Mixed models in R using the lme4 package
Part 6: Interactions

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Interactions of covariates and grouping factors

- For longitudinal data, having a random effect for the slope w.r.t. time by subject is reasonably easy to understand.
- Although not generally presented in this way, these random effects are an interaction term between the grouping factor for the random effect (`Subject`) and the time covariate.
- We can also define interactions between a categorical covariate and a random-effects grouping factor.
- Different ways of expressing such interactions lead to different numbers of random effects. These different definitions have different levels of complexity, affecting both their expressive power and the ability to estimate all the parameters in the model.

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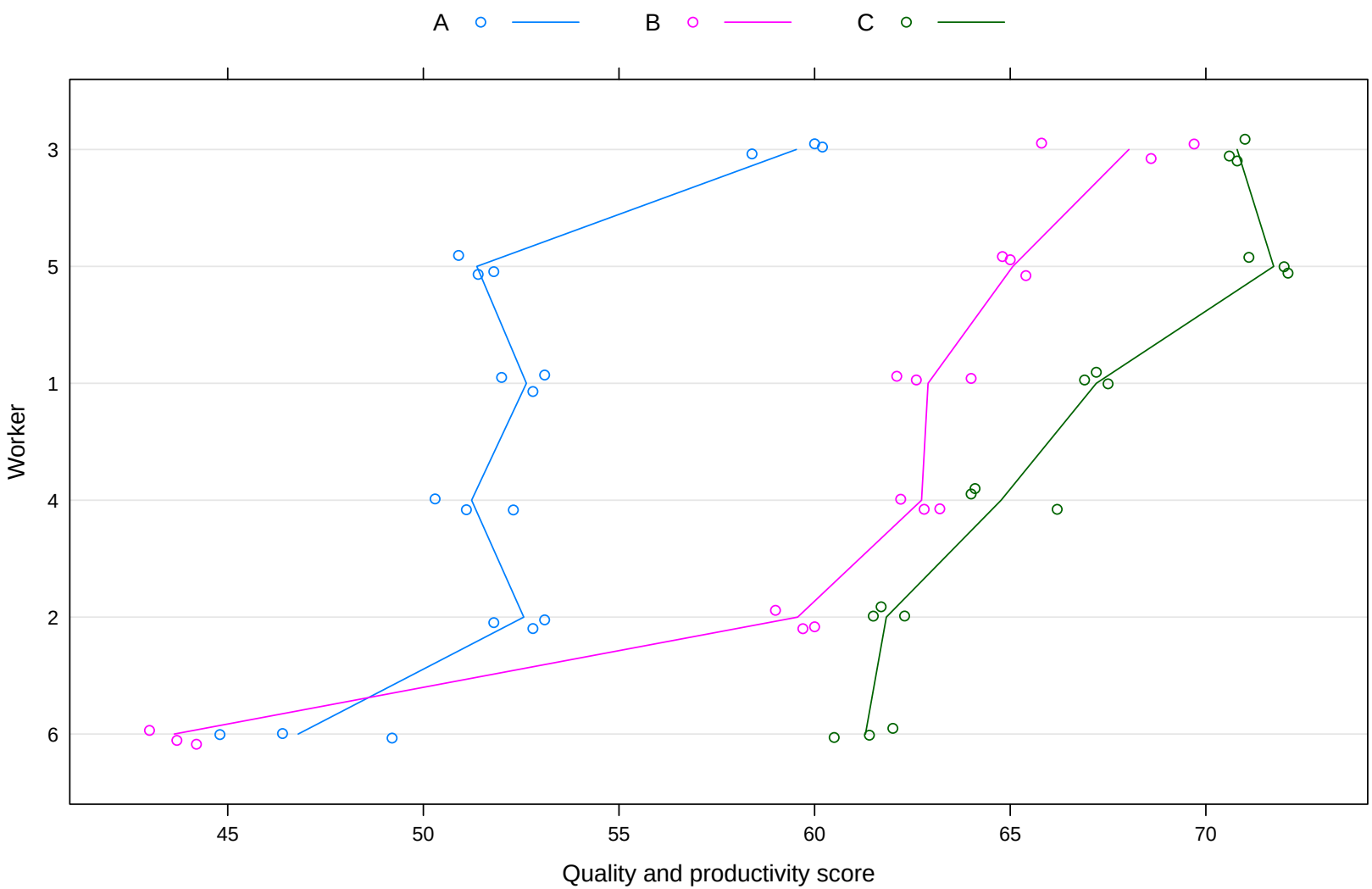
Machines data

- Milliken and Johnson (1989) provide (probably artificial) data on an experiment to measure productivity according to the machine being used for a particular operation.
- In the experiment, a sample of six different operators used each of the three machines on three occasions — a total of nine runs per operator.
- These three machines were the specific machines of interest and we model their effect as a fixed-effect term.
- The operators represented a sample from the population of potential operators. We model this factor, (`Worker`), as a random effect.
- This is a replicated "subject/stimulus" design with a fixed set of stimuli that are themselves of interest. (In other situations the stimuli may be a sample from a population of stimuli.)

Machines data plot



Comments on the data plot

- There are obvious differences between the scores on different machines.
- It seems likely that `Worker` will be a significant random effect, especially when considering the low variation within replicates.
- There also appears to be a significant `Worker:Machine` interaction. `Worker` 6 has a very different pattern w.r.t. machines than do the others.
- We can approach the interaction in one of two ways: define simple, scalar random effects for `Worker` and for the `Worker:Machine` interaction or define vector-valued random effects for `Worker`

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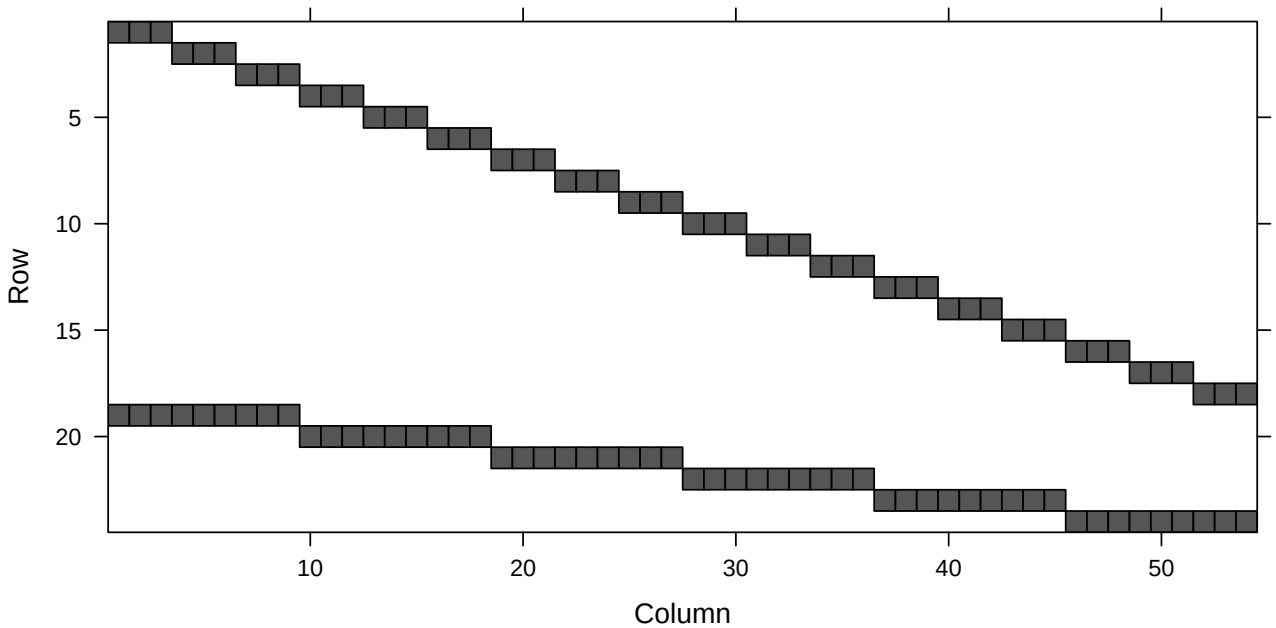
Random effects for subject and subject:stimulus

```
Linear mixed model fit by REML
Formula: score ~ Machine + (1 | Worker) + (1 | Worker:Machine)
   Data: Machines
   AIC   BIC logLik deviance REMLdev
 227.7 239.6 -107.8    225.5   215.7
Random effects:
 Groups         Name        Variance Std.Dev.
 Worker:Machine (Intercept) 13.90946 3.72954
 Worker         (Intercept) 22.85849 4.78105
 Residual                    0.92463 0.96158
Number of obs: 54, groups: Worker:Machine, 18; Worker, 6
Fixed effects:
            Estimate Std. Error t value
(Intercept)   52.356      2.486  21.063
MachineB       7.967      2.177   3.660
MachineC      13.917      2.177   6.393
```

Characteristics of the scalar interaction model

- The model incorporates simple, scalar random effects for `Worker` and for the `Worker:Machine` interaction.
- These two scalar random-effects terms have $q_1 = q_2 = 1$ so they contribute $n_1 = 6$ and $n_2 = 18$ random effects for a total of $q = 24$. There are 2 variance-component parameters.
- The random effects allow for an overall shift in level for each worker and a separate shift for each combination of worker and machine. The unconditional distributions of these random effects are independent. The unconditional variances of the interaction random effects are constant.
- The main restriction in this model is the assumption of constant variance and independence of the interaction random effects.

Model matrix $\boldsymbol{Z}^{\mathsf{T}}$ for the scalar interaction model

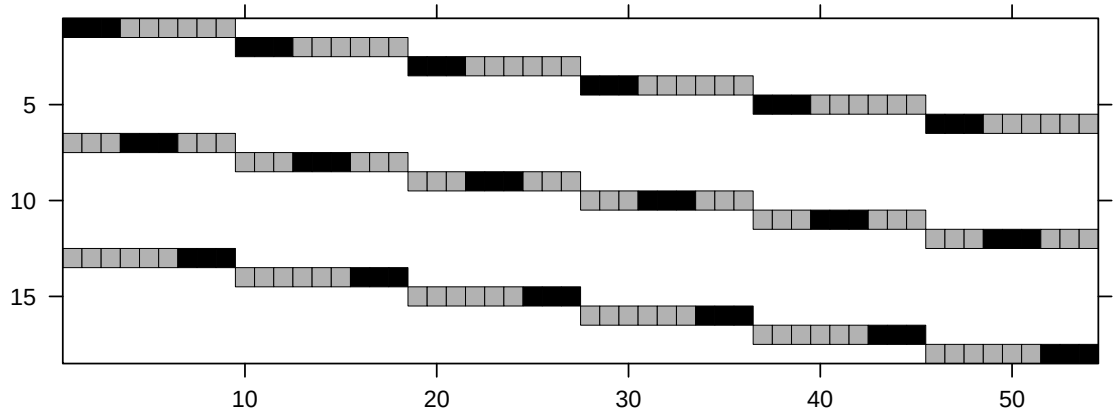


- Because we know these are scalar random effects we can recognize the pattern of a balanced, nested, two-factor design, similar to that of the model for the `Pastes` data.

Vector-valued random effects by subject

```
Linear mixed model fit by REML
Formula: score ~ Machine + (0 + Machine | Worker)
   Data: Machines
   AIC   BIC logLik deviance REMLdev
 228.3 248.2 -104.2    216.6   208.3
Random effects:
 Groups   Name     Variance Std.Dev. Corr
 Worker   MachineA 16.64097 4.07933
          MachineB 74.39556 8.62529  0.803
          MachineC 19.26756 4.38948  0.623 0.771
 Residual           0.92463 0.96158
Number of obs: 54, groups: Worker, 6
Fixed effects:
            Estimate Std. Error t value
(Intercept)   52.356      1.681  31.150
MachineB       7.967      2.421   3.291
MachineC      13.917      1.540   9.037
```

Characteristics of the vector-valued r.e. model



- We use the specification `(0 + Machine|Worker)` to force an "indicator" parameterization of the random effects.
- In this image the 1's are black. The gray positions are non-systematic zeros (initially zero but can become nonzero).
- Here $k = 1$, $q_1 = 3$ and $n_1 = 6$ so we have $q = 18$ random effects but $q_1(q_1 + 1)/2 = 6$ variance-component parameters to estimate.

Comparing the model fits

- Although not obvious from the specifications, these model fits are nested. If the variance-covariance matrix for the vector-valued random effects has a special form, called *compound symmetry*, the model reduces to model `fm1`.
- The p-value of 6.5% may or may not be significant.

```
> fm2M <- update(fm2, REML = FALSE)
> fm1M <- update(fm1, REML = FALSE)
> anova(fm2M, fm1M)
```

```
Data: Machines
Models:
fm1M: score ~ Machine + (1 | Worker) + (1 | Worker:Machine)
fm2M: score ~ Machine + (0 + Machine | Worker)
     Df     AIC     BIC  logLik  Chisq Chi Df Pr(>Chisq)
fm1M  6  237.27  249.20 -112.64
fm2M 10  236.42  256.31 -108.21 8.8516      4    0.06492
```

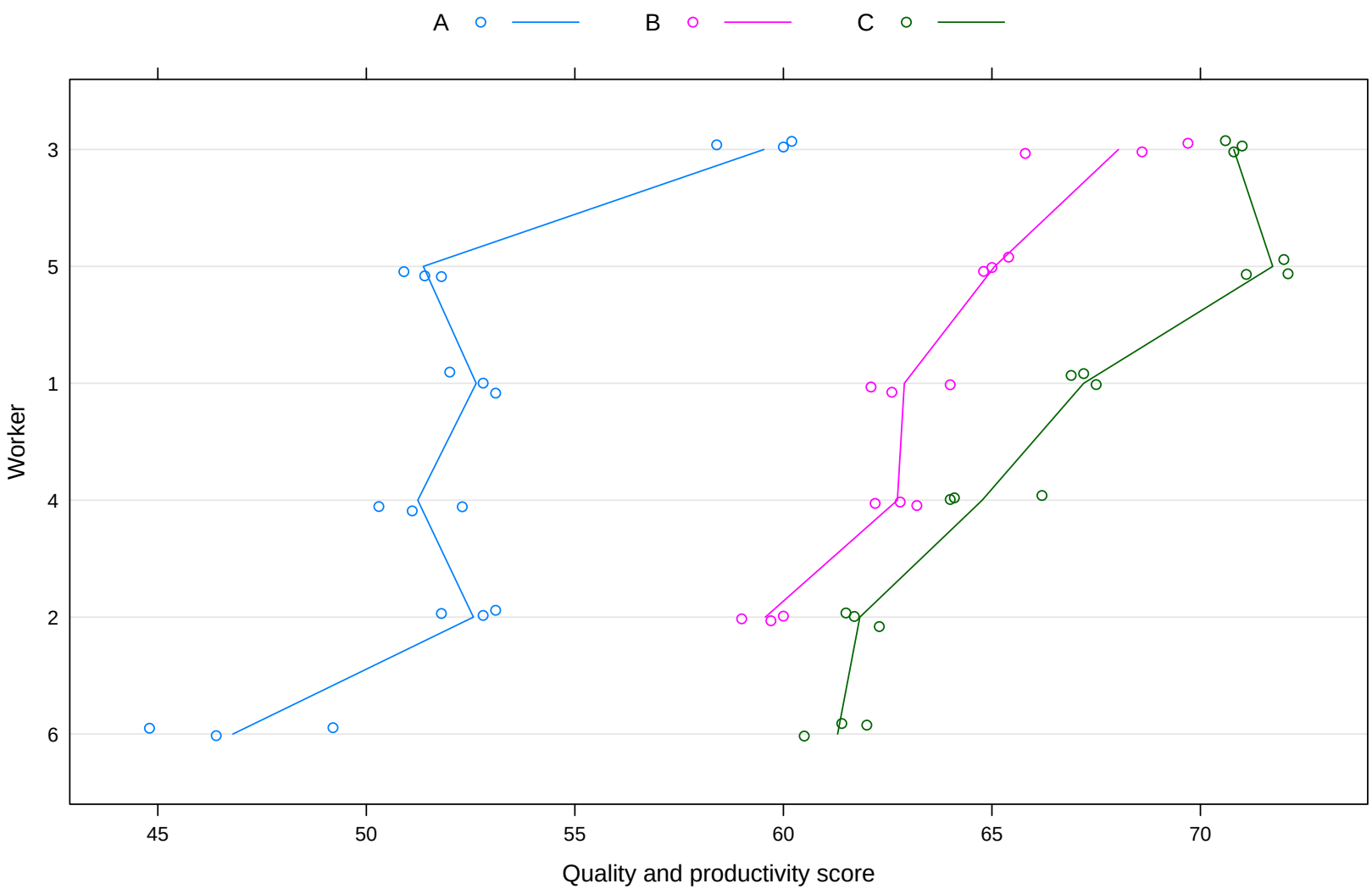
Model comparisons eliminating the unusual combination

- In a case like this we may want to check if a single, unusual combination (`Worker` 6 using `Machine` "B") causes the more complex model to appear necessary. We eliminate that unusual combination.

```
> Machines1 <- subset(Machines, !(Worker == "6" & Machine ==
+     "B"))
> xtabs(~Machine + Worker, Machines1)
```

```
       Worker
Machine 1 2 3 4 5 6
      A 3 3 3 3 3 3
      B 3 3 3 3 3 0
      C 3 3 3 3 3 3
```

Machines data after eliminating the unusual combination



Model comparisons without the unusual combination

```
> fm1aM <- lmer(score ~ Machine + (1 | Worker) + (1 |
+     Worker:Machine), Machines1, REML = FALSE)
> fm2aM <- lmer(score ~ Machine + (0 + Machine | Worker),
+     Machines1, REML = FALSE)
> anova(fm2aM, fm1aM)
```

```
Data: Machines1
Models:
fm1aM: score ~ Machine + (1 | Worker) + (1 | Worker:Machine)
fm2aM: score ~ Machine + (0 + Machine | Worker)
      Df     AIC     BIC  logLik  Chisq Chi Df Pr(>Chisq)
fm1aM  6 208.554 220.145 -98.277
fm2aM 10 208.289 227.607 -94.144 8.2655      4    0.08232
```

Trade-offs when defining interactions

- It is important to realize that estimating scale parameters (i.e. variances and covariances) is considerably more difficult than estimating location parameters (i.e. means or fixed-effects coefficients).
- A vector-valued random effect term having q_i random effects per level of the grouping factor requires $q_i(q_i+1)/2$ variance-covariance parameters to be estimated. A simple, scalar random effect for the interaction of a "random-effects" factor and a "fixed-effects" factor requires only 1 additional variance-covariance parameter.
- Especially when the "fixed-effects" factor has a moderate to large number of levels, the trade-off in model complexity argues against the vector-valued approach.
- One of the major sources of difficulty in using the `lme4` package is the tendency to overspecify the number of random effects per level of a grouping factor.

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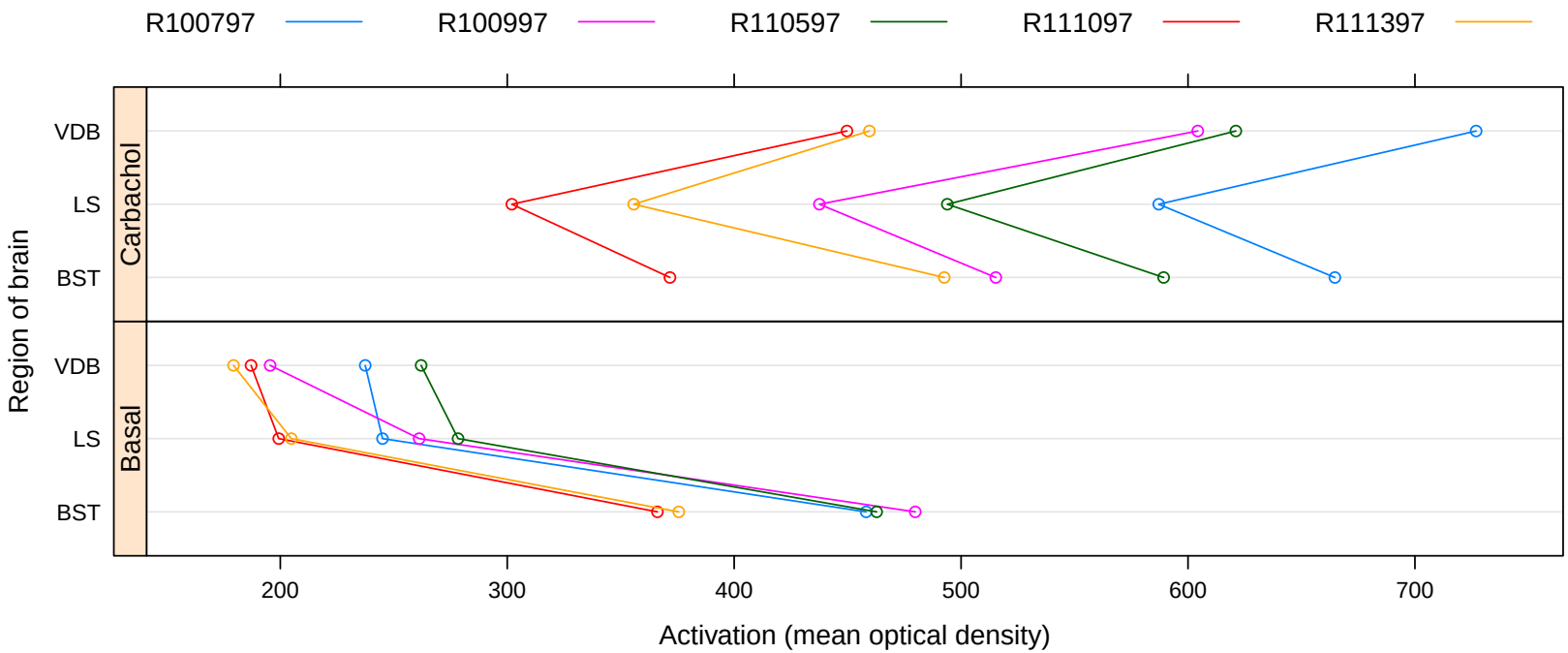
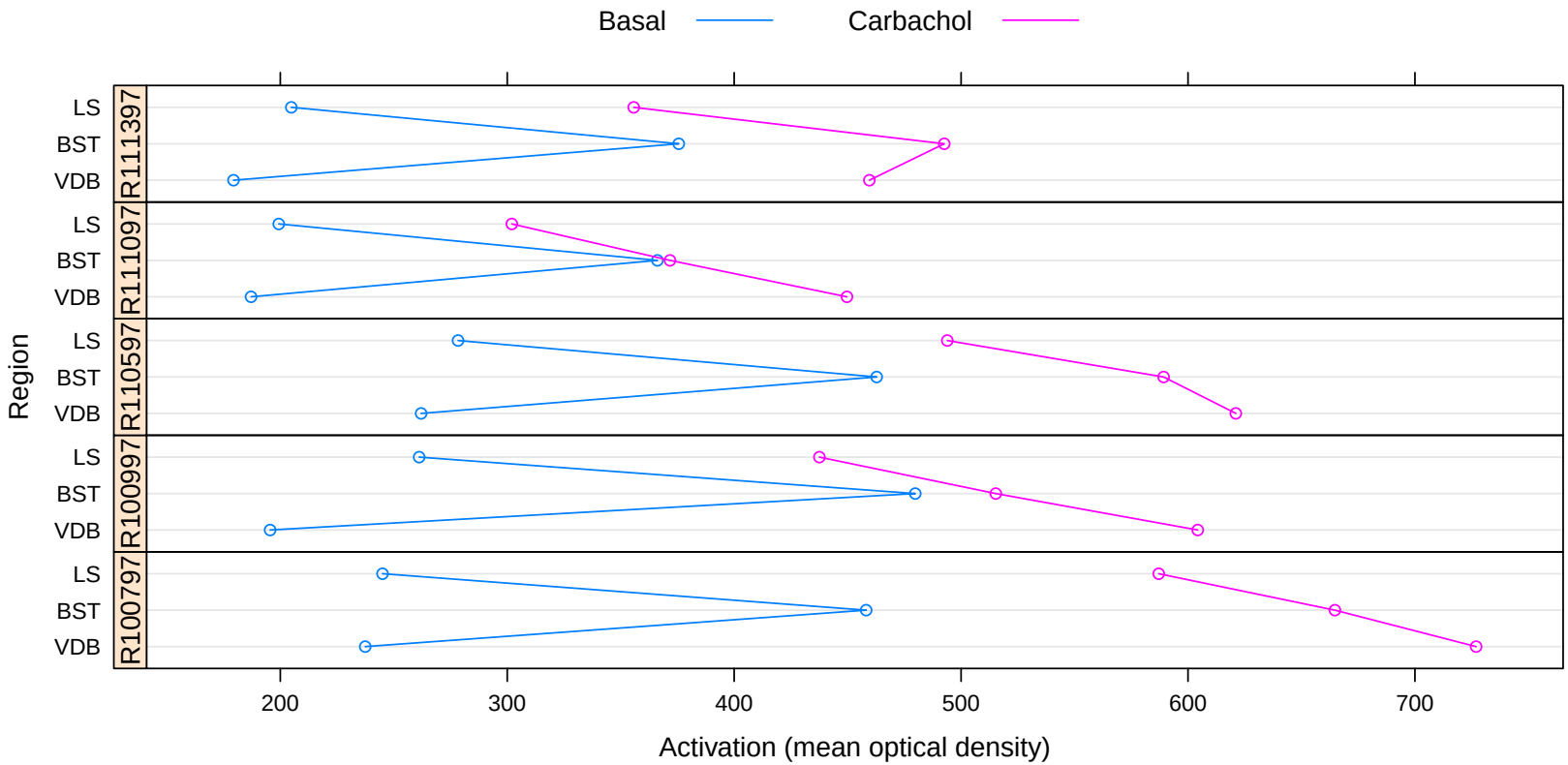
Brain activation data from West, Welch and Gałecki (2007)



- In the experiment seven different regions of five rats' brains were imaged in a basal condition (after injection with saline solution) and after treatment with the drug Carbachol. The data provided are from three regions.
- This representation of the data is similar to the figure on the cover of West, Welch and Gałecki (2007).

Brain activation data in an alternative layout



- The animals have similar patterns of changes but different magnitudes.

Reproducing the models from West et al.

- These data are analyzed in West et al. (2007) allowing for main effects for treatment and region, a fixed-effects interaction of these two factors and vector-valued random effects for the intercept and the treatment by animal.
- Note that this will require estimating three variance component parameters from data on five animals.
- Their final model also allowed for different residual variances by treatment. We won't discuss that here.
- We choose the order of the levels of `region` to produce the same parameterization of the fixed effects.

```
'data.frame': 30 obs. of  4 variables:
 $ animal   : Factor w/ 5 levels "R100797","R100997",..: 4 4 4 4 4 4 5
 $ treatment: Factor w/ 2 levels "Basal","Carbachol": 1 1 1 2 2 2 1 1 1
 $ region   : Factor w/ 3 levels "VDB","BST","LS": 2 3 1 2 3 1 2 3 1 2
 $ activate : num  366 199 187 372 302 ...
```

Model 5.1 from West et al.

```
Linear mixed model fit by REML
Formula: activate ~ region * treatment + (1 | animal)
   Data: ratbrain
   AIC   BIC logLik deviance REMLdev
 291.3 302.5 -137.6    325.3   275.3
Random effects:
 Groups   Name        Variance Std.Dev.
 animal   (Intercept) 4849.8   69.64
 Residual             2450.3   49.50
Number of obs: 30, groups: animal, 5
Fixed effects:
                            Estimate Std. Error t value
(Intercept)                   212.29      38.21   5.556
regionBST                     216.21      31.31   6.906
regionLS                       25.45      31.31   0.813
treatmentCarbachol            360.03      31.31  11.500
regionBST:treatmentCarbachol -261.82      44.27  -5.914
regionLS:treatmentCarbachol  -162.50      44.27  -3.670
```

Model 5.2 from West et al.

```
Linear mixed model fit by REML
Formula: activate ~ region * treatment + (treatment | animal)
   Data: ratbrain
   AIC   BIC logLik deviance REMLdev
 269.2 283.2 -124.6    292.7   249.2
Random effects:
 Groups   Name                Variance Std.Dev. Corr
 animal   (Intercept)         1284.3   35.837
          treatmentCarbachol  6371.3   79.821   0.801
 Residual                      538.9   23.214
Number of obs: 30, groups: animal, 5
Fixed effects:
                             Estimate Std. Error t value
(Intercept)                    212.29      19.10  11.117
regionBST                      216.21      14.68  14.726
regionLS                        25.45      14.68   1.733
treatmentCarbachol             360.03      38.60   9.328
regionBST:treatmentCarbachol  -261.82      20.76 -12.610
regionLS:treatmentCarbachol   -162.50      20.76  -7.826
```

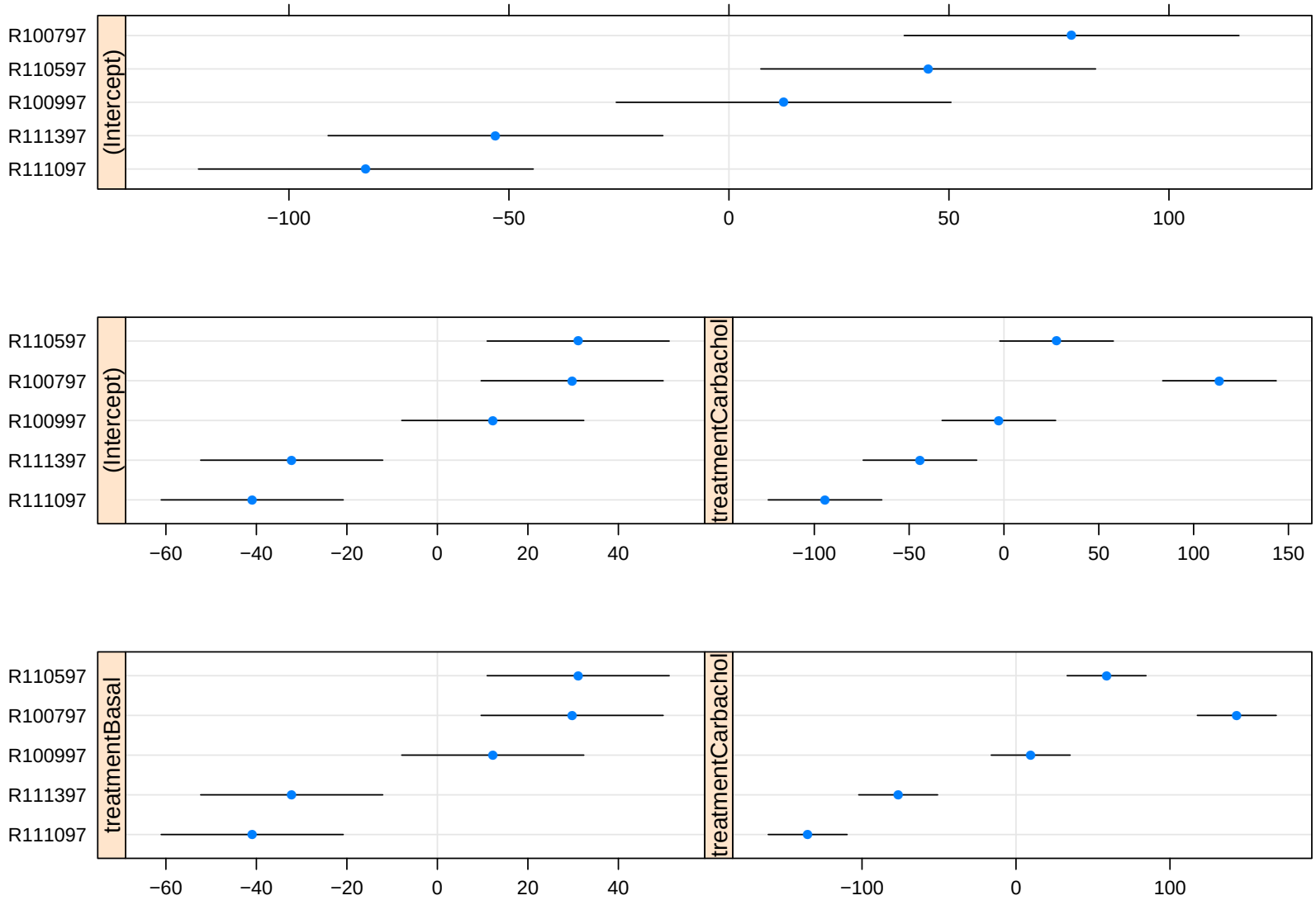
A variation on model 5.2 from West et al.

```
Linear mixed model fit by REML
Formula: activate ~ region * treatment + (0 + treatment | animal)
   Data: ratbrain
   AIC   BIC logLik deviance REMLdev
 269.2 283.2 -124.6    292.7   249.2
Random effects:
 Groups   Name                Variance Std.Dev. Corr
 animal   treatmentBasal       1284.3   35.837
          treatmentCarbachol 12238.1  110.626  0.902
 Residual                       538.9   23.214
Number of obs: 30, groups: animal, 5
Fixed effects:
                             Estimate Std. Error t value
(Intercept)                    212.29      19.10  11.117
regionBST                      216.21      14.68  14.726
regionLS                        25.45      14.68   1.733
treatmentCarbachol             360.03      38.60   9.328
regionBST:treatmentCarbachol  -261.82      20.76 -12.610
regionLS:treatmentCarbachol   -162.50      20.76  -7.826
```

Simple scalar random effects for the interaction

```
Linear mixed model fit by REML
Formula: activate ~ region * treatment + (1 | animal) + (1 | animal:tre
   Data: ratbrain
   AIC   BIC logLik deviance REMLdev
 274.7 287.3 -128.4    302.1   256.7
Random effects:
 Groups           Name        Variance Std.Dev.
 animal:treatment (Intercept) 3185.7   56.442
 animal           (Intercept) 3575.5   59.796
 Residual                      538.9   23.214
Number of obs: 30, groups: animal:treatment, 10; animal, 5
Fixed effects:
                             Estimate Std. Error t value
(Intercept)                    212.29      38.21   5.556
regionBST                      216.21      14.68  14.726
regionLS                        25.45      14.68   1.733
treatmentCarbachol             360.03      38.60   9.328
regionBST:treatmentCarbachol  -261.82      20.76 -12.610
regionLS:treatmentCarbachol   -162.50      20.76  -7.826
```

Prediction intervals for the random effects



Is this "overmodeling" the data?

- The prediction intervals for the random effects indicate that the vector-valued random effects are useful, as does a model comparison.

```
Data: ratbrain
Models:
m51M: activate ~ region * treatment + (1 | animal)
m52M: activate ~ region * treatment + (treatment | animal)
     Df     AIC     BIC  logLik  Chisq Chi Df Pr(>Chisq)
m51M  8  341.34  352.55 -162.67
m52M 10  312.72  326.73 -146.36 32.615      2  8.276e-08
```

- However, these models incorporate many fixed-effects parameters and random effects in a model of a relatively small amount of data. Is this too much?
- There are several ways we can approach this:
  - Simplify the model by considering the difference in activation under the two conditions within the same animal:region combination (i.e. approach it like a paired t-test).
  - Model the five animals with fixed effects and use F-tests.
  - Assess the precision of the variance estimates (done later).

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Considering differences

- Before we can analyze the differences at each `animal:region` combination we must first calculate them.
- We could do this by subsetting the `ratbrain` data frame for the `"Basal"` and `"Carbachol"` levels of the `treatment` factor and forming the difference of the two `activate` columns. For this to be correct we must have the same ordering of levels of the `animal` and `region` factors in each half. It turns out we do but we shouldn't count on this (remember "Murphy's Law"?).
- A better approach is to reshape the data frame (but this is complicated) or to use `xtabs` to align the levels. First we should check that the data are indeed balanced and unreplicated.

Checking for balanced and unreplicated; tabling activate

- We saw the balance in the data plots but we can check too

```
> ftable(xtabs(~treatment + region + animal, ratbrain))
```

```
                  animal R100797 R100997 R110597 R111097 R111397
treatment region
Basal     VDB                  1       1       1       1       1
          BST                  1       1       1       1       1
          LS                   1       1       1       1       1
Carbachol VDB                  1       1       1       1       1
          BST                  1       1       1       1       1
          LS                   1       1       1       1       1
```

- In xtabs we can use a two-sided formula to tabulate a variable

```
> ftable(atab <- xtabs(activate ~ treatment + animal +
+     region, ratbrain))
```

```
                region    VDB    BST     LS
treatment animal
Basal     R100797       237.42 458.16 245.04
          R100997       195.51 479.81 261.19
          R110597       262.05 462.79 278.33
          R111097       187.11 366.19 199.31
          R111397       179.38 375.58 204.85
Carbachol R100797       726.96 664.72 587.10
```

Taking differences

- The atab object is an array with additional attributes

```
xtabs [1:2, 1:5, 1:3] 237 727 196 604 262 ...
- attr(*, "dimnames")=List of 3
 ..$ treatment: chr [1:2] "Basal" "Carbachol"
 ..$ animal   : chr [1:5] "R100797" "R100997" "R110597" "R111097"
 ..$ region   : chr [1:3] "VDB" "BST" "LS"
- attr(*, "class")= chr [1:2] "xtabs" "table"
- attr(*, "call")= language xtabs(formula = activate ~ treatment +
```

- Use apply to take differences over dimension 1

```
> (diffs <- as.table(apply(atab, 2:3, diff)))
```

```
          region
animal       VDB    BST     LS
  R100797 489.54 206.56 342.06
  R100997 408.78  35.48 176.37
  R110597 359.02 126.46 215.60
  R111097 262.59   5.52 102.71
  R111397 280.20 117.00 150.89
```

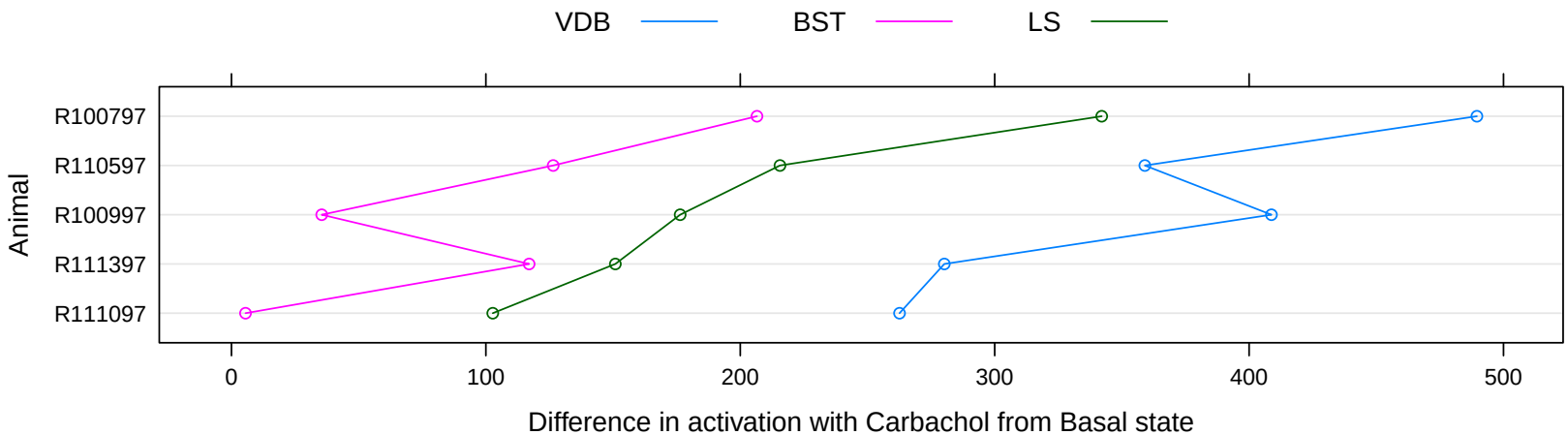
Taking differences (cont'd)

- Finally, convert the table of differences to a data frame.

```
> str(diffs <- as.data.frame(diffs))

'data.frame': 15 obs. of  3 variables:
 $ animal: Factor w/ 5 levels "R100797","R100997",..: 1 2 3 4 5 1 2 3 4
 $ region: Factor w/ 3 levels "VDB","BST","LS": 1 1 1 1 1 2 2 2 2 2 ...
 $ Freq  : num  490 409 359 263 280 ...

> names(diffs)[3] <- "actdiff"
```



A model for the differences

```
Linear mixed model fit by REML
Formula: actdiff ~ region + (1 | animal)
   Data: diffs
   AIC   BIC logLik deviance REMLdev
 147.4 150.9 -68.68    162.3   137.4
Random effects:
 Groups   Name        Variance Std.Dev.
 animal   (Intercept) 6209.9   78.803
 Residual             1562.2   39.524
Number of obs: 15, groups: animal, 5
Fixed effects:
            Estimate Std. Error t value
(Intercept)   360.03      39.42   9.132
regionBST    -261.82      25.00 -10.474
regionLS     -162.50      25.00  -6.501

Correlation of Fixed Effects:
          (Intr) rgnBST
regionBST -0.317
regionLS  -0.317  0.500
```

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Using fixed-effects for the animals

- There are five experimental units (animals) in this study. That is about the lower limit under which we could hope to estimate variance components.
- We should compare with a fixed-effects model.
- If we wish to evaluate coefficients for `treatment` or `region` we must be careful about the "contrasts" that are used to create the model. However, the analysis of variance table does not depend on the contrasts.
- We use `aov` to fit the fixed-effects model so that a summary is the analysis of variance table.
- The fixed-effects anova table is the sequential table with main effects first, then two-factor interactions, etc. The anova table for an `lmer` model gives the contributions of the fixed-effects after removing the contribution of the random effects, which include the `animal:treatment` interaction in model `m52`.

Fixed-effects anova versus random effects

```
> summary(m52f <- aov(activate ~ animal * treatment +
+     region * treatment, ratbrain))
```

```
                  Df Sum Sq Mean Sq F value    Pr(>F)
animal             4 126197   31549  58.544 2.376e-09
treatment          1 358347  358347 664.965 1.844e-14
region             2 100998   50499  93.708 1.465e-09
animal:treatment   4  40384   10096  18.734 6.973e-06
treatment:region   2  87352   43676  81.047 4.244e-09
Residuals         16   8622     539
```

```
> anova(m52)
```

```
Analysis of Variance Table
                  Df Sum Sq Mean Sq F value
region             2 100998   50499  93.708
treatment          1  18900   18900  35.072
region:treatment   2  87352   43676  81.047
```

- Except for the `treatment` factor, the anova tables are nearly identical.

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- It is possible to fit complex models to balanced data sets from carefully designed experiments but one should always be cautious of creating a model that is too complex.
- I prefer to proceed incrementally, taking time to examine data plots, rather than starting with a model incorporating all possible terms.
- Some feel that one should be able to specify the analysis (and, in particular, the analysis of variance table) before even beginning to collect data. I am more of a model-builder and try to avoid dogmatic approaches.
- For the `ratbrain` data I would be very tempted to take differences and analyze it as a randomized blocked design.