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Testing Binomiality of Chemical Reaction Networks Using Comprehensive Gröbner Systems

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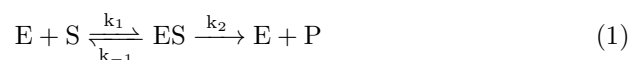
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Abstract. We consider the problem of binomiality of the steady state ideals of biochemical reaction networks. We are interested in finding polynomial conditions on the parameters such that the steady state ideal of a chemical reaction network is binomial under every specialisation of the parameters if the conditions on the parameters hold. We approach the binomiality problem using Comprehensive Gröbner systems. Considering rate constants as parameters, we compute comprehensive Gröbner systems for various reactions. In particular, we make automatic computations on n-site phosphorylations and biomodels from the Biomodels repository using the grobcov library of the computer algebra system Singular.

Keywords: Binomial ideals · Toric varieties · Chemical reaction networks · Mass action kinetics · Scientific computation · Symbolic computation · Gröbner bases · Comprehensive Gröbner bases

1 Introduction

A *chemical reaction* is a transformation between two sets of chemical objects called chemical *complexes*. The objects that form a chemical complex are chemical *species*. In fact, complexes are formal sums of chemical species representing the left and the right hand sides of chemical reactions. A *chemical reaction network* is a set of chemical reactions. For example



is a chemical reaction network with one reversible reactions and one non-reversible reaction. This reaction network is a well-known network, called the *Michaelis–Menton* reaction network.

A *kinetics* of a chemical reaction network is an assignment of a rate function to each reaction in the network. The rate function depends on the concentrations of the species. A kinetics for a chemical reaction network is called *mass-action* if

for each reaction in the network, the rate function is a monomial in terms of the concentrations of the species, such that the exponents are given by the numbers of molecules of the species consumed in the reaction, multiplied by a constant called *rate constant*. In the Michaelis–Menton reaction, k_1, k_{-1}, k_2 are the rate constants. In this article, we assume mass-action kinetics.

A system of autonomous ordinary differential equations can be used to describe the change in the concentration of each species over time in a reaction. For example, in the Michaelis–Menton reaction, let the variables s, p, c, e represent the concentrations of the species S, P, ES, E respectively. The ordinary differential equations (ODEs) describing change of the concentrations of the species for this reaction network are the following:

$$\dot{s} = f_s = -k_1se + k_{-1}c, \quad (2)$$

$$\dot{p} = f_p = k_2c, \quad (3)$$

$$\dot{c} = f_c = k_1se - (k_{-1} + k_2)c, \quad (4)$$

$$\dot{e} = -f_c. \quad (5)$$

Solutions of the polynomials f_s, f_p, f_c and $-f_c$ give us the concentrations of the species in which the system is in equilibrium. In fact, the solutions of f_s, f_p, f_c and $-f_c$ are called the steady states of the chemical reaction network. Accordingly, the ideal generated by f_s, f_p, f_c and $-f_c$, i.e., $I = \langle f_s, f_p, f_c, -f_c \rangle \subseteq \mathbb{K}[k_1, k_{-1}, k_2][s, p, c, e]$, where \mathbb{K} is a field, is called the *steady state ideal* of the Michaelis–Menton network. For a thorough introduction on chemical reaction network theory, refer to Feinberg’s Book [22] and his lecture notes [21]. We follow the notation of Feinberg’s book in this article.

A *binomial ideal* is an ideal that is generated by a set of binomials. In this article, we consider the problem of binomiality of steady state ideals when the rate constants are specialised over a field extension of \mathbb{K} , that is, when the rate constants have been assigned values from an extension of \mathbb{K} , typically the closure of \mathbb{K} . More precisely, we are interested in conditions over the rate constants (typically given by polynomial equations on rate constants), such that for every values of the rate constants in the extension field, the steady state ideal is binomial under those conditions. In this article, we often use parameters instead of rate constants, an indication that they can be specialised. Therefore, we consider the *parametric binomiality problem*.

Let us consider the steady state ideal of the Michaelis–Menton reaction:

$$I = I = \langle f_s, f_p, f_c \rangle \subseteq \mathbb{K}[k_1, k_{-1}, k_2][s, p, c, e], \quad (6)$$

given by Equations (2)–(4). One can observe that $f_c = -f_s + f_p$. Hence, $I = \langle f_s, f_p \rangle$. Having fixed the term ordering induced by $c > s > e$, one may consider further reducing f_s by f_p , i.e., $f_s - f_p = (k_{-1} - k_1)c - k_1se$. As the rate constants in a chemical reaction take values, $k_{-1} - k_1$ may vanish. In this case, if the leading term of $f_s - f_p$ vanishes, then it will be a monomial, and therefore, the reduced Gröbner basis of I will be the monomial ideal generated by $\{k_2c, -k_1se\}$, given that $k_2 \neq 0$ and $k_{-1} \neq 0$. This example shows that the Gröbner basis of the

steady state ideal (and the steady states of the reaction) can change depending on the values of the rate constants. Therefore, we must consider distinct cases for the parameters when analysing a reaction network. Thinking purely in terms of computer algebra, this example illustrates the idea behind *Comprehensive Gröbner bases*. In this article, we investigate the conditions on the parameters of a steady state ideal (or equivalently on the rate constants of a reaction) such that the steady state ideal is binomial when those conditions on the parameters hold.

In the literature, a slightly different notions of binomiality has been considered. Eisenbud and Sturmfels in [16] call an ideal binomial if it is generated by polynomials with at most two terms. Some authors, e.g., Pérez-Milán et al. [40], have studied the binomiality of steady state ideals according to the definition in [16]. However, in this article, our definition does not include those ideals that include monomials. This difference in the definition, obviously, affects the steady state variety of binomial chemical reaction networks in practice.

Binomial ideals and toric varieties have rich history in chemical reaction networks theory. Binomiality corresponds to detailed balance, which is a very important concept in thermodynamics. Detailed balance means that at thermodynamic equilibrium, the forward and backward rates should be equal for all reactions. Detailed balance has been historically used by Einstein [15], Wegscheider [49] and by Onsager [38]. Some of the subsystems of molecular devices can satisfy binomiality conditions. Another interesting point to study binomiality is because the analysis of properties such as multi-stationarity and stability are easier to establish for binomial systems. Toricity, also known as complex, or cyclic, or semi-detailed balance is also known since Boltzmann that has used it as a sufficient condition for deriving his famous H-theorem [2]. Toricity implies binomiality, but the converse is not true. A toric variety is indeed irreducible, however a binomial steady state ideal may have an irreducible variety, which would not be toric. However, every variety of a binomial ideal includes a toric variety as its irreducible component. A toric system must obey constraints on the rates constants, such as the well known Wegscheider—Kolmogorov condition, which implies the equality of the products of forward and backward rates constants in cycles of reversible reactions.

Mathematicians have considered binomiality and toricity and investigated their properties thoroughly, among them existing literature are the work by Fulton [23], Sturmfels [46] and Eisenbud et al. [16]. Binomiality implies *detailed balancing* of reversible chemical reactions, which has been studied by Gorban et al. [24,25] and Grigoriev and Weber [28]. Toric dynamical systems have been studied by Feinberg [20] and Horn and Jackson [30]. Over the real numbers Craciun et al. have studied the toricity problem in [9]. In the latter work, it has been shown that *complex balanced systems* are the same as toric dynamical systems, although *toric steady states* are different from that. Binomiality implies much simpler criteria for multistationarity [14,45].

Pérez-Milán, et al. presented a sufficient linear algebra conditions with inequalities for binomiality of the steady state ideals [41]. The idea in the latter

has been developed in [39], where MESSI reactions have been introduced. Conradi and Kahle have proved in [8] that for homogenous ideals the latter sufficient condition is necessary as well, and introduced an algorithm for that case. Their algorithm has been implemented in Maple and Macaulay II in [32,31]. A geometric view towards toricity of chemical reaction networks has been given by Grigoriev et al. in [27], where shifted toricity has been introduced, algorithms presented for testing shifted toricity and complexity bounds and experimental results are discussed. In [27], the two main tools from computer algebra, quantifier elimination [12,26,50] and Gröbner bases [5,6,18,19] are used. Also recently, the authors introduced a first order logic test for toricity [44]. An efficient linear algebra method for testing unconditional binomiality has been presented in [43] and a graph-theoretical equivalent of the method is given in [42].

Testing binomiality of an ideal is a difficult problem, both from a theoretical and a practical point of view. A typical method to test binomiality is via computing a Gröbner basis. It has been shown that computing a Gröbner basis is EXPSPACE-complete [36], which shows the difficulty of the binomiality problem from the computational point of view. The approach proposed for testing binomiality of steady state ideals in [41,8] relies on linear algebra. In this approach the computations are done without considering the values of the parameters. Also large matrices are constructed in this approach.

Existing work on binomiality of chemical reaction networks typically ignores specialisation of the parameters, often treating them as variables and carrying on the computations. For instance, fixing an ordering in which the parameters are smaller than the variables, e.g., lexicographic ordering, one may consider computing a Gröbner basis of the steady state ideal and then eliminating the variables. Then the elimination ideal will be in the ring of parameters and may result in conditions on the parameters such that the original ideal is binomial. However, this approach does not consider the fact that in the process of computations, some terms can be vanished, if parameters are specialised.

In contrast, our approach is to use comprehensive Gröbner bases, which considers specialisations of the parameters. A comprehensive Gröbner basis of an ideal is a finite set of polynomials on the parameters and the variables, such that it is a Gröbner basis under every value assignment in the parameters. Therefore, a steady state ideal is binomial if its comprehensive Gröbner basis is binomial. This observation reduces testing binomiality of a steady state ideal under specialisation into testing binomiality of a comprehensive Gröbner basis. Computing a comprehensive Gröbner basis results in a partitioning of the ambient space into certain varieties and computations of certain set of polynomials associated to each of those varieties, such that if the parameters are specialised from the variety, the associated polynomial set is a Gröbner basis. Such a partition with its associated polynomial sets is called a Gröbner system. Computing comprehensive Gröbner bases is at least as difficult as computing Gröbner bases. Hence, testing binomiality via comprehensive Gröbner bases is a hard problem.

The concept of comprehensive Gröbner bases has been introduced by Weispfenning in his seminal work [51]. He later introduced canonical comprehensive

Gröbner bases in [52]. A source of introduction to comprehensive Gröbner basis is Becker and Weispfenning's book [1]. Weispfenning also worked on the relation between comprehensive Gröbner bases and regular rings [53]. Later, several authors worked on the topic and introduced more efficient algorithms and polished the theory of comprehensive Gröbner bases. Suzuki-Sati's approach to Gröbner bases is presented in [47]. Montes has worked extensively on comprehensive Gröbner bases, introduced several algorithms and developed the theory [37,11]. In particular, Montes' book, the Gröbner Cover [35] is a great source for computations, among other interesting aspects, that can be used as a guide to the Singular library `grobcov.lib` [13] for computing comprehensive Gröbner bases. Among the most efficient algorithms for computing comprehensive Gröbner bases are the algorithms given by Kapur et al.[34,33]. Dehghani and Hashemi studied Gröbner walk and FGLM for comprehensive Gröbner bases [10,29] and implemented several algorithms for computing comprehensive Gröbner bases and related topics in Maple [29].⁴

To the best of our knowledge, to this date, comprehensive Gröbner bases have not been used in chemical reaction networks theory. Previous studies on binomiality of steady state ideals have considered Gröbner bases, linear algebra on stoichiometric matrices, etc., however, never have considered the change in the polynomials during computations when the values are assigned to the parameters. For instance, it is known that detailed balancing holds under some polynomial conditions on the parameters. However, the fact that specialisation of the rate constants may affect the computations has not been considered. The authors' previous work on toricity [27,44] considers the toricity problem when the parameters have already been assigned real positive values. Other articles of the authors have considered unconditional binomiality, that is, when the rate constants are considered variables [43,42]. The present article is the original work that considers specialisation of the parameters and uses comprehensive Gröbner bases to study the binomiality under specialisations.

The plan of the article is as follows. Section 1 gives an introduction to the necessary concepts of chemical reaction network theory, reviews the literature and presents the idea of the present article. Section 2 explains the preliminaries required on comprehensive Gröbner systems, explains the main concepts and sketches the idea behind computing comprehensive Gröbner bases. Section 3 includes the main computations, where we show our computations on n -phosphorylations and biochemical reactions and present the benchmarks. We furthermore compare our computations using comprehensive Gröbner bases with some earlier work on the binomiality problem that does not take into account the specialisation of the rate constants. In Section 4 we summarise our results and draw some conclusions.

⁴ https://amirhashemi.iut.ac.ir/sites/amirhashemi.iut.ac.ir/files//file_basepage/pggw_0.txt

2 Preliminaries on Comprehensive Gröbner System

We review the required definitions, theorems and an algorithm on comprehensive Gröbner systems, mainly from the original work of Weispfenning [51] and Kapur, et al.'s work [34].

Let \mathbb{K} be a field, $R = \mathbb{K}[U] = \mathbb{K}[u_1, \dots, u_m]$ be the ring of polynomials over \mathbb{K} in the indeterminates u_1, \dots, u_m and let $S = \mathbb{K}[U][X] = \mathbb{K}[u_1, \dots, u_m][x_1, \dots, x_n]$ be the ring of polynomials over $\mathbb{K}[U]$ with the indeterminates x_1, \dots, x_n . Assume that $X \cap U = \emptyset$. We call u_1, \dots, u_m the parameters of the ring S and x_1, \dots, x_n the variables of S . In fact, the coefficients of every polynomial in S are themselves polynomials in parameters. For every $\alpha = (\alpha_1, \dots, \alpha_n) \in \mathbb{N}^n$, by X^α we denote $x_1^{\alpha_1} \dots x_n^{\alpha_n}$ and by U^α we denote $u_1^{\alpha_1} \dots u_m^{\alpha_m}$. In this paper, \mathbb{K} is either \mathbb{R} or \mathbb{C} . By the variety of an ideal I (or a set of polynomials F), we mean the set of solutions of the ideal I (or the set of polynomials F) and we denote it by $V(I)$ (or $V(F)$).

Let $<_1$ and $<_2$ be term orders on $\mathbb{K}[U]$ and $\mathbb{K}[X]$, respectively. We define a block order $<$ produced by the latter on $\mathbb{K}[U][X]$. Firstly, define $u_i < x_j$ for all $1 \leq i \leq m, 1 \leq j \leq n$. Secondly, define $X^{\alpha_1} U^{\beta_1} < X^{\alpha_2} U^{\beta_2}$ if either $X^{\alpha_1} < X^{\alpha_2}$ or $(X^{\alpha_1} = X^{\alpha_2} \wedge U^{\alpha_1} < U^{\alpha_2})$. A polynomial of the form $c_\alpha p(U) X^\alpha$, where $\alpha \in \mathbb{N}^n$, $c_\alpha \in \mathbb{K}$ and $p(U) \in R$, is called a term in $\mathbb{K}[U][X]$. A monomial is a term of the form X^α . Leading monomial, leading term and leading coefficient of the polynomials in $\mathbb{K}[U][X]$ are defined with respect to the block ordering $<$.

A specialisation of S is a ring-homomorphism from the ring of parameters $R = \mathbb{K}[U]$ into some field \mathbb{L} , i.e., $\sigma : R \rightarrow \mathbb{L}$. Obviously \mathbb{K} is embedded in \mathbb{L} . We consider \mathbb{L} to be an algebraically closed field in this paper. Every specialisation is uniquely determined by its restriction to \mathbb{K} and its images on the parameters u_1, \dots, u_m and vice versa. A specialisation $\sigma : R \rightarrow \mathbb{L}$ has a canonical extension to a ring-homomorphism $\bar{\sigma} : S \rightarrow \mathbb{L}[x_1, \dots, x_n]$, i.e., for every $f = \sum_{i \in I} a_i(U) X^{\alpha_i}$, $\bar{\sigma}(f) = \sum_{i \in I} \sigma(a_i(U)) X^{\alpha_i}$, where $a_i(U) \in R$ and X^{α_i} is a monomial in $\mathbb{K}[X]$. Following Weispfenning's notation, we denote $\bar{\sigma}$ by σ as well. Specialisation of a set of polynomials F by σ , denoted by $\sigma(F)$, is defined to be the set of specialisations of the polynomials in F . Accordingly, a specialisation of an ideal I by σ is defined, and is denoted by $\sigma(I)$. Following Kapur, et al. [34], in this paper we only consider specialisations induced by the elements $a \in \mathbb{L}^m$, that is, $\sigma_a : f \rightarrow f(a)$, where $f \in R$.

Below we mention the definition of comprehensive Gröbner system and comprehensive Gröbner basis, which are due to Weispfenning. We follow Kapur et al's notation in [34].

Definition 1 (Comprehensive Gröbner System). *Let I be an ideal in S generated by a finite set $F \subseteq S$ and \mathbb{L} be an algebraically closed field containing \mathbb{K} . Assume that $V_1, W_1, \dots, V_r, W_r$ are varieties in \mathbb{L}^n , and G_1, \dots, G_r are finite sets of polynomials in S . A set of tripiles $\mathcal{G} = \{(V_1, W_1, G_1), \dots, (V_r, W_r, G_r)\}$ is called a comprehensive Gröbner system of I on $V = \bigcup_{i=1}^r V_i \setminus W_i$, if for every $a \in V$ and every specialisation σ_a of S , $\sigma_a(G_i)$ is a Gröbner basis of $\sigma_a(I)$ in $\mathbb{L}[X]$ when a is in $V(V_i) \setminus V(W_i)$, for $i = 1, \dots, r$. If $V = \mathbb{L}^m$, we simply call*

\mathcal{G} a comprehensive Gröbner system of I . Each (V_i, W_i, G_i) is called a branch of \mathcal{G} . A comprehensive Gröbner system \mathcal{G} of I is called faithful, if every element of G_i is in I .

Definition 2 (Comprehensive Gröbner Basis). Let I be an ideal in S and \mathbb{L} be an algebraically closed field containing \mathbb{K} . Assume that V is a subset of \mathbb{L}^m . A finite subset G of I is called a comprehensive Gröbner basis of I on V , if for all specialisations $\sigma_a : R \rightarrow \mathbb{L}$ of S , where $a \in V$, the set $\sigma_a(G)$ is a Gröbner basis of the ideal generated by $\sigma_a(I)$ in $\mathbb{L}[X]$. If $V = \mathbb{L}^m$, we simply call G a comprehensive Gröbner basis of I . A comprehensive Gröbner basis G of I is called faithful, if every element of G is in I .

Having defined comprehensive Gröbner bases, Weispfenning proved the existence of a comprehensive Gröbner basis for every ideal in S [51]. In the latter reference, he gave a non-constructive proof first, and an algorithm later.

Following the first algorithm proposed by Weispfenning, algorithms for computing a comprehensive Gröbner basis essentially construct a faithful comprehensive Gröbner system $\mathcal{G} = \{(V_1, W_1, G_1), \dots, (V_r, W_r, G_r)\}$. Then the union $G = \cup_{i=1}^r G_i$ will be a comprehensive Gröbner basis. Roughly speaking, the varieties V_i and W_i are typically obtained by considering the monomials that are vanished by specialisations, and simultaneously, using a Gröbner basis computation algorithm, a Gröbner basis under the conditions imposed by the specialisations is computed. Below we present a modified version of Kapur, et al.’s algorithm by Dehghani and Hashemi from [29]. “Other cases” in line 16 of the algorithm refers to those cases that the Gröbner basis is 1. Dehghani and Hashemi group all those cases together with the aim of speeding the computations up. In line 13, MDBasis computes a minimal Dickson basis for a given set of polynomials in S . For more details, refer to [29].

3 Testing Binomiality of Chemical Reaction Networks Using Comprehensive Gröbner Systems

In this section we present computations on biochemical networks, using comprehensive Gröbner bases, in order to test binomiality of the corresponding steady state ideals.

In [16,9,39], the authors call an ideal binomial if there exists a basis for the ideal whose polynomials have at most two terms. In particular, as it is discussed in the latter references, one can see that an ideal is binomial if and only if its reduced Gröbner bases with respect to every term order is binomial. Our definition of binomiality is as in [42,43], which is slightly different from [16,9,39]. We call an ideal binomial if there exists a basis for the ideal whose polynomials have exactly two terms. That is, we do not consider monomials in the basis. Similar to the definition of binomiality in [16,9,39], one can easily observe that, for the case of our definition, an ideal is binomial if and only if its reduced Gröbner bases with respect to every term order is binomial. In terms of parametric polynomial rings, i.e., $\mathbb{K}[U][X]$, we discuss the binomiality using

Algorithm 1 PGBMAIN

Input: 1. $N, W \subseteq \mathbb{K}[U]$ finite; 2. $F \subseteq \mathbb{K}[U][X]$ finite

Output: PGB a Gröbner system of F on $V(N) \setminus V(W)$

- 1: $PGB := \emptyset$
- 2: **if** $V(N) \setminus V(W) = \emptyset$ **then**
- 3: **return** \emptyset
- 4: **end if**
- 5: $G := \text{ReducedGroebnerBasis}(F \cup N, <)$
- 6: **if** $1 \in G$ **then**
- 7: **return** $\{(N, W, \{1\})\}$
- 8: **end if**
- 9: $G_r := G \cap \mathbb{K}[U]$
- 10: **if** $V(G_r) \setminus V(W) = \emptyset$ **then**
- 11: **return** PGB
- 12: **else**
- 13: $G_m := \text{MDBasis}(G \setminus G_r)$
 $h = \text{lcm}(h_1, \dots, h_k)$ with $h_i = \text{LC}_{<_1}(g_i)$ for each $g_i \in G_m$
- 14: **if** $V(G_r) \setminus V(W \times \{h\}) \neq \emptyset$ **then**
- 15: $PGB := PGB \cup \{G_r, W \times \{h\}, G_m\}$
- 16: **end if**
- 17: **return** $PGB \cup \bigcup_{h_i \in \{h_1, \dots, h_k\}} \text{PGBMAIN}(G_r \cup \{h_i\}, W \times \{h_1 h_2 \dots h_{i-1}\}, G \setminus G_r) \cup \{(\text{Other Cases}, \{1\})\}$
- 18: **end if**

a comprehensive Gröbner system. That is in particular the case for the steady state ideals of chemical reaction networks.

As computing a comprehensive Gröbner basis is done via computing the branches of a comprehensive Gröbner system, we basically compute the latter and check the binomiality of the Gröbner basis at each branch. Then a comprehensive Gröbner basis of a steady state ideal will be binomial if and only if the Gröbner basis at each branch of a comprehensive system is binomial. One can consider the generic comprehensive Gröbner bases, introduced in [51], however as it is mentioned in the latter reference, computing a generic comprehensive Gröbner basis is not feasible in practice.

In this paper, for our computations on the steady state ideals of the chemical reaction networks, we consider $\mathbb{L} = \overline{\mathbb{K}}$, the algebraic closure of \mathbb{K} . In practice, for the computation purpose, the coefficient field is considered to be \mathbb{Q} , extended by the parameters, i.e., $\mathbb{Q}(k_1, \dots, k_m)$; hence the comprehensive Gröbner system computations are carried out over $\mathbb{Q}(k_1, \dots, k_m)[x_1, \dots, x_n]$.

Our computations are carried out via version 4.2.0 of the computer algebra system Singular [13]⁵, the grobcov package (whose latest version is available at A. Montes' website)⁶. For instructions on the grobcov package we refer the reader to the book [35] and examples by A. Montes. We have done fully automated

⁵ <http://www.singular.uni-kl.de>

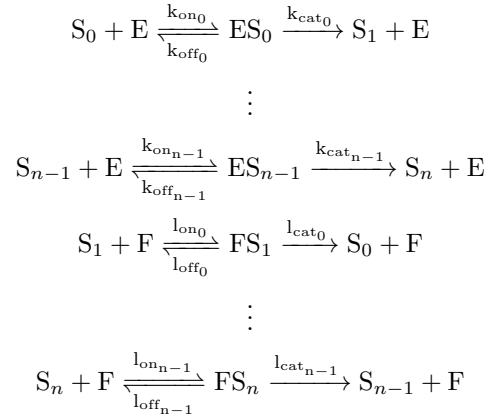
⁶ <https://mat.upc.edu/en/people/antonio.montes>

computations on sets of examples, in particular on biochemical models from the BioModels' repository [7]⁷. Our computations have been done on a 2.48 MHz AMD EPYC 7702 64-Core Processor in a Debian GNU/Linux 10 machine with 211 gB memory.

3.1 n -Site Phosphorylation

Multisite phosphorylation–dephosphorylation cycles or n -site phosphorylations (for $n \in \mathbb{N}$) are studied by Wang and Sontag in [48] in terms of multi-stationarity. Pérez-Milán et al. in [40] have shown that for every $n \in \mathbb{N}$, n -site phosphorylation has a binomial steady state. As mentioned earlier, in the latter reference, the authors did not take into account the specialisations of the constant rates. In this subsection, we first do some reductions on a basis of the steady state ideal of n -phosphorylations and prove its binomiality. This essentially gives us the unconditional binomiality of n -phosphorylation, defined and investigated in [43,42]. Our algebraic manipulations below are simple and avoid the criterion presented by Pérez-Milán et al. in [40].

Using Wang and Sontag's notation in [48] for the variables and parameters, for a fixed positive integer n , the n -site phosphorylation reaction network is the following.



The parameters of the reaction network are $k_{\text{on}_0}, \dots, k_{\text{on}_{n-1}}, k_{\text{off}_0}, \dots, k_{\text{off}_{n-1}}, k_{\text{cat}_0}, \dots, k_{\text{cat}_{n-1}}, l_{\text{on}_0}, \dots, l_{\text{on}_{n-1}}, l_{\text{off}_0}, \dots, l_{\text{off}_{n-1}}, l_{\text{cat}_0}, \dots, l_{\text{cat}_{n-1}}$. Let the variables $s_0, \dots, s_n, c_0, \dots, c_{n-1}, d_1, \dots, d_n, e, f$ represent the concentrations of the species $S_0, \dots, S_n, ES_0, \dots, ES_{n-1}, FS_1, \dots, FS_n, E, F$ respectively. The ODEs describing change of the concentrations of the species for this reaction network are

⁷ <https://www.ebi.ac.uk/biomodels>

the following:

$$\begin{aligned}
\dot{s}_0 &= P_0 = -k_{\text{on}_0} s_0 e + k_{\text{off}_0} c_0 + l_{\text{cat}_0} d_1, \\
\dot{s}_i &= P_i = -k_{\text{on}_i} s_i e + k_{\text{off}_i} c_i + k_{\text{cat}_{i-1}} c_{i-1} - l_{\text{on}_{i-1}} s_i f + l_{\text{off}_{i-1}} d_i + l_{\text{cat}_i} d_{i+1}, \\
&\quad i = 1, \dots, n-1, \\
\dot{c}_j &= Q_j = k_{\text{on}_j} s_j e - (k_{\text{off}_j} + k_{\text{cat}_j}) c_j, \quad j = 0, \dots, n-1, \\
\dot{d}_k &= R_k = l_{\text{on}_{k-1}} s_k f - (l_{\text{off}_{k-1}} + l_{\text{cat}_{k-1}}) d_k, \quad k = 1, \dots, n.
\end{aligned}$$

The ODEs for s_n, e and f are linear combinations of the above ODEs, hence they are redundant and we skip them in this article.

In order to show unconditional binomiality of the steady state ideal of n -phosphorylation, we perform reductions on the the generators of the steady state ideal so that a binomial basis is obtained. First of all, note that polynomials Q_j and R_k are already binomial. Reducing P_0 with respect to Q_0 , we obtain

$$\begin{aligned}
P'_0 &= P_0 + Q_0 \\
&= -k_{\text{on}_0} s_0 e + k_{\text{off}_0} c_0 + l_{\text{cat}_0} d_1 \\
&\quad + k_{\text{on}_0} s_0 e - (k_{\text{off}_0} + k_{\text{cat}_0}) c_0 \\
&= l_{\text{cat}_0} d_1 + k_{\text{cat}_0} c_0,
\end{aligned}$$

which is a binomial.

Now we reduce P_i with respect to P'_0, Q_j and R_k as follows. First we reduce P_i with respect to R_i

$$\begin{aligned}
P_i + R_i &= \\
&\quad -k_{\text{on}_i} s_i e + k_{\text{off}_i} c_i + k_{\text{cat}_{i-1}} c_{i-1} - l_{\text{on}_{i-1}} s_i f + l_{\text{off}_{i-1}} d_i + l_{\text{cat}_i} d_{i+1} \\
&\quad + l_{\text{on}_{i-1}} s_i f - (l_{\text{off}_{i-1}} + l_{\text{cat}_{i-1}}) d_i \\
&= -k_{\text{on}_i} s_i e + k_{\text{off}_i} c_i + k_{\text{cat}_{i-1}} c_{i-1} + l_{\text{cat}_i} d_{i+1} - l_{\text{cat}_{i-1}} d_i.
\end{aligned}$$

Then we reduce the result with respect to Q_i

$$\begin{aligned}
P_i + R_i + Q_i &= \\
&\quad -k_{\text{on}_i} s_i e + k_{\text{off}_i} c_i + k_{\text{cat}_{i-1}} c_{i-1} + l_{\text{cat}_i} d_{i+1} - l_{\text{cat}_{i-1}} d_i \\
&\quad + k_{\text{on}_i} s_i e - (k_{\text{off}_i} + k_{\text{cat}_i}) c_i \\
&= k_{\text{cat}_{i-1}} c_{i-1} + l_{\text{cat}_i} d_{i+1} - l_{\text{cat}_{i-1}} d_i + k_{\text{cat}_i} c_i.
\end{aligned}$$

For $i = 1$, the above can be reduced with respect to P'_0

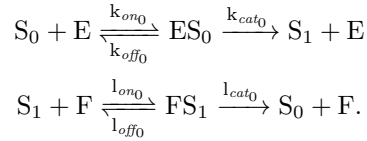
$$\begin{aligned}
P'_1 &= P_1 + R_1 + Q_1 - P'_0 = k_{\text{cat}_0} c_0 + l_{\text{cat}_1} d_1 - l_{\text{cat}_0} d_1 + k_{\text{cat}_1} c_1 \\
&\quad - (l_{\text{cat}_0} d_1 + k_{\text{cat}_0} c_0) \\
&= l_{\text{cat}_1} d_1 + k_{\text{cat}_1} c_1,
\end{aligned}$$

which is a binomial.

Similarly, for $i = 2, \dots, n$, P_i can be reduced to a binomial with respect to R_i , Q_I and P'_{i-1} . Therefore, a binomial basis can be obtained this way for the steady state ideal.

As the algebraic manipulations above do not consider into account the specialisations of the parameters, we computed comprehensive Gröbner system of the steady state ideals for the cases $n = 1, 2$ to test the binomiality under specialisations. 1-site phosphorylation and 2-site phosphorylations have been studied in [40] using the criteria presented in that article as well.

Example 1 (1-site phosphorylation, [40], Example 2.1)



Let the variables representing the change of the concentrations of the species $S_0, S_1, \text{ES}_0, \text{FS}_1, E, F$ be s_0, s_1, c_0, d_1, e, f respectively, and let the parameters be $k_{\text{on}_0}, k_{\text{off}_0}, k_{\text{cat}_0}, l_{\text{on}_0}, l_{\text{off}_0}, l_{\text{cat}_0}$.

The steady state ideal for 1-site phosphorylation reaction is generated by

$$\begin{aligned} \dot{s}_0 &= -k_{\text{on}_0}s_0e + k_{\text{off}_0}c_0 + l_{\text{cat}_0}d_1, \\ \dot{s}_1 &= -k_{\text{on}_1}s_1e + k_{\text{off}_1}c_1 + k_{\text{cat}_0}c_0 - l_{\text{on}_0}s_1f + l_{\text{off}_0}d_1, \\ \dot{c}_0 &= k_{\text{on}_0}s_0e - (k_{\text{off}_0} + k_{\text{cat}_0})c_0, \\ \dot{d}_1 &= l_{\text{on}_0}s_1f - (l_{\text{off}_0} + l_{\text{cat}_0})d_1. \end{aligned}$$

We skip the ODEs for e and f as they are linear combination of the other ODEs. Renaming the variables as

$$s_0 = x_1, s_1 = x_2, c_0 = x_3, d_1 = x_4, e = x_5, f = x_6,$$

we computed the comprehensive Gröbner system for the steady state ideal using Singular. It contains 25 branches, out of which 6 are binomial. We recall that in this article, a binomial ideal is an ideal that is generated by a set of binomials (not including monomials). For the last branch, V_{25} and W_{25} are the zero sets of the following sets of polynomials in $\mathbb{Q}[k_{\text{on}_0}, k_{\text{off}_0}, k_{\text{cat}_0}, l_{\text{on}_0}, l_{\text{off}_0}, l_{\text{cat}_0}][x_1, \dots, x_6]$ respectively:

$$\begin{aligned} &\{l_{\text{cat}_0}, k_{\text{on}_0}\}, \\ &\{k_{\text{off}_0}k_{\text{cat}_0}l_{\text{on}_0} + k_{\text{cat}_0}^2l_{\text{on}_0}\}. \end{aligned}$$

The corresponding Gröbner basis is

$$\begin{aligned} &\{f_1 = k_{\text{cat}_0}x_3, \\ &\quad f_2 = l_{\text{on}_0}x_2x_6 - l_{\text{off}_0}x_4\}, \end{aligned}$$

which obviously is not binomial.

An example of a branch with binomial Gröbner basis is branch 24, for which V_{24} and W_{24} are the zero sets of the following sets, respectively:

$$\begin{aligned} &\{k_{\text{off}_0} + k_{\text{cat}_0}, k_{\text{on}_0}\}, \\ &\{l_{\text{on}_0} k_{\text{cat}_0}\}. \end{aligned}$$

The corresponding Gröbner basis is

$$\begin{aligned} f_1 &= k_{\text{cat}_0} x_3 + l_{\text{cat}_0} x_4, \\ f_2 &= l_{\text{on}_0} x_2 x_6 + (-l_{\text{off}_0} - l_{\text{cat}_0}) x_4. \end{aligned}$$

Example 2 (2-site phosphorylation, [40], Example 3.13) *The steady state ideal for the 2-site phosphorylation reaction is generated by*

$$\begin{aligned} \dot{s}_0 &= P_0 = -k_{\text{on}_0} s_0 e + k_{\text{off}_0} c_0 + l_{\text{cat}_0} d_1, \\ \dot{s}_1 &= P_1 = -k_{\text{on}_1} s_1 e + k_{\text{off}_1} c_1 + k_{\text{cat}_0} c_0 - l_{\text{on}_0} s_1 f + l_{\text{off}_0} d_1 + l_{\text{cat}_1} d_2, \\ \dot{c}_0 &= Q_0 = k_{\text{on}_0} s_0 e - (k_{\text{off}_0} + k_{\text{cat}_0}) c_0, \\ \dot{c}_1 &= Q_1 = k_{\text{on}_1} s_1 e - (k_{\text{off}_1} + k_{\text{cat}_1}) c_1, \\ \dot{d}_1 &= R_1 = l_{\text{on}_0} s_1 f - (l_{\text{off}_0} + l_{\text{cat}_0}) d_1, \\ \dot{d}_2 &= R_2 = l_{\text{on}_1} s_2 f - (l_{\text{off}_1} + l_{\text{cat}_1}) d_2, \end{aligned}$$

where the variables are

$$s_0, s_1, s_2, c_0, c_1, d_1, d_2, e, f$$

and the parameters are

$$k_{\text{on}_0}, k_{\text{on}_1}, k_{\text{off}_0}, k_{\text{off}_1}, k_{\text{cat}_0}, k_{\text{cat}_1}, l_{\text{on}_0}, l_{\text{on}_1}, l_{\text{off}_0}, l_{\text{off}_1}, l_{\text{cat}_0}, l_{\text{cat}_1}.$$

We have computed a comprehensive Gröbner system for this system using Singular. It has 1187 branches, out of which 36 are binomial. The last branch of the comprehensive Gröbner system is as follows. V_{1187} is the zero set of $l_{\text{off}_1} + l_{\text{cat}_1}$ and W_{1187} is the zero set of the following polynomial:

$$\begin{aligned} &k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_0} k_{\text{off}_1} k_{\text{cat}_0} k_{\text{cat}_1} l_{\text{on}_0} l_{\text{on}_1} l_{\text{off}_0} l_{\text{cat}_0} l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_0} k_{\text{off}_1} k_{\text{cat}_0} k_{\text{cat}_1} l_{\text{on}_0} l_{\text{on}_1} l_{\text{cat}_0}^2 l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_0} k_{\text{cat}_0} k_{\text{cat}_1}^2 l_{\text{on}_0} l_{\text{on}_1} l_{\text{off}_0} l_{\text{cat}_0} l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_0} k_{\text{cat}_0} k_{\text{cat}_1}^2 l_{\text{on}_0} l_{\text{on}_1} l_{\text{cat}_0}^2 l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_1} k_{\text{cat}_0}^2 k_{\text{cat}_1} l_{\text{on}_0} l_{\text{on}_1} l_{\text{off}_0} l_{\text{cat}_0} l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{off}_1} k_{\text{cat}_0}^2 k_{\text{cat}_1} l_{\text{on}_0} l_{\text{on}_1} l_{\text{cat}_0}^2 l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_0}^2 k_{\text{cat}_1}^2 l_{\text{on}_0} l_{\text{on}_1} l_{\text{off}_0} l_{\text{cat}_0} l_{\text{cat}_1} \\ &+ k_{\text{on}_0} k_{\text{on}_1} k_{\text{cat}_0}^2 k_{\text{cat}_1}^2 l_{\text{on}_0} l_{\text{on}_1} l_{\text{cat}_0}^2 l_{\text{cat}_1}. \end{aligned}$$

Renaming the variables as

$$s_0 = x_1, s_1 = x_2, s_2 = x_3, c_0 = x_4, c_1 = x_5, d_1 = x_6, d_2 = x_7, e = x_8, f = x_9,$$

the Gröbner basis for every specialisation of the parameters in $V_{1187} \setminus W_{1187}$ is the following.

$$\begin{aligned}
 f_1 &= k_{cat_1} x_5 - l_{cat_1} x_7, \\
 f_2 &= k_{cat_0} x_4 - l_{cat_0} x_6, \\
 f_3 &= l_{on_1} x_3 x_9, \\
 f_4 &= l_{on_0} x_2 x_9 + (-l_{off_0} - l_{cat_0}) x_6, \\
 f_5 &= (k_{on_1} l_{off_0} + k_{on_1} l_{cat_0}) x_6 x_8 + (-k_{off_1} l_{on_0}) x_5 x_9 + (-l_{on_0} l_{cat_1}) x_7 x_9, \\
 f_6 &= (k_{on_1}) x_2 x_8 + (-k_{off_1}) x_5 + (-l_{cat_1}) x_7, \\
 f_7 &= (k_{on_0}) x_1 x_8 + (-k_{off_0}) x_4 + (-l_{cat_0}) x_6, \\
 f_8 &= (l_{on_1} l_{off_0} + l_{on_1} l_{cat_0}) x_3 x_6, \\
 f_9 &= (k_{on_1} k_{off_0} k_{cat_1} l_{cat_0} + k_{on_1} k_{cat_0} k_{cat_1} l_{cat_0}) x_2 x_6 \\
 &\quad + (-k_{on_0} k_{off_1} k_{cat_0} l_{cat_1} - k_{on_0} k_{cat_0} k_{cat_1} l_{cat_1}) x_1 x_7, \\
 f_{10} &= (k_{on_0} k_{off_1} l_{on_0} l_{cat_1} + k_{on_0} k_{cat_1} l_{on_0} l_{cat_1}) x_1 x_7 x_9 \\
 &\quad + (-k_{on_1} k_{off_0} k_{cat_1} l_{off_0} - k_{on_1} k_{off_0} k_{cat_1} l_{cat_0}) x_4 x_6 \\
 &\quad + (-k_{on_1} k_{cat_1} l_{off_0} l_{cat_0} - k_{on_1} k_{cat_1} l_{cat_0}^2) x_6^2, \\
 f_{11} &= (k_{on_0} k_{off_1} k_{cat_0} l_{on_1} l_{off_0} l_{cat_1} + k_{on_0} k_{off_1} k_{cat_0} l_{on_1} l_{cat_0} l_{cat_1} \\
 &\quad + k_{on_0} k_{cat_0} k_{cat_1} l_{on_1} l_{off_0} l_{cat_1} + k_{on_0} k_{cat_0} k_{cat_1} l_{on_1} l_{cat_0} l_{cat_1}) x_1 x_3 x_7.
 \end{aligned}$$

One can observe that the above branch of the comprehensive Gröbner system is not binomial.

We carried on the computations for comprehensive Gröbner system of the steady state ideal of n -phosphorylation for $n = 2, 3, 4, 5$ in Singular with the time limit of six hours. The results of the computations are summarised in Table 1. In this table, DNF refers to did not finish.

Table 1: Comprehensive Gröbner System of n -Phosphorylations

	#branches	#binomial branches	% of binomial branches	time(s)
2-phosph.	1187	36	3.03	24
3-phosph.	57857	216	0.37	2231
4-phosph.	-	-	-	DNF
5-phosph.	-	-	-	DNF

As the number of variables and parameters grow drastically when n increases, comprehensive Gröbner system computations did not finish in a reasonable time period for $n \geq 4$.

We also computed a comprehensive Gröbner system of 2-phosphorylation in Maple, using Dehghani and Hashemi's PWWG package⁸, which uses a modification of Kapur et al.'s algorithm so that the branches with Gröbner basis $\{1\}$

⁸ https://amirhashemi.iut.ac.ir/sites/amirhashemi.iut.ac.ir/files//file_basepage/pggw_0.txt

are ignored [29]. According to the authors' experiments in [29], this modification results in speed-up of the computations. However, even for 2-phosphorylation the computations did not finish in six hours in Maple.

As we see from the computations in this subsection, there are several branches of the n -phosphorylations that are not binomial. This means that for certain values of the rate constants, n -phosphorylation is not binomial, while the computations without taking into account the specialisations of the rate constants leads to the binomiality.

3.2 BioModels

Our main benchmark for computing comprehensive Gröbner system of steady state ideals, are the biochemical models from the BioModels repository [7], which is typically used for such computations. As a first example, we present biomodel 629 and the corresponding computations in the following example.

Example 3 (BIOMD000000629, [7]) *The corresponding ODEs for biomodel 629 are the following;*

$$\begin{aligned} \dot{x}_1 &= -k_2x_1x_3 + k_3x_2, \\ \dot{x}_2 &= k_2x_1x_3 - k_3x_2 - k_4x_2x_4 + k_5x_5, \\ \dot{x}_3 &= -k_2x_1x_3 + k_3x_2, \\ \dot{x}_4 &= -k_4x_2x_4 + k_5x_5, \\ \dot{x}_5 &= k_4x_2x_4 - k_5x_5, \end{aligned}$$

where k_1, \dots, k_5 are the parameters and x_1, \dots, x_5 are the variables. Comprehensive Gröbner system computation over the ring $\mathbb{Q}[k_1, \dots, k_5][x_1, \dots, x_5]$ in Singular results in 10 branches with the following conditions and Gröbner bases.

Table 2: Comprehensive Gröbner System of BIOMD000000629

branch	V	W	GB
1	0	k_2k_4	$k_4x_2x_4 - k_5x_5, k_2x_1x_3 - k_3x_2$
2	k_4	k_2k_5	$k_5x_5, k_2x_1x_3 - k_3x_2$
3	k_5, k_2	k_2	$k_2x_1x_3 - k_3x_2$
4	k_5, k_4, k_2	k_3	k_3x_2
5	k_5, k_4, k_3, k_2	1	0
6	k_4, k_2	k_3k_5	k_5x_5, k_3x_2
7	k_4, k_3, k_2	k_5	k_5x_5
8	k_2	k_5, k_4, k_3	$k_3k_5x_5, k_3x_2$
9	k_3, k_2	k_4	$k_4x_2x_4 - k_5x_5$
10	k_5, k_2	k_3k_4	k_3x_2

There are three branches with binomial Gröbner basis for biomodel 629. All the branches have either monomial or binomial Gröbner basis.

In Table 3, we present the results of our computations for some biomodels from the Biomodels repository [7]. As computing comprehensive Gröbner system of systems with large number of variables is very expensive, we have considered those biomodels that have relatively small number of species (correspondingly, relatively small number of variables), so that the computations took less than ten minutes for those biomodels. In Table 3, one can find the number of branches of the corresponding comprehensive Gröbner systems, the number of branches that are binomial, and their percentage. Except for biomodels 271 and 519 that have no binomial branch, all other biomodels have at least one binomial branch. For two biomodels (283 and 486), at least half of their branches are binomial.

The largest biomodel we have considered is the model 26. We note that this model is a MAPK reaction network. It has been studied in [17], where the authors associated a graph to the CRN and used a trick based on vertex cover in order to reduce the number of the polynomials in the steady state ideal into 2 polynomials.

Table 3: Branches of Comprehensive Gröbner Systems of Biomodels

model	#branches	#binomial branches	% of binomial branches
26	46870	164	0.35
40	35	6	17.00
92	10	4	40.00
101	81	11	13.40
104	4	1	25.00
156	25	5	20.00
159	36	6	16.66
178	24	2	8.33
194	19	5	26.31
233	18	5	27.78
267	12	2	16.67
271	92	0	0.00
272	44	7	15.91
282	18	4	22.22
283	2	1	50.00
289	351	43	12.25
321	26	5	19.23
363	15	2	13.33
459	40	9	22.50
486	3	2	66.67
519	128	0	0.00
546	15	1	6.67
629	10	4	40.00

4 Conclusion

We address the problem of binomiality of the steady state ideal of a chemical reaction network. The binomiality problem has been widely considered in the literature of mathematics and chemical reaction network theory and is still an active research area. Finding binomiality and toricity is a hard problem from both a theoretical and a practical point of view. The computational methods typically rely on Gröbner bases..

The authors have recently investigated binomiality and toricity in several papers. We have given efficient algorithms for testing toricity in [27]. We also have considered the binomiality from a first-order logic point of view and gave efficient computational results and studied biomodels systematically via quantifier elimination [44,27]. Other than those, we have considered the concept of unconditional binomiality, which considers rate constants as variables, and gave polynomial time linear algebra and graph theoretical approaches for detecting binomiality [42,43].

The existing work on binomiality of steady state ideals do not take into account the effect of assigning values to the rate constants during the computations. In the present work, we consider the problem of binomiality when the parameters can be specialised. Our approach to this parametric binomiality problem is naturally based on comprehensive Gröbner bases. We make systematic computations on n -phosphorylations and biomodels and detect the branches of the Gröbner systems that are binomial. Our computations via comprehensive Gröbner systems show that in several cases, the comprehensive Gröbner bases for steady state ideals are not binomial, while using other methods, e.g., considering rate constants as variables or doing computations without considering the effect of specialisation, one may consider those steady state ideal as binomial ideals.

As in this paper the concept of comprehensive Gröbner bases is used for the first time on chemical reaction network theory, we propose using this approach for studying further properties of chemical reaction networks.

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