Software Design for Population Pharmacokinetic Analysis

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Outline

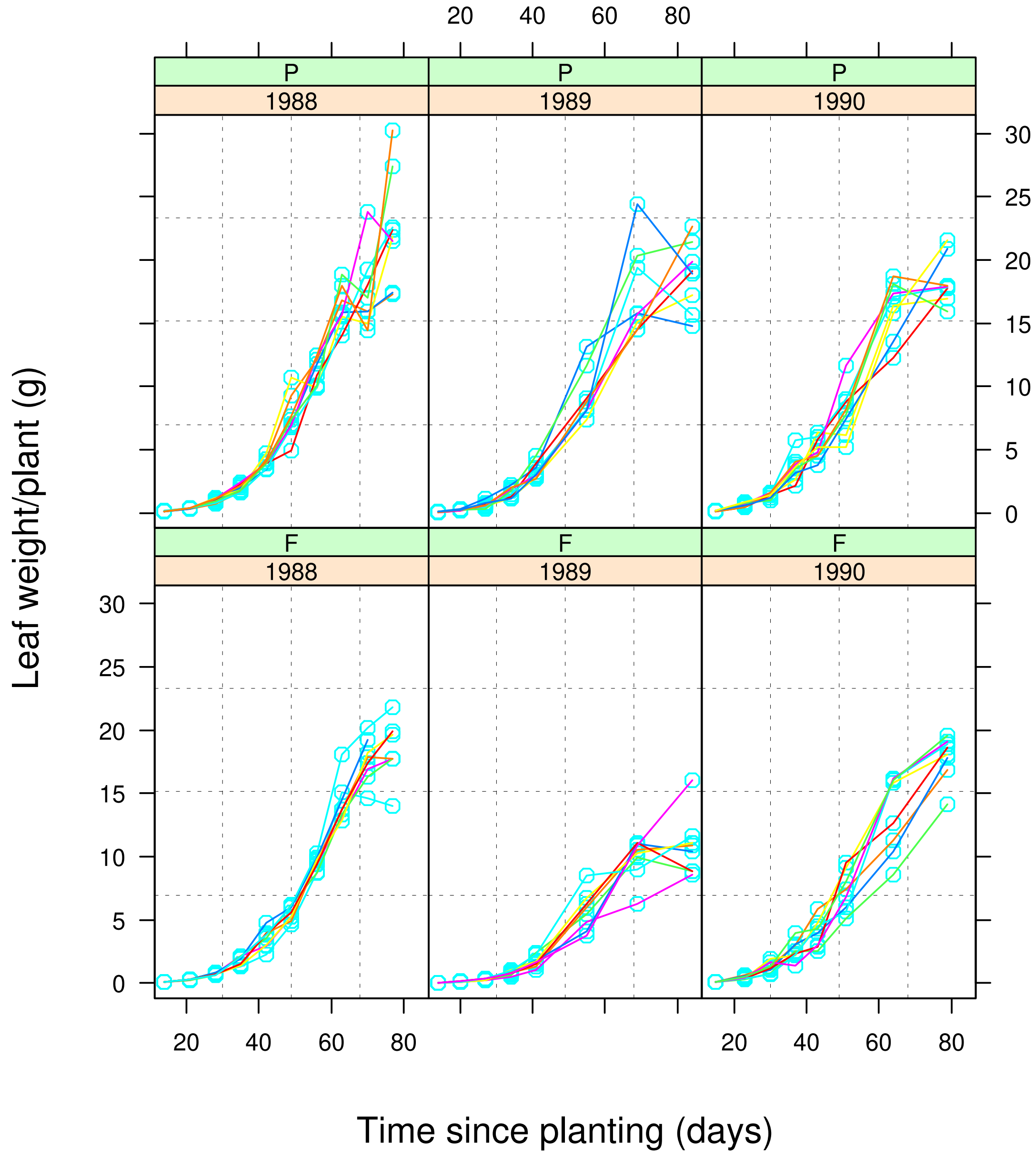
Will describe software for nonlinear mixed-effects modeling showing

- Objects for grouped data
- Objects for within-subject models
- Objects for within-subject variance functions
- Covariate modeling
- Comparing models

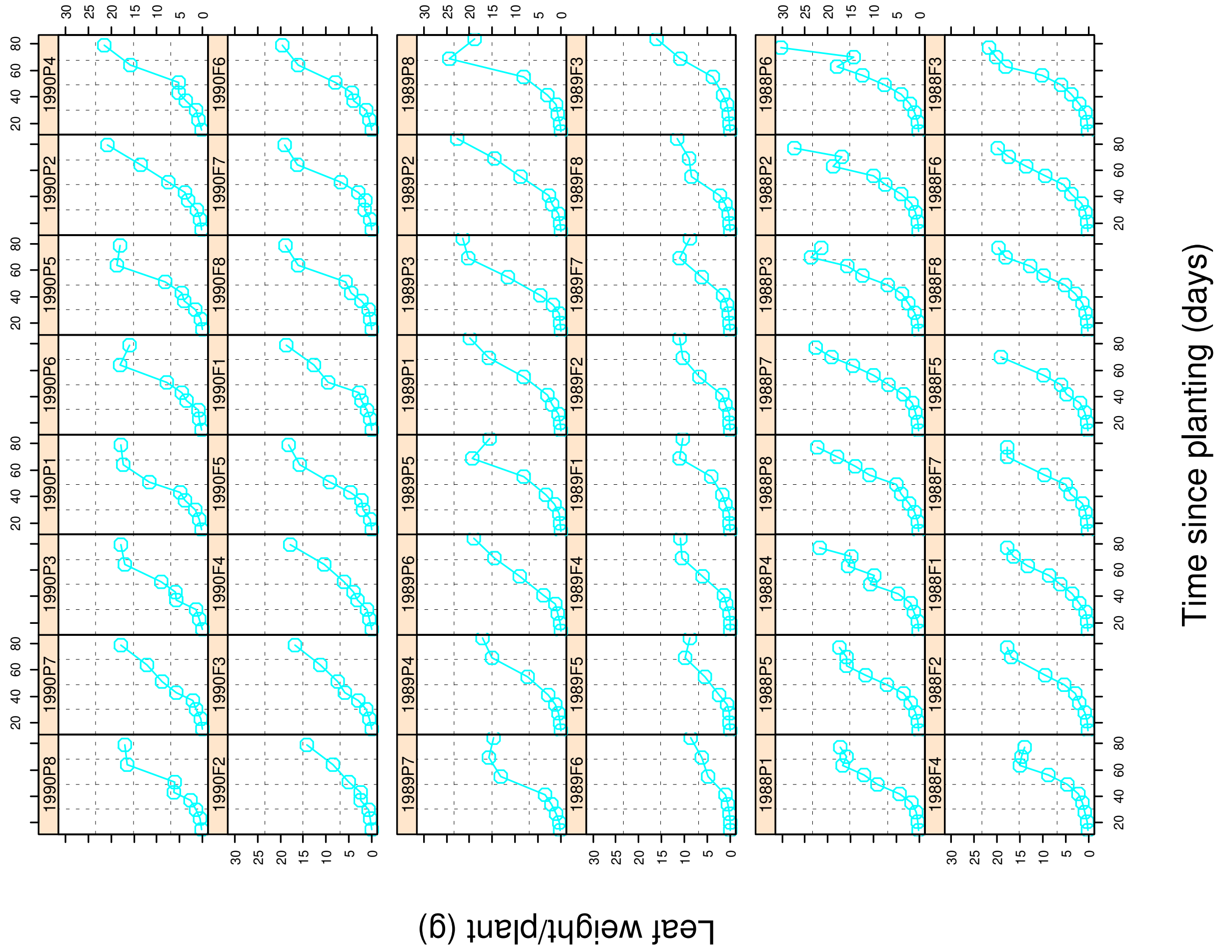
Emphasis on easy transition from simple to complicated models and informative graphical display wherever possible.

Example - Soybean growth

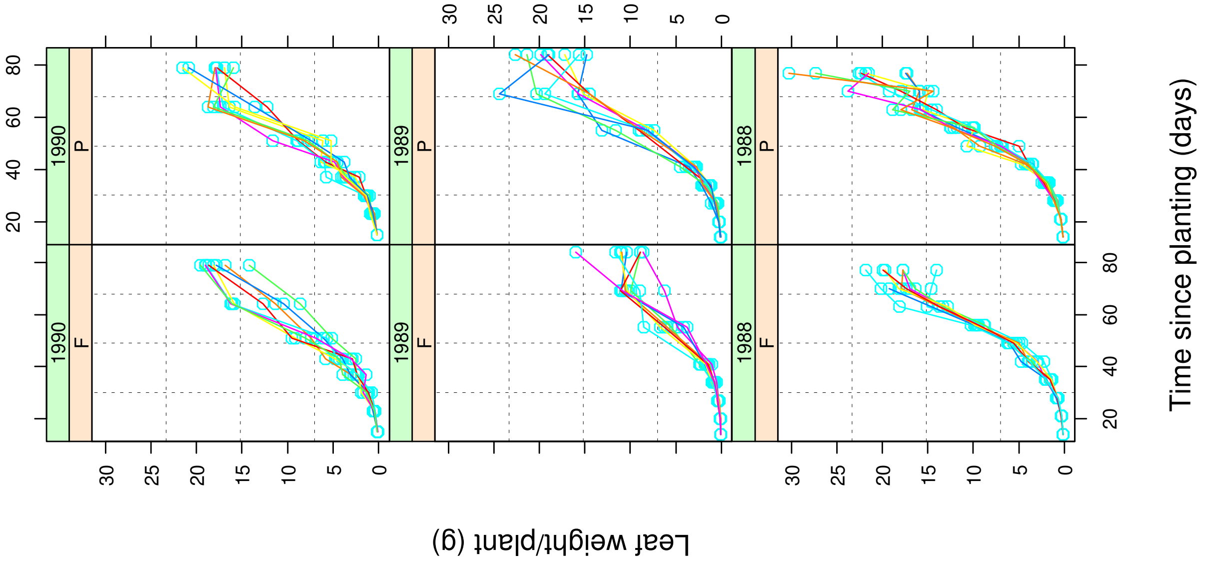
Eight plots each for 2 varieties of soybean in 3 years (Davidian and Giltinan, 1995)



Each plot separately



Comparing varieties within years



Code for Soybean plots

```
> Soybean <-
+  groupedData(formula = weight ~ time | Plot,
+    data = read.table("Soybean", header = TRUE),
+    outer = ~ Year * Variety,
+    labels = list(x = "Time since Planting",
+                  y = "Leaf weight/plant"),
+    units = list(x = "(days)", y = "(g)"))
> plot(Soybean, outer = TRUE)
> plot(Soybean, layout = c(8, 6),
+   between = list(y = c(0, 0.5)))
> plot(Soybean, outer = ~ Variety * Year)
```

Characteristics of the Soybean Data

- Sigmoidal shape wrt time. D&G suggest a *logistic function* for the intra-group model.

$$\theta_1 / \left[1 + \exp\left(\frac{\theta_2 - t}{\theta_3} \right) \right]$$

- Two *outer* factors - `Year` and `Variety`.
- Probably an interaction in these factors when modeling the asymptote (θ_1) for the weight.
- Greater level of "noise" when response is greater. May want to model intra-group variance.
- Design could lead to serial correlation for the intra-group noise.

`groupedData` objects in general

- Provide the table of data values and a display formula

```
response ~ primary | groups
```

- Can contain labels and units for primary and response
- Can contain information on the roles of other covariates
- The groups are sorted according to a summary function (`max`, by default) applied to the response. Outer factors are preserved in the sorting.

`selfStart` objects for nonlinear models

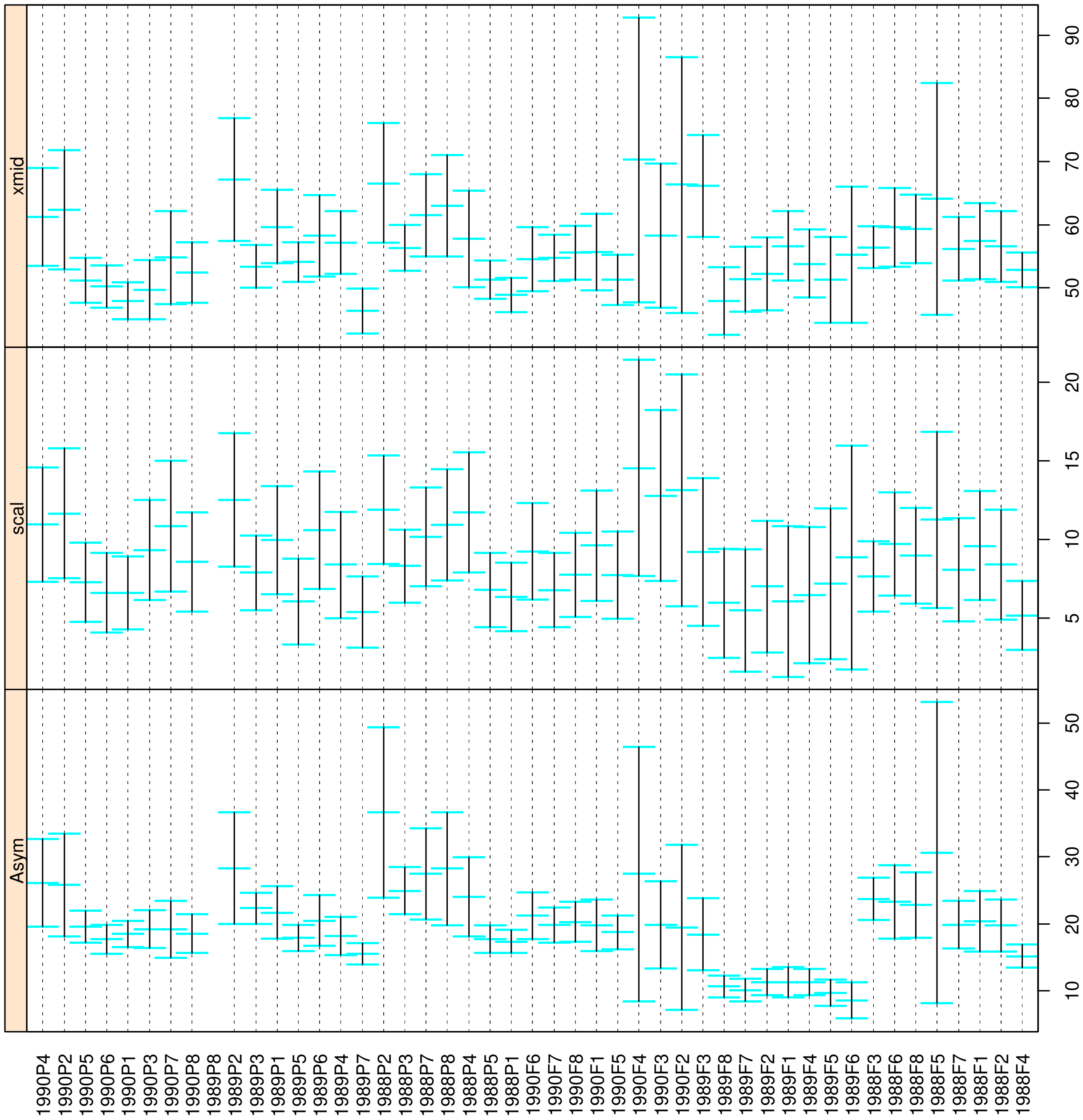
- A class for nonlinear regression models with “initial” functions.
- Contains the model function itself (possibly derivatives too).
- Before starting iterations, “initial” is called to create initial parameter estimates
- Described in Venables and Ripley (1996). (Interface to “initial” function will change in **nlme** 3.0.)
- `logistic` is a selfStart model for the logistic function.

Separate fits to each soybean plot

```
> Soybean.lis <- nlsList(logistic, Soybean)
> coef(Soybean.lis)
             Asym      xmid      scal
1988F4  15.152181  52.83510  5.177737
1988F2  19.746046  56.57598  8.407161
. . .
1988P2  36.644323  66.54816 11.912636
1988P6 163.038801 104.87821 17.924085
1989P7  15.471780  46.34263  5.393812
. . .
1989P8         NA        NA        NA
. . .
1990P4  26.129500  61.19955 10.971970
```

- Roles of variables can be inferred from display formula
- Did not converge on one plot (1989P8) and gave unusual estimates on another (1988P6).

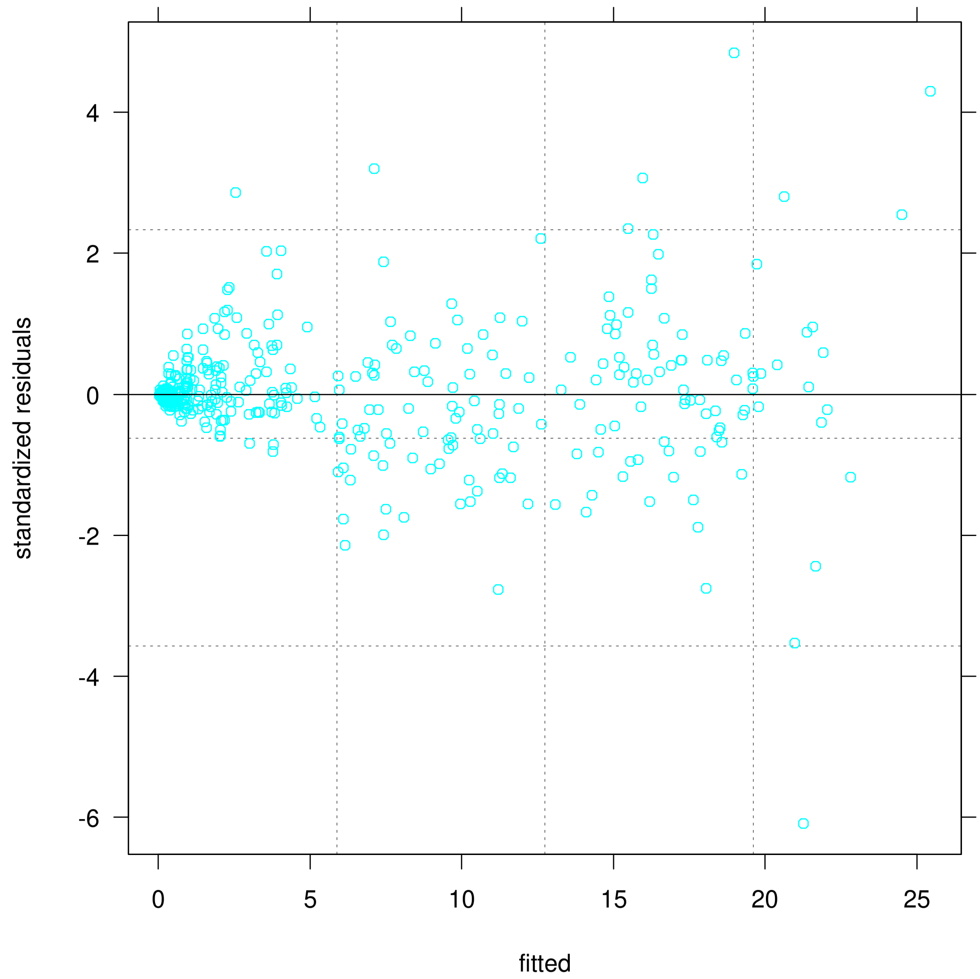
Comparing parameter estimates




```
plot(intervals(Soybean.lis), omitGroups = "1988P6")
```

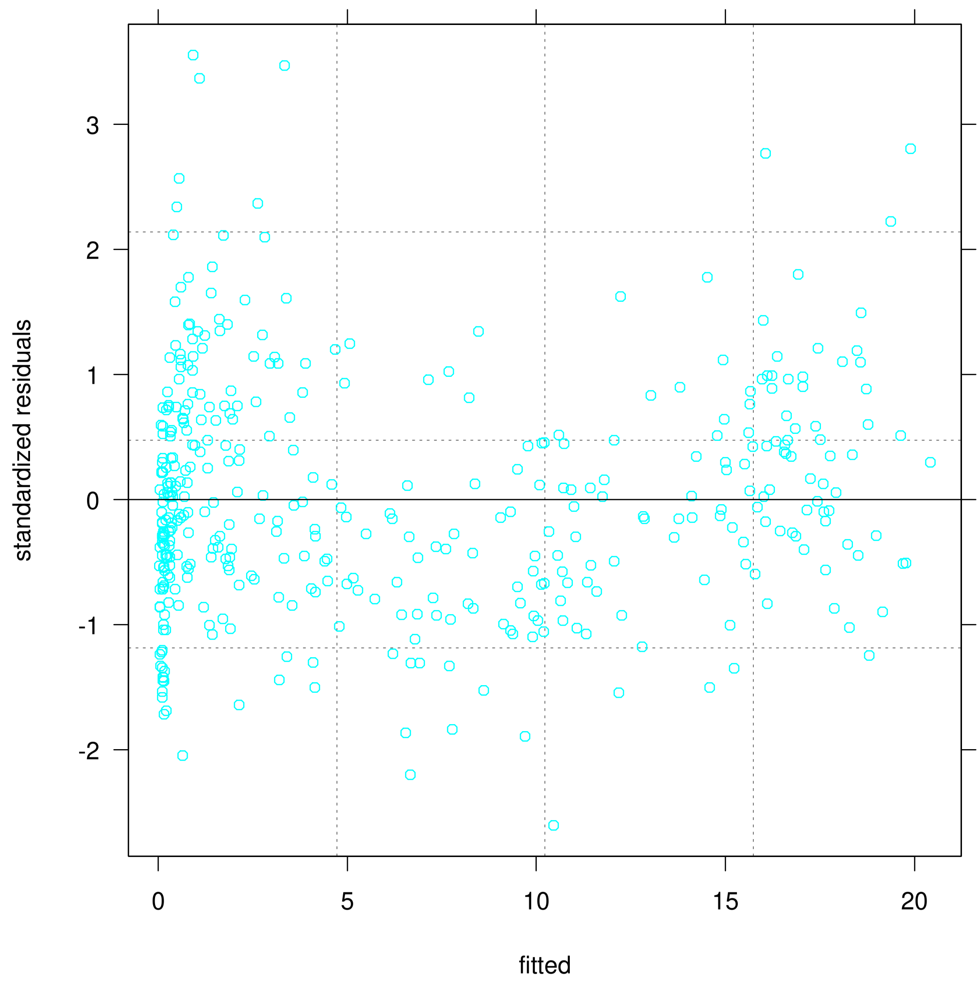
An initial mixed-effects model

```
> Soybean.nlme <- nlme(Soybean.lis)
> Soybean.nlme
Call:
  Model: weight ~ logistic(time, Asym, xmid, scal)
  Fixed: list(Asym ~ ., xmid ~ ., scal ~ .)
 Random: list(Asym ~ ., xmid ~ ., scal ~ .)
 Groups: ~ Plot
   Data: Soybean
...
> plot(Soybean.nlme, resid(., type = "st") ~ fitted(.))
```



Modeling heteroscedasticity

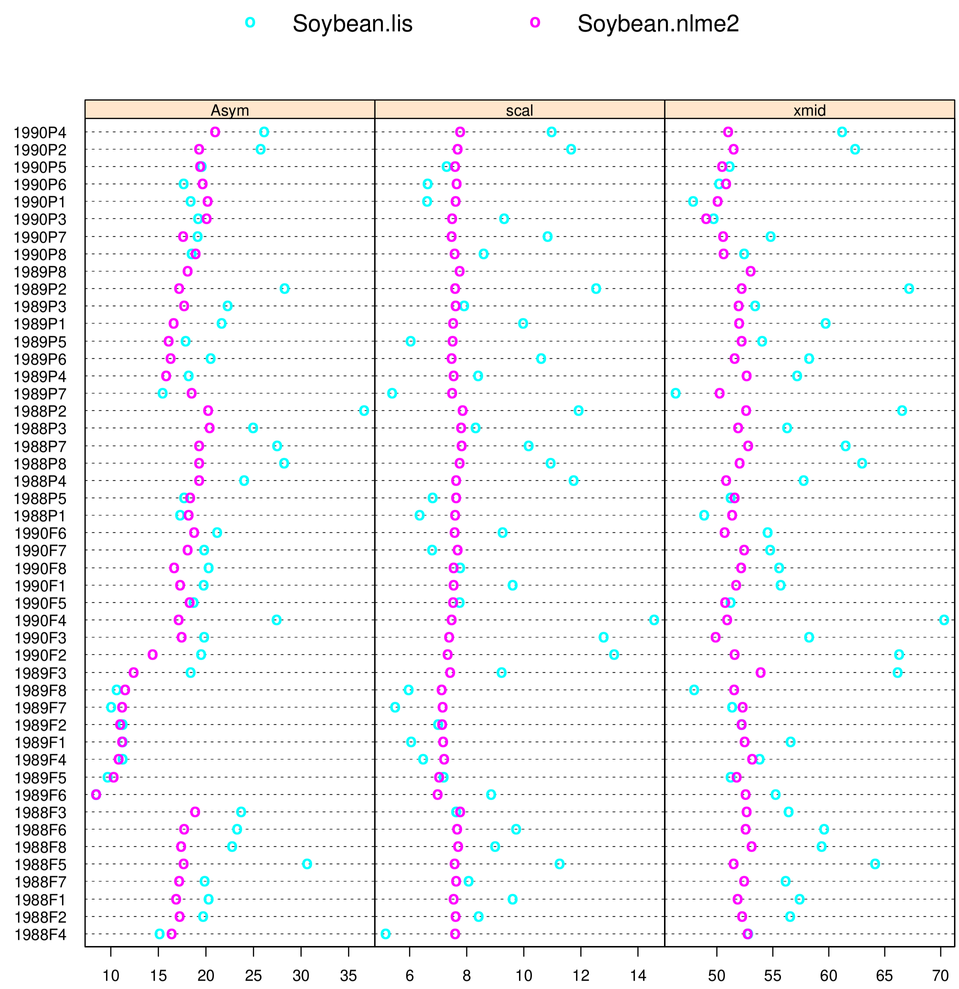
```
> Soybean.nlme2 <- update(Soybean.lis, varF = varFPower())
> summary(Soybean.nlme2)
Call:
  Model: weight ~ logistic(time, Asym, xmid, scal)
  Fixed: list(Asym ~ ., xmid ~ ., scal ~ .)
...
 Variance Function Structure: Power of fitted value
 Parameter estimates:
[1] 0.9388794
...
> plot(Soybean.nlme2, resid(., type = "st") ~ fitted(.))
```



Comparing models

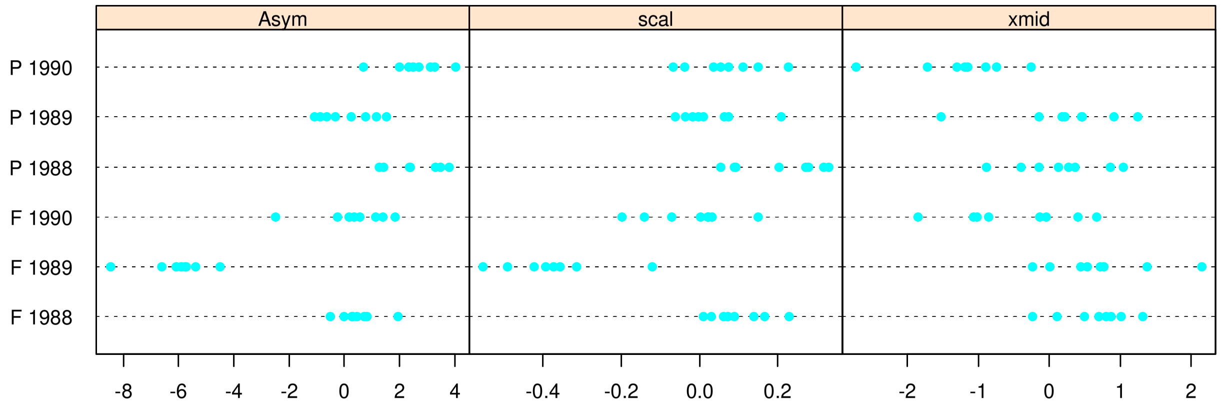
Models can be compared analytically or graphically

```
> anova(Soybean.nlme, Soybean.nlme2, test = T)
              Model df    AIC    BIC  logLik    Test  ChiSq P-val
 Soybean.nlme     1 10 1499.7 1539.9 -739.84
Soybean.nlme2     2 11  737.3  781.6 -357.67 1 vs. 2 764.33     0
> plot(compareFits(Soybean.lis, Soybean.nlme2),
       omitGroups = "1988P6", layout = c(3,1))
```



Covariate modeling

```
> plot(random.effects(Soybean.nlme2, aug = T), outer = ~ Year * Variety)
```




```
>  # fixed effects depending on year only
> Soybean.nlme3 <- update(Soybean.nlme2,
+    fixed = list(Asym ~ Year, xmid ~ Year, scal ~ Year))
> anova(Soybean.nlme2, Soybean.nlme3)
              Model df    AIC    BIC  logLik    Test  ChiSq    P-val
 Soybean.nlme2     1 11 737.03 781.26 -357.52
 Soybean.nlme3     2 17 683.98 752.34 -324.99  1 vs. 2 65.053 4.21e-12
> # no longer need random effect for scal
> # continue examining random effects versus covariates
> Soybean.nlme4 <- update(Soybean.nlme3,
+   fixed = list(Asym ~ Year * Variety,
+                xmid ~ Year + Variety, scal ~ Year),
+   random = list(Asym ~ .))
```

Final result

```
> summary(Soybean.nlme4)
Call:  Model: weight ~ ll(time, Asym, xmid, scal)
  Fixed: list(Asym ~ Year * Variety,
              xmid ~ Year + Variety, scal ~ Year)
 Random: list(Asym ~ .)
 Groups:  ~ Plot
   Data: Soybean
. . .
Fixed Effects Estimate(s):
                          Value Std.Error   z-value
    Asym.(Intercept) 19.4337563 0.9386001 20.705044
       Asym.Year1989 -8.8421762 1.0551015 -8.380403
       Asym.Year1990 -3.7077747 1.1583028 -3.201041
        Asym.Variety  1.6232548 1.0217624  1.588681
Asym.Year1989Variety  5.5705385 1.1522732  4.834390
Asym.Year1990Variety  0.1473987 1.1570482  0.127392
    xmid.(Intercept) 54.8147656 0.7427505 73.799707
       xmid.Year1989 -2.2383957 0.9562405 -2.340829
       xmid.Year1990 -4.9711801 0.9587453 -5.185089
        xmid.Variety -1.2971909 0.4077588 -3.181270
    scal.(Intercept)  8.0633659 0.1448889 55.652079
       scal.Year1989 -0.8952299 0.1980641 -4.519901
       scal.Year1990 -0.6733403 0.2087876 -3.225001
. . .
> anova(Soybean.nlme1, Soybean.nlme2, Soybean.nlme3, Soybean.nlme4,
+       test = F)
                Model df    AIC    BIC  logLik
  Soybean.nlme1     1 10 1499.7 1539.9 -739.84
  Soybean.nlme2     2 11  737.0  781.3 -357.52
  Soybean.nlme3     3 17  684.0  752.3 -324.99
  Soybean.nlme4     4 16  616.3  680.6 -292.15
```

Object-oriented aspects of the approach

- The data, the model function, the fitted models and its derived quantities (residuals, random effects estimates, . . .) are all represented as objects.
- An object can encapsulate both information and behaviour. An important type of behaviour is “plot yourself”.
- Combining data with models produces initial fits. All fitted models should have “update yourself” methods to refine the fit.