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Analysis of Random Intercept and Slope Model (RISM) for Data of Repeated Measures from Hy-Line White Laying Hens

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A B S T R A C T

In animal science, sequential variation on quantitative traits during a certain time period should be precisely identified for regulating managerial conditions in animal experimental data. This study was conducted in order to investigate the effect of including some covariates on performance of covariance structures, fixed and random effects on the scope of random intercept and slope model (RISM) in order to improve model quality criteria. In repeated measurement data of laying hens, cumulative egg weight (CEW) per hen as a dependent variable was recorded per week, and treatment, time and treatment x time interaction effects were added as independent variables. Time effect was considered as a continuous variable in RISM. For better improving quality of RISM, feed intake (FI), feed conversation ratio (FCR), and egg mass (EGGM) per week were also included as covariates. Model quality criteria like -2 Res Log Likelihood, Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), and Corrected Akaike's Information Criterion (AICC) criterion were used to identify best covariance structure among Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Unstructured (UN), First-Order Autoregressive (AR(1)), Unstructured correlation (UNR), Heterogeneous First-Order Autoregressive (ARH(1)), Toeplitz (TOEP) and Heterogeneous Toeplitz (TOEPH) with/without adding covariates. The explanation proportion of 90% in the dependent variable (CEW) was estimated for CSH, UNR, ARH(1), TOEPH, and UN as an outcome of adding covariates, which was prominently higher than the RISM without adding covariates. The significant differences in parameter estimates of fixed and random effects were recorded between the RISM with and without covariates. In repeated measures design, adding covariates in improving quality criteria of RISM could be recommended for data of laying hens

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INTRODUCTION

Repeated measures are multiple sequential responses taken from the same experimental unit (animal) over a period of the certain time (Littell *et al.*, 2000). The favourable examples for these measures in animal science are the growth-time and lactation-time data collected consecutively across time to define the growth and lactation curves (Akbas *et al.*, 2011; Waheed *et al.*, 2016). Describing sequential variation on quantitative (continuous) traits such as live weight and body measurements during the time period is of vital importance in order to regulate managerial conditions in animal experiment data. The description is probable in the violation of Spherity assumption with the use of multivariate approaches like profile analysis and mixed model approaches compared to classical approaches (Univariate or Repeated ANOVA) in a repeated measures design.

A basic assumption (non-missing data) for the classical approach is that measurements for all the animals should be taken at all the time periods during the experiment and animals with missing data should be excluded from the data set (Eyduran and Akbas, 2015). Repeated ANOVA is a desirable tool for statisticians in the validation of Spherity assumption, but its statistical performance declined when the significant deviations are present from the assumption (Eyduran *et al.*, 2013). In this case, being the best alternative, profile analysis (repeated MANOVA) approach is more preferable one compared to classical approach with non-missing data (Eyduran *et al.*, 2008); however, the efficiency of this

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approach reduces due to the fact that the number of observations (n) in each level of treatments is lesser than the number of repeated measurements (level of time=p) in the repeated measures design (Tabachnick and Fidell, 2007). Mixed model methodology with random (between and within animals) and fixed (time and treatment) effects is a superior approach not only for identifying variation between-animals but also for defining variation within-animals by specifying many covariance structures with/without missing data in the correlated design (Eyduran *et al.*, 2013). In the repeated measures designs, Kaps and Lamberson (2004) reported that a random coefficient regression approach, which is an efficient approach like mixed model approach in heterogeneous variance-covariance, had some advantages such that it can be applied when unequal distances between measurements are available as well as there are animals having different observation numbers across time period. Its basic assumption is that each animal has its own regression. Similarly in RISM, one of special cases in the data of repeated measures, it is assumed that each animal has its own intercept and slope over time within the scope of mixed model theory since all animals cannot show the alteration at same proportions over time.

The authors highlighted that the time effect was identified as both discrete and continuous variables in the data of repeated measures (Kaps and Lamberson, 2004). In recent years, the number of statistical applications on mixed and random coefficient regression model approaches for animal data has been increasing in repeated measures designs (Orhan *et al.*, 2010; Eyduran *et al.*, 2013).

In the study, we tested the suitability of homogenous and heterogeneous covariance structures between repeated measurements of data concerning laying hens, and evaluated the effect of adding some covariates in quality criteria of RISM where a time effect was specified as a continuous variable.

MATERIALS AND METHODS

The experiment was conducted based on protocols by Mustafa Kemal University, Ethical Commission Report (Date: 30.04.2013 Decision Number: 2013-5/5).

Animals, diets, and feeding treatments

Totally eighty 56 week-old Hy-Line White laying hens (commercial type) having nearly similar initial body weight (1360.6±14.25 g) were divided randomly into 5 groups (control group and 4 experimental groups) including 16 in each one and kept individually in cages sized 35 x 40 x 45 cm. Carrot leaves were obtained for any farm in Kırıkhan / Hatay after fruit harvesting. These leaves were stored and maintained for air drying in clean surface without any microbiological contamination and sunshine effect. Carrot leaves were used after dried and powdered by using 1-mm-sieve opening mill. Hens were fed with basal diets (commercial) (171 g crude protein and 2817 Kcal ME kg^{-1}) supplemented with powders of 0 (control), 1, 2, 4 and 8 g carrot leaves from 56 to 64 weeks age (Table I). Feeds were offered limited by 100 g per hen and water was available *ad lib*. Birds were exposed to 16 hours day light and 19-22 °C ambient temperature in poultry house during experimental period of 8 weeks.

Table I.- Experimental layer diet (Phase I).

Feed ingredients	%
Corn	47.8
Full fat soya	17.9
Sunflower meal	9.7
Barley	7.0
Corn gluten meal	7.6
$CaCO_3$	8.3
DCP (17.5%)	0.9
Methionine&Lysine	0.1
$NaHCO_3$&NaCl	0.3
Mineral and Vitamin premix*	0.4
Calculated composition	
ME, kcal kg^{-1}	2817
Crude protein, %	17.1
Lysine, %	0.65
Methionine + cystine, %	0.57
Ca, %	3.0
P (available), %	0.7

*Per kg diet included 7000 IU Vitamin A, 2000 IU Vitamin D_3, 15 mg Vitamin E, 2 mg Vitamin K_3, 4 mg Vitamin B_2, 10 mg Vitamin B_{12}, 60 mg Mn, 50 mg Zn, 25 mg Fe, 15 mg Cu, 0.25 mg Co, 1 g Iodine, 0.2 mg Se

Growth parameters

Body weights of hens were observed at the start and end of study. Feed intake (FI), egg number (EGGN), and egg weight for each hen were recorded daily; and then, egg mass (EGGM) and rate (EGGR) were determined. Feed conversion ratio (FCR) was found as a division of total feed intake by total egg mass.

Testing the validity of multivariate normal distribution

In order to test the validity of multivariate normal distribution for the evaluated data, ordered squares of the mahalanobis distances calculated individually for each (experimental unit) animal were estimated by using PROC IML of SAS program as reported earlier by Eyduran and Akbas (2010). When more than or half of the ordered mahalanobis distances estimated from 78 animals were found to be less than $X^2_{p:0.50}$ (α=%50), the assumption regarding multivariate normal distribution for the poultry data was satisfied (Alpar, 2003). $X^2_{8:0.50}$ table value for a time effect of 8 levels was 7.344. 65.38% of the 78 ordered squares of mahalanobis distance values was less than the table value of 7.344, which signifies that the assumption for the interpreted poultry data was valid.

General linear mixed model

In repeated measures data, general linear mixed models were considerably preferred. A linear mixed model can be written as in Eq. 1

$$Y_i = X_i\beta + Z_i u_i + e_i \qquad (1)$$

Where, *(Y_i)* values are normally distributed and *(ß)* regression parameter which is the same for all the animals is included as a fixed effect in the model. *(u_i)* is animals' own slopes from each other independently and included as a random effect in the model, *($u_i \sim N(0,G)$)*. The presence of *(u_i)* in model explains that there is heterogeneity between animals based on *(ß)*. *$X_i(n_i x p)$* and *$Z_i(n_i x q)$* are design matrices of fixed and random effects. *(e_i)* is error vector, as well as *$ei \sim N(0,R_i)$* and *$R_i = Cov(e_i)$* can be expressed. In brief, if random effects are assumed to be distributed normally,

$$E\begin{bmatrix} u_i \\ e_i \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \text{and} Var\begin{bmatrix} u_i \\ e_i \end{bmatrix} = \begin{bmatrix} G & 0 \\ 0 & R \end{bmatrix} \qquad (2)$$

(Kincaid, 2005).

In mixed model methodology, there are some special cases, like random intercept and slope models. Detail information of random intercept and slope model was presented below. In the repeated measures design, variation between animals at initial time periods was wider than variation between animals as time progressed. For this reason, RISM points should be specified as random in the model. In the context, two-stage model can be written as follows;

First stage model:

$$Y_{ij} = \beta_{0j} + \beta_{1j} X_{ij} + e_{ij} \qquad (3)$$

Second stage model:

$$\beta_{0j} = \gamma_{00} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

and

$$\begin{pmatrix} u_{0j} \\ u_{1j} \end{pmatrix} = u_j \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_0^2 & \sigma_{10} \\ \sigma_{10} & \sigma_1^2 \end{pmatrix}\right)$$

(Anderson, 2013).

The explained proportion by random effects in dependent variable is called intra-class correlation coefficient *(ρ)* in RISM. The coefficient can be estimated by the following equation.

$$\rho = \frac{\sigma_{u0}^2 + \sigma_{u1}^2}{\sigma_{u0}^2 + \sigma_{u1}^2 + \sigma_e^2} \qquad (4)$$

(Moerbeek and Teerenstra, 2011).

Variance-covariance structures in general linear mixed model

Within the scope of mixed model methodology implemented in the repeated measures design, there are homogenous and heterogeneous variance-covariance structures specified to model sequential relationship between measurements. Examples of homogenous covariance structures are Compound Symmetry (CS), Variance Component (VC), Toeplitz (TOEP), and First-order Autoregressive (AR(1)). Heterogeneous covariance structures are Unstructured (UN), Banded Main Diagonal (UN(1)), Heterogeneous Compound Symmetry (CSH), Heterogeneous Toeplitz (TOEPH), Heterogeneous First-order Autoregressive (ARH(1)), First-order Factor Analytic (FA(1)), Huynh-Feldt (HF), Ante-dependence (ANTE(1)), and Unstructured Correlation (UNR) (Iyit, 2008; Cetin, 2009). In the detection of the ideal covariance structure for the evaluated poultry data,-2 Res Log Likelihood, Akaike's Information Criteria (AIC), Corrected Akaike's Information Criterion (AICC), and Bayesian Information Criteria (BIC) were used. Both AIC and BIC can be preferred for large samples; whereas, BIC based on sample size and number of parameters can be suggested for small samples (Littell *et al.*, 2000; Çetin, 2009). Covariance structures investigated in this study were CS, UN, AR(1), TOEP, CSH, ARH(1), TOEPH, and UNR., respectively. In information criteria, smaller is better.

In this study, feed intake (FI), feed conversion ratio (FCR) and egg mass (EGGM) variables were specified as covariates. Time was adopted as a continuous variable for RISM. Cumulative egg weight (CEW) per hen was taken into account as a dependent variable. In order to determine the independent variables notably affecting CEW, we considered two main parts for RISM. First, all

Table II.- Results of goodness of fit criteria estimated for various variance-covariance structures.

Covariance Structure	With the Covariate				Without the Covariate			
	-2 Res Log Likelihood	AIC	AICC	BIC	-2 Res Log Likelihood	AIC	AICC	BIC
CS	5034.7	5040.7	5040.7	5047.8	7210.8	7216.8	7216.8	7223.9
UN	**5023.6**	**5031.6**	**5031.6**	**5041.0**	**7183.4**	**7191.4**	**7191.4**	**7200.9**
AR(1)	5034.7	5040.7	5040.7	5047.8	7210.8	7216.8	7216.8	7223.9
TOEP	5034.7	5040.7	5040.7	5047.8	7210.8	7216.8	7216.8	7223.9
CSH	**5023.6**	**5031.6**	**5031.6**	**5041.0**	**7183.4**	**7191.4**	**7191.4**	**7200.9**
UNR	**5023.6**	**5031.6**	**5031.6**	**5041.0**	**7183.4**	**7191.4**	**7191.4**	**7200.9**
ARH(1)	**5023.6**	**5031.6**	**5031.6**	**5041.0**	**7183.4**	**7191.4**	**7191.4**	**7200.9**
TOEPH	**5023.6**	**5031.6**	**5031.6**	**5041.0**	**7183.4**	**7191.4**	**7191.4**	**7200.9**

Table III.- The significance results of the fixed effects in RISM.

Covariance structure	With the Covariate[1] TRT F	TIME F	TRTxTIME F	FI F	FCR F	EGGM F	Without the Covariate TRT F	TIME F	TRTxTIME F
CS	8.31****	29.44****	1.03	72.36****	29.27****	8423.77****	2.55*	3364.53****	0.51
UN	8.52****	28.02****	0.79	70.85****	25.73****	8858.93****	1.45	5485.08****	0.83
AR(1)	8.31****	29.44****	1.03	72.36****	29.27****	8423.96****	2.55*	3363.79****	0.51
TOEP	8.31****	29.44****	1.03	72.36****	29.27****	8423.76****	2.55*	3364.53****	0.51
CSH	8.52****	28.02****	0.79	70.85****	25.73****	8858.97****	1.45	5485.09****	0.83
UNR	8.52****	28.02****	0.79	70.85****	25.73****	8858.97****	1.45	5485.09****	0.83
ARH(1)	8.52****	28.02****	0.79	70.85****	25.73****	8858.97****	1.45	5485.09****	0.83
TOEPH	8.52****	28.02****	0.79	70.85****	25.73****	8858.97****	1.45	5485.09****	0.83

$^{*}p<0.05$, $^{****}p<0.0001$

[1]FI, feed intake; FCR, feed conversion ratio; EGGM, egg mass.

variables included in RISM without covariates were treatment (TRT), time (TIME), and treatment x time interaction (TRTxTIME) for several covariance structures, CS, UN, AR(1), TOEP, CSH, ARH(1), TOEPH and UNR, respectively. Second, all variables included in RISM with covariates were treatment (TRT), time (TIME), treatment x time interaction (TRTxTIME), as well as feed intake (FI), feed conversion ratio (FCR), and egg mass (EGGM) covariates for several covariance structures, CS, UN, AR(1), TOEP,CSH, ARH(1), TOEPH, and UNR, respectively. The data of the repeated measures were analysed by using PROC MIXED procedure of SAS version 9.4 (SAS, 2014) program.

RESULTS AND DISCUSSION

Table II illustrates summary results of goodness of fit criteria estimated for various variance-covariance structures between repeated measurements in the scope of RISM where time effect was considered as a continuous variable.

According to the results obtained from Table II; UN, CSH, UNR, ARH(1) and TOEPH heterogeneous covariance structures gave the lowest goodness of fit criteria in modeling sequential variability in CEW between repeated measurements with/without covariates. With including the covariates, *viz.*, FI, FCR, and EGGM -2 Res Log Likelihood, AIC, AICC and BIC goodness of fit criteria were remarkably reduced by approximately more than 2000 in comparison with not including it. Eyduran *et al.* (2013) remarked that the addition of covariate would improve model quality criteria for both missing and non-missing repeated measures data. The investigators estimated, in non-missing data, the best model fit for ANTE(1) covariance structure. Similarly, only one covariate was also specified by Wang and Goonewardene (2004) for merely non-missing data.

In the scope of RISM, the significance results of the fixed effects for homogenous and heterogeneous variance-covariance structures in the data of the repeated measures are summarized in Table III.

When the time effect was examined as a continuous variable in the general linear mixed model, the fixed effects of treatment and time on CEW were found very

Table IV.- Summary results of variance components estimated for the best covariance structures.

Covariance Structures	Covariance Parameter	Subject	Estimate	Standard Error	Z	Pr >Z
	With the Covariate					
UN	σ_1^2	Laying hens(Treatment)	168.96	34.97	4.83	<.0001
	σ_{12}	Laying hens(Treatment)	-89.83	35.03	-2. 56	0.0103
	σ_2^2	Laying hens(Treatment)	389.78	64.64	6.03	<.0001
	σ_e^2	Laying hens(Treatment)	60.37	3.95	15.29	<.0001
CSH, UNR, ARH(1), TOEPH	σ_1^2	Laying hens(Treatment)	168.95	34.97	4.83	<.0001
	σ_2^2	Laying hens(Treatment)	389.78	64.63	6.03	<.0001
	ρ	Laying hens(Treatment)	-0.35	0.11	-3.08	0.0021
	σ_e^2	Laying hens(Treatment)	60.37	3.95	15.29	<.0001
	Without the Covariate					
UN	σ_1^2	Laying hens(Treatment)	5935.07	1248.75	4.75	<.0001
	σ_{12}	Laying hens(Treatment)	-1454.82	456.88	-3.18	0.0015
	σ_2^2	Laying hens(Treatment)	1572.03	269.00	5.84	<.0001
	σ_e^2	Laying hens(Treatment)	2690.15	174.74	15.39	<.0001
CSH,UNR, ARH(1), TOEPH	σ_1^2	Laying hens(Treatment)	5935.27	1248.75	4.75	<.0001
	σ_2^2	Laying hens(Treatment)	1572.03	269.00	5.84	<.0001
	ρ	Laying hens(Treatment)	-0.48	0.10	-4.65	<.0001
	σ_e^2	Laying hens(Treatment)	2689.85	174.70	15.40	<.0001

significantly (P<0.0001) for all covariance structures specified under the work. Additionally, a statistically significant effect was obtained in covariates like FCR, FI, and EGGM. When the covariates were excluded from the general linear mixed model, the treatment x time interaction effect had an insignificant effect on CEW for eight covariance structures implemented in RISM where only fixed effects were analyzed. On the other hand, the extremely inflated F values of time effect were produced for all the covariance structures as an outcome of excluding covariates (P<0.0001), and a significant influence of treatment factor on CEW was found for CS, AR(1), and TOEP covariance structure. Compared with excluding the covariates, it was found that the goodness of fit was much improved by including the covariates, which was in agreement with those of Eyduran *et al.* (2013).

Table IV illustrates summary results of variance components with regard to UN, CSH, UNR, AR(1), and TOEPH which were identified to be the best covariance structures for the RISM built with/without specifying covariates.

When Table IV was examined, parameter estimates, their standard errors and significance levels of the models with the covariates were found more different compared to those of the models without the covariates. Parameter estimates of variance components for the models with the covariates were much smaller in comparison with the models without the covariates (Table IV). In both cases, UN structure had four parameters, like in CSH, UNR, ARH(1), and TOEPH. In the output of MIXED procedure, UN(i,j) illustrates the covariance between i. and j. measurements. For instance, in the model with covariates, σ_1^2 is a variance of the measurements obtained in time 1, and became equal to UN (1,1)=168.96; σ_{12} is a covariance between the measurements taken in time 1 and time 2, and was found as: UN (2,1)=-89.83; σ_3^2 is variance of random error term.

Proportions of total variation (intra-class correlation, see Eq. 6) explained by laying hens (Treatment) and time effects included as random effects in RISM were estimated as $\rho=0.90$ and $\rho=0.70$ in case of adding and excluding covariates for CSH, UNR, ARH(1), TOEPH and UN structures, respectively. A specification of covariates for the covariance structures with the explained variation of $\rho=0.90$ provided more advantages compared with those without covariates. Covariance structures in modeling heterogeneity of repeated measures data with eight time levels per animal are given below. Variance-covariance presentations for random effects are shown in Table V.

From the matrix presentation of Table V, it was understood noticeably that parameter estimates displayed in variance-covariance matrices for random effects of the RISM with covariates (FCR, FI, and EGGM) were very much lower than the estimates made for those without covariates.

Table V.- Presentation of variance-covariance matrices of random effects of the models from several covariance structures.

Covariance structures	With the covariate	Without the covariate
UN	$G=\begin{bmatrix}168.96 & -89.83\\ -89.83 & 389.78\end{bmatrix}$	$G=\begin{bmatrix}5935.07 & -1454.82\\ -1454.82 & 1572.03\end{bmatrix}$
CSH, UNR, ARH(1), TOEPH	$G=\begin{bmatrix}168.95 & -89.82\\ -89.82 & 389.78\end{bmatrix}$	$G=\begin{bmatrix}5935.27 & -1454.89\\ -1454.89 & 1572.03\end{bmatrix}$

CONCLUSION

In mixed models quite easily applied in repeated measures data, RISM as a specification of mixed models takes account of individual variations by including animal effect to the model. In the study, the presence of covariates in RISM had a very improving effect on the estimates of fixed and random effects compared to the absence of them. The results showed that addition of significant covariates contributing to RISM models was reasonable.

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Statement of conflict of interest

Authors have declared no conflict of interest.

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