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# Parametric Toricity of Steady State Varieties of Reaction Networks

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## Abstract

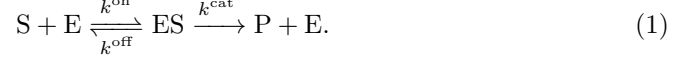
We study real steady state varieties of the dynamics of chemical reaction networks. The dynamics are derived using mass action kinetics with parametric reaction rates. The models studied are not inherently parametric in nature. Rather, our interest in parameters is motivated by parameter uncertainty, as reaction rates are typically either measured with limited precision or estimated. We aim at detecting toricity and shifted toricity, using a framework that has been recently introduced and studied for the non-parametric case over both the real and the complex numbers. While toricity requires that the variety specifies a subgroup of the direct power of the multiplicative group of the underlying field, shifted toricity requires only a coset. In the non-parametric case these requirements establish real decision problems. In the presence of parameters we must go further and derive necessary and sufficient conditions in the parameters for toricity or shifted toricity to hold. Technically, we use real quantifier elimination methods. Our computations on biological networks here once more confirm shifted toricity as a relevant concept, while toricity holds only for degenerate parameter choices.

## 1 Introduction

We study the kinetics of reaction networks in the sense of *Chemical Reaction Network Theory* [22]. This covers also biological networks that are not reaction networks in a strict sense, e.g., epidemic models and signaling networks. The kinetics of reaction networks is given by ordinary differential equations (ODE)  $\dot{\mathbf{x}} = \mathbf{f}$  with polynomial vector

field  $\mathbf{f} \in \mathbb{Z}[\mathbf{k}, \mathbf{x}]$ , where  $\mathbf{k}$  are positive scalar reaction rates and  $\mathbf{x}$  are concentrations of species over time. Such ODE are typically derived using mass action kinetics [22, Sect. 2.1.2]. For fixed choices  $\mathbf{k}^* \in \mathbb{R}_{>0}^s$ , the real variety  $V_{\mathbf{k}^*}(\mathbf{f}) = \{ \mathbf{x}^* \in \mathbb{R}^n \mid \mathbf{f}(\mathbf{k}^*, \mathbf{x}^*) = 0 \}$  describes the set of steady states of the system.

One famous example is the Michaelis–Menten network [39], which describes an enzymatic reaction as follows:



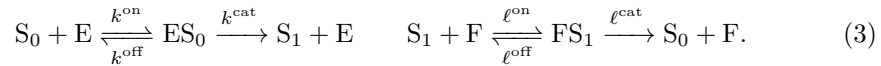
Here one has reaction rates  $\mathbf{k} = (k^{\text{on}}, k^{\text{off}}, k^{\text{cat}})$  and species concentrations  $\mathbf{x} = (x_1, \dots, x_4)$  for the substrate S, the enzyme E, the enzyme-substrate complex ES, and the product P, respectively. The vector field of the ODE is given by  $\mathbf{f} = (f_1, \dots, f_4)$  as follows, where  $f_2 = -f_3$ :

$$\begin{aligned} f_1 &= -k^{\text{on}}x_1x_2 + k^{\text{off}}x_3 \\ f_2 &= -k^{\text{on}}x_1x_2 + (k^{\text{off}} + k^{\text{cat}})x_3 \\ f_3 &= k^{\text{on}}x_1x_2 - (k^{\text{off}} + k^{\text{cat}})x_3 \\ f_4 &= k^{\text{cat}}x_3. \end{aligned} \quad (2)$$

For an intuition about mass action kinetics consider the reaction  $\text{S} + \text{E} \xrightarrow{k^{\text{on}}} \text{ES}$  in (1). The summand  $-k^{\text{on}}x_1x_2$  in the differential equation  $\dot{x}_1 = f_1 = -k^{\text{on}}x_1x_2 + k^{\text{off}}x_3$  describes a decrease of the concentration  $x_1$  of S that is proportional to the product  $x_1x_2$  of concentrations of S and E with a positive proportionality factor  $k^{\text{on}}$ . The product  $x_1x_2$  of concentrations models the probability that one molecule of S and one molecule of E encounter each other in a perfectly stirred reactor.

For steady state of the Michaelis–Menten kinetics,  $f_4$  in (2) imposes  $x_3 = 0$ . Biologically speaking, steady state requires that the concentration of the enzyme-substrate complex become zero. Next,  $f_1, \dots, f_3$  impose that either  $x_1 = 0$  and  $x_2$  can be freely chosen, or vice versa. That is, the concentration of either substrate or enzyme must become zero. The concentration  $x_4$  of the product can always be freely chosen. It turns out that  $V_{\mathbf{k}}(\mathbf{f}) \neq \emptyset$ , and  $V_{\mathbf{k}}(\mathbf{f})$  does not depend on  $\mathbf{k}$  at all.

Let us look at 1-site phosphorylation [53, 43], which gives a slightly more complex network as follows:



Here we have  $\mathbf{k} = (k^{\text{on}}, \dots, \ell^{\text{cat}})$ ,  $\mathbf{x} = (x_1, \dots, x_6)$  for concentrations of species  $\text{S}_0, \text{S}_1, \text{ES}_0, \text{FS}_1, \text{E}, \text{F}$ , respectively. The vector field of the ODE is given by  $\mathbf{f} = (f_1, \dots, f_6)$  with

$$\begin{aligned} f_1 &= -k^{\text{on}}x_1x_5 + k^{\text{off}}x_3 + \ell^{\text{cat}}x_4 \\ f_3 &= k^{\text{on}}x_1x_5 - (k^{\text{cat}} + k^{\text{off}})x_3 \end{aligned}$$

$$f_4 = \ell^{\text{on}} x_2 x_6 - (\ell^{\text{cat}} + \ell^{\text{off}}) x_4. \quad (4)$$

Similarly to  $f_2$  in (2),  $f_2, f_5, f_6$  here are linear combinations of  $\mathbf{f}' = (f_1, f_3, f_4)$  and thus  $V_{\mathbf{k}}(\mathbf{f}) = V_{\mathbf{k}}(\mathbf{f}')$ . In contrast to the Michaelis–Menten kinetics we now find steady states where all species concentrations are non-zero. One such steady state is

$$\mathbf{x}^* = \left( 1, 1, 1, \frac{k^{\text{cat}}}{\ell^{\text{cat}}}, \frac{k^{\text{cat}} + k^{\text{off}}}{k^{\text{on}}}, \frac{k^{\text{cat}} \ell^{\text{cat}} + k^{\text{cat}} \ell^{\text{off}}}{\ell^{\text{cat}} \ell^{\text{on}}} \right)^T. \quad (5)$$

Notice that this particular steady state exists uniformly in  $\mathbf{k}$  and that denominators cannot vanish, due to our requirement that  $\mathbf{k} > 0$ .

For the non-parametric case, i.e., for fixed  $\mathbf{k}^* \in \mathbb{R}_{>0}^s$ , comprehensive computational experiments on reaction networks in [28] have identified *shifted toricity* as a structural property that occurs frequently but not generally. Assuming that  $V_{\mathbf{k}^*}(\mathbf{f})$  is irreducible, the set  $V_{\mathbf{k}^*}(\mathbf{f})^* = V_{\mathbf{k}^*}(\mathbf{f}) \cap \mathbb{R}^{*n}$  is *shifted toric* if it forms a multiplicative coset of  $\mathbb{R}^{*n}$  [29]. Here  $\mathbb{R}^*$  is the multiplicative group of the field of real numbers, and  $\mathbb{R}^{*n}$  is its direct power. For the sake of this clear and simple algebraic setting, we do not take into consideration the positivity of  $\mathbf{x}$  here. Instead, shifted tori can be algorithmically intersected with the positive first orthant later on.

The notion of shifted toricity historically originates from the consideration of additive groups. In our setting, the “shift” is geometrically not a translation but a scaling of the torus. For the natural sciences, structural properties like shifted toricity provide *qualitative* insights into nature, as opposed to quantitative information like numeric values of coordinates of some fixed points. For symbolic computation, our hope is that structural properties can be exploited for the development of more efficient algorithms.

Our program for this article is the generalization of the concept of shifted toricity to the parametric case, along with the development of suitable computational methods, accompanied by computational experiments. For instance, for our 1-site phosphorylation we will automatically derive in Sect.4.4 that

- (i)  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a coset for all admissible choices of  $\mathbf{k}$ , and
- (ii)  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a group if and only if  $k^{\text{on}} - k^{\text{off}} = \ell^{\text{on}} - \ell^{\text{off}} = k^{\text{cat}} = \ell^{\text{cat}}$ .

Chemical reaction network theory [22] generally studies specific structural properties of networks like (1) and (3), such as our shifted toricity. There is a consensus in chemical reaction network theory that meaningful structural properties of networks would not refer to specific values of the rate constants  $\mathbf{k}$ , as Feinberg explicitly states in his excellent textbook: *The network itself will be our object of study, not the network endowed with a particular set of rate constants* [22, p.19]. In reality, exact rate constants are hardly ever known. They are either measured in experiments with a certain finite precision, or they are estimated, often only in terms of orders of magnitude. Furthermore, even if we had perfect positive real values for the rate constants  $\mathbf{k}$ , recall that according to mass action kinetics their co-factors are products of certain species concentrations  $\mathbf{x}$ , which only approximate probabilities as they would hold under hypothetical ideal conditions. Hence, we are looking primarily for results like (i) above.

Result (ii) might seem appealing from a mathematical viewpoint, but it has hardly any relevance in nature. Bluntly speaking, a metabolism whose functioning depends on any of the equations in (ii) could not be evolutionarily successful.

What is the motivation for looking at admissible parameter values at all? Why not just derive yes/no decisions under suitable existential or universal quantification of the parameters? First, just as the equations in (ii) hardly ever hold in reality, the same arguments support the hypothesis that derived inequalities, in the sense of logically negated equations, in  $\mathbf{k}$  would hardly ever fail and may thus be acceptable. Second, we are working in real algebra here. Even if there are no order inequalities in the input, they will in general be introduced by the computation. For instance, when asking whether there exists  $x_1 \in \mathbb{R}$  such that  $x_1^2 = k_1 - 10^6 k_2$ , an equivalent condition is given by  $k_1 \geq 10^6 k_2$ . Such a condition that one reaction rate be larger than another by several orders of magnitude is meaningful and might provide useful insights into a model. It should be clear at this point that our parametric considerations are not aimed at uniform treatment of families of similar problems. Rather, we are concerned with a formally clean treatment of parameter uncertainty.

Let us summarize the main characteristics of our approach taken here:

1. Our domain of computation are the real numbers in contrast to the complex numbers. This is the natural choice for reaction networks. It allows us to consequently use the information  $\mathbf{k} > 0$  throughout the computation. There is a perspective to discover further polynomial ordering inequalities in  $\mathbf{k}$  with the derivation of equivalent conditions for shifted toricity, even though the input is purely equational.
2. We take a logic approach, using polynomial constraints, arbitrary Boolean combinations of these constraints, and first-order quantification. In this way, the logical connection between the occurring constraints is shifted from metamathematical reasoning to object mathematics. This ensures that human intuition is not mixed up with automatically derived results. The long-term goal is to develop robust fully automatic methods and to make corresponding implementations in software accessible to natural scientists. Technically, we employ real quantifier elimination methods, normal form computations, and various simplification techniques.
3. Our approach aims at the geometric shape of the real variety in contrast to the syntactic shape of generators of the polynomial ideal. On the one hand, there is a strong relation between toricity of the variety and binomiality of the ideal [18], and Gröbner bases are mature symbolic computation tool in this regard. The relation between toricity and binomiality has even been generalized to shifted toricity [29, 28]. On the other hand, real quantifier elimination methods are an equally mature tool, and they allow to operate directly on the real steady state variety, which is the object of interest from the point of view of natural sciences. Particularly with parameters, order inequalities enter the stage. They should not be ignored, and their derivation from the ideal would not be straightforward.

Our definitions of toricity and shifted toricity are inspired by Grigoriev and Milman’s work on *binomial varieties* [29]. In joint work with Grigoriev and others, we have systematically applied them to both complex and real steady state varieties of reaction networks [28]. We have furthermore studied the connection between complex and real shifted toricity [45]. Toric dynamical systems have been studied by Feinberg [20] and by Horn and Jackson [32]. Craciun et al. [12] showed that toric dynamical systems correspond to *complex balancing* [22]. There are further definitions in the literature, where the use of the term “toric” is well motivated. Gatermann et al. considered *deformed toricity* for steady state ideals [23]. The exact relation between the principle of complex balancing and various definitions of toricity has obtained considerable attention in the last years [43, 24, 40]. Complex balancing itself generalizes *detailed balancing*, which has widely been used in the context of chemical reaction networks [21, 22, 32]. Gorban et al. [26, 25] related reversibility of chemical reactions in detailed balance to binomiality of the corresponding varieties. Historically, the principle of detailed balancing has attracted considerable attention in the sciences. It was used by Boltzmann in 1872 in order to prove his H-theorem [2], by Einstein in 1916 for his quantum theory of emission and absorption of radiation [17], and by Wegscheider [55] and Onsager [41] in the context of *chemical kinetics*, which led to Onsager’s Nobel prize in Chemistry in 1968. Pérez-Millán et al. [43] consider steady state ideals with binomial generators. They present a sufficient linear algebra condition on the *stoichiometry matrix* of a reaction network in order to test whether the steady state ideal has binomial generators. Conradi and Kahle proposed a corresponding heuristic algorithm. They furthermore showed that the sufficient condition is even equivalent when the ideal is homogenous [11, 34, 33]. Based on the above-mentioned linear algebra condition, MESSI systems have been introduced in [42]. Another linear algebra approach to binomiality has been studied in [44]. Recently, binomiality of steady state ideals was used to infer network structure of chemical reaction networks out of measurement data [54].

Bradford et al. [5, 6] and England et al. [19] have worked on multistationarity of reaction networks with parametric rate constants. Pérez-Millán et al., in their above-mentioned work [43], have also discussed the parametric case, remarkably, already in 2012. We have taken various of our examples in the present article from [43], which allows the reader to directly compare our results obtained here over the real numbers with the existing ones over the complex numbers.

In Sect. 2, we make precise our notions of toricity and shifted toricity. We choose a strictly formal approach leading to characterizing first-order logic formulas over the reals. This prepares the application of real quantifier elimination methods. In Sect. 3, we summarize basic concepts from real quantifier elimination theory and related simplification techniques to the extent necessary to understand our computational approach. In Sect. 4, we present systematic computations on biological networks taken from the literature and from established biological databases for such models [8]. In Sect. 5, we summarize our findings and draw conclusions.

## 2 Tori Are Groups, and Shifted Tori Are Cosets

We start with some notational conventions. For a vector  $\mathbf{v} = (v_1, \dots, v_n)$  equations  $\mathbf{v} = 0$  have to be read as  $v_1 = 0 \wedge \dots \wedge v_n = 0$ , which is equivalent to  $\mathbf{v} = (0, \dots, 0)$ . Inequalities  $\mathbf{v} \neq 0$  have to be read as  $v_1 \neq 0 \wedge \dots \wedge v_n \neq 0$ , which is *not* equivalent to  $\mathbf{v} \neq (0, \dots, 0)$ . Similarly, inequalities  $\mathbf{v} > 0$  serve as shorthand notations for  $v_1 > 0 \wedge \dots \wedge v_n > 0$ . Other ordering relations will not occur with vectors. All arithmetic on vectors is component-wise. Logic formulas as above are mathematical objects that can contain equations. For better readability we use “ $\doteq$ ” to express equality between formulas.

Consider polynomials  $\mathbf{f} \in \mathbb{Z}[\mathbf{k}, \mathbf{x}]^m$  with parameters  $\mathbf{k} = (k_1, \dots, k_s)$  and variables  $\mathbf{x} = (x_1, \dots, x_n)$ . For fixed choices  $\mathbf{k}^* \in \mathbb{R}_{>0}^s$  of  $\mathbf{k}$ , the corresponding real variety of  $\mathbf{f}$  is given by

$$V_{\mathbf{k}^*}(\mathbf{f}) = \{ \mathbf{x}^* \in \mathbb{R}^n \mid \mathbf{f}(\mathbf{k}^*, \mathbf{x}^*) = 0 \}. \quad (6)$$

We consider the multiplicative group  $\mathbb{R}^* = \mathbb{R} \setminus \{0\}$ , note that the direct product  $\mathbb{R}^{*n}$  establishes again a group, and define

$$V_{\mathbf{k}^*}(\mathbf{f})^* = V_{\mathbf{k}^*}(\mathbf{f}) \cap \mathbb{R}^{*n} \subseteq \mathbb{R}^{*n}. \quad (7)$$

This set  $V_{\mathbf{k}^*}(\mathbf{f})^*$  is a *torus* if it forms an irreducible subgroup of  $\mathbb{R}^{*n}$ . For this purpose, we allow ourselves to call  $V_{\mathbf{k}^*}(\mathbf{f})^*$  irreducible if  $V_{\mathbf{k}^*}(\mathbf{f})$  is irreducible, equivalently, if  $\langle \mathbf{f}(\mathbf{k}^*, \mathbf{x}) \rangle$  is a prime ideal over  $\mathbb{R}$ . More generally,  $V_{\mathbf{k}^*}(\mathbf{f})^*$  is a *shifted torus* if it forms an irreducible coset of  $\mathbb{R}^{*n}$  [29, 28].

In this article, we focus on the discovery of coset and group structures. This is only a very mild limitation, as a closer look at the geometric relevance of the irreducibility requirement shows: If we discover a coset but irreducibility does not hold, then we are, from a strictly geometrical point of view, faced with finitely many shifted tori instead of a single one. If we disprove the coset property and irreducibility does not hold, then some but not all of the irreducible components might be shifted tori, and they could be discovered via decomposition of the variety. The same holds for groups vs. tori.

It should be noted that the primality of  $\langle \mathbf{f}(\mathbf{k}^*, \mathbf{x}) \rangle$  over  $\mathbb{R}$  in contrast to  $\mathbb{Q}$  is a computationally delicate problem already in the non-parametric case. Starting with integer coefficients, prime decomposition would require the construction of suitable real extension fields during computation. Our parametric setting would require in addition the introduction of suitable finite case distinctions on the vanishing of coefficient polynomials in  $\mathbf{k}$ .

The definition typically used for a set  $C \subseteq \mathbb{R}^{*n}$  to form a coset of  $\mathbb{R}^{*n}$  goes as follows: There exists  $\mathbf{g} \in \mathbb{R}^{*n}$  such that  $\mathbf{g}^{-1}C$  forms a subgroup of  $\mathbb{R}^{*n}$ . We are going to use a slightly different but equivalent characterization:  $\mathbf{g}^{-1}C$  forms a subgroup of  $\mathbb{R}^{*n}$  for all  $\mathbf{g} \in C$ . A proof for the equivalence can be found in [28, Proposition 21]. We now present four first-order logic formulas  $\varphi_1, \dots, \varphi_4$ . They state, uniformly in  $\mathbf{k}$ , certain properties that can be combined to express that  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a coset or a group:

1. *Non-emptiness*

There exists  $\mathbf{x} \in \mathbb{R}^{*n}$  such that  $\mathbf{x} \in V_{\mathbf{k}}(\mathbf{f})$ :

$$\varphi_1 \doteq \exists \mathbf{x}(\mathbf{x} \neq 0 \wedge \mathbf{f} = 0). \quad (8)$$

2. *Shifted completeness under inverses*

For all  $\mathbf{g}, \mathbf{x} \in \mathbb{R}^{*n}$ , if  $\mathbf{g}, \mathbf{g}\mathbf{x} \in V_{\mathbf{k}}(\mathbf{f})$ , then  $\mathbf{g}\mathbf{x}^{-1} \in V_{\mathbf{k}}(\mathbf{f})$ :

$$\begin{aligned} \varphi_2 \doteq \forall \mathbf{g} \forall \mathbf{x} (\mathbf{g} \neq 0 \wedge \mathbf{x} \neq 0 \wedge \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g}] = 0 \wedge \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{x}] = 0 \\ \longrightarrow \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{x}^{-1}] = 0). \end{aligned} \quad (9)$$

Here  $[\mathbf{x} \leftarrow \mathbf{t}]$  denotes substitution of terms  $\mathbf{t}$  for variables  $\mathbf{x}$ . In the equation  $\mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{x}^{-1}] = 0$  we tacitly drop the principal denominator of the left hand side to obtain a polynomial. This is admissible due to the premise that  $\mathbf{x} \neq 0$ .

3. *Shifted completeness under multiplication*

For all  $\mathbf{g}, \mathbf{x}, \mathbf{y} \in \mathbb{R}^{*n}$ , if  $\mathbf{g}, \mathbf{g}\mathbf{x}, \mathbf{g}\mathbf{y} \in V_{\mathbf{k}}(\mathbf{f})$ , then  $\mathbf{g}\mathbf{x}\mathbf{y} \in V_{\mathbf{k}}(\mathbf{f})$ :

$$\begin{aligned} \varphi_3 \doteq \forall \mathbf{g} \forall \mathbf{x} \forall \mathbf{y} (\mathbf{g} \neq 0 \wedge \mathbf{x} \neq 0 \wedge \mathbf{y} \neq 0 \wedge \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g}] = 0 \wedge \\ \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{x}] = 0 \wedge \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{y}] = 0 \longrightarrow \mathbf{f}[\mathbf{x} \leftarrow \mathbf{g} \cdot \mathbf{x} \cdot \mathbf{y}] = 0). \end{aligned} \quad (10)$$

4. *Neutral element*

$(1, \dots, 1) \in V_{\mathbf{k}}(\mathbf{f})$ :

$$\varphi_4 \doteq \mathbf{f}[\mathbf{x} \leftarrow (1, \dots, 1)] = 0. \quad (11)$$

In these terms we can define formulas  $\sigma$  and  $\tau$ , which state the  $V_{\mathbf{k}}(\mathbf{f})^*$  is a coset or group, respectively:

$$\sigma \doteq \varphi_1 \wedge \varphi_2 \wedge \varphi_3, \quad \tau \doteq \varphi_2 \wedge \varphi_3 \wedge \varphi_4. \quad (12)$$

For the non-parametric case, these formulas have been derived and discussed in [28, Sect. 3.2]. In the absence of parameters they were logic sentences, which are either true or false over the real numbers. Real decision procedures were used to automatically derive either “true” or “false.” In our parametric setting here, they contain  $\mathbf{k}$  as free variables and thus establish exact formal conditions in  $\mathbf{k}$ , which become either “true” or “false” after making choices of real values for  $\mathbf{k}$ .

### 3 Real Quantifier Elimination and Simplification

In the presence of parameters, the natural generalization of a decision procedure is an effective *quantifier elimination* procedure for the real numbers [15, 48, 49]. In fact, most real decision procedures are actually quantifier elimination procedures themselves, which apply quantifier elimination to their parameter-free input and subsequently evaluate the variable-free quantifier elimination result to either “true” or “false.” Plenty of approaches have been proposed for real quantifier elimination,



e.g. [50, 10, 27, 38, 1, 56, 57, 35], but only few of them have led to publicly available implementations with a long-term support strategy [13, 7, 47, 9, 51].

Given a first-order formula  $\varphi$  built from polynomial constraints with integer coefficients, quantifier elimination computes a formula  $\varphi'$  that is equivalent to  $\varphi$  over the reals, formally  $\mathbb{R} \models \varphi \longleftrightarrow \varphi'$ , but does not contain any quantifiers. We allow ourselves to call  $\varphi'$  *the result* of the quantifier elimination, although it is not uniquely determined by  $\varphi$ .

The following example, which is discussed in more detail in [48, Sect. 2.1], gives a first idea: On input of

$$\varphi \doteq \forall x_1 \exists x_2 (x_1^2 + x_1 x_2 + k_2 > 0 \wedge x_1 + k_1 x_2^2 + k_2 \leq 0), \quad (13)$$

quantifier elimination computes the result  $\varphi' \doteq k_1 < 0 \wedge k_2 > 0$ , which provides a necessary and sufficient condition in  $\mathbf{k}$  for  $\varphi$  to hold. Another application of quantifier elimination has been used already in the introduction of this article: Consider  $\mathbf{f} = (f_1, f_3, f_4)$  with  $f_1, f_3, f_4$  as in (4). Then compute  $\varphi_2, \dots, \varphi_4$  as in (9)–(11) and  $\tau$  as in (12). On input of  $\tau$ , quantifier elimination delivers the result  $\tau' \doteq k^{\text{on}} - k^{\text{off}} = \ell^{\text{on}} - \ell^{\text{off}} = k^{\text{cat}} = \ell^{\text{cat}}$ . This is a necessary and sufficient condition in  $\mathbf{k}$  for  $V_{\mathbf{k}}(\mathbf{f})^*$  to form a graph, which has already been presented in (ii) on p.3.

For an existential formula like  $\varphi_1$  in (8), quantifier elimination computes a result  $\varphi'_1$  that provides necessary and sufficient conditions in  $\mathbf{k}$  for the existence of choices for  $\mathbf{x}$  that satisfy the constraints in  $\varphi_1$ . By definition, quantifier elimination does not derive any information on possible choices of  $\mathbf{x}$ . In other words, quantifier elimination talks about solvability, not about solutions. However, quantifier elimination via virtual substitution [38, 56, 35, 49], which we use here primarily, can optionally provide sample solutions for  $\mathbf{x}$ . This is known as *extended quantifier elimination* [36]. We have used extended quantifier elimination to compute the uniform steady state  $\mathbf{x}^*$  in (5) in the introduction, besides the actual quantifier elimination result “true.”

Successful practical application of quantifier elimination by virtual substitution goes hand in hand with strong and efficient automatic simplification of intermediate and finite results. We use essentially a collection of techniques specified in [14, Sect. 5.2] as the “standard simplifier.” In particular, we exploit the concept of an *external theory* introduced in [14] with  $\mathbf{k} > 0$  as our theory. This means that all simplifications are performed modulo the assumption  $\mathbf{k} > 0$  without explicitly adding this information to the input formula  $\varphi$ . As a consequence, the quantifier elimination result  $\varphi'$  is equivalent only modulo  $\mathbf{k} > 0$ , formally  $\mathbb{R} \models \mathbf{k} > 0 \longrightarrow (\varphi \longleftrightarrow \varphi')$ .<sup>1</sup>

Note that, in contrast to  $\mathbf{k} > 0$  for the rate constants, we never require  $\mathbf{x} > 0$  for the species concentrations although chemical reaction network theory assumes both to be positive. The reason is that the concepts of toricity used here have been defined in terms of varieties and multiplicative groups without any reference to order. It might be interesting to review these concepts with respect to the particular situation encountered here. However, this is beyond the scope of this article and should be settled in a non-parametric context first.

<sup>1</sup>Alternatively, one could temporarily introduce constants  $\mathbf{k}$  and state equivalence in an extended theory of real closed fields:  $\text{Th}(\mathbb{R}) \cup \{\mathbf{k} > 0\} \models \varphi \longleftrightarrow \varphi'$ . This point of view is common in algebraic model theory and has been taken in [14].

We convert our final results to disjunctive normal form [14, Sect. 7] and apply simplification methods based on Gröbner bases [14, Sect. 4.3]. A disjunctive normal form is a finite case distinction over systems of constraints. It has been our experience that users prefer such a presentation of the computed information in comparison to arbitrary boolean combinations, even at the price of larger output. In general, this normal form computation can get quite expensive in time and space, because quantifier elimination by virtual substitution on universal formulas like  $\varphi_2, \dots, \varphi_4$  in (9)–(11) tends to produce conjunctions of disjunctions rather than vice versa. Luckily, our results are rather small.

Having said this, we have devised *quantifier elimination-based simplification* as another heuristic simplification step for our results  $\psi$  here. It checks via quantifier elimination for every single constraint  $\gamma$  in  $\psi$  whether

$$\mathbb{R} \models \forall \mathbf{k}(\mathbf{k} > 0 \longrightarrow \gamma) \longleftrightarrow \text{true} \quad \text{or} \quad \mathbb{R} \models \exists \mathbf{k}(\mathbf{k} > 0 \wedge \gamma) \longleftrightarrow \text{false}. \quad (14)$$

When such constraints  $\gamma$  are found, they are replaced in  $\psi$  with the respective truth value, and then the standard simplifier in applied to  $\psi$  once more. Quantifier elimination-based simplification preserves disjunctive normal forms.

As an example consider  $\mathbf{k} = (k_{12}, k_{13}, k_{21}, k_{23}, k_{31}, k_{32})^T$  and  $\psi \doteq \gamma_1 \vee \gamma_2$ , where

$$\begin{aligned} \gamma_1 &\doteq k_{31} - k_{32} = 0 \\ \gamma_2 &\doteq 16k_{12}k_{21} + 8k_{12}k_{23} + 8k_{13}k_{21} + 4k_{13}k_{23} + k_{31}^2 - 2k_{31}k_{32} + k_{32}^2 \leq 0. \end{aligned} \quad (15)$$

If one recognizes that  $k_{31}^2 - 2k_{31}k_{32} + k_{32}^2 = (k_{31} - k_{32})^2$  and furthermore takes into consideration that  $\mathbf{k} > 0$ , it becomes clear that  $\gamma_2$  is not satisfiable. The argument can be seen as a generalization of sum-of-squares decomposition, which is not supported within our simplification framework [14]. Quantifier elimination-based simplification recognizes that the condition on the right hand side of (14) holds for  $\gamma_2$ . It replaces  $\gamma_2$  with “false” in  $\psi$ , which yields  $\gamma_1 \vee \text{false}$ . Finally, the standard simplifier is applied, and  $\gamma_1$  is returned.

## 4 Computational Experiments

All our computations have been conducted on an AMD EPYC 7702 64-Core Processor. On the software side, we have used SVN revision 5797 of the computer algebra system Reduce with its computer logic package Redlog [30, 31, 13]. Reduce is open source and freely available on SourceForge.<sup>2</sup> On these grounds, we have implemented systematic Reduce scripts, which essentially give algorithms and could be turned into functions as a next step. In few places, global Redlog options have been adjusted manually in order to optimize the efficiency of quantifier elimination for a particular example. The scripts and the log files of the computations are available as supplementary material with this article.

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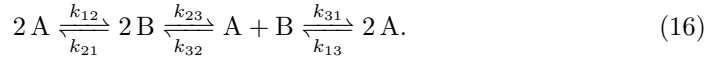
<sup>2</sup><https://sourceforge.net/projects/reduce-algebra/>

Table 1: Problem sizes and computation times for Sect. 4.1–Sect. 4.3

Sect.	network	<b>k</b>	<b>x</b>	<b>f</b>	# quantifiers			time
					$\varphi_1$	$\varphi_2$	$\varphi_3$	
4.1	Triangle	6	2	2	2	4	6	0.845 s
4.2	EnvZ-OmpR	14	9	9	9	18	27	2.172 s
4.3	TGF- $\beta$	8	6	6	6	12	18	26.477 s

## 4.1 An Artificial Triangle Network

We start with an artificial network introduced by Pérez-Millán et al. [43, p.1033, Ex. 2.3]:



There are reaction rates  $\mathbf{k} = (k_{12}, k_{13}, k_{21}, k_{23}, k_{31}, k_{32})^T$  and species concentrations  $\mathbf{x} = (x_1, x_2)^T$  for abstract species A and B, respectively. Its kinetics is described by an ODE  $\dot{\mathbf{x}} = \mathbf{f}$  with a polynomial vector field  $\mathbf{f} = (f_1, f_2)^T$  as follows:

$$f_1 = f_2 = (-2k_{12} - k_{13})x_1^2 + (2k_{21} + k_{23})x_2^2 + (k_{31} - k_{32})x_1x_2. \quad (17)$$

We form  $\varphi_1$  according to (8), and extended quantifier elimination yields  $\varphi'_1 \doteq \text{true}$  along with a uniform witness

$$\mathbf{x}^* = \left( 1, -\frac{\sqrt{16k_{12}k_{21}+8k_{12}k_{23}+8k_{13}k_{21}+4k_{13}k_{23}+k_{31}^2-2k_{31}k_{32}+k_{32}^2-k_{31}+k_{32}}}{4k_{21}+2k_{23}} \right)^T. \quad (18)$$

Notice that  $\mathbf{k} > 0$  ensures that the denominator cannot vanish.

Next, we consider  $\varphi_2$  and obtain  $\varphi'_2 \doteq k_{31} - k_{32} = 0$  with the help of quantifier elimination-based simplification. In fact, this is the example for quantifier elimination-based simplification discussed in the previous section. From  $\varphi_3$  we also obtain  $\varphi'_3 \doteq k_{31} - k_{32} = 0$ .

Hence,  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a coset of  $\mathbb{R}^{*2}$  if and only if  $\mathbb{R} \models \sigma'$ , where

$$\sigma' = k_{31} - k_{32} = 0. \quad (19)$$

The same condition has been derived with a different method in [43]. For  $V_{\mathbf{k}}(\mathbf{f})^*$  to form even a subgroup of  $\mathbb{R}^{*2}$  we must add to  $\sigma'$  the condition  $\varphi_4 \doteq \mathbf{f}[\mathbf{x} \leftarrow (1, 1)] = 0$ . This yields

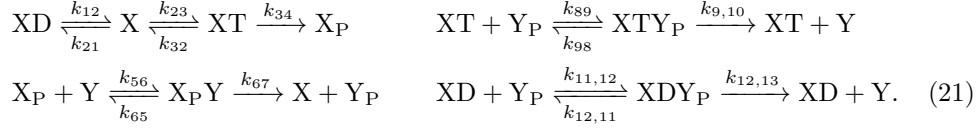
$$\tau' \doteq k_{31} - k_{32} = 0 \wedge 2k_{12} + k_{13} - 2k_{21} - k_{23} = 0. \quad (20)$$

The overall CPU time for the computations in this section was 0.867 s. Details on input problem sizes can be found in Tab. 1.

## 4.2 Escherichia Coli Osmoregulation System

Our next example is a model of the escherichia coli osmoregulation system (EnvZ-OmpR). It has been introduced by Shinar and Feinberg [46, (S60)] in the supporting

online material] and also discussed in [43, p.1043, Example 3.15]:



There are 14 reaction rates  $\mathbf{k}$  and species concentrations  $\mathbf{x} = (x_1, \dots, x_9)^T$  for XD, X, XT,  $\text{X}_\text{P}$ , Y,  $\text{X}_\text{P}\text{Y}$ ,  $\text{Y}_\text{P}$ ,  $\text{XTY}_\text{P}$ ,  $\text{XDY}_\text{P}$ , respectively. Its kinetics is described by an ODE  $\dot{\mathbf{x}} = \mathbf{f}$  with a polynomial vector field  $\mathbf{f} = (f_1, \dots, f_9)^T$  as follows:

$$\begin{aligned}
f_1 &= -k_{12}x_1 + k_{21}x_2 - k_{11,12}x_1x_7 + (k_{12,11} + k_{12,13})x_9 \\
f_2 &= k_{12}x_1 + (-k_{21} - k_{23})x_2 + k_{32}x_3 + k_{67}x_6 \\
f_3 &= k_{23}x_2 + (-k_{32} - k_{34})x_3 - k_{89}x_3x_7 + (k_{98} + k_{9,10})x_8 \\
f_4 &= k_{34}x_3 - k_{56}x_4x_5 + k_{65}x_6 \\
f_5 &= -k_{56}x_4x_5 + k_{65}x_6 + k_{9,10}x_8 + k_{12,13}x_9 \\
f_6 &= k_{56}x_4x_5 + (-k_{65} - k_{67})x_6 \\
f_7 &= k_{67}x_6 - k_{89}x_3x_7 + k_{98}x_8 - k_{11,12}x_1x_7 + k_{12,11}x_9 \\
f_8 &= k_{89}x_3x_7 + (-k_{98} - k_{9,10})x_8 \\
f_9 &= k_{11,12}x_1x_7 + (-k_{12,11} - k_{12,13})x_9.
\end{aligned} \quad (22)$$

We compute  $\varphi'_1 \doteq \varphi'_2 \doteq \varphi'_3 \doteq \sigma \doteq \text{true}$ , which means that  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a coset for all admissible choices of reaction rates  $\mathbf{k}$ . Again, extended quantifier elimination delivers, in addition to  $\varphi'_1$ , a uniform parametric witness  $\mathbf{x}^*$  for the non-emptiness of  $V_{\mathbf{k}}(\mathbf{f})^*$ . We obtain the following equivalent condition in  $\mathbf{k}$  for  $V_{\mathbf{k}}(\mathbf{f})^*$  to form even a group:

$$\begin{aligned}
\varphi'_4 &\doteq \tau \doteq k_{89} - k_{9,10} - k_{98} = 0 \wedge k_{12,13} - k_{67} + k_{89} - k_{98} = 0 \wedge \\
&k_{12,13} - k_{56} + k_{65} + k_{89} - k_{98} = 0 \wedge k_{12,13} - k_{34} + k_{89} - k_{98} = 0 \wedge \\
&k_{12,13} - k_{23} + k_{32} + k_{89} - k_{98} = 0 \wedge k_{12} - k_{21} = 0 \wedge \\
&k_{11,12} - k_{12,11} - k_{12,13} = 0.
\end{aligned} \quad (23)$$

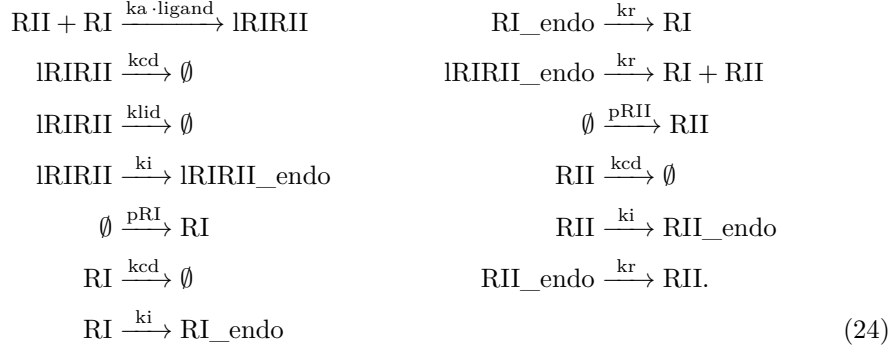
The overall CPU time for the computations in this section was 0.651 s. Details on input problem sizes can be found in Tab. 1.

### 4.3 TGF- $\beta$ Pathway

The TGF- $\beta$  signaling pathway plays a central role in tissue homeostasis and morphogenesis, as well as in numerous diseases such as fibrosis and cancer [52]. It is featured as model no. 101 in the BioModels repository [8].<sup>3</sup> We consider here a variant, which ignores a discrete event changing ligand concentration at time  $t = 2500$ . A non-parametric instance of this variant has been studied in [28] with respect to toricity

<sup>3</sup><https://www.ebi.ac.uk/biomodels/BIOMD0000000101>

and in [37] with respect to multiple time scale reduction.



There are 8 parameters  $\mathbf{k}$  and species concentrations  $\mathbf{x} = (x_1, \dots, x_6)^T$  corresponding to RI, RII, IRIRII, IRIRII\_endo, RI\_endo, RII\_endo, respectively. The dynamics of the network is described by an ODE  $\dot{\mathbf{x}} = \mathbf{f}$  with a polynomial vector field  $\mathbf{f} = (f_1, \dots, f_6)^T$  as follows:

$$\begin{aligned}
f_1 &= -\text{ka} \cdot \text{ligand} \cdot x_1 x_2 - \text{kcd} \cdot x_1 - \text{ki} \cdot x_1 + \text{kr} \cdot x_4 + \text{kr} \cdot x_5 + \text{pri} \\
f_2 &= -\text{ka} \cdot \text{ligand} \cdot x_1 x_2 - \text{kcd} \cdot x_2 - \text{ki} x_2 + \text{kr} \cdot x_4 + \text{kr} \cdot x_6 + \text{prii} \\
f_3 &= \text{ka} \cdot \text{ligand} \cdot x_1 x_2 - \text{kcd} \cdot x_3 - \text{ki} \cdot x_3 - \text{klid} \cdot x_3 \\
f_4 &= \text{ki} \cdot x_3 - \text{kr} \cdot x_4 \\
f_5 &= \text{ki} \cdot x_1 - \text{kr} \cdot x_5 \\
f_6 &= \text{ki} \cdot x_2 - \text{kr} \cdot x_6.
\end{aligned} \tag{25}$$

For fixed choices  $\mathbf{k}^*$  of parameters as specified in the BioModels repository we had shown in [28] that  $V_{\mathbf{k}^*}(\mathbf{f})^*$  is not a coset. Our parametric approach here allows to investigate to what extent this negative result depends on the specific choices  $\mathbf{k}^*$ . We compute  $\varphi'_1 \doteq \text{true}$  along with a witness for  $V_{\mathbf{k}}(\mathbf{f})^* \neq \emptyset$  for all admissible choices of  $\mathbf{k}$ . Next, we obtain  $\varphi'_2 \doteq \varphi'_3 \doteq \text{false}$ , i.e., shifted completeness under inverses and multiplication fails for all admissible choices of  $\mathbf{k}$ . It follows that  $\sigma \doteq \tau \doteq \text{false}$ , i.e.,  $V_{\mathbf{k}}(\mathbf{f})^*$  is generally not a coset and not a group.

The synthesis and degradation reactions<sup>4</sup> in (24) cause absolute summands in  $f_1$  and  $f_2$  in the dynamics (25). Although there is a connection between cosets and the existence of binomial generators of the ideal, those summands are not an immediate reason to exclude cosets. Consider, e.g., the abstract example  $\mathbf{g} = (-x_1 - x_2 + k_1, x_2 + x_3 + k_2)$ , where  $V_{\mathbf{k}}(\mathbf{g})^*$  is a coset for all admissible choices of  $k_1, k_2$ . On the other hand, we have mentioned in the introduction that toricity is related to complex balance. TGF- $\beta$  cannot not have complex balance, because there is a nonzero flux through the system: receptors are produced, they cycle, and are degraded. One cannot transfer information without dissipation. This observation generally applies to signaling models.

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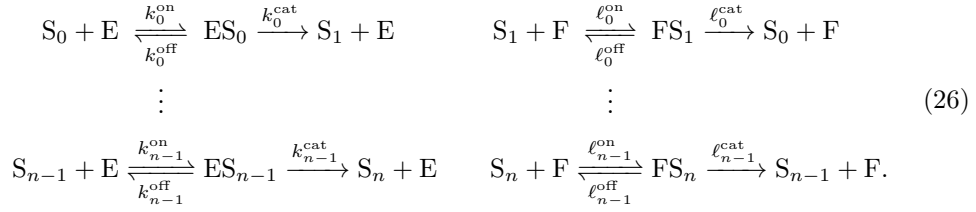
<sup>4</sup>i.e., the ones with “ $\emptyset$ ” on their left hand side or right hand side, respectively

The overall CPU time for the computations in this section was 26.477 s. Details on input problem sizes can be found in Tab. 1.

#### 4.4 $n$ -Site Phosphorylation-Dephosphorylation Cycle

The  $n$ -site phosphorylation network in the form discussed here has been taken from Wang and Sontag [53]. Pérez-Millán et al. have discussed  $n$ -site phosphorylation for generic  $n$  [43, Sect. 4.1]; the cases  $n = 1$  and  $n = 2$  are discussed explicitly as Ex. 2.1 and Ex. 3.13, respectively. We have used the case  $n = 1$  in the introduction.

For a fixed positive integer  $n$ , the  $n$ -site phosphorylation reaction network is given by



Its dynamics is described by the following ODE with  $6n$  parameters  $\mathbf{k}_n = (k_0^{\text{on}}, \dots, \ell_{n-1}^{\text{cat}})$  and  $3n + 3$  variables

$$\mathbf{x}_n = (s_0, \dots, s_n, c_0, \dots, c_{n-1}, d_1, \dots, d_n, e, f) \tag{27}$$

for concentrations of species  $S_0, \dots, S_n, ES_0, \dots, ES_{n-1}, FS_1, \dots, FS_n, E, F$ , respectively:

$$\begin{aligned}
 \dot{s}_0 &= -k_0^{\text{on}} s_0 e + k_0^{\text{off}} c_0 + \ell_0^{\text{cat}} d_1 \\
 \dot{s}_i &= -k_i^{\text{on}} s_i e + k_i^{\text{off}} c_i + k_{i-1}^{\text{cat}} c_{i-1} - \ell_{i-1}^{\text{on}} s_i f + \ell_{i-1}^{\text{off}} d_i + \ell_i^{\text{cat}} d_{i+1} \\
 \dot{c}_j &= k_j^{\text{on}} s_j e - (k_j^{\text{off}} + k_j^{\text{cat}}) c_j \\
 \dot{d}_k &= \ell_{k-1}^{\text{on}} s_k f - (\ell_{k-1}^{\text{off}} + \ell_{k-1}^{\text{cat}}) d_k, \\
 &\quad i = 1, \dots, n-1, \quad j = 0, \dots, n-1, \quad k = 1, \dots, n.
 \end{aligned} \tag{28}$$

Let  $\mathbf{f}_n = (f_1, \dots, f_{3n-1})$  denote the vector field of (28). We may ignore here the equations for  $\dot{s}_n, \dot{e},$  and  $\dot{f}$ , whose right hand sides are linear combinations of  $\mathbf{f}_n$ .

For  $n \in \{1, \dots, 5\}$  we obtain the following computational results:

- (i)  $V_{\mathbf{k}}(\mathbf{f})^* \neq \emptyset$  for all admissible choices of  $\mathbf{k}$ ; we also obtain a uniform witness in terms of  $\mathbf{k}$ ;
- (ii)  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a coset for all admissible choices of  $\mathbf{k}$ ;
- (iii)  $V_{\mathbf{k}}(\mathbf{f})^*$  forms a group if and only if

$$\bigwedge_{i=0}^{n-1} k_i^{\text{on}} - k_i^{\text{off}} = \ell_i^{\text{on}} - \ell_i^{\text{off}} = k_i^{\text{cat}} = \ell_i^{\text{cat}}. \tag{29}$$

Table 2: Problem sizes and computation times for n-site phosphorylation in Sect.4.4

$n$	$ \mathbf{k} $	$ \mathbf{x} $	$ \mathbf{f} $	# quantifiers			time
				$\varphi_1$	$\varphi_2$	$\varphi_3$	
1	6	6	2	6	12	18	0.500 s
2	12	9	5	9	18	27	1.131 s
3	18	12	8	12	24	36	5.911 s
4	24	15	11	15	30	45	33.790 s
5	30	18	14	18	36	54	3963.204 s
$\geq 6$	$6n$	$3(n+1)$	$3n-1$	$3(n+1)$	$6(n+1)$	$9(n+1)$	$> 6$ h

Wang and Sontag, in their article [53], were interested in quantitative information on the numbers of steady states of the dynamics (28). Our results here provide qualitative information on the structure of the set of steady states. We could automatically deduce that there is always at least one steady state, for which we find a uniform witness in  $\mathbf{k}$ . In fact, extended quantifier elimination could even enumerate steady states, because one can exclude in the input formula the ones already found, and rerun. More important, we know that the set  $S \subseteq \mathbb{R}^{*n}$  of all steady states forms a coset. That is, for all choices of  $\mathbf{k}$  and all  $\mathbf{g} \in S$ , the set  $G = \mathbf{g}^{-1}S$  is complete under component-wise multiplication and inverses. The set  $S$  itself has this completeness property only for choices of parameters satisfying the equations (29) exactly, which one cannot expect from a practical point of view.

As one possible application of our results, assume that experiments have delivered three steady states  $\mathbf{x}_1, \dots, \mathbf{x}_3$ . Then, e.g., the following are steady states, too:

$$\mathbf{x}_1(\mathbf{x}_1^{-1}\mathbf{x}_2 \cdot \mathbf{x}_1^{-1}\mathbf{x}_3) = \mathbf{x}_1^{-1}\mathbf{x}_2\mathbf{x}_3, \quad \mathbf{x}_1(\mathbf{x}_1^{-1}\mathbf{x}_2)^{-1} = \mathbf{x}_1^2\mathbf{x}_2. \quad (30)$$

Here we use multiplication with  $\mathbf{x}_1^{-1}$  for switching from  $S$  to  $G$ , exploit there completeness under multiplication and inverses, respectively, and finally use multiplication with  $\mathbf{x}_1$  for switching back to  $S$ .

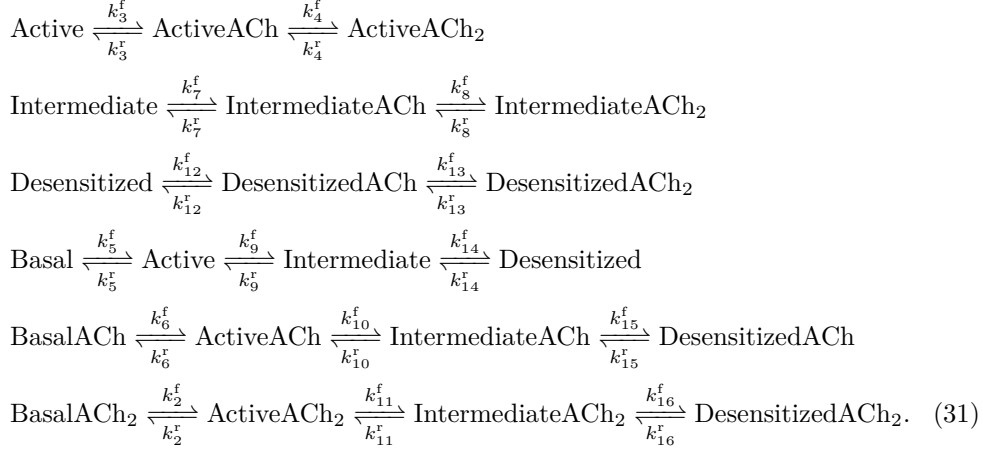
The computation times are collected in Tab. 2. The formula  $\varphi_3$  for  $n = 5$  is the formally largest quantifier elimination problem considered in this article. We have eliminated here 54 real quantifiers in an 84-dimensional space, which took 1 h 6 min. For  $n \geq 6$ , the computations did not finish within 6 hours.

## 4.5 Excitatory Post-Synaptic Potential Acetylcholine Event

The excitatory post-synaptic potential acetylcholine event model (EPSP-ACh) has been introduced by Edelstein et al. [16]. It also appears as model no. 1 in the BioModels repository [8]:<sup>5</sup>



<sup>5</sup><https://www.ebi.ac.uk/biomodels/BIOMD0000000001>



There are 34 reaction rates  $\mathbf{k}$  and species concentrations  $\mathbf{x} = (x_1, \dots, x_{12})^T$  for BasalACh<sub>2</sub>, IntermediateACh, ActiveACh, Active, BasalACh, Basal, DesensitizedACh<sub>2</sub>, Desensitized, IntermediateACh<sub>2</sub>, DesensitizedACh, Intermediate, ActiveACh<sub>2</sub>, respectively. The kinetics is described by an ODE  $\dot{\mathbf{x}} = \mathbf{f}$  with a polynomial vector field  $\mathbf{f} = (f_1, \dots, f_{12})^T$  as follows:

$$\begin{aligned}
f_1 &= k_1^f x_5 - k_1^r x_1 - k_2^f x_1 + k_2^r x_{12} \\
f_2 &= k_7^f x_{11} - k_7^r x_2 - k_8^f x_2 + k_8^r x_9 + k_{10}^f x_3 - k_{10}^r x_2 - k_{15}^f x_2 + k_{15}^r x_{10} \\
f_3 &= k_4^r x_{12} + k_6^f x_5 - k_6^r x_3 - k_{10}^f x_3 + k_{10}^r x_2 + k_3^f x_4 - k_3^r x_3 - k_4^f x_3 \\
f_4 &= k_5^f x_6 - k_5^r x_4 - k_9^f x_4 + k_9^r x_{11} - k_3^f x_4 + k_3^r x_3 \\
f_5 &= k_0^f x_6 - k_6^f x_5 + k_6^r x_3 - k_0^r x_5 - k_1^f x_5 + k_1^r x_1 \\
f_6 &= -k_0^f x_6 - k_5^f x_6 + k_5^r x_4 + k_0^r x_5 \\
f_7 &= k_{13}^f x_{10} - k_{13}^r x_7 + k_{16}^f x_9 - k_{16}^r x_7 \\
f_8 &= -k_{12}^f x_8 + k_{12}^r x_{10} + k_{14}^f x_{11} - k_{14}^r x_8 \\
f_9 &= k_8^f x_2 - k_8^r x_9 + k_{11}^f x_{12} - k_{11}^r x_9 - k_{16}^f x_9 + k_{16}^r x_7 \\
f_{10} &= k_{12}^f x_8 - k_{12}^r x_{10} - k_{13}^f x_{10} + k_{13}^r x_7 + k_{15}^f x_2 - k_{15}^r x_{10} \\
f_{11} &= -k_7^f x_{11} + k_7^r x_2 + k_9^f x_4 - k_9^r x_{11} - k_{14}^f x_{11} + k_{14}^r x_8 \\
f_{12} &= -k_4^r x_{12} - k_{11}^f x_{12} + k_{11}^r x_9 + k_2^f x_1 - k_2^r x_{12} + k_4^f x_3. \quad (32)
\end{aligned}$$

In the presentation of the model in the BioModels repository, occurrences of reaction rates  $\mathbf{k}$  are generally multiplied with the volume of a compartment  $\text{comp}_1$ . This amounts in (32) to a corresponding factor for all  $\mathbf{f}$ , which would not affect our computations here and can be equivalently dropped. It is noteworthy that our framework would allow to handle occurrences of various different compartment volumes as extra parameters in  $\mathbf{k}$ .

Our computations for this model did not finish within 24 hours, even when fixing all forward reaction rates  $k_i^f$  to their values specified in the BioModels repository. This



is a bit surprising, because with regard to  $|\mathbf{k}|$ ,  $|\mathbf{x}|$ , and  $|\mathbf{f}|$ , the problem is smaller than 5-site phosphorylation, which we successfully computed in the previous section. Furthermore,  $\mathbf{f} = 0$  is a system of parametric *linear* equations. It seems that there is an immense combinatorial explosion in the size of parametric coefficient polynomials caused by iterated solving for certain variables and plugging in.

## 5 Conclusions

Geometric definitions of shifted toricity and toricity of a real steady state variety  $V$  require that  $V \cap \mathbb{R}^{*n}$  forms a multiplicative coset or group, respectively. We have proposed a formal framework, based on first-order logic and real quantifier elimination, to test this in the presence of parameters. Computational experiments succeeded on dynamics of reaction networks with up to 54 species and 30 parameters.

With all our computations on real-world networks here, we have found that the coset property is independent of the choice of parameters. This result is desirable from the viewpoint of chemical reaction theory, which postulates that relevant properties of networks do not depend on reaction rates. Given the coset property, the stronger group property holds only for degenerate choices of parameters in the sense that they satisfy algebraic equations. In the context of our framework, this is not too surprising. The equivalent conditions in the parameters for the group property are obtained by plugging in 1 for all species concentrations in the defining equations of  $V$ . Our conclusion is that the coset property without algebraic conditions on the parameters is the relevant concept.

We have used above a strict notion of *algebraic*, which excludes order inequalities. Recall that we had advertised in the introduction that our approach is capable of producing semi-algebraic conditions on the parameters, which can include inequalities. Such inequalities come into existence during quantifier elimination as sign conditions on discriminants of non-linear polynomials. With the Triangle network in Sect. 4.1 they almost made their way into the output but were removed in the last moment by quantifier elimination-based simplification. One of them has been presented in (15). Beyond that, our computations did not produce any order constraints on the parameters. It is an interesting question, maybe also for the natural sciences, whether there is a systematic reason for their absence. A positive answer would also support alternative purely algebraic approaches to toricity, e.g., based on binomial ideals.

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