Testing the Need for a Random Effects Modelin in a Two Compartment Model

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Abstract

The objective of this paper is to find a simple way to test whether random effects are needed in a nonlinear mixed effects model. We proposed a test statistic, approximately an F random variable, from the fixed parameter approach which compares the residual sum of squares from the full model and the reduced model. From the difference of exponentials model simulations, the empirical size of the test is slightly higher than the nominal level α. The test offers very good power for detection. The achieved power depends on the error variance, the population coefficient of variation (CV) of the random effects, and the number of random effects in the model. For a fixed error variance, power increases as the population CV increases and/or the number of random effects increases. From our sensitivity analysis the performance of these test statistics is similar when the model has two rate constants that are almost equal, or when the model is close to a one compartment model.

Keywords: Compartment model, Difference of exponentials model, Fixed parameter approach, Nonlinear mixed effects mode

1. Introduction

A nonlinear mixed effects model is often used to model repeated-measurement response data. In these types of studies, one is usually interested in estimating the underlying population response curve. Individuals are randomly sampled from the population as a whole, so the parameters could be considered as random effects. Variance-covariance parameters are also specified for these random effects. Treating the parameters as fixed and equal for all individuals implies the variances of these parameters are zero. Therefore testing whether random effects are needed is a test of whether the parameter's variance is non-zero. The objective of this research is to find a simple approximate way to test for non-zero variance-covariance parameters.

Under the null hypothesis, the true value of a parameter is on the boundary of the parameter space defined by the alternative hypothesis. In the case of the linear mixed effects model [1], where random effects are associated with parameters in the mean response only, Stram and Lee [2], applying results of Self and Liang [3], showed that the likelihood ratio test statistic for non-zero variance components under the assumption of normality does not follow a χ^2 distribution, but instead has the distribution of a mixture of χ^2 random variables. Morgan et al. [4] developed Stram and Lee's test by using a different approach namely reparameterizing the covariance matrix of random effects. They compared the maximum likelihood approach to a fixed parameter approach. They found that the F test from the fixed parameter approach is an exact test given the normality assumption. It is simple to implement and invariant to the behavior of the parameters not being tested. Power can be approximated by using Satterthwaite's approximation. However, from their simulations, the fixed parameter approach F test had slightly lower power than the likelihood ratio test.

The same idea applies in principle to the case of a non-linear mixed effects model. However, the non-linearity of the model causes several complications, even under normality assumptions; as discussed by Davidian and Giltinan [5]. Approximate methods depend on the particular model used and may be computationally intensive. Zeng and Davidian [6] adapted a simple method for testing variance components associated with random regression parameters in the linear random coefficient models suggested by Swamy [7] and Morgan et al. [4]. They concluded that the approximated test based on χ^2 random variable achieves the correct α level and exhibits fairly good power for detection of moderate to large departures from the homogeneity assumption.

2. A General Non-linear Mixed Effects Model

Several different nonlinear mixed effects models have been proposed in recent years (Lindstrom and Bates, [8]; Vonesh and Carter, [9]; Davidian and Gallant, [10]; Wakefield, Smith, Racine-Poon and Gelfand, [11]; Pinheiro and Bates, [12]; Davidian and Giltinan, [5]). We slightly modified the model proposed in Pinheiro and Bates [12]. This model is a hierarchical model. At the first stage the jth observation on the ith individual is modeled as:

$$y_{ij} = f(\beta_i, x_{ij}) + \varepsilon_{ij}, i = 1,...,m; j = 1,...n_i$$

where f is a nonlinear function of an individual parameter vector β_i and the covariate vector x_{ij}, ε_{ij} is a normally distributed noise term, m is the total number of individuals, and n_i is the number of observation in the ith individual. For the second stage, the individual parameter vector is modeled as:

$$\beta_{ij} = A_{ij}\beta + B_{ij}b_i, \quad b_i \sim (0, D)$$

where β is a p-dimensional vector of fixed population parameters, b_i is a q-dimensional random effects vector associated with the ith individual, A_{ij} and B_{ij} are design matrices for the fixed and random effects respectively, and D is a variance-covariance matrix. It is also assumed that observations made on different individuals are independent and that the ε_{ij} are independent of b_i.

The vector b_i can be partitioned as $b_i = (b_{1,i}, b_{2,i})'$ where $b_{2,i}$ contains the r elements that are of interest to test as fixed and $b_{1,i}$ contains the other (q-r) elements in the model. The matrix D can be partitioned accordingly:

$$D = \begin{bmatrix} D_{11} & D_{12} \\ D_{12}' & D_{22} \end{bmatrix}$$

where $D_{11} = Var(b_{1,i})$, $D_{22} = Var(b_{2,i})$, and $D_{12} = Cov(b_{1,i}, b_{2,i})$. To test whether the variance associated with the parameters in $b_{2,i}$ are zero, the hypothesis can be written as:

$$H_0 : LDL' = 0 \qquad (1)$$

where $L = (0_{(q-r)\times(q-r)}, I_{r\times r})$. Under the null hypothesis, D_{22} equal zero implies D_{12} is zero.

3. Fixed Parameter Approach

The fixed parameter approach treats the parameters as fixed but different for every individual. Swamy [7] suggested this approach as a preliminary test as a diagnostic for whether the assumptions of the random coefficient regression model are reasonable. A model is fit using ordinary least squares (OLS) in which all parameters are estimated as different across individuals. Then, a model in which the parameters are equal across individuals is fit by OLS. The residual sum of squares between these two models is then compared and forms a test. We will follow the fixed parameter approach in the non-linear model and investigate this approximate test with regard to its correct α level and power.

Let SSE_F denote the residual sum of squares when the model in which all parameters are different across individuals is fit, and has $\sum n_i - mr$ degrees of freedom. SSE_R is the residual sum of squares when the model in which all parameters are equal across individuals is fit and has $\sum n_i - r$ degrees of freedom. Let $Q = SSE_R - SSE_F$, the difference in the residual sum of squares between these two

models. For testing the hypothesis in (1), this approach yields the test statistic of the form:

$$TS = \frac{Q/r(m-1)}{SSE_F / \sum n_i - mr}$$

This test is approximated as an F random variable with r(m-1) and $\sum n_i - mr$ degrees of freedom under the null hypothesis.

4. Simulation Study

We conducted simulations to evaluate the performance of the test statistic from the fixed parameter approach by consider its empirical size and power under certain conditions. The simulation is based on the model:

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

where A_i is normal with mean 1.5. b_i and d_i are normal with mean 0.0065 and 0.044 respectively. A_i, b_i and d_i are considered random effects with Pearson's correlation coefficient (ρ) between any relevant pair of random parameters is -.90, 0, or .90. 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. $V_0 = 5.50287 \times 10^{-6}$, $10 \times V_0$, $100 \times V_0$, and $1000 \times V_0$. 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, 1000 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}. When only one random effect is considered, the results are shown in Table 1.

The model we propose for the flux rate profile of the porcine flaps experiment is the difference of exponentials model [13]. 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 $d \geq b$. Since d is greater than b, this model can be considered as a two compartment model with a faster absorption constant rates than elimination constant rates. 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.

The empirical size of the test slightly increases when the variance of the error term increases. It is greater than level .05 but it is still within three standard errors of the nominal level. When variance of the error terms equal $V_0 = 5.50287 \times 10^{-6}$, the achieved power is very high and close to one in all random effects when CV is only .01. If the error variance is $10 \times V_0$, the achieved power is close to one when CV is .05. If the error variance is $100 \times V_0$ the achieved power is close to one when CV is .10. If the error variance is $1000 \times V_0$, the achieved power is close to one when CV is .10 for only when A or b is random. The information from 8 individuals each at 23 time points is sufficient to allow detection of slight departures from the null hypothesis. The test offers very good power for detection. Power increases as the population CV increases as expected. The random effect d is the slowest effect to achieve a higher power with an increase in the population CV, in contrast with the random effect A that is the fastest effect to achieve the desired power.

Table 1. Simulation results : the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160} = 1.622$) when a single random effect is considered at different levels of the population CV and variance of error terms.

Var(ε_{ij})	Random Effect	CV = 0	CV = .01	CV = .05	CV = .10
$V_0 = 5.50287 \times 10^{-6}$	A	.068	1.0	1.0	1.0
	(Median)	(1.018)	(37.733)	(922.520)	(3709.266)
	b	.068	1.0	1.0	1.0
	(Median)	(1.018)	(20.643)	(498.480)	(2023.392)
	d	.068	.992	1.0	1.0
	(Median)	(1.018)	(7.433)	(162.317)	(655.374)
$10 \times V_0$	A	.069	.978	1.0	1.0
	(Median)	(1.018)	(4.730)	(92.742)	(369.158)
	b	.069	.906	1.0	1.0
	(Median)	(1.018)	(3.052)	(50.875)	(203.448)
	d	.069	.552	1.0	1.0
	(Median)	(1.018)	(1.655)	(17.103)	(66.047)
$100 \times V_0$	A	.070	.345	.999	1.0
	(Median)	(1.021)	(1.418)	(10.275)	(37.768)
	b	.070	.215	.993	1.0
	(Median)	(1.021)	(1.226)	(5.953)	(21.217)
	d	.070	.115	.868	.991
	(Median)	(1.021)	(1.082)	(2.656)	(7.551)
$1000 \times V_0$	A	.092	.108	.720	.980
	(Median)	(1.047)	(1.087)	(2.040)	(4.934)
	b	.092	.094	.473	.916
	(Median)	(1.047)	(1.074)	(1.588)	(3.163)
	d	.092	.095	.198	.577
	(Median)	(1.047)	(1.052)	(1.220)	(1.744)

Tables 2 and 3 show the preliminary study of 1000 Monte Carlo replications when two or more random effects are in the model and they are negatively correlated, independent, or positively correlated (ρ= -.90, 0, .90 respectively) at the error variance $100 \times V_0$, and $1000 \times V_0$, respectively. Not surprisingly, the power increases when more random effects terms are in the model. In Table 2, with ρ=0 and CV= .01, the power increases by .157 (.502-.345) when A and b are both random, compared to when only A is random (Table 1). Similarly, the power increases by .056 (.401-.345) when A and d are both random effects, compared to when only effect A is random (Table 1). When b is the only random effect in the model, adding d as an additional random effect slightly increases the power form .215 to .259. Adding both b and d as random effects in the model that has only A as a random effect increases the power about the same amount as adding only b effect. Similar pattern when CV = .01 and .05 is presented in Table 3.

When random effects are highly negatively or highly positively correlated, we observe that positive correlation between each random pair of effects causes the power to be lower than the independent random effects case when (A,b), (b,d), and (A,b,d) are random but not for (A,d). Negative correlation between (A,b) and (b,d) causes the power to be higher than when they are independent random but not for (A,d). For example, when CV=.01 the power when both A and b are random is .165, .502, and .698, respectively, when ρ = .90, 0, and -.90. If both A and d are random when CV= .01, the power is .547, .401, and .225, respectively, when ρ=.90, 0, and -.90. Similar results were obtained in Table 3 when the error variance is $1000 \times V_0$.

Table 2. Simulation results: the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160}$ = 1.622) When more than one random effect are considered at different levels of the population CV and variance of error term equal $100 \times V_0$.

	Random Effects	CV = .01	CV = .05	CV = .10
$\rho = .90$	A,b	.165	.994	1.0
	(Median)	(1.201)	(5.161)	(17.826)
	A,d	.547	1.0	1.0
	(Median)	(1.707)	(17.085)	(65.045)
	b,d	.193	.997	1.0
	(Median)	(1.228)	(5.762)	(20.571)
	A,b,d	.301	1.0	1.0
	(Median)	(1.335)	(10.041)	(37.186)
$\rho = 0$	A,b	.502	1.0	1.0
	(Median)	(1.623)	(15.166)	(57.910)
	A,d	.401	1.0	.999
	(Median)	(1.486)	(12.137)	(45.191)
	b,d	.259	1.0	1.0
	(Median)	(1.298)	(7.674)	(28.059)
	A,b,d	.546	1.0	1.0
	(Median)	(1.677)	(17.090)	(66.105)
$\rho = -.90$	A,b	.698	1.0	1.0
	(Median)	(2.032)	(25.631)	(100.295)
	A,d	.225	.994	1.0
	(Median)	(1.267)	(6.721)	(23.288)
	b,d	.303	1.0	1.0
	(Median)	(1.355)	(9.189)	(34.781)

5. Sensitivity Analysis

The performance of the approximate F-test was also evaluated at other different values of the absorption rate parameter d. First, when $d^* = d/2 = 0.022$ and secondly when $d^* = 4 \times d = 0.176$. Since b = .0065 for both cases, then the first model can be considered as a model where two constant rates are almost equal (a Gamma model when two constant rates are equal), and the second model can be considered as a model that comes close to the one compartment model (a model when d approaches to infinity). Simulations were conducted at the error variance $10 \times V_0$ for both cases. When only one random effect is considered, the empirical size and power are shown in Table 4.

The empirical size of the test for both models is about .07. The achieved power is very high and close to one in all random effects when CV is .05. Power increases as the CV increases. The random effect d is the slowest effect to achieve a higher power with an increase in CV for both models. The random effect A is the fastest effect to achieve the desired power for the model with $d^* = 0.176$. Both A and b are the quickest to achieve the desired power for the model with $d^* = 0.022$.

Table 3. Simulation results: the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160} = 1.622$) when more than one random effect are considered at different levels of the population CV and variance of error terms equal $1000 \times V_0$.

	Random Effects	CV = .01	CV = .05	CV = .10
$\rho = .90$	A,b	.103	.410	.903
	(Median)	(1.073)	(1.507)	(2.786)
	A,d	.127	.864	.993
	(Median)	(1.126)	(2.767)	(7.826)
	b,d	.100	.456	.918
	(Median)	(1.074)	(1.549)	(3.048)
	A,b,d	.108	.689	.988
	(Median)	(1.072)	(1.945)	(4.793)
$\rho = 0$	A,b	.126	.846	.998
	(Median)	(1.114)	(2.561)	(7.030)
	A,d	.116	.765	.993
	(Median)	(1.103)	(2.209)	(5.693)
	b,d	.101	.576	.980
	(Median)	(1.078)	(1.752)	(3.863)
	A,b,d	.119	.896	1.0
	(Median)	(1.122)	(2.748)	(66.105)
$\rho = -.90$	A,b	.143	.945	1.0
	(Median)	(1.157)	(3.639)	(11.473)
	A,d	.101	.530	.939
	(Median)	(1.076)	(1.688)	(3.466)
	b,d	.103	.661	.984
	(Median)	(1.096)	(1.962)	(4.551)

Table 4. Simulation results: the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160} = 1.622$) when a single random effect is considered at different levels of the population CV and variance of error terms equal $10 \times V_0$ for $d^* = 0.022$, and $d^* = 0.176$

d*	Random Effects	CV = 0	CV = .01	CV = .05	CV = .10
0.022	A	.067	.904	1.0	1.0
	(Median)	(1.018)	(3.038)	(50.682)	(198.417)
	b	.067	.915	1.0	1.0
	(Median)	(1.018)	(3.026)	(50.752)	(202.534)
	d	.067	.715	1.0	1.0
	(Median)	(1.018)	(2.046)	(26.185)	(102.708)
0.176	A	.068	.992	1.0	1.0
	(Median)	(1.035)	(7.485)	(159.961)	(640.095)
	b	.068	.912	1.0	1.0
	(Median)	(1.035)	(3.032)	(50.859)	(202.788)
	d	.068	.324	.998	.998
	(Median)	(1.035)	(1.385)	(9.770)	(36.470)

Table 5. Simulation results: the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160}$ = 1.622) when more than one random effect are considered at different levels of the population CV and variance of error terms equal $10 \times V_0$ for d* = 0.022.

	Random Effects	CV= .01	CV = .05	CV = .10
ρ = .90	A,b	.602	1.0	1.0
	(Median)	(1.786)	(19.789)	(76.130)
	A,d	.990	1.0	1.0
	(Median)	(6.411)	(132.528)	(526.178)
	b,d	.810	1.0	1.0
	(Median)	(2.404)	(34.578)	(135.949)
	A,b,d	.946	1.0	1.0
	(Median)	(3.376)	(60.273)	(238.023)
ρ = 0	A,b	.989	1.0	1.0
	(Median)	(5.014)	(98.288)	(395.961)
	A,d	.964	1.0	1.0
	(Median)	(4.106)	(77.407)	(310.201)
	b,d	.981	1.0	1.0
	(Median)	(4.076)	(76.416)	(305.277)
	A,b,d	.996	1.0	1.0
	(Median)	(6.116)	(125.743)	(499.374)
ρ = -.90	A,b	.992	1.0	1.0
	(Median)	(8.295)	(181.673)	(726.113)
	A,d	.593	1.0	1.0
	(Median)	(1.774)	(19.415)	(75.661)
	b,d	.992	1.0	1.0
	(Median)	(5.574)	(116.201)	(467.617)

Tables 5 and 6 show the power when two or more random effects are in the model and they are negatively, independent, or positively correlated (ρ = -.90, 0, .90 respectively) at the error variance $10 \times V_0$ for d* = 0.022 and d* = 0.176 respectively. The power increases when more random effect terms are in the models. When random effects are highly negatively or highly positively correlated, we observe that positive correlation between each random pairs of effects causes the power to be lower than the independent random effects case when (A,b), (b,d), and (A,b,d) are random but not for (A,d) for both models. Negative correlation between (A,b) and (b,d) causes the power to be higher than when they are independent random but not for (A,d) for both models. For example, when CV = .01 and d* = 0.022, the power when both A and b are random is .602, .989, and .992, respectively, when ρ = -.90, 0, .90. Similar results were obtained in Table 6 when d* = 0.176.

Table 6. Simulation results: the proportion of times the null hypothesis is rejected at level 0.05 ($F_{.95,21,160}$ = 1.622) when more than one random effect are considered at different levels of the population CV and variance of error terms equal $10 \times V_0$ for d* = 0.176.

	Random Effects	CV = .01	CV = .05	CV = .10
$\rho = .90$	A,b	.987	1.0	1.0
	(Median)	(4.957)	(99.270)	(394.322)
	A,d	.998	1.0	1.0
	(Median)	(9.304)	(205.114)	(815.640)
	b,d	.929	1.0	1.0
	(Median)	(3.232)	(56.903)	(222.910)
	A,b,d	.997	1.0	1.0
	(Median)	(6.597)	(141.152)	(560.222)
$\rho = 0$	A,b	1.0	1.0	1.0
	(Median)	(9.5614)	(213.113)	(854.044)
	A,d	.998	1.0	1.0
	(Median)	(7.913)	(169.891)	(687.277)
	b,d	.956	1.0	1.0
	(Median)	(3.346)	(60.753)	(241.080)
	A,b,d	.999	1.0	1.0
	(Median)	(10.114)	(222.472)	(901.780)
$\rho = -.90$	A,b	.999	1.0	1.0
	(Median)	(14.075)	(329.347)	(1330.202)
	A,d	.991	1.0	1.0
	(Median)	(6.396)	(132.766)	(525.588)
	b,d	.948	1.0	1.0
	(Median)	(3.466)	(61.865)	(249.087)

6. Example

We applied the method we proposed 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 7 and the profile fitting is shown in Figure 1.

Table 7. 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.

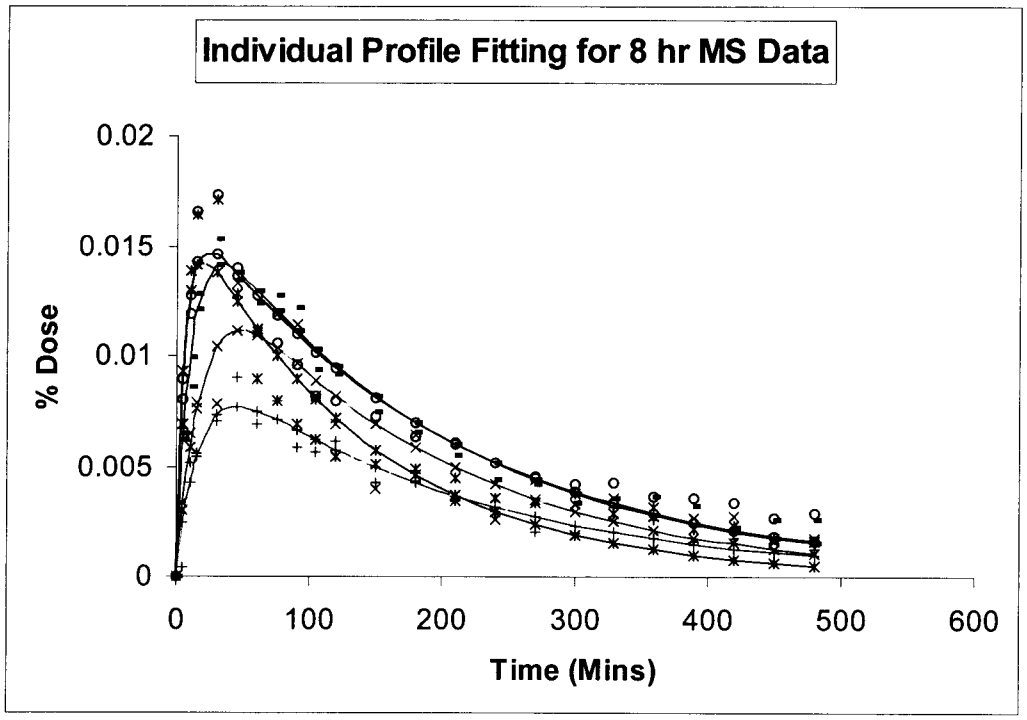

Figure 1. Individual profile fitting for 5 replications for 8 hr MS data (original scale)

7. Conclusion and Discussion

To model and to estimate an underlying population response curve from repeated-measurement response data, a nonlinear mixed effects model is often used. Its parameters might be considered as random effects since individuals are randomly sampled from the population. A simple way to test whether random effects are needed is therefore of interest to investigate. We proposed a test statistic, approximately an F random variable, from the fixed parameter approach which compares the residual sum of squares from the full model (the model in which all parameters are different across individuals) and the reduced model (the model in which all parameters are equal across individuals).

From the difference of exponentials model simulations, the empirical size of the test is slightly higher than the nominal level α. The test offers very good power for detection. The achieved power depends on the error variance, the population coefficient of variation (CV) of the random effects, and the number of random effects in the model. For a fixed error variance, power increases as the population CV increase and/or the number of random effects increases. The random effect d is the slowest and the random effect A is the fastest parameter to achieve a higher power with an increase in CV when only one random effect is considered. When more than one independent random effects are considered, adding parameter d as an additional random effect slightly increases the power. High positive or negative correlation between each pair of effects causes the power to be lower or higher respectively, than the independent random effects case except for the pair (A,d). From our sensitivity analysis the performance of these test statistics is similar when the model has two rate constants that are almost equal, or when the model is close to a one compartment model. However, now A and b are the quickest to achieve a higher power for the approximate gamma model.

8. References

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