

DigiSem
Wir beschaffen und
digitalisieren



^b
**UNIVERSITÄT
BERN**
Universitätsbibliothek Bern

Dieses Dokument steht Ihnen online zur Verfügung
dank DigiSem, einer Dienstleistung der
Universitätsbibliothek Bern.

Kontakt: Gabriela Scherrer
Koordinatorin digitale Semesterapparate
E-Mail digisem@ub.unibe.ch, Telefon 031 631 93 26

José C. Pinheiro
Douglas M. Bates

Mixed-Effects Models in S and S-PLUS

With 172 Illustrations



Springer



José C. Pinheiro
Department of Biostatistics
Novartis Pharmaceuticals
One Health Plaza
East Hanover, NJ 07936-1080
USA
jose.pinheiro@pharma.novartis.com

Douglas M. Bates
Department of Statistics
University of Wisconsin
Madison, WI 53706-1685
USA
bates@stat.wisc.edu

Series Editors:

J. Chambers
Bell Labs, Lucent
Technologies
600 Mountain Ave.
Murray Hill, NJ 07974
USA

W. Eddy
Department of Statistics
Carnegie Mellon University
Pittsburgh, PA 15213
USA

W. Härdle
Institut für Statistik und
Ökonometrie
Humboldt-Universität zu Berlin
Spandauer Str. 1
D-10178 Berlin
Germany

S. Sheather
Australian Graduate School
of Management
University of New South
Wales
Sydney NSW 2052
Australia

L. Tierney
School of Statistics
University of Minnesota
Vincent Hall
Minneapolis, MN 55455
USA

Library of Congress Cataloging-in-Publication Data
Pinheiro, José C.

Mixed-effects models in S and S-PLUS / José C. Pinheiro, Douglas M. Bates
p. cm. — (Statistics and computing)
Includes bibliographical references and index.
ISBN 0-387-98957-9 (alk. paper)
I. Bates, Douglas M. II. Title. III. Series.
QA76.73.S15P56 2000
005.13'3—dc21

99-053566

Printed on acid-free paper.

© 2000 Springer Verlag New York, LLC

All rights reserved. This work may not be translated or copied in whole or in part without the written permission of the publisher (Springer-Verlag New York, LLC, 175 Fifth Avenue, New York, NY 10010, USA), except for brief excerpts in connection with reviews or scholarly analysis. Use in connection with any form of information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed is forbidden. The use of general descriptive names, trade names, trademarks, etc., in this publication, even if the former are not especially identified, is not to be taken as a sign that such names, as understood by the Trade Marks and Merchandise Marks Act, may accordingly be used freely by anyone.

Printed in the United States of America. (HAM)

9 8 7 6 5

SPIN 10995662

Springer Verlag is a part of *Springer Science+Business Media*

springeronline.com

Contents

Preface	vii
I Linear Mixed-Effects Models	1
1 Linear Mixed-Effects Models	3
1.1 A Simple Example of Random Effects	4
1.1.1 Fitting the Random-Effects Model With <code>lme</code>	8
1.1.2 Assessing the Fitted Model	11
1.2 A Randomized Block Design	12
1.2.1 Choosing Contrasts for Fixed-Effects Terms	14
1.2.2 Examining the Model	19
1.3 Mixed-Effects Models for Replicated, Blocked Designs . . .	21
1.3.1 Fitting Random Interaction Terms	23
1.3.2 Unbalanced Data	25
1.3.3 More General Models for the Random Interaction Effects	27
1.4 An Analysis of Covariance Model	30
1.4.1 Modeling Simple Linear Growth Curves	30
1.4.2 Predictions of the Response and the Random Effects	37
1.5 Models for Nested Classification Factors	40
1.5.1 Model Building for Multilevel Models	44
1.6 A Split-Plot Experiment	45
1.7 Chapter Summary	52
Exercises	52

2	Theory and Computational Methods for LME Models	57
2.1	The LME Model Formulation	58
2.1.1	Single Level of Grouping	58
2.1.2	A Multilevel LME Model	60
2.2	Likelihood Estimation for LME Models	62
2.2.1	The Single-Level LME Likelihood Function	62
2.2.2	Orthogonal-Triangular Decompositions	66
2.2.3	Evaluating the Likelihood Through Decompositions	68
2.2.4	Components of the Profiled Log-Likelihood	71
2.2.5	Restricted Likelihood Estimation	75
2.2.6	Multiple Levels of Random Effects	77
2.2.7	Parameterizing Relative Precision Factors	78
2.2.8	Optimization Algorithms	79
2.3	Approximate Distributions	81
2.4	Hypothesis Tests and Confidence Intervals	82
2.4.1	Likelihood Ratio Tests	83
2.4.2	Hypothesis Tests for Fixed-Effects Terms	87
2.4.3	Confidence Intervals	92
2.5	Fitted Values and Predictions	94
2.6	Chapter Summary	94
	Exercises	96
3	Describing the Structure of Grouped Data	97
3.1	The Display Formula and Its Components	97
3.2	Constructing groupedData Objects	101
3.2.1	Roles of Other Experimental or Blocking Factors	104
3.2.2	Constructors for Balanced Data	108
3.3	Controlling Trellis Graphics Presentations of Grouped Data	110
3.3.1	Layout of the Trellis Plot	110
3.3.2	Modifying the Vertical and Horizontal Scales	113
3.3.3	Modifying the Panel Function	114
3.3.4	Plots of Multiply-Nested Data	116
3.4	Summaries	120
3.5	Chapter Summary	130
	Exercises	130
4	Fitting Linear Mixed-Effects Models	133
4.1	Fitting Linear Models in S with <code>lm</code> and <code>lmList</code>	134
4.1.1	The <code>lmList</code> Function	139
4.2	Fitting Linear Mixed-Effects Models with <code>lme</code>	146
4.2.1	Fitting Single-Level Models	146
4.2.2	Patterned Variance-Covariance Matrices for the Random Effects: The <code>pdMat</code> Classes	157
4.2.3	Fitting Multilevel Models	167
4.3	Examining a Fitted Model	174

4.3.1	Assessing Assumptions on the Within-Group Error . . .	174
4.3.2	Assessing Assumptions on the Random Effects . . .	187
4.4	Chapter Summary	196
	Exercises	197
5	Extending the Basic Linear Mixed-Effects Model	201
5.1	General Formulation of the Extended Model	202
5.1.1	Estimation and Computational Methods	202
5.1.2	The GLS model	203
5.1.3	Decomposing the Within-Group Variance–Covariance Structure	205
5.2	Variance Functions for Modeling Heteroscedasticity	206
5.2.1	<code>varFunc</code> classes in <code>nlme</code>	208
5.2.2	Using <code>varFunc</code> classes with <code>lme</code>	214
5.3	Correlation Structures for Modeling Dependence	226
5.3.1	Serial Correlation Structures	226
5.3.2	Spatial Correlation Structures	230
5.3.3	<code>corStruct</code> classes in <code>nlme</code>	232
5.3.4	Using <code>corStruct</code> Classes with <code>lme</code>	239
5.4	Fitting Extended Linear Models with <code>gls</code>	249
5.5	Chapter Summary	266
	Exercises	267
II	Nonlinear Mixed-Effects Models	271
6	NLME Models: Basic Concepts and Motivating Examples	273
6.1	LME Models vs. NLME Models	273
6.2	Indomethicin Kinetics	277
6.3	Growth of Soybean Plants	287
6.4	Clinical Study of Phenobarbital Kinetics	294
6.5	Chapter Summary	300
	Exercises	301
7	Theory and Computational Methods for NLME Models	305
7.1	The NLME Model Formulation	306
7.1.1	Single-Level of Grouping	306
7.1.2	Multilevel NLME Models	309
7.1.3	Other NLME Models	310
7.2	Estimation and Inference in NLME Models	312
7.2.1	Likelihood Estimation	312
7.2.2	Inference and Predictions	322
7.3	Computational Methods	324
7.4	Extending the Basic NLME Model	328

7.4.1	General model formulation	328
7.4.2	Estimation and Computational Methods	329
7.5	An Extended Nonlinear Regression Model	332
7.5.1	General Model Formulation	333
7.5.2	Estimation and Computational Methods	334
7.6	Chapter Summary	336
8	Fitting Nonlinear Mixed-Effects Models	337
8.1	Fitting Nonlinear Models in S with <code>nls</code> and <code>nlsList</code>	338
8.1.1	Using the <code>nls</code> Function	338
8.1.2	Self-Starting Nonlinear Model Functions	342
8.1.3	Separate Nonlinear Fits by Group: The <code>nlsList</code> Function	347
8.2	Fitting Nonlinear Mixed-Effects Models with <code>nlme</code>	354
8.2.1	Fitting Single-Level <code>nlme</code> Models	354
8.2.2	Using Covariates with <code>nlme</code>	365
8.2.3	Fitting Multilevel <code>nlme</code> Models	385
8.3	Extending the Basic <code>nlme</code> Model	391
8.3.1	Variance Functions in <code>nlme</code>	391
8.3.2	Correlation Structures in <code>nlme</code>	395
8.3.3	Fitting Extended Nonlinear Regression Models with <code>gnls</code>	401
8.4	Chapter Summary	409
	Exercises	410
	References	415
A	Data Used in Examples and Exercises	423
A.1	Alfalfa—Split-Plot Experiment on Varieties of Alfalfa	425
A.2	Assay—Bioassay on Cell Culture Plate	425
A.3	BodyWeight—Body Weight Growth in Rats	427
A.4	Cefamandole—Pharmacokinetics of Cefamandole	427
A.5	CO ₂ —Carbon Dioxide Uptake	428
A.6	Dialyzer—High-Flux Hemodialyzer	429
A.7	DNase—Assay Data for the Protein DNase	429
A.8	Earthquake—Earthquake Intensity	430
A.9	ergoStool—Ergometrics Experiment with Stool Types	431
A.10	Glucose2—Glucose Levels Following Alcohol Ingestion	432
A.11	IGF—Radioimmunoassay of IGF-I Protein	433
A.12	Indometh—Indomethacin Kinetics	433
A.13	Loblolly—Growth of Loblolly Pine Trees	434
A.14	Machines—Productivity Scores for Machines and Workers . .	435
A.15	Oats—Split-plot Experiment on Varieties of Oats	435
A.16	Orange—Growth of Orange Trees	436
A.17	Orthodont—Orthodontic Growth Data	436

A.18 Ovary—Counts of Ovarian Follicles	437
A.19 Oxboys—Heights of Boys in Oxford	437
A.20 Oxide—Variability in Semiconductor Manufacturing	437
A.21 PBG—Effect of Phenylbiguanide on Blood Pressure	438
A.22 PBIB—A Partially Balanced Incomplete Block Design	439
A.23 Phenobarb—Phenobarbitol Kinetics	440
A.24 Pixel—Pixel Intensity in Lymphnodes	440
A.25 Quinidine—Quinidine Kinetics	441
A.26 Rail—Evaluation of Stress in Rails	443
A.27 Soybean—Soybean Leaf Weight over Time	443
A.28 Spruce—Growth of Spruce Trees	444
A.29 Theoph—Theophylline Kinetics	444
A.30 Wafer—Modeling of Analog MOS Circuits	448
A.31 Wheat2—Wheat Yield Trials	448

B S Functions and Classes 451

ACF	451
ACF.lme	452
anova.lme	453
coef.lme	455
coef.lmList	457
fitted.lme	458
fixef	459
gapply	460
getGroups	461
gls	462
gnls	464
groupedData	466
gsummary	469
intervals	471
intervals.lme	471
intervals.lmList	473
lme	474
lmeControl	476
lmList	478
logLik	479
nlme	479
nlmeControl	483
nlsList	485
pairs.lme	486
plot.lme	488
plot.nfnGroupedData	490
plot.nmGroupedData	492
plot.Variogram	494
predict.lme	495

qqnorm.lme	497
ranef	498
ranef.lme	499
ranef.lmList	501
residuals.lme	503
selfStart	504
selfStart.default	505
selfStart.formula	506
Variogram	507
Variogram.lme	508

C A Collection of Self-Starting Nonlinear Regression

Models	511
C.1 SSasymp—The Asymptotic Regression Model	511
C.1.1 Starting Estimates for SSasymp	511
C.2 SSasympOff—Asymptotic Regression with an Offset	512
C.2.1 Starting Estimates for SSasympOff	512
C.3 SSasympOrig—Asymptotic Regression Through the Origin	513
C.3.1 Starting Estimates for SSasympOrig	513
C.4 SSbiexp—Biexponential Model	514
C.4.1 Starting Estimates for SSbiexp	515
C.5 SSfol—First-Order Compartment Model	516
C.5.1 Starting Estimates for SSfol	516
C.6 SSfpl—Four-Parameter Logistic Model	517
C.6.1 Starting Estimates for SSfpl	518
C.7 SSlogis—Simple Logistic Model	519
C.7.1 Starting Estimates for SSlogis	519
C.8 SSmicmen—Michaelis-Menten Model	520
C.8.1 Starting Estimates for SSmicmen	521

Index	523
--------------	------------