These slides illustrate a few example R commands that can be useful for the analysis of repeated measures data.

We focus on the experiment designed to compare the effectiveness of three strength training programs.

```
#Read the data

d=read.delim("http://www.public.iastate.edu/
~dnett/S511/RepeatedMeasures.txt")
head(d)

  Program Subj Time Strength
1       3    1    2       85
2       3    1    4       85
3       3    1    6       86
4       3    1    8       85
5       3    1   10       87
6       3    1   12       86
```

```
#Create factors

d$Program=as.factor(d$Program)
d$Subj=as.factor(d$Subj)
d$Timef=as.factor(d$Time)

head(d)
  Program Subj Time Strength Timef
1       3    1    2       85     2
2       3    1    4       85     4
3       3    1    6       86     6
4       3    1    8       85     8
5       3    1   10       87    10
6       3    1   12       86    12
```

```
# Compute sample means

means = tapply(d$Strength,list(d$Time,d$Program),mean)

means
          1        2     3
2  79.6875 81.04762 79.75
4  80.5625 81.66667 79.95
6  80.8125 81.90476 80.00
8  81.0000 82.52381 80.05
10 81.2500 82.61905 79.80
12 81.1250 82.71429 79.60
14 81.1250 83.09524 79.60
```

THESE ARE BLUES OF

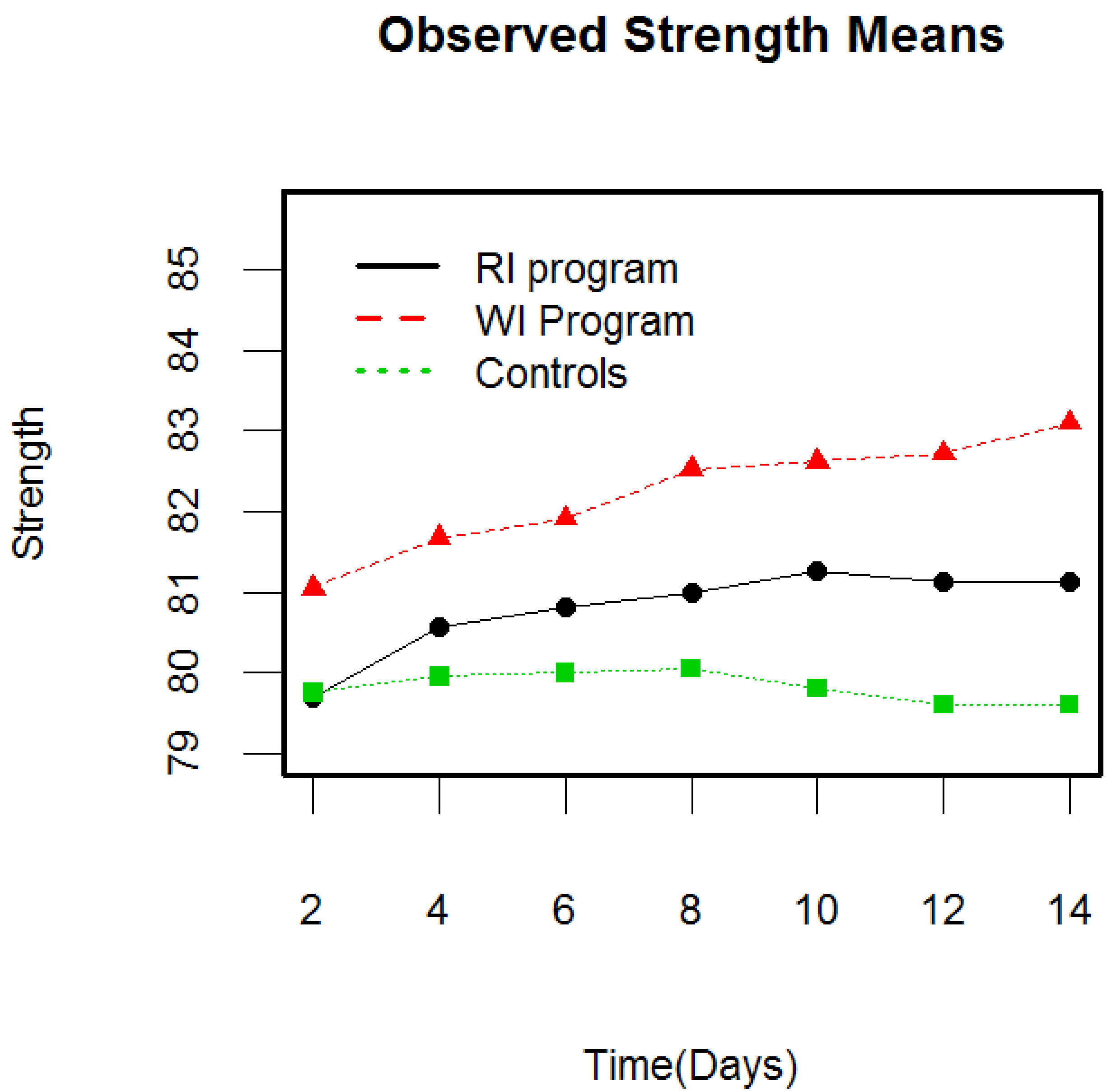
$$\mu_{ik} = \mu + \alpha_i + \tau_k + \gamma_{ik}$$

FOR THE CELL MEAN MODELS WE CONSIDER FOR THESE DATA.

```
#  Make a profile plot of the means

x.axis = unique(d$Time)

par(fin=c(6.0,6.0),pch=18,mkh=.1,mex=1.5,
    cex=1.2,lwd=3)
matplot(c(2,14), c(79,85.7), type="n",
       xlab="Time(Days)", ylab="Strength",
       main= "Observed Strength Means")
matlines(x.axis,means,type='l',lty=c(1,2,3))
matpoints(x.axis,means, pch=c(16,17,15))
legend(2.1,85.69,legend=c("RI program",
      'WI Program','Controls'),
       lty=c(1,2,3),col=1:3,bty='n')
```



Observed Strength Means
RI program
WI Program
Controls
Strength
79
80
81
82
83
84
85
2
4
6
8
10
12
14
Time(Days)

- **The following code illustrates how to specify different models for the variance-covariance of the response vector.**

- **We will begin with each model specification followed by a description of the model variance-covariance matrix associated with that model specification. Then output from each model fit will be examined.**

- **At first, we will assume the same structure for the mean in each case (one mean for each combination of program and time, a cell means model). Later we will look into different models for the mean.**

This code fits a linear mixed effects model with independent random effects for each subject. The resulting variance-covariance structure for the response vector is block diagonal. Each block has a compound symmetric structure. There is one block for each subject.

```
lme(Strength ~ Program*Timef,data=d,
    random= ~ 1|Subj)
```

$\mathrm{Var}(\boldsymbol{y})$ is block diagonal with blocks

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

This code fits a general linear model. The variance-covariance structure for the response vector is block diagonal. Each block has a compound symmetric structure. There is one block for each subject. This code fits a model for the response vector that is identical to the model obtained using the previous lme code.

```
gls(Strength ~ Program*Timef,data=d,
  correlation = corCompSymm(form=~1|Subj))
```

$\mathrm{Var}(\boldsymbol{y})$ is block diagonal with blocks

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho & \rho & \rho \\ \rho & \rho & 1 & \rho & \rho & \rho & \rho \\ \rho & \rho & \rho & 1 & \rho & \rho & \rho \\ \rho & \rho & \rho & \rho & 1 & \rho & \rho \\ \rho & \rho & \rho & \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & \rho & \rho & \rho & 1 \end{bmatrix}$$

To match with previous variance components, note that

$$\sigma^2 = \sigma_e^2 + \sigma_s^2 \qquad \sigma^2\rho = \sigma_s^2 \;\Leftrightarrow \rho = \frac{\sigma_s^2}{\sigma^2} = \frac{\sigma_s^2}{\sigma_e^2 + \sigma_s^2}.$$

This code fits a general linear model. The variance-covariance structure for the response vector is block diagonal. Each block has an AR(1) structure. There is one block for each subject.

```
gls(Strength ~ Program*Timef,data=d,
    correlation = corAR1(form=~1|Subj))
```

$\mathrm{Var}(\boldsymbol{y})$ is block diagonal with blocks

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 & \rho^4 & \rho^5 & \rho^6 \\ \rho & 1 & \rho & \rho^2 & \rho^3 & \rho^4 & \rho^5 \\ \rho^2 & \rho & 1 & \rho & \rho^2 & \rho^3 & \rho^4 \\ \rho^3 & \rho^2 & \rho & 1 & \rho & \rho^2 & \rho^3 \\ \rho^4 & \rho^3 & \rho^2 & \rho & 1 & \rho & \rho^2 \\ \rho^5 & \rho^4 & \rho^3 & \rho^2 & \rho & 1 & \rho \\ \rho^6 & \rho^5 & \rho^4 & \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

This code fits a general linear model. The variance-covariance structure for the response vector is block diagonal. Each block is a general symmetric, positive definite variance-covariance matrix. There is one block for each subject.

```
gls(Strength ~ Program*Timef,data=d,
    correlation = corSymm(form=~1|Subj),
    weight = varIdent(form = ~ 1|Timef))
```

$\mathrm{Var}(\boldsymbol{y})$ is block diagonal with blocks

$$\sigma^2 \ \text{diag}(\delta_1, ..., \delta_7) \begin{bmatrix} 1 & & & & & & \\ & 1 & & & \rho_{ij} & & \\ & & 1 & & & & \\ & & & 1 & & & \\ & & & & 1 & & \\ & \rho_{ij} & & & & 1 & \\ & & & & & & 1 \end{bmatrix} \text{diag}(\delta_1, ..., \delta_7)$$

$$
= \sigma^2 \begin{bmatrix}
\delta_1^2 & & & & & & \\
& \delta_2^2 & & & \rho_{ij}\delta_i\delta_j & & \\
& & \delta_3^2 & & & & \\
& & & \delta_4^2 & & & \\
& & & & \delta_5^2 & & \\
& \rho_{ij}\delta_i\delta_j & & & & \delta_6^2 & \\
& & & & & & \delta_7^2
\end{bmatrix}
$$

Identifiability Constraint : $\delta_1 \equiv 1$

- To understand the reason for an identifiability constraint, notice that an arbitrary positive definite 7×7 covariance matrix depends on only

$$7+6+5+4+3+2+1 = \frac{7(7+1)}{2} = 28$$

parameters. However, we have $\sigma^2, \; 6+5+4+3+2+1 = 21 \; \rho_{ij}$ parameters, and $\delta_1, \ldots, \delta_7$.

- That's 29 parameters for a symmetric positive definite matrix that depends on at most 28 parameters.

- Thus, R chooses to set δ_1 to 1.

- Without such a constraint, it is easy to use different values of the parameters to define the same matrix. For example,

$$\left[\begin{array}{cc} 3 & -1 \\ -1 & 7 \end{array}\right] = 3\left[\begin{array}{cc} 1 & -\frac{1}{3} \\ -\frac{1}{3} & \frac{7}{3} \end{array}\right] = 1\left[\begin{array}{cc} 3 & -1 \\ -1 & 7 \end{array}\right]$$

σ^2	3	1
δ_1	1	$\sqrt{3}$
δ_2	$\sqrt{\frac{7}{3}}$	$\sqrt{7}$
ρ_{12}	$\frac{-1}{3\sqrt{\frac{7}{3}}}$	$\frac{-1}{\sqrt{21}}$

If you are interested in learning about how to fit other variance-covariance structures in R, the following help commands will be useful.

?corClasses

?varClasses

?pdClasses

```
# Use the lme function. This application
# assumes that each subject has a different
# identification value

library(nlme)
d.lme = lme(Strength ~ Program*Timef,
    random= ~ 1|Subj, data=d,
    method="REML")

summary(d.lme)

Linear mixed-effects model fit by REML
 Data: d
       AIC      BIC    logLik
  1466.820 1557.323 -710.4101

Random effects:
 Formula: ~1 | Subj
        (Intercept) Residual
StdDev:    3.098924 1.094017
```

RANK(X) = 21

SAMPLE SIZE FOR REML LIKELIHOOD IS 57x7 - 21 = 378

$-2\ell(\hat{\underset{\sim}{\Theta}}) + 2(21+2)$

$\ell(\hat{\underset{\sim}{\Theta}})$

$-2\ell(\hat{\underset{\sim}{\Theta}}) + (21+2)\log(378)$

RANK(X)

#VAR PARAMETERS

$\hat{\sigma}_S$ $\hat{\sigma}_E$

```
Fixed effects: Strength ~ Program * Timef
                          Value Std.Error  DF   t-value p-value
(Intercept)            79.68750 0.8215916 324  96.99162  0.0000
Program2                1.36012 1.0905540  54   1.24718  0.2177
Program3                0.06250 1.1022808  54   0.05670  0.9550
Timef4                  0.87500 0.3867933 324   2.26219  0.0243
Timef6                  1.12500 0.3867933 324   2.90853  0.0039
Timef8                  1.31250 0.3867933 324   3.39328  0.0008
Timef10                 1.56250 0.3867933 324   4.03962  0.0001
Timef12                 1.43750 0.3867933 324   3.71645  0.0002
Timef14                 1.43750 0.3867933 324   3.71645  0.0002
Program2:Timef4        -0.25595 0.5134169 324  -0.49853  0.6185
Program3:Timef4        -0.67500 0.5189377 324  -1.30073  0.1943
Program2:Timef6        -0.26786 0.5134169 324  -0.52171  0.6022
Program3:Timef6        -0.87500 0.5189377 324  -1.68614  0.0927
Program2:Timef8         0.16369 0.5134169 324   0.31883  0.7501
Program3:Timef8        -1.01250 0.5189377 324  -1.95110  0.0519
Program2:Timef10        0.00893 0.5134169 324   0.01739  0.9861
Program3:Timef10       -1.51250 0.5189377 324  -2.91461  0.0038
Program2:Timef12        0.22917 0.5134169 324   0.44636  0.6556
Program3:Timef12       -1.58750 0.5189377 324  -3.05913  0.0024
Program2:Timef14        0.61012 0.5134169 324   1.18835  0.2356
Program3:Timef14       -1.58750 0.5189377 324  -3.05913  0.0024
```

$\hat{\beta}$ $\hat{\Sigma}$ =

THIS PART NOT ALWAYS RIGHT

NOT TEST OF TIME MAIN EFFECTS

```
Number of Observations: 399
Number of Groups: 57
anova(d.lme)
```

	numDF	denDF	F-value	p-value
~~(Intercept)~~	~~1~~	~~324~~	~~38242.27~~	~~<.0001~~
Program	2	54	3.07	0.0548
Timef	6	324	7.37	<.0001
Program:Timef	12	324	2.99	0.0005

SAFER TO CONSTRUCT YOUR OWN TESTS USING EQUATIONS BELOW. THIS IS A TYPE I ANOVA TABLE

$$\hat{\underset{\sim}{\beta}}_{\hat{\Sigma}} = (X'\hat{\Sigma}^{-1}X)^{-1}X'\hat{\Sigma}^{-1}y \leftarrow \text{fixef(d.lme)}$$

$$\widehat{VAR}(\hat{\underset{\sim}{\beta}}_{\hat{\Sigma}}) = (X'\hat{\Sigma}^{-1}X)^{-1} \leftarrow \text{vcov(d.lme)}$$

$$\widehat{VAR}(C\hat{\underset{\sim}{\beta}}_{\hat{\Sigma}}) = C(X'\hat{\Sigma}^{-1}X)^{-1}C'$$

$$F = (C\hat{\underset{\sim}{\beta}}_{\hat{\Sigma}})'[C(X'\hat{\Sigma}^{-1}X)^{-1}C']^{-1}C\hat{\underset{\sim}{\beta}}_{\hat{\Sigma}} / q$$

$$q = \text{RANK}(C) = \text{nrow}(C) = \text{numerator df}$$

```
#  Use the gls( ) function to fit a
#  model where the errors have a
#  compound symmetry covariance structure
#  within subjects. Random effects are
#  not used to induce correlation.

d.glscs = gls(Strength ~ Program*Timef,data=d,
              correlation = corCompSymm(form=~1|Subj),
              method="REML")
summary(d.glscs)

Generalized least squares fit by REML
  Model: Strength ~ Program * Timef
  Data: d
       AIC      BIC    logLik
  1466.820 1557.323 -710.4101
```

SAME AS FOR THE lme FIT OF THIS MODEL

```
Correlation Structure: Compound symmetry
 Formula: ~1 | Subj
 Parameter estimate(s):
      Rho
0.8891805
```

$\hat{\rho}$

$\hat{\underset{\sim}{\beta}}$ $\hat{\Sigma}$

```
Coefficients:
                    Value Std.Error  t-value p-value
(Intercept)      79.68750 0.8215916 96.99162  0.0000
Program2          1.36012 1.0905540  1.24718  0.2131
Program3          0.06250 1.1022808  0.05670  0.9548
Timef4            0.87500 0.3867933  2.26219  0.0243
Timef6            1.12500 0.3867933  2.90853  0.0038
Timef8            1.31250 0.3867933  3.39328  0.0008
Timef10           1.56250 0.3867933  4.03962  0.0001
Timef12           1.43750 0.3867933  3.71645  0.0002
Timef14           1.43750 0.3867933  3.71645  0.0002
Program2:Timef4  -0.25595 0.5134169 -0.49853  0.6184
Program3:Timef4  -0.67500 0.5189377 -1.30073  0.1941
Program2:Timef6  -0.26786 0.5134169 -0.52171  0.6022
Program3:Timef6  -0.87500 0.5189377 -1.68614  0.0926
```

```
Program2:Timef8    0.16369 0.5134169  0.31883  0.7500
Program3:Timef8   -1.01250 0.5189377 -1.95110  0.0518
Program2:Timef10   0.00893 0.5134169  0.01739  0.9861
Program3:Timef10  -1.51250 0.5189377 -2.91461  0.0038
Program2:Timef12   0.22917 0.5134169  0.44636  0.6556
Program3:Timef12  -1.58750 0.5189377 -3.05913  0.0024
Program2:Timef14   0.61012 0.5134169  1.18835  0.2354
Program3:Timef14  -1.58750 0.5189377 -3.05913  0.0024

Residual standard error: 3.286366
Degrees of freedom: 399 total; 378 residual
```

$\hat{\sigma}$

$399 - 21$

```
anova(d.glscs)
Denom. DF: 378
              numDF  F-value p-value
(Intercept)       1 38242.27  <.0001
Program           2     3.07  0.0478
Timef             6     7.37  <.0001
Program:Timef    12     2.99  0.0005
```

```
# Try an auto regressive covariance
# structures across time within
# subjects

d.glsar = gls(Strength ~ Program*Timef,data=d,
              correlation = corAR1(form=~1|Subj),
              method="REML")
summary(d.glsar)

Generalized least squares fit by REML
  Model: Strength ~ Program * Timef
  Data: d
       AIC      BIC    logLik
  1312.804 1403.306 -633.4018

Correlation Structure: AR(1)
 Formula: ~1 | Subj
 Parameter estimate(s):
     Phi
0.951777
```

$\hat{\rho}$

SAME CALCULATIONS AS BEFORE BUT WITH A NEW VALUE OF MAXIMIZED LOG LIKELIHOOD

SAME $\hat{\beta}$ BUT NEW SEs.

Coefficients: $\hat{\Sigma}$

	Value	Std.Error	t-value	p-value
(Intercept)	79.68750	0.8200605	97.17271	0.0000
Program2	1.36012	1.0885218	1.24951	0.2123
Program3	0.06250	1.1002267	0.05681	0.9547
Timef4	0.87500	0.2546762	3.43573	0.0007
Timef6	1.12500	0.3557980	3.16191	0.0017
Timef8	1.31250	0.4305201	3.04864	0.0025
Timef10	1.56250	0.4911919	3.18104	0.0016
Timef12	1.43750	0.5426737	2.64892	0.0084
Timef14	1.43750	0.5874975	2.44682	0.0149
Program2:Timef4	-0.25595	0.3380490	-0.75715	0.4494
Program3:Timef4	-0.67500	0.3416840	-1.97551	0.0489
Program2:Timef6	-0.26786	0.4722748	-0.56716	0.5709
Program3:Timef6	-0.87500	0.4773531	-1.83302	0.0676
Program2:Timef8	0.16369	0.5714584	0.28644	0.7747
Program3:Timef8	-1.01250	0.5776033	-1.75293	0.0804
Program2:Timef10	0.00893	0.6519923	0.01369	0.9891
Program3:Timef10	-1.51250	0.6590031	-2.29513	0.0223
Program2:Timef12	0.22917	0.7203275	0.31814	0.7506
Program3:Timef12	-1.58750	0.7280732	-2.18041	0.0298

```
Program2:Timef14  0.61012 0.7798251  0.78238  0.4345
Program3:Timef14 -1.58750 0.7882106 -2.01406  0.0447


Residual standard error: 3.280242
Degrees of freedom: 399 total; 378 residual
anova(d.glsar)
Denom. DF: 378
              numDF  F-value p-value
(Intercept)       1 39707.71  <.0001
Program           2     3.27  0.0390
Timef             6     4.22  0.0004
Program:Timef    12     1.17  0.3000
```

$\hat{\sigma}$

```
#  Use an arbitray covariance matrix for
#  observations at different time
#  points within subjects

d.gls = gls(Strength ~ Program*Timef,data=d,
            correlation = corSymm(form=~1|Subj),
            weight = varIdent(form = ~ 1|Timef),
            method="REML")
summary(d.gls)
```

$-2\ell(\hat{\underset{\sim}{\theta}}) + (21+28)\log(378)$

```
Generalized least squares fit by REML
  Model: Strength ~ Program * Timef
  Data: d
       AIC      BIC    logLik
  1332.896 1525.706 -617.4479
```

$-2\ell(\hat{\underset{\sim}{\theta}}) + 2(21+28)$

```
Correlation Structure: General
 Formula: ~1 | Subj
 Parameter estimate(s):
 Correlation:
  1     2     3     4     5     6
2 0.960
3 0.925 0.940
4 0.872 0.877 0.956
5 0.842 0.860 0.937 0.960
6 0.809 0.827 0.898 0.909 0.951
7 0.797 0.792 0.876 0.887 0.917 0.953
```

ρ_{ij}

VALUES

```
Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | Timef
 Parameter estimates:
       2        4        6        8       10       12       14
1.000000 1.038706 1.104345 1.071331 1.173700 1.157128 1.203170
```

$\hat{\delta}_1$ $\hat{\delta}_2$ . . . . $\hat{\delta}_7$

SAME $\hat{\beta}$ & $\hat{\Sigma}$ BUT NEW SEs

Coefficients:

	Value	Std.Error	t-value	p-value
(Intercept)	79.68750	0.7407750	107.57315	0.0000
Program2	1.36012	0.9832807	1.38325	0.1674
Program3	0.06250	0.9938539	0.06289	0.9499
Timef4	0.87500	0.2149042	4.07158	0.0001
Timef6	1.12500	0.3119398	3.60647	0.0004
Timef8	1.31250	0.3921652	3.34680	0.0009
Timef10	1.56250	0.4689837	3.33167	0.0009
Timef12	1.43750	0.5059335	2.84128	0.0047
Timef14	1.43750	0.5394644	2.66468	0.0080
Program2:Timef4	-0.25595	0.2852569	-0.89727	0.3701
Program3:Timef4	-0.67500	0.2883242	-2.34111	0.0197
Program2:Timef6	-0.26786	0.4140587	-0.64691	0.5181
Program3:Timef6	-0.87500	0.4185111	-2.09075	0.0372
Program2:Timef8	0.16369	0.5205474	0.31446	0.7533
Program3:Timef8	-1.01250	0.5261448	-1.92438	0.0551
Program2:Timef10	0.00893	0.6225138	0.01434	0.9886
Program3:Timef10	-1.51250	0.6292077	-2.40382	0.0167
Program2:Timef12	0.22917	0.6715597	0.34125	0.7331
Program3:Timef12	-1.58750	0.6787810	-2.33875	0.0199

```
Program2:Timef14  0.61012 0.7160675   0.85204  0.3947
Program3:Timef14 -1.58750 0.7237674  -2.19338  0.0289
```

`Residual standard error: 2.9631` $\hat{\sigma}$

```
Degrees of freedom: 399 total; 378 residual
anova(d.gls)
Denom. DF: 378
              numDF  F-value p-value
(Intercept)       1 47713.21  <.0001
Program           2     2.77  0.0639
Timef             6     6.99  <.0001
Program:Timef    12     1.57  0.0989
```

Compare the fit of various covariance
structures.

```
anova(d.gls, d.glscs)
         Model df      AIC      BIC    logLik   Test  L.Ratio p-value
d.gls        1 49 1332.896 1525.706 -617.4479
d.glscs      2 23 1466.820 1557.323 -710.4101 1 vs 2 185.9245  <.0001

anova(d.gls, d.glsar)
         Model df      AIC      BIC    logLik   Test  L.Ratio p-value
d.gls        1 49 1332.896 1525.706 -617.4479
d.glsar      2 23 1312.803 1403.306 -633.4018 1 vs 2 31.90777  0.1962
```

$\ell(\hat{\underset{\sim}{\theta}})$

$\ell(\hat{\underset{\sim}{\theta}}_0)$

$-2\log\Lambda$

$= 2\ell(\hat{\underset{\sim}{\theta}}) - 2\ell(\hat{\underset{\sim}{\theta}}_0)$

TO GET p-VALUE, COMPARE TO

$\chi^2_{49-23} = \chi^2_{26}$

```
# Treat time as a continuous variable and
# fit quadratic trends in strength
# over time

d.time = gls(Strength ~ Program+Time+
   Program*Time+I(Time^2)+Program*I(Time^2),
   data=d,
   correlation = corAR1(form=~1|Subj),
   method="REML")

summary(d.time)

Generalized least squares fit by REML
  Model: Strength ~ Program + Time + Program * Time +
I(Time^2) + Program *       I(Time^2)
  Data: d
       AIC      BIC    logLik
  1315.507 1359.134 -646.7534
```

PROGRAM	MEAN = QUADRATIC FUNCTION OF TIME = x
1	$\beta_0 + \beta_1 x + \beta_2 x^2$
2	$\beta_0 + \delta_{02} + (\beta_1 + \delta_{12}) x + (\beta_2 + \delta_{22}) x^2$
3	$\beta_0 + \delta_{03} + (\beta_1 + \delta_{13}) x + (\beta_2 + \delta_{23}) x^2$

```
Correlation Structure: AR(1)
 Formula: ~1 | Subj
 Parameter estimate(s):
      Phi
0.9522692
```

$\hat{\rho}$

Coefficients:

		Value	Std.Error	t-value	p-value
(Intercept)	$\hat{\beta}_0$	78.90542	0.8912542	88.53301	0.0000
Program2	$\hat{\delta}_{02}$	1.58737	1.1830220	1.34180	0.1804
Program3	$\hat{\delta}_{03}$	0.66537	1.1957430	0.55645	0.5782
Time	$\hat{\beta}_1$	0.43031	0.1315124	3.27199	0.0012
I(Time^2)	$\hat{\beta}_2$	-0.01942	0.0076344	-2.54327	0.0114
Program2:Time	$\hat{\delta}_{12}$	-0.13728	0.1745653	-0.78639	0.4321
Program3:Time	$\hat{\delta}_{13}$	-0.32572	0.1764424	-1.84607	0.0656
Program2:I(Time^2)	$\hat{\delta}_{22}$	0.01176	0.0101336	1.16049	0.2466
Program3:I(Time^2)	$\hat{\delta}_{23}$	0.01209	0.0102426	1.18052	0.2385

```
Residual standard error: 3.279999
Degrees of freedom: 399 total; 390 residual
anova(d.time)
Denom. DF: 390
                  numDF  F-value p-value
(Intercept)           1 39659.69  <.0001
Program               2     3.27  0.0391
Time                  1    12.69  0.0004
I(Time^2)             1     7.18  0.0077
Program:Time          2     4.75  0.0092
Program:I(Time^2)     2     0.88  0.4166
```

$\hat{\sigma}$

TESTS $H_0: \delta_{22} = \delta_{23} = 0$

NULL SAYS COEFFICIENT OF TIME^2

IS THE SAME FOR ALL THREE PROGRAMS

```
# To compare the continuous time model to the
# model where we fit a different mean at each
# time point, we must compare likelihood values
# instead of REML likelihood values.

d.glsarmle = gls(Strength ~ Program*Timef,
   data=d,
   correlation = corAR1(form=~1|Subj),
   method="ML")

d.timemle = gls(Strength ~ Program+ Time+
      Program*Time+I(Time^2)+Program*I(Time^2),
   data=d,
   correlation = corAR1(form=~1|Subj),
   method="ML")

anova(d.glsarmle, d.timemle)
           Model df      AIC      BIC    logLik   Test  L.Ratio p-value
d.glsarmle     1 23 1296.492 1388.238 -625.2458
d.timemle      2 11 1281.437 1325.315 -629.7183 1 vs 2 8.945125  0.7076
```

```
#  Do not fit different quadratic trends
#  for different programs

d.timemle = gls(Strength ~ Program+Time+
      Program*Time+I(Time^2), data=d,
   correlation = corAR1(form=~1|Subj),
   method="ML")

anova(d.glsarmle, d.timemle)

           Model df      AIC      BIC    logLik   Test  L.Ratio p-value
d.glsarmle     1 23 1296.492 1388.238 -625.2458
d.timemle      2  9 1279.216 1315.117 -630.6081 1 vs 2 10.72470  0.7075
```

SIMPLER MODEL WITH A COEFFICIENT ON $TIME^2$ THE SAME FOR ALL THREE PROGRAMS LOOKS ADEQUATE RELATIVE TO THE FULL CELL MEANS MODEL.

```
#  Fit a model with random regression coefficients
#  for individual subjects

d.timer = lme(Strength ~ Program+Time+
      Program*Time+I(Time^2),
   random = ~ Time + I(Time^2) | Subj,
   data=d,
   correlation = corAR1(form=~1|Subj),
   control=list(msMaxIter=100),
   method="REML")
```

$$\underset{\sim}{b}_{ij} = \begin{bmatrix} b_{0ij} \\ b_{1ij} \\ b_{2ij} \end{bmatrix} \overset{iid}{\sim} N(\underset{\sim}{0}, \Sigma_{\underset{\sim}{b}})$$

$$\beta_0 + b_{01j} + (\beta_1 + b_{11j})\, x + (\beta_2 + b_{21j})\, x^2$$

$$\beta_0 + \delta_{02} + b_{02j} + (\beta_1 + \delta_{12} + b_{12j})\, x + (\beta_2 + b_{22j})\, x^2$$

$$\beta_0 + \delta_{03} + b_{03j} + (\beta_1 + \delta_{13} + b_{13j})\, x + (\beta_2 + b_{23j})\, x^2$$

d.timer
Linear mixed-effects model fit by REML
  Data: d
  Log-restricted-likelihood: -637.0981

  Fixed: Strength ~ Program + Time + Program * Time + I(Time^2)

$\hat{\beta}_0$ (Intercept)	$\hat{\delta}_{02}$ Program2	$\hat{\delta}_{03}$ Program3	$\hat{\beta}_1$ Time	I(Time^2) $\hat{\beta}_2$
79.17786184	1.23186773	0.30103181	0.29462862	-0.01087514

$\hat{\delta}_{12}$ Program2:Time	Program3:Time $\hat{\delta}_{13}$
0.04705013	-0.13634751

Random effects:
 Formula: ~Time + I(Time^2) | Subj
 Structure: General positive-definite, Log-Cholesky parametrization

	StdDev	Corr	
(Intercept)	2.435205146	(Intr)	Time
Time	0.083560882	0.986	
I(Time^2)	0.005844736	-0.451	-0.413
Residual	1.451700610 $\hat{\sigma}$		

CAN COMPUTE $\hat{\Sigma}_{\underline{b}}$ FROM THESE

```
Correlation Structure: AR(1)
 Formula: ~1 | Subj
 Parameter estimate(s):
      Phi
0.7672073
Number of Observations: 399
Number of Groups: 57
```

$\hat{\rho}$

```
fixef(d.timer)

  (Intercept)      Program2      Program3          Time     I(Time^2)
  79.17786184    1.23186773    0.30103181    0.29462862   -0.01087514

Program2:Time Program3:Time
   0.04705013   -0.13634751
```

EACH ROW IS ONE $\underset{\sim}{b}'_{ij}$ VECTOR

```
ranef(d.timer)
   (Intercept)            Time     I(Time^2)
1   4.36120788  0.1506892044 -1.482481e-03
2  -0.66822714 -0.0242457678 -5.946353e-04
3  -1.98939356 -0.0679391585  2.130498e-03
4   3.20033334  0.1101934789 -1.284287e-03
5   0.06168899  0.0023445249  4.229756e-04
```

6	-2.48115876	-0.0871809434	-1.536516e-03
7	-0.17728408	-0.0033522833	3.299436e-03
8	-3.36666714	-0.1163086953	1.380470e-03
9	-0.77467305	-0.0229830327	3.899628e-03
10	-0.82040204	-0.0273901177	1.702806e-03
11	0.77419357	0.0281727603	1.788654e-03
12	-2.06939153	-0.0698564540	2.615701e-03
13	2.17709296	0.0750139662	-1.243322e-03
14	1.43182191	0.0419766118	-8.434318e-03
15	0.49657353	0.0173900116	-7.603326e-04
16	-1.18629379	-0.0407438258	1.178443e-03
17	2.33644091	0.0783388866	-3.636774e-03
18	-1.39239840	-0.0484070315	5.358528e-05
19	-0.02323497	-0.0002146880	9.337472e-04
20	-0.38713026	-0.0111258578	2.211710e-03
21	-0.89163905	-0.0306024159	8.168185e-04
22	3.17832641	0.1108398304	-1.556342e-04
23	1.08549647	0.0359933861	-2.314019e-03
24	0.64497519	0.0202910707	-2.504246e-03
25	1.26010207	0.0481090718	4.670353e-03
26	-3.44476711	-0.1196613972	6.122401e-04

```
27  2.01520483  0.0708054518  1.130032e-04
28 -0.99733972 -0.0311737140  3.529689e-03
29  3.87721106  0.1314515238 -4.784980e-03
30 -2.88738111 -0.0958539834  4.524976e-03
31 -3.00487285 -0.1039155375  8.583371e-04
32  3.34548126  0.1141778993 -2.800330e-03
33 -0.25912561 -0.0068153540  2.568338e-03
34 -2.77555992 -0.0976719084 -2.197173e-04
35 -2.68590182 -0.0963014338 -2.503327e-03
36  2.50886247  0.0808065101 -7.569840e-03
37  1.25824159  0.0406710443 -3.029020e-03
38 -5.13073594 -0.1743223349  4.982952e-03
39  0.37870040  0.0097142511 -3.475527e-03
40  3.23755456  0.1074241367 -6.106997e-03
41  1.30142073  0.0463002799  8.941384e-04
42 -1.97387203 -0.0680401159  1.122287e-03
43 -1.13096183 -0.0357805086  4.128329e-03
44  5.61815932  0.1935763609 -3.106655e-03
45 -0.23127824 -0.0075690566  7.509660e-04
46  1.28170665  0.0472952992  3.014230e-03
47 -1.47090355 -0.0499452880  1.421987e-03
```

```
48 -0.88768978 -0.0293982386  1.282170e-03
49  0.97002432  0.0304384938 -3.745478e-03
50  0.27632027  0.0118046144  2.581628e-03
51 -2.63396237 -0.0904744258  1.666682e-03
52  0.80293223  0.0266056657 -1.124724e-03
53 -1.60630477 -0.0563999403 -6.950414e-05
54 -0.79109912 -0.0285059974 -1.242500e-03
55  2.71979799  0.0909662456 -4.312172e-03
56 -1.71087648 -0.0551439598  4.356512e-03
57 -0.74934489 -0.0240671146  2.524044e-03
```

```
coef(d.timer)
```

```
   (Intercept) Program2  Program3      Time    I(Time^2) Program2:Time
1     83.53907 1.231868 0.3010318 0.4453178 -0.012357626    0.04705013
2     78.50963 1.231868 0.3010318 0.2703829 -0.011469780    0.04705013
3     77.18847 1.231868 0.3010318 0.2266895 -0.008744647    0.04705013
4     82.37820 1.231868 0.3010318 0.4048221 -0.012159431    0.04705013
5     79.23955 1.231868 0.3010318 0.2969731 -0.010452169    0.04705013
6     76.69670 1.231868 0.3010318 0.2074477 -0.012411661    0.04705013
7     79.00058 1.231868 0.3010318 0.2912763 -0.007575709    0.04705013
8     75.81119 1.231868 0.3010318 0.1783199 -0.009494674    0.04705013
9     78.40319 1.231868 0.3010318 0.2716456 -0.006975516    0.04705013
10    78.35746 1.231868 0.3010318 0.2672385 -0.009172339    0.04705013
11    79.95206 1.231868 0.3010318 0.3228014 -0.009086491    0.04705013
12    77.10847 1.231868 0.3010318 0.2247722 -0.008259444    0.04705013
```

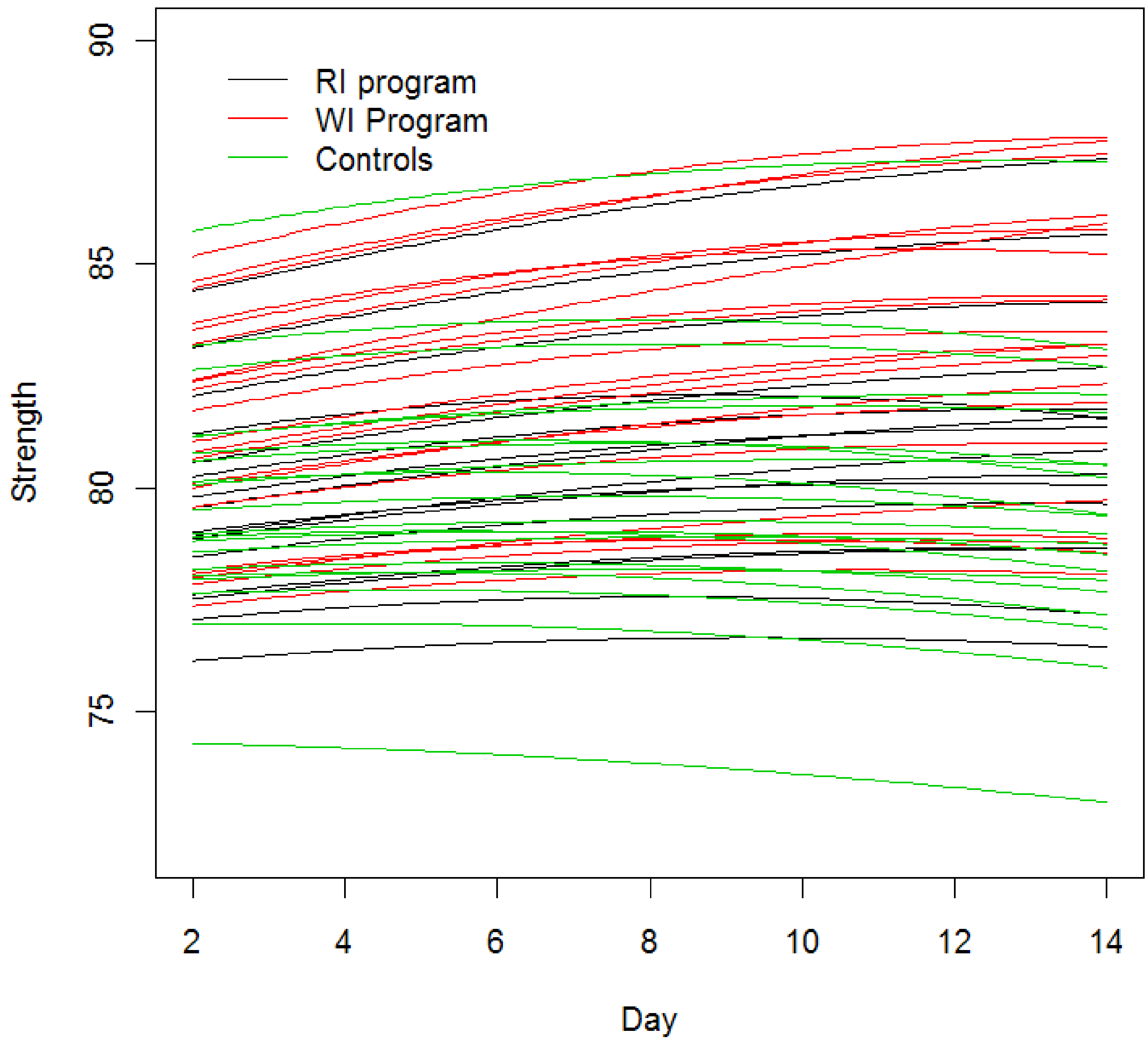
13	81.35495	1.231868	0.3010318	0.3696426	-0.012118466	0.04705013
14	80.60968	1.231868	0.3010318	0.3366052	-0.019309462	0.04705013
15	79.67444	1.231868	0.3010318	0.3120186	-0.011635477	0.04705013
16	77.99157	1.231868	0.3010318	0.2538848	-0.009696702	0.04705013
17	81.51430	1.231868	0.3010318	0.3729675	-0.014511918	0.04705013
18	77.78546	1.231868	0.3010318	0.2462216	-0.010821559	0.04705013
19	79.15463	1.231868	0.3010318	0.2944139	-0.009941397	0.04705013
20	78.79073	1.231868	0.3010318	0.2835028	-0.008663434	0.04705013
21	78.28622	1.231868	0.3010318	0.2640262	-0.010058326	0.04705013
22	82.35619	1.231868	0.3010318	0.4054684	-0.011030779	0.04705013
23	80.26336	1.231868	0.3010318	0.3306220	-0.013189164	0.04705013
24	79.82284	1.231868	0.3010318	0.3149197	-0.013379391	0.04705013
25	80.43796	1.231868	0.3010318	0.3427377	-0.006204792	0.04705013
26	75.73309	1.231868	0.3010318	0.1749672	-0.010262905	0.04705013
27	81.19307	1.231868	0.3010318	0.3654341	-0.010762141	0.04705013
28	78.18052	1.231868	0.3010318	0.2634549	-0.007345456	0.04705013
29	83.05507	1.231868	0.3010318	0.4260801	-0.015660125	0.04705013
30	76.29048	1.231868	0.3010318	0.1987746	-0.006350168	0.04705013
31	76.17299	1.231868	0.3010318	0.1907131	-0.010016807	0.04705013
32	82.52334	1.231868	0.3010318	0.4088065	-0.013675474	0.04705013
33	78.91874	1.231868	0.3010318	0.2878133	-0.008306807	0.04705013
34	76.40230	1.231868	0.3010318	0.1969567	-0.011094862	0.04705013
35	76.49196	1.231868	0.3010318	0.1983272	-0.013378471	0.04705013
36	81.68672	1.231868	0.3010318	0.3754351	-0.018444984	0.04705013
37	80.43610	1.231868	0.3010318	0.3352997	-0.013904165	0.04705013
38	74.04713	1.231868	0.3010318	0.1203063	-0.005892193	0.04705013
39	79.55656	1.231868	0.3010318	0.3043429	-0.014350671	0.04705013
40	82.41542	1.231868	0.3010318	0.4020528	-0.016982141	0.04705013
41	80.47928	1.231868	0.3010318	0.3409289	-0.009981006	0.04705013

42	77.20399	1.231868	0.3010318	0.2265885	-0.009752857	0.04705013
43	78.04690	1.231868	0.3010318	0.2588481	-0.006746816	0.04705013
44	84.79602	1.231868	0.3010318	0.4882050	-0.013981800	0.04705013
45	78.94658	1.231868	0.3010318	0.2870596	-0.010124179	0.04705013
46	80.45957	1.231868	0.3010318	0.3419239	-0.007860914	0.04705013
47	77.70696	1.231868	0.3010318	0.2446833	-0.009453158	0.04705013
48	78.29017	1.231868	0.3010318	0.2652304	-0.009592974	0.04705013
49	80.14789	1.231868	0.3010318	0.3250671	-0.014620622	0.04705013
50	79.45418	1.231868	0.3010318	0.3064332	-0.008293516	0.04705013
51	76.54390	1.231868	0.3010318	0.2041542	-0.009208462	0.04705013
52	79.98079	1.231868	0.3010318	0.3212343	-0.011999868	0.04705013
53	77.57156	1.231868	0.3010318	0.2382287	-0.010944649	0.04705013
54	78.38676	1.231868	0.3010318	0.2661226	-0.012117645	0.04705013
55	81.89766	1.231868	0.3010318	0.3855949	-0.015187317	0.04705013
56	77.46699	1.231868	0.3010318	0.2394847	-0.006518632	0.04705013
57	78.42852	1.231868	0.3010318	0.2705615	-0.008351100	0.04705013

	Program3:Time
1	-0.1363475
2	-0.1363475
3	-0.1363475
4	-0.1363475
5	-0.1363475
6	-0.1363475
7	-0.1363475
8	-0.1363475
9	-0.1363475
10	-0.1363475
11	-0.1363475
12	-0.1363475

13	-0.1363475
14	-0.1363475
15	-0.1363475
16	-0.1363475
17	-0.1363475
18	-0.1363475
19	-0.1363475
20	-0.1363475
21	-0.1363475
22	-0.1363475
23	-0.1363475
24	-0.1363475
25	-0.1363475
26	-0.1363475
27	-0.1363475
28	-0.1363475
29	-0.1363475
30	-0.1363475
31	-0.1363475
32	-0.1363475
33	-0.1363475
34	-0.1363475
35	-0.1363475
36	-0.1363475
37	-0.1363475
38	-0.1363475
39	-0.1363475
40	-0.1363475
41	-0.1363475

42	-0.1363475
43	-0.1363475
44	-0.1363475
45	-0.1363475
46	-0.1363475
47	-0.1363475
48	-0.1363475
49	-0.1363475
50	-0.1363475
51	-0.1363475
52	-0.1363475
53	-0.1363475
54	-0.1363475
55	-0.1363475
56	-0.1363475
57	-0.1363475


RI program
WI Program
Controls
Strength
90
85
80
75
Day
2
4
6
8
10
12
14

```
# Do we need the AR(1) structure in the
# random coefficients model?

d.timeru = lme(Strength ~ Program+Time+
      Program*Time+I(Time^2),
   random = ~ Time + I(Time^2) | Subj,
   data=d,
   method="REML")

anova(d.timer,d.timeru)
         Model df      AIC      BIC    logLik   Test  L.Ratio p-value
d.timer      1 15 1304.196 1363.765 -637.0981
d.timeru     2 14 1318.074 1373.672 -645.0372 1 vs 2 15.87827   1e-04

# The more complicated model is preferred.
# Keep the AR(1) structure.
```