UPPSALA
UNIVERSITET

Evaluation of the nonparametric estimation method in NONMEM VIβ

Rada Savic, Maria Kjellsson and Mats Karlsson

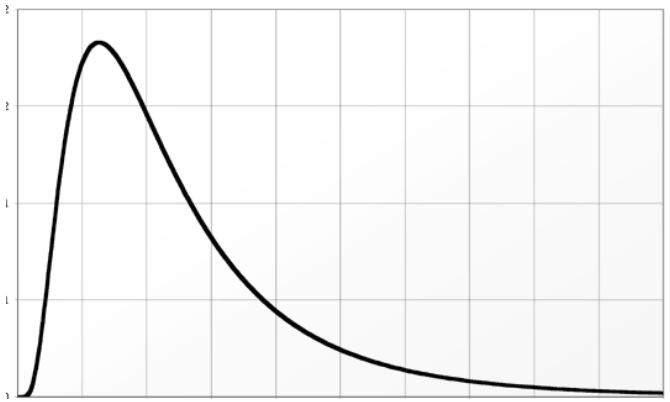
Division of Pharmacokinetics and Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University
Sweden

UPPSALA UNIVERSITET

Statistical methods for population analysis

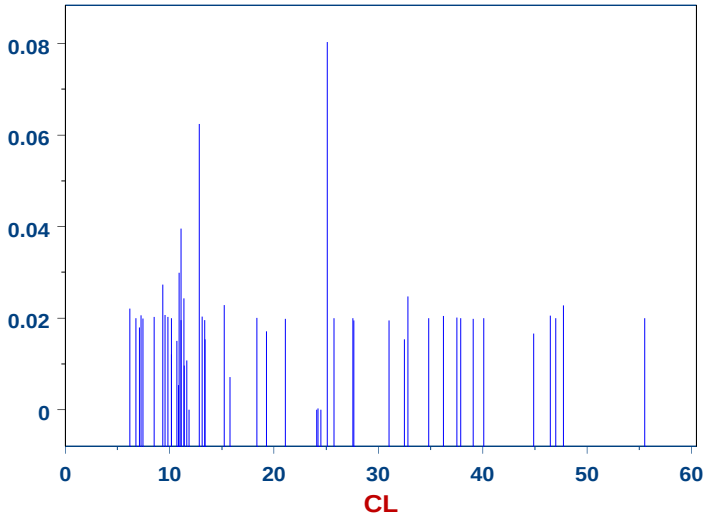
✓ Parametric methods

- *assumed shape of parameter distribution*
- ***normal** or transformation of normal (usually)*
- ***mean** and **variance***
- *imprecision estimates (SE)*



✓ Nonparametric methods

- *no assumptions regarding the distribution shape*
- ***discrete, non-continuous***
- *collection of **finite number of values** for all parameters along with **the estimated probabilities***
- *no imprecision estimates*



UPPSALA UNIVERSITET

Search for nonparametric distribution How NONMEM VIβ does it?

1. Search for support points

- ✓ ***NONMEM runs parametric step (FO/FOCE)***
- ✓ ***Computes the Empirical Bayes Estimates* (EBEs)**
- ✓ **The EBEs** are taken as the support points for the nonparametric distribution

2. Probability estimation

NONMEM recomputes:

- ✓ the joint probability
- ✓ the marginal cumulative probability for each parameter distribution

NONMEM output

NONPARAMETRIC ESTIMATE **

MINIMUM VALUE OF OBJECTIVE FUNCTION **

-1010.387 → **NPOFV** – as OFV for mixture model

$n_{\text{mixtures}} = n_{\text{subjects}}$

EXPECTED VALUE OF ETA **********

ETA1	ETA2
-3.66E-01	-6.15E-03

→ New set of ***typical parameter estimates***

COVARIANCE MATRIX OF ETA *****

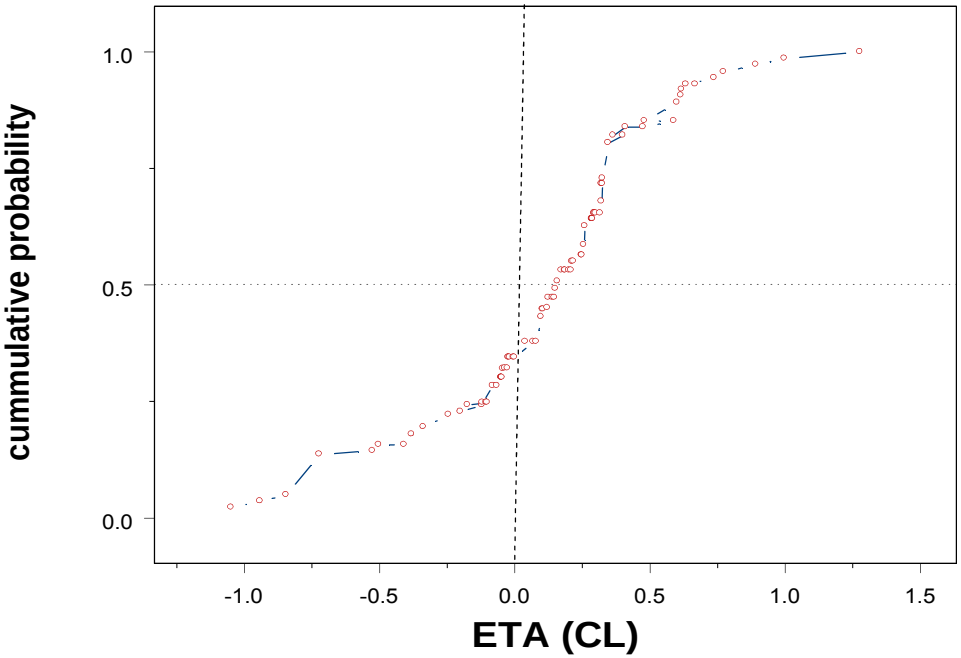
	ETA1	ETA2
ETA1		
+	3.40E-01	
ETA2		
+	-5.53E-02	2.85E-01

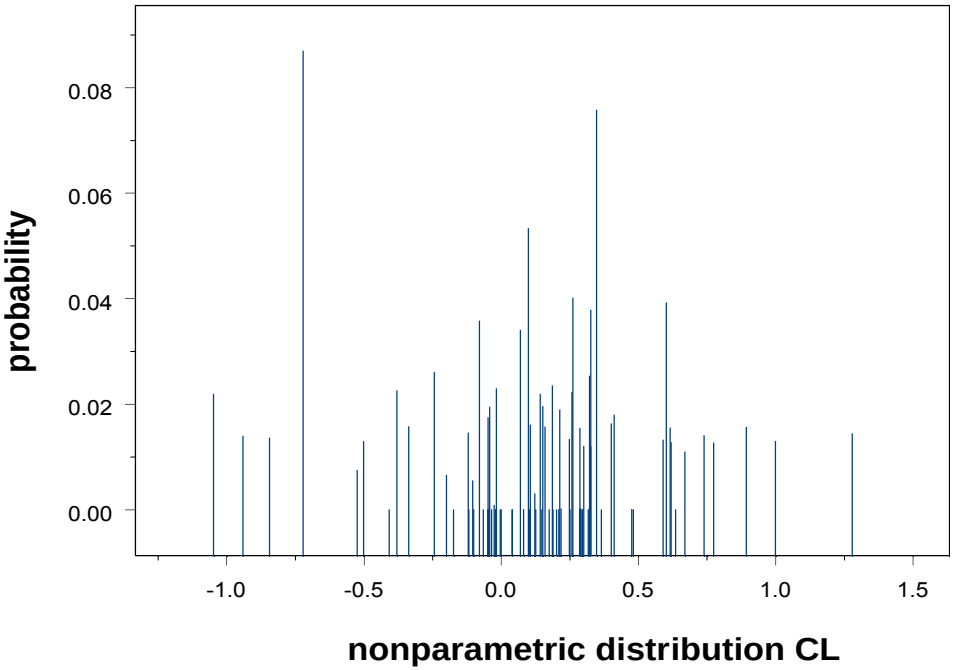
→ Nonparametric ***Ω matrix***

UPPSALA UNIVERSITET

NONMEM output – nonparametric distribution

- ✓ ***Cumulative marginal density function*** for each parameter distribution
- ✓ ***Joint probability*** for vector of parameters





UPPSALA
UNIVERSITET

Aim

Aim

to explore the performance of the
nonparametric estimation method in NONMEM VIβ

Method

a Monte Carlo simulation study

Emphasis

✓ *the analysis of data with*
non-normal distribution of random effects

✓ *the analysis of data with*
misspecification ín residual error magnitude

UPPSALA
UNIVERSITET

the analysis of data with

non-normal distribution of random effects

UPPSALA UNIVERSITET

Simulation settings

Simulated PK DATA

- ✓ **One compartment *iv* bolus model**
- ✓ **3 observations** per individual (early / mid / late sample)
- ✓ **100 datasets** for each condition
- ✓ **Random effects distribution** - 4 different types
  - Log-normal
  - Quadromodal

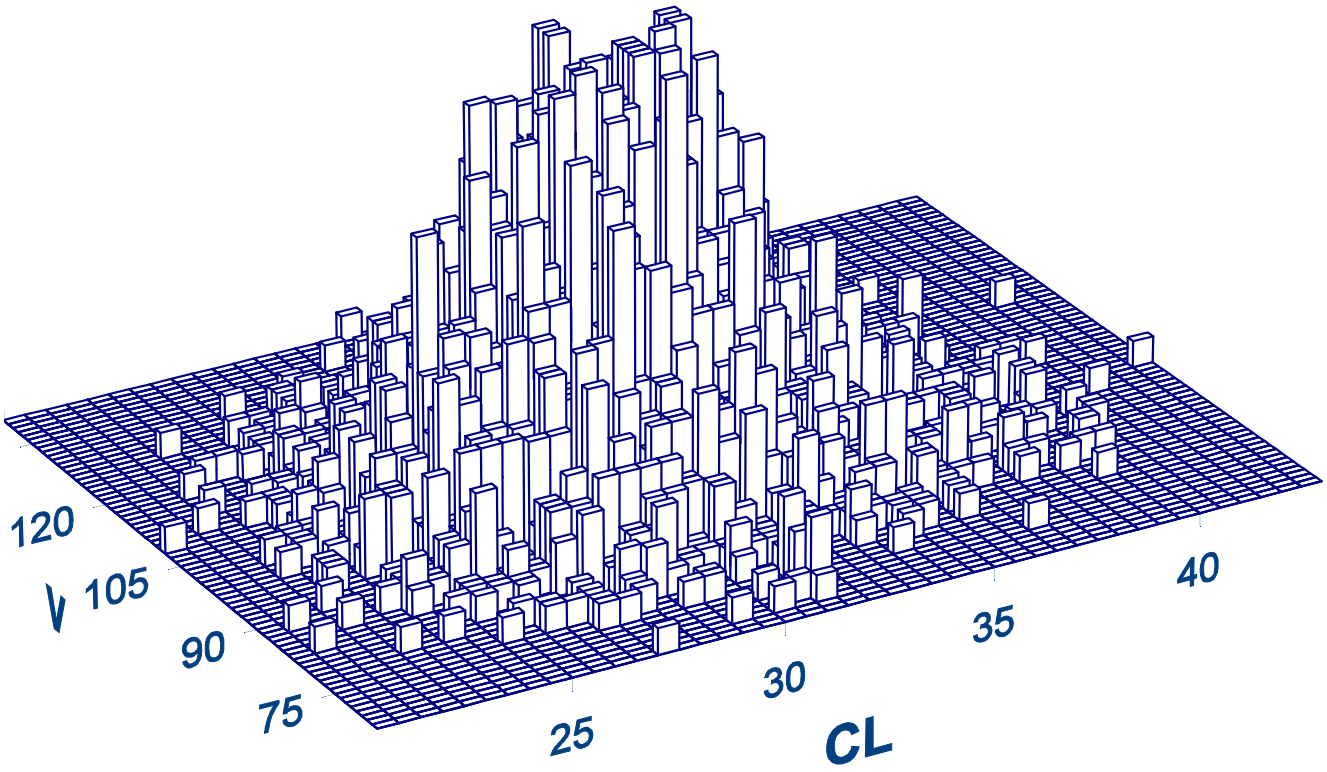
  } *will discuss today*
  - Trimodal
  - Heavy-tailed

  } *will be available at the web*

UPPSALA
UNIVERSITET

Random effects distributions

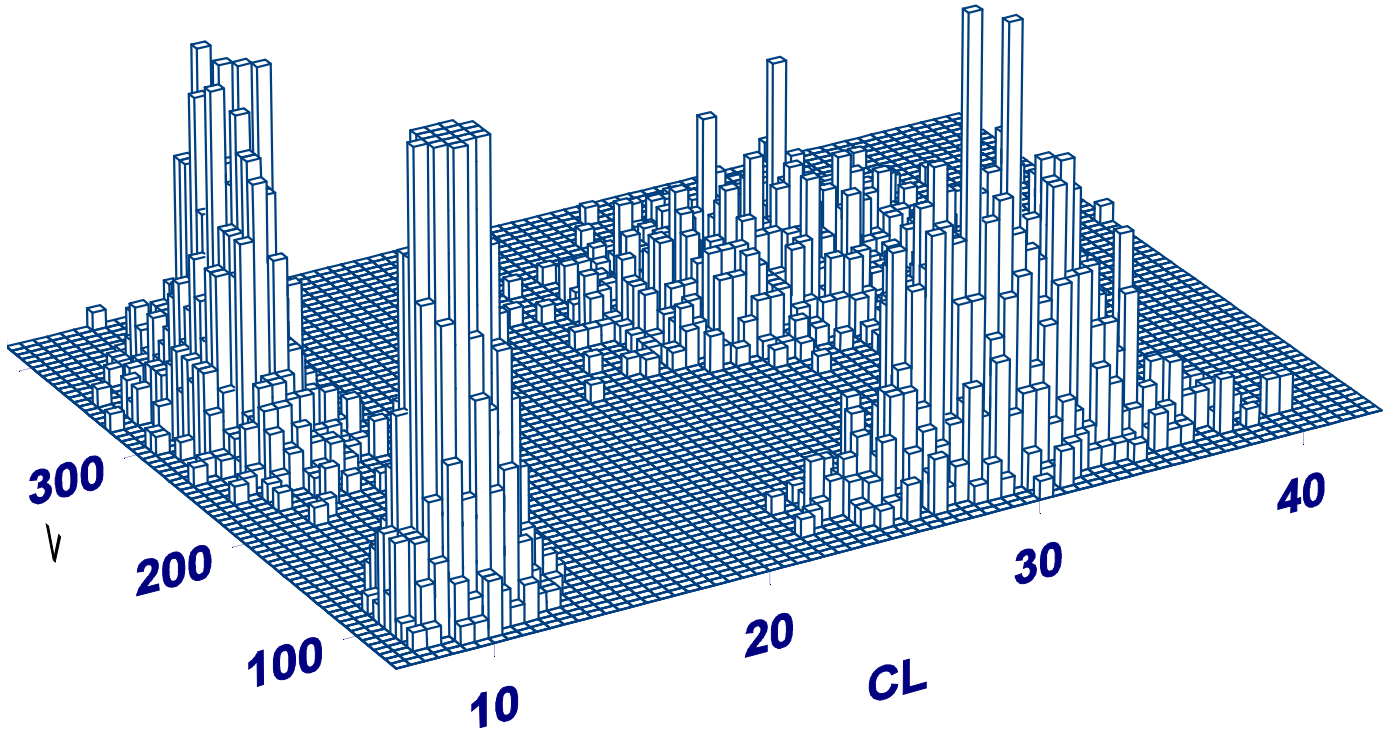
1. Log-normal



UPPSALA
UNIVERSITET

Random effects distributions

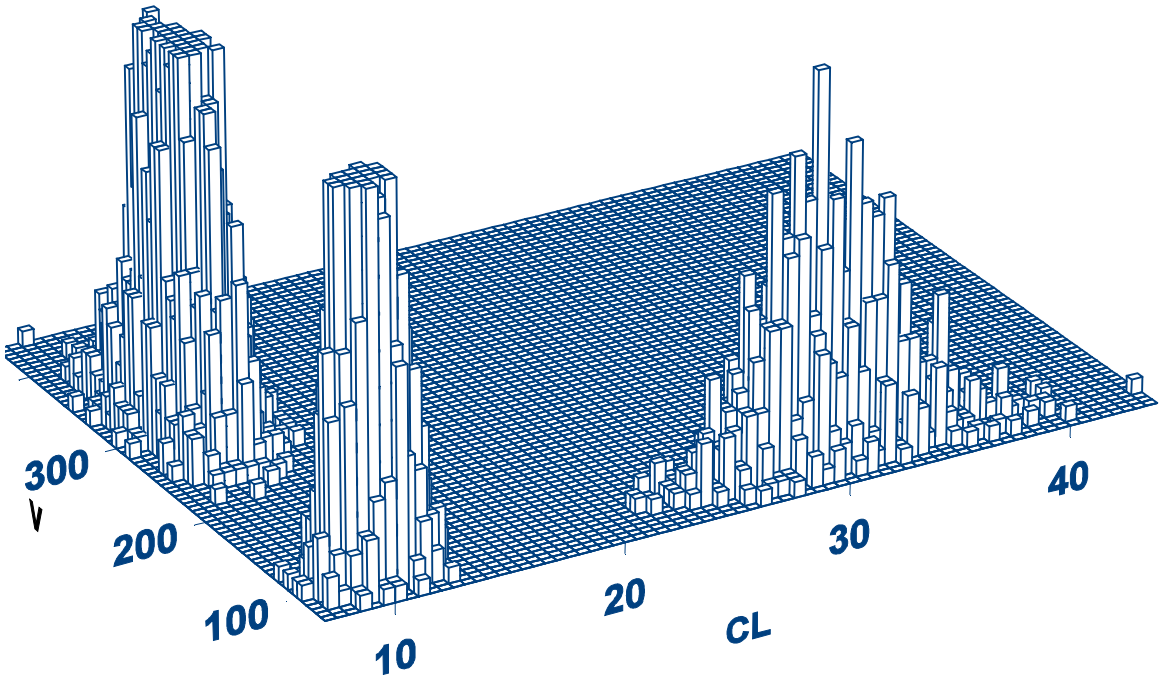
2. ”quadromodal” distribution



UPPSALA
UNIVERSITET

Random effects distributions

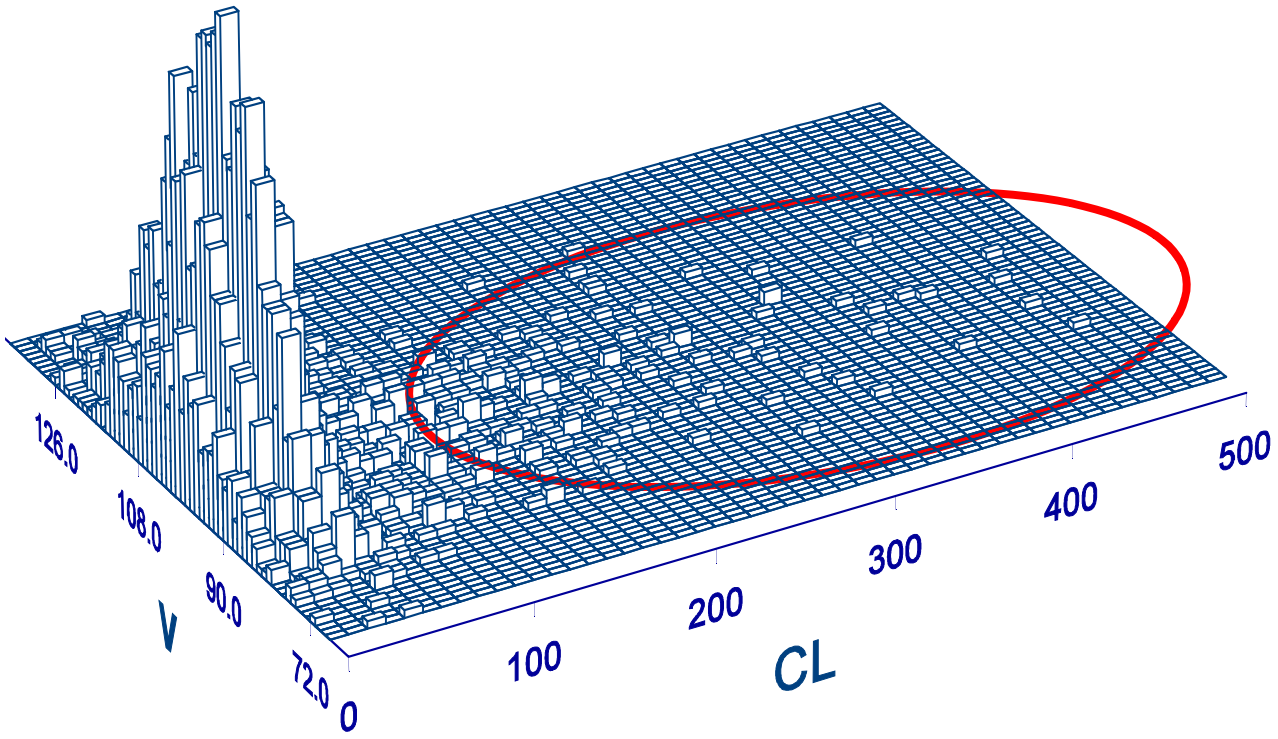
3. ”trimodal” distribution



UPPSALA
UNIVERSITET

Random effects distributions

4. Heavy-tailed distribution



UPPSALA
UNIVERSITET

Analysis

Models fitted to the data — *Parameter distribution*

1. **PARAMETRIC** ..... The Log-normal

2. **MIXTURE ($MIX)** ..... The TRUE one (quadromodal)

3. **NONPARAMETRIC** ..... The nonparametric (EBEs – points of support)

based on the *incorrectly* assumed Log-normal distribution

UPPSALA UNIVERSITET

Results evaluation

Estimated parameter distributions were

1. ***evaluated*** *at the* 10_{th}, 25_{th}, 50_{th}, 75_{th}, 90_{th} percentile
2. ***compared to*** the ***true*** distribution at the same percentiles

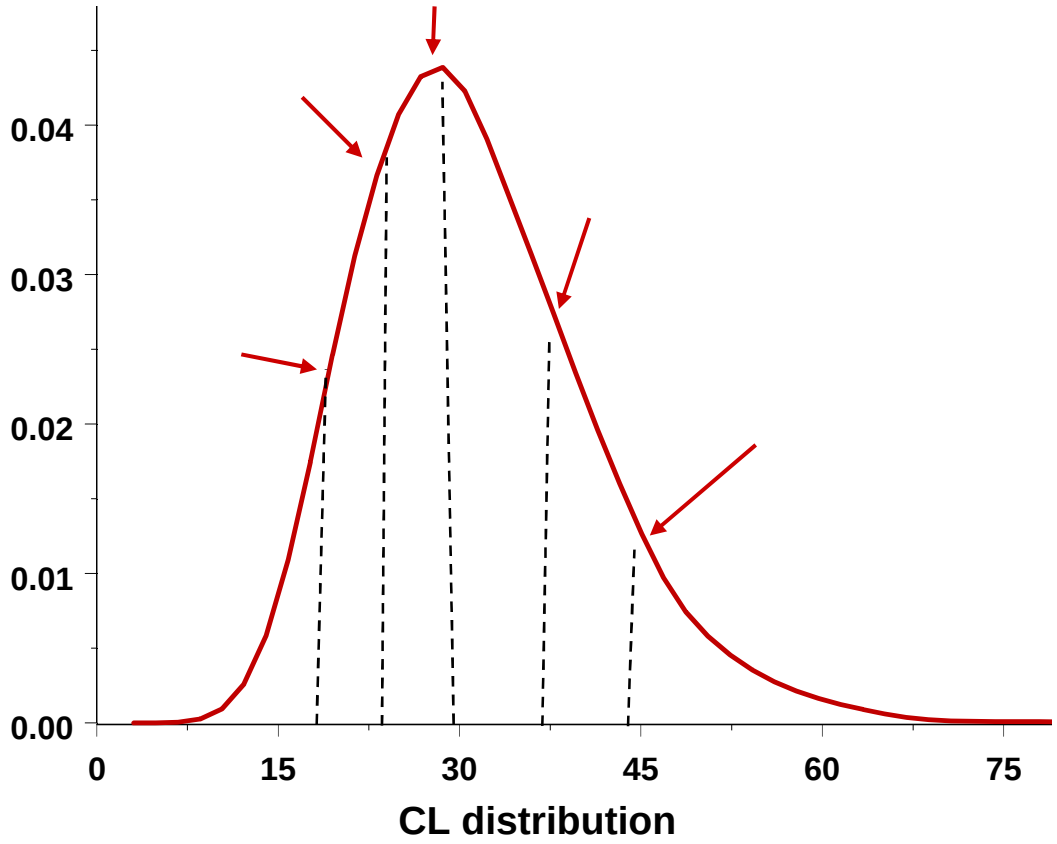
Relative estimation error (REE)

$$REE = \frac{P_{est} - P_{true}}{P_{true}}$$

P_{est} – estimated parameter value

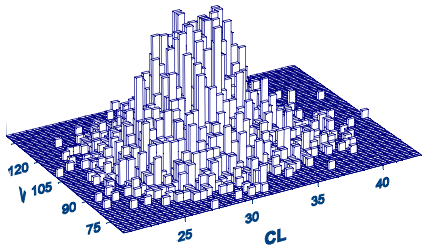
P_{true} – true parameter value

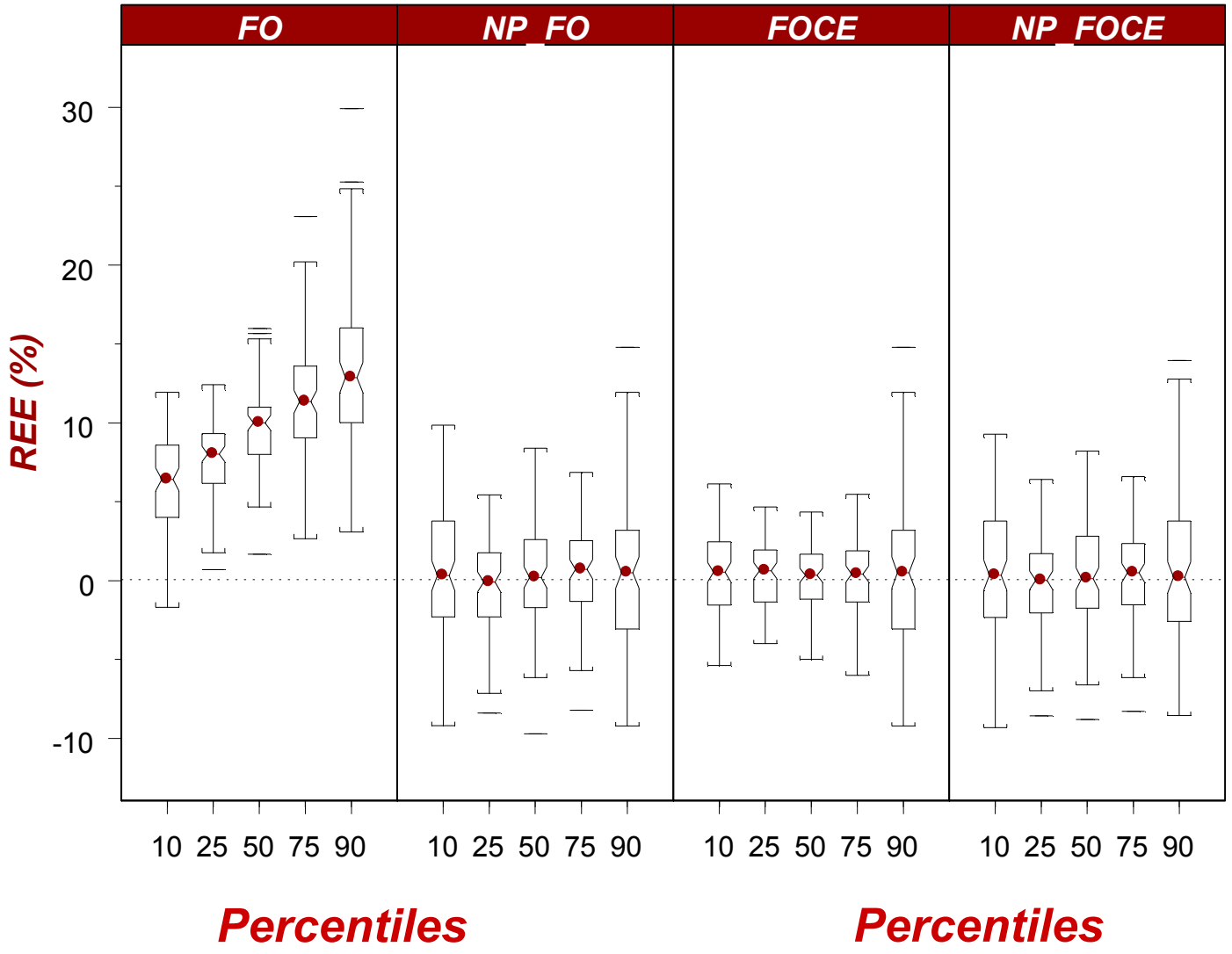
(*at the given percentiles*)



UPPSALA UNIVERSITET

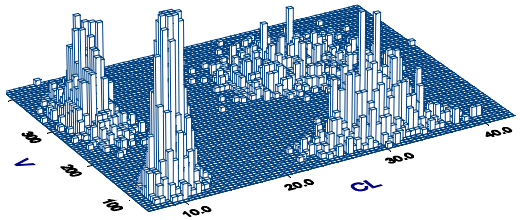
Results: Log-normal -CL

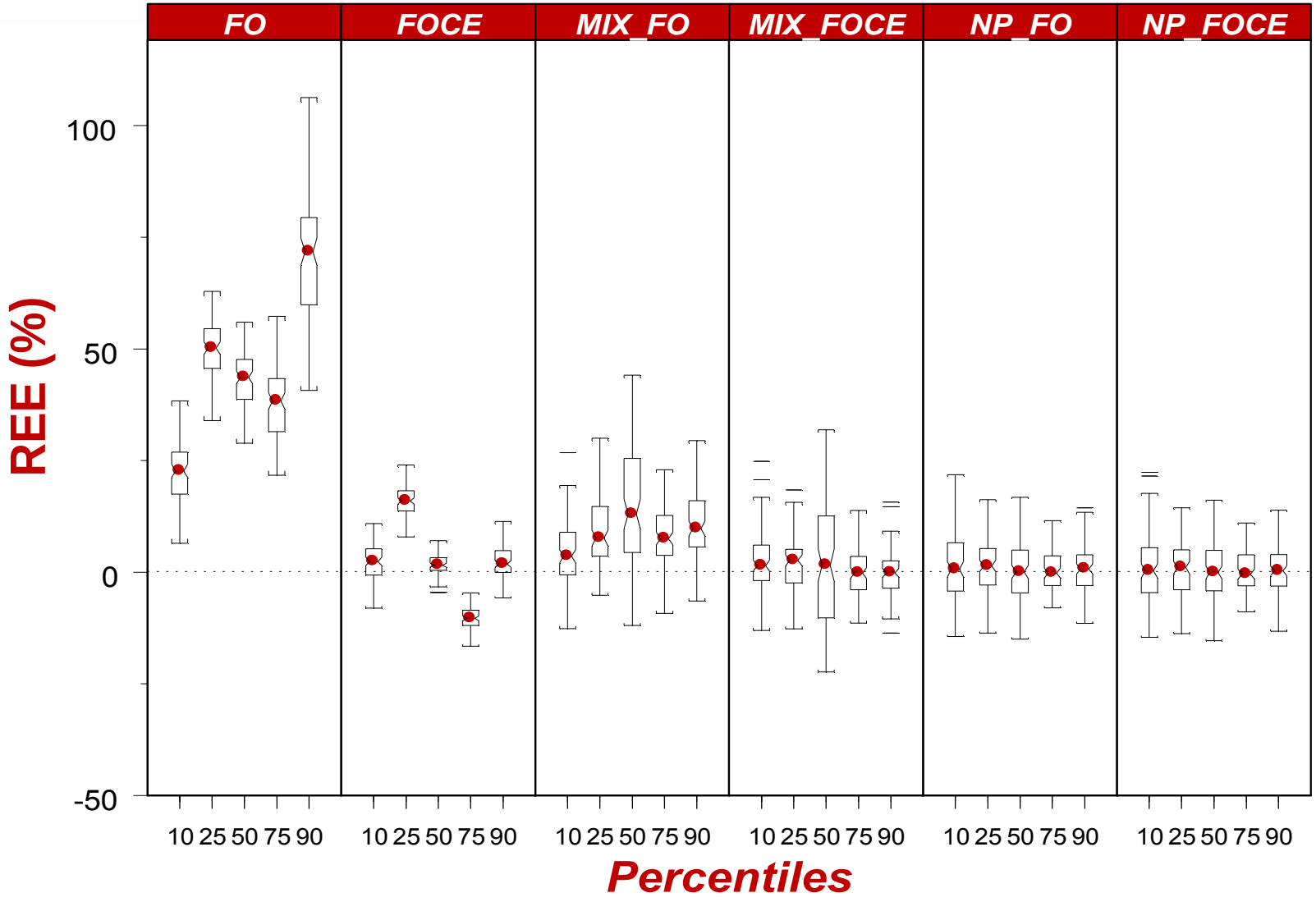




UPPSALA UNIVERSITET

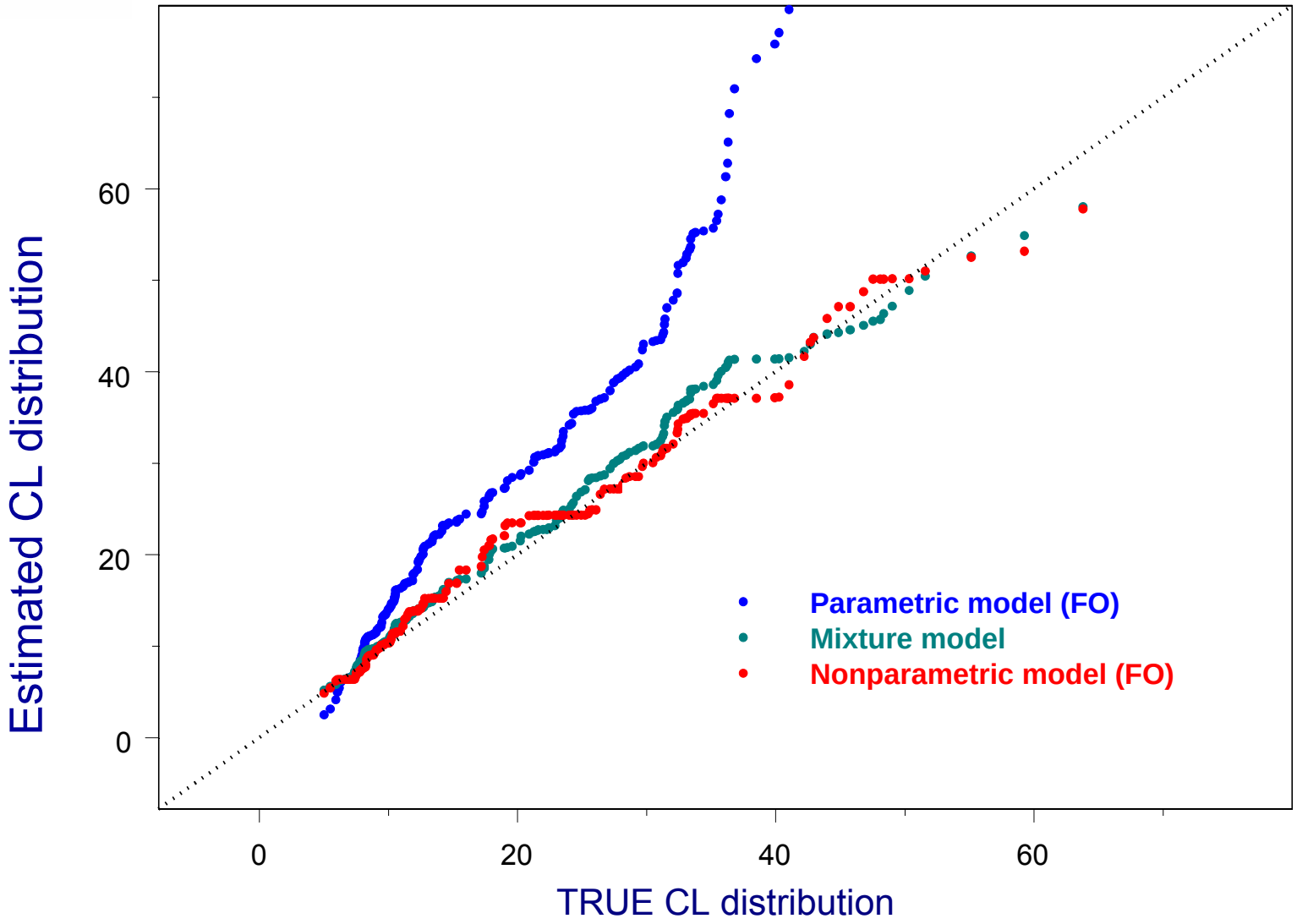
Results: quadromodal - CL





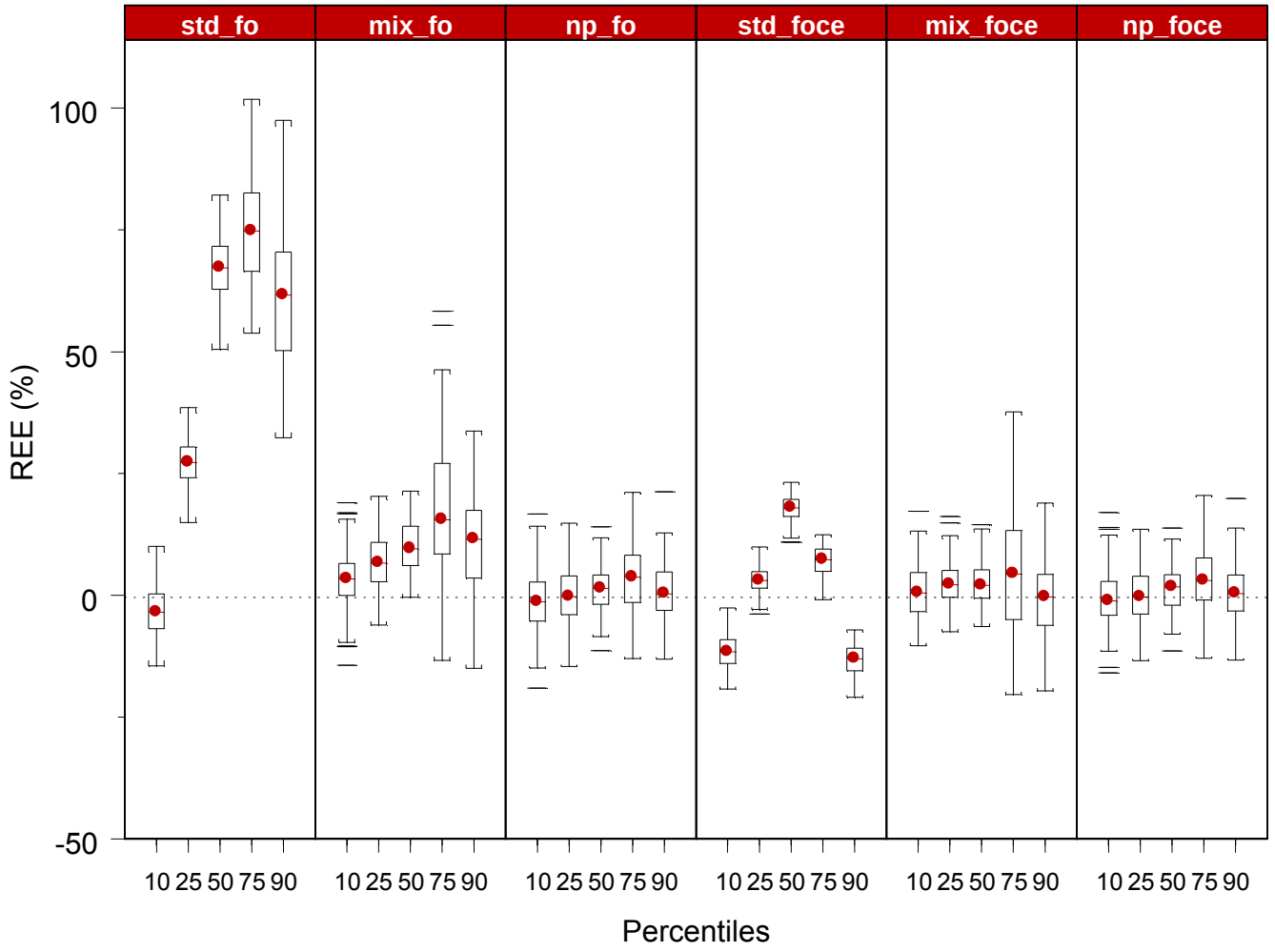
UPPSALA UNIVERSITET

quadromodal: QQ plots - CL



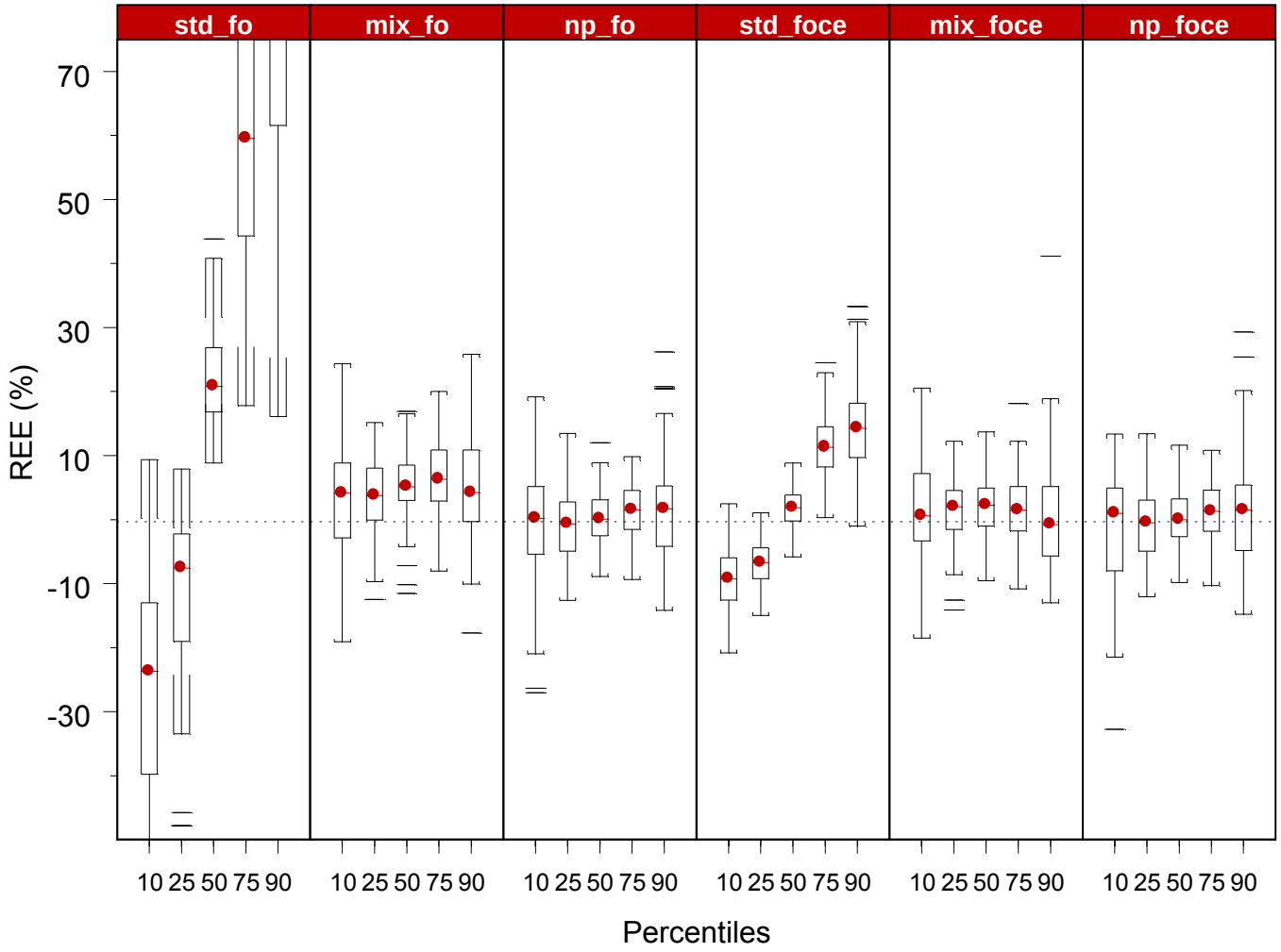
UPPSALA UNIVERSITET

Results: trimodal - CL



UPPSALA UNIVERSITET

Results: heavy-tailed - CL



UPPSALA
UNIVERSITET

Results cont.

- ✓ **With both, FO and FOCE**, the nonparametric parameter distribution **matched the TRUE parameter distribution** in *all studied cases*

- ✓ **With less informative data and/or smaller population**, relative bias in parameter estimates is increasing for all methods, but **the same trend remains**

UPPSALA
UNIVERSITET

the analysis of data with

misspecification ín residual error magintude

UPPSALA UNIVERSITET

Background

Residual (intraindividual) variability (RV):

- Assay error
- Model misspecification
- Individual biology
- Study conduct

Nonparametric approach has to specify the RV magnitude a priori

The ways to handle this :

The past : RV was fixed to the **assay error**

The present : RV is estimated with the parametric program and fixed to that

Option in NONMEM (the future way ?):

✓ *possibility of estimating RV magnitude distribution (ETA on EPSILON)*

⇒ With NONMEM, the ***nonparametric distribution of RV*** can be estimated

UPPSALA
UNIVERSITET

Aim

Aim

to explore the sensitivity of the nonparametric estimation method in NONMEM VIβ to the misspecification in residual error magnitude

Questions to answer:

- ✓ *Is it sensitive?*
- ✓ *Can we benefit from the nonparametric distribution in residual error magnitude?*

UPPSALA
UNIVERSITET

Data

In addition to previous simulation settings:

(with underlying log-normal parameter distribution)

2 mixtures in residual error magnitude:

1. 80 % of population – 30 % residual variability (CV%)
2. 20 % of population - 100% residual variability (CV%)

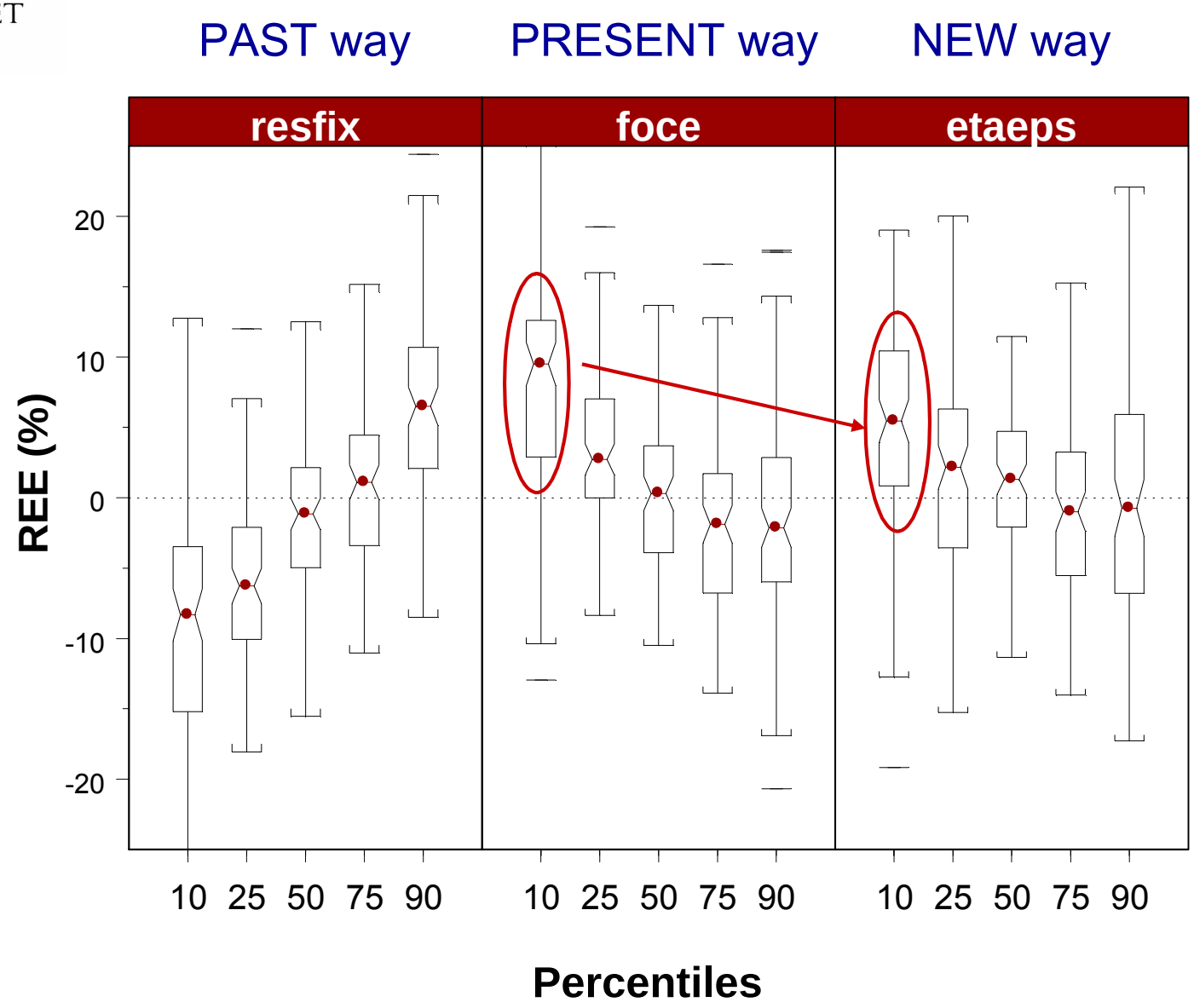
UPPSALA
UNIVERSITET

Analysis

Models fitted to the data	*Mimic:*
1. RV **fixed** *apriori to the 30%*	The past way
2. RV **estimated**	The present way
3. ***Nonparametric distribution*** **in RV** estimated	Advanced NONMEM way

UPPSALA UNIVERSITET

Results – CL distribution



UPPSALA
UNIVERSITET

Conclusions

- ✓ NONPARAMETRIC estimation method in NONMEM VIβ is ***sensitive*** to the misspecification in the residual error magnitude

- ✓ We ***can*** **benefit** from nonparametric distributions of random effects in residual error magnitude (eta on epsilon)

UPPSALA
UNIVERSITET

Potential use of $NONP

- ✓ ***an aid*** in building of parametric models, especially when the EBE distribution may be misleading or non-informative

- ✓ ***replacement of the final parametric model***, especially when the FO method is used

UPPSALA
UNIVERSITET

What's going on in Uppsala more ...

- Evaluation of this method with ***real data sets***
- *Development of a bootstrap method for the* ***imprecision measurement*** of the nonparametric distributions estimates

UPPSALA
UNIVERSITET

Acknowledgments

Professor Stuart Beal