Nonlinear Mixed Effects Modeling: 20 Years Later

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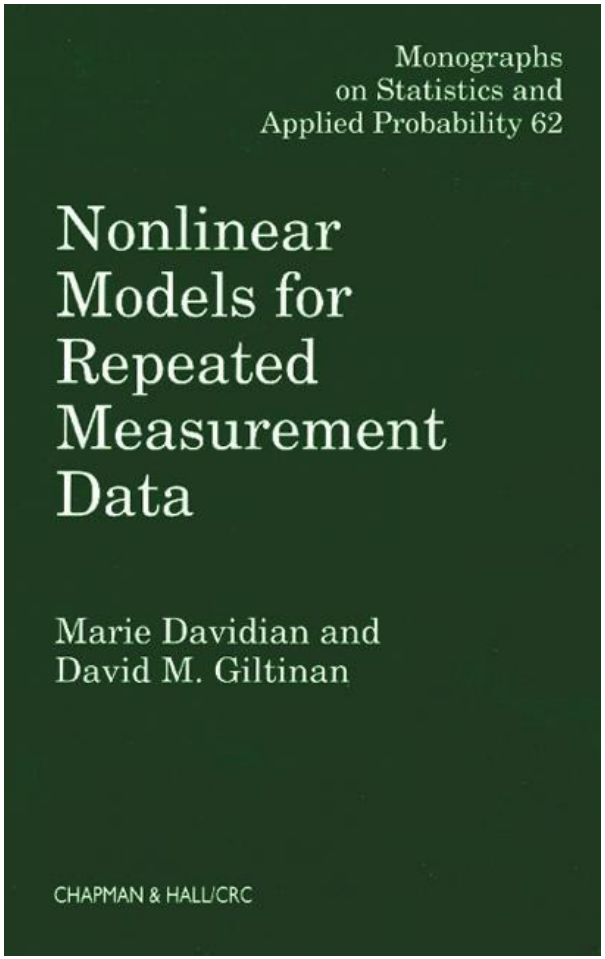
1995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on Statistics and
Applied Probability 62
Nonlinear
Models for
Repeated
Measurement
Data
Marie Davidian and
David M. Giltinan
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How I Got There

- PhD, *1987*, Statistics, University of North Carolina-Chapel Hill
- Assistant Professor, Department of Statistics, North Carolina State University
- Around *1989* , *Soybean growth study* (Section 11.2)
- *Very different* application, *same problem. . .*

Partners in Crime

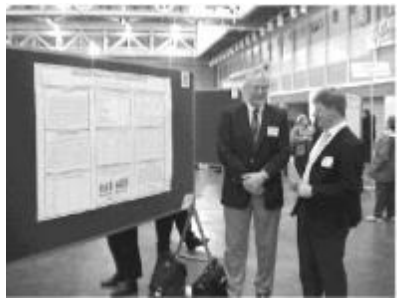
Pre-1995

- Davidian, M. and Giltinan, D.M. (1993). Some simple methods for estimating intraindividual variability in nonlinear mixed effects models. *Biometrics*, 49, 59–73.
- Davidian, M. and Giltinan, D.M. (1993). Some general estimation methods for nonlinear mixed effects models. *Journal of Biopharmaceutical Statistics*, 3, 23–55.
- Davidian, M. and Gallant, A.R. (1992). Smooth nonparametric maximum likelihood for population pharmacokinetics, with application to quinidine. *Journal of Pharmacokinetics and Biopharmaceutics*, 20, 529–556.
- Davidian, M. and Gallant, A.R. (1993). The nonlinear mixed effects model with a smooth random effects density. *Biometrika*, 80, 475–488.

Statisticians Get Involved

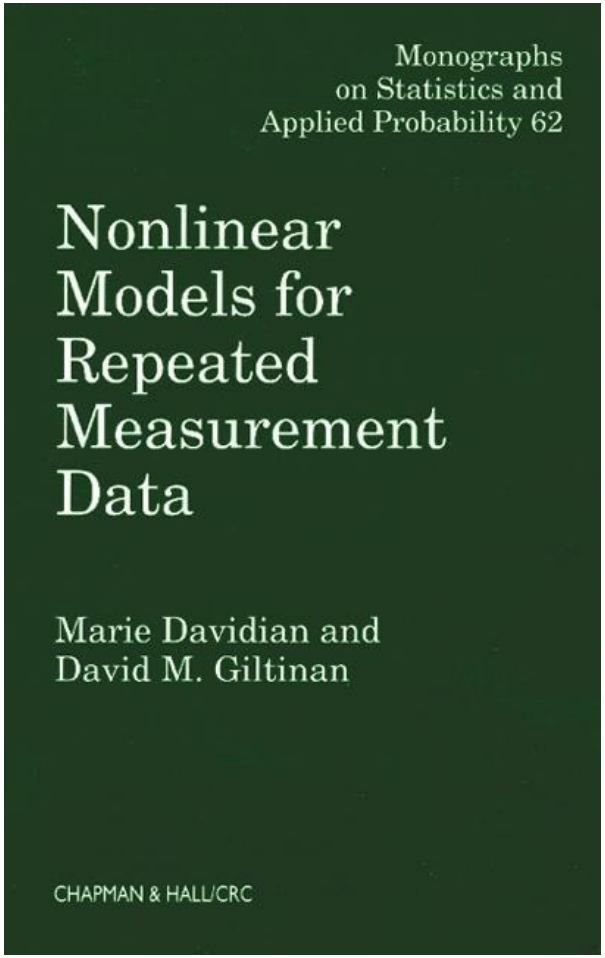







- Lindstrom, M. J. and Bates, D. M. (1990). Nonlinear mixed effects models for repeated measures data. *Biometrics*, 46, 673-687.
- Pinheiro, J. C., and Bates, D. M. (1995). Approximations to the log-likelihood function in the nonlinear mixed-effects model. *Journal of Computational and Graphical Statistics*, 4, 12–35.
- Wakefield, J. (1996). The Bayesian analysis of population pharmacokinetic models. *Journal of the American Statistical Association*, 91, 62–75 (submitted 1993).
- Vonesh, E. F. (1992). Non-linear models for the analysis of longitudinal data. *Statistics in Medicine*, 11, 1929–1954.
- Wolfinger, R. (1993). Laplace's approximation f nonlinear mixed models. *Biometrika*, 80, 791–795.

1995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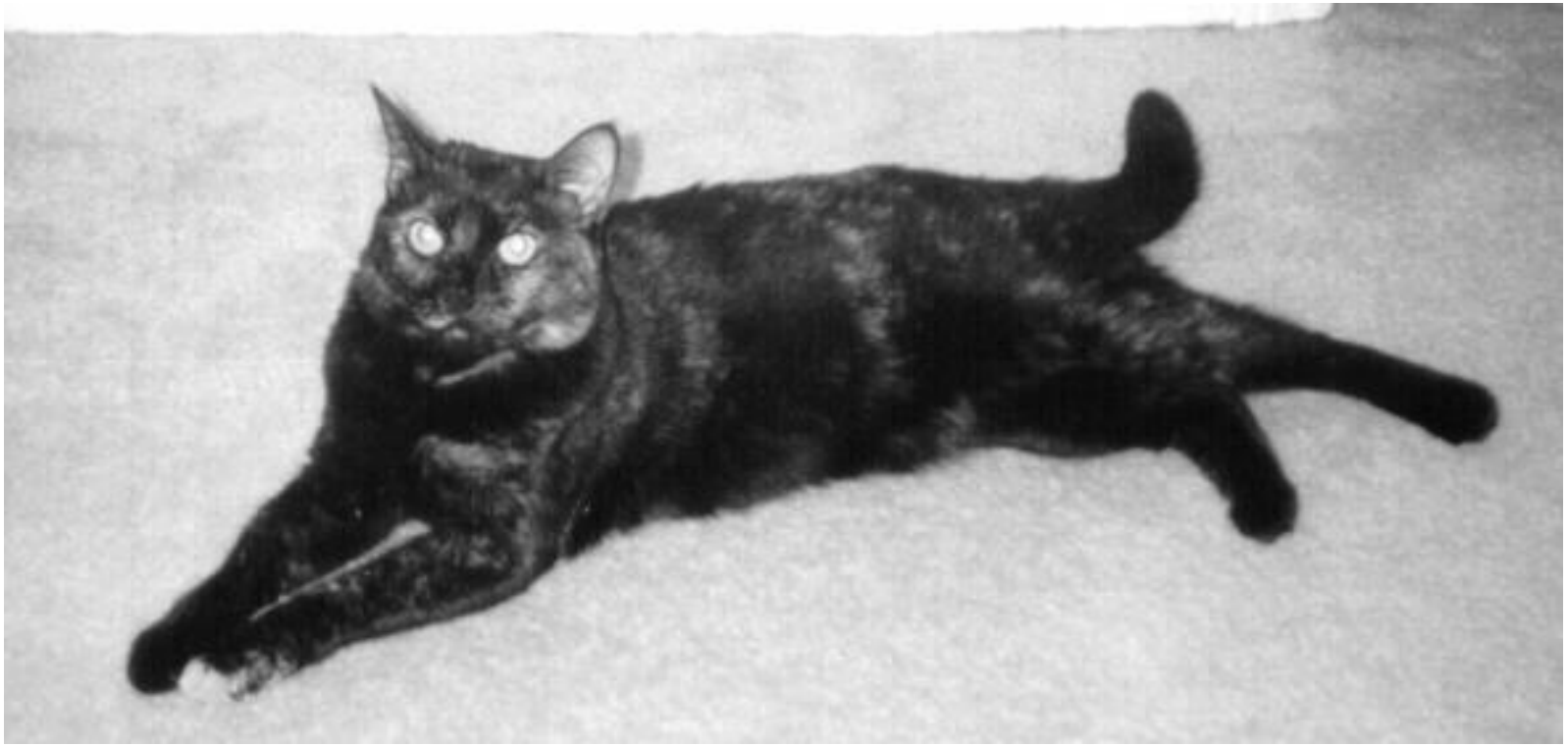
Clarification



Kitty
1989 – 2011

December 1994

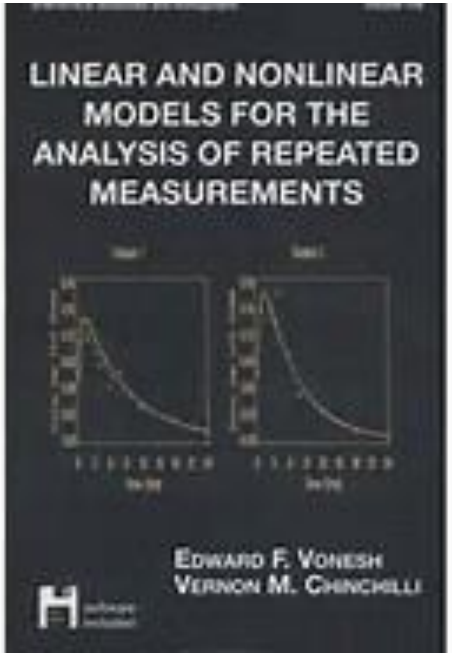
Cottonwood Café, Boston, Massachusetts

January 7, 1995

January 7, 1995

June 1995

1996 – NLMEMs Are A Hot Topic



Biopharmaceutical Applied Statistics Symposium (BASS) III, 1996, San Diego, California

More Statisticians






- Gelman, A., Bois, F., and Jiang, J. (1996). Physiological pharmacokinetic analysis using population modeling and informative prior distributions. *JASA*, 91, 1400–1412. (*MCSim*)
- Rosner, G. L. and Mueller, P. (1997). Bayesian population pharmacokinetic-pharmacodynamic analysis using mixture models. *Journal of Pharmacokinetics and Biopharmaceutics*, 25, 209–233.
- Galecki, A. T. (1998). NLMEM: New SAS/IML macro for hierarchical nonlinear models. *Computer Methods and Programs in Biomedicine*, 55, 207–16.
- Wu, H. and Ding, A. (1999). Population HIV-1 dynamics in vivo: Applicable models and inferential tools for virological data from AIDS clinical trials. *Biometrics*, 55, 410–418.

Late 1990s/Early 2000s – Explosion of Interest

- Roe, D. J. (1997). Comparison of population pharmacokinetic modeling methods using simulated data: Results from the Population Modeling Workgroup. *Statistics in Medicine*, 16, 1241–1262.
- Racine-Poon, A. and Wakefield, J. (1998). Statistical methods for population pharmacokinetic modelling. *Statistical Methods in Medical Research*. 7, 63-84.
- Wolfinger, R. D. (1999). Fitting nonlinear mixed models with the new NLMIXED procedure. Cary, NC: SAS Institute, 1999. (Paper 287). (*proc nlmixed*)
- Pinheiro, J. C. and D. M. Bates. (2000). *Mixed-Effects Models in S and S-PLUS*. New York, Springer. (*nlme*)
- Lunn, D. J., Best, N., Thomas, A., Wakefield, J., and Spiegelhalter, D. (2002). Bayesian analysis of population PK/PD models: General concepts and software. *Journal of Pharmacokinetics and Pharmacodynamics*, 29, 271–307 (*PKBugs*)

2003 – Update

Davidian, M. and Giltinan, D. M. (2003). Nonlinear models for repeated measurements: An overview and update. Editor's Invited paper, *Journal of Agricultural, Biological, and Environmental Statistics*, 8, 387-419.

Data and Model

Data: $i = 1, \ldots, N$ subjects

- Concentrations $Y_{i1}, \ldots, Y_{in_i}$ at times $t_{i1} < \cdots < t_{in_i}$
- *Within-subject* conditions of observation U_i (doses, dosing intervals, etc)
- *Subject characteristics* Z_i (covariates; could vary over time), e.g., weight, age, gender, renal function, genetic

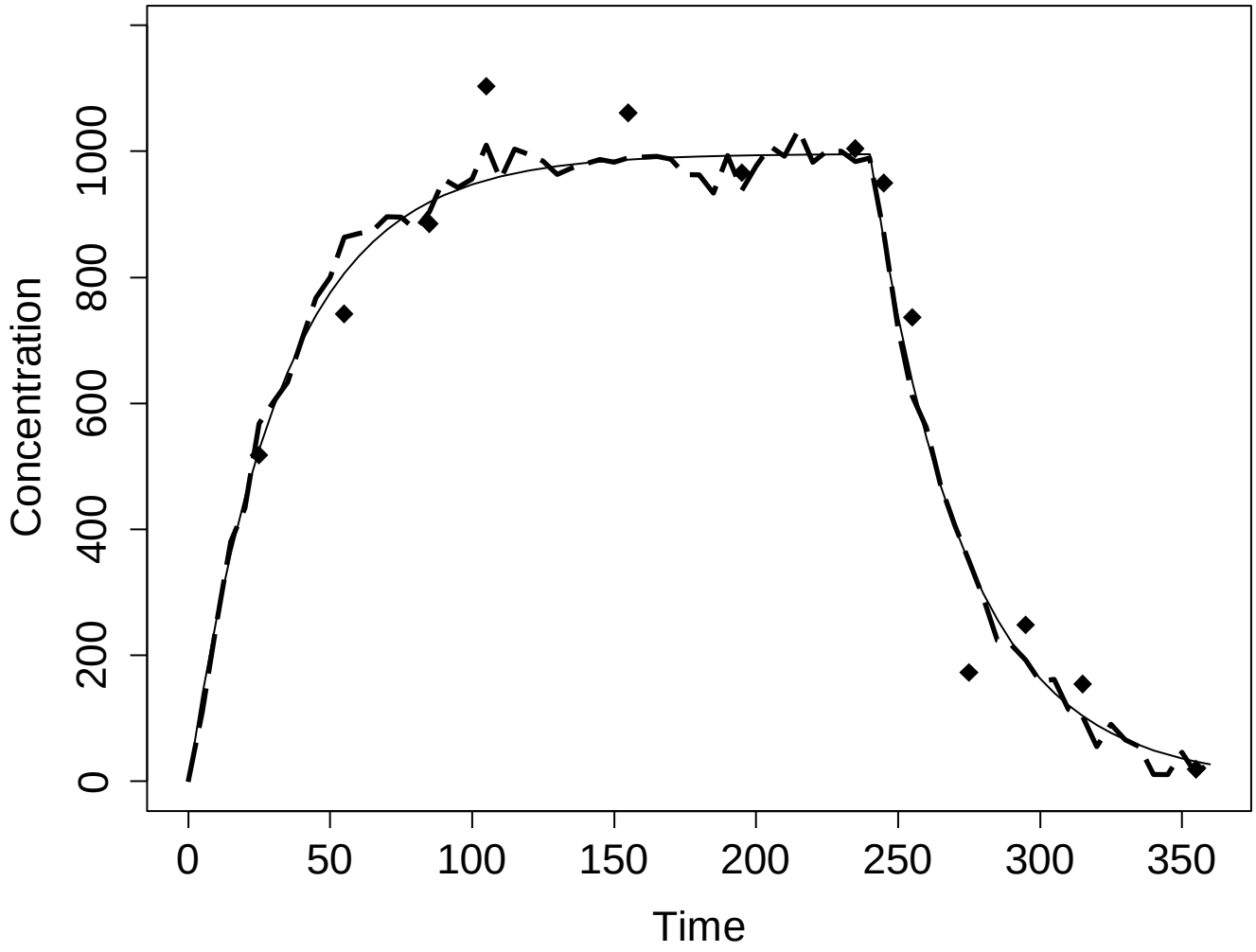
Individual model: $Y_{ij} = f(t_{ij}, U_i, \varphi_i) + e_{ij}$

- *PK model* f
- *Subject-specific* PK parameters φ_i

Population model: $\varphi_i = d(Z_i, \theta, \eta_i)$

- *Fixed effects* θ
- *Random effects* η_i (often assumed *normal* but need not be)

Conceptual Perspective



Conceptual Perspective

Y_{ij} at times t_{ij} are *intermittent* observations (possibly *measured with error*) on an *subject-specific stochastic process*

$$Y_i(t, U_i) = f(t, U_i, \varphi_i) + e_{R,i}(t, U_i) + e_{M,i}(t, U_i)$$

$$e_i(t, U_i) = e_{R,i}(t, U_i) + e_{M,i}(t, U_i)$$

- $f(t, U_i, \varphi_i)$ is i's "*inherent tendency*" of concentration over time under conditions U_i
- $e_{R,i}(t, U_i)$ mean-zero *deviation* of *realization* of process, *auto-correlated* over time
- $e_{M,i}(t, U_i)$ mean-zero *measurement error deviation*
- *Assumptions* on $e_{R,i}(t, U_i)$ and $e_{M,i}(t, U_i)$ lead to assumptions on $e_i(t, U_i)$ and thus on e_{ij}

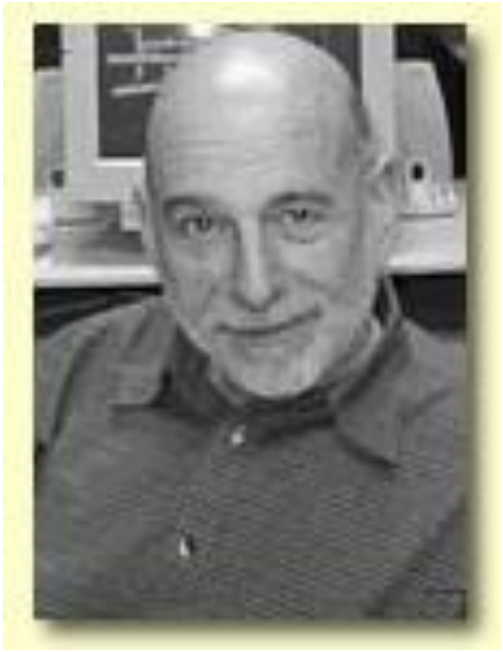
Ongoing Methodological Challenges

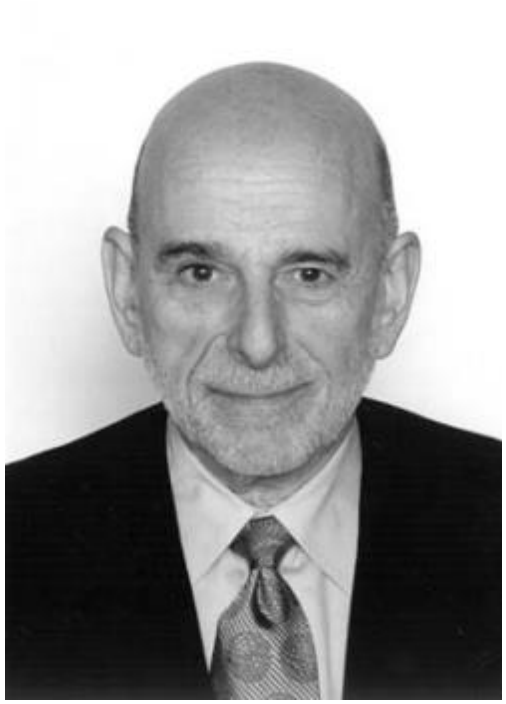
- Computational strategies for implementation (likelihood/Bayesian)
- Measurement error in covariates (Z_i)
- Missing covariates (Z_i)
- Censoring (Y_{ij}, Z_i)
- Joint modeling of PK/PD and survival/clinical outcomes
- Modeling and simulation
- Population model specification/covariate selection (d, Z_i)
- High-dimensional covariates (Z_i) (e.g., genetic association with PK)
- . . .

20 Years Later

- The nonlinear mixed effects model is now a *routine framework* for *both* statisticians and pharmacokineticists
- Involves *pharmacological* and *statistical* components
- Further progress will continue to benefit from *collaboration*

Dedication





Lewis B. Sheiner
1940 – 2004