



Unified analytic and computational methods for population pharmacokinetic analysis of single dose data

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Outline

- Pharmacokinetics and role of Population PK
- PKtools
- Motivation
- Example analysis using PKtools

Pharmacokinetics

- Analysis of pharmacokinetic (PK) data is concerned with defining the relationship between the dosing regimen and the body's exposure to drug as indicated by the concentration time curve or summaries there of (i.e. AUC).
- A second goal is to determine if exposure differs among subpopulations (young-old, sick-well) based on subject specific covariates (age, size, concomitant medications, kidney function) requiring a change in dose.

Population PK

- PK analysts routinely carry out complex statistical analyses of datasets to estimate exposure. This data may be fairly sparse.
- The general tool of choice is the family of nonlinear mixed effects models.
 - The nonlinear component of this family of models reflects the kinetic theory.
 - The mixed effects component deals with the sources of variation, with particular concern for within- vs between-individual variation.

PKtools

- `PKtools` is an R package that provides access to frequentist and Bayesian estimation methods for population PK, through NLME ([7]), NONMEM ([1]) and WinBUGS ([9]).
- A set of graphical and statistical functions to aid with analysis are also available.
- `RunNLME`, `RunNM`, and `RunWB`, run NLME, NONMEM and WinBUGS, respectively.

RunNLME, RunNM, and RunWB

- To access the three 'Run' programs the user only needs to identify:
 - The statistical model to be fit.
 - A PK dataset, including; patient id, dose, draw times and concentrations.
 - The list of variable names.
 - The RunWB program requires some additional WinBUGS arguments.
- Ex: RunWB(inputStructure, data, nameData, WBargs)



The Run programs

- Output data objects from the three “Run” programs include: parameter estimates, residuals, and predicted values,
 - for use in other `PKtools` functions,
 - for further manipulation in R, and
 - for export.

Other PKtools functions

- `AICcomp` which prints the AIC, AIC_c (small sample AIC) and the objective function ($-2 \times$ the log likelihood) from NONMEM and NLME for a list of models;
- `paramEst` and `indEst` print the population and individual parameter estimates, respectively, based on maximum likelihood (NONMEM), generalized least squares (NLME) and Bayesian estimates using MCMC (WinBUGS);
- `HTMLtools` and `tex`, respectively, output HTML and Latex/MikTex report files of population and individual estimates and diagnostic plots for the users choice of estimation method.



Motivation

- Browne and Draper [3] recommend a hybrid analysis combining frequentist and Bayesian methods.
 - After choosing the model(s) of interest using frequentist methods,
 - make a final run using Bayesian MCMC methods to get parameter estimates.



Step 1: Model Selection using frequentist methods

- Trustworthy model selection methods are available for hierarchical models in the frequentist paradigm.
- These methods can be used to view a lot of models quickly.
- Thus we recommend maximum likelihood (ML) or generalized least squares (GLS) for the choice of a final model or models.

Bias in ML/GLS estimates

- In the general case of a nonlinear mixed model in which the stage I model is nonlinear and the random effects enter nonlinearly, the marginal distribution for y can not be evaluated in closed form. Frequentist methods approximate the marginal distribution for y [8].
- Variance parameters estimates for ML/GLS tend to be biased downward as they do not recognize the estimation error of the mean parameters and further the variances of the mean parameters and random effects are biased downward as their estimation does not recognize the estimation error in the variance parameters [5].

Bias(RMSE) following simulation by Bennett and Wakefield [2].

3 Concentrations	NLME	NONMEM (Laplacian)	NONMEM (Conditional)	WinBUGS
μ_{LC}	.0859(.110)	.0105(.0786)	.0382(.0843)	.00162(.0758)
μ_{LV}	-.0529(.0749)	.00633(.0528)	.0108(.0545)	.00413(.0579)
$\log(\sqrt{(\Sigma_{LC})})$	-.144(.193)	-.0968(.163)	-.100(.163)	.00632(.133)
$\log(\sqrt{(\Sigma_{LV})})$	-.0760(.227)	-.112(.265)	-.0988(.248)	-.0528(.184)
$\log(\sigma)$.0204(.0961)	.0198(.0928)	.0166(.0901)	.0299(.102)
runs	130	124	126	200
12 Concentrations				
μ_{LC}	.0182(.0670)	-.00224(.0616)	.00676(.0596)	.00499(.0735)
μ_{LV}	-.0195(.0509)	.00546(.0486)	.00834(.0510)	.000575(.0470)
$\log(\sqrt{(\Sigma_{LC})})$	-.0627(.131)	-.0768(.133)	-.0807(.137)	-.0000862(.105)
$\log(\sqrt{(\Sigma_{LV})})$	-.0245(.133)	-.0378(.142)	-.0352(.143)	-.00296(.132)
$\log(\sigma)$.00185(.0310)	.00114(.0307)	.00388(.0330)	.00754(.0353)
runs	198	88	92	200

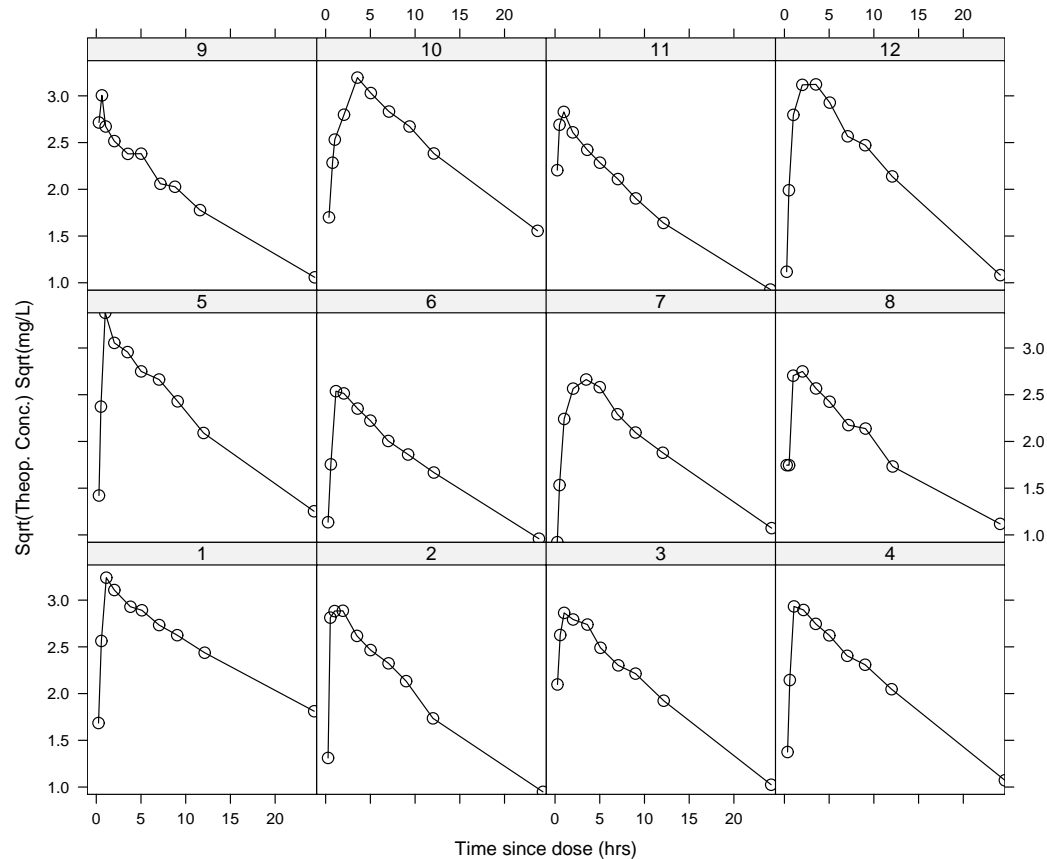
Step 2: Parameter Estimates using Bayesian MCMC

- Bayesian estimates using MCMC are exact thus confidence limits achieve the defined coverage.
- MCMC methods easily adapts to censoring in the data.
- Standard errors for individual level parameter estimates can be calculated.
- Concerns over the choice of prior for Bayesian estimation can be allayed by implementing a sensitivity analysis.

Hybrid analysis using PKtools

- Lets consider the theophylline data set with intensive sampling (11 samples) over a 24 hour period after a single oral dose for each of 12 subjects [6].
Measurements at time zero were not included in this analysis.
- This is a well studied data set known to follow a one compartment model with 1st order absorption with parameters absorption rate coefficient (K_a), apparent volume of distribution (V) and Clearance (Cl).

Trellis plot of Concentration vs Time Data



```
trplot(x=NM,yvarlab=nameData$yvarlab,  
xvarlab=nameData$xvarlab, pages=1)
```

Statistical Model

Stage I Model

$$g(y_{ij}) = g[f(x_{ij}, \beta_i)] + e_{ij} \quad e_{ij} \sim (0, \sigma^2 I)$$

Stage II Model

$$\beta_i = A_i \beta + B_i b_i \quad b_i \sim (0, D)$$

Stage III Model

- The uncertainty regarding the parameters β , σ^2 , and D is modelled through prior distributions.



Goals for Theophylline Analysis

1. to estimate the mean and variances for the population and individual PK parameters,
2. to determine if V or Cl should be modelled as a function of weight, and
3. to show that exposure for a new patient defined by the predicted drug concentration versus time curve is consistent with the current data.

Listing of models

	fixed parameters	random parameters
0	$\log(Ka), \log(V), \log(Cl)$	$\log(Cl)$
1	$\log(Ka), \log(V), \log(V)=f(WT), \log(Cl),$ $\log(Cl)=f(WT)$	$\log(Cl)$
2	$\log(Ka), \log(V), \log(V)=f(WT), \log(Cl)$	$\log(Cl)$
3	$\log(Ka), \log(V), \log(V)=f(WT), \log(Cl)$	$\log(Ka), \log(Cl)$
4	$\log(Ka), \log(V), \log(Cl)$	$\log(Ka), \log(Cl)$
5	$\log(Ka), \log(V), \log(Cl)$	$\log(Ka), \log(V), \log(Cl)$
6	$\log(Ka), \log(V), \log(Cl)$	$\text{diag}(\log(Ka), \log(V), \log(Cl))$
7	$\log(Ka), \log(V), \log(V)=f(WT), \log(Cl)$	$\text{diag}(\log(Ka), \log(V), \log(Cl))$

Note $f(WT)$ is defined as $\beta_0 + \beta_1 \times WT$.

Model Selection

- We chose AIC_c since prediction was the goal and $n/K = (\text{number of values}) / (\text{number of parameters}) = 120/10 < 40$.
- `AICcomp(PKNLMEobjects=PKNLMEobjects, NONMEMobjects=NONMEMobjects)`.
PKNLMEobjects and NONMEMobjects contain ordered lists of the PKNLME and NONMEM objects for models 0 to 7.

Model Selection Criteria

	AIC		AICc		Objective Function		
	NONMEM	NLME	NONMEM	NLME	NONMEM	NLME	K
0	-138.18	82.89	-137.65	83.41	-148.18	72.89	5.00
1	314.19	65.76	315.19	66.76	300.19	51.76	7.00
2	-153.35	64.14	-152.61	64.88	-165.35	52.14	6.00
3	-148.01	9.97	-146.71	11.27	-164.01	-6.03	8.00
4	-202.05	17.87	-201.05	18.87	-216.05	3.87	7.00
5	-217.92	0.43	-215.90	2.45	-237.92	-19.57	10.00
6	-211.81	6.46	-210.81	7.46	-225.81	-7.54	7.00
7	-217.13	10.94	-215.83	12.24	-233.13	-5.06	8.00

Burnham and Anderson [4] suggest that a difference in AIC of ≤ 2 is not credible, while a difference of 4-7 is definite and that of > 10 is very strong.

Final Model

- Model 5 is the winner with the minimum AIC_c .
- Model 7 was the next best model in NONMEM; variance for $\log(Ka)$ was very near zero, a boundary for variance and not likely to be a stable model.

paramEst

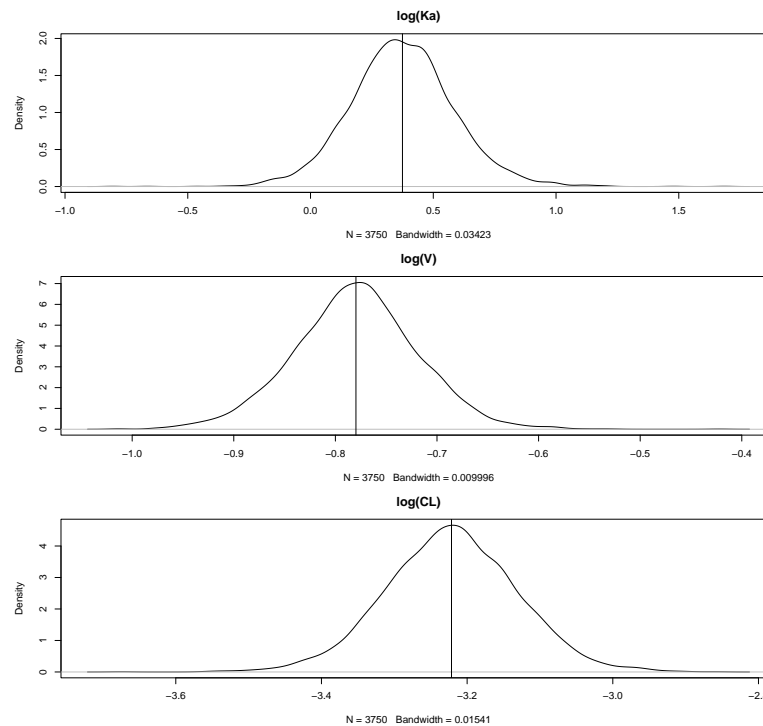
- `paramEst` gives population parameter estimates for all three methods.
- `paramEst(PKNLMEobject=results.nlme5, NMobject=results5, WBobject=WB2)` where `results.nlme5`, `results5`, `WB2` are the PKNLME, NONMEM and WinBUGS objects.

Population Parameter Estimates

	NONMEM		NLME		WinBUGS	
	Estimates	(se)	Estimates	(se)	Estimates	(se)
log(Ka)	0.36	0.41	0.35	0.2	0.37	0.21
log(V)	-0.78	0.1	-0.79	0.044	-0.78	0.05
log(Cl)	-3.2	0.22	-3.2	0.077	-3.2	0.082
D[1,1]	0.43	0.75	0.41	NA	0.48	0.28
D[1,2]	-0.013	0.046	-0.011	NA	-0.016	0.042
D[2,2]	0.014	0.044	0.014	NA	0.022	0.014
D[1,3]	-0.02	0.16	-0.019	NA	-0.02	0.07
D[2,3]	0.029	0.054	0.029	NA	0.033	0.02
D[3,3]	0.062	0.057	0.06	NA	0.071	0.039
sigma2	0.029	0.0042	0.028	NA	0.03	0.0046

Parameter Estimation from WinBUGS via RunWB

- WinBUGS gives the full distributions that can be summarized by statistics or shown graphically.



indEst

- `indEst` gives individual parameter estimates for all three methods.
- `indEst(PKNLMEobject=results.nlme5, NMobject=results5, WBobject=WB2, outputType="R")` where `results.nlme5`, `results5`, `WB2` are the PKNLME, NONMEM and WinBUGS objects for the model 5.

Individual Level Estimates from Model 5

$\text{Log}(\hat{K}a_i)$		NONMEM	NLME	WinBUGS
	1	0.39	0.39	0.42
	2	0.56	0.57	0.56
	3	0.76	0.77	0.78
$\text{Log}(\hat{V}_i)$		NONMEM	NLME	WinBUGS
	1	-1.05	-1.06	-1.04
	2	-0.76	-0.76	-0.77
	3	-0.77	-0.77	-0.77
$\text{Log}(\hat{C}l_i)$		NONMEM	NLME	WinBUGS
	1	-3.77	-3.78	-3.78
	2	-3.15	-3.16	-3.15
	3	-3.17	-3.18	-3.19

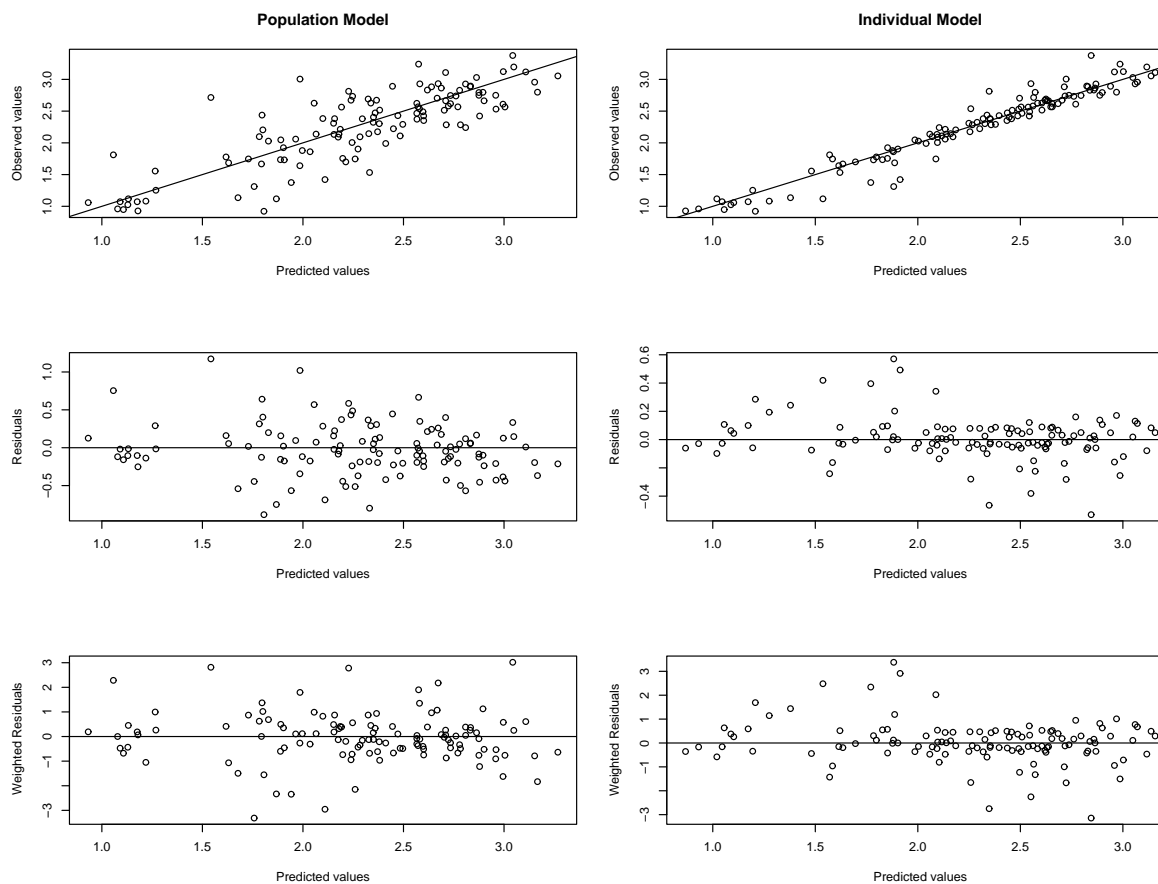
Distributions of Individual Cls from WinBUGS

	N	Mean	Med	S	2.5%	97.5%	Min	Max
1	7998	0.023	0.023	0.0022	0.019	0.027	0.016	0.031
2	7998	0.043	0.043	0.0032	0.037	0.05	0.032	0.056
3	7998	0.041	0.041	0.003	0.036	0.047	0.031	0.054

Model Diagnostics

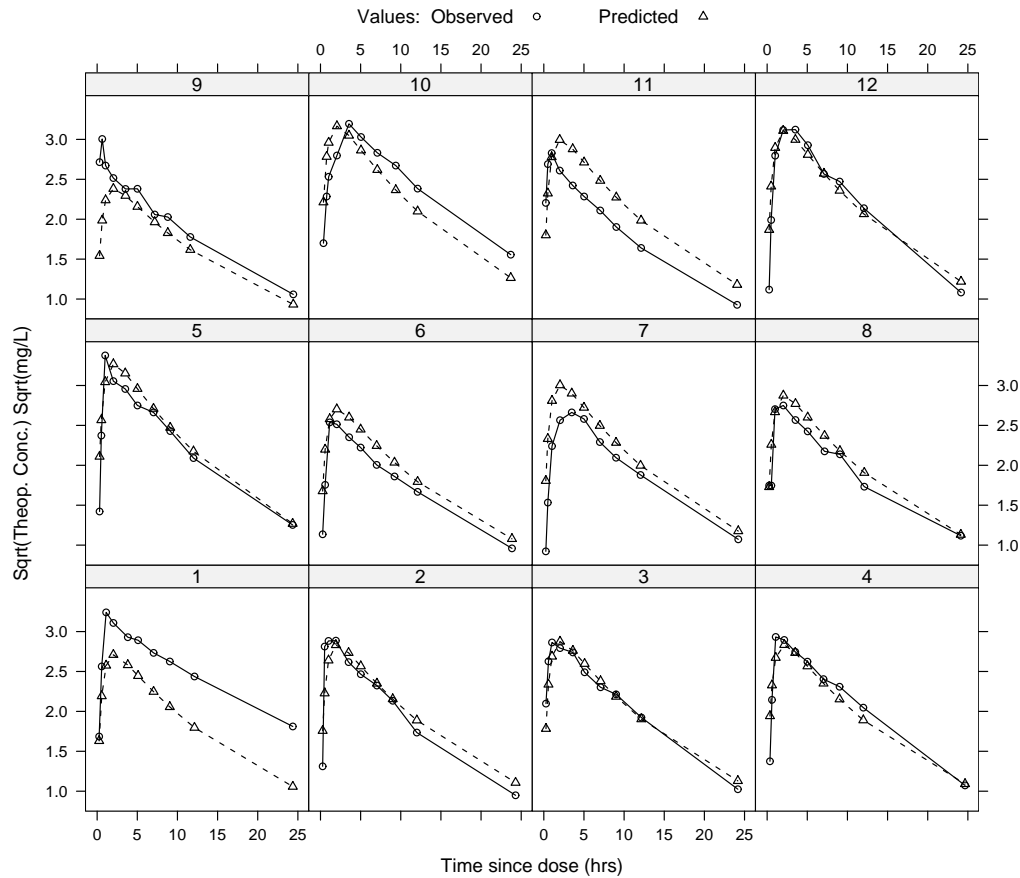
- Diagnostic plots are designed to assess the adequacy of the model and are provided by `PKtools` for all three estimation methods.
- `PKtools` produces
 - Observed vs predicted values and residuals versus predicted values for both the population (marginal) and individual (conditional) levels.
 - Concentration vs time for the observed data and predicted values from the population and individual level models.
 - QQplots for the population and individual level and the Stage II model.
 - Individual Random effects vs covariate plots.

Predicted vs Observed and Residual vs Predicted Plots



`diagplot(NM)`, NM is the NONMEM object.

Population Predicted and Observed Values vs Time Plots



```
diagtrplot(x=NM, level="p", xvarlab=nameData$xvarlab,  
yvarlab=nameData$yvarlab, pages=1)
```

Summary

- The PKtools library provides an R interface for analysis of single dose population PK data to NLME, NONMEM, and WinBUGS.
- This interface facilitates the use of hybrid likelihood-based and Bayesian methods in analyses.
- In the theophylline example we showed that using PKtools the user could easily implement frequentist methods to chose the model and Bayesian MCMC methods to get the parameter estimates.



Collaborators

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