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Extensive and automatic assumption assessment of pharmacometric models

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Aim

- For model assumptions testable on data provide
  - Probability of violation
  - Impact of violation
  - Guidance for change

- To be achieved through the PsN tool ”QA”

Linearize

Covariate model

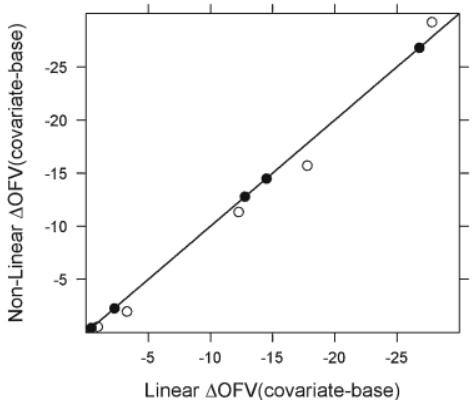
- Univariate (SCM)
- FREM

Parameter variability

- Additional etas
- Covariances
- Semi-parametric

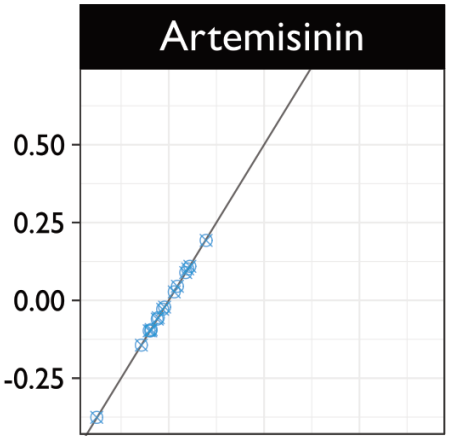
Case-deletion

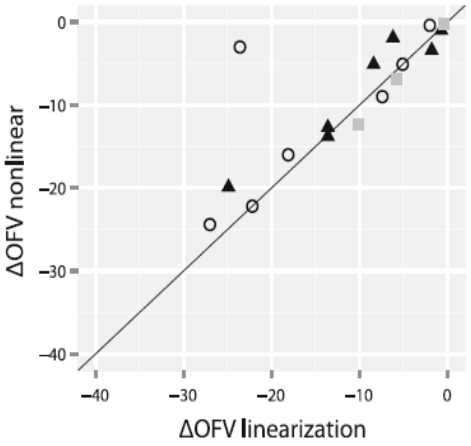
- Influential individuals



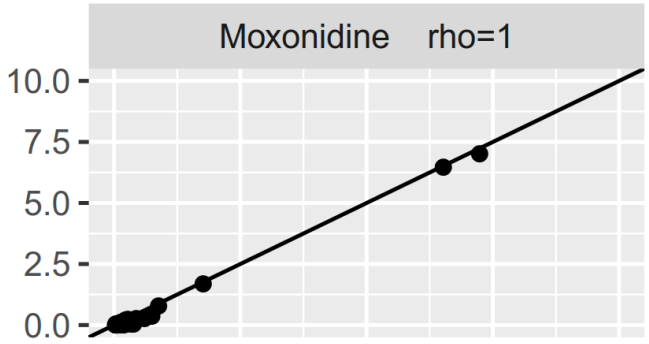
Khandelwal et al.
AAPS J 2011

Yngman et al
P-I-68





Svensson & Karlsson
JPKPD 2014

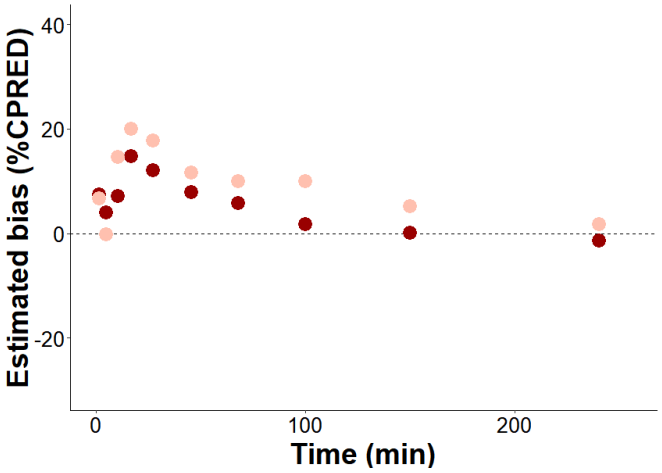


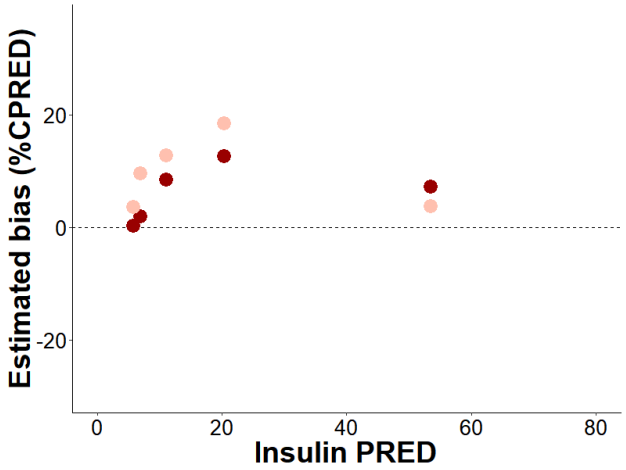
Nordgren et al
P-IV-38

Resmod

Structural model

- TIME
- TAD
- PRED

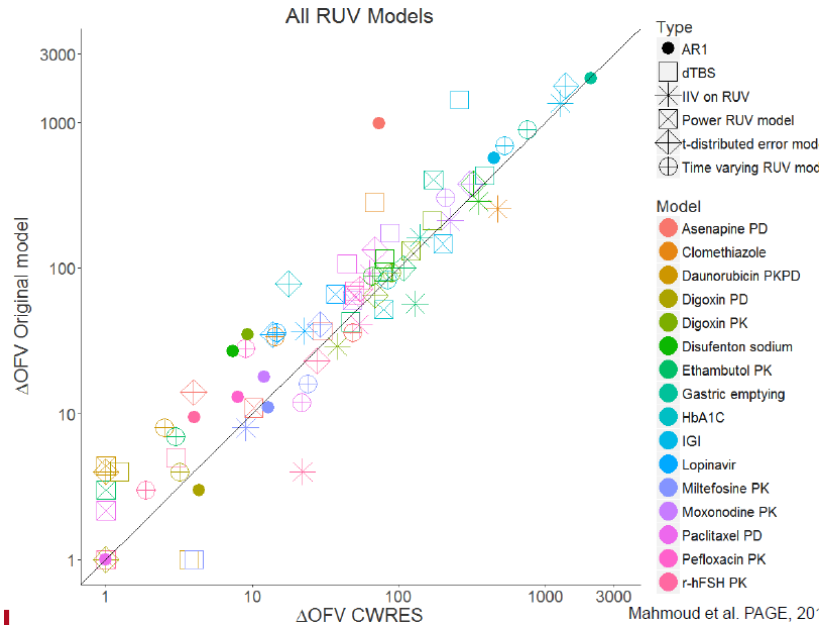




Ibrahim et al. Model-based post-processing of CWRES for assessment of prediction bias P-II-49

Residual variability

- IIV-in-RUV
- Time-varying RUV
- dTBS
- Autocorrelation
- Power
- t-distribution

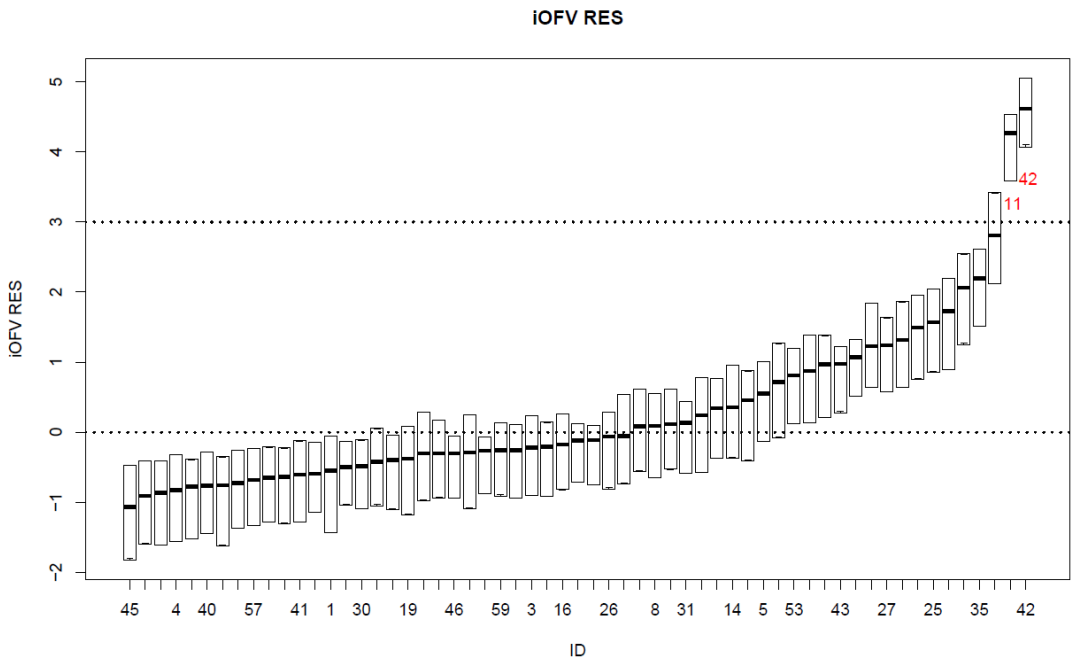


Ibrahim et al. PAGE 2017

Simeval

Outliers

- Individual outliers
- Parameter outliers
- Observation outliers



	Individual level		Observation level
ID	OFV outliers (SD)	EBE NPDE outliers (ETA numbers)	CWRES outliers
11	3.887		
25			1
42	5.587		1
48			1

Largajolli et al, PAGE 2014

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 26, No. 2, 1998

Assumption Testing in Population Pharmacokinetic Models: Illustrated with an Analysis of Moxonidine Data from Congestive Heart Failure Patients

Mats O. Karlsson,[1,4] E. Niclas Jonsson,[1] Curtis G. Wiltse,[2] and Janet R. Wade[3]

Quality assurance

qa run1.mod -parameters=CL,V,KA -cont=AGE,CLCR,WT -cat=SEX,ACE -add_etas=ALAG1

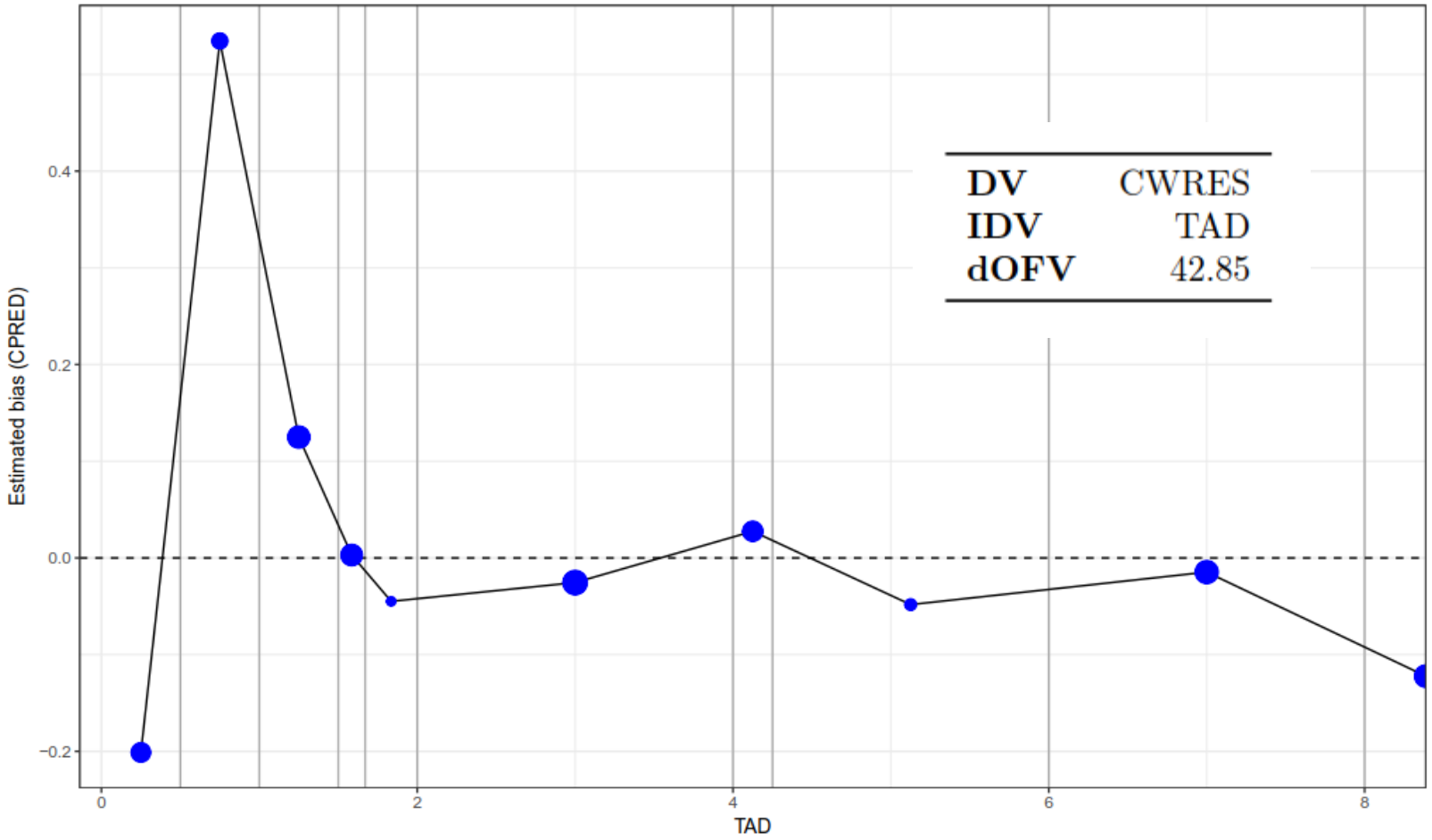
Run started: 2018-05-29 14:56:51

Run finished: 2018-05-29 15:16:14

	OFV
Nonlinear base model	-753.900553826191
Linearized base model before estimation	-753.900553694691
Linearized base model after estimation	-754.904143210669
Sum of individual OFV values	-754.904143210669

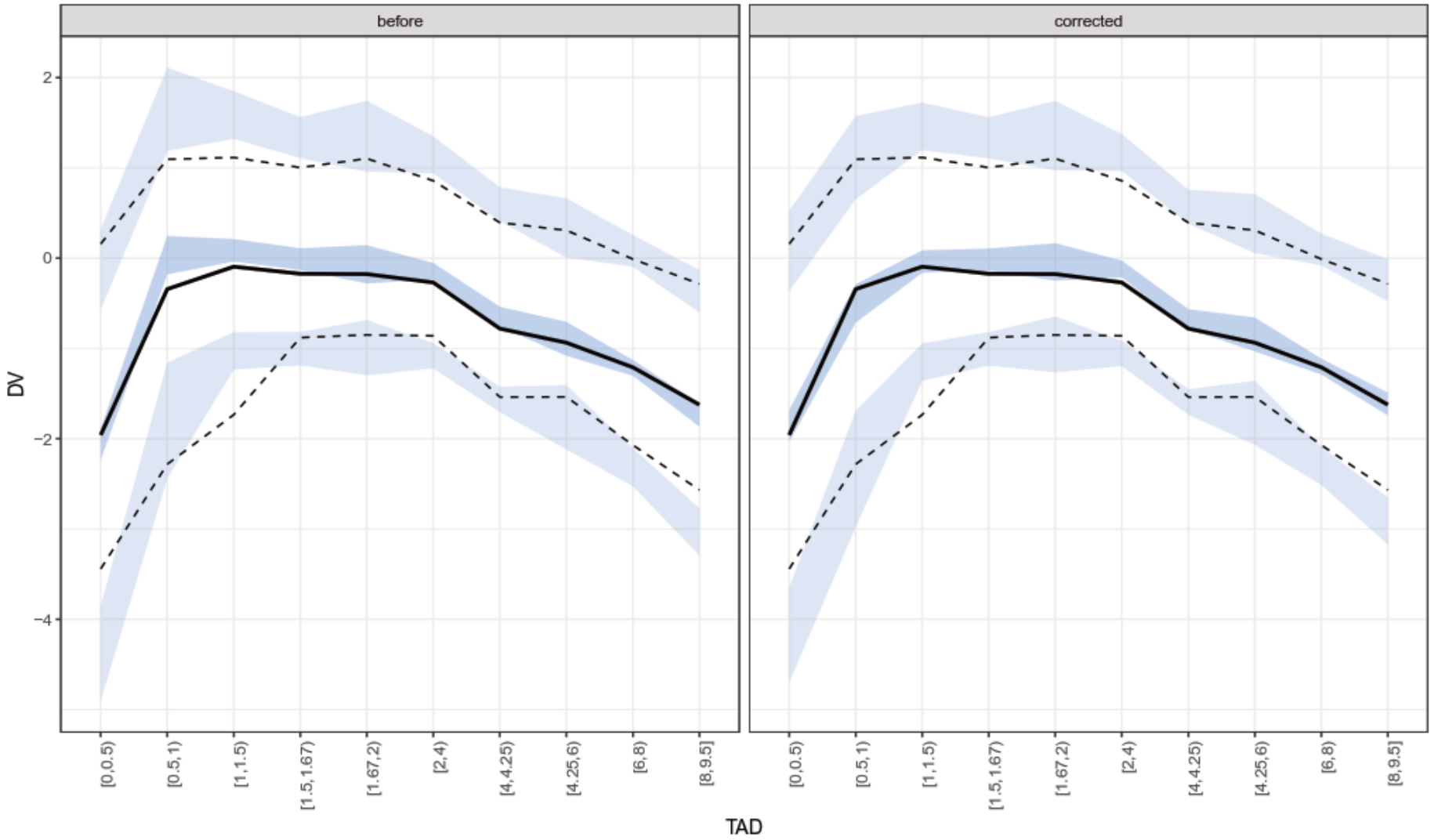
Overview

	dOFV	Additional parameters
Structural Model		
TIME	18.1	9
TAD	42.9	9
PRED	14.2	9
Parameter Variability Model		
Full OMEGA Block	2.6	2
Box-Cox Transformation	22.8	7
Additional ETA	128.0	1
t-distribution	1.4	7
Interoccasion variability	NA	
Covariates		
FREM	40.0	15
CLACE-2	3.0	1
Residual Error Model		
tdist	286.5	1
tad varying	230.7	2
Influential Individuals		
None		
Outliers		
Subject 505	2.4	



Estimated structural bias on the population prediction (CPRED) scale vs. binned time after dose (TAD).

Ibrahim et al. Model-based post-processing of CWRES for assessment of prediction bias P-II-49



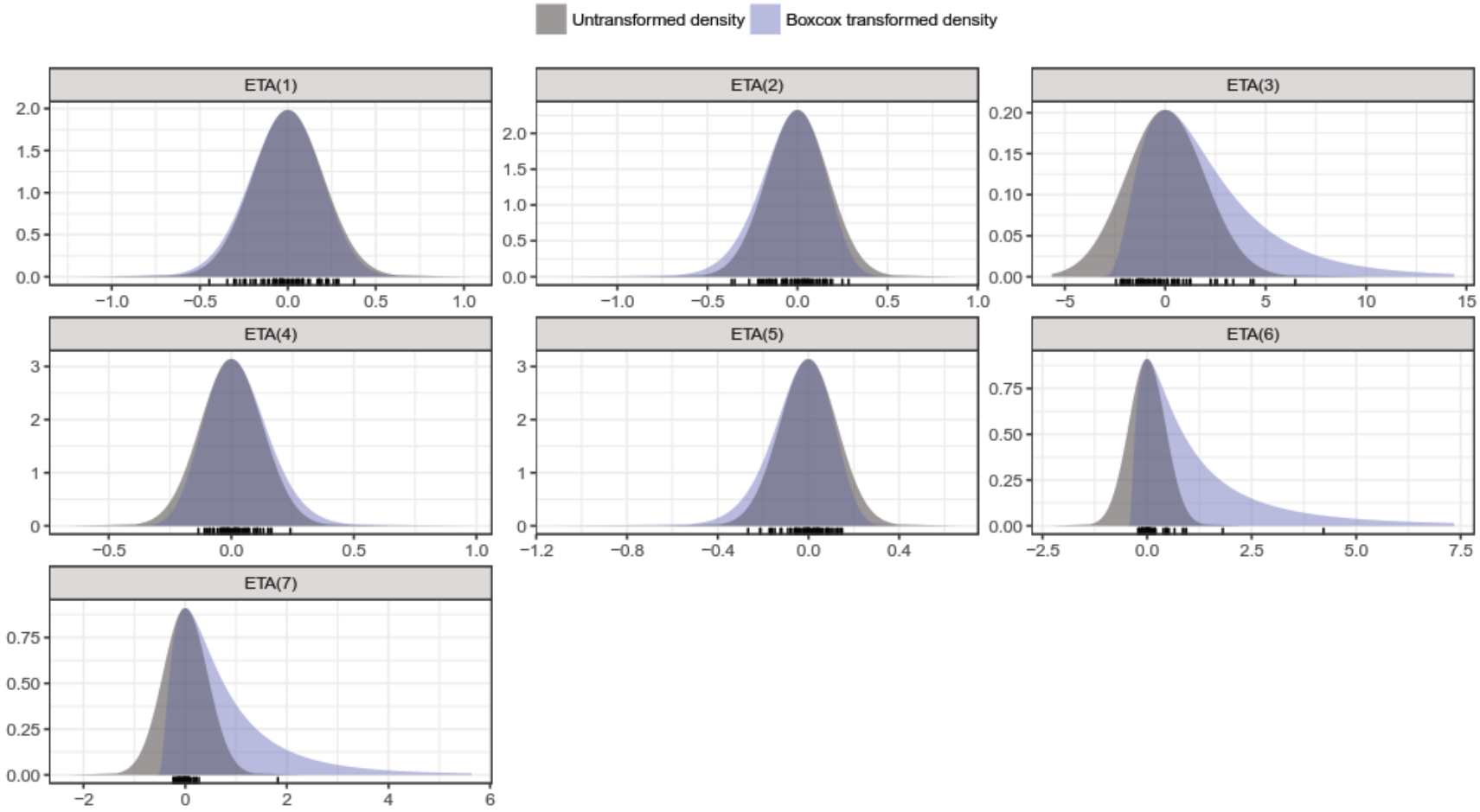
VPC of observations (DV) vs. binned time after dose (TAD) before and after correcting for the estimated structural bias by TAD bin.

Additional etas

	Added	New SD	Old SD
ETA(1)	No	0.21	0.20
ETA(2)	No	0.19	0.15
ETA(3)	No	0.85	1.65
ETA(4)	No	0.14	0.13
ETA(5)	No	0.14	0.13
ETA(6)	No	0.87	0.71
ETA(7)	No	0.87	0.71
ALAG1	Yes	1.97	
dOFV	**128.0**		

Box-Cox Transformation

	Lambda	New SD	Old SD
ETA(1)	-0.32	0.20	0.20
ETA(2)	-0.86	0.17	0.15
ETA(3)	0.29	1.96	1.65
ETA(4)	1.13	0.13	0.13
ETA(5)	-1.46	0.13	0.13
ETA(6)	2.28	0.44	0.71
ETA(7)	1.77	0.44	0.71
dOFV	**22.8**		

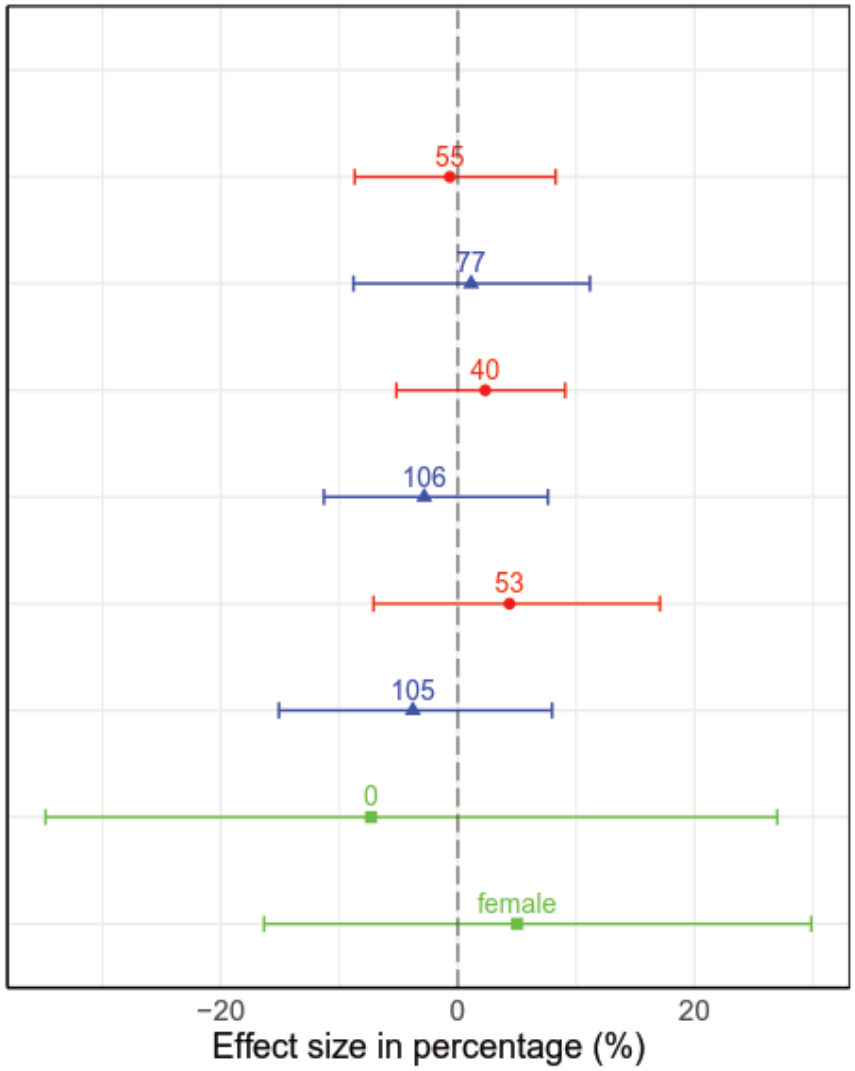


Density of the Box-Cox transformed random effect in comparison with the density of the original (untransformed) random effect. The rug below the densities indicates the empirical Bayes estimates for the transformed random effect.

Covariates

Covariate	dOFV	Coefficient
CLACE-2	2.97	-0.083
CLAGE-4	1.69	-0.004
CLCLCR-4	0.00	0.000
CLSEX-2	0.68	0.047
CLWT-4	0.41	0.001
KAACE-2	0.06	0.110
KAAGE-4	0.10	0.008
KACLCR-4	0.52	0.006
KASEX-2	0.71	-0.456
KAWT-4	1.40	0.015
VACE-2	0.03	-0.009
VAGE-4	0.31	0.002
VCLCR-4	0.31	-0.001
VSEX-2	0.43	-0.037
VWT-4	1.13	-0.002
sum(SCMu)	**10.76**	
FREM	**40.04**	

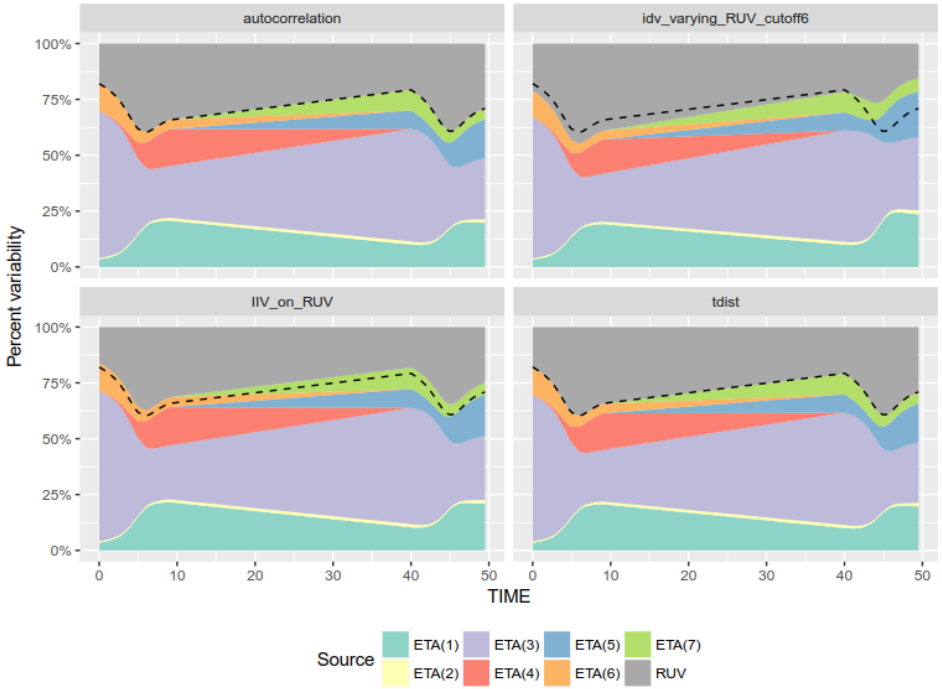
Covariate effects on parameter CL



COVARIATE	MEAN	EXPECTED
AGE	65 years	−0.67 % [−8.7, +8.26]
		+1.13 % [−8.81, +11.2]
CLCR	68 ml/min	+2.32 % [−5.18, +9.07]
		−2.83 % [−11.3, +7.61]
WT	79 kg	+4.37 % [−7.11, +17.1]
		−3.79 % [−15.1, +7.96]
ACE	1	−7.32 % [−34.8, +27]
SEX	male	+5.01 % [−16.4, +29.9]

Residual Error Model

Model	dOFV	Additional parameters	Parameter values
tdist	286.5	1	df=3.070
tad varying	230.7	2	sdeps_0-t0=1.357,sdeps_t0-10=0.651,t0=1.67
IIV on RUV	215.9	1	%CV=42.678
time varying	86.0	2	sdeps_0-t0=1.109,sdeps_t0-50=0.671,t0=41.58
autocorrelation	12.8	1	half-life=0.141

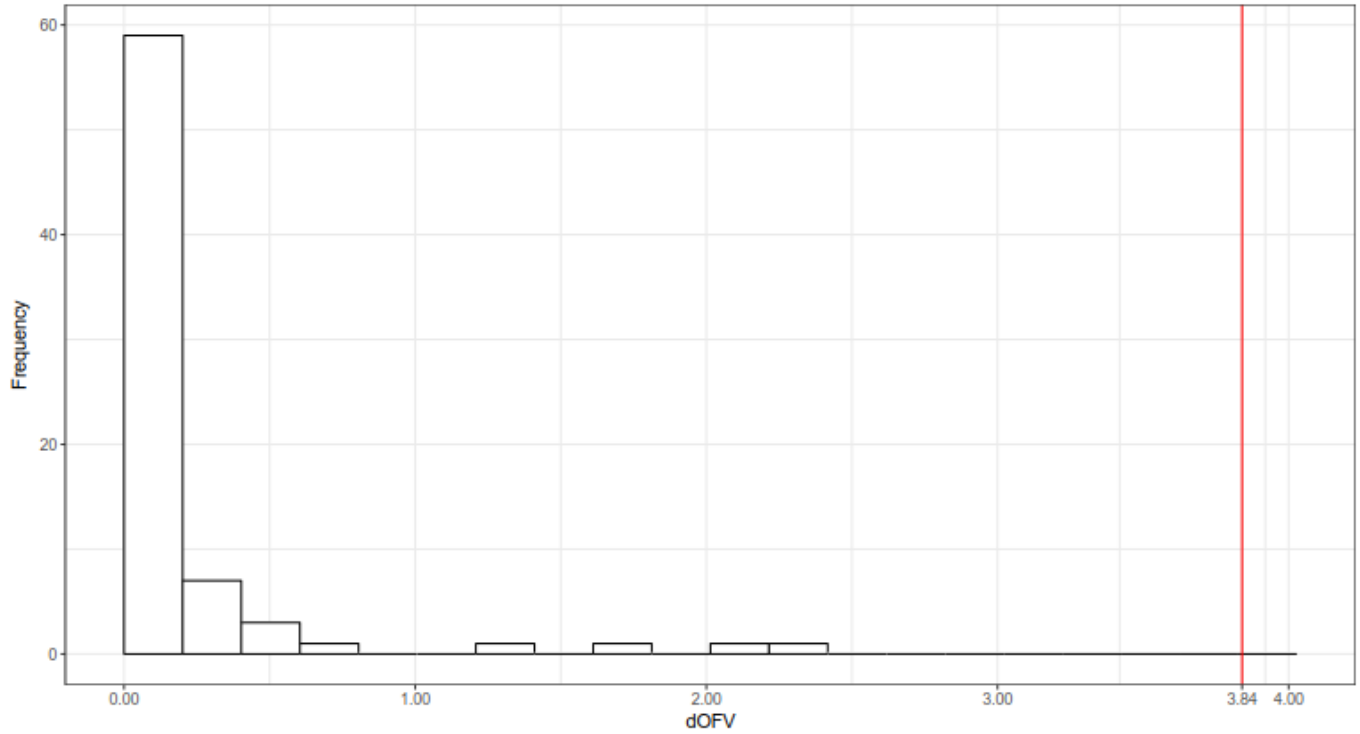


Ueckert et al. Understanding sources of variability: The variability attribution plot; P-II-16

Influential Individuals

No influential individuals detected

Subjects identified as significantly influencing the model fit for all other subjects and their influence in terms of improvement in OFV for other subjects when excluding them during the fit.

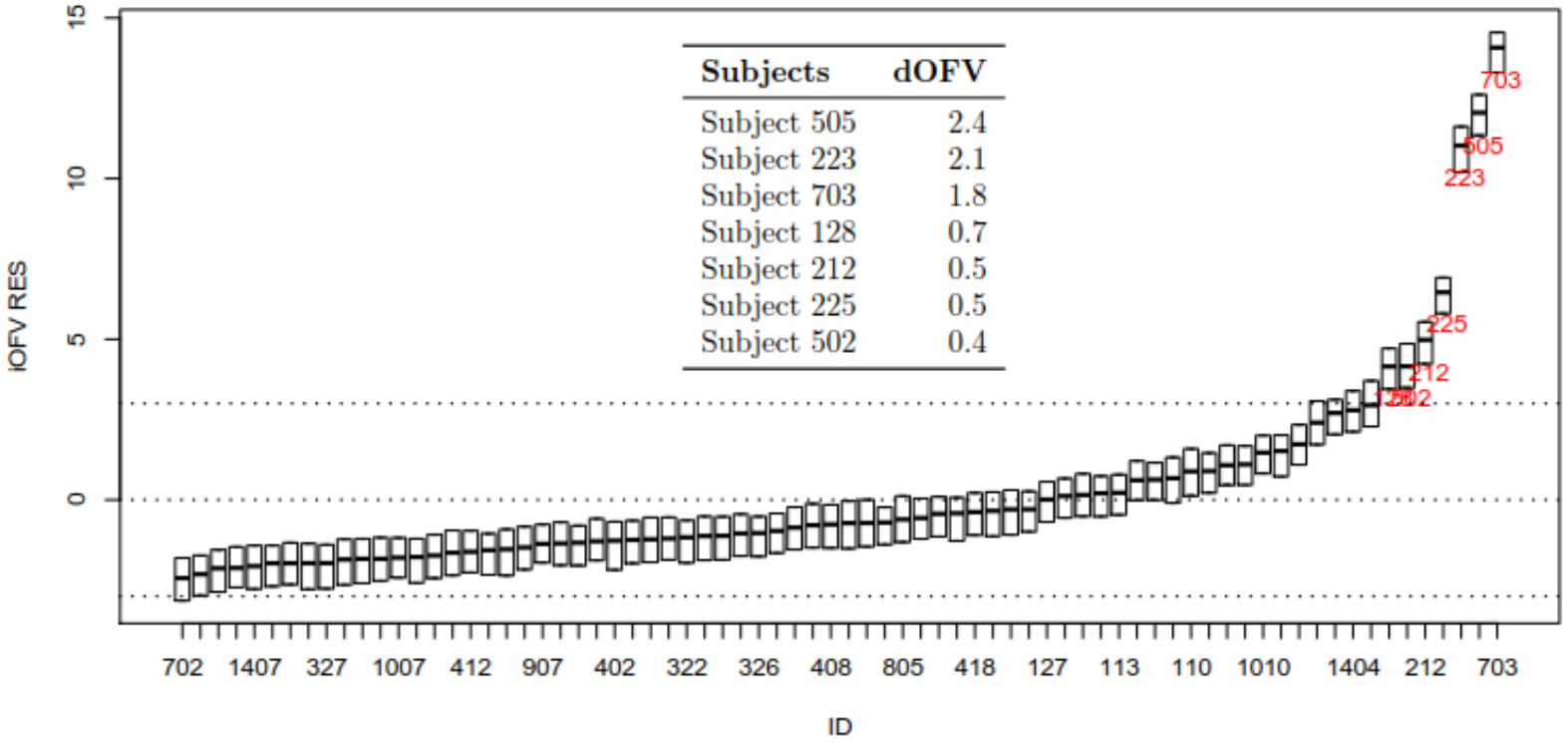


Distribution of OFV improvements (dOFV) when excluding specific subjects during the fit.

Nordgren et al. P-IV-38
Faster methods for case deletion diagnostics: dOFV and linearized dOFV

Outliers

Subjects	dOFV
Subject 505	2.4
Subject 223	2.1
Subject 703	1.8
Subject 128	0.7
Subject 212	0.5
Subject 225	0.5
Subject 502	0.4



Range of deviation of individual OFVs between observed and simulated data for all subjects in standard deviations from the expected fit (iOFV RES). High iOFV RES values indicate subjects for which the model describe the data worse than expected.

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tad varying	230.7	2
Influential Individuals		
None		
Outliers		
Subject 505	2.4	

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QA limitations

- Cannot handle categorical data
- Cannot handle some model types
  - e.g. mixture models, MTIME, …
- Cannot handle all coding practises

Aoki et al. Second order Taylor expansion of likelihood-based models for fast covariate and random effect model building. P-III-05

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Thanks for testing and advice

- Colleagues at Uppsala Pharmacometrics Group and Roche

Dev. Pharmacol. Ther. *8:* 374–383 (1985)

Neonatal Population Pharmacokinetics of Phenobarbital Derived from Routine Clinical Data[1]

Thaddeus H. Grasela, Jr.[a], *Steven M. Donn*[b]

	dOFV	Additional parameters
Structural Model		
TIME	7.7	9
PRED	6.5	9
Parameter Variability Model		
Full OMEGA Block	2.6	1
Box-Cox Transformation	2.2	2
Additional ETA	NA	
t-distribution	0.0	2
Interoccasion variability	NA	
Covariates		
FREM	4.5	4
CLAPGR-4	2.5	1
Residual Error Model		
dtbs	13.9	2
time varying	8.0	2
Influential Individuals		
None		
Outliers		
Subject 42	0.4	