STATISTICS
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Handout 12

Introduction to Nonlinear Mixed Models

- **Introduction to Generalized Linear Mixed Models and Nonlinear Mixed Models**

- **Fitting a Generalized Linear Mixed Model Using the GLIMMIX Procedure**

- **Fitting a Nonlinear Mixed Model using the NLMIXED Procedure**

Generalized Linear Mixed Models and Nonlinear Mixed Models

Objectives

- Assumptions of linear mixed models.
- Situations where linear mixed model assumptions are violated.
- Generalized linear mixed models.
- Nonlinear mixed models.

General Linear Models (GLM)

unknown fixed effect

$$y = X\beta + \varepsilon$$

unknown
random error

known design matrix

assume $\varepsilon \sim iid\ N(0, \sigma^2 I_n)$

therefore $E(y) = X\beta$, $Var(y) = \sigma^2 I_n$

Linear Mixed Models (LMM)

Random effects. specified in the RANDOM statement

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\boldsymbol{\gamma} + \boldsymbol{\varepsilon}$$

Design matrix for random effects

Not required to be independent or homogeneous.
Specified in the REPEATED statement for non-default structures

$$\boldsymbol{\gamma} \sim N(\mathbf{0}, \mathbf{G}), \;\; \boldsymbol{\varepsilon} \sim N(\mathbf{0}, \mathbf{R})$$

$$\Rightarrow \quad E(\mathbf{y}) = \mathbf{X}\boldsymbol{\beta}, \quad Var(\mathbf{y}) = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \mathbf{R} = \mathbf{V}$$

Linear Mixed Models Assumptions

- Random effects and residuals are normally distributed with mean zero and covariance matrices **G** and **R**, respectively.

- Random effects and model errors are independent of each other.

- The means (expected values) of the responses are linearly related to the predictor variables (linear in terms of fixed-effects parameters).

Examples of Linear Mixed Models

Linear mixed models can be appropriate when you have the following:

- random effects
  - blocks, machines, operators, centers, teachers
- correlated errors
  - repeated measures data
- both random effects and correlated errors

Normal Assumption Is Violated – An Example with Binomial Data

A clinical trial study involved two drug treatments and eight clinics.

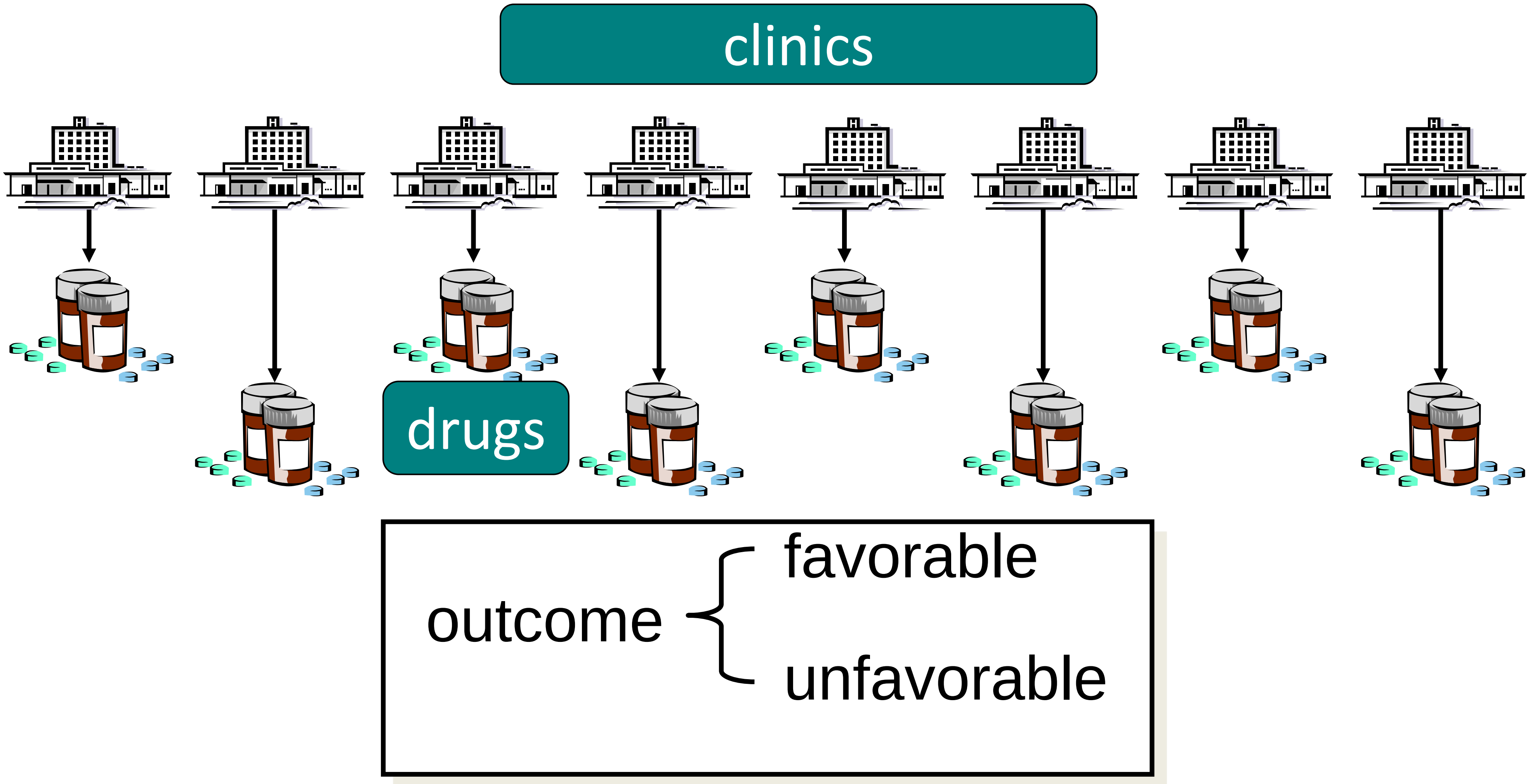
The eight clinics represented a sample from a larger target population.

At each clinic, subjects were randomly assigned to receive one of the two treatments.

Each subject was classified as having a favorable or unfavorable response to the treatment.

Is the response binary or continuous or discrete?
Does this violate the normal assumption of a linear mixed model?

Normal Assumption Is Violated – An Example with Binomial Data



Normal Assumption Is Violated – An Example with Count Data

A split plot experiment was conducted to compare various treatments for improving damaged rangeland.

The whole plot treatments were various management methods. They were applied in RCBD.

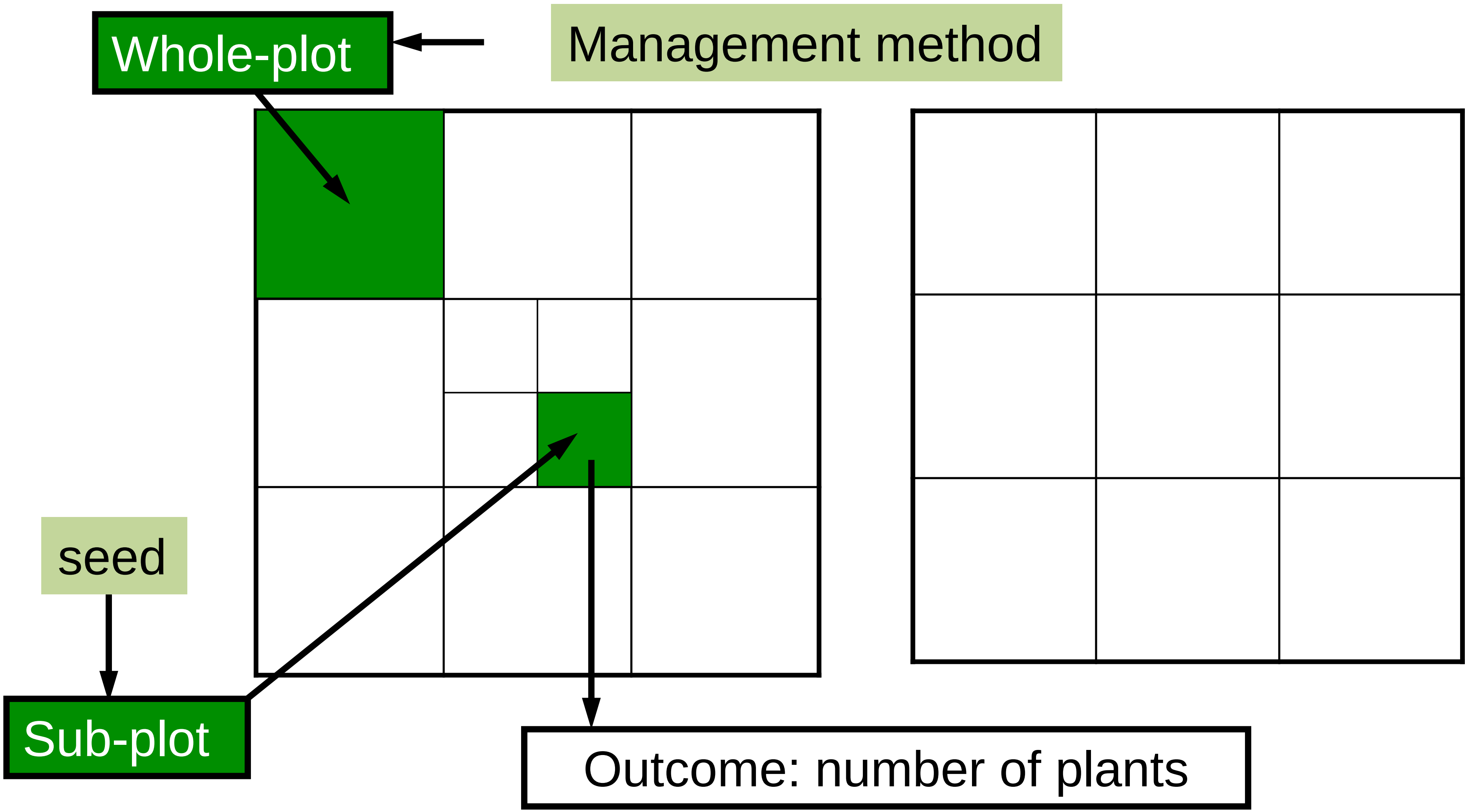
The plot units are plots of land of equal sizes within a block.

Each whole plot was split into 4 subplots and different seed mixes were applied to the subplot units.

The response variable of interest was botanical composition, measured by the number of plants of various species present in a given plot.

Is the response binary or continuous or discrete?
Does this violate the normal assumption of a linear mixed model?

Normal Assumption Is Violated – An Example with Count Data



Orange Tree Growth Example

A botanist is studying growth patterns in 5 randomly selected orange trees.

The trunk circumferences (y) of these 5 orange trees, measured at 7 time points (in weeks), since planted (x) are recorded.

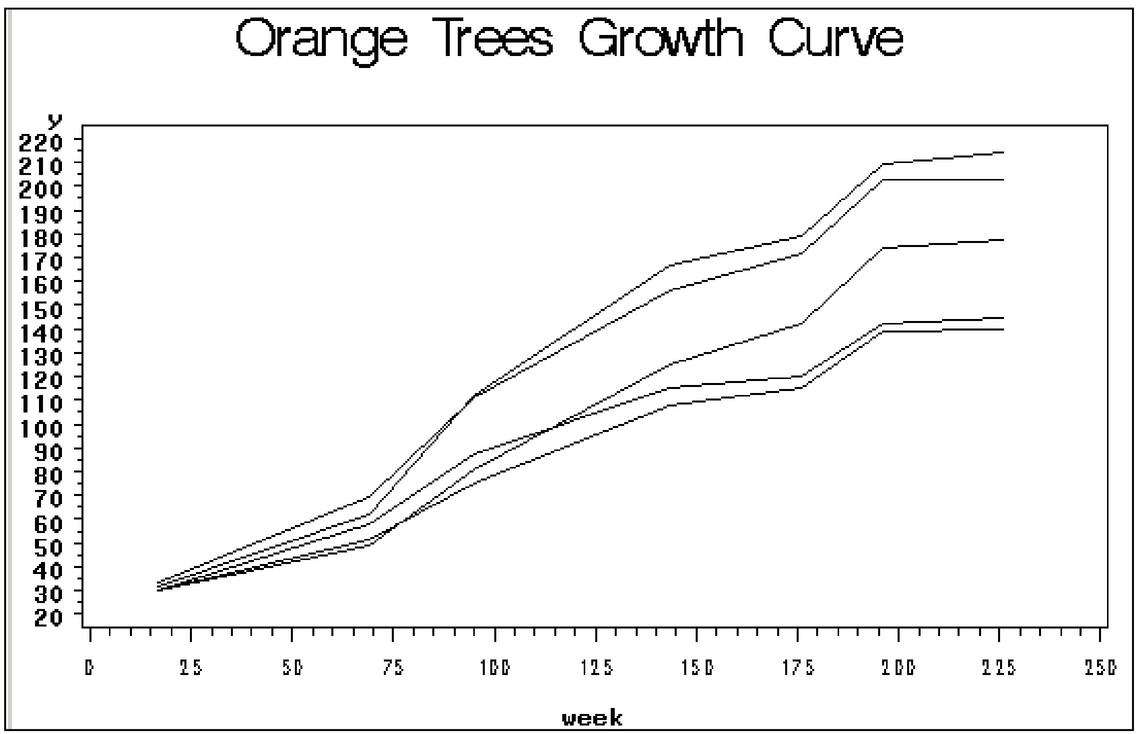
Logistic growth model might be appropriate.

$$y_{ij} = \frac{\beta_1}{1 + \beta_2 e^{-\beta_3 x_{ij}}} + \varepsilon_{ij}$$

In addition to this, the variation of the upper horizontal asymptote (the thickest a tree can get) among different trees, which is a random effect, may need to be modeled.

Is this a nonlinear mixed model?

Linearity Assumption Is Violated – Orange Tree Growth Example



$$y_{ij} = \frac{\beta_1 + u_i}{1 + \beta_2 e^{-\beta_3 x_{ij}}} + \varepsilon_{ij}$$

Linear Mixed Models Estimation Methods

The estimation methods for linear mixed models are shown below:

- Maximum likelihood or restricted maximum likelihood for covariance parameter estimates
- Generalized least squares method for fixed-effect parameter estimates

The MIXED Procedure

General form of the MIXED procedure:

```
PROC MIXED options;
     CLASS variables;
     MODEL dependent=fixed-effects / options;
     RANDOM random-effects / options;
     REPEATED <repeated-effect> / options;
RUN;
```

- Multiple random effects are allowed in one RANDOM statement.
- Multiple RANDOM statements are possible.
- Only one REPEATED statement is allowed.

Generalized Linear Models (GzLM)

– *Generalization* is from linear models:

- Allow data from exponential family of distributions

$$f(y) = \exp\{\frac{y\theta - b(\theta)}{a(\phi)} + c(y,\phi)\}$$

where θ is the location parameter and ϕ is the dispersion parameter

  – discrete response: Bernoulli, binomial, Poisson, negative binomial, geometric

  – continuous response: normal, gamma, inverse Gaussian, beta

– *Linearity* is achieved through the link function.

- A transformation of the mean (link function) is linearly related to the independent variables.

  linear predictor $\eta = X\beta$

- Link functions are monotonic.

  link function $g(\mu) = \eta$

$Var(y) = V(\mu)a(\phi)$

Examples of GzLMs

Responses	Distribution	Mean	Variance	Link	Model
Continuous	Normal	μ	σ^2	μ	$\mu = X\beta$
Dichotomous	Binary	μ	$\mu(1-\mu)$	$\log[\mu/(1-\mu)]$	$\log[\mu/(1-\mu)] = X\beta$
Binomial count	Binomial	$n\mu$	$n\mu(1-\mu)$	$\log[\mu/(1-\mu)]$	$\log[\mu/(1-\mu)] = X\beta$
Count	Poisson	μ	μ	$\log(\mu)$	$\log(\mu) = X\beta$
Count	Negative Binomial	μ	$\mu+k\mu^2$	$\log(\mu)$	$\log(\mu) = X\beta$

Examples of Continuous Response Variables

Example	Assumed Distributions	Possible Models	Possible Procedures
yield, blood pressure, height, weight, temperature	normal	linear regression, ANOVA	REG, GLM, MIXED*†, GENMOD†, GLIMMIX*†
salaries, home values, concentration	Gamma, lognormal, other	Gamma regression, linear regression on transformed response	GENMOD†, GLIMMIX*†, For the transformed response: REG, GLM, MIXED*†
proportions of gas expenditure	beta	beta regression	GLIMMIX*†

* can also be used for models with random effects.

† can also be used for data with correlated errors.

Examples of Discrete Response Variables

Example	Assumed Distributions	Possible Models	Possible Procedures
yes/no, good/bad, live/dead	binary	logistic regression	LOGISTIC, GENMOD†, GLIMMIX*†
number of patients with side effects out of patients treated	binomial	logistic regression	LOGISTIC, GENMOD†, GLIMMIX*†
excellent/good/fair/poor, very satisfied/somewhat satisfied/not satisfied, low/medium/high	multinomial	ordinal regression	LOGISTIC, GENMOD, GLIMMIX*
favorite brand: A/B/C/None	multinomial	multinomial regression	LOGISTIC, GLIMMIX*
number of emergency room visits, number of birds observed	Poisson, negative binomial	Poisson regression, negative binomial regression	GENMOD†, GLIMMIX*†

* can also be used for models with random effects.

† can also be used for data with correlated errors.

Generalized Linear Mixed Models (GzLMMs)

GzLMMs enable modeling random effects and correlated errors for nonnormal data.

- A linear predictor can contain random effects:

  $\eta = X\beta + Z\gamma$

- The random effects are normally distributed.
- The conditional mean, $\mu|\gamma$, relates to the linear predictor through a link function:

  $g(\mu|\gamma) = \eta$

- The conditional distribution (given γ) of the data belongs to the exponential family of distributions.

Examples of GzLMMs

Responses	Distribution	Mean	Variance	Link	Model
Continuous	Normal	μ	σ^2	μ	$\mu = X\beta+Z\gamma$
Dichotomous	Binary	μ	$\mu(1-\mu)$	$\log[\mu/(1-\mu)]$	$\log[\mu/(1-\mu)] = X\beta+Z\gamma$
Binomial count	Binomial	$n\mu$	$n\mu(1-\mu)$	$\log[\mu/(1-\mu)]$	$\log[\mu/(1-\mu)] = X\beta+Z\gamma$
Count	Poisson	μ	μ	$\log(\mu)$	$\log(\mu) = X\beta+Z\gamma$
Count	Negative Binomial	μ	$\mu+k\mu^2$	$\log(\mu)$	$\log(\mu) = X\beta+Z\gamma$

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Bernoulli Distribution

$f(y) = \pi^{y} (1-\pi)^{1-y}$ for $y=0$ or 1

Rewriting this

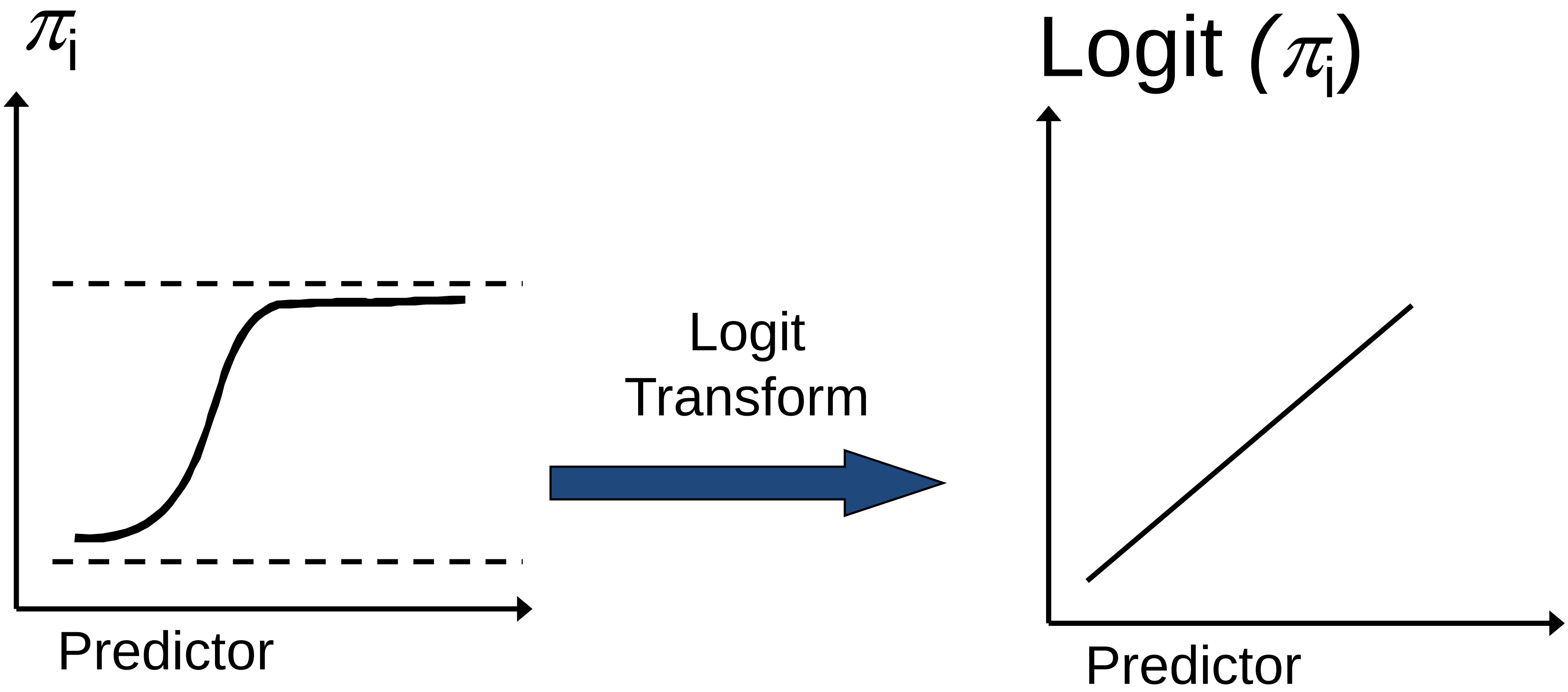
$f(y) = \exp(y*\ln(\pi) + (1-y)*\ln(1-\pi))$

$= \quad \exp\left(y * ln\left(\frac{\pi}{1-\pi}\right) + \ln(1-\pi)\right)$

link function is $\theta = ln\left(\frac{\pi}{1-\pi}\right)$

Logit Link Function for Binary Response

$$logit(\pi) = log\left(\frac{\pi}{1-\pi}\right)$$



Examples of Generalized Linear Models

Model	Distribution	Mean	Variance	Link	Inverse Link Function
linear regression	Normal	μ	σ^2	(identity) μ	identity
logistic regression	Binomial	π	$\pi(1-\pi)/n$	(logit) $\log[\pi/(1-\pi)]$	$\dfrac{1}{1+e^{-\text{logit}}}$
Poisson regression	Poisson	λ	λ	(log) $\log(\lambda)$	exponential

Generalized Linear Mixed Models

Unknown fixed effects

Unknown random effects

$$y = X\beta + Z\gamma + \varepsilon$$

Design matrix for fixed effects

Design matrix for random effects

Random normal errors

Assume $\gamma \sim \mathrm{MVN}(0, \mathrm{G}),\ \varepsilon \sim \mathrm{MVN}(0, \mathrm{R})$

The conditional mean and variance are

$$E(y \mid \gamma) = \mu = \mathrm{X}\beta + Z\gamma,\ \ Var(y \mid \gamma) = \mathrm{R} = \mathrm{Var}(\varepsilon)$$

Generalized Linear Mixed Models

The generalized linear mixed model is

$$g(E(y \mid \gamma)) = g(\mu) = X\beta + Z\gamma$$

where $g(\mu)$ is the link function and μ is the conditional mean, $E(y \mid \gamma)$.

You apply a link function to the conditional mean.

To obtain the parameter estimates, you must obtain marginal log-likelihood function which is a challenge.

GLIMMIX procedure uses the linearization technique to approximate the model as a linear mixed model.

NLMIXED procedure uses numerical techniques to integrate out the random effects to obtain the function.

Nonlinear Mixed Models

$$y_{ij} = f(x_{ij}, \beta, u_i) + e_{ij}$$

where

f is some nonlinear function

y_{ij} is the j^{th} observation on the i^{th} subject

x_{ij} is a known vector of independent variables

β is an unknown vector of fixed-effect parameters

u_i is the unknown vector of random effect parameters

e_{ij} are unknown random errors.

Generalization Patterns

Less General → More General

linear mixed models (LMM) → generalized linear mixed models (GLMM) → nonlinear mixed models (NLMM)

linear mixed models (LMM) ↕ PROC MIXED

generalized linear mixed models (GLMM) ↕ PROC GLIMMIX

nonlinear mixed models (NLMM) ↕ PROC NLMIXED

Question

Which of the following is **false**?

a. Linear mixed models (LMM) and general linear models (GLM) are special cases of generalized linear mixed models (GLMM).
b. Generalized linear mixed models handle normal and some types of nonnormal data.
c. Linear mixed models handle normal and some types of nonnormal data.
d. Nonlinear mixed models handle normal and some types of nonnormal data.

PROC GLIMMIX versus PROC MIXED

PROC GLIMMIX
- BY
- CLASS
- CONTRAST
- ESTIMATE
- FREQ
- ID
- LSMEANS
- LSMESTIMATE
- MODEL
- NLOPTIONS
- OUTPUT
- PARMS
- RANDOM
- WEIGHT
- <Programming Statements>

PROC MIXED
- BY
- CLASS
- CONTRAST
- ESTIMATE
- ID
- LSMEANS
- MODEL
- PARMS
- RANDOM
- REPEATED
- WEIGHT

The GLIMMIX Procedure

General form of the GLIMMIX procedure:

PROC GLIMMIX *options* **;**

…programming statements…

CLASS *variables***;**

MODEL *response=fixed-effects / dist= link= options***;**

RANDOM *random-effects / options***;**

RANDOM *_residual_ / options***;**

RUN;

The GLIMMIX Procedure

PROC GLIMMIX <options> ;

BY variables ;

CLASS variables ;

CONTRAST 'label' contrast-specification <, contrast-specification> <, ...> </ options>;

COVTEST <'label'> <test-specification> </ options> ;

EFFECT effect-specification ;

ESTIMATE 'label' contrast-specification <**(**divisor**=***n***)**>
<, 'label' contrast-specification <**(**divisor**=***n***)**>> <, ...> </ options> ;

FREQ variable ;

ID variables ;

LSMEANS fixed-effects </ options> ;

LSMESTIMATE fixed-effect <'label'> values <divisor**=**>
<, <'label'> values <divisor**=**n>> <, ...> </ options> ;

MODEL response<**(**response-options**)**> **=** <fixed-effects> </ model-options>;

MODEL events/trials **=** <fixed-effects> </ model-options>;

OUTPUT <**OUT=**SAS-data-set>
<keyword<**(**keyword-options**)**> <**=**name>>...
<keyword<**(**keyword-options**)**> <**=**name>> </ options> ;

PARMS **(**value-list**)** ...</ options> ;

RANDOM random-effects </ options> ;

SLICE model-effect </ options> ;

STORE <**OUT=**>*item-store-name* </ **LABEL=**'*label*'> ;

Selected Features of PROC GLIMMIX

The GLIMMIX procedure enables the following:

- statistical graphs via ODS Graphics
- programming statements
- multiple comparison adjustment in the ESTIMATE statement (ADJUST=)
- custom hypothesis tests among least squares means (LSMESTIMATE statement)
- odds ratio computations (ODDSRATIO or OR) in the MODEL statement and the LSMEANS statement
- presentation of the least squares means on the original scale (ILINK) and differences by lines (LINES)
- additional covariance structures

continued...

Selected Features of PROC GLIMMIX

- METHOD=QUAD or METHOD=LAPLACE to request maximum likelihood estimation method
- New bias-corrected empirical (“sandwich”) covariance estimator (EMPIRICAL=MBN)
- Covariance matrix diagnostics (COVB(DETAILS))
- The COVTEST statement to make inference about covariance parameters
- Step-down multiplicity adjustment options
- FIRSTORDER suboptions for DDFM=KR
- OUTDESIGN= to write **X** or **Z** matrix to an output SAS data set
- Experimental EFFECT statement to define constructed effects
- Nonpositional syntax for LSMESTIMATE, CONTRAST and ESTIMATE statements.

GLMM Formulation and PROC GLIMMIX

$$g(\mu\,|\,\gamma) = \mathbf{X}\beta + \mathbf{Z}\gamma$$

LINK= option

MODEL statement

RANDOM statement

$Y|\gamma$ ~ exponential family

DIST= option

$\text{var}(\gamma) = G$

Options in the RANDOM statement

$\text{Var}(y|\,\gamma)=A_\mu^{1/2}\,R\,A_\mu^{1/2}$

RANDOM _RESIDUAL_ statement

g(.) : the differentiable monotonic link function

μ : the expected value of y

A_μ : variance of the response as a function of the mean

Estimation Methods in PROC GLIMMIX

- Pseudo-Likelihood (or Linearization) – default method
  - uses first-order Taylor series to approximate the model as a series of linear mixed models
  - can fit complex models.
  - likelihood is for an approximated linear mixed model. There is no true likelihood, so there are no likelihood ratio tests.
  - variance estimates for random effects might be biased, especially for binary outcome and few clusters or small number of observations per cluster.

Estimation Methods in PROC GLIMMIX

- Maximum-Likelihood (quadrature or Laplace)
  - log-likelihood of the data is computed so model comparisons are possible based on information criteria.
  - the pseudo-likelihood bias is avoided.
  - cannot be implemented for models with the R-side random effects.
  - for the quadrature method, there are some limitations for the G-side random effects.
    - METHOD=QUAD : random effect should be proceed with SUBJECT. Nested subject can only be possible with limitations
    - METHOD=LAPLACE : random effects can be crossed. It can be used for unbounded variance components

Questions

(1) Mixed models are not only used for situations when there are random effects. They are also commonly used for data with correlated errors, such as repeated measures data, where you might or might not have random effects.

- ❍ True
- ❍ False

(2) PROC GLIMMIX does not have a REPEATED statement, therefore it cannot be used to model data with correlated errors.

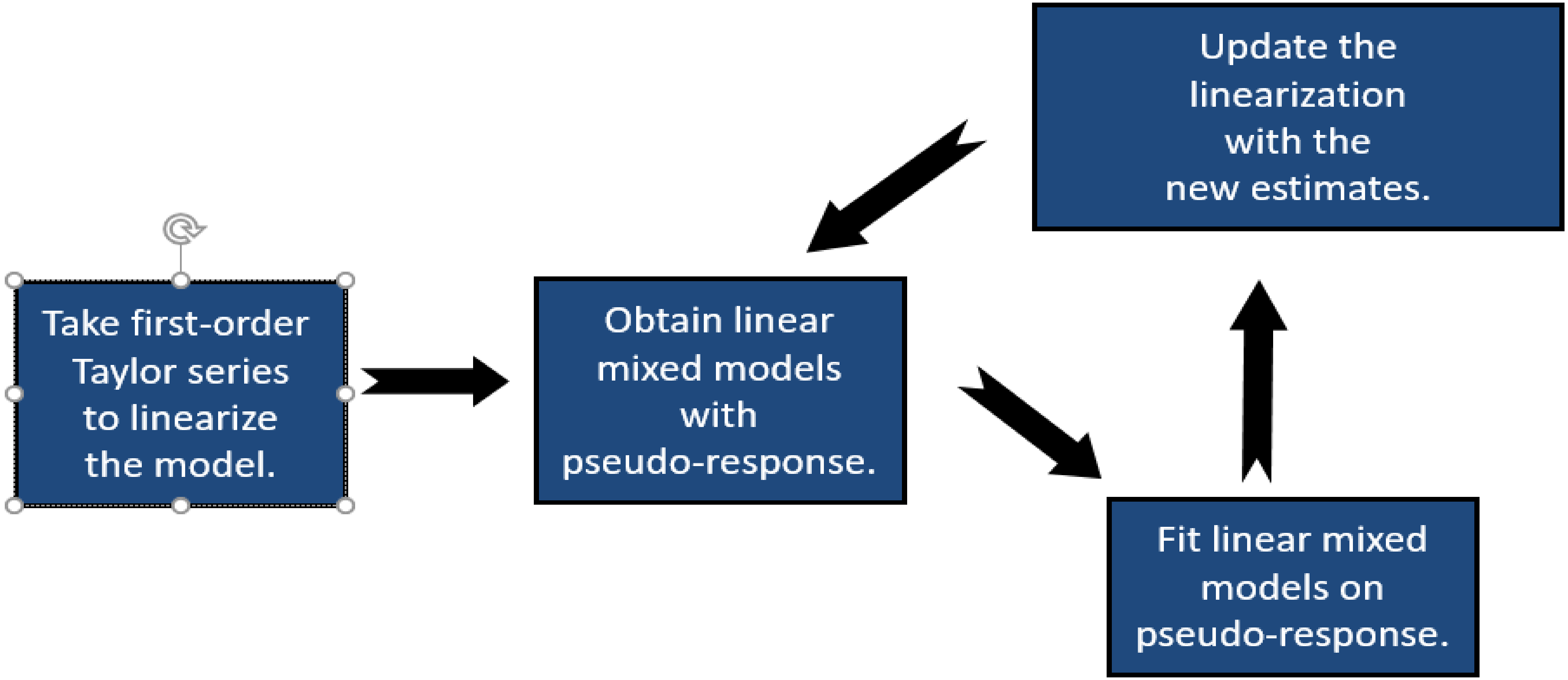
- ❍ True
- ❍ False

(3) The maximum likelihood estimation method in PROC GLIMMIX enables you to

a. fit any type of generalized linear mixed models using this estimation method.
b. perform likelihood ratio tests for nested models.
c. use PROC GLIMMIX rather than PROC NLMIXED for all models that can be fit in PROC NLMIXED.
d. model R-side random effects.

Fitting a Generalized Linear Mixed Model Using the GLIMMIX Procedure

– Fit a logistic regression model with random effects using the GLIMMIX procedure.



Binomial Example

Data was collected for several insurance agents who provided different promotion programs to existing policy holders. The goal was to try to have new policies added to the existing policies with these promotions and evaluate which promotional program is more effective. The added or not added response was recorded for each policy holder. Data is stored in a SAS data set called policy.

The variables are:
Agent: the insurance agent identification number
Promotions: the promotion programs
Holders: the number of existing policy holders
New: the number of new policies added

Binomial Policy, The Model

$$newadded_{ij}|agents \sim Binomial(n_{ij}, p_{ij})$$

i=1,2,3, j=1,2,….,10

$$\eta_{ij} = log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \mu + \alpha_i + A_j$$

Promotion effect, fixed

link function logit(p_{ij})

Agent effect, random

Obs	agent	promotions	holders	new
1	1	A	36	25
2	1	B	37	27
3	1	C	35	10
4	2	A	20	6
5	2	B	32	10
6	2	C	28	4
7	3	A	23	5
8	3	B	19	12
9	3	C	22	4
10	4	A	23	14
11	4	B	24	9
12	4	C	25	5
...				

Then $p_{ij} = \frac{e^{logit}}{1+e^{logit}} = \frac{1}{1+e^{-logit}}$

Fitting a Model for a Binomial Response Using the GLIMMIX Procedure

Fit Statistics	
-2 Res Log Pseudo-Likelihood	58.35
Generalized Chi-Square	27.46
Gener. Chi-Square / DF	1.02

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error
Intercept	agent	0.1867	0.1244

Solutions for Fixed Effects

Effect	promotions	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		-1.4402	0.2265	9	-6.36	0.0001
promotions	A	1.3291	0.2281	18	5.83	<.0001
promotions	B	1.4247	0.2258	18	6.31	<.0001
promotions	C	0	.	.	.	.

Type III Tests of Fixed Effects

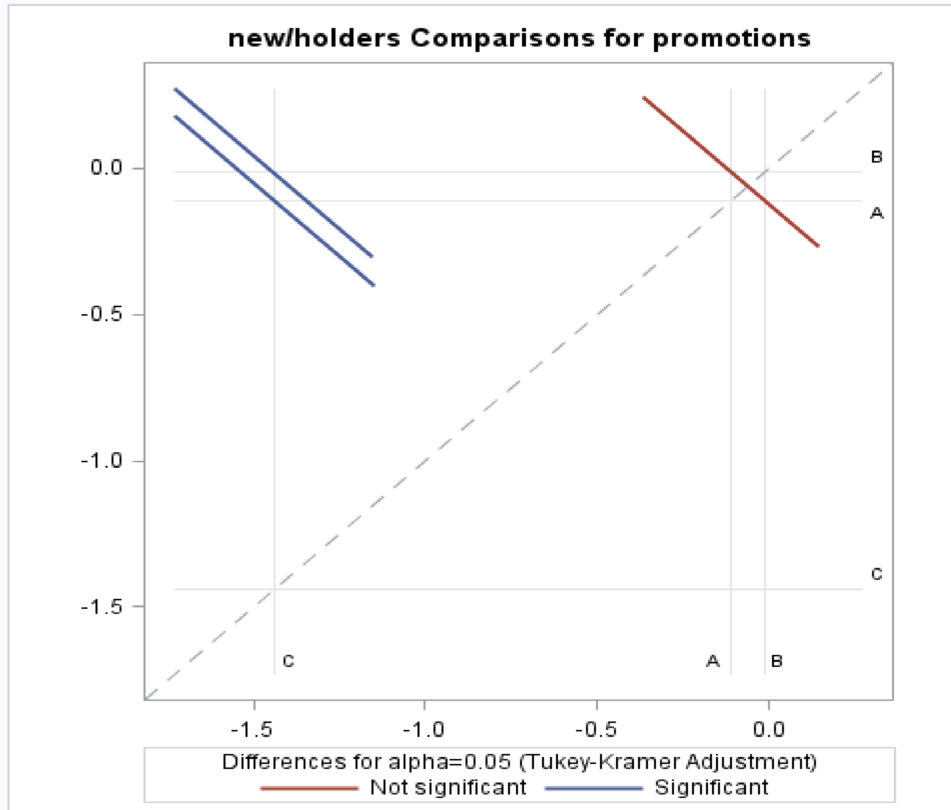
Effect	Num DF	Den DF	F Value	Pr > F
promotions	2	18	23.03	<.0001

promotions Least Squares Means

promotions	Estimate	Standard Error	DF	t Value	Pr > |t|
A	-0.1111	0.2005	18	-0.55	0.5863
B	-0.01548	0.1981	18	-0.08	0.9385
C	-1.4402	0.2265	18	-6.36	<.0001

Differences of promotions Least Squares Means
Adjustment for Multiple Comparisons: Tukey-Kramer

promotions	_promotions	Estimate	Standard Error	DF	t Value	Pr > |t|	Adj P
A	B	-0.09560	0.2008	18	-0.48	0.6397	0.8833
A	C	1.3291	0.2281	18	5.83	<.0001	<.0001
B	C	1.4247	0.2258	18	6.31	<.0001	<.0001



Policyexample.sas

Question

How do you best interpret the variance estimate of 0.1867 for agent?

a. The agent variance is 0.1867.
b. The agent variance in terms of the probability of adding a new policy is 0.1867.
c. The variance among agents in terms of the probability of adding a new policy on the logit scale is estimated to be 0.1867.

Fitting a Model for a Binomial Response Using the GLIMMIX Procedure

promotions	_promotions	Estimate	Standard Error	DF	t Value	Pr > |t|	Adj P	Alpha	Lower	Upper	Adj Lower	Adj Upper	Odds Ratio	Lower Confidence Limit for Odds Ratio	Upper Confidence Limit for Odds Ratio	Adj Lower Odds Ratio	Adj Upper Odds Ratio
A	B	-0.09560	0.2008	18	-0.48	0.6397	0.8833	0.05	-0.5174	0.3262	-0.6080	0.4168	0.909	0.596	1.386	0.544	1.517
A	C	1.3291	0.2281	18	5.83	<.0001	<.0001	0.05	0.8499	1.8083	0.7470	1.9112	3.778	2.339	6.100	2.111	6.761
B	C	1.4247	0.2258	18	6.31	<.0001	<.0001	0.05	0.9502	1.8992	0.8483	2.0011	4.157	2.586	6.680	2.336	7.397

Obs	agent	promotions	holders	new	pred	predilink	residual	resilink
1	1	A	36	25	0.56179	0.63687	0.24896	0.05758
2	1	B	37	27	0.65739	0.65867	0.31605	0.07106
3	1	C	35	10	-0.76730	0.31706	-0.14478	-0.03135
4	2	A	20	6	-0.60330	0.35359	-0.23446	-0.05359
5	2	B	32	10	-0.50770	0.37573	-0.26958	-0.06323
6	2	C	28	4	-1.93239	0.12649	0.14817	0.01637
7	3	A	23	5	-0.29547	0.42667	-0.85550	-0.20927
8	3	B	19	12	-0.19987	0.45020	0.73280	0.18138
9	3	C	22	4	-1.62456	0.16458	0.12540	0.01724
10	4	A	23	14	-0.08997	0.47752	0.52576	0.13117
11	4	B	24	9	0.00562	0.50141	-0.50563	-0.12641
12	4	C	25	5	-1.41906	0.19481	0.03310	0.00519
13	5	A	22	10	-0.02250	0.49438	-0.15934	-0.03983
14	5	B	23	12	0.07310	0.51827	0.01391	0.00347
15	5	C	23	6	-1.35159	0.20561	0.33831	0.05526
16	6	A	28	10	-0.49860	0.37787	-0.08817	-0.02073
17	6	B	29	10	-0.40300	0.40059	-0.23224	-0.05576
18	6	C	28	4	-1.82769	0.13851	0.03640	0.00434

Tukey-Kramer Grouping for promotions Least Squares Means (Alpha=0.05)

LS-means with the same letter are not significantly different.

promotions	Estimate	
B	-0.01548	A
		A
A	-0.1111	A
C	-1.4402	B

Least Squares Means Estimates

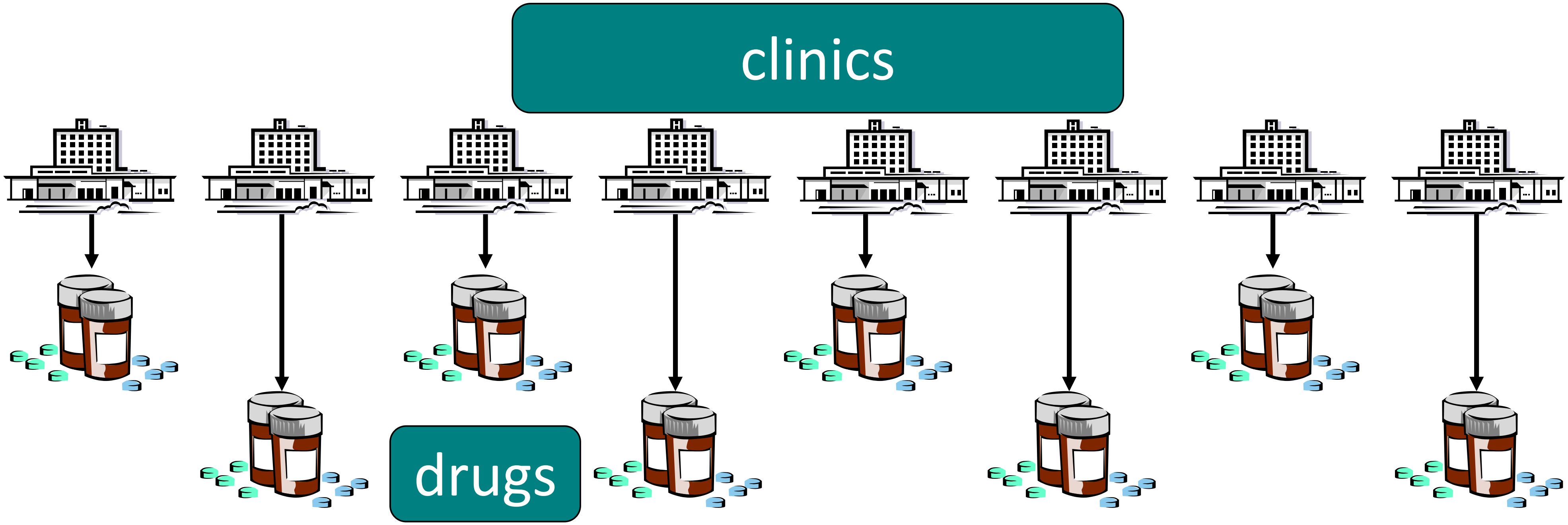
Effect	Label	Estimate	Standard Error	DF	t Value	Pr > |t|
promotions	avg(A, B) vs. C	1.3769	0.2036	18	6.76	<.0001

Least Squares Means Estimates

Effect	Label	Estimate	Standard Error	DF	t Value	Pr > |t|
promotions	A	-0.1111	0.2005	18	-0.55	0.5863

Policyexample.sas

Drug Study Example



outcome { favorable / unfavorable

Drug Study Example (favorableExample)

A clinical trial study involved 2 drug treatments and 8 clinics.

The eight clinics represented a sample from a large target population; therefore, **clinic** is a random effect. At each clinic i, n_{i1} subjects were randomly assigned to receive treatment 1 and n_{i2} subjects were randomly assigned to receive treatment 2. Each subject was classified as having a favorable or unfavorable response to the treatment.

The objective of the study was to determine the effect of treatment on the probability of a favorable response across a population of clinics.

Clinic: clinic where the study is performed

Trt: treatment (1=drug or 0=control)

Fav: number of favorable responses

Unfav: number of unfavorable responses

n: total number of subjects (n=fav+unfav)

FavorableExample Data

clinic	trt	fav	unfav	n
1	1	11	25	36
1	0	10	27	37
2	1	16	4	20
2	0	22	10	32
3	1	14	5	19
3	0	7	12	19
4	1	2	14	16
4	0	1	16	17
5	1	6	11	17
5	0	0	12	12
6	1	1	10	11
6	0	0	10	10
7	1	1	4	5
7	0	1	8	9
8	1	4	2	6
8	0	6	1	7

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Drug Study, The Model

$$fav_{ij} \mid c_i \sim Binomial(n_{ij}, p_{ij})$$

$i = 1$ to 8 (**`clinic`**)

$j = 1, 2$ (**`trt`**)

trt effect, fixed

$$\eta_{ij} = \log\left(\frac{p_{ij}}{1 - p_{ij}}\right) = \mu + t_j + c_i + (ct)_{ij}$$

link function logit(p_{ij})

clinic effect, random

trt*clinic effect, random

Fitting a Generalized Linear Mixed Model Using PROC GLIMMIX

Fit Statistics	
-2 Res Log Pseudo-Likelihood	50.30
Generalized Chi-Square	13.55
Gener. Chi-Square / DF	0.97

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error
Intercept	clinic	2.0103	1.2716
trt	clinic	0.06057	0.2043

Type III Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	1	7	5.06	0.0592

trt Least Squares Means

trt	Estimate	Standard Error	DF	t Value	Pr > |t|	Mean	Standard Error Mean
0	-1.1650	0.5657	7	-2.06	0.0784	0.2378	0.1025
1	-0.4164	0.5606	7	-0.74	0.4818	0.3974	0.1343

Differences of trt Least Squares Means

trt	_trt	Estimate	Standard Error	DF	t Value	Pr > |t|	Odds Ratio
0	1	-0.7485	0.3326	7	-2.25	0.0592	0.473

For overall fit in binomial distribution, Pearson chisquare/df should be close to 1.

The odds of having favorable response for Ttrt 0 is 47.3% of the odds for trt 1

Trt 1 is 2.11 times the odds in terms of having favorable response comparing with Trt 0.

FavorableExample.sas

Fitting a Generalized Linear Mixed Model Using PROC GLIMMIX

Fit Statistics	
-2 Res Log Pseudo-Likelihood	81.44
Generalized Chi-Square	30.69
Gener. Chi-Square / DF	1.10

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error
Intercept	center	0.6176	0.3181

Solutions for Fixed Effects

Effect	group	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		-0.8071	0.2514	14	-3.21	0.0063
group	A	-0.4896	0.2034	14	-2.41	0.0305
group	B	0	.	.	.	.

Type III Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
group	1	14	5.79	0.0305

The odds of side effect occurrence for Group A is 0.613 times the odds for Group B

OR (Odds Ratio) is significant.

group Least Squares Means

group	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Mean	Standard Error Mean	Lower Mean	Upper Mean
A	-1.2966	0.2601	14	-4.99	0.0002	0.05	-1.8544	-0.7388	0.2147	0.04385	0.1354	0.3233
B	-0.8071	0.2514	14	-3.21	0.0063	0.05	-1.3462	-0.2679	0.3085	0.05363	0.2065	0.4334

Differences of group Least Squares Means

group	_group	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper	Odds Ratio	Lower Confidence Limit for Odds Ratio	Upper Confidence Limit for Odds Ratio
A	B	-0.4896	0.2034	14	-2.41	0.0305	0.05	-0.9259	-0.05322	0.613	0.396	0.948

RandominterceptExample.sas

Questions

(1) In PROC GLIMMIX, the dependent variable in the events/trials format implies a binomial distribution. You do not need to specify the DIST= option.

❍ True

❍ False

(2) In PROC GLIMMIX, if the dependent variable y has values 0/1, then you do not need to specify the DIST= option in the MODEL statement because the default distribution for this situation is binary.

❍ True

❍ False

Fitting a Nonlinear Mixed Model using the NLMIXED Procedure

Objectives

- Fit a nonlinear mixed model using the NL
- MIXED procedure.

Orange Tree Growth Example

A botanist is studying the growth patterns in five randomly selected orange trees.

The trunk circumferences of these five orange trees measured at seven time points (in weeks since planted) are recorded and stored in a SAS dataset ***trees***.

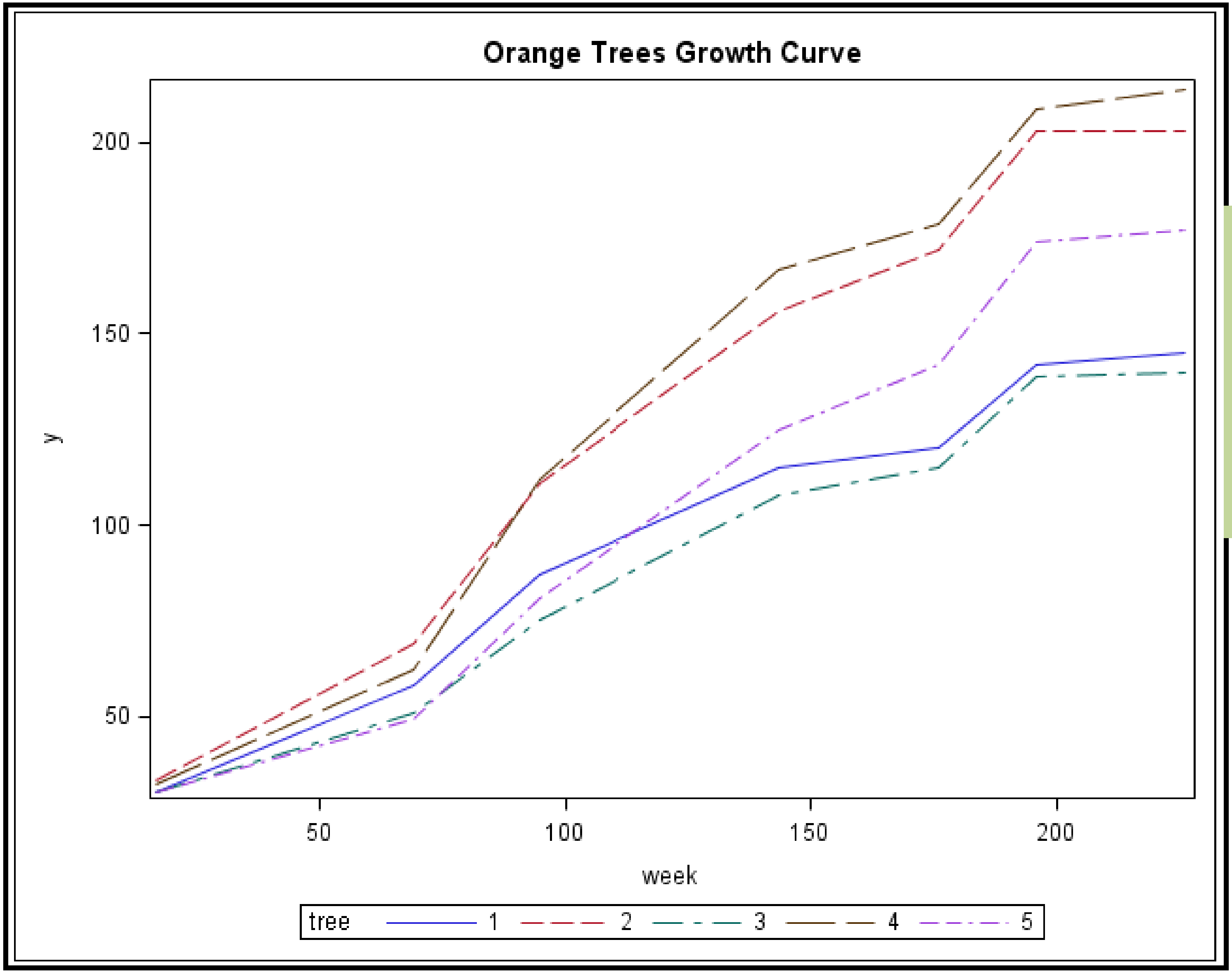
<u>The variables in the data set are:</u>

Y: trunk circumference measurements in millimeters

Tree: trees' identification number (1,2,3,4, and 5)

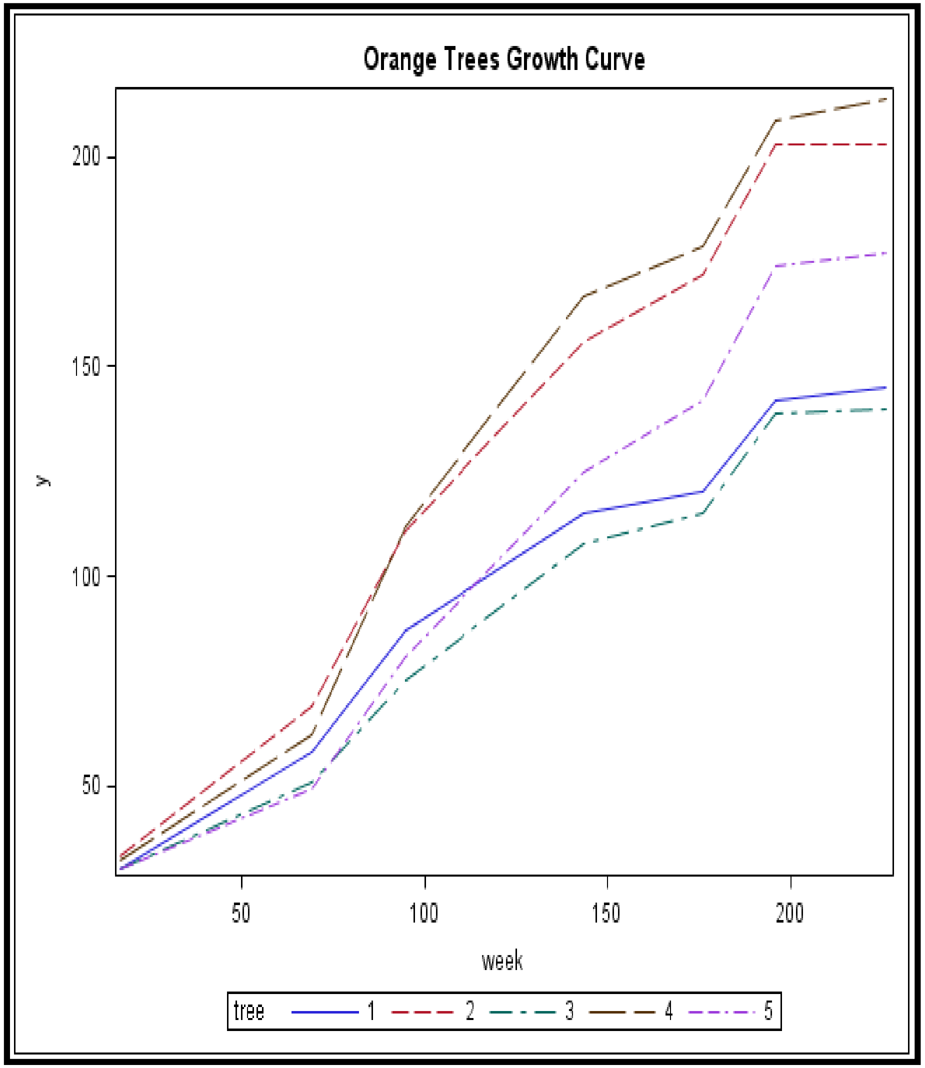
Week: the number of weeks since planting when the measurements were taken

Orange Tree Growth Example



tree	week	y
1	16.86	30
1	69.14	58
1	94.86	87
……		

Orange Tree Growth Model



$$E[Y_{ij}] = \frac{\beta_1 + u_i}{1 + \beta_2 \exp(-\beta_3 x_{ij})}$$

$$u_i \sim N(0, \sigma_u^2), \quad i = 1 \text{ to } 5$$

$$Var[Y_{ij} \mid u_i] = \sigma^2$$

u_i: random term for tree to tree

β_1 – upper horizontal asymptote

$\dfrac{\beta_1}{1+\beta_2}$ – y intercept

β_3 – shape

The bigger the value, the steeper the curve

The NLMIXED Procedure

General form of the NLMIXED procedure:

```
PROC NLMIXED options;
      PARMS parameters and starting values;
       programming statements
      MODEL dependent ~ distribution;
      RANDOM random-effects ~ distribution
                  SUBJECT=variable <options>;
      ESTIMATE 'label' expression;
      PREDICT expression;
RUN;
```

Programming statements enable you to code the log-likelihood function in PROC NLMIXED using DATA step statements.

Model Assumptions in PROC NLMIXED

- The conditional distribution of the data given the random effects can be normal, binary, binomial, Poisson, or of any general form.

- The means (expected values) of the responses and the predictor variables can have any nonlinear relationship.

- Random effects can enter the model nonlinearly.

- Random effects follow a normal distribution.

Estimation Method in PROC NLMIXED

The maximum-likelihood method

- obtains the marginal log-likelihood by quadrature, Laplace, or some other methods, then obtains the maximum-likelihood estimates
- makes model comparisons possible based on information criteria
- cannot be implemented for models with the R-side random effects.

Fitting a Nonlinear Mixed Model Using the NLMIXED Procedure

This demonstration illustrates the concepts discussed previously.

PROC NLMIXED can be used to fit some generalized linear mixed models and nonlinear mixed models.

- ❍ True
- ❍ False

TreeExample.sas

PROC NLMIXED versus PROC MIXED

– The models fit by PROC NLMIXED can be viewed as generalizations of the random coefficient models fit by PROC MIXED.

– PROC NLMIXED allows the random coefficients to enter the model nonlinearly;

PROC MIXED does not.

– PROC MIXED assumes normally distributed data;

PROC NLMIXED allows normal, binomial, Poisson, or any likelihood programmable with SAS statements.

– PROC MIXED performs ML or REML estimations;

PROC NLMIXED only performs ML.

– PROC NLMIXED has no CLASS or REPEATED statement, only allows one RANDOM statement, and requires one SUBJECT= variable;

PROC MIXED is just the opposite.

PROC NLMIXED versus PROC GLIMMIX

– PROC NLMIXED does not have CLASS or RANDOM _RESIDUAL_ statements;

PROC GLIMMIX can handle CLASS statements and the R-side random effects.

– PROC NLMIXED does not support more than one RANDOM statement or more than one SUBJECT= variable;

PROC GLIMMIX supports multiple RANDOM statements and multiple SUBJECT= variables.

– PROC GLIMMIX determines starting values intelligently;

PROC NLMIXED assumes starting value of 1.

– PROC GLIMMIX has a dedicated algorithm for METHOD=LAPLACE, and therefore allows for larger class of models;

PROC NLMIXED treats LAPLACE as a special case of quadrature.