Chapter 6

Repeated Measures Data
and Random Parameter Models

Part of the Iowa State University NSF/ILI project

Beyond Traditional Statistical Methods


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January 13, 2001
17h 21min
Chapter 6 Objectives

• Understand applications of growth curve models to describe the results of statistical studies in which repeated measures are made on a sample of units from some population or process.

• Explore different kinds of models for repeated measure data.
  ▶ Empirical
  ▶ Mechanistic (e.g., from systems of differential equations)

• Understand how to fit nonlinear regression models.

• Understand the different sources of variability in repeated measures data.

• Become familiar with methods for data analysis and inference for repeated measure data.
Plot of Laser Operating Current as a Function of Time

Percent Increase in Operating Current

Hours

0 1000 2000 3000 4000
Laser Test Data

- Measured percentage increase in operating current over time for GaAs lasers tested at 80°C.

- Fifteen (15) devices each measured every 250 hours up to 4000 hours of operation.

- For these device and the corresponding application, a $D_f = 10\%$ increase in current was the specified failure level.

- Engineers wanted to predict life of lasers operating at 10°C.
Constant-Rate Growth Model

- For some types of growth, rate will be approximately constant:

\[
\frac{dy(t)}{dt} = \beta_1
\]

- With \( y(0) = \beta_0 \), this simple differential equation has the solution

\[
y(t) = \beta_0 + \beta_1 t
\]

where \( \beta_0 \) is the intercept and \( \beta_1 \) is the slope (growth rate).

- This linear model is useful describe certain growth patterns.
Plasma Concentrations of Indomethicin Following Bolus Intravenous Injection

![Graph showing plasma concentrations of indomethicin over time.](image-url)
Plasma Concentrations of Indomethicin Following Bolus Intravenous Injection

• Blood plasma concentrations of indomethicin following bolus intravenous injection.

• Data from Kwan et al. (1976) “Kinetics of indomethicin absorption, elimination, and enterohepatic circulation in man.” Also, page 18 of Davidian and Giltinan (1995)

• Data collected on six human volunteers at 11 time points from 15 minutes to 8 hours.

• Pharmacokinetic researchers need to know the rate of passing to elimination and the time (or expected time) until a specified level of indomethicin is left.

• Interest centers on the identification of demographic and physiological characteristics explaining the variability in drug response—information to be used in choosing effective dosage regimes.
Plasma Concentrations of Indomethicin Following Intravenous Injection
Two-Compartment Model for Blood Plasma Concentrations of Indomethicine Following Bolus Intravenous Injection
Compartmental Model for
Indomethicin Absorption and Elimination

- A two-compartment model provides a useful model to describe the concentration in the blood over time.

- The following differential equations describe the two compartment model

\[
\frac{dA_1(t)}{dt} = -k_1 A_1(t), \quad \text{and} \quad \frac{dA_2(t)}{dt} = k_1 A_1(t) - k_2 A_2(t).
\]

- Then, using standard methods for solving systems of linear differential equations, the concentration in the blood at time \( t \) is

\[
A_2(t) = \theta_2 \exp(-k_2 t) - \theta_1 \exp(-k_1 t)
\]

\[
\theta_1 = A_1(0) k_1 / (k_1 - k_2)
\]

\[
\theta_2 = \theta_1 + A_2(0)
\]

Splus has the biexponential function for this model.
Biexponential Function

plot.function(biexp, 1:8, A1=20.96, A2=3.0, lrc1=-0.87, lrc2=.08)
Serum Concentrations of Theophylline Following Oral Administration

Time since drug administration (Hours)

Concentration (mg/L)
Serum Concentrations of Theophylline Following Oral Administration

• Data from Boeckmann et al. (1992). Theophylline is an anti-asthmatic agent.

• Data collected on twelve subjects. Serum concentrations were measured at 11 time points from 15 minutes to 24 hours.

• Dosage was varied in proportion to body weight.
Trellis Plot of Serum Concentrations of Theophylline Following Oral Administration

Time since drug administration (hr).

Theophylline concentration (mg/L)
Two-Compartment Model
for Theophylline Absorption and Elimination Following Oral Administration

\[ k_2 = \frac{V}{Cl} \]

Stomach          Blood
\[ A_1 \rightarrow k_1 \rightarrow A_2 \]

Elimination
Two-Compartment Model
for Theophylline Absorption and Elimination
Following Oral Administration

- The following two-compartment (gut and blood) model is used to describe the concentration in the blood as a function of time.

\[
\frac{dA_1(t)}{dt} = -k_1 A_1(t), \quad \text{and} \quad \frac{dA_2(t)}{dt} = k_1 A_1(t) - \frac{Cl}{V} A_2(t)
\]

where

- \( A_1(t) \) is the amount in the stomach at time \( t \).
- \( A_2(t) \) is the concentration in the blood at time \( t \).
- The rate \( k_1 \) has units 1/hour.
- Clearance \( Cl \) has units L/hr/kg.
- Volume of distribution \( V \) has units L/kg.
- The elimination rate \( k_2 = \frac{Cl}{V} \) has units 1/hour.
Two-Compartment Model for Theophylline Absorption and Elimination

- With initial conditions $A_1(0) = \text{Dose}$ and $A_2(0) = 0$, the concentration in the blood as a function of time is obtained by solving the system of differential equations to give:

$$A_2(t) = \frac{\text{Dose} \times k_1}{V(k_1 - Cl/V)} \left[ \exp \left( - \frac{Cl}{V} t \right) - \exp(-k_1 t) \right]$$

- The amount left in the stomach at time $t$ is

$$A_1(t) = \text{Dose} \times \exp(-k_1 t)$$

- The model fit to the blood concentration data was reparameterized as

$$A_2(t) = \frac{\text{Dose} \times \exp(\theta_1) \exp(\theta_2)}{\exp(\theta_3)[\exp(\theta_1) - \exp(\theta_2)]} \{\exp[-\exp(\theta_2)t] - \exp[-\exp(\theta_1)t]\}$$

where $\theta_1 = \log(k_1)$, $\theta_2 = \log(Cl/V)$, $\theta_3 = \log(Cl)$, are unrestricted in sign.

Splus has function `first.order.log` function for this model.
First Order Log Function

plot.function(first.order.log, time=1:25, Dose=8, lCl=-3.17, lka = -0.18, lke=-2.24)
Device-B Power Drop

Accelerated Degradation Test Results

at 150°C, 195°C, and 237°C

(Use conditions 80°C)
Device-B Power Drop
Accelerated Test Results

- RF amplifier IC device, used in a satellite communications system.
- System life was designed to be between 10 and 15 years.
- A six-month test at high temperature was to be used to predict life at 80°C junction temperature.
- The physics/chemistry of the failure mechanism was well-understood.
Simple One-Step Chemical Reaction

\[ \text{A}_1 \xrightarrow{k_1} \text{A}_2 \]
Device-B Power Drop
Simple One-Step Chemical Reaction
Leading to Failure

• $A_1(t)$ is the amount of harmful material available for reaction at time $t$

• $A_2(t)$ is proportional to the amount of failure-causing compounds at time $t$.

• Simple one-step chemical reaction:

\[ A_1 \xrightarrow{k_1} A_2 \]

• Power drop proportional to $A_2(t)$

• The rate equations for this reaction are

\[ \frac{dA_1}{dt} = -k_1 A_1 \quad \text{and} \quad \frac{dA_2}{dt} = k_1 A_1 \]
Device-B Power Drop
Simple One-Step Chemical Reaction
Leading to Failure (contd.)

• Solution to system of differential equations:

\[ A_1(t) = A_1(0) \exp(-k_1 t) \]
\[ A_2(t) = A_2(0) + A_1(0) [1 - \exp(-k_1 t)] \]

where \( A_1(0) \) and \( A_2(0) \) are initial conditions.

• If \( A_2(0) = 0 \), then \( \lim_{t \to \infty} A_2(t) = A_1(0) \) and the solution for \( A_2(t) \) (the function of primary interest) can be reexpressed as

\[ A_2(t) = A_1(0) [1 - \exp(-k_1 t)] \]

A simple 1-step diffusion process has the same solution.
The Arrhenius model describing the effect that temperature has on the rate of a simple one-step chemical reaction is

\[ R(\text{temp}) = \gamma_0 \exp\left(\frac{-E_a}{k_B \times (\text{temp} + 273.16)}\right) \]

where temp is temperature in °C and \( k_B = 8.6 \times 10^{-5} \) is Boltzmann’s constant in units of electron volts per °C.

The pre-exponential factor \( \gamma_0 \) and the reaction activation energy \( E_a \) are characteristics of the product or material.

The Acceleration Factor between temp and \( \text{temp}_U \) is

\[ A\mathcal{F}(\text{temp}) = A\mathcal{F}(\text{temp}, \text{temp}_U, E_a) = \frac{R(\text{temp})}{R(\text{temp}_U)} \]

When \( \text{temp} > \text{temp}_U \), \( A\mathcal{F}(\text{temp}, \text{temp}_U, E_a) > 1 \).
Simple Reversible Chemical Reaction

\[ \text{Simple Reversible Chemical Reaction} \]
Simple Reversible Chemical Reaction

- The rate equations for this reaction are
  \[
  \frac{dA_1}{dt} = -k_1 A_1 + k_2 A_2 \quad \text{and} \quad \frac{dA_2}{dt} = k_1 A_1 - k_2 A_2
  \]

- In this model the failure causing reaction is reversible. With
  \( A_2(0) = 0 \), the solution of the system of differential equations for this model gives, for \( A_2 \)
  \[
  A_2(t) = A_1(0) \frac{k_1}{k_1 + k_2} \{ 1 - \exp[-(k_1 + k_2)t] \}.
  \]
Orange Tree Circumference Growth

- Data collected by measuring trunk circumference on five different trees grown in Riverside, California, between 1969 and 1973.

- Measurements taken at 118, 484, 664, 1004, 1231, 1372, and 1582 days.

- Researchers are interested in characterizing the tree-to-tree variability and seeking explanations for why some trees grow faster than others.

- Data from Draper and Smith (1981), page 524.
Orange Tree Circumference Growth

![Graph showing growth in trunk circumference over time since December 31, 1968]

- X-axis: Time since December 31, 1968 (days)
- Y-axis: Trunk circumference (mm)
- Multiple lines representing different trees or conditions, each line showing the growth pattern over time.
Trellis Plot of Orange Tree Circumference Growth

Time since December 31, 1968 (days).

Trunk circumference (mm)
Logistic (Autocatalytic) Model

• For some types of growth, growth rate will increase to a point and then decline.

• The following differential equation has rate depending on has a basic rate, \( \kappa \), current size \( f \), and a limiting size \( \alpha \).

\[
\frac{dy(t)}{dt} = Asym \times scale \times y(t) \times [Asym - y(t)].
\]

• This differential equation has the general solution

\[
y(t) = Asym / \{1 + \exp[-(t - T50)/scale] \}
\]

where \( Asym \) is the asymptote, \( T50 \) is the time at which 50% growth has been achieved, and \( scale \) is a scale parameter describing the steepness of the growth curve.

• This S-shaped “logistic” curve is a useful curve to describe certain growth patterns.

Splus has the logistic function for this model.
Orange Tree Circumference Growth Data and Fitted Logistic Function
Logistic Function

plot.function(logistic,1:1500,Asym=207,T50=861,scal=379)

Orange Tree Circumference Growth
Fatigue Crack Size Observations for Alloy-A
(Bogdanoff & Kozin 1985)

Bogdonoff-Kozin Fatigue Crack Growth Data

![Graph showing fatigue crack growth data for Alloy-A](image-url)
Notched “Compact” Fatigue Test Specimen
Alloy-A Fatigue Crack-Size Data


• Suppose investigators wanted to:
  ▶ Estimate materials parameters related to crack growth.
  ▶ Estimate time (measured in number of cycles) at which 50% of the cracks would reach 1.6 inches.
  ▶ Assess adequacy of the Paris model to describe crack growth rate.
Fatigue Crack Size Observations for Alloy-A
(Bogdanoff & Kozin 1985)
Fatigue Crack Size Observations for Alloy-A and Nonlinear Least Squares Paris Law Fit

Bogdonoff-Kozin Fatigue Crack Growth Data
Degradation Data in Reliability Analysis

- Sometimes possible to measure degradation directly over time
  - Continuously.
  - At specific points in time.

- Degradation is natural response for some tests.

- Degradation data can provide considerably more reliability information than censored failure-time data (especially with few or no failures).

- Direct observation of the degradation process allows direct modeling of the failure-causing mechanism.
Paris Crack Growth Model

- The Paris model is

\[ \frac{d a(t)}{d t} = C \times [\Delta K(a)]^m \]

is a commonly used empirical model to describe the growth of fatigue cracks over some range of size.

- \( C > 0 \) and \( m > 0 \) are materials properties

- \( K(a) \) is the stress intensity function. Form of \( K(a) \) depends on applied stress, part dimensions, and geometry.

- To model a two-dimensional edge-crack in a plate with a crack that is small relative to the width of the plate (say less than 3%), \( K(a) = \text{Stress} \sqrt{\pi a} \) and the solution to the resulting differential equation is

\[
a(t) = \begin{cases} 
\left\{ a(0) \right\}^{1-m/2} + (1-m/2) \times C \times \left( \text{Stress} \sqrt{\pi} \right)^m \times t \frac{2}{2-m}, & m \neq 2 \\
 a(0) \times \exp \left[ C \times \left( \text{Stress} \sqrt{\pi} \right)^2 \times t \right], & m = 2
\end{cases}
\]
Paris Model with no Variability

Cycles

Crack Size (mm)

0 20000 40000 60000 80000

0.0 0.2 0.4 0.6 0.8

6-40
Paris Model with Unit-to-Unit Variability in Initial Crack Size but with Fixed Materials Parameters and Constant Stress
Models for Variation in Degradation and Failure Time

If all manufactured units were identical, operated at exactly the same time, under exactly the same conditions, and in exactly the same environment, and if every unit failed as it reached a particular critical level of degradation, then all units would fail at exactly the same time.

- Need to identify and model important sources of variability in the degradation process.

- Quantities that might be modeled as random include:
  - Initial conditions (flaw size, amount of material).
  - Materials parameters (related to degradation rate).
  - Level of degradation at which unit will fail.

- Stochastic process variability (e.g., stress of other environmental variables changing over time).
Paris Model with Unit-to-Unit Variability in the Initial Crack Size and Materials Parameters but Constant Stress
Paris Model with Unit-to-Unit Variability in the Initial Crack Size and Materials Parameters and Stochastic Stress

![Graph showing crack size over cycles with variability]

Crack Size (mm)

Cycles

0 20000 40000 60000 80000

0.0 0.2 0.4 0.6 0.8

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General Response Path Model

- $D_{ij} = D(t_{ij}, \beta_{1i}, \ldots, \beta_{ki})$ is the degradation path for unit $i$ at time $t$ (measured in hours, cycles, etc.).

- Observed sample path of unit $i$ at time $t_j$ is

  $$y_{ij} = D_{ij} + \epsilon_{ij}, \quad i = 1, \ldots, n, \quad j = 1, \ldots, m_i$$

- Residuals $\epsilon_{ij} \sim \text{NOR}(0, \sigma_e)$ describe a combination of measurement error and model error.

- For unit $i$, $\beta_{1i}, \ldots, \beta_{ki}$ is a vector of $k$ unknown parameters.

- Some of the $\beta_{1i}, \ldots, \beta_{ki}$ are random from unit to unit. Model appropriate function of $\beta_{1i}, \ldots, \beta_{ki}$ with multivariate normal distribution (MVN) with parameters $\mu_\beta$ and $\Sigma_\beta$. 
Estimation of Degradation Model Parameters

- The likelihood for the random-parameter path model is $L(\mu_\beta, \Sigma_\beta, \sigma_\epsilon|\text{DATA})$

$$= \prod_{i=1}^{n} \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \left[ \prod_{j=1}^{m_i} \frac{1}{\sigma_\epsilon} \phi_{\text{nor}}(\zeta_{ij}) \right] f_\beta(\beta_{1i}, \ldots, \beta_{ki}; \mu_\beta, \Sigma_\beta) d\beta_{1i}, \ldots, d\beta_{ki}$$

where $\zeta_{ij} = [y_{ij} - \mathcal{D}(t_{ij}, \beta_{1i}, \ldots, \beta_{ki})]/\sigma_\epsilon$ and $f_\beta(\beta_{1i}, \ldots, \beta_{ki}; \mu_\beta, \Sigma_\beta)$ is the multivariate normal distribution density function.

- Each evaluation of $L(\mu_\beta, \Sigma_\beta, \sigma_\epsilon|\text{DATA})$ will, in general, require numerical approximation of $n$ integrals of dimension $k$.

- Maximization of $L(\mu_\beta, \Sigma_\beta, \sigma_\epsilon|\text{DATA})$ computationally difficult.
Alloy-A Fatigue Crack Size Observations and Fitted Paris-Rule Model
Estimates of Fatigue Data Model Parameters for Alloy-A

• Splus gives the following approximate ML estimates.

\[ \hat{\mu}_\beta = \begin{pmatrix} 5.17 \\ 3.73 \end{pmatrix}, \quad \hat{\Sigma}_\beta = \begin{pmatrix} .251 & -.194 \\ -.194 & .519 \end{pmatrix} \]

and \( \hat{\sigma}_\epsilon = .0034 \).

• Here \( \beta_1 = C, \beta_2 = m \).
Estimates $\hat{\beta}_1^i$ Versus $\hat{\beta}_2^i$, $i = 1, \ldots, 21$ and Contours for the Fitted Bivariate Normal Distribution
Models Relating Degradation and Failure

- “Soft failures” are defined to occur at a specified degradation level.

- In some products there is a gradual loss of performance (e.g., decreasing light output from a fluorescent light bulb).

- Use fixed $D_f$ to denote the critical level defining failure for a degradation path.
Alloy-A Fatigue Crack Size Observations and Fitted Paris-Rule Model
Evaluation of $F(t)$
Distribution of Time to First Crossing

- **Direct evaluation of $F(t)$**: Closed forms available for simple problems (e.g., a single random variable and other special cases).

- **Numerical integration**: Useful for a small number of random variables (e.g., 2 or 3).

- **FORM (first order) approximation**: Rapid computation, but uncertain approximation. Used frequently in engineering problems with large number of random variables.

- **Monte Carlo simulation**: General method. Needs much computer time to evaluate small probabilities. Can use importance sampling.

Estimate failure probabilities by evaluating at ML estimates.
Evaluation of $F(t)$ by Numerical Integration

- The failure (crossing probability) can be expressed as

$$
Pr(T \leq t) = F(t) = F(t; \theta_\beta) = \Pr[D(t, \beta_1, \ldots, \beta_k) > D_f].
$$

- If $(\beta_1, \beta_2)$ follows a bivariate normal distribution with parameters $\mu_{\beta_1}, \mu_{\beta_2} \sigma_{\beta_1}^2, \sigma_{\beta_2}^2, \rho_{\beta_1, \beta_2}$, then $P(T \leq t)$

$$
= \int_{-\infty}^{\infty} \Phi_{\text{nor}} \left[ - \frac{g(D_f, t, \beta_1) - \mu_{\beta_2|\beta_1}}{\sigma_{\beta_2|\beta_1}} \right] \frac{1}{\sigma_{\beta_1}} \phi_{\text{nor}} \left( \frac{\beta_1 - \mu_{\beta_1}}{\sigma_{\beta_1}} \right) d\beta_1
$$

where $g(D_f, t, \beta_1)$ is the value of $\beta_2$ for given $\beta_1$, that gives $D(t) = D_f$.

- Method generalizes to multivariate normal, but requires correspondingly higher-order integration.
Bootstrap Estimates of $F(t) = \Pr(T \leq t)$
Degradation Estimate of $F(t)$ with Pointwise Two-Sided 90% and 80% Bootstrap Bias-Corrected Percentile Confidence Intervals, Based on the Crack-Size Data Censored at $t_c = .12$. The Nonparametric Estimate of $F(t)$ Indicated by Dots
> Indometh.lis <- nlsList(data=Indometh, 
+  conc ~ biexp(time, A1, A2,lrc1,lrc2), cluster= ~ Subject)

<table>
<thead>
<tr>
<th>A1</th>
<th>A2</th>
<th>lrc1</th>
<th>lrc2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1915405</td>
<td>2.029278</td>
<td>-1.78783</td>
<td>0.5793801</td>
</tr>
<tr>
<td>0.4986587</td>
<td>2.827599</td>
<td>-1.63598</td>
<td>0.8010547</td>
</tr>
<tr>
<td>1.675421</td>
<td>5.46662</td>
<td>-0.4123908</td>
<td>1.749457</td>
</tr>
<tr>
<td>0.2543484</td>
<td>2.19826</td>
<td>-1.603379</td>
<td>0.242206</td>
</tr>
<tr>
<td>0.2915201</td>
<td>3.566077</td>
<td>-1.506703</td>
<td>1.040773</td>
</tr>
<tr>
<td>0.9683424</td>
<td>3.002198</td>
<td>-0.8732972</td>
<td>1.088059</td>
</tr>
</tbody>
</table>

> Indometh.nlme <- nlme(Indometh.lis)
> plot(Indometh.nlme)
Fitted Values of Plasma Concentrations of Indomethicin Following Intravenous Injection
Plasma Concentrations of Indomethacin
Estimates of Random Parameters

A1

A2

lrc1

lrc2
```
> anova(Indometh.nlme)

           Value Std.Error  z ratio
   A1     0.6357129 0.1662857 3.823016
   A2     2.8531937 0.3378634 8.444815
  lrc1   -1.2759586 0.2095212 -6.089878
  lrc2    0.8755098 0.1214845  7.206762

> summary(Indometh.nlme)

Call:
  Model: conc ~ biexp(time, A1, A2, lrc1, lrc2)
  Fixed: list(A1 ~ ., A2 ~ ., lrc1 ~ ., lrc2 ~ .)
  Random: list(A1 ~ ., A2 ~ ., lrc1 ~ ., lrc2 ~ .)
Cluster: ~ Subject
  Data: Indometh

Estimation Method: ML
Convergence at iteration: 10
Approximate Loglikelihood: 64.00883
AIC:  -98.01766
BIC:  -65.17284
```
Variance/Covariance Components Estimate(s):
  Structure: matrixlog
  Standard Deviation(s) of Random Effect(s)
    A1     A2     lrc1    lrc2
    0.3871147 0.7758602 0.482693  0.2686875
  Correlation of Random Effects
    A1     A2     lrc1
    A2  0.4592938
    lrc1 0.9481822 0.1532631
    lrc2 0.6822219 0.9628043 0.4145663

  Cluster Residual Variance: 0.004846928

Fixed Effects Estimate(s):
  Value  Approx. Std. Error z ratio(C)
    A1    0.6357129 0.1662857  3.823016
    A2    2.8531937 0.3378634  8.444815
   lrc1  -1.2759586 0.2095212 -6.089878
   lrc2    0.8755098 0.1214845  7.206762
Conditional Correlation(s) of Fixed Effects Estimates

A1    A2    lrc1
A2  0.4113891
lrc1 0.9124454  0.1079738
lrc2 0.6766042  0.9075225  0.3778523

Random Effects (Conditional Modes):

<table>
<thead>
<tr>
<th></th>
<th>A1</th>
<th>A2</th>
<th>lrc1</th>
<th>lrc2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.45701638</td>
<td>-0.83383053</td>
<td>-0.44839015</td>
<td>-0.33416642</td>
</tr>
<tr>
<td>2</td>
<td>-0.06417292</td>
<td>-0.01969095</td>
<td>-0.08463536</td>
<td>-0.01916071</td>
</tr>
<tr>
<td>3</td>
<td>0.66019886</td>
<td>1.14263995</td>
<td>0.66151125</td>
<td>0.46508815</td>
</tr>
<tr>
<td>4</td>
<td>0.12355803</td>
<td>-0.93905219</td>
<td>0.38035935</td>
<td>-0.24158791</td>
</tr>
<tr>
<td>5</td>
<td>-0.41411192</td>
<td>0.54533293</td>
<td>-0.69578056</td>
<td>0.06801642</td>
</tr>
<tr>
<td>6</td>
<td>0.15154433</td>
<td>0.10460080</td>
<td>0.18693548</td>
<td>0.06181046</td>
</tr>
</tbody>
</table>

Standardized Population-Average Residuals:

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<th>Min</th>
<th>Q1</th>
<th>Med</th>
<th>Q3</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3.535373</td>
<td>-0.4377011</td>
<td>0.002928057</td>
<td>0.4082834</td>
<td>3.651327</td>
</tr>
</tbody>
</table>

Number of Observations: 66
Number of Clusters: 6
> predict(Indometh.nlme, data=Indometh, cluster= ~ Subject)

    cluster  fit.cluster  fit.population
     1       1         1.48507448        2.15868605
     2       1         1.01869476        1.41221653
     3       1         0.71290557        0.98721718
     4       1         0.51172529        0.73967401
     5       1         0.37871768        0.59048273
     6       1         0.19006862        0.38720959
     7       1         0.11632430        0.27726326
     8       1         0.08966846        0.20830885
     9       1         0.07365166        0.15743964
    10       1         0.06137793        0.11907827
    11       1         0.04292379        0.06813162
    12       2         2.10886906        2.15868605
    13       2         1.37579502        1.41221653

  ...
Fitted Values of Serum Concentrations of Theophylline Following Oral Administration
Fitted Values of Orange Tree Circumference Growth
Trellis Plot of the Results of an Experiment to Compare Two Genotypes of Soybeans

Leaf weight/plant (g) vs. Days after planting for three years: 1988, 1989, and 1990.
Summary

- Repeated measure data occur in many different areas of application from biological to engineering.

- For many purposes, it is better to have a mechanistic (e.g., one derived from kinetics) but empirical models can also be useful.

- Modeling the unit-to-unit variability in model parameters is useful for answering many important questions about variability in the population or process being studied.

- Modern software (e.g., the Splus function \texttt{nlme}) make it easy to fit nonlinear regression models with random parameters to reflect unit-to-unit variability.

- It is also possible to fit models with autocorrelated residual terms.