MIXED EFFECTS MODELING OF SPARSE DATA: A COMPARISON OF THREE SOFTWARE PACKAGES

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Sparse Data

- Pediatric trials.
- Poor trial designs.
- Therapeutic drug monitoring.

Implications*

- High bias and poor precision of parameter estimates.
- Simplification of PK model leads to poor estimates.

Available solutions*

- Fixing of some parameters.
- Use of prior information by modeling with dense data from other studies.

*Brian P. Booth and Jogarao V.S. Gobburu, J Clin Pharmacol, 2003. **43** : p. 1307-1315.

Software available

- NONMEM
- SAS™ (PROC NLMIX)
- SPLUS (NLME)
- PKBUGS
- KINETICA™
- NPEM/ NPAG

Sparse data situation

The data comprises of steady-state serum digoxin concentration in Egyptian pediatric patients (n=40).

- Route: Intravenous bolus.
- Dose: 10 µg/kg/day divided into two equal doses.
- Sampling: 2 samples/patient (0.5 - 18 h).

OBJECTIVE

- To compare analysis of NONMEM with
  - PKBUGS (Ver 2).
  - KINETICA™ (Ver 4.0.2).
    - Fixed effects
    - Random effects
    - Precision

Brief overview

- NONMEM is a parametric approach based on analytical approximation of the expression for likelihood.
- PKBUGS involves a full Bayesian estimation using the Markov Chain Monte Carlo simulation performed with Gibbs sampler.
- KINETICA™ is a software package which applies an iterative Expectation-Maximization (EM) algorithm to perform mixed effects modeling.

ESTIMATION

NONMEM (Ver V) – Digital Fortran Compiler 6.5

- The data were analyzed with 1 and 2 compartment models and the best model was chosen.
- Models were parameterized as Clearances (CL1,CL2) and Volumes of distribution (V1,V2), which is the mechanistic choice as well as rate constants (ke, k12 and k21).
- Inter/Intra-individual variability: Log-normal/Additive
- Method: FOCE

PKBUGS (Ver 2.0)

- The data was analyzed using a two compartment model.
- Parameterization - Clearances (CL1,CL2) and Volumes (V1, V2).
- Informative priors – Adult population mean, BSV and the associated precision were obtained from literature* and body-weight scaled .
- A prior mean of 1 and a coefficient of variation of 100% was set for τ which represents the prior for residual error.

*Hornestam, B., et al., Eur J Clin Pharmacol, 2003. **58**(11): p. 747-55.

- Inter/Intra-individual variability: Log-normal/Additive.
- Method:Three independent chains with dispersed initial values were run for 24001 iterations.
- Burn-in: 4001
- Refresh: 1
- Thin: 100
- Assessment of convergence:
  - Graphic history of the chains
  - Brooks-Gelman-Rubin (bgr) diagnostic
  - Autocorrelation

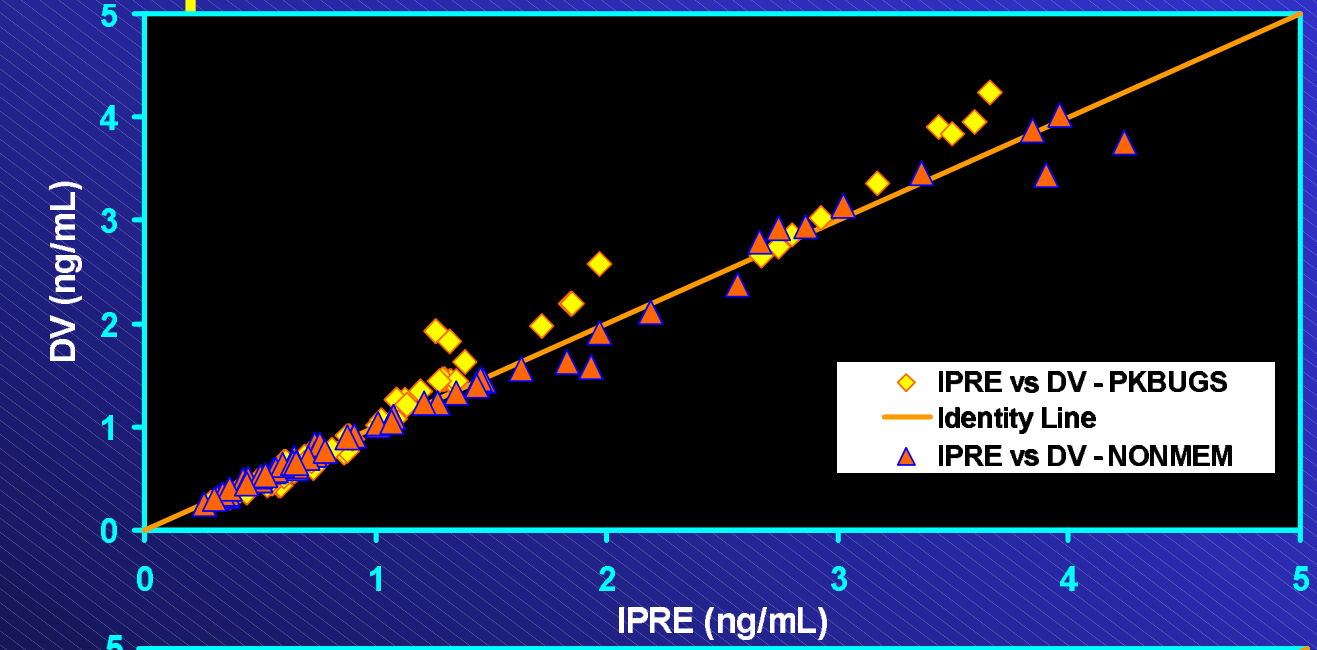
KINETICA™ (Ver 4.0.2)

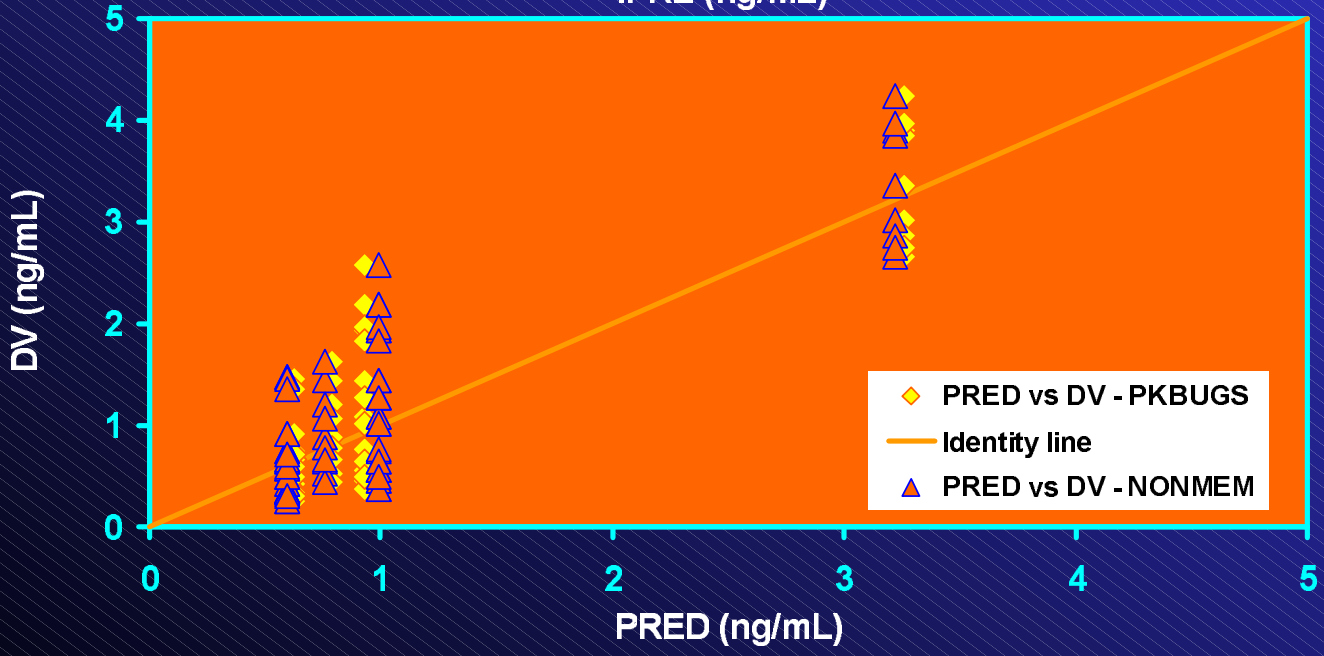
- The data was analyzed using a two compartment model.
- Parameterization - Volume (V1) and Rate Constants (K10, K12 and K21).
- Inter/Intra-individual variability: Log–normal/Additive

RESULTS

- A two compartment model was shown to fit the data better than one compartment model using NONMEM.
- For further comparisons between the software platforms a two compartment model was considered.

Comparison of NONMEM and PKBUGS





FIXED EFFECTS

	NONMEM Mean (95% CI)*	PKBUGS Median (Credible Interval)†
CL1 $L.h^{-1}.kg^{-1}$	0.37 (0.32, 0.42)	0.37 (0.31, 0.45)
CL2 $L.h^{-1}.kg^{-1}$	0.46 (0.31, 0.62)	0.64 (0.28, 1.65)
V1 $L.kg^{-1}$	1.42 (1.21,1.63)	1.16 (0.40, 2.75)
V2 $L.kg^{-1}$	9.11 (4.52,13.70)	8.66 (3.05, 78.18)

∗CI: Conventional confidence intervals define a range for the expectation of an estimate in frequently repeated experiments.

†Credible Interval: Statement in Bayesian framework concerning the probability of an unknown population parameter falling in a specified interval in this experiment.

RANDOM EFFECTS

Between Subject Variance

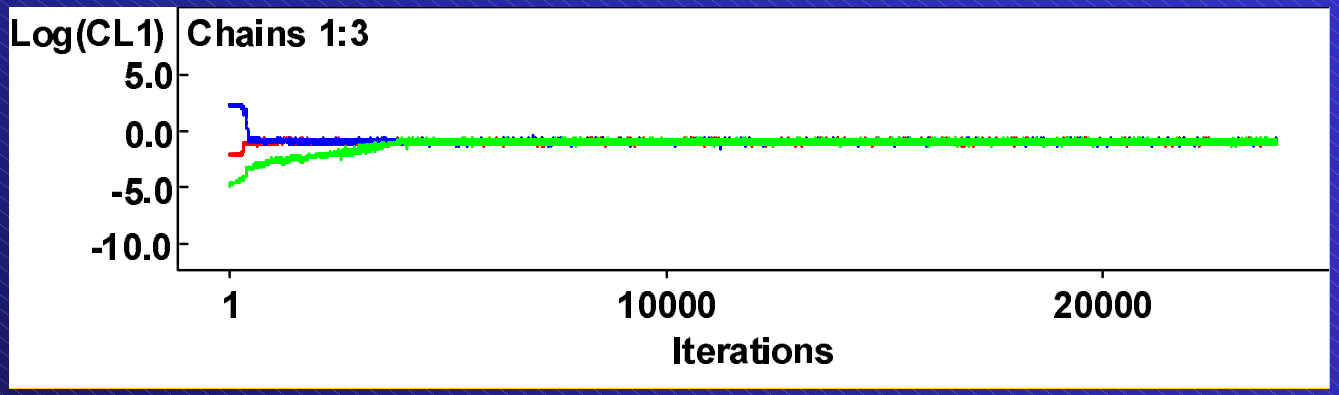
	NONMEM Mean (95% CI)*	PKBUGS Median (Credible Interval)†
ω_{CL1}	0.14 (0.09, 0.20)	0.18 (0.10, 0.33)
ω_{CL2}	0.53 (*-0.06*, 1.11)	0.68 (0.26, 2.27)
ω_{V1}	~ 0	0.66 (0.25, 2.34)
ω_{V2}	~ 0	0.92 (0.31, 3.90)

Residual Error

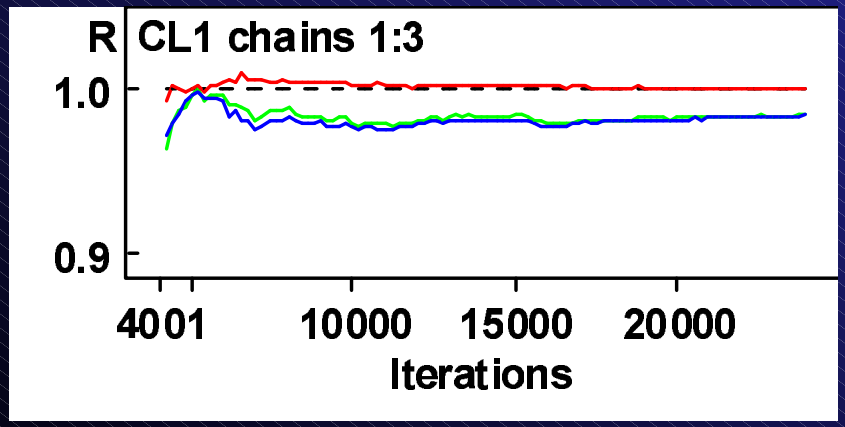
	NONMEM Mean (95% CI)*	PKBUGS Median (Credible Interval)†
σ	0.12 (0.11, 0.13)	0.34 (0.26, 0.44)

Assessment of convergence for PKBUGS analysis

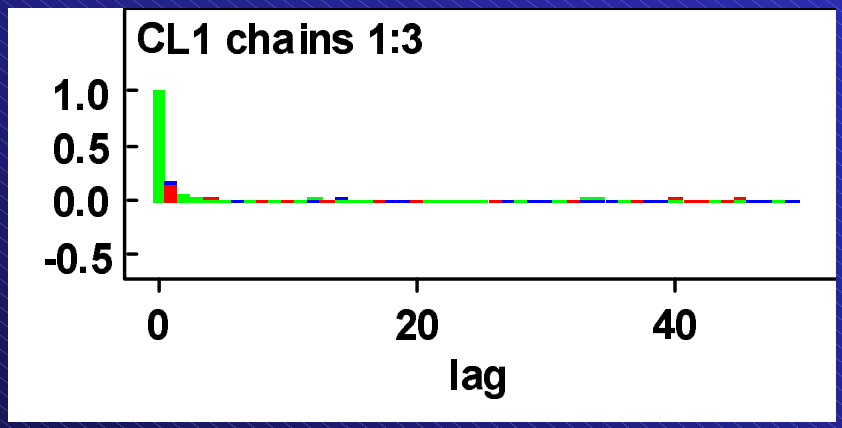
History



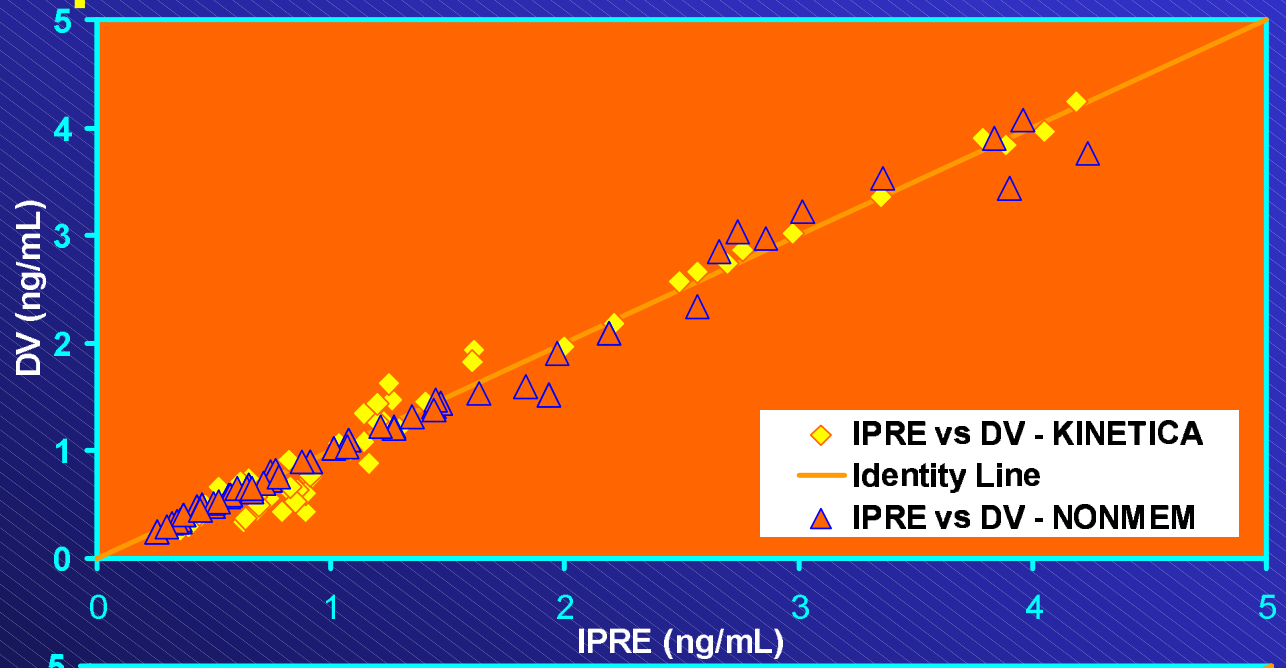
BGR diagnostic

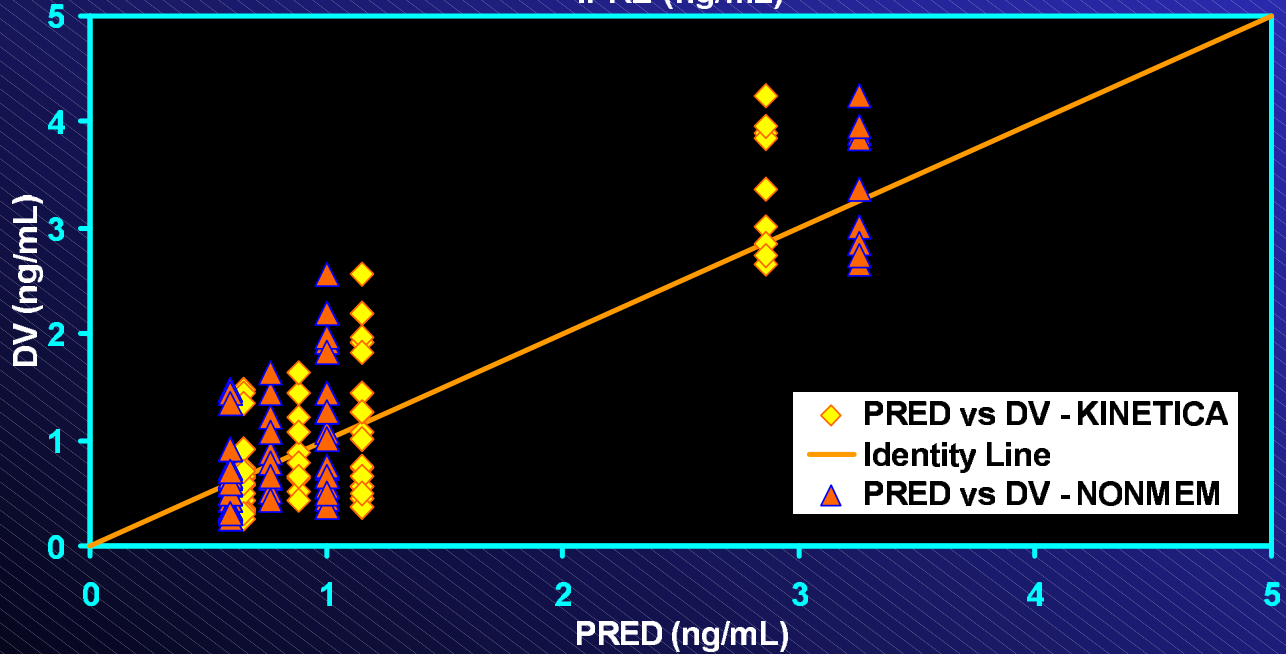


Autocorrelation



Comparison of NONMEM and KINETICA™





FIXED EFFECTS

		NONMEM Mean (SE)	KINETICA™ Mean (SE)
V1	$L.kg^{-1}$	1.41 (0.08)	1.82 (1.05)
k_e	h^{-1}	0.26 (0.02)	0.19 (0.03)
k_{12}	h^{-1}	0.31 (0.06)	0.25 (0.12)
k_{21}	h^{-1}	0.05 (0.03)	0.05 (0.04)

RANDOM EFFECTS

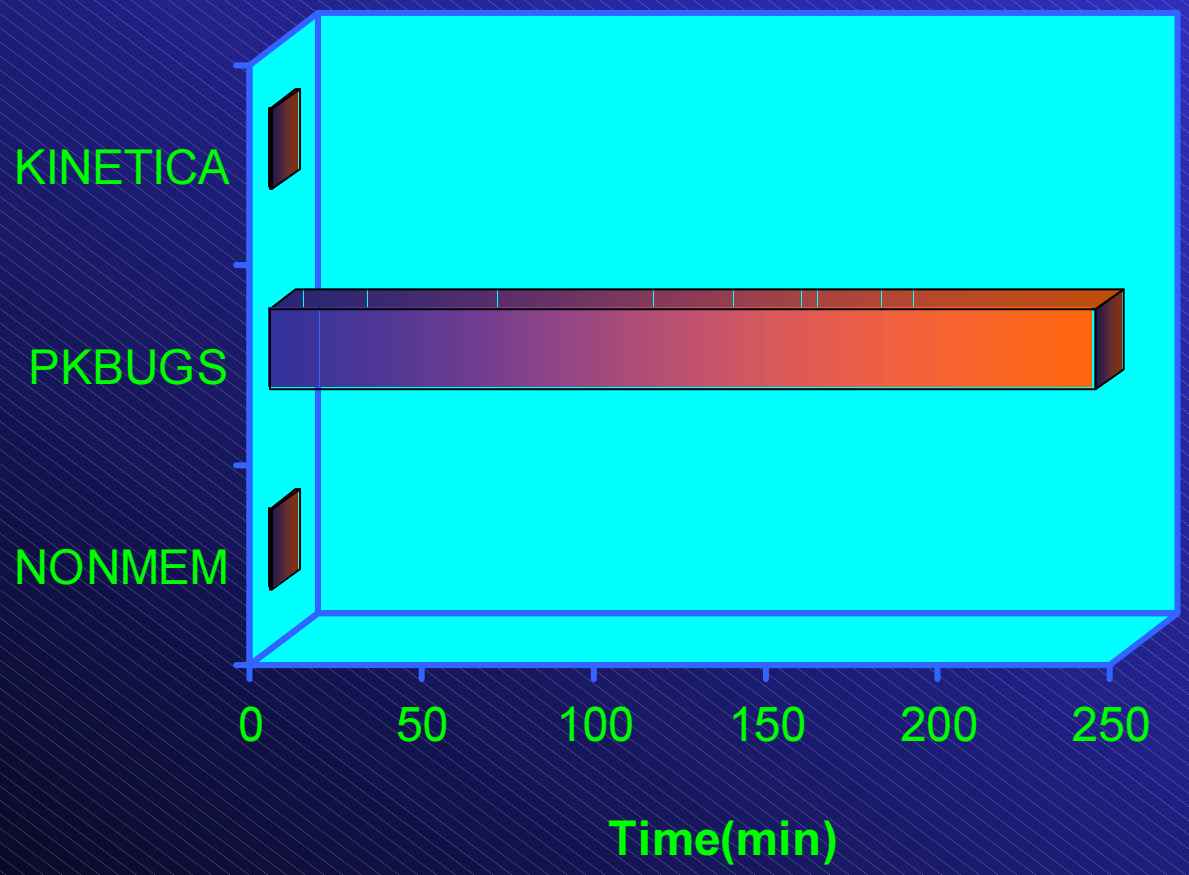
Between Subject Variance

	NONMEM Mean (SE)	KINETICA™ Mean (SE)
ω_{V1}	[0 FIX]	0.23 [NE]
ω_{ke}	0.14 (0.03)	0.0004 [NE]
ω_{k12}	0.35 (0.21)	0.01 [NE]
ω_{k21}	[0 FIX]	0.04 [NE]

Residual Error

	NONMEM Mean (SE)	KINETICA™ MEAN (SE)
σ	0.12 (0.0006)	0.07 (0.03)

Comparison of the analysis time across the software platforms



SUMMARY

NONMEM

- Reasonable estimates can be obtained.
- Analysis time very short.
- Reparametrization is easy and quick.
- Requires good initial estimates for successful minimization.
- Requires fixing of certain parameters or unreasonable estimates obtained.
- The 95% CI are narrow and symmetric always.

PKBUGS

- Estimates all the parameters.
- The 95% credible intervals are wider and realistic.
- Does not require good initial starting values.
- Requires prior information for successful analysis.
- Requires methods to ascertain convergence.
- Computationally intensive and requires long analysis time.
- Reparametrization not a standard feature

KINETICA™

- Reasonable estimation of the fixed effects is possible without need to fix.
- Analysis time very short.
- Requires good initial estimates for successful analysis.
- Does not estimate the SE associated with BSV.
- Reparametrization not a standard feature.

CONCLUSION

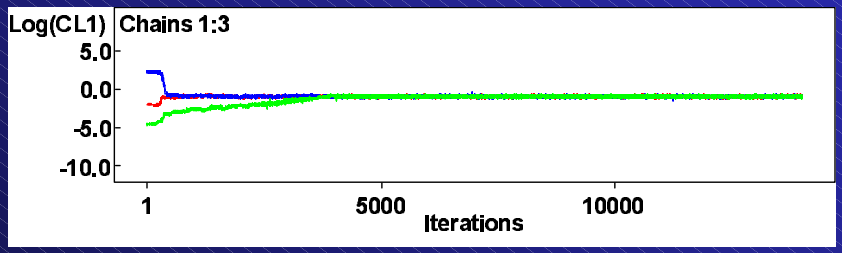
- The population mean estimates of the pharmacokinetic parameters are similar across different software platforms.
- Better estimates of BSV are obtained with PKBUGS.
- The choice of the software for analysis depends on:
  - The nature of the data.
  - Available prior information.
  - Time available for analysis.

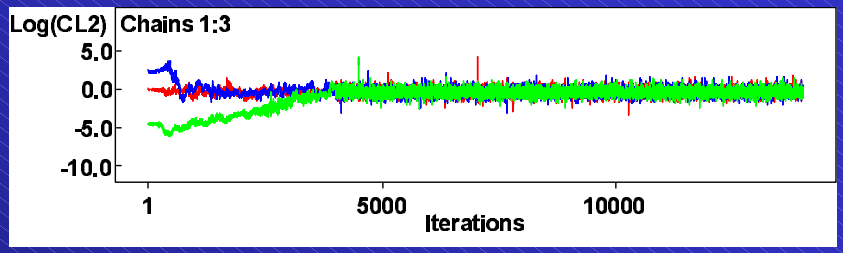
Acknowledgements

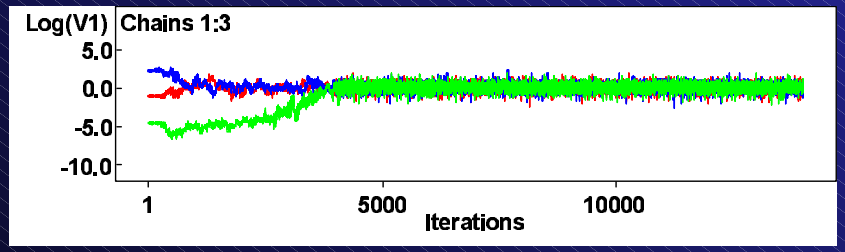
- Prof. Hartmut Derendorf
- Dr. Venkatesh Atul Bhattaram
- Hao Zhu & Qi Liu
- ECPAG committee

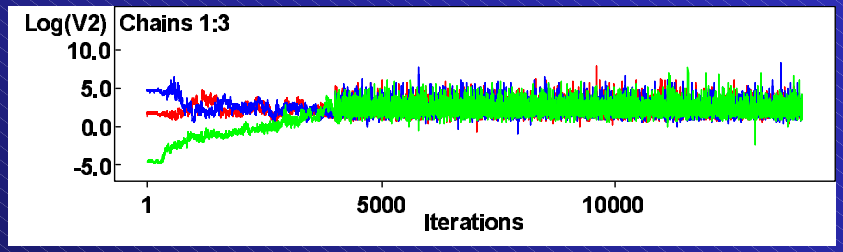
Assessment of convergence for PKBUGS analysis

History

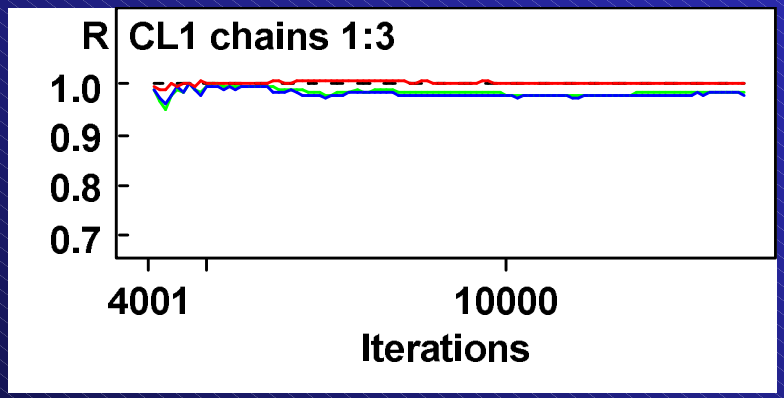


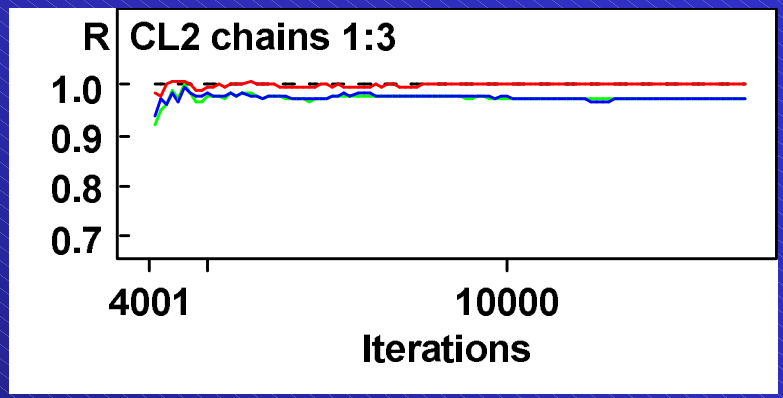


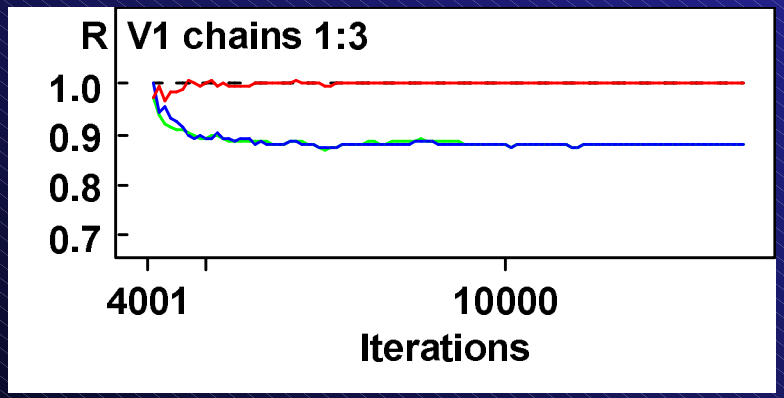


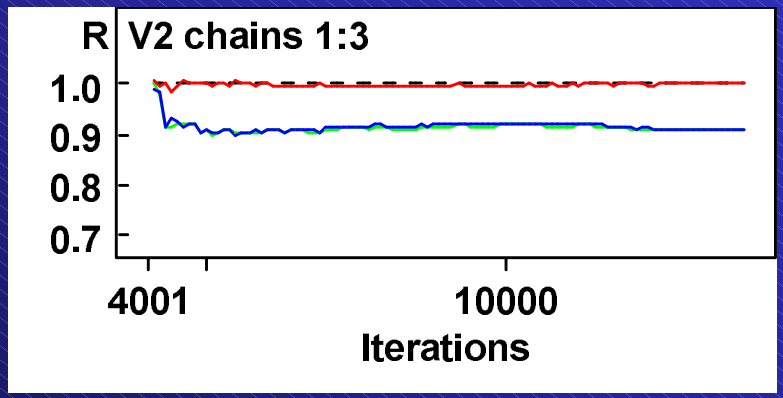


Brooks-Gelman-Rubin diagnostic









Autocorrelation