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Fitting Nonlinear Regression Models with Correlated Errors to Individual Pharmacodynamic Data Using SAS Software

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Nonlinear regression is widely used in pharmacokinetic and pharmacodynamic modeling by applying nonlinear ordinary least squares. Although the assumption of independent errors is frequently not fulfilled, this has received scant attention in the pharmacokinetic literature. As in linear regression, leaving correlation of errors out of account leads to an underestimation of the standard deviations of parameter estimates. On the other hand, the use of models that accommodate correlated errors requires more care and more computation. This paper describes a method to fit log-normal functions to individual response curves containing correlated errors by means of statistical software for time series. A sample computer program is given in which the SAS/ETS procedure MODEL is used. In particular, the problem of finding appropriate starting values for nonlinear iterative algorithms is considered. A linear weighted least squares approach for initial parameter estimation is developed. The adequacy of the method is investigated by means of Monte Carlo simulations. Furthermore, the statistical properties of nonlinear least squares with and without accommodating correlated errors are compared. Time action profiles of a long-acting insulin preparation injected subcutaneously in humans are analyzed to illustrate the usefulness of the method proposed.

KEY WORDS: nonlinear regression; pharmacodynamic data; log-normal curves; correlated errors; nonlinear least squares; starting values; simulation.

INTRODUCTION

A general representation of individual pharmokinetic or pharmacodynamic data is a nonlinear regression model

$$y_t = f(t, \theta) + u_t \tag{1}$$

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where y_t are the measured curve points, t is the time, f is a nonlinear time function, θ is a vector of unknown parameters and u_t are random errors. In standard nonlinear regression using ordinary least squares (OLS) it is assumed that the u_t are independent and identically distributed with mean zero and variance σ_u^2, in symbols

$$u_t \; iid(0, \sigma_u^2) \tag{2}$$

Some important statistical considerations involved in the fitting of nonlinear regression equations in pharmacokinetic applications are treated by Boxenbaum *et al.* (1). Several generalizations of the stringent assumption, Eq. (2) are possible. The most important are heteroscedastic errors, i.e., unequal error variances, and correlated errors. Heteroscedasticity is widely considered in the pharmacokinetic literature (2,3) entailing the development of a special estimation method called extended least squares (ELS) (4). Although this method is sensitive to outliers and model misspecification and could lead to an inconsistent estimator (5), the application of ELS is popular in pharmacokinetic research. While the second important generalization of Eq. (2), i.e., allowing correlated errors, appears frequently in econometrics, environmetrics and other fields, it has received only little attention in the pharmacokinetic literature. It is also possible that both violations of the *iid* assumption occur together, which makes it difficult to model the error structure adequately.

A case in which the independence of errors cannot be assumed, is presented by pharmacodynamic studies using the euglycemic glucose-clamp technique (6). In such studies blood glucose concentration is held constant after subcutaneous injection of insulin preparations by varying glucose infusion rates (GIR) automatically (Biostator) or manually. This permits an indirect measurement of the time action profiles of the insulin preparation studied. The glucose-clamp algorithm employed by the Biostator results in correlated data. An example of such a GIR curve is shown in Fig. 3 (see the example below for more details).

In this paper we demonstrate that methods for time series analysis (7,8) can be applied to correlated pharmacodynamic data such as GIR curves. The serial dependence of data values is taken into account by modeling the errors as stationary autoregressive (AR) processes of order p

$$u_t = \sum_{j=1}^{p} \varphi_j u_{t-j} + \varepsilon_t \tag{3}$$

where $\varepsilon_t \; iid(0, \sigma_u^2)$, φ_j for $j = 1, \ldots, p$ are the AR parameters, and $t = 1, \ldots, n$ are equally spaced time points. In practice, a value for the order p must be chosen. For this, the Box-Jenkins method (7,8) can be applied. A brief overview of this method is given by Seber and Wild (9).

Since GIR data represent unimodal curves, gamma and log-normal functions (10,11) have some advantages over the more commonly used poly-exponentials (12,13). In this paper the log-normal function

$$f(t) = at^{-1}\, e^{-b[\log(t)-c]^2} \tag{4}$$

is used, which has desirable properties to describe *GIR* curves (13). The use of this function yields Model Eq. (1) with Eq. (4) inserted for f, $\theta = (a, b, c)'$, and Eq. (3) for u_t. Taking Eq. (3) into account is more accurate than nonlinear OLS applied to Eq. (1), but requires more care and more computation. In the following, practical problems of fitting this model to real data are considered. In particular, a method of finding starting values for the nonlinear iterative algorithms is proposed. A sample computer program using SAS software (14,15) is given in the Appendix. The adequacy of the proposed method as well as advantages of taking correlated errors into account are investigated by means of Monte Carlo simulations. An example of fitting log-normal curves with AR errors of order 3 to GIR data is given to illustrate the usefulness of the method proposed.

A LINEAR WEIGHTED LEAST SQUARES APPROACH TO OBTAIN INITIAL ESTIMATES

The common nonlinear estimation procedures are iterative algorithms requiring appropriate starting values to ensure a successful fit. The problem of finding suitable initial estimates is an important but neglected issue in nonlinear regression analysis (16). For the development of an initial estimation procedure for log-normal curves one can make use of the fact that the log-normal function in Eq. (4) can be linearized via logarithmic transformation. Applying the log transformation to both sides of Eq. (4) yields the mathematically equivalent expression

$$g(x) = \alpha + \beta x + \gamma x^2 \tag{5}$$

where $g = \log(f)$, $x = \log(t)$, and

$$\begin{aligned} \alpha &= \log(a) - bc^2 \\ \beta &= 2bc - 1 \\ \gamma &= -b \end{aligned} \tag{6}$$

Hence, if $f(t)$ would be observable, a perfect fit could be obtained by applying linear OLS to Eq. (5). However, in Model Eq. (1) the values $f(t)$ are corrupted by additive errors, resulting in the observed values y_t. Applying the log transformation to y_t involves several problems. First, some of the y_t possibly are not positive due to negative errors u_t. Second, the log

transformation of some curve patterns caused by the autocorrelation structure can produce highly biased data. The first problem can be easily solved by substituting small positive values, e.g., 0.0001, for negative y_t. However, this replacement increases the bias of the data transformation. Hence, using OLS for such log-transformed data will in general produce an inadequate fit. However, the goodness-of-fit can be improved by choosing suitable weights and applying linear weighted least squares (WLS) for initial parameter estimation in Eq. (5). Appropriate weights which diminish the bias of the log transformation are obtained by the observed y_t themselves together with some prior information about the time course. For example, if one knows that within an initial period of, say, $t_0 = 20$ min the true curve points are close to zero, one can choose very small weights or disregard these data by choosing the weights 0. Thus, the weights can be described by

$$w_t = \begin{cases} 0 & \text{if } t \leq t_0 \\ 0.0001 & \text{if } y_t \leq 0 \\ y_t & \text{otherwise} \end{cases} \tag{7}$$

For application of linear WLS to Model Eq. (5) a standard linear regression program such as PROC REG (14) can be used. To obtain the initial parameter estimates for Model Eq. (4) a transformation back into the original scale is necessary. Solving Eq. (6) for a, b, c yields

$$\begin{aligned} a &= \exp\left(\alpha - \frac{(\beta+1)^2}{4\gamma}\right) \\ b &= -\gamma \\ c &= -\frac{\beta+1}{2\gamma} \end{aligned} \tag{8}$$

Having computed the starting values in the original scale by means of Eq. (8), in principle, any nonlinear regression program can be used for the final nonlinear fit. However, due to the correlated errors [Eq. (3)], some special computations are required. These can be done easily by using the SAS/ETS procedure MODEL (15). This procedure in the SAS module, developed for econometrics and time series analysis, is also suitable for pharmacokinetic modeling (17). In comparison to other better known nonlinear programs such as NLIN (14) the procedure MODEL has some advantages. A variety of error structures such as AR and autoregressive moving average (ARMA) processes can be modeled, a quality that is required here. In addition, one does not have to specify derivatives, simultaneous equations can be considered, and MODEL can be used for simulations.

MONTE CARLO SIMULATIONS

Simulated Data

To evaluate the adequacy of the proposed method of obtaining starting values, log-normal curves with additive normally distributed AR(1) errors were simulated within the period $t \in [0,1000]$ using the parameter values

$$\begin{aligned} a &= 1000 \\ b &= 1 \\ c &= 6 \\ \sigma_u^2 &= 1 \end{aligned} \tag{9}$$

Using additionally the AR parameter $\varphi = 0.9$ and the number of time points $n = 1000$ ($t = 1, \ldots, 1000$) the simulated data resemble the GIR profiles recorded in pharmacodynamic studies. The relatively high error variance $\sigma_u^2 = 1$ was chosen to investigate the properties of estimation procedures in nonoptimal situations possibly occurring in the practice of glucose-clamp studies. In the simulations presented here the error variance was not varied, which would be necessary if one wants to investigate the usefulness of the estimation method for short response curves. In this paper, attention is focused on log-normal curves with similar properties as GIR data. To analyze the effect of φ and n, additional parameter combinations were considered using $\varphi = 0.1$, $\varphi = 0.5$, and $n = 100$ ($t = 10, \ldots, 1000$) yielding $2 \times 3 = 6$ sets of parameters. A sample of $n = 100$ is small in this case because the resulting curve can be masked due to the high error variance. For each of the parameter sets $s = 1000$ replications were made, resulting in 6000 simulated log-normal curves in all. A log-normal function was fitted to each simulated curve by applying the linear WLS approach to obtain starting values and then using nonlinear least squares. Final nonlinear estimations were done with (NLAR) and without (NL) accommodating correlated errors. An example of such a simulated curve is shown in Fig. 1, where $\varphi = 0.9$ and $n = 1000$ were used. The curve fitting procedure is illustrated by plotting the retransformed initial curve estimate as well as the final NLAR fit.

Adequacy of the Starting Values

The initial parameter estimates obtained by the linear WLS approach can serve as starting values if they ensure a successful and fast convergence of the nonlinear iterative scheme. All simulations with a sample of $n = 1000$ resulted in a successful fit for both methods. For $n = 100$ and $\varphi = 0.9$ the NL method failed to converge in 23 of 1000 replications, while the NLAR method failed in 39 cases. For $\varphi = 0.5$ no convergence was achieved in 1

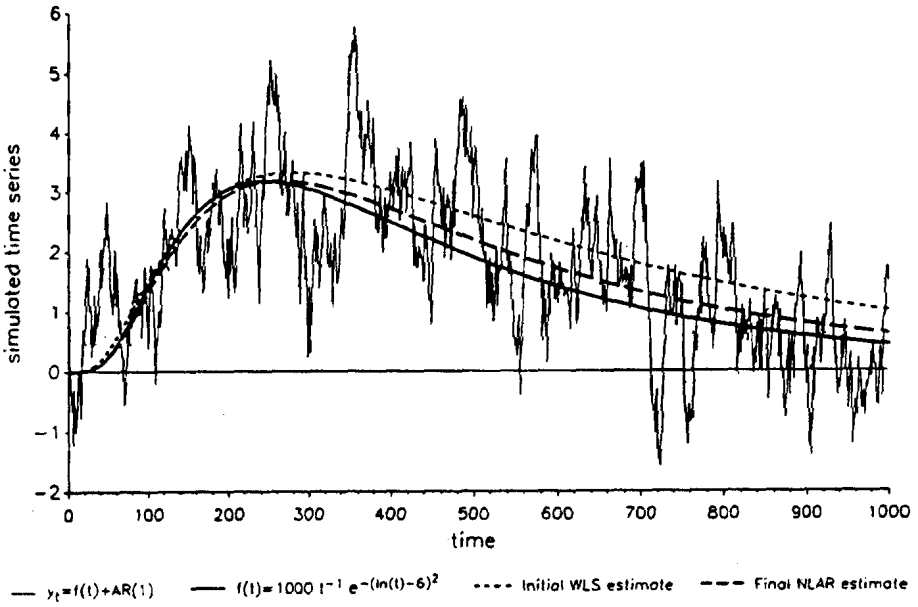

Fig. 1. Example of a simulated log-normal curve corrupted by correlated errors with initial linear WLS and final NLAR estimates.

replication by the NLAR method. All other replications converged for $n=100$.

Hence, in more than 99% of the simulations the starting values produced a successful fit for both nonlinear algorithms. The number of simulations without convergence was slightly higher for NLAR than for NL due to the larger number of parameters. The only case in which a noteworthy number of replications did not converge was $n=100$ and $\varphi=0.9$ showing that for highly correlated data with the error variance considered a large number of time points is necessary. Hence, the simulations indicate that the starting values obtained by the linear WLS approach in general ensure a fast and successful fit for log-normal curves with autocorrelated errors if a sufficient number of time points is available.

Comparison of NL and NLAR

In the context of linear regression it is well known that OLS remains unbiased and consistent even if errors are positively correlated (18). However, standard deviations of parameter estimates are underestimated by OLS leading to invalid tests and confidence intervals if ordinary t and F distributions are used (18). Generalized least squares (GLS) is unbiased, consistent and, in general, more efficient than OLS. The situation in nonlinear regression is more complicated, because explicit equations for the moments of nonlinear parameter estimators do not exist. Boxenbaum *et al.* (1), using simulations and Glasbey (19), investigating logistic curves, found that the underestimation of standard deviations also holds for nonlinear regressions

when correlation of errors is disregarded. In the following, the general properties of the NL and the NLAR method are investigated and compared for the simulated log-normal curves in dependence on the level of correlation given by φ and the number of time points n.

Let β be a parameter and $\hat{\beta}_r$ its estimate from replication r, then the percentage error of the estimation is defined as

$$e_r = \frac{\hat{\beta}_r - \beta}{\beta} \times 100 \tag{10}$$

The bias of the estimation is described by the mean percentage error (MPE)

$$MPE = \frac{1}{s} \sum_{r=1}^{s} e_r \tag{11}$$

where s is the total number of replications ($s = 1000$ in this paper).

The precision of the estimation is described by the mean absolute percentage error ($MAPE$)

$$MAPE = \frac{1}{s} \sum_{r=1}^{s} |e_r| \tag{12}$$

Finally, the percentage improvement (PI) in precision of NLAR over NL is defined as

$$PI = \frac{MAPE(\text{NL}) - MAPE(\text{NLAR})}{MAPE(\text{NL})} \times 100 \tag{13}$$

To investigate bias, precision and improvement of standard errors the same definitions hold when the unknown true values β in Eq. (10) are replaced

Table I. Bias and Precision of NL and NLAR Parameter Estimates

	$n=100$						$n=1000$					
	a		b		c		a		b		c	
φ	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR
A. Bias (MPE) of NL and NLAR parameter estimates												
0.1	0.6	0.6	1.9	1.9	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.0
0.5	2.1	2.1	4.5	4.6	0.4	0.4	0.1	0.1	0.7	0.6	0.0	0.0
0.9	10.6	8.6	25.1	25.5	1.2	0.9	1.2	1.2	3.2	3.1	0.2	0.2
B. Precision ($MAPE$) of NL and NLAR parameter estimates												
0.1	5.7	5.7	15.5	15.5	1.1	1.1	1.8	1.8	4.7	4.7	0.4	0.4
0.5	9.3	9.3	25.5	25.6	1.9	1.9	3.0	3.0	7.4	7.4	0.6	0.6
0.9	23.2	21.9	52.8	52.0	4.2	4.2	7.4	7.4	19.9	19.9	1.4	1.4
C. Percentage improvement (PI) of NLAR parameter estimates												
0.1	−0.02		−0.01		−0.02		+0.00		−0.03		+0.00	
0.5	−0.00		−0.25		−0.00		−0.03		−0.11		−0.04	
0.9	+5.70		+1.36		+5.70		+0.18		+0.18		+0.17	

Table II. Bias and Precision of NL and NLAR Standard Errors

	$n=100$						$n=1000$					
	SE(a)		SE(b)		SE(c)		SE(a)		SE(b)		SE(c)	
φ	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR	NL	NLAR
	A. Bias (*MPE*) of NL and NLAR standard errors											
0.1	−7.8	−0.8	−10.9	−4.3	−9.9	−3.0	−10.4	−1.2	−7.5	+2.0	−9.7	−0.5
0.5	−41.8	−4.1	−47.8	−15.8	−47.0	−15.4	−43.1	−1.9	−41.2	+1.5	−42.6	−0.9
0.9	−76.4	−29.8	−80.2	−51.2	−78.9	−38.8	−77.9	−6.2	−78.7	−10.5	−77.8	−6.1
	B. Precision (*MAPE*) of NL and NLAR standard errors											
0.1	9.1	11.1	15.8	16.1	19.6	20.0	10.4	3.7	7.9	5.4	10.1	6.2
0.5	42.0	16.3	48.0	27.0	49.4	34.4	43.2	5.2	41.2	8.0	42.6	9.2
0.9	84.6	47.7	80.7	58.4	82.5	59.5	77.9	12.3	78.7	20.4	77.8	24.5
	C. Percentage improvement (*PI*) of NLAR standard errors											
0.1	−21.2		−2.2		−1.7		+64.8		+32.0		+39.2	
0.5	+61.3		+43.8		+30.3		+88.0		+80.5		+78.3	
0.9	+43.6		+27.6		+27.9		+84.1		+74.1		+68.5	

by the empirical standard deviation computed from the simulations. In Tables IA–IIC the *MPE*, *MAPE*, and *PI* of NL and NLAR for the estimates of the three function parameters a, b, c, and their standard errors are given. The *PI* of the NLAR standard errors is also shown in Fig. 2.

The following conclusions can be drawn from Tables IA–IIC and Fig. 2. Bias and precision of NL and NLAR are comparable concerning the parameter estimates (Tables IA–IC). Only in the case $n=100$, $\varphi=0.9$ NLAR shows a slight advantage (Table IC). However, it should be noted that both NL and NLAR perform very poorly in this case. Recall that for this parameter set the starting values sometimes did not produce a successful fit, which

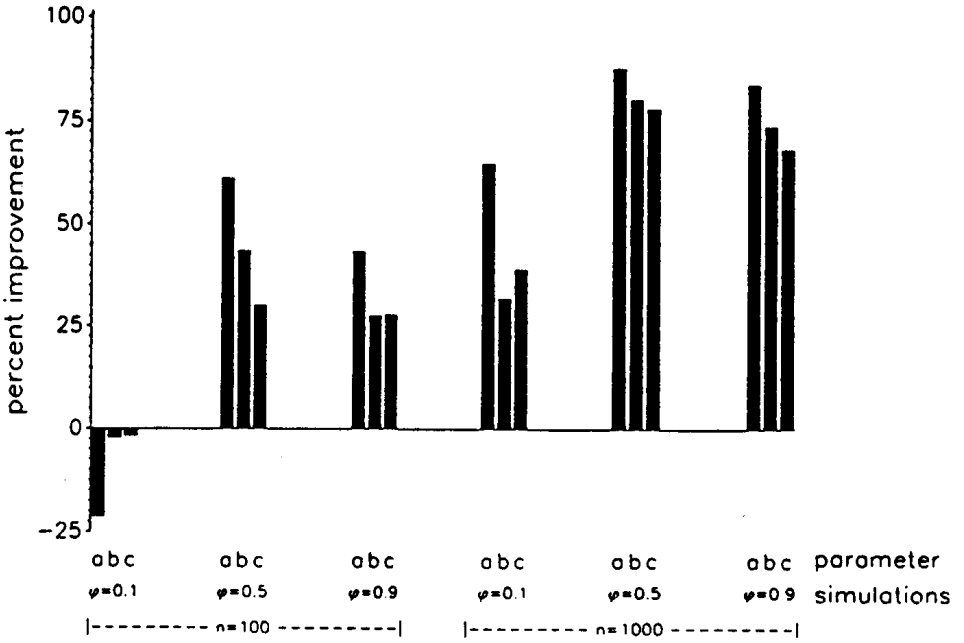

Fig. 2. Percentage improvement in precision of NLAR vs NL standard errors.

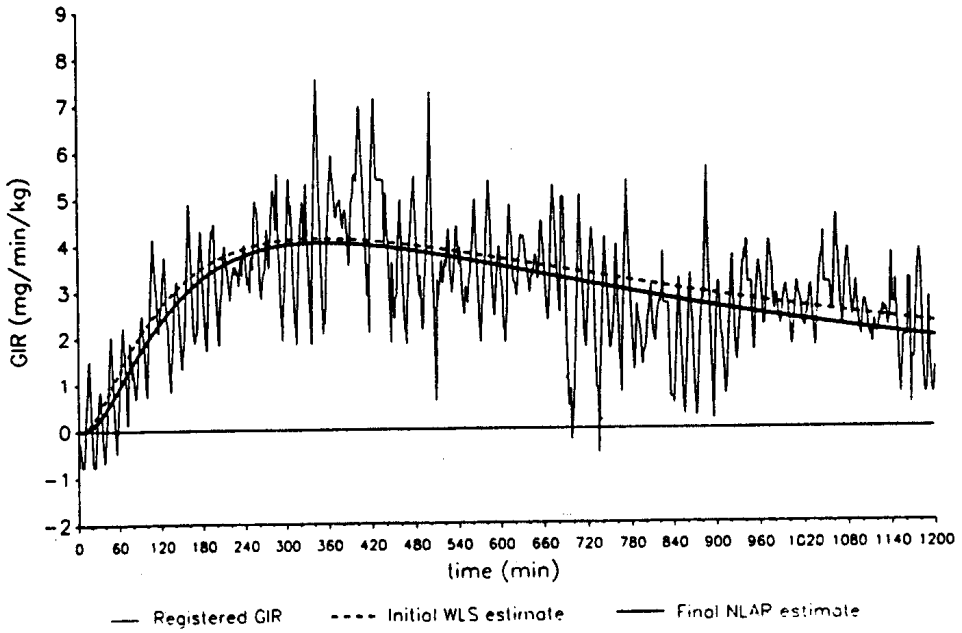

Fig. 3. Example of a GIR curve registered during an euglycemic glucose-clamp study with initial linear WLS and final NLAR fit of a log-normal function.

is not surprising in this light of the high *MPE* and *MAPE* of the estimates. As in linear regression, standard deviations are considerably underestimated by NL (Table IIA). NLAR performs far better, although bias and precision are not satisfactory for $n = 100$ (Tables IIA, IIB). While the insufficient properties of the NL standard errors are comparable for $n = 100$ and $n = 1000$, the NLAR standard errors improved with increasing number of time points. The highest *PI* of NLAR was obtained in the case of moderate autocorrelation ($\varphi = 0.5$, Table IIC, Fig. 2).

In summary, the properties of NL and NLAR are comparable concerning parameter estimation but NL underestimates standard deviations substantially. The NLAR standard errors are adequate if the curve considered contains a sufficient number of time points.

EXAMPLE

The method described was applied to real GIR data recorded during an euglycemic glucose-clamp study. To investigate the dose-response characteristics of a long-acting insulin preparation (NPH insulin: Humulin N, Eli Lilly, Indianapolis, IN) 8 healthy subjects were connected to a Biostator (20). Each subject received in random order three subcutaneous insulin injections into the abdominal wall using three different doses. GIR necessary to keep blood glucose constant at 5 mmol/l thereafter were recorded each minute for 20 hr thereafter. To each of the 24 GIR curves log-normal functions with autoregressive errors of order $p = 3$ were fitted. This order is

suitable for most GIR curves shown by application of the Box-Jenkins method (7,9). As an example the initial and final estimation for one of the GIR curves are illustrated in Fig. 3. The NLAR estimates (SE in parentheses) of the log-normal function parameters in this case are: $\hat{a}=$ 2381.8 (108), $\hat{b}=0.477$ (0.055), $\hat{c}=6.903$ (0.112). In comparison, the NL method resulted in: $\hat{a}=2378.9$ (45), $\hat{b}=0.478$ (0.023), $\hat{c}=6.901$ (0.047). In the light of the simulations, we can conclude that the standard errors of the NL method are too small. A sample computer program using the SAS code to perform the necessary calculations is given in the Appendix.

In this study the summary measures curve maximum (C_{max}), time to curve maximum (t_{max}), and area under the curve (AUC) are of interest. These can be calculated from the log-normal function parameters by

$$t_{max}=\exp\left(c-\frac{1}{2b}\right)$$

$$C_{max}=a\exp\left(\frac{1}{4b}-c\right) \tag{14}$$

$$AUC=a\sqrt{\pi/b}$$

For the example shown in Fig. 3 the summary measures computed by means of Eqs. (14) are $t_{max}=349$ min, $C_{max}=4.04$ mg/min per kg, and $AUC=$ 6111 mg/kg. Table III contains the means and standard deviations of the summary measures at each dose level (units per kg body weight). From the results in Table III it can be concluded that there are no obvious dose effects on t_{max} while the C_{max} and AUC values tend to increase with increasing dose level.

DISCUSSION

This paper addresses practical problems of fitting nonlinear regression models with correlated errors to individual pharmacodynamic time series

Table III. Means and SDs for Summary Measures of GIR Curves

	Means (SD) for dose		
	0.2 U/kg	0.4 U/kg	0.8 U/kg
t_{max} (min)	259 (81)	241 (51)	270 (48)
C_{max} (mg/min per kg)	3.69 (1.96)	4.93 (1.37)	6.43 (2.05)
AUC (mg/kg)	3566 (1850)	4334 (2214)	9804 (7351)

data. The problem of finding suitable starting values for the nonlinear iterative algorithms is solved by a linear WLS approach in the context of log-normal curves. Although the adequacy of the approach is shown only in the case of log-normal functions it can be assumed that the method is also applicable to other equations, e.g., gamma curves, perhaps by choosing alternative weights. By using the initial estimates of the WLS approach as starting values the nonlinear fitting can be performed conveniently by means of the SAS/ETS procedure MODEL (15).

The method described is suitable for unimodal curves with errors forming a stationary time series, i.e., the errors are correlated but have homoscedastic variances. The number of time points must be sufficiently large, so that a reasonable time series model can be fitted to the errors. In the case of pharmacokinetic data containing only a few time points and heteroscedastic variances the method will fail because the error structure cannot be described by means of time series methods. For such data it is more appropriate to use OLS and correct the standard errors. Gallant (21) gives an estimated asymptotic covariance matrix for the OLS estimate which can be used even in the case of nonstationarity.

The use of nonlinear functions for the description of time action profiles has a number of advantages. First, a large number of curve points can be summarized by a small number of function parameters containing the relevant information. Second, important summary measures can be calculated from the function parameters even if the curve considered is corrupted by autoregressive noise. In this case a direct computation of summary measures is not adequate. Third, the computation of the total AUC is possible, which requires a mathematical or pharmacokinetic model in any case.

The comparison of the statistical properties of the nonlinear least squares methods with and without accommodating correlated errors showed similar conditions as in the linear case. Whereas the parameter estimates are comparable, disregarding correlated errors leads to a substantial underestimation of standard deviations. Hence, models taking the correlation structure into account should be used if one is interested in valid standard errors.

In summary, we demonstrated that methods of nonlinear regression analysis combined with time series analysis can be applied to individual correlated pharmacodynamic data with stationary time series errors. Standard software for time series can be used for calculations.

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APPENDIX

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*************************************************************************
*          FIT OF A LOGNORMAL CURVE TO CORRELATED DATA                  *
*             BY USING NONLINEAR LEAST SQUARES AND                      *
*       A LINEAR WLS APPROACH FOR OBTAINING STARTING VALUES             *
*************************************************************************

   * NOTE: The data set 'CURVE' must contain at least 2 Variables:      *
   *         1) t for the time points and                                *
   *         2) Y for the curve points used.                            *;

*-------------------------------------------------------------------*
|                        Initial Estimation                         |
*-------------------------------------------------------------------*;
*--------------------- *Log-Transformation*-----------------------*;
data lin;  set curve;
   if Y<=0.0001 then Y=0.0001;
   G  = log(Y);
   X1 = log(t);
   X2 = log(t)**2;
   w  = Y;
   if  0<t<=10 then w=0;        *  1-10 min: weights=0          *;
   if 10<t<=20 then w=0.0001;   * 11-20 min: weights=0.0001     *;
run;
*-------------------- *Linear WLS Estimation* --------------------*;
proc reg data=lin outest=wlspar noprint;
   model G=X1 X2;
   weight w;
run;

*------------ *Retransformation of Initial Estimates*  ------------*;
data wlspar;
   set wlspar(keep=intercep x1 x2);
   A = exp(intercep-(x1+1)**2/(4*x2));
   B = -x2;
   C = -(x1+1)/(2*x2);
   PHI1 =  1.4;                  * Suitable starting values   ;
   PHI2 = -0.5;                  * for the parameters of      *;
   PH13 = -0.1;                  * AR(3) errors               *;
run;
*-------------------------------------------------------------------*
|                        Final Estimation                           |
*-------------------------------------------------------------------*;

title 'Nonlinear Fit of Lognormal Curve with AR(3) Errors';
proc model data=curve;
   var Y T;
   parms A B C PHI1 PHI2 PHI3;
   f=A * T**(-1) * exp(-B*(log(T)-C)**2);
   Y=f+PHI1*zlag1(Y-f)+PHI2*zlag2(Y-f)+PHI3*zlag3(Y-f);
   fit Y / estdata=wlspar out=fit outpredict outest=est outs=sigma dw;
```

```
   solve Y / estdata=est out=func simulate random=0;
   range T=1 to 1200;
run;
*-------------------------------------------------------------*
|                          Plot                               |
*-------------------------------------------------------------*;
data fit;    set fit;                          rename Y=Yhat;
data func;   set func;                         rename Y=fhat;
data plot;   merge curve fit func;             by t;
run;
title f=swissl h=2 'Nonlinear Fit of Lognormal Curve with AR(3) Errors';
proc gplot data=plot;
   plot (Y Yhat fhat)*t / overlay vref=0;
run;
```

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