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Determination of Best Variance-Covariance Structure in Mixed Model (SAS Proc Mixed) with Various Parameter Estimation Methods

Adile TATLIYER TUNAZ[1]*
Kahramanmaras Sutcu Imam University, Agriculture Faculty, Department of Animal Science, Kahramanmaras
(orcid.org/0000-0002-4239-7072)
e-mail: atatliyer@ksu.edu.tr

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Abstract: The aim of this study was to compare the covariance structures by using Maximum Likelihood (ML), Restricted Maximum Likelihood (REML) and Minimum Variance Quadratic Unbiased Estimator (MIVQUE) in the estimation methods in repeated measures design with mixed model approach. In the study, live weight (birth, 30th, 60th, 90th, 120th day) values of 60 head Kilis goats from birth to 120 days old were used as research data. For the purpose of evaluate of the relationship among the data, Compound symmetry (CS), Variance components (VC), (First-order autoregressive (AR(1)), Unstructured (UN), Toeplitz (TOEP), Heterogenous compound symetry (CSH), Heterogenous first-order autoregressive (ARH(1)), Heterogenous toeplitz (TOEPH), First-Order Autoregressive Moving-Avarege (ARMA(1,1)), Toeplitz With Two Bands (TOEP(2)), First-order factor analytic (FA(1)), Equal Diagonal Factor Analytic (FA1(1)), Unstructured correlations (UNR), Banded Unstructured (UN(1)), Ante-Depence (ANTE(1)) covariance structures were used. The most appropriate covariance structure was selected according to 2Ln(L), AIC, AICC and BIC information criteria in modeling the relationship between data in all three estimation methods (ML, REML and MIVQUE0), UN and UNR covariance structures were determined as the most appropriate covariance structures, although they gave the same results.

Keywords: General Lineer Mixed model, parameter estimations, variance-covariance structure.

Farklı Parametre Tahmin Yöntemleriyle En İyi Varyans-Kovaryans Yapısının Karışık Modelde (SAS Proc Mixed) Belirlenmesi

Öz: Bu çalışmanın amacı, tekrarlı ölçümlü deneme desenlerinde genel doğrusal karışık model yaklaşımı ile En Çok Olabilirlik (ML), Kısıtlanmış En Çok Olabilirlik (REML) ve Minimum Varyanslı Kuadratik Sapmasız Tahminleyici (MIVQUE) parametre tahmin yöntemleri kullanılarak farklı varyans-kovaryans yapılarının karşılaştırılmasıdır. Çalışmada, 60 baş Kilis keçisinin doğumdan itibaren 120 günlük yaşa kadarki canlı ağırlık (doğum, 30., 60., 90., 120. gün) değerleri araştırma verisi olarak kullanılmıştır. Bu amaçla, Bileşik simetri, Varyans bileşenleri, Birinci dereceden otoregresif, Yapılandırılmamış, Toeplitz, Heterojen bileşik simetri, Heterojen birinci dereceden otoregresif, Heterojen toeplitz, Hareketli ortalamalı birinci dereceden otoregresif , İki şeritli Toeplitz , Birinci dereceden faktör analitik, Eşit köşegenli faktör analitik , Yapılandırılmamış korelasyonlu, Şeritli Ana Diagonal Yapılandırılmamış ve Birinci dereceden anti-bağımlı kovaryans modelleri kullanılmıştır. En uygun kovaryans yapısının seçiminde 2Ln(L), AIC, AICC, BIC bilgi ölçütleri kullanılmıştır. Her üç tahmin yönteminde de UN ve UNR kovaryans yapıları aynı sonuçları vermekle birlikte en uygun kovaryans yapılar olarak belirlenmiştir.

Anahtar Kelimeler: Genel doğrusal karışık model, parametre tahminleri, varyans-kovaryans yapısı.

1. Indroduction

Repeated measures design is a design consisting of taking more than one measurement (consecutive measurements) over time from the experimental unit or data obtained from the same experimental unit under different conditions. Milk yield records from a cow during the lactation period, and live weights recorded during the growth period in small ruminants can be cited as examples for repeated measurement experimental designs, which are increasingly used today in the field of agriculture. Because in repeated measurement designs; using classical methods such as analysis of variance, the assumption of constant relationships between observations and errors are independent from each other brings some limitations (Ser et al., 2013). However, Ser (2011) reported that if classical methods (Repeated Measures Analysis of Variance-RANOVA, Multivariate Analysis of Variance MANOVA) are preferred in the analysis of repeated measures designs, missing observations in the data set and ignoring individual changes in measurements obtained over time are disadvantages of classical methods. Mixed model and Generalized Estimating Equations (GEE) approaches, which have strong analysis capability in data analysis by using appropriate variance-covariance structures and providing great convenience in case of unbalanced data structure, are defined as modern methods (Wu & Zhang, 2006; Ser, 2011; Ser & Bati, 2015).

General Linear Mixed Models, which have a flexible structure by giving more effective results in the analysis of unbalanced data and thus increase the power of the test, are models in which both fixed effects and random effects are used together. Littell et al. (2000) indicated that random effects were defined as the variances and covariances of the observations, while the fixed effects were defined as the expected values of the observations. The variance-covariance structure changes according to the structure of the observations. If the selected covariance structure is simpler, the first type of error increases and therefore the standard error gets smaller (Bati, 2017). However, Hanford (2005) reported that selecting the covariance structure in a very complex way may reduce the power and effect of the test. If the variance values of variance-covariance structures along the diagonal in matrix forms are the same, it is defined as a homogeneous variance-covariance structure, while if the variance values change along the diagonal, it is defined as a homogeneous variance-covariance structure (İyit, 2008). While CS, VC, AR (1), (ARMA (1,1), TOEP, TOEP (2) structures are homogeneous covariance structures, CSH, ARH (1), TOEPH, UN, UN (1), FA (1), UNR, ANTE (1), FA1 (1) are heterogeneous covariance structures (Iyit, 2008).

Various methods are used in the covariance parameter estimation of variance-covariance matrices in the general linear mixed model. The most commonly used estimation methods in research are ML, REML and MIVQUE (Kincaid, 2005; Akbaş ve ark., 2001; Anderson, 2013).

This study, different from the study conducted by Ser et al. (2013), is to determine the most appropriate covariance structure and parameter estimation by using the advantages of the general linear mixed model in the analysis of repetitive measures data on growth traits.

2. Materials and Methods

2.1. Materials

The material of this study is the live weight records of 60 head Kilis goats born in March 2018, raised in a private enterprise in Gaziantep. Body weight records continued until the 120th day of age at one-month intervals from birth, and obtained from the same individuals (Sample size n = 60 * 5 = 300) at 5 different times (live weight at the time of birth, live weight on day 30, live weight on day 60, body weight on day 90 and live weight on day 120).

2.2. Methods

General linear mixed model

The expression of the mixed model in matrix form in which both fixed and random effects are combined is as follows:

$$Y = X\beta + Zu + \varepsilon \qquad (1)$$

In the equation here, Y =n × 1 is dimensional vector containing the observation values for the traits and y ~ MVN (μ, V) with a mean of μ, the variance-covariance matrix V shows a normal distribution. $X = n \times p$ dimensional incidence matrix for fixed effect ; $\beta = p \times 1$ dimensional coefficients of the fixed effects (p: total number of fixed effect factors); $Z = n \times q$ dimensional incidence matrix for random effects ; $u = q \times 1$ dimensional coefficients of the random effects $(u \sim MVN(0,G))$; $\varepsilon = n \times 1$ dimensional is the random error vector and it is $e \sim MVN(0,R)$ and $R = Cov(e)$ (Verbeke and Molenbergs, 2000; Kincaid, 2005).

G = q × q is the variance-covariance matrix of the random effects, and R = n × n is the variance-covariance matrix of the dimensional error. Expected values of *u, ε* and *y* are *E(u) = 0; E(ε)=0 ve E(y)=Xβ*. Under the assumption that *Cov (u, ε) = 0, var (u) = G, var (e) = R,* the variance of the general linear mixed model is obtained as *var (y) = ZGZ` + R* (Hanford, 2005). In line with these explanations, the variance-covariance matrix of observation values (Y) and random effects (u, e) can be shown as follows;

$$V\begin{bmatrix} Y \\ u \\ e \end{bmatrix} = \begin{bmatrix} V & Z'G & R \\ GZ' & G & 0 \\ R & 0 & R \end{bmatrix}$$

Based on the equation var (y) = ZGZ` + R in the mixed linear model, the most commonly used methods in parameter estimation of covariance matrices are REML, ML and MIVQUE (Fusel et al., 2015; Kayabaşar & Fırat, 2016).

Parameter Estimation Methods: Maximum Likelihood (ML), Restricted Maximum Likelihood (REML) and Minimum Variance Quadratic Unattended Estimation (MIVQUE)

ML method does not take into account the degree of freedom of fixed effects while estimating error variance. Based on the equation V = ZGZ '+ G in the mixed model, the likelihood function of Y except for constants in ML is as follows:

$$L(Y) = -0.5\log\left[V\right] - 0.5(Y - Xb)'V^{-1}(Y - Xb) \quad (2)$$

is happening. The main purpose in ML method is to maximize L (Y). In the equation *Y=Xβ+Zu+ε,*

$$\begin{bmatrix} tr(\hat{P}Z_1Z_1'\,\hat{P}Z_1Z_1' & tr(\hat{P}Z_1Z_1'\,\hat{P}Z_2Z_2') \\ tr(\hat{P}Z_2Z_2'\hat{P}Z_1Z_1') & tr(\hat{P}Z_2Z'\hat{P}Z_2Z') \end{bmatrix}\begin{bmatrix} \hat{\sigma}_i^2 \\ \hat{\sigma}_e^2 \end{bmatrix} = \begin{bmatrix} y'\hat{P}Z_1Z_1'\,\hat{P}_y \\ y'\hat{P}Z_2Z_2'\,\hat{P}_y \end{bmatrix}$$

with solution

$$\hat{V} = \hat{\sigma}_i^2 V_1 + \hat{\sigma}_e^2 V_2 \quad (3)$$

and is obtained. from here;

$$\hat{\sigma}_e^2 = (Y'Y - \hat{b}'X'Y - \sum_{i=1}^{q}\hat{u}_i{}'Z'Y)/N \quad (4)$$

and $\hat{\sigma}_i^2 = (\hat{u}_i{}'\hat{u}_i + trT_{ii})/q_i$ (5)

is obtained.

REML method has the same quadratic form as MIVQUE and ML methods, but the expected values of these forms are different. While REML and ML methods require the assumption of normality, the MIVQUE method does not require (Türkan, 2008; Orhan, 1992). Although ML observation values use the log function of Y, REML uses the log function of error contrasts in the form of k'Y. Here is k'X=0 ve k'Y= k'Xb= 0

Mixed model matrix in REML:

$$\begin{bmatrix} X'R^{-1}X & Z'R^{-1}X \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{bmatrix}\begin{bmatrix} \beta \\ u \end{bmatrix} = \begin{bmatrix} X'R^{-1}Y \\ Z'R^{-1}Y \end{bmatrix}$$

is and obtained in the form;

$$\hat{\sigma}_e^2 = (Y'Y - \hat{b}'X'Y' - \sum_{i=1}^{q}\hat{u}_i'Z_iY)/(N - r(x)) \quad (6)$$

$$\hat{\sigma}_a^2 = (\hat{u}_i{}'\hat{u}_i + trC_{ii}\hat{\sigma}_e^2)/q_i \quad (7)$$

As can be seen from equations of $\hat{\sigma}_e^2$, the difference between ML and REML, REML takes into account r (x), which is the degree of freedom of fixed effects, while ML neglects it (Orhan, 1992).

In comparing the models used, among from the goodness of fit criteria's (Likelihood information criterion (-2Res Log Likelihood, 2Ln(L)), Akaike information criterion (AIC), Bayesian information criterion (BIC) or Schwarz information criterion (SIC) and Corrected Akaike information criterion (AICC)) AIC, BIC and AICC were used. Moser (2004) reported that since the 2Ln (L) information criterion does not take into account the number of parameters, AIC and BIC information criteria are generally used in the variance-covariance model selection. Accordingly, the information criteria used in the study:

$$AIC = -2Ln(L) + 2k \quad (8)$$

$$AICC = AIC + \frac{2k(k+1)}{n-k-1} \quad (9)$$

$$BIC = -2Ln(L) + kLn(n) \quad (10)$$

In the above equations, k = the number of random effect parameters in the variance-covariance matrix and n = the number of observations (Konishi & Kitagawa, 2008). In this study, general linear mixed model analyzes were performed using the PROC MIXED procedure of the SAS (version 9.0) program.

3. Results and Discussion

Descriptive statistics regarding the data (fixed effects) used in the study are as specified in Table 1. The change in the body weight of goats in terms of gender is as shown in Figure 1.

Table 1. Descriptive statistics for fixed effects
Çizelge 1. *Sabit etkilere ait tanımlayıcı istatistikler*

Fixed Effects		N	$\bar{X} \pm S$	Min	Max	95% Confidence intervals Min	95% Confidence intervals Max
Gender	Male	150	13.11±7.21	2.00	29.50	11.95	14.28
	Female	150	11.86±6.40	2.00	29.00	10.83	12.89
Birth Type	Single	160	12.76±7.08	2.00	29.50	11.66	13.87
	Twin	140	12.17±6.56	2.00	29.50	11.07	13.27

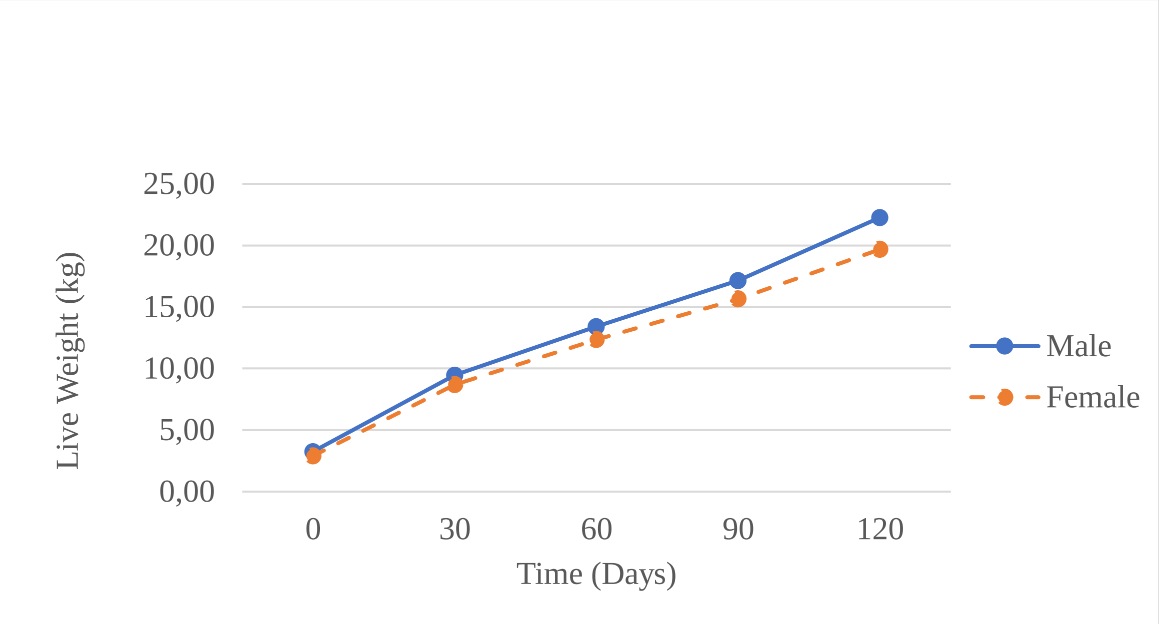

Figure 1. Change of body weight of the sexes over time
Şekil 1*. Cinsiyetlere ait canlı ağırlık ortalamalarının zamana göre değişimi*

In order to compare the most appropriate covariance structure and parameter estimation method in the mixed model used in the study, the results of AIC, AICC and BIC goodness of fit criteria are shown in Table 2.

The structure giving the smallest AIC, AICC and BIC values according to Table 2 has been determined as the most suitable structure (Bati, 2017). The structure that gives the smallest value according to Table 2 is the UN and UNR structures, which have heterogeneous structures in all three parameter estimation methods. At the same time, the UN and UNR covariance structures gave the same results. Ser et al. (2013) reported that the UN covariance structure has a heterogeneous structure and that it can be a good choice for the researcher when the number of repeated measurements is low, and does not require any assumptions. Ser et al. (2013) reported that the most suitable covariance structure is the UN structure in their study, and similar results were obtained in the present study. The number of iterations and their convergence in comparing parameter estimation methods and covariance are also informative (Bati, 2017). In this study, while ML estimation method provided convergence with UN and UNR covariance structures with 5 iterations, REML provided 4 iterations. On the other hand, MIVQUE predicted with a single iteration. Ser et al. (2013) indicated that REML and ML give better results if REML, ML and MIVQUE are evaluated together. At the same time, the researchers stated that while MIVQUE provides convergence with a single iteration, the estimation results obtained from MIVQUE are also considered as the initial value in REML and ML.

Table 2. Results of the goodness of fit criteria for different covariance structures in ML, REML and MIVQUE methods
Çizelge 2. *ML, REML ve MIVQUE yöntemlerinde farklı kovaryans yapılarının uyum iyiliği ölçütleri sonuçları*

Covariance Structures	ML			REML			MIVQUE		
	AIC	**AICC**	**BIC**	**AIC**	**AICC**	**BIC**	**AIC**	**AICC**	**BIC**
CS	1481.4	1481.9	1498.1	1469.9	1470.0	1474.1	1469.9	1470.0	1474.1
VC	1514.0	1514.3	1528.6	1502.7	1502.7	1504.8	1502.7	1502.7	1504.8
AR(1)	1439.8	1440.3	1456.6	1429.0	1429.1	1433.2	1429.1	1429.1	1433.3
UN	**1266.9**	**1270.3**	**1310.9**	**1262.2**	**1263.9**	**1293.6**	**1269.7**	**1271.4**	**1301.1**
TOEP	1443.7	1444.7	1466.8	1433.1	1433.3	1443.6	1433.9	1434.1	1444.4
CSH	1298.0	1299.1	1323.1	1292.3	1292.6	1304.9	1304.0	1304.3	1316.5
ARH(1)	1292.8	1293.9	1318.0	1287.0	1287.3	1299.6	1611.4	1611.7	1624.0
TOEPH	1294.2	1295.8	1325.6	1288.5	1289.1	1307.3	1300.7	1301.3	1319.5
FA(1)	1271.0	1272.9	1304.5	1266.0	1266.8	1287.0	1401.4	1402.2	1422.3
FA1(1)	1417.3	1418.4	1442.4	1407.7	1408.0	1420.3	1490.0	1490.3	1502.5
ARMA(1,1)	1440.7	1441.3	1459.6	1430.0	1430.1	1436.3	1525.5	1525.6	1531.8
TOEP(2)	1449.7	1450.2	1466.4	1439.1	1439.1	1443.3	1523.5	1523.6	1527.7
UNR	**1266.9**	**1270.3**	**1310.9**	**1262.2**	**1263.9**	**1293.6**	**1269.7**	**1271.4**	**1301.1**
UN(1)	1352.8	1353.7	1375.9	1346.2	1346.4	1356.7	1350.5	1350.7	1361.0
ANTE(1)	1282.2	1283.9	1313.6	1276.7	1277.4	1295.6	1280.5	1281.1	1299.3

In this study, UN and UNR covariance structures gave the same results for fixed effects with ML, REML and MIVQUE parameter estimation methods. Hence, only the UN covariance structure and the results regarding the significance of the fixed effects are shown in Table 3.

Table 3. Statistical significance results of fixed effects
Çizelge 3. *Sabit etkilerin istatistiksel önemlilik sonuçları*

Estimation Methods	Gender		Time	
	F	P	F	P
ML	5.92	0.0181	525.67	<.0001
REML	5.72	0.0201	516.92	<.0001
MIVQUE	5.58	0.0215	516.91	<.0001

Gender and time used as fixed effects in the study were found to be statistically significant in all three models ($p < 0.0001$).

Anderson (2013) reported that the number of fixed effects in the model affected the results of ML and REML parameter estimation methods based on likelihood. In the study, the researcher stated that if the number of fixed effects is ≤ 4, the ML method could give better results, while if the number of fixed effects is> 4, REML would be preferred. According to Anderson (2013), ML may be preferred regarding the data structure used in this study. However, ML, REML and MIVQUE showed similar performances in the selection of covariance structures in terms of goodness of fit criteria.

Yavuz Yurdigül (2014) conducted a simulation study to compare the performance of ANOVA, ML and REML methods and reported that the ML method was more consistent. The results obtained in this study were similar to their results.

Akbaş et al. (2001), in their study on weekly body weights of Japanese quails, stated that general linear mixed models should be preferred in determining the appropriate variance covariance structures, and stated that the most suitable structure in the study was the UN structure. Their results from the study are consistent with this study. Wang and Goonewardene (2004), on the other hand, proposed a general linear mixed model in the analysis of experimental designs with repeated measures and reported that the most appropriate variance-covariance structure was ANTE (1) in their study.

The results of the parameter estimation of the UN covariance structure under different parameter estimation methods are as indicated in Table 4.

Table 4. Results for parameter estimates of the UN covariance structure

Çizelge 4. *UN kovaryans yapısının parametre tahminlerine ilişkin sonuçları*

Covariance structure	Covariance Parameters	Estimation methods	Estimate	Std. Error	Z	p
	UN(1,1)		0.3265	0.05966	5.47	<.000
	UN(2,1)		0.2881	0.1561	1.85	0.0649
	UN(2,2)		4.1731	0.7625	5.47	<.0001
	UN(3,1)		1.0346	0.2700	3.83	0.0001
	UN(3,2)		2.2748	0.8846	2.57	0.0101
	UN(3,3)		9.9870	1.8241	5.48	<.0001
	UN(4,1)		1.1242	0.3046	3.69	0.0002
UN $\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \end{bmatrix}$	UN(4,2)	ML	1.4301	0.9656	1.48	0.1386
	UN(4,3)		8.3210	1.8167	4.58	<.0001
	UN(4,4)		12.8705	2.3512	5.47	<.0001
	UN(5,1)		0.5235	0.3228	1.62	0.1049
	UN(5,2)		-0.4629	1.0991	-0.42	0.6736
	UN(5,3)		4.1896	1.7791	2.35	0.0185
	UN(5,4)		8.1510	2.1931	3.72	0.0002
	UN(5,5)		17.1960	3.1433	5.47	<.0001
	UN(1,1)		0.3363	0.06226	5.40	<.0001
	UN(2,1)		0.2973	0.1614	1.84	0.0654
	UN(2,2)		4.2481	0.7828	5.43	<.0001
	UN(3,1)		1.0564	0.2786	3.79	0.0001
	UN(3,2)		2.3177	0.9080	2.55	0.0107
	UN(3,3)		10.1606	1.8714	5.43	<.0001
	UN(4,1)		1.1475	0.3143	3.65	0.0003
UN $\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \end{bmatrix}$	UN(4,2)	REML	1.4586	0.9910	1.47	0.1411
	UN(4,3)		8.4664	1.8639	4.54	<.0001
	UN(4,4)		13.0930	2.4120	5.43	<.0001
	UN(5,1)		0.5367	0.3333	1.61	0.1073
	UN(5,2)		-0.4664	1.1279	-0.41	0.6792
	UN(5,3)		4.2650	1.8253	2.34	0.0195
	UN(5,4)		8.2935	2.2499	3.69	0.0002
	UN(5,5)		17.4917	3.2244	5.42	<.0001
	UN(1,1)		0.4988	0.1994	2.50	0.0062
	UN(2,1)		0.3720	0.2553	1.46	0.1452
	UN(2,2)		4.2351	0.7881	5.37	<.0001
	UN(3,1)		1.1239	0.4057	2.77	0.0056
	UN(3,2)		2.2974	0.9121	2.52	0.0118
	UN(3,3)		10.1330	1.8732	5.41	<.0001
	UN(4,1)		1.1282	0.4384	2.57	0.0101
UN $\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \end{bmatrix}$	UN(4,2)	MIVQUE	1.3515	0.9782	1.38	0.1671
	UN(4,3)		8.3520	1.8351	4.55	<.0001
	UN(4,4)		12.8919	2.3490	5.49	<.0001
	UN(5,1)		0.2443	0.5266	0.46	0.6427
	UN(5,2)		-0.8466	1.1155	-0.76	0.4479
	UN(5,3)		3.8776	1.7480	2.22	0.0265
	UN(5,4)		7.8194	2.1165	3.69	0.0002
	UN(5,5)		16.7446	3.0128	5.56	<.0001

In conclusion, in repeated measure studies, the flexible structure of the mixed linear model allows the comparison of different covariance structures as well as the comparison of different parameter estimation methods, providing great convenience to researchers.

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