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A multilevel nonlinear mixed-effects approach to model growth in pigs

A. B. Strathe,* A. Danfær,* H. Sørensen,† and E. Kebreab‡

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ABSTRACT: Growth functions have been used to predict market weight of pigs and maximize return over feed costs. This study was undertaken to compare 4 growth functions and methods of analyzing data, particularly one that considers nonlinear repeated measures. Data were collected from an experiment with 40 pigs maintained from birth to maturity and their BW measured weekly or every 2 wk up to 1,007 d. Gompertz, logistic, Bridges, and Lopez functions were fitted to the data and compared using information criteria. For each function, a multilevel nonlinear mixed effects model was employed because it allowed for estimation of all growth profiles simultaneously, and different sources of variation (i.e., sex, pig, and litter effects) were incorporated directly into the parameters. Furthermore, variance in-homogeneity and within-pig correlation were introduced to the functions. Inclusion of a variance of power function and a continuous autoregressive process of first order rendered a substantially improved fit to data for all 4 growth functions. The Lopez function provided the best fit to the data set and was used for characterizing mean growth curves for the 3 sexes (barrows, boars, and gilts). It was estimated that the maximum growth rate occurs at 117, 134, and 96 kg of BW for barrows, boars, and gilts, respectively. Hence, the gilts reached their maximum growth rate at an earlier stage in life compared with boars. Mature size of pigs varied systematically with sex and was estimated to be 466, 537, and 382 kg of BW for the barrows, boars, and gilts, respectively. These estimates are significantly affected by the duration of the experimental period, and it is recommended that future studies looking at estimating the mature size in animals are conducted long enough so that the BW visually stabilizes. Furthermore, studies should consider adding continuous autoregressive process when analyzing nonlinear mixed models with repeated measures.

Key words: growth, multilevel mixed effect model, sigmoidal function

INTRODUCTION

Growth functions have been extensively used to describe the size vs. age relationship in pigs, and thus many functions are presented in the literature including polynomials (Wellock et al., 2004). It is expected that the growth curve of an individual pig deviates from that of the population that must be modeled. Furthermore, some of the pigs might share similar genetic background because they are littermates; thus, specification of pig within litter relationship (i.e., nested random effects) is necessary to model the hierarchical data structure. Body weight recordings, which are taken on the same individual, are not independent. Statistical issues such as heteroskedastic and serial correlated errors in relation to modeling animal growth curves have previously been described, but solutions to circumvent this problem have not been proposed (Wang and Zuidhof, 2004). Recent developments in statistical theory and computational power allow for specification of multilevel nonlinear mixed effect models (NLME; Pinheiro and Bates, 2000). These models have been described previously to express age vs. size relations in pigs and broilers (e.g., Craig and Schinckel, 2001; Wang and Zuidhof, 2004). Comparison among growth curves of different sexes ranging from 20 to 120 kg of BW has received some attention, and an elegant modeling approach was presented by Andersen and Pedersen (1996). However, analysis of growth patterns beyond 120 kg of BW is limited and

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could potentially yield valuable biological insights into swine growth of different sexes (Knap, 2000).

Therefore, the objectives of the present investigation were to 1) specify multilevel NLME-models including variance functions and correlation structures for dealing with repeated measures growth data that enable comparison between different growth functions in their ability to describe pig growth; and 2) characterize growth patterns of different sexes based on the best performing growth model.

**MATERIALS AND METHODS**

All experimental procedures complied with the Danish Ministry of Justice, Law No. 382 (June 10, 1987) and Act No. 726 (September 9, 1993), regarding animal experimentation and care.

**Animals and Diets**

The data used in this analysis were part of a serial slaughter experiment designed to determine growth capacity and energy and nutrient utilization in growing pigs. The experimental pigs used in this study were crosses of Yorkshire × Landrace sows and Duroc boars. The pigs were fed 7 diets in the corresponding intervals: 4 to 7 wk, 7 wk to 25 kg, 25 to 45 kg, 45 to 65 kg, 65 to 100 kg, 100 to 150 kg and 150 kg to maturity. The chemical composition of the diets is presented in Table 1. The pigs were individually housed under thermoneutral conditions and given ad libitum access to feed and water during the entire growth period to maximize growth. All pigs were weighed at birth, weaning, and weekly thereafter until approximately 150 kg of BW and then every second week (biweekly) until the time of slaughter. The data set consisted of 40 animals from 17 litters, which were of 3 sexes (barrow, boar, and gilt). The 3 sexes were represented by 11, 16, and 13 pigs, respectively. There were a minimum of 25 and maximum 65 with an average of 36 data points per pig available for the analysis. Thus, a total of 1,431 BW recordings were used. The average BW and SD are calculated by grouping measurements into weekly and after 150 kg of BW into alternate-week groups for each sex. These average growth curves with error bars are plotted as a function of age for each of the 3 sexes in Figure 1.

**Growth Functions**

Four sigmoid growth functions are considered in the data analysis and will be referred to as the Gompertz, logistic, Bridges, and Lopez (Gompertz, 1825; Robertson, 1908; Bridges et al., 1986; Lopez et al., 2000; Eq. [1] to [4], respectively). The growth functions are parameterized as follows:

\[
W = W_0 \exp \left( \frac{W_f}{W_0} \ln \left( \frac{W_f}{W_0} \right) \right); \quad [1]
\]

\[
W = \frac{W_f \times W_0}{W_0 - (W_f - W_0) \times \exp(-k \times Age)}; \quad [2]
\]

\[
W = W'_0 + W_f \times \left( 1 - \exp(-k \times Age^n) \right); \quad \text{and} \quad [3]
\]

\[
W = \frac{W_0 \times K^n + W_f \times Age^n}{K^n + Age^n}, \quad [4]
\]
where $W$ denotes the expected BW at a given age, $W_j$ is the asymptotic BW (kg) of the pigs, $W_0$ is the initial BW (kg), $k$ is a rate constant ($d^{-1}$), $K$ is the age to approximately one-half maximum BW (d), and $n$ is a dimensionless exponent.

**Multilevel Nonlinear Mixed Models**

The factors pig and litter are considered random because specific levels for these effects are not of interest. However, both sources of variation contribute to the variability in the observed data as shown in Figure 1. The multilevel model representation is used because data are organized according to clusters (i.e., some observations originate from the same litter, and within that litter data are clustered longitudinally according to each pig). The multilevel concept refers to the tree-type structure of the data. Thus, effects of litter and pig need to be included in the NLME models as nested random effects.

Let $W_{jk}$ denote the BW of $j$th ($1 \leq j \leq n_j$) pig originating from $i$th ($1 \leq i \leq n_i$) litter on $k$th ($1 \leq k \leq n_p$) day during the test. For clarity the parameter vector $\varphi = (W_j, W_0, k, n)$ is introduced. In NLME models the fixed and random effects are incorporated directly into the parameters and thus written in the following way:

$$W_{jk} = f(\varphi_{ij}, \text{age}_{jk}) + e_{ijk}$$

where $f$ is a known nonlinear growth function (as described above) of age$_{ijk}$, a known continuous variable and of the parameter vector $\varphi_{ij}$ and model error $e_{ijk}$. $d$ refers to the number of parameters in the given growth function. The litter and pig random effects, ($b_i$) and ($b_{ij}$), are assumed independent of each other and independent of the within pig errors $e_{ijk}$. The $\beta$ are the fixed effects affecting the curve parameters due to sex (barrow, boar, and gilt) and are introduced through 3 dummy variables: $x_1$, $x_2$, and $x_3$, respectively. The Gompertz and logistic functions have 3 parameters, whereas Bridges and Lopez are 4-parameter functions. This means that the variance-covariance matrices $\Psi_1$ and $\Psi_2$ are $3 \times 3$ or $4 \times 4$ dimensional matrices when all parameters are included with a random individual effect. It makes biological sense to assume that individual random effects are correlated because a pig with larger birth weight than the population might also have a larger mature BW. This assumes that the random effects related to birth and final BW are correlated positively. The specifications of $\Psi$ are essential because full unstructured $\Psi$ lead to a difficult optimization problem, and we therefore assume that the $\Psi$ are diagonal matrices. If full unstructured $\Psi$ for the 4 parameter functions are specified, an additional 12 parameters need to be estimated (i.e., 6 parameters per matrix). Thus, to make sure convergence occurs for all candidate functions, diagonal elements in $\Psi$ were set to zero. The term $\Lambda_{ij} = I_{ij}$ was also initially assumed [i.e., the within-pig errors $e_{ij}$ are independent, identical and $N(0, \sigma^2 I_{ij})$]
random vectors \((I_{ij}, \text{an identity matrix})\). This is referred to as the basic model. Thus, in the beginning of the model building phase, constraints are introduced for avoiding nonidentifiability but extensions are described below. Nonlinear regression relies heavily on good starting values for the parameters to converge properly, and thus the following 4-step approach was adopted: first, starting values for initial and asymptotic BW are visually estimated from graphical inspection of Figure 1. Second, these values are held fixed, whereas a nonlinear optimization scheme iteratively minimizes the mean square error for each sex and estimates the last parameter(s) in the growth functions. Third, all the fixed effect parameters in the growth function are allowed to vary during final parameter estimation without random effects. Finally, the parameter values from the last nonlinear optimization step are transferred as starting values to the NLME estimations procedure. These methods work on an approximation to the likelihood function for the NLME model (Pinheiro and Bates, 2000; Littell et al., 2006). The estimation routine fits a set of linear estimation equations using a linear mixed model estimation (LME) routine as computing engine at each stage (Pinheiro and Bates, 2000). In the first stage of LME iterations the random effects are initialized by setting them to zero, and thus, initial estimates of variance parameters (\(\Psi, \sigma^2\)) are not necessary. All statistical computations were implemented in R (R Development Core Team, 2007), and parameter estimation was carried out by means of the NLME-library (Pinheiro et al., 2007). The R-language was chosen because it is an open source language; however, SAS (SAS Inst. Inc., Cary, NC) is commonly used in animal science; therefore, codes based on R and SAS are presented in Appendix 1. The SAS implementation uses the %nlinmix version 8.

**Extension of the Basic Model.** Model diagnostics are a central part of modeling because plotting the residuals against predicted values reveals whether the variance is constant and systematic deviations (serial correlation) are present visually. Moreover, residual and empirical auto-correlation plots can be used to diagnose violations of model assumptions. The basic model fit suggests that the within-pig variability increased with increasing BW and auto-correlation is also present. This section presents extensions of the basic model due to shortcomings of the current model formulation. Extensions imposed on the basic model formulation apply to all growth models because all functions should be compared on the same basis. The assumption that \(\Lambda_{ij} = I_{ij}\) has to be relaxed to correct misspecifications of the basic models. The matrix \(\Lambda_{ij}\) can be decomposed into a variance structure component and a correlation structure component that allows specification of model variance heterogeneity and serial correlation (Pinheiro and Bates, 2000). As mentioned earlier, the variance of the within-pig residuals increased with increasing expected values, suggesting variance heterogeneity in the data. Therefore, variance of the within-pig errors was modeled using a variance function (i.e., a function that describes the variance of errors through covariates). An obvious candidate covariate is the predicted values of the within-pig errors are dependent on both the fixed effects \(\beta\) and random effects \(b_i\) and \(b_{ij}\). The data suggest a variance function, which expresses the variance as a power (VP) of the expected values \((e_{ijk})\), 

\[
\text{Var}(e_{ijk}) = \sigma^2 e_{ijk}^{2\delta}.
\]

A fixed \(\delta\) value of 0.5 was used, which specifies a model where the variance of a measurement increases linearly with the predicted BW value. Thus, the variance weights are defined as the inverse of the variance function values (i.e., \(1 / \sigma^2 e_{ijk}^{2\delta}\), which are used to weight the errors \(e_{ijk}\)). The NLME-library provides several other variance functions for modeling heteroskedasticity of the within-group errors using covariates (Pinheiro et al., 2007).

To define the appropriate correlation structure for the within-pig residuals, it is important to realize that the BW measurements are unequally spaced in time and differ among pigs. Adapting a continuous time autoregressive process of first order [\(\text{CAR}(1)\)] to the within-pig errors has the properties for dealing with unequally spaced observations. The \(\text{CAR}(1)\) process is a generalization of an autoregressive process of first order and has the following correlation function (Littell et al., 2006):

\[
h(\tau, \phi) = \phi^\tau = \phi^{(A_{ij} - A_{ij})}, \quad [6]
\]

where \(\phi \geq 0\) is the single correlation parameter and \(\tau\) expresses the absolute distance between 2 observations on the same individual e.g., \(\tau = |A_{ij} - A_{ij}|\). The \(\text{CAR}(1)\) process is driven by random variables or innovations that are assumed to be independent and normally distributed. The innovations can be considered as the residuals in the \(\text{CAR}(1)\) process.

The best performing model was used for subsequent analysis based on the following goodness-of-fit indicators: Akaike information criterion (\(\text{AIC}\)), Bayesian information criterion (\(\text{BIC}\)), and residual SD. Likelihood ratio tests (\(\text{LRT}\)) are used for nested model (Pinheiro and Bates, 2000). Model reductions are done in 2 steps. First, the random part of the model was reduced followed by the systematic part. At each step the last significant factor was identified and removed from the model. This was done successively until the final model was obtained. Parameter estimates are presented with corresponding 95% confidence intervals. When additional traits (i.e., points of inflection) are calculated as function of the fixed effect estimates \(g(\beta)\), the corresponding SE is obtained by means of the delta method. The method approximates the SE of a transformation \(g(\beta)\) of a random variable \(\beta = (\beta_1, \beta_2, ...\), given estimates of the mean and covariance matrix of \(\beta\). The delta method expands the differentiable function \(g(\beta)\) of a random variable about its mean, with a first-order
Taylor approximation, and then takes the variance (Oehlert, 1992). The codes for fitting the VP + CAR(1) version of the Lopez model are presented in Appendix 1.

RESULTS AND DISCUSSION

Comparison of Growth Functions

Four growth functions with 3 or 4 parameters were fitted to growth data and compared for their accuracy of prediction. Literature search and the review by Welllock et al. (2004) shows that there are several other functions that can be of interest. However, all 4 functions chosen have been used previously to describe growth in pigs, although the Gompertz function has been the most popular. The results of fitting the 4 models to data are presented in Table 2 for the basic model formulation and extensions [i.e., VP and VP + CAR(1)]. The results indicate the following ranking of the growth functions: Lopez, Bridges, Gompertz, and logistic, independent of modifications of the error structure. A recent study by Schulin-Zeuthen et al. (2008) introduced the Schumacher growth function for interpreting growth data and compared it with the Gompertz and Weibull growth functions. For each of the 5 data sets, the AIC was least for Weibull, which supports usage of 4 parameter functions for modeling BW vs. age relations in pigs. Schinckel et al. (2006) showed that Lopez produced a marginally better fit for pig growth data than the Weibull and Bridges growth functions. The current analysis provides evidence that the 4-parameter functions perform better than the 3-parameter functions, independent of modifications to the error structure of the models. The results of the current study contradict the conclusion reached by Knap (2000) after reanalyzing 8 previously published data sets. The author reported that the Gompertz function was adequate to model BW vs. age relationships in pigs. Part of the discrepancies can be explained by frequency of BW registrations (sampling) and duration of the experiment. In the first instance, only 1 of the reanalyzed data sets contained weekly measurements of BW [i.e., data from Andersen and Pedersen (1996)]. Second, none of the included experiments studied growth beyond 350 d of age, whereas the reported results from this experiment lasted more than 2 yr (Figures 1 and 2). It was also observed that the Gompertz function had a tendency to overestimate the BW at time zero heavily by predicting birth weights of around 10 kg. This was also noted by Schulin-Zeuthen et al. (2008). The point of utilizing semi-mechanistic growth models is that the parameters can be assigned biological meaning, but if the parameter estimate(s) are out of biological range as for the Gompertz function, then it may be argued that they lose their interpretation and validity.

Characterizing Pig Growth Using the Lopez Function

Random Effects. The results presented in this section are all based on reductions of the Lopez growth function. It is essential that the variance structure is modeled properly when biological inference regarding growth profiles of different sexes or other sources of variation are explored, and thus the VP + CAR(1) version of the Lopez model was used. The result of this analysis is presented in Table 3 along with AIC and BIC values for the reduced models. Parameter estimates for the final model, which are estimated by restricted maximum likelihood, are presented in Table 4 with approximate 95% confidence intervals.

When comparing the growth functions, information that some pigs share in common are included (i.e., littersmates). These variance components in \( \Psi_I \) were small compared with those in the \( \Psi_2 \) and thus were removed from the model. Significance of the changes imposed on the Lopez model can be ascertained by LRT. Based

### Table 2. Comparison of 4 sigmoid models fitted to growth data of pigs in terms of goodness-of-fit indicators, including Akaike information criterion (AIC), Bayesian information criterion (BIC), and residual SD (RSD)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Model</th>
<th>df</th>
<th>AIC</th>
<th>BIC</th>
<th>RSD, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Gompertz</td>
<td>16</td>
<td>10,724.5</td>
<td>10,793.0</td>
<td>8.91</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>16</td>
<td>11,939.7</td>
<td>12,008.2</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>Bridges</td>
<td>21</td>
<td>10,059.3</td>
<td>10,148.9</td>
<td>6.59</td>
</tr>
<tr>
<td></td>
<td>Lopez</td>
<td>21</td>
<td>9,861.4</td>
<td>9,950.9</td>
<td>6.45</td>
</tr>
<tr>
<td>VP(^2)</td>
<td>Gompertz</td>
<td>16</td>
<td>10,069.3</td>
<td>10,137.8</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>16</td>
<td>11,765.4</td>
<td>11,833.9</td>
<td>1.32</td>
</tr>
<tr>
<td></td>
<td>Bridges</td>
<td>21</td>
<td>9,522.0</td>
<td>9,611.6</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Lopez</td>
<td>21</td>
<td>8,905.4</td>
<td>9,040.0</td>
<td>0.53</td>
</tr>
<tr>
<td>VP + CAR(1)(^3)</td>
<td>Gompertz</td>
<td>17</td>
<td>7,141.9</td>
<td>7,215.7</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>Logistic</td>
<td>17</td>
<td>7,474.2</td>
<td>7,547.9</td>
<td>4.30</td>
</tr>
<tr>
<td></td>
<td>Bridges</td>
<td>22</td>
<td>7,095.8</td>
<td>7,190.6</td>
<td>1.22</td>
</tr>
<tr>
<td></td>
<td>Lopez</td>
<td>22</td>
<td>7,051.5</td>
<td>7,146.3</td>
<td>0.82</td>
</tr>
</tbody>
</table>

1Model degrees of freedom, which is equal to the number of parameters.
2Variance of power specification.
3Variance of power and first-order continuous autoregressive process.
on the LRT with 4 df, the effect of litter was not significant \((P = 0.11)\), and thus \(\Psi_1\) was not significantly different from zero. This source of variation could be important if more information was available. Further model reductions were initialized by setting the variance components in \(\Psi_2 = \text{diag}(\sigma_1^2, \sigma_2^2, \sigma_3^2, \sigma_4^2)\) one by one equating to zero to identify the appropriate variance structure for the structural parameters in Eq. [4]. The inter-pig variation in the parameter value that describes the mature size \((W_f)\) was highly significant \((P < 0.001)\), which was quantified by the variance component \((\sigma_1^2)\). The variation between pigs in the parameter that describes initial BW \((W_0)\) of pigs \((\sigma_2^2)\) was not significantly different from zero \((P = 0.97)\). The age at approximately one-half maximum BW \((K)\) varies from individual to individual \((\sigma_3^2, P < 0.001)\). The exponent \((n)\) that determines the sigmoid shape in Eq. [4] was not affected by the pig-to-pig variation \((P = 0.97)\). The second main objective of the study was to model and describe growth patterns of different sexes of pigs; therefore, it is important to have an adequate quantification of the source of variation imposed by each pig and to understand which of the parameters in the Lopez function varies with individual pigs. Moreover, it further underlines the necessity to separate the variation between pigs from the within-pig-variation when fitting nonlinear models to growth data obtained from a population of pigs. Failure to include this information adequately in the modeling process will produce biased estimates and SE of the parameters (Pinheiro and Bates, 2000).

**Fixed Effects.** The systematic effect of sex on the mean curve parameters \(\beta = (\beta_{11}, \beta_{12}, \ldots, \beta_{43})\) that affects the shape of the estimated population growth profiles was investigated. \(W_0\) was not affected by sex \((P = 0.99)\). The estimated birth weight of 1.78 \((\text{SE} = 0.174)\)

![Selected growth profiles of 9 pigs (3 per sex; symbol). The Lopez function was used to produce population- (solid lines) and pig-specific (dotted lines) curves.](image-url)
kg by the Lopez function was similar to mean birth weight of 1.86 kg of 40 pigs represented in the data set. Furthermore, conducting a 1-way ANOVA on the birth weights of these pigs also showed that the sex effect was not significant ($P = 0.69$). This suggested that there was a good correspondence between conclusions based on the Lopez-NLME analysis and the simple ANOVA.

The asymptotic BW of the pigs, $W_f$, showed systematic differences between sexes ($P < 0.001$). A qualitative interpretation of Figure 1 and Figure 2 is that gilts have a distinct growth patterns compared with other sexes, and it seems that they do not grow as large as the barrows or boars, which the estimates of $W_f$ also confirm. The estimates of the 3 sexes [barrow: 466 (SE = 18.4), boar: 537 (SE = 17.2), gilt: 382 (SE = 13.9), kg] seem to display a reasonable mature BW of barrows, boars, and gilts, respectively. These estimates are much larger than previously reported in the literature [e.g., Knap (2000)], which was partly a consequence of genetic, nutrititional, and environmental improvements of Danish meat-type pigs and partly due to the duration of the experimental period as stated previously. When growth data containing only a BW of less than 200 kg were analyzed by sigmoid growth functions, caution should be taken in the interpretation of the asymptotic value (i.e., mature size). This problem can be illustrated by fitting the final Lopez model to a subset of data where all information above 365 d of age was excluded. This resulted in $W_f$ estimates of 406 (SE = 19.4), 471 (SE = 21.2), and 354 (SE = 15.4) kg for barrows, boars, and gilts, respectively. Thus, the value of $W_f$ shifted downwards, and it may be recommended that future studies looking at estimating the mature size of animals are conducted long enough so that BW stabilizes visually.

The age at approximately half maximum was also affected by sex ($P < 0.001$). The dimensional exponent ($n$) in the Lopez function was not affected by sex ($P = 0.99$). Lopez et al. (2000) presented methods for calculating inflection points ($t^*, BW^*$) when $d^2W/dt^2$ is zero, and the dimensional exponent is $n > 1$. These estimates are presented in Table 5. The maximum growth rate for the boars was reached at 135 kg of BW which agrees very well with results obtained by Tauson et al. (1998),

Table 3. Successive test for random and fix effects based on likelihood ratio-test and Akaike information criterion (AIC) and Bayesian information criterion (BIC) for the reduced Lopez models

<table>
<thead>
<tr>
<th>Item</th>
<th>AIC</th>
<th>BIC</th>
<th>LRatio $^1$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random effect of pig</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptotic BW: $\sigma_1^2$</td>
<td>7,051.1</td>
<td>7,109.1</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial BW: $\sigma_2^2$</td>
<td>7,047.5</td>
<td>7,131.8</td>
<td>0.51</td>
<td>0.97</td>
</tr>
<tr>
<td>One-half maximal growth: $\sigma_3^2$</td>
<td>7,050.0</td>
<td>7,107.9</td>
<td>12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dimensionless exponent: $\sigma_4^2$</td>
<td>7,047.5</td>
<td>7,131.8</td>
<td>0.51</td>
<td>0.97</td>
</tr>
<tr>
<td>Fixed effect of sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptotic BW: $\beta_1 = \beta_2 = \beta_3$</td>
<td>7,077.6</td>
<td>7,130.2</td>
<td>42.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial BW: $\beta_2 = \beta_3$</td>
<td>7,039.3</td>
<td>7,102.5</td>
<td>0.24</td>
<td>0.99</td>
</tr>
<tr>
<td>One-half maximal growth: $\beta_3 = \beta_4 = \beta_5$</td>
<td>7,069.3</td>
<td>7,121.9</td>
<td>33.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^1$LRatio: likelihood ratio for the 2 Lopez models [e.g., LRatio = 2[log(L2) – log(L1)]]

Table 4. Parameter estimates for the final Lopez model with 95% confidence limits

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Lower</th>
<th>Estimate</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solutions for fixed effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptotic BW barrows</td>
<td>kg</td>
<td>429.5</td>
<td>466.3</td>
<td>503.1</td>
</tr>
<tr>
<td>Asymptotic BW boars</td>
<td>kg</td>
<td>503.6</td>
<td>537.1</td>
<td>570.7</td>
</tr>
<tr>
<td>Asymptotic BW gilts</td>
<td>kg</td>
<td>354.8</td>
<td>382.1</td>
<td>409.3</td>
</tr>
<tr>
<td>Initial BW</td>
<td>kg</td>
<td>1.444</td>
<td>1.782</td>
<td>2.120</td>
</tr>
<tr>
<td>One-half maximal growth barrows</td>
<td>d</td>
<td>247.5</td>
<td>264.3</td>
<td>280.8</td>
</tr>
<tr>
<td>One-half maximal growth boars</td>
<td>d</td>
<td>271.3</td>
<td>286.1</td>
<td>300.7</td>
</tr>
<tr>
<td>One-half maximal growth gilts</td>
<td>d</td>
<td>219.5</td>
<td>232.5</td>
<td>245.6</td>
</tr>
<tr>
<td>Dimensionless exponent</td>
<td></td>
<td>1.941</td>
<td>1.985</td>
<td>2.029</td>
</tr>
<tr>
<td>Solutions for random effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptotic BW pig: $\sigma_1$</td>
<td>kg</td>
<td>19.52</td>
<td>30.40</td>
<td>47.35</td>
</tr>
<tr>
<td>One-half maximal growth: $\sigma_1$</td>
<td>d</td>
<td>2.688</td>
<td>8.187</td>
<td>24.94</td>
</tr>
<tr>
<td>Correlation structure – CAR(1)</td>
<td></td>
<td>0.990</td>
<td>0.993</td>
<td>0.994</td>
</tr>
<tr>
<td>Within-group SE</td>
<td>kg</td>
<td>0.704</td>
<td>0.822</td>
<td>0.961</td>
</tr>
</tbody>
</table>

1LRatio: likelihood ratio for the 2 Lopez models [e.g., LRatio = 2[log(L2) – log(L1)]]
Figure 3. Each row in plot region presents diagnostic plots for the Lopez function according to the extensions imposed on the basic model formulation. In the left column, the residuals or continuous AR(1) innovations are plotted as a function of fitted values, and in the right column, the empirical autocorrelation functions are presented. AR = autoregressive.
who reported that boars of similar breed reached the maximal rate of protein retention at about the same BW. It can be noted that the maximum growth rate (inflection point) of the boars are reached later in life compared with the gilts, which are caused by differences in the parameter values ($\beta_3$, $\beta_2$, $\beta_3$), the age at approximately half maximum BW. The results of the current growth analysis showing growth profiles of 9 pigs of 3 sexes with the estimated populations and pig-specific curves for the final Lopez model are given in Figure 2. The NLME-models provide the possibility of fitting all growth profiles simultaneously and thus partition variation between pigs from variation within pigs (under the assumption that all pigs are sampled from the same homogenous populations). Therefore, it was possible to observe that some pig-specific growth profiles deviate from the population curve, whereas others follow the population curve.

**Modeling Correlation in Repeated Measure Growth Data**

The fit of the 4 growth functions to data as presented in Table 2 was improved by adding the VP specification without introduction of a new parameter, which gives evidence of heterogeneity of residual variance. The VP + CAR(1) gives a substantial improvement of fit to data across all growth functions. This calls for a description of the error structure (e.g., $\Lambda_{ij}$) because measurements taken on the same animal are not independent. As mentioned earlier, growth data show an inherent underlying relationship. Measures made on the individual animal are likely to be more correlated than measures made on different individuals, and spatial correlation exists because measurements made closely in time tend to be highly correlated compared with measures made further distant in time. As a result, all growth functions yield a substantial improvement of fit to data by incorporating a CAR(1)-process into the models. Wang and Zuidhof (2004) discussed the same issue in their analysis of growth in chickens without resolving it and encouraged development of more advanced correlations structures for NLME models. Figure 3 presents the residuals as function of fitted values along with the empirical autocorrelation function for the basic model and VP. For the VP + CAR(1) model specification the CAR(1) innovations are presented instead. It is clear from inspection of the first row of diagnostic plots (basic model formulation) that the assumptions of variance homogeneity and independent errors were violated. The heteroskedastic errors were corrected by introducing the VP-specification, but this did not remove the strong auto-correlation in the residuals. A combination of a VP and CAR(1) specification produced innovations that were homoskedastic and independent based on the empirical autocorrelation and corresponding 95% confidence bands. The average autocorrelation could be calculated using Eq. [6]. The average distance between measurements was 9.5 d, and thus the average correlation between 2 following measurements was $0.993^{0.5} = 0.935$, which was very substantial.

As mentioned earlier, we have chosen to implement all models in the R-language utilizing the NLME library (Pinheiro et al., 2007). The NLME modeling of growth in pigs has previously been approached in SAS, utilizing the NLMIXED procedure (Craig and Schinckel, 2001; Kebreab et al., 2007). However, the NLMIXED procedure only offers a single RANDOM and no REPEATED statement (Littell et al., 2006). Thus, specification of multilevel NLME models with variance weights and correlation structures, which were required to give a complete description of growth data, is not possible within the framework of the NLMIXED procedure. Most animal scientists use SAS for analysis; therefore, we have implemented the multilevel NLME Lopez model with VP + CAR(1) specification in SAS as well. This is possible by means of the %NLINMIX macro where the latest version of the macro (NLMM 8.0 SAS) is used (Moser, 2004; Littell et al., 2006); however, the SAS syntax is more technical compared with the NLME function in R (Appendix 1).

In conclusion, 4 different growth functions (Gompertz, logistic, Bridges, and Lopez) have been fitted successfully to growth data obtained from 40 pigs of 3 sexes originating from 17 litters. The models were specified as multilevel nonlinear mixed effect models that allow inclusion of nested random effects and fixed effects of sex on the parameters in the growth functions. The growth analysis has also revealed that inclusion of a continuous auto-regressive process of first order considerably improved the fit to data for all models. This can be attributed to removal of the serial correlated errors, and

### Table 5. Calculated traits for the final Lopez model with 95% confidence limits

<table>
<thead>
<tr>
<th>Item</th>
<th>Unit</th>
<th>Lower</th>
<th>Estimate</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflection point barrows: t*</td>
<td>d</td>
<td>142.6</td>
<td>151.2</td>
<td>159.7</td>
</tr>
<tr>
<td>Inflection point boars: t*</td>
<td>d</td>
<td>156.5</td>
<td>163.6</td>
<td>170.8</td>
</tr>
<tr>
<td>Inflection point gilts: t*</td>
<td>d</td>
<td>126.2</td>
<td>133.0</td>
<td>139.8</td>
</tr>
<tr>
<td>Inflection point barrows: BW*</td>
<td>kg</td>
<td>108.3</td>
<td>117.0</td>
<td>125.7</td>
</tr>
<tr>
<td>Inflection point boars: BW*</td>
<td>kg</td>
<td>126.7</td>
<td>134.6</td>
<td>142.5</td>
</tr>
<tr>
<td>Inflection point gilts: BW*</td>
<td>kg</td>
<td>89.6</td>
<td>96.1</td>
<td>102.7</td>
</tr>
</tbody>
</table>

* t* and BW* are inflection points (i.e., the time and BW at maximum growth rate calculated from the fixed effect parameter estimates).
thus inclusion of a continuous auto-regressive process of first order is recommended when modeling frequently sampled growth data. The Lopez function has provided the best fit to data and is used for estimating the population growth curves related to the different sexes. The 3 sexes clearly differ in the parameters, describing the asymptotic weight and the age at approximately half maximum BW.

LITERATURE CITED


Appendix 1

The R and SAS code for fitting nonlinear mixed model with specification of variance power and a continuous first-order autoregressive process using the Lopez function as an example is given below. Comments are provided that describe the specific details of the procedures used. The SAS code explanations are given between /* and */, whereas the R code explanations are given by #.

The following code is for R, S, and S-PLUS implementation.

```
# The groupedData function defines the hierarchical data structure
growth <- groupedData(Weight ~ Age | Litter/Pig_no, data = growth)
M <- nlme(model = Weight ~ (W0*K^n + Wm*Age^n)/(K^n + Age^n))
, data = growth

#The fixed argument specifies the structure for fixed effects. In this #case the intercept (-1) has been removed from equations to produce #estimates of the population effects
,fixed = list(W0-Sex-1, K-Sex-1, n-Sex-1, Wm-Sex-1)
# In the random argument the pdDiag function specifies diagonal #variance-covariance matrices for the random effects
,random = pdDiag(W0 + K + n + Wm -1)
# The weight argument specifies the variance function to be used. In #this case the “power of the mean” function is used, which is fixed at #0.5
,weights = varPower(form = -fitted(.), fixed = 0.5)
# The corr argument specifies the CAR(1) process
```
The following code is for SAS (Version 8 or higher) implementation.

/*NLINMIX is a SAS macro for fitting nonlinear mixed models using PROC NLIN and PROC MIXED. It requires SAS/STAT Version 8 */
/* include the macro from file */
%nlinmix(data = A,
/*The model = argument defines the mean growth function. Due to multiple statements ending
with semi-colons, the entire argument is enclosed with the %str() macro. The variables ending
with _Litter and _Pig are the random effects. The variables _barrow*(Sex = "barrow"),
_boar*(Sex = "boar") and _gilt*(Sex = "gilt") are fixed effect parameters influencing shape of
growth curves due to gender. The syntax *(Sex = "") is used to construct a design matrix for
the fixed effects. */
model = %str(
    W0 = W0_barrow*(Sex = "barrow") + W0_boar*(Sex = "boar") + W0_gilt*(Sex = "gilt") + b1_Litter + b1_Pig;
    K = K_barrow*(Sex = "barrow") + K_boar*(Sex = "boar") + K_gilt*(Sex = "gilt") + b2_Litter + b2_Pig;
    n = n_barrow*(Sex = "barrow") + n_boar*(Sex = "boar") + n_gilt*(Sex = "gilt") + b3_Litter + b3_Pig;
    Wm = Wm_barrow*(Sex = "barrow") + Wm_boar*(Sex = "boar") + Wm_gilt*(Sex = "gilt") + b4_Litter + b4_Pig;
    predv = (((W0*K**n + Wm*Age**n)/(K**n + Age**n));
),
/*Starting values for fixed effects are listed in the parms argument. The model and parms arguments in %nlinmix is similar to PROC NLIN */
parms = %str(W0_barrow = 1.7 W0_boar = 1.7 W0_gilt = 1.7
    K_barrow = 264 K_boar = 283 K_gilt = 244
    n_barrow = 1.94 n_boar = 1.94 n_gilt = 1.94
    Wm_barrow = 455 Wm_boar = 510 Wm_gilt = 393),
/*The derivs argument is used to specify the variance weights but it may also be used to specify
partial derivatives with respect to parameters. If they are not specified, these are calculated
using the finite difference method */
derive = %str(
    wt = 1/predv**2*0.5;
),
/*The stmts argument specifies the PROC MIXED statements to be executed for each iteration.
The response variable must be declared as pseudo_y where y is the response variable in the
input dataset i.e. weight. In the model statement the options noint, notest, solution and cl
must be specified */
stmts = %str(
    class Litter Pig_no;
    model pseudo_Weight = d_W0_barrow d_W0_boar d_W0_gilt
d_K_barrow d_K_boar d_K_gilt
d_n_barrow d_n_boar d_n_gilt
d_Wm_barrow d_Wm_boar d_Wm_gilt / noint notest solution cl;
    /* In the random statements the options subject, type and solution must be specified. Note,
that the structure VC is used to specify diagonal variance-covariance matrices for the random
effects */
    random d_b1_Litter d_b2_Litter d_b3_Litter d_b4_Litter / subject = Litter type = VC solution;
    random d_b1_Pig d_b2_Pig d_b3_Pig d_b4_Pig / subject = Pig_no(Litter) type = VC solution;
    /*The SP(POW) correlation structure declares the CAR(1) process for the within-pig residuals */
Repeated / Subject = Pig_no(Litter) Type = SP(POW)(Age);
weight wt;
),
/*The expand argument is used to employ a first-order Taylor expansion around the current estimates of fixed effects and the conditional modes of the random effects. The procopt are used for numerical specifications to the PROC MIXED call */
expand = eblup,
procopt = %str(maxiter = 100 method = ml)
)