

**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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17h 5min

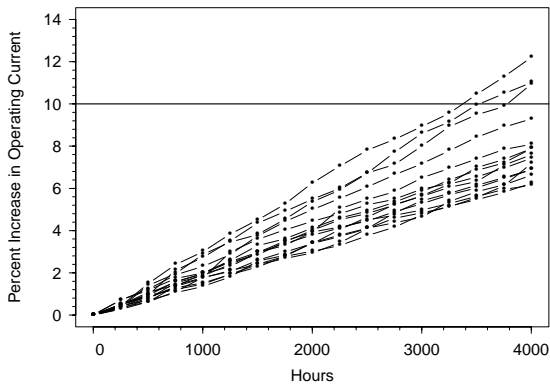
6-1

**Repeated Measures Data and Random Parameter Models**  
**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.

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**Plot of Laser Operating Current as a Function of Time**



6-3

**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.

6-4

**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

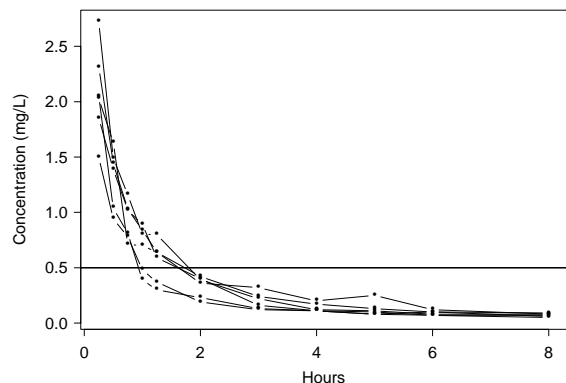
$$y(t) = \beta_0 + \beta_1 t$$

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

- This linear model is useful describe certain growth patterns.

6-5

**Plasma Concentrations of Indomethicin Following Bolus Intravenous Injection**



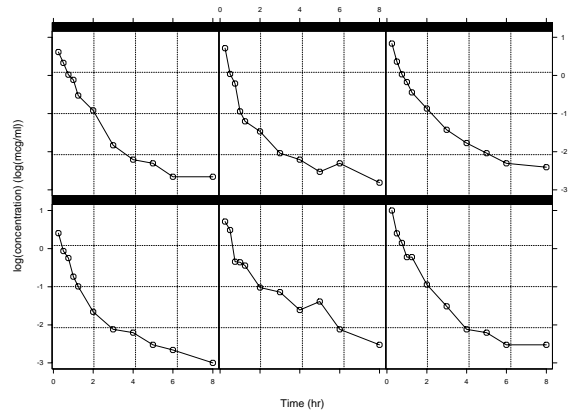
6-6

### Plasma Concentrations of Indomethacin Following Bolus Intravenous Injection

- Blood plasma concentrations of indomethacin following bolus intravenous injection.
- Data from Kwan et al. (1976) "Kinetics of indomethacin 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 indomethacin 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.

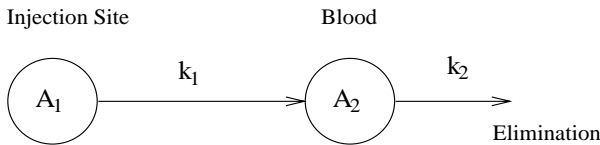
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### Plasma Concentrations of Indomethacin Following Intravenous Injection



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### Two-Compartment Model for Blood Plasma Concentrations of Indomethacin Following Bolus Intravenous Injection



6-9

### Compartmental Model for Indomethacin Absorption and Elimination

- A two-compartment model provides 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

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

$$\theta_1 = A_1(0)k_1 / (k_1 - k_2)$$

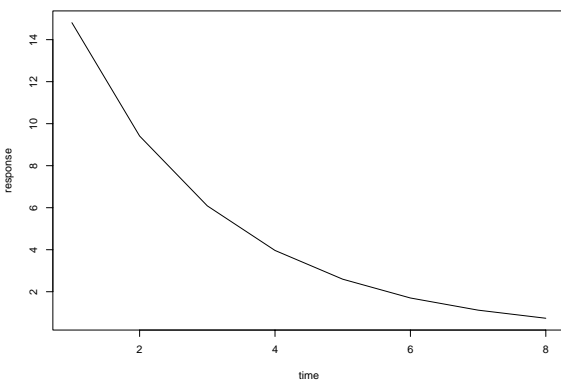
$$\theta_2 = \theta_1 + A_2(0)$$

Splus has the biexponential function for this model.

6-10

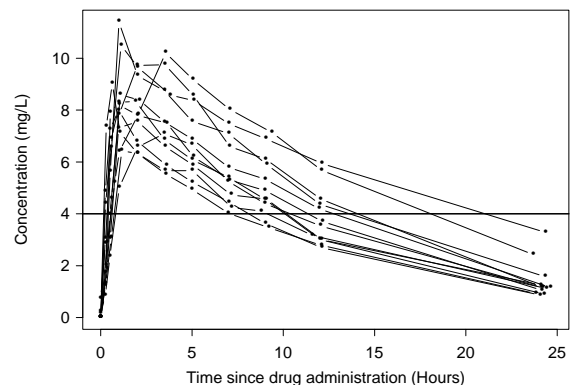
### Biexponential Function

```
plot.function(biexp,1:8,A1=20.96, A2=3.0, lrc1=-0.87, lrc2=.08)
```



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### Serum Concentrations of Theophylline Following Oral Administration



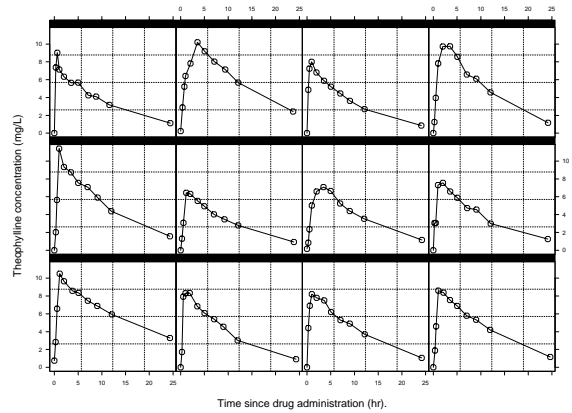
6-12

### 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.

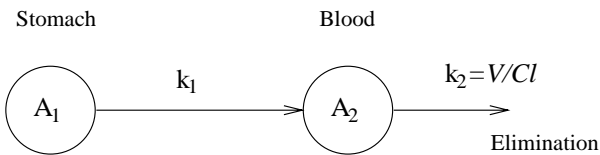
6-13

### Trellis Plot of Serum Concentrations of Theophylline Following Oral Administration



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



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### 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  $k_2 = Cl/V$  has units 1/hour.

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### 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

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

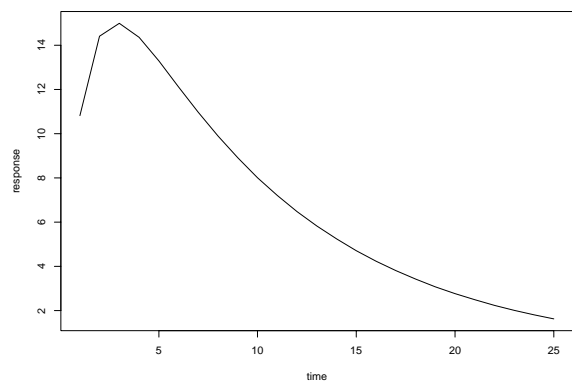
where  $\theta_1 = \log(k_1)$ ,  $\theta_2 = \log(Cl/V)$ ,  $\theta_3 = \log(Cl)$ , are unrestricted in sign.

Spplus has function `first.order.log` function for this model.

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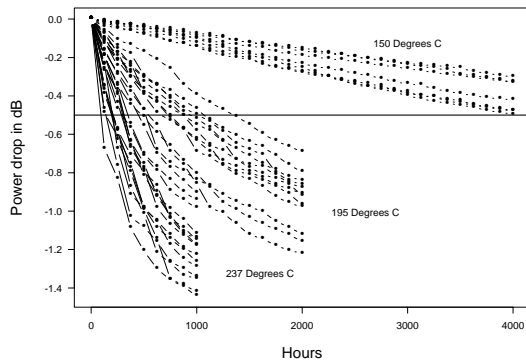
### First Order Log Function

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



6-18

**Device-B Power Drop  
Accelerated Degradation Test Results  
at 150°C, 195°C, and 237°C  
(Use conditions 80°C)**



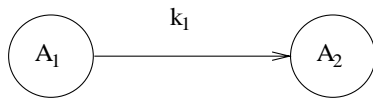
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**Device-B Power Drop  
Accelerated Test Results**

- 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.

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**Simple One-Step Chemical Reaction**



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**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

$$\frac{dA_1}{dt} = -k_1 A_1 \quad \text{and} \quad \frac{dA_2}{dt} = k_1 A_1$$

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**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  $\lim_{t \rightarrow \infty} A_2(t) = A_1(0)$  and the solution for  $A_2(t)$  (the function of primary interest) can be re-expressed as

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

A simple 1-step diffusion process has the same solution.

6-23

**Acceleration of Degradation**

- The Arrhenius model describing the effect that temperature has on the rate of a simple one-step chemical reaction is

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

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

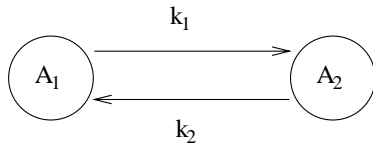
- The pre-exponential factor  $\gamma_0$  and the reaction activation energy  $E_a$  are characteristics of the product or material.
- The Acceleration Factor between  $\text{temp}$  and  $\text{temp}_U$  is

$$\mathcal{AF}(\text{temp}) = \mathcal{AF}(\text{temp}, \text{temp}_U, E_a) = \frac{\mathcal{R}(\text{temp})}{\mathcal{R}(\text{temp}_U)}$$

When  $\text{temp} > \text{temp}_U$ ,  $\mathcal{AF}(\text{temp}, \text{temp}_U, E_a) > 1$ .

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### Simple Reversible Chemical Reaction



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### 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  $A_2$

$$A_2(t) = A_1(0) \frac{k_1}{k_1 + k_2} \{1 - \exp[-(k_1 + k_2)t]\}.$$

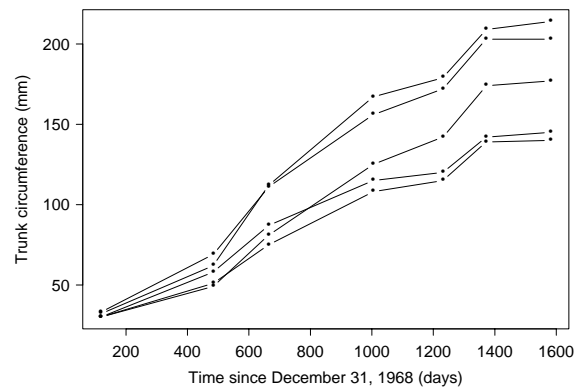
6-26

### 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.

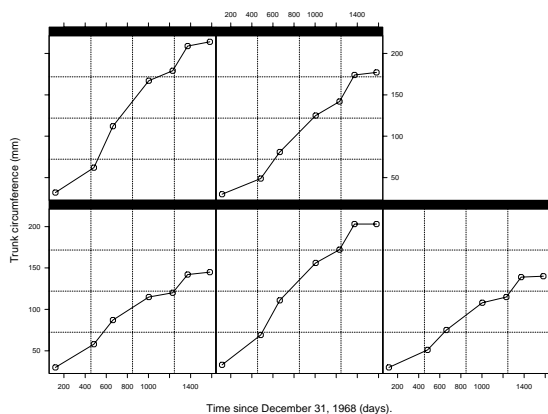
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### Orange Tree Circumference Growth



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### Trellis Plot of Orange Tree Circumference Growth



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### 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 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

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

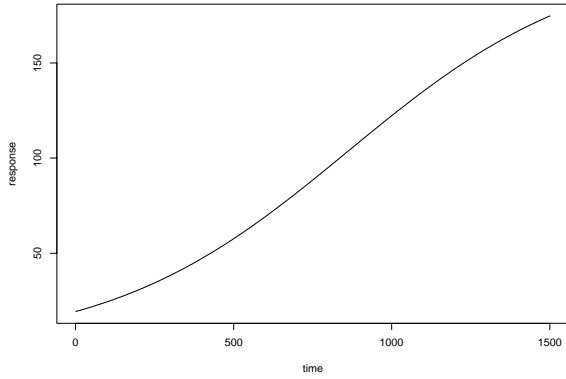
where  $Asym$  is the asymptote,  $T50$  is the time at which 50% growth has been achieved, and  $scale$  is a scale parameter describing the steepness of the growth curve.

- This S-shaped "logistic" curve is a useful curve to describe certain growth patterns.

Plus has the logistic function for this model.

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### Orange Tree Circumference Growth Data and Fitted Logistic Function

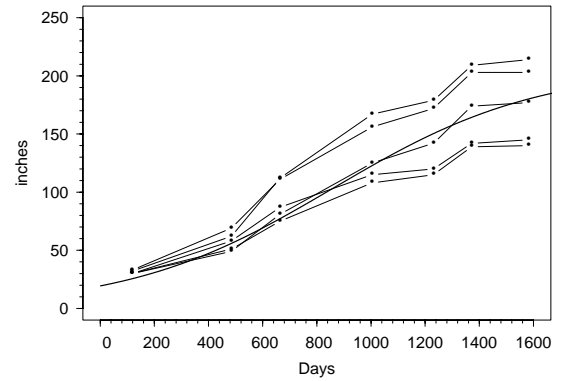


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### Logistic Function

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

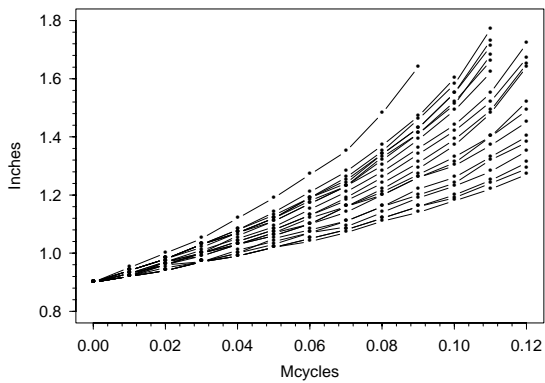
### Orange Tree Circumference Growth



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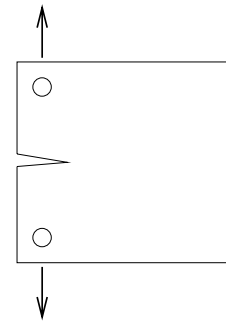
### Fatigue Crack Size Observations for Alloy-A (Bogdanoff & Kozin 1985)

#### Bogdanoff-Kozin Fatigue Crack Growth Data



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### Notched "Compact" Fatigue Test Specimen



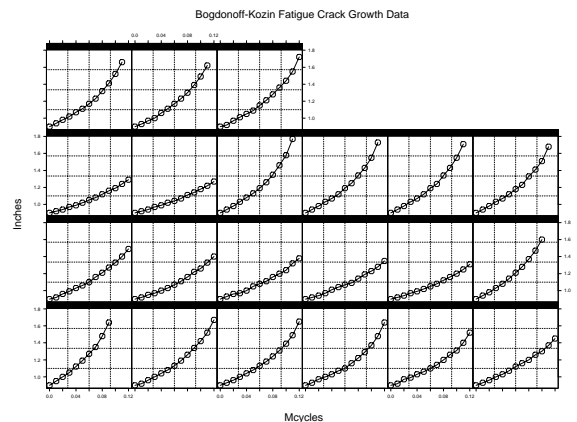
6-34

### Alloy-A Fatigue Crack-Size Data

- Data from Hudak, Saxena, Bucci, and Malcolm (1978) Bogdanoff and Kozin (1985, page 242), and Lu and Meeker (1993).
- 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.

6-35

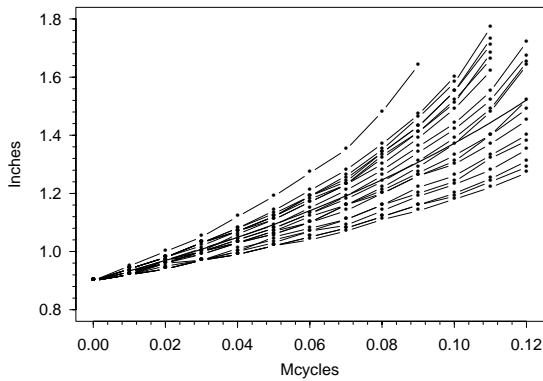
### Fatigue Crack Size Observations for Alloy-A (Bogdanoff & Kozin 1985)



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**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

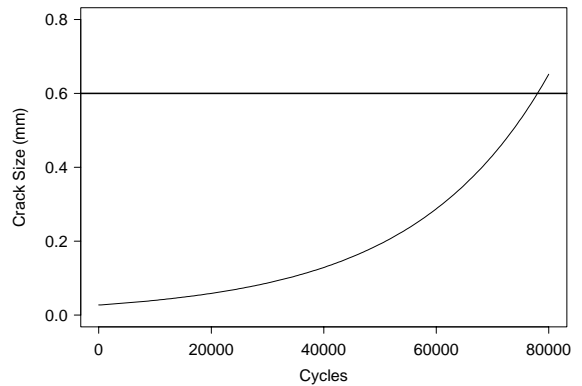
$$\frac{da(t)}{dt} = C \times [\Delta K(a)]^m$$

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

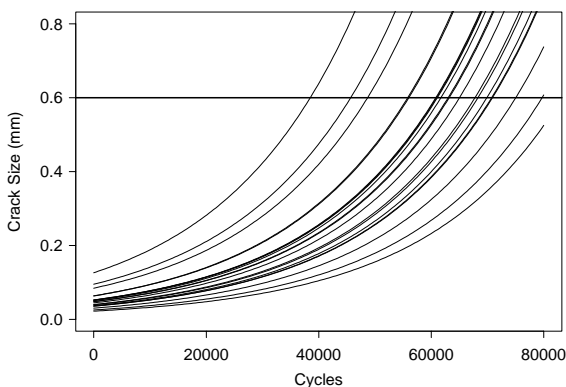
- $C > 0$  and  $m > 0$  are materials properties
- $K(a)$  is the stress intensity function. Form of  $K(a)$  depends on applied stress, part dimensions, and geometry.
- To model a two-dimensional edge-crack in a plate with a crack that is small relative to the width of the plate (say less than 3%),  $K(a) = \text{Stress}\sqrt{\pi a}$  and the solution to the resulting differential equation is

$$a(t) = \begin{cases} \left[ \{a(0)\}^{1-m/2} + (1-m/2) \times C \times (\text{Stress}\sqrt{\pi})^m \times t \right]^{\frac{2}{2-m}}, & m \neq 2 \\ a(0) \times \exp [C \times (\text{Stress}\sqrt{\pi})^2 \times t], & m = 2 \end{cases}$$

**Paris Model with no Variability**



**Paris Model with Unit-to-Unit Variability in Initial Crack Size but with Fixed Materials Parameters and Constant Stress**

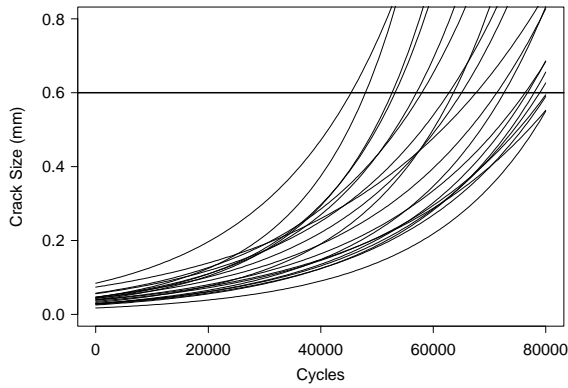


**Models for Variation in Degradation and Failure Time**

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.

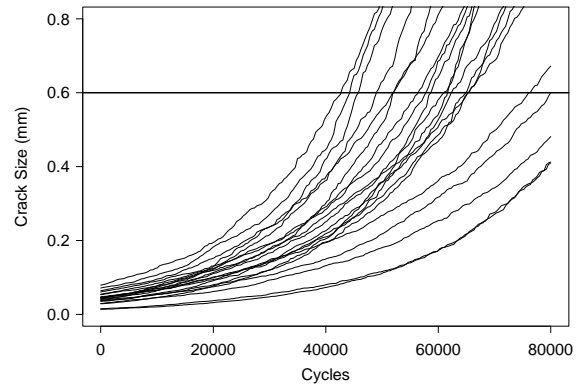
- Need to identify and model important sources of variability in the degradation process.
- Quantities that might be modeled as random include:
  - ▶ Initial conditions (flaw size, amount of material).
  - ▶ Materials parameters (related to degradation rate).
  - ▶ Level of degradation at which unit 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**



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**Paris Model with Unit-to-Unit Variability in the Initial Crack Size and Materials Parameters and Stochastic Stress**



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**General Response Path Model**

- $\mathcal{D}_{ij} = \mathcal{D}(t_{ij}, \beta_{1i}, \dots, \beta_{ki})$  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

$$y_{ij} = \mathcal{D}_{ij} + \epsilon_{ij}, \quad i = 1, \dots, n, \quad j = 1, \dots, m_i$$

- Residuals  $\epsilon_{ij} \sim \text{NOR}(0, \sigma_\epsilon)$  describe a combination of measurement error and model error.
- For unit  $i$ ,  $\beta_{1i}, \dots, \beta_{ki}$  is a vector of  $k$  unknown parameters.
- Some of the  $\beta_{1i}, \dots, \beta_{ki}$  are random from unit to unit. Model appropriate function of  $\beta_{1i}, \dots, \beta_{ki}$  with multivariate normal distribution (MVN) with parameters  $\mu_\beta$  and  $\Sigma_\beta$ .

6-45

**Estimation of Degradation Model Parameters**

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

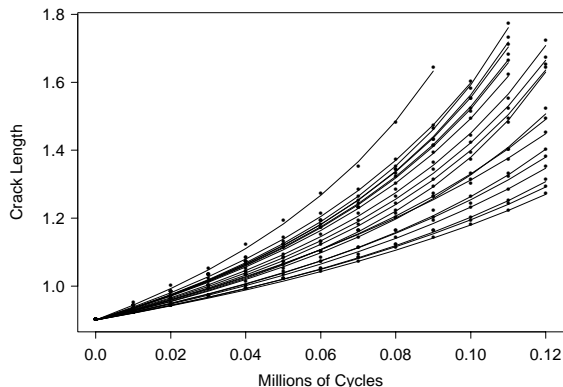
$$= \prod_{i=1}^n \int_{-\infty}^{\infty} \dots \int_{-\infty}^{\infty} \left[ \prod_{j=1}^{m_i} \frac{1}{\sigma_\epsilon} \phi_{\text{NOR}}(\zeta_{ij}) \right] f_\beta(\beta_{1i}, \dots, \beta_{ki}; \mu_\beta, \Sigma_\beta) d\beta_{1i}, \dots, d\beta_{ki}$$

where  $\zeta_{ij} = [y_{ij} - \mathcal{D}(t_{ij}, \beta_{1i}, \dots, \beta_{ki})] / \sigma_\epsilon$  and  $f_\beta(\beta_{1i}, \dots, \beta_{ki}; \mu_\beta, \Sigma_\beta)$  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.

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**Alloy-A Fatigue Crack Size Observations and Fitted Paris-Rule Model**



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**Estimates of Fatigue Data Model Parameters for Alloy-A**

- Splus gives the following approximate ML estimates.

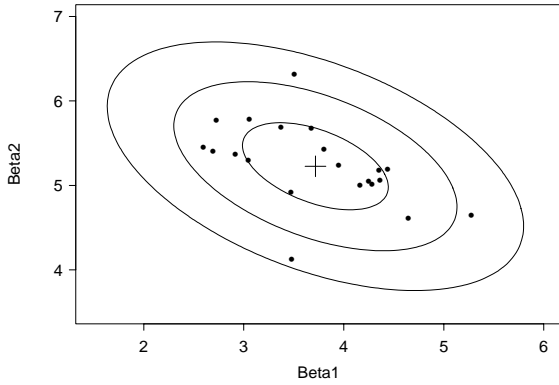
$$\hat{\mu}_\beta = \begin{pmatrix} 5.17 \\ 3.73 \end{pmatrix}, \quad \hat{\Sigma}_\beta = \begin{pmatrix} .251 & -.194 \\ -.194 & .519 \end{pmatrix}$$

and  $\hat{\sigma}_\epsilon = .0034$ .

- Here  $\beta_1 = C$ ,  $\beta_2 = m$ .

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**Estimates  $\hat{\beta}_{1i}$  Versus  $\hat{\beta}_{2i}$ ,  $i = 1, \dots, 21$  and Contours for the Fitted Bivariate Normal Distribution**



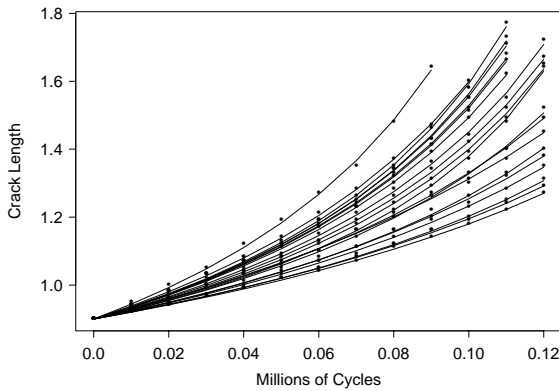
6-49

**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  $\mathcal{D}_f$  to denote the critical level defining failure for a degradation path.

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**Alloy-A Fatigue Crack Size Observations and Fitted Paris-Rule Model**



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**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.

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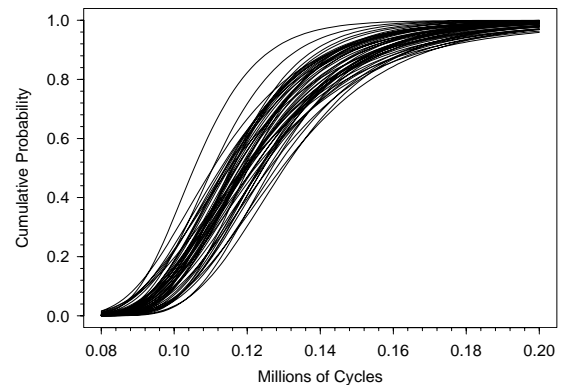
**Evaluation of  $F(t)$  by Numerical Integration**

- The failure (crossing probability) can be expressed as
 
$$\Pr(T \leq t) = F(t) = F(t; \theta_\beta) = \Pr[\mathcal{D}(t, \beta_1, \dots, \beta_k) > \mathcal{D}_f].$$
- 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  $P(T \leq t)$ 

$$= \int_{-\infty}^{\infty} \Phi_{\text{nor}} \left[ -\frac{g(\mathcal{D}_f, t, \beta_1) - \mu_{\beta_2|\beta_1}}{\sigma_{\beta_2|\beta_1}} \right] \frac{1}{\sigma_{\beta_1}} \phi_{\text{nor}} \left( \frac{\beta_1 - \mu_{\beta_1}}{\sigma_{\beta_1}} \right) d\beta_1$$
 where  $g(\mathcal{D}_f, t, \beta_1)$  is the value of  $\beta_2$  for given  $\beta_1$ , that gives  $\mathcal{D}(t) = \mathcal{D}_f$ .
- Method generalizes to multivariate normal, but requires correspondingly higher-order integration.

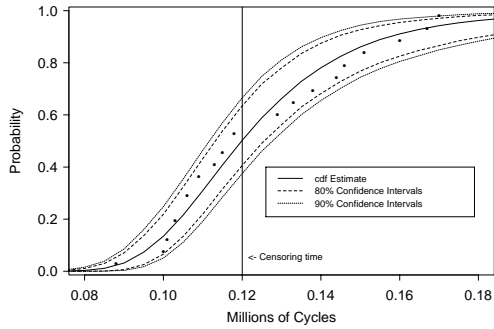
6-53

**Bootstrap Estimates of  $F(t) = \Pr(T \leq t)$**



6-54

**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**



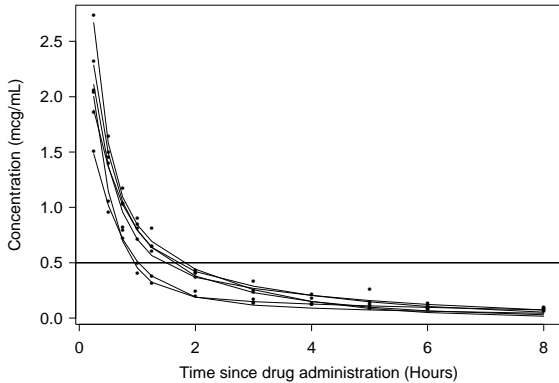
6-55

```
> Indometh.lis <- nlsList(data=Indometh,
+ conc ~ biexp(time, A1, A2,lrc1,lrc2), cluster= ~ Subject)
      A1      A2      lrc1      lrc2
0.1915405 2.029278 -1.78783 0.5793801
      A1      A2      lrc1      lrc2
0.4986587 2.827599 -1.635984 0.8010547
      A1      A2      lrc1      lrc2
1.675421 5.46662 -0.4123908 1.749457
      A1      A2      lrc1      lrc2
0.2543484 2.19826 -1.603379 0.242206
      A1      A2      lrc1      lrc2
0.2915201 3.566077 -1.506703 1.040773
      A1      A2      lrc1      lrc2
0.9683424 3.002198 -0.8732972 1.088059

> Indometh.nlme <- nlme(Indometh.lis)
> plot(Indometh.nlme)
```

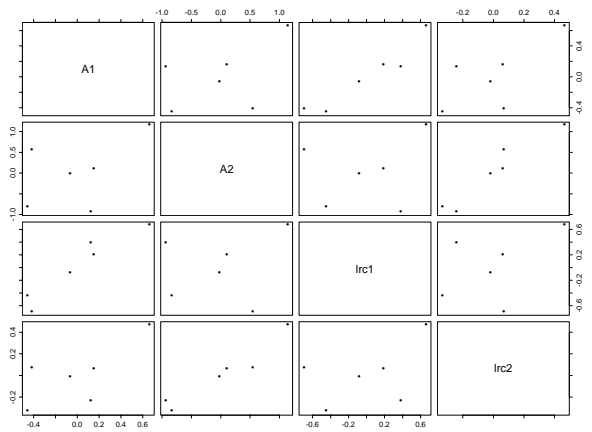
6-56

**Fitted Values of Plasma Concentrations of Indomethicin Following Intravenous Injection**



6-57

**Plasma Concentrations of Indomethicin Estimates of Random Parameters**



6-58

```
> 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:
nlme::nlme(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
```

6-59

```
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
```

6-60

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):

	A1	A2	lrc1	lrc2
1	-0.45701638	-0.83383053	-0.44839015	-0.33416642
2	-0.06417292	-0.01969095	-0.08463536	-0.01916071
3	0.66019886	1.14263995	0.66151125	0.46508815
4	0.12355803	-0.93905219	0.38035935	-0.24158791
5	-0.41411192	0.54533293	-0.69578056	0.06801642
6	0.15154433	0.10460080	0.18693548	0.06181046

Standardized Population-Average Residuals:

	Min	Q1	Med	Q3	Max
	-3.535373	-0.4377011	0.002928057	0.4082834	3.651327

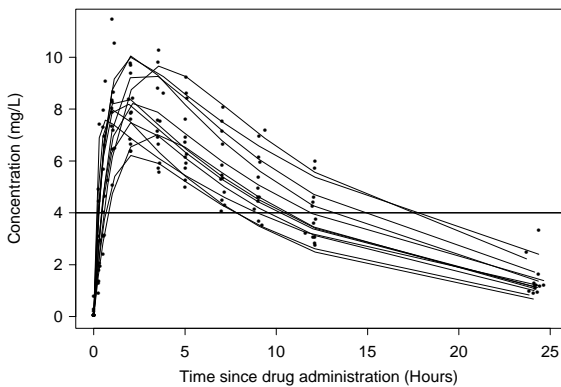
Number of Observations: 66

Number of Clusters: 6

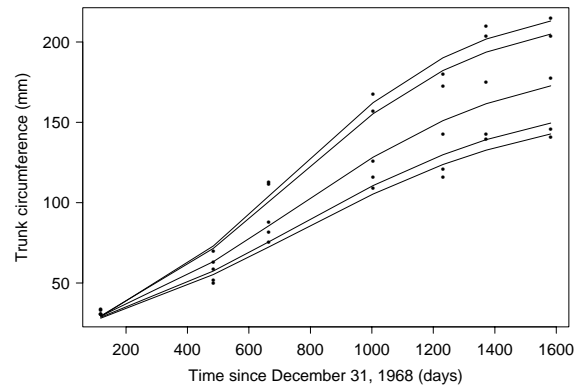
```
> predict(Indometh.nlm, data=Indometh, cluster= ~ Subject)
```

	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
.			
.			
.			
65	6	0.10451084	0.11907827
66	6	0.05331376	0.06813162

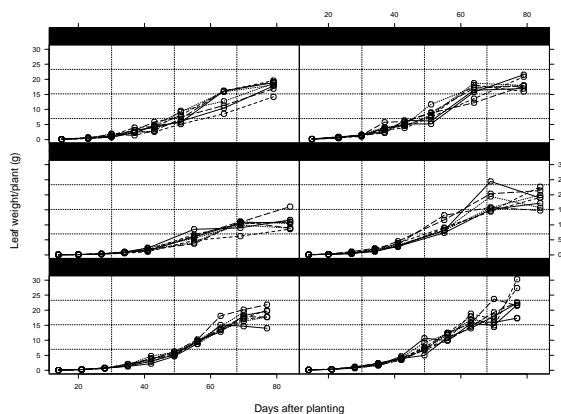
Fitted Values of Serum Concentrations of Theophylline Following Oral Administration



Fitted Values of Orange Tree Trunk Circumference Growth



Trellis Plot of the Results of an Experiment to Compare Two Genotypes of Soybeans



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 `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.