Efficient and Informed Model Development for NLME Models with Poor Parameter Identifiability

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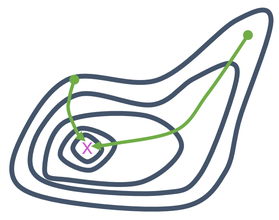
Problem

- Poor parameter identifiability can lead to convergence issues and unreliable prediction due to inflated RSEs.
- This slows model development and undermines confidence in simulation outcomes.

Hill = 23.7 (947% RSE)

Approach

- Use of dMod[1] in IQRtools as deterministic framework combining trust-region optimization with profile likelihood analysis to detect and resolve non-identifiabilities.
- Implemented using analytically derived gradients and Hessians for high precision.
- Inter-individual variability is modeled using a penalized likelihood, enabling efficient and robust estimation.



Impact

- In a malaria PK/PD model, our approach identified a poorly identifiable Hill coefficient.
- Profile likelihood guided parameter fixing, resulting in a stable, interpretable model.
- The framework improves model reliability, supports informed decisions, and reduces development time.

IQRtools integrates gradient-based optimization and profile likelihoods with population modeling

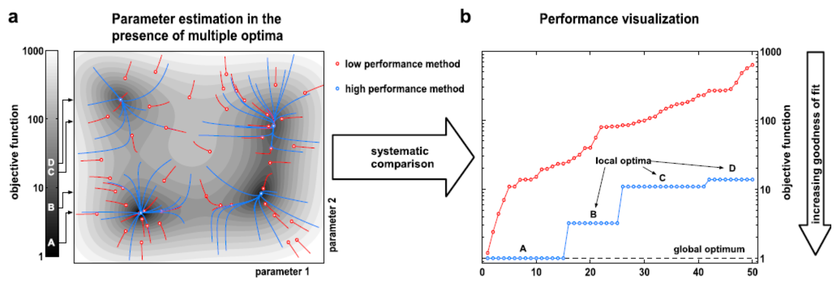
IQRmodel syntax for consistent model description

- Versatile modeling syntax compatible with formats of typically used tools in QSP and PMX.
- A PK model library is available in the documentation material.

```
********** MODEL NAME
Linear 1-compartmental PK model

********** MODEL NOTES
Linear 1-compartmental PK model with initial single dose

********** MODEL STATES
d/dt(Ac) = -CL/Vc*Ac + INPUT1
Ac(0)    = 0

********** MODEL PARAMETERS
CL = 20  # (L/hour) Clearance
Vc = 32  # (L)      Central volume

********** MODEL VARIABLES
Cc = Ac/Vc * 1000   # (ng/mL) Plasma concentration
```

Highly efficient parameter estimation

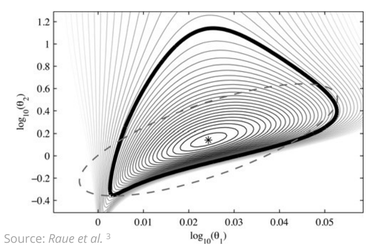
- State-of-the-art optimization using analytically derived sensitivity equations,
- Deterministic optimization combined with,
- Global sampling of initial guesses.



Source: *Raue et al.* [2]

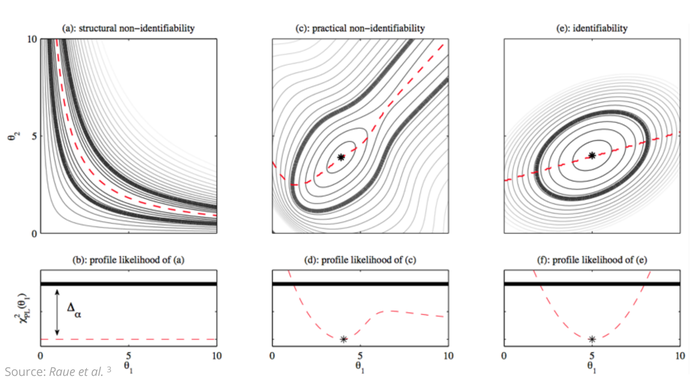
Identification of structural and practical non-identifiability

- Nonlinear likelihood function shape is not captured by the Fisher information matrix.
- Likelihood profiling characterizes the parameter identifiability and characterization of the parameter identifiability.



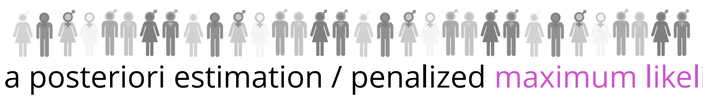
Source: *Raue et al.* [3]

$$\mathrm{PL}_j(p) = \max_{\theta \in \{\theta \mid \theta_j = p\}} \ln L(Y \mid \theta)$$



Source: *Raue et al.* [3]

How we deal with variability of parameters between virtual patients



- Maximum a posteriori estimation / penalized maximum likelihood estimation.

$$f(\mu) f(x \mid \mu) = \pi(\mu) L(\mu) = \frac{1}{\sqrt{2\pi}\sigma_m} \exp\left(-\frac{1}{2}\left(\frac{\mu - \mu_0}{\sigma_m}\right)^2\right) \prod_{j=1}^{n} \frac{1}{\sqrt{2\pi}\sigma_v} \exp\left(-\frac{1}{2}\left(\frac{x_j - \mu}{\sigma_v}\right)^2\right)$$

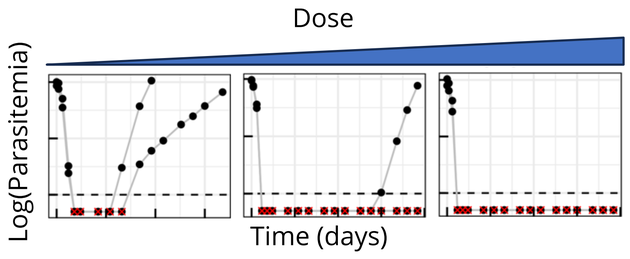
Application Example: Malaria PD Modeling

In malaria PK/PD modeling, parasite killing is described by a .model linking drug concentration to the parasite elimination rate.

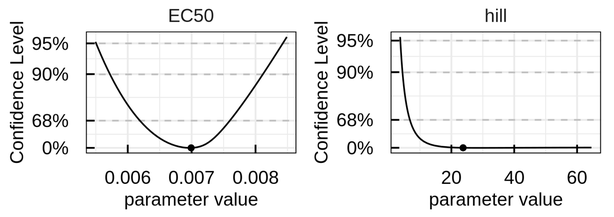
$$\frac{dP}{dt} = \left(GR - Emax \frac{Cc^{hill}}{Cc^{hill} + EC_{50}^{hill}}\right) \cdot P$$

Example 1: Preclinical study

Objective:
Characterize the PK/PD relationship in SCID mice infected with *P. falciparum* to support human dose prediction.



- Hill coefficient poorly identified (hill = 23.7, 947% RSE) due to limited data support.
- In trial simulations this causes instability from extreme parameter values.
- Profile likelihood analysis reveals a right-open shape for hill.

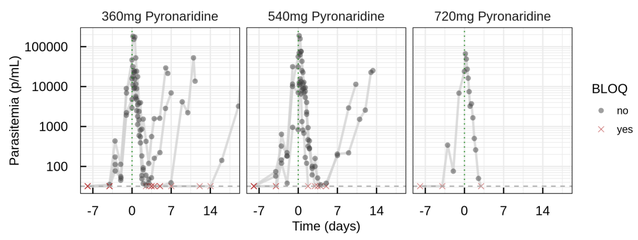


Parameter	Hill estimated	Hill fixed
GR	0.03 (FIX)	0.03 (FIX)
EMAX	0.24 (FIX)	0.24 (FIX)
EC50	0.00699 (13%)	0.007 (12%)
hill	23.7 (950%)	20 (FIX)
omega(EMAX)	0.1 (FIX)	0.1 (FIX)
omega(EC50)	0.3 (FIX)	0.3 (FIX)
error_ADD1	0.75 (7.4%)	0.75 (7.4%)
OBJ	245	245
BIC	265	260

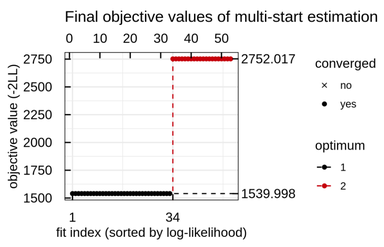
Fixing hill to 20 improved model identifiability while accounting for variability in EC50.

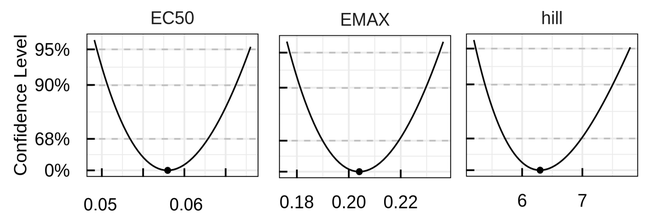
Example 2: Clinical Phase 1b Study [4]

Objective:
Characterize the PK/PD relationship between pyronaridine blood concentrations and *P. falciparum* parasitemia in healthy volunteers with induced blood-stage malaria, to inform dose prediction in African children.



Multi-start optimization revealed two optima with distinct objective function values. Profile likelihoods show well-behaved, symmetric shapes for all parameters.





Parameter estimates are consistent across tools (vs. Monolix), supporting model robustness.

Parameter	dMod	Monolix
GR	0.0871 (4.1%)	0.0856 (3.9%)
EMAX	0.204 (7.3%)	0.201 (3.9%)
EC50	0.0058 (8.3%)	0.00575 (11%)
hill	6.3 (11%)	6.62 (2.4%)
omega(GR)	0.1 (FIX)	0.1 (FIX)
omega(EMAX)	0.2 (FIX)	0.0996 (29%)
omega(EC50)	0.2 (FIX)	0.273 (29%)
error_ADD1	1.04 (3.2%)	1.02 (3.4%)

dMod in IQRtools

- ✓ **Enables robust parameter estimation through deterministic optimization and profile likelihood analysis.**
- ✓ **Supports identifiability assessment, leading to reliable models and faster development.**

References:
[1] Kaschek D, Mader W, Fehling-Kaschek M, Rosenblatt M, Timmer J. Dynamic modeling, parameter estimation, and uncertainty analysis in R. J Stat Softw. 2019;88(10):1–32. doi:10.18637/jss.v088.i10
[2] Raue A, Schilling M, Bachmann J, et al. Lessons learned from quantitative dynamical modeling in systems biology. PLoS One. 2013;8(9):e74335. doi:10.1371/journal.pone.0074335
[3] Raue A, Kreutz C, Maiwald T, Klingmüller U, Timmer J. Addressing parameter identifiability by model-based experimentation. IET Syst Biol. 2011;5(2):120–130. doi:10.1049/iet-syb.2010.0030
[4] Barber BE, Webster R, Potter AJ, et al. Characterising the blood-stage antimalarial activity of pyronaridine in healthy volunteers experimentally infected with Plasmodium falciparum. Int J Antimicrob Agents. 2024;64:107196. doi:10.1016/j.ijantimicag.2023.107196

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