Motivation: Mathematical description of biological reaction networks by differential equations leads to large models whose parameters are calibrated in order to optimally explain experimental data. Often only parts of the model can be observed directly. Given a model that sufficiently describes the measured data, it is important to infer how well model parameters are determined by the amount and quality of experimental data. This knowledge is essential for further investigation of model predictions. For this reason a major topic in modeling is identifiability analysis.

Results: We suggest an approach that exploits the profile likelihood. It enables to detect structural non-identifiabilities, which manifest in functionally related model parameters. Furthermore, practical non-identifiabilities are detected, that might arise due to limited amount and quality of experimental data. Last but not least confidence intervals can be derived. The results are easy to interpret and can be used for experimental planning and for model reduction.

Availability: An implementation is freely available for MATLAB and the PottersWheel modeling toolbox at http://web.me.com/andreas.raue/profile/software.html.

Contact: andreas.raue@me.com

Supplementary information: Supplementary data are available at Bioinformatics online.

1 INTRODUCTION

Inferring cell biological questions by mathematical modeling of reaction networks became a popular and powerful approach (Kitano, 2005). Tools to build models for complex reaction networks and calibrate model parameters to experimental data are available (Maiwald and Timmer, 2008; Schmidt and Jirstrand, 2006). Statistical tests were established to evaluate, whether a model can explain experimental data sufficiently, as well as to compare the performance of different models or model extensions, e.g. Ghosh and Samanta (2001).

Furthermore, it is usually desired to use an established model for prediction of: model parameters such as rate constants or initial concentrations; model trajectories such as time-courses of experimentally unobserved species concentrations; model behaviour under changed environmental conditions such as altered network structure or different external stimulation. Since the considered models are parametric, these predictions depend intrinsically on the previously calibrated model parameters. Due to technical limitations, e.g. availability of specific antibodies, biological reaction networks are often only partially observable. This means that not all species incorporated in a model can be measured directly. Given a certain amount and quality of experimental data measured under specific experimental conditions, it is not assured that model parameters can be estimated unambiguously. Frequently, experimental data are insufficient considering the size of the model which results in parameters that are non-identifiable (Swameye et al., 2003). Even identifiable parameters can only be determined within confidence intervals, which contain the true value of the parameter with a desired probability (Lehmann and Leo, 1983). If model parameters are not well determined also model predictions are not. Consequently, the biological question that should be answered by the model, might not be addressable. Our aim is to develop an approach that enables evaluating which parameters are identifiable, thus inferring which model predictions are feasible. Provided that parameters are identifiable, the question that follows is how large their confidence intervals are, which indicates how reliable a model prediction is.

After introducing parameter estimation and discussing how confidence intervals can be derived, different types of identifiability are formulated. A brief overview of existing approaches for identifiability analysis including their assets and drawbacks is given. Subsequently, a novel approach for identifiability analysis by exploiting the profile likelihood will be introduced. This approach is able to detect both structural and practically non-identifiable parameters and simultaneously calculates confidence intervals. Since large models are under consideration, the approach needs to be computationally feasible and its output should be
interpretable even if depending on a high-dimensional parameter space. Furthermore, the approach can be used for experimental planning to suggest additional measurements that efficiently reduce parameter uncertainties and for model reduction to tailor the model complexity to the information given by the experimental data. Usage and benefit of the approach will be illustrated by applying it to a model of the JAK-STAT signaling pathway, that is calibrated to experimental data.

2 PROBLEM STATEMENT

Given a model $M$ describing $n$ species concentrations $x_i$ in a reaction network by a system of ordinary differential equations (ODE)

$$\dot{\tilde{x}}(t) = f(\tilde{x}(t), \bar{u}(t), \bar{p})$$

(1)

$$\tilde{y}(t) = g(\tilde{x}(t), \bar{\theta}) + \tilde{\epsilon}(t)$$

(2)

with internal model states $\tilde{x}(t)$, an externally given stimulus $\bar{u}(t)$, dynamic parameters $\bar{p}$, an $m$-dimensional mapping $g$ of the internal model states to the observables $\tilde{y}(t)$ involving scaling and offset parameters $\bar{\theta}$. The measurement noise $\tilde{\epsilon}(t)$ is assumed to be normally distributed. For partially observed models, the dimension $m$ of observations is smaller than the dimensions $n$ of internal model states. Together with the initial concentrations $\tilde{x}(0)$ for Equation (1), we define

$$\theta = \{\bar{p}, \tilde{x}(0), \tilde{\theta}\}$$

(3)

as set of parameters necessary to fully specify $M$. For parameters in biological reaction networks, e.g. rate constants or initial concentrations usually $\theta \in \mathbb{R}^n \setminus \{0\}$. To avoid the natural lower bound of zero, logarithmic parameter values will be used in the following.

2.1 Parameter estimation

The agreement of experimental data with the observables predicted by the model is measured by an objective function, commonly the weighted sum of squared residuals

$$\chi^2(\theta) = \sum_{k=1}^{m} \sum_{i=1}^{n} \frac{y^D_{ki} - y_{ki}(\theta, t)}{\sigma^2_{ki}}^2$$

(4)

where $y^D_{ki}$ denotes $d$ data-points for each observable $k$, measured at time-points $t_i$, $\sigma^2_{ki}$ are the corresponding measurement errors and $y_{ki}(\theta, t)$ the $k$-th observable as predicted by parameters $\theta$ for time-point $t_i$. The parameters can be estimated numerically by

$$\hat{\theta} = \arg\min \chi^2(\theta).$$

(5)

For normally distributed observational noise $\tilde{\epsilon} \sim N(0, \sigma^2)$, this corresponds to the maximum likelihood estimate (MLE) of $\theta$ and

$$\chi^2(\theta) = \text{const} - 2 \log(L(\theta))$$

(6)

where $L(\theta)$ is the likelihood. In the following, $\chi^2$ will be used as placeholder for the likelihood. Furthermore, an appropriate model $M$ that sufficiently describes the available experimental data is assumed.

2.2 Confidence intervals

A confidence interval $[\sigma_i^{-}, \sigma_i^{+}]$ of a parameter estimate $\hat{\theta}_i$ to a confidence level $\alpha$ signifies that the true value $\theta_i$ is located within this interval with probability $\alpha$. In the following, asymptotic and finite sample confidence intervals will be introduced.

2.2.1 Asymptotic confidence intervals

Confidence intervals can be derived from the curvature of the likelihood, e.g. the Hessian matrix

$$H = \nabla^2 \chi^2(\theta)$$

(7)

Using the covariance matrix $C = 2^{-1} H^{-1}$ of the parameter estimates, asymptotic confidence intervals are given by

$$\sigma_i^{+} = \hat{\theta}_i \pm \sqrt{\chi^2(a, df)} C_{ii}$$

(7)

where $\chi^2(a, df)$ is the $a$ quantile of the $\chi^2$-distribution with $df$ degrees of freedom, as explained in Press et al. (1990). The choice of $df$ yields two different types of confidence intervals: $df = 1$ gives pointwise confidence intervals that hold individually for each parameter, $df = \#\theta$ being the number of parameters gives simultaneous confidence intervals that hold jointly for all parameters.

Asymptotic confidence intervals are a good approximation of the actual uncertainty of $\hat{\theta}_i$ if the amount of experimental data is large compared to $\#\theta$ and/or the measurement noise is small. They are exact if the observables $\tilde{y}$ depend linearly on $\theta$. However, even for the simplest reaction network the observables $\tilde{y}$ depend nonlinearly on $\theta$ and the amount and quality of experimental data is often insufficient. Therefore, asymptotic confidence intervals might not be appropriate (Joshi et al., 2006).

2.2.2 Finite sample confidence intervals

Confidence intervals can be also derived using a threshold in the likelihood. These so called likelihood-based confidence intervals are defined by a confidence region

$$\{\theta | \chi^2(\theta) - \chi^2(\hat{\theta}) < \Delta_a\}$$

(7)

whose borders represent confidence intervals (Meeker and Escobar, 1995). The threshold $\Delta_a$ is the $a$ quantile of the $\chi^2$-distribution and represents with $df = 1$ and $df = \#\theta$ pointwise, respectively, simultaneous confidence intervals to a confidence level $\alpha$ [see Equation (7)]. Likelihood-based confidence intervals are considered superior to asymptotic confidence intervals for finite samples (Neale and Miller, 1997).

2.3 Identifiability

A parameter $\theta_i$ is identifiable, if the confidence interval $[\sigma_i^{-}, \sigma_i^{+}]$ of its estimate $\hat{\theta}_i$ is finite. Two phenomena accounting for parameters to be non-identifiable will be discussed here. Structural non-identifiability is related to the model structure independent of experimental data which is extensively discussed, e.g. Cobelli and DiStefano III (1980). In contrast, practical non-identifiability also takes into account the amount and quality of measured data, that was used for parameter calibration. Practical non-identifiability is less clearly defined in literature, therefore an independent definition will be given.

2.3.1 Structural non-identifiability

A structural non-identifiability arises from a redundant parameterization in the formal solution of $\tilde{x}(t)$, due to an insufficient mapping $g$ of
Definition 1. A parameter estimate \( \hat{\theta} \) is *structurally non-identifiable* if the internal model states \( \bar{x} \) to observables \( \bar{y} \) in Equation (2). The set of ambiguous parameters \( \delta_{ab} \subset \theta \) may be varied without changing the observables \( \bar{y}(t) \), hence keeping \( \chi^2(\theta) \) on a constant value. Consequently, the parameter estimates \( \delta_{ab} \) and, respectively, the internal model states \( \bar{x}(t) \) affected by these parameters are not uniquely identified. Confidence intervals of a structurally non-identifiable parameter \( \theta_i \in \delta_{ab} \) are infinite \([-\infty, +\infty]\) in log-linearizable parameter space considered here. Hence, its value cannot be estimated at all. A direct detection of a redundant parameterization manifests as functional relations \( h \) between the parameters \( \theta_{ab} \), representing a manifold with constant \( \chi^2 \) in parameter space

\[
\chi^2(\theta) = \chi^2(\hat{\theta}) \leftrightarrow h(\theta_{ab}) = 0. \tag{9}
\]

In a two-dimensional parameter space, a practical non-identifiability, the flattening out of the likelihood can continue along a functional relation. The confidence interval of a practically non-identifiable parameter is not necessarily extended infinitely to both sides. There can be a finite upper or lower bound of the confidence interval \( [\sigma^{\hat{\theta}_i}_i, \sigma^\theta_i] \) where either \( \sigma^{\hat{\theta}_i}_i = -\infty \) or \( \sigma^\theta_i = +\infty \).

### 3 EXISTING METHODS

Various methods exist to detect structural non-identifiability by a priori analyzing the system equations (1) and (2), such as the Power Series Expansion (Pohjanpalo, 1978), the Volterra and Generating Power Series Approach (Lecourtier et al., 1987), the Similarity Transform Approach (Vajda et al., 1998b) or differential algebraic methods (e.g. Ljung and Glad, 1994). Unfortunately, these methods become rapidly infeasible with increasing model size (Margaria et al., 2001; White et al., 2001). Practical non-identifiability cannot be detected, since experimental data are disregarded.
or Fisher information matrix (Jacquez and Greif, 1985; Vajda et al., 1989a; Yao et al., 2003). These methods are appropriate if functional relations $h$ between the parameters emerging from structural non-identifiability are linear. This is often not the case for reaction networks modeled by ODE, because observables depend non-linearly on the parameters. Practical non-identifiability cannot be detected, because a quadratic approximation is not able to explain increasing but limited behavior of $x^2(\theta)$ as mentioned earlier.

An approach to detect structural non-identifiability by the corresponding functional relations was introduced by Hengl et al. (2007). It is able to detect flatness of likelihood for arbitrary models, but is not intended to detect practical non-identifiability.

Similar to a clear formal definition, an approach for explicit testing of practical non-identifiability is not available to our knowledge. In the following, we introduce a general approach to analyze arbitrary models for structural and practical non-identifiability.

4 APPROACH

The idea of the approach is to explore the parameter space for each parameter in the direction of the least increase in $x^2$. For a structurally non-identifiable parameter this means to follow the functional relations $h(\theta_{ub})=0$. In case of a practically non-identifiable parameter, the aim is to detect directions where the likelihood flattens out.

A useful concept for this task is the profile likelihood (PL) $x^2_{PL}$. (Murphy and van der Vaart, 2000; Venzon and Moolgavkar, 1988).

It can be calculated for each parameter individually by

$$x^2_{PL}(\theta_i) = \min_{\theta_{ub}} x^2(\theta)$$

meaning re-optimization of $x^2(\theta)$ with respect to all parameters except for each value of parameter $\theta_i$. Hence, the profile likelihood keeps $x^2$ as small as possible alongside $\theta_i$. Figure 1 illustrates that the likelihood is explored in the desired way to detect non-identifiabilities. An algorithm to calculate $x^2_{PL}$ is described in the Supplementary Material.

Structural non-identifiable parameters are characterized by a flat profile likelihood [Equation (9)]. The profile likelihood of a practically non-identifiable parameter has a minimum, but is not exceeding a threshold $\Delta_0$ for increasing and/or decreasing values of $\theta_i$. In contrast, the profile likelihood of an identifiable parameter exceeds $\Delta_0$ for both increasing and decreasing values of $\theta_i$. The points of passover represent likelihood-based confidence intervals as defined in Equation (8) (Royston, 2007). By following the change of parameters $\theta_{ub}$ along $x^2_{PL}(\theta)$, the functional relations $h(\theta_{ub})=0$ corresponding to a structural non-identifiability can be recovered.

Experimental planning To improve certainty of a specific model prediction, it would be valuable to suggest additional measurements that efficiently resolve non-identifiability and narrow the confidence interval of a parameter $\theta_i$ affecting this issue. The set of trajectories along the profile likelihood of $\theta_i$ reveals spots where the uncertainty of $\theta_i$ has the largest impact on the model. Additional measurements at these spots are likely to efficiently reduce this uncertainty. The amplitude of variability of the trajectories at these spots allows to assess the necessary precision of a new measurement to provide adequate data that is able to improve parameter identification.

The impact of new measurements can be evaluated by Monte Carlo simulations. To this aim, the described analysis of the profile likelihood is repeated, taking into account additional simulated data. The resulting change of the profile likelihood and correspondingly the resolution of non-identifiability and the narrowing of the likelihood-based confidence intervals allow to justify the effort of new measurements to gain a more confident model prediction.

Model reduction The approach can be used for model reduction by considering a threshold $\Delta_0$ with $df=1$ [see Equation (8)]. Assume that a parameter $\theta_i$ is practically non-identifiable for decreasing parameter value. Consider a reduced model $M^*$ with simplified kinetics concerning $\theta_i$, e.g. for mass action kinetics by removing the corresponding reaction. In this case, the threshold $\Delta_0$ corresponds to a likelihood ratio test of the reduced model $M^*$ against the original model $M$ to a significance level $1-\alpha$. Falling below this threshold, the profile likelihood indicates that it is not possible to dismiss $M^*$ in favor of $M$, based on the available experimental data.

5 APPLICATION

To illustrate usage and benefit of the approach, it was applied to a model of the JAK-STAT signaling pathway inspired by Swameye et al. (2003), which is calibrated to the experimental data available at http://webber.physik.uni-freiburg.de/~jet/PNAS_Swameye_Data/ (dataset 1). The model represents the STAT signaling cascade including nuclear shuttling upon stimulation with Erythropoietin: phosphorylation of cytoplasmatic STAT $(\Delta_2)$ triggered by active Erythropoietin receptor pEpoR $(u)$; homo-dimerization of pSTAT $(\Delta_2)$; import of the pSTAT:pSTAT complex $(\Delta_3)$ into the nucleus; dissociation and dephosphorylation of npSTAT npSTAT $(\Delta_4)$ and export to cytoplasm (Fig. 2). A spline interpolation of pEpoR measurements serves as external stimulus $u$. The double arrowhead denotes a delay reaction modeled by a linear chain approximation.

\[x_{\theta_i} = -p_1 x_{\theta_i} u + 2 p_4 x_4^2 \]

\[x_{\theta_i} = +p_1 x_{\theta_i} u - p_2 x_2^2 - p_3 x_3 \]

\[x_{\theta_i} = +p_1 x_{\theta_i} - p_4 x_4^2 \]

\[x_{\theta_i} = +p_1 x_{\theta_i} - p_4 x_4^2 \]

Fig. 2. Network structure of the model and observables calibrated to experimental data. A spline interpolation of pEpoR measurements serves as external stimulus $u$. The double arrowhead denotes a delay reaction modeled by a linear chain approximation.
where the superscript $τ$ denotes a delay reaction implemented by a linear chain approximation, yielding an effective delay $τ = 10/μ_4$ with 10 intermediate steps (MacDonald, 1976). Experimentally observable quantities are phosphorylated STAT in cytoplasm ($y_1$) and total STAT in cytoplasm ($y_2$), both measured in arbitrary units by quantitative western blotting. Two compartments are considered in the model: the cytoplasm and the nucleus with 1400 μm$^3$ and 450 μm$^3$. Species concentrations are modeled in nanometer. Besides the dynamic parameters $p_1$ to $p_4$ and scaling parameters $s_1$ and $s_2$, the initial concentration $x_1(0)$ belongs to the parameters $θ$ that need to be calibrated by the experimental data. The initial values of species $x_2$ to $x_4$ are assumed to be equal to zero. The model is implemented and calibrated using the PottersWheel fitting toolbox (Maiwald and Timmer, 2008), resulting trajectories of observables are shown in Figure 2.

Calculating the profile likelihood takes $54 ± 18$ s per parameter, using an implementation of the approach embedded in the PottersWheel fitting toolbox (1 GHz CPU, 2 GB RAM), which is described in the Supplementary Material. The resulting plots of profile likelihood versus parameter reveal four structurally non-identifiable parameters $p_2$, $x_1(0)$, $s_1$, $s_2$ by their flat profile likelihood, see Figure 3, upper panel.

**Structural non-identifiability** The functional relations $\hat{h}$ connecting these structurally non-identifiable parameters can be recovered from the changes of the remaining parameters, while calculating the profile likelihood of the structurally non-identifiable parameters, as shown in Figure 4. Using, for example, $x_{1P}^2$, the manifold can be characterized as

\[
\begin{align*}
  h_1(θ_{sub}) &= p_2 \cdot x_1(0) - const = 0 \\
  h_2(θ_{sub}) &= x_1(0) - const = 0 \\
  h_3(θ_{sub}) &= p_2 \cdot x_1(0) - const = 0
\end{align*}
\]

which is compliant with analytical considerations given in Timmer et al. (2004). Recovering the functional relations unambiguously from the change of parameters along the profile likelihood is only possible if the corresponding manifold is one-dimensional. This is because one parameter is fixed at a time while computing the profile likelihood. To recover functional relations that correspond to manifolds with dimension larger than one, a further analysis of the structurally non-identifiable parameters is necessary, e.g. the approach by Hengl et al. (2007).

The variability of the internal model states $\vec{x}$ imposed by this structural non-identifiability can be analyzed by plotting the trajectories for parameter values along the profile likelihoods of the structural non-identifiable parameters (Fig. 5). All internal model states can only be identified up to a common factor. This implies that the structural non-identifiability is derived from the fact that no information about absolut concentration is included in the experimental data.

**Practical non-identifiability** Thresholds $Δα=0.68$ for both pointwise and simultaneous $1−σ$ confidence intervals are displayed.
The profile likelihood reveals that parameter $p_3$ is practically non-identifiable for increasing parameter values. This indicates that the amount and quality of the experimental data provided does not contain enough information to yield an upper limit for the rate of nuclear import $p_3$. The variability of the predicted model observables $\tilde{y}$ along the profile likelihood of $p_3$ remains consistent with the measurement errors, as shown in Figure 6. Nevertheless, a lower confidence bound can be derived.

Confidence intervals Table 1 compares finite sample confidence intervals derived from the profile likelihood and asymptotic confidence intervals derived from the Hessian matrix. For identifiicable parameters the discrepancies are small. Working in logarithmic parameter space linearizes the functional relations given in Equation (11). In this case, asymptotic approximation leads to large but nevertheless finite confidence intervals for the structurally non-identifiable parameters. The largest discrepancy occurs for practically non-identifiable parameters, where asymptotic confidence intervals are significantly smaller than likelihood-based confidence intervals. Asymptotic confidence intervals are also indicated in Figure 3 by gray parabolas.

Experimental planning To resolve the structural non-identifiability between parameters $p_2, x_1(0), x_2, x_4$, a measurement of absolut concentration is necessary as mentioned earlier. Figure 5 shows trajectories for parameters along this non-identifiability. Spots of largest variability suggest where and when a measurement of a species most efficiently determines theses parameters: $x_1$ at times $t=0$ or $t>50$, $x_2$ to $x_4$ at times $5 < t < 30$. The trajectories of the internal model states $\tilde{x}$ along the profile likelihood of the practically non-identifiable parameter $p_3$ shown in Figure 6 comprises large antipodal variability of species $x_2$ and $x_3$, revealing that the experimental setup is inappropriate to estimate this parameter with confidence. Therefore, an additional measurement to discriminate phosphorylated STAT species $x_2$ and $x_3$ is suggested, e.g. the fraction of dimerized pSTAT relative to total phosphorylated STAT in cytoplasm $x_3/(x_2 + x_3)$ between 5 and 30 min. If no further quantities than $y_1$ and $y_3$ can be measured directly, a refined measurement of phosphorylated STAT in cytoplasm $(y_3)$ at times $t > 50$ or of total STAT in cytoplasm $(y_2)$ at times $t > 30$ where largest variability of the observables occurs are the best options. To evaluate the impact of additional measurements on identifiability and confidence intervals, we assume hypothetic measurements yielding an initial concentration of unphosphorylated STAT in cytoplasm $x_1(0) = 200 \pm 20 \text{nM}$ and a fraction of $x_3/(x_2 + x_3) = 0.90 \pm 0.05$ at time $t = 20 \text{min}$. The recalculated profile likelihood reveals, that parameters $p_2, x_1(0), x_2, x_4$ become structurally identifiable (Fig. 3, lower panel), by measuring only one of them. This accentuates the benefit of knowing the functional relations between structurally non-identifiable parameters, as given in Equation (11). Parameter $p_3$ becomes practically identifiable, only previously structurally non-identifiable parameter $p_2$ remains practically non-identifiable.

### Table 1. Likelihood-based confidence intervals $\sigma_{PL}$ derived from the profile likelihood are compared with asymptotic confidence intervals $\sigma_{Hess}$ derived from the Hessian matrix [see Equation (7)]

<table>
<thead>
<tr>
<th>Name</th>
<th>$\hat{p}$</th>
<th>Non-identifiability</th>
<th>$\sigma_{PL}$</th>
<th>$\sigma_{Hess}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p_1$</td>
<td>+0.31</td>
<td>Structural</td>
<td>+0.12</td>
<td>+0.50</td>
</tr>
<tr>
<td>$p_2$</td>
<td>-1.00</td>
<td>Practical</td>
<td>-1.14</td>
<td>-1.14</td>
</tr>
<tr>
<td>$p_3$</td>
<td>-0.49</td>
<td>Structural</td>
<td>-1.14</td>
<td>-0.15</td>
</tr>
<tr>
<td>$p_4$</td>
<td>+0.42</td>
<td>Structural</td>
<td>+0.15</td>
<td>+0.78</td>
</tr>
<tr>
<td>$x_1(0)$</td>
<td>+0.31</td>
<td>Structural</td>
<td>+0.31</td>
<td>+0.31</td>
</tr>
<tr>
<td>$x_2$</td>
<td>-0.21</td>
<td>Structural</td>
<td>+0.31</td>
<td>+0.31</td>
</tr>
<tr>
<td>$x_3$</td>
<td>-0.34</td>
<td>Structural</td>
<td>+0.31</td>
<td>+0.31</td>
</tr>
</tbody>
</table>

Values are given in orders of magnitude and correspond to $\sigma = \pm 1$ simultaneous confidence intervals.

6 DISCUSSION

Exploiting the profile likelihood is a powerful approach to infer parameter uncertainties in a high-dimensional parameter space. Since it is a systematic and directed exploration, it has less computational cost than sampling parameter space randomly, which gets intractable for high dimensions. The profile likelihood can be calculated for each parameter separately. Thereby it is possible to restrict the analysis to the parameters relevant for the biological question. Moreover, this allows to perfectly parallelize the approach, which is a major benefit for its scalability. An analysis of the runtime of the approach for a test case model is shown in the Supplementary Material. The approach can be applied to any parameter estimation problem, where a likelihood or a similar objective criterion is

![Fig. 5. Trajectories of internal model states $\tilde{x}$ for parameter values along the structural non-identifiability. All internal model states can only be identified up to a common factor.](image)

![Fig. 6. Trajectories of observables $\tilde{y}$ and internal model states $\tilde{x}$ along the profile likelihood of the practically non-identifiable parameter $p_3$. Please note, that species $x_2$ and $x_3$ change antipodal.](image)
available, e.g. partial differential equations (PDE) or stochastic differential equations (SDE).

The approach results in easily interpretable plots of profile likelihood versus parameter. It can be automated, but an explicit advantage is that the output might be evaluated visually. This gives insight into a complex and high-dimensional parameter space. Structural non-identifiabilities originating from incomplete observation of the internal model states can be detected. Arising from limited amount and quality of experimental data, also practical non-identifiabilities can be inferred. Bridging the gap between identifiability and confidence intervals, the profile likelihood allows to derive likelihood-based confidence intervals for each parameter. Functional relations between parameters occurring due to non-identifiabilities can be recovered. The results of the approach can be used on the one hand to design new experiments that efficiently resolve non-identifiability and narrow confidence intervals and on the other hand to facilitate model reduction. Thus, identifiability analysis ensures that the model complexity is tailored to the information content given by the experimental data. Whether a model that is not well determined by the experimental data, should be reduced or additional data should be measured depends on the biological issue to be addressed.

The approach was applied to a model of the JAK-STAT signaling pathway. Non-identifiable parameters were detected, revealing limitations in the experimental setup. Additional measurements that efficiently improve parameter identification were suggested and validated.

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