Friday, Apr 29

Nonlinear Regression With Random Effects

Example: The model we specified for the `Sitka` data can be written as

$$E(Y_{ij}) = \beta_0 + \beta_1 o_{ij} + \beta_2 w_{ij} + \beta_3 o_{ij} w_{ij} + \delta_i + \gamma_i w_{ij},$$

where o_{ij} is an indicator for if the observation is from the ozone treatment condition and w_{ij} is weeks. We can also write this model as

$$E(Y_{ij}) = \underbrace{\beta_0 + \beta_1 o_{ij} + \delta_i}_{\beta_{0ij}} + \underbrace{(\beta_2 + \beta_3 o_{ij} + \gamma_i)}_{\beta_{1ij}} w_i,$$

or

$$E(Y_{ij}) = \beta_{0ij} + \beta_{1ij} w_{ij},$$

to show that the model assumes a linear relationship between expected size and weeks, but where the "intercept" β_{0ij} depends on the treatment condition and tree, and the "slope" β_{1ij} depends on the treatment condition and tree because

$$\begin{aligned}\beta_{0ij} &= \beta_0 + \beta_1 o_{ij} + \delta_i \\ \beta_{1ij} &= \beta_2 + \beta_3 o_{ij} + \gamma_i.\end{aligned}$$

Models with random effects written in this way are sometimes called "random coefficient" models. The coefficients β_{0ij} and β_{1ij} are random (due to δ_i and γ_i) but may also depend on one or more explanatory variables (such as treatment condition via o_{ij}).

The `nlme` function from the **nlme** package can estimate a linear or nonlinear regression model with random coefficients (assuming a normally-distributed response variable and random parameters). We estimated a model for the `Sitka` data as follows.

```r
library(MASS)
library(lme4)
m <- lmer(exp(size) ~ treat * I(Time/7) + (1 + I(Time/7) | tree),
  data = Sitka, REML = FALSE)
summary(m)$coefficients
```

```
                     Estimate Std. Error t value
(Intercept)          -305.123     31.251  -9.764
treatozone            110.675     37.799   2.928
I(Time/7)              17.565      1.685  10.424
treatozone:I(Time/7)   -5.516      2.038  -2.707
```

I am using `REML = FALSE` to use maximum likelihood rather than *restricted* maximum likelihood (REML) for estimation so that we can compare the results with `nlme`, which only uses maximum likelihood.

```r
library(nlme)
m <- nlme(exp(size) ~ b0 + b1 * I(Time/7),
  fixed = b0 + b1 ~ treat,
  random = b0 + b1 ~ 1 | tree,
  start = c(0,0,0,0), data = Sitka)
summary(m)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: exp(size) ~ b0 + b1 * I(Time/7)
  Data: Sitka
   AIC  BIC logLik
  3947 3978  -1965

Random effects:
 Formula: list(b0 ~ 1, b1 ~ 1)
 Level: tree
 Structure: General positive-definite, Log-Cholesky parametrization
               StdDev  Corr
b0.(Intercept) 148.699 b0.(I)
b1.(Intercept)   8.266 -0.987
Residual        19.575

Fixed effects:  b0 + b1 ~ treat
                 Value Std.Error  DF t-value p-value
b0.(Intercept) -305.12     31.41 313  -9.714  0.0000
b0.treatozone   110.68     37.99 313   2.913  0.0038
b1.(Intercept)   17.56      1.69 313  10.371  0.0000
b1.treatozone    -5.52      2.05 313  -2.693  0.0075
 Correlation:
               b0.(I) b0.trt b1.(I)
b0.treatozone  -0.827
b1.(Intercept) -0.980  0.810
b1.treatozone   0.810 -0.980 -0.827

Standardized Within-Group Residuals:
     Min       Q1      Med       Q3      Max
-2.96548 -0.38922 -0.05501  0.38267  4.82179

Number of Observations: 395
Number of Groups: 79
```

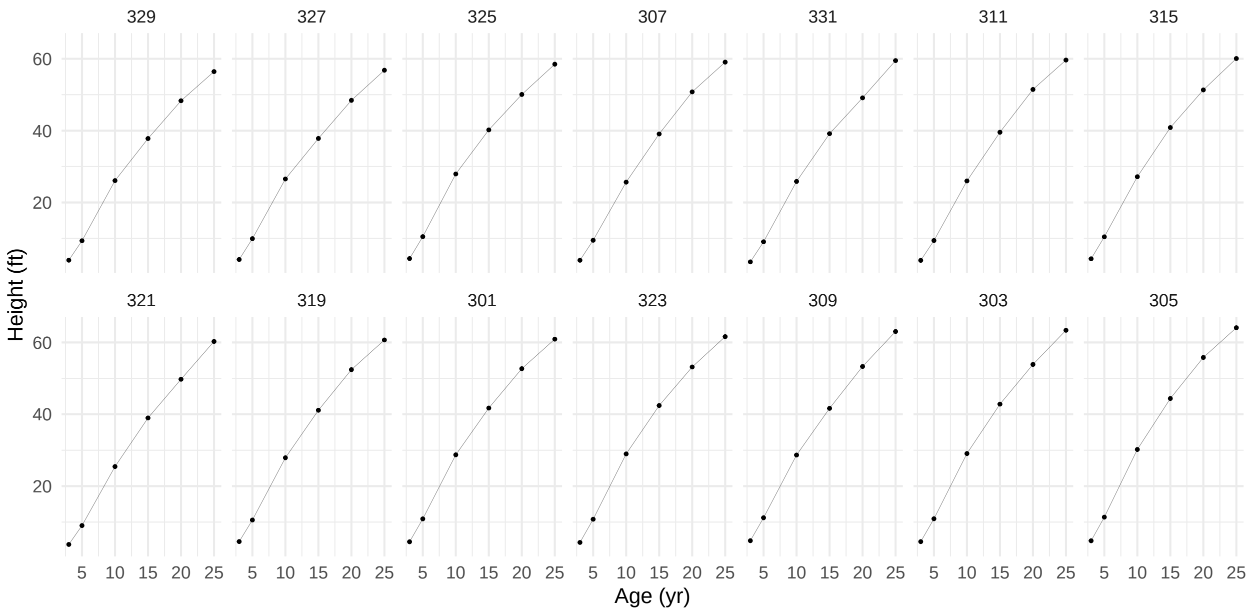
The `nlme` function is like `nls` in that it needs starting values for the (fixed) parameters, but since the model is linear we do not need particularly good starting values.

Example: Now consider a *nonlinear* regression model with random effects for the `Loblolly` data that come with R.

```
head(Loblolly)
```

```
Grouped Data: height ~ age | Seed
   height age Seed
1    4.51   3  301
15  10.89   5  301
29  28.72  10  301
43  41.74  15  301
57  52.70  20  301
71  60.92  25  301
```

```
p <- ggplot(Loblolly, aes(x = age, y = height)) +
  geom_line(aes(group = Seed), alpha = 0.5, size = 0.01) +
  geom_point(size = 0.5) + facet_wrap(~ Seed, ncol = 7) +
  ylab("Height (ft)") + xlab("Age (yr)") + theme_minimal()
plot(p)
```



Suppose we want to estimate the nonlinear growth model

$$E(H) = \theta_1 + (\theta_2 - \theta_1)e^{-a\log(2)/\theta_3},$$

where H and a are height and age, respectively, θ_1 is the asymptote as $a \to \infty$, and θ_2 is an “intercept” parameter, and θ_3 is the age at which the tree is half way between $E(H) = \theta_2$ and $E(H) = \theta_1$. To allow for differences between trees with respect to θ_1 and θ_3 (but not θ_2) we could write the model as

$$E(H_{ij}) = \theta_{1i} + (\theta_2 - \theta_{1i})e^{-a_{ij}\log(2)/\theta_{3i}},$$

where H_{ij} and a_{ij} are now the height and age of the j-th observation of the i-th tree.

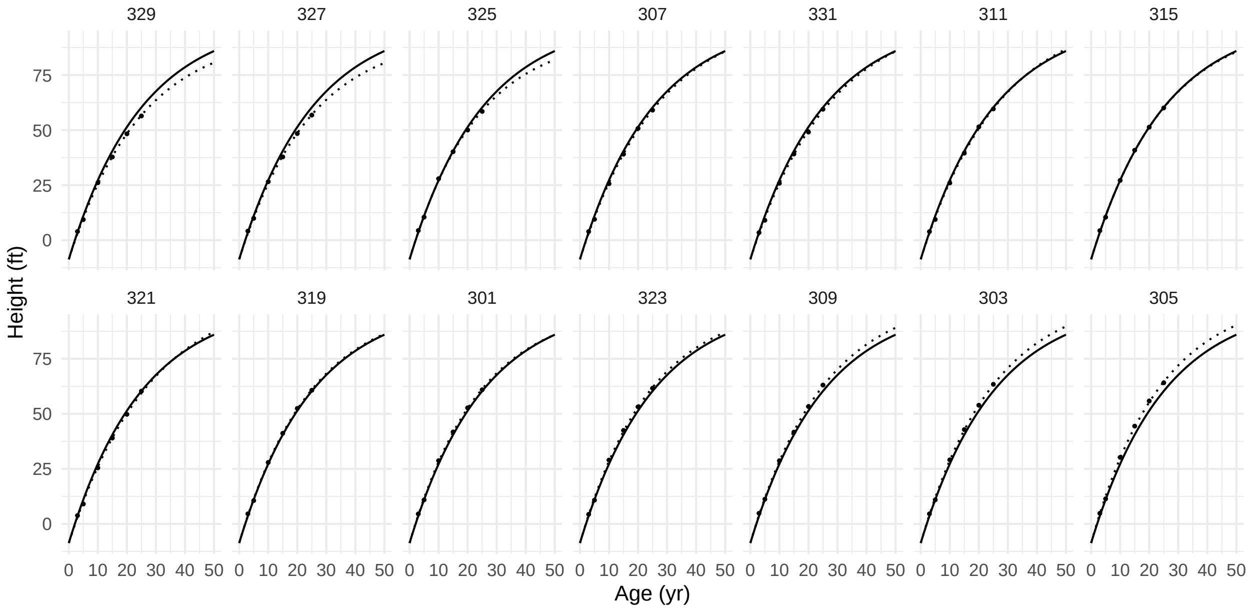
```
m <- nlme(height ~ t1 + (t2 - t1) * exp(-age * log(2)/t3),
  fixed = t1 + t2 + t3 ~ 1,
  random = t1 + t3 ~ 1 | Seed,
  start = c(t1 = 100, t2 = 0, t3 = 15),
  data = Loblolly)
summary(m)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: height ~ t1 + (t2 - t1) * exp(-age * log(2)/t3)
  Data: Loblolly
    AIC   BIC logLik
  239.1 256.1 -112.5

Random effects:
 Formula: list(t1 ~ 1, t3 ~ 1)
 Level: Seed
 Structure: General positive-definite, Log-Cholesky parametrization
         StdDev Corr
t1       5.4054 t1
t3       1.2334 0.769
Residual 0.6462

Fixed effects:  t1 + t2 + t3 ~ 1
    Value Std.Error DF t-value p-value
```

```
t1 101.03    2.4708 68   40.89       0
t2  -8.71    0.2850 68  -30.55       0
t3  17.48    0.6289 68   27.79       0
 Correlation:
   t1    t2
t2 0.615
t3 0.918 0.698

Standardized Within-Group Residuals:
     Min        Q1       Med        Q3       Max
-1.88049 -0.59420 -0.04009  0.70784  1.47988

Number of Observations: 84
Number of Groups: 14
```

We can plot the estimated growth curves (both per tree and average) as follows.

```
d <- expand.grid(age = seq(0, 50, length = 100), Seed = unique(Loblolly$Seed))

d$yhat.ind <- predict(m, newdata = d, level = 1) # individual tree
d$yhat.avg <- predict(m, newdata = d, level = 0) # average tree

p <- ggplot(Loblolly, aes(x = age, y = height)) +
  geom_line(aes(y = yhat.ind), data = d, linetype = 3) +
  geom_line(aes(y = yhat.avg), data = d) +
  geom_point(size = 0.5) + facet_wrap(~ Seed, ncol = 7) +
  ylab("Height (ft)") + xlab("Age (yr)") + theme_minimal()
plot(p)
```



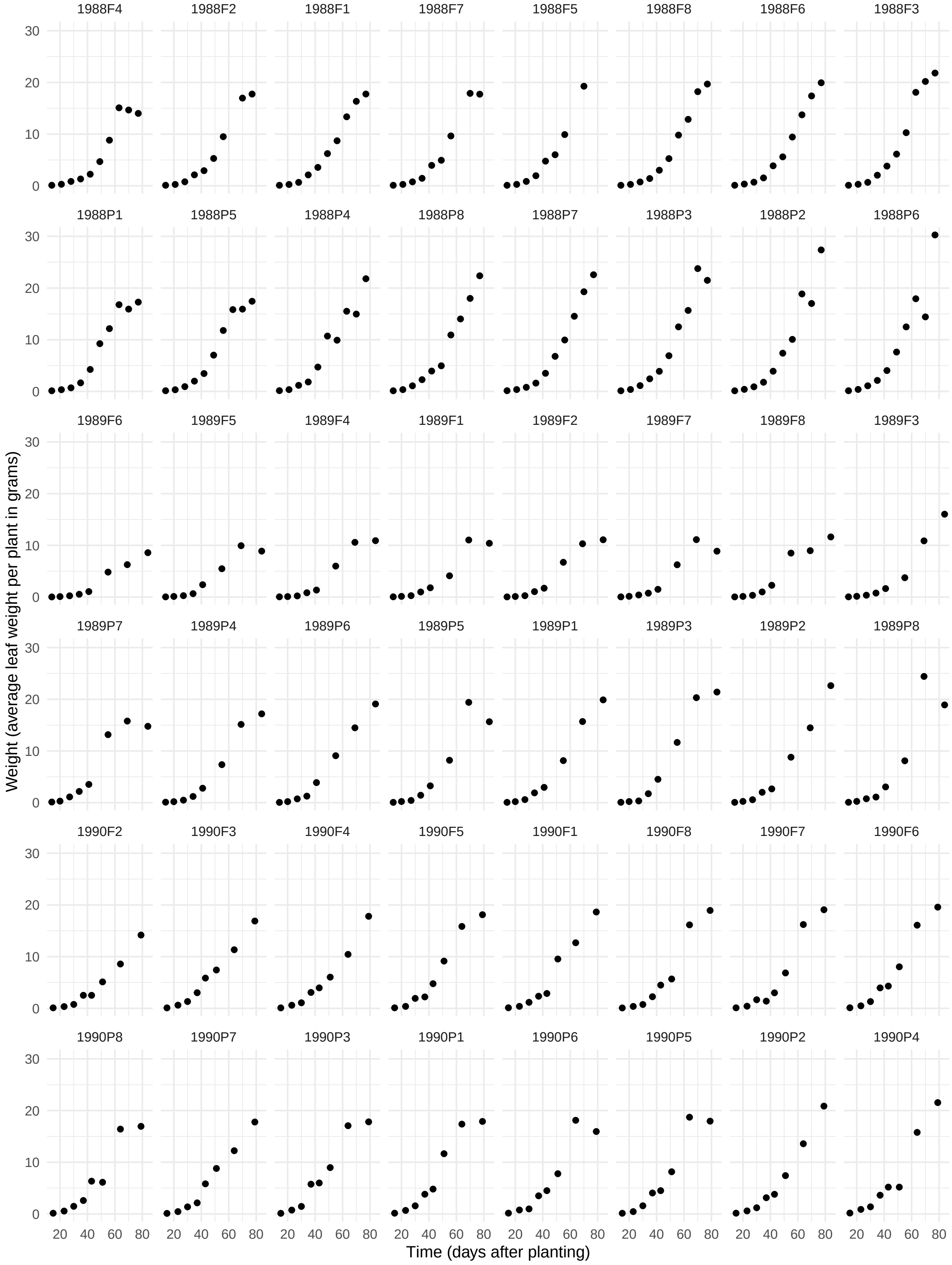
Example: The data frame `Soybean` from the **nlme** package has data from an experiment looking at soybean growth.

```
head(Soybean)
```

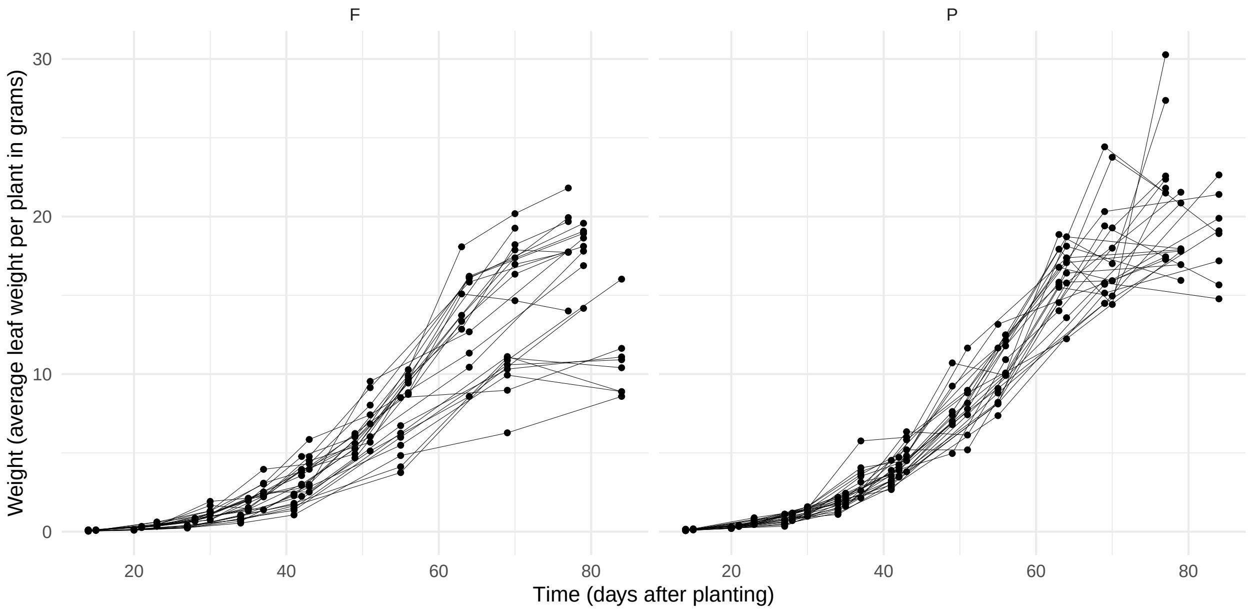
```
Grouped Data: weight ~ Time | Plot
    Plot Variety Year Time weight
```

```
1 1988F1       F 1988   14  0.106
2 1988F1       F 1988   21  0.261
3 1988F1       F 1988   28  0.666
4 1988F1       F 1988   35  2.110
5 1988F1       F 1988   42  3.560
6 1988F1       F 1988   49  6.230
```

```
p <- ggplot(Soybean, aes(x = Time, y = weight)) +
  geom_point() + facet_wrap(~ Plot, ncol = 8) +
  labs(x = "Time (days after planting)",
    y = "Weight (average leaf weight per plant in grams)") +
  theme_minimal()
plot(p)
```


1988F4
1988F2
1988F1
1988F7
1988F5
1988F8
1988F6
1988F3
1988P1
1988P5
1988P4
1988P8
1988P7
1988P3
1988P2
1988P6
1989F6
1989F5
1989F4
1989F1
1989F2
1989F7
1989F8
1989F3
1989P7
1989P4
1989P6
1989P5
1989P1
1989P3
1989P2
1989P8
1990F2
1990F3
1990F4
1990F5
1990F1
1990F8
1990F7
1990F6
1990P8
1990P7
1990P3
1990P1
1990P6
1990P5
1990P2
1990P4
0
10
20
30
20
40
60
80
Weight (average leaf weight per plant in grams)
Time (days after planting)

```
p <- ggplot(Soybean, aes(x = Time, y = weight)) +
  geom_point(size = 1) + facet_wrap(~ Variety) +
  geom_line(aes(group = Plot), size = 0.1) +
  labs(x = "Time (days after planting)",
    y = "Weight (average leaf weight per plant in grams)") +
  theme_minimal()
plot(p)
```



Consider a logistic growth model which can be written as

$$E(W) = \frac{\theta_1}{1 + e^{-(t-\theta_2)/\theta_3}},$$

where θ_1 is the asymptote as $t \to \infty$, θ_2 is the time at which the expected weight is $\theta_1/2$, and θ_3 is inversely related to the steepness of the curve at θ_2. We could assume that each parameter varies by plot, and is also affected by variety as follows.

```
m <- nlme(weight ~ theta1 / (1 + exp(-(Time - theta2) / theta3)), data = Soybean,
 fixed = theta1 + theta2 + theta3 ~ Variety,
 random = theta1 + theta2 + theta3 ~ 1 | Plot,
 start = c(20, 0, 60, 0, 10, 0),
 control = nlmeControl(msMaxIter = 1000))
summary(m)$tTable
```

```
                      Value Std.Error  DF t-value   p-value
theta1.(Intercept) 16.9466    1.0308 359 16.4410  1.121e-45
theta1.VarietyP     4.5664    1.4630 359  3.1212  1.947e-03
theta2.(Intercept) 54.8759    1.0561 359 51.9630 4.219e-169
theta2.VarietyP     0.1828    1.4504 359  0.1260  8.998e-01
theta3.(Intercept)  8.2284    0.4748 359 17.3304  2.526e-49
theta3.VarietyP     0.3741    0.6345 359  0.5896  5.558e-01
```

In more complex models getting the inferences you want from a `nlme` object can be a bit tricky. Functions like `contrast` and `emmeans` will not work with a `nlme` object. But you can use the `lincon` function, although you need to tell it how to extract the parameter estimates from `nlme` (it needs to use the `fixef` function). Here we can get results like those returned by `summary`.

```
trtools::lincon(m, fest = fixef)
```

```
                   estimate     se   lower  upper  tvalue  df    pvalue
theta1.(Intercept)  16.9466 1.0232 14.9412 18.952 16.5620 Inf 1.311e-61
theta1.VarietyP      4.5664 1.4523  1.7199  7.413  3.1442 Inf 1.666e-03
theta2.(Intercept)  54.8759 1.0483 52.8212 56.931 52.3455 Inf 0.000e+00
theta2.VarietyP      0.1828 1.4398 -2.6391  3.005  0.1269 Inf 8.990e-01
theta3.(Intercept)   8.2284 0.4713  7.3046  9.152 17.4580 Inf 2.994e-68
theta3.VarietyP      0.3741 0.6299 -0.8605  1.609  0.5939 Inf 5.525e-01
```

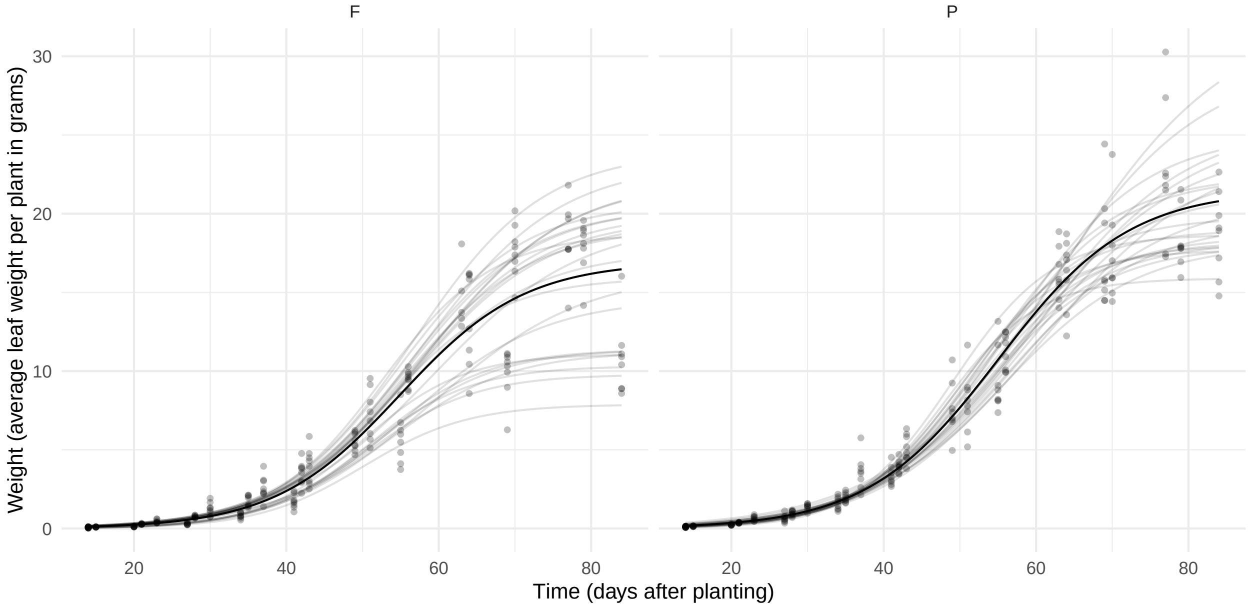
The estimate of mean θ_1 parameter for the F variety is given by `theta1.(Intercept)`. But the estimate of the mean θ_1 parameter for the P variety is the sum of the `theta1.(Intercept)` and `theta1.VarietyP` parameters. This can be obtained as follows.

```
trtools::lincon(m, a = c(1,1,0,0,0,0), fest = fixef)
```

```
                estimate    se lower upper tvalue  df    pvalue
(1,1,0,0,0,0),0    21.51 1.031 19.49 23.53  20.87 Inf 9.498e-97
```

Again we can plot this model as we did with the `Loblolly` data/model, although setting up the data frame is a little more complicated because plots and variety are not crossed.

```
library(dplyr)
library(tidyr)
d <- Soybean %>% dplyr::select(Plot, Variety) %>% unique() %>%
  group_by(Plot, Variety) %>% tidyr::expand(Time = seq(14, 84, length = 100))
d$yhat.ind <- predict(m, newdata = d, level = 1)
d$yhat.avg <- predict(m, newdata = d, level = 0)

p <- ggplot(Soybean, aes(x = Time, y = weight)) +
  geom_line(aes(y = yhat.ind, group = Plot), data = d, alpha = 0.125) +
  geom_line(aes(y = yhat.avg), data = d) +
  geom_point(size = 1, alpha = 0.25) + facet_wrap(~ Variety) +
  labs(x = "Time (days after planting)",
    y = "Weight (average leaf weight per plant in grams)") + theme_minimal()
plot(p)
```

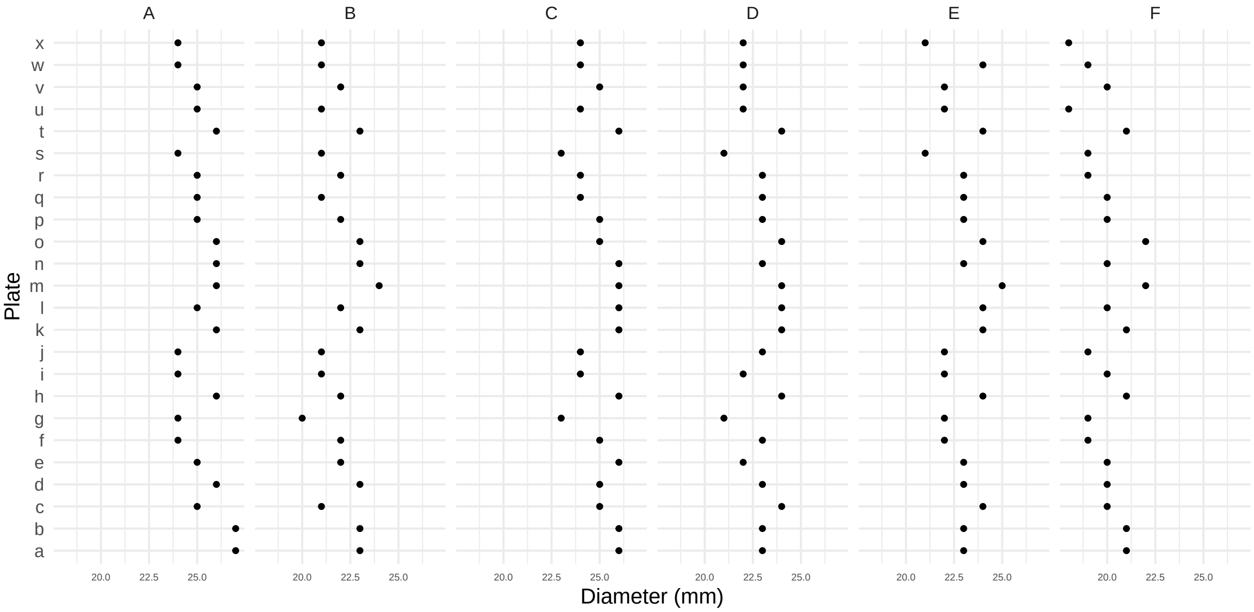


Crossed Random Effects

Crossed random effects might be specified when two (or more) factors modeled as having random effects are crossed (i.e., having a "factorial design" structure).

Example: Six samples of penicillin were tested using 24 plates. The response varaible was the diameter of the zone of inhibition of the growth of a bacteria.

```
p <- ggplot(Penicillin, aes(x = plate, y = diameter)) +
  geom_point(size = 1) + facet_wrap(~ sample, ncol = 6) +
  coord_flip() + theme_minimal() +
  theme(axis.text.x = element_text(size = 5)) +
  labs(y = "Diameter (mm)", x = "Plate")
plot(p)
```



Let Y_{ij} denote the diameter of inhibition for the i-th sample ($i = 1, 2, \ldots, 6$) and the j-th plate ($j = 1, 2, \ldots, 26$). A model might be

$$E(Y_{ij}) = \beta_0 + \delta_i + \zeta_j \quad \text{or} \quad Y_{ij} = \beta_0 + \delta_i + \zeta_j + e_{ij}.$$

where δ_i and ζ_j are sample-specific and plate-specific effects, respectively. Here we will model both as random effects, each with an independent normal distribution. Note that we don't have any fixed effects.

```
m <- lmer(diameter ~ (1 | plate) + (1 | sample), data = Penicillin)
summary(m)
```

```
Linear mixed model fit by REML ['lmerMod']
Formula: diameter ~ (1 | plate) + (1 | sample)
   Data: Penicillin

REML criterion at convergence: 330.9

Scaled residuals:
    Min      1Q  Median      3Q     Max
-2.0792 -0.6714  0.0629  0.5838  2.9796

Random effects:
 Groups   Name        Variance Std.Dev.
 plate    (Intercept) 0.717    0.847
 sample   (Intercept) 3.731    1.932
 Residual             0.302    0.550
Number of obs: 144, groups:  plate, 24; sample, 6

Fixed effects:
            Estimate Std. Error t value
(Intercept)   22.972      0.809    28.4
```

Example: Consider the following data from a study that examined mating success with multiple combinations of male and female salamanders.

```
library(hglm.data)
data(salamander)
head(salamander, 12)
```

```
   Season Experiment TypeM TypeF Cross Male Female Mate
1  Summer          1     R     R    RR    1      1    1
2  Summer          1     W     R    RW   14      1    1
3  Summer          1     R     R    RR    5      1    1
4  Summer          1     W     R    RW   11      1    0
5  Summer          1     R     R    RR    4      1    1
6  Summer          1     W     R    RW   15      1    1
7  Summer          1     R     R    RR    5      2    1
8  Summer          1     W     R    RW   15      2    1
9  Summer          1     R     R    RR    3      2    1
10 Summer          1     W     R    RW   13      2    1
11 Summer          1     R     R    RR    1      2    1
12 Summer          1     W     R    RW   12      2    1
```

The question here is how the combination female and male salamanders in terms of population (W = "White Side", R = "Rough Butt") affects mating success, while accounting for individual differences in the salamanders themselves.

```
salamander$Cross <- relevel(salamander$Cross, ref = "WR")
m <- glmer(Mate ~ Cross + (1 | Male) + (1 | Female),
  family = binomial, data = salamander)
summary(m)
```

```
Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) [glmerMod
]
 Family: binomial  ( logit )
Formula: Mate ~ Cross + (1 | Male) + (1 | Female)
   Data: salamander

     AIC      BIC   logLik deviance df.resid
   430.6    453.9   -209.3    418.6      354

Scaled residuals:
   Min     1Q Median     3Q    Max
-2.051 -0.616  0.271  0.597  2.551

Random effects:
 Groups Name        Variance Std.Dev.
 Male   (Intercept) 1.04     1.02
 Female (Intercept) 1.17     1.08
Number of obs: 360, groups:  Male, 60; Female, 60

Fixed effects:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.896      0.446   -4.25  2.1e-05 ***
CrossRR        2.904      0.561    5.18  2.2e-07 ***
CrossRW        2.202      0.588    3.75  0.00018 ***
CrossWW        2.886      0.549    5.26  1.4e-07 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
        (Intr) CrssRR CrssRW
CrossRR -0.716
CrossRW -0.771  0.678
CrossWW -0.709  0.521  0.661
```

Nested Random Effects

Nested factors occur when they form a *hierarchical* structure. For example, in the Sitka data the levels of tree are nested within levels of treat (i.e., ozone or control), and in the Soybean data the levels of Plot are nested within levels of Variety. Nested random effects when the levels of one factor, modeled as a random effect, are nested within the levels of another factor that is also modeled as a random effect.

Example: The Pastes data frame from the **lme4** package is from a study of the strength of chemical pastes. Paste was delivered in a cask, and there were three casks per batch, and 10 batches. Two tests were run per cask.

```
head(Pastes, 12)
```

```
   strength batch cask sample
1      62.8     A    a    A:a
2      62.6     A    a    A:a
```

```
3       60.1     A    b    A:b
4       62.3     A    b    A:b
5       62.7     A    c    A:c
6       63.1     A    c    A:c
7       60.0     B    a    B:a
8       61.4     B    a    B:a
9       57.5     B    b    B:b
10      56.9     B    b    B:b
11      61.1     B    c    B:c
12      58.9     B    c    B:c
```

Note that levels of `cask` are not the same between batches — i.e., cask `a` in batch `A` is *not* the same as cask `a` in batch `B`, for example. The `sample` variable was created to identify a particular `cask`. We could model these data as

$$E(Y_{ijk}) = \beta_0 + \delta_i + \zeta_{ij},$$

where Y_{ijk} is k-th ($k = 1, 2$) test a paste from the j-th ($j = 1, 2, 3$) cask from the i-th batch ($i = 1, 2, \dots, 10$). So here δ_i is the effect of the i-th batch, and ζ_{ij} is the effect of the j-th cask from the i-th batch.

```
m <- lmer(strength ~ (1|batch) + (1|cask:batch), data = Pastes)
summary(m)
```

```
Linear mixed model fit by REML ['lmerMod']
Formula: strength ~ (1 | batch) + (1 | cask:batch)
   Data: Pastes

REML criterion at convergence: 247

Scaled residuals:
    Min      1Q  Median      3Q     Max
-1.4798 -0.5156  0.0095  0.4720  1.3897

Random effects:
 Groups     Name        Variance Std.Dev.
 cask:batch (Intercept) 8.434    2.904
 batch      (Intercept) 1.657    1.287
 Residual               0.678    0.823
Number of obs: 60, groups:  cask:batch, 30; batch, 10

Fixed effects:
            Estimate Std. Error t value
(Intercept)   60.053      0.677    88.7
```

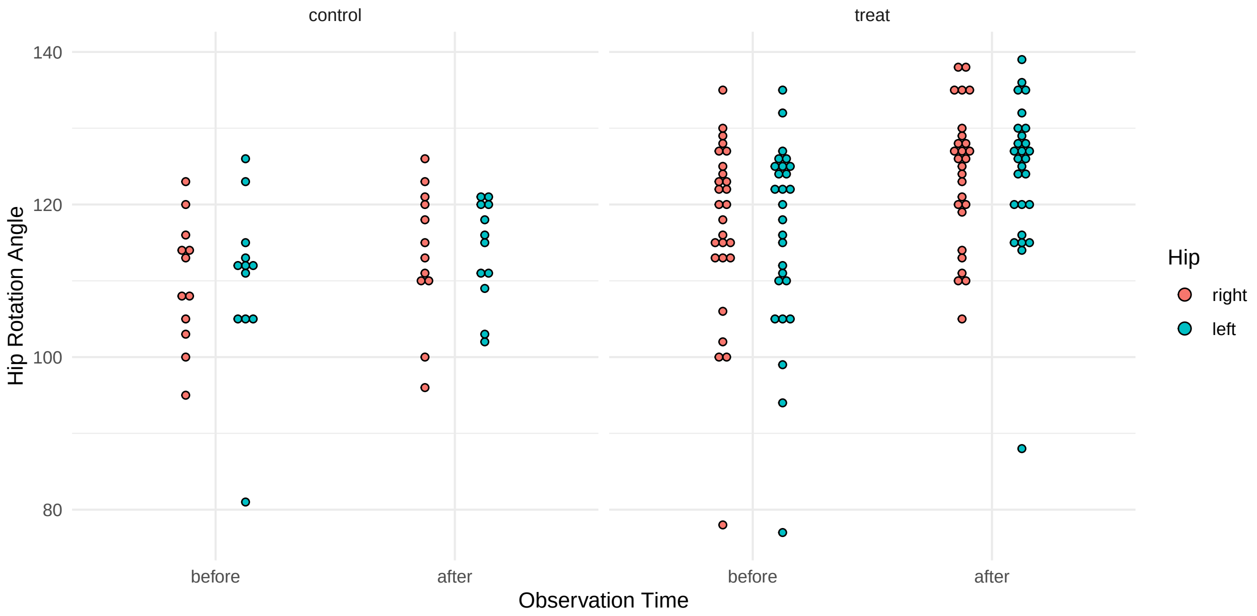
Note that you could use `sample` in place of `cask:batch`.

Example: Consider the following data from an experiment on the treatment of arthritis.

```
myhips <- faraway::hips %>% pivot_longer(cols = c(fbef,faft,rbef,raft),
   names_to = "obs", values_to = "angle") %>%
   mutate(time = rep(c("before","after"), n()/2)) %>%
   mutate(variable = rep(c("flexion","flexion","rotation","rotation"), n()/4)) %>%
   mutate(time = factor(time, levels = c("before","after")))
head(myhips,10)
```

```
# A tibble: 10 x 7
   grp   side  person obs   angle time   variable
   <fct> <fct> <fct>  <chr> <dbl> <fct>  <chr>
 1 treat right 1      fbef    125 before flexion
 2 treat right 1      faft    126 after  flexion
 3 treat right 1      rbef     25 before rotation
 4 treat right 1      raft     36 after  rotation
 5 treat left  1      fbef    120 before flexion
 6 treat left  1      faft    127 after  flexion
 7 treat left  1      rbef     35 before rotation
 8 treat left  1      raft     37 after  rotation
 9 treat right 2      fbef    135 before flexion
10 treat right 2      faft    135 after  flexion
```

```
p <- ggplot(subset(myhips, variable == "flexion"), aes(x = time, y = angle, fill = side)) +
   theme_minimal() + geom_dotplot(binaxis = "y", stackdir = "center", binwidth = 1,
      position = position_dodge(width = 0.5)) + facet_wrap(~ grp) +
   labs(x = "Observation Time", y = "Hip Rotation Angle", fill = "Hip")
plot(p)
```



Here for each of two response variables (flexion and rotation) we have two observations (before and after) for each hip (side) for each person. Here we specify a random effect for each person and a random effect for each hip within each person. Here we will consider the rotation response variable. Note that I am assuming that there is not, on average, an effect of left versus right side.

```
m <- lmer(angle ~ time * grp + (1|person) + (1|person:side),
   subset = variable == "rotation", data = myhips)
summary(m)
```

```
Linear mixed model fit by REML ['lmerMod']
Formula: angle ~ time * grp + (1 | person) + (1 | person:side)
   Data: myhips
 Subset: variable == "rotation"

REML criterion at convergence: 1033

Scaled residuals:
    Min      1Q  Median      3Q     Max 
-2.0275 -0.5006  0.0254  0.4548  1.8289 
```

```
Random effects:
 Groups      Name        Variance Std.Dev.
 person:side (Intercept) 33.1     5.76    
 person      (Intercept) 27.6     5.25    
 Residual                18.0     4.24    
Number of obs: 156, groups:  person:side, 78; person, 39

Fixed effects:
                   Estimate Std. Error t value
(Intercept)          25.000      2.105   11.88
timeafter             0.958      1.224    0.78
grptreat             -0.222      2.529   -0.09
timeafter:grptreat    5.634      1.471    3.83

Correlation of Fixed Effects:
            (Intr) timftr grptrt
timeafter   -0.291              
grptreat    -0.832  0.242       
tmftr:grptr  0.242 -0.832 -0.291
```

What is the estimated change in expected rotation from before to after treatment in each group?

```
trtools::contrast(m,
  a = list(time = "after", grp = c("control","treat")),
  b = list(time = "before", grp = c("control","treat")),
  cnames = c("control","treat"))
```

```
        estimate     se  lower upper tvalue  df    pvalue
control   0.9583 1.2238 -1.440 3.357  0.783 Inf 4.336e-01
treat     6.5926 0.8159  4.993 8.192  8.080 Inf 6.468e-16
```

The icc_specs function from the **specr** package can be used to produce estimates concerning the "variance components" (i.e., the variance due to person, side, and error).

```
specr::icc_specs(m)
```

```
          grp  vcov    icc percent
1 person:side 33.14 0.4210   42.10
2      person 27.59 0.3506   35.06
3    Residual 17.97 0.2284   22.84
```