2AMS10 - Solution Exam 05-11-2021

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Data Description

A multi-site randomized controlled trial was conducted to investigate the effect of three different cognition training's on the cognitive performance of independent-living elderly (i.e., 65 years and older). The study included 2802 participants collected from six different area's of the United States. They were randomly allocated to one of four different trainings (memory, reasoning, speed, and a control). They study investigated the performance on memory, reasoning, and speed. The participants were first tested on cognition before they undergone a cognition training (the so-called baseline period) and they were tested four times after training. The first time just after the training session and then approximately annually. The goal is to understand if the treatment has an influence on the cognitive trajectories of the participants.

1. Trial design variables:
   (a) `SITE`: indicating an area of the USA
   (b) `ID`: indicating a participant number
   (c) `DAYS`: the number of days measured from the time of the training
   (d) `PERIOD`: a categorical variable indicating the period of the observation
   (e) `ORDER`: a numerical support variable for the period
   (f) `TRT`: A treatment indicator with four levels (1 = memory; 2 = reasoning; 3 = speed; 4 = control)
2. Participant baseline characteristics:
   (a) `SEX`: a binary variable indicating the sec of the participant (0 = male; 1 = female)
   (b) `AGEC`: a categorical variable for age group ($0 = [65, 70)$; $1 = [70, 75)$; $2 = \geq 75$)
3. Response variables:
   (a) `HVLT`: Hopkins verbal learning test
   (b) `AVLT`: Auditory verbal learning test
   (c) `WORD`: A speed score measuring the number of correct words out of 30 tested words

Questions

1. In this exercise we will focus on the response `HVLT` in the sixth site (`SITE` = 6), observed at the first and second moment after training (i.e., post-training and first annual moment). We will consider the factors subject (`ID`), period (`PERIOD`) and training (`TRT`). Make sure that you create an appropriate data set or otherwise use an appropriate selection statement for the analysis questions.

   (a) Write down the **full** ANOVA model in mathematical terms with all relevant assumptions (assuming balanced design).

   Answer: Let us denote the HVLT response of the k-th subject (`ID`) receiving the i-th treatment (`TRT`) at j-th period (`PERIOD`) as y_{ijk}. Then the proposed ANOVA model is given by:

$$y_{ijk} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + c_{k(i)} + \varepsilon_{ijk},$$

   where,

$$\begin{aligned}
\mu =& \text{mean effect}, \\
\alpha_i =& \text{fixed effect of the } i\text{-th treatment}, \\
\beta_j =& \text{fixed effect of the } j\text{-th period}, \\
\alpha\beta_{ij} =& \text{fixed interaction of the } i\text{-th treatment and the } j\text{-th period}, \\
c_{k(i)} =& \text{random effect of the } i\text{-th period on the } k\text{-th subject}, \\
\varepsilon_{ijk} =& \text{random error in observation.}
\end{aligned}$$

   Since there are 4 treatments and 2 periods, relevant assumptions for the model are:

$$\begin{aligned}
\sum_{i=1}^{4} \alpha_i =& 0; \\
\beta_1 + \beta_2 =& 0; \\
\sum_{i=1}^{4} \alpha\beta_{ij} =& 0 \quad \text{for all } i; \\
c_{k(i)} \sim& N\left(0, \sigma^2_{I(T)}\right); \quad \text{and} \\
\varepsilon_{ijk} \overset{i.i.d}{\sim}& N(0, \sigma^2_R).
\end{aligned}$$

   (b) Provide the expected mean squares of this ANOVA model in mathematical terms, give the variance component estimators, and provide the F-test for all terms in the model (assuming a balanced design again).

   Answer: For calculating the expected mean squares of this ANOVA model, we prepare the following table:

	Q_T	Q_P	Q_{TP}	$\sigma^2_{I(T)}$	σ^2_R	df
T	JK	0	0	J	1	I-1
P	0	IK	0	0	1	J-1
TP	0	0	K	0	1	(I-1)(J-1)
I(T)	0	0	0	J	1	I(K-1)
Res	0	0	0	0	1	I(J-1)(K-1)

where, I, J and K denote the number of treatment, period and subject respectively. In our case $I = 4$ and $J = 2$. Therefore from the table, the expected mean squares are given by:

$$\begin{aligned}
\mathbb{E}\left[MS_T\right] =& Q_T + J\sigma^2_{I(T)} + \sigma^2_R;\\
\mathbb{E}\left[MS_P\right] =& Q_P + \sigma^2_R;\\
\mathbb{E}\left[MS_{TP}\right] =& Q_{TP} + \sigma^2_R;\\
\mathbb{E}\left[MS_{I(T)}\right] =& J\sigma^2_{I(T)} + \sigma^2_R;\\
\mathbb{E}\left[MS_R\right] =& \sigma^2_R.
\end{aligned}$$

Therefore the variance component estimators are:

$$\begin{aligned}
\hat{\sigma}^2_R =& MS_R, \quad \text{and}\\
\hat{\sigma}^2_{I(T)} =& \left[MS_{I(T)} - MS_R\right]/I(K-1).
\end{aligned}$$

F-tests for the variance component is:

$$\begin{aligned}
&H_0 : \sigma^2_{I(T)} = 0 \quad \text{v/s} \quad H_1 : \text{not } H_0.\\
&\text{Test Statistic:} F = \frac{MS_{I(T)}}{MS_R} \sim F_{df\left(MS_{I(T)}\right), df(MS_R)}.
\end{aligned}$$

(c) Determine the quadratic term mathematically for the effect of training in the expected mean square for training. Thus determine the first term of $\mathbb{E}[MS_{\text{TRT}}]$.

Answer: The quadratic term for the effect of training in the mean square training can be obtained from the table as:

$$Q_T = \mathbb{E}\left[MS_T - MS_{I(T)}\right]$$

. Using the assumptions for the fixed interaction effects, simplifying the summands of $SS_{I(T)}$,

$$\bar{y}_{i.k} - \bar{y}_{i..} = c_{k(i)} + \bar{\varepsilon}_{i.k} - \bar{c}_{.(i)} - \bar{\varepsilon}_{i..}\ .$$

Similarly,

$$\bar{y}_{i..} - \bar{y}_{...} = \alpha_i + \left(\bar{c}_{.(i)} + \bar{\varepsilon}_{i..} - \bar{c}_{.(.)} - \bar{\varepsilon}_{...}\right).$$

Since $\bar{\varepsilon}_{i.k} \sim N\left(0, \frac{1}{2}\sigma_R^2\right)$, taking expectation over $SS_{I(T)}$ we have

$$\begin{aligned}
\mathbb{E}\left[SS_{I(T)}\right] &= \sum_{i=1}^{4}\sum_{j=1}^{2}\sum_{k=1}^{K}\left[\mathbb{E}\left(c_{k(i)} - \bar{c}_{.(i)}\right)^2 + \mathbb{E}\left(\bar{\varepsilon}_{i.k} - \bar{\varepsilon}_{i..}\right)^2\right] \\
&= 8(K-1)\sigma_{I(T)}^2 + 8(K-1)\frac{\sigma_R^2}{2} \\
&= 4(K-1)\left[2\sigma_{I(T)}^2 + \sigma_R^2\right].
\end{aligned}$$

The covariance terms produce 0 since the terms are independent. Therefore

$$\mathbb{E}\left[MS_{I(T)}\right] = 2\sigma_{I(T)}^2 + \sigma_R^2$$

On the other hand $\bar{c}_{.(i)} \sim N\left(0, \frac{1}{K}\sigma_{I(T)}^2\right)$ and $\bar{\varepsilon}_{i..} \sim N\left(0, \frac{1}{2K}\sigma_R^2\right)$. Taking expectation over SS_T,

$$\begin{aligned}
\mathbb{E}\left[SS_T\right] &= \sum_{i=1}^{4}\sum_{j=1}^{2}\sum_{k=1}^{K}\left[\alpha_i^2 + \mathbb{E}\left(\bar{c}_{.(i)} - \bar{c}_{.(.)}\right)^2 + \mathbb{E}\left(\bar{\varepsilon}_{i..} - \bar{\varepsilon}_{...}\right)^2\right] \\
&= 2K\sum_{i=1}^{4}\alpha_i^2 + 6K\frac{\sigma_{I(T)}^2}{K} + 6K\frac{\sigma_R^2}{2K} \\
&= 2K\sum_{i=1}^{4}\alpha_i^2 + 3\left[2\sigma_{I(T)}^2 + \sigma_R^2\right].
\end{aligned}$$

Other covariance terms produce 0 using their independence structure. Therefore

$$\mathbb{E}\left[MS_T\right] = \frac{2K}{3}\sum_{i=1}^{4}\alpha_i^2 + 2\sigma_{I(T)}^2 + \sigma_R^2\ .$$

Hence the quadratic term for the training effect is

$$Q_T = \frac{2K}{3}\sum_{i=1}^{4}\alpha_i^2.$$

(d) Since the design is not entirely balanced, what ANOVA estimation technique would you recommend for your ANOVA model? Explain your answer.

Answer: Firstly we can find a ordering between the factors as subject (ID), training (TRT), period (PERIOD). Moreover, the degrees of freedom for training and period are 4 and 2 respectively making ML estimation techniques less applicable in this situation. So we can use Type 1 ANOVA estimation technique for the unbalanced case.

(e) Fit your ANOVA model and provide the complete ANOVA table. Based on this table, do you believe there is evidence for a training effect? Explain your answer.

Answer: We use the following code:

```
PROC MIXED DATA = ANOVA METHOD = TYPE1;
        CLASS ID TRT PERIOD;
        MODEL HVLT = TRT PERIOD TRT*PERIOD/SOLUTION;
        RANDOM ID(TRT);
RUN;
```

Type 1 Analysis of Variance								
Source	**DF**	**Sum of Squares**	**Mean Square**	**Expected Mean Square**	**Error Term**	**Error DF**	**F Value**	**Pr > F**
PERIOD	1	2192.176805	2192.176805	Var(Residual) + 0.0628 Var(ID(TRT)) + Q(PERIOD,TRT,PERIOD*TRT)	0.0334 MS(ID(TRT)) + 0.9666 MS(Residual)	531.44	189.36	<.0001
TRT	3	320.732917	106.910972	Var(Residual) + 1.9372 Var(ID(TRT)) + Q(TRT,PERIOD*TRT)	1.03 MS(ID(TRT)) - 0.03 MS(Residual)	470.72	2.59	0.0525
PERIOD*TRT	3	91.079545	30.359848	Var(Residual) + 0.0628 Var(ID(TRT)) + Q(PERIOD*TRT)	0.0334 MS(ID(TRT)) + 0.9666 MS(Residual)	531.45	2.62	0.0499
ID(TRT)	478	19329	40.437223	Var(Residual) + 1.8808 Var(ID(TRT))	MS(Residual)	421	3.82	<.0001
Residual	421	4453.668470	10.578785	Var(Residual)	.	.	.	.

Figure 1: Output SAS model

In Figure 1 we see that F-test suggests that `TRT` does not have an effect on the outcome. However, `TRT*PERIOD` seems to be significant.

In short: treatment (on its own) does not have an effect.

(f) Based on you ANOVA model, calculate the correlation between the two scores of participants with their 95% confidence intervals? Explain your opinion on the strength of this correlation.

Answer: We run the same code and now use the output given in Figure 2. Furthermore we use the theory on slide 37 on ANOVA. We see that:

$$\sigma_G^2 = 15.8758,\ \sigma_R^2 = 10.5788,\ MS_B = 40.437223,\ MS_W = 10.578785,\ C_n = 1.8808,$$

and $df_B = 478, df_W = 421$. Thus we have that:

$$F_L = 0.83115$$
$$F_U = 1.20449$$
$$F = MS_B/MS_W = 3.82248$$
$$\hat{ICC} = 0.600$$
$$LCL = \frac{F/F_U - 1}{F/F_U + c_n - 1} = 0.5361$$
$$UCL = 0.6568.$$

This means that more than half of the observed variation in the data can be explained by the differences between the subjects. This is a fair correlation between two subsequent measurements.

Type 1 Analysis of Variance								
Source	DF	Sum of Squares	Mean Square	Expected Mean Square	Error Term	Error DF	F Value	Pr > F
TRT	3	339.403643	113.134548	Var(Residual) + 1.9372 Var(ID(TRT)) + Q(TRT,PERIOD,TRT*PERIOD)	1.03 MS(ID(TRT)) - 0.03 MS(Residual)	470.72	2.74	0.0430
PERIOD	1	2173.506079	2173.506079	Var(Residual) + 0.0628 Var(ID(TRT)) + Q(PERIOD,TRT*PERIOD)	0.0334 MS(ID(TRT)) + 0.9666 MS(Residual)	531.43	187.75	<.0001
TRT*PERIOD	3	91.079545	30.359848	Var(Residual) + 0.0628 Var(ID(TRT)) + Q(TRT*PERIOD)	0.0334 MS(ID(TRT)) + 0.9666 MS(Residual)	531.45	2.62	0.0499
ID(TRT)	478	19329	40.437223	Var(Residual) + 1.8808 Var(ID(TRT))	MS(Residual)	421	3.82	<.0001
Residual	421	4453.668470	10.578785	Var(Residual)	.	.	.	.

Covariance Parameter Estimates	
Cov Parm	Estimate
ID(TRT)	15.8758
Residual	10.5788

Figure 2: Output SAS model

(g) To investigate any effect of training conduct a likelihood ratio test. Formulate the null and alternative hypotheses in mathematical terms, report the value of the test statistic, degrees of freedom, and its P-value. Do you believe there is a training effect? Explain your answer.

Answer: We are now testing the following:

$$H_0 : \alpha_i = 0 \; \forall i \text{ and } (\alpha\beta)_{ij} = 0 \; \forall i, j \qquad \text{vs.} \qquad H_1 = \exists i \; \alpha_i \neq 0 \text{ or } \exists i, j \; (\alpha\beta)_{ij} \neq 0.$$

We now estimate the model with an without `TRT` using Maximum Likelihood estimation and find:

$$LL_{\text{full}} = 5359.6, \; LL_{\text{reduced}} = 5374.7.$$

We thus have a statistic $LRT = 5374.7 - 5359.6 = 15.1$. The degrees of freedom is the difference in the number of estimated parameters: 6, and therefore gives a p-value of 0.0195. This means that we reject the null-hypotheses and therefore there is some effect of `TRT` on the outcome.

2. In this exercise we will analyze the response on reasoning (`WORD`) at baseline and at post training using

several marginal mixed models. We will concentrate on the variables subject (`ID`), location (`SITE`), period (`PERIOD`), training (`TRT`), sex (`SEX`), and age group (`AGEC`), although these variables will not be used in all questions.

(a) Fit a marginal model with PERIOD and TRT and their two-factor interaction as fixed effects, assuming that the participants have an unstructured variance covariance matrix. Provide the SAS code and report the output of the overall test statistics and the residual variance-covariance matrix. Explain why the interaction effect TRT*PERIOD could not be tested.

Answer: The output is shown in Figure 3. The interaction effect could not be estimated since the effects are not crossed: when PERIOD="Baseline", then TRT always equals 4.

Covariance Parameter Estimates		
Cov Parm	**Subject**	**Estimate**
UN(1,1)	ID	23.9047
UN(2,1)	ID	21.6078
UN(2,2)	ID	27.6593

Fit Statistics	
-2 Res Log Likelihood	29394.1
AIC (Smaller is Better)	29400.1
AICC (Smaller is Better)	29400.1
BIC (Smaller is Better)	29417.9

Figure 3: Overall test statistics and residual variance-covariance matrix.

(b) Based on the model in 2(a), formulate the null hypothesis and the alternative hypothesis for an effect of training from baseline to post training. Determine the effect sizes with their 95% confidence intervals for each of the four trainings. Report whether the cognition training has increased the response.

Answer: The null hypothesis is that there is no effect for TRT, i.e. that $b_i = 0$ for $i \in \{1, 2, 3, 4\}$, where b_i is the effect of TRT i. The alternative hypothesis, then, is that there is an effect, i.e. that there is some $i \in \{1, 2, 3, 4\}$ such that $b_i \neq 0$. We run the following code:

```
PROC MIXED DATA=MARGINAL;
        CLASS ID PERIOD TRT;
        MODEL WORD = PERIOD TRT/SOLUTION DDFM=SAT CL;
        REPEATED PERIOD/SUBJECT=ID TYPE=UN;
RUN;
```

The output for the fixed effects is shown in Figure 4. We see that for TRT=2, 0 lies outside the confidence interval, so that we reject the null hypothesis.

Solution for Fixed Effects										
Effect	PERIOD	TRT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept			10.9454	0.1406	3992	77.86	<.0001	0.05	10.6698	11.2210
PERIOD	Baseline		-1.4493	0.1135	2564	-12.77	<.0001	0.05	-1.6718	-1.2269
PERIOD	Post		0	.	.	.	.	.	.	.
TRT		1	-0.02403	0.1597	2539	-0.15	0.8804	0.05	-0.3372	0.2892
TRT		2	2.3590	0.1608	2540	14.67	<.0001	0.05	2.0437	2.6743
TRT		3	-0.1436	0.1593	2540	-0.90	0.3674	0.05	-0.4559	0.1687
TRT		4	0	.	.	.	.	.	.	.

Figure 4: Solutions for fixed effects.

(c) Fit a marginal model with SITE, PERIOD, TRT, SEX, and AGEC and with all twofactor interactions with TRT (except of course for interaction TRT*PERIOD) using the unstructured variance-covariance stucture. Determine whether you can reduce the complexity of the variance-covariance matrix and the fixed effects. Provide your model selection approach, your final marginal model, and the details of how you came to this model.

Answer: We apply the model selection strategy as described in Slides 71 and 72 of *LDA_Linear Mixed Models Final.pdf*. We start with the overspecified model that includes all potential fixed effects (apart from TRT*PERIOD, since we already know from (a) that this effect cannot be tested).

```
PROC MIXED DATA=MARGINAL;
        CLASS ID SITE PERIOD TRT AGEC SEX;
        MODEL WORD = SITE PERIOD SEX AGEC TRT SITE*TRT SEX*TRT AGEC*TRT/SOLUTION DDFM=SAT;
        REPEATED PERIOD/SUBJECT=ID TYPE=UN;
RUN;
```

Then, we select the covariance structure using REML estimation. We compare covariance structures UN and CS using the LRT which rejects CS in favor of UN. Hence, we keep covariance structure UN.

```
ODS OUTPUT FITSTATISTICS=FULL1;
PROC MIXED DATA=MARGINAL;
        CLASS ID SITE PERIOD TRT AGEC SEX;
        MODEL WORD = SITE PERIOD SEX AGEC TRT SITE*TRT SEX*TRT AGEC*TRT/SOLUTION DDFM=SAT;
        REPEATED PERIOD/SUBJECT=ID TYPE=UN;
RUN;


ODS OUTPUT FITSTATISTICS=NULL1;
PROC MIXED DATA=MARGINAL;
```

```
        CLASS ID SITE PERIOD TRT AGEC SEX;
        MODEL WORD = SITE PERIOD SEX AGEC TRT SITE*TRT SEX*TRT AGEC*TRT/SOLUTION DDFM=SAT;
        REPEATED PERIOD/SUBJECT=ID TYPE=CS;
RUN;

DATA FULL1;
        SET FULL1;
        WHERE DESCR = "-2 Res Log Likelihood";
        MIN2L_F = VALUE;
        KEEP MIN2L_F;
RUN;
DATA NULL1;
        SET NULL1;
        WHERE DESCR = "-2 Res Log Likelihood";
        MIN2L_N = VALUE;
        KEEP MIN2L_N;
RUN;
DATA LRT1;
        MERGE FULL1 NULL1;
        LRT = MIN2L_N - MIN2L_F;
        DF  = 1;
        P        = 1-PROBCHI(LRT,DF);
RUN;
PROC PRINT DATA=LRT1;
RUN;
```

We then use ML estimation to select fixed effects. The Type 3 tests for fixed effects show that the effect SEX*TRT has p-value 0.71, which is the highest among the interaction effects, so we start by testing whether this effect can be eliminated. We again use the LRT to compare the full model to the eliminated model. The following code gives a p-value of 0.24, which indeed tells us that this effect can be eliminated.

```
ODS OUTPUT FITSTATISTICS=FULL1;
PROC MIXED DATA=MARGINAL METHOD=ML;
        CLASS ID SITE PERIOD TRT AGEC SEX;
        MODEL WORD = SITE PERIOD SEX AGEC TRT SITE*TRT SEX*TRT AGEC*TRT/SOLUTION DDFM=SAT;
        REPEATED PERIOD/SUBJECT=ID TYPE=UN;
RUN;
```

```
ODS OUTPUT FITSTATISTICS=NULL1;
PROC MIXED DATA=MARGINAL METHOD=ML;
        CLASS ID SITE PERIOD TRT AGEC SEX;
        MODEL WORD = SITE PERIOD SEX AGEC TRT SITE*TRT AGEC*TRT/SOLUTION DDFM=SAT;
        REPEATED PERIOD/SUBJECT=ID TYPE=UN;
RUN;

DATA FULL1;
        SET FULL1;
        WHERE DESCR = "-2 Log Likelihood";
        MIN2L_F = VALUE;
        KEEP MIN2L_F;
RUN;
DATA NULL1;
        SET NULL1;
        WHERE DESCR = "-2 Log Likelihood";
        MIN2L_N = VALUE;
        KEEP MIN2L_N;
RUN;
DATA LRT1;
        MERGE FULL1 NULL1;
        LRT = MIN2L_N - MIN2L_F;
        DF  = 1;
        P        = 1-PROBCHI(LRT,DF);
RUN;
PROC PRINT DATA=LRT1;
RUN;
```

After that, we apply LRT again to test whether the effects can be eliminated using the LRT. Each of these tests results in a p-value below 0.05. The final model contains the effects SITE, PERIOD, SEX, AGEC, TRT, SITE*TRT, and AGEC*TRT and has unstructured residual covariance.

3. In this exercise we will analyze the trial data using several subject-specific mixed models for the responde on memory (`AVLT`). We will built polynomial time profiles and use the different trainings (`TRT`) to understand how training affect the the time profile. Here we will only use the observations after training (no baseline data). Create an appropriate data set and make a new time variable: `TIME=DAYS/365`.

(a) Fit a linear time profile for each patient separately and assume that the residuals are independent. The coefficients of the linear time profile are assumed dependent. Provide the SAS code, the output of this model, and report the conclusions about the training.

Answer: We use the following code:

```
PROC MIXED DATA=LMM;
        CLASS ID SITE TRT;
        MODEL AVLT = TRT TIME TRT*TIME/ SOLUTION DDFM=SAT;
        RANDOM INT TIME/SUBJECT=ID TYPE=UN;
RUN;
```

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TRT	3	2575	5.23	0.0013
TIME	1	2032	245.87	<.0001
TIME*TRT	3	2032	0.55	0.6481

Figure 5: Output SAS model

In Figure 5 you can see that the null hypothesis for no effect of time× trt cannot be rejected, while the null hypothesis for no effect of trt and the null hypothesis for no effect of time are rejected with a significance level of 0.05 (this happens even if you adjust for multiple testing). From this we can conclude that there is a significant effect for trt and time, but not for the interaction. Note that Bonferonni and Sidak both have a value $\alpha_k \approx 0.016$ for $k = 3$, so the conclusion stays the same.

(b) For the model in (a) determine the time point for which variability in AVLT is minimal when the reasoning training (TRT=2) is applied. Report this time point and provide an estimate of the minimal variation.

Answer: Using the theory on slide 34 on Linear Mixed Models we have:

$$\min_t\{\sigma(t)\} = (1-\rho^2)\tau_0^2 + \sigma_R^2 = 113.74903093$$
$$\arg\min_t\{\sigma(t)\} = -\rho\frac{\tau_0}{\tau_1} = -3.49.$$

(c) Calculate the 95% upper finite sample prediction limit for the control training. Report the formula as function of years.

Answer:

$$\hat{\mu}(t) = \hat{\beta}_0 + \hat{\beta}_t \cdot t = 44.91 + 0.87 \cdot t$$

$$\hat{\sigma}^2(t) = \hat{\tau}_0^2 + 2\hat{\tau}_{01} \cdot t + \hat{\tau}_1^2 + \hat{\sigma}_R^2 = 89.75 + 2 \cdot 1.48 \cdot t + 0.42 \cdot t^2 + 29.16$$

$$\hat{\eta}^2(t) = \mathrm{Var}(\hat{\beta}_0) + 2\mathrm{Cov}(\hat{\beta}_0\hat{\beta}_1) \cdot t + \hat{\beta}_1 \cdot t^2 = 0.18 - 2 \cdot 0.01 + 0.01 \cdot t^2$$

$$UPL(t) = \hat{\mu}(t) + z_{0.95}\sqrt{\hat{\sigma}^2(t) + \hat{\eta}^2(t)} = 44.91 + 0.87 \cdot t + 1.64\sqrt{119.09 + 2.94 \cdot t + 0.43 \cdot t^2}$$

Please note that the normal distribution Z can be used here as the degrees of freedom is high, and since the normal distribution is two-tailed, the $1 - \alpha/2$ quantile is used.