Parameter identifiability analysis through likelihood profiles with COPASI

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Parameter Estimation

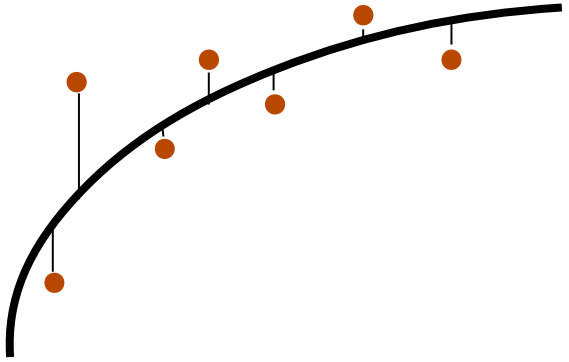
- ***Given a set of data, adjust a model's parameter values such that the distance between the model behaviour and the data is minimal***
- An essential part of parameter estimation consists on the application of numerical optimisation algorithms.
- In particular, many parameter estimation applications rely on either of the following

  minimisation of a least squares function

  minimisation of other distance measure

Least-squares methods

- The sum of squares of residuals (SSR) measures distance of model to data:



$$SSR = \sum (\chi - f(\boldsymbol{x}, \boldsymbol{k}))^2$$

- If residuals are normally distributed then *SSR* approximates the log-likelihood

Parameter Identifiability

- Not all parameters are equally *identifiable*
- *Unidentifiability* is the extent to which parameters are not identifiable
- **Structural Unidentifiability**
  - Some parameters cannot be identified uniquely individually, but can be identified in groups
  - Is detected from the equations by analysis (symbolic manipulation)
- **Practical Unidentifiability**
  - Some parameters cannot be identified given a specific data set, but with additional data are identifiable
  - Can be detected by numerical methods

One-dimensional likelihood profiles

$$LP(p_i) = min_{p_{j \neq i}}(SSR(p_j))$$

- Re-optimizing all parameters $p_{j \neq i}$ for fixed values of p_i around the solution
- Confidence intervals for each parameter can be estimated based on likelihood contours (C_{LC})or on likelihood ratios (C_{LR}), *e.g.*:

$$C_{LR} = \{ p : SSR(p) \leq SSR(\hat{p}) e^{\chi^2_\alpha / n} \}$$

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REVIEW ARTICLE

Profile likelihood in systems biology

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Keywords
parameter estimation; prediction; profile likelihood; propagation of errors; uncertainty

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Inferring knowledge about biological processes by a mathematical description is a major characteristic of Systems Biology. To understand and predict system's behavior the available experimental information is translated into a mathematical model. Since the availability of experimental data is often limited and measurements contain noise, it is essential to appropriately translate experimental uncertainty to model parameters as well as to model predictions. This is especially important in Systems Biology because typically large and complex models are applied and therefore the limited experimental knowledge might yield weakly specified model components. Likelihood profiles have been recently suggested and applied in the Systems Biology for assessing parameter and prediction uncertainty. In this article, the profile likelihood concept is reviewed and the potential of the approach is demonstrated for a model of the erythropoietin (EPO) receptor.

Profile likelihood in COPASI

- First described by Schaber
- Easily carried out by coupling parameter scan with parameter estimation
- Scan p_i around its optimal value and carry out a parameter estimation of all other parameters

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Easy parameter identifiability analysis with *COPASI*

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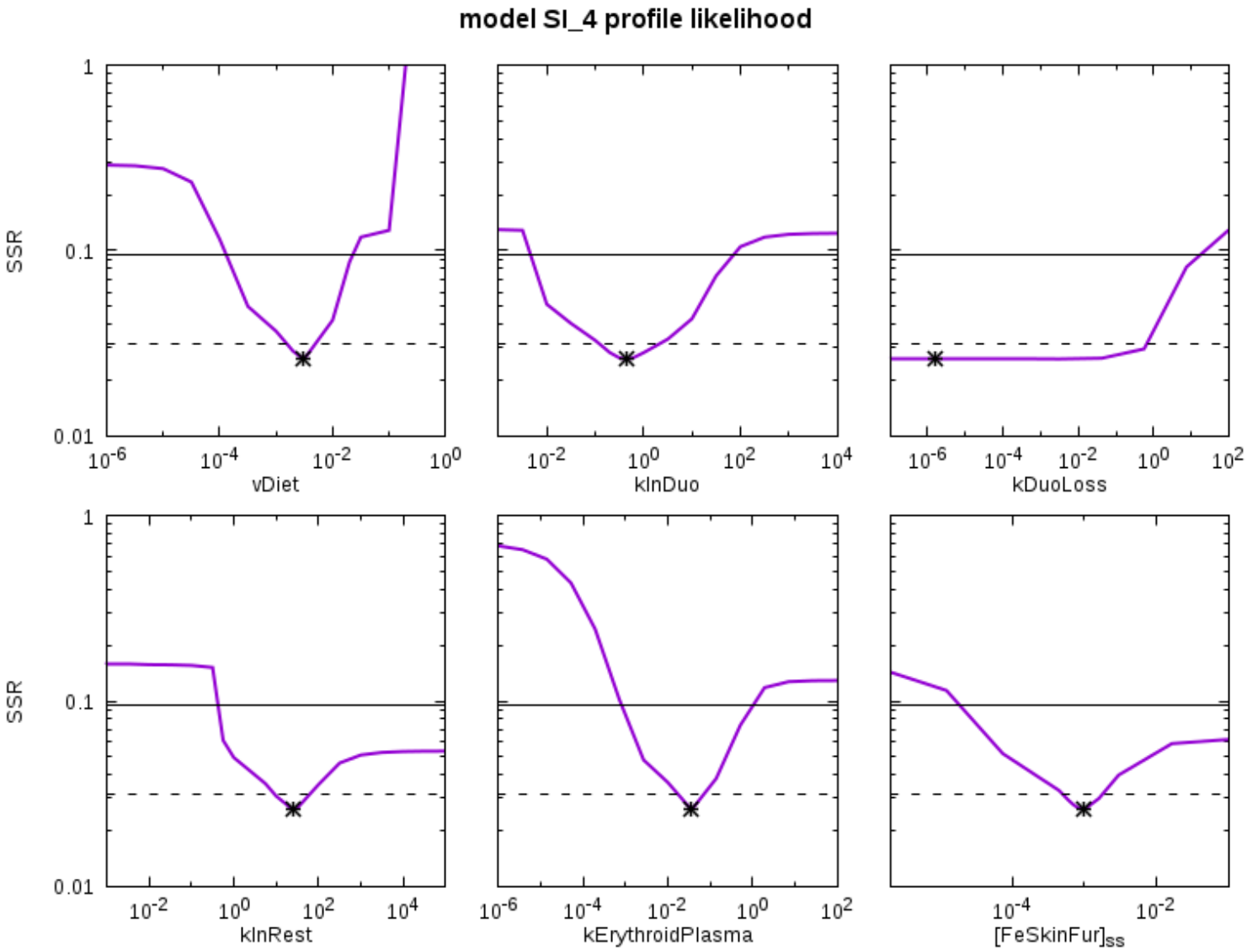
ABSTRACT

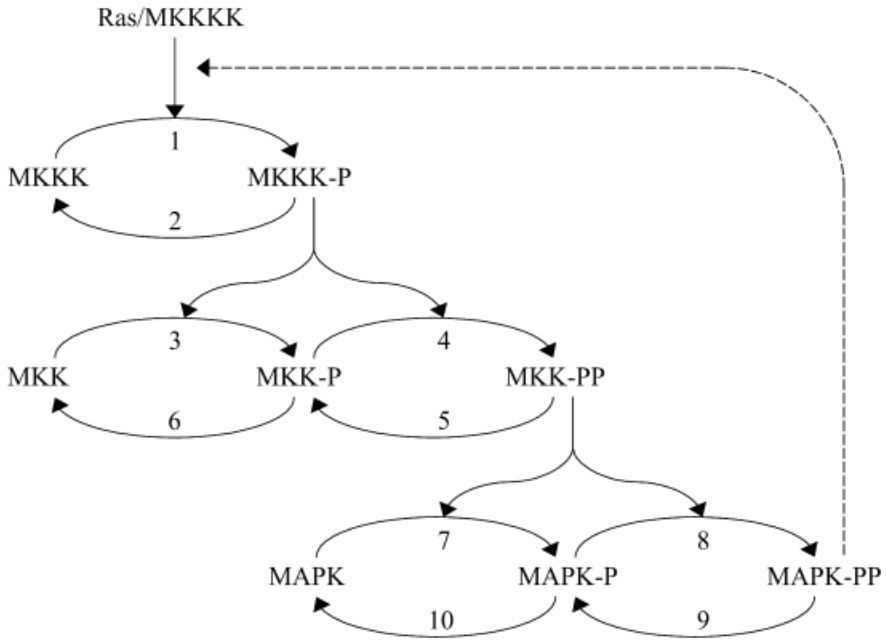
Background and scope: Differential equation systems modeling biochemical reaction networks can only give quantitative predictions, when they are in accordance with experimental data. However, even if a model can well recapitulate given data, it is often the case that some of its kinetic parameters can be arbitrarily chosen without significantly affecting the simulation results. This indicates a lack of appropriate data to determine those parameters. In this case, the parameter is called to be practically non-identifiable. Well-identified parameters are paramount for reliable quantitative predictions and, therefore, identifiability analysis is an important topic in modeling of biochemical reaction networks. Here, we describe a hidden feature of the free modeling software *COPASI*, which can be exploited to easily and quickly conduct a parameter identifiability analysis of differential equation systems by calculating likelihood profiles. The proposed combination of an established method for parameter identifiability analysis with the user-friendly features of *COPASI* offers an easy and rapid access to parameter identifiability analysis even for non-experts.

Availability: COPASI is freely available for academic use at http://www.copasi.org.

Example


model SI_4 profile likelihood
SSR
1
0.1
0.01
vDiet
klnDuo
kDuoLoss
klnRest
kErythroidPlasma
[FeSkinFur]ss

Biomodels 10



Kholodenko BN. (2000) Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. *Eur J Biochem.* 267(6):1583-8

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