if the solution set is empty (when it is not a sample point assessing the non-emptiness is provided) and compute sample points per connected components. The polynomial system we need to solve is out of reach to the software implementing all the aforementioned methods. None of them was able to solve our problem within a full month of computation.

1.3. Contributions

We investigate some structural properties of the polynomial system to solve and in particular the degree pattern of our polynomial constraints *w.r.t.* the involved variables. By leveraging this degree pattern, we simplify significantly the first steps of the Cylindrical Algebraic Decomposition algorithm and show that *on the system we need to solve*, the classical complexity growth one is faced does not occur. We push forward this investigation and show how to exploit even better the degree patterns of intermediate data to find even stronger simplifications. In the end, after those simplifications, we obtain a polynomial system with less variables which can be solved rather easily (within a few seconds) by the RAGLIB Maple package. These simplifications are based on a careful geometric analysis of the solution set to the system we need to solve. This analysis enables us to find more compact ways to describe their projection on coordinate subspaces thanks to the degree patterns we already mentioned. In Section 2, we recall the self-replicator model of the bioreactor under consideration and show how using Routh-Hurwitz criterion, lead to polynomial system solving issues. In Section 3, we describe how we leverage degree patterns in our problem to solve our polynomial system. The last section gives more details about the data manipulated during our computations.

2. Self-replicator model for bacterial growth

2.1. Model definition

We consider a self-replicator mathematical model representing bacterial growth [31], which is described in this paper in a simplified manner. A more detailed description of the dynamical system can be found in [28], with a thorough analysis of the biological principles and assumptions behind its derivation. In the model, the bacterial culture in the bioreactor has constant volume \mathcal{V}_{ext} , and is subject to an inflow of fresh medium rich in substrate. The medium is supplied at constant volumetric flow rate F (measured in liters per hour) and with substrate concentration s_{in} (measured in grams per liter). The bioreactor is also subject to an outflow of same volumetric flow rate F of bacterial culture, containing substrate, microbial cells and metabolites of interest. The quantities in the bioreactor are given in concentrations with respect to the culture volume \mathcal{V}_{ext} :

- s : the concentration of substrate, which is used by bacteria to grow and to produce the compounds of interest.
- \mathcal{V} : the volume of the bacterial population.
- x : the concentration of the compound of interest.

The composition of the bacterial culture is described at the cell level as in [33], and thus the quantities are mass fractions of the total bacterial volume:

- p : mass fraction of precursor metabolites, used to produce biomass and the compound of interest.
- r : mass fraction of proteins of the gene expression machinery, responsible for the production of biomass.
- m : mass fraction of proteins of the metabolic machinery, responsible for the uptake of substrate from the medium, and the production of compounds of interest.

As, in nature, the precursor metabolites p occupy a negligible fraction of the cell, the cellular mass is assumed to be described by m and r , such that $m + r = 1$. The system can be externally controlled through two essential parameters:

- $u \in [0, 1]$: the allocation control, which decides whether the precursors are being used to produce proteins r or m . In nature, the allocation of resources is governed by natural mechanisms optimized by evolution. In biotechnological processes, this parameter can be controlled through biosynthetic methods able to affect the expression of RNA polymerase [11, 15]. As this paper focuses on the steady-state behavior of the system, u is a constant parameter.
- $D > 0$: the dilution rate (defined as the ratio of in-flow rate to culture volume F/V_{ext}).

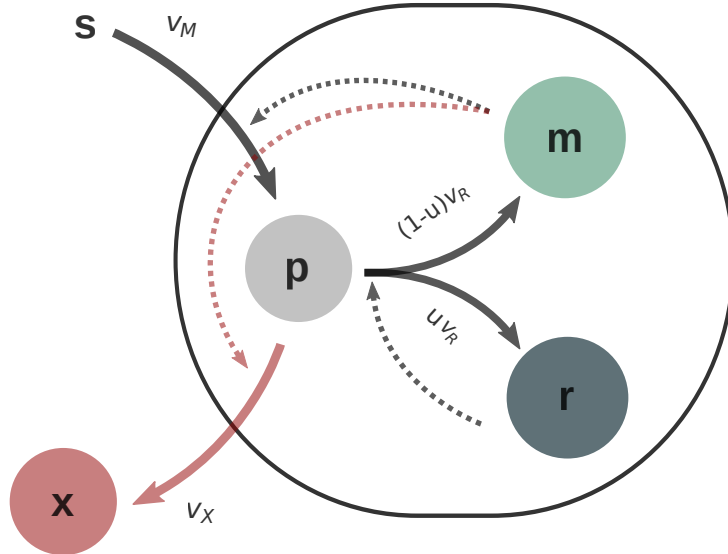


FIGURE 1. Extended coarse-grained self replicator model [33].

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The dynamical model is

$$\left\{ \begin{array}{l} \dot{s} = D(s_{in} - s) - v_M(s, m) \frac{\mathcal{V}}{\mathcal{V}_{ext}}, \\ \dot{p} = v_M(s, m) - v_R(p, r) - v_X(p, m) - \mu(p, r)p, \\ \dot{r} = u v_R(p, r) - \mu(p, r)r, \\ \dot{m} = (1 - u) v_R(p, r) - \mu(p, r)m, \\ \dot{x} = v_X(p, m) \frac{\mathcal{V}}{\mathcal{V}_{ext}} - Dx, \\ \dot{\mathcal{V}} = (\mu(p, r) - D) \mathcal{V}. \end{array} \right. \quad (\text{S}_{\text{original}})$$

The functions v_M , v_R and v_X are defined according to Michaelis-Menten kinetics [17], and linear in the concentrations m and r [21], such that

$$\begin{aligned} v_M(s, m) &\doteq k_2 m \frac{s}{K_2 + s}, \\ \mu(p, r) = v_R(p, r) &\doteq r \frac{p}{K + p}, \\ v_X(p, m) &\doteq k_1 m \frac{p}{K_1 + p}. \end{aligned} \quad (2.1)$$

As the system is analyzed in a steady-state regime, the control is fixed to a constant parameter $u = u^*$. Thus, the set of parameters is defined as $\theta \doteq (K, k_1, K_1, k_2, K_2, u^*, D)$, which is subject to the constraints

$$K > 0, \quad k_1 > 0, \quad K_1 > 0, \quad k_2 > 0, \quad K_2 > 0, \quad 1 \geq u^* \geq 0, \quad D > 0. \quad (2.2)$$

Using $m + r = 1$, we can express $m = 1 - r$, and thus remove m from the dynamical model. Additionally, by analyzing the dynamics of the quantities $s + (p+1)\mathcal{V} + x$ and $s + (p+r/u^*)\mathcal{V} + x$, we can see that they both tend asymptotically to the constant value s_{in} when $t \rightarrow \infty$. Thus, the ω -limit set (i.e. the set of points that can be limit of subtrajectories of the system) is characterized as follows.

Proposition 2.1. *The ω -limit set of any solution of system (S_{original}) lies in the hyperplane*

$$\Omega_1 \doteq \{(s, p, r, x, \mathcal{V}) \in \mathbb{R}^5 : s + (p+1)\mathcal{V} + x = s_{in}\}. \quad (2.3)$$

Moreover, under a constant allocation control $u(t) \equiv u$, this is also true for the hyperplane

$$\Omega_2 \doteq \left\{ (s, p, r, x, \mathcal{V}) \in \mathbb{R}^5 : s + \left(p + \frac{r}{u^*}\right) \mathcal{V} + x = s_{in} \right\}, \quad (2.4)$$

for $u^* \neq 0$.

The latter implies that, for every trajectory, r converges to u^* asymptotically, and x can be expressed in terms of the remaining states as

$$x = s_{in} - s - (p+1)\mathcal{V}. \quad (2.5)$$

The case $u^* = 0$ is excluded from the study for its triviality, as it is rather simple to analyze. Indeed, for this case, the hyperplane $s + (p + m/(1 - u^*))\mathcal{V} + x = s_{in}$ can be used for a similar study. Without loss of generality, a change of variables can be made that allows to omit the

constants s_{in} and \mathcal{V}_{ext} from the model. Thus, the asymptotic behavior of the original system ($S_{original}$) can be studied through its limiting system given by

$$\begin{cases} \dot{s} = D(1 - s) - v_M(s, 1 - u^*)\mathcal{V}, \\ \dot{p} = v_M(s, 1 - u^*) - v_X(p, 1 - u^*) - (p + 1)v_R(p, u^*), \\ \dot{\mathcal{V}} = (v_R(p, u^*) - D)\mathcal{V}, \end{cases} \quad (S)$$

In order to ensure that the original system ($S_{original}$) converges to the equilibria of the limiting system (S), an additional analysis is required. The reader can refer to [28] for an application of the theory of asymptotically autonomous systems [24].

2.2. Stability of the equilibrium of interest

In (S), there is a single equilibrium of interest $(s^*, p^*, \mathcal{V}^*)$, as the other existing equilibrium (usually referred to as the *washout* equilibrium) is characterized by having $\mathcal{V}^* = 0$, which does not allow for bacterial growth and metabolite production. By solving $\dot{s} = \dot{p} = \dot{\mathcal{V}} = 0$, we obtain the steady-state values in terms of the system parameters θ .

Proposition 2.2. *The equilibrium of interest is*

$$\begin{cases} p^*(\theta) = \frac{DK}{u^* - D} \\ s^*(\theta) = K_2 \frac{k_1(1 - u^*) \frac{p^*(\theta)}{K_1 + p^*(\theta)} - (p^*(\theta) + 1)u^* \frac{p^*(\theta)}{K + p^*(\theta)}}{k_2(1 - u^*) - k_1(1 - u^*) \frac{p^*(\theta)}{K_1 + p^*(\theta)} - (p^*(\theta) + 1)u^* \frac{p^*(\theta)}{K + p^*(\theta)}} \\ \mathcal{V}^*(\theta) = \frac{D(1 - s^*(\theta))(K_2 + s^*(\theta))}{k_2(1 - u^*)s^*(\theta)} \end{cases} \quad (2.6)$$

As the variables represent concentrations and biomass, they are non-negative quantities. Thus, additional inequalities are required for the existence of the equilibrium, which can be obtained by enforcing $(s^*, p^*, \mathcal{V}^*) > 0$:

$$1 > u^* > D, \quad 1 > s^*(\theta) > 0. \quad (2.7)$$

The steady state is thus determined by 7 variables. In order to study the local stability of the equilibrium, we compute the eigenvalues over \mathbb{C} of the Jacobian matrix

$$\begin{bmatrix} -D - \frac{\partial}{\partial s^*} v_M(s^*, 1 - u^*)\mathcal{V}^* & 0 & -v_M(s^*, 1 - u^*) \\ \frac{\partial}{\partial s^*} v_M(s^*, 1 - u^*) & \frac{\partial}{\partial p^*} v_X(p^*, 1 - u^*) - v_R(p^*, u^*) & 0 \\ 0 & -\frac{\partial}{\partial p^*} v_R(p^*, u^*)(p^* + 1) & 0 \\ & \frac{\partial}{\partial p^*} v_R(p^*, u^*)\mathcal{V}^* & 0 \end{bmatrix} \quad (2.8)$$

and check whether their real part is negative. The characteristic polynomial is

$$P(\lambda) = \frac{\mathcal{V}^* k_2^2 s^* (u^* - 1)^2 u^* \left(\frac{p^*}{K + p^*} - 1 \right) \left(\frac{s^*}{K_2 + s^*} - 1 \right)}{(K + p^*)(K_2 + s^*)^2} \quad (2.9)$$

$$+ \left(-\frac{(p^* + 1)u^* \left(\frac{p^*}{K + p^*} - 1 \right)}{K + p^*} + \frac{k_1(u^* - 1) \left(\frac{p^*}{K_1 + p^*} - 1 \right)}{K_1 + p^*} + \lambda + D \right) \left(\frac{\mathcal{V}^* k_2 (u^* - 1) \left(\frac{s^*}{K_2 + s^*} - 1 \right)}{(K_2 + s^*)} + D + \lambda \right) \lambda. \quad (2.10)$$

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Defining

$$\begin{aligned}\phi_1(\theta) &= \frac{\mathcal{V}^* k_2^2 s^* (u^* - 1)^2 u^* \left(\frac{p^*}{K+p^*} - 1\right) \left(\frac{s^*}{K_2+s^*} - 1\right)}{(K+p^*)(K_2+s^*)^2}, & \phi_2(\theta) &= -\frac{(p^*+1)u^* \left(\frac{p^*}{K+p^*} - 1\right)}{K+p^*}, \\ \phi_3(\theta) &= \frac{k_1(u^* - 1) \left(\frac{p^*}{K_1+p^*} - 1\right)}{K_1+p^*}, & \phi_4(\theta) &= \frac{\mathcal{V}^* k_2(u^* - 1) \left(\frac{s^*}{K_2+s^*} - 1\right)}{(K_2+s^*)},\end{aligned}\tag{2.11}$$

that satisfy $\phi_i(\theta) > 0$ for $i \in \{1, \dots, 4\}$, we see that the characteristic polynomial can be expressed as

$$P(\lambda) = \phi_1 + (\phi_2 + \phi_3 + \lambda + D)(\phi_4 + D + \lambda)\lambda \tag{2.12}$$

$$= \lambda^3 + (2D + \phi_2 + \phi_3 + \phi_4)\lambda^2 \tag{2.13}$$

$$+ (D^2 + D\phi_2 + D\phi_3 + D\phi_4 + \phi_2\phi_4 + \phi_3\phi_4)\lambda + \phi_1. \tag{2.14}$$

The Routh-Hurwitz criteria for degree-three polynomials states that the roots of a degree-three polynomial $\lambda^3 + \alpha_2\lambda^2 + \alpha_1\lambda + \alpha_0$ belong to the open left complex plane if and only if

$$\alpha_2 > 0, \quad \alpha_0 > 0 \quad \text{and} \quad \alpha_1\alpha_2 > \alpha_0.$$

For (2.14), since all ϕ_i 's are positive, the stability criteria reads

$$(2D + \phi_2 + \phi_3 + \phi_4)(D^2 + D\phi_2 + D\phi_3 + D\phi_4 + \phi_2\phi_4 + \phi_3\phi_4) - \phi_1 > 0. \tag{2.15}$$

In order to prove the latter, we can prove that no state-parameter combination satisfies the negation of the condition,

$$(2D + \phi_2 + \phi_3 + \phi_4)(D^2 + D\phi_2 + D\phi_3 + D\phi_4 + \phi_2\phi_4 + \phi_3\phi_4) - \phi_1 \leq 0. \tag{POL}$$

Ultimately, the stability of the steady state of interest can be computed by showing that the set of solutions of this system in terms of $\theta \in \mathbb{R}^7$ is empty. We performed an exhaustive numerical exploration—by fixing the parameters θ to random values satisfying the constraints—that failed to find regions of instability, suggesting that (POL) has no solution, and thus the equilibrium of interest is stable. Routh-Hurwitz criterion reduces the study of the local stability of an equilibrium to an algebraic problem. In some cases, depending on the complexity of the dynamical system (such as its dimension and non-linearity), such a problem may be solved analytically. The difficulty in our case stems from the large number of non-zero coefficients of the right-hand side of (POL) in the standard monomial basis. Using the tailored computer algebra methods described in the next section allows us to obtain the local stability of the family of equilibria of interest:

Theorem 2.3. *On a dense subset of the set of admissible parameters $\theta = (K, k_1, K_1, k_2, K_2, u^*, D)$, the equilibrium $(s^*(\theta), p^*(\theta), \mathcal{V}^*(\theta))$ is locally stable.*

The Maple worksheet used to prove the result is available online ¹ as a companion notebook of the current paper. It makes an intensive use of the RAGLIB package.

3. Computer algebra analysis of stability

Instead of solving the system of inequalities *w.r.t.* $(s^*, p^*, \mathcal{V}^*)$, we parametrize both the constraints and the equation (POL) in terms of (K, k_1, \mathcal{V}^*) , where K , k_1 and \mathcal{V}^* can be obtained

¹See ct.gitlabpages.inria.fr/gallery/stability/stability.html

by solving $\dot{s} = \dot{p} = \dot{V} = 0$, as done in (2.6). Additionally, we define

$$K'_1 = K_1 + p^*, \quad K'_2 = K_2 + s^* \quad (3.1)$$

and thus, the new set of variables becomes $\theta' = (s^*, p^*, K'_1 - p^*, k_2, K'_2 - s^*, u^*, D) \in \mathbb{R}^7$, and the resulting system of inequalities become

$$\begin{aligned} K > 0, \quad k_1 > 0, \quad K'_1 - p^* > 0, \quad k_2 > 0, \quad K'_2 - s^* > 0, \\ 1 > u^* > D > 0, \quad 1 > s^* > 0, \quad \text{and } \mathcal{C} < 0. \end{aligned} \quad (3.2)$$

where \mathcal{C} is a polynomial of total degree 13 involving the above 7 variables, whose number of non-zero coefficients in the standard monomial basis is 164. To determine the stability of the system, one needs to decide whether this system of polynomial inequalities is inconsistent, *i.e.* whether the set of solutions of this system in \mathbb{R}^7 is empty or not. The rest of the section is devoted to proving the following result, from which Theorem 2.3 proceeds.

Proposition 3.1. *The semi-algebraic set defined by (3.2) is empty.*

As a consequence, for any admissible values of the parameters in the dense subset defined by $\mathcal{C} < 0$, all equilibria of the dynamical system are locally stable, which is Theorem 2.3. Feeding `HasRealSolutions` with the above system (3.2) without further simplification does not allow to obtain a solution in *reasonable time*.² The crucial observation to obtain a computationally tractable proof of Proposition 3.1 is related to the degree pattern of the input system. Indeed, observe that the system (3.2) involves 12 polynomial inequalities in the polynomial ring $\mathbb{Q}[s^*, p^*, K'_1, k_2, K'_2, u^*, D]$ but only two of them have positive degree in K'_1 . In other words, amongst the 13 inequalities, 10 lie actually in $\mathbb{Q}[s^*, p^*, k_2, K'_2, u^*, D]$. This gives rise to the following idea: one may reduce our initial problem (deciding the consistency of the system (3.2)) to the study of some semi-algebraic set defined by polynomial inequalities in $\mathbb{Q}[s^*, p^*, k_2, K'_2, u^*, D]$. Hence, we are in the process of *eliminating* the variable K'_1 from (3.2), that is computing polynomial inequalities that would define the *projection* of the solution set to (3.2) on the $(s^*, p^*, k_2, K'_2, u^*, D)$ coordinate space. A key tool for algebraic elimination is the resultant of two univariate polynomials, which we now recall.

Let f and g be two polynomials in $R[x]$ where R is a ring of respective degree p and q . The resultant associated to (f, g) is the determinant of the Sylvester matrix which is the one obtained by stacking on each row the coefficients of the polynomials $x^i f$ and $x^j g$ for $0 \leq i \leq q - 1$ and $0 \leq j \leq p - 1$ (see e.g. [3, Chapter 4]). This resultant is 0 if and only if f and g have a gcd of positive degree. The discriminant of a polynomial f is the resultant of f and its derivative $\frac{\partial f}{\partial x}$ divided by an appropriate power of the leading coefficient of f (see e.g. [3, Chapter 4]). When dealing with polynomials f and g in $\mathbb{Q}[x_1, \dots, x_n]$, one can see them as polynomials in $\mathbb{Q}[x_1, \dots, x_{n-1}][x_n]$. The resultant (resp. discriminant) associated to (f, g) (resp. f) is then denoted by $\text{resultant}(f, g, x_n)$ (resp. $\text{discriminant}(f, x_n)$). Note that they lie in $\mathbb{Q}[x_1, \dots, x_{n-1}]$ (as does the leading coefficient of f *w.r.t.* x_n which we denote by $\text{lc}(f, x_n)$). These are the tools we use to describe the projection on a subspace of coordinates of a semi-algebraic set. This process is the one which is used by the Cylindrical Algebraic Decomposition algorithm and its so-called “open” Cylindrical Algebraic Decomposition which applies to systems of strict inequalities [23]. Let now f_1, \dots, f_s be polynomials in $\mathbb{Q}[x_1, \dots, x_n]$ and let $S \subset \mathbb{R}^n$ be the semi-algebraic set defined by

$$f_1 > 0, \dots, f_s > 0 \quad (3.3)$$

with $f_i \in \mathbb{Q}[x_1, \dots, x_{n-1}]$ for $1 \leq i \leq t$ and $\deg(f_j, x_n) > 0$ for all $t+1 \leq j \leq s$. Note that since S is open for the Euclidean topology, whenever it is not empty, its projection on the (x_1, \dots, x_{n-1})

²Computation not terminated after one month on an Intel(R) Xeon(R) Gold 6244 CPU @ 3.60GHz with 1.5 To of RAM.

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coordinate space is open too. Let S' be the semi-algebraic set defined by

$$\begin{aligned} f_i &> 0 && \text{for } 1 \leq i \leq t, \text{ and} \\ \text{resultant}(f_i, f_j, x_n) &\neq 0, \text{discrim}(f_i, x_n) \neq 0, \\ \text{lc}(f_i, x_n) &\neq 0 && \text{for } t+1 \leq i \leq j \leq s. \end{aligned} \tag{3.4}$$

By [23], there exist connected components C_1, \dots, C_ℓ of S' such that $C_1 \cup \dots \cup C_\ell$ is semi-algebraic and dense in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space. We call **OpenCAD**, the operator which, given the polynomial system $f_1 > 0, \dots, f_s > 0$ and the variable x_n as inputs, computes the polynomial system (3.4). Hence, in order to decide the consistency over the reals of the system of inequalities (3.3), it suffices to

- (a) compute from it the system of polynomial inequations and inequalities (3.4) using **OpenCAD**;
- (b) compute at least one sample point per connected component in the semi-algebraic set S' defined by (3.4) – this is what the command **PointsPerComponents** from the **RAGLIB** package is designed for;
- (c) letting $\alpha_1, \dots, \alpha_r$ be those sample points, solve the *univariate* system of polynomial inequalities

$$f_1(\alpha_i, x_n) > 0, \dots, f_t(\alpha_i, x_n) > 0.$$

If the system is not consistent over the reals then one can conclude that S is empty (in other words, the system (3.3) is not consistent over the reals).

Launching this computation on system (3.2) is still not computationally tractable. To further reduce computations, we rely on the following property of the system, which can easily be checked on the *Maple* worksheet attached with the paper.

Lemma 3.2. *In system (3.2), only two polynomials have positive degree in K'_1 : one has degree 2 in K'_1 , and the other one has degree 1 in K'_1 .*

We assume from now on that $\deg(f_s, x_n) = 2$ (so f_s has real roots if and only if its discriminant is non-negative) and $\deg(f_i, x_n) = 1$ for $t+1 \leq i \leq s-1$. We let C be a connected component of S' that is contained in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space. In other words, for any $\alpha \in C \subset \mathbb{R}^{n-1}$, there exists $\vartheta \in \mathbb{R}$ such that $f_i(\alpha, \vartheta) > 0$ for $t+1 \leq i \leq s$. By definition of S' , the discriminant of f_s does not vanish over C . We then consider the two possible cases:

- when $\text{discrim}(f_s, x_n)$ is negative over C , for any $\alpha \in C$, $f_s(\alpha, x_n)$ has no real root and is then positive;
- when $\text{discrim}(f_s, x_n)$ is positive over C , for any $\alpha \in C$, $f_s(\alpha, x_n)$ has exactly two real roots with multiplicity one and there exists ϑ such that $f_s(\alpha, \vartheta)$ is positive.

Note that the leading coefficient of f_s did not play any role in the above observations. This leads us to consider the semi-algebraic set S'' which is defined by

$$\begin{aligned} f_i &> 0 && \text{for } 1 \leq i \leq t, \text{ and} \\ \text{resultant}(f_i, f_j, x_n) &\neq 0, \text{discrim}(f_i, x_n) \neq 0, \\ \text{lc}(f_i, x_n) &\neq 0 && \text{for } t+1 \leq i \leq j \leq s-1. \end{aligned} \tag{3.5}$$

Note also that the only difference is that we do not consider the leading coefficient of f_s anymore. The connected components of S'' are unions of some connected components of S' and some connected components of the intersection of S' with the vanishing set of $\text{lc}(f_s)$. Moreover, by definition of S'' , over any connected component C of S'' , the discriminant polynomial $\text{discrim}(f_s, x_n)$ is sign invariant.

Proposition 3.3. *Assume that the semi-algebraic set S is non-empty. Then, there exists a connected component C of S'' such that any $\alpha \in C$ which does not cancel $\text{lc}(f_s, x_n)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space.*

Proof. Consider the semi-algebraic set defined by $f_1 > 0, \dots, f_{s-1} > 0$. Running the algorithm `OpenCAD`($[f_1, \dots, f_{s-1}], x_n$) builds a polynomial system which is the same as system (3.4) without the constraints $\text{discrim}(f_s, x_n) \neq 0$ and $\text{resultant}(f_i, f_s, x_n) \neq 0$ for $1 \leq i \leq s-1$. Let C be a connected component of S'' . By [23], there exist finitely many continuous semi-algebraic maps (i.e. maps whose graphs are semi-algebraic sets) ξ_1, \dots, ξ_k from C to \mathbb{R} such that the cylinder $C \times \mathbb{R}$ is the disjoint union of cells defined as

- either the graph of one of the map ξ_i for $1 \leq i \leq k$,
- or a band of the cylinder

$$B_i = \{(\alpha, \vartheta) \mid \alpha \in C \text{ and } \xi_i(\alpha) < \vartheta < \xi_{i+1}(\alpha)\}$$

for $0 \leq i \leq k$ with $\xi_0 = -\infty$ and $\xi_{k+1} = +\infty$ by convention,

over which the polynomials f_1, \dots, f_{s-1} are sign invariant (because the system output by `OpenCAD`($[f_1, \dots, f_{s-1}], x_n$) is contained in (3.4), and then defines a dense open semi-algebraic of S''). Note that, geometrically (see [23]), for $\alpha \in C$, $\xi_1(\alpha), \dots, \xi_k(\alpha)$ is the ordered sequence of roots of the univariate polynomials $f_{t+1}(\alpha, x_n), \dots, f_{s-1}(\alpha, x_n)$. Assume now that C has a non-empty intersection with the projection of S on the (x_1, \dots, x_{n-1}) subspace of coordinates (note that if S is non-empty, there exists such a connected component C of S'' since S and S'' are both open for the Euclidean topology). Let α be in this intersection such that $\text{lc}(f_s)$ does not vanish at α (such a point α exists because C is open for the Euclidean topology as well as the projection of S and the solution set to $\text{lc}(f_s, x_n) \neq 0$). In other words, there exists ϑ such that

$$f_1(\alpha, \vartheta) > 0, \dots, f_s(\alpha, \vartheta) > 0.$$

Let B_i be the band which contains (α, ϑ) . Consider now $\alpha' \in C$ and assume that $\text{lc}(f_s, x_n)(\alpha') \neq 0$. We need to prove that there exists $\vartheta' \in \mathbb{R}$ such that $(\alpha', \vartheta') \in S$. Note that, by the sign invariance property over the band B_i of f_1, \dots, f_{s-1} , we already know that there exists ϑ' such that $f_j(\alpha', \vartheta') > 0$ for $1 \leq j \leq s-1$. Hence, what is missing is a control on the sign of f_s .

Lemma 3.4. *Assume that there exists a continuous semi-algebraic path $\gamma : [0, 1] \rightarrow C$ such that $\gamma(0) = \alpha$ and $\gamma(1) = \alpha'$ such that for any $v \in [0, 1]$, $\text{lc}(f_s, x_n)$ does not vanish at $\gamma(v)$, with α in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space. Then, for any $v \in [0, 1]$, $\gamma(v)$ lies in the projection of S on the (x_1, \dots, x_n) -space.*

Proof. Note that for any $v \in [0, 1]$, and any $\xi_i(\gamma(v)) < \vartheta_v < \xi_{i+1}(\gamma(v))$, the following holds:

$$f_1(\gamma(v), \vartheta_v) > 0, \dots, f_{s-1}(\gamma(v), \vartheta_v) > 0.$$

Recall also that, by definition of S'' , the discriminant $\text{discrim}(f_s, x_n)$ is sign invariant over C . If it is negative, then for any $v \in [0, 1]$, $f_s(\gamma(v), x_n)$ has no root in \mathbb{R} (because we have assumed that $\text{lc}(f_s, x_n)$ does not vanish at $\gamma(v)$). Since, by construction, $f_s(\gamma(0), x_n)$ is positive over \mathbb{R} , we deduce that for any $v \in [0, 1]$, $f_s(\gamma(0), x_n)$ is positive over \mathbb{R} (else, by continuity of γ , there would exist some v' such that $f_s(\gamma(v'), x_n)$ has some real root while $\text{lc}(f_s, x_n)$ does not vanish at $\gamma(v')$, which would contradict our assumption of the negativity of $\text{discrim}(f_s, x_n)$ over C). Assume now that $\text{discrim}(f_s, x_n)$ is positive over C . As above, we need to prove that for any $v \in [0, 1]$, there exists $\vartheta_v \in B_i$ such that $f_s(\gamma(v), \vartheta_v) > 0$. We start with $v = 0$. We already know by construction that there exists $\xi_i(\gamma(0)) < \vartheta < \xi_{i+1}(\gamma(0))$ such that $f_s(\gamma(0), \vartheta) > 0$. Assume by contradiction that there exists $v' \in [0, 1]$ such that for any $\xi_i(\gamma(v')) < \vartheta' < \xi_{i+1}(\gamma(v'))$, it holds that $f_s(\gamma(v'), \vartheta') \leq 0$. By continuity of γ , the set of such reals v' is closed in $[0, 1]$. We let v'_{\min} be the smallest element of this set. By continuity of the ξ_i 's we deduce that either

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$f_s(\gamma(v'_{\min}), \xi_i(\gamma(v'_{\min}))) = 0$ or $f_s(\gamma(v'_{\min}), \xi_{i+1}(\gamma(v'_{\min}))) = 0$. Recall that there exists some $t + 1 \leq j \leq s - 1$ such that ξ_i maps $\alpha \in C$ to the r -th root of f_j . In other words, the gcd of $f_s(\gamma(v'_{\min}), x_n)$ and $f_j(\gamma(v'_{\min}), x_n)$ has degree ≥ 1 . This implies that for some j , the resultant polynomial $\text{resultant}(f_j, f_s, x_n)$ vanishes at $\gamma(v'_{\min})$. This is a contradiction since C is a connected component of S'' , defined by (3.4) which contains the constraint $\text{resultant}(f_j, f_s, x_n) \neq 0$. This ends the proof of the above lemma. \square

Assume now that any continuous semi-algebraic path in C linking α to α' meets the vanishing set of $\text{lc}(f_s, x_n)$. Note that since the vanishing set of $\text{lc}(f_s, x_n)$ has dimension at most $n - 1$, one takes a continuous semi-algebraic path linking α to α' whose intersection with the vanishing set of $\text{lc}(f_s, x_n)$ is finite.

$$\gamma(0) = \alpha, \gamma(1) = \alpha' \text{ and } \#\{v \in [0, 1] \mid \text{lc}(f_s, x_n)(\gamma(t)) = 0\} < \infty \quad (3.6)$$

Hence, there exist $\{v_1, \dots, v_N\} \subset [0, 1]$ such that

$$\{v_1, \dots, v_N\} = \{v \in [0, 1] \mid \text{lc}(f_s, x_n)(\gamma(t)) = 0\}$$

and we define $v_0 = 0$ and $v_{N+1} = 1$. We let γ_j be the semi-algebraic continuous path $v \in]v_j, v_{j+1}[\rightarrow \gamma(v)$ for $0 \leq j \leq N$. We are going to apply the next lemma to each path γ_j .

Lemma 3.5. *Let $\gamma : [0, 1] \rightarrow C$ be a semi-algebraic continuous map such that*

- *for all $v \in [0, 1[, \text{lc}(f_s, x_n)$ does not vanish at $\gamma(v)$ but does at $\gamma(1)$;*
- *$\gamma(0)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space.*

Then, for all $v \in [0, 1]$, $\gamma(v)$ also lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space.

Proof. Applying Lemma 3.4, we deduce that for any $w \in]0, 1[, \gamma(w)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate subspace. Recall that, by construction, for any $w \in]0, 1[,$ there exists ϑ_w in the band B_i (i.e. $\xi_i(\gamma(w)) < \vartheta_w < \xi_{i+1}(\gamma(w))$) such that

$$f_{t+1}(\gamma(w), \vartheta_w) > 0, \dots, f_{s-1}(\gamma(w), \vartheta_w) > 0, f_s(\gamma(w), \vartheta_w) > 0$$

and that for $\xi_i(\gamma(w)) < \vartheta < \xi_{i+1}(\gamma(w))$, the following holds

$$f_{t+1}(\gamma(w), \vartheta) > 0, \dots, f_{s-1}(\gamma(w), \vartheta) > 0, f_s(\gamma(w), \vartheta) > 0.$$

By continuity of γ , the equality $\gamma(1) = \lim_{w \rightarrow 1}(\gamma(w))$ holds. We are going to prove that $\gamma(1)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate subspace. By assumption, $\text{lc}(f_s, x_n)$ vanishes at $\gamma(1)$. Note that, by definition of the discriminant of a quadratic polynomial, this implies that $\text{discrim}(f_s, x_n)$ is positive at $\gamma(1)$. Also, $\text{discrim}(f_s, x_n)$ is sign invariant over $\gamma([0, 1])$ (since the inequation constraint $\text{discrim}(f_s, x_n) \neq 0$ is part of the polynomial system (3.4)). Hence, we can deduce that $\text{discrim}(f_s, x_n)$ is positive $\gamma([0, 1])$. Recall that we established that, for all $w \in]0, 1[, \gamma(w)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space. Hence, for $w \in]0, 1[,$ the univariate polynomial $f_s(\gamma(w), x_n)$ has two real roots – let us denote them by $\rho_1(\gamma(w))$ and $\rho_2(\gamma(w))$ – and the locus where it is positive meets the interval $]\xi_i(\gamma(w)), \xi_{i+1}(\gamma(w))]$. Assume by contradiction that $\gamma(1)$ does not lie in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space. Then, by continuity of γ, ξ_i, ξ_{i+1} and the two roots ρ_1 and ρ_2 of $f_s(\gamma(\cdot), x_n)$ we deduce that one of the two roots $\rho_1(\gamma(1))$, or $\rho_2(\gamma(1))$ coincides with either $\xi_i(\gamma(1))$ or $\xi_{i+1}(\gamma(1))$. By definition of the ξ_i 's, this implies that the resultant polynomial $\text{resultant}(f_r, f_s, x_n)$ (for $t + 1 \leq r \leq s - 1$) vanishes at $\gamma(1)$. This is a contradiction since this resultant polynomial cannot vanish over $\gamma([0, 1])$ (by definition of S''). Hence we deduce that $\gamma(1)$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space as requested. \square

We eventually apply inductively Lemmas 3.4 and 3.5 to the semi-algebraic continuous paths γ_j (up to translating and scaling $[v_j, v_{j+1}]$ to $[0, 1]$). We deduce that $\gamma_j([v_j, v_{j+1}])$ lies in the projection of S on the (x_1, \dots, x_{n-1}) coordinate space for $0 \leq j \leq N$. We then deduce that $\gamma(1) = \alpha'$ lies in this projection, which ends the proof of Proposition 3.3. \square

Denoting `ModifiedOpenCAD` a procedure which takes as input f_1, \dots, f_s as above and returns the system of polynomial constraints as in (3.4). By Proposition 3.3, it suffices to compute sample points $\alpha_1, \dots, \alpha_\ell$ per connected components of the semi-algebraic set defined by (3.4) at which $\text{lc}(f_s, x_n)$ do not vanish – recall that doing so is the purpose of the `PointsPerComponents` command of RAGLIB – and decide the univariate system of polynomial inequalities

$$f_{t+1}(\alpha_i, x_n) > 0, \dots, f_s(\alpha_i, x_n) > 0$$

has real solutions (which is easily done with real root isolation algorithms). Running this computation does not provide any result in a reasonable time, even when one takes advantage of special simplifications which we make explicit in the next section. However, note that one can apply `OpenCAD` to (3.4) which provides a new system of polynomial inequalities/inequations. Computing sample points per connected components for the semi-algebraic set defined by this new system is done within a minute on a standard laptop with `PointsPerComponents` (when exploiting some simplifications which we make explicit in the next section). Next, one can “lift” those points by instantiating x_1, \dots, x_{n-2} in (3.4) and solve the obtained univariate polynomial systems of constraints. This will provide sample points per connected components of the semi-algebraic set defined by (3.4), which can be lifted as sketched above and finally solve our decision problem. These latter steps take a few second. All in all, these computations prove that the semi-algebraic set defined by (3.2) is empty, which is Proposition 3.1.

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