Detecting a Random Component in a Two Compartment Model: An Independent Random Effects Simulation Study

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Abstract

The coefficient of variations (CV) of each individual estimate and for all possible combinations of the estimates are used to see which parameters should be random in a nonlinear mixed effects model. From the difference of exponentials model simulations, when only one parameter is random, the sample CV of the corresponding estimate will be the highest rank and its mean is close to the population CV. When more than two independent random effects are considered, the corresponding sample CV of the individual estimate equally shares the highest and the mean of each individual CV estimate and their combinations are close to the population CV. An example on isolated perfused porcine skin flaps data is also presented and the multivariate coefficient of variation was applied to indicate which parameter appears to be random. The optimum solution agrees with other model selection criteria, e.g., AICC, AIC, or BIC.

Keywords: compartment model, difference of exponentials model, fixed parameter approach, multivariate coefficient of variation, nonlinear mixed effects model

1. Introduction and Motivation

A nonlinear mixed effects model is often used to model repeated-measures response data. In these types of studies, one is usually interested in estimating the underlying population response curve. Since individuals are randomly sampled from the population as a whole, the parameters could be considered as random effects.

Budsaba and Smith [1] proposed an approximate F statistics test from the fixed parameter approach, which compares the residual sum of squares from the full model and the reduced model, to test whether random effects are needed. From the difference of exponentials model simulations, the test offers very good results.

To choose which parameters should have random effects in a nonlinear mixed effects model, Pinheiro et al. [2] start with all parameters as mixed effects and then examine the eigenvalues of the estimated variance-covariance matrix. If one, or more, are close to zero, then the associated eigenvector(s) would then give an estimate of the linear combination of the parameters that could be considered as fixed.

The strategy we suggest here for determining the random effects in a non linear mixed effects model is to use the sample coefficient of variation of each individual estimate ($\mathrm{CV}(\hat{\theta})$) and CV for all possible combinations of the estimates. CV for more than one estimator will be defined later and denoted by $\mathrm{CV}(\hat{\theta}_1,\ldots,\hat{\theta}_k)$. For example, if a model has 3 parameters, A, b, and d, we calculate $\mathrm{CV}(\hat{A})$, $\mathrm{CV}(\hat{b})$, $\mathrm{CV}(\hat{d})$, $\mathrm{CV}(\hat{A},\hat{b})$, $\mathrm{CV}(\hat{A},\hat{d})$, $\mathrm{CV}(\hat{b},\hat{d})$, and $\mathrm{CV}(\hat{A},\hat{b},\hat{d})$. We expect that $\mathrm{CV}(\hat{A})$ will have the highest value when A is the only random parameter in the model. Similarly, $\mathrm{CV}(\hat{b})$ or $\mathrm{CV}(\hat{d})$ will have the highest value when only b or d, respectively, is a random parameter in the model. When two

or more random parameters are in the model, we want to investigate the performance of those CVs under certain conditions, e.g., CV($\hat{A}$), CV($\hat{b}$), and CV($\hat{A},\hat{b}$) will have the highest value when both A and b are random.

The motivation of using the sample CV of an estimator to detect the corresponding random parameter after the significance of the approximate F test can be considered as follows:

Suppose in a single factor balanced ANOVA model II,

$$y_{ij} = \mu_i + \varepsilon_{ij}$$

where μ_i are independent $N(\mu_.,\sigma_\mu^2)$,

ε_{ij} are independent $N(0_.,\sigma^2)$,

μ_i and ε_{ij} are independent random variables, i = 1,...,k groups and j = 1,...,n replications.

From this model, $\overline{Y}_{i.}$ is an estimator of the random parameter μ_i. The expectation and variance of $\overline{Y}_{i.}$ is as follows:

$$E(\overline{Y}_{i.}) = \mu_.$$

$$V(\overline{Y}_{i.}) = \sigma_\mu^2 + \frac{\sigma^2}{n}$$

Hence, the population CV($\overline{Y}_{i.}$) is defined by:

$$\text{CV}(\overline{Y}_{i.}) = \frac{(\sigma_\mu^2 + \frac{\sigma^2}{n})^{1/2}}{\mu}$$

The population CV($\overline{Y}_{i.}$) can be estimated by the sample CV($\overline{Y}_{i.}$) which is defined by:

$$\text{CV}(\overline{Y}_{i.}) = \frac{[\sum_{i=1}^{k}(\overline{Y}_{i.} - \overline{Y}_{..})^2/(k-1)]^{1/2}}{|\overline{Y}_{..}|}$$

Hence the usual F statistics can be stated in term of the sample CV($\overline{Y}_{i.}$) as follows:

$$\text{F} = [n(\overline{Y}_{..})^2 CV^2(\overline{Y}_{i.})] \text{ /MS (Within Group)}$$

We can see that the larger the value of sample $CV^2(\overline{Y}_{i.})$, the larger the value of F. If the null hypothesis is false, the noncentral parameter [3] of F is:

$$\phi = n\frac{\sum_{i=1}^{k}(\mu_{i.} - \mu_{..})^2}{\sigma^2} \qquad (1)$$

The term $\sum_{i=1}^{k}(\mu_{i.} - \mu_{..})^2$ in (1) can be estimated by $(\overline{Y}_{..})^2$ (k–1) $CV^2(\overline{Y}_{i.})$, and then the larger the value of $CV^2(\overline{Y}_{i.})$, the larger the value of ϕ. Hence the sample CV of the estimator of a random parameter can be used as an index to determine whether the parameter is random after the significance of an F test. The same idea can also be applied in a nonlinear mixed effects model.

2. Multivariate Coefficient of Variation

Some CV-like methods for k samples have been reported in the literature. These include the arithmetic mean of standard deviation over the grand mean, the CV based on variation within samples (the square root of the error mean square from an analysis of variance over the grand mean), and the CV based on variation among samples (the square root of the added variance component among samples in an analysis of variance over the grand mean) [4]. The pooled coefficient of variation across samples for homogeneity of variance test (Bartlett's test) is defined by $[\sum_{i=1}^{k} f_i(CV_i)^2/f]^{1/2}$, where f_i is the degrees of freedom of sample i and f is the total degrees of freedom, and other pooled coefficients (e.g. $C\overline{R}V$) [5].

Chow and Tse [6] investigated estimators for the common CV for a balanced k sample in bioavailability/ bioequivalence studies. The arithmetic mean of CV, the pooled CV as in [5], the least square regression function of S_i and $\overline{Y}_i$, the moment estimator under one-way random effects model, etc, were compared asymptotically.

For the multivariate case, the literature is lacking. We use the univariate CV as an expansion to the multivariate variables. The proposed multivariate coefficient of variation is defined as:

$$CV(Y_1,\ldots,Y_k) = \{\frac{1}{k}(\mu_1,\ldots,\mu_k)\{Cov(Y_1,\ldots,Y_k)\}^{-1}(\mu_1,\ldots,\mu_k)^T\}^{-\frac{1}{2}}$$

For example:

$$\upsilon(Y_1,Y_2) = \{\frac{1}{2}(\mu_1,\mu_2)\{Cov(Y_1,Y_2)\}^{-1}((\mu_1,\mu_2)^T\}^{-\frac{1}{2}}$$

$$\upsilon(Y) = \{(\mu)^2\{Var(Y)\}^{-1}\}^{-\frac{1}{2}}$$
$$= \sigma/\mu$$

Note that when $(Y_1,\ldots,Y_k)$ are mutually independent, the reciprocal of the mutivariate CV squared is the arithmetic mean of each univariate reciprocal CV squared.

The sample coefficient of variation for k random variables $(Y_1,\ldots,Y_k)$ is then given by:

$$CV(Y_1,\ldots,Y_k)=\{\frac{1}{k}(\bar{Y}_1,\ldots,\bar{Y}_k)\{\hat{Cov}(Y_1,\ldots,Y_k)\}^{-1}(\bar{Y}_1,\ldots,\bar{Y}_k)^T\}^{-\frac{1}{2}}$$

For example:

$$CV(Y_1,Y_2) = \{\frac{1}{2}(\bar{Y}_1,\bar{Y}_2)\{\hat{Cov}(Y_1,Y_2)\}^{-1}(\bar{Y}_1,\bar{Y}_2)^T\}^{-\frac{1}{2}}$$

$$\mathrm{CV}(Y) = \{(\bar{Y})^2\{\hat{Var}(Y)\}^{-1}\}^{-\frac{1}{2}}$$
$$= S/\bar{Y}$$

Similar to the population value, when $(Y_1,\ldots,Y_k)$ are mutually independent, the reciprocal of the sample mutivariate CV squared is the arithmetic mean of each sample univariate reciprocal CV squared.

3. Simulation Study

To see the performance of the proposed sample CV, the multivariate sample CV is calculated. The simulation is based on the model:

$$y_{ij} = A_i\{exp(-b_i t_{ij}) - exp(-d_i t_{ij})\} + \varepsilon_{ij}, \quad (2)$$
$$i = 1,\ldots,8;\ j = 1,\ldots,23$$

where A_i is Normal with mean 1.5, and b_i and d_i are normal with mean 0.0065 and 0.044 respectively. The random effects are independent in this preliminary study. The independent normal random variables ε_{ij} have mean zero and four choices of variance, i.e. V_0 = 5.50287 × 10^{-6}, 10 × V_0, 100 × V_0, and 1000 × V_0. These error terms are also independent of random effects. The model and its parameters including the approximate value of the error terms variance were generated based on a porcine skin flaps experiment. With these scenarios and several choices of the coefficients of variation (CV) of the random effects across individuals, 1,000 Monte Carlo replications were realized at time (t_{ij}) = {0, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480}.

The model (2) we propose for the flux rate profile of the porcine flaps experiment is the difference of exponentials model [7]. This model is a compartment model. Compartment models are commonly used in pharmacokinetics, where the exchange of materials in biological systems is studied. A system is divided into compartments, and it is assumed that the rates of flow of drugs between compartments follow first order kinetics, so that the rate of transfer to a receiving compartment is proportional to the concentration in the supplying compartment. The transfer coefficients, which are assumed constant with respect to time, are called rate constants.

The reciprocal of a rate constant is called a time constant. Our model has two constant rates (b and d). We also assume that d ≥ b. Since d is greater than b, this model can be considered as a two compartment model with a faster absorption constant rate than elimination constant rate. A is mathematically explained as a function of b, d, and an initial unobservable quantity of the supplying compartment. This model allows the response to be zero at time zero.

At each replication of 1,000 Monte Carlo runs, sample CV of all subsets of the estimates were obtained and ranked by ascending order. We investigated the sample CV of these estimates when all parameters are fixed, and for all possible combinations of independent random effects (one, two, or three random parameters) with several choices of the error variance, i.e. $V_0 = 5.50287\times10^{-6}$, $10\times V_0$, $100\times V_0$, and $1000\times V_0$. Error terms are also independent of the random effects. Three choices of υ, the population CV of each random effects across individuals, i.e. .01, .05, and .10 were studied. These CV values (.01, .05 and .10) were chosen according to the pilot porcine skin flaps experiment.

Table 1. shows the result when all parameters are fixed. CV $(\hat{d})$ is about 90% of the time in the highest rank for all choices of the error variance except for the error variance $1000\times V_0$, which is about 85%. This means that when all parameters are fixed, CV$(\hat{d})$ is more likely to have the highest value.

Presence of random effects are considered in Tables 2, 3, 4, and 5. Each table presents results of simulations for several values of υ (the population CV of each random independent effect) and when one, two, or all three of the effects are random with the error variance of V_0 = 5.50287 × 10^{-6}, $10\times V_0$, $100\times V_0$, and $1000\times V_0$, respectively.

At V_0 (Table 2), when only one parameter is random, we observe that at least 98% of the time, the corresponding CV will be the highest. When the error variance is increased from 10 times to 1000 times V_0 in Tables 3-5, we observe that to attain the highest rank, usually the population CV (υ) of the random parameter should increase correspondingly.

When only two independent random parameters are considered at V_0 (Table 2), the corresponding sample CVs of estimators are the highest rank (about 50% for each individual estimate). For example, when A and b are independent random parameters, we observe that CV($\hat{A}$) and CV($\hat{b}$) are the highest, 50% of the time when υ = .01. Similar results were obtained when υ = .05 or υ = .10, and when A and d, or b and d are random parameters.

When the error variance is increased to $10\times V_0$ (Table 3), $100\times V_0$ (Table 4), and $1000\times V_0$ (Table 5), to attain the highest value of the corresponding CVs of estimators, the population CV (υ) of each random parameter has to be increased also.

If all parameters are independently random at variance level V_0 (Table 2), CV($\hat{A}$), CV($\hat{b}$) and CV($\hat{d}$) share the highest rank with the amount being 31-35% of the time (υ = .10). To see this pattern, when the error variance increases, the population CV of each random parameter has to increase (e.g. υ = .05 in Table 3).

Figures 1- 3 show the means of the sample CV of the estimator(s) at the error variance V_0 when the population CV of each independent random effect is, respectively, .01, .05, and .10. In each figure, the means of CV of the estimator(s) when all parameters are fixed, is shown at the upper left corner. For this error variance, means of CV of the estimator(s) under fixed effects are all within the dashed septagon for all values of υ (.01, .05, and .10), then we can see the pattern of the sample CV of the estimator(s) clearly. For example, when only one random effect is considered, the mean of the sample CV of the corresponding estimator is highest and close to the population CV. When both A and b are independent random, the mean of CV($\hat{A}$), CV($\hat{b}$), and CV($\hat{A},\hat{b}$) are all highest and close to the population CV. When all parameters are independently random, all means of the sample CV are close to the population CV.

At the error variance $10 \times V_0$, means of CV of the estimator(s) under fixed effects are all within the dashed septagon when the population CV = .05 and .10. Then, we can see the same pattern as for the case when the error variance is V_0 for the population CV = .05 and .10 only. Similar results were obtained when the error variance is $100 \times V_0$. The mean of CV of the corresponding estimator(s) is highest and close to the population CV when the population CV is .05 and .10. It is also clearer when the population CV = .10 than when the population CV = .05.

When the error variance is $1000 \times V_0$, we cannot see this pattern anymore since under the fixed effects model, all means of CV of estimator(s) are not inside the dashed septagon.

Table. 1 The proportion of times that the sample CV of the estimator(s) has the highest value when all parameters are fixed and Var(ε_{ij}) = $5.50287 \times 10^{-6} = V_0$.

	V_0	$10 \times V_0$	$100 \times V_0$	$1000 \times V_0$
CV($\hat{A}$)	.011	.012	.017	.075
CV($\hat{b}$)	.086	.087	.086	.080
CV($\hat{d}$)	.903	.901	.897	.845
CV($\hat{A},\hat{b}$)	.000	.000	.000	.000
CV($\hat{A},\hat{d}$)	.000	.000	.000	.000
CV($\hat{b},\hat{d}$)	.000	.000	.000	.000
CV($\hat{A},\hat{b},\hat{d}$)	.000	.000	.000	.000

Table. 2 The proportion of times that the sample CV of the estimator(s) has the highest value at different population CV (υ) and Var(ε_{ij}) = $5.50287 \times 10^{-6} = V_0$.

Random Effect(s)		υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.981	1.00	1.00
b	CV($\hat{b}$)	.980	1.00	1.00
d	CV($\hat{d}$)	.996	1.00	1.00
A,b	CV($\hat{A}$)	.503	.515	.515
	CV($\hat{b}$)	.497	.485	.485
A,d	CV($\hat{A}$)	.476	.528	.527
	CV($\hat{d}$)	.524	.472	.473
b,d	CV($\hat{b}$)	.469	.528	.527
	CV($\hat{d}$)	.531	.472	.473
A,b,d	CV($\hat{A}$)	.307	.342	.346
	CV($\hat{b}$)	.280	.317	.314
	CV($\hat{d}$)	.431	.341	.340

Table. 3 The proportion of times that the sample CV of the estimator(s) has the highest value at different population CV (υ) and Var(ε_{ij}) = $10 \times V_0$.

Random Effect(s)		υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.460	1.00	1.00
	CV($\hat{d}$)	.504	.000	.000
b	CV($\hat{b}$)	.476	.999	1.00
	CV($\hat{d}$)	.521	.001	.000
d	CV($\hat{d}$)	.953	1.00	1.00
A,b	CV($\hat{A}$)	.299	.507	.510
	CV($\hat{b}$)	.318	.493	.490
A,d	CV($\hat{A}$)	.271	.511	.521
	CV($\hat{d}$)	.715	.489	.479
b,d	CV($\hat{b}$)	.292	.503	.552
	CV($\hat{d}$)	.703	.497	.478
A,b,d	CV($\hat{A}$)	.173	.331	.351
	CV($\hat{b}$)	.176	.301	.303
	CV($\hat{d}$)	.651	.368	.346

Table. 4 The proportion of times that the sample CV of the estimator(s) has the highest value at different population CV (υ) and Var(ε_{ij}) = $100 \times V_0$.

Random Effect(s)		υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.065	.763	.978
	CV($\hat{b}$)	.074	.014	.000
	CV($\hat{d}$)	.861	.223	.022
b	CV($\hat{b}$)	.132	.753	.978
	CV($\hat{d}$)	.857	.246	.022
d	CV($\hat{b}$)	.078	.015	.002
	CV($\hat{d}$)	.895	.970	.997
A,b	CV($\hat{A}$)	.051	.445	.501
	CV($\hat{b}$)	.122	.443	.499
A,d	CV($\hat{A}$)	.060	.394	.472
	CV($\hat{b}$)	.079	.002	.000
	CV($\hat{d}$)	.861	.604	.528
b,d	CV($\hat{b}$)	.126	.383	.471
	CV($\hat{d}$)	.859	.617	.529
A,b,d	CV($\hat{A}$)	.055	.241	.308
	CV($\hat{b}$)	.093	.224	.278
	CV($\hat{d}$)	.852	.535	.414

Table. 5 The proportion of times that the sample CV of the estimator(s) has the highest value at different population CV (υ) and Var(ε_{ij}) = $1000 \times V_0$.

Random Effect(s)		υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.081	.199	.473
	CV($\hat{b}$)	.079	.053	.030
	CV($\hat{d}$)	.840	.748	.497
b	CV($\hat{b}$)	.088	.188	.451
	CV($\hat{d}$)	.840	.746	.504
d	CV($\hat{d}$)	.840	.867	.910
	CV($\hat{b}$)	.079	.057	.025
A,b	CV($\hat{A}$)	.086	.169	.341
	CV($\hat{b}$)	.080	.148	.292
	CV($\hat{d}$)	.834	.683	.367
A,d	CV($\hat{A}$)	.090	.189	.303
	CV($\hat{b}$)	.080	.045	.013
	CV($\hat{d}$)	.830	.766	.684
b,d	CV($\hat{b}$)	.086	.154	.270
	CV($\hat{d}$)	.834	.777	.687
A,b,d	CV($\hat{A}$)	.076	.135	.216
	CV($\hat{b}$)	.079	.096	.167
	CV($\hat{d}$)	.845	.769	.617

4. An Example

We applied the method we propose to the methyl salicylate data (MS). 400 $\mu g / cm^2$ of $^{14}C - MS$ in ethanol were topically applied to 8 isolated perfused porcine skin flaps and experiments terminated at 8 hrs. Perfusate was collected over time (5,10,20,30,45,60,75,90,105,120 minutes and then every 30 minutes until termination of the experiment). Perfusate flux profiles were fitted to an exponential difference model,

$y_{ij} = A_i(\exp(-b_i t_{ij}) - \exp(-d_i t_{ij})) + \varepsilon_{ij}$. We performed the statistics test from 5 flaps for the final analysis since three flaps are outliers. Prior to analysis, time was converted to hours and percent of dose was multiplied by 100.

The individual estimates are shown in Table 6.

Table. 6 Parameter estimates for each flap of 8 hr. MS data.

Flap	$\hat{A}$	$\hat{b}$	$\hat{d}$
1	1.0516	0.3007	3.6095
2	1.6230	0.3397	3.2220
3	1.7346	0.4414	10.1435
4	1.7642	0.3076	5.6908
5	1.7109	0.2978	9.4859

The approximate F statistics test is 18.419 with p-value close to 0 since $F_{(.95,12,100)}$ =1.850. The result suggests that a random effects model is needed for these data under model assumptions.

Model selection to see which pararmeter should be considered random by using the multivariate coefficient of variation is presented in Table 7.

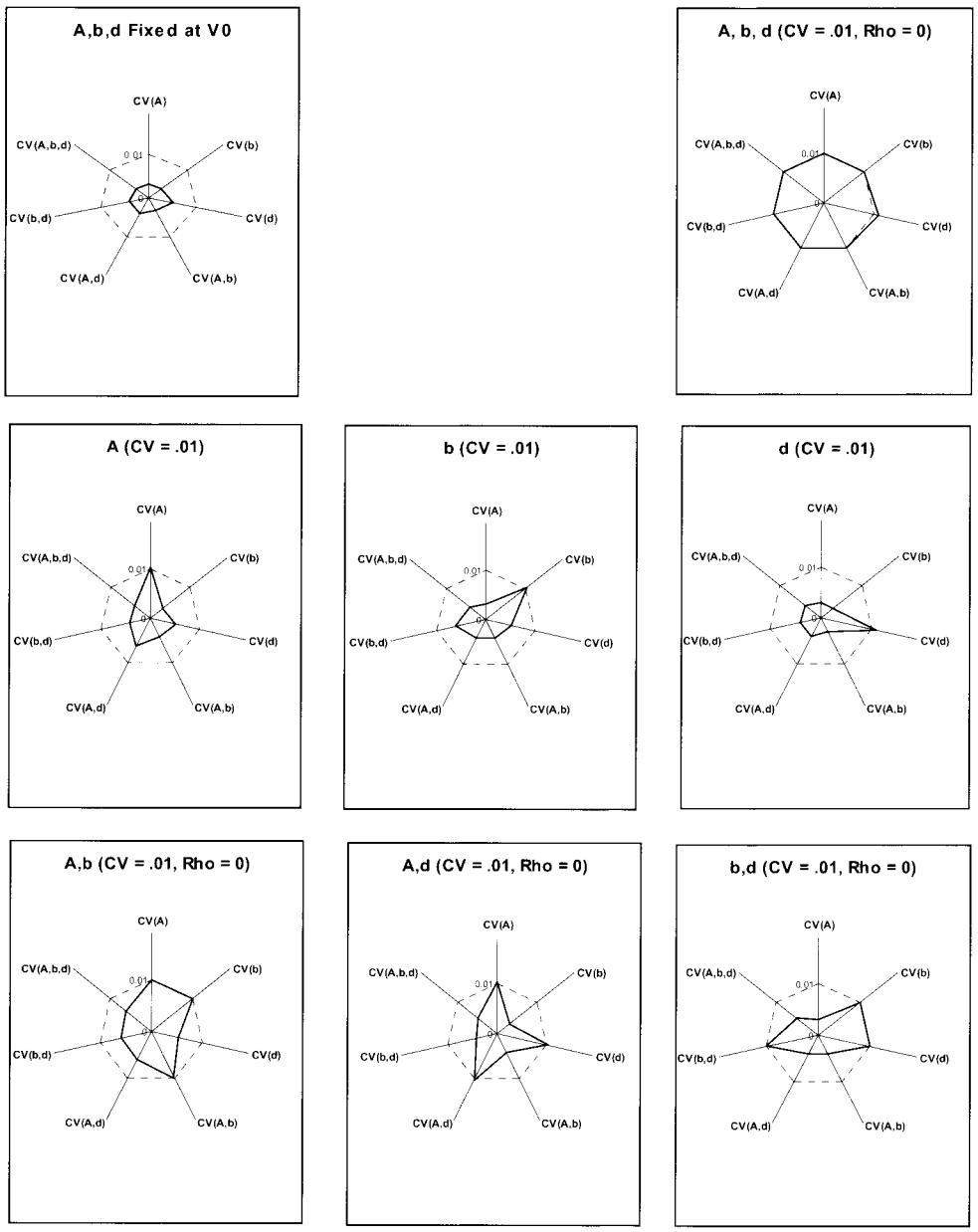

Figure 1: Means of the sample CV of the estimator(s) with fixed parameters and when one, two, or three independent effect are random at the population CV = .01 and Var(ε_{ij}) = 5.50287×10^{-6}

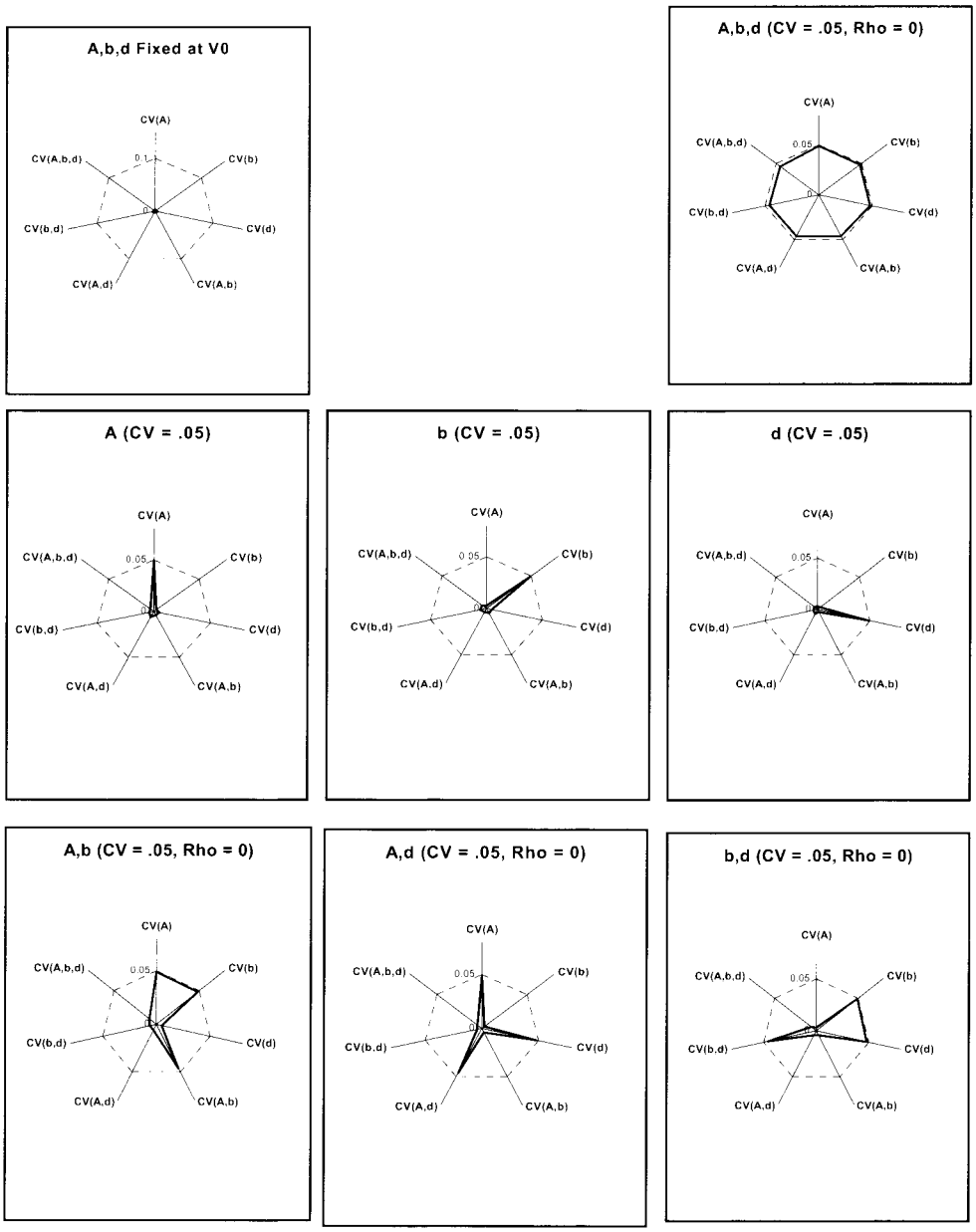

Figure 2: Means of the sample CV of the estimator(s) when fixed parameters and when one, two, or three independent effect are random at the population CV = .05 and $\mathrm{Var}(\varepsilon_{ij}) = 5.50287 \times 10^{-6}$

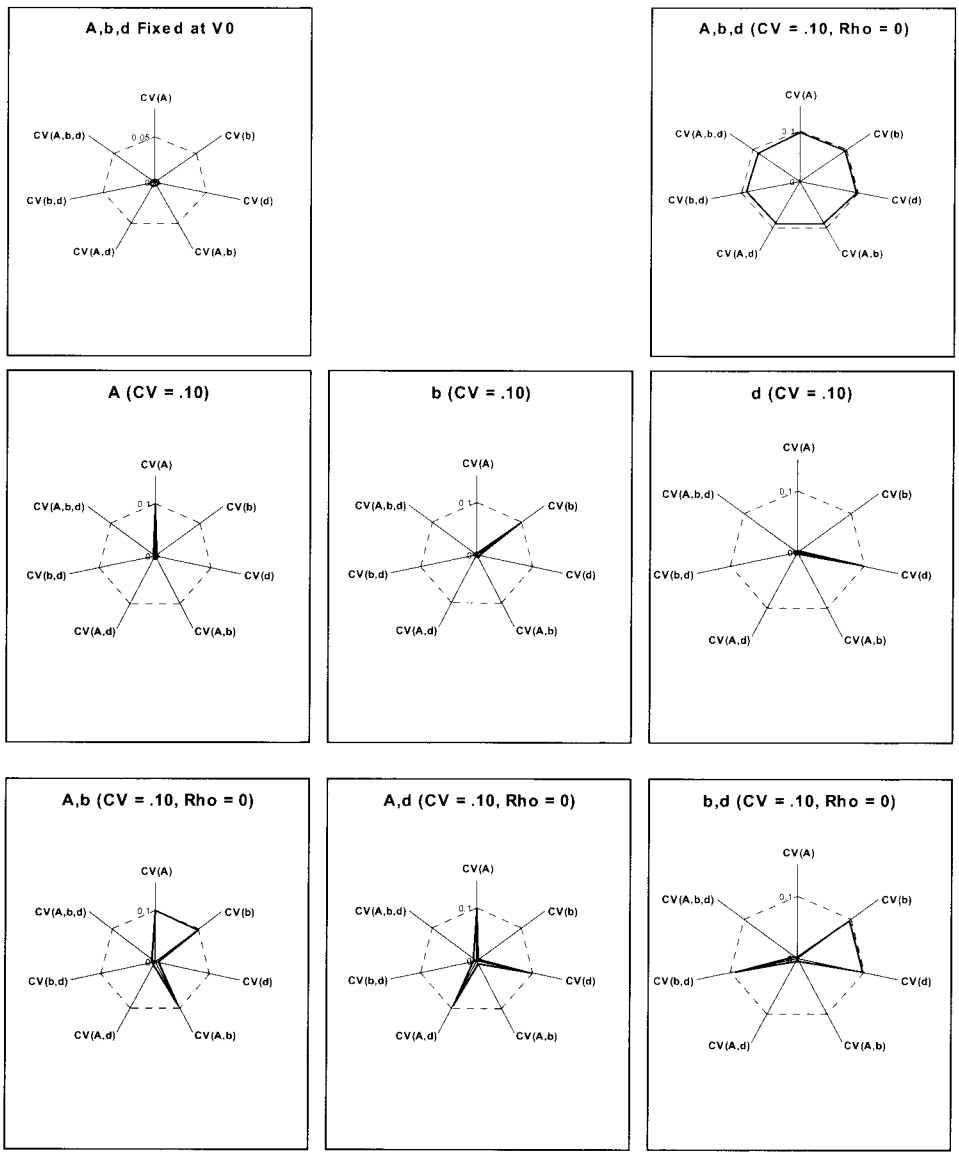

Figure 3: Means of the sample CV of the estimator(s) when fixed parameters and when one, two, or three independent effect are random at population CV = .10 and Var(ε_{ij}) = 5.50287×10^{-6}

Table. 7 Sample multivariate CV of the estimates from 8 hr MS data.

Estimate(s)	CV
$\hat{A}$	0.1892
$\hat{b}$	0.1792
$\hat{d}$	0.5034
$\hat{A},\hat{b}$	0.2133
$\hat{A},\hat{d}$	0.2606
$\hat{b},\hat{d}$	0.2505
$\hat{A},\hat{b},\hat{d}$	0.2384

The sample CV($\hat{d}$) is highest (0.5034), follow by CV($\hat{A},\hat{d}$) and CV($\hat{b},\hat{d}$) (0.2606 and 0.2505, respectively). This might suggest a model with only d random, or a model with d and one other parameter. For example, a model with A and d random, or a model with b and d random, compared to a model with all parameters random. The fixed parameter approach then will be used to form an approximate F test for model selection.

The full model here is the model with all parameters random. The reduced model I is the model with only d random, the other reduced model II and III are the models with $\hat{A}$ and $\hat{d}$ random, and the model with $\hat{b}$ and $\hat{d}$ random. The statistics test, critical values of the F random variable, and p-values are shown in Table 8.

Table. 8 Test statistics, F and p-value for testing the full model and the reduced model for 8 hr MS data.

Reduced Model	TS	F	p-value
I (d random)	5.80	2.03	.0000
II (A, d random)	1.86	2.46	.1229
III(b, d random)	1.68	2.46	.1612

The results in Table 8 indicate that the model with A and d random and the model with b and d random are not different from the model with all parameters random. Based on the sample multivariate CV and the p-values from the test, we then conclude that the model with b and d random is appropriate for this data.

Akaike's Information Criterion (AIC), a finite-sample corrected version of AIC(AICC), and Schwarz's Bayesian Information Criterion (BIC) were examined for this data set. The order of AICC, AIC, and BIC from smallest to largest for all combinations of random terms in the model obtained from PROC NLMIXED of SAS are shown in Table 9.

Table.9 Order of AICC, AIC and BIC for all combination of random terms in the model for 8 MS data.

Random	AICC	AIC	BIC
b,d	-108.0	-109.1	-111.8
A,d	-107.4	-108.4	-111.2
d	-92.0	-92.5	-94.5
A,b	-87.9	-89.0	-91.7
A	-82.9	-83.5	-85.4
A,b,d	-41.2	-43.4	-47.3
b	-40.2	-40.8	-42.7
None	-26.5	-26.8	-28.4

The multivariate coefficient of variation criteria agree with AICC, AIC, or BIC for the best model selection as expected. The final model is:

$$y_{ij} = A_i(\exp(-b_i t_{ij}) - \exp(-d_i t_{ij})) + \varepsilon_{ij},$$

where $A_i = \alpha$, $b_i = \beta + b_i^*$, and $d_i = \delta + d_i^*$. Note that $\alpha, \beta,$ and δ denote fixed effects parameters, b_i^* and d_i^* denote random effects parameters with an unknown covariance matrix. By assuming that the conditional model for the data and the joint distribution of b_i^* and d_i^* are normal, the maximum likelihood estimates of the parameters were obtained from PROC NLMIXED with Newton-Raphson Ridge optimization technique and integral approximations by adaptive Gaussian quadrature. Results are shown in Table 10.

Table. 10 Parameter estimates of the model with b and d random from 8 hr MS data.

Parameter	Estimate	SE	p-value
α	1.6978	0.0613	.0001
β	0.3673	0.0355	.0019
δ	6.1918	1.5811	.0296
σ_{ε}^2	0.0157	0.0022	.0054
σ_b^2	0.0044	0.0034	.2780
σ_d^2	11.1502	7.7217	.2445
σ_{bd}	-0.0854	0.1179	.5209

From Table 10, with only 5 replications, there is no evidence to argue that both $\hat{\sigma}_b^2$ and $\hat{\sigma}_d^2$ are marginally significant even though a model with b and d random is the most appropriate. There does not appear to be a significant covariance between them also, as seen by the estimate of σ_{bd}. The final profile fitting is shown in Figure 4.

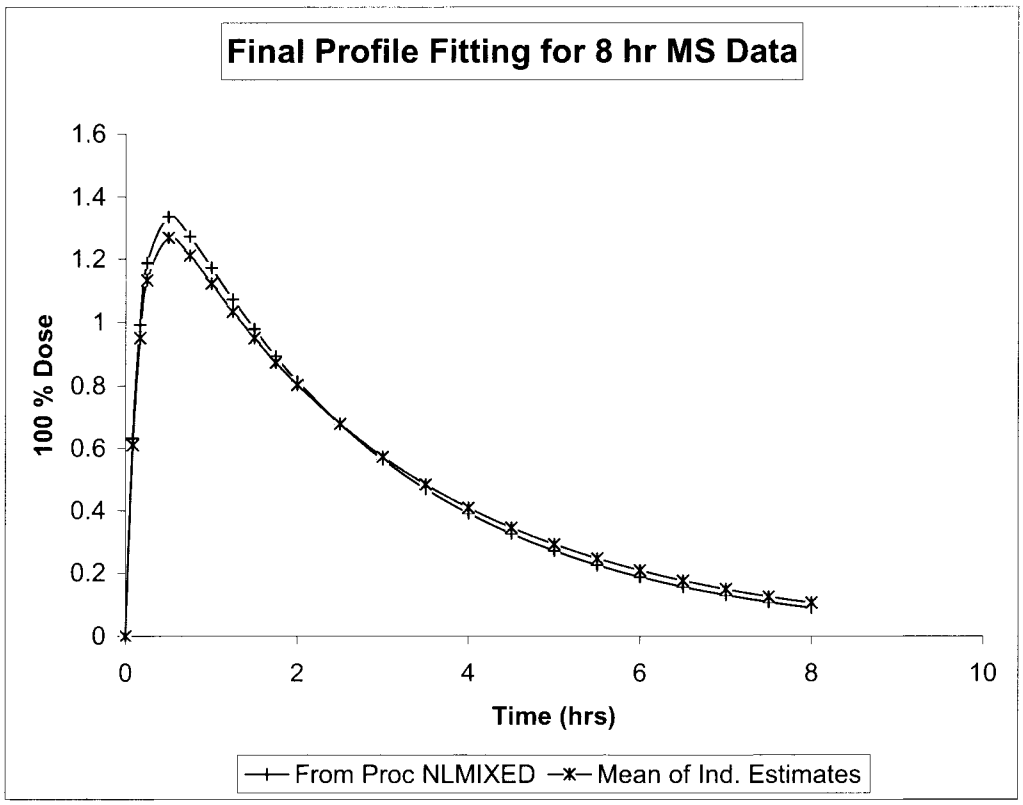

Figure 4: Final profile fitting from estimates of PROC NLMIXED for 8 hr MS data.

5. Conclusion and Discussion

Multvariate coefficients of variation for individual estimate and for all combination of estimates were used to determine which effects have a random component after the significance of the approximate F statistics test for testing whether random effects are needed. From the difference of exponentials model simulations, when all parameters are fixed and the sample CV is calculated, CV($\hat{d}$) is likely to have the highest value. The

characteristics of the estimates summarized here, can be seen clearly when the error variance is small enough. If the error variance is increased, to attain the same characteristic, the population CV of random parameters should be increased also.

When only one parameter is random, the sample CV of the corresponding estimate will be the highest rank most of the time. When more than two independent random effects are considered, the corresponding sample CV of the individual estimates equally share the highest.

With only one random effect, the mean of the sample CV of the corresponding estimate is highest and close to the population CV. When two independent random effects are considered, the mean of each individual CV estimate and their combination are highest and close to the population CV. If all parameters are independent and random, the mean CV of all estimators and their combinations are close to the population value.

When all parameters are fixed, CV($\hat{A}$) is likely to have the highest value for the approximate gamma model but CV($\hat{d}$) is likely to have the highest value when the model is close to a one compartment model.

An example for the difference of exponentials model is given, and the fixed parameter approach statistics test then is used to test whether random effects are needed. The multivariate sample coefficient of variation is applied to indicate which parameter appears to be random. Then, the fixed parameter approach is performed to pick up the appropriate model. The optimum solution agrees with other model selection criteria, e.g., AICC, AIC, or BIC. More simulation studies should be conducted to see the performance of the multivariate coefficient of variation we proposed here when random effects are correlated.

6. References

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