

## BIOS 6612 final exam

A study was conducted to determine the effect of an antagonist MDL 72222 on the change in blood pressure experienced by a sample of rabbits with increasing dosage of phenylbiguanide (PBG). For the study, each of five rabbits was exposed to increasing doses of phenylbiguanide after having either a placebo or the HD5-antagonist MDL 72222 administered. The variables in the data set are:

- Rabbit: a factor with levels 1 to 5 identifying the subject.
- Treatment: a factor with levels 'Placebo' and 'MDL 72222' indicating the treatment administered.
- dose: a numeric vector giving the dose of PBG administered.
- deltaBP: a numeric vector giving the outcome, change in blood pressure.

The data for Rabbit=1 is printed below:

```
## Grouped Data: deltaBP ~ dose | Rabbit
##   deltaBP   dose Treatment Rabbit
## 1    0.50    6.25   Placebo      1
## 2    4.50   12.50   Placebo      1
## 3   10.00   25.00   Placebo      1
## 4   26.00   50.00   Placebo      1
## 5   37.00  100.00   Placebo      1
## 6   32.00  200.00   Placebo      1
## 31    1.25    6.25  MDL 72222      1
## 32    0.75   12.50  MDL 72222      1
## 33    4.00   25.00  MDL 72222      1
## 34    9.00   50.00  MDL 72222      1
## 35   25.00  100.00  MDL 72222      1
## 36   37.00  200.00  MDL 72222      1
```

Answer the following questions based on this data set. Output from R is given, but you are free to fit any models necessary yourself, in SAS or R, to help you answer the questions **unless specifically instructed otherwise**. Some output may be intentionally blanked out: you are intended to fill in the missing components if needed to answer questions, based on other information given.

1. A linear mixed effects model was fitted to this data with a random intercept for Rabbit. This is Model 1; output appears below.

```
# Model 1
mod1 <- lme(deltaBP ~ dose*Treatment,
            random=~1|Rabbit,
            data=PBG)
```

```
summary(mod1)

## Linear mixed-effects model fit by REML
## Data: PBG
##      AIC      BIC    logLik
## 400.9387 413.0908 -194.4694
##
## Random effects:
## Formula: ~1 | Rabbit
##      (Intercept) Residual
## StdDev:      2.14037 5.735298
##
## Fixed effects: deltaBP ~ dose * Treatment
##
##              Value Std.Error DF   t-value p-value
## (Intercept)    4.180348  1.7446163  52   2.396142  0.0202
## dose          0.142903  0.0154724  52   9.235945  0.0000
## TreatmentMDL 72222 -4.288955  2.0627406  52  -2.079251  0.0425
## dose:TreatmentMDL 72222 -0.005959  0.0218813  52  -0.272322  0.7865
## Correlation:
##              (Intr) dose   TMDL72
## dose              -0.582
## TreatmentMDL 72222 -0.591  0.492
## dose:TreatmentMDL 72222  0.412 -0.707 -0.696
##
## Standardized Within-Group Residuals:
##      Min      Q1      Med      Q3      Max
## -2.2444284 -0.6080561 -0.2439825  0.3231946  2.7545985
##
## Number of Observations: 60
## Number of Groups: 5

anova(mod1)

##              numDF denDF   F-value p-value
## (Intercept)      1    52  85.93657 <.0001
## dose             1    52 163.56558 <.0001
## Treatment        1    52   9.98783 0.0026
## dose:Treatment   1    52   0.07416 0.7865
```

- Interpret the interaction between the dose and Treatment variables. Is this interaction significant? Provide a test statistic and p-value to support your conclusion. **(10 points)**
- Calculate the estimated ICC for this data. Interpret the estimate. **(10 points)**
- Now consider a linear regression model for this data with the same fixed effects but no random effect.

```
mod0 <- lm(deltaBP ~ dose*Treatment, data=PBG)
anova(mod0)

## Analysis of Variance Table
##
```

```
## Response: deltaBP
##              Df Sum Sq Mean Sq  F value    Pr(>F)
## dose          1 5380.3  5380.3 146.1233 < 2.2e-16 ***
## Treatment     1  328.5   328.5   8.9227  0.004174 **
## dose:Treatment 1    2.4    2.4   0.0663  0.797819
## Residuals    56 2061.9    36.8
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Compare this ANOVA table with the ANOVA table for Model 1 above; *ignore any differences in output format due to this model using `Lm()` with no random effect and Model 1 using `Lme()` including a random effect*. Why are they similar? **(4 points)**

2. Model 2 is fitted to the data, exchanging the linear effect for dose with a categorical one.

```
mod2 <- lme(deltaBP ~ as.factor(dose)*Treatment,
             random=~1|Rabbit,
             data=PBG)

summary(mod2)

## Linear mixed-effects model fit by REML
## Data: PBG
##      AIC      BIC    logLik
## 320.0336 346.2304 -146.0168
##
## Random effects:
## Formula: ~1 | Rabbit
##      (Intercept) Residual
## StdDev:      2.46726 3.848636
##
## Fixed effects: deltaBP ~ as.factor(dose) * Treatment
##                                     Value Std.Error DF   t-value
## (Intercept)                      1.00  2.044474 44   0.489123
## as.factor(dose)12.5                1.35  2.434091 44   0.554622
## as.factor(dose)25                  4.60  2.434091 44   1.889822
## as.factor(dose)50                 16.40  2.434091 44   6.737627
## as.factor(dose)100                26.80  2.434091 44  11.010269
## as.factor(dose)200                26.20  2.434091 44  10.763770
## TreatmentMDL 72222                 0.68  2.434091 44   0.279365
## as.factor(dose)12.5:TreatmentMDL 72222 -1.34  3.442325 44  -0.389272
## as.factor(dose)25:TreatmentMDL 72222  -3.98  3.442325 44  -1.156195
## as.factor(dose)50:TreatmentMDL 72222 -13.88  3.442325 44  -4.032158
## as.factor(dose)100:TreatmentMDL 72222 -11.28  3.442325 44  -3.276855
## as.factor(dose)200:TreatmentMDL 72222  -1.68  3.442325 44  -0.488042
##                                     p-value
## (Intercept)                      0.6272
## as.factor(dose)12.5                0.5820
## as.factor(dose)25                  0.0654
## as.factor(dose)50                  0.0000
```

```

## as.factor(dose)100          0.0000
## as.factor(dose)200          0.0000
## TreatmentMDL 72222          0.7813
## as.factor(dose)12.5:TreatmentMDL 72222 0.6990
## as.factor(dose)25:TreatmentMDL 72222 0.2538
## as.factor(dose)50:TreatmentMDL 72222 0.0002
## as.factor(dose)100:TreatmentMDL 72222 0.0021
## as.factor(dose)200:TreatmentMDL 72222 0.6279
## Correlation:
##                               (Intr) a.()12 a.()25 a.()50 a.()10
## as.factor(dose)12.5          -0.595
## as.factor(dose)25            -0.595  0.500
## as.factor(dose)50            -0.595  0.500  0.500
## as.factor(dose)100           -0.595  0.500  0.500  0.500
## as.factor(dose)200           -0.595  0.500  0.500  0.500  0.500
## TreatmentMDL 72222          -0.595  0.500  0.500  0.500  0.500
## as.factor(dose)12.5:TreatmentMDL 72222 0.421 -0.707 -0.354 -0.354 -0.354
## as.factor(dose)25:TreatmentMDL 72222 0.421 -0.354 -0.707 -0.354 -0.354
## as.factor(dose)50:TreatmentMDL 72222 0.421 -0.354 -0.354 -0.707 -0.354
## as.factor(dose)100:TreatmentMDL 72222 0.421 -0.354 -0.354 -0.354 -0.707
## as.factor(dose)200:TreatmentMDL 72222 0.421 -0.354 -0.354 -0.354 -0.354
##                               a.()20 TMDL72 a.()127 a.()257
## as.factor(dose)12.5
## as.factor(dose)25
## as.factor(dose)50
## as.factor(dose)100
## as.factor(dose)200
## TreatmentMDL 72222          0.500
## as.factor(dose)12.5:TreatmentMDL 72222 -0.354 -0.707
## as.factor(dose)25:TreatmentMDL 72222 -0.354 -0.707  0.500
## as.factor(dose)50:TreatmentMDL 72222 -0.354 -0.707  0.500  0.500
## as.factor(dose)100:TreatmentMDL 72222 -0.354 -0.707  0.500  0.500
## as.factor(dose)200:TreatmentMDL 72222 -0.707 -0.707  0.500  0.500
##                               a.()57 a.()107
## as.factor(dose)12.5
## as.factor(dose)25
## as.factor(dose)50
## as.factor(dose)100
## as.factor(dose)200
## TreatmentMDL 72222
## as.factor(dose)12.5:TreatmentMDL 72222
## as.factor(dose)25:TreatmentMDL 72222
## as.factor(dose)50:TreatmentMDL 72222
## as.factor(dose)100:TreatmentMDL 72222 0.500
## as.factor(dose)200:TreatmentMDL 72222 0.500 0.500
##
## Standardized Within-Group Residuals:
##           Min           Q1           Med           Q3           Max
## -1.73841154 -0.41355540  0.06431518  0.40703912  2.39129789
##

```

```
## Number of Observations: 60
## Number of Groups: 5

anova(mod2)

##               numDF denDF  F-value p-value
## (Intercept)         1    44 85.94376 <.0001
## as.factor(dose)       5    44 81.30602 <.0001
## Treatment            1    44 22.18039 <.0001
## as.factor(dose):Treatment  5    44  5.67019 4e-04
```

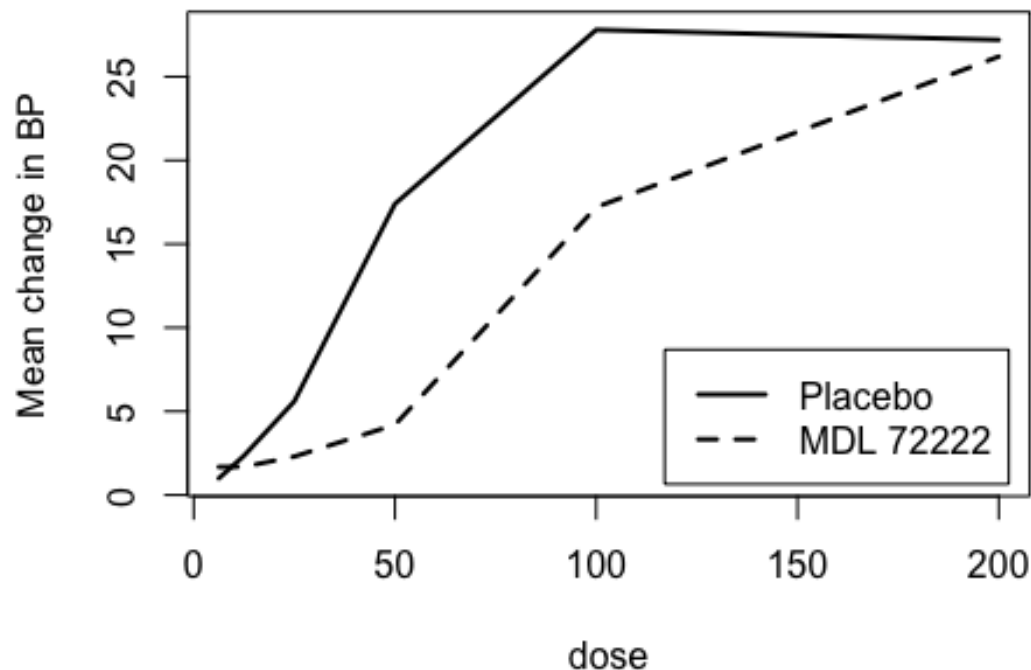
- (a) Should dose be treated as categorical or continuous in this model? Justify your answer: include the results of a formal statistical test. The following additional output may be helpful: **(6 points)**

```
## refitting model(s) with ML (instead of REML)

## Data: PBG
## Models:
## mod1: deltaBP ~ dose * Treatment + (1 | Rabbit)
## mod2: deltaBP ~ as.factor(dose) * Treatment + (1 | Rabbit)
##      Df    AIC    BIC  logLik deviance Chisq Chi Df Pr(>Chisq)
## mod1  6  XXXXXX  XXXXXX -190.29   XXXXXX
## mod2 14  XXXXXX  XXXXXX -163.76   XXXXXX
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

- (b) Using Model 2, what is the average deltaBP value estimated for subjects at Treatment='MDL 72222' and dose=50? **(10 points)**
- (c) Using results from Model 2, provide an interpretation of the effect of dose, Treatment, and their interaction on mean glucose levels; give p-values to support your conclusions. **(14 points)**

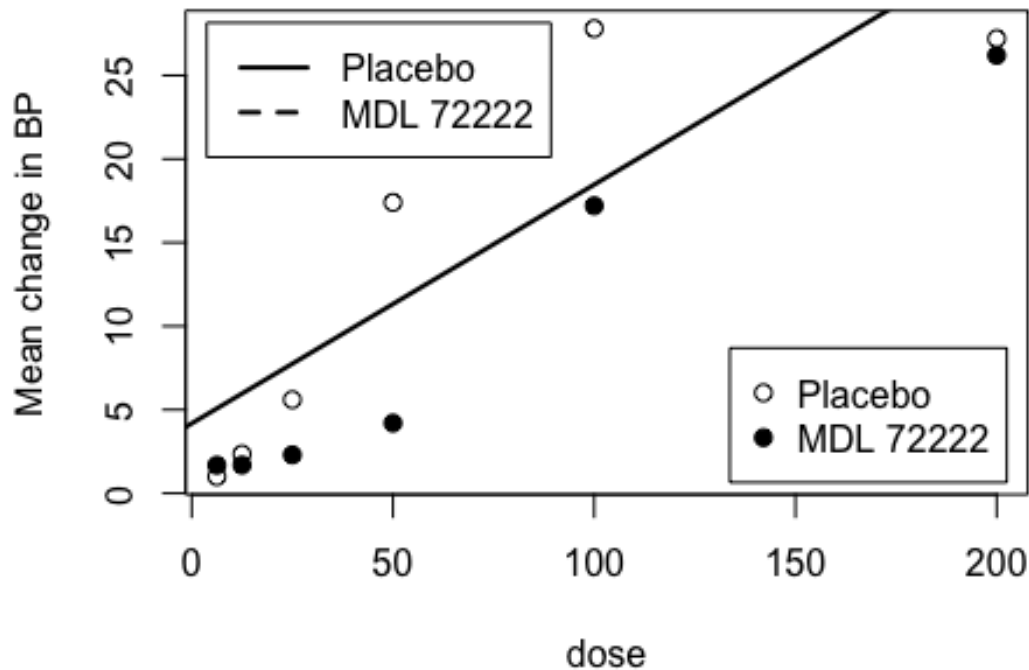
3. A plot of mean change in BP with dose for each Treatment appears below.



- (a) If we think about each point on this plot as a fitted value from some regression model for the data, then what variables would be included in this model, and what form would each take (e.g., categorical, continuous)? **(8 points)**
- (b) Estimated fixed effects parameters from Model 1 appear in the table below.

##	Value	Std.Error	DF	t-value	p-value
## (Intercept)	4.1803	1.7446	52	2.3961	0.0202
## dose	0.1429	0.0155	52	9.2359	0.0000
## TreatmentMDL 72222	-4.2890	2.0627	52	-2.0793	0.0425
## dose:TreatmentMDL 72222	-0.0060	0.0219	52	-0.2723	0.7865

Draw the fitted mean curve for Treatment='MDL 72222' corresponding to Model 1 on the plot below, which shows the mean curve for Treatment='Placebo' for this model, along with the mean change in BP at each time for each treatment group. (This doesn't need to be exact, just show approximately where the curve should be.) **(12 points)**



- (c) Another variable in the data set, Run, indexes repeated measurements within each rabbit at each treatment condition. A researcher has erroneously used this as the subject variable and obtained the following table from a RMANOVA analysis.

```
##
## Error: as.factor(Run)
##           Df Sum Sq Mean Sq F value Pr(>F)
## Treatment  1  328.5    328.5    5.87 0.0417 *
## Residuals  8  447.7     56.0
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Error: Within
##           Df Sum Sq Mean Sq F value    Pr(>F)
## as.factor(dose)      5   6022   1204.3   86.727 < 2e-16 ***
## as.factor(dose):Treatment  5    420    84.0    6.048 0.000294 ***
## Residuals          40    555    13.9
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Use this to calculate the estimated random intercept variance for this model. **Do not** fit this model to answer the question. (10 points)

4. Now consider a polynomial trend model for the effect of dose. The table below gives values of AIC and BIC for orthogonal polynomial models for the effect of dose on mean glucose levels; the models also include Treatment and the interaction between dose and Treatment.

##	Model	df	AIC	BIC	logLik	Test	L.Ratio	p-value
##	.L	1 6	392.5815	405.1475	-190.2907			
##	.Q	2 8	353.7388	370.4936	-168.8694	1 vs 2	42.84264	<.0001
##	.C	3 10	350.4396	371.3831	-165.2198	2 vs 3	7.29917	0.0260
##	^4	4 12	351.6234	376.7555	-163.8117	3 vs 4	2.81623	0.2446
##	^5	5 14	355.5118	384.8327	-163.7559	4 vs 5	0.11157	0.9457

- (a) Which model is best according to AIC? What about BIC? Why are these answers different? Note that R bases the BIC penalty on total number of observations rather than number of independent subjects. **(8 points)**
- (b) Assuming the fitting methods used are correct, were these models fitted using ML or REML? Justify your answer. **(8 points)**