Thailand Statistician
July 2006; 4: 63-83
http://statassoc.or.th
Contributed paper

Detecting a Random Component in a Two Compartment Model: Correlated Random Effect Simulation Study

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Received: 1 August 2006
Accepted: 19 September 2006

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 correlated 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

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, so the parameters could be considered as random effects.

Budsaba and Smith [2] proposed an approximate F test statistics from the fixed parameter approach to test whether random effects are needed. From the difference of exponentials model simulations, the test offers a good power.

To choose which parameters should be random in a nonlinear mixed effects model, Pinheiro et al. [5] 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 (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 CV $(\hat{\theta}_1,\ldots,\hat{\theta}_k)$. For example, if a model has 3 parameters, A, b, and d, we calculate CV($\hat{A}$), CV($\hat{b}$), CV($\hat{d}$), CV($\hat{A},\hat{b}$), CV($\hat{A},\hat{d}$), CV($\hat{b},\hat{d}$), and CV($\hat{A},\hat{b},\hat{d}$). We expect that CV($\hat{A}$) will have the highest value when A is the only 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. Since $E(\overline{Y}_{i.}) = \mu_.$ and $V(\overline{Y}_{i.}) = \sigma_\mu^2 + \frac{\sigma^2}{n}$. Hence, the population CV($\overline{Y}_{i.}$) is defined by:

CV($\overline{Y}_{i.}$) = $\frac{(\sigma_{\mu}^2 + \frac{\sigma^2}{n})^{1/2}}{\mu}$, and can be estimated by the sample CV($\overline{Y}_{i.}$) which is defined by: 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 follow: F =$[n(\overline{Y}_{..})^2 CV^2(\overline{Y}_{i.})]$ /MS(Within Group). We can see that the larger value of sample $CV^2(\overline{Y}_{i.})$, the larger value of F. If the null hypothesis is false, the noncentral parameter [4] of F is:

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

The term $\sum_{i=1}^{k}(\mu_{i.} - \mu..)^2$ in (1) can be estimated by by ($\overline{Y}_{..}$)^2 (k–1) CV^2($\overline{Y}_{i.}$), and then the larger value of CV^2($\overline{Y}_{i.}$), the larger 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.

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, and the CV based on variation among samples [6].

Chow and Tse [3] investigated estimators for the common CV for balanced k sample in bioavailability/bioequivalence studies. The arithmetic mean of CV, the pooled CV as in Worley et al. [7], 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:

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

For example:

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

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

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

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

For example;

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

$$\text{CV}(\bar{Y}) = \{(\bar{Y})^2\{\hat{V}ar(Y)\}^{-1}\}^{-\frac{1}{2}} = S/\bar{Y}$$

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:

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

where A_i is normal with mean 1.5. b_i and d_i are normal with mean 0.0065 and 0.044 respectively. The random effects are positively or negatively highly correlated. 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 the 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 [1]. 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 correlated random effects (one, two, or three random parameters) with Pearson's correlation coefficient (ρ) between any relevant pair of random parameters is .90 or -.90. 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 $1000 \times V_0$, that is about 85%. This means that when all parameters are fixed, CV $(\hat{d})$ is more likely to have the highest value.

Presence of correlated random effects are considered in Tables 2, 3, 4, and 5. Each table presents result of simulations for several values of υ (the population CV of each random 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.

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 × 10-6 = V_0.

	V_0	10 × V_0	100 × V_0	1000 × 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

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 most of the times, the population CV (υ) of the random parameter should increase correspondingly.

When only two positively correlated parameters are present at V_0 (Table 2), we observe that the CV of the corresponding estimators have the highest rank most of the time when ρ = .90. For example, when A and b are positively correlated, CV $(\hat{A},\hat{b})$ is the highest about 84 %, 85 %, and 84 % of the time, respectively, when υ = .01, .05, and .10. When ρ = -.90, we observe that CV of the estimator corresponding with each individual random parameter has the highest rank most of the time. For example, when A and b are negatively correlated, CV($\hat{A}$) and CV($\hat{b}$) has the highest, respectively, about 51 % and 49 % of the time for all values of υ.

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 × 10^{-6} = V_0 .

Random Effect(s)		$\rho = -.90$			$\rho = .90$		
		υ = .01	υ = .05	υ = .10	υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.981	1.00	1.00	.981	1.00	1.00
b	CV($\hat{b}$)	.980	1.00	1.00	.980	1.00	1.00
d	CV($\hat{d}$)	.996	1.00	1.00	.996	1.00	1.00
A,b	CV($\hat{A}$)	.509	.508	.513	.070	.075	.078
	CV($\hat{b}$)	.484	.492	.487	.073	.074	.078
	CV($\hat{A},\hat{b}$)	.004	.000	.000	.841	.851	.844
A,d	CV($\hat{A}$)	.429	.515	.520	.117	.084	.080
	CV($\hat{d}$)	.569	.485	.480	.180	.076	.075
	CV($\hat{A},\hat{d}$)	.000	.000	.000	.703	.840	.845
b,d	CV($\hat{b}$)	.431	.516	.518	.099	.080	.079
	CV($\hat{d}$)	.567	.484	.482	.179	.075	.076
	CV($\hat{b},\hat{d}$)	.000	.000	.000	.722	.845	.845
A,b,d	CV($\hat{A}$)				.017	.010	.009
	CV($\hat{b}$)				.008	.011	.010
	CV($\hat{d}$)				.075	.013	.010
	CV($\hat{A},\hat{b}$)				.216	.121	.123
	CV($\hat{A},\hat{d}$)				.089	.129	.124
	CV($\hat{b},\hat{d}$)				.094	.102	.098
	CV($\hat{A},\hat{b},\hat{d}$)				.501	.614	.626

Similar results with the bivariate positively correlated effects were obtained when all parameters are positively correlated at the error variance level V_0 (Table 2), CV($\hat{A},\hat{b},\hat{d}$) is the highest 50 % , 61 % , and 63 % of the time, respectively, when υ = .01, .05, and .10.

When the error variance is increased to $10 \times V_0$ (Table 3), similar results to the case when the error variance equals V_0 were obtained. For positively correlated parameters, the sample CV of the corresponding estimators is the highest most of the time when υ is only .01. This is not true for this particular υ (.01) if parameter d is also random variable, as well as either A, b or (A,b) are random. We observe that the sample CV of the corresponding estimators will be highest most of the time when υ is .05 or .10. For example, CV($\hat{A}, \hat{d}$) is the highest 79 % and 82 % of the time, respectively, when υ is .05 and .10. CV($\hat{b}, \hat{d}$) is the highest 79 % and 83 % of the time, respectively, when υ is .05 and .10. CV($\hat{A}, \hat{b}, \hat{d}$) is the highest 56 % and 61 % of the time, respectively, when υ is .05 and .10.

For the negatively correlated parameters with the error variance equals $10 \times V_0$ (Table 3), the sample CV of the estimator corresponding with each individual random parameter has the highest rank most of the time when υ = .05 and υ = .10 only. For example, when A and b are negatively correlated, CV($\hat{A}$) and CV($\hat{b}$) has the highest, respectively, about 50-51 % and 49-50 % of the time for υ = .05 and .10.

If we increases the error variance to be $100 \times V_0$ (Table 4) the corresponding sample CV of estimator(s) will be the highest most of the time when the population CV is also increased. For example, when A and b are positively correlated, CV($\hat{A}, \hat{b}$) is the highest most of the time when υ = .05 and .10. When (A,d), (b,d), or (A,b,d) are positively correlated, respectively, CV($\hat{A}, \hat{d}$),CV($\hat{b}, \hat{d}$), and CV($\hat{A}, \hat{b}, \hat{d}$) will be the highest most of the time when υ = .10. This is also true when the error variance is $1000 \times V_0$ (Table 5), for only A and b are random parameters with υ = .10 but it is not true with this particular υ (.10) when (A,d), (b,d) or (A,b,d) are random parameters.

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)		$\rho = -.90$			$\rho = .90$		
		υ = .01	υ = .05	υ = .10	υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.460	1.00	1.00	.460	1.00	1.00
	CV($\hat{d}$)	.504	.000	.000	.504	.000	.000
b	CV($\hat{b}$)	.476	.999	1.00	.476	.999	1.00
	CV($\hat{d}$)	.521	.001	.000	.521	.001	.000
d	CV($\hat{d}$)	.953	1.00	1.00	.953	1.00	1.00
A,b	CV($\hat{A}$)	.271	.506	.499	.034	.076	.079
	CV($\hat{b}$)	.296	.491	.501	.050	.074	.076
	CV($\hat{d}$)	.302	.001	.000	.238	.000	.000
	CV($\hat{A},\hat{b}$)	.123	.002	.000	.665	.848	.845
A,d	CV($\hat{A}$)	.107	.472	.508	.175	.090	.088
	CV($\hat{d}$)	.713	.528	.492	.598	.125	.089
	CV($\hat{A},\hat{b}$)	.164	.000	.000	.120	.000	.000
	CV($\hat{A},\hat{d}$)	.000	.000	.000	.104	.785	.823
b,d	CV($\hat{b}$)	.165	.484	.512	.171	.090	.087
	CV($\hat{d}$)	.709	.516	.488	.580	.120	.085
	CV($\hat{b},\hat{d}$)	.001	.000	.000	.152	.790	.828
A,b,d	CV($\hat{A}$)				.026	.009	.011
	CV($\hat{b}$)				.016	.007	.008
	CV($\hat{d}$)				.394	.035	.015
	CV($\hat{A},\hat{b}$)				.465	.183	.127
	CV($\hat{A},\hat{d}$)				.007	.102	.120
	CV($\hat{b},\hat{d}$)				.027	.101	.112
	CV($\hat{A},\hat{b},\hat{d}$)				.065	.563	.607

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)		$\rho = -.90$			$\rho = .90$		
		υ = .01	υ = .05	υ = .10	υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.065	.763	.978	.065	.763	.978
	CV($\hat{b}$)	.074	.014	.000	.074	.014	.000
	CV($\hat{d}$)	.861	.223	.022	.861	.223	.022
b	CV($\hat{b}$)	.132	.753	.978	.132	.753	.978
	CV($\hat{d}$)	.857	.246	.022	.857	.246	.022
d	CV($\hat{d}$)	.895	.970	.997	.895	.970	.997
A,b	CV($\hat{A}$)	.023	.415	.495	.006	.059	.070
	CV($\hat{b}$)	.047	.432	.497	.035	.063	.067
	CV($\hat{d}$)	.632	.099	.004	.577	.080	.005
	CV($\hat{A},\hat{b}$)	.293	.047	.004	.379	.780	.846
A,d	CV($\hat{A}$)	.006	.238	.418	.024	.188	.110
	CV($\hat{d}$)	.676	.693	.580	.644	.442	.198
	CV($\hat{A},\hat{b}$)	.291	.056	.002	.308	.026	.000
	CV($\hat{A},\hat{d}$)	.000	.000	.000	.000	.343	.692
b,d	CV($\hat{b}$)	.036	.278	.441	.046	.171	.107
	CV($\hat{d}$)	.660	.673	.557	.640	.426	.184
	CV($\hat{A},\hat{b}$)	.302	.041	.002	.307	.020	.000
	CV($\hat{b},\hat{d}$)	.001	.002	.000	.006	.383	.709
A,b,d	CV($\hat{A}$)				.005	.025	.015
	CV($\hat{b}$)				.025	.009	.009
	CV($\hat{d}$)				.592	.237	.069
	CV($\hat{A},\hat{b}$)				.372	.374	.225
	CV($\hat{A},\hat{d}$)				.000	.032	.090
	CV($\hat{b},\hat{d}$)				.005	.058	.099
	CV($\hat{A},\hat{b},\hat{d}$)				.001	.265	.493

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)		$\rho = -.90$			$\rho = .90$		
		υ = .01	υ = .05	υ = .10	υ = .01	υ = .05	υ = .10
A	CV($\hat{A}$)	.081	.199	.473	.081	.199	.473
	CV($\hat{b}$)	.079	.053	.030	.079	.053	.030
	CV($\hat{d}$)	.840	.748	.497	.840	.748	.497
b	CV($\hat{b}$)	.088	.188	.451	.088	.188	.451
	CV($\hat{d}$)	.840	.746	.504	.840	.746	.504
d	CV($\hat{d}$)	.840	.867	.910	.840	.867	.910
A,b	CV($\hat{A}$)	.034	.089	.268	.031	.048	.070
	CV($\hat{b}$)	.030	.087	.253	.026	.035	.040
	CV($\hat{d}$)	.619	.519	.290	.630	.482	.256
	CV($\hat{A},\hat{b}$)	.314	.299	.180	.311	.431	.616
A,d	CV($\hat{A}$)	.030	.064	.165	.033	.104	.205
	CV($\hat{d}$)	.639	.653	.656	.633	.630	.576
	CV($\hat{A},\hat{b}$)	.303	.261	.166	.306	.249	.128
	CV($\hat{A},\hat{d}$)	.000	.000	.000	.000	.007	.090
b,d	CV($\hat{b}$)	.028	.051	.154	.026	.065	.137
	CV($\hat{d}$)	.630	.610	.576	.635	.635	.568
	CV($\hat{A},\hat{b}$)	.308	.308	.237	.303	.267	.138
	CV($\hat{b},\hat{d}$)	.001	.000	.001	.004	.020	.150
A,b,d	CV($\hat{A}$)				.035	.055	.054
	CV($\hat{b}$)				.025	.021	.019
	CV($\hat{d}$)				.631	.532	.387
	CV($\hat{A},\hat{b}$)				.306	.380	.437
	CV($\hat{A},\hat{d}$)				.000	.000	.009
	CV($\hat{b},\hat{d}$)				.003	.006	.030
	CV($\hat{A},\hat{b},\hat{d}$)				.000	.006	.064

When A and b are negatively correlated at the error variance $100 \times V_0$ (Table 4), CV($\hat{A}$) and CV($\hat{b}$) is the highest most of the time (about 42 - 43 % for both CV($\hat{A}$) and CV($\hat{b}$) when υ = .05 and about 50 % for both CV($\hat{A}$) and CV($\hat{b}$) when υ = .10.

At the error variance $100 \times V_0$, if parameter d is also random variable as well as either A or b. We observe that when (A,d) or (b,d) are negatively correlated, respectively, CV($\hat{A}$), CV($\hat{d}$) and CV($\hat{b}$), CV($\hat{d}$) will be in the highest rank most of the time when υ = .10 (Table 4). We cannot observe this pattern when the error variance is $1000 \times V_0$ (Table 5).

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 correlated effect is, respectively, .01, .05, and .10. In each figure, means of CV of the estimator(s) when all parameters are fixed is shown at the upper left corner. With this V_0 = 5.50287 $\times$ 10^{-6}, the means of CV of the estimator(s) under fixed effects are all within the dashed septagon for all values of the population CV (.01, .05, and .10) then we can see the pattern of the sample CV of the estimator(s) clearly. The performance of CV of the estimator(s) when the random effects are highly positively correlated (ρ = .90) is different from when the random effects are highly negatively correlated (ρ = -.90). For example, when A and b are positively correlated, the mean of CV($\hat{A},\hat{b}$), CV($\hat{A}$), and CV($\hat{b}$) are highest. The mean of CV($\hat{A},\hat{b}$) is the highest while the mean of CV($\hat{A}$) and CV($\hat{b}$) are close to the population CV. If A and b are negatively correlated, only the mean of CV($\hat{A}$) and CV($\hat{b}$) are highest and close to the population CV.

At the error variance $10 \times V_0$, the 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.

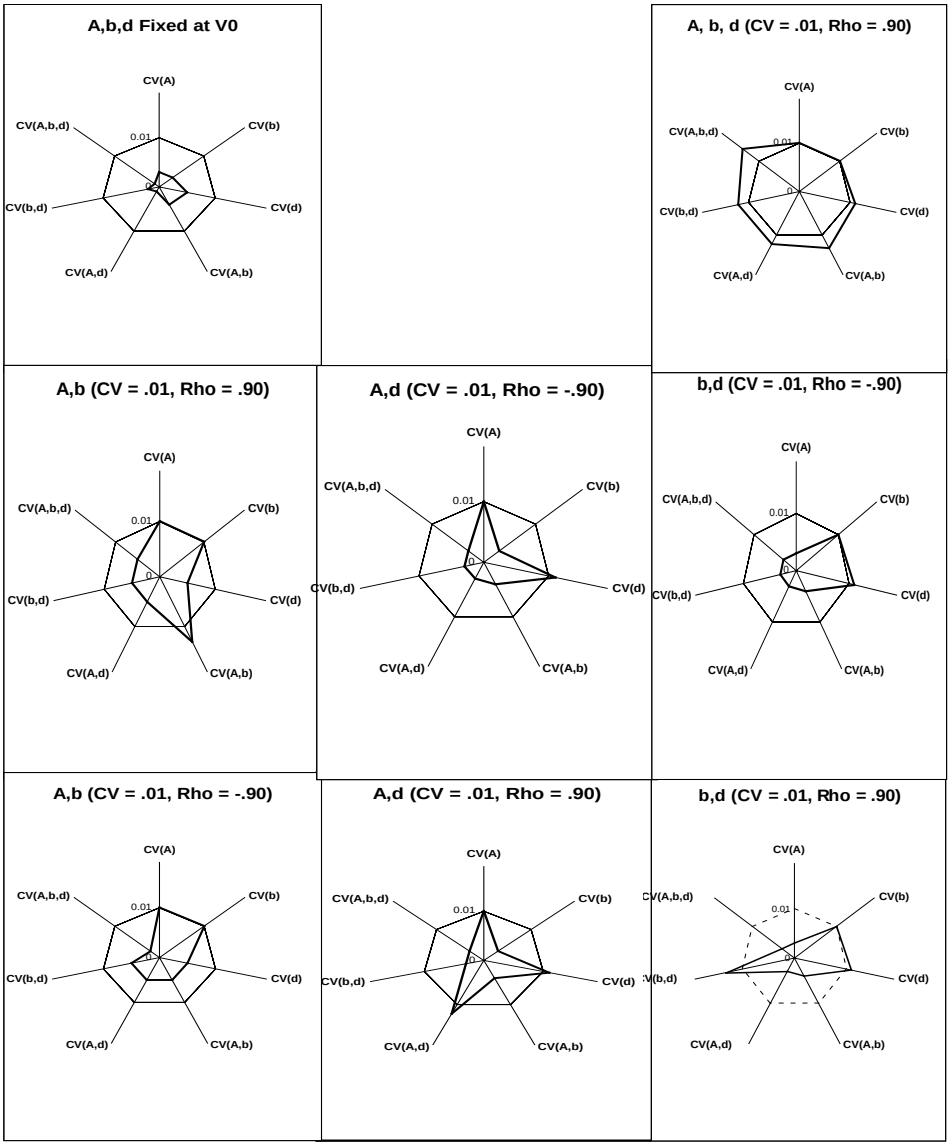

Figure 1: Mean of the sample CV of the estimator(s) when all parameters are fixed and when two or more correlated effects are considered, each with the population CV = .01 and Var(ε_{ij}) = 5.50287×10^{-6}

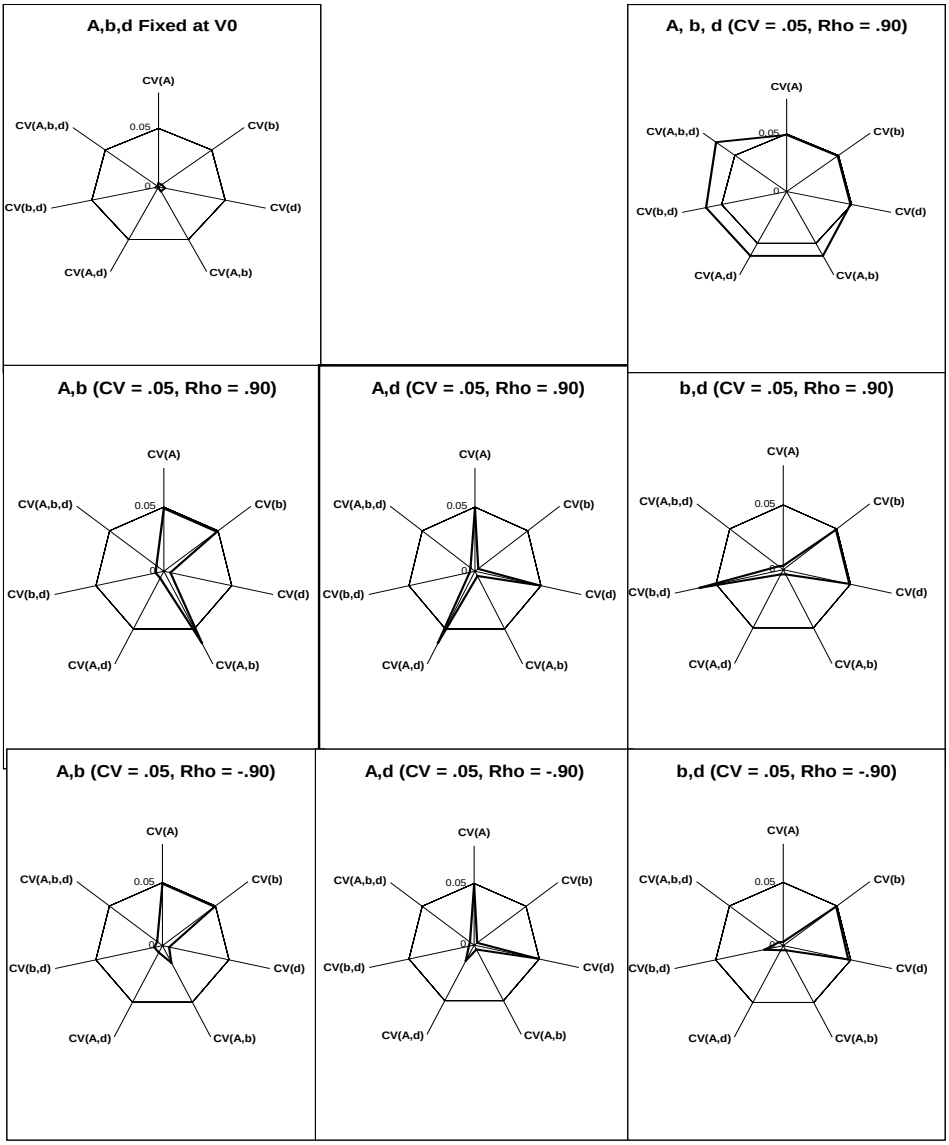

Figure 2. Mean of the sample CV of the estimator(s) when all parameters are fixed and when two or more correlated effects are considered, each with the population CV = .05 and Var(ε_{ij}) = 5.50287×10^{-6}

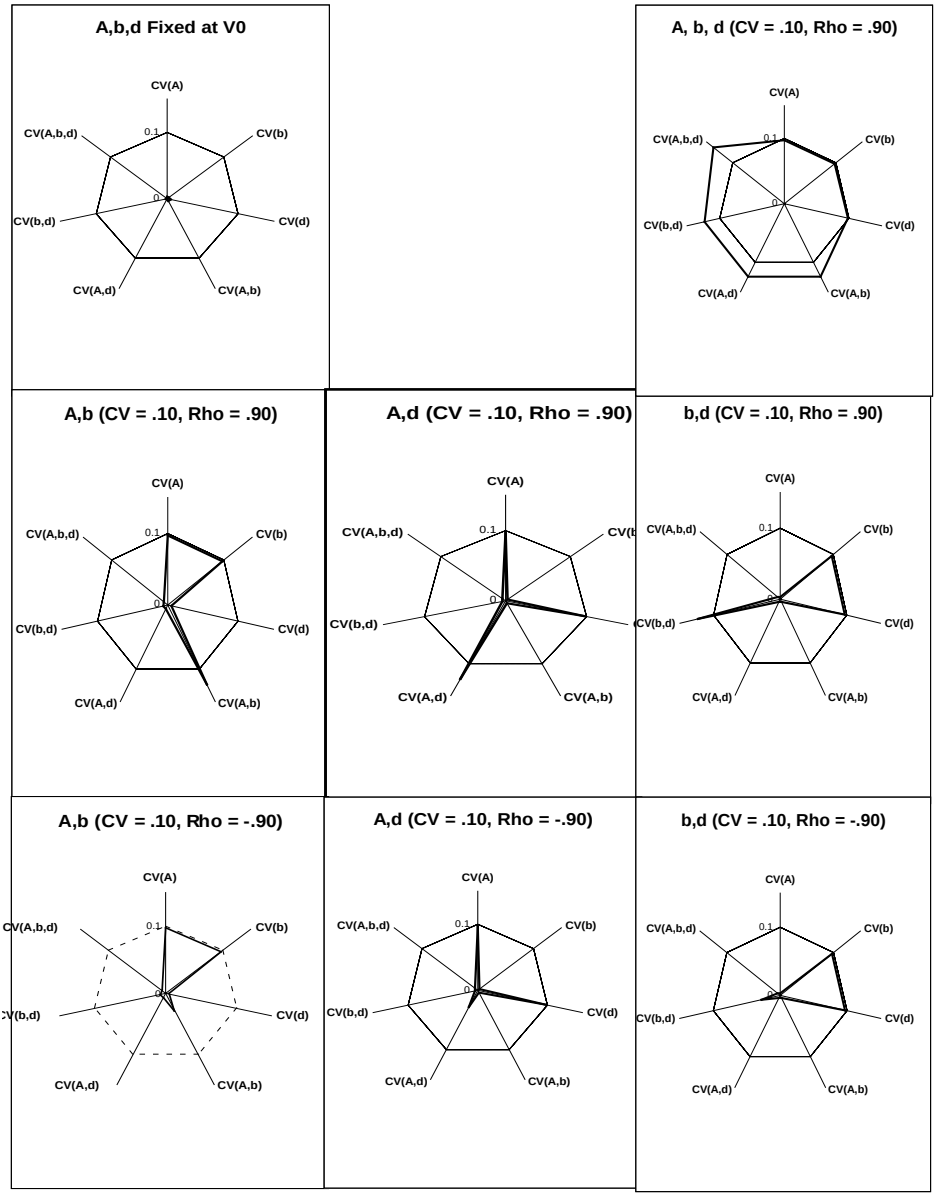

Figure 3. Mean of the sample CV of the estimator(s) when all parameters are fixed and when two or more correlated effects are considered, each with the population CV = .10 and Var(ε_{ij}) = 5.50287×10^{-6}

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 the population CV = .05 but when the error variance is $1000 \times V_0$, we cannot see this pattern anymore since under fixed effects model, all means of CV of estimator(s) are not inside the dash septagon.

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 test statistic 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 test statistic 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.

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). We might suggest the model with only d random, or the model with d and one other parameter. For example, the model with A and d random, or the model with b and d random, compared to the 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 test statistics (TS), critical values of the F random variable, and p-values are shown in Table 8.

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.

Table 8. Test statistics (TS), 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

Table 9. Order of AICC, AIC and BIC for all combination of random term 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

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

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 term in the model obtained from PROC NLMIXED of SAS are shown in Table 9.

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

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

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.

From Table 10, 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.

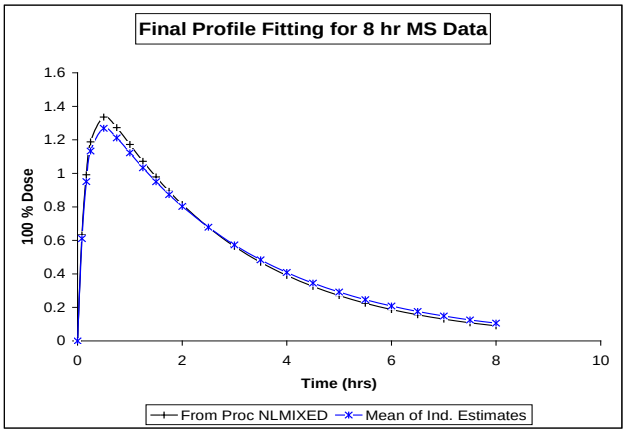

Figure 4. Final profile fitting from estimates of PROC NLMIXED for 8 hr MS data.

5. Conclusion and Discussion

Multivariate coefficient of variation for each individual estimate and for all combinations of estimates were used to determine which effects have a random component after the significance of the approximate F test statistics. 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 positively correlated random effects are considered, the CV of the corresponding estimators have the highest rank most of the time. However, when two negatively correlated random effects are considered, the CV of the estimator corresponding with each individual random parameter has the highest rank most of the time.

With only one random effect, the mean of the sample CV of the corresponding estimate is highest and close to the population CV. The performance of CV of the estimator(s) when the random effects are highly positively correlated is different from when the random effects are highly negatively correlated.

An example for the difference of exponentials model is given, and the fixed parameter approach test statistic then be 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 independent and/or non-normally distributed.

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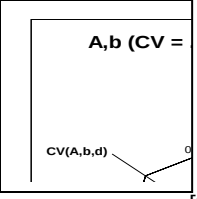

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