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On structural and practical identifiability: Current status and update of results

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Identifiability of parameters in dynamical systems is a fundamental concept of mathematical modelling in systems biology and systems medicine. Both the structurally inherent identifiability of parameters in models and the practical identifiability of parameters, which arises from insufficient available data, play crucial roles in the development of useful models. Here, we provide an overview of recent developments in the field of structural identifiability analysis of models based on ordinary differential equations, emphasising its importance for accurate parameter estimation. We extend an existing benchmark study by comparing the methods for structural identifiability analysis with the recently developed *StrucID*, showing it to be a fast, efficient and intuitive algorithm. Furthermore, this review highlights the challenges in practical identifiability analysis and the need for benchmarking with real-world models using experimental data. The potential benefits of standardising documentation for benchmarking models with experimental data and practical non-identifiabilities are stressed.

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Introduction

Mathematical modelling of biological and medical questions and understanding of complex dynamical systems and their behaviour is highly dependent on the identifiability of the used system. Since "On structural and practical identifiability" [1] was published in 2021, the topic gained popularity, both in the theoretical and in the experimental community. Several mathematical algorithms have been developed and extended to analyse identifiability for distinguishing *bad*, *good* and *useful* models. Identifiability constitutes one property of a (partially observed) dynamical system, represented by a system of ordinary differential equations (ODEs)

$$\dot{x} = f(x, \theta, u), \tag{1}$$

with n model states $x(t)$, a set of p unknown parameters θ that have to be estimated from experimental data, and external and possibly unknown stimuli $u(t)$. To map the model states to time-resolved experimental data y^{D}, the observation function

$$y = g(x, \theta, t) \tag{2}$$

is employed yielding the model trajectories y. Typically, the number of observables m is smaller than the number of states n, rendering the system partially observed.

Comparing the experimental data y^{D} with the model trajectories y yields a measure of agreement between the model and the data. Commonly, a likelihood using normally or log-normally distributed noise is defined and maximum likelihood estimation is performed to estimate the model parameters.

Structural identifiability plays an important role in the development of informative models. It is especially linked to parameter estimation. Non-identifiable parameters can greatly hamper parameter estimation performance, create a flat likelihood landscape leading to feeble or impossible maximum likelihood estimation and can cause inefficient or infeasible Markov chain Monte Carlo sampling [2]. More importantly it often leads to biased, inaccurate and coupled estimates of the parameters. Even estimates of identifiable parameters can be biased if other parameters are non-identifiable.

A parameter θ_i is globally structurally identifiable, if for all parameter sets, θ

$$y(\theta) = y(\theta') \Rightarrow \theta_i = \theta_i' \quad (3)$$

holds [3,4]. Thus, a parameter θ_i is structurally non-identifiable if one can change it without any influence on trajectories y as all possible changes can be fully compensated by the other parameters. Local structural identifiability is defined similar to global structural identifiability, with the difference in limiting the condition to a local neighbourhood $\eta(\theta)$.

Structural identifiability analysis is ideally conducted a priori as it requires no experimental data. This proactive approach can substantially enhance model development and experimental design.

The concept of structural identifiability is strongly related to the concept of observability of a dynamical system. While a system is identifiable if its trajectories are unique for differing parameters, observability of a system refers to the ability of determining the model states uniquely given the measured observables [5–10]. A state $x(\tau)$ is called observable if it can be uniquely determined from the output vector $y(t)$ and known input vector $u(t)$ in the interval $t_0 \leq \tau \leq t_f$, where t_f is a finite time. This concept is more commonly used in the field of engineering [11,12].

In contrast to structural identifiability, practical identifiability is a data-dependent property, which complicates the definition of the problem itself, and in turn also the analysis of this property. One approach defines a parameter as practically identifiable, if, for a given confidence level α, confidence intervals based on the χ^2-distribution are finite [13]. This definition has faced criticism due to the inherent arbitrariness of choosing the confidence level that designates a parameter as practically non-identifiable [14]. Nevertheless, it remains the sole definition that offers a clear criterion while considering the actual data. Other definitions tend to not answer the question of practical identifiability binary but by use of a degree of practical identifiability. This degree of practical identifiability is to some extend comparable with the confidence level chosen in the first definition. The most common influences on the degree of identifiability are the noise level, the amount of available data and the information content and dynamics in the sampled time points. Independent of the different definitions, a model or a parameter that is practically identifiable is always structurally identifiable. In the case of infinite, noiseless and highly informative data, practical identifiability analysis results in structural identifiability analysis.

Here, we discuss recent developments and extend the existing work on structural identifiability analysis. We further highlight the importance of practical identifiability. Our aim is to foster a collaborative effort within the research community to facilitate the analysis of practical identifiability, ultimately enabling it to be as straightforward to assess as structural identifiability in the coming years.

On recent developments in structural identifiability research

In the review "On structural and practical identifiability" [1], it is discussed that the analysis of structural identifiability is no longer a major bottleneck for the development of dynamical models. Various methods have been developed [10,15–35] and previously been reviewed [36–38].

In the past two years, further methods have been developed [11,12,39–41]. Furthermore, some previously published methods have been refined, including StrucID and STRIKE-GOLDD [42–48]. StrucID and STRIKE-GOLDD have already been discussed in "On structural and practical identifiability" [1]. Several of the methods and toolboxes cannot only be used to analyse structural identifiability, but also to find identifiable parameter combinations to reparameterise an initially non-identifiable model [8,22,23,41,45].

In addition to these methodological advances, the analysis of structural identifiability has been performed in various applications, often motivated by the study of infectious disease models in the wake of the COVID-19 pandemic [49–52], but not limited to this [53–56]. The analysis of structural identifiability in these applications suggests a welcome shift towards a more rigorous study of this model property in model development. This can both benefit model reduction [54] as well as experimental design [55] and should be standard practice in any model development process.

In general, we would like to emphasise that the analysis of structural identifiability is no longer a bottleneck in the development of useful models. The existence of fast and reliable methods for the identification of structurally non-identifiable parameters allows scientists to perform this analysis frequently within the model development process across multiple programming languages.

The most notable challenges in using structural identifiability methods in the past have been the limited applicability of some methods to specific problem and model conditions and the computational effort necessary for assessing the structural identifiability of realistically large models. A comprehensive assessment of the different methods mentioned above is so far lacking; however, Rey Barreiro et al. [57] have recently published a study comparing twelve different methods in seven different programming languages. In the following, this analysis will be extended.

On efficient and fast identification of structural identifiability

The benchmark study by Rey Barreiro et al. [57] compares the applicability and computational effort of twelve different methods ([12,21–23,26,27,31,35,41,45,48]) written in seven different programming languages. The authors give an overview of the underlying theoretical aspects, software accessibility and user-friendliness of each tool and evaluate their performance using 25 case studies based on 21 models with varying inputs.

The authors decided to exclude numerical or data-based methods from their analysis. Specifically, two methods mentioned in "On structural and practical identifiability" [1] are missing: the data-based profile likelihood and a method called StrucID [58] utilising the sensitivity matrix that does not need any experimental data.

Analogous to the presentation of the other tools in the mentioned study, we shortly summarise the theoretical background behind StrucID [42,43,58,59] and discuss software accessibility and user-friendliness. Furthermore, the results of the existing benchmark study are collected and compared with StrucID.

The sensitivity matrix approach

The definition of structural identifiability in Eq. (3) suggests analysing it with the help of output sensitivities. The model is not identifiable if the output is not sensitive to the parameters, meaning the trajectory does not change when a parameter changes. Using the model definition from before in Eqs. (1) and (2), this property is checked by calculating the so-called sensitivity matrix $\mathcal{S}$ of size $(N \cdot m) \times p$ that contains changes of the m different observations in dependence on p parameters for N discrete time points:

$$\mathcal{S} = \begin{pmatrix} \frac{\partial y_1}{\partial \theta_1}(t_0) & \cdots & \frac{\partial y_1}{\partial \theta_n}(t_0) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_m}{\partial \theta_1}(t_0) & \cdots & \frac{\partial y_m}{\partial \theta_n}(t_0) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_1}{\partial \theta_1}(t_N) & \cdots & \frac{\partial y_1}{\partial \theta_n}(t_N) \\ \vdots & \vdots & \vdots \\ \frac{\partial y_m}{\partial \theta_1}(t_N) & \cdots & \frac{\partial y_m}{\partial \theta_n}(t_N) \end{pmatrix} \tag{4}$$

The sensitivity matrix entries are given by

$$\frac{\partial y}{\partial \theta} = \frac{\partial g}{\partial x}\frac{\partial x}{\partial \theta} + \frac{\partial g}{\partial \theta}. \tag{5}$$

The only term not directly given by the model equations is $\frac{\partial x}{\partial \theta}$ as only the differential equations are known. But, as $\frac{\partial}{\partial \theta}\left(\frac{\mathrm{d}x}{\mathrm{d}t}\right) = \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\partial x}{\partial \theta}\right)$ in this case, one can obtain $\frac{\partial x}{\partial \theta}$ by numerical integration over time with randomly chosen parameters. Due to the numerical integration, the calculated sensitivity matrix is a local property, to extend the analysis it is advised to calculate several sensitivity matrixes for different parameter values.

Once the sensitivity matrix is determined, three different cases can occur.

1. The sensitivity matrix $\mathcal{S}$ is of full rank, thus the rank equals the number of parameters. In this case, the model is locally structurally identifiable as the numerical integration is based on local conditions.
2. A complete column of $\mathcal{S}$ is zero. In this case, the observable is completely independent of the parameter belonging to that column, hence the model is structurally non-identifiable.
3. Different columns of $\mathcal{S}$ are linearly dependent and the matrix does not have full rank. In this case, the contributing parameters are coupled and the model is structurally non-identifiable.

All of these three cases can be found by calculating the rank of the matrix and in the implementation of StrucID this is achieved by means of singular value decomposition. Here, a threshold is used to determine if a singular value is zero as due to numerics, no singular value will be exactly zero.

The sensitivity matrix approach by itself does not give the option to automatically calculate an identifiable reparametrization. Nevertheless, one can determine the groups in which the non-identifiable parameters show up as each group belongs to one zero-valued singular value. In addition, the results of the identifiability analysis can be used to perform a reduced symbolic computation of identifiable parameter combinations, which now can be evaluated quickly in comparison with an analysis of the whole problem [59].

Software accessibility and usability

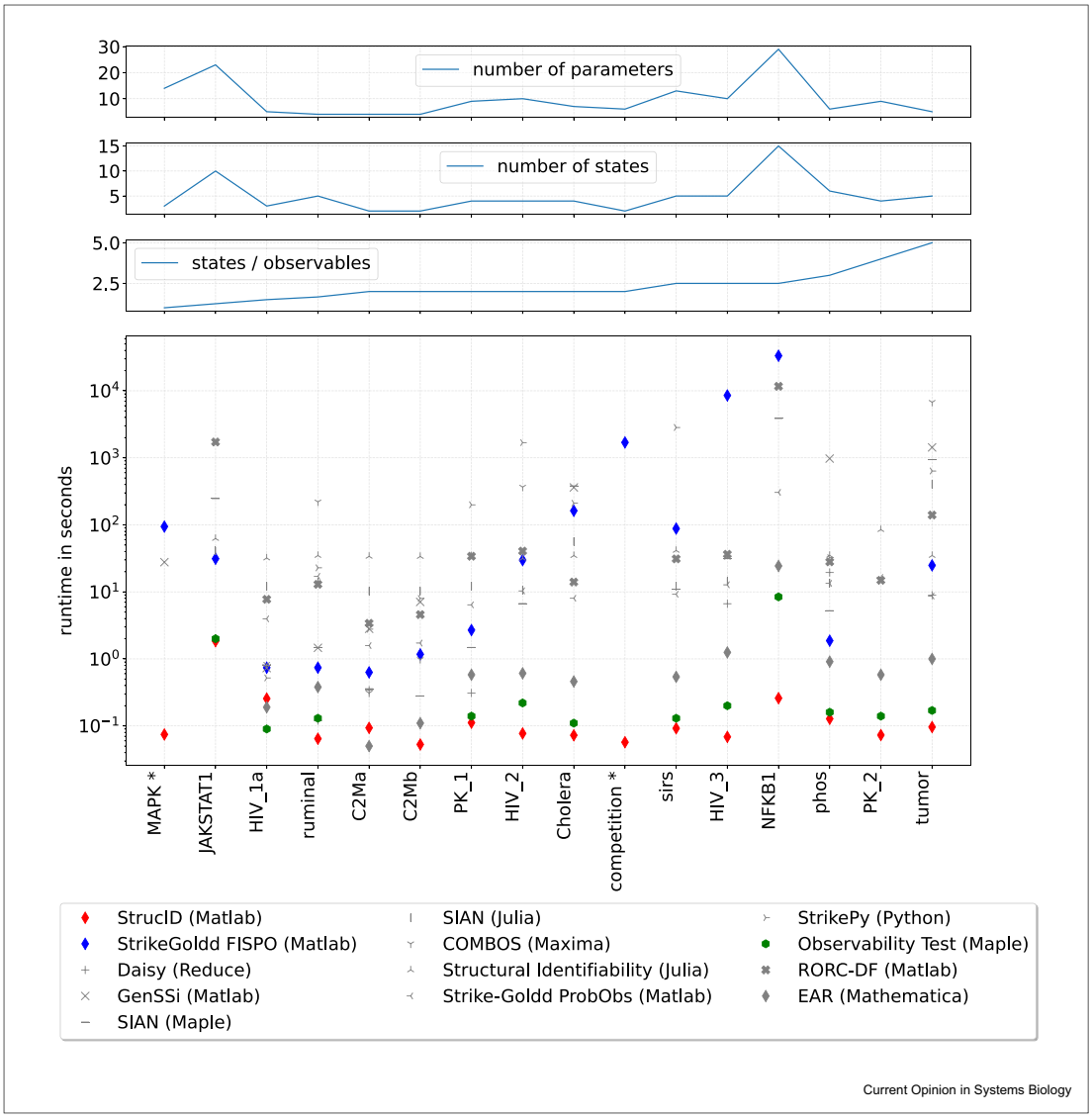
StrucID is written in Matlab and the source code as well as a compiled version to accommodate users without Matlab access are available on Github (https://github.com/jdstigter/StrucID). Furthermore, the StrucID analysis is integrated in the D2D framework (https://

github.com/Data2Dynamics/d2d). The software does cover rational and non-rational models with known and unknown analytic inputs. Identifiability of initial conditions can be tested, but for known initial conditions these can be provided in the input file and are used to inform the numeric integration. The input needed for a StrucID analysis is easily readable and user-friendly and the complete model structure has to be provided in a single .txt file.

Benchmarking StrucID

To test, whether we will be able to compare our run times for StrucID with the values published in Ref. [57], the STRIKE-GOLDD FISPO algorithm was used to compare computational setups. Using the same setup as for StrucID, sixteen models of different complexity were analysed. The calculations with StrucID and the run times were compared with those documented in the benchmark study [57]. In Appendix

Figure 1



Comparison of performance of different structural identifiability methods including StrucID. The upper panels show the number of parameters, number of states and states over observables for each model, the parameters are given in Table A.2. The models are ordered by states over observables. In the lower panel, the run times of StrucID (red) for the different benchmark models as presented in Ref. [57] are plotted. The run times for StrucID are significantly lower and show less dependence on the structure of the model. For the PK_2 model, the analysis in STRIKE-GOLDD was stopped as it took longer than the limit of 36 h. In grey, the run times for the different methods as given in the benchmark study are plotted. The observability test written in Maple (green) [22] also achieves fast run times but is only suitable for rational models. The two non-rational models are marked with an asterisk. Comparing the quantities in the upper panels with the run times shows that there is no way to easily predict the run time beforehand, thus a method that is mostly independent of model size or complexity is advantageous. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

A, the results of the comparison are shown in detail and it shows that the two setups are sufficiently comparable to compare the StrucID results with all other methods analysed in the benchmark study.

In Figure 1 and Table A.1, a comparison between the run times of StrucID and the methods analysed in the benchmark study is shown. A detailed presentation of the used models is given in Ref. [57], the models cover a wide range of states and amount of measured outputs, as well as different inputs. Most of the models are rational, thus also feasible with the second STRIKE-GOLDD algorithm, but the competition and the mitogen-activated protein kinase model have been included as non-rational models. For the analysis, each model was analysed once and the time was measured via the Matlab function tic-toc using one core. The results were compared in terms of detected non-identifiabilities and computational time.

For all models, StrucID yields fast results and for the models analysed in this paper, the results were checked in terms of detected non-identifiable parameters and no false results, neither false positive nor false negative results were found. For most of the models, the observability test written in Maple, based on the probabilistic algorithm presented in Ref. [22] yields comparably fast results as StrucID but for the non-rational competition and MAPK model, the probabilistic algorithm is not suitable. For these non-rational models, none of the other benchmarked algorithms gives comparable run times to StrucID.

We conclude that adding this method to the already known methods solves the problem of analysing structural identifiability in ODE models fast enough so it can be integrated in the modelling workflow and a priori assist with model design.

Besides the fast identifiability analysis, StrucID can also assist in fast reparametrization of models. After the identifiability analysis, the analytic calculations that are, for example, performed by STRIKE-GOLDD can be reduced to only include the parameters that cause the model to be non-identifiable. This leads to a smaller number of Lie derivatives that need to be calculated and highly improves the analysis.

On the still challenging problem of practical identifiability analysis

While structural identifiability analysis no longer hampers model development, it becomes more and more apparent that proper practical identifiability analysis can be a challenge for typical tasks of dynamical modelling. A model parameter is termed practically non-identifiable when it's structurally identifiable but does not have finite confidence intervals. Approaching a biological question with a practically non-identifiable model can be cumbersome for the interpretation of results and quality of model predictions, although for several cases predictive power can still be given [60]. Most prominently, the iterative model development process, including multiple parameter optimisation runs for each iteration, can be problematic and time-consuming when parameters are practically non-identifiable, which is why practical identifiability analysis has become standard inside the systems biology modelling community [1,61]. Moreover, importance of practical identifiability was shown in the fields of growth models [62,63], ecological population models [64] or animal science [65]. Recently, in the context of partial differential equation models, practical identifiability was even suggested as an additional criterion for model selection [66].

During the last couple of years, several approaches to address practical identifiability analysis in dynamical models have been reported [14]. However, both computationally fast and comprehensive solution remains elusive. In particular, we see three challenges to be faced:

(i) **Performance trade-off of practical identifiability methods:** Profile likelihood [13] remains the most accurate practical identifiability method but is often computationally expensive since step-wise optimisation is necessary. Approximate alternatives, such as the method of Lagrangian multipliers [67–70], or the Cluster Gauss–Newton method [71] in the context of physiologically based pharmacokinetic models, offer faster solutions. However, by construction, these approaches may lead to wrong conclusions regarding the practical identifiability of a parameter. Similar to the Fisher's information matrix–based confidence intervals, the approximation typically leads to confidence intervals that are computed to be smaller than by the *true* profile likelihood obtained by step-wise optimisation.

(ii) **Benchmark problems for practical identifiability analysis:** Following current scientific standards, the final results of a research project are reported and the potentially long way of achieving these results is typically not documented. In the field of mathematical modelling, this means that publicly available model collections, as for example [72], are already in a reasonable state concerning the issue of practical identifiability. While this is in general desirable, it implies a situation with a lack of well-documented problems for testing and developing new approaches for practical identifiability analysis. Generation of such a practical identifiability oriented benchmark collection would not only support the development of new algorithms but also comparing them with each other as it has already become the standard for structural identifiability analysis. To provide quick access for as many as possible modelling environments that provide practical identifiability approaches, project documentation should orient on the

PEtab structure [73]. Although real-world scenarios apparently are the best for testing approaches in real-world application, a recent idea of simulating realistic data sets based on given model structures and parameters [74] could be helpful to create practical identifiability test scenarios. In particular, this could be combined with models from the BioModels database [75] where the focus is typically not on providing proper data sets along with the model definition.

Given a practical identifiability benchmark collection and proper analysis tools, the next step is to distinguish and classify typical scenarios of practical identifiability. One basic step of documenting such problems was taken with the main focus of showing how to cure them in a statistically sound manner by means of the profile likelihood [76]. The usage of 2D profile likelihoods [77,78] can be very helpful to understand and describe the interdependence of model parameters connected to a practical non-identifiability. However, most informative is the analysis of *parameter paths*, i.e. the set of parameter values along the profile likelihood [13,79]. As demonstrated in Ref. [76], parameter paths are essential for proper interpretation of non-identifiabilities and model reduction. To our eyes, the information content of the parameter paths is currently undervalued by the community.

(iii) **A priori prediction of practical identifiability:** The practical identifiability of a model is only defined in conjunction with experimental data. Nevertheless, there are approaches that aim to assess the expected results of the practical identifiability analysis of a model without experimental data [80,81], meaning purely based on the model's structure as it is typically done for structural identifiability analysis. Although these approaches are in early stages of development, we expect the task of a priori practical identifiability analysis to be intensively discussed in the near future. Within the iterative process of model generation [1], it will constitute a remarkable milestone. It will not only guide a priori selection of useful models but also support experimental design regarding potential parameters of the model that are cumbersome to determine with precision.

To summarise, the development of tools for practical identifiability analysis is still in its infancy. It is conceptually challenging because of the mathematical and statistical complexity of the task. Furthermore, the data-based problem statement needs biological interpretation and the amount of reported case scenarios is low.

Conclusion

Structural identifiability of nonlinear dynamic models can be analysed efficiently with currently available methods. The recent development in benchmarking of these methods further shows that methods for various model types exist. Adding up to this, the here presented analysis of StrucID shows that there is a method available that is able to perform analyses of the vast majority of currently used models in less than a minute. Thus, the problem of structural identifiability analysis is effectively solved for all practical purposes. It should be a standard part of the model development workflow in systems biology and no longer constitutes a bottleneck.

As stated in the last review [1], the actual challenge lies in the analysis of practical identifiability. The recent review on practical identifiability [14] also highlights the importance of that topic and summarises advances and new methodology. Despite these novel approaches, a both fast and reliable method to analyse practical identifiability is still lacking. We are also missing a set of real-world scenarios, i.e. models with experimental data, where new methods for practical identifiability analysis could be tested on and compared with each other. Without such a collection, benchmarking of methods that are designed to analyse identifiability issues that occur only when data are involved sounds ambiguous. We hope that the aspects highlighted in this section will help to circumvent this situation and foster the development of efficient and comprehensive tools in the near future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Comparison of the computational setups

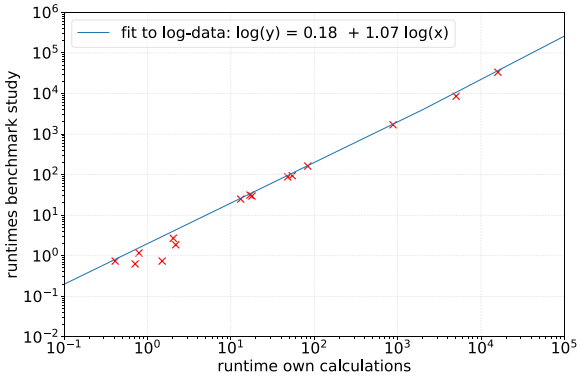
To analyse whether our computational setup is comparable with the one used in the benchmark study [57], our own calculations with the STRIKE-GOLDD FISPO algorithm were compared with the ones reported in the study (also see Table A.1). As computational time scales exponentially with complexity of the model, the two run time series should show a linear dependence on the log-log scale. For comparable results, the slope of the linear dependence should be close to one and the offset close to zero.

To determine slope and offset, both data series were logarithmised and fitted with a linear regression; the results are shown in Figure A.1. We find

$$\log(\text{runtimes}_{\text{bench.}}) = 0.18(13)\,\text{s} + 1.07(3)\cdot\log(\text{runtimes}_{\text{own}}). \quad \text{(A.1)}$$

that the slope is close to one and shows that the setups produce comparable results.

Figure A.1



Comparison of the run times for STRIKE-GOLDD FISPO as given in the benchmark study with our own calculations. As expected, the run times show a linear dependence on the log-log scale and the slope is close to one, thus the setups give comparable results.

Table A.1

Run times for the different methods in seconds. Strike-Goldd (own) refers to the local computations made to compare the local StrucID results with the ones from the benchmark study. Strike-Goldd (benchmark) lists the results from the benchmarking paper [57]. For the PK_2 model, the Strike-Goldd computations took longer than 36 h and were terminated. In the table, this is denoted by *None*.

Model	StrucID	Strike-Goldd (own)	Strike-Goldd (benchmark)
HIV_1a	0.256	0.41	0.74
C2Ma	0.09	0.71	0.63
C2Mb	0.05	0.79	1.17
Ruminal	0.06	1.50	0.74
PK_1	0.11	2.04	2.69
Phos	0.13	2.18	1.87
Tumour	0.1	13.1	24.86
JAKSTAT1	1.84	16.98	31.26
HIV_2	0.08	17.92	29.79
SIRS	0.09	48.11	87.98
MAPK	0.07	54.47	94.219
Cholera	0.07	83.53	162.26
Competition	0.06	881.14	1696.29
HIV_3	0.07	5030.162	8528
NFKB1	0.26	15 931.81	33 345
PK_2	0.07	None	None

MAPK, mitogen-activated protein kinase; SIRS, systemic inflammatory response syndrome.

Table A.2

Number of parameters and states, as well as calculated states over observables for the analysed models. These properties are also plotted in Figure 1 as different measures for the size of the models.

Model	Parameters	States	States/observables
HIV_1a	5	3	1.5
C2Ma	4	2	2
C2Mb	4	2	2
ruminal	4	5	1.67
PK_1	9	4	2
phos	6	6	3
tumour	5	5	5
JAKSTAT1	23	10	1.25
HIV_2	10	4	2
sirs	13	5	2.5
MAPK	14	3	1
Cholera	7	4	2
competition	6	2	2
HIV_3	10	5	2.5
NFKB1	29	15	2.5
PK_2	9	4	4

MAPK, mitogen-activated protein kinase; SIRS, systemic inflammatory response syndrome.

Data availability

Data will be made available on request.

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Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

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