



Effect of Miss-specified Covariance Structures on Estimated Fixed Effect Parameters from Non-Linear Mixed Effects Models for PK Data

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INTRODUCTION

This paper is an extension of the work done by Pfizer statisticians who reported on the effect of miss-specified covariance structures on linear mixed effects models, they showed that using an over-simplified between subject variance structures leads to a marked underestimation of the standard errors of the treatment effect. We are now interested to see if this is true with respect to non-linear mixed effects models which are commonly used pharmacometrics.

METHODS

A computer simulation study is performed using **NONMEM V** to illustrate our goal.

STRUCTURAL MODEL

We simulated drug concentration data from a first order absorption with oral dosing structural model with one compartment disposition and first-order elimination.

$$C_{it} = [D_i \cdot F_i \cdot Ka_i \cdot Ke_i / CL_i (Ka_i - Ke_i)] * [e^{-Ke_i t} - e^{-Ka_i t}]$$

- C_{it} is the concentration of the i th subject at time t
- D is the dose level,
- $Ke = CL/V$, is the elimination rate constant for subject i
- Ka is the absorption rate constant
- CL is the clearance for subject i
- F is the bioavailability for subject i and treatment j .

STATISTICAL MODEL

Statistical model used is an Non-Linear Mixed Effect Model with Additive error structure ,

$$Y_{it} = c_{it} + e_{it}$$

SIMULATION

Simulation study is performed based on the 2 formulation (R, T), two sequence (TRTR, RTRT) four period crossover design.

1000 Dataset each with 24 subjects, 12 per sequence where simulated, with **True Values**, $CL=3.5L/h$, $Ka=.473/h$, $VD=31.5L$, $FR=0.8$, $FT=1.0$.

Dense sampling plan was chosen where, there are 14 samples per subject at time : 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 24 /hr .

Two different types of **Covariance** structures are fit for between subject variability with respect to the random effects to see the effects of Miss-specification.

Block Matrix: Where subjects were allowed to vary between TRT groups and are **correlated**.

Diagonal: Where subjects were allowed to vary between TRT groups and are **uncorrelated**.

Block Matrix (Complex Structure)	Diagonal (Simplified Structure)
$\begin{bmatrix} \sigma_1^2 & \rho\sigma_1\sigma_2 \\ \rho\sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix}$	$\begin{bmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{bmatrix}$

SCENARIO'S

Three different scenarios regarding between subject variability were used for our purpose.

- Data was simulated and analyzed using **NONMEM V**.

SCENARIO	Scenario 1	Scenario 2	Scenario 3
Fixed Effects	Clearance Volume Ka	Clearance Volume	
Random Effects	Bioavailability	Bioavailability Ka	Clearance Volume Ka
Simulated Model	Block Matrix	Block Matrix	Diagonal
Analysis Model (1) Not Miss-specified (N.M)	Block Matrix	Block Matrix	Diagonal
Analysis Model (2) Miss-specified (M.M)	Diagonal	Diagonal	Block Matrix

EVALUATION OF STATISTICAL PERFORMANCE

Statistical performance of these model are now evaluated and compared based on 3 main criterion.

1. STANDARD ERRORS

Estimated standard errors of the PK parameters averaged across all 1000 dataset for the N.M and M.M model for the 3 scenarios are computed.

S.E's obtained from the N.M models are considered as 'Gold – Standards' as their coverage probability was close to nominal (Table 2).

Comparisons are made with respect to the S.E's (N.M vs. M.M). To understand how much effect does miss-specification have on them.

2. COVERAGE PROBABILITIES (C.P)

90% confidence interval ($\hat{\theta} \pm 1.644 * S.E$) are calculated for each of the PK parameters for each dataset.

The S.E's which are used to compute the confidence interval above are the estimates provided from the **NONMEM cov** step.

Coverage probability is calculated as the proportion of 90% confidence interval that correctly brackets the true parameter values for a given scenario.

A correct analysis should provide us with a coverage probability of 90%.

3. BIAS

Bias is calculated as the mean difference in the observed PK estimates averages across 1000 datasets to the 'True Values'.

RESULTS

S.E	SCENARIO 1		SCENARIO 2		SCENARIO 3	
	N.M	M.M	N.M	M.M	N.M	M.M
PARMS						
KA	0.0008	0.0008	0.004	0.004	0.006	0.006
CL	4.36	0.32	9.05	0.37	0.02	0.03
VD	39.25	2.96	41.51	3.40	1.95	3.06
F1	1.25	0.11	2.60	0.13	Fixed	
F2	1.03	0.08	2.06	0.093	Fixed	

Table 1 (Comparing Standard Errors): Compares the average estimated Standard Errors obtained using the true model to the estimated model for the 3 scenarios.

For Scenario 1 and 2, we can see that there is a drastic reduction (upto 80%) of the average estimated standard errors for the M.M models for all PK parameters when compared to the N.M model standard errors.

There is an increase in the S.E's for 'volume' under the M.M model for scenario 3.

C.P	SCENARIO 1		SCENARIO 2		SCENARIO 3	
PARMS	N.M	M.M	N.M	M.M	N.M	M.M
KA	92	91	88	87	70	77
CL	85	17	78	15	88	91
VD	85	18	78	15	88	90
F1	83	21	71	20	Fixed	
F2	85	19	79	16	Fixed	

Table 2 (Comparing Coverage Probabilities):

Compares the coverage probability obtained using the N.M model to the M.M model for the 3 scenarios.

We notice that the coverage for the N.M model is close to 90% for all the 3 scenarios. Validating that the estimated S.E's with respect to the N.M model are correct and can be used now as the 'Gold-Standard'.

There is a drop in the coverage probability for 'Volume', 'Clearance' and 'Bioavailability' with respect to miss-specified models for scenario 1 and 2.

Thereby suggesting that the S.E's are too small to cover the true estimates.

Scenario 3, we see that the C.P has increased slightly for N.M model when compared to the M.M model suggesting that it might do slightly better under miss-specification.

BIAS	SCENARIO 1		SCENARIO 2		SCENARIO 3	
PARMS	N.M	M.M	N.M	M.M	N.M	M.M
KA	.009	.008	.004	.002	.5	.3
CL	21	21	21	21	0.23	0.32
VD	22	21	21	22	0.64	0.54
F1	21	22	22	21	Fixed	
F2	21	21	21	21	Fixed	

Table 3 (Comparing Bias): Percent Reduction/Increase [(Obs-True)/Obs] is calculated.

We notice that there is a slight bias for the estimates of our parameters, but Magnitude of percent Increase/Reduction for the PK parameter estimates is much smaller when compared to the magnitude of reduction of their S.E's.

We can conclude that the drop in coverage for the miss-specified (for cases 1 and 2) models can be contributed mainly due to underestimated Standard errors rather than the Bias.

CONCLUSIONS

If the model is correctly specified we see that the standard errors are appropriately estimated, and we achieve a coverage close to 90%.

Miss-specification of covariance structures did affect the outcome when bioavailability was the random effect in the model, resulting in the drastic underestimation of the standard errors of clearance and volume.

Scenario 3 might seem to suggest that using a block matrix (M.M model) for the between subject variability might perform better compared to a diagonal structure (N.M), but be leave this for further investigation.