The Effect of Collinearity on Parameter Estimates in Nonlinear Mixed Effect Models

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Received December 18, 1998; accepted January 29, 1999

Purpose. To demonstrate how correlations among predictor variables in a population pharmacokinetic model affect the ability to discern which covariates should enter into the structural pharmacokinetic model.

Methods. Monte Carlo simulation was used to generate multiple-dose concentration-time data similar to that seen in a Phase III clinical trial. The drugs' pharmacokinetics were dependent on two covariates. Five data sets were simulated with increasing correlation between the two covariates. All data sets were analyzed using NONMEM both with and without inclusion of the covariates in the structural pharmacokinetic model. Summary measures for ill-conditioning and sensitivity analysis were used to examine how increasing correlation among covariates affects the accuracy and precision of the parameter estimates.

Results. When covariates were included in the structural pharmacokinetic model and the correlation between covariates increased, the standard error of the parameter estimates increased and the value of parameter estimates themselves became increasingly biased. When the correlation between predictor variables was 0.75, the standard errors of the parameter estimates were too large to declare statistical significance.

Conclusions. Correlations among predictor variables greater than 0.5 when entered into the model simultaneously should be a warning to researchers because the (1) the accuracy of the parameter estimates themselves may be biased and (2) the precision of the estimates may be inflated due to ill-conditioning.

KEY WORDS: NONMEM; regression diagnostics; sensitivity analysis; reformulation; validation

INTRODUCTION

One goal for nonlinear mixed effect modeling is to identify covariates that are predictors for pharmacokinetic parameters and to incorporate these covariates into the population model in a manner that yields good predictive power for future observations. A general modeling process was outlined by Maitre *et al.* (1) and expanded upon by Mandema *et al.* (2). A key element in these approaches is the filtering of covariates that have no relationship to the parameters of interest. Common screening methods include multiple linear regression (MLR), generalized additive models (GAMs)[3], or to skip the linear model screening step and proceed directly to nonlinear model development, the idea being that model development will screen out unimportant variables.

Often the predictor variables themselves are ignored during the model building process. It is common knowledge that correlation among the covariates in linear regression will affect the precision of the regression parameter estimates, possibly leading to parameter estimates that are artificially statistically non-significant (3). This effect is referred to as collinearity[4] and is due to the inherent instability of inverting a near singular matrix. When two correlated covariates enter into a linear model simultaneously, compared to the case where either variable is entered in the model alone, one or more of the following may occur: (1) one or more of the regression parameter estimates becomes statistically non-significant, (2) one or more of the regression parameter estimates exhibit a sign change that may or may not be physically possible, or (3) the parameter estimates associated each covariate differ substantially. Collinearity can also affect parameter estimates in the nonlinear mixed effect model building process when covariates are entered into the structural pharmacokinetic model. The purpose of this article is to demonstrate how the correlation between covariates can affect the parameter estimates reported by a nonlinear mixed effect modeling software package.

Theory for Nonlinear Models

Consider the general nonlinear model:

$$Y_i = f(X_i, \hat{\theta}) + e_i \quad i = 1, 2, \ldots n \tag{1}$$

where Y_i is the ith response associated with a px1 vector of parameter estimates $\hat{\theta}$ and predictor variables X_i and e_i is normally distributed random error with mean 0 and variance σ^2. One common method to estimate the variance of $\hat{\theta}$ is from the diagonal elements of

$$\text{Var}(\hat{\theta}) = \sigma^2[J^T J]^{-1} = \sigma^2\left[\left(\frac{\partial}{\partial\theta_1}, \ldots \frac{\partial}{\partial\theta_p}\right)^T \left(\frac{\partial}{\partial\theta_1}, \ldots \frac{\partial}{\partial\theta_p}\right)\right]^{-1},$$

where J is the gradient matrix. Collinearity arises from two sources: model collinearity and data collinearity. Model based collinearity arises when the columns of J are correlated with each other. A classic example of model collinearity is found with the E_{max} pharmacodynamic model in which E_{max} is conditionally linear on EC_{50} (4). Parameters that are conditionally linear on other parameters will have correlated parameter estimates because one or more columns in J can be expressed as a (near) linear combination of other columns in J. Another type of collinearity is data-based collinearity wherein there is a high degree of correlation among predictor variables. This is not an issue with the models with a single predictor variable. Consequently collinearity will be due solely to the model. However when X is an nxq matrix of predictor variables that enter into the structural model and one or more columns of X can be written as a near linear combination of any other column in X, then the columns of J will be correlated indirectly as a result of X entering into the model. With population pharmacokinetic models, both model-based and data-based collinearity

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[3] Collinearity also affects the ability of GAMs to model the underlying functional relationship (20). At least in the MLR case, diagnosis and correcting for collinearity has been addressed (3), whereas no such diagnostics have been reported for GAMs. It is not the purpose of this paper to examine the effect of collinearity of GAMs but its adverse effects needed to be pointed out.

[4] Collinearity is also referred to as multicollinearity or ill-conditioning.

0724-8741/99/0500-0709$16.00/0

can occur simultaneously, unless of course no covariates are included in the structural model, in which case only model-based collinearity can occur.

The adverse effects of collinearity manifest primarily in affecting the parameter estimates and their standard errors. When the predictors are uncorrelated, the values of the parameter estimates remain unchanged regardless of any other predictor variables included in the model. When the predictors are correlated, the value of a regression parameter depends on which other parameters are entered into the model and which others are not, i.e., it destroys the uniqueness of the parameter estimate. Thus, when collinearity is present "*a regression coefficient does not reflect any inherent effect of the particular predictor variable on the response variable but only a marginal or partial effect, given whatever other correlated predictor variables are included in the model*" (5). Correlation between predictor variables in and of itself does not mean that a good fit cannot be obtained nor does that predictions of new observations are poorly inferred, provided the inferences are made within the sample space of the data set upon which the model was derived. What it means is that the estimated regression coefficients tend to widely vary from one data set to the next. During drug development there may be many different clinical trials in different populations, if the same variables are collected in these studies and they are correlated with each other, the situation may occur wherein one analysis identifies a particular covariate as being important, but another analysis using a different data set does not.

Matrix instability may occur during the inversion of the J^TJ matrix, such that small changes in J lead to large changes in the parameter estimates and their standard errors. In NONMEM (6) two matrices are computed in calculating the covariance matrix: S, the sum of S_j matrices calculated for each individual where S_j is equal to J^TJ evaluated at the final parameter estimates and R, the matrix of partial second derivatives evaluated at the final parameter estimates. Assuming that the errors are normally distributed, as the sample size increased towards infinity, then R and S converge to the same matrix and the inverse of either estimates the covariance matrix. If normality is not assumed (the default option with NONMEM) the matrix $R^{-1}SR^{-1}$ is used to compute the covariance matrix. Collinearity increases the degree of instability in inverting R and S.

Summary Measures for Ill-Conditioning and Collinearity

A variety of summary measures are available for assessing the degree of collinearity in a linear regression, most of which actually reflect the degree of instability in inverting the X'X matrix. Similar measures can be applied to nonlinear regression. For example, Magel and Hertsgaard (7) used variance decomposition proportions (3) and the condition number of J^6J to assess the instability of nonlinear regression parameter estimates. Of interest in NONMEM is the stability in inverting the R and/or *S* matrices since these are the matrices that are inverted in the default case for estimating the covariance matrix (6).

All matrix inversions are dependent on the determinant of the matrix and the square root of the determinant is a general measure of the overall "volume" of a matrix. The square root of the determinant ranges from 0 when the columns of the matrix are perfectly correlated to 1 when the columns are uncorrelated. Thus the square root of the determinant of the R matrix may be a useful summary measure. However, the determinant, denoted $|\cdot|$, is extremely sensitive to scaling such that $|\alpha A| = \alpha_p|A|$, e.g., a 10 fold change in A results in a 10_p-fold change in the determinant of A (8). NONMEM limits the format of the output to exponential notation with four places, two of which are behind the decimal. Hence, attempting to determine the determinant of the R matrix is risky business in general, but especially so with NONMEM output.

An alternative is to examine ρ, the pxp correlation matrix. All the information contained in R is contained in ρ. Also, the ρ matrix outputted by NONMEM is of sufficient precision that it can be worked on with little rounding error. Thus it is a better measure of stability than R. The index number of ρ, IN, is defined as

$$IN = \sqrt{\frac{l_1}{l_p}} \tag{2}$$

where l_1 and l_p are the largest and smallest eigenvalues of ρ (9). Related to the index number is simply the ratio of the largest and smallest eigenvalue. A matrix that is ill-conditioned has a large index number whereas a matrix that is well-conditioned has a index number near one. Gleason and Staelin (10) proposed the Redundancy Number to quantify the degree of collinearity:

$$\varphi = \sqrt{\frac{\sum_{i=1}^{p} l_i^2 - p}{p(p-1)}} \tag{3}$$

where l_i is the ith eigenvalue of the correlation matrix. φ ranges from 0 when the columns of ρ are uncorrelated to 1 when the columns are perfectly correlated. Kullback (11) presented the Information Statistic, *I*, defined as:

$$I = -\frac{1}{2}\ln(|\rho|) \tag{4}$$

and the Divergence Statistic, *D*, defined as:

$$D = \sum_{i=1}^{p} \frac{1 - l_i}{2l_i}. \tag{5}$$

Both *I* and *D* range from 1 when all the columns are uncorrelated to ∞ when the columns are perfectly correlated. These statistics fail to identify which columns are collinear and simply indicate that collinearity is present (3). If multicollinearity is present wherein a function of one or more columns is collinear with a function of one or more other columns, then these statistics will fail to identify that collinearity. Also, there has been no research as to at what point does a summary measure indicate "significant collinearity". Regardless of these problems (some of which may be remedied), they are useful tools for comparing data sets.

Belsley and Oldford (12) proposed using sensitivity analysis to determine how collinearity can affect the resulting parameter estimates. They propose adding small alterations to the predictor variables and examining how this affects the resulting parameter estimates. Then using Monte Carlo simulation and repeating this process many times, plotting the parameter estimates against each other can be used as a diagnostic to indicate

Table 1. Summary Statistics for Pharmacokinetic Parameters and Covariates Generated by Monte Carlo Simulation

	Theoretical value	Correlation between covariates				
		0	0.25	0.5	0.75	0.95
Clearance (L/h)	Log-Normal Distribution					
Mean	100	106	107	107	107	107
Standard Deviation		57	57	57	57	57
CV (%)	50	54	54	54	53	54
Min		22	22	22	22	22
Median		94	94	94	93	94
Max		394	396	397	400	403
Volume of Distribution (L)	Log-Normal Distribution					
Mean	400	460	460	460	460	460
Standard Deviation		252	252	252	252	252
CV (%)	50	54	55	55	55	55
Min		90	89	90	89	90
Median		400	400	400	400	400
Max		1879	1879	1879	1879	1879
Absorption Rate Constant (Ka, h^{-1})	Log-Normal Distribution					
Mean	0.80	0.81	0.81	0.81	0.81	0.81
Standard Deviation		0.08	0.08	0.08	0.08	0.08
CV (%)	10	9	9	9	9	9
Min		0.61	0.61	0.61	0.61	0.61
Median		0.81	0.81	0.81	0.81	0.81
Max		1.06	1.06	1.06	1.06	1.06
Covariate #1 (X_1)	Log-Normal Distribution					
Mean	145	145	145	145	145	145
Standard Deviation		36	36	36	36	36
CV (%)	25	24	24	24	24	24
Min		33	33	33	33	33
Median		142	142	142	142	142
Max		257	257	257	257	257
Covariate #2 (X_2)	Normal Distribution					
Mean	28	29	28	28	28	28
Standard Deviation		4.5	4.4	4.4	4.2	4.2
CV (%)	15	16	16	15	15	15
Min		17	17	17	17	19
Median		28	28	28	28	28
Max		46	48	47	48	45

how instability in one parameter can lead to instability in another.

Example

Five data sets were simulated using a one-compartment model with absorption. Drug (40 mg) was given daily for 10 days. Pharmacokinetic parameters and covariates were simulated with the following characteristics,

$$F = 1$$

$$Cl \sim LN(100\ L/h,\ 50\%\ CV)$$

$$V_d \sim LN(400\ L,\ 50\%\ CV)$$

$$K_a \sim LN(0.8\ h^{-1},\ 10\%\ CV)$$

$$\text{Height } (X_1) \sim LN(145\ cm,\ 25\%\ CV)$$

$$\text{Age } (X_2) \sim N(28\ yr.,\ 15\%\ CV)$$

where LN and N indicate log-normal and normal distribution, respectively, and CV is coefficient of variation. Correlation between pharmacokinetic parameters and covariates was defined as:

$$\rho = \begin{array}{c} \\ Cl \\ V_d \\ K_a \\ X_1 \\ X_2 \end{array} \begin{array}{c} \begin{array}{ccccc} Cl & V_d & K_a & X_1 & X_2 \end{array} \\ \begin{bmatrix} 1 & 0.7 & 0 & 0.3 & 0.25 \\ & 1 & 0 & 0 & 0 \\ & & 1 & 0 & 0 \\ & & & 1 & r \\ & & & & 1 \end{bmatrix} \end{array},$$

where r is the correlation between X_1 and X_2, which varied from 0 to 0.95. Random deviates were generated using the method of Johnson (13).

Five-hundred (500) subjects were simulated with two to four plasma samples collected at random time intervals after drug administration anywhere between day 1, time 0 to day 11, time 0. This sampling scheme simulated the situation where a patient can simply walk in and have their blood drawn without an appointment. The sample collection time was recorded and exact. The analytical assay had a constant CV of 7.5% and a limit of quantification of 0.1 ng/ml. Samples less than the LOQ

Table 2. Correlation Among Variables Generated Using Monte Carlo Simulation

	Cl	V_d	Ka	Cov1	Cov2
Correlation between X_1 and X_2 = 0					
Cl	1.000	0.586	0.078	0.291	0.209
V_d		1.000	0.008	−0.091	−0.060
Ka			1.000	0.079	0.048
X_1				1.000	−0.059
X_2					1.000
Correlation between X_1 and X_2 = 0.25					
	Cl	Vd	Ka	Cov1	Cov2
Cl	1.000	0.585	0.078	0.296	0.214
V_d		1.000	0.008	−0.091	−0.074
Ka			1.000	0.079	0.056
X_1				1.000	0.180
X_2					1.000
Correlation between X_1 and X_2 = 0.50					
	Cl	V_d	Ka	Cov1	Cov2
Cl	1.000	0.585	0.078	0.301	0.223
V_d		1.000	0.008	−0.095	−0.086
Ka			1.000	0.079	0.063
X_1				1.000	0.432
X_2					1.000
Correlation between X_1 and X_2 = 0.75					
	Cl	Vd	Ka	Cov1	Cov2
Cl	1.000	0.584	0.078	0.307	0.239
V_d		1.000	0.008	−0.090	−0.093
Ka			1.000	0.079	0.070
X_1				1.000	0.703
X_2					1.000
Correlation between X_1 and X_2 = 0.95					
	Cl	Vd	Ka	Cov1	Cov2
Cl	1.000	0.584	0.078	0.312	0.260
V_d		1.000	0.008	−0.091	−0.090
Ka			1.000	0.079	0.075
X_1				1.000	0.936
X_2					1.000

Note: Correlation between Cl and Vd = 0.7. Correlation between Cl and X_1 = 0.30. Correlation between Cl and X_2 = 0.25. Values in Bold indicate significantly different from zero.

were defined as missing. Each data set was simulated using PROC IML in SAS® (14).

The data were analyzed with NONMEM, version 4 (6). The structural base model was a one-compartment model with absorption. Cl, V_d, and K_a were modeled assuming a log-normal distribution and residual error was modeled with a constant CV error structure. Cl was modeled with

$$Cl = \theta(1) * X_1 + \theta(2) * X_2$$

and without covariates in the structural model

$$Cl = \theta(1).$$

Each of the five data sets (with r = 0, 0.25, 0.5, 0.75, and 0.95) was fit using the same model. NONMEM could not estimate the correct covariance structure using an unstructured covariance matrix so a diagonal covariance structure was assumed. Inter-subject variability on K_a could not be adequately modeled so this was removed from the model. For each data set all of the summary measures for ill-conditioning were calculated to assess the stability of the parameter estimate. All calculations were done using Gauss 3.2 (15).

The method of Belsley and Oldford (12) was also applied to the data. Uniform random error of ±5 cm and ±2 yr. were added to X_1 and X_2, respectively, and the data reanalyzed. This process was repeated 30 times. Scatter plots and whisker plots were generated to examine the conditional and marginal distribution of the eta's, respectively.

RESULTS

Tables 1 and 2 show the summary statistics and correlations between variables for the five data sets, respectively, and indicate that the data sets generated have the sampling characteristics defined *a priori*. Note that the only real difference between the data sets was due to the correlation between X_1 and X_2. Table 3 shows a summary of the NONMEM output without using the covariates in the model. Parameter estimates were near their theoretical values, but were not exact, with clearance tending to be underestimated, and K_a and V_d overestimated. Inter-subject variability was near the true value, but residual error was higher than theoretical values. There was no difference among parameter estimates or objective function values for the five data sets.

Table 3 shows a summary of the NONMEM output without using the covariates in the model. The parameter estimates were near the theoretical values for all five data sets but were not exact. In all five cases, clearance tended to be underestimated, and Ka and V_d overestimated. The intersubject variability was near the true value, but residual error was higher than theoretical values. There was no difference among parameter estimates or objective function values for the five data sets.

Table 4 shows a summary of the NONMEM output with covariates included in the model. There was a distinct trend that as the correlation between X_1 and X_2 increased (1) the standard errors of parameter estimates increased and (2) the value of the parameter estimates themselves decreased for θ(1), whereas θ(2), θ(3) and θ(4) increased. When the correlation between covariates was 0.75 or greater, θ(1) was not statistically different than zero. There was no change in inter-subject variability, but there was a slight increase in residual error as the correlation between X_1 and X_2 increased.

Table 5 shows the summary measures for the data sets with and without covariate inclusion. Without covariates in the model there was little change in the summary measures as the correlation between covariates increased. There was evidence that some degree of instability in matrix inversion was occurring, but to what degree was unclear. When clearance was modeled as a function of the covariates, all summary statistics showed that collinearity dramatically increased as the correlation increased. The least and most sensitive statistic appeared to be Redundancy Number and the condition number, respectively. However, the Redundancy Number was the only statistic that was monotonically increasing with increasing correlation between covariates.

Figures 1–3 show the results of the sensitivity analysis. Fig. 1 is a whisker plot of the marginal distribution of the theta's (θ) as a function of the correlation between X_1 and X_2. Only the distribution of θ(4), the θ related to K_a, was unaffected by the correlation between X_1 and X_2. Surprisingly, the mean

Table 3. NONMEM Output Without Using Covariates in Model

	Correlation between covariates				
	0.00	0.25	0.50	0.75	0.95
Number of Iterations	26	25	25	27	25
Objective Function	6699.8	6696.8	6703.4	6698.6	6697.6
Parameter Estimates (Standard Error)					
Clearance = θ(1) * exp(eta(1))	82.6 (2.23)	82.6 (2.23)	82.7 (2.22)	82.7 (2.21)	82.7 (22.0)
V_d = θ(2) * exp(eta(2))	495 (21)	495 (21)	495 (20.8)	495 (20.7)	495 (20.7)
K_a = θ(3)	1.16 (0.104)	1.15 (0.104)	1.15 (0.104)	1.15 (0.103)	1.15 (0.102)
Inter-Individual Variance (CV%)					
Eta(1) = Clearance	0.206 (48)	0.206 (48)	0.206 (48)	0.207 (48)	0.207 (48)
Eta(2) = V_d	0.260 (54)	0.261 (54)	0.261 (54)	0.263 (55)	0.264 (55)
Eta(3) = K_a	0.215 (49)	0.216 (49)	0.218 (49)	0.222 (50)	0.230 (51)
Residual Error Variance (CV%)	0.0288 (17)	0.0286 (17)	0.0286 (17)	0.0283 (17)	0.0279 (17)

Table 4. NONMEN Output with Covariates Included in Model

	Correlation between covariates				
	0.00	0.25	0.50	0.75	0.95
Number of Iterations	31	27	33	35	38
Objective Function	6319.2	6390.7	6488.9	6567.0	6670.9
Parameter Estimates (Standard Error)					
Clearance = f(θ(1), θ(2), X_1, X_2) * exp(eta(1))					
θ(1)	0.236 (0.072)	0.235 (0.082)	0.208 (0.098)	0.158 (0.122)	0.166 (0.109)
θ(2)	1.87 (0.345)	1.86 (0.394)	1.98 (0.475)	2.22 (0.594)	2.15 (0.528)
V_d = θ(3)	459 (19)	466 (19.8)	475 (21.4)	483 (23.6)	493 (28.1)
Ka = θ(4)	1.12 (0.097)	1.13 (0.098)	1.14 (0.103)	1.16 (0.109)	1.19 (0.120)
Inter-Individual Variance (CV%)					
Eta(1) = Clearance	0.175 (44)	0.177 (44)	0.178 (44)	0.177 (44)	0.172 (43)
Eta(2) = Volume of Distribution	0.249 (53)	0.253 (45)	0.253 (45)	0.249 (53)	0.237 (52)
Residual Error Variance (CV%)	0.0298 (17)	0.0299 (17)	0.0312 (18)	0.0328 (18)	0.0359 (19)

Note: Clearance Modeled as θ(1) * X_1 + θ(2) * X_2. Values in Bold indicate value equal to zero using 95% confidence interval approach.

Table 5. Summary Statistics Based on Correlation Matrix

Data set without covariates	Correlation between covariates				
Statistic	0	0.25	0.5	0.75	0.95
Redundancy Number	0.379	0.376	0.374	0.373	0.372
Index of Matrix	4.623	4.572	4.500	4.488	4.424
Square Root(Determinant)	0.202	0.207	0.210	0.211	0.213
Information Statistic	1.598	1.576	1.560	1.555	1.547
Divergence Statistic	5.4	5.3	5.2	5.2	5.1
Condition Number	21	20	20	20	20
Data set with covariates	Correlation between covariates				
Statistic	0	0.25	0.5	0.75	0.95
Redundancy Number	0.373	0.429	0.447	0.475	0.495
Index of Matrix	6.175	17.008	20.123	23.452	18.820
Square Root(Determinant)	0.193	0.051	0.041	0.033	0.036
Information Statistic	1.647	2.967	3.192	3.417	3.325
Divergence Statistic	7.3	45.6	61.0	77.9	49.9
Condition Number	38	289	405	550	354

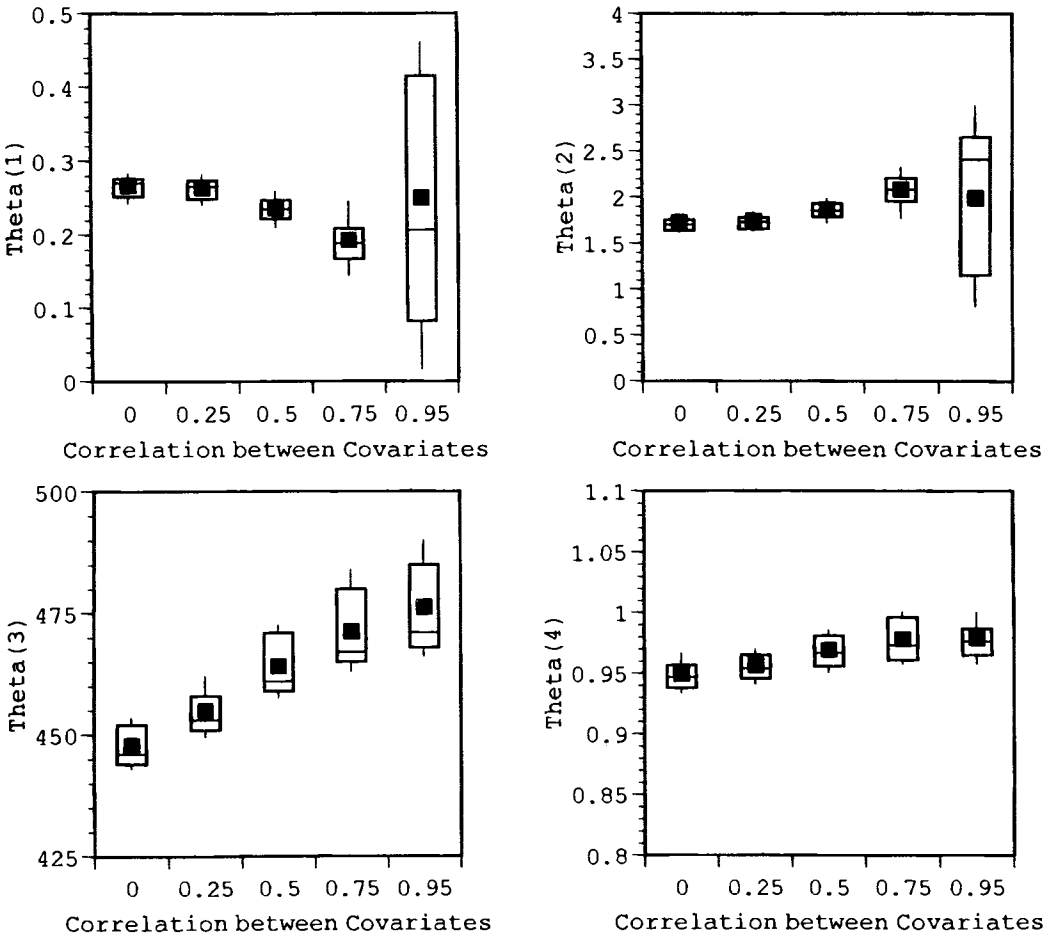

Fig. 1. Whisker plot of the marginal distribution of the theta's as a function of the correlation between X_1 and X_2. Each (x, y) datapoint was generated using Monte Carlo simulation (n = 30) wherein ±5 and ±2 units uniformly distributed random error was added to X_1 and X_2, respectively. The lowest, middle, and second highest, and highest box points represent the 10th, 25th, 75th, and 90th quartile. Means are represented by symbols. Legend: Cl = $[\theta(1)X_1 + \theta(2) *X_2] *\exp(\text{eta}(1))$, $V_d = \theta(3) *\exp(\text{eta}(2))$, $K_a = \theta(4)$.

values obtained with Monte Carlo simulation were closer to the theoretical value of 0.8 h^{-1} than the original data set was with $\theta(4) \sim 1.2\ h^{-1}$. For the remaining theta's, as the correlation between X_1 and X_2 increased so did their respective CVs. When the correlation between X_1 and X_2 was 0.75, the CV of the theta's had doubled relative to when X_1 and X_2 were uncorrelated. However, when the correlation between X_1 and X_2 was less than or equal to 0.50, the CV of the theta's was relatively stable. There was little change in the mean value of $\theta(2)$ as the correlation between X_1 and X_2 increased, but the mean value of $\theta(1)$ fluctuated as the correlation between X_1 and X_2 increased. There was also a distinct trend that as the correlation between X_1 and X_2 increased so did the mean of $\theta(3)$, the θ associated with volume of distribution, getting further and further removed from the true value of 400 L. Thus even when the covariates did not enter into the function for V_d, their presence significantly influenced the mean and variance of the eta associated with V_d. Figs. 2 and 3 show the correlation matrix between the theta's expressed as a scatter plot matrix when the predictor variables were uncorrelated and when the correlation between X_1 and X_2 was 0.75, respectively. Both Figures clearly show a significant correlation between all the theta's regardless of the correlation between the predictor variables. Correlation between the theta's even when the covariates were uncorrelated indicated that model collinearity influenced the final value of the parameter estimates. Sensitivity analysis was able to identify which of the theta's were affected by model based collinearity and showed that when there was a high degree of collinearity between predictors, small changes in the predictor variables can lead to large changes in the parameter estimates.

DISCUSSION

The purpose of this study was to examine how correlation among covariates affects the accuracy and precision of NONMEM parameter estimates. These results show that two types of collinearity may be present in any nonlinear mixed effects model: model-based and data-based collinearity. Both modes of collinearity affect the point estimate itself and variance of estimates. This should not be surprising given that as X_1 and X_2 became more and more correlated, they began to measure the same variable. Sensitivity analysis of the predictor variables

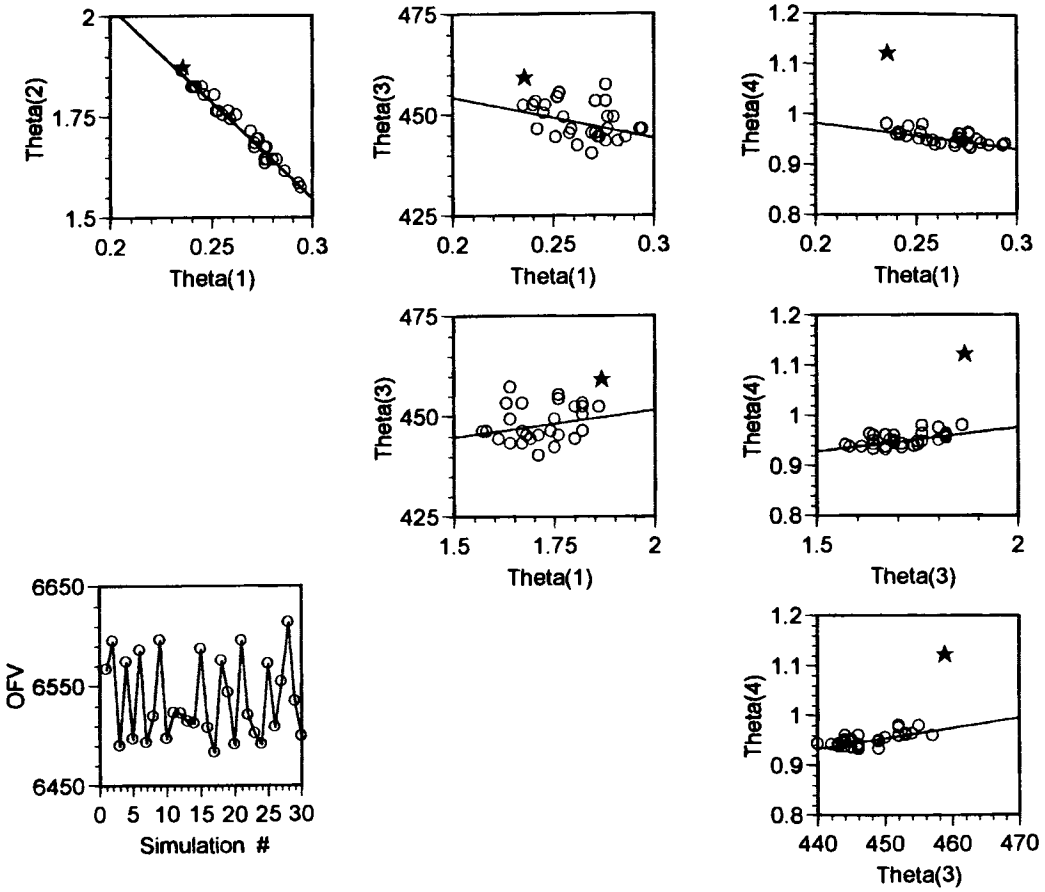

Fig. 2. Scatter plot matrix of correlation between eta's when the covariates were uncorrelated. Each (x, y) datapoint was generated using Monte Carlo simulation (n = 30) wherein ±5 and ±2 units uniformly distributed random error was added to X_1 and X_2, respectively. The star indicates the original value of the eta's. The lower left plot shows the objective function for each Monte Carlo iteration. Legend: Cl = [θ(1) X_1 + θ(2) *X_2] *exp(eta(1)), V_d = θ(3) *exp(eta(2)), K_a = θ(4).

indicated that when the correlation among covariates was large (approximately greater than 0.5) small changes in the predictor variables lead to large changes in the parameter estimates making their final values unreliable. When the correlation between X_1 and X_2 was 0.75, the parameter estimate associated with X_1 became statistically non-significant.

Sensitivity analysis offers a convenient method to determine which parameter estimates are affected by collinearity and how changes in one parameter may lead to changes in another parameter. This diagnostic demonstrated that, even though X_1 and X_2 appeared in the structural model through θ(1) and θ(2), respectively, the correlation between them influenced not only θ(1) and θ(2), but θ(3) as well. The fact that increasing correlation affected θ(3) is suggestive of model-based collinearity. Surprisingly, Monte Carlo sensitivity analysis produced parameter estimates nearer the true value associated with K_a than did the original data set. It would appear prudent to use this technique as part of the model validation process to ensure that parameter estimates are stable to small changes in the covariates.

Various summary measures were presented which summarized the degree of instability in the matrix inversion. All of these statistics, except the Information statistic which requires calculation of the determinant of the correlation matrix, can be computed by hand directly from NONMEM output. Although increasing collinearity did not lead to a monotonic increase in ill-conditioning as indicated by the summary measures, the results clearly show that as the correlation between two covariates increased to above 0.5, numerical stability in the parameter estimates became an issue.

What was not discussed in this paper is once collinearity has been identified in a model, how do you remove it? That question remains to be answered and further research is needed before one becomes available. One possible solution to remove model-based collinearity is the reformulating approach suggested by Simonoff *et al.* (16,17). However, for data-based collinearity only speculation can be made at this time. One approach may be to use techniques used in the linear case, such as ridge regression (5), or to use some type of principal components transformation (9). Another solution might be to transform correlated covariates into a single composite vector thereby eliminating one source of collinearity. For example, height and weight could be transformed to body surface area (18) or body mass index (19).

This study was limited to the case of two covariates showing a high degree of correlation. Future research should examine how a small to moderate degree of correlation ($\rho<0.4$) among a large number of covariates affects the parameter estimates.

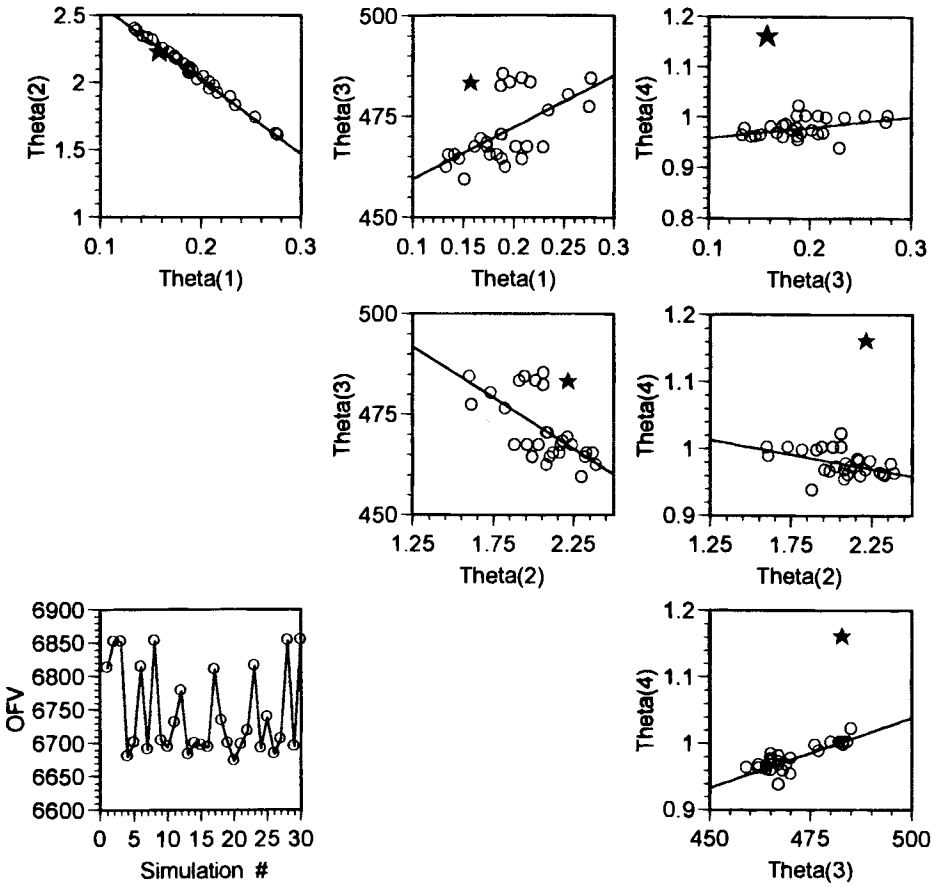

Fig. 3. Scatter plot matrix of correlation between eta's when the correlation between covariates was 0.75. Each (x, y) datapoint was generated using Monte Carlo simulation (n = 30) wherein ±5 and ±2 units uniformly distributed random error was added to X_1 and X_2, respectively. The star indicates the original value of the eta's. The lower left plot shows the objective function for each Monte Carlo iteration. Legend: Cl = [θ(1) X_1 + θ(2) *X_2] *exp(eta(1)), V_d = θ(3) *exp(eta(2)), K_a = θ(4).

Other areas include how collinearity affects the precision of parameter estimates such that the analyst can gauge how the observed model compares to a model that has absolutely no collinearity. In summary, these results indicate that population pharmacokinetic analysis should involve greater analysis of the predictor variables prior to their introduction into the structural pharmacokinetic model. The bottom line is that models which include covariates showing a high degree of correlation, greater than 0.5, when included in the model at the same time may indicate that one or both are not relevant to the structural model even when in fact they are.

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