

Higher-order Lie symmetries in identifiability and predictability analysis of dynamic modelsBenjamin Merkt,¹ Jens Timmer,^{1,2,3} and Daniel Kaschek^{1,*}¹*Institute of Physics, Freiburg University, Freiburg 79104, Germany*²*Freiburg Centre for Systems Biology (ZBSA), Freiburg University, Freiburg 79104, Germany*³*BIOSS Centre for Biological Signaling Studies, Freiburg University, Freiburg 79104, Germany*

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Parameter estimation in ordinary differential equations (ODEs) has manifold applications not only in physics but also in the life sciences. When estimating the ODE parameters from experimentally observed data, the modeler is frequently concerned with the question of parameter identifiability. The source of parameter nonidentifiability is tightly related to Lie group symmetries. In the present work, we establish a direct search algorithm for the determination of admitted Lie group symmetries. We clarify the relationship between admitted symmetries and parameter nonidentifiability. The proposed algorithm is applied to illustrative toy models as well as a data-based ODE model of the NF κ B signaling pathway. We find that besides translations and scaling transformations also higher-order transformations play a role. Enabled by the knowledge about the explicit underlying symmetry transformations, we show how models with nonidentifiable parameters can still be employed to make reliable predictions.

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I. INTRODUCTION

Modeling of dynamic systems by ordinary differential equations (ODEs) has always been concerned with the problem of unknown parameters in the model equations. As opposed to other fields, in the life sciences *a priori* unknown parameters like reaction velocities, association rates, dissociation rates, etc., can often not be measured directly. The system under investigation is only observable as a whole and cannot be dissected into isolated reactions. Therefore, the parameters need to be determined by parameter estimation, which relies on a certain amount of time-resolved measurements for at least a subset of system components.

In this procedure, the modeler is frequently confronted with the problem of nonidentifiable parameters, i.e., given the observed data there exists a submanifold in parameter space describing, in terms of an objective value, the data equally or almost equally well: these cases are denoted as structural or practical nonidentifiability [1].

In Ref. [2], a data-based approach is utilized to identify submanifolds of equal objective values, thus being able to detect nonidentifiabilities. A complementary data-based approach employing the profile likelihood is presented in Ref. [1], giving a precise definition of structural and practical identifiability in terms of parameter profiles. On the other hand, *a priori* data-independent analytical methods can be applied to directly test the model equations for structural nonidentifiability. The authors of [3,4] introduced two methods which can be applied to study the identifiability of ODE models. However, these do not yield algorithms to automatically detect structural nonidentifiabilities. The approach presented in Refs. [5–7]

relies on differential algebra methods and can be employed to study the input-output relation between the parameters and the predicted observation. If a unique solution exists, the model is structurally identifiable. This approach is purely algebraic. However, as the method relies on Buchberger's algorithm to solve the equations, its complexity grows rapidly with the size of the model and quickly becomes infeasible. Additionally, the model is expected to be in minimal form, which is often not fulfilled. In such cases, the model has to be manually transformed before the analysis can be applied.

A drawback of all the above techniques is that they do not elucidate the fundamental source of the structural nonidentifiabilities. In Ref. [8] it was shown that the admittance of Lie transformations is equivalent to the existence of similarity transformations [4] and thus equivalent to structural nonidentifiability of the model. To concretize this statement, let

$$\begin{aligned}\dot{\mathbf{x}}(t) &= f(\mathbf{x}(t), \boldsymbol{\theta}_{\text{dyn}}, \mathbf{u}(t)), & \mathbf{x}(0) &= \boldsymbol{\theta}_{\text{ini}}, \\ \mathbf{y}(t) &= g(\mathbf{x}(t), \boldsymbol{\theta}_{\text{obs}})\end{aligned}\quad (1)$$

be a dynamic system with states $\mathbf{x} \in \mathbb{R}^m$, dynamic parameters $\boldsymbol{\theta}_{\text{dyn}} \in \mathbb{R}^{p'}$, inputs $\mathbf{u} \in \mathbb{R}^q$, and initial conditions $\boldsymbol{\theta}_{\text{ini}} \in \mathbb{R}^m$. In general, the observation $\mathbf{y} \in \mathbb{R}^{p''}$ is an arbitrary function of the states \mathbf{x} and observational parameters $\boldsymbol{\theta}_{\text{obs}} \in \mathbb{R}^{p''}$. Then, an admitted Lie symmetry is a continuous group of transformations Ψ of the states \mathbf{x} and parameters $\boldsymbol{\Theta} = (\boldsymbol{\theta}_{\text{dyn}}, \boldsymbol{\theta}_{\text{ini}}, \boldsymbol{\theta}_{\text{obs}}) \in \mathbb{R}^p$, $p = m + p' + p''$:

$$\begin{aligned}\Psi : \quad \mathbb{R}^{m+p+q} \times \mathcal{G} &\longrightarrow \mathbb{R}^{m+p+q} \\ (\mathbf{x}, \boldsymbol{\Theta}, \mathbf{u}; \epsilon) &\longmapsto (\mathbf{x}^*, \boldsymbol{\Theta}^*, \mathbf{u}^*),\end{aligned}$$

such that the observation \mathbf{y} is unchanged for each element ϵ in the Lie group \mathcal{G} . I.e., it must hold that

$$\forall \epsilon \in \mathcal{G} : g(\mathbf{x}^*(t), \boldsymbol{\theta}_{\text{obs}}^*) = g(\mathbf{x}(t), \boldsymbol{\theta}_{\text{obs}}), \quad (2)$$

where $\mathbf{x}(t)$ and $\mathbf{x}^*(t)$ implicitly depend on the parameters $(\boldsymbol{\theta}_{\text{ini}}, \boldsymbol{\theta}_{\text{dyn}})$ and $(\boldsymbol{\theta}_{\text{ini}}^*, \boldsymbol{\theta}_{\text{dyn}}^*)$. This illustrates the relation between Lie groups of transformations and structural nonidentifiability: Although the parameters are changed by the transformation

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Ψ , the observation stays invariant. Equation (2) can also be expressed using the infinitesimal generators \mathbf{X} of Ψ , forming the Lie algebra \mathfrak{g} :

$$\forall \mathbf{X} \in \mathfrak{g} : \mathbf{X} \cdot g(\mathbf{x}, \theta_{\text{obs}}) = 0.$$

The advantage of the latter formulation is that it yields a condition for admitted symmetries which can be exploited to explicitly calculate the transformations.

Generally, the challenge of finding symmetries is approached by two methods. The first one, introduced by [9], is based on differential algebra combined with probabilistic sampling. The sampling is employed to investigate the rank of the variational system of the ODEs in order to identify the set of nonidentifiable parameters. This identification is computationally efficient as it is polynomial in time. Furthermore, having identified the subset of nonidentifiable parameters, it is possible to determine the associated Lie algebra generators from the maximal singular minor of the Jacobian. A Mathematica implementation of the algorithm was presented in Ref. [10].

The second approach is a more direct method employing an explicit polynomial *Ansatz* for the generator. This leads to a determining system for the coefficients which specify the *Ansatz*. The authors of [11,12] applied this approach to compute the reduced system of ODEs, especially for scaling and Möbius transformations, and to define coordinates leaving the steady states of a dynamic system invariant. Translational and scaling symmetries were also investigated by [13], pointing out the close relation between nondimensionalization and Lie group symmetries. Both groups work with Maple implementations. Translation, scaling, and affine transformations were also studied by [14] and used to compute a minimal set of observations which make the model identifiable. In Ref. [8] the determining system is solved by methods available in Mathematica with applications to observation functions with scalings.

The approach presented in this work has the same starting point as the methods used in Refs. [8,11–14]; however, it differs in three major aspects. First, instead of using random specializations, we develop a method to solve the determining equations by directly transforming the rational expressions to a linear system. Second, by applying the proposed algorithm [15] to three examples, we demonstrate the significance of higher-order generators which to our knowledge were not discussed before. Third, we show that the knowledge of the explicit underlying symmetries that we gain by the proposed algorithm enables us to determine reliable model predictions although model parameters are nonidentifiable.

The work is structured as follows: Sec. II recapitulates Lie group theory and illustrates the algorithm as being implemented in Python with the libraries SymPy [16] for symbolic mathematics and SciPy and NumPy for numerical calculations. Section III introduces several examples demonstrating the relevance of higher-order transformations. In this context, we also study a data-based ODE model of the NF κ B signaling pathway. Besides determining and discussing the intrinsic symmetries of the dynamic system, we infer quantities which can be reliably predicted despite the structural nonidentifiabilities in the model.

II. METHODS

For a simplified notation, Eq. (1) is rewritten in a form where the input $\mathbf{u}(t)$ and parameters θ are absorbed in the state vector $\mathbf{x}(t)$:

$$\begin{aligned} \dot{x}_i(t) &= f_i(\mathbf{x}(t)), \quad i = 1, \dots, m, \\ x_i(t) &= \Theta_i, \quad i = m + 1, \dots, m + p, \\ x_i(t) &= u_i(t), \quad i = m + p + 1, \dots, m + p + q. \end{aligned} \quad (3)$$

In the following, we call $n = m + p + q$ the total number of states. Hereby, the ODE model becomes

$$\dot{\mathbf{x}}(t) = f(\mathbf{x}(t)), \quad (4a)$$

$$\mathbf{y}(t) = g(\mathbf{x}(t)). \quad (4b)$$

If the biological system is in steady state at the start of the experiment, this has to be accounted for by the additional condition

$$f(\mathbf{x}_0) = 0, \quad (5)$$

where $\mathbf{x}_0 = \mathbf{x}(t = 0)$, which introduces an additional constraint for the parameters.

A. Theory of Lie groups of transformations

We adopt the definition of [17] for a Lie group of transformations.

Definition 1. Let $\mathbf{x} = (x_1, \dots, x_n) \in D \subset \mathbb{R}^n$, $S \subset \mathbb{R}$ with $0 \in S$ and let $\phi : S \times S \rightarrow S$ be a law of composition. A mapping

$$\mathbf{x}^* = \Psi(\mathbf{x}, \epsilon) \in D$$

with $\mathbf{x} \in D$ and $\epsilon \in S$ is called a *Lie group of transformations* if it satisfies the following.

- (i) For all $\epsilon \in S$, the mapping $\Psi(\cdot, \epsilon)$ is one to one.
- (ii) S together with ϕ forms a group with identity element zero.
- (iii) For all $\mathbf{x} \in D$ we have $\Psi(\mathbf{x}, 0) = \mathbf{x}$.
- (iv) If $\mathbf{x}^* = \Psi(\mathbf{x}, \epsilon)$ and $\mathbf{x}^{**} = \Psi(\mathbf{x}^*, \delta)$, then $\mathbf{x}^{**} = \Psi(\mathbf{x}, \phi(\epsilon, \delta))$.
- (v) S is an interval in \mathbb{R} and ϕ is analytic.
- (vi) $\Psi(\mathbf{x}, \epsilon)$ is smooth in \mathbf{x} and analytic in ϵ .

A Lie group of transformations is said to be *admitted* by ODE model (4) if for every solution $\mathbf{x}(t)$ and every $\epsilon \in S$ the transformed function $\mathbf{x}^*(t) = \Psi(\mathbf{x}(t), \epsilon)$ is also a solution of the system.

For every Lie group of transformations, the *infinitesimal generator* is a differential operator defined as

$$\mathbf{X} = \sum_{i=1}^n \eta_i(\mathbf{x}) \frac{\partial}{\partial x_i}$$

with $\eta(\mathbf{x}) = \left. \frac{\partial \Psi(\mathbf{x}, \epsilon)}{\partial \epsilon} \right|_{\epsilon=0}$. The functions $\eta_i(\mathbf{x})$ are called *infinitesimals* of the transformation.

Theorem 1 [17]. By utilizing the infinitesimal generator, the corresponding transformation can be written as

$$\mathbf{x}^* = \Psi(\mathbf{x}, \epsilon) = \exp[\epsilon \mathbf{X}] \mathbf{x}. \quad (6)$$

Hence, the infinitesimal generator is an equivalent representation of a Lie group of transformations.

Each component of the state vector $\mathbf{x}(t)$ in system (4) is a function of time. Therefore, a transformation of $\mathbf{x}(t)$ also induces a transformation of the time derivatives $\dot{\mathbf{x}}(t)$. In order to compute the explicit transformation of $\dot{\mathbf{x}}(t)$, the infinitesimal generator is extended such that the transformation (6) also acts on the derivatives:

$$\mathbf{X}' = \sum_{i=1}^n \eta_i(\mathbf{x}) \frac{\partial}{\partial x_i} + \sum_{i=1}^n \eta'_i(\mathbf{x}) \frac{\partial}{\partial \dot{x}_i}. \quad (7)$$

The transformation of the derivatives is now represented by the infinitesimals $\eta'_i(\mathbf{x})$ which are calculated by

$$\eta'_i(\mathbf{x}) = \sum_{j=1}^n \dot{x}_j \frac{\partial \eta_i}{\partial x_j}(\mathbf{x})$$

[18]. This prolonged infinitesimal generator enables the formulation of an explicit criterion for admitted Lie groups of transformations.

Theorem 2 [17,18]. The system of ordinary differential equations (4) admits a Lie group of transformations defined by the infinitesimal generator $\mathbf{X} = \sum_{i=1}^n \eta_i(\mathbf{x}) \frac{\partial}{\partial x_i}$ if and only if

$$\begin{aligned} \mathbf{X}' \cdot (\dot{x}_k - f_k(\mathbf{x})) &= 0, \quad k = 1, \dots, m, \\ \mathbf{X} \cdot (y_{k'} - g_{k'}(\mathbf{x})) &= 0, \quad k' = 1, \dots, n^* \end{aligned} \quad (8)$$

whenever $\dot{\mathbf{x}} = f(\mathbf{x})$ and $g(\mathbf{x}) = 0$.

The steady state equation (5) imposes additional constraints for the parameter values. Therefore, it could, in principle, also restrict the admitted symmetries. This has to be accounted for by the third symmetry condition:

$$\mathbf{X} \cdot f_k(\mathbf{x}) = 0, \quad k = 1, \dots, m \quad \text{whenever} \quad f_k(\mathbf{x}) = 0.$$

However, it can be shown (see Appendix A, Theorem A1) that this is fulfilled whenever Eq. (8) holds and, consequently, the steady state equation (5) does not require additional considerations. If the initial concentrations are given by general algebraic expressions, these can be treated similarly to the observation functions. For details see [14].

If \mathbf{X}_i and \mathbf{X}_j are two infinitesimal generators satisfying Eq. (8), then also every linear combination $\mu_i \mathbf{X}_i + \mu_j \mathbf{X}_j$ is admitted by the system of ODEs. Therefore, its solution set defines a linear vector space of admitted generators. Furthermore, it can be shown [18] that the *Lie bracket*

$$[\mathbf{X}_i, \mathbf{X}_j] = \mathbf{X}_i \cdot \mathbf{X}_j - \mathbf{X}_j \cdot \mathbf{X}_i$$

also yields an infinitesimal generator which is admitted. The vector space of admitted generators together with the Lie bracket forms a *Lie algebra*, denoted by \mathfrak{g} .

B. Calculation of symmetry groups

1. Rational differential equations

In the following, a method for solving the determining equations (8) is derived. Theorem 2 states that a system of

the form of Eq. (4) admits a Lie group of transformations $\tilde{\mathbf{x}} = \Psi(\mathbf{x}, \epsilon)$ if and only if

$$\begin{aligned} \sum_{j=1}^n \dot{x}_j \frac{\partial \eta_k}{\partial x_j}(\mathbf{x}) - \sum_{i=1}^n \eta_i(\mathbf{x}) \frac{\partial f_k}{\partial x_i}(\mathbf{x}) &= 0, \quad k = 1, \dots, m, \\ \sum_{i=1}^n \eta_i(\mathbf{x}) \frac{\partial g_{k'}}{\partial x_i}(\mathbf{x}) &= 0, \quad k' = 1, \dots, n^* \end{aligned} \quad (9)$$

holds for all solutions $\mathbf{x}(t)$ of the system where $\eta_i(\mathbf{x})$ are the infinitesimals of the transformations. Equation (9) defines a system of coupled partial differential equations for these infinitesimals. If a solution to this system is found, the admitted transformations can be computed by Eq. (6). However, Eq. (9) cannot be solved analytically for general differential equations. Therefore, in the following, we consider rational differential equations and observation functions of the form

$$\begin{aligned} \dot{x}_k &= f_k(\mathbf{x}) = \frac{P^k(\mathbf{x})}{Q^k(\mathbf{x})} \quad k = 1, \dots, m, \\ y_{k'} &= g_{k'}(\mathbf{x}) = \frac{R^{k'}(\mathbf{x})}{S^{k'}(\mathbf{x})} \quad k' = 1, \dots, n^*, \end{aligned} \quad (10)$$

where $P^k(\mathbf{x})$, $Q^k(\mathbf{x})$, $R^{k'}(\mathbf{x})$, and $S^{k'}(\mathbf{x})$ are multivariate polynomial expressions. Hereby, a large class of ODE models is covered. In particular, mass action, Michaelis-Menten, and Hill kinetics are included. The derivatives of the input $\mathbf{u}(t)$ are generally unknown. Therefore, the terms in Eq. (9) containing $\dot{\mathbf{u}}$ have to vanish and, consequently, it must hold that $\frac{\partial \eta_k}{\partial x_j}(\mathbf{x}) = 0$ for $k = 1, \dots, m$ and $j = m + p + 1, \dots, n$. Taken together, if Eq. (10) is plugged into Eq. (9), the conditions become

$$\sum_{j=1}^m \frac{P^j}{Q^j} \frac{\partial \eta_k}{\partial x_j} - \sum_{i=1}^n \eta_i \frac{P^k Q^k - P^k Q^k_{x_i}}{Q^{k^2}} = 0, \quad k = 1, \dots, m, \quad (11a)$$

$$\sum_{i=1}^n \eta_i \frac{R^{k'} S^{k'} - R^{k'} S^{k'}_{x_i}}{S^{k'^2}} = 0, \quad k' = 1, \dots, n^*, \quad (11b)$$

where the subscripts x_i denote partial derivatives with respect to that variable. Note that, due to the structure of these conditions, whenever a set of infinitesimals $\eta_i, i = 1, \dots, n$ is admitted, also the infinitesimals $\eta'_i = \theta_j \eta_i, i = 1, \dots, n$ are admitted. The next step is to choose an *Ansatz* for the infinitesimals $\eta_i(\mathbf{x}), i = 1, \dots, n$. This corresponds to a restriction to a subclass of symmetries the admitted transformations are sought in.

2. Polynomial generators

Many elementary transformations are generated by infinitesimals which are simple powers of the variable. Examples are

$$x_i^* = x_i + \epsilon, \quad \mathbf{X} = \frac{\partial}{\partial x_i} \quad (\text{translation})$$

$$x_i^* = e^\epsilon x_i, \quad \mathbf{X} = x_i \frac{\partial}{\partial x_i} \quad (\text{scaling})$$

$$\begin{aligned}
 x_i^* &= \frac{x_i}{1 - \epsilon x_i}, & \mathbf{X} &= x_i^2 \frac{\partial}{\partial x_i} \quad (\text{Möbius}) \\
 & \vdots \\
 x_i^* &= \frac{x_i}{[1 - (p-1)\epsilon x_i^{p-1}]^{\frac{1}{p-1}}}, & \mathbf{X} &= x_i^p \frac{\partial}{\partial x_i} \quad (\text{higher order}).
 \end{aligned}$$

Although the structures of these common transformations are rather different, their infinitesimals are given by similar expressions of the form x_i^d , $d \in \mathbb{N}$. This motivates the polynomial *Ansatz*

$$\eta_i(x_i) = \sum_{d=0}^{d_{\max}} r_{i,d} x_i^d, \quad i = 1, \dots, n. \quad (12)$$

The goal is then to determine the coefficients $r_{i,d}$ for which the corresponding transformation is admitted. If plugged into Eq. (11a), the first sum reduces to a single term because $\frac{\partial \eta_k}{\partial x_j} = 0$ for $j \neq k$. Consequently, the conditions can be multiplied by the denominators Q^{k^2} and $S^{k'^2}$, respectively, to obtain

$$\begin{aligned}
 P^k Q^k \frac{\partial \eta_k}{\partial x_k} - \sum_{i=1}^n \eta_i [P_{x_i}^k Q^k - P^k Q_{x_i}^k] &= 0, \quad k = 1, \dots, m, \\
 \sum_{i=1}^n \eta_i [R_{x_i}^{k'} S^{k'} - R^{k'} S_{x_i}^{k'}] &= 0, \quad k' = 1, \dots, n^*.
 \end{aligned} \quad (13)$$

With *Ansatz* (12), these equations define polynomial expressions which can always be rearranged into the form

$$\sum_{i_1, \dots, i_n} c_{i_1, \dots, i_n}(\mathbf{r}) x_1^{i_1} \cdots x_n^{i_n} = 0,$$

where \mathbf{r} is a vector containing all parameters $r_{i,d}$ and the coefficients c_{i_1, \dots, i_n} are linear in \mathbf{r} . Since the polynomial vanishes if and only if all its coefficients vanish, condition (9) is equivalent to the linear system

$$\mathbf{C} \cdot \mathbf{r} = 0,$$

where the entries of the matrix \mathbf{C} are computed by the differential equations and observation functions via Eq. (13). Consequently, the problem of finding structural nonidentifiabilities in an ODE model was turned into the problem of solving a linear system of size $N_r = n(d_{\max} + 1)$. However, there can be admitted transformations which are not covered by *Ansatz* (12). In order to also detect these symmetries using the presented approach, a more general *Ansatz* is required. The intuitive generalization of the infinitesimals is to allow multivariate polynomials where the infinitesimal of state x_i can also depend on other variables $x_{j \neq i}$. Hereby, the most general polynomial *Ansatz* is given by

$$\begin{aligned}
 \eta_i(\mathbf{x}) &= \sum_{d_1, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_1^{d_1} \cdots x_{m+p}^{d_{m+p}} \\
 i &= 1, \dots, m \quad (\text{concentrations}), \\
 \eta_i(\mathbf{x}) &= \sum_{d_{m+1}, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_{m+1}^{d_{m+1}} \cdots x_{m+p}^{d_{m+p}}
 \end{aligned}$$

$i = m + 1, \dots, m + p$ (parameters),

$$\eta_i(\mathbf{x}) = \sum_{d_1, \dots, d_n=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_1^{d_1} \cdots x_n^{d_n}$$

$i = m + p + 1, \dots, n$ (inputs).

The necessary calculations for solving Eq. (9) are analogous to the case of univariate polynomial generators. For details, the reader is referred to Appendix B.

In summary, we have derived an algorithm to automatically and efficiently search for admitted symmetries in rational ODE models. Unlike the methods used in Refs. [11–14], no random specializations of the determining equations (8) and (11) are utilized but they are converted to a linear system which can be solved directly. Once the form of the infinitesimal generator is chosen and the expressions are combined into the form of Eq. (13), the algorithm performs two major steps. First, the terms in the polynomials are rearranged and combined such that the coefficients which are required to vanish can be extracted. Although these calculations are *a priori* symbolic, they can be performed in a linear vector space because each term in the polynomials is fully defined by its coefficients and exponents. Because the coefficients are always linear in the parameters, both can be represented by a real vector. This step can be performed independently for each differential equation and observation function and, therefore, allows for parallel evaluation. In the second step, the system of linear equations as being defined by the coefficients is solved. This yields the set of infinitesimals which generate admitted transformations. Note that these infinitesimals only generate a basis and every linear combination is also admitted. The solution for the parameters is then plugged into the infinitesimal *Ansatz* which, in turn, fully defines the admitted transformations. The computational complexity of the two algorithm steps is bounded by $\mathcal{O}(N_r^2)$ and $\mathcal{O}(N_r^3)$, respectively, where N_r is the total number of constants in the *Ansatz*. Further details on the computational complexity with univariate and multivariate generators are presented in Appendix C.

III. APPLICATION

In the following, the algorithm introduced above is applied to example ODE models highlighting different aspects of the general theory. In particular, the significance of higher-order generators is demonstrated. For details on how these examples are analyzed with our Python implementation see [15].

A. Higher-order symmetries in simple examples

As a simple example, consider the chemical reaction



which is modeled by the differential equation

$$\dot{A}(t) = -2k A^2(t). \quad (14)$$

We assume that A is measurable on a relative scale and the observation saturates for high values:

$$A^{\text{obs}}(t) = s_1 \frac{A(t)}{1 + s_2 A(t)}. \quad (15)$$

If the univariate polynomial *Ansatz* (12) is used to solve the symmetry condition (13) for this system, two distinct solutions are found.

1. Solution 1

The first solution is given by the infinitesimals

$$\eta_A = A, \quad \eta_k = -k, \quad \eta_{s_1} = -s_1, \quad \eta_{s_2} = -s_2,$$

which results in the infinitesimal generator

$$X = A \frac{\partial}{\partial A} - k \frac{\partial}{\partial k} - s_1 \frac{\partial}{\partial s_1} - s_2 \frac{\partial}{\partial s_2}.$$

It corresponds to a scaling of species *A* by

$$A^* = \exp[\epsilon \mathbf{X}]A = e^\epsilon A,$$

together with a reversed scaling of the parameters

$$k^* = e^{-\epsilon} k, \quad s_1^* = e^{-\epsilon} s_1, \quad s_2^* = e^{-\epsilon} s_2.$$

The scaled species *A** satisfies the same ODE because all the scaling factors *e^ϵ* cancel out in the differential equation (14). Furthermore, in the observation function (15), the scaling is compensated by the transformation of the parameters *s₁* and *s₂* leaving *A^{obs}* invariant. The admittance of this transformation expresses the fact that the unit in which *A* is measured is not determined due to the relative measurement.

2. Solution 2

The second solution of the determining equations (13) is given by the infinitesimals

$$\eta_A = A^2, \quad \eta_k = 0, \quad \eta_{s_1} = 0, \quad \eta_{s_2} = 1,$$

which generate the Möbius transformation

$$A^* = \frac{A}{1 - \epsilon A}, \quad s_2^* = s_2 + \epsilon. \tag{16}$$

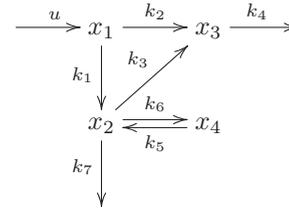
In this case, it is not immediately obvious that the transformed concentration *A** solves the same differential equation. However, if also the time derivative of the transformation

$$\frac{\partial A^*}{\partial t} = \dot{A}^* = \frac{\dot{A}}{(1 - \epsilon A)^2}$$

is plugged into Eq. (14) it is indeed fulfilled. Note that by Theorems 1 and 2 this is equivalent to calculating $\dot{A}^* = \exp[\epsilon \mathbf{X}']\dot{A}$, where \mathbf{X}' is the extended infinitesimal generator (7). On the other hand, the observation *A^{obs}* is not altered because the transformation of *A* and the second factor in Eq. (15) have the same structure and if the transformations (16) are plugged in the transformation parameter ϵ cancels out. In fact, the second factor in Eq. (15) itself can be viewed as an element of the transformation group with transformation parameter $\epsilon = -s_2$.

This example pinpoints one source of second order symmetries. The quadratic rate expression $-2kA^2$ of Eq. (14), generated by the bimolecular reaction, is preserved by the Möbius transformation because of its quadratic generator. On the other hand, the observation function allows the interpretation as a transformation, corresponding to a measurement technique that is affected by saturation effects.

In general, observation functions can also compensate transformations which do not have the same structure, as demonstrated in the following example taken from [9]:



Here, the input function *u(t)* is assumed to be known and *x₂* and *x₃* are measurable on a relative scale. This results in the following linear ODE model:

$$\begin{aligned} \dot{x}_1 &= u - (k_1 + k_2)x_1, & x_2^{\text{obs}} &= s_2 x_2, \\ \dot{x}_2 &= k_1 x_1 - (k_3 + k_6 + k_7)x_2 + k_5 x_4, & x_3^{\text{obs}} &= s_3 x_3, \\ \dot{x}_3 &= k_2 x_1 + k_3 x_2 - k_4 x_3, \\ \dot{x}_4 &= k_6 x_2 - k_5 x_4. \end{aligned} \tag{17}$$

Because *u(t)* is known, it cannot be transformed and $\eta_u = 0$ must hold. The system does not admit symmetries which are generated by univariate polynomial infinitesimals. However, the application of one of the more general multivariate *Ansatz* functions reveals an admitted transformation which is determined by the infinitesimal generator

$$\begin{aligned} \mathbf{X} &= k_1 k_2 \left(\frac{\partial}{\partial k_1} - \frac{\partial}{\partial k_2} \right) - k_3 (k_1 + k_2) \left(\frac{\partial}{\partial k_3} - \frac{\partial}{\partial k_7} \right) \\ &\quad - k_2 s_2 \frac{\partial}{\partial s_2} + k_1 s_3 \frac{\partial}{\partial s_3} + k_2 x_2 \frac{\partial}{\partial x_2} \\ &\quad - k_1 x_3 \frac{\partial}{\partial x_3} + k_2 x_4 \frac{\partial}{\partial x_4}. \end{aligned} \tag{18}$$

The necessary computations take about 15 s on a standard PC, which is due to the high number of constants required in the multivariate polynomial *Ansatz*. In order to construct the explicit transformation $x_i^* = \exp[\epsilon \mathbf{X}]x_i$ for this symmetry, it has to be slightly modified and integrated, which can be found in Ref. [9]. However, even without the explicit transformation it can be seen from the infinitesimals $\eta_{x_2} = k_2 x_2$ and $\eta_{x_3} = -k_1 x_3$ that the transformations of *x₂* and *x₃* are not of the scaling type but also depend on the parameters *k₁* and *k₂*.

B. Symmetries of a complex signaling pathway

In a next step, the presented method is applied to an ODE model of the NFκB signaling pathway. The parameters occurring in the ODE model, i.e., initial conditions, rate constants, and observation parameters, are *a priori* unknown. Therefore, in a modeling application, they would need to be determined from experimental data. However, every parameter involved in a symmetry transformation of the ODE cannot be uniquely determined from this data because the observation is left invariant. Note that the scope of this paper is not to make conclusions about the function of the NFκB pathway. Here, it is solely used as a complex, interesting example to demonstrate the relationship between nonidentifiability and the various underlying symmetry transformations.

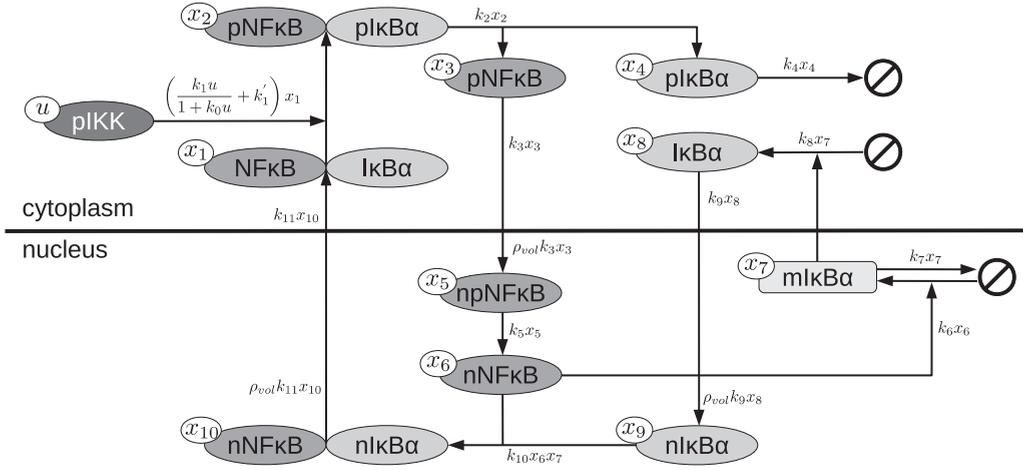


FIG. 1. Reaction scheme of the NF κ B signaling pathway. NF κ B is bound in a complex with I κ B α in the cytoplasm. Complex phosphorylation by pIKK leads to complex dissociation, I κ B α degradation, and NF κ B shuttling to the nucleus. The associated reactions are indicated by arrows labeled by reaction flow expressions.

Figure 1 shows a graphical representation of the analyzed NF κ B model. NF κ B is a transcription factor that is prevented from exerting its activity by its inhibitor I κ B α , with which it is bound in a complex in the cell cytoplasm. Upon stimulation, the complex is phosphorylated by pIKK and dissociates into phosphorylated NF κ B and I κ B α . Whereas I κ B α is degraded, NF κ B shuttles into the nucleus, where it induces gene expression. Besides NF κ B target genes associated with apoptosis, NF κ B induces also gene expression of its own inhibitor, I κ B α , leading to the production of I κ B α mRNA and translation into the I κ B α protein. These I κ B α proteins shuttle into the nucleus, forming complexes with NF κ B which are transported back into the cytoplasm. Depending on the duration of the activating pIKK signal, this cycle begins again, resulting in characteristic NF κ B oscillations. In the model, each of the reactions is associated with a mathematical expression for the reaction flow, indicated as arrow labels in Fig. 1. See Ref. [15] for the comprehensive list of differential equations.

Protein levels of NF κ B are measured independently in the cytoplasm and the nucleus but the measurement technique does not distinguish between single proteins and protein complexes. Phosphorylation of NF κ B and I κ B α is measured in the cytoplasm only. Again, the measurement technique does not distinguish complexes from single molecules. This results in the following observation functions:

$$\begin{aligned} \text{NF}\kappa\text{B}_{\text{cyt}}^{\text{obs}} : y_1 &= s_1(x_1 + x_2 + x_3) + I_{0,\text{cyt}}, \\ \text{NF}\kappa\text{B}_{\text{nuc}}^{\text{obs}} : y_2 &= s_2(x_{10} + x_5 + x_6) + I_{0,\text{nuc}}, \\ \text{pNF}\kappa\text{B}_{\text{cyt}}^{\text{obs}} : y_3 &= s_3(x_2 + x_3), \\ \text{pI}\kappa\text{B}\alpha_{\text{cyt}}^{\text{obs}} : y_4 &= s_4(x_2 + x_4). \end{aligned} \quad (19)$$

Here, the species x_i are numbered according to Fig. 1. The observation parameters $s_1, s_2, s_3, s_4, I_{0,\text{cyt}}$, and $I_{0,\text{nuc}}$ in Eq. (19) are unknown.

The analysis with *Ansatz* (12) and $p_{\text{max}} = 2$ yields five admitted transformations while the computation time is on the order of 1 s. The first four are regular scaling symmetries.

(i) Because there are only relative observations in Eq. (19), it is possible to scale all the internal variables as long as this is compensated by an inverse transformation of the observation parameters:

$$x_i^* = e^\epsilon x_i, \quad i = 1, \dots, 10, \quad s_j^* = e^{-\epsilon} s_j, \quad j = 1, \dots, 4.$$

Here, x_i stands for every concentration in the model except pIKK. In addition, because complex formation in the nucleus described by the reaction flow

$$v = k_{10}x_9x_6$$

involves a product of species, one scaling factor has to be compensated by $k_{10}^* = e^{-\epsilon} k_{10}$.

(ii) The second scaling symmetry is introduced by the factor ρ_{vol} . Because the only measurement in the nucleus has a separate scaling factor, the species in the nucleus can be scaled independently from those in the cytoplasm, i.e., the transformation

$$\rho_{\text{vol}}^* = e^\epsilon \rho_{\text{vol}}, \quad k_i^* = e^{-\epsilon} k_i, \quad s_2^* = e^{-\epsilon} s_2$$

with $i = 6, 10, 11$ and

$$\begin{aligned} x_5^* &= e^\epsilon x_5, & x_6^* &= e^\epsilon x_6, \\ x_9^* &= e^\epsilon x_9, & x_{10}^* &= e^\epsilon x_{10} \end{aligned}$$

is admitted.

(iii) Another symmetry is

$$x_7^* = e^\epsilon x_7, \quad k_6^* = e^\epsilon k_6, \quad k_8 = e^{-\epsilon} k_8.$$

It is admitted because neither is mI κ B α observed nor is its scale coupled to any other concentrations.

(iv) Finally, a fourth admitted scaling transformation is

$$u^* = e^\epsilon u, \quad k_0^* = e^{-\epsilon} k_0, \quad k_1^* = e^{-\epsilon} k_1$$

because these variables only occur as products with each other.

In addition to the scalings, the model admits the higher-order transformation

$$u^* = \frac{u}{1 - \epsilon u}, \quad k_0^* = k_0 + \epsilon. \quad (20)$$

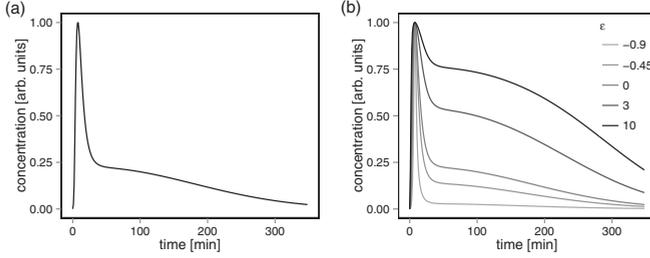


FIG. 2. Different time courses of pIKK. (a) pIKK activation as expected from the literature. (b) Transformation (20) applied to the expected activation for different values of ϵ (renormalized to a peak height of 1).

This solution pinpoints another source for second order transformations. The Möbius transformation generated by $\phi(x) = x^2$ and the Michaelis–Menten-like rate expression

$$v = k_1 x_1 \frac{u}{1 + k_0 u}$$

coincide structurally and, thus, are able to compensate each other. Because the transformation is admitted, a change of the input by transformation (20) results in the same model response and does not change the observation. To illustrate this, Fig. 2(a) shows the time course of pIKK employed as input function in the ODE model. The activation starts with a strong peak in the first 30 min, which is followed by a slower decay starting at about 25% of the peak activation and requiring approximately 6 h for complete deactivation. In Fig. 2(b), transformation (20) is applied to the input for different values of ϵ . This illustrates that the observation remains invariant for inputs which are qualitatively very different. For negative values of ϵ , the plateau is almost removed and the activation is dominated by a sharp peak. On the other hand, for positive values of ϵ , the input becomes more sustained.

C. Reliable model predictions despite structural nonidentifiability

As described in Ref. [14], in case of a model with nonidentifiable variables, Lie group analysis can be utilized to find additional measurements which would make these variables identifiable. However, even if the nonidentifiabilities are not removed by additional experiments, the model can still be employed to make accurate predictions because for every structural nonidentifiability the presented method also yields the underlying transformation. To this end, it is tested if a candidate prediction $y^{\text{pred}}(t) = h(\mathbf{x}(t))$ admits all transformations which are admitted by the model, i.e., it must hold that

$$\mathbf{X} \cdot [y^{\text{pred}} - h(\mathbf{x})] = 0$$

for all infinitesimal generators \mathbf{X} . If this is fulfilled, the predicted quantity is not affected by the admitted transformations, similar to the case of observation functions. Furthermore, if we allow transformations of y^{pred} by assuming $\eta_{y^{\text{pred}}} \neq 0$, it can be detected if a prediction is possible only modulo some specific transformation.

As an example, consider again the NF κ B model of Fig. 1 together with the quantity

$$N_{\text{rel}}^{\text{pred}} : z_1 = \frac{\rho_{\text{vol}}(x_1 + x_2 + x_3)}{x_5 + x_6 + x_{10}},$$

which gives the ratio between the absolute numbers of NF κ B molecules in the cytoplasm and nucleus. If this is analyzed with the presented method, it is revealed that all transformations are admitted by the expression with $\eta_{N_{\text{rel}}^{\text{pred}}} = 0$. Therefore, the quantity can be predicted by the model although all the occurring variables are structurally nonidentifiable. Another example is that of the quantities

$$\text{pIkB}\alpha^{\text{pred}} : z_2 = x_2 + x_4, \quad \text{mIkB}\alpha^{\text{pred}} : z_3 = x_7, \quad (21)$$

which describe the total concentration of phosphorylated IkB α molecules and of IkB α mRNA. These predictions are not possible on an absolute scale. However, by introducing the additional infinitesimals

$$\eta_{\text{pIkB}\alpha^{\text{pred}}} = z_2, \quad \eta_{\text{mIkB}\alpha^{\text{pred}}} = z_3,$$

the symmetries are preserved. These infinitesimals generate scaling transformations, which means that it is possible to predict the relative time courses of the quantities in Eq. (21) despite the structural nonidentifiabilities in the model.

IV. DISCUSSION

Structural nonidentifiabilities in ODE models are generated by admitted transformations, meaning that parameters can be simultaneously transformed in a way that the observed quantities are not altered. Therefore, in order to detect structural nonidentifiability, the search for admitted transformations in the model equations is a promising approach. For this purpose, Lie group theory is a suitable framework as it is capable of handling a large variety of classes of transformations in a uniform way. This is achieved by reformulating every transformation in terms of its infinitesimal generator. Hereby, the necessary calculations can be performed in a linear space, the Lie algebra, which enables the formulation of a compact criterion to guarantee invariance of the observed quantities. The set of coupled partial differential equations arising from this criterion cannot be solved in general. However, in many practical applications, the ODE model consists only of rational equations. In particular, this holds for chemical reaction networks based on mass action, Michaelis–Menten, or Hill kinetics. Furthermore, all of the most frequent transformations are generated by polynomial infinitesimal generators. Based on these assumptions, the criterion for admitted transformations can be reformulated as a set of linear equations. The algorithm we developed to obtain the admitted infinitesimal generators exploits these assumptions to automatically and efficiently search for structural nonidentifiabilities in rational ODE models. To this end it does not rely on random specializations as previous methods but directly converts the conditions to a linear system which can then be solved. As the presented method is independent of any measured data, it is not capable of finding practical nonidentifiabilities which arise due to uncertainties in a given set of measurements. In order to detect also this type of nonidentifiability, a data-based method like the one presented in Ref. [1] has to be utilized.

In the present work, we employed the proposed algorithm in two ways as being illustrated on an ODE model of the NF κ B signal transduction pathway with ten state variables, four observables, one input, and 20 parameters. First, given the observation functions, the algorithm is applied to determine admitted symmetry transformations. The parameters involved in these transformations are structurally nonidentifiable. Most of the found symmetries are of scaling type. Since the determination of protein levels occurs mostly on a relative scale, these observables are compatible with the intrinsic symmetries, yielding nonidentifiable parameters. However, we demonstrated that also Möbius transformations play an important role. This is due to its possible interpretation as saturating observation function or Michaelis–Menten-like rate expression. While saturation of measurement signals frequently occurs due to technical limitations, Michaelis–Menten rates are employed for modeling enzymatic reactions. Both scenarios are frequently found in various applications, underlining the practical relevance of the second order symmetries.

We also tested the performance of the differential algebra for identifiability of systems [7] and exact arithmetic rank [10] methods on our examples. Although they consistently found the same parameters as being nonidentifiable, they give no hint to the underlying transformation. However, this information is crucial for the second application of the proposed method, where we detect quantities which can be predicted by the model even if structural nonidentifiabilities are present. Such a prediction is possible if the corresponding expression is invariant under all admitted transformations or if it is varied with some specific, known transformation.

The limitation of the presented method in terms of feasibility depends on two factors, which are the size of the analyzed model and the size of the infinitesimal generator. While the number of necessary constants quickly rises for multivariate generators, it only grows linearly for the most common transformations like translations, scalings, and Möbius transformations. Therefore, in the latter case, the algorithm can be applied to large models with as much as hundreds of variables.

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APPENDIX A: SYMMETRIES AND STEADY STATE CONDITIONS

Theorem A1 (symmetries of steady state conditions). Let $\eta_i(\mathbf{x})$, $i = 1, \dots, n$ be a set of infinitesimals and let the transformation $x_k^* = \exp[\epsilon \eta_k(\mathbf{x}) \frac{\partial}{\partial x_k}] x_k$, $k = 1, \dots, n$ be admitted by the differential equations $\dot{\mathbf{x}} = f(\mathbf{x}(t))$. Then the transformation is admitted by the steady state condition $f(\mathbf{x}_0) = 0$.

Proof. Because the transformation is admitted by the differential equations, Eq. (8) of the main text holds, which means that

$$\sum_{i=1}^n \eta_i \frac{\partial f_k}{\partial x_i} - \sum_{j=1}^n \frac{\partial \eta_k}{\partial x_j} \dot{x}_j = 0 \quad \text{whenever} \\ \dot{\mathbf{x}} = f(\mathbf{x}) \quad \forall k. \quad (\text{A1})$$

Now let $\mathbf{x}_0 \in \mathbb{R}^n$ be a fixed point with $f(\mathbf{x}_0) = 0$ and hence $\dot{\mathbf{x}}_0 = 0$. If this is plugged into Eq. (A1), we see that

$$\sum_{i=1}^n \eta_i \left. \frac{\partial f_k}{\partial x_i} \right|_{\mathbf{x}=\mathbf{x}_0} - \sum_{j=1}^n \frac{\partial \eta_k}{\partial x_j} \dot{x}_{0j} \\ = \sum_{i=1}^n \eta_i \left. \frac{\partial f_k}{\partial x_i} \right|_{\mathbf{x}=\mathbf{x}_0} = 0 \quad \forall k.$$

Therefore, the symmetry condition

$$\sum_{i=1}^n \eta_i \frac{\partial f_k}{\partial x_i} = 0 \quad \text{whenever} \quad f(\mathbf{x}) = 0 \quad \forall k$$

is fulfilled and the transformation is admitted by the steady state condition. ■

APPENDIX B: MULTIVARIATE POLYNOMIAL GENERATORS

In the most general polynomial *Ansatz*, each infinitesimal $\eta_i(\mathbf{x})$ is given by a multivariate polynomial in all variables. However, as mentioned in Sec. II, the infinitesimals of the concentrations x_i , $i = 1, \dots, m$ cannot depend on the inputs $\mathbf{u}(t)$. In addition, parameters Θ are time-independent states. In order to conserve this independence, the infinitesimals of the Θ transformations can only depend on other parameters. Consequently, the most general polynomial *Ansatz* is

$$\eta_i(\mathbf{x}) = \sum_{d_1, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_1^{d_1} \cdots x_{m+p}^{d_{m+p}} \\ i = 1, \dots, m \quad (\text{concentrations}), \\ \eta_i(\mathbf{x}) = \sum_{d_{m+1}, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_{m+1}^{d_{m+1}} \cdots x_{m+p}^{d_{m+p}} \quad (\text{B1}) \\ i = m+1, \dots, m+p \quad (\text{parameters}), \\ \eta_i(\mathbf{x}) = \sum_{d_1, \dots, d_n=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_1^{d_1} \cdots x_n^{d_n} \\ i = m+p+1, \dots, n, \quad (\text{inputs}).$$

With these infinitesimals, the first sum in the symmetry condition (11a) does not reduce to a single term. Therefore, the equation has to be multiplied by $Q^k \prod_{l=1}^n Q^l$ to obtain a polynomial condition:

$$0 = \sum_{j=1}^m \frac{\partial \eta_k}{\partial x_j} Q^k \left[\prod_{l \neq j} Q^l \right] P^j \\ - \sum_{i=1}^n \eta_i \left[\prod_{l \neq k} Q^l \right] [P_{x_i}^k Q^k - P^k Q_{x_i}^k], \\ k = 1, \dots, m.$$

Analogously to the case of univariate polynomial generators, this can be translated into a linear system for the constants \mathbf{r} by rearranging the terms of the polynomial. The number of

constants $r_{i,\mathbf{p}}$ in the *Ansatz* is given by

$$N_r = \sum_{d=0}^{d_{\max}} \left[m \binom{m+p+d-1}{d} + p \binom{p+d-1}{d} + q \binom{n+d-1}{d} \right], \quad (\text{B2})$$

where $\binom{\cdot}{\cdot}$ denotes binomial coefficients. This shows that for this general *Ansatz* the size of the linear system \mathbf{C} grows rapidly with the number of variables and eventually becomes infeasible for large systems.

A set of infinitesimals which is smaller than Eq. (B1) but still covers a large class of transformations is given by

$$\begin{aligned} \eta_i(\mathbf{x}) &= \sum_{d_k, d_{m+1}, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_i^{d_i} x_{m+1}^{d_{m+1}} \dots x_{m+p}^{d_{m+p}} \\ & i = 1, \dots, m \quad (\text{concentrations}), \\ \eta_i(\mathbf{x}) &= \sum_{d_{m+1}, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_{m+1}^{d_{m+1}} \dots x_{m+p}^{d_{m+p}} \\ & i = m+1, \dots, m+p \quad (\text{parameters}), \\ \eta_i(\mathbf{x}) &= \sum_{d_k, d_{m+1}, \dots, d_{m+p}=0}^{|\mathbf{d}|=d_{\max}} r_{i,\mathbf{d}} x_i^{d_i} x_{m+1}^{d_{m+1}} \dots x_{m+p}^{d_{m+p}} \\ & i = m+p+1, \dots, n, \quad (\text{inputs}), \end{aligned} \quad (\text{B3})$$

i.e., each infinitesimal $\eta_i(\mathbf{x})$ is given by a multivariate polynomial in the corresponding variable x_i and all parameters x_{m+1}, \dots, x_{m+p} . Similarly to the case of univariate polynomial generators, condition (9) can be reduced to Eq. (13) because either $\frac{\partial \eta_i}{\partial x_j} = 0$ or $f_j(\mathbf{x}) = 0$ for $j \neq k$ in the first sum. Therefore, the condition for admitted transformations can also

be reduced to a linear system by multiplication of Q^{k^2} . In this case, the number of constants $r_{i,\mathbf{d}}$ in the *Ansatz* is

$$N_r = \sum_{d=0}^{d_{\max}} \left[m \binom{p+d}{d} + p \binom{p+d-1}{p} + q \binom{p+d}{d} \right] \quad (\text{B4})$$

and therefore only grows with the number of parameters p and not with the total number of variables $n = m + p + q$.

APPENDIX C: COMPUTATIONAL COMPLEXITY

The algorithm described in the main text consists of two major steps. In the first step, the polynomials

$$\begin{aligned} P^k Q^k \frac{\partial \eta_k}{\partial x_k} - \sum_{i=1}^n \eta_i [P_{x_i}^k Q^k - P^k Q_{x_i}^k] &= 0, \quad k = 1, \dots, m, \\ \sum_{i=1}^n \eta_i [R_{x_i}^{k'} S^{k'} - R^{k'} S_{x_i}^{k'}] &= 0, \quad k' = 1, \dots, n^* \end{aligned}$$

[see Eq. (13)] must be reordered such that the exponents of the single summands are unique. The infinitesimals η_k and their derivatives $\frac{\partial \eta_k}{\partial x_k}$ occur only linearly in these equations. Therefore, the number of summands in these equations grows with $\mathcal{O}(N_r)$, where N_r is the total number of constants in the polynomial *Ansatz*. Because all the terms have to be compared to each other for the reduction to a linear system, the complexity of this step is bounded by $\mathcal{O}(N_r^2)$. Finally, the lower upper decomposition which is used to solve the linear system has a time complexity of $\mathcal{O}(N_r^3)$. Consequently, the complexity of the presented algorithm is polynomial in the number of constants N_r which in turn is linear in the number of variables n for the univariate polynomial *Ansatz* and given by Eqs. (B2) and (B4) for the multivariate *Ansätze*.

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