Logistic nonlinear mixed effects model for estimating growth parameters

S. E. Aggrey[1]

Poultry Genetics and Biotechnology Laboratory, Department of Poultry Science and Institute of Bioinformatics, University of Georgia, Athens 30602

ABSTRACT This study was undertaken to apply the logistic model with nonlinear mixed effects to model growth in Japanese quail. Nonlinear mixed models (NLMM) allow for the inclusion of random factors in a linear manner, which accounts for the between-individual variability and heterogeneous variance. A fixed effects model (M1) was compared with NLMM containing either 1 (M2) or 2 (M3) random effects using the residual error variance, −2 log-likelihood, Akaike information criterion, and Bayesian information criterion as the criteria for evaluating these alternative models. In M2, the between-bird variability was modeled by varying the asymptotic BW, which led to a 57% reduction in the residual variance compared with M1 in males. In M3, the between-bird variation was partitioned into variances due to varying asymptotic BW and the age at the inflection point. The residual variance in M3 was reduced by about 72 and 38% compared with M1 and M2, respectively, in males. The correlation coefficient between the actual and predicted BW for M1, M2, and M3 were 0.9887, 0.9955, and 0.9975, respectively. Similar results were found in females. The model evaluation criteria indicated that the mixed effect models fitted the data better than the fixed effect model because they account for between-bird variation. The use of NLMM is recommended for modeling growth data in poultry because the predicted BW at different ages is more accurate than using the mean prediction function of the fixed effect model.

Key words: growth, nonlinear mixed effect model, fixed effect, random effect

INTRODUCTION

Modeling growth is a complex process because it entails describing longitudinal measurements with few parameters with biological interpretation. The growth pattern of most species can be described by a single sigmoid phase, and nonlinear models (**NLM**) have often been chosen to describe such growth curves (Aggrey, 2002), whereas spline regression models have been used to describe preasymptotic growth (Aggrey, 2002, 2004). With longitudinal data, the variance of observations may increase with time (age), and repeated measurements of an individual over time are correlated. The nonindependence of data violates a key assumption underlying many statistical procedures and has been ignored in most traditional NLM, which are considered as fixed effect models.

A solution to ameliorate this problem is the use of hierarchical nonlinear mixed effect models (**NLMM**). Mixed effects models for longitudinal data such as growth have become of interest because of their flexible covariance structure and their ability to handle unbalanced data (Lindstrom and Bates, 1990). A NLMM makes it possible to account for random covariates before testing for fixed effects and control (in part) autocorrelation in repeated measures (Lindstrom and Bates, 1990; Pinheiro and Bates, 1995). Nonlinear mixed effect models also account for multiple sources of heterogeneity in data through the inclusion of random effects in the models (Hall and Clutter, 2004). Thus, each parameter in the NLMM can be represented by a fixed effect that pertains to the population or for the mean value of the parameter, as well as a random effect that pertains to the differences between the value of the parameter fitted for each individual, and the mean value of the parameter, the fixed effect. The random effects are modeled by describing their distribution and thereby avoiding the problem of overparameterization. Nonlinear mixed effect models have been applied to growth data (Lindstrom and Bates, 1990; Schinckel et al., 2005), physiological-response curves (Peek et al., 2002), survivorship kingship curves (Karban, 1997), and developmental patterns (Knight et al., 1991).

The objectives of the present study were to model longitudinal measurements of growth using the NLMM approach and evaluate the efficacies of NLMM and the conventional NLM methodologies using the logistic growth model.

MATERIALS AND METHODS

Data

Aggrey et al. (2003) first reported the BW data used in the present study. Growth data were from a population of 183 unselected Japanese quail. The birds were generated from 30 pairs. Chicks were hatched, wing banded, and reared in standard quail brooders. Birds were fed a diet containing 28% CP and 2,947 kcal of ME/kg. They had ad libitum access to feed and water. Individual hatch and weekly weights were measured on all birds until 8 wk of age. Aggrey et al. (2003) described details of husbandry and management practices. Birds were sexed at 6 wk of age according to plumage pattern.

The General Logistic Model

The well-known logistic model (Robertson, 1923) serves as the basic growth model. The statistical expectation of the logistic model is expressed as:

$$W_{it} = A/[1 + \exp\text{-}K(t - t^*)] \qquad [1]$$

where W_{it} is the expected BW of individual i at time (age) t wk, A is the asymptotic BW, K is the exponential growth rate, and t^* is the age at the inflection point. The point of inflection, t^*, can be estimated as

$$t^* = (1/K)\ln[A - (W_0/W_0)], \qquad [2]$$

where W_0 is the weight at hatch.

NLMM

The nonlinear model for BW can be expressed as

$$Y_{ij} = f\left(\boldsymbol{\beta}_{ij}, \mathbf{u}_{ij}\right) + \varepsilon ij, \; \varepsilon ij \sim N\left(0, \sigma_e^2\right), \qquad [3]$$

where Y_{ij} is the jth observation (BW) on the ith individual ($i = 1,\ldots, M$, $j = 1,\ldots,m_i$); M is the total number of individuals, and m_i is the number of observations on the ith individual; f is the nonlinear function relating BW to age and other possible covariates $\mathbf{u}_{ij}$ varying with individual; $\boldsymbol{\beta}_{ij}$ is a vector with the parameters of the nonlinear function; ε_{ij} is the residual term; and σ_e^2 is the variance for the residuals.

The $\boldsymbol{\beta}_{ij}$ vector may be modeled in a second stage (Lindstrom and Bates, 1990; Pinheiro and Bates, 1995) as the sum of 2 components: a fixed (population) component, $\boldsymbol{\beta}$, common to all individuals, and a random component, $\mathbf{b}$, specific to each individual. Therefore:

$$\boldsymbol{\beta}_{ij} = \mathbf{A}_{ij}\boldsymbol{\beta} + \mathbf{B}_{ij}\mathbf{b}_i, \, \mathbf{b}_i \sim N\left(0, \sigma_u^2\right), \qquad [4]$$

where $\mathbf{A}_{ij}$ and $\mathbf{B}_{ij}$ are design matrices for the fixed and random effects, respectively; $\boldsymbol{\beta}$ is a p-dimensional vector of fixed population parameters; $\mathbf{b}_i$ is a q-dimensional random effects vector associated with individual i (not varying with j), and σ_u^2 is the variance of the random effects. It is assumed that observations made on different individuals are independent, and ε_{ij} is independent of $\mathbf{b}_i$. The logistic model, in terms of fixed and random effects, can now be written as

$$W_{it} = (A + u_{i1})/\{1 + \exp\text{-}K[t - (t^* + u_{i2})]\}. \qquad [5]$$

The 3 fixed-effect parameters to be estimated are A, K, and t^*. The 2 random-effect parameters are u_{i1} and u_{i2}, and they enter the model linearly. Fitting u_{i1} allows for between-bird variation in mature BW, whereas fitting u_{i2} allows for between-bird variation at the point of inflection. The random parameters u_{i1} and u_{i2} are assumed to have a mean of zero with a 2×2 unstructured covariance matrix.

Statistical Analysis

Body weight measurements from 0 to 8 wk on 102 males and 81 females were used in the analysis. The same data were fitted to the fixed (**M1**; equation [1]) and random (equation [5]) effects growth models using the NLMIXED procedure in SAS (SAS Institute, 1996). The mixed effects model (equation [5]) was first fitted with 1 random effect (**M2**; u_{i1}) and thereafter with 2 random effects (**M3**; u_{i1} and u_{i2}). Under normality assumptions, alternative models were evaluated by the -2 log-likelihood, Akaike information criterion (Akaike, 1974), Bayesian information criterion (Schwartz, 1978) and the residual variance $\left(\sigma_e^2\right)$. Smaller Akaike or Bayesian information criteria or σ_e^2 values indicate a better fit of the model to the data. The correlation between actual and predicted BW was performed using the CORR procedure (SAS Institute, 1996). Japanese quail exhibit sexual dimorphism in growth (Aggrey and Cheng, 1994) and therefore the data were analyzed by sex.

RESULTS AND DISCUSSION

The means and standard deviation for BW at different ages for both sexes are shown in Table 1. There was no sexual dimorphism for BW until after 4 wk of age where females were consistently heavier than their male counterparts. The estimates of logistic growth parameters obtained with fixed and mixed effects models for both sexes are presented in Table 2. In M2, the between-bird variability was modeled by varying the asymptotic BW. In M3, the between-bird variability was modeled by varying both the asymptotic BW and the age at the inflection point.

Table 1. Mean and standard deviation of BW at different ages in a randombred Japanese quail population

Age (wk)	BW (g)	
	Male (n = 102)	Female (n = 81)
0	5.41 ± 0.51	5.44 ± 0.47
1	18.92 ± 2.78	19.07 ± 3.28
2	39.91 ± 4.57	40.23 ± 5.80
3	64.07 ± 5.84	64.66 ± 7.08
4	84.87 ± 6.44	87.14 ± 7.54
5	96.13 ± 7.09	101.94 ± 7.94
6	100.39 ± 6.16	116.59 ± 10.69
7	101.98 ± 6.00	127.83 ± 10.78
8	104.06 ± 6.05	130.81 ± 9.58

The growth parameter estimates for both the fixed and random effects models were similar because the expected means of the mixed effect model is the same as that of the fixed effect model and the data were balanced for all birds. The SE for residual variance was lowest in M3 followed by M2, with M1 being the greatest. In M2, the error variation was partitioned into within-bird variation $\left(\sigma_e^2\right)$ and between-bird variation $\left(\sigma_{u1}^2\right)$. The residual variance in the males was reduced by about 56% in M2 compared with M1, indicating an improvement in the accuracy of estimating the growth

parameters. The log-likelihood, Akaike and Bayesian information criteria were all lower in M2 compared with M1, suggesting a better fit of M2 to the data. In M3, the between-bird variation was further partitioned into variance due to varying asymptotic BW $\left(\sigma_{u1}^2\right)$, variance due to varying the age at the inflection point $\left(\sigma_{u2}^2\right)$, and the covariance among them $\left(\sigma_{u1u2}\right)$. By incorporating 2 random effects in the model, the residual variance further declined. The residual variance in M3 males was reduced by about 72 and 38% compared with M1 and M2, respectively. From M3, it appears that the large proportion of the between-bird variation was accounted for by σ_{u1}^2 even though σ_{u2}^2 was also significant ($P < 0.0001$). The covariance between the 2 random effects was negative and not significant. A similar phenomenon was observed in the females. Judging from criteria of fit of the models, M3 was the best model compared with M2 and M1, and NLMM fit the data better than NLM because the variance-covariance partitioning associated with the random effects allowed for the separation of the between-bird variation from the within-bird variation. The goodness of fit between actual and predicted BW for M1, M2, and M3 for males are presented in Figure 1. The correlation coefficient between the actual and predicted BW for M1, M2, and

Table 2. Growth parameter and standard error estimates from mixed logistic growth models

Parameter[1]	Fixed model[2]			Mixed model[3]			Mixed model[4]		
	Estimate ± SE	t value	Pr > |t|	Estimate ± SE	t value	Pr > |t|	Estimate ± SE	t value	Pr > |t|
Male									
A (g)	103.53 ± 0.35	298.18	<0.0001	103.50 ± 0.59	175.76	<0.0001	103.59 ± 0.57	180.93	<0.0001
K (g/wk)	1.02 ± 0.01	71.52	<0.0001	1.02 ± 0.01	107.56	<0.0001	1.02 ± 0.01	135.94	<0.0001
t* (wk)	2.50 ± 0.02	154.94	<0.0001	2.50 ± 0.01	232.99	<0.0001	2.50 ± 0.02	127.38	<0.0001
σ_e^2 (g²)	30.02 ± 1.40	21.42	<0.0001	13.31 ± 0.66	20.20	<0.0001	8.31 ± 0.44	18.88	<0.0001
σ_{u1}^2 (g²)				29.94 ± 4.57	6.56	<0.0001	30.04 ± 4.54	6.62	<0.0001
σ_{u2}^2 (wk²)							0.03 ± 0.01	5.90	<0.0001
σ_{u1u2} (g, wk)							−0.12 ± 0.11	−1.19	0.2741
−2 Log-likelihood	5,728			5,237			5,031		
AIC	5,736			5,247			5,045		
BIC	5,755			5,260			5,063		
Female									
A (g)	132.41 ± 0.90	147.63	<0.0001	132.38 ± 1.20	110.25	<0.0001	132.43 ± 1.18	112.70	<0.0001
K (g/wk)	0.77 ± 0.01	51.49	<0.0001	0.77 ± 0.01	83.63	<0.0001	0.77 ± 0.01	95.65	<0.0001
t* (wk)	3.18 ± 0.03	97.34	<0.0001	3.18 ± 0.02	157.92	<0.0001	3.18 ± 0.03	110.23	<0.0001
σ_e^2 (g²)	67.13 ± 3.52	19.09	<0.0001	25.60 ± 1.42	18.00	<0.0001	19.51 ± 1.16	16.81	<0.0001
σ_{u1}^2 (g²)				92.06 ± 15.47	5.95	<0.0001	93.00 ± 16.00	5.81	<0.0001
σ_{u2}^2 (wk²)							0.04 ± 0.01	4.48	<0.0001
σ_{u1u2} (g, wk)							−0.34 ± 0.28	−1.20	<0.2331
−2 Log-likelihood	5,136			4,655			4,582		
AIC	5,145			4,665			4,596		
BIC	5,162			4,677			4,612		

[1]A = asymptotic BW; K = exponential growth rate; t* = age at the inflection point; σ_e^2 = residual BW variance; σ_{u1}^2 = the individual variance in A within the population; σ_{u2}^2 = the individual variance in t* within the population; σ_{u1u2} = individual covariance between random effects; AIC = Akaike information criterion; BIC = Bayesian information criterion.

[2]M1: no random effect.

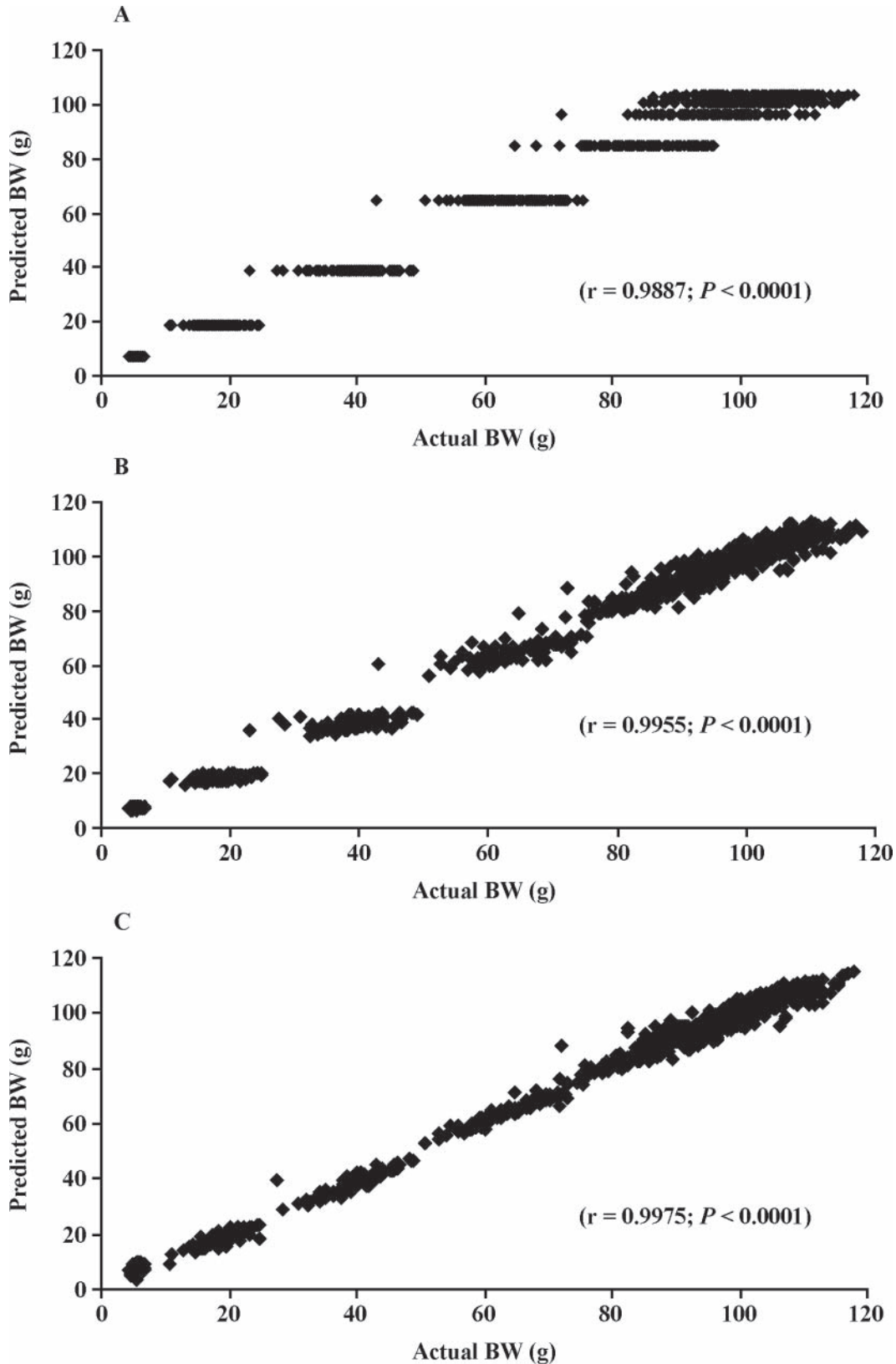[3]M2: 1 random effect.

[4]M3: 2 random effects.

Figure 1. Goodness of fit between actual and predicted body weights for fixed and random models using the mixed logistic growth model: A) Fixed effect model (M1: no random effect); B) random effect model (M2: 1 random effect: asymptotic BW); and C) random effect model (M3: 2 random effects: asymptotic BW and point of inflection).

M3 are 0.9887, 0.9955, and 0.9975, respectively. An important point to consider in modeling mixed effects is to avoid overparameterization. If all parameters are considered mixed (both random and fixed), the eigenvalues of the estimated covariance of the effects must be examined to ascertain if one or more are close to

zero. The associated eigenvectors for such eigenvalues will suggest the linear combination of parameters that may be treated as fixed. In addition, low estimated values of some random values and high correlation among random values may all suggest which effects need to be treated as fixed.

Accuracy of prediction of growth models is necessary especially when alternative treatments are under consideration (Aggrey, 2008), and stochastic modeling of random effects of nonlinear functions could allow for accurate predictions. The appeal of NLMM is obvious because of its flexibility in including the variance-covariance structure, which is not identified by the traditional regression approach. With random effects considered, the predicted BW at different ages are expected to be closer to the observed values than those predicted by the mean response function because the random effect estimation process utilizes all observed information, whereas the mean response predicated does not. Nevertheless, the mixed model does not account for all the heterogeneous variances and correlation across age, because the q-dimensional random effects vector associated with an individual does not vary with observations. Random regression procedures allow, among other things, accounting for heterogeneity of variance in measurement error over time; however, their constraint is in fitting a nonlinear model.

The present study suggests that NLMM improve the accuracy of prediction of BW at different ages compared with traditional NLM, and the addition of random effects into fixed effect models partitions the error variance into residual variance and between-bird variance.

ACKNOWLEDGMENTS

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