

Calculation of confidence and prediction intervals for PK and PD models

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INTRODUCTION

Background

Confidence in model predictions is an important aspect for the utility of pharmacokinetic (PK) and pharmacodynamic (PD) models in the decision-making processes, e.g., for defining safety margins or selecting doses. Available fitting tools typically provide information about the confidence for the estimated model parameters, but information about the confidence around the primary result, e.g., the predicted concentration-time or exposure-response curve, is not directly available (Table 1).

Table 1. Overview on PK/PD estimation/simulation software

Software	Model type	Estimation	Simulation	Prediction confidence
NONMEM/Xpose	closed form and ODE	yes	yes	no
Monolix/MlxPlore/Simulx	closed form and ODE	yes	yes	no
Berkeley Madonna	closed form and ODE	no	yes (limited)	no
WinNonLin	closed form and ODE	yes	yes	no
PFIM	closed form and ODE	no	no	no

Objective

- The objective of this project was to develop a single-interface framework for data fitting, confidence and prediction interval derivation for user-specified, closed-form functions with visualization of the results.

IMPLEMENTATION

A parameter estimation and confidence interval calculation toolbox was implemented in R and is accessed via the single function "parameter.estimation".

Data

ID	Wt	Dose	Time	Conc
9	86.4	3.1	0.30	7.37
9	86.4	3.1	0.63	9.03
9	86.4	3.1	1.05	7.14
9	86.4	3.1	2.02	6.33
9	86.4	3.1	3.53	5.66
9	86.4	3.1	5.02	5.67
9	86.4	3.1	7.17	4.24
9	86.4	3.1	8.80	4.11
9	86.4	3.1	11.60	3.16
9	86.4	3.1	24.43	1.12

Model

```
pk.lcpt.oral <-  
function(x, ka, ke, V)  
{  
  y <- ka/(V * (ka-ke)) *  
    (exp(-ke*x) -  
    exp(-ka*x))  
  return(y)  
}
```

parameter.estimation()

```
output <- parameter.estimation(  
  data = data,  
  model = pk.lcpt.oral,  
  errmod = 'prop',  
  
  estmethod = 'mle',  
  init = list(ka=2.5, ke=0.1, V=0.3),  
  
  CImethod = 'sim',  
  xsupport = seq(0.01, 24.01, by = 0.1)  
)
```

Input parameters for parameter estimation and confidence calculation:

- Error model (errmod)
- Estimation method (estmethod)
- Initial parameter estimates (init)
- Confidence interval (CI) calculation method (CImethod)
- Vector of independent variable values for which to calculate CI (xsupport)

Output

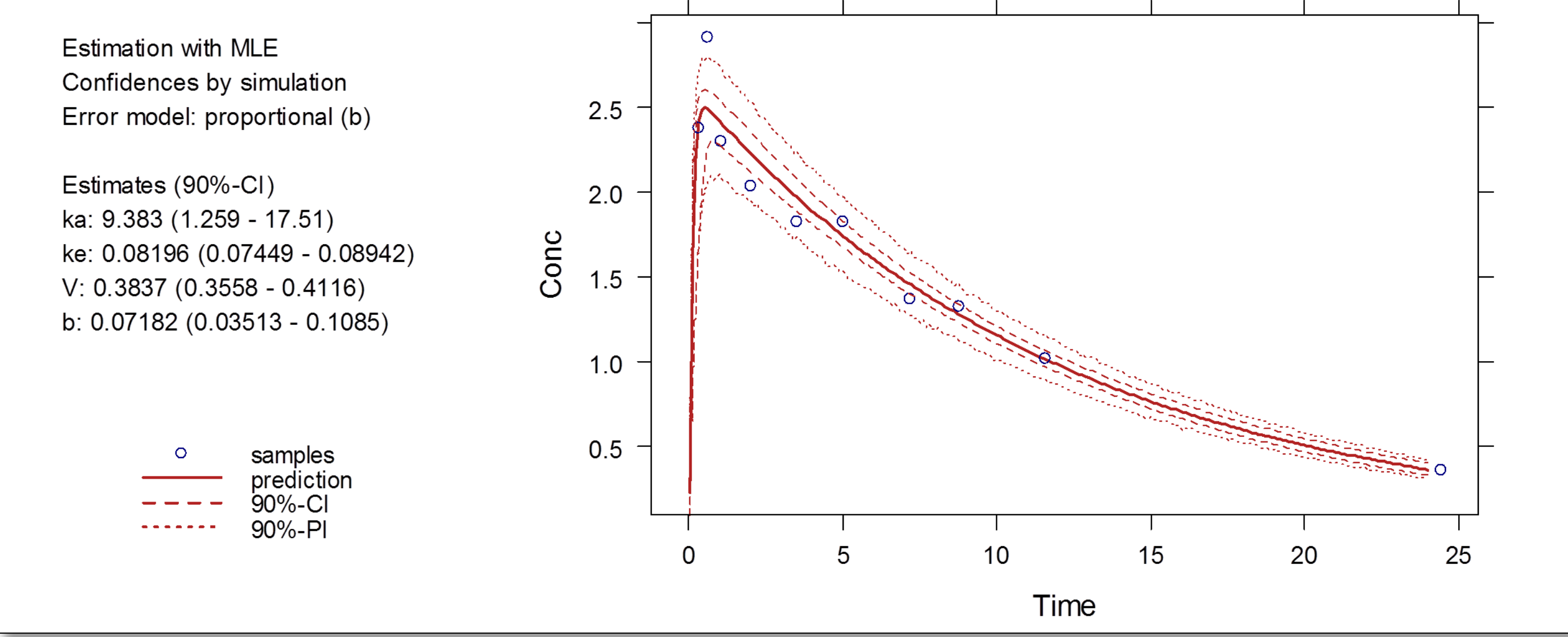


Figure 1. Dose-response data example

Dose response example

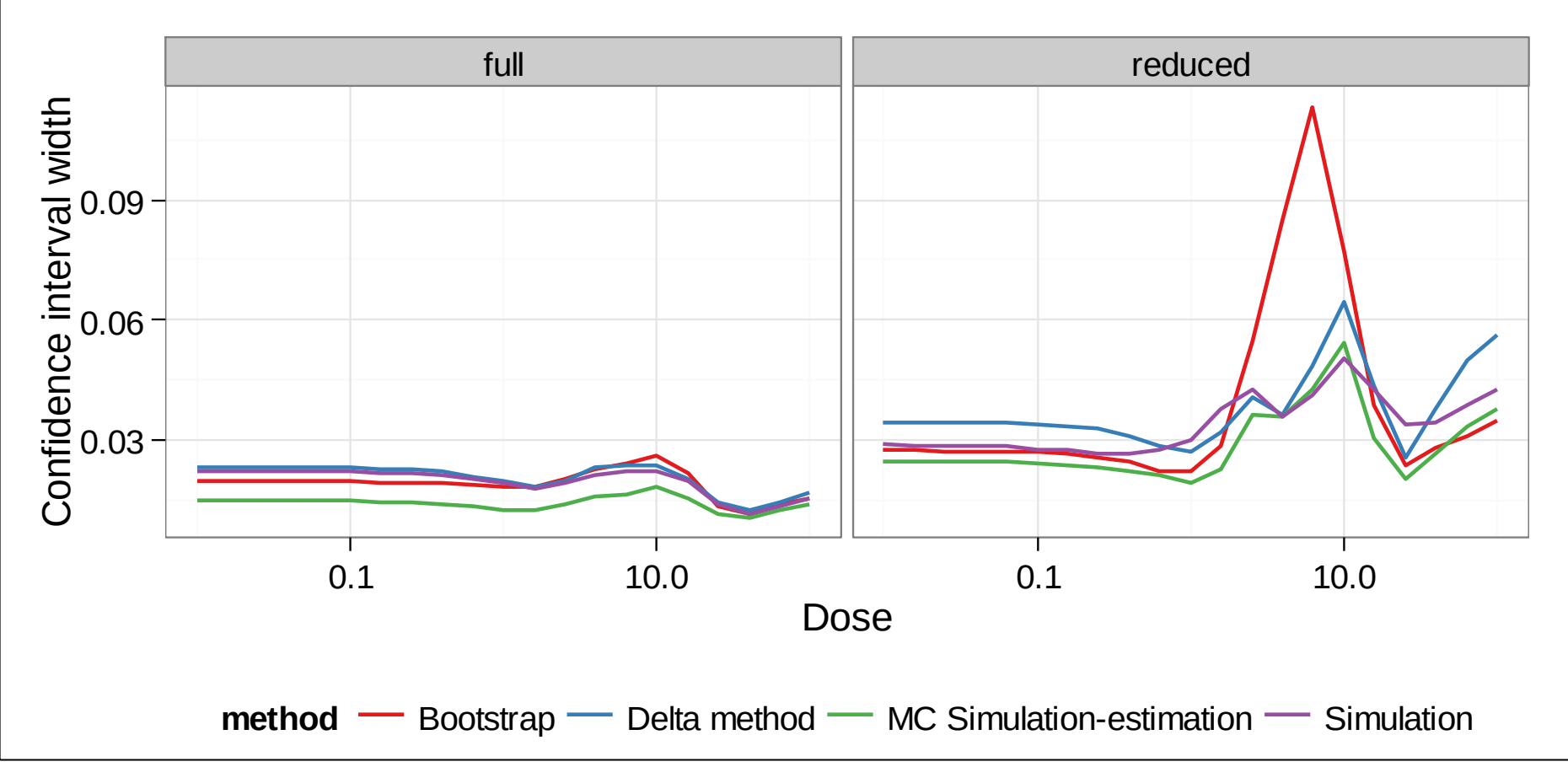
The full data set contains 10 replicates per tested dose or placebo (n=50). A reduced data set was created as a random subset (n=20) of the full data set (red circles in Figure 1).

- Confidence intervals are comparable for different calculation methods but calculation times differ considerably (Table 4).
- When using only limited data, bootstrapping estimates a wide confidence interval (Figure 2).

Table 4. Calculation times

Method	Calculation time (s)
Delta method	0.32
Simulation (k=1000)	0.92
MC simulation-estimation (k=1000)	212.60
Bootstrap (k=1000)	224.53

Figure 2. Differences in calculated CIs



PARAMETER ESTIMATION METHODS

Non-linear least squares or maximum likelihood estimation (MLE) are implemented. Non-linear least squares is faster but limited to an additive error model requiring data/model transformation for other error models. The standard deviation of the residuals is used as an estimator of the residual error.

ERROR MODELS

An additive, proportional, combined (additive + proportional), or an exponential error can be applied when using MLE.

Table 2 shows the impact of the error model on parameter estimates for the PK example shown above.

Table 2. Parameter estimates and estimation errors for different error models

error model	structural parameters			s.d. of residual error		
	ka	ke	V	a	b	e
additive	8.87 (44%)	0.087 (15%)	0.377 (5.2%)	0.161 (29%)		
proportional	9.38 (49%)	0.082 (5.2%)	0.384 (4.1%)		0.072 (29%)	
combined	9.38 (54%)	0.082 (5.3%)	0.384 (4.5%)	3e-09 (n.d.)	0.072 (27%)	
exponential	9.84 (53%)	0.081 (5.2%)	0.387 (4%)			0.069 (29%)

CONFIDENCE INTERVAL CALCULATION

The implemented CI calculation methods are listed and compared in Table 3.

Table 3. Implemented CI calculation methods

Inputs	Calculus				Notes
SIMULATION					
Parameter estimates, covariance matrix	1) Sample k sets of parameters	2) Predict for each parameter set	3) CI based on distribution of predictions		Relies on estimated covariance matrix
DELTA METHOD^{1,2}					
Parameter estimates, covariance matrix, Jacobian matrix	Translate uncertainty in parameters into uncertainty in predictions via Jacobian matrix $Var[f(x, \theta)] = \frac{\partial f}{\partial \theta} \cdot \Sigma \cdot \left(\frac{\partial f}{\partial \theta}\right)^T$				Assumes symmetric CI intervals for predictions, fast
MONTE-CARLO (MC) SIMULATION²					
Parameter estimates	1) Simulate k datasets	2) Re-estimate parameter set for each simulated dataset	3) Predict for each parameter set	4) CI based on distribution of predictions	More calculation time needed, unclear how to handle failed estimations
BOOTSTRAPPING³					
Observed data	1) Bootstrap k datasets	2) Re-estimate parameter set for each simulated dataset	3) Predict for each parameter set	4) CI based on distribution of predictions	Non-parametric approach, more calculation time needed, unclear how to handle failed estimations

COMPARISON OF CI CALCULATION METHODS

CONCLUSIONS

The R framework can be used for any closed-form function in PK/PD modeling and includes various tools for study design, data fitting, prediction, and result visualization. Further development of the tool will include

- extension to ODE models,
- extension to population-based models (mixed effects models), and
- extension taking non-normal distribution of parameters into account.

Different methods for estimation or confidence calculation besides different error structures are implemented and can be instructionally compared.

REFERENCES

- Bonate, P.L., Pharmacokinetic-pharmacodynamic modeling and simulation. 2011, New York: Springer.
- Lavielle, M., Mixed effects models for the population approach: Models, tasks, methods and tools. 2014: Chapman and Hall/CRC.
- Efron, B, Bootstrap methods: Another look at the jackknife, Annals of Statistics 7: 1-26, 1997