Algorithm to find new identifiable reparametrizations of parametric rational ODE models

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Abstract

Structural identifiability concerns the question of which unknown parameters of a model can be recovered from (perfect) input-output data. If all of the parameters of a model can be recovered from data, the model is said to be identifiable. However, in many models, there are parameters that can take on an infinite number of values but yield the same input-output data. In this case, those parameters and the model are called unidentifiable. The question is then what to do with an unidentifiable model. One can either adjust the model, if experimentally feasible, or try to find a reparametrization to make the model identifiable. In this paper, we take the latter approach. While existing approaches to find identifiable reparametrizations were limited to scaling reparametrizations or were not guaranteed to find a globally identifiable reparametrization even if it exists, we significantly broaden the class of models for which we can find a globally identifiable model with the same input-output behavior as the original one. We also prove that, for linear models, a globally identifiable reparametrization always exists and show that, for a certain class of linear compartmental models, an explicit reparametrization formula exists. We illustrate our method on several examples and provide detailed analysis in supplementary material on github.

I. Introduction

Structural (local) identifiability is a property of an ODE model with parameters

$$\begin{cases} \bar{x}' = \bar{f}(\bar{x}, \bar{\alpha}, \bar{u}) \\ \bar{y} = \bar{g}(\bar{x}, \bar{\alpha}, \bar{u}), \end{cases}$$

as to whether the parameters $\bar{\alpha}$ can be uniquely determined (or determined up to finitely many choices) from the inputs $\bar{u}$ and outputs $\bar{y}$ of the model. If a parameter is not locally identifiable, then it is not possible to estimate its numerical values from measurements of the outputs. Non-identifiability occurs rather frequently in models used in practice [2]. Therefore, it is important to develop theory and algorithms that can remove non-identifiability. Achieving only local identifiability for a model (finitely many parameter values fit the data) can still be problematic for many algorithms and software packages for parameter estimation. This is because these algorithms typically cannot find all of the multiple parameter values that fit the data, and multiple values can fit into the physically meaningful ranges [2]. As a result, errors in such methods can easily be much higher than for globally identifiable models, see the locally identifiable Biohydrogenation, Mammillary 4, and SEIR models in the tables in [3]. Therefore, it is important to find a globally rather than just locally identifiable reparametrization.

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In this paper, we discuss closely related properties called global and local input-output (IO) identifiability, which concern determining the parameters from IO-equations, i.e. the equations relating the inputs and the outputs obtained by eliminating the state variables. Global (resp., local) IO-identifiability and global (resp., local) identifiability are not logically equivalent. However, there are sufficient conditions for the equivalence, see [29], which can be checked algorithmically and often (but not always) hold in practical models.

We propose a new method of reparametrizing an ODE model to achieve at least local structural IO-identifiability of the parameters of the reparametrized system. Whenever possible within the framework of our approach, this allows us to find a globally IO-identifiable reparametrization. However, there are ODE models for which no globally IO-identifiable reparametrizations exist regardless of the approach taken, see [27, Section IV.A]. Maple code for our illustrating examples can be found in [23]. We also prove a new general result that, for linear models with or without inputs, a globally IO-identifiable reparametrization always exists. Additionally, for a class of linear compartmental models without inputs, we obtain explicit reparametrization formulas.

Efficient algorithms are available for finding scaling [11] or, more generally, linear reparametrizations or linear reparametrizations [14, 25]. Further refinements are available for scaling reparametrizations of linear compartmental models [1, 21]. Several approaches have been proposed for producing locally identifiable reparametrizations [8, 15, 20], which succeed in finding nontrivial parametrizations for models from the literature but are not guaranteed to produce a reparametrization if it exists. Another recent approach [27] gives an algorithm for reparametrizing the model preserving its structure. This approach has shown to be practical in many cases. However, it has a noticeable drawback. In particular, the requirement in [27] to preserve the structure can result in not being able to find an IO globally identifiable reparametrization when it exists; see [27, Section IV.B] or Section E from our paper for examples, which is a limitation of that approach that we do not have in our proposed approach.

The paper is organized as follows. Basic definitions, including IO-identifiability, are given in Section III. Our main algorithm is in Section IV. We illustrate the algorithm in Section V using toy models, a Lotka-Volterra model with input, a chemical reaction network model, a biohydrogenation model, which is rational (non-polynomial), a bilinear model with input, and a linear compartmental model for which no scaling reparametrization exists. In Section VI, based on our algorithm, we establish the existence of globally IO-identifiable reparametrizations for linear models, and we also provide new general explicit reparametrization formulas, which we discovered using our software.

II. Problem statement

Given an ODE system

$$\Sigma(\bar{\alpha}) := \begin{cases} \bar{x}' = \bar{f}(\bar{x}, \bar{\alpha}, \bar{u}) \\ \bar{y} = \bar{g}(\bar{x}, \bar{\alpha}, \bar{u}), \end{cases} \tag{1}$$

where $\bar{f}$ and $\bar{g}$ are rational functions over $\mathbb{Q}(\bar{\alpha})$, find $\bar{\beta}$ in the algebraic closure of $\mathbb{Q}(\bar{\alpha})$ and $\bar{w}$ in the algebraic closure of $\mathbb{Q}(\bar{x}, \bar{\alpha}, \bar{u}, \bar{u}', \bar{u}'', \ldots)$ such that

- there exist $\bar{F}, \bar{G}$ in $\mathbb{Q}(\bar{w}, \bar{\beta}, \bar{u}, \bar{u}', \bar{u}'', \ldots)$ with $|\bar{F}| = |\bar{w}|$ and $|\bar{G}| = |\bar{y}|$ such that

$$\begin{cases} \bar{w}' = \bar{F}(\bar{w}, \bar{\beta}, \bar{u}, \bar{u}', \bar{u}'', \ldots) \\ \bar{y} = \bar{G}(\bar{x}, \bar{\beta}, \bar{u}, \bar{u}', \bar{u}'', \ldots). \end{cases} \tag{2}$$

  We will denote this system by $\tilde{\Sigma}(\bar{\beta})$.

- all parameters $\bar{\beta}$ in $\tilde{\Sigma}(\bar{\beta})$ are at least locally IO-identifiable and
- the IO-equations of $\Sigma(\bar{\alpha})$ and $\tilde{\Sigma}(\bar{\beta})$ are the same.

Sometimes in the literature, the ground field is taken to be $\mathbb{C}$ instead of $\mathbb{Q}$. The reader may substitute $\mathbb{C}$ for $\mathbb{Q}$ everywhere in this paper. We prefer to work with the rational numbers as they are more amenable to machine computations.

III. Definitions and notation

In this section, we recall the standard terminology from differential algebra that is used in working with IO-identifiability.

1. A *differential ring* $(R, ')$ is a commutative ring with a derivation $' : R \to R$, that is, a map such that, for all $a, b \in R$, $(a+b)' = a' + b'$ and $(ab)' = a'b + ab'$.
2. The *ring of differential polynomials* in the variables $x_1, \ldots, x_n$ over a field K is the ring $K[x_j^{(i)} \mid i \geqslant 0,\ 1 \leqslant j \leqslant n]$ with a derivation defined on the ring by $(x_j^{(i)})' := x_j^{(i+1)}$. This differential ring is denoted by $K\{x_1, \ldots, x_n\}$.
3. An ideal I of a differential ring $(R, ')$ is called a *differential ideal* if, for all $a \in I$, $a' \in I$. For $F \subset R$, the smallest differential ideal containing the set F is denoted by $[F]$.
4. For an ideal I and element a in a ring R, we denote $I : a^\infty = \{r \in R \mid \exists \ell : a^\ell r \in I\}$. This set is also an ideal in R.
5. An ideal P of a commutative ring R is said to be prime if, for all $a, b \in R$, if $ab \in P$ then $a \in P$ or $b \in P$.
6. Given Σ as in (II), we define the differential ideal of Σ as $I_\Sigma = [Q\bar{x}' - \bar{f}, Q\bar{y} - \bar{g}] : Q^\infty \subset \mathbb{Q}(\bar{\alpha})\{\bar{x}, \bar{y}, \bar{u}\}$, where Q is the common denominator of $\bar{f}$ and $\bar{g}$. By [10, Lemma 3.2], I_Σ is a prime differential ideal.
7. A *differential ranking* on $K\{x_1, \ldots, x_n\}$ is a total order $>$ on $X := \{x_j^{(i)} \mid i \geqslant 0,\ 1 \leqslant j \leqslant n\}$ satisfying:
   - for all $x \in X$, $x' > x$ and
   - for all $x, y \in X$, if $x > y$, then $x' > y'$).

   It can be shown that a differential ranking on $K\{x_1, \ldots, x_n\}$ is always a well order. The ranking is *orderly* if moreover for all i, j, o_1, and o_2, if $o_1 > o_2$, then $x_i^{(o_1)} > x_j^{(o_2)}$.
8. For $f \in K\{x_1, \ldots, x_n\} \backslash K$ and differential ranking $>$,
   - $\operatorname{lead}(f)$ is the element of $\{x_j^{(i)} \mid i \geqslant 0, 1 \leqslant j \leqslant n\}$ appearing in f that is maximal with respect to $>$.
   - The leading coefficient of f considered as a polynomial in $\operatorname{lead}(f)$ is denoted by $\operatorname{in}(f)$ and called the initial of f.
   - The separant of f is $\frac{\partial f}{\partial \operatorname{lead}(f)}$, the partial derivative of f with respect to $\operatorname{lead}(f)$.
   - The rank of f is $\operatorname{rank}(f) = \operatorname{lead}(f)^{\deg_{\operatorname{lead}(f)} f}$.
   - For $S \subset K\{x_1, \ldots, x_n\} \backslash K$, the set of initials and separants of S is denoted by H_S.
   - for $g \in K\{x_1, \ldots, x_n\} \backslash K$, say that $f < g$ if $\operatorname{lead}(f) < \operatorname{lead}(g)$ or $\operatorname{lead}(f) = \operatorname{lead}(g)$ and $\deg_{\operatorname{lead}(f)} f < \deg_{\operatorname{lead}(g)} g$.
9. For $f, g \in K\{x_1, \ldots, x_n\} \backslash K$, f is said to be reduced w.r.t. g if no proper derivative of $\operatorname{lead}(g)$ appears in f and $\deg_{\operatorname{lead}(g)} f < \deg_{\operatorname{lead}(g)} g$.
10. A subset $\mathcal{A} \subset K\{x_1, \ldots, x_n\} \backslash K$ is called *autoreduced* if, for all $p \in \mathcal{A}$, p is reduced w.r.t. every element of $\mathcal{A} \setminus \{p\}$. One can show that every autoreduced set has at most n elements (like a triangular set but unlike a Gröbner basis in a polynomial ring).
11. Let $\mathcal{A} = \{A_1, \ldots, A_r\}$ and $\mathcal{B} = \{B_1, \ldots, B_s\}$ be autoreduced sets such that $A_1 < \ldots < A_r$ and $B_1 < \ldots < B_s$. We say that $\mathcal{A} < \mathcal{B}$ if

- $r > s$ and $\operatorname{rank}(A_i) = \operatorname{rank}(B_i)$, $1 \leqslant i \leqslant s$, or
- there exists q such that $\operatorname{rank}(A_q) < \operatorname{rank}(B_q)$ and, for all i, $1 \leqslant i < q$, $\operatorname{rank}(A_i) = \operatorname{rank}(B_i)$.

12. An autoreduced subset of the smallest rank of a differential ideal $I \subset K\{x_1, \ldots, x_n\}$ is called a *characteristic set* of I. One can show that every non-zero differential ideal in $K\{x_1, \ldots, x_n\}$ has a characteristic set. Note that a characteristic set does not necessarily generate the ideal.

Definition 1 (IO-identifiability)**.** The smallest field k such that

- $\mathbb{Q} \subset k \subset \mathbb{Q}(\bar{\alpha})$ and
- $I_\Sigma \cap \mathbb{Q}(\bar{\alpha})\{\bar{y}, \bar{u}\}$ is generated as a differential ideal by $I_\Sigma \cap k\{\bar{y}, \bar{u}\}$

is called *the field of globally IO-identifiable functions*.

We call $h \in \mathbb{Q}(\bar{\alpha})$ *globally IO-identifiable* if $h \in k$. We also call $h \in \mathbb{Q}(\bar{\alpha})$ *locally IO-identifiable* if h is in the algebraic closure of the field k.

Definition 2 (IO-equations)**.** Given a differential ranking on the differential variables $\bar{y}$ and $\bar{u}$, the *IO-equations* are defined as the monic characteristic presentation of the prime differential ideal $I_\Sigma \cap \mathbb{Q}(\bar{\alpha})\{\bar{y}, \bar{u}\}$ with respect to this ranking (see [29, Definition 6 and Section 5.2] for more details). For a given differential ranking, such a monic characteristic presentation is unique [4, Theorem 3].

Let $\bar{\beta}$ generate the field of globally IO-identifiable functions of the parameters. The tuple $\bar{\beta}$ can be computed as the set of coefficients of input-output equations, which are a canonical (still can depend on the choice of ranking the variables) characteristic set of the projection of (1) to the $(\bar{u}, \bar{y})$-variables [29, Corollary 1]. On a computer, this can be done, for instance, in MAPLE using `RosenfeldGroebner` or `ThomasDecomposition`. An implementation that further simplifies $\bar{\beta}$ is available at https://github.com/pogudingleb/AllIdentifiableFunctions as a part of [26].

IV. Main algorithm

We break down our approach into the following several **steps**, which we describe and justify in detail in Theorem 1:

1. Find input-output equations, view them as algebraic equations E, and compute the rational parametrization of the variety V defined by $(E) : H_E^\infty$ induced by the Lie derivatives of the output variables.
2. Create a polynomial system of equations based on the computed parametrization solutions of which provide another rational parametrization of V but now over (the algebraic closure of) the field of identifiable functions. Pick a solution, and therefore, a locally IO-identifiable rational parametrization of V. Whenever it exists, pick such a solution that results in a globally IO-identifiable rational parametrization of V.
3. Reconstruct a locally (or globally if it exists) IO-identifiable ODE system from the new rational parametrization, cf. [6].
4. By comparing the two rational parametrizations of V, find the corresponding change of state variables using Gröbner bases.

Theorem 1. *There is an algorithm solving the local IO-identifiable reparametrization problem from Section II for system (1), whose detailed steps are given in the proof. Furthermore,*

- *as in [27, Theorem 1], if the sum of the orders with respect to the $\bar{y}$-variables of the IO-equations is equal to the dimension of the model, the state variables of the reparametrized system can be expressed as algebraic functions of $\bar{x}$ and $\bar{\alpha}$.*
- *If the ODE system (1) has a globally IO-identifiable reparametrization whose Lie derivatives have monomial support being a subset of the monomial support of the Lie derivatives for (1), then we can find this globally IO-identifiable reparametrization of (1).*

Proof. We follow the four steps outlined above.

1. **Rational parametrization of IO-equations.** By computing Lie derivatives of $\bar{y}, \ldots, \bar{y}^{(n)}$ using (II), for each i, we can write $y_s^{(i)}$ as a rational function to fix in the rest to work for rational ODEs
$$h_{s,i}\left(\hat{x}, \bar{\alpha}, \bar{u}, \ldots, \bar{u}^{(i)}\right) = \frac{\sum_{m \in M_1} m(\bar{\alpha}) \cdot p_{s,m}\left(\hat{x}, \bar{u}, \ldots, \bar{u}^{(i)}\right)}{\sum_{m \in M_2} m(\bar{\alpha}) \cdot q_{s,m}\left(\hat{x}, \bar{u}, \ldots, \bar{u}^{(i)}\right)} \quad (3)$$
for some sets M_1 and M_2 of polynomials m in the indeterminates $\bar{\alpha}$, where $\hat{x}$ are the variables from $\bar{x}$ that explicitly appear in the Lie derivatives for $\bar{y}, \ldots, \bar{y}^{(n)}$, and the p's and q's are polynomials over $\mathbb{Q}$. Let
$$Y_s\left(\bar{\beta}, \bar{y}, \ldots, \bar{y}^{(n_s)}, \bar{u}, \ldots, \bar{u}^{(n_s)}\right) = 0, \quad 1 \leqslant s \leqslant |\bar{y}| \quad (4)$$
be the input-output equations E with respect to an *orderly* ranking on $\mathbb{Q}\{\bar{y}\}$, where here we write $|\bar{y}|$ for the length of the tuple of variables $\bar{y}$. Note that the rational functions $h_{s,i}$ considered as functions from the affine space $\mathbb{A}^{|\hat{x}|}$ with $\hat{x}$ coordinates to the affine $(n_1 + \ldots + n_{|\bar{y}|})$-space is a rational parametrization over $\mathbb{Q}(\bar{\beta})\langle\bar{u}\rangle$ $h : \mathbb{A}^{|\hat{x}|} \to V$ of the affine variety V defined over $\mathbb{Q}(\bar{\beta})\langle\bar{u}\rangle$ by the input-output equations: V is the zero set of the ideal
$$I_V := (E) : H_E^\infty.$$
Since I_Σ is a prime differential ideal, the differential ideal $I_\Sigma \cap \mathbb{Q}(\bar{\beta})\{\bar{y}, \bar{u}\}$ is prime. Since E is a characteristic set of $I_\Sigma \cap \mathbb{Q}(\bar{\beta})\{\bar{y}, \bar{u}\}$, we have
$$I_\Sigma \cap \mathbb{Q}(\bar{\beta})\{\bar{y}, \bar{u}\} = [E] : H_E^\infty.$$

By Rosenfeld's lemma from differential algebra [18, Lemma III.8.5], the polynomial ideal I_V is prime as well, and so V is an irreducible affine variety.

If $|\hat{x}| = \dim V$, define $\tilde{x} := \hat{x}$. If $|\hat{x}| > \dim V$, then we look for a linear change of variables $\hat{x} = A\tilde{x}$ for some matrix over $\mathbb{Q}$ of rank $\dim V$ defining a linear map $L : \mathbb{A}^{\dim V} \to \mathbb{A}^{|\hat{x}|}$ so that $h \circ L : \mathbb{A}^{\dim V} \to V$ is a parameterization of V. On general grounds, almost any A works.

We then have

$$n_1 + \ldots + n_{|\bar{y}|} = \operatorname{trdeg} \mathbb{Q}(\bar{\alpha})\langle \bar{y}, \bar{u}\rangle / \mathbb{Q}(\bar{\alpha})\langle \bar{u}\rangle = |\tilde{x}|. \quad (5)$$

Let $M = \{m_1, \ldots, m_q\}$. Note that

$$Y_s\left(\bar{\beta}, \bar{y}, \ldots, \bar{y}^{(n_s)}, \bar{u}, \ldots, \bar{u}^{(n_s)}\right)|_{\bar{y}^{(i)} = h_{s,i}, 1 \leqslant i \leqslant n_s} = 0 \quad (6)$$

holds for all s, $1 \leqslant s \leqslant |\bar{y}|$.

2. **Rational parametrization over identifiable parameters.** Consider the new indeterminates $z_1, \ldots, z_q$ and the rational functions

$$H_{s,i}(\bar{z}, \tilde{x}, \bar{u}, \ldots, \bar{u}^{(i)}) := h_{s,i}|_{L(\tilde{x}) = \hat{x},\ m_j = z_j, 1 \leqslant j \leqslant q}, \quad 0 \leqslant i \leqslant n_s.$$

By (6), the system of polynomial equations (after clearing out the denominators)

$$Y_s(\bar{\beta}, H_{s,0}, \ldots, H_{s,n_s}, \bar{u}, \ldots, \bar{u}^{(n)})|_{y_s^{(i)} = h_{s,i}} = 0 \quad (7)$$

in the variables $z_1, \ldots, z_q$ has a solution in $\mathbb{Q}(\bar{\alpha})$. Since the coefficients of the system belong to $\mathbb{Q}(\bar{\beta})$, it has a solution $\bar{\gamma}$ in the algebraic closure of $\mathbb{Q}(\bar{\beta})$.

3. **Identifiable ODE realization of the IO-equations given the new rational parametrization.** Consider now

$$H_{s,0}(\bar{\gamma}, \bar{w}, \bar{u}), \ldots, H_{s,n_s}(\bar{\gamma}, \bar{w}, \bar{u}, \ldots, \bar{u}^{(n_s)}), \quad (8)$$

in which we replaced $\tilde{x}$ by the new indeterminates $\bar{w}$, and try to find an explicit ODE system (cf. [6])

$$\begin{cases} \bar{w}' = F(\bar{\gamma}, \bar{w}, \bar{u}, \ldots, \bar{u}^{(n+1)}), \\ \bar{y} = G(\bar{\gamma}, \bar{w}, \bar{u}, \ldots, \bar{u}^{(n+1)}) \end{cases} \quad (9)$$

so that the input-output equations of (38) coincide with (4) as follows by making sure that (8) are the Lie derivatives of $\bar{y}$. We have

$$H_{1,1} = \bar{y}' = H_{1,0}' = \frac{\partial H_{1,0}}{\partial \bar{w}}\bar{w}' + \sum \frac{\partial H_{1,0}}{\partial \bar{u}}\bar{u}' = \frac{\partial H_{1,0}}{\partial \bar{w}}F + \frac{\partial H_{1,0}}{\partial \bar{u}}\bar{u}'$$

$$\vdots$$

$$H_{1,n_1} = y^{(n_1)} = H_{1,n_1-1}' = \frac{\partial H_{1,n_1-1}}{\partial \bar{w}}\bar{w}' + \sum \frac{\partial H_{1,n_1-1}}{\partial \bar{u}}\bar{u}' = \frac{\partial H_{1,n_1-1}}{\partial \bar{w}}F + \sum_{i=0}^{n} \frac{\partial H_{1,n_1-1}}{\partial \bar{u}^{(i)}}\bar{u}^{(i+1)}$$

$$\vdots$$

Define an $(n_1 + \ldots + n_{|\bar{y}|})$-vector

$$H = \begin{pmatrix} H_{1,1} - \sum_{i=0}^{n} \frac{\partial H_{1,0}}{\partial \bar{u}^{(i)}}\bar{u}^{(i+1)} \\ \vdots \\ H_{1,n_1} - \sum_{i=0}^{n} \frac{\partial H_{1,n_1-1}}{\partial \bar{u}^{(i)}}\bar{u}^{(i+1)} \\ \vdots \\ H_{|\bar{y}|,1} - \sum_{i=0}^{n} \frac{\partial H_{|\bar{y}|,0}}{\partial \bar{u}^{(i)}}\bar{u}^{(i+1)} \\ \vdots \\ H_{|\bar{y}|,n_{|\bar{y}|}} - \sum_{i=0}^{n} \frac{\partial H_{|\bar{y}|,n_{|\bar{y}|}-1}}{\partial \bar{u}^{(i)}}\bar{u}^{(i+1)} \end{pmatrix}$$

and an $(n_1 + \ldots + n_{|\bar{y}|}) \times |\bar{w}|$-matrix (see (5))

$$dH = \left(\frac{\partial H_{1,0}}{\partial \bar{w}}, \ldots, \frac{\partial H_{1,n_1-1}}{\partial \bar{w}}, \ldots, \frac{\partial H_{|\bar{y}|,0}}{\partial \bar{w}}, \ldots, \frac{\partial H_{|\bar{y}|,n_1-1}}{\partial \bar{w}}\right)^T$$

Then the above translates into a linear system in F:

$$dH \cdot F = H.$$

What if $\det dH$ is zero? Then go back and choose a different tuple $\bar{\gamma}$ satisfying (5) and additionally $\det dH \neq 0$.

4. **Corresponding change of variables.** This step is done as [27, Section III, step 4], which computationally is: solving the system of polynomial equations (after clearing out the denominators) $H_{s,i} = h_{s,i}|_{L(\tilde{x}) = \hat{x}}$ for $\bar{w}$. This can be done, for instance, by doing a Gröbner basis computation with an elimination monomial ordering. □

V. Explaining the approach using examples

In this section, we illustrate our approach using a series of examples, intentionally beginning with toy linear models to show the basics first. The non-linear examples are Lotka-Volterra models with input, a polynomial chemical reaction network model, a rational (non-polynomial) biohydrogenration model, and a bilinear model with input. We end the section with a linear compartmental model with input, for which the prior method of finding scaling identifiable reparametrizations failed but our more general method succeeded.

A. Turning local into global identifiability

Consider the system

$$\begin{cases} x_1' = ax_1, \\ x_2' = bx_2, \\ y = x_1 + x_2, \end{cases} \quad (10)$$

and so $\bar{x} = (x_1, x_2)$, $\bar{y} = y$, and $\bar{\alpha} = (a, b)$. There is no $\bar{u}$. The input-output equation is

$$y'' - (a + b)y' + ab \cdot y = 0. \quad (11)$$

Therefore, $\bar{\beta} = (a + b, a \cdot b)$ and the identifiable functions are $K := \mathbb{Q}(a + b, a \cdot b)$, and so a and b are algebraic of degree 2 over K, therefore, are only locally identifiable. The approach from Section IV will proceed as follows. For $i = 0, 1, 2$, we will compute $y^{(i)}$ as a function $h_i(x_1, x_2, a, b)$:

$$\begin{aligned} y &= h_0(x_1, x_2, a, b) = x_1 + x_2, \\ y' &= h_1(x_1, x_2, a, b) = x_1' + x_2' = ax_1 + bx_2, \\ y'' &= h_2(x_1, x_2, a, b) = x_1'' + x_2'' = a^2x_1 + b^2x_2, \end{aligned} \tag{12}$$

and so $\hat{x} = (x_1, x_2)$, $\tilde{x} = \hat{x}$, and $M = \{1, a, b, a^2, b^2\}$. The equations (12) induce the following parametrization of the plane induced by (11), where, since the equation is linear, $(E) : H_E^\infty = (E)$:

$$Y_2 - (a + b)Y_1 + ab \cdot Y_0 = 0, \tag{13}$$

$$\begin{aligned} Y_0 &= x_1 + x_2, \\ Y_1 &= ax_1 + bx_2, \\ Y_2 &= a^2x_1 + b^2x_2. \end{aligned}$$

We now define

$$\begin{aligned} H_0 &= z_1w_1 + z_2w_2, \\ H_1 &= z_3w_1 + z_4w_2, \\ H_2 &= z_5w_1 + z_6w_2. \end{aligned} \tag{14}$$

and search for a reparametrization of (13) of the form defined by (14):

$$(z_5w_1 + z_6w_2) - (a + b)(z_3w_1 + z_4w_2) + ab(z_1w_1 + z_2w_2) = 0,$$

arriving at the following solution set in the z-variables:

$$z_5 = -abz_1 + (a + b)z_3, \quad z_6 = -abz_2 + (a + b)z_4.$$

This solution set has 4 free variables, $z_1, \ldots, z_4$. For the simplicity of the next steps, let us make the following choice:

$$z_1 = 1, \; z_2 = 0, \; z_3 = 0, \; z_4 = 1,$$

which we can adjust later if necessary if the choice makes the next steps degenerate (a non-degenerate choice always exists according to Section IV). So, we have $z_5 = -ab$ and $z_6 = a + b$, which turns (14) into

$$\begin{aligned} H_0 &= w_1, \\ H_1 &= w_2, \\ H_2 &= -abw_1 + (a + b)w_2. \end{aligned} \tag{15}$$

We now construct an ODE realization of (13) from parametrization $Y_0 = H_0, Y_1 = H_1, Y_2 = H_2$ from (15) using the following equations:

$$\begin{aligned} w_1 &= H_0 = y_1, \\ w_1' &= H_0' = y' = H_1 = w_2, \\ w_2' &= H_1' = (y')' = y'' = H_2 = -abw_1 + (a + b)w_2. \end{aligned}$$

Thus, we finally have

$$\begin{cases} w_1' = w_2, \\ w_2' = (a + b) \cdot w_2 - a \cdot b \cdot w_1, \\ y = w_1, \end{cases}$$

We now find the conversion from the x-variables to the w-variables:

$$\begin{cases} w_1 = H_0 = Y_0 = x_1 + x_2, \\ w_2 = H_1 = Y_1 = ax_1 + bx_2. \end{cases}$$

B. Making choices for the non-vanishing of $\det dH$

Consider the system

$$\begin{cases} x_1' = ax_2, \\ x_2' = bx_1, \\ y = x_1, \end{cases} \tag{16}$$

so $\bar{x} = (x_1, x_2)$, $\bar{y} = (y)$, $\bar{\alpha} = (a, b)$, and we have no $\bar{u}$. The input-output equation is

$$y'' - ab \cdot y = 0. \tag{17}$$

Therefore, $\bar{\beta} = (ab)$ and ab is globally identifiable but neither a nor b is identifiable. Following the approach from Section IV, let us begin by computing Lie derivatives of $\bar{y}$. We have

$$\begin{aligned} y &= h_0(x_1, x_2, a, b), = x_1, \\ y' &= h_1(x_1, x_2, a, b) = x_1' = ax_2, \\ y'' &= h_2(x_1, x_2, a, b) = x_1'' = ax_2' = abx_1. \end{aligned} \tag{18}$$

We have $\hat{x} = (x_1, x_2)$, $\tilde{x} = \hat{x}$, and $M = \{1, a, ab\}$. Equations (18) induce the following parametrization of the plane defined by the input-output equation, where, since the equation is linear, $(E) : H_E^\infty = (E)$:

$$Y_2 - ab \cdot Y_0 = 0, \tag{19}$$

$$\begin{aligned} Y_0 &= x_1, \\ Y_1 &= ax_2, \\ Y_2 &= abx_1. \end{aligned}$$

We now define

$$\begin{aligned} H_0 &= z_1w_1, \\ H_1 &= z_2w_2, \\ H_2 &= z_3w_1. \end{aligned} \tag{20}$$

and search for a reparametrization of (19) of the form defined by (20):

$$z_3w_1 - abz_1w_1 = 0,$$

arriving at the following solution set in the z-variables: $z_3 = abz_1$. This solution set has 2 free variables, z_1 and z_2. For the simplicity of the next steps, let us make the following choice: $z_1 = 1, z_2 = 0$, which we can adjust later if necessary if the choice makes the next steps degenerate (a non-degenerate choice always exists according to Section IV). So, we have $z_3 = ab$, which turns (20) into

$$\begin{aligned} H_0 &= w_1, \\ H_1 &= 0, \\ H_2 &= abw_1. \end{aligned} \tag{21}$$

We now construct an ODE realization of (19) from parametrization $Y_0 = H_0, Y_1 = H_1, Y_2 = H_2$ from (21) using the following equations:

$$
\begin{aligned}
y &= H_0 = w_1,\\
w_1' &= H_0' = y' = H_1 = 0.
\end{aligned}
$$

However, we cannot find an ODE for w_2 because it does not appear in the H_i's. So, let us instead choose a non-zero value for z_2, e.g., $z_2 = 1$. Then we have

$$
\begin{aligned}
H_0 &= w_1,\\
H_1 &= w_2,\\
H_2 &= abw_1.
\end{aligned}
\tag{22}
$$

and so we obtain:

$$
\begin{aligned}
y &= H_0 = w_1,\\
w_1' &= H_0' = y' = H_1 = w_2,\\
w_2' &= H_1' = (y')' = y'' = H_2 = abw_1.
\end{aligned}
$$

Thus, we finally have

$$
\begin{cases}
w_1' = w_2,\\
w_2' = abw_1,\\
y = w_1,
\end{cases}
$$

We now find the conversion from the x-variables to the w-variables:

$$
\begin{cases}
w_1 = H_0 = Y_0 = x_1,\\
w_2 = H_1 = Y_1 = ax_2.
\end{cases}
$$

C. Lotka-Volterra examples with input

Consider the system

$$
\begin{cases}
x_1' = ax_1 - bx_1x_2 + u,\\
x_2' = -cx_2 + dx_1x_2,\\
y = x_1
\end{cases}
\tag{23}
$$

with two state variables $\bar{x} = (x_1, x_2)$, four parameters $\bar{\alpha} = (a, b, c, d)$, one output $\bar{y} = y$, and one input $\bar{u} = u$. The input-output equation is

$$
yy'' - y'^2 - dy'y^2 + cyy' + uy' + ady^3 + duy^2 - acy^2 - u'y - cuy = 0. \tag{24}
$$

So, we have that the field of IO-identifiabile functions is $\mathbb{Q}(d, c, ad, ac) = \mathbb{Q}(a, c, d)$. A computation (in MAPLE) shows that $(E) = (E) : H_E^\infty$ in this case. The Lie derivatives of the y-variable are as follows:

$$
\begin{aligned}
y &= x_1,\\
y' &= -bx_1x_2 + ax_1 + u,\\
y'' &= u' - bdx_1^2x_2 - bux_2 + au\\
&\quad + \left(b^2x_2^2 + (-2a + c)bx_2 + a^2\right)x_1
\end{aligned}
\tag{25}
$$

We then have $\tilde{x} = \hat{x} = (x_1, x_2)$, and we now define

$$
\begin{aligned}
H_0 &= z_1w_1\\
H_1 &= z_2w_1w_2 + z_3u + z_4w_1\\
H_2 &= z_5w_1^2w_2 + z_6w_1w_2^2 + z_7uw_2 + z_8w_1w_2\\
&\quad + z_9u + z_{10}u' + z_{11}w_1
\end{aligned}
\tag{26}
$$

Making the substitution $y = H_0, y' = H_1, y'' = H_2$ into (24), we obtain the following polynomial system in $z_1, \ldots, z_{11}$:

$$
\begin{cases}
-dz_1^2z_2 + z_1z_5 = 0\\
adz_1^3 - dz_1^2z_4 = 0\\
z_1z_6 - z_2^2 = 0\\
cz_1z_2 + z_1z_8 - 2z_4z_2 = 0\\
-duz_1^2z_3 - acz_1^2 + duz_1^2 + cz_1z_4 + z_1z_{11} - z_4^2 = 0\\
uz_1z_7 - 2uz_3z_2 + uz_2 = 0\\
(cuz_3 - cu + u'z_{10} - u')z_1 + u(z_9 - 2z_3z_4 + z_4) = 0\\
-u^2z_3^2 + u^2z_3 = 0
\end{cases}
\tag{27}
$$

In the above, u and u' are considered to be in the ground field for solving purposes, so these do not vanish. Also, if $z_1 = 0$, then (26) is degenerate. So, we may assume that $z_1 \neq 0$. To preserve input, we may also assume $z_3 \neq 0$ (so, $z_3 = 1$). Solving system (27) in MAPLE with these assumptions, we arrive at the following solution set, in which z_1, z_7, z_{10} play the role of free variables:

$$
z_2 = z_1z_7,\quad z_3 = 1,\quad z_4 = az_1,\quad z_5 = dz_1^2z_7,\quad z_6 = z_1z_7^2,
$$
$$
z_8 = (2a - c)z_1z_7,\quad z_9 = \frac{au + (1 - z_{10})u'}{u},\quad z_{11} = a^2z_1.
$$

Choosing (since, for us, it is sufficient to pick a solution) $z_1 = z_7 = z_{10} = 1$, we obtain

$$
z_2 = z_3 = z_6 = 1,\ z_4 = z_9 = a,\ z_5 = d,\ z_8 = 2a - c,\ z_{11} = a^2.
$$

Substituting into (25), we obtain

$$
\begin{aligned}
H_0 &= w_1,\\
H_1 &= (a + w_2)w_1 + u,\\
H_2 &= dw_1^2w_2 + \left(w_2^2 + (2a - c)w_2 + a^2\right)w_1 + (a + w_2)u + u'.
\end{aligned}
$$

With the above, we now solve

$$
\begin{aligned}
y &= H_0 = w_1,\\
w_1' &= H_0',\\
(w_1w_2 + aw_1)' &= H_1' = H_2.
\end{aligned}
$$

and obtain the following reparametrized system

$$
\begin{cases}
w_1' = aw_1 + w_1w_2 + u\\
w_2' = -cw_2 + dw_1w_2
\end{cases}
$$

and to find the variable conversion, we solve the system

$$
\begin{aligned}
x_1 &= h_0 = H_0 = w_1,\\
-bx_1x_2 + ax_1 + u &= h_1 = H_1 = w_1w_2 + aw_1 + u,
\end{aligned}
$$

(we omitted the the equation with H_2 because the first two were already sufficient, and the additional one is too big to display and does not change the outcome) finding the following:

$$\begin{cases} w_1 = x_1, \\ w_2 = -bx_2. \end{cases} \tag{28}$$

Here is another Lotka-Volterra model with input [12]

$$\begin{cases} x_1' = ax_1 - bx_1x_2 + ux_1, \\ x_2' = -cx_2 + dx_1x_2 + ux_2, \\ y = x_1. \end{cases}$$

We omit the details because they are mostly the same as in the previous Lotka-Volterra model. The globally IO-identifiable parameters are a, d, c. According to our code, the same change of variables (28) results in the following globally IO-identifiable reparametrization:

$$\begin{cases} w_1' = aw_1 + w_1w_2 + uw_1, \\ w_2' = -cw_2 + dw_1w_2 + uw_2, \\ y = w_1. \end{cases}$$

D. Chemical reaction network example

Consider the following example based on [13, Example 5]:

$$\begin{cases} x_1' = (2k_1 + k_4)x_2^2 - (k_2 + 2k_6)x_1^2 + (k_5 - k_3)x_1x_2, \\ x_2' = -x_1', \\ y = x_1. \end{cases}$$

And, using our code, we obtain the following reparametrized model equations with globally IO-identifiable parameters:

$$\begin{cases} w_1' = \dfrac{(4k_1 + k_3 + 2k_4 - k_5)^2}{2k_1 + k_4} w_2^2 \\ \qquad - \dfrac{(8k_2 + 16k_6)k_1 + (4k_2 + 8k_6)k_4 + (k_3 - k_5)^2}{4(2k_1 + k_4)} w_1^2, \\ w_2' = \dfrac{w_1'}{2}, \\ y = w_1 \end{cases} \tag{29}$$

and the following linear change of variables resulting in (29):

$$\begin{cases} w_1 = x_1, \\ w_2 = \dfrac{k_3 - k_5}{2(4k_1 + k_3 + 2k_4 - k_5)} x_1 - \dfrac{2k_1 + k_4}{4k_1 + k_3 + 2k_4 - k_5} x_2. \end{cases} \tag{30}$$

E. Biohydrogenation model

Consider the following rational ODE model

$$\begin{cases} x_4' = -\dfrac{k_5x_4}{k_6 + x_4}, \\ x_5' = \dfrac{k_5x_4}{k_6 + x_4} - \dfrac{k_7x_5}{k_8 + x_5 + x_6}, \\ x_6' = \dfrac{k_7x_5}{k_8 + x_5 + x_6} - k_9x_6\dfrac{(k_{10} - x_6)}{k_{10}}, \\ x_7' = k_9x_6\dfrac{k_{10} - x_6}{k_{10}}, \\ y_1 = x_4, \quad y_2 = x_5, \end{cases}$$

(see [24, system (3), Supplementary Material 2], initial conditions are assumed to be unknown, the choice of outputs is as in https://maple.cloud/app/6509768948056064).

We have $\bar{x} = (x_4, x_5, x_6, x_7)$, $\bar{y} = (y_1, y_2)$, $\bar{\alpha} = (k_5, k_6, k_7, k_8, k_9, k_{10})$, and there is no $\bar{u}$. Our MAPLE code shows that the field of globally IO-identifiable functions is generated by

$$k_5, \quad k_6, \quad k_7, \quad A := k_9^2, \quad B := \frac{k_{10}}{k_9}, \quad C := k_9\frac{2k_8 + k_{10}}{k_{10}}.$$

We can see from this list that all parameters in this model $k_5, \ldots, k_{10}$ are at least locally IO-identifiable. Therefore, the approach from [27] will leave this model as is, and so will not improve the identifiability properties of the model. In what follows, we will show how our approach makes the model globally IO-identifiable. Our MAPLE code then finds that the resulting reparametrized system is

$$\begin{cases} w_1' = -k_5\dfrac{w_1}{k_6 + w_1}, \\ w_2' = \dfrac{((k_5 - k_7)w_2 + k_5w_3)w_1 - k_6k_7w_2}{(w_2 + w_3)(k_6 + w_1)}, \\ w_3' = \dfrac{\frac{1}{B}w_2w_3^2 - Cw_2w_3 + \left(\frac{BC^2 - AB}{4} + k_7\right)w_2 + \frac{1}{B}w_3^3 - Cw_3^2 + \frac{BC^2 - AB}{4}w_3}{w_2 + w_3}, \\ y_1 = w_1, \quad y_2 = w_2 \end{cases} \tag{31}$$

under the following change of variables: change of variables

$$\begin{cases} w_1 = x_4, \\ w_2 = x_5, \\ w_2 = k_8 + x_6. \end{cases}$$

Using SIAN [9], we have also checked to see that all parameters (and initial conditions) in (31) are globally identifiable. The algorithm from [27] cannot find this reparametrization because it has a different structure, e.g., a smaller number of state variables, among other things.

F. Bilinear model with input

Consider the model [19, Example 1]:

$$\begin{cases} x_1' = -p_1x_1 + p_2u, \\ x_2' = -p_3x_2 + p_4u, \\ x_3' = -(p_1 + p_3)x_3 + (p_4x_1 + p_2x_2)u, \\ y = x_3. \end{cases}$$

Our computation shows that the globally IO-identifiable functions are $p_1p_3, p_2p_4, p_1 + p_3$ and that the following change of variables

$$\begin{cases} w_1 = p_2x_2 + p_4x_1, \\ w_2 = -p_1p_2x_2 - 2p_1p_4x_1 - 2p_2p_3x_2 - p_3p_4x_1, \\ w_3 = x_3 \end{cases}$$

results in the following reparametrized globally IO-identifiable ODE system:

$$\begin{cases} w_1' = (p_1+p_3)w_1 + 2p_2p_4u + w_2, \\ w_2' = (-2p_1^2 - 5p_1p_3 - 2p_3^2)w_1 - 3p_2p_4(p_1+p_3)u + (-2p_1 - 2p_3)w_2, \\ w_3' = -(p_1+p_3)w_3 + uw_1, \\ y = w_3 \end{cases}$$

On the other hand, if one follows the algorithm from [27], one would arrive at the following system of equations and inequations in the unknowns $\widetilde{p_1}, \widetilde{p_2}, \widetilde{p_3}, \widetilde{p_4}$:

$$\begin{cases} p_1p_3 = \widetilde{p_1}\widetilde{p_3}, \\ p_2p_4 = \widetilde{p_2}\widetilde{p_4}, \\ p_1 + p_3 = \widetilde{p_1} + \widetilde{p_3}, \\ \widetilde{p_1}\widetilde{p_2}\widetilde{p_4} - \widetilde{p_2}\widetilde{p_3}\widetilde{p_4} \neq 0. \end{cases}$$

with solutions sought over the algebraic closure of the field $\mathbb{Q}(p_1p_3, p_2p_4, p_1+p_3)$. This system does not have solutions over $\mathbb{Q}(p_1p_3, p_2p_4, p_1+p_3)$ and the method from [27] would just pick a value for $\widetilde{p_2}$, say, $\widetilde{p_2} = 1$, and so $\widetilde{p_4} = p_2p_4$. Thus the method from [27] would arrive at the following ODE model, which is locally but not globally IO-identifiable:

$$\begin{cases} w_1' = -p_1w_1 + u, \\ w_2' = -p_3w_2 + p_2p_4u, \\ w_3' = -(p_1+p_3)w_3 + (p_2p_4w_1 + w_2)u, \\ y = w_3. \end{cases}$$

Here the limitation of [27] that prevents the method from achieving global IO-identifiability is the requirement to keep the same monomial structure in each equation of the reparametrized vs. original ODE model, cf. [27, Section IV.B].

G. *Linear compartmental model with input*

We consider a model that does *not* have an identifiable scaling reparametrization according to [21] and thus could not be reparametrized using that approach. We, however, are able to find a linear reparametrization using our approach.

$$\begin{cases} x_1' = a_{11}x_1 + a_{12}x_2 + u_1 \\ x_2' = a_{22}x_2 + a_{23}x_3 \\ x_3' = a_{31}x_1 + a_{32}x_2 + a_{33}x_3 \\ y_1 = x_1. \end{cases} \tag{32}$$

The IO-equation is

$$y''' - (a_{11}+a_{22}+a_{33})y'' - u_1'' + ((a_{11}+a_{33})a_{22} + a_{11}a_{33} - a_{23}a_{32})y' + (a_{22}+a_{33})u_1' + (-a_{11}a_{22}a_{33} + a_{11}a_{23}a_{32} - a_{12}a_{23}a_{31})y + (-a_{22}a_{33} + a_{23}a_{32})u_1 = 0.$$

The coefficients of this equation generate the field of globally IO-identifiable functions. After simplifying these generators using https://github.com/pogudingleb/AllIdentifiableFu we obtain

$$a_{11},\ a_{12}a_{23}a_{31},\ a_{22}+a_{33},\ a_{22}a_{33} - a_{23}a_{32}$$

as generators of the field of globally IO-identifiable functions. To reparametrize (32), our next step is to find the Lie derivatives, which are:

$$\begin{aligned} y &= x_1, \\ y' &= a_{11}x_1 + a_{12}x_2 + u_1, \\ y'' &= a_{11}^2x_1 + a_{11}a_{12}x_2 + a_{12}a_{22}x_2 + a_{12}a_{23}x_3 + u_1' + a_{11}u_1, \\ y''' &= (a_{11}^3 + a_{12}a_{23}a_{31})x_1 \\ &\quad + (a_{11}^2a_{12} + a_{11}a_{12}a_{22} + a_{12}a_{22}^2 + a_{12}a_{23}a_{32})x_2 \\ &\quad + (a_{11}a_{12}a_{23} + a_{12}a_{22}a_{23} + a_{12}a_{23}a_{33})x_3 \\ &\quad + u_1'' + a_{11}u_1' + a_{11}^2u_1, \end{aligned}$$

which, with undetermined coefficients, takes the form

$$\begin{aligned} H_0 &= w_1z_1, \\ H_1 &= z_2u_1 + z_3w_1 + z_4w_2, \\ H_2 &= z_5u_1 + z_6u_1' + z_7w_1 + z_8w_2 + z_9w_3, \\ H_3 &= z_{10}u_1 + z_{11}u_1' + z_{12}u_1'' + z_{13}w_1 + z_{14}w_2 + z_{15}w_3. \end{aligned} \tag{33}$$

Since the IO-equation E is linear, $(E) = I : H_E^\infty$, so we will be substituting the above H's into E to obtain the following system of linear equations in $z_1, \ldots, z_{15}$, which we solve and obtain

$$\begin{aligned} z_{15} &= (a_{11}+a_{22}+a_{33})z_9, \\ z_{14} &= (a_{23}a_{32} - a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33})z_4 \\ &\quad + (a_{11}+a_{22}+a_{33})z_8, \\ z_{13} &= (a_{11}a_{22}a_{33} - a_{11}a_{23}a_{32} + a_{12}a_{23}a_{31})z_1 \\ &\quad - (a_{11}a_{22} - a_{11}a_{33} - a_{22}a_{33} + a_{23}a_{32})z_3 \\ &\quad + (a_{11}+a_{22}+a_{33})z_7 \\ z_{12} &= -\big((a_{11}a_{22} + a_{11}a_{33} + a_{22}a_{33} - a_{23}a_{32})u_1z_2 \\ &\quad - (a_{11}+a_{22}+a_{33})(u_1z_5 + u_1'z_6) + (a_{23}a_{32} - a_{22}a_{33})u_1 \\ &\quad + (z_{11} + a_{22} + a_{33})u_1' + u_1z_{10} - u_1''\big)/u_1'', \end{aligned}$$

with $z_1, \ldots, z_{11}$ being free variables. We choose the following values for the free variables:

$$z_1 = z_2 = z_4 = z_6 = z_9 = z_{10} = z_{11} = 1, \quad z_3 = z_5 = z_8 = a_{11},\ \ z_7 = a_{11}^2.$$

Substituting this entire solution in (33) and using the relationship $H_0' = H_1$, $H_1' = H_2$, $H_2' = H_3$, we obtain the following reparametrized system:

$$\begin{cases} w_1' = a_{11}w_1 + w_2 + u_1 \\ w_2' = w_3 \\ w_3' = a_{12}a_{23}a_{31}w_1 + (a_{23}a_{32} - a_{22}a_{33})w_2 + (a_{22}+a_{33})w_3, \\ y_1 = w_1. \end{cases}$$

We find the resulting (non-scaling) linear reparameterization:

$$\begin{cases} w_1 = x_1, \\ w_2 = a_{12}x_2, \\ w_3 = a_{12}a_{22}x_2 + a_{12}a_{23}x_3 \end{cases}$$

by setting equal (33) with the found z-values to the Lie derivatives and solving the resulting equations for w_1, w_2, w_3.

VI. Linear models

In this section, we focus on finding globally IO-identifiable reparametrizations of linear ODE models. Theorem 2 gives a general existence result of such reparametrizations based on analyzing our algorithm. Theorems 3 and 4 provide explicit globally IO-identifiable reparametrization formulas for linear compartmental models with single and multiple outputs, respectively. Each of these explicit results is preceded by small examples that we calculated using our software and that gave a hint on what the general result should look like.

A. General existence result

Theorem 2. *Every model (1) in which $\bar{f}$ and $\bar{g}$ are linear has a globally IO-identifiable linear reparametrization obtained by a linear change of variables. Moreover, this reparametrization can be found using the algorithm from Section IV.*

Proof. Since $\bar{f}$ and $\bar{g}$ are linear, the IO-equations are linear in $\bar{y}, \bar{y}', \ldots, \bar{y}^{(n)}$, and so the corresponding variety V is a hyperplane. The Lie derivatives of $\bar{y}$ are also linear in $\bar{x}$ (though could be non-linear in $\bar{\alpha}$, like in (12)). The embedding L from step 1 is linear. Since the coefficients of the monomials in the Lie derivatives are replaced by new indeterminates, the resulting system (7) is linear in the unknowns $z_1, \ldots, z_q$ (and is also consistent), and so it has a solution $\bar{\gamma}$ in $\mathbb{Q}(\bar{\beta})$ itself (without taking the algebraic closure). Since $\mathbb{Q}(\bar{\beta})$ is the field of globally IO-identifiable functions, $\bar{\gamma}$ is globally IO-identifiable.

With this solution $\bar{\gamma}$, the algorithm then proceeds to construct an ODE realization with the new Lie derivatives. This step is done by solving a consistent system of linear equations, and so the result is an ODE system with globally IO-identifiable parameters. Finally, the change of variables from the original $\bar{x}$ to the new $\bar{w}$ is linear as it can be found by setting the old and new expressions of the Lie derivatives of $\bar{y}, \bar{y}', \ldots, \bar{y}^{(n)}$, which are all linear (in $\bar{x}$ and $\bar{w}$, respectively). □

B. Linear Compartmental Models

Definition 3. Let G be a directed graph with vertex set V and set of directed edges E. Each vertex $i \in V$ corresponds to a compartment in our model and an edge $j \to i$ denotes a direct flow of material from compartment j to compartment i. Also introduce three subsets of the vertices $In, Out, Leak \subseteq V$ corresponding to the set of input compartments, output compartments, and leak compartments respectively. To each edge $j \to i$, we associate an independent parameter a_{ij}, the rate of flow from compartment j to compartment i. To each leak node $i \in Leak$, we associate an independent parameter a_{0i}, the rate of flow from compartment i leaving the system.

We associate a matrix A, called the *compartmental matrix* to the graph and the set $Leak$ in the following way:

$$A_{ij} = \begin{cases} -a_{0i} - \sum_{k:i\to k\in E} a_{ki} & \text{if } i = j \text{ and } i \in Leak \\ -\sum_{k:i\to k\in E} a_{ki} & \text{if } i = j \text{ and } i \notin Leak \\ a_{ij} & \text{if } j \to i \text{ is an edge of } G \\ 0 & \text{otherwise} \end{cases}$$

Then we construct a system of linear ODEs with inputs and outputs as follows:

$$\dot{x}(t) = Ax(t) + u(t) \qquad y_i(t) = x_i(t) \text{ for } i \in Out \tag{34}$$

where $u_i(t) \equiv 0$ for $i \notin In$. The resulting model is called a *linear compartmental model*.

For a model as in (34) where there is a leak in every compartment (i.e. $Leak = V$), it can greatly simplify the representation to use the fact that the diagonal entries of A are the only places where the parameters a_{0i} appear. Since these are algebraically independent parameters, we can introduce a new algebraically independent parameter a_{ii} for the diagonal entries (i.e. we make the substitution $a_{ii} = -a_{0i} - \sum_{k:i\to k\in E} a_{ki}$) to get generic parameter values along the diagonal. Identifiability questions in such a model are equivalent to identifiability questions in the model with this reparametrized matrix.

We will be considering graphs that have some special connectedness properties. We define these properties now.

Definition 4. A *path* from vertex i_k to vertex i_0 in a directed graph G is a sequence of vertices $i_0, i_1, i_2, \ldots, i_k$ such that $i_{j+1} \to i_j$ is an edge for all $j = 0, \ldots, k-1$. To a path $P = i_0, i_1, i_2, \ldots, i_k$, we associate the monomial $a^P = a_{i_0 i_1} a_{i_1 i_2} \cdots a_{i_{k-1} i_k}$, which we refer to as a *monomial path*.

Definition 5. A directed graph G is *strongly connected* if there exists a directed path from each vertex to every other vertex.

C. Linear models without inputs

In this section, we give a general technique to reparameterize a linear model without any inputs, but with one or more outputs.

Example 1. Consider the following model:

$$\begin{aligned} \dot{x}_1 &= a_{11}x_1 + a_{12}x_2 + a_{13}x_3 \\ \dot{x}_2 &= a_{21}x_1 + a_{22}x_2 + a_{23}x_3 \\ \dot{x}_3 &= a_{31}x_1 + a_{32}x_2 + a_{33}x_3 \\ y_1 &= x_1 \end{aligned}$$

Here the identifiable functions are

$$\begin{aligned} &a_{11} + a_{22} + a_{33}, \\ &-a_{11}a_{22} - a_{11}a_{33} + a_{12}a_{21} + a_{13}a_{31} - a_{22}a_{33} + a_{23}a_{32}, \\ &a_{11}a_{22}a_{33} - a_{11}a_{23}a_{32} - a_{33}a_{12}a_{21} + a_{12}a_{23}a_{31} \\ &\qquad + a_{13}a_{32}a_{21} - a_{22}a_{13}a_{31} \end{aligned}$$

as these are the coefficients of the characteristic polynomial (up to sign). Using the linear reparameterization:

$$
\begin{aligned}
X_1 &= x_1\\
X_2 &= a_{11}x_1 + a_{12}x_2 + a_{13}x_3\\
X_3 &= (a_{11}^2 + a_{12}a_{21} + a_{13}a_{31})x_1\\
&\quad + (a_{11}a_{12} + a_{22}a_{12} + a_{13}a_{32})x_2\\
&\quad + (a_{11}a_{13} + a_{12}a_{23} + a_{13}a_{33})x_3
\end{aligned}
$$

we obtain the following reparameterized system:

$$
\begin{aligned}
\dot{X}_1 &= X_2\\
\dot{X}_2 &= X_3\\
\dot{X}_3 &= (a_{11}a_{22}a_{33} - a_{11}a_{23}a_{32} - a_{33}a_{12}a_{21} + a_{12}a_{23}a_{31}\\
&\quad + a_{13}a_{32}a_{21} - a_{22}a_{13}a_{31})X_1\\
&\quad + (-a_{11}a_{22} - a_{11}a_{33} + a_{12}a_{21} + a_{13}a_{31} - a_{22}a_{33} + a_{23}a_{32})X_2\\
&\quad + (a_{11} + a_{22} + a_{33})X_3
\end{aligned}
$$

C.1. Reparametrization formula for linear systems with one output

We will now derive an explicit formula for globally IO-identifiable reparametrization of a linear ODE system with one output.

Theorem 3. *Consider a linear system over $\bar{x} = x_1, \ldots, x_n$:*

$$
\begin{cases}
\dot{\bar{x}} = A\bar{x}\\
y_1 = x_1 = C\bar{x},
\end{cases}
$$

where the graph corresponding to A is strongly connected and there is at least one leak and C is the matrix where the $(1, 1)$ entry is 1 and all other entries are zero. Then using the linear reparameterization $X = Px$ given by:

$$
\begin{cases}
X_1 = x_1\\
X_i = \sum_{j=1}^{n} p_{ij}x_j, \quad i = 2, \ldots, n,
\end{cases}
$$

where p_{ij} is the sum of all monomial paths of length $i-1$ from j to 1,

$$p_{ij} = \sum_{\text{length}=i-1} a_{1k_1}a_{k_1k_2}\cdots a_{k_lj}$$

we get a reparameterized globally IO-identifiable (and, by [28, Theorem 1] globally identifiable as well) ODE system:

$$
\begin{aligned}
\dot{X}_1 &= X_2\\
\dot{X}_2 &= X_3\\
&\vdots\\
\dot{X}_{n-1} &= X_n\\
\dot{X}_n &= -c_0X_1 - c_1X_2 - \ldots - c_{n-1}X_n
\end{aligned}
\tag{35}
$$

where c_i is the $n-i^{th}$ coefficient of the characteristic polynomial of A, $i = 1, \ldots, n$. The matrix P is the $n\times n$ observability matrix:

$$
\begin{pmatrix}
C\\
CA\\
\vdots\\
CA^{n-1}
\end{pmatrix}
$$

Proof. A direct calculation shows that

$$y_1^{(n)} + c_{n-1}y_1^{(n-1)} + \ldots + c_1\dot{y}_1 + c_0y_1 = 0 \tag{36}$$

is the IO-equation of (35). This can be shown using the Laplace Transform/Transfer Function approach (see [5] for more details). This input-output equation is irreducible and of minimal order by [22, Theorem 3]. Notice the reparameterized system can be factored as:

$$
\dot{X} = \begin{pmatrix}
0 & 1 & 0 & 0 & \cdots & 0\\
0 & 0 & 1 & 0 & \cdots & 0\\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots\\
-c_0 & -c_1 & -c_2 & -c_3 & \cdots & -c_{n-1}
\end{pmatrix} X = \tilde{A}X.
$$

This is a standard result from differential equations on converting an n^{th} order linear ODE (i.e. the input-output equation (36)): into a first order system of n ordinary differential equations via the procedure:

$$
\begin{aligned}
X_1 &= y_1\\
X_2 &= \dot{y}_1 = \dot{X}_1\\
X_3 &= \ddot{y}_1 = \dot{X}_2\\
&\vdots\\
\dot{X}_n &= y_1^{(n)} = -c_{n-1}y_1^{(n-1)} - \ldots - c_1\dot{y}_1 - c_0y_1\\
&= -c_0X_1 - c_1X_2 - \ldots - c_{n-1}X_n
\end{aligned}
$$

Now we show that this procedure leads to the linear reparameterization $\bar{X} = P\bar{x}$ given above. We have:

$$
\begin{aligned}
X_1 &= y_1 = x_1 = C\bar{x}\\
X_2 &= \dot{X}_1 = \dot{x}_1 = a_{11}x_1 + a_{12}x_2 + \ldots + a_{1n}x_n = CA\bar{x}\\
X_3 &= \dot{X}_2 = \ddot{X}_1 = \ddot{x}_1 = a_{11}\dot{x}_1 + a_{12}\dot{x}_2 + \ldots + a_{1n}\dot{x}_n\\
&= a_{11}(a_{11}x_1 + a_{12}x_2 + \ldots + a_{1n}x_n)\\
&\quad + a_{12}(a_{21}x_1 + a_{22}x_2 + \ldots + a_{2n}x_n) + \ldots\\
&\quad + a_{1n}(a_{n1}x_1 + a_{n2}x_2 + \ldots + a_{nn}x_n) = CA^2\bar{x}\\
X_4 &= \dot{X}_3 = \ddot{X}_2 = \dddot{X}_1 = \dddot{x}_1 = a_{11}\ddot{x}_1 + a_{12}\ddot{x}_2 + \ldots + a_{1n}\ddot{x}_n\\
&= a_{11}(a_{11}\dot{x}_1 + a_{12}\dot{x}_2 + \ldots + a_{1n}\dot{x}_n)\\
&\quad + a_{12}(a_{21}\dot{x}_1 + a_{22}\dot{x}_2 + \ldots + a_{2n}\dot{x}_n) + \ldots\\
&\quad + a_{1n}(a_{n1}\dot{x}_1 + a_{n2}\dot{x}_2 + \ldots + a_{nn}\dot{x}_n) = CA^3\bar{x}\\
&\vdots\\
X_n &= CA^{n-1}\bar{x}
\end{aligned}
$$

Thus the matrix P is the n by n observability matrix:

$$
\begin{pmatrix}
C\\
CA\\
\vdots\\
CA^{n-1}
\end{pmatrix}
$$

We can write $\dot{x}_1, \ldots, \dot{x}_n$ in terms of paths:

$$\dot{x}_i = \sum_{j=1}^{n} p_{ij}x_j$$

for $i = 1, \dots, n$, p_{ij} is the monomial path of length 1 from j to i. Then $\ddot{x}_i = \sum_{j=1}^{n} p_{ij}\dot{x}_j$, which is:

$$\ddot{x}_i = \sum_{j=1}^{n} p_{ij} \sum_{k=1}^{n} p_{jk} x_k$$

which works out to: $\ddot{x}_i = \sum_{j=1}^{n} p_{ij} x_j$ where p_{ij} is the sum of all monomial paths of length 2 from j to i,

$$p_{ij} = \sum_{\text{length}=2} a_{ik_1} a_{k_1 j}$$

We have that $x_i^{(n)} = \sum_{j=1}^{n} p_{ij} x_j^{(n-1)}$ (by linearity) and now assume that:

$$x_i^{(n-1)} = \sum_{j=1}^{n} p_{ij} x_j$$

where p_{ij} is the sum of all monomial paths of length $n-1$ from j to i. Then

$$x_i^{(n)} = \sum_{j=1}^{n} p_{ij} \sum_{k=1}^{n} p_{jk} x_k$$

which works out to: $x_i^{(n)} = \sum_{j=1}^{n} p_{ij} x_j$, where p_{ij} is the sum of all monomial paths of length n from j to i,

$$p_{ij} = \sum_{\text{length}=n} a_{1k_1} a_{k_1 k_2} \dots a_{k_l j}. \qquad \square$$

Corollary 1. *The reparametrization in Theorem 3 yields X_i that are linearly independent (in particular, are not zero) for $i = 1, \dots, n$.*

Proof. To show linear independence of the X_i, it is sufficient to show that the Jacobian of the linear reparametrization is generically full rank. The Jacobian is given by the matrix P. This is the observability matrix:

$$\begin{pmatrix} C \\ CA \\ \vdots \\ CA^{n-1} \end{pmatrix}$$

where C has $(1,1)$ entry equal to 1, all others zero. A $n-$compartment model is structurally observable if and only if the rank of the observability matrix is n [16]. From [7, Theorem 1], a compartmental model is structurally observable if and only if it is output connectable, which means there exists a path from every vertex to the output. Since G is strongly connected by assumption, it is thus output connectable and this structurally observable, so the rank of the observability matrix is n. $\square$

C.2. Reparametrization formula for linear systems with multiple outputs

Example 2. Consider the following model:

$$\begin{aligned}
\dot{x}_1 &= a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + a_{14}x_4 + a_{15}x_5 \\
\dot{x}_2 &= a_{21}x_1 + a_{22}x_2 + a_{23}x_3 + a_{24}x_4 + a_{25}x_5 \\
\dot{x}_3 &= a_{31}x_1 + a_{32}x_2 + a_{33}x_3 + a_{34}x_4 + a_{35}x_5 \\
\dot{x}_4 &= a_{41}x_1 + a_{42}x_2 + a_{43}x_3 + a_{44}x_4 + a_{45}x_5 \\
\dot{x}_5 &= a_{51}x_1 + a_{52}x_2 + a_{53}x_3 + a_{54}x_4 + a_{55}x_5 \\
y_1 &= x_1 \\
y_2 &= x_2
\end{aligned}$$

Using the linear reparameterization:

$$\begin{aligned}
X_1 &= x_1 \\
X_2 &= x_2 \\
X_3 &= \dot{x}_1 = a_{11}x_1 + a_{12}x_2 + a_{13}x_3 + a_{14}x_4 + a_{15}x_5 \\
X_4 &= \dot{x}_2 = a_{21}x_1 + a_{22}x_2 + a_{23}x_3 + a_{24}x_4 + a_{25}x_5 \\
X_5 &= \ddot{x}_1 = a_{11}\dot{x}_1 + a_{12}\dot{x}_2 + a_{13}\dot{x}_3 + a_{14}\dot{x}_4 + a_{15}\dot{x}_5 = \dots
\end{aligned}$$

we obtain the following reparameterized system:

$$\begin{aligned}
\dot{X}_1 &= X_3 \\
\dot{X}_2 &= X_4 \\
\dot{X}_3 &= X_5 \\
\dot{X}_4 &= \ddot{X}_2 \\
\dot{X}_5 &= \dddot{X}_1
\end{aligned}$$

The expressions for $\ddot{X}_2$ and $\dddot{X}_1$ on the right-hand side can then be written in terms of $X_1, ..., X_5$, but we do not include these as the expressions get too big to fit on a page.

We can now generalize to the case of multiple outputs and write a reparametrized linear system.

Theorem 4. *Consider*

- *a linear system over $\bar{x} = x_1, \dots, x_n$:*

$$\begin{cases} \dot{\bar{x}} = A\bar{x} \\ y_i = x_i, \quad i = 1, \dots, m \end{cases}$$

- *C the diagonal $m \times n$ matrix in which the (i,i) entry is 1 for $i = 1, \dots, m$, all other entries are zero*
- *the matrix P given by the first n rows of the observability matrix:*

$$\begin{pmatrix} C \\ CA \\ \vdots \\ CA^{n-1} \end{pmatrix} \tag{37}$$

If the matrix P is invertible, then, using the linear reparameterization $\bar{X} = P\bar{x}$, we obtain a globally IO-identifiable reparametrized ODE system

$$\dot{X} = PAP^{-1}X.$$

Remark 1. In coordinates, the new variables are given by

$$\begin{aligned} X_1 &= x_1, \ldots, X_m = x_m \\ X_{m+1} &= \dot{X}_1 = \dot{x}_1 \\ &\vdots \\ X_{2m} &= \dot{X}_m = \dot{x}_m \\ X_{2m+1} &= \dot{X}_{m+1} = \ddot{X}_1 = \ddot{x}_1 \\ &\vdots \\ X_n &= \dot{X}_{n-m} = \ddot{X}_{n-2m} = \ldots = X^{(k)}_{n-km} = x^{(k)}_{n-km}, \end{aligned} \tag{38}$$

where $k \geqslant 0$ is an integer such that $m \geqslant n - km > 0$. The reparameterized globally IO-identifiable ODE system is:

$$\begin{cases} \dot{X}_1 = X_{m+1}, \dot{X}_2 = X_{m+2}, \ldots, \dot{X}_{m+1} = X_{2m+1}, \ldots, \dot{X}_{n-m} = X_n \\ \dot{X}_{n-m+1} = \ddot{X}_{n-m+1-m}, \ldots, \dot{X}_n = \ddot{X}_{n-m} \end{cases} \tag{39}$$

Remark 2. It would be interesting to know for what classes of linear systems, the matrix P is invertible. For instance, it is invertiblein Example 2. On the other hand, if A is the zero matrix and $m < n$, then P is not invertible.

Proof. Note that we trivially set $X_1 = x_1, \ldots, X_m = x_m$ as we do not want to change the outputs. Following this same technique as in Theorem 3, we can describe our reparametrization (38) in terms of C and powers of A. We have that

$$\begin{aligned} &(X_1, \ldots, X_m) = C\bar{x}, \\ &(X_{m+1}, \ldots, X_{2m}) = CA\bar{x}, \ldots, (X_{n-m}, \ldots, X_n) = CA^k\bar{x}. \end{aligned}$$

This gives the first n rows of the observability matrix in (37). Our reparametrization in (38) gives the right-hand-side expressions for $\dot{X}_1, \ldots, \dot{X}_{n-m}$, etc, in (39) by setting them equal to $X_{m+1}, \ldots, X_n$ until all variables X_i have been exhausted. The expressions for $\dot{X}_{n-m+1}, \ldots, \dot{X}_n$ in (39) can be obtained by taking derivatives of the first $n - m$ equations in (39), as the variables $X_{n-m+1}, \ldots, X_n$ appear in the first $n - m$ equations on the right-hand side of (39) since $n - m + 1 < n$ for $m > 1$. This introduces second order derivatives (and higher) of the variables $X_1, \ldots, X_n$. To get the precise form of the right-hand-side of (39) in terms of X, we use the linear reparametrization $X = Px$ and get the reparametrized ODE system $\dot{X} = PAP^{-1}X$.

What's only left to prove is that this reparametrized ODE system is, in fact, a globally IO-identifiable reparametrization. Note that each of the expressions $X_1, \ldots, X_n$ can themselves be written in terms of $y_1, \ldots, y_m$ or their derivatives as follows:

$$\begin{cases} X_i = x_i = y_i, & i = 1, \ldots, m, \\ X_j = \dot{X}_{j-m} = \dot{y}_{j-m}, & j = m+1, \ldots, 2m, \\ X_k = \dot{X}_{k-m} = \ddot{y}_{k-2m}, & k = 2m+1, \ldots, 3m, \\ \quad\vdots \end{cases}$$

Thus, we can use substitution to obtain that the equations in $\dot{X}_{n-m+1}, \ldots, \dot{X}_n$ in (39) are m IO-equations. As the coefficients of the IO-equations are globally IO-identifiable by definition, we have a globally IO-identifiable reparametrization. ☐

Remark 3. Theorem 3 can be seen as a special case of Theorem 4 for the case where $m = 1$, and we thus get a single input-output equation in our identifiable reparametrization.

VII. Conclusion and Future work

We have presented a new algorithm for finding globally identifiable reparametrizations of ODE models, which has wider applicability than the existing methods. Our algorithm relies on solving systems of polynomial equations to find reparametrizations. Typically, the fewer unknowns there are, the more efficient this polynomial solving is. Some biological models, such as the glucose-insulin model from [17], involve high-degree but relatively sparse polynomials. Developing an approach that takes advantage of sparsity would significantly improve the efficiency of the current algorithm.

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