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RESEARCH ARTICLE

On the Origins and Rarity of Locally but Not Globally Identifiable Parameters in Biological Modeling

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ABSTRACT Structural identifiability determines the possibility of estimating the parameters of a model by observing its output in an ideal experiment. If a parameter is structurally *locally* identifiable, but not globally (SLING), its true value cannot be uniquely inferred because several equivalent solutions exist. In biological modeling it is sometimes assumed that local identifiability entails global identifiability, which is convenient because local identifiability tests are typically less computationally demanding than global tests. However, this assumption has never been investigated beyond demonstrating the existence of counter-examples. To clarify this matter, in this paper we began by asking *how often* a structurally locally identifiable parameter is *not* globally identifiable in systems biology. To answer this question empirically we assembled a collection of 102 mathematical models from the literature, with a total of 763 parameters. We analysed their identifiability, determining that approximately 5% of the parameters are SLING. Next we investigated how the SLING parameters arise, tracing their origin to particular features of the model equations. Finally, we investigated the possibility of obtaining false estimates. Some of the solutions that are mathematically equivalent to the true one involved parameters and/or initial conditions with negative values, which are not biologically meaningful. In other cases the true solution and the equivalent one were in the same range. These results provide insight about a previously unexplored hypothesis, and suggest that in most (albeit not all) systems biology applications it suffices to test for structural local identifiability.

INDEX TERMS Computational methods, dynamic models, nonlinear systems, observability, structural identifiability, systems biology.

I. INTRODUCTION

Dynamic mathematical models are extensively used for understanding, describing, and predicting the behavior of biological processes over time [1], [2]. In many applications model dynamics are given by nonlinear ordinary differential equations (ODEs) with unknown parameters, whose values are obtained by finding the best fit between model output and measured data obtained from identification experiments [3]. The outcome of this task, known as model calibration or parameter estimation, may be termed successful if the resulting estimates correspond to the true values of the unknown model parameters [4]. A requirement for successful parameter estimation is structural identifiability, which is the theoretical possibility of determining the parameter values from data in an ideal experiments [5]. Lack of identifiability may lead to inaccurate estimates of mechanistically meaningful parameters, as well as to the inability to make correct predictions about certain variables.

If a model is structurally *globally* identifiable (SGI), the structural identifiability problem has a unique solution in the whole parameter space, corresponding to the true parameter

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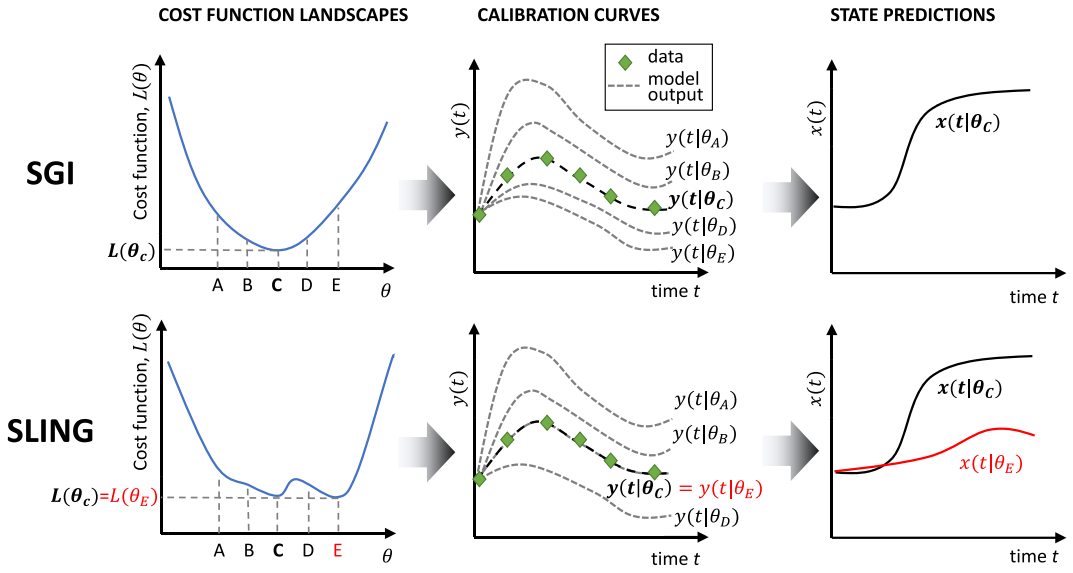

FIGURE 1. Illustration of the difference between a SGI and a SLING parameter. For a SGI parameter θ (upper row), the cost function (left column) that measures the distance between the measured data and the model simulation has a unique minimum, that corresponds to the nominal value θ_C. Hence, model simulations with parameter values other than the nominal differ from the measured data (center column), and the model calibration process correctly estimates θ_C. This enables the correct simulation of unmeasured state variables, or of output variables in different conditions (right column). In contrast, if a parameter is SLING (lower row) there are at least two indistinguishable minima of the cost function, one for θ_C and another for θ_E (left). As a result, the calibration process may infer the correct parameter value θ_C, but it could also erroneously infer the value that yields an equivalent solution, θ_E (center). The latter case may lead to wrong simulations (right).

vector. This is the most desirable situation. In contrast, if a model is structurally unidentifiable (SU), there are infinite parameter vectors that generate identical output trajectories [6]. When there is a finite number of parameter vectors that yield the same input-output data, the model is structurally *locally* identifiable (SLI). If the number of possible solutions of a SLI parameter is exactly one, then the parameter is also SGI. When there are multiple solutions (each of which may lead to different dynamic responses of the unmeasured variables of the model), the model is structurally locally but not globally identifiable (SLING). The difference between SGI and SLING models is illustrated in Fig. 1.

Assessing whether a model (or a specific parameter) is SLI is typically easier than checking whether it is SGI [7]. Furthermore, it is often the case that a SLI parameter is also SGI. Hence in many applications only structural local identifiability is checked. However, the question of whether such test is actually sufficient, or it may lead to confounding results, has seldom been investigated. An early example of investigation of the sources of structural non-uniqueness in parameter estimation of local identifiable models appeared in [8], where a large family of compartmental models was analysed. More recently, a method to find all numerical solutions for local identifiable parameters was presented in [9]. The method was applied to two different biological models, a simple compartmental model with three states and a HIV model [10], which we include in our analyses.

In many studies the goal is to estimate parameters and state variables that are not directly measurable [11], [12], [13]. It is important to determine whether a parameter is SLING, and, if that is indeed the case, to find if there are multiple local solutions within the physically meaningful parameter bounds – a situation that could lead to wrong parameter estimates. In a biomedical context, some parameter values may be used to discriminate a pathological state from a normal state, and failing to estimate their true values could result in wrong diagnoses or treatments.

However, the extent to which a SLI parameter in a biological model can be expected to be SGI or SLING is still unclear. Here we aim at shedding light on this matter. To this end, we begin by collecting and curating a large collection of mathematical models from the literature of several biological areas. We analyse their structural identifiability, classifying their parameters as either SU, SGI, or SLING, and quantifying the percentage of parameters belonging to each class. Next, we have a closer look at the SLING parameters, in order to investigate the modeling practices from which they originate.

The remainder of this paper is organized as follows. Section II describes the theoretical background and the methodologies used to analyse structural identifiability, locally and globally. Section III presents the results of our analyses. Lastly, Section IV discusses the results and summarizes the conclusions.

II. METHODS

A. MODELING FRAMEWORK

We consider deterministic models described by ordinary differential equations, which are typically nonlinear. We restrict ourselves to models with rational equations, since it is generally not possible to analyse the structural global identifiability of nonrational models. Most systems biology models are of this type, and some of those that are not can be rewritten in rational form. That is, our models will be of the form:

$$\mathcal{M}: \begin{cases} \dot{x}(t) = f(x(t), u(t), \theta), \\ y(t) = h(x(t), u(t), \theta), \\ x(0) = x^0(\theta) \end{cases} \tag{1}$$

where $x(t) \in \mathbb{R}^n$ is the state vector, $u(t) \in \mathbb{R}^q$ is the input vector, $\theta \in \mathbb{R}^p$ is the parameter vector, and $y(t) \in \mathbb{R}^m$ is the output vector. The output represents the measurement functions, which are typically but not always a subset of the state variables. Both input and output are known, while the parameters are unknown. Vector elements will be written with subindices, e.g. θ_i, x_j. We will sometimes omit the dependence on time for convenience, i.e. we may write x instead of $x(t)$.

B. STRUCTURAL IDENTIFIABILITY CONCEPTS

We will analyse the structural identifiability of models of the type (1). We distinguish between local and global identifiability as follows:

Definition 1: Structural Global Identifiability: a parameter θ_i of a dynamic model $\mathcal{M}$ is structurally globally identifiable (SGI) or uniquely structurally identifiable if, for any admissible inputs and almost all parameter vectors θ_i^* in the parameter space Θ, the equation $y(t, \theta_i) = y(t, \theta_i^*)$ implies $\theta_i = \theta_i^*$. A model, $\mathcal{M}$, is said to be globally structurally identifiable if every parameter θ_i is globally structurally identifiable.

Definition 2: Structural Local Identifiability: a parameter θ_i of a dynamic model $\mathcal{M}$ is structurally locally identifiable (SLI) if, for almost all values θ_i^* and almost all initial conditions, the equation $y(t, \theta_i) = y(t, \theta_i^*)$ implies that θ_i has a finite number of solutions that generate identical output trajectories, $y(t)$.

Note that SGI parameters are also SLI. If a parameter is SLI but not SGI, we call it SLING (structurally locally but not globally identifiable). If none of the above conditions hold, the parameter is *structurally unidentifiable* (SU). A model is said to be SGI (respectively, SLI) if all its parameters are SGI (resp., at least SLI). If it has at least one SU parameter, the model is called SU.

C. THE DIFFERENTIAL ALGEBRA APPROACH TO STRUCTURAL IDENTIFIABILITY ANALYSIS

A differential algebra approach can be used to distinguish between local and global identifiable models [6], [14]. Differential algebra relies on finding algebraic equations that relate the model parameters with the inputs and outputs. Let us denote the input-output map of the system (1) given an initial state x^0 [9] as:

$$y = \Phi_{x^0}(\theta, u) \tag{2}$$

The input-output map is the core of the research on structural identifiability of dynamical models such as (1). We will define the number of solutions of locally identifiable models by means of equation (2). Thus, an alternative characterization of a locally identifiable model is as follows:

Definition 3: Structurally locally identifiable model. Consider a mathematical model (1) with a parameter space Θ and a parameter vector $\tilde{\theta}$. The model is locally identifiable at $\tilde{\theta}$ if there exists an open neighborhood Θ_0 of $\tilde{\theta}$ in Θ such that for all initial conditions $x^0 \in \mathbb{R}^n$, there is a unique parameter vector $\hat{\theta}$ in Θ_0 satisfying the following equation:

$$\Phi(x^0, \hat{\theta}, u) = \Phi(x^0, \tilde{\theta}, u) \tag{3}$$

This definition implies that it is possible to uniquely determine the parameter vector within an open neighborhood of a point in the parameter space. Likewise, this definition states that there is a finite number of solutions that are isolated in different open sets of the entire parameter space.

Let us introduce an equivalence class [9] characterized as an isomorphism relationship between the vector of solutions of the equality (3). We write the binary relation known as the equivalence relation on the parameter space Θ as $\Re$. Given an element $\tilde{\theta} \in \Theta$, $\Re$ defines some disjoint sets as equivalence classes in Θ. The equivalence class associated to a parameter vector $\tilde{\theta}$ is the set

$$[\tilde{\theta}] = \{\theta^i \in \Theta \,|\, \theta^i \,\Re\, \tilde{\theta}\} \tag{4}$$

Two parameter vectors θ^i and θ^j belong to the same equivalence class if and only if they are equivalent, so the equivalence class of a vector θ^j is:

$$[\theta^j] = \{\theta^i \in \Theta \,|\, \theta^i \sim \theta^j\} \tag{5}$$

In SGI models there is no equivalence class, since no θ^i exists that satisfies the $\Re$ relation with $\tilde{\theta}$. In SLI models, each member of these equivalence classes represents a numerical solution for the identification problem, and all such solutions yield the same output trajectories.

D. ANALYZING STRUCTURAL GLOBAL IDENTIFIABILITY WITH SIAN

There are currently a number of methodologies that adopt a differential algebra approach to structural identifiability analysis [7]. Here we have used SIAN (Structural Identifiability ANalyser), an open-source software tool that combines differential algebra methods with the Taylor series approach [15], [16]. We have chosen it for its speed and reliability, as well as for the possibility of including as a parameter in the analysis the initial conditions of the state variables, x^0.

SIAN introduces a numeric-randomized algorithm [15] based on Taylor series and Zarisky topology. It constructs a

map that relates parameter values and initial conditions with the output functions of the model (1). After reducing the map by applying Taylor series, the identifiability problem is defined as a topological question about the map's fibers [15]. Instead of considering a generic fiber, SIAN randomly selects a point to get the fiber. This last step is correct given a certain probability that is estimated by the algorithm. Eventually, the problem boils down to checking if there is at least one set of values of the unknowns that satisfies each equation in the system of polynomial equations and inequalities. SIAN performs this step by computing the Gröbner basis of the system [17].

E. CHARACTERIZING NON-UNIQUE SOLUTIONS

Once we have classified a given parameter as SLING, we need to determine $[\tilde{\theta}]$, i.e. all admissible solutions of a locally identifiable parameter. In contrast to the analysis of structural identifiability, there is no standard procedure to perform this task. In the remainder of this section, we describe how we have carried it out.

1) REVISITING A METHOD TO OBTAIN ALL ADMISSIBLE SOLUTIONS OF A SLING PARAMETER

Our starting point is the method introduced in [9]. It starts by calculating the input-output equations of the model 1, extracting the exhaustive summary from them [18]. This leads to a system of polynomial equations with a constant unknown value in one side. Substituting the parameters of the previous system with numerical values, we obtain a numerical solution for the constant term of the polynomial system. At this point, the problem of determining $[\tilde{\theta}]$ is reduced to finding every possible combination of numerical values of the parameters that satisfies the system of polynomial equations. Each of these combinations is a member of the equivalence class $[\tilde{\theta}]$.

2) EXTENSIONS TO THE CORE METHOD

In [9] the aforementioned procedure was performed using DAISY [19] to compute the input-output equations. Here we have worked instead with the StructuralIdentifiability toolbox (SI.jl) [20], which is usually faster than DAISY [7]. After obtaining the input-output equations in the command prompt of SI.jl, we have to derive the exhaustive summary of the model, which depends only on the parameters. The number of equivalent solutions is found with the Maple structural identifiability toolbox [21], which is available in MapleCloud.

Once the exhaustive summary has been obtained, and the number of equivalent solutions is determined, we solve the polynomial system using one of the following approaches:

a: NUMERICAL COMPUTATIONS

This method computes numerical approximations for both algebraic and transcendental equations. It is implemented in Nsolve, a built-in function in Mathematica [22]. It relies on a combination of iterative algorithms, such as the Newton-Raphson and bisection methods, as well as homotopy continuation techniques for tracking multiple solutions in nonlinear systems. This approach ensures both the accuracy and the efficiency of the numerical solutions found during the computations.

b: SYMBOLIC COMPUTATIONS

Complementary, we also applied symbolic equation-solving techniques [23] in Matlab to solve algebraic and transcendental systems of equations. This method integrates algebraic, analytic, and heuristic strategies, such as factorization, variable elimination, and Gröbner basis methods. Specifically for polynomial systems, this function could apply Gröbner basis to transform the polynomial equation system into an equivalent yet simpler set, which is then readily solved using backward substitution techniques.

c: BRUTE FORCE SEARCH

Both approaches mentioned above have computational limitations when analyzing large systems of equations. While we have found that method (a) is significantly more efficient than method (b), neither approach is able to effectively handle systems consisting of more than ten equations. When we encountered these limitations in some complex models, we tried to surmount them by implementing a brute-force method consisting of testing every possible combination for the parameters – within some tolerance – in order to find the solution of the system. We restricted the search for possible solutions to an interval, which makes sense for parameters that are physically or biologically restricted to some numerical values. For example, some parameters in infectious models are restricted to values within the interval [0, 1].

III. RESULTS

A. MODELS

We assembled a diverse collection of models from different areas, with the aim of obtaining a representative subset of the systems biology literature. To this end we collected 102 biological models, which we classified as belonging to one of 10 different areas: virology, cellular signaling, physiology, metabolism, pharmacokinetics, gene expression, immunology, tumor modeling, epidemiology, and microbial communities. Additionally, we included a group named "general cases", consisting of models that do not describe specific biological processes, but more general behaviors that are common to different types of biosystems (e.g. basic compartmental models). Some models were retrieved from the Github repositories of several structural identifiability toolboxes [7], and the remaining ones were taken from the literature on biological modeling. All models are listed in table 1, along with their references and some key features such as the total number of parameters and the number of parameters that are locally but not globally identifiable. Their implementations are provided at https://github.com/Xabo-RB/Local-Global-Models.

TABLE 1. List of the models and their main features. The first column displays a short name for the model. The second one ('Ref.') shows its original publication, and indicates with "G*" those models directly taken from GitHub repositories of identifiability toolboxes, which do not refer to any previous paper: GenSSI2(G1), ObservabilityTest(G2), SIAN.jl(G3), STRIKE-GOLDD(G4) and Structural-Identifiability(G5). The third column shows the number of parameters ("#θ") along with the number of SLING parameters (in red parentheses). The fourth column ("Cause") refers to the groups explained in section III-C, (1) parameters with exponents, (2) symmetry-breaking control inputs, (3) recurring products, and (4) other. The last column indicates whether the equivalent solutions might be confounded with the actual solution ('Yes') or not ('No').

Short name	Ref.	#θ(SLING)	Case	Confounding
General				
C2M	[24]	4		
Degrad	**G1**	3		
DegradPoly	**G1**	3		
HiDimNLn	[25]	22		
C1996	[26]	5		
CG1992	[27]	6		
A2006	**G2**	1		
BF2004	**G2**	5		
Campb2016	**G2**	7		
GRV1990	[28]	4		
Juricic	**G2**	12		
KD1999	[29]	14		
L2003	**G2**	8		
LLW1987	[30]	4(2)	4	Yes
MW2000	**G2**	14		
R1986	[31]	9		
V1987	[32]	5		
Verhulst	**G2**	4		
D_ex3	[25]	5(3)	2	Yes
D_mamil3	[33]	5(4)	2	Yes
SlowFast	[34]	3(3)	3	Yes
Crauste	**G5**	13		
QWWC	**G5**	6		
2DOF	[35]	7		
CR	[36]	3		
Vajda1989	[28]	4		
FHN_obs	[37]	3		
Gene Expression				
Gene p53	[2]	25(1)	1	No
Transf2st	[38]	3		
Transf4st	**G1**	5		
Transf4stT	**G1**	6		
Bruno2016	[39]	6		
Goodwin	[40]	7(2)	4	Yes
GoodwObs	[40]	6		
Physiology				
Bilirubin1	[41]	7		
Bilirubin2	[41]	7(6)	2	Yes
βIG	[42]	5(1)	1	No
Cholesterol1	[41]	5		
Cholesterol2	[41]	4		
Thyroid	[41]	7		
CC1993	[43]	9		
OralGluc	[33]	5		
1Aintegral	[42]	3		
1BPropInt	[42]	3		
1CNonLin	[42]	3		
Bolie_A	[44]	5		
Bolie_B	[44]	5		
Microbial				
gLotkaVolt	[45]	6		
PhaCock	[46]	12		
gLV-QSMI	[47]	9		
cLV1	[48]	15		
cLV2	[48]	12		

Short name	Ref.	#θ(SLING)	Case	Confounding
Virology				
HIV 1	[10]	5		
HIV 2	[10]	10(2)	4	Yes
HIV 3	[49]	10		
Metabolism				
Glycolysis	[50]	5		
Biohydrog	[51]	6(3)	4	No
RumLipoly	[51]	3		
BlQiao2004	[52]	19		
PharmaKin.				
PK 1	[36]	9		
PK 2	[53]	9		
PKPoly	[54]	7		
Pivast	[55]	8		
Pivast_ss	[55]	7		
Inmunol.				
CGV1990	[56]	5		
TCRJoaoE	[57]	6		
TCRBach	[58]	3		
LeukLeon21	[59]	14		
Tumor				
TuHu19	[60]	21		
TuPillis07	[61]	25		
TuGarcia20	[62]	6		
Tumor	[63]	5		
Epidem.				
SEUIR	[64]	5		
Cholera	[65]	7		
WSP1985	[66]	7		
SEIRT	[67]	3(2)	3	Yes
SEIR2T	[67]	3		
TreatT	[67]	5(1)	3	No
SEIR1	[68]	4(3)	3	No
SEIR2	[69]	4		
SEIR4	[70]	6		
SEIR5	[70]	5		
SEIR11	[71]	5(4)	3	No
SEIR16	[72]	5(1)	3	No
SEIR32	[73]	5		
SEIR33	[74]	10		
SEIR34	[75]	6(3)	3	No
SEIR36ref	[71]	12		
SIR6	[76]	4		
SIR19	[77]	4		
SIR21	[72]	5		
SIR22	[78]	7		
SIR24	[79]	5		
SEAIJRC	[69]	8		
SIAR	[80]	18		
SIR_R0	**G3**	2		
Cellular signalling				
NFkB 2	[81]	6		
Phospho	[82]	6		
JAKSTAT1	[83]	23		
ChReNet	[82]	6		
Fujita	[84]	15		
FujitaSS10	**G4**	16		

B. PROPORTION OF SLING PARAMETERS

Overall, we obtained that in 86 out of 102 models all the SLI parameters were also SGI. In the remaining 16 models, at least one parameter has an equivalent class where there exists more than one admissible solution for the same output data. Thus, in approximately 16% of the models there is at

least one SLING parameter; we will refer to them as SLING models.

The 102 models have a total of 763 parameters. There are 499 SGI parameters (i.e., 65% of parameters have a unique solution), 223 SU parameters (i.e., 29% of parameters have an infinite number of admissible solutions), and 41 SLING parameters (i.e., for 5% of the parameters a $\Re$ relation that contains equivalent solutions exists). That is, only 7.6% of the SLI parameters are SLING; in other words, if a parameter is SLI, it is also SGI in 92.4% of the cases. These numbers are summarized in figure 2.

C. HOW SLING PARAMETERS ORIGINATE

We have divided the 16 SLING models into four groups, depending on the main feature that explains the reason for the existence of SLING parameters. These features are the existence of: (1) parameters with exponents, (2) symmetry-breaking control inputs, (3) recurring products in compartmental models, and (4) other causes.

1) PARAMETERS WITH EXPONENTS

The first group includes models that have a parameter with an exponent other than one. An example is the βIG model included in our collection, which has the following equations:

$$\begin{cases} \dot{G}(t) = u_0 + u(t) - (C + S_i I(t))G(t), \\ \dot{\beta}(t) = \beta(t)\left(\dfrac{1.458 \cdot 10^{-5}}{1 + \left(\dfrac{8.4}{G(t)}\right)^{1.7}} - \dfrac{1.736 \cdot 10^{-5}}{1 + \dfrac{G(t)^{8.4}}{4.8}}\right), \\ \dot{I}(t) = p\beta(t) \cdot \dfrac{G(t)^2}{\alpha^2 + G(t)^2} - \gamma I(t), \\ y(t) = G(t), \end{cases} \tag{6}$$

Since the parameter α only appears as α^2, it may have a negative or a positive value and still have the same effect on the model dynamics. This is the simplest case of a SLING parameter. It is trivially easy to fix – replacing α^2 with $\tilde{\alpha} = \alpha^2$ yields a SGI parameter – and it is not potentially confounding, since parameters are typically restricted to positive values.

2) SYMMETRY-BREAKING CONTROL INPUTS

The second type of cause is less intuitive. For several models with external inputs, we have found that removing the input makes some parameters SU, while including it makes them SLING. Thus, the existence of a known input breaks a symmetry that was preventing a parameter from being identifiable, but it only manages to make it SLI, not SGI. We confirmed this characteristic by testing variations of the same model, with and without the control variable. In our collection there are three models with this feature, *D_ex3*, *D_mamil3*, and *bilirubin2*, with a total of 13 SLING parameters. As an example, we show below the equations of the *D_ex3* model, where in the presence of an input $u(t)$ there are 3 SLING parameters: $p4$, $p6$, and $p7$.

$$\begin{cases} \dot{x1} = -p1 \cdot x1 + p2 \cdot x2 + u(t), \\ \dot{x2} = p3 \cdot x1 - p4 \cdot x2 + p5 \cdot x3, \\ \dot{x3} = p6 \cdot x1 - p7 \cdot x3, \\ y(t) = x1, \end{cases} \tag{7}$$

3) RECURRING PRODUCTS IN COMPARTMENTAL MODELS

Another source of SLING parameters is the existence of the same terms in the equations of several state variables, in a way that is typical of compartmental models such as the ones commonly used in epidemiology. Said terms consist of combinations of the product of a parameter and a state. Parameters typically affected include β and γ, which correspond to the transmission rate and to the average infectious period, respectively. Typical states involved in these terms are, for example, $S(t)$ and $E(t)$, i.e. the compartments of susceptible and exposed individuals. An epidemiological model that consists of these variables would be completely built as an addition or subtraction of the product of the variables, $\pm\beta \cdot S(t)$, $\pm\gamma \cdot E(t)$. This model structure has been found in every epidemiological model analysed in this research. Since these products appear in at least two differential equations in the model, we refer to this feature as the existence of *recurring products*. An example is given by the following model, *SEIR1* [68], which has three SLING parameters, β, ν, and ψ, and only one SGI, γ:

$$\begin{cases} \dot{S} = -\beta \cdot S \cdot I, \\ \dot{E} = \beta \cdot S \cdot I - \nu \cdot E, \\ \dot{I} = \nu \cdot E - \psi \cdot I - (1 - \psi) \cdot \gamma \cdot I, \\ \dot{R} = \gamma \cdot Q + (1 - \psi) \cdot \gamma \cdot I, \\ \dot{Q} = -\gamma \cdot Q + \psi \cdot I, \\ y(t) = Q, \end{cases} \tag{8}$$

4) OTHER

The last group includes four models for which we were not able to identify a clear cause for the existence of SLING parameters. These models are from different areas and have no obvious shared features.

D. ASSESSMENT OF THE POSSIBILITY OF CONFUSION

In this section we apply the methods described in Section II-E to find all the possible the values of the parameters with an equivalence class, in order to assess the risk of confounding the true values with the spurious ones. That is, our goal is to find, given a nominal or 'true' value of a SLING parameter, every other possible solution, in order to determine if they exist within the range of admissible – i.e. biologically feasible – parameter bounds.

To this end, for each SLING parameter we must define an open neighborhood Θ_F that contains its admissible numerical values. Defining the range of values requires prior knowledge about the parameter. In some cases the parameter values are constrained to a specific range of values, e.g. between [0,1].

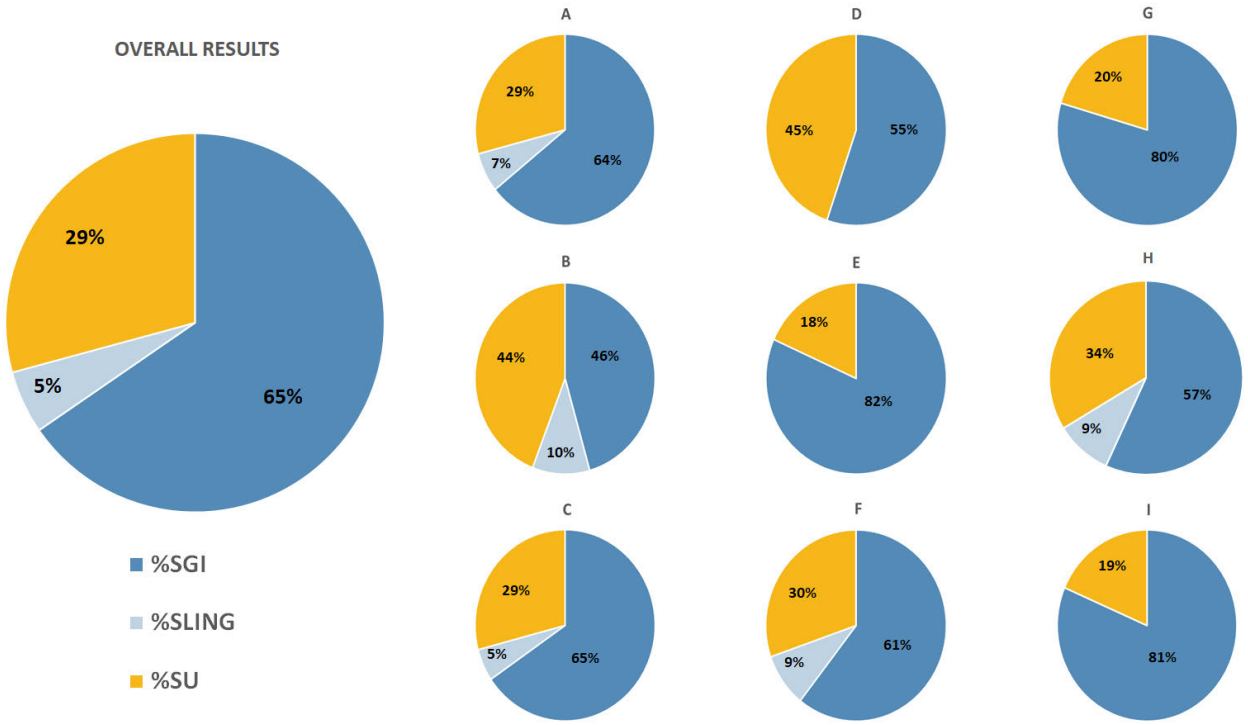

FIGURE 2. Characterization of the structural identifiability of model parameters. Left: overall. Right: by biological area. A: general cases; B: physiology; C: gene expression; D: pharmacokinetics; E: cellular signaling; F: metabolism; G: immunology and tumor modeling; H: epidemiology and virology; I: microbial communities.

In other cases, the feasible values are determined by the specific circumstances of the model context. For example, if α is a parameter that refers to a clearance rate constant (the fraction of a chemical that is removed from a compartment, such as blood) then its value must be within zero and one. Hence, if α is a SLING parameter in a model, but only the true solution is in $\Theta_F = [0, 1]$, while the equivalent solution(s) lie outside this range, we may conclude that there is no risk of inferring the wrong value.

To find all possible solutions for the SLING parameters in our study, we first attempted to use approaches (a–b) in Section II-E, which yield exact solutions. However, some models were too complex for these approaches; in those cases we used the brute-force method (c) to search for approximate solutions within an interval of numerical values with biological meaning.

We classified the equivalent solutions $[\tilde{\theta}]$ in two groups: 'confounding' (those for which the equivalent solutions are contained within the admissible interval of parameter numerical values, $[\tilde{\theta}] \subset \Theta_F$), and 'not confounding' (i.e., $[\tilde{\theta}] \not\subset \Theta_F$). The results are summarized in the 'Confounding' column of Table 1, which indicates whether the equivalent values of the parameters can be confounded with the true one or not, and in Fig. 3, which classifies the SLING parameters according to the possibility of confusion of their numerical solutions. Overall, among the 763 parameters included in the models there are 41 SLING parameters (5% of the total); 24 of them (3%) have at least two equivalent solutions in Θ_F (which means that it is possible to confuse the true and the equivalent value) and 17 (2%) have solutions out of this admissible span Θ_F (there is no possibility of confusion).

1) NOT CONFOUNDING

In some of the models in which there is no possibility of confusion, the equivalence class originates from parameters with even exponents (case 1 in Table 1). Thus, equivalent solutions consisting of real negative numbers exist. Since parameters are expected to be positive numbers, the only one solution in the biologically admissible space Θ_F is the true one.

In other cases, the equivalence class originates from the existence of recurring products in the equations (case 3 in Table 1), as is typical of epidemiological models. Some of these models have a specific feasible range of values (Θ_F) for the SLING parameters; this is the case of TreatT, SEIR1, SEIR 11, SEIR16, and SEIR 34. For example, SEIR1 [68] has three SLING parameters: infection rate β, isolation rate ψ, and latency coefficient w. Since the first two are percents, their values must be between 0 and 1. The third one, $1/w$, represents the period it takes for a person to go from exposed to infected, measured in days. The authors of this model defined w between $1/10$ and $1/21$. Thus, $\Theta_F = \{\beta \in (0, 1], \psi \in (0, 1], w \in [1/10, 1/21]\}$. Since we found no solution within these ranges, we concluded that there is no possibility of

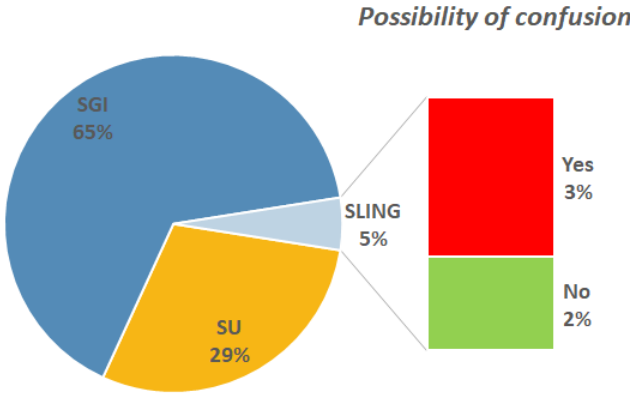

FIGURE 3. Total parameters disaggregated by identifiability results and the possibility of confusion of SLING parameters.

confusion since the SLING parameters are uniquely defined in Θ_F. As an additional example, the SEIR16 model has one SLING parameter which is the transfer rate from exposed to infected individuals. In [72] it is stated that the numerical value should be between $[0.263, 0.78]$. Even when we expanded the range to $(0, 1]$, we found no solution in $\Theta_F = \{\epsilon \in (0, 1]\}$.

2) CONFOUNDING

In 8 out of 16 SLING models we found that at least one SLING parameter has equivalent solutions within the feasible range of numerical values Θ_F. In total, there are 24 SLING parameters with possibility of confusion. We have found a common pattern among these potentially confounding parameters: the numerical values of the equivalent solutions are interchangeable among parameters (e.g. either $\theta_i = 2$ and $\theta_j = 3$, or $\theta_i = 3$ and $\theta_j = 2$). For example, the Bilirubin2 model has 6 SLING parameters, whose nominal values are $\{k_{21} = 21, k_{31} = 1, k_{41} = 8, k_{12} = 3, k_{13} = 25, k_{14} = 21\}$. The parameters are divided into two groups, (k_{21}, k_{31}, k_{41}) and (k_{12}, k_{13}, k_{14}), with each parameter having three possible solutions, corresponding to their own true value and those of the other parameters in the group. Thus the equivalent solutions are as follows: $\{(k_{21} = 1, k_{31} = 8, k_{41} = 21), (k_{12} = 25, k_{13} = 21, k_{14} = 3)\}$, $\{(k_{21} = 8, k_{31} = 1, k_{41} = 21), (k_{12} = 21, k_{13} = 25, k_{14} = 3)\}$, $\{(k_{21} = 1, k_{31} = 21, k_{41} = 8), (k_{12} = 25, k_{13} = 3, k_{14} = 21)\}$, and so on, resulting in six possible combinations of parameters, with each parameter having three possible numerical values.

This compensatory phenomenon occurs for each model with SLING parameters. In the example above we have assumed that all parameters can have values in [1] and [25], and hence we have classified the case as confounding. This may be a conservative assumption. If the researcher has some prior knowledge of the relative values of the parameters, such as e.g. that θ_i should be within a different range than θ_j, or that $\theta_i \leq \theta_j$, this additional information could constrain the admissible values of the parameters further, leading to a model that is uniquely identifiable within the admissible ranges.

IV. DISCUSSION

The motivation for this work was to shed light on the difference between local and global structural identifiability in biological modeling. Our first goal was to quantify how likely is it for a SLI parameter to *not* be also SGI. We refer to such parameters with the new acronym SLING. Since it is not possible to analyse every model in the literature, we assembled a set of models and analysed their structural identifiability. In order to make this set as representative as possible of the existing diversity in biological modeling, we selected case studies from different areas: physiology, gene expression, pharmacokinetics, cellular signaling, metabolism, immunology, tumor modeling, epidemiology, virology, microbiology, and generic model structures. Admittedly, our choice of models is subjective, and a different selection would probably not yield the exact same results. However, our results showed a remarkably consistent trend common to all areas. In qualitative terms, all areas had a minority of unidentifiable (SU) parameters, a majority of SGI parameters (which are also SLI), and very few or no SLING parameters. Quantitatively speaking, the percentage of SLING parameters across all areas was approximately 5%. Thus, it may be concluded that SLING parameters are rare, although not nonexistent.

A second goal was to explain mathematically the features that make a parameter SLING. To this end, we analysed every SLING case individually, which allowed us to find a number of common features that can cause this result. While one of them – the existence of parameters with even exponents – is trivial, the others are less obvious.

Thirdly, we assessed the possibility of obtaining wrong estimates of SLING parameters, i.e. of confounding their true values with equivalent local solutions. This may happen when the equivalent solutions are within the range of biologically admissible values. In our tests, this risk for confusion was present for more than half of the SLING parameters, which represents roughly 3% of all the parameters in the models. However, this number could be lowered if additional knowledge about the parameter values is available, which is often the case. Overall, these figures suggest that, by performing a structural local identifiability analysis and assuming that local identifiability makes it possible to uniquely determine the parameter values, one can expect to obtain correct results in at least 97% of the cases.

An interesting aspect that we have not mentioned yet is the role played by initial conditions. When identifiability is analysed with a structural approach, the results are valid for generic values of the initial conditions. Thus, if a parameter is structurally identifiable, it will be so for almost all values of the initial conditions, i.e. except possibly for a set of measure zero. While there may exist a specific numerical value of an initial condition from which the model loses identifiability (thus rendering a locally or globally identifiable model unidentifiable), we regard such case as a practical or numerical (not structural) issue. Thus, the structural identifiability results reported in this paper do not change depending on the initial conditions.

On the other hand, since the initial conditions of unmeasured state variables can be regarded as unknown parameters, it is possible to investigate whether they are SLING. In fact, our analyses revealed that the identifiability of the initial conditions followed similar patterns as that of the other parameters. We found that, if a equation contained one or more SLING parameters, there was typically a SLING initial condition involved. However, since the primary focus of our investigation was on the parameters appearing in the differential equations, we did not include the initial conditions as parameters in the results reported in our paper. Such analysis could be pursued as future work.

Lastly, it should be noted that, in order to determine whether a parameter is SGI or not, we need to perform a structural global identifiability analysis. Currently this task can only be performed systematically and reliably for rational models [7]. Hence, in this study we did not consider nonrational models, which are a small but non-negligible fraction of all published models. Including those models in the analysis is a possible avenue for future work, which may be pursued when the maturity of structural global identifiability methods allows it. Furthermore, a complete mathematical characterization of all possible causes of SLING parameters, including those cases for which we could not find a discernible pattern, would also be a desirable goal.

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DATA AND CODE AVAILABILITY

Implementations of the models are available at https://github.com/Xabo-RB/Local-Global-Models.

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