Two New User-Friendly Approaches to Assess Pharmacometric Model Identifiability

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Introduction

In pharmacometric modelling, it is often important to know whether the data is sufficiently rich to identify the parameters of a proposed model. While it may be possible to assess this based on the results of a model fit, it may be difficult to disentangle identifiability issues from other model fitting and numerical problems. Furthermore, it can be of value to ascertain identifiability beforehand from study design.

The parameters of a model are identifiable if two different parameter vectors always lead to two different model outputs. In practice one often focuses on local unidentifiability, characterized by a curve in parameter space of constant model output. The tangent to the curve is the unidentifiable direction.

Several methods are available to assess parameter identifiability, such as DAISY [1], Aliasing [2] or the $DESIGN option in NONMEM [3]. However, they are sometimes limited in scope (both regarding the models to which they can be applied and the issues that can be identified) and may make unrealistic assumptions. Also, they may be difficult to use, and implementations are not always available.

Objectives

The aim of this work was to develop two new methods for identifiability analysis prior to model optimization that address these drawbacks. Their use is illustrated with an example problem.

Application

The methods were applied to a quasi-equilibrium (QE) approximation to a Target Mediated Drug Disposition (TMDD) model, describing leukaemia inhibitory factor (LIF) data in sheep, with parameter values, sample times and dose levels obtained from Abraham et al. [4]. The output consisted of the PK concentration at the reported sample times.

Model structure and parameter values

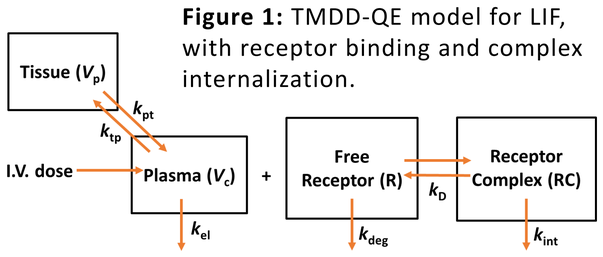


Figure 1: TMDD-QE model for LIF, with receptor binding and complex internalization.

Table 1: Model parameters, from Abraham et al. [4].

Parameter	Abbreviation	Value	Unit
Elimination rate constant	k_{el}	1.49	h^{-1}
Central and peripheral volume	$V_c = V_p$	51.2	mL/kg
Tissue distribution rate constant	$k_{pt} = k_{tp}$	0.389	h^{-1}
Equilibrium dissociation constant	k_D	1.22	nM
Initial receptor concentration	B_{max}	8.19	nM
Internalization rate constant	k_{int}	3.16	h^{-1}
Degradation rate constant	k_{deg}	0.67	h^{-1}

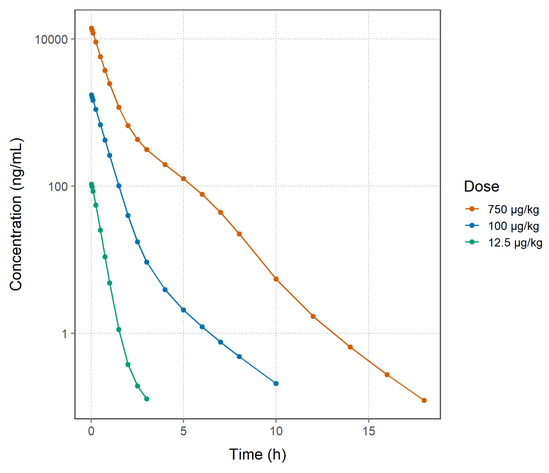


Figure 2: Plasma concentration profiles and sampling points.

Methods

Two methods for local identifiability were developed, based on well-known matrices.

Methods were implemented in R [5] and validated on standard examples (data on file). To reduce numerical approximation errors, implementations optionally make use of symbolic calculations. The methods were applied to a TMDD-QE model (Fig. 1 and Table 1) with seven structural parameters, at three individual dose levels (12.5, 100, 750 µg/kg) separately, or to all three combined.

Method 1 (Fig. 3a-c)

The Sensitivity Matrix Method (SMM) uses the matrix of derivatives of the model outputs with respect to the structural parameters. Unidentifiable directions in parameter space correspond to vectors in the null space of this matrix. As the null space is difficult to determine numerically, several proxy indicators were developed that identify near-singularities of the matrix and the corresponding parameter vectors.

- The Skewing Angle, which measures the absolute angle between the images of the parameter vectors under the sensitivity matrix;
- The Minimal Parameter Relations, listing the parameter vectors closest to singularity. Their vector norms (M-norm) indicate the level of identifiability;
- The Least Identifiable Parameter(s), indicating the parameters closest to dependence on the others.

Method 2 (Fig. 3d)

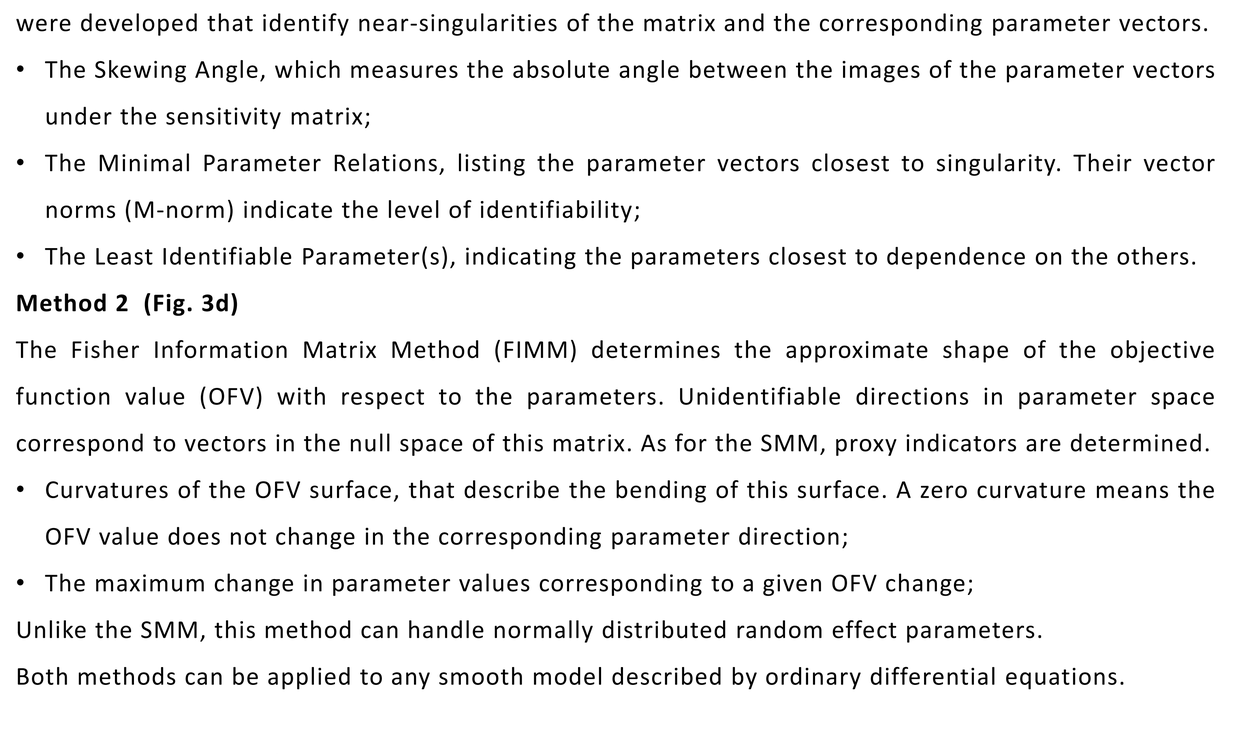
The Fisher Information Matrix Method (FIMM) determines the approximate shape of the objective function value (OFV) with respect to the parameters. Unidentifiable directions in parameter space correspond to vectors in the null space of this matrix. As for the SMM, proxy indicators are determined.

- Curvatures of the OFV surface, that describe the bending of this surface. A zero curvature means the OFV value does not change in the corresponding parameter direction;
- The maximum change in parameter values corresponding to a given OFV change;

Unlike the SMM, this method can handle normally distributed random effect parameters.

Both methods can be applied to any smooth model described by ordinary differential equations.

Figure 3: Illustration of the methods.



Results

Results from each of the three individual dose levels showed identifiability issues with both methods (Fig. 4). Even at the highest dose level, where the model traversed all phases of the TMDD profile, there were two unidentifiable directions, involving the nonlinear binding parameters. All parameters became identifiable in a scenario where the dose levels were combined.

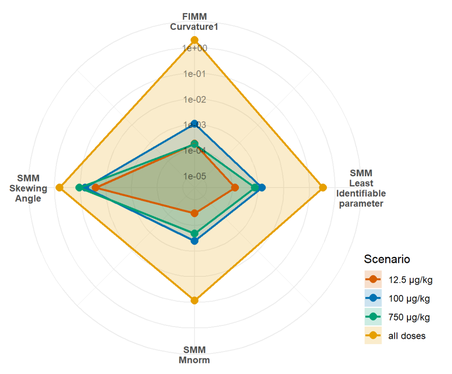


Figure 4: Composite model identifiability visualization from SMM (skewing angle, M-norm, Least identifiable parameter) and FIMM (curvature), on a log scale.
All indicators have low values for the single dose level scenarios, indicating non-identifiability, and higher ones for all dose levels combined, showing identifiability.

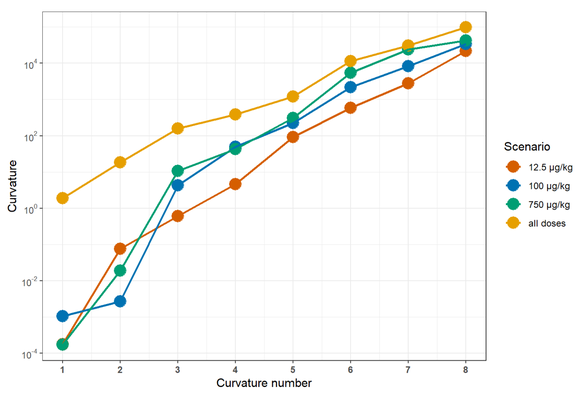


Figure 5: FIMM results: Curvature 1-8 for scenarios for each single dose level and for a scenario with all three dose levels combined. These confirm the radar plot summary and demonstrate that the TMDD-QE model becomes identifiable only in a scenario where the three dose levels are combined.

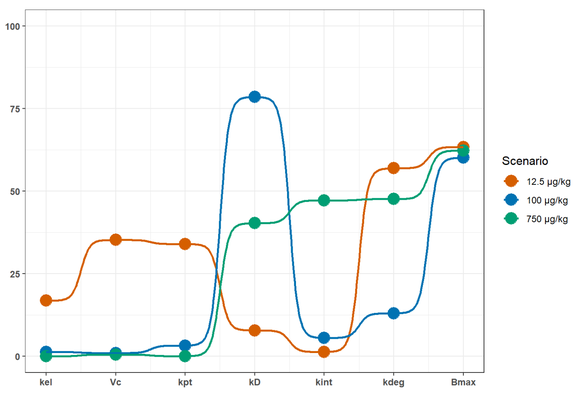


Figure 6: SMM results: minimal parameter relation per unidentifiable scenario (so excluding the "all doses" case). High values indicate the parameter is badly identifiable. This shows that different combinations of parameters are badly identifiable for the individual dose levels.

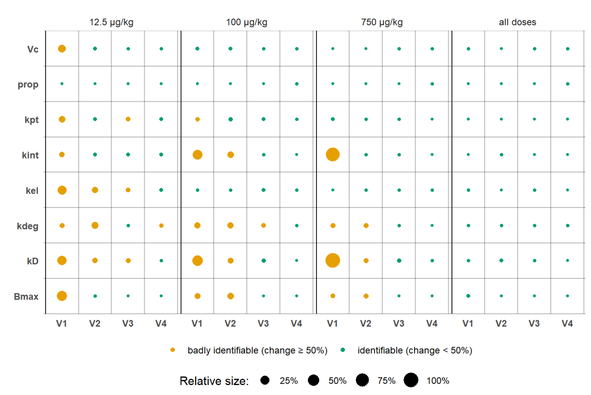


Figure 7: FIMM results: size of relative parameter change corresponding to significant change in OFV, per scenario and first four curvatures. Orange color and large sizes indicate bad identifiability, while green indicates parameter changes below 50%. This confirms the SMM results and shows identifiability for the combined scenario.

Conclusion

Two new methods were developed for identifiability analysis and were applied to a TMDD-QE example model from literature. They can be applied to any smooth model described by ordinary differential equations. They can detect any local identifiability issues and find the corresponding directions in parameter space. The methods provide a set of indicators that characterize identifiability on a continuous rather than categorical scale and are best assessed in combination. Both methods are easy to use and will be publicly available. They require as input a definition of the model, its parameters, sample times and dosing levels and times. Actual observations are not required.

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