1. (a) The model in this problem is $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$ with $\boldsymbol{\beta} = (\mu, \alpha_1, \alpha_2, \beta_1, \beta_2)'$ and

$$oldsymbol{X} = \left(oldsymbol{1}_{20 imes 1}, egin{bmatrix} oldsymbol{1}_{10 imes 1} \ oldsymbol{0}_{10 imes 1} \end{bmatrix} egin{bmatrix} oldsymbol{0}_{10 imes 1} \ oldsymbol{1}_{10 imes 1} \end{bmatrix} egin{bmatrix} oldsymbol{1}_{2 imes 1} \ oldsymbol{0}_{6 imes 1} \ oldsymbol{0}_{6 imes 1} \ oldsymbol{0}_{6 imes 1} \ oldsymbol{1}_{4 imes 1} \end{bmatrix}
ight)$$

Because $rank(\mathbf{X}) = 3$, one possible full rank matrix is

$$egin{aligned} (oldsymbol{x}_1,oldsymbol{x}_2,oldsymbol{x}_3) = \left(oldsymbol{1}_{20 imes 1},egin{bmatrix} oldsymbol{1}_{10 imes 1} \ oldsymbol{0}_{10 imes 1} \end{bmatrix} egin{bmatrix} oldsymbol{1}_{2 imes 1} \ oldsymbol{0}_{8 imes 1} \ oldsymbol{1}_{6 imes 1} \ oldsymbol{0}_{4 imes 1} \end{bmatrix}
ight) \end{aligned}$$

We can compute orthogonal columns using Gram-Schmidt Orthogonalization method:

$$egin{aligned} m{w}_1 &= m{x}_1; \ m{w}_2 &= (m{I} - m{P}_{m{w}_1}) m{x}_2 = rac{1}{2} egin{bmatrix} m{1}_{10 imes 1} \ -m{1}_{10 imes 1} \end{bmatrix} \ m{w}_3 &= (m{I} - m{P}_{[m{w}_1, m{w}_2]}) m{x}_3 = egin{bmatrix} 0.8 \cdot m{1}_{2 imes 1} \ -0.2 \cdot m{1}_{8 imes 1} \ 0.4 \cdot m{1}_{6 imes 1} \ -0.6 \cdot m{1}_{4 imes 1} \end{bmatrix} \end{aligned}$$

So a model matrix W with orthogonal columns is $W = (w_1, w_2, w_3)$.

(b) Compute $P_W y$:

$$(\boldsymbol{W}'\boldsymbol{W})^{-1} = \begin{bmatrix} \begin{pmatrix} \boldsymbol{w}_1' \\ \boldsymbol{w}_2' \\ \boldsymbol{w}_3' \end{pmatrix} (\boldsymbol{w}_1, \boldsymbol{w}_2, \boldsymbol{w}_3) \end{bmatrix}^{-1} = \begin{bmatrix} \boldsymbol{w}_1' \boldsymbol{w}_1 \\ \boldsymbol{w}_2' \boldsymbol{w}_2 \\ \boldsymbol{w}_3' \boldsymbol{w}_3 \end{bmatrix}^{-1}$$

$$= \begin{bmatrix} 20 \\ 5 \\ 4 \end{bmatrix}^{-1} = \begin{bmatrix} \frac{1}{20} \\ \frac{1}{5} \\ \frac{1}{4} \end{bmatrix}$$

$$\mathbf{W}'\mathbf{y} = \begin{pmatrix} \mathbf{w}_{1}' \\ \mathbf{w}_{2}' \\ \mathbf{w}_{3}' \end{pmatrix} \cdot \mathbf{y} = \begin{bmatrix} \mathbf{w}_{1}'\mathbf{y} \\ \mathbf{w}_{2}'\mathbf{y} \\ \mathbf{w}_{3}'\mathbf{y} \end{bmatrix}$$

$$= \begin{bmatrix} \sum_{i} \sum_{j} \sum_{k} y_{ijk} \\ \frac{1}{2} (\sum_{j} \sum_{k} y_{1jk} - \sum_{j} \sum_{k} y_{2jk}) \\ 0.8 \cdot \sum_{k} y_{11k} - 0.2 \cdot \sum_{k} y_{12k} + 0.4 \cdot \sum_{k} y_{21k} - 0.6 \cdot \sum_{k} y_{22k} \end{bmatrix}$$

$$= \begin{bmatrix} 100 \\ -4 \\ 6.4 \end{bmatrix}$$

$$P_{W}y = W(W'W)^{-1}W'y$$

$$= (w_{1}, w_{2}, w_{3}) \begin{bmatrix} \frac{1}{20} & & \\ & \frac{1}{5} & \\ & & \frac{1}{4} \end{bmatrix} \begin{bmatrix} 100 \\ -4 \\ 6.4 \end{bmatrix}$$

$$= 5w_{1} - 0.8w_{2} + 1.6w_{3}$$

$$= \begin{bmatrix} 5.88 \cdot \mathbf{1}_{2\times 1} \\ 4.28 \cdot \mathbf{1}_{8\times 1} \\ 6.04 \cdot \mathbf{1}_{6\times 1} \\ 4.44 \cdot \mathbf{1}_{4\times 1} \end{bmatrix}$$

(c) The Type II sum of squares for factor B is $S(B|1, A) = y'(P_3 - P_2)y$ where $P_3y = P_Wy$ and from part (b)

$$P_2 \mathbf{y} = P_{[\mathbf{w}_1, \mathbf{w}_2]} \mathbf{y}$$

$$= (\mathbf{w}_1, \mathbf{w}_2) \begin{bmatrix} \frac{1}{20} & \\ & \frac{1}{5} \end{bmatrix} \begin{bmatrix} 100 \\ -4 \end{bmatrix}$$

$$= 5\mathbf{w}_1 - 0.8\mathbf{w}_2$$

$$= \begin{bmatrix} 4.6 \cdot \mathbf{1}_{10 \times 1} \\ 5.4 \cdot \mathbf{1}_{10 \times 1} \end{bmatrix}$$

SO

$$S(B|1, A) = \mathbf{y}'(\mathbf{P}_3 - \mathbf{P}_2)\mathbf{y} = \mathbf{y}'\mathbf{P}_3\mathbf{y} - \mathbf{y}'\mathbf{P}_2\mathbf{y} = ||\mathbf{P}_3\mathbf{y}||^2 - ||\mathbf{P}_2\mathbf{y}||^2$$

= $(5.88^2 \times 2 + 4.28^2 \times 8 + 6.04^2 \times 6 + 4.44^2 \times 4) - (4.6^2 \times 10 + 5.4^2 \times 10)$
= 10.24

2. (a) For the jth woman treated with the ith drug,

$$W = \text{Var}(y_{ij1}, y_{ij2}, y_{ij3}, y_{ij4})'$$

$$= \begin{bmatrix} \sigma_w^2 + \sigma_e^2 & \sigma_w^2 & \sigma_w^2 & \sigma_w^2 \\ \sigma_w^2 & \sigma_w^2 + \sigma_e^2 & \sigma_w^2 & \sigma_w^2 \\ \sigma_w^2 & \sigma_w^2 & \sigma_w^2 + \sigma_e^2 & \sigma_w^2 \\ \sigma_w^2 & \sigma_w^2 & \sigma_w^2 & \sigma_w^2 + \sigma_e^2 \end{bmatrix}$$

$$= \sigma_w^2 \mathbf{1}_{4\times4}^{\prime} + \sigma_e^2 \mathbf{I}_{4\times4}^{\prime}.$$

We know that Var(y) is block diagonal with blocks W. There are a total of $3 \cdot 5 = 15$ blocks, so that

$$\operatorname{Var}(\boldsymbol{y}) = \boldsymbol{I}_{15 \times 15} \otimes \boldsymbol{W} = \boldsymbol{I}_{15 \times 15} \otimes (\sigma_w^2 \mathbf{1} \mathbf{1}_{4 \times 4}' + \sigma_e^2 \boldsymbol{I}_{4 \times 4}).$$

(b) The null hypothesis of no drug-by-time interactions is $H_0: \mu_{ij} - \mu_{ij*} = \mu_{i*j} - \mu_{i*j*}$ for all $i \neq i*$ and $j \neq j*$. The test statistic F = 7.12 on (6,36) degrees of freedom with p < 0.001. We reject the null hypothesis and conclude that there is significant evidence for drug-by-time interactions on heart rate.

- (c) The null hypothesis for testing the same mean heart rate 15 minutes after treatment for all three drugs is $H_0: \mu_{14} = \mu_{24} = \mu_{34}$. The test statistic F = 1.11 on (2, 17.1) degrees of freedom with p = 0.352 > 0.05. We fail to reject the null hypothesis and conclude that there is no significant evidence for the same mean heart rate 15 minutes after treatment for all three drugs.
- (d) An approximate 95% confidence interval for $\mu_{14} \mu_{24}$ is (-13.77, 2.57) with df = 17.1 by the SAS code below.

Note: for part (c-d), df = 17.1 was computed by Cochran-Satterthwaite since it is for the difference between simple effects with different whole-plot factors. The easiest way to get this is to use SAS with method=satterthwaite option.

SAS code:

```
proc import datafile="./HeartRate.txt"
 dbms=TAB replace out=d;
proc print data=d (obs=14);
run;
proc mixed;
class woman drug time;
model y=drug time drug*time /ddfm = satterthwaite;
random woman(drug);
contrast "same mean for drug A B C at 15 min"
drug 1 -1 0 drug*time 0 0 0 1 0 0 0 -1 0 0 0 0,
drug 1 0 -1 drug*time 0 0 0 1 0 0 0 0 0 0 -1;
estimate "drug A - drug B at 15 min"
 drug 1 -1 0 drug*time 0 0 0 1 0 0 0 -1 0 0 0 0 /cl;
run;
R code:
library(MASS)
library(nlme)
library(dplyr)
> d <- read.table("http://dnett.github.io/S510/HeartRate.txt", header = T)</pre>
> dt <- factor((dtime + 5) / 5) # Levels of time.
> fit <- lme(y ~ drug * t, random = ~1 | woman / drug, data = d)</pre>
> anova(fit)
           numDF denDF F-value p-value
              1 36 2900.7782 <.0001
(Intercept)
                    12 1.3517 0.2955
drug
               3
t
                    36
                          10.2159 0.0001
drug:t
                    36
                          7.1153 <.0001
> # Function from Dr. Nettletons Notes
> test=function(lmout,C,d=0,df){
    b=fixed.effects(lmout)
    V=vcov(lmout)
    dfn=nrow(C)
    Cb.d=C %*% b - d
    Fstat=drop(t(Cb.d)%*%solve(C%*%V%*%t(C))%*%Cb.d/dfn)
     pvalue=1-pf(Fstat,dfn,df)
```

```
cbind(Fstat=Fstat,pvalue=pvalue)
+ }
> C1 \leftarrow matrix(c(0, 1, 0, 0, 0, 0, 0, 0, 0, 1, 0,
                 0, 0, 1, 0, 0, 0, 0, 0, 0, 0, 1), byrow=T,nrow = 2)
> test(fit,C1,df=17.1) # df computed by Cochran-Satterthwaite via SAS.
        Fstat
               pvalue
[1,] 1.109573 0.3523058
> # Function from Dr. Nettletons Notes
> ci <- function(lmeout, C, df, a = 0.05) {
   b = fixed.effects(lmeout)
    V = vcov(lmeout)
    Cb = C %*% b
   se = sqrt(diag(C %*% V %*% t(C)))
   tval = qt(1 - a / 2, df)
   low = Cb - tval * se
   up = Cb + tval * se
   m = cbind(C, Cb, se, low, up)
   dimnames(m)[[2]] = c(paste("c", 1 : ncol(C), sep = ""),
                         "estimate", "se", paste(100 * (1 - a), "% Conf.", sep = ""), "limits")
   return(m)
+ }
> C2 \leftarrow matrix(c(0, -1, 0, 0, 0, 0, 0, 0, 0, -1, 0), nrow = 1)
> ci(fit, C2, 17.1) # df computed by Cochran-Satterthwaite via SAS.
     c1 c2 c3 c4 c5 c6 c7 c8 c9 c10 c11 c12 estimate
[1,] 0 -1 0 0 0 0 0 0 0 -1
     95% Conf. limits
[1,] -13.76676 2.566758
```

3. (a) Under a compound symmetry assumption,

$$\boldsymbol{W} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix},$$

where the REML estimates for the heart rate data are $\hat{\sigma} = 6.12$ and $\hat{\rho} = 0.777$. $(\hat{\sigma}_s^2 = 29.13, \hat{\sigma}_e^2 = 8.36)$

- (b) Using R, AIC = 317.92 and BIC = 344.12. Using SAS, AIC = 293.9 and BIC = 295.3.
- (c) Under an AR(1) assumption,

$$m{W} = \sigma^2 egin{bmatrix} 1 &
ho &
ho^2 &
ho^3 \
ho & 1 &
ho &
ho^2 \
ho^2 &
ho & 1 &
ho \
ho^3 &
ho^2 &
ho & 1 \end{bmatrix},$$

where the REML estimates for the heart rate data are $\hat{\sigma} = 6.00$ and $\hat{\rho} = 0.828$.

- (d) Using R, AIC = 313.94 and BIC = 340.14. Using SAS, AIC = 289.9 and BIC = 291.4.
- (e) Under a general symmetry assumption,

$$\mathbf{W} = \sigma^2 \begin{bmatrix} 1 & \rho_{12}\delta_2 & \rho_{13}\delta_3 & \rho_{14}\delta_4 \\ \rho_{12}\delta_2 & \delta_2^2 & \rho_{23}\delta_2\delta_3 & \rho_{24}\delta_2\delta_4 \\ \rho_{13}\delta_3 & \rho_{23}\delta_2\delta_3 & \delta_3^2 & \rho_{34}\delta_3\delta_4 \\ \rho_{14}\delta_4 & \rho_{24}\delta_2\delta_4 & \rho_{34}\delta_3\delta_4 & \delta_4^2 \end{bmatrix},$$

where the REML estimates for the heart rate data are

$$\hat{\sigma} = 6.10,$$

$$\hat{\delta}_2 = 1.08, \quad \hat{\delta}_3 = 0.995, \quad \hat{\delta}_4 = 0.928,$$

$$\hat{\rho}_{12} = 0.850, \quad \hat{\rho}_{13} = 0.889, \quad \hat{\rho}_{14} = 0.625,$$

$$\hat{\rho}_{23} = 0.870, \quad \hat{\rho}_{24} = 0.631, \quad \hat{\rho}_{34} = 0.794.$$

- (f) Using R, AIC = 322.85 and BIC = 364.01. Using SAS, AIC = 298.8 and BIC = 305.9.
- (g) The model with an AR(1) correlation structure has the smallest AIC and BIC of the three (regardless of whether you used R or SAS). Consequently, the AR(1) correlation structure is preferred for this dataset.
- (h) There are several ways to find a 95% confidence interval for $\mu_{14} \mu_{24}$ using the model with an AR(1) correlation structure. In question 2 (f), we used a split-plot design to get a confidence interval, for which it is clear that we should compute the degrees of freedom using Cochran-Satterthwaite. However, it is less clear for the model using AR(1). Regardless of which degrees of freedom you use, you should have $\mu_{14} \mu_{24} = -5.6$ with $\sqrt{\widehat{\mathrm{Var}}(\widehat{\mu_{14} \mu_{24}})} = 3.795$.

We can use the Cochran-Satterthwaite method in SAS by specifying the "ddfm = satterthwaite" option, which gives the interval (-13.54, 2.34) based on df = 19.2. The default "ddfm" method in SAS uses df = 36, which gives the interval (-13.30, 2.10).

In R, gls computes df = n - rank(X) = 48, which leads to the interval (-13.23, 2.03).

Of these intervals, I would prefer the one where the degrees of freedom are computed by Cochran-Satterthwaite because it is the widest and hence the most conservative in terms of inference about the value of $\mu_{14} - \mu_{24}$.

SAS code:

```
proc mixed;
    class woman drug time;
    model y = drug time drug*time;
```

```
repeated time / subject = woman type = cs r rcorr;
run;
proc mixed;
     class woman drug time;
     model y = drug time drug*time / ddfm = satterthwaite;
     repeated time / subject = woman type = ar(1) r rcorr;
     estimate 'drug A - drug B at 15 minutes'
          drug 1 -1 0 drug * time 0 0 0 1 0 0 0 -1 0 0 0 0 / cl;
run;
proc mixed;
     class woman drug time;
     model y = drug time drug*time;
     repeated time / subject = woman type = un r rcorr;
run;
R code:
attach(d)
woman <- as.factor(woman)</pre>
drug <- as.factor(drug)</pre>
time <- as.factor(time)</pre>
model.cs <- gls(y ~ drug * time,</pre>
                correlation = corCompSymm(form = ~1 | woman),
                method = "REML")
model.ar <- gls(y ~ drug * time,</pre>
                correlation = corAR1(form = ~1 | woman),
                method = "REML")
model.sy <- gls(y ~ drug * time,</pre>
                correlation = corSymm(form = ~1 | woman),
                weight = varIdent(form = ~1 | time),
                method = "REML")
summary(model.cs)
getVarCov(model.cs)
summary(model.ar)
getVarCov(model.ar)
summary(model.sy)
getVarCov(model.sy)
ci.gls <- function(lmeout, C, df, a = 0.05) {</pre>
  b = coef(lmeout)
  V = vcov(lmeout)
  Cb = C \%*\% b
  se = sqrt(diag(C %*% V %*% t(C)))
  tval = qt(1 - a / 2, df)
  low = Cb - tval * se
  up = Cb + tval * se
 m = cbind( Cb, se, low, up)
  dimnames(m)[[2]] = c("estimate", "se", paste(100 * (1 - a), "% Conf.", sep = ""), "limits")
  return(m)
}
ci.gls(model.ar, C2, 19.2) # Cheated and took Cochran-Satterthwaite df value from SAS.
ci.gls(model.ar, C2, 36) # Default df method in SAS.
ci.gls(model.ar, C2, 48) # Default df method in R.
```

4. The model we used in this problem is $y = X\beta + \epsilon$ where

$$\boldsymbol{y} = \begin{bmatrix} y_{11} \\ y_{12} \\ y_{21} \\ y_{31} \end{bmatrix}, \ \boldsymbol{X} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 0 \end{bmatrix}, \ \boldsymbol{\beta} = \begin{bmatrix} \mu_1 \\ \mu_2 \end{bmatrix}, \ \boldsymbol{\epsilon} = \begin{bmatrix} \epsilon_{11} \\ \epsilon_{12} \\ \epsilon_{21} \\ \epsilon_{31} \end{bmatrix} \text{ and } \boldsymbol{\epsilon} \sim N \left(\boldsymbol{0}_{4 \times 1}, \boldsymbol{\Sigma} = \begin{bmatrix} 4 & 2 & 0 & 0 \\ 2 & 4 & 0 & 0 \\ 0 & 0 & 4 & 0 \\ 0 & 0 & 0 & 4 \end{bmatrix} \right)$$

(a) The expected total weight gained by a calf from birth to 12 weeks of age is $\mu_1 + \mu_2$ (which is estimable because $E(y_{11} + y_{12}) = \mu_1 + \mu_2$).

The BLUE of $\mu_1 + \mu_2 = (1,1)\boldsymbol{\beta}$ is

$$(1,1)\hat{\boldsymbol{\beta}}_{\text{BLUE}} = (1,1)(\boldsymbol{X}'\boldsymbol{\Sigma}^{-1}\boldsymbol{X})^{-}\boldsymbol{X}'\boldsymbol{\Sigma}^{-1}\boldsymbol{y}$$

$$= (1,1)\left(\begin{bmatrix} 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{3} & -\frac{1}{6} & 0 & 0 \\ -\frac{1}{6} & \frac{1}{3} & 0 & 0 \\ 0 & 0 & \frac{1}{4} & 0 \\ 0 & 0 & 0 & \frac{1}{4} \end{bmatrix} \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 0 \end{bmatrix} \right)^{-1}$$

$$\times \begin{pmatrix} 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{1}{3} & -\frac{1}{6} & 0 & 0 \\ -\frac{1}{6} & \frac{1}{3} & 0 & 0 \\ 0 & 0 & \frac{1}{4} & 0 \\ 0 & 0 & 0 & \frac{1}{4} \end{pmatrix} \boldsymbol{y}$$

$$= (1,1)\begin{pmatrix} \frac{151}{3} \\ \frac{161}{3} \end{pmatrix}$$

$$= 104$$

(b) According to the model and the correlation description,

$$\begin{bmatrix} \mathbf{y} \\ y_{22} \\ y_{32} \end{bmatrix} \sim N \begin{pmatrix} \begin{bmatrix} \mathbf{X}\boldsymbol{\beta} \\ \mu_2 \\ \mu_2 \end{bmatrix}, \begin{bmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} \end{bmatrix} \end{pmatrix} \text{ where } \begin{bmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} \end{bmatrix} = \begin{bmatrix} 4 & 2 & 0 & 0 & 0 & 0 \\ 2 & 4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & 0 & 2 & 0 \\ 0 & 0 & 0 & 4 & 0 & 2 \\ \hline 0 & 0 & 2 & 0 & 4 & 0 \\ 0 & 0 & 0 & 2 & 0 & 4 \end{bmatrix}$$

The BLUP of $\mathbf{u} = (y_{22}, y_{32})$ is the BLUE of $E(\mathbf{u}|\mathbf{y})$.

$$\begin{split} E(\boldsymbol{u}|\boldsymbol{y}) &= \begin{bmatrix} \mu_2 \\ \mu_2 \end{bmatrix} + \boldsymbol{\Sigma}_{21} \boldsymbol{\Sigma}_{11}^{-1} (\boldsymbol{y} - \boldsymbol{X}\boldsymbol{\beta}) \\ &= \begin{bmatrix} \mu_2 \\ \mu_2 \end{bmatrix} + \begin{bmatrix} 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 2 \end{bmatrix} \begin{bmatrix} \frac{1}{3} & -\frac{1}{6} & 0 & 0 \\ -\frac{1}{6} & \frac{1}{3} & 0 & 0 \\ 0 & 0 & \frac{1}{4} & 0 \\ 0 & 0 & 0 & \frac{1}{4} \end{bmatrix} \begin{pmatrix} \boldsymbol{y} - \begin{bmatrix} \mu_1 \\ \mu_2 \\ \mu_1 \\ \mu_1 \end{bmatrix} \end{pmatrix} \\ &= \begin{bmatrix} \mu_2 \\ \mu_2 \end{bmatrix} + \frac{1}{2} \begin{bmatrix} y_{21} - \mu_1 \\ y_{31} - \mu_1 \end{bmatrix} \end{split}$$

From part (a), the BLUE of
$$\boldsymbol{\beta} = (\mu_1, \mu_2)'$$
 is $\hat{\boldsymbol{\beta}}_{\text{BLUE}} = \begin{bmatrix} \hat{\mu}_2 \\ \hat{\mu}_2 \end{bmatrix} = \begin{pmatrix} \frac{151}{3} \\ \frac{161}{3} \end{pmatrix}$, so

$$\hat{E}(\boldsymbol{u}|\boldsymbol{y}) = \begin{bmatrix} \hat{\mu}_2 \\ \hat{\mu}_2 \end{bmatrix} + \frac{1}{2} \begin{bmatrix} y_{21} - \hat{\mu}_1 \\ y_{31} - \hat{\mu}_1 \end{bmatrix}$$
$$= \begin{pmatrix} 52.5 \\ 54.5 \end{pmatrix}$$

Therefore the BLUP of y_{22} and y_{32} are 52.5 and 54.5 respectively.