Homework 4 - BIOS 6643 Analysis of Longitudinal Data

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Question 1

Complex MLE estimation in LMM requires computational optimization approaches, the goal here is to implement a basic Newton-Raphson algorithm in R. The following data are an i.i.d sample from a Cauchy(θ,1) distribution: 1.77, -0.23, 2.76, 3.80, 3.47, 56.75, -1.34, 4.24, -2.44, 3.29, 3.71, -2.40, 4.53, -0.07, -1.05, -13.87, -2.53, -1.75, 0.27, 43.21.

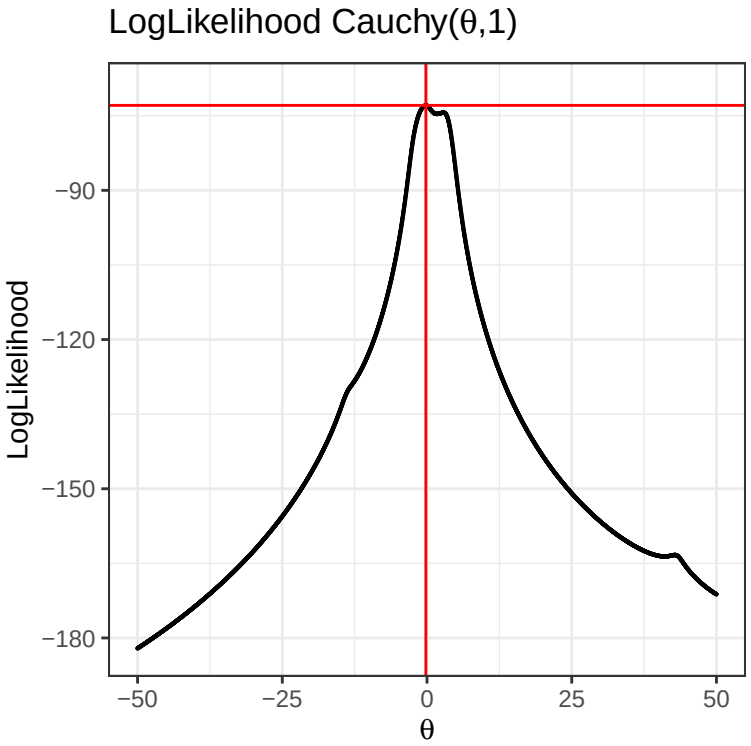
Part A: Graph the log likelihood function.

The likelihood function of the Cauchy(θ,1) distribution is:

$$\frac{1}{\pi^n}\frac{1}{\prod[1+(x_i-\theta)^2]}$$

and the loglikelihood is:

$$-nlog(\pi)-\sum_i^n log(1+(x_i-\theta)^2)$$



From the plot of log-likelihood the maximum log-likelihood values is -72.92, and the optimal theta is -0.2.

Part B

Find (and write an R program) to find the MLE for θ using the Newton-Raphson method.

The equation for the Newton-Raphson method in general form is as follows:

$$x_i = x_{i-1} - \frac{f(x_{i-1})}{f'(x_{i-1})}$$

Translating this to finding the MLE of θ:

$$\hat{\theta}_i = \hat{\theta}_{i-1} - \frac{logL'(\hat{\theta}_{i-1})}{logL''(\hat{\theta}_{i-1})} = \hat{\theta}_{i-1} - \frac{S(\hat{\theta}_{i-1})}{I(\hat{\theta}_{i-1})}$$

What finding an MLE the score $S(\theta)$, the derivative of the log-likelihood, should equal 0, $S(\theta) = 0$. $I(\theta)$ is the Fisher observed information from the data.

Check the code appendix for the function.

Part C Try all of the following starting points: -11,-1,0,1.5,4,4.7,7,8,and 38.

Table 1: Cauchy Location Parameter Estimate

Starting Theta	Estimate
-11.0	-0.193
-1.0	-0.193
0.0	-0.193
1.5	1.714
4.0	2.817
4.7	-0.193
7.0	41.041
8.0	-0.193
38.0	42.795

PART D Discuss your results. Is the mean of the data a good starting point?

When using the mean as the starting point the estimate is 54.877. The mean is not a good starting point in this case, as the convergence is relatively far off from the true maximum of around -0.2 given from the maximum likelihood plot. The Newton-Raphson method is extremely sensitive to the starting point.

Question 2

In a paragraph explain the difference between a general linear model or multiple regression (GLM; not a generalized linear model like a logistic regression or GLM; not a generalized linear model like a logistic regression or Poisson, which will be discussed later) and a linear mixed model (LMM).

A general linear model only has fixed effects, while a linear mixed model includes both fixed and random effects. The random effects of the linear mixed model allows the model to account for differences between subjects. A simple example would be measuring something like cholesterol levels through time. A general linear model (fixed effects only) may include covariates such as time, BMI, smoking status, sex, race, etc. Every individual will follow the same regression line based on those covariates. In a linear mixed model random effect which account for subject differences, such as someone tending to have higher or lower cholesterol at start (random intercept) can be included to better model change over time. A better fit may be found by including random slopes as well for each subject if cholesterol trajectory is found to be different between subjects.

Question 3

In a short paragraph, explain the difference between a profiled likelihood and a restricted likelihood for a linear mixed model, and how and why they are used.

In a profile likelihood you maximize the likelihood by fixing every other parameter and only allowing one to vary. Doing this maximizes the single parameter you allowed to vary. You can then repeat this process for every other parameter incrementally, plugging in the estimates for parameters which have already been maximized. The downside to this method is that variance estimates are biased downward. The restricted likelihood (REML) allows for estimating parameters which are not biased regardless of sample size. The downside for the REML method compared to profile likelihood is that you can only compare REML model using a likelihood ratio of both models have the same set of fixed effects.

Profile likelihood - maximize likelihood by fixing every other parameter and only allow one to vary and maximize that using a grid search. After getting that maximum repeat each process for each parameter in the set of likelihood parameter.

Restricted maximum likelihood - REML has property that your standard error are unbiased regardless of sample size, so generally is in situations where were trying to get unbiased estimates of errors when sample sizes are small. Loglikelihood are not valid for reduced in full REML models. Can only compare REML models that have the same set of fixed effects.

Part 2ish

Investigator wants to understand whether Cortisol (a stress hormone) secretion differs in women suffering from depression. Cortisol was measured every 10 minutes for a period of 24 hours starting at 9 am. 26 patients and 26 controls were collected in the study. Although the data were collected every 10 minutes for a period of 24 hours on each subject (144 observations), the investigators were interested in differences in the circadian pattern between the groups. Data was divided into 6 blocks of 4 hours and averaged to obtain a set of "block means".

Question 4

Part A Fit a multiple linear regression to investigate how mean cortisol values change over the day (categorical time) and how the average cortisol levels differ by group (no interaction for this model). This will be used to anchor the comparisons later in the assignment.

Table 2: MLR Cortisol

Term	Estimate	Std.Error	95% Conf.Low	95% Conf.High	P-Value
(Intercept)	3.0501	0.5088	2.0489	4.0513	5.7451e-09
timeTime2	3.9697	0.6662	2.6589	5.2806	6.9911e-09
timeTime3	10.0791	0.6662	8.7682	11.3899	$<$ 2.22e-16
timeTime4	6.1979	0.6662	4.8870	7.5087	$<$ 2.22e-16
timeTime5	4.4042	0.6662	3.0934	5.7151	1.7017e-10
timeTime6	1.7518	0.6662	0.4410	3.0627	0.0089779
casecontrolp	0.9211	0.3846	0.1643	1.6779	0.0172285

Table 1 shows the output of the multiple linear regression where mean cortisol is the outcome and time and casecontrol are covariates. Time is factored into 6 different levels, where time 1 is the reference.

Part B Provide a table of mean differences from the 6th time period along with SE's of the differences. Interpret two of the coefficients. You do not need to conduct inference.

Table 3: MLR Cortisol - Time 6 Reference

Term	Estimate	Std.Error	95% Conf.Low	95% Conf.High	P-Value
(Intercept)	4.8020	0.5088	3.8008	5.8031	$<$ 2.22e-16
timeTime1	-1.7518	0.6662	-3.0627	-0.4410	0.00897790
timeTime2	2.2179	0.6662	0.9071	3.5287	0.00097714
timeTime3	8.3273	0.6662	7.0164	9.6381	$<$ 2.22e-16
timeTime4	4.4461	0.6662	3.1352	5.7569	1.1726e-10
timeTime5	2.6524	0.6662	1.3415	3.9632	8.5630e-05
casecontrolp	0.9211	0.3846	0.1643	1.6779	0.01722849

Table 2 shows the output of the multiple linear regression where time 6 is the reference group. For term timeTime1 this is the mean difference between cortisol at time 1 and cortisol at time 6. Interpreting this it means cortisol is 1.7518 units higher at time 6 compared to time 1. For the term casecontrolp this is the mean difference between the control (reference) group and women with depression. Interpreting this

it means cortisol is 0.9211 units higher for women with depression compared to women without depression (control).

Part C Will these standard error be too big or small and why?

Standard error is found with the equation:

$$Std.Error = \frac{\sigma}{\sqrt{n}}$$

For a study at a single instance n is generally the number of subjects. For this study because subjects each have 6 time points (assuming balanced data) n refers to all instances where cortisol was measured for each subject, 52×6, which mean $n = 312$.

Table 4: MLR Cortisol - Time 6 Ref. Variances

Intercept	Time 1	Time 2	Time 3	Time 4	Time 5	Group P
1.294317	2.218829	2.218829	2.218829	2.218829	2.218829	0.7396097

Table 3 shows the variances for each estimate. Given that each estimate is relatively low compared to the variances the standard errors (which were used to calculate variance) may be too large to make a meaningful interpretation, as subjects may have significantly different mean cortisol measurements between each other.

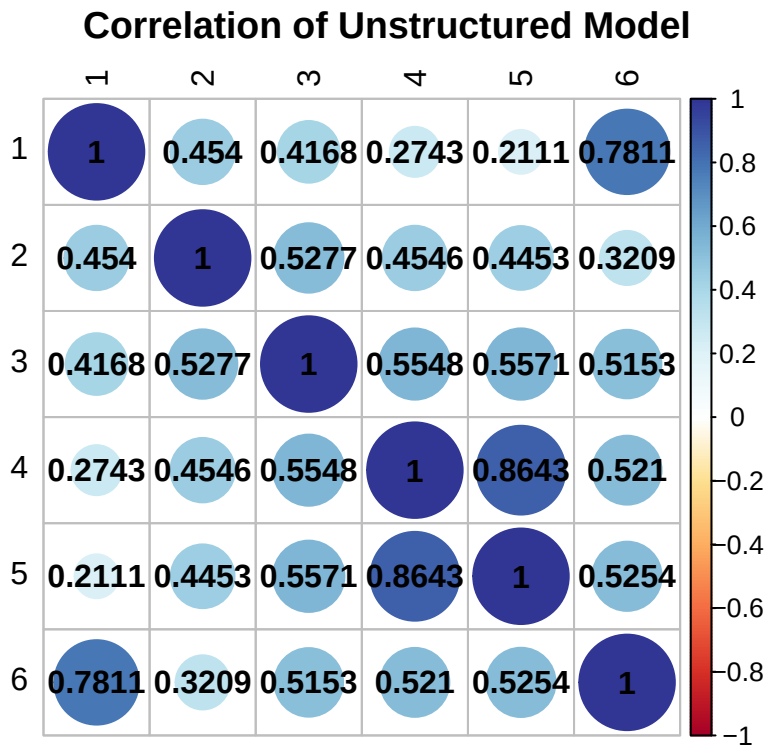
Question 5

Part A Fit a linear mixed model assuming categorical time and group with an unstructured variance-covariance structure using method=REML (the default). Print out the correlation matrix and interpret the general patterns of the correlation in the errors for an individual.

Table 5: LMM Unstructured Var-Cov

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.1311	0.6060	1.9433	4.3190	4.3174e-07
timeTime2	3.9697	0.5074	2.9753	4.9641	8.4296e-14
timeTime3	10.0791	0.5244	9.0514	11.1068	$<$ 2.22e-16
timeTime4	6.1979	0.5849	5.0514	7.3444	$<$ 2.22e-16
timeTime5	4.4042	0.6099	3.2089	5.5995	4.1222e-12
timeTime6	1.7518	0.3213	1.1221	2.3815	1.0258e-07
casecontrolp	0.7591	0.7254	-0.6627	2.1808	0.2962

Table 4 shows the fixed effects for the linear mixed effects model with unstructured variance-covariance.



The above plot shows the correlation structure for the linear mixed model with unstructured variance-covariance. Because the correlation structure is unstructured each time point correlation is different and has no general pattern. This is reflected in the standard errors, where each time point has a unique standard error.

Part B Provide a table of mean differences from the 6th time period along with SE's of the differences. Interpret two of the coefficients. You do not need to conduce inference.

Table 6: LMM Unstructured Var-Cov - Time 6 Ref.

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	4.8830	0.6060	3.6951	6.0708	1.7812e-14
timeTime1	-1.7518	0.3213	-2.3815	-1.1221	1.0258e-07
timeTime2	2.2179	0.5658	1.1089	3.3269	0.00010954
timeTime3	8.3273	0.4780	7.3903	9.2642	$<$ 2.22e-16
timeTime4	4.4461	0.4752	3.5146	5.3775	$<$ 2.22e-16
timeTime5	2.6524	0.4730	1.7253	3.5795	4.6086e-08
casecontrolp	0.7591	0.7254	-0.6627	2.1808	0.29619701

Table 5 shows the output of the linear mixed model with unstructured variance-covariance where time 6 is the reference group.

- For term timeTime1 this is the mean difference between cortisol at time 1 and cortisol at time 6. Interpreting this it means cortisol is 1.7518 units higher at time 6 compared to time 1. This estimate is identical to that of the MLR model from question 4, but the standard error is smaller at 0.3213

compared to the MLR model's standard error of 0.6662. In other words the estimate of the LMM with unstructured variance-covariance is more precise.

- For term timeTime2 this is the mean difference between cortisol at time 2 and cortisol at time 6. Interpreting this is means cortisol is 2.2179 units higher at time 2 compared to time 6. This estimate is identical to that of the MLR model from question 4, but the standard error is smaller at 0.5658 compared to the MLR model's standard error of 0.6662. In other words the estimate of the LMM with unstructured variance-covariance is more precise.

Part C What is the estimate difference in mean cortisol levels (and SE) between the depressed and non-depressed groups. Interpret the finding in a sentence. You do not need to conduct inference.

From table 4 (or 5, they are equivalent for the casecontrol variable) the estimate difference between the control group and the depressed group is 0.7591. This means that cortisol is 0.7591 units higher in the depressed group. The estimate is smaller than the estimate from the MLR model, but has a higher standard error of 0.7254 compared to the MLR model's standard error of 0.3846.

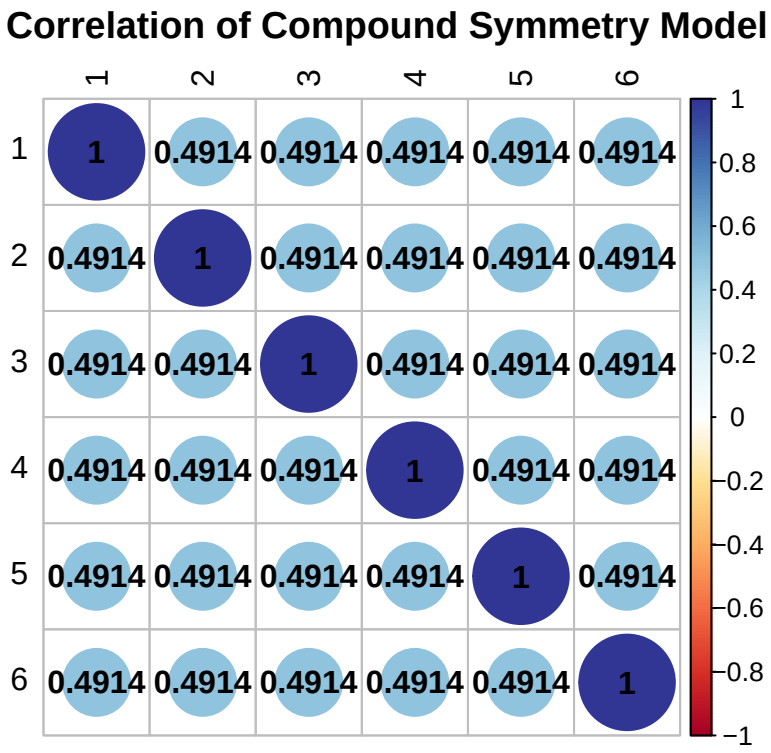
Question 6

Part A Fit a linear mixed model assuming categorical time and group with a compound symmetry structure using method=REML (the default). Print out the correlation matrix and interpret the general patterns of the correlation in the errors for an individual.

Table 7: LMM Compound Symmetry Var-Cov

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.0501	0.5938	1.8864	4.2139	4.9916e-07
timeTime2	3.9697	0.4770	3.0348	4.9047	2.9358e-15
timeTime3	10.0791	0.4770	9.1441	11.0140	$<$ 2.22e-16
timeTime4	6.1979	0.4770	5.2629	7.1328	$<$ 2.22e-16
timeTime5	4.4042	0.4770	3.4693	5.3392	$<$ 2.22e-16
timeTime6	1.7518	0.4770	0.8169	2.6868	0.00028364
casecontrolp	0.9211	0.7180	-0.4861	2.3283	0.20050032

Table 6 shows the fixed effects for the linear mixed effects model with compound symmetry variance-covariance structure.



The above plot shows the correlation structure for the linear mixed model with compound symmetry variance-covariance structure. Because the correlation structure is compound symmetric each correlation (besides the variances) is the same value. This is reflected in the standard error, where each time point standard error has the same value of 0.4770.

Part B Provide a table of mean differences from the 6th time period along with SE's of the differences. Interpret two of the coefficients. You do not need to conduct inference.

Table 8: LMM Compound Symmetry Var-Cov - Time 6 Ref.

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	4.8020	0.5938	3.6382	5.9657	1.4528e-14
timeTime1	-1.7518	0.4770	-2.6868	-0.8169	0.00028364
timeTime2	2.2179	0.4770	1.2829	3.1529	4.9628e-06
timeTime3	8.3273	0.4770	7.3923	9.2622	$<$ 2.22e-16
timeTime4	4.4461	0.4770	3.5111	5.3810	$<$ 2.22e-16
timeTime5	2.6524	0.4770	1.7174	3.5873	5.8875e-08
casecontrolp	0.9211	0.7180	-0.4861	2.3283	0.20050032

Table 7 shows the output of the linear mixed model with compound symmetry variance-covariance where time 6 is the reference group. Because the variance-covariance structure is compound symmetric each SE for time points are the same.

- For term timeTime1 this is the mean difference between cortisol at time 1 and cortisol at time 6. Interpreting this it means cortisol is 1.7518 units higher at time 6 compared to time 1. This estimate

is identical to that of the MLR model from question 4, but the standard error is smaller at 0.4770 compared to the MLR model's standard error of 0.6662. In other words the estimate of the LMM with compound symmetry variance-covariance is more precise.

- For term timeTime2 this is the mean difference between cortisol at time 2 and cortisol at time 6. Interpreting this it means cortisol is 2.2179 units higher at time 2 compared to time 6. This estimate is identical to that of the MLR model from question 4, but the standard error is smaller at 0.4770 compared to the MLR model's standard error of 0.6662. In other words the estimate of the LMM with compound symmetry variance-covariance is more precise.

Part C What is the estimated difference in mean cortisol levels (and SE) between the depressed and non-depressed groups. Interpret the finding in a sentence. You do not need to conduct inference.

From table 4 (or 5, they are equivalent for the casecontrol variable) the estimate difference between the control group and the depressed group is 0.9211. This means that cortisol is 0.9211 units higher in the depressed group. This estimate is identical to the MLR model, but has a higher standard error of 0.7180 compared to the MLR model's standard error of 0.3846.

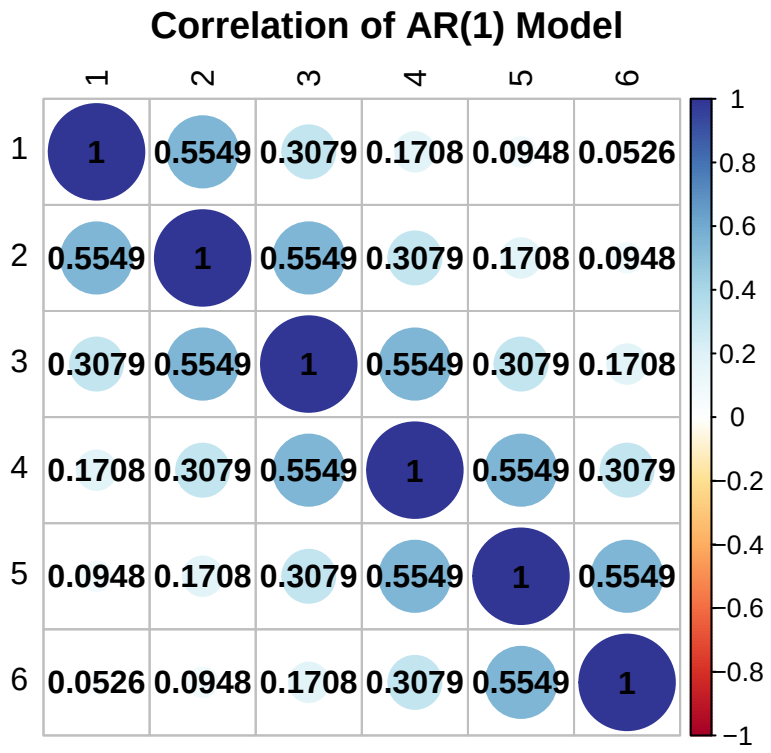
Question 7

Part A Fit a linear mixed model assuming categorical time and group with an AR(1) structure using method=REML (the default). Print out the correlation matrix and interpret the general patterns of the correlation in the errors for an individual.

Table 9: LMM AR(1) Var-Cov

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.1384	0.5646	2.0318	4.2449	5.9331e-08
timeTime2	3.9697	0.4484	3.0909	4.8486	$<$ 2.22e-16
timeTime3	10.0791	0.5591	8.9832	11.1750	$<$ 2.22e-16
timeTime4	6.1979	0.6120	4.9984	7.3974	$<$ 2.22e-16
timeTime5	4.4042	0.6395	3.1509	5.6575	3.2512e-11
timeTime6	1.7518	0.6542	0.4696	3.0340	0.0078104
casecontrolp	0.7446	0.6096	-0.4502	1.9393	0.2228629

Table 8 shows the fixed effects for the linear mixed effects model with AR(1) variance-covariance.



The above output shows the correlation structure for the linear mixed model with AR(1) variance-covariance. As time points get further from each other the correlation decreases. Each standard error is different, which is reflected by each covariance being different. This is likely not a good structure for this data set, as time 6 and time 1 have very little correlation even though they are actually the same distance from each other as the other consective time points.

Part B Provide a table of mean differences from the 6th time period along with SE's of the differences. Interpret two of the coefficients. You do not need to conduct inference.

Table 10: LMM AR(1) Var-Cov - Time 6 Ref.

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	4.8902	0.5646	3.7837	5.9968	2.7585e-16
timeTime1	-1.7518	0.6542	-3.0340	-0.4696	0.00781044
timeTime2	2.2179	0.6395	0.9646	3.4712	0.00059886
timeTime3	8.3273	0.6120	7.1278	9.5268	$<$ 2.22e-16
timeTime4	4.4461	0.5591	3.3502	5.5420	3.6193e-14
timeTime5	2.6524	0.4484	1.7735	3.5313	8.8967e-09
casecontrolp	0.7446	0.6096	-0.4502	1.9393	0.22286293

Table 9 shows the output of the linear mixed model with AR(1) variance-covariance where time 6 is the reference group.

- For term timeTime1 this is the mean difference between cortisol at time 1 and cortisol at time 6. Interpreting this is means cortisol is 1.7518 units higher at time 6 compared to time 1. This estimate

is identical to that of the MLR model from question 4, but the standard error is slightly smaller at 0.6542 compared to the MLR model's standard error of 0.6662. In other words the estimate of the LMM with AR(1) variance-covariance is more precise.
- For term timeTime2 this is the mean difference between cortisol at time 2 and cortisol at time 6. Interpreting this it means cortisol is 2.2179 units higher at time 2 compared to time 6. This estimate is identical to that of the MLR model from question 4, but the standard error is slightly smaller at 0.6395 compared to the MLR model's standard error of 0.6662. In other words the estimate of LMM with AR(1) variance-covariance is slightly more precise.

Part C What is the estimated difference in mean cortisol levels (and SE) between the depressed and non-depressed groups. Interpret the finding in a sentence. You do not need to conduct inference.

From table 4 (or 5, they are equivalent for the casecontrol variable) the estimate difference between the control group and the depressed group is 0.7446. This means that cortisol is 0.7446 units higher in the depressed group. This estimate is smaller compared to the MLR model, but has a higher standard error of 0.6096 compared to the MLR model's standard error of 0.3846.

Question 8

Write a paragraph comparing and contrasting the parameter estimates for β (the mean differences) and the standard errors across the difference variance-covariance structures.

Between the different variance-covariance structures the time points all have the same estimates. Between the MLR model and the unstructured LMM the standard errors for the time coefficients decrease. Between the MLR model and the compound symmetry LMM the standard errors for the time coefficients decrease (and are all the same). Between the unstructured and compound symmetry LMMs the standard errors are smaller in the compound symmetry model. Between the MLR model and the AR(1) model the standard errors are all smaller in the AR(1) model. Between the unstructured LMM and the AR(1) LMM some time points have higher standard errors and some have lower between the models. Between the compound symmetry model and the AR(1) model the compound symmetry model has smaller standard errors for all time points.

The intercept and casecontrol coefficients change between variance-covariance structure. Between the MLR and the unstructured LMM the intercept is higher in the MLR model and the casecontrol coefficient is higher in the unstructured model. Standard error for both of these is smaller in the MLR model. Between the MLR and the compound symmetry LMM the estimates are identical, and the compound symmetry has higher standard error. Between the MLR and AR(1) models the intercept is higher in the AR(1) model and the casecontrol coefficient is higher in the MLR model. Standard error is higher in the AR(1) model. Between the compound symmetry LMM and the unstructured LMM the intercept is higher in the unstructured model and the casecontrol coefficient is higher in the compound symmetry model. Between the unstructured model and the AR(1) model the intercept is higher in the AR(1) model and the casecontrol coefficient is higher in the unstructured model. The standard error is higher for both coefficients in the unstructured model. Between the compound symmetry LMM and the AR(1) LMM the intercept is higher in the AR(1) model and for the case control coefficient it is higher in the compound symmetry model. The standard errors are higher in the compound symmetry models.

Question 9

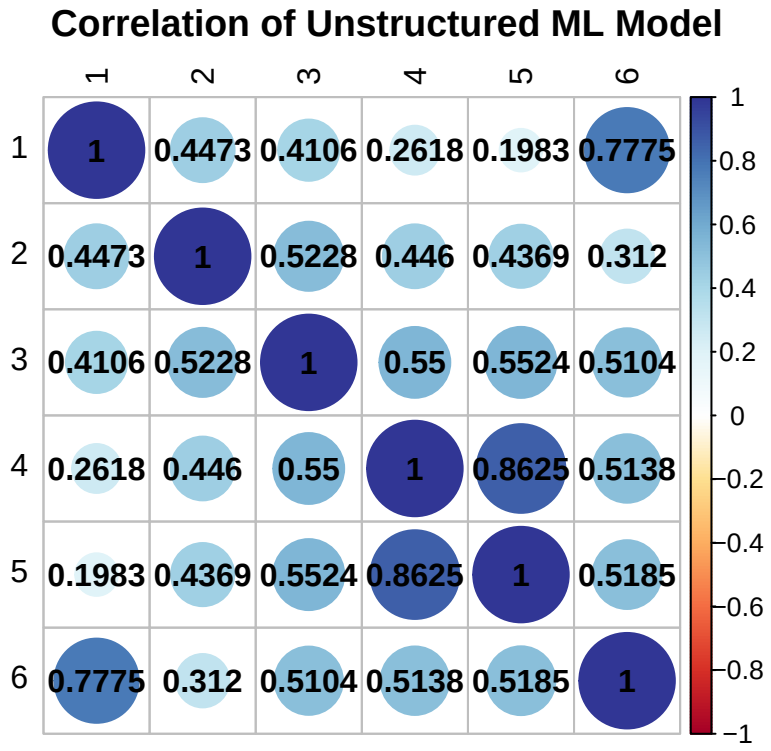
Refit the models using method = ML and compare and contrast the findings with the different estimation approaches. How were the β coefficients impacted (if at all)? How were the SE estimates (and variance-covariance structures) impacted by the different methods (if at all)? Explain.

Question 5 Refit

Table 11: LMM Unstructured Var-Cov ML

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.1325	0.6023	1.9521	4.3129	3.6379e-07
timeTime2	3.9697	0.5083	2.9735	4.9660	9.2795e-14
timeTime3	10.0791	0.5249	9.0503	11.1079	$<$ 2.22e-16
timeTime4	6.1979	0.5874	5.0465	7.3493	$<$ 2.22e-16
timeTime5	4.4042	0.6122	3.2043	5.6041	4.9000e-12
timeTime6	1.7518	0.3225	1.1198	2.3839	1.1396e-07
casecontrolp	0.7563	0.7182	-0.6514	2.1641	0.29315

Table 11 shows the fixed effects for the linear mixed effects model with unstructured variance-covariance when the maximum likelihood method is used. Compared to the REML method all time point coefficients are the same and the intercept and casecontrol coefficients are slightly different. Standard errors for the time points increased slightly, and standard errors for intercept and casecontrol decreased slightly.



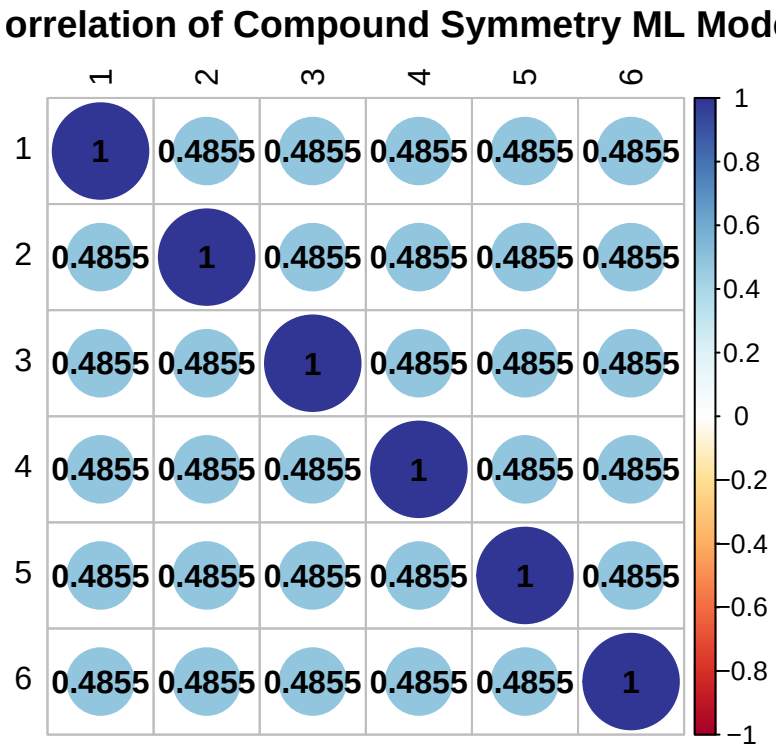
The correlations at each time point decreased slightly for the ML method compared to the REML method.

QUESTION 6 REFIT

Table 12: LMM Compound Symmetry Var-Cov ML

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.0501	0.5905	1.8928	4.2074	4.3348e-07
timeTime2	3.9697	0.4778	3.0333	4.9062	3.2237e-15
timeTime3	10.0791	0.4778	9.1426	11.0156	$< 2.22e-16$
timeTime4	6.1979	0.4778	5.2614	7.1344	$< 2.22e-16$
timeTime5	4.4042	0.4778	3.4677	5.3407	$< 2.22e-16$
timeTime6	1.7518	0.4778	0.8154	2.6883	0.00029009
casecontrolp	0.9211	0.7121	-0.4745	2.3167	0.19679936

Table 12 shows the fixed effects for the linear mixed effects model with compound symmetry variance-covariance structure. The estimates are the same between the REML and ML methods. The standard errors slightly increased for the time point coefficients and decreased slightly or the intercept and casecontrol estimates.



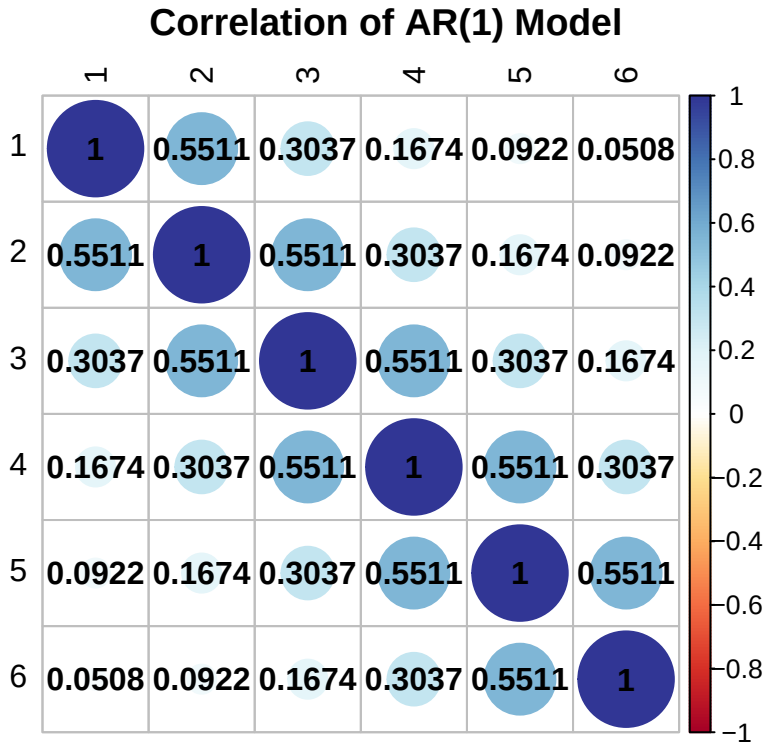
The correlation is smaller in the ML method compared to the REML method.

QUESTION 7 Refit

Table 13: LMM AR(1) Var-Cov

Term	Estimate	Std.Error	95% Conf.Low	95% Conf. High	P-Value
(Intercept)	3.1374	0.5626	2.0347	4.2402	5.4151e-08
timeTime2	3.9697	0.4492	3.0894	4.8501	< 2.22e-16
timeTime3	10.0791	0.5594	8.9827	11.1755	< 2.22e-16
timeTime4	6.1979	0.6117	4.9989	7.3969	< 2.22e-16
timeTime5	4.4042	0.6387	3.1523	5.6561	3.1035e-11
timeTime6	1.7518	0.6532	0.4717	3.0320	0.0077141
casecontrolp	0.7465	0.6061	-0.4414	1.9344	0.2190467

Table 13 shows the fixed effects for the linear mixed effects model with AR(1) variance-covariance. The time estimates are the same between both methods. The intercept is higher in the REML method and the casecontrol coefficient is higher in the ML method. The direction of change for the standard errors vary between methods.



Between the REML and ML methods the direction of change for the correlations vary between time points.