

Introduction to Nonlinear Mixed-Effects Models for Longitudinal Data

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ABSTRACT

Nonlinear mixed-effects models are models in which one or more coefficients of the model enter in a nonlinear manner, such as appearing in the exponent of the growth function. This talk is intended for users already familiar with linear mixed-effects models who are interested in extending their modeling options to include more complex functions. Unlike linear mixed-effects models for longitudinal data, nonlinear mixed-effects models enable researchers to apply a wide range of nonlinear growth functions to data, including multi-phase functions. This talk reviews the syntax for the NLMIXED procedure for fitting a variety of nonlinear mixed-effects models.

INTRODUCTION

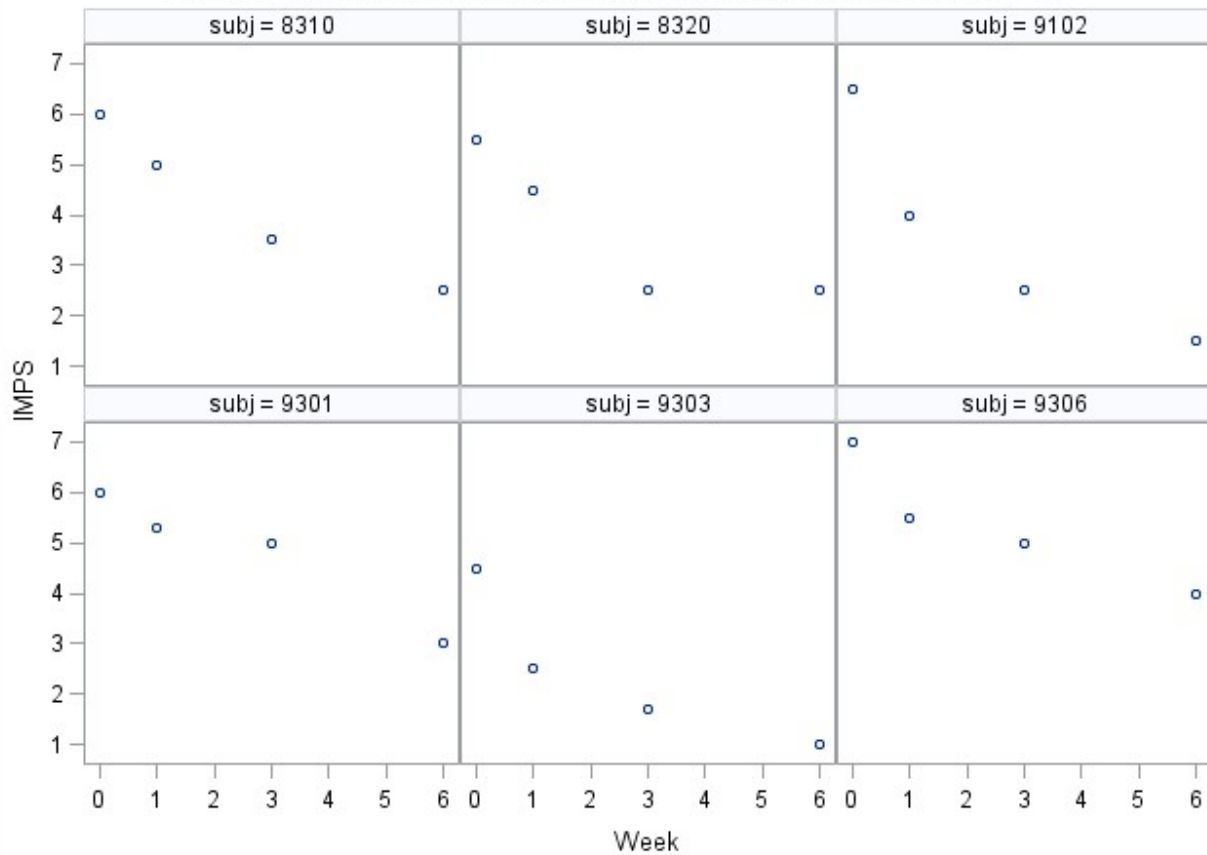
Behavioral studies can require repeated assessments of a target behavior to understand its developmental progression. Repeated measures reflect individual differences in the target response as it evolves, either according to time or to changes in experimental conditions. These differences may be reflected in dissimilar behavioral courses, such as those marked by different rates of change or differences in the timing of transition from one distinct developmental phase to another. Nonlinear mixed-effects models provide a flexible framework for the study of many kinds of complex behaviors often studied in the behavioral and social sciences. This paper provides an introduction to these models and presents examples of different types of complex patterns of change, including growth that follows two distinct phases of development. Syntax is provided for fitting different nonlinear growth models using SAS® PROC NLMIXED, a procedure that allows users to tailor a growth function to a particular measured response.

NONLINEAR MIXED-EFFECTS MODELS

Nonlinear mixed-effects models (Davidian & Giltinan, 2003) offer a general structure for characterizing repeated measures data. An extension of linear mixed-effects models developed for normally distributed response data and for which coefficients of the model are strictly linear, nonlinear mixed-effects models provide a means for users to specify models that may better describe a measured response whose pattern of change is complex.

For example, repeated measures data for 437 patients (Lorr & Klatt, 1966) show individual differences in a global rating assessment of severity of illness, beginning with a baseline assessment (week 0) and reported on weekly thereafter for up to 6 weeks. Higher scores on the 7-point rating scale correspond to relatively poor functioning. The patients were assigned to either a treatment group in which patients received one of three psychiatric drugs or to a control group in which patients received a placebo. Figure 1 displays the raw scores for six patients, with separate plots for individuals assigned to a drug or to the placebo condition.

Item 79 of the Inpatient Multidimensional Psychiatric Scale (IMPS)



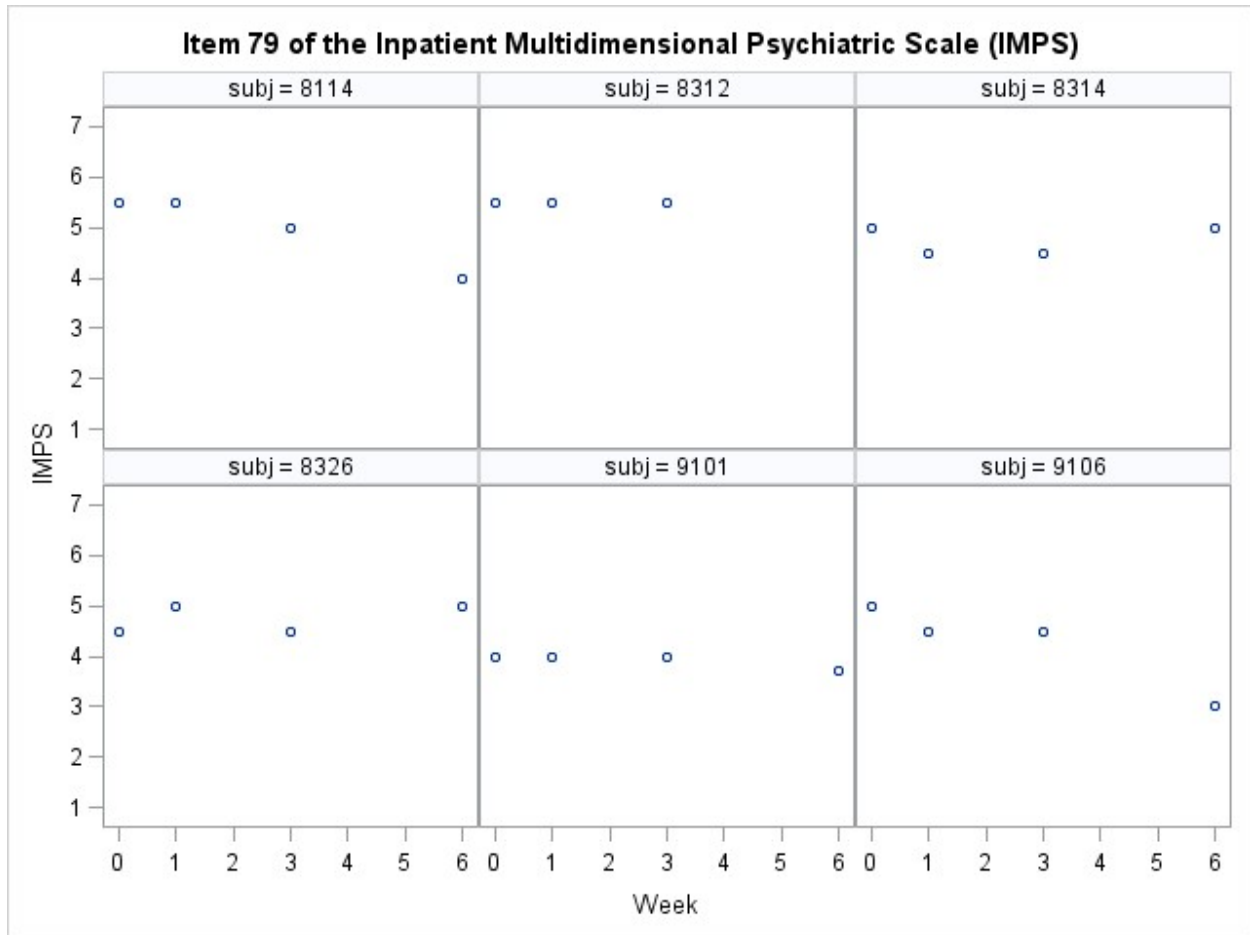


Figure 1

As shown in the displays, individual differences are apparent. For instance, among those receiving a therapeutic drug, many patients showed an overall improvement in ratings with time but at different rates, with some patients showing improvements earlier than others. In the control group, responses exhibit patterns that differ from those of the treatment group, with individual trajectories lacking the more apparent path to improvement illustrated by patients receiving a psychiatric drug. What is apparent with these data is that there is a general course in the responses of individuals within the same group, yet within groups, individuals differ in their response levels and rates of change.

Nonlinear mixed-effects models are well suited to the analysis of these data. A nonlinear mixed-effects model is a subject-specific model in which a general growth model is assumed to characterize the population, but the coefficients of the growth model can be unique to the individual. For the illness rating data, a nonlinear mixed-effects model is specified in which a common growth function is assumed for all patients, but one or more of the coefficients of the function vary between both groups and patients within groups to evaluate important differences related to the treatment conditions. Thus, the model provide a meaningful way to parameterize differences between the treatment groups, as well as individual differences in aspects of the responses both within and between treatment groups.

In a different study, participants provided four measures of salivary cortisol, a stress hormone, over the course of a day (Ryff & Almeida, 2017). For many people, morning cortisol levels increase shortly after waking, followed by a general decreasing response level over the course of the day. Similar to the illness ratings, there is a similar pattern of

response across people, but individual differences in cortisol measures apparent, as illustrated in Figure 2.

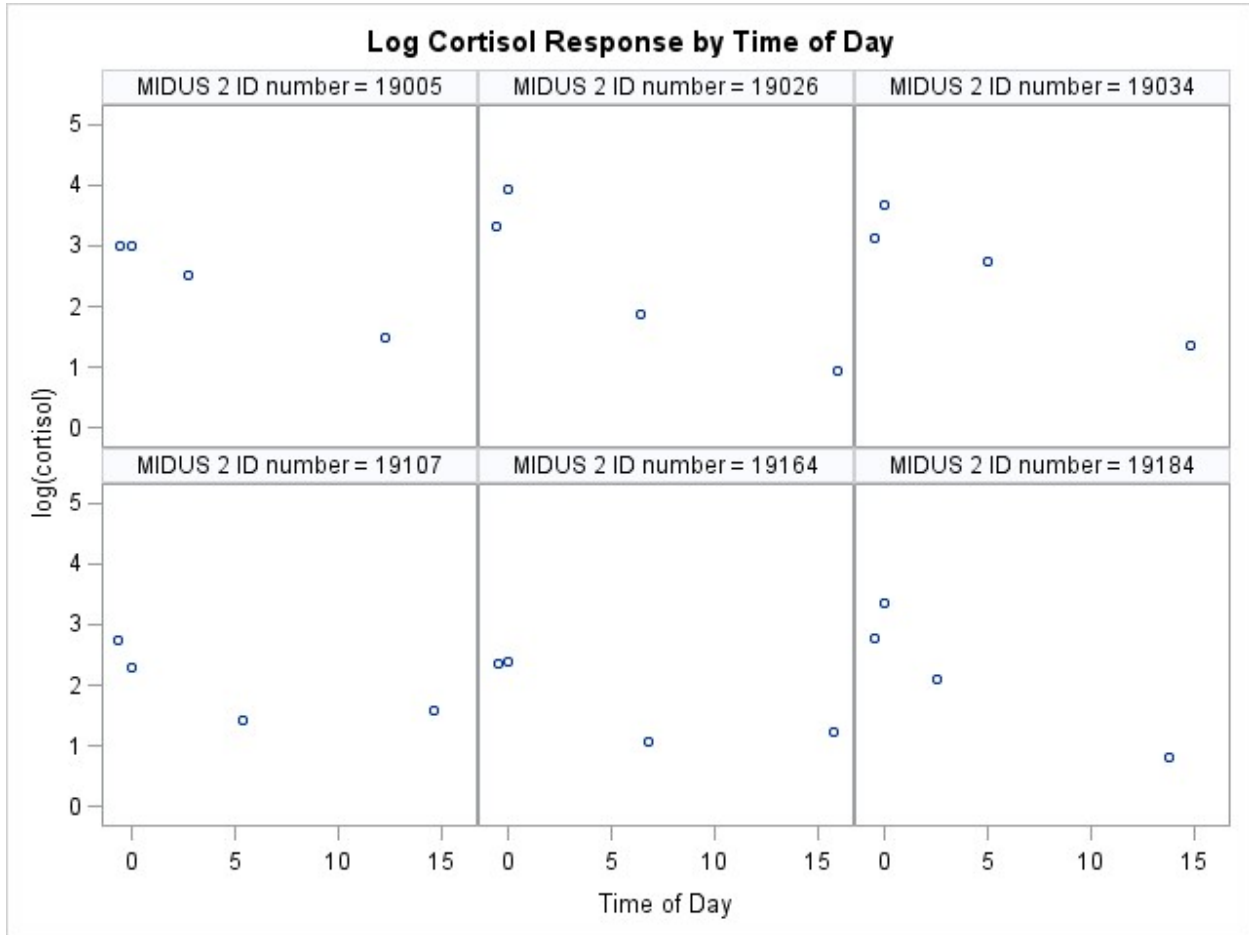


Figure 2

FITTING AN EXPONENTIAL GROWTH MODEL TO ILLNESS RATINGS

PROC NL MIXED syntax for fitting a logistic growth curve model to the illness severity ratings is:

```

title1 'exponential growth model';
PROC NL MIXED;
PARMS
f10 = 0.97          f11 = 0.01          f20 = 0.53
f21 = -0.2529      f30 = 0.12          f31 = 0.15
s1 = 0.0004
c21 = 0.009        s2 = 0.308
se = 0.077;
b1=f10 + f11*tx + u1;
b2=f20 + f21*tx + u2;
b3=f30 + f31*tx;
pred = b2-(b2-b1)*exp(-b3*week);

MODEL imps79b ~ normal(pred,se);
RANDOM u1 u2 ~ NORMAL([0,0],[s1,c21,s2]) SUBJECT=id;
bounds s1 s2 se >= 0;

```

FITTING A TWO-PHASE MIXED-EFFECTS MODEL TO CORTISOL MEASURES

PROC NL MIXED syntax for fitting a linear-quadratic growth curve model to the cortisol measures is:

```
title1 'linear-quadratic growth model';
proc nlmixed;
parms
f00   =    2.92   f10   =    0.591
f20   =   -0.21  f30   =    0.007
tau0  =   -1.53
s2u0  =    0.19
cu1u0 =    0.03      s2u1 =    0.13
cu2u0 =   -0.008    cu2u1 =   -0.003      s2u2 =    0.001;
s2e = .1;
tau = 0;
a0 = f00 + u0;
a1 = f10 + u1;
b1 = f20 + u2;
b2 = f30;
bounds s2u0 s2u1 s2u2 >0;
if (CORTpctime <= tau) then predv = a0 + a1*CORTpctime ;
if (CORTpctime > tau) then predv = a0 + a1*tau + b1*(CORTpctime-tau) +
b2*(CORTpctime*CORTpctime - tau*tau);
model logcort ~ normal(predv,s2e);
random u0 u1 u2 ~ normal([0,0,0],[s2u0,
                                cu1u0,s2u1,
                                cu2u0,cu2u1,s2u2]) subject=m2id;
```

CONCLUSION

Nonlinear mixed-effects models, like linear mixed-effects models, are subject-specific models that assume a common trajectory for the population. A growth model is specified that is assumed to be common to all individuals but one or more of the coefficients of the model are unique to the individual. SAS PROC NL MIXED allows for estimation of these models in which users may specify the growth function directly. This naturally includes nonlinear growth models where one or more of the model coefficients can enter a growth model in a nonlinear way. Estimation of these models is not necessarily straightforward, however, and so careful consideration should be made about the suitability of a given model in describing a set of data. Paper 332-2012, "*Tips and Strategies for Mixed Modeling with SAS/STAT® Procedures*" offers many helpful suggestions.

Some aspects of fitting a linear mixed-effects model for longitudinal data are not so routine when fitting a nonlinear mixed-effects model but are possible. For instance, Harring and Blozis (2014) and Blozis and Harring (2018) show how PROC NL MIXED can be used to fit nonlinear mixed-effects models where the level-1 residual covariance structure does not necessarily assume independence of the residuals with constant variance across occasions. They show how to fit nonlinear mixed-effects models allowing for heterogeneity of variance or covariances between residuals.

Generalized linear mixed-effects models, estimated using PROC GLIMMIX, allow for a wide range of continuous and discrete distributions. PROC NL MIXED also includes a number of alternative response distributions, and so the procedure may be used to fit generalized nonlinear mixed-effects models.

Finally, with increasing model complexity often comes increasing computational demands. Sometimes it is suggested that users rely on a first-order linearization method available in

PROC NL MIXED (specify method=FIRO). Although suitable in some circumstances, models estimated using this procedure can generate results that are consistent with a different statistical model, namely a structure latent curve model. Unlike a nonlinear mixed-effects model that is a subject-specific model, a structured latent curve model is a population-average model, and so it has a very different interpretation (Blozis & Harring, 2016).

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Figure 1. Severity of Illness Ratings for Treatment (upper figure) and Control (lower figure)

Figure 2. Log-Cortisol Response for a Single Day

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