indometh1.R:

```
library(nlme)
library(lattice)
trellis.device(color=F)
plot(Indometh)
plot(Indometh,outer=~1)
m1.nls <- nls(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
summary(m1.nls)
plot(m1.nls,Subject~resid(.),abline=0)
plot(m1.nls, resid(.) ~ fitted(.) | Subject, abline = 0,grid=F)
m1.lis <- nlsList(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
coef(m1.lis)
plot(intervals(m1.lis))
#again, the following didn't work without providing starting values
# it appears to be a bug
#m1.nlme <- nlme(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh,
# fixed= th1+th2+th3+th4~1,
# random=pdDiag(th1+th2+th3+th4~1) )
getInitial(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
m1.nlme <- nlme(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh,
 fixed= th1+th2+th3+th4~1,
 random=pdDiag(th1+th2+th3+th4~1),
 start=c(th1=2.7734071,  th2=0.8863545,  th3=0.6067352, th4=-1.0919293 ) )
summary(m1.nlme)
m2.nlme <- update(m1.nlme,random=pdDiag(th1+th2+th3~1) )
anova(m1.nlme,m2.nlme)
m3.nlme <- update(m2.nlme,random=pdSymm(th1+th2+th3~1) )
summary(m3.nlme)
m4.nlme <- update(m3.nlme,random=pdBlocked(list(th1+th2~1,th3~1)) )
anova(m3.nlme,m4.nlme)
anova(m2.nlme,m4.nlme)
summary(m4.nlme)
plot(m4.nlme,id=.05,adj=-1,grid=F)
plot(augPred(m4.nlme,level=0:1))
```

Output from indometh1.R:

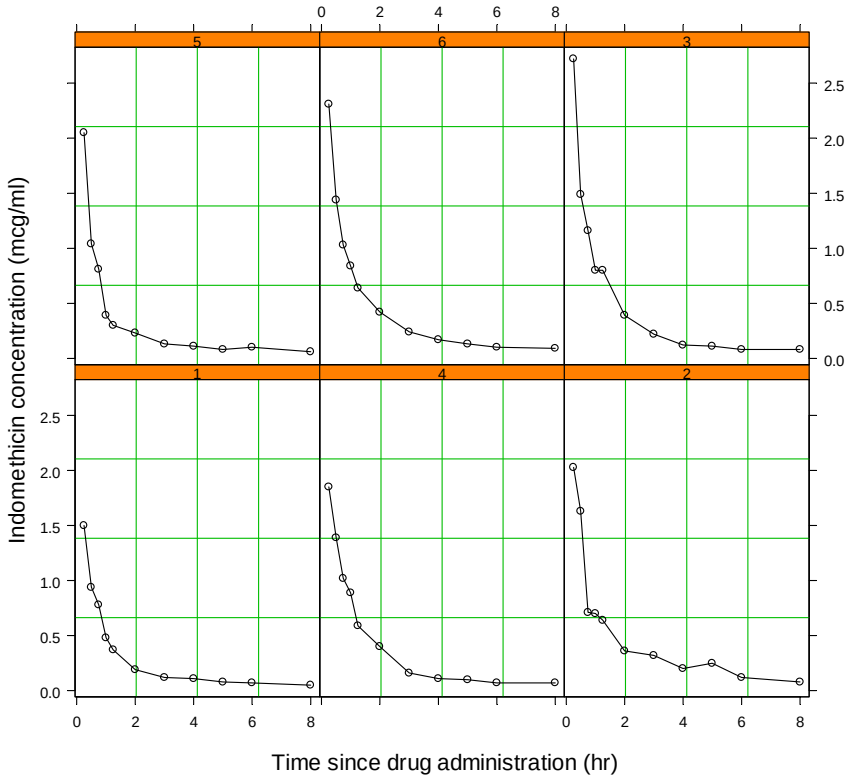
```
> library(nlme)
> library(lattice)
> trellis.device(color=F)
> plot(Indometh)
> plot(Indometh,outer=~1)
> m1.nls <- nls(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
> summary(m1.nls)

Formula: conc ~ SSbiexp(time, th1, th2, th3, th4)

Parameters:
    Estimate Std. Error t value Pr(>|t|)
th1   2.7734     0.2533  10.951 3.97e-16 ***
th2   0.8864     0.2222   3.988 0.000178 ***
th3   0.6067     0.2671   2.272 0.026598 *
th4  -1.0919     0.4089  -2.671 0.009658 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.1745 on 62 degrees of freedom

Number of iterations to convergence: 0
```

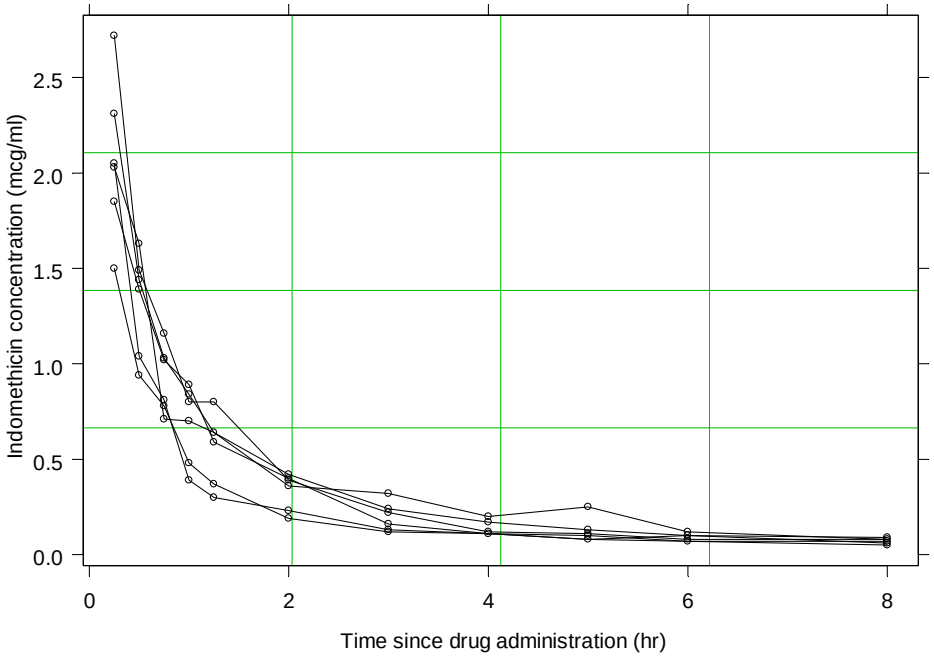
```
Achieved convergence tolerance: 3.303e-07

> plot(m1.nls,Subject~resid(.),abline=0)
> plot(m1.nls, resid(.) ~ fitted(.) | Subject, abline = 0,grid=F)
> m1.lis <- nlsList(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
> coef(m1.lis)
       th1       th2       th3        th4
1 2.029277 0.5793887 0.1915475 -1.7877849
4 2.198132 0.2423124 0.2545223 -1.6026859
2 2.827673 0.8013195 0.4989175 -1.6353512
5 3.566103 1.0407660 0.2914970 -1.5068522
6 3.002250 1.0882119 0.9685230 -0.8731358
3 5.468312 1.7497936 1.6757522 -0.4122004
> plot(intervals(m1.lis))
> #again, the following didn't work without providing starting values
> # it appears to be a bug
> #m1.nlme <- nlme(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh,
> # fixed= th1+th2+th3+th4~1,
> # random=pdDiag(th1+th2+th3+th4~1) )
> getInitial(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh)
       th1        th2        th3        th4
 2.7734071  0.8863545  0.6067352 -1.0919293
> m1.nlme <- nlme(conc~SSbiexp(time,th1,th2,th3,th4),data=Indometh,
+  fixed= th1+th2+th3+th4~1,
+  random=pdDiag(th1+th2+th3+th4~1),
+  start=c(th1=2.7734071,  th2=0.8863545,  th3=0.6067352, th4=-1.0919293 ) )
> summary(m1.nlme)
Nonlinear mixed-effects model fit by maximum likelihood
  Model: conc ~ SSbiexp(time, th1, th2, th3, th4)
 Data: Indometh
       AIC       BIC   logLik
  -91.18904 -71.48214 54.59452

Random effects:
 Formula: list(th1 ~ 1, th2 ~ 1, th3 ~ 1, th4 ~ 1)
 Level: Subject
 Structure: Diagonal
              th1       th2       th3          th4   Residual
StdDev: 0.5713799 0.1580998 0.1115626 7.689272e-06 0.08149489

Fixed effects: th1 + th2 + th3 + th4 ~ 1
         Value Std.Error DF   t-value p-value
th1  2.8275704 0.2639932 57 10.710770   0e+00
th2  0.7734360 0.1100173 57  7.030131   0e+00
th3  0.4612438 0.1127820 57  4.089694   1e-04
th4 -1.3445564 0.2311956 57 -5.815666   0e+00
 Correlation:
    th1    th2    th3
th2  0.055
th3 -0.102  0.630
th4 -0.139  0.577  0.834

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-3.1734048 -0.3562738 -0.1286094  0.3427745  3.0022624

Number of Observations: 66
Number of Groups: 6
> m2.nlme <- update(m1.nlme,random=pdDiag(th1+th2+th3~1) )
> anova(m1.nlme,m2.nlme)
        Model df       AIC       BIC   logLik   Test      L.Ratio p-value
m1.nlme     1  9 -91.18904 -71.48214 54.59452
m2.nlme     2  8 -93.18904 -75.67180 54.59452 1 vs 2 1.037959e-08  0.9999
```

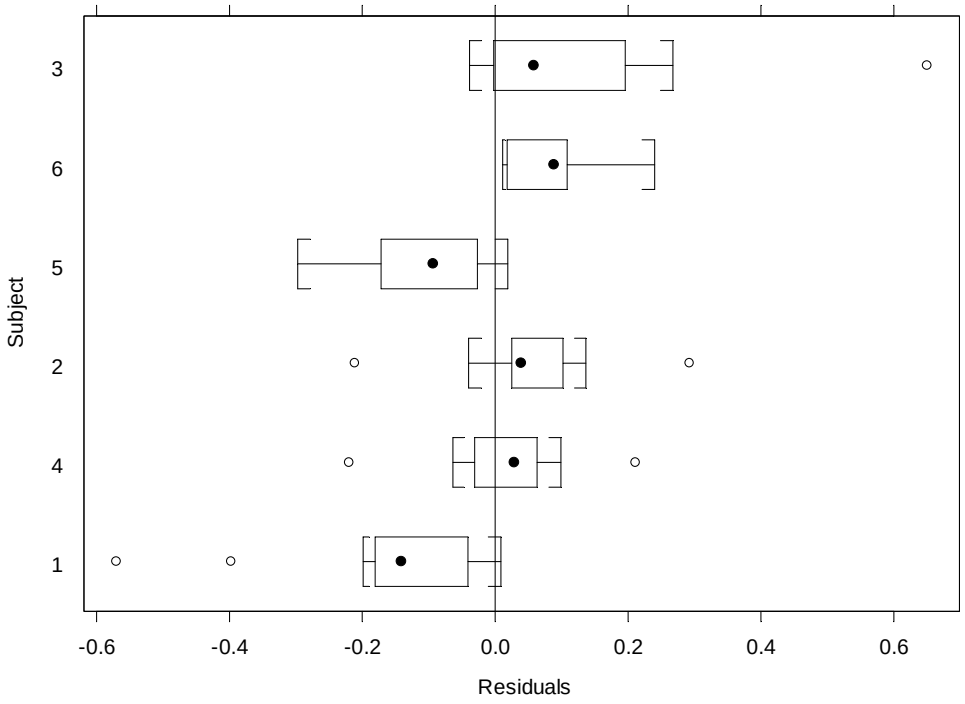
```
> m3.nlme <- update(m2.nlme,random=pdSymm(th1+th2+th3~1) )
> summary(m3.nlme)
Nonlinear mixed-effects model fit by maximum likelihood
  Model: conc ~ SSbiexp(time, th1, th2, th3, th4)
 Data: Indometh
       AIC       BIC  logLik
  -94.94661 -70.86041 58.4733

Random effects:
 Formula: list(th1 ~ 1, th2 ~ 1, th3 ~ 1)
 Level: Subject
 Structure: General positive-definite
         StdDev     Corr
th1      0.69045574 th1   th2
th2      0.17903517 0.932
th3      0.15371598 0.471 0.118
Residual 0.07807092

Fixed effects: th1 + th2 + th3 + th4 ~ 1
         Value Std.Error DF   t-value p-value
th1  2.8148379 0.3123823 57  9.010876       0
th2  0.8292887 0.1138548 57  7.283740       0
th3  0.5613588 0.1216462 57  4.614686       0
th4 -1.1406655 0.1714575 57 -6.652762       0
 Correlation:
    th1    th2    th3
th2  0.636
th3  0.164  0.591
th4 -0.110  0.524  0.765

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-3.47928698 -0.40288346  0.02753556  0.44197127  2.92931776

Number of Observations: 66
Number of Groups: 6
> m4.nlme <- update(m3.nlme,random=pdBlocked(list(th1+th2~1,th3~1)) )
> anova(m3.nlme,m4.nlme)
        Model df       AIC       BIC   logLik   Test   L.Ratio p-value
m3.nlme     1 11 -94.94661 -70.86041 58.47331
m4.nlme     2  9 -98.15690 -78.45000 58.07845 1 vs 2 0.7897149  0.6738
> anova(m2.nlme,m4.nlme)
        Model df       AIC      BIC   logLik   Test L.Ratio p-value
m2.nlme     1  8 -93.18904 -75.6718 54.59452
m4.nlme     2  9 -98.15690 -78.4500 58.07845 1 vs 2 6.96786  0.0083
> summary(m4.nlme)
Nonlinear mixed-effects model fit by maximum likelihood
  Model: conc ~ SSbiexp(time, th1, th2, th3, th4)
 Data: Indometh
       AIC    BIC   logLik
  -98.1569 -78.45 58.07845

Random effects:
 Composite Structure: Blocked

 Block 1: th1, th2
 Formula: list(th1 ~ 1, th2 ~ 1)
 Level: Subject
 Structure: General positive-definite
    StdDev    Corr
th1 0.7196259 th1
th2 0.1486626 1
```

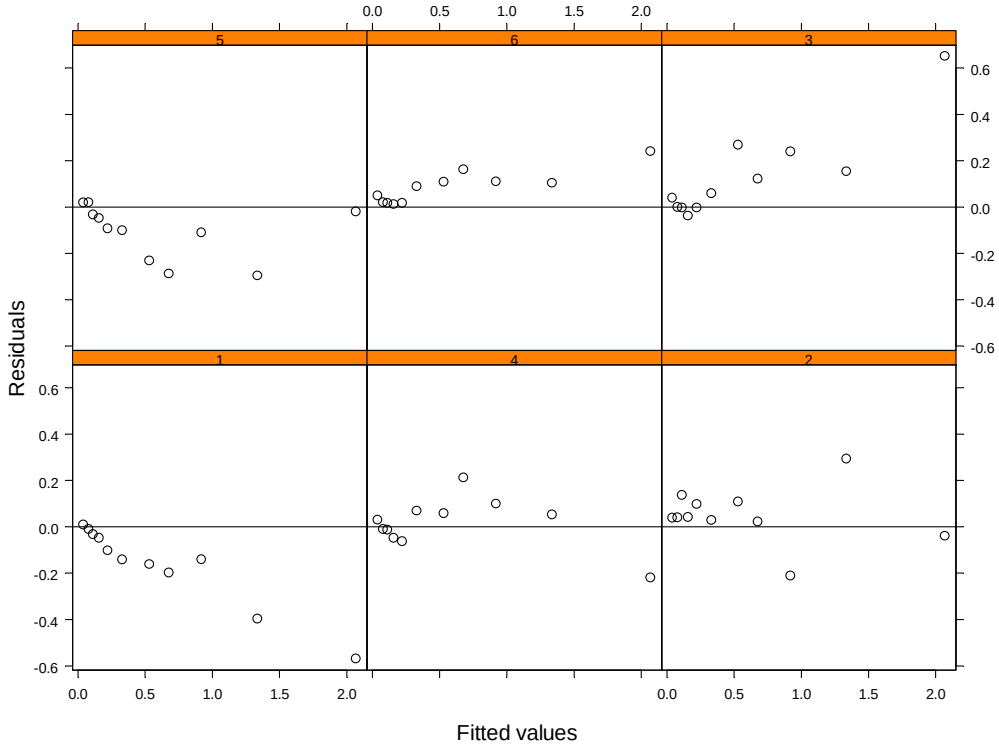
```
 Block 2: th3
 Formula: th3 ~ 1 | Subject
              th3   Residual
StdDev: 0.2129434 0.07820026

Fixed effects: th1 + th2 + th3 + th4 ~ 1
         Value Std.Error DF   t-value p-value
th1  2.7830610 0.3270846 57  8.508689       0
th2  0.8979139 0.1106839 57  8.112417       0
th3  0.6577986 0.1428049 57  4.606274       0
th4 -1.0003642 0.1499714 57 -6.670367       0
 Correlation:
    th1    th2    th3
th2  0.602
th3 -0.058  0.556
th4 -0.109  0.570  0.702

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-3.4587653 -0.4372662  0.1096675  0.5042423  3.0571610

Number of Observations: 66
Number of Groups: 6
> plot(m4.nlme,id=.05,adj=-1,grid=F)
> plot(augPred(m4.nlme,level=0:1))
>
```

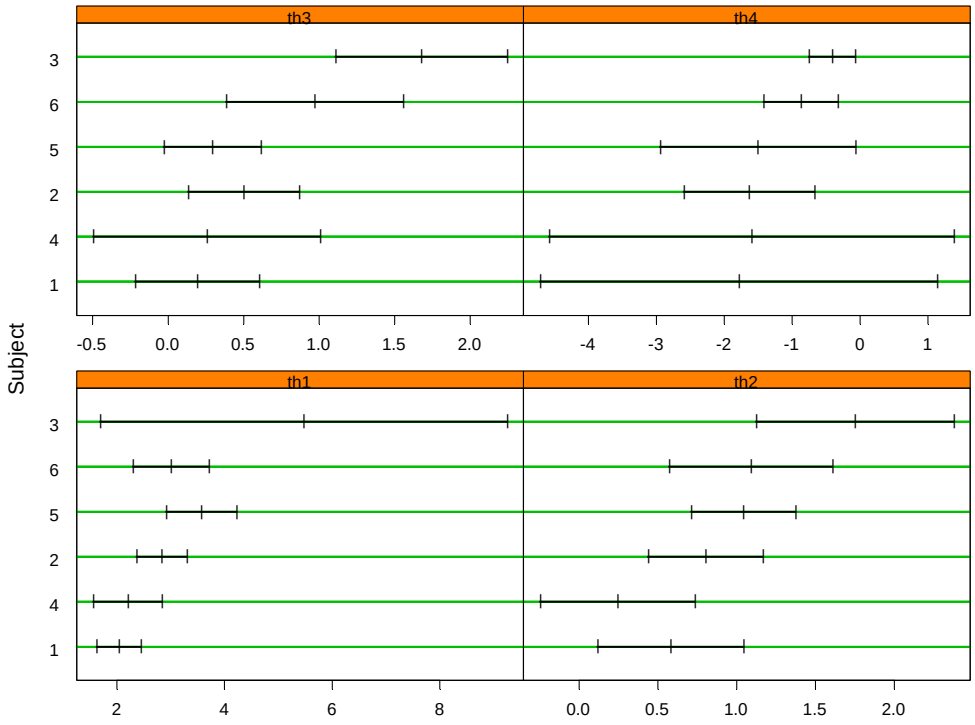
Plots from indometh1.R:

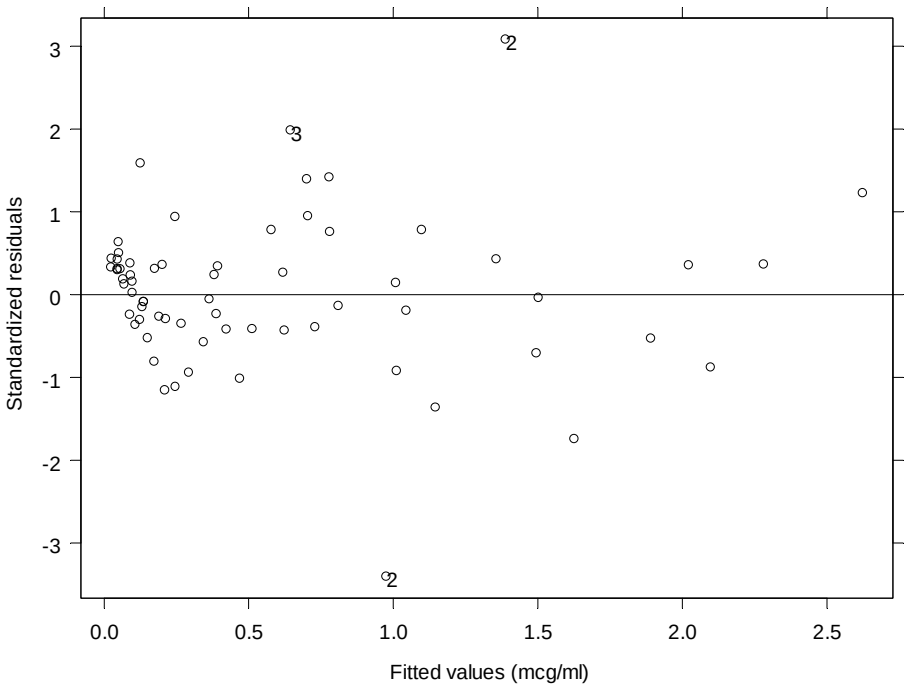

5
6
3
1
4
2
Indomethicin concentration (mcg/ml)
Time since drug administration (hr)

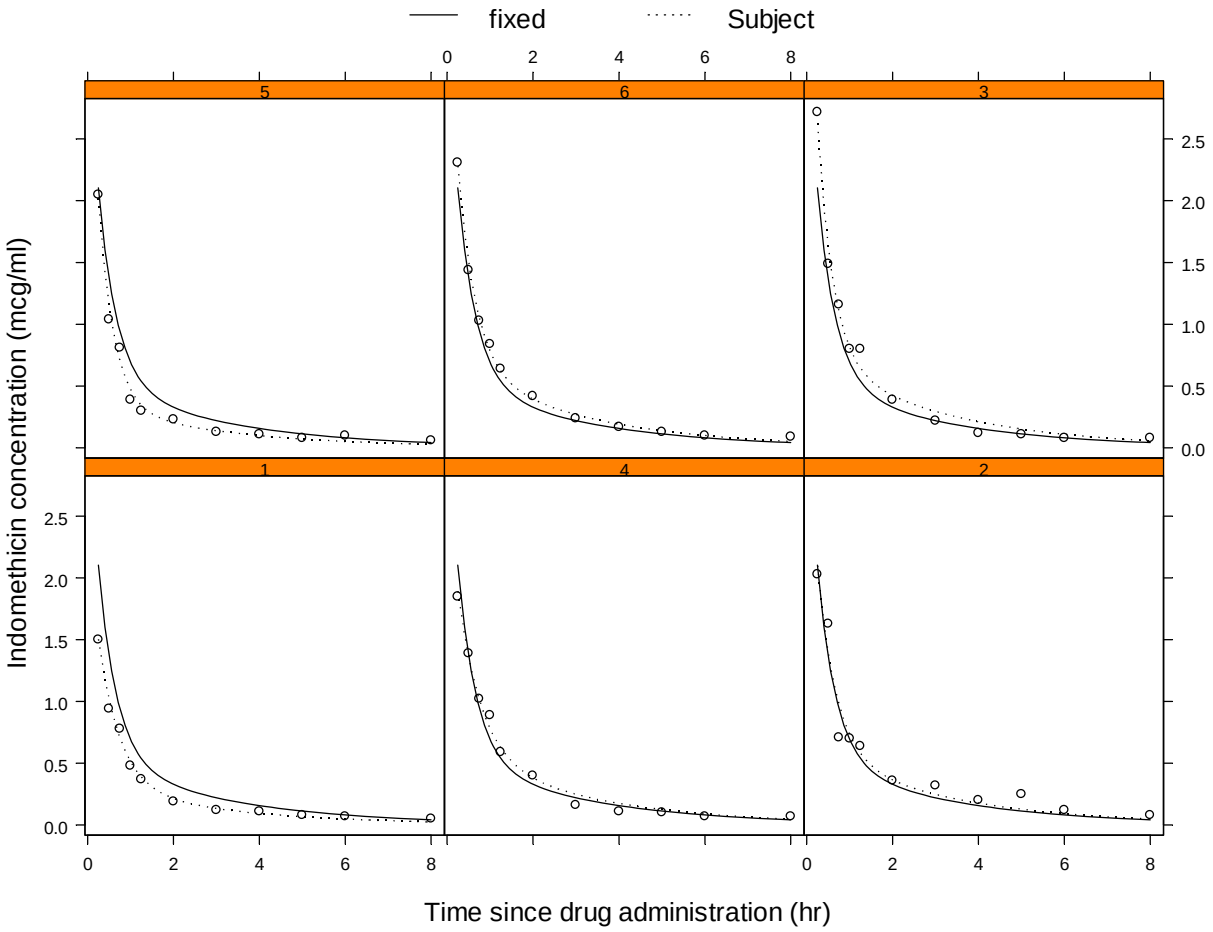

Indomethicin concentration (mcg/ml)
Time since drug administration (hr)


Subject
3
6
5
2
4
1
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
Residuals


5
6
3
1
4
2
Residuals
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
0.0
0.5
1.0
1.5
2.0
Fitted values


th3
th4
th1
th2
Subject
3
6
5
2
4
1
-0.5
0.0
0.5
1.0
1.5
2.0
-4
-3
-2
-1
0
1
2
4
6
8


Standardized residuals
Fitted values (mcg/ml)
3
2
1
0
-1
-2
-3
0.0
0.5
1.0
1.5
2.0
2.5


fixed
Subject
5
6
3
1
4
2
Indomethicin concentration (mcg/ml)
Time since drug administration (hr)
0
2
4
6
8
0.0
0.5
1.0
1.5
2.0
2.5