Towards an automated reduction method for polynomial ODE models in cellular biology

François Boulier, François Lemaire, Alexandre Sedoglavic, Aslı Grimaud

Towards an automated reduction method for polynomial ODE models in cellular biology

François Boulier, François Lemaire, Alexandre Sedoglavic and Aslı Ürgüplü

Abstract. This paper presents the first version of an algorithmic scheme dedicated to the model reduction problem, in the context of polynomial ODE models derived from generalized chemical reaction systems. This scheme, which relies on computer algebra, is implemented within a new MAPLE package. It is applied over an example. The qualitative analysis of the reduced model is afterwards completely carried out, proving the practical relevance of our methods.

Mathematics Subject Classification (2000). 12H05, 37N25, 62P10.

Keywords. computer algebra, differential algebra, cellular biology, system modeling.

1. Introduction

This paper is concerned by the model reduction problem in cellular biology. The concerned modeling approach is the well-established one, based on nonlinear differential equations [34, 10]. However, this paper only considers parametric polynomial ordinary differential equation (ODE) systems, derived from generalized chemical reaction systems by means of the mass-action law [30].

When modeling cellular processes by this approach, one rapidly gets very complicated overparameterized systems. Fitting methods to determine parameter values become difficult to carry out and unreliable. The parameters which reproduce some behaviour of interest are usually far from unique [46, 45]. Because of these reasons, the ODE systems need to be reduced for further analysis.

The model reduction problem is common in biological modeling. Though not formulated in these terms, most of the approaches listed in [13] address this

issue, in particular the one that considers the qualitative simulations of genetic networks [12]. Even in our particular setting, many methods exist for the model reduction, including lumping, sensitivity analysis and multiple time-scale analysis [37]. Among all these methods, this paper is concerned by the quasi-steady state approximation (QSSA) [31], combined with reparameterization techniques. In our setting, the QSSA relies on the assumption that some of the chemical reactions are much faster than the other ones. Its principle is simple: focusing on the dynamics of the slow reactions, assuming that the fast ones are at quasi-equilibrium. The QSSA has two advantages: it reduces the number of ODE occuring in the system under study and it transforms stiff ODE systems into non stiff ones. Even in the setting of chemical reaction systems, the QSSA has been extensively studied [44, 47, 3].

The authors are developing software which aim is to make the model reduction process as automatic as possible. This paper presents a first version, still incomplete, of such a software. It carries out the following steps:

1. definition of the chemical reaction system to be studied ;
2. approximation by QSSA of the ODE system derived from the input system, leading to a raw reduced model ;
3. reduction of the parameter set of the raw reduced model, leading to a reduced model.

This software is implemented in the new MABSys package of the MAPLE computer algebra system. The QSSA step applies the method presented in [6], which makes algorithmic the equivalent methods of [44, 47, 3]. The reduction of the parameter set is an exact reduction step, relying on the computation of the system Lie symmetries. It relies on the ExpandedLiePointSymmetry MAPLE package [41, 42]. All these methods are presented in section 2.

In order to prove the relevance of our methods, an example, borrowed from [8, 7], is completely carried out in section 3. This example features a single gene regulated by an order n polymer of its own protein (the integer number n is a parameter of this model). The non reduced model involves $n + 3$ ODE depending on $2\,n + 5$ parameters. An interesting value is $n = 8$, which leads to a medium size system. The reduced model involves 3 ODE and $n + 6$ parameters only. Its qualitative analysis is carried out and one proves that the model exhibits Poincaré-Andronov-Hopf bifurcations if and only if $n \geq 9$. Observe that this problem is already solved in [8, 7] but with only a sketched proof in the case $n \geq 9$, a different reduction in the case $n \leq 8$, and much less automatic computations.

2. The methods

2.1. Performing QSSA by means of differential elimination

For differential systems arising from generalized chemical reactions systems, there exists a standard way to perform the QSSA, provided that the set of chemical reactions is divided in two parts: the fast ones and the slow ones.

As far as we know, the first clear relationship between this method and the Tikhonov theorem [31, Theorem 3.1] was established in [44]. Afterwards, close variants of the same method were rediscovered more or less independently [47, 3]. Though all these papers present methods, none of them is fully presented in an algorithmic manner. This may at least partly be due to the fact that some steps of the methods require the inversion of a matrix over a residue class ring, a non obvious task which may imply splitting cases. Indeed, it turns out that the whole method is equivalent to a differential elimination process, as shown for the first time in [6]. See section 4 for an introduction to differential elimination.

Algorithm 1 DifferentialModelReduction($\dot{X} = N\,V$)

Input: The initial parametric ODE system $\dot{X} = N\,V$ derived from a generalized chemical reaction system involving n chemical species and p reactions. The stoichiometry matrix N has dimension $n \times p$ and integer entries. The vector X of dependent variables has dimension n. The vector of reaction rates V has dimension n. Its entries are power products of system parameters and dependent variables. Each reaction rate of V (hence each column of N) is assumed to be tagged "fast" or "slow".

Output: a list of dynamical systems in the dependent variables X obtained by quasi-steady state approximation from the initial system or **Fail**.

1: Split N into two matrices N_f (columns of the fast reactions) and N_s (columns of the slow reactions). Split V into V_f and V_s so that the initial ODE model writes

$$\dot{X} = N_\mathrm{s}\,V_\mathrm{s} + N_\mathrm{f}\,V_\mathrm{f}\,.$$

2: By (say) Gaussian elimination, determine a maximal linearly independent set of columns of N_f and remove the other ones, giving $\overline{N}_\mathrm{f}$. Update the vector of reaction rates V_f, giving a new vector $\overline{V}_\mathrm{f}$, such that the initial ODE model writes as follows. The entries of $\overline{V}_\mathrm{f}$ are linear combinations of elements of V_f with rational number coefficients.

$$\dot{X} = N_\mathrm{s}\,V_\mathrm{s} + \overline{N}_\mathrm{f}\,\overline{V}_\mathrm{f}\,.$$

3: Build a vector F of new dependent variables, having the same dimension as $\overline{V}_\mathrm{f}$.

4: Build the following DAE of the differential polynomial ring $K\{X \cup F\}$ where K is the field of the rational fractions in the system parameters:

$$\dot{X} = N_\mathrm{s}\,V_\mathrm{s} + \overline{N}_\mathrm{f}\,F\,, \quad \overline{V}_\mathrm{f} = 0\,. \tag{2.1}$$

5: $\mathscr{R}$:= a ranking $F \gg X$ eliminating F w.r.t. X.

6: $[C_1, \ldots, C_t]$:= Rosenfeld-Gröbner$((2.1), \mathscr{R})$

7: If there exists some dependent variable X_i and some regular differential chain C_k such that $\mathsf{NF}(X_i, C_k)$ is not a rational fraction in the variables X then **Fail**.

8: **Return** the list $\dot{X} = \mathsf{NF}(\dot{X}, C_k)$ for $1 \le k \le t$.

The DifferentialModelReduction algorithm is summarized in Algorithm 1. One illustrates it over a famous example: the beginning of the Henri-Michaelis-Menten reduction of the basic enzymatic reaction system:

$$E + S \xrightarrow[k_2]{k_1} C \xrightarrow{k_3} E + P \, . \tag{2.2}$$
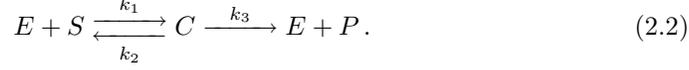
The initial system of ODE writes: $\dot{X} = N V$ i.e.

$$\begin{pmatrix} \dot{E} \\ \dot{C} \\ \dot{S} \\ \dot{P} \end{pmatrix} = \begin{pmatrix} -1 & 1 & 1 \\ 1 & -1 & -1 \\ -1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \cdot \begin{pmatrix} k_1 \, E \, S \\ k_2 \, C \\ k_3 \, C \end{pmatrix} \tag{2.3}$$

where X is the vector of the chemical species, N is the system stoichiometry matrix and V is the vector of the reaction rates. The stoichiometry matrix is built as follows: it involves one row per species and one column per reaction. The entry at row r, column c is the number of molecules of species r produced by the reaction c (i.e. the number of times species r occurs on the reaction right-hand side minus the number of times it occurs on the reaction left-hand side). The rate of a reaction is the product of the left-hand side species (with multiplicities) times the reaction rate constant (the parameter over the arrow).

Split the stoichiometry matrix N into two matrices N_f and N_s putting the columns which correspond to fast reactions in N_f and the ones which correspond to slow reactions in N_s. Split accordingly the rows of the vector V into two vectors V_f and V_s. One gets a formula $\dot{X} = N_s \, V_s + N_f \, V_f$. Over system (2.3), one gets:

$$\begin{pmatrix} \dot{E} \\ \dot{C} \\ \dot{S} \\ \dot{P} \end{pmatrix} = \begin{pmatrix} 1 \\ -1 \\ 0 \\ 1 \end{pmatrix} \cdot \begin{pmatrix} k_3 \, C \end{pmatrix} + \begin{pmatrix} -1 & 1 \\ 1 & -1 \\ -1 & 1 \\ 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} k_1 \, E \, S \\ k_2 \, C \end{pmatrix} \, . \tag{2.4}$$

Determine a maximal linearly independent set of columns of N_f (i.e. a basis of that matrix) and remove the other ones, giving a new matrix $\overline{N}_f$. Update the vector of reaction rates V_f, giving a new vector $\overline{V}_f$ such that $N_f \, V_f = \overline{N}_f \, \overline{V}_f$. Over the example, removing the second column, one gets a new formula $\dot{X} = N_s \, V_s + \overline{N}_f \, \overline{V}_f$ which is equivalent to formula (2.3):

$$\begin{pmatrix} \dot{E} \\ \dot{C} \\ \dot{S} \\ \dot{P} \end{pmatrix} = \begin{pmatrix} 1 \\ -1 \\ 0 \\ 1 \end{pmatrix} \cdot \begin{pmatrix} k_3 \, C \end{pmatrix} + \begin{pmatrix} -1 \\ 1 \\ -1 \\ 0 \end{pmatrix} \cdot \begin{pmatrix} k_1 \, E \, S - k_2 \, C \end{pmatrix} \, . \tag{2.5}$$

Replace the vector $\overline{V}_f$ by a vector F of new dependent variables F_i. The slow variety[1] is defined by letting the entries of $\overline{V}_f$ all equal to zero. The DAE to be

---

[1] More precisely, its approximation M_0, following the notations of [31, Sect. 1.4].

considered for quasi-steady state approximation is

$$\dot{X} = N_{\mathrm{s}} V_{\mathrm{s}} + \overline{N}_{\mathrm{f}} F, \qquad \overline{V}_{\mathrm{f}} = 0. \tag{2.6}$$

Over the example, one gets:

$$\begin{pmatrix} \dot{E} \\ \dot{C} \\ \dot{S} \\ \dot{P} \end{pmatrix} = \begin{pmatrix} 1 \\ -1 \\ 0 \\ 1 \end{pmatrix} \cdot \begin{pmatrix} k_3\, C \end{pmatrix} + \begin{pmatrix} -1 \\ 1 \\ -1 \\ 0 \end{pmatrix} \cdot \begin{pmatrix} F_1 \end{pmatrix}, \qquad \begin{pmatrix} k_1\, E\, S - k_2\, C \end{pmatrix} = 0. \tag{2.7}$$

Expand this system in order to get a set of differential polynomials in the differential polynomial ring $K\{X \cup F\}$ where $K = \mathbb{Q}(k_1, k_2, k_3)$ and, using a ranking $F \gg X$ eliminating the new unknowns F, simplify it by means of a differential elimination process. One gets the following system:

$$\left[F_1 = \frac{k_3\, k_1\, E\, S\, (k_1\, S + k_2)}{k_2\, (k_1\, S + k_1\, E + k_2)}, \quad \dot{E} = \frac{k_1^2\, E^2\, k_3\, S}{k_2\, (k_1\, S + k_1\, E + k_2)}, \quad \dot{P} = \frac{k_3\, k_1\, E\, S}{k_2}, \right.$$

$$\left. \dot{S} = -\frac{k_3\, k_1\, E\, S\, (k_1\, S + k_2)}{k_2\, (k_1\, S + k_1\, E + k_2)}, \quad C = \frac{k_1\, E\, S}{k_2} \right]$$

Readers used to the Michaelis-Menten formula do probably not recognize it in the above result. Indeed, some further simplifications need to be done but these simplifications are actually not related to the QSSA. They involve considerations on initial conditions and parameter renaming. See [6] for a complete study.

2.2. Reduction of the parameter set and reparameterization

Two packages are available for reducing the parameter set and reparameterizing differential systems. The first one is the ExpandedLiePointSymmetry package which is not specifically designed for the manipulation of biochemical systems. The second one is the MABSys package which is mostly oriented for the manipulation of models coming from biochemical reactions. They perform automatically two kinds of changes of coordinates:

1. changes of coordinates which reduce the number of parameters (by computing Lie symmetries of the differential system) ;
2. changes of coordinates which make some parameters appear as factors in the right-hand sides of differential equations (by computing Lie symmetries of the nondifferential system which defines the system steady points).

To illustrate these features, consider the following ODE, which is borrowed from system (3.4) and slightly simplified:

$$\dot{G} = \theta\, (1 - G) - \alpha\, G.$$

Greek letters denote parameters. The solutions of the steady point equation $0 = \theta\, (1 - G) - \alpha\, G$ are not changed when α and θ are both multiplied by any nonzero

constant λ. This suggests to replace α by $\alpha\,\theta$, which leads to the new ODE:

$$\dot{G} = \theta\,(1 - G - \alpha\,G).$$

The parameter θ appears as a factor of the right-hand side of the ODE. The steady point does not depend on θ anymore. Now, the ODE is left unchanged when the time t is multiplied by λ and θ is divided by λ. This suggests to replace t by t/θ. This leads to the new ODE:

$$\dot{G} = 1 - G - \alpha\,G.$$

An important feature of the MABSys package is that it restricts itself to symmetries of type scaling because they preserve the positivity of the system variables and parameters: a crucial property for studying the system qualitative behaviour.

An important issue is not yet satisfactorily solved: the parameters that can be removed or rewritten by means of symmetries is not uniquely defined. Designing a package interface which precisely defines the package output is thus far from easy. Different choices may lead to different systems which lead to qualitative analyses of various difficulties.

3. The example

One considers the genetic circuit depicted in Figure 1. The single gene is regulated by an order n polymer of its own protein. The integer number n is a parameter of the system. This study was motivated by the activity of a working group aiming at modeling the circadian clock of the green alga *ostreococcus tauri*. See [35] for a survey on circadian rhythms and [19, Chapter 9] or [24, 21] for more general texts about oscillations in biology.

The addressed question is: does there exist biologically meaningful (i.e. positive) parameter values which make this circuit oscillate ? A related but easier problem consists of searching for the existence of parameter and variable positive values which give rise to Poincaré-Andronov-Hopf bifurcations. See [29, Chapter 11], or [28, Section I.16]. In the neighborhood of a Poincaré-Andronov-Hopf bifurcation indeed, a stable steady point of the model under study gives birth to a small stable limit cycle under some general hypotheses. Note that searching for Poincaré-Andronov-Hopf bifurcations is not as general as searching for limit cycles: first, some Poincaré-Andronov-Hopf bifurcations (the subcritical ones) do not imply the existence of stable limit cycles; second, there may exist limit cycles not related to Poincaré-Andronov-Hopf bifurcations.

Our approach is decomposed in three parts. First one reduces the initial model to a three-variable model by means of quasi-steady state approximation. Second, one reduces the parameter set of the three-variable model. Third one proves by computer algebra methods that Poincaré-Andronov-Hopf bifurcation occur for positive values of the parameters if and only if $n \geq 9$. As pointed out
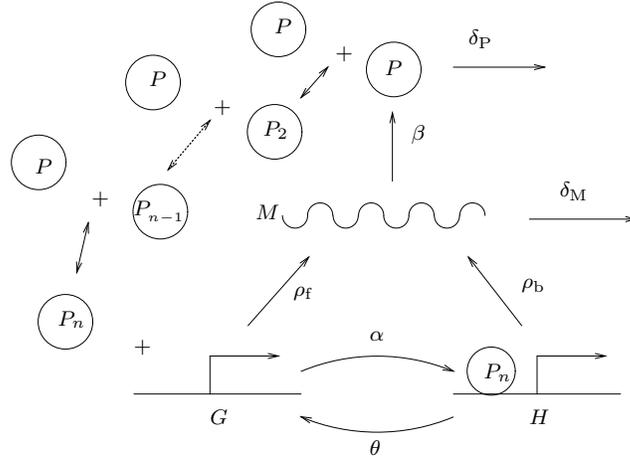
FIGURE 1. A single gene regulated by a polymer of its own protein.

previously, this is not sufficient to prove the presence of limit cycles in the case $n \geq 9$. However, this result is confirmed by extensive numerical simulations.

Other approaches could have been applied. There exist software packages such as AUTO or XPPAUT [14, 18] which locate Poincaré-Andronov-Hopf bifurcations by means of numerical calculations. They allow one to evidence the existence of Poincaré-Andronov-Hopf bifurcations but not to prove their absence, and thus cannot be used to discard a model. Moreover, they can only tackle particular values of n. Theoretically, the existence or the absence of Poincaré-Andronov-Hopf bifurcations can be decided algebraically [17, 49, 23, 22, 36]. In particular, it can be decided by means of computer algebra methods which rely on Sturm sequences computations and algebraic elimination. Practitioners usually seem to avoid these methods because of their huge complexity in the worst case. See however [1, 50] for applications in biology. In particular, the QEPCAD [9] package, which is based on quantifier elimination methods, could not solve the problem addressed in this section. The REDLOG package [15] and the software described in [17] rely on QEPCAD for the quantifier elimination process. An attempt to solve the addressed problem using the RAGLib library [16] did not succeed. According to specialists, these methods are optimized to tackle the worst case while our problems exhibit more generic features.

The abstract model depicted in Figure 1 is closely related to models studied by Goodwin and Griffith in the 60's [25, 26, 27]. It features a negative feedback loop, one of the core ingredients for generating oscillations [19]. Griffith considered a model of a gene regulated by a polymer formed of n copies of its own protein. The same problem is studied here, but in a slightly more general case, where gene activation is not assumed to be fast. Although we do focus here on biology, it should

be stressed that a cooperativity of order 9 is not as unrealistic as it may seem. In particular, gene regulation by an octamer has been reported [43]. Moreover, an effective cooperativity of order 9 may also be obtained as a consequence of reducing a higher-dimensional, more realistic, model to that of Figure 1. Finally, our conclusions are consistent with those of Griffith [19, Pages 244–246] and of other works devoted to more sophisticated variants of the Goodwin model [39, 40, 33].

In the next sections, all the computations are sketched. A detailed trace of these computations is available at [20].

3.1. The initial model

The model of Figure 1 is translated as a system of generalized chemical reactions (observe that transcription and translation are not balanced reactions). The variables G and H represent the state of the gene. The mRNA concentration and the concentration of the protein translated from the mRNA are represented respectively by M and P. The n types of polymers of P are denoted by $P = P_1, P_2, \ldots, P_n$. Greek letters and k_i^-, k_i^+ ($1 \leq i \leq n-1$) represent parameters:

$$G + P_n \underset{\theta}{\overset{\alpha}{\rightleftharpoons}} H, \quad G \xrightarrow{\rho_{\mathrm{f}}} G + M, \quad H \xrightarrow{\rho_{\mathrm{b}}} H + M,$$

$$M \xrightarrow{\beta} M + P, \quad M \xrightarrow{\delta_{\mathrm{M}}} \varnothing, \quad P \xrightarrow{\delta_{\mathrm{P}}} \varnothing, \tag{3.1}$$

$$P_i + P \underset{k_i^-}{\overset{k_i^+}{\rightleftharpoons}} P_{i+1} \quad (1 \leq i \leq n - 1).$$
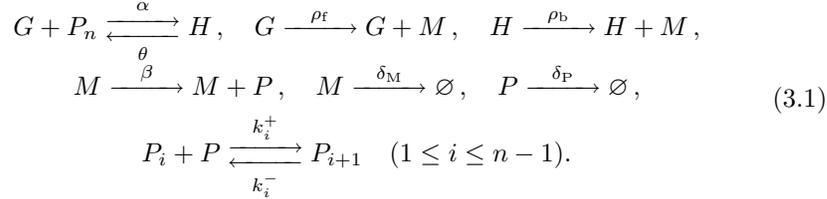
This generalized chemical reaction system can now be canonically translated as a system of parametric ordinary differential equations, denoting $A_i = (k_i^- P_{i+1} - k_i^+ P_i P)$. Variables $G, H, M, P = P_1, \ldots, P_n$ are dependent variables. They all represent species concentrations except G and H, which should rather be viewed as "random variables".

$$
\begin{aligned}
\dot{G} &= \theta H - \alpha G P_n, \\
\dot{H} &= -\theta H + \alpha G P_n, \\
\dot{M} &= \rho_{\mathrm{f}} G + \rho_{\mathrm{b}} H - \delta_{\mathrm{M}} M, \\
\dot{P} &= \beta M - \delta_{\mathrm{P}} P + 2 A_1 + A_2 + \cdots + A_{n-1}, \\
\dot{P}_i &= -A_{i-1} + A_i \qquad\qquad (2 \leq i \leq n - 1), \\
\dot{P}_n &= -A_{n-1} + \theta H - \alpha G P_n.
\end{aligned}
\tag{3.2}
$$

This system involves $n + 3$ differential equations depending on $2\,n + 5$ parameters.

3.2. The raw reduced model

In order to apply a quasi-steady state approximation, it is assumed that the $n - 1$ chemical reactions describing the polymerization of the protein are fast compared to the other ones. Then, according to the technique sketched in section 2.1, one gets an approximation of system (3.2) by replacing each expression A_i by a new

dependent variable F_i $(1 \leq i \leq n-1)$ and by augmenting this system by the $n-1$ following algebraic equations:

$$0 \ = \ k_i^+ \, P \, P_i - k_i^- \, P_{i+1}, \qquad (1 \leq i \leq n-1). \qquad (3.3)$$

It is now sufficient to eliminate the F_i from the so obtained differential-algebraic system.

The MABSys package allows us to define the initial model and to compute the raw reduced model. Unfortunately, computations cannot be performed by keeping a symbolic value for n (this is a classical restriction of symbolic computation methods). However, the MABSys package can be applied for many different values of n and the general formula can be inferred.

Computations are as follows. The chemical reaction system (3.1) is entered by using the NewReaction function. Then the ModelReduce function (which is an enhanced implementation of DifferentialModelReduction, based on the RegularChains package) is applied. Then, H is replaced by $\gamma_0 - G$, introducing a new positive parameter γ_0. Last n new K_i parameters are introduced for legibility with the convention $K_0 = 1$.

$$K_i = \frac{k_1^+ \cdots k_i^+}{k_1^- \cdots k_i^-}.$$

The obtained raw reduced model writes:

$$\begin{aligned}
\dot{G} &= \theta \, (\gamma_0 - G) - \alpha \, K_{n-1} \, P^n \, G, \\
\dot{M} &= \rho_{\mathrm{b}} \, (\gamma_0 - G) + \rho_{\mathrm{f}} \, G - \delta_{\mathrm{M}} \, M, \\
\dot{P} &= \frac{n \, \theta \, (\gamma_0 - G) - n \, \alpha \, K_{n-1} \, P^n \, G - \delta_{\mathrm{P}} \, P + \beta \, M}{\displaystyle\sum_{i=0}^{n-1} (i+1)^2 \, K_i \, P^i}.
\end{aligned} \qquad (3.4)$$

Observe that, in principle, there is no need to introduce the K_i parameters since this simplification should be performed in the next section. However, the MABSys package does not find this particular change of coordinates but a slightly more complicated one. We chose to perform this natural simplification interactively for the sake of the legibility of our paper.

3.3. The reduced model

The raw reduced model (3.4) can now be simplified by rescaling all parameters and variables. Observe that computations are not completely automatic: the practitionner needs to choose the parameters to keep and the ones to eliminate.

Computations are made in two main steps as follows. The first step uses the function RemoveParameterByScalings which is an interface to some functionnalities of the ExpandedLiePointSymmetry package. It removes the two parameters β and δ_{P}. The second step uses MABSys. The CylindrifySteadyPoints function is called in order to make some parameters appear as factors in the right-hand sides of the differential equations. Thus, these parameters do not appear anymore in the algebraic steady points system. For $n \geq 2$, two further changes of coordinates are

applied interactively for the sake of the legibility of the result (the case $n = 1$ is slightly different, see [20]). In all cases, the reduced model writes:

$$
\begin{aligned}
\dot{G} &= \theta\,(\gamma_0 - G - G\,P^n), \\
\dot{M} &= ((\rho_{\mathrm{f}} - 1)\,G + \gamma_0 - M)\,\delta_{\mathrm{M}}, \\
\dot{P} &= \frac{M - P + n\,\rho_{\mathrm{b}}\,(\gamma_0 - G - G\,P^n)}{n^2\,\alpha^{n-1}\,P^{n-1} + \displaystyle\sum_{i=0}^{n-2}(i+1)^2\,K_i\,\alpha^i\,P^i}.
\end{aligned}
\tag{3.5}
$$

The changes of coordinates, summarized below, are obtained by composing the ones automatically computed by the MABSys package with the extra ones, performed interactively. The old variables are expressed as functions of the new (overlined) ones. The bars are removed afterwards for legibility. For $n \geq 2$, the change of variables are as follows (they are slightly different in the case $n = 1$, see [20]):

$$
M = \frac{\overline{M}\,\overline{\alpha}\,\overline{\delta}_{\mathrm{P}}}{\overline{K}_{n-1}\,\overline{\beta}}, \qquad t = \frac{\overline{t}}{\overline{\delta}_{\mathrm{P}}}, \qquad\qquad P = \frac{\overline{P}\,\overline{\alpha}}{\overline{K}_{n-1}},
$$

$$
G = \frac{\overline{G}\,\overline{\rho}_{\mathrm{b}}\,\overline{\alpha}}{\overline{K}_{n-1}\,\overline{\theta}}, \qquad \alpha = \frac{\overline{K}_{n-1}\,\overline{\theta}\,\overline{\delta}_{\mathrm{P}}}{\overline{\alpha}^n}, \qquad\qquad \theta = \overline{\theta}\,\overline{\delta}_{\mathrm{P}},
$$

$$
\rho_{\mathrm{f}} = \frac{\overline{\rho}_{\mathrm{f}}\,\overline{\theta}\,\overline{\delta}_{\mathrm{M}}\,\overline{\delta}_{\mathrm{P}}^2}{\overline{\rho}_{\mathrm{b}}\,\overline{\beta}}, \qquad \rho_{\mathrm{b}} = \frac{\overline{\theta}\,\overline{\delta}_{\mathrm{M}}\,\overline{\delta}_{\mathrm{P}}^2}{\overline{\rho}_{\mathrm{b}}\,\overline{\beta}}, \qquad\qquad \delta_{\mathrm{M}} = \overline{\delta}_{\mathrm{M}}\,\overline{\delta}_{\mathrm{P}},
\tag{3.6}
$$

$$
\gamma_0 = \frac{\overline{\gamma}_0\,\overline{\rho}_{\mathrm{b}}\,\overline{\alpha}}{\overline{K}_{n-1}\,\overline{\theta}}, \qquad K_{n-1} = \overline{K}_{n-1}^{n-1}, \quad K_i = \overline{K}_i\,\overline{K}_{n-1}^i \quad (1 \leq i < n).
$$

3.4. Qualitative analysis of the reduced model

In this section and the next ones, one proves the following proposition.

Proposition 3.1. *For positive values of the variables and parameters, the reduced model (3.5) exhibits a Poincaré-Andronov-Hopf bifurcation if and only if $n \geq 9$.*

Though the MABSys package provides functions related to the qualitative analysis of differential systems (in particular, functions for studying the presence of Poincaré-Andronov-Hopf bifurcations), most of the study performed in this section needed to be performed interactively.

3.4.1. The steady point equations. One computes a Gröbner basis of the ideal generated by the right-hand sides of the differential equations (3.5) w.r.t. the lexicographical ordering $G > M > \gamma_0$. The other variables and parameters are considered as algebraically independent elements of the base field of the equations.

Observe that one does not need to distinguish the roles of the variables from the ones of the parameters at this step. The zeroes of this system provide the steady points of system (3.5). In general, one cannot compute a Gröbner basis if a symbolic n is left as an exponent, but in our case, a generic Gröbner basis exists. The ordering was chosen carefully in order to achieve two important properties:

1. the leading monomials are plain variables ;
2. the right-hand sides of the Gröbner basis equations are positive.

The first property implies that the quotient ring defined by the Gröbner basis is a free algebra: a polynomial ring. The second property implies that there are no constraints on the values that can be assigned to the variables and parameters occuring in the right-hand sides of the Gröbner basis equations.

Computations were performed using the Basis function of the MAPLE Groebner package. The leading monomials appear on the left-hand sides of the equations:

$$\gamma_0 = \frac{P\,(1 + P^n)}{P^n + \rho_{\mathrm{f}}}, \quad M = P, \quad G = \frac{P}{P^n + \rho_{\mathrm{f}}}.$$

3.5. The Jacobian matrix

In order to study Poincaré-Andrononv-Hopf bifurcations of system (3.5), one needs to consider the Jacobian matrix of that system, evaluated over the system steady points. Thanks to the striking properties of the Gröbner basis computed in the above paragraph, one just needs to replace each element of the generic Jacobian matrix by its normal form w.r.t. the Gröbner basis and to forget the steady point equations. The normal form of the Jacobian matrix writes as follows:

$$J = \begin{pmatrix} -\theta\,(1 + P^n) & 0 & -\dfrac{n\,\theta\,P^n}{P^n + \rho_{\mathrm{f}}} \\ (-1 + \rho_{\mathrm{f}})\,\delta_{\mathrm{M}} & -\delta_{\mathrm{M}} & 0 \\ -\dfrac{n\,\rho_{\mathrm{b}}\,(1 + P^n)}{B} & \dfrac{1}{B} & -\dfrac{n^2\,\rho_{\mathrm{b}}\,P^n + P^n + \rho_{\mathrm{f}}}{B\,(P^n + \rho_{\mathrm{f}})} \end{pmatrix}$$

where $B = n^2\,\alpha^{n-1}\,P^{n-1} + \displaystyle\sum_{i=0}^{n-2}(i + 1)^2\,K_i\,\alpha^i\,P^i$.

The parameters α and K_i only occur in B. It is thus possible to assign arbitrary positive values to B without perturbating the values of the other expressions involved in the matrix elements. One can thus consider B as a new parameter.

3.6. If $n \leq 8$ then no Poincaré-Andronov-Hopf bifurcation arises

In order to prove that no Poincaré-Andronov-Hopf bifurcation arises for positive values of variables and parameters whenever $n \leq 8$, it is sufficient to prove that the three Hurwitz determinants $c_{0,0}$, $c_{1,0}$ and $c_{2,0}$ are positive, thanks to Proposition 4.4 and Definition 4.6. These determinants are defined as follows:

$$c_{0,0} = 1, \quad c_{1,0} = a_1, \quad c_{2,0} = a_1\,a_2 - a_3.$$

where $x^3 + a_1 x^2 + a_2 x + a_3$ denotes the characteristic polynomial of the matrix J. The determinant $c_{0,0}$ is positive. The determinant $c_{1,0}$ is positive also since its numerator and denominator are linear combinations of power products of positive variables and parameters, with positive coefficients:

$$c_{1,0} = \frac{\theta\, B\, P^{2\,n} + (1 + n^2\, \rho_{\mathrm{b}} + \delta_{\mathrm{M}}\, B + \theta\, B + \theta\, \rho_{\mathrm{f}}\, B)\, P^n + (1 + \delta_{\mathrm{M}}\, B + \theta\, B)\, \rho_{\mathrm{f}}}{B\, (P^n + \rho_{\mathrm{f}})}.$$

In the sequel, one proves that $c_{2,0}$ is positive if $n \leq 8$. The denominator $B\,(P^n + \rho_{\mathrm{f}})^2$ of this rational fraction is positive. The numerator is a sum of 59 monomials, only two of which have negative coefficients:

$$-n\, \delta_{\mathrm{M}}\, \theta\, \rho_{\mathrm{f}}\, B\, P^n\, (P^n + \rho_{\mathrm{f}}).$$

One thus studies the positivity of the numerator, which is a polynomial in P^n. One performs a change of coordinates, renaming P^n as P. This polynomial has the form

$$d_0\, \rho_{\mathrm{b}}^2 + d_1\, \rho_{\mathrm{b}} + d_2$$

where d_0 and d_1 are linear combinations of power products of positive variables and parameters, with positive coefficients. Thus $c_{2,0}$ is positive for each $\rho_{\mathrm{b}} > 0$ if and only if d_2 is nonnegative. One thus studies the nonnegativity of d_2, factoring out its positive coefficient $P + \rho_{\mathrm{f}}$. This polynomial has the form:

$$\frac{d_2}{P + \rho_{\mathrm{f}}} = e_0\, \rho_{\mathrm{f}} + e_1$$

where e_1 is a linear combination of power products of positive variables and parameters, with positive coefficients. Thus d_2 is nonnegative for each $\rho_{\mathrm{f}} > 0$ if and only if e_0 is nonnegative. One thus studies the nonnegativity of e_0, which has the form:

$$e_0 = f_0\, P^2 + f_1\, P + f_2$$

where f_0 and f_2 are linear combinations of power products of positive variables and parameters, with positive coefficients. Thus e_0 is nonnegative if and only if e_0 (viewed as a univariate polynomial in P) has no nonnegative root. Since f_2/f_0 is the product of the roots, the two roots have the same sign and are nonzero. For both roots to be positive, it is necessary and sufficient to have f_1 negative (since f_1 is the opposite of the sum of the roots) and a positive discriminant of e_0 w.r.t. P (in order to have real roots). These polynomials write:

$$\frac{f_1}{\theta} = 2\, B\, (B\, \delta_{\mathrm{M}} + 1)\, \theta + (\delta_{\mathrm{M}}\, B)^2 + (2 - n)\, \delta_{\mathrm{M}}\, B + 1$$

and

$$\frac{\mathrm{disc}\,(e_0,\, P)}{\theta^2} = -4\, n\, B\, (\delta_{\mathrm{M}}\, B)\, (\delta_{\mathrm{M}}\, B + 1)\, \theta$$
$$+ (\delta_{\mathrm{M}}\, B)^4 - 2\, n\, (\delta_{\mathrm{M}}\, B)^3 + (n^2 - 4\, n - 2)(\delta_{\mathrm{M}}\, B) - 2\, n\, (\delta_{\mathrm{M}}\, B) + 1.$$

Denoting $\delta_M B$ by δ, one has e_0 nonnegative if and only if the conditions $0 < \theta < \theta_0$ and $0 < \theta < \theta_1$ are not satisfied simultaneously, i.e. if and only if θ_0 and θ_1 are not positive simultaneously, where:

$$
\begin{aligned}
\theta_0 &= \delta^4 - 2\,n\,\delta^3 + (n^2 - 4\,n - 2)\,\delta^2 - 2\,n\,\delta + 1, \\
\theta_1 &= -\delta^2 + (n-2)\,\delta - 1.
\end{aligned}
$$

These two polynomials are reciprocal polynomials. Thus, denoting $\lambda = \delta + 1/\delta$, one has:

$$
\begin{aligned}
\theta_0/\delta^2 &= \lambda^2 - 2\,n\,\lambda + n^2 - 4\,n - 4, \\
\theta_1/\delta &= -\lambda + n - 2.
\end{aligned}
$$

For θ_1 to be positive, it is necessary that $n > \lambda + 2$. For θ_0 to be positive, it is necessary that $n < \lambda + 2 - 2\sqrt{\lambda + 2}$ or $n > \lambda + 2 + 2\sqrt{\lambda + 2}$. Thus, for both θ_0 and θ_1 to be positive, it is necessary that $n > \lambda + 2 + 2\sqrt{\lambda + 2}$. Since $\lambda = \delta + 1/\delta$ with $\delta > 0$, one has $\lambda \geq 2$ whence $n > 8$. Thus $c_{2,0}$ is positive if and only if $n \leq 8$. This concludes the proof of the left to right implication of Proposition 3.1.

### 3.7. If $n \geq 9$ then Poincaré-Andronov-Hopf bifurcation arise
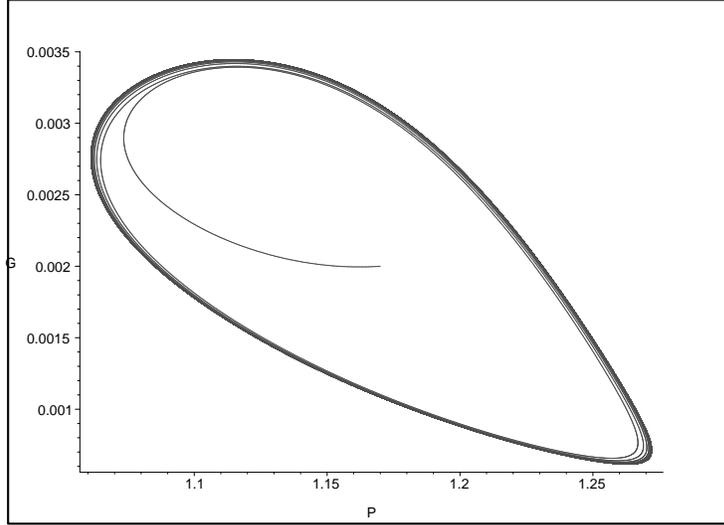
FIGURE 2. A limit cycle between $P(t)$ (horizontally) and $G(t)$ (vertically) obtained by simulating system (3.5) numerically. The parameter values are: $n = 15$, $\delta_M = 1/2$, $\theta = 1/20$, $\rho_f = 600$, $\rho_b = 1/40$, $\gamma_0 = 1/50$, $\alpha = 6/25$ and $K_i = 1$ for each $1 \leq i < n$. The initial values are: $P(0) = 1.17$, $M(0) = 0.8$ and $G(0) = 0.002$.

Let n be an integer number greater than or equal to 9. One exhibits a Poincaré-Andronov-Hopf bifurcation by applying Proposition 4.5. Take $\delta = 1$. Then, since $\delta = \delta_M B$ one can take $\delta_M = 1/2$ and $B = 2$ (observe that B denotes

an expression that is greater than 1). The conditions $\theta < \theta_0$ and $\theta < \theta_1$ then permit to take $\theta = 1/20$. Then the polynomial e_0 has two positive roots (in the P variable) and one can take the value $P = 10$, which is enclosed between the two roots of e_0, in order to ensure $e_0 < 0$. Now, the curve $d_2 = 0$ is a decreasing function of n, bounded by (say), 600. Taking $\rho_{\mathrm{f}} = 600$ thus ensures that $d_2 < 0$. The positive root of $d_0\,\rho_{\mathrm{b}}^2 + d_1\,\rho_{\mathrm{b}} + d_2 = 0$ provides a value of ρ_{b} which cancels $c_{2,0}$. Its analytic formula is:

$$\rho_{\mathrm{b}} = \frac{-3843 + \sqrt{1461560\,n + 1640961}}{20\,n^2}.$$

These values ensure that $c_{0,0} > 0$, $c_{1,0} > 0$, $c_{2,0} = 0$ and $c_{2,1} = -a_3 < 0$ i.e. that a Poincaré-Andronov-Hopf bifurcation occurs. This concludes the proof of Proposition 3.1. Figure 2 shows an oscillation in the neighborhood of a Poincaré-Andronov-Hopf bifurcation.

4. Appendix

4.1. On differential elimination

The differential elimination theory is a subtheory of the differential algebra [38, 32]. See also [48]. The differential elimination processes that are presented in this paper take as input two parameters: a system of polynomial (thus nonlinear) differential equations, ordinary or with partial derivatives[2] and a *ranking*. They produce on the output an equivalent finite set of polynomial differential systems, which are simpler, in the sense that they involve some differential equations which are consequences of the input system but were somehow hidden. The output may consist of more than one differential system because the differential elimination process may need to split cases. The set of the differential equations which are consequences of the input system forms a so-called *differential ideal* of some *polynomial differential ring*. Since this ideal is an infinite set, a natural question arises: how does the process select the finitely many differential equations which appear in the output system ? This is indeed the role of the rankings.

A *differential ring* (resp. field) is a ring (resp. field) R endowed with a derivation (this paper is restricted to the case of a single derivation but the theory is more general) i.e. a unitary mapping $R \rightarrow R$ such that (denoting $\dot{a}$ the derivative of a):

$$\widehat{(a+b)} = \dot{a} + \dot{b}, \quad \widehat{(a\,b)} = \dot{a}\,b + a\,\dot{b}. \tag{4.1}$$

Observe that, theoretically, the derivation is an abstract operation. For legibility, one views it as the derivation w.r.t. the time t. Algorithmically, one is led to manipulate finite subsets of some *differential polynomial ring* $R = K\{U\}$ where K is the differential field of coefficients (in practice, $K = \mathbb{Q}$, $\mathbb{Q}(t)$ or $\mathbb{Q}(k_1, \ldots, k_r)$ where the k_i denote parameters that would be assumed to be algebraically independent)

---

[2]This paper is only concerned by the ordinary case.

and U is a finite set of *dependent variables*[3]. The elements of R, the *differential polynomials* are just polynomials in the usual sense, built over the infinite set, denoted ΘU, of all the derivatives of the dependent variables.

Definition 4.1. A *differential ideal* of a differential ring R is an ideal of R, stable under the action of the derivation.

Let F be a finite subset of a differential ring R. The set of all the finite linear combinations of various orders derivatives of elements of F, with elements of R for coefficients, is a differential ideal. It is called the differential ideal generated by F. An ideal $\mathfrak{A}$ is said to be *radical* if $a \in \mathfrak{A}$ whenever there exists some nonnegative integer p such that $a^p \in \mathfrak{A}$. The radical of an ideal $\mathfrak{A}$ is the set of all the ring elements a power of which belongs to $\mathfrak{A}$. The radical of a (differential) ideal is a radical (differential) ideal.

Theorem 4.2. *Let R be a differential polynomial ring and F be a finite subset of R. A differential polynomial p of R lies in the radical of the differential ideal generated by F if and only if it vanishes over every analytic solution of F.*

Proof. [38, chap. II, §7, 11] or [4]. □

The *Rosenfeld-Gröbner* algorithm [5] solves the membership problem to radical differential ideals. To present it, one needs to define the concept of *ranking*.

Definition 4.3. If U is a finite set of dependent variables, a *ranking* over U is a total ordering over the set ΘU of all the derivatives of the elements of U which satisfies: $a < \dot{a}$ and $a < b \Rightarrow \dot{a} < \dot{b}$ for all $a, b \in \Theta U$.

Let U be a finite set of dependent variables. A ranking such that, for every $u, v \in U$, the ith derivative of u is greater than the jth derivative of v whenever $i > j$ is said to be *orderly*. If U and V are two finite sets of dependent variables, one denotes $U \gg V$ every ranking such that any derivative of any element of U is greater than any derivative of any element of V. Such rankings are said to *eliminate* U w.r.t. V.

Assume that some ranking is fixed. Then one may associate with any differential polynomial $f \in K\{U\} \setminus K$ the greatest (w.r.t. the given ranking) derivative $v \in \Theta U$ such that $\deg(f, v) > 0$. This derivative is called the *leading derivative* or the *leader* of f.

Rankings permit to define leaders. Leaders permit to use differential polynomial as rewrite (substitution) rules. Assume that $f = a_d v^d + \cdots + a_1 v + a_0$ is a differential polynomial with leader v (the coefficients a_i are themselves differential polynomials). Then the equation $f = 0$ can be written:

$$v^d \quad \longrightarrow \quad -\frac{a_{d-1} v^{d-1} + \cdots + a_1 v + a_0}{a_d} \, . \tag{4.2}$$

---

[3]In the differential algebra theory, the terminology *differential indeterminates* is preferred to *dependent variables* for derivations are abstract and differential indeterminates are not even assumed to correspond to functions. In order not to mix different expressions in this paper, the second expression, which seems to be more widely known, was chosen.

It can be used afterwards as a rule to simplify any differential polynomial g such that $\deg(g, v) \geq d$ or $\deg(g, v^{(k)}) > 0$ where $v^{(k)}$ denotes any proper derivative of v. There are precise algorithms for performing these sorts of substitution by finite sets of rewrite rules: Ritt's reduction algorithm or the *normal form* algorithm [4, algorithm NF].

The *Rosenfeld-Gröbner* algorithm gathers as input a finite system F of differential polynomials and a ranking. It returns a finite family (possibly empty) $C_1, \ldots, C_r$ of finite subsets of $K\{U\} \setminus K$, called *regular differential chains*. Each system C_i defines a differential ideal $\mathfrak{C}_i$ (it is a *characteristic set* of $\mathfrak{C}_i$) in the sense that, for any $f \in K\{U\}$, we have

$$f \in \mathfrak{C}_i \quad \text{iff} \quad \mathsf{NF}(f, C_i) = 0. \tag{4.3}$$

The relationship with the radical $\mathfrak{A}$ of the differential ideal generated by F is the following:

$$\mathfrak{A} \;=\; \mathfrak{C}_1 \cap \cdots \cap \mathfrak{C}_r. \tag{4.4}$$

When $r = 0$ we have $\mathfrak{A} = K\{U\}$. Combining both relations, one gets an algorithm to decide membership in $\mathfrak{A}$. Indeed, given any $f \in K\{U\}$ we have:

$$f \in \mathfrak{A} \quad \text{iff} \quad \mathsf{NF}(f, C_i) = 0, \quad 1 \leq i \leq r. \tag{4.5}$$

The differential ideals $\mathfrak{C}_i$ do not need to be prime. They are however necessarily radical. The $\mathsf{NF}(\,\cdot\,, C_i)$ function permits to compute canonical representatives of the residue classes of the differential ring $R/\mathfrak{C}_i$.

4.2. On Poincaré-Andronov-Hopf bifurcations

4.2.1. Non parametric systems. Let $\dot{x} = F(x)$ be a differential system in m dependent variables. The steady points of the differential system are the zeros of the system (that we assume to be polynomial or rational) $F(x) = 0$. To each steady point, one may associate a linear system $\dot{x} = J\,x$ where J is the $m \times m$ jacobian matrix of the differential system, evaluated over the steady point. The stability of the steady state is determined by the eigenvalues of J. It is stable if and only if all eigenvalues have negative real parts. Thus to each steady point, one may associate the characteristic polynomial $C(\sigma) = \sigma^m + a_1\,\sigma^{m-1} + \cdots + a_m$ $(a_0 = 1)$ of J. Thanks to the Routh-Hurwitz criterion, the stability of the steady points can be studied by analyzing the sign of the Hurwitz determinants $c_{k,0}$. These ones can be directly computed from the coefficients of the characteristic polynomial, as shown below. Following [28, Section I.13], compute the Sturm sequence:

$$p_0(\omega) = \Re\left(\frac{C(i\,\omega)}{i^m}\right), \quad p_1(\omega) = -\Im\left(\frac{C(i\,\omega)}{i^m}\right) \tag{4.6}$$

$$p_{k+2}(\omega) = -\operatorname{rem}(p_k, p_{k+1}, \omega) \qquad (k \geq 0).$$

Denote $p_k(\omega) = c_{k,0}\,\omega^{m-k} + c_{k,1}\,\omega^{m-k-2} + c_{k,2}\,\omega^{m-k-4} + \cdots$ Observe that the computation of p_k must be performed carefully (e.g. using subresultant sequences) to ensure that $c_{k,0}$ actually is a Hurwitz determinant. See [17]. Indeed,

$$c_{0,0} = 1, \quad c_{1,0} = a_1, \quad c_{2,0} = a_1\,a_2 - a_3, \quad \ldots, \quad c_{m,0} = a_m\,c_{m-1,0}.$$

The two following propositions are well known. The first one is nearly a corollary to the Routh Theorem [28, Theorem 13.4].

Proposition 4.4. *With the same notations, if all the Hurwitz determinants $c_{k,0}$ are positive, apart perhaps $c_{m,0}$, then J has no pure imaginary eigenvalue.*

Proof. If all the Hurwitz determinants $c_{k,0}$ are positive $(0 \leq k < m)$ then they are *a fortiori* nonzero. Assume J has pure imaginary eigenvalues $\pm i\,\bar{\omega}$ (they are necessarily conjugate). These values $\pm\bar{\omega}$ are then common zeros of p_0 and p_1. The gcd of p_0 and p_1 has thus degree greater than or equal to 2. This gcd is the last nonzero polynomial in the sequence $p_0, \ldots, p_{m-1}$. Thus one polynomial p_k with $0 \leq k < m$ must vanish identically. Therefore the corresponding Hurwitz determinant $c_{k,0}$ must vanish also.   □

Proposition 4.5. *With the same notations, if all the Hurwitz determinants $c_{k,0}$ are positive $(0 \leq k \leq m-2)$ and $c_{m-1,0} = 0$ and $c_{m-2,1} < 0$ then all the eigenvalues of J have negative real parts except a purely imaginary conjugate pair.*

Proof. The polynomial p_{m-1} has the special form $p_{m-1} = c_{m-1,0}\,\omega$. We have $c_{m-1,0} = 0$. Then p_0 and p_1 have a degree two gcd, p_{m-2}, which has the special form $p_{m-2} = c_{m-2,0}\,\omega^2 + c_{m-2,1}$. We have $c_{m-2,1} < 0$ and $c_{m-2,0} > 0$ thus, the common roots $\pm\bar{\omega}$ of p_0 and p_1 are real. Therefore J has one pair of purely imaginary conjugate eigenvalues $\pm i\,\bar{\omega}$. Now, compute the Sturm sequence (4.6) over the polynomial $\bar{C}(\sigma) = C(\sigma)/(\sigma^2 + \bar{\omega}^2)$. This Sturm sequence $\bar{p}_0, \bar{p}_1, \ldots, \bar{p}_{\bar{m}}$ can actually be derived from that of C:

$$\bar{p}_0(\omega) = \frac{p_0}{\sigma^2 + \bar{\omega}^2}, \quad \bar{p}_1(\omega) = \frac{p_1}{\sigma^2 + \bar{\omega}^2}, \quad \ldots, \quad \bar{p}_{\bar{m}}(\omega) = c_{m-2,0}.$$

All the corresponding Hurwitz determinants are positive. According to the Routh Theorem [28, Theorem 13.4], all the roots of $\bar{C}$ have negative real parts. This concludes the proof of the proposition.   □

For $m = 3$ we have $c_{m-2,1} = -a_3$. For $m = 4$ we have $c_{m-2,1} = -a_1\,a_4$.

4.2.2. Parametric systems. The differential systems encountered in biological modelling involve parameters. Let $\dot{x} = F(x, \theta)$ be a differential system in m variables and p parameters θ. If some real values are assigned to the parameters then one gets a system such as the one described in the previous section. If these real values continuously vary then the steady points and their associated eigenvalues continuously vary also.

Definition 4.6. With notations as above, a Poincaré-Andronov-Hopf bifurcation arises for a steady point when all the eigenvalues associated to the steady point have negative real parts except one complex conjugate pair, which crosses the imaginary axis because of a variation in the system parameters.

In computer algebra, an important point is to avoid to compute the steady points, i.e. not to solve the system $F(x, \theta) = 0$. The Hurwitz determinants can be computed generically. They depend on the system parameters. Their sign is studied

modulo the ideal I generated by the polynomial system $F(x, \theta) = 0$. The absence of Poincaré-Andronov-Hopf bifurcation is established, thanks to Proposition 4.4 and Definition 4.6, by proving that the Hurwitz determinants $c_{0,0}, \ldots, c_{m-1,0}$ are positive for all x and θ, considering that x and θ satisfy $F(x, \theta) = 0$ plus, usually, some extra (positivity) conditions such as $x, \theta > 0$.

The Hurwitz determinants $c_{k,0}$ get reformulated by computing their normal forms $\bar{c}_{k,0}$ w.r.t. any Gröbner basis of the ideal I. Reference books for the Gröbner basis theory are [11, 2]. Indeed, the difference $c_{k,0} - \bar{c}_{k,0}$ belongs to I. Over any steady point of the differential system, it is thus zero, thus the two polynomials $c_{k,0}$ and $\bar{c}_{k,0}$ have the same value hence the same sign.

In practice moreover, Gröbner bases can be computed in dimension zero. Computing in dimension zero corresponds to some generic computation, which may be false for particular values of the system variables and parameters. However, in biological models, parameters (and thus variables) have no accurate values and zero dimensional computing makes sense.

5. Conclusion

We have presented the first version of an algorithmic scheme dedicated to the model reduction problem. By carrying out a complete medium size example, including its qualitative analysis, we have proven that computer algebra tools may be most useful in biological modeling. Embedding these methods in an easy to use package should help practitioners to model cellular processes by means of a much wider variety of functions than the classical Michaelis-Menten or Hill functions, and to make the hypotheses leading to model reductions more explicit than they do. However, the model reduction part of our package still needs many improvements. It also misses tools which make automatic the small set of heuristics which permitted us to carry out the qualitative analysis of our example.

References

[1] Hirokazu Anai. Algebraic Methods for Solving Real Polynomial Constraints and their Applications in Biology. In *Proceedings of Algebraic Biology 2005*, pages 139–147, 2005.

[2] Thomas Becker and Volker Weispfenning. *Gröbner Bases: a computational approach to commutative algebra*, volume 141 of *Graduate Texts in Mathematics*. Springer Verlag, 1991.

[3] Matthew R. Bennet, Dmitri Volfson, Lev Tsimring, and Jeff Hasty. Transient Dynamics of Genetic Regulatory Networks. *Biophysical Journal*, 92:3501–3512, May 2007.

[4] François Boulier and François Lemaire. A computer scientist point of view on Hilbert's differential theorem of zeros. *Submitted to Applicable Algebra in Engineering, Communication and Computing*, 2007. `http://hal.archives-ouvertes.fr/hal-00170091`.

[5] François Boulier, Daniel Lazard, François Ollivier, and Michel Petitot. Representation for the radical of a finitely generated differential ideal. In *ISSAC'95: Proceedings of the 1995 international symposium on Symbolic and algebraic computation*, pages 158–166, New York, NY, USA, 1995. ACM Press. `http://hal.archives-ouvertes.fr/hal-00138020`.

[6] François Boulier, Marc Lefranc, François Lemaire, and Pierre-Emmanuel Morant. Model Reduction of Chemical Reaction Systems using Elimination, 2007. Presented at the international conference MACIS 2007, `http://hal.archives-ouvertes.fr/hal-00184558`, submitted to Mathematics in Computer Science.

[7] François Boulier, Marc Lefranc, François Lemaire, and Pierre-Emmanuel Morant. Applying a rigorous quasi-steady state approximation method for proving the absence of oscillations in models of genetic circuits. In K. Horimoto et al., editor, *Proceedings of Algebraic Biology 2008*, number 5147 in LNCS, pages 56–64. Springer Verlag Berlin Heidelberg, 2008.

[8] François Boulier, Marc Lefranc, François Lemaire, Pierre-Emmanuel Morant, and Aslı Ürgüplü. On proving the absence of oscillations in models of genetic circuits. In K. Horimoto H. Anai and T. Kutsia, editors, *Proceedings of Algebraic Biology 2007*, volume 4545 of *LNCS*, pages 66–80. Springer Verlag Berlin Heidelberg, 2007. `http://hal.archives-ouvertes.fr/hal-00139667`.

[9] Christopher W. Brown. QEPCAD B: a program for computing with semi-algebraic sets using CADs. *SIGSAM Bulletin*, 37(4):97–108, 2003. `http://www.cs.usna.edu/~qepcad/B/QEPCAD.html`.

[10] Emery D. Conrad and John J. Tyson. Modeling Molecular Interaction Networks with Nonlinear Differential Equations. In Zoltan Szallasi, Jörg Stelling, and Vipul Periwal, editors, *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*, pages 97–124. Cambridge, Massachussets: The MIT Press, 2006.

[11] David Cox, John Little, and Donal O'Shea. *Ideals, Varieties and Algorithms. An introduction to computational algebraic geometry and commutative algebra*. Undergraduate Texts in Mathematics. Springer Verlag, New York, 1992.

[12] Hidde de Jong, Johannes Geiselmann, Céline Hernandez, and Michel Page. Genetic Network Analyzer: qualitative simulation of genetic regulatory networks. *Bioinformatics*, 19(3):336–344, 2003.

[13] Hidde de Jong and Delphine Ropers. Qualitative Approaches to the Analysis of Genetic Regulatory Networks. In Zoltan Szallasi, Jörg Stelling, and Vipul Periwal, editors, *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*, pages 125–147. Cambridge, Massachussets: The MIT Press, 2006.

[14] Eusebius Doedel. AUTO software for continuation and bifurcation problems in ODEs. `http://indy.cs.concordia.ca/auto`, 1996.

[15] Andreas Dolzmann and Thomas Sturm. Redlog: computer algebra meets computer logic. *SIGSAM Bulletin*, 31(2):2–9, 1997.

[16] Mohab Safey El Din. RAGLib (Real Algebraic Library Maple package). `http://www-calfor.lip6.fr/~safey/RAGLib`, 2003.

[17] M'Hammed El Kahoui and Andreas Weber. Deciding Hopf bifurcations by quantifier elimination in a software–component architecture. *Journal of Symbolic Computation*, 30(2):161–179, 2000.

[18] Bard Ermentrout. *Simulating, Analyzing, and Animating Dynamical Systems: A Guide to XPPAUT for Researchers and Students*, volume 14 of *Software, Environments, and Tools*. SIAM, 2002.

[19] C. P. Fall, E. S. Marland, J. M. Wagner, and John J. Tyson. *Computational Cell Biology*, volume 20 of *Interdisciplinary Applied Mathematics*. Springer Verlag, 2002.

[20] François Boulier and François Lemaire and Alexandre Sedoglavic and Aslı Ürgüplü. Supplementary data. `http://hal.archives-ouvertes.fr/hal-00307915/fr/`, 2008.

[21] Jean-Pierre Françoise. *Oscillations en biologie*, volume 46 of *Mathématiques et Applications*. Springer Verlag, 2005.

[22] Karin Gatermann, Markus Eiswirth, and Anke Sensse. Toric Ideals and graph theory to analyze Hopf bifurcations in mass action systems. *Journal of Symbolic Computation*, 40:1361–1382, 2005.

[23] Karin Gatermann and Serkan Hosten. Computational algebra for bifurcation theory. *Journal of Symbolic Computation*, 40:1180–1207, 2005.

[24] Albert Goldbeter. *Biochemical Oscillations and Cellular Rhythms: The Molecular Bases of Periodic and Chaotic Behaviour*. Cambridge University Press, 2004. New Edition.

[25] B. C. Goodwin. *Temporal Organization in Cells*. Academic Press, London, 1963.

[26] B. C. Goodwin. In *Advances in Enzyme Regulation*, volume 3, page 425, Oxford, 1965. Pergamon Press.

[27] J. S. Griffith. Mathematics of Cellular Control Processes. I. Negative Feedback to One Gene. *Journal of Theoretical Biology*, 20:202–208, 1968.

[28] Ernst Hairer, Syvert Paul Norsett, and Gerhard Wanner. *Solving ordinary differential equations I. Nonstiff problems*, volume 8 of *Springer Series in Computational Mathematics*. Springer–Verlag, New York, 2nd edition, 1993.

[29] Jack K. Hale and Hüseyin Koçak. *Dynamics and Bifurcations*, volume 3 of *Texts in Applied Mathematics*. Springer–Verlag, New York, 1991.

[30] F. Horn and R. Jackson. General mass action kinetics. *Archive for Rational Mechanics and Analysis*, 47:81–116, 1972.

[31] Petar Kokotovic, Hassan K. Khalil, and John O'Reilly. *Singular Perturbation Methods in Control: Analysis and Design*. Classics in Applied Mathematics 25. SIAM, 1999.

[32] Ellis Robert Kolchin. *Differential Algebra and Algebraic Groups*. Academic Press, New York, 1973.

[33] Gen Kurosawa, Atsushi Mochizuki, and Yoh Iwasa. Comparative Study of Circadian Clock Models, in Search of Processes Promoting Oscillation. *Journal of Theoretical Biology*, 216:193–208, 2002.

[34] J. C. Leloup and A. Goldbeter. Modeling the molecular regulatory mechanism of circadian rhythms in Drosophila. *Bioessays*, 22:84–93, 2000.

[35] C. Robertson McClung. Plant Circadian Rhythms. *The Plant Cell*, 18:792–803, April 2006.

[36] Wei Niu and Dongming Wang. Algebraic Approaches to Stability Analysis of Biological Systems. *Mathematics in Computer Science*, 1:507–539, 2008.

[37] Miles S. Okino and Michael L. Mavrovouniotis. Simplification of Mathematical Models of Chemical Reaction Systems. *Chemical Reviews*, 98(2):391–408, 1998.

[38] Joseph Fels Ritt. *Differential Algebra*. Dover Publications Inc., New York, 1950. `http://www.ams.org/online_bks/coll33`.

[39] Peter Ruoff and Ludger Rensing. The Temperature–Compensated Goodwin Model Simulates Many Circadian Clock Properties. *Journal of Theoretical Biology*, 179:275–285, 1996.

[40] Peter Ruoff, Merete Vinsjevik, Saadat Mohsenzadeh, and Ludger Rensing. The Goodwin Model: Simulating the Effet of Cycloheximide and Heat Shock on the Sporulation Rhythm of *Neurospora crassa*. *Journal of Theoretical Biology*, 196:483–494, 1999.

[41] Alexandre Sedoglavic. Reduction of Algebraic Parametric Systems by Rectification of their Affine Expanded Lie Symmetries. In K. Horimoto H. Anai and T. Kutsia, editors, *Proceedings of Algebraic Biology 2007*, volume 4545 of *LNCS*, pages 277–291, 2007.

[42] Alexandre Sedoglavic and Aslı Ürgüplü. Expanded Lie Point Symmetry (MAPLE package). `http://www.lifl.fr/~sedoglav/Software`, 2007.

[43] William Selleck, Ryan Howley, Qiaojun Fang, Vladimir Podolny, Michael G. Fried, Stephen Buratowski, and Song Tan. A histone fold TAF octamer within the yeast TFIID transcriptional coactivator. *Nature Structural Biology*, 8(8):695–700, 2001.

[44] Vincent Van Breusegem and George Bastin. Reduced order dynamical modelling of reaction systems: a singular perturbation approach. In *Proceedings of the 30th IEEE Conference on Decision and Control*, pages 1049–1054, Brighton, England, December 1991.

[45] George von Dassow and Elie Meir. Exploring modularity with dynamical models of gene networks. In G. Schlosser and G. P. Wagner, editors, *Modularity in Development and Evolution*, pages 245–287. University of Chicago Press, 2003.

[46] George von Dassow, Elie Meir, E. M. Munro, and G. M. Odell. The segment polarity network is a robust developmental module. *Nature*, 406:188–192, 2000.

[47] Nishith Vora and Prodromos Daoutidis. Nonlinear model reduction of chemical reaction systems. *AIChE Journal*, 47(10):2320–2332, 2001.

[48] Dongming Wang. *Elimination Practice: Software Tools and Applications*. Imperial College Press, London, 2003.

[49] Dongming Wang and Bican Xia. Stability Analysis of Biological Systems with Real Solution Classification. In *proceedings of ISSAC 2005*, pages 354–361, Beijing, China, 2005.

[50] Hiroshi Yoshida, Hirokazy Anai, Shigeo Orii, and Katsuhisa Horimoto. Inquiry into Conditions for Cell-Type Diversity of Multicellular Organisms by Quantifier Elimination. pages 105–113, 2005.

François Boulier
LIFL, University Lille I, 59655 Villeneuve d'Ascq, France
e-mail: `Francois.Boulier@lifl.fr`

François Lemaire
LIFL, University Lille I, 59655 Villeneuve d'Ascq, France
e-mail: `Francois.Lemaire@lifl.fr`

Alexandre Sedoglavic
LIFL, University Lille I, 59655 Villeneuve d'Ascq, France
e-mail: `Alexandre.Sedoglavic@lifl.fr`

Aslı Ürgüplü
LIFL, University Lille I, 59655 Villeneuve d'Ascq, France
e-mail: `Asli.Urguplu@lifl.fr`