Analyzing Event History Data with nlme in S

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PAGE Meeting, Pamplona Spain, June 17, 2005

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Outline

- Motivation: pkNLME library
- Example: Analgesic data
- pkGroupedData extension of groupedData class
- Fitting compartment models to event history data with nlme
- Conclusions

Motivation

- Primary software for population PK analysis: NONMEM
  - standalone Fortran software with comprehensive PK/PD library
  - suited for event history data format
  - limited capabilities for graphics (diagnostics, data, etc) and extensibility (e.g., bootstrap, likelihood profiling)
  - requires different programming environments for additional capabilities (e.g., Xpose, WFN, PDx-Pop)

- New numerical methods for fitting NLME models available – difficult to implement in NONMEM

Motivation (cont.)

- S language (and its dialects, SPLUS and R)
  - integrated, flexible, extensible programming environment for statistical graphics and modeling
  - efficient calculations in use of vectorized form
  - less suitable for recursive calculations
- Methods for mixed-effects models is available in NLME library (Pinheiro and Bates, 2000)
  - groupedData class
  - limited capabilities for PK modeling (vectorized form)

Example: PK clinical trial with analgesic drug

- Clinical trial with 91 patients submitted to four different dose regimens of an analgesic drug: 50 mg bid, 100 mg bid, 200 mg bid, and 400 mg od – 22 to 24 patients per dose group
- Blood concentrations of drug measured on first day non-steady-state and after four weeks in the trial steady-state: six concentration measurements taken over about six hours on each occasion
- Data available on five demographic variables: sex, race, age, weight, and height
- PK model: two-compartment model with zero-order absorption
- Main objective: determine impact of demographic covariates on PK parameters
- For confidentiality, data presented was simulated using same design and PK model as in original clinical trial

Analgesic example (cont.)

```
ANALGESIC STUDY 01 NONMEM INPUT FILE (SBJ WITH MISSING WEIGHT, RACE IGNORED)
ID,EVID,AMT,TIME,SEX,RACE,AGE,WGT,HT,SS,II,DV
1.0,1.0,400.00000,9.25000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,0.00000
1.0,0.0,0.0,9.75000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,7.51500
1.0,0.0,0.0, 10.30000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,7.07800
1.0,0.0,0.0, 11.25000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,12.15100
1.0,0.0,0.0, 12.23300,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,2.23100
1.0,0.0,0.0, 13.25000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,1.99020
1.0,0.0,0.0, 15.25000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,0.54854
1.0,1.0,400 728.63000,1.0,1.0,61.00000,72.50000,175.00000,1.0,24.00000,0.00000
1.0,0.0,0.0,752.33000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,0.18974
1.0,1.0,400 752.63000,1.0,1.0,61.00000,72.50000,175.00000,0.0,0.0,0.00000
...
```

A pkGroupedData class

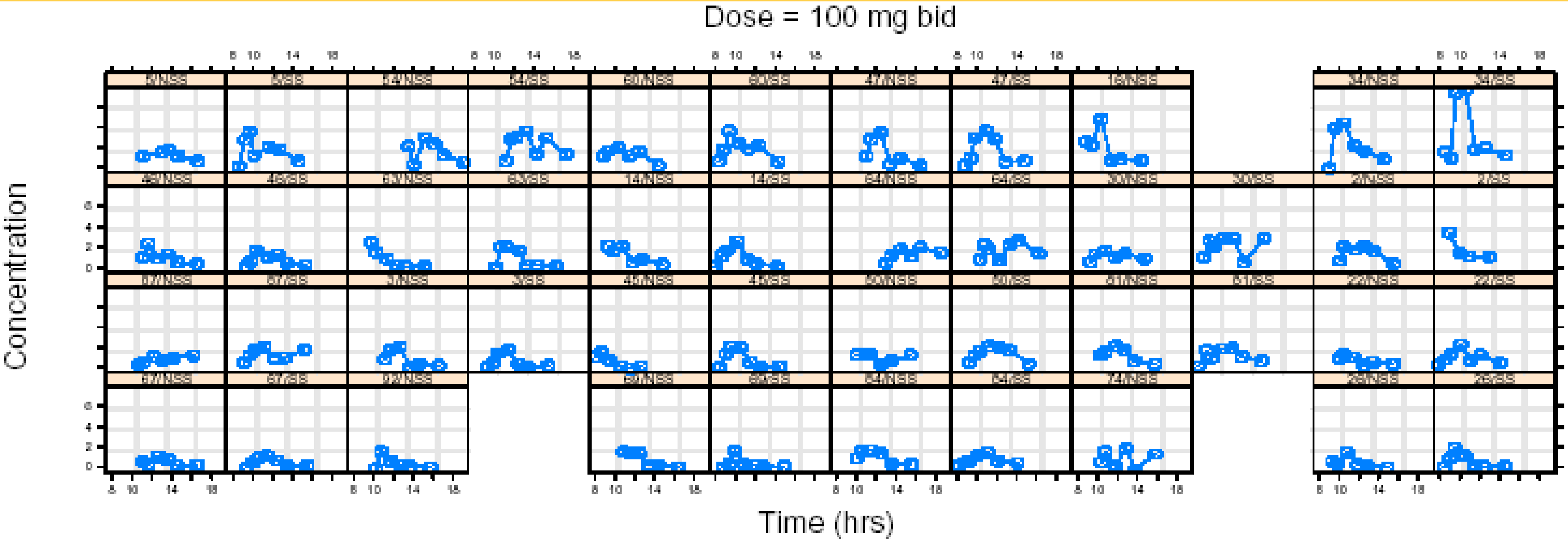
- groupedData class
  - included in NLME library
  - extended data frame to represent data with one or more nested levels of grouping (e.g. longitudinal data, repeated measures)
  - available methods for displaying, summarizing, and modeling

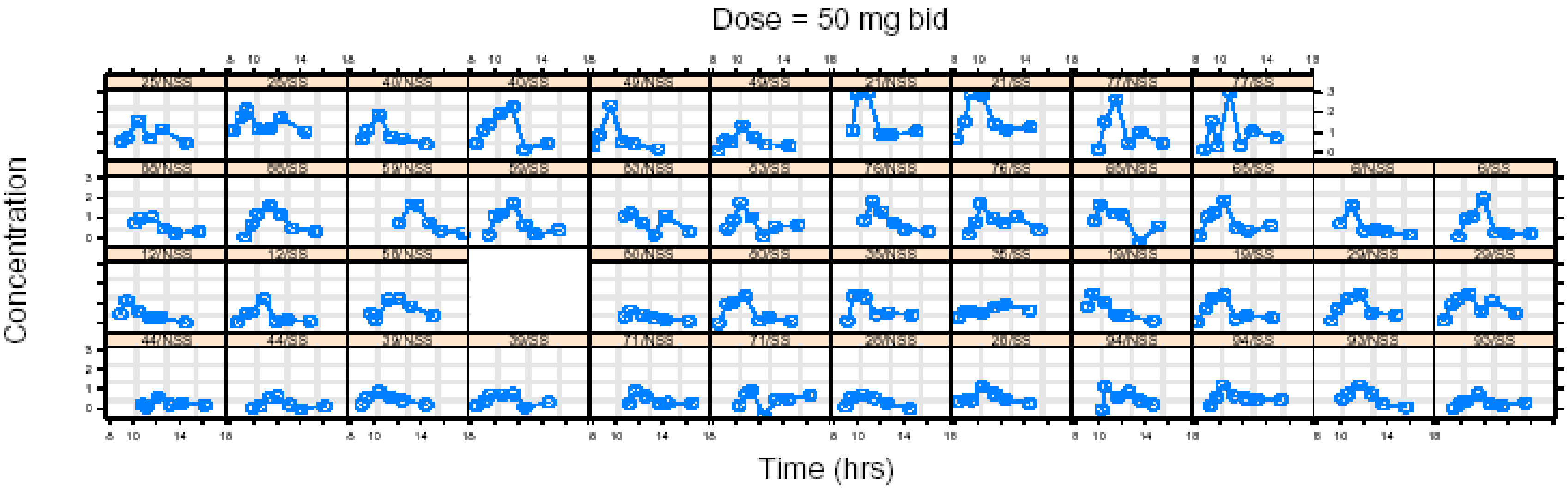
- pkGroupedData class
  - included in pkNLME library
  - Constructor function to read NONMEM data files into S objects
  - inherits all groupedData methods
  - specialized information stored with the object for later plotting and modeling (e.g., role of special variables like SS, II, …)

Analgesic data as pkGroupedData

```
> ## reading data from NONMEM file and creating object
> Analg <- pkGroupedData(DV ~ TIME | ID, "Analgesic.dat")
> Analg[1:10,]
PK Grouped Data: DV ~ TIME | ID
   ID EVID AMT    TIME SEX RACE AGE  WGT  HT SS II       DV
 1  1    1 400   9.250   1    1  61 72.5 175  0  0  0.00000
 2  1    0   0   9.750   1    1  61 72.5 175  0  0  7.51500
 3  1    0   0  10.300   1    1  61 72.5 175  0  0  7.07800
 4  1    0   0  11.250   1    1  61 72.5 175  0  0 12.15100
 5  1    0   0  12.233   1    1  61 72.5 175  0  0  2.23100
 6  1    0   0  13.250   1    1  61 72.5 175  0  0  1.99020
 7  1    0   0  15.250   1    1  61 72.5 175  0  0  0.54854
 8  1    1 400 728.630   1    1  61 72.5 175  1 24  0.00000
 9  1    0   0 752.330   1    1  61 72.5 175  0  0  0.18974
10  1    1 400 752.630   1    1  61 72.5 175  0  0  0.00000
```

Plots of Analgesic data





Fitting Population PK models with nlme

- Current capabilities: small number of functions implementing
  - single-dose first-order one-compartment: SSfol – self-starting model (vectorized form)
  - multiple-dose first-order one-compartment: quinModel – wrapper to recursive function written in C
  - multiple-dose bolus injection one-compartment: phenoModel – wrapper to recursive function written in C

- Once PK model is fitted, have access to all capabilities in nlme: e.g., diagnostic plots, model building and updating, confidence intervals, tests, predictions methods

pkNLME: extending PK modeling capabilities in nlme

- Objective: allow population PK modeling capabilities in nlme similar to NONMEM
- Allow use of history data format as in NONMEM, for modeling and internal data representation (pkGroupedData)
- Library of simple compartment models using recursive calculations consistent with event history format – wrappers to C functions
- Embedded in S environment, benefiting from existing syntax, libraries, and other capabilities in language

Model functions: oneComp, twoComp and threeComp

- Event-driven updating

- Similar input requirements
  - ID, EVID, TIME, AMT, RATE, SS, II, ADDL, DV, …

- Allowing three types of administration, specified via argument TYPE

- Allowing multiple routes of administrations in the same data

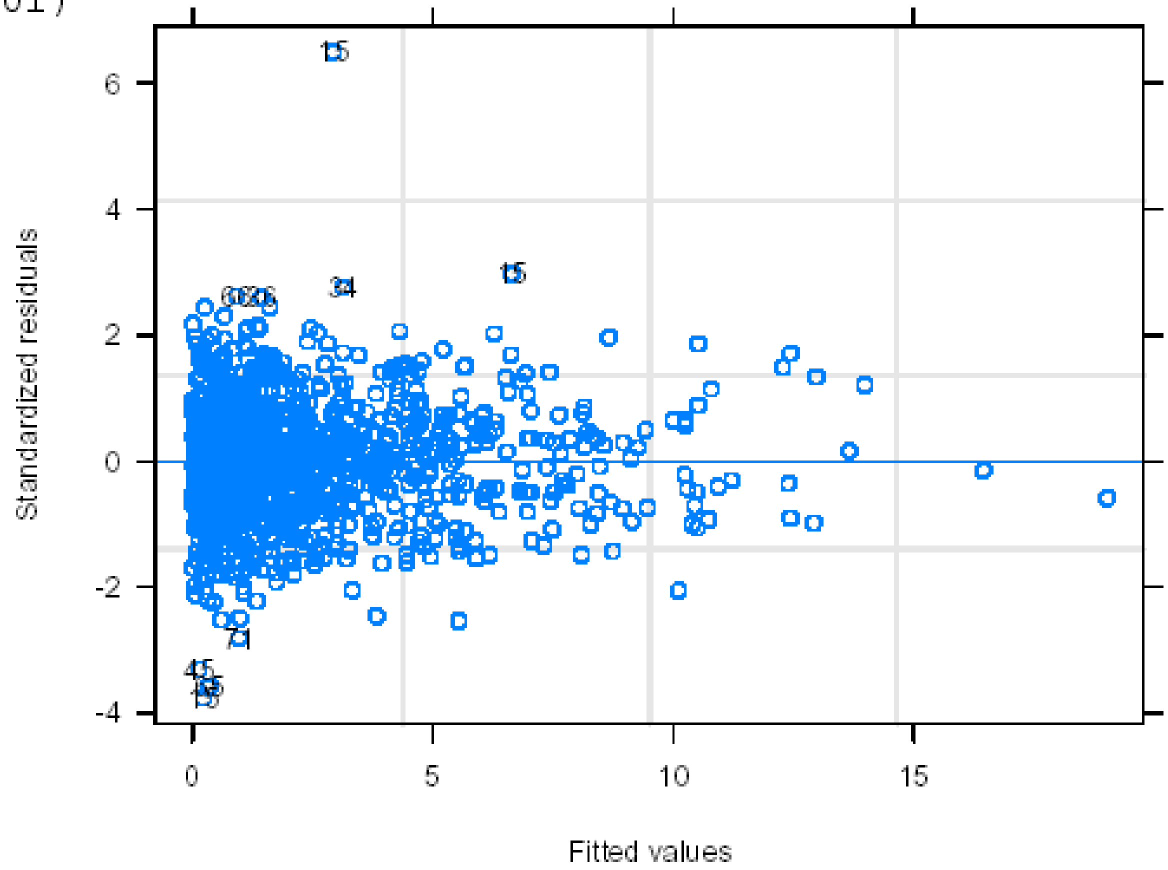
Modeling Analgesic data

- No built-in function available in NLME for two-compartment zero-rdero input model; can use twoComp2 function (version of twoComp with desired parameterization

```
➢> fm1Analg <- nlme(DV ~ twoComp2(lV, lCl, lV2, lQ, TIME = TIME, EVID = EVID,
+     AMT = AMT, RATE = AMT/2, SS = SS, II = II, ID = ID, TYPE = 2),
+     data=Analg, fixed = lCl + lV + lQ + lV2 ~ 1, random = pdDiag(lCl + lV ~ 1),
+     weights = varPower(fixed = 1), groups = ~ ID, start=c(2, 3, 2, 3),
+     na.action = na.include, naPattern = ~ EVID == 0)
> fm1Analg
. . .
  Log-likelihood: -1227.8
  Fixed: lCl + lV + lQ + lV2 ~ 1
    lCl      lV      lQ     lV2
 2.3477 3.0306 2.0432 3.0753
. . .
```

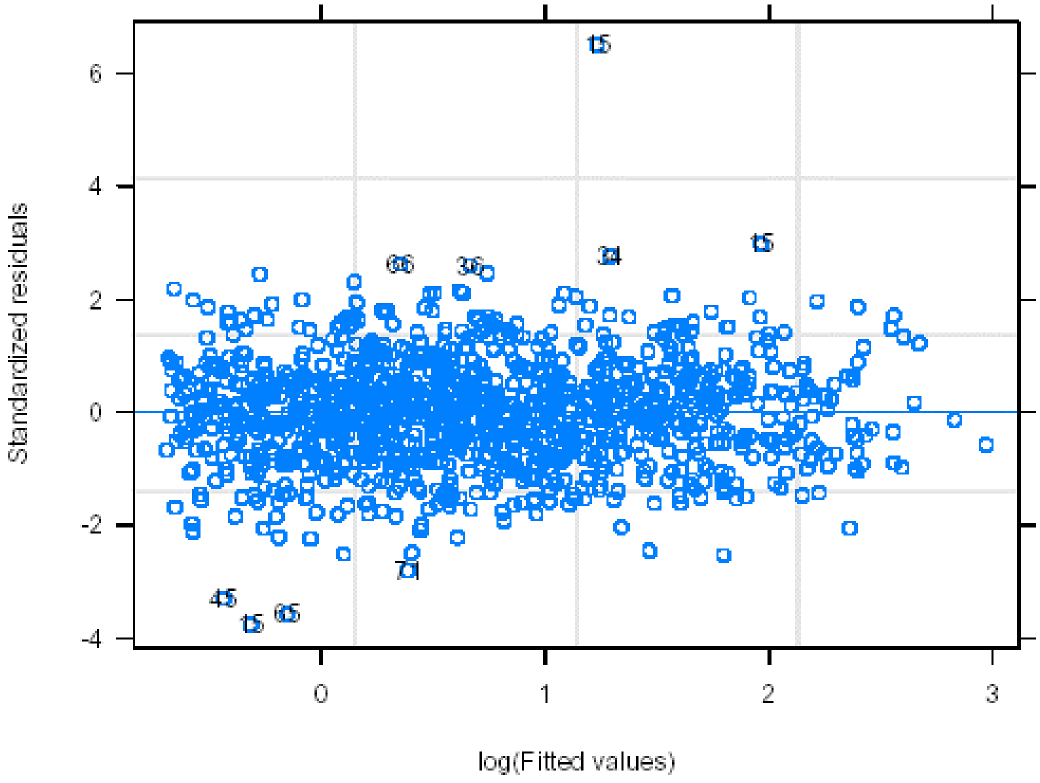
Assessing the quality of Analgesic fit

```
> plot(fm1Analg, id = 0.01)
```



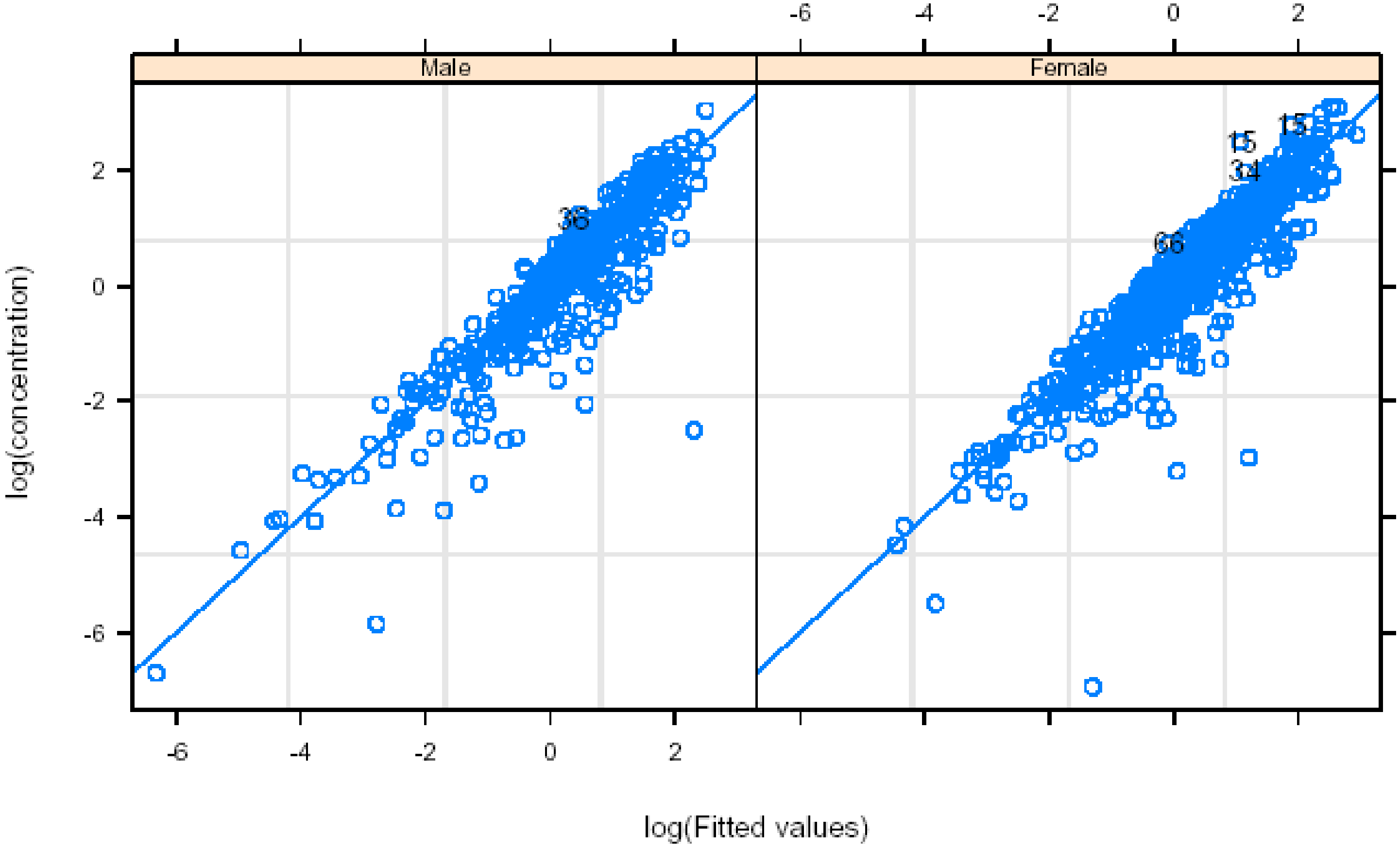
Assessing the quality of Analgesic fit (cont.)

```
> plot(fm1Analg, form = resid(., type = "p") ~ log(fitted(.) + 0.5), id = 0.01)
```



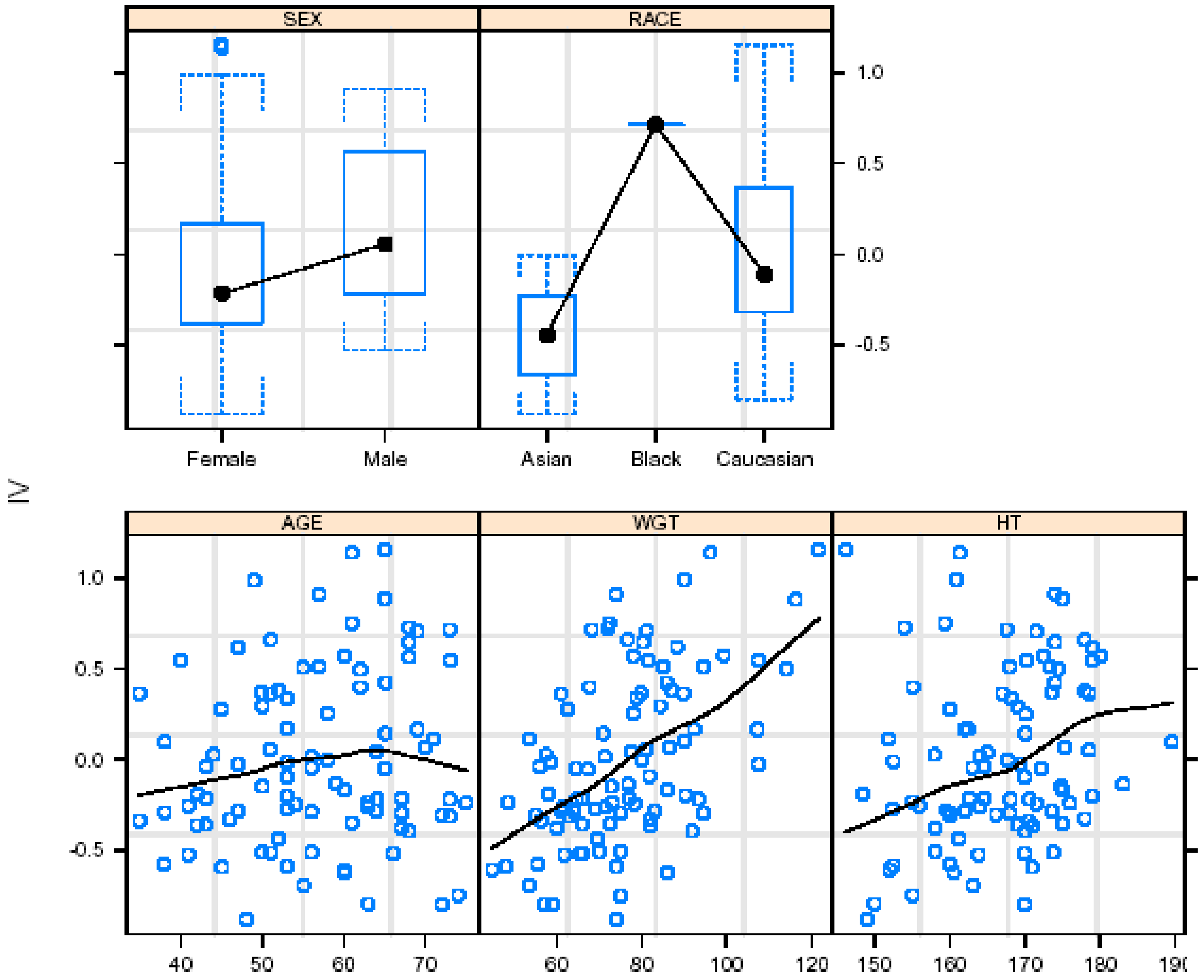
Assessing the quality of Analgesic fit (cont.)

```
> plot(fm1Analg, log(DV) ~ log(fitted(.)) | SEX, abline = c(0,1), id = 0.01,
+   xlab = "log(Fitted values)", ylab = "log(concentration)")
```



Incorporating covariates in Analgesic model

```
> plot(ranef(fm1Analg, aug = T), form = lV ~ AGE + WGT + HT + SEX + RACE)
```



Incorporating covariates in Analgesic model (cont.)

```
> fm2Analg <- update(fm1Analg, fixed = list(lCl + lQ + lV2 ~ 1, lV ~ I(WGT/75)),
+    start = c(fm1Analg[c(1,3,4,2)], 0))
> anova(fm1Analg, fm2Analg)
        Model df    AIC    BIC    logLik   Test  L.Ratio  p-value
fm1Analg   1  7  2469.6 2504.9  -1227.8
fm2Analg   2  8  2432.7 2473.0  -1208.4 1 vs 2   38.86   <.0001
```

Conclusions

- S provides an integrated environment for statistical modeling software development
- NLME library in S includes comprehensive set of tools for fitting, analyzing, and exploring mixed-effects models
- For NONMEM users, event history format is main difficulty in using nlme for PK/PD modeling
- pkNLME project is aimed at addressing these issues and making nlme a viable alternative to NONMEM within S programming environment
- New numerical methods in S can also be incorporated