User-friendly parameter identifiability methods with a workflow to guide model development, using categorical and continuous scales

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Introduction

- Parameter identifiability methods assess whether the parameters of a model are uniquely determined by the observations. While the success of a model fit can provide some information on this, it can be valuable to determine identifiability before attempting a fit, or to separate identifiability from other issues.
- Traditional identifiability methods provide a single categorical (yes/no) answer [1-3] to the question of identifiability, often assuming idealized data. In many cases this is not very informative, and identifiability depends on study design (e.g., dose levels or sampling times) and parameter values.
- Indicators on a continuous scale characterizing level of identifiability and taking design limitations into account can provide more detailed and relevant information to guide model development.

Application

PK model: one-compartmental linear PK model with first order absorption, in 3 scenarios (**Figure 1**):

- A: all parameters are identifiable.
- B: lower absorption rate → identifiability problem.
- C: unidentifiable by adding bioavailability parameter F=1.

MAPK model: mitogen-activated protein kinase (MAPK) model (**Figure 2**)[6]: 3 state variables (all observed), 14 parameters, and 3 subjects with (artificially chosen) baselines:

- Subject 1: 100% dephosphorylated (**Figure 3**).
- Subject 2: 99% dephosphorylated.
- Subject 3: 100% phosphorylated.

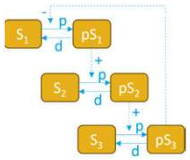

Figure 2: MAPK model diagram. Species S_i with phosphorylated states pS_i; p = phosphorylation; d = dephosphorylation; solid arrow = mass flow; dashed arrow = effect, positive or negative as indicated.

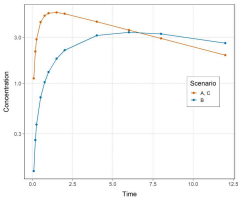

Figure 1: PK model time profiles.

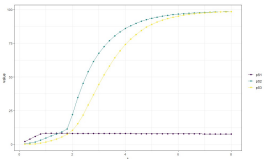

Figure 3: MAPK time profiles for subject 1.

Objectives

1) To present new methods that characterize identifiability on a continuous scale;
2) To describe a workflow for employing parameter identifiability analyses in model development;
3) To demonstrate the application of the methods to an intuitive and a complex example.

Methods

- We present two newly developed methods [4,5] that characterize identifiability with *categorical* and *continuous* indicators (**Figure 4**), namely the Sensitivity Matrix (SM) Method (SMM) and Fisher Information Matrix (FIM) Method (FIMM). They assess *practical* identifiability by restricting the observed quantities to user-selected time points (in contrast to *structural* analysis that assumes an idealized design).
- SMM examines the SM, consisting of the derivatives of the model output with respect to its parameters, evaluated at a finite set of time points. Local unidentifiability is formally characterized by non-trivial null space of SM. Continuous indicators are the skewing angle, M-norm, and L-norm.
- FIMM computes the FIM at a given parameter point and observation times. Local unidentifiability is formally characterized by a zero curvature of the log-likelihood surface, corresponding to a zero eigenvalue of the FIM. Continuous indicators are curvatures and relative parameter changes (RPC).

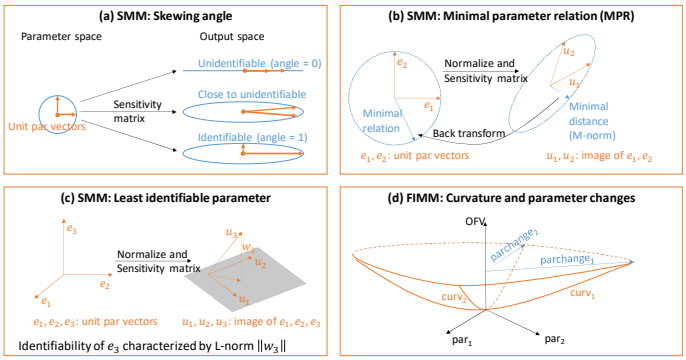

Figure 4: Illustration of the methods and indicators.

Results

Workflow: We propose three processes for different stages of model development, involving identifiability analyses before or after model estimation (**Figure 5**):

- **Before development**: structural identifiability analysis on the initial model(s), followed by practical identifiability analysis, considering study design. This helps to determine a modelling strategy by providing an a priori check to see which models could be supported by the data and informs which biologically relevant parameters can be identified from the data. A categorical test is useful in this stage, followed by a continuous one.
- **During development**: repeat these analyses at key steps. Structural analysis can be skipped if model complexity did not increase. Continuous test are most useful.
- **After development**: practical identifiability analysis with continuous indicators, to assess model quality.

PK model: categorical yes/no answers of SMM and FIMM to the identifiability question are valuable in case of structural unidentifiability (scenario C in **Table 1**): if a model is categorically unidentifiable, then it needs to be redefined or additional analytes need to be measured to resolve this. Continuous indicators provide more detail and may indicate badly identifiable cases (B in **Table 1**). This may be due to study design limitations or the values of the parameters. The remedy is to change the model or adapt the design. Continuous indicators are subject to interpretation by the analyst and therefore require some experience in their application.

In line with expectations, all categorical and continuous indicators indicated identifiability for scenario A and unidentifiability for C. For B, categorical indicators showed identifiability, but continuous ones indicated this scenario was less identifiable than A (**Table 1**).

MAPK model: strongest identifiability was shown for subject 1 (baseline 100% dephosphorylated) and the three subjects combined (**Figure 6**), while the other two cases were less identifiable, with indicators near zero (especially subject 3).

This example shows that the methods can be applied to more complex cases as well.

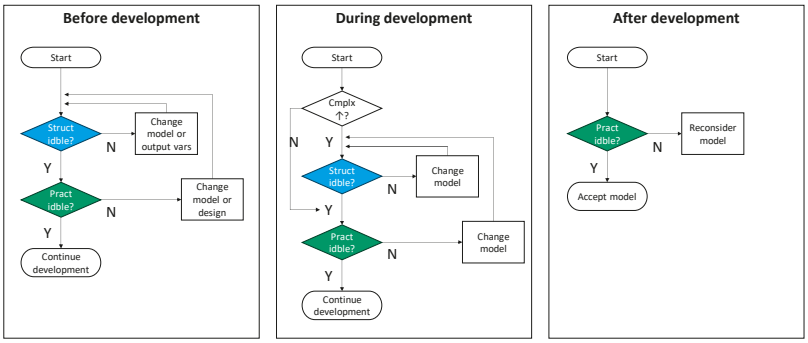

Figure 5: Workflow. struct idble = structurally identifiable; pract idble = practically identifiable; vars = variables; cmplx ↑ = increase in model complexity; Y = yes; N = no.

Scenario	A	B	C
Nullity	0	0	1
Skewing Angle	0.77	0.29	5.60e-06
M-norm	0.26	0.038	5.40e-09
MPR (%) $(CL, V, k_a, (F))$	(-42, 34.3, 84)	(-32.8, 61.9, 71.3)	(57.5, 57.5, 0, 58.1)
L-norm	V: 0.59, k_a: 0.64, CL: 0.85	V: 0.088, k_a: 0.1, CL: 0.27	F: 3.7e-16, V: 5.7e-16, CL: 1.3e-15, k_a: 0.64
Smallest curvature	0.86	0.0035	-5.90e-13
RPC (%) $(CL, V, k_a, (F), \sigma^2)$	(5.4, -5.2, -10, 0)	(-44, 83, 95, 0)	(58, 58, 7.6e-13, 0, 58)

Table 1: results of SMM and FIMM for the PK model. Scenario A is identifiable, C (with bioavailability parameter) is unidentifiable, and B (slow absorption) is badly identifiable.
Good identifiability corresponds with high skewing angle (0-1), M-norm (0-1), L-norm (0-1) and curvature (0-∞). The minimal parameter relation (MPR) and relative parameter change (RPC) show the least identifiable parameter directions of scenarios B and C to involve (CL, V, k_a) and (CL, V, F), respectively. MPR and RPC list F only for scenario C.

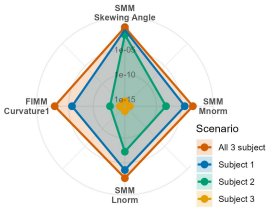

Figure 6: MAPK model. Composite model identifiability visualization from SMM (skewing angle, M-norm, Least identifiable parameter) and FIMM (curvature), on a log scale. High values indicate better identifiability.

Conclusion

- Two newly developed methods for parameter identifiability, SMM and FIMM, are implemented [7] in R [8].
- FIMM provides the clearest and most useful answers.
- SMM is an intuitive method that is computationally more efficient than FIMM, but the cut-off between identifiability and unidentifiability is more difficult to establish.
- The availability of the methods, together with the workflow recommendation, facilitate the addition of parameter identifiability analysis to the toolbox of the modeler to diagnose over-parameterization and assess a model's suitability in relation to study design.

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