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A generalized Michaelis-Menten equation for the analysis of growth

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ABSTRACT: The functional form $W = (W_0 K^c + W_f t^c)/(K^c + t^c)$, where W is body size at age t , W_0 and W_f are the zero- and infinite-time values of W , respectively, and K and c are constants, is derived. This new generalized Michaelis-Menten-type equation provides a flexible model for animal growth capable of describing sigmoidal and diminishing returns behavior. The parameters of the nonlinear model are open to biological interpretation and can be used to calculate reliable estimates of growth traits, such as maximum or average postnatal growth rates. To evaluate the new model, the derived equation and standard growth functions such as the Gompertz and Richards were used to fit 83 growth data sets of different animal species (fish, mice, hamsters, rats, guinea pigs, rabbits, cats, dogs, broilers, turkeys, sheep, goats, pigs, horses, and cattle) with a large range in body size. A comparative study was car-

ried out based on mathematical, statistical, and biological characteristics of the models. The statistical goodness-of-fit achieved with the new model was similar to that of Richards, and both were slightly superior to the Gompertz. The new model differed from the others with respect to some of the estimated growth traits, but there were highly significant correlation coefficients between estimates obtained with the different models, and the ranking of animals based on growth parameters computed with the new function agreed with the rankings computed by the other models. Therefore, the new model, with its variable inflection point, was able to adequately describe growth in a wide variety of animals, to fit a range of data showing sigmoidal growth patterns, and to provide satisfactory estimates of traits for quantifying the growth characteristics of each type of animal.

Key Words: Animal Species, Growth, Growth Curves, Mathematical Models, Nonlinear Equations, Sigmoidal Functions

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Introduction

Growth functions have been used extensively to represent changes in size with age, so that the genetic potential of animals for growth can be evaluated and nutrition matched to possible growth. In models of animal production systems, growth curves are used to provide estimates of daily feed requirements for growth. These estimates are used in calculating total feed requirements, which sets an upper limit to feed intake when animals are given ad libitum access to high-quality feeds.

An appropriate growth function conveniently summarizes the information provided by observations on

an animal into a small set of parameters that can be interpreted biologically and used to derive other relevant growth traits. A number of nonlinear functions have been used to describe growth in fish, poultry, and mammals (Parks, 1982; France and Thornley, 1984; France et al., 1996a). Despite the number of growth functions reported in the literature, derivatives of the commonly used functions are unable to describe the corresponding mean growth-rate curve (Taylor, 1980a), emphasizing the need for obtaining growth functions with the same overall shapes as the observed data.

The use of growth functions is usually empirical, and the form of the function is chosen by its ability to fit the data. However, a growth function can characterize some underlying physiological or biochemical mechanism or constraint (Von Bertalanffy, 1957; France and Thornley, 1984). Such growth functions can be expressed in the “rate is a function of state” form, in which the instantaneous growth rate is a function of the organism’s size. An equation in this form can usually be

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interpreted biologically and meaning can be ascribed to its parameters, unlike equations in which growth rate is purely an empirical function.

In this paper, the functional form of a generalized Michaelis-Menten-type equation is derived as a growth function. This function is evaluated using growth data for fish and several farm and laboratory animals and compared with the Gompertz and Richards functions.

Mathematical Model Derivation

The equation may be derived by assuming the system is closed with no inputs or outputs, the quantity of growth machinery is constantly working at a rate (increase of biomass [W, kg] per unit of time) proportional to the substrate level S (kg) with proportionality μ , μ changes with time according to a simple rational function, and growth is irreversible. Formalizing the above, therefore:

$$dW/dt = \mu S \tag{1}$$

with

$$\mu = ct^{c-1}/(K^c + t^c) \tag{2}$$

where t denotes age in weeks (or any other unit of time such as days, months, years), μ is in units of week⁻¹, and c (dimensionless) and K (wk) are positive constants. The conditions $c > 0$, $K > 0$ have to be satisfied because μ cannot be negative as growth is irreversible. K is the time when half-maximal growth is achieved. Equation [2] permits μ to decrease continually ($c \leq 1$) or to increase to reach a maximum and then decrease again ($c > 1$). μ is plotted for different values of c in Figure 1.

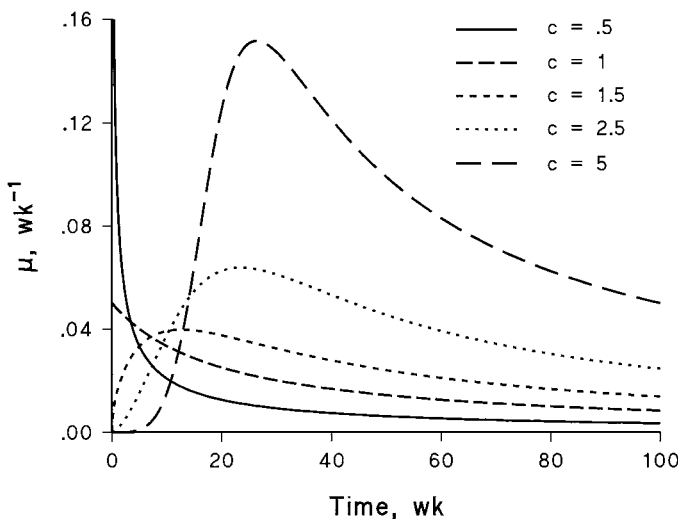


Figure 1. The range of behavior of the new growth function. The graph shows the value of the fractional growth rate (μ) against time with $K = 20$, and for five values of c .

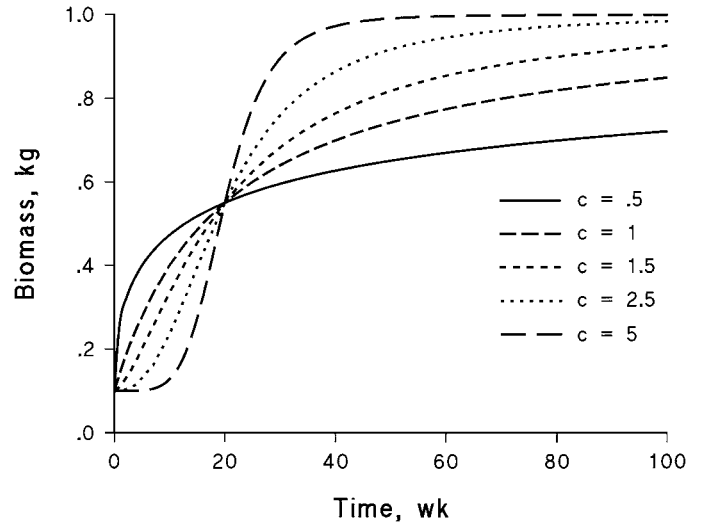


Figure 2. The range of behavior of the new growth function. The graph shows biomass against time with $W_0 = .1$, $W_f = 1$, $K = 20$, and for five values of c .

On substituting for μ using Eq. [2], writing S as $W_f - W$ and integrating Eq. [1] yields:

$$\int_{W_0}^W (W_f - W)^{-1} dW = \int_0^t ct^{c-1}/(K^c + t^c)^{-1} dt \tag{3}$$

giving:

$$W = (W_0 K^c + W_f t^c)/(K^c + t^c) \tag{4}$$

where W_0 and W_f are the zero- and infinite-time values of biomass W , respectively.

A point of inflection (t^* , W^*) occurs when d^2W/dt^2 is zero. This is possible only if $c > 1$ and occurs at a time

$$t^* = K[(c - 1)/(c + 1)]^{1/c} \tag{5}$$

i.e.,

$$W^* = [(1 + 1/c)W_0 + (1 - 1/c)W_f]/2 \tag{6}$$

The growth function (Eq. [4]) is illustrated in Figure 2 for a range of values of c and shows both diminishing returns and sigmoidal behavior. All lines are heading toward the same asymptotic value and, because they share the same K , they all cross at the same point. However, the points of inflection are variable for the curves shown in Figure 2 and occur at 6.8, 14.2, and 18.4 wk for $c = 1.5$, 2.5, and 5, respectively.

Special Cases

When the parameter c equals 1, μ varies with time t as follows:

$$\mu = 1/(t + K), \tag{7}$$

where $K (> 0)$ is the inverse of μ_{max} . The growth equation becomes:

$$W = (W_0K + W_f t)/(K + t). \quad [8]$$

Equation [8] is a rectangular hyperbola (see Figure 2 for $c = 1$) and, when W_0 equals zero, is in the form of the well-known Michaelis-Menten equation of enzyme kinetics (Michaelis and Menten, 1913) with time replacing substrate concentration. The growth rate decreases continually (see Figure 1 for $c = 1$), and there is no point of inflection (Figure 2).

If μ is not allowed to vary with time as in Eq. [2] but is held constant, then Eq. [1] with S written as $W_f - W$ now yields on integration:

$$W = W_f - (W_f - W_0)e^{-\mu t}. \quad [9]$$

Equation [9] is the monomolecular growth function (France and Thornley, 1984), representing a growth rate that decreases continually, and therefore is a curve with no point of inflection.

Model Evaluation

Data Sets

Growth data recorded for 83 animals, most of them reported in the literature, were used for model evaluation. Given the diversity of animal species (with mature weights ranging from $< .040$ kg [mouse] to $> 1,100$ kg [Charolais bull]), data were grouped in seven sets of similar characteristics. Data set 1 comprised observations for fish reported by Hightower and Heppell (1996), relating fish length in centimeters (either standard or total length as defined by Ricker [1979]) to age in years. Data for the ensuing fishes were used: three tilefish (*Lopholatilus chamaeleonticeps*), two canary rockfish (*Sebastes pinniger*), one darkblotched rockfish (*Sebastes cramerii*), one Pacific ocean perch (*Sebastes alutus*), one vermilion snapper (*Rhomboplites aurorubens*), two weakfish (*Cynoscion regalis*), one Black sea bass (*Centropristis striata*), one snowy grouper (*Epinephelus niveatus*), and two gag grouper (*Mycteroperca microlepis*). Growth data reported by Altman and Dittmer (1964) and Parks (1982) for eight laboratory animals were in a data set corresponding to two hamsters, three mice, and three rats. These data related live weight in grams to age in weeks. Set 3 comprised growth data for six pet animals (two cats, two guinea pigs, and two rabbits) reported by Altman and Dittmer (1964). Weight-age data for five poultry animals (two broilers, one laying hen, and two Eastern wild turkeys) were in data set 4 (Altman and Dittmer, 1964; Parks, 1982). Set 5 comprised growth data for 16 breeds of dogs, with mature weight ranging from 2.5 (Pomeranian) to 60 kg (Great Dane) (Kirk, 1966). The dog breeds were Pomeranian, Pekingese, Boston, Dachshund, Fox terrier, Scottish terrier, Beagle, Cocker, Bulldog, Chow Chow,

Poodle, Collie, Setter, Hound, German shepherd, and Great Dane. Data set 6 comprised weight-age data for different farm animal species, with observations for six breeds of sheep (Merino d'Arles, Berrichon, Suffolk, Merino, Shetland, and Welsh mountain) (Brody, 1945; Prud'hom, 1976; Friggens et al., 1997), two breeds of goats (Saanen and Toggenburg) (Altman and Dittmer, 1964), three pigs (one Dutch Landrace boar and two commercial Landrace \times Large White pigs) (Walstra, 1980; Whittemore et al., 1988), and one castrated male Percheron horse (Brody, 1945). Finally, set 7 comprised data reported in the literature (Brody, 1945; Altman and Dittmer, 1964; Fraysse and Darré, 1990) for six breeds of cattle (Ayrshire, Jersey, Guernsey, Holstein, Charolais, and French Frison), with adult weights ranging from 450 to 1,100 kg, and also growth data recorded for 16 Holstein heifers bred at the Centre for Dairy Research (CEDAR, Reading, U.K.) as replacements for the experimental herd, with weights recorded from birth to 40 mo of age. In data sets 3, 4, 5, 6, and 7 weight was in kilograms and age in weeks. The observed graphical depiction resulting from plotting body size (length or weight) against age is shown in Figure 3 for all the animals.

Model Fitting

Four models were fitted to the data by nonlinear regression using the NLIN procedure of the SAS package (1988). The models were the generalized Michaelis-Menten (GMM) model (Eq. [4]), its special case with parameter $c = 1$ (Eq. [8]), and the well-known growth functions of Gompertz and Richards, using the equations described by France and Thornley (1984):

$$\text{Gompertz} \quad W = W_0 \exp[\mu_0(1 - e^{-Dt})/D] \quad [10]$$

$$\text{Richards} \quad W = \frac{W_0 W_f}{[W_0^n + (W_f^n - W_0^n)e^{-kt}]^{1/n}}, \quad [11]$$

where W_f , W_0 , W , and t are as above and μ_0 , D , k , and n are parameters as defined by France and Thornley (1984). These equations were chosen as representative of functions that fit sigmoidal growth with a fixed (Gompertz) and a variable (Richards) inflection point, and also because Eq. [10] and [11] were derived by France and Thornley (1984) using an approach similar to that followed in the previous section.

Several possible starting values were specified for each parameter, so that the NLIN procedure evaluated the model at each combination of initial values on the grid, using for the first iteration of the fitting process the combination yielding the smallest residual sum of squares (SAS, 1988). The initial values supplied were different for each data set, and the selection of the starting values was based on visual inspection of the plots of weight (length for fish) vs time. The uniqueness of the final solution achieved in each case was checked

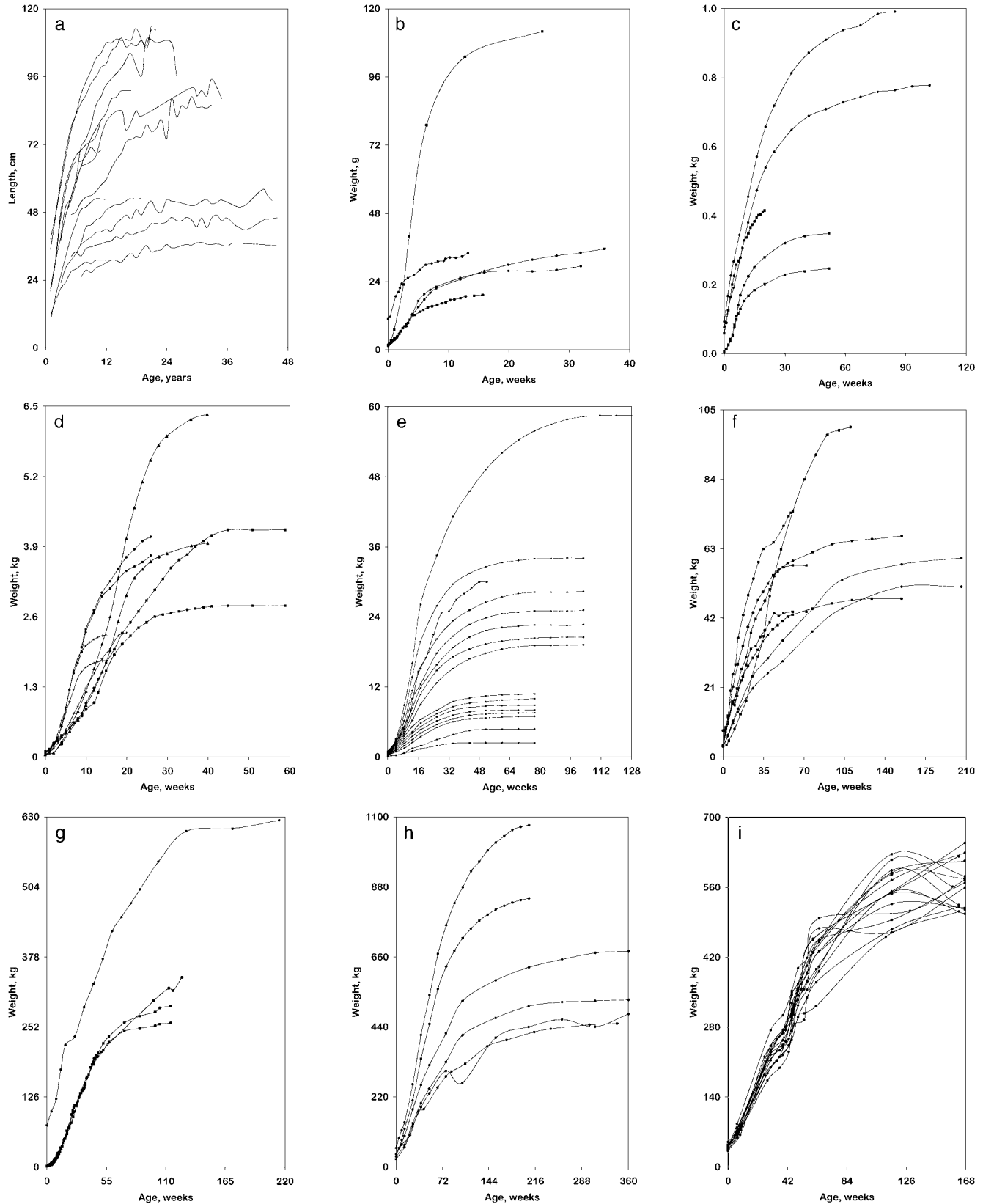


Figure 3. Plots of the growth data used to evaluate the new model (see text for sources and details): (a) Data for different fish species (data set 1). (b) Data for mice (circles) and hamsters (squares) (data set 2). (c) Data for rats (squares, data set 2) and for guinea pigs (circles, data set 3). (d) Data for cats (squares) and rabbits (circles) (data set 3); and for broilers (crosses) and turkeys (triangles) (data set 4). (e) Data for 16 breeds of dogs (data set 5). (f) Data for sheep (squares) and goats (circles) (data set 6). (g) Data for pigs (squares) and a horse (circles) (data set 6). (h) Data for six breeds of cattle (data set 7). (i) Data for Holstein heifers (data set 7).

by changing the initial parameter estimates within a reasonable range for each group of animals.

Growth Parameters

Estimates of growth parameters obtained with the different models were compared. The growth parameters used were initial weight (W_0), final weight (W_f), maximum growth rate (ΔW_{max}), average growth rate during postnatal life ($\langle \Delta W \rangle$), and the time at which 50% of the final weight is achieved (t_{50}). The maximum growth rate is the slope at the point of inflection and was calculated as dW/dt at t^* (when d^2W/dt^2 is zero). The average growth rate during postnatal life ($\langle \Delta W \rangle$) was defined by Richards (1959) as the average height of the curve resulting from plotting dW/dt against W for the entire growing interval, and it is calculated from the following expression:

$$\langle \Delta W \rangle = \frac{1}{W_f - W_0} \int_{W_0}^{W_f} \frac{dW}{dt} dW. \quad [12]$$

The time at which 50% of the final weight is achieved (t_{50}) is calculated by substituting $.5W_f$ for W in the equations relating W to time for each model (Eq. [4], [8], [10], and [11]). The growth curve parameter estimates and calculated traits obtained with the new model for each of the animal species examined are given in Table 1.

Statistical Analyses

To evaluate the ability of each model to describe the data without systematically over- or underestimating any section of the curve, the number of runs of sign of the residuals (Motulsky and Ransnas, 1987) was calculated. A run is a sequence of residuals with the same sign (positive or negative). Because the number of observations (N) was different for each individual, the number of runs of sign was expressed as a percentage of the maximum number possible (i.e., $N - 1$). The probability for the occurrence of too few (indicating clustering of residuals with the same sign or systematic bias) or too many (indicating negative serial correlation) runs of sign was determined using the test for runs described by Draper and Smith (1981). Serial correlation was examined using the Durbin-Watson statistic, and its level of significance was determined as described by Draper and Smith (1981). A number of statistics were used to evaluate the general goodness-of-fit of each model. Proportion of variation accounted for (R^2) was calculated as $1 - \text{RMS}/s_y^2$, where **RMS** is the residual mean square and s_y^2 is the total variance of the y-variable. The residual sum of squares (**RSS**) was used to compare two different equations (models) when fitted to the same set of data, so that the fit with the lower RSS was, in principle, superior. The statistical significance of the difference between models in terms of the goodness-of-fit of the same data was assessed by using

the F -tests described by Motulsky and Ransnas (1987) for comparing two models either with the same or a different number of parameters.

The mean square prediction error (**MSPE**) defined by Bibby and Toutenburg (1977) was used to calculate mean prediction error (square root of the MSPE), as a measure of the degree of the discrepancy (error) between two models in the estimation of growth parameters. Furthermore, the MSPE was partitioned into overall bias, slope deviation, and random (lack of linear correlation) variation components, according to the MSPE analysis proposed by Bibby and Toutenburg (1977). The Spearman rank correlation coefficient (SAS, 1988) was used to evaluate the similarity between models in ranking the animals according to growth parameters, and the concordance correlation coefficient (Lin, 1989) was used to measure the degree of reproducibility among models in the parameters estimates.

Results

Evaluation of the Simple Michaelis-Menten Model

The special case of the model derived herein for $c = 1$ is the well-known Michaelis-Menten equation with time rather than substrate concentration as the independent variable. All growth data were fitted by both the generalized model and its special case, to evaluate whether the simpler model was an acceptable growth function. However, the solution obtained by fitting the simple model could not be considered satisfactory for at least 40 curves (48% of cases), because the SE for the estimates of one or more parameters could not be assessed, resulting in singularity of the Jacobian matrix, and giving an inconsistent solution with large SE for the other parameters. This problem was detected when the final estimate for one of the parameters approached a prescribed limit. When data were fitted without any restriction, the solution tended to converge to a negative value for W_0 (birth weight), which is nonsensical. When the condition that W_0 had to be greater than zero was imposed, the final solution gave $W_0 = 0$, but then the SE of this parameter could not be estimated, and large SE were obtained for the other parameters of the model.

Fitting the generalized model and examining the SE of parameter c allows a t -test to be performed to determine whether or not c is significantly greater than unity. The estimate of parameter c was always greater than 1 (so all curves tended to be sigmoidal). Using the t -test, it could be determined whether this value ($c = 1$) was within the 95% confidence interval of parameter c calculated from its asymptotic standard error. This occurred only in 11 cases (out of 83, 13.3%), indicating that over 85% of the cases were not appropriately described by the simpler model. This was confirmed by evaluating the goodness-of-fit of both models, because the residual sum of squares was always greater when fitting the special case. The F -test of Motulsky and

Table 1. Growth parameters and traits estimated with the new growth function for the different animal species (average, minimum, and maximum values)

Animal species	number of observations (N)	Birth weight (W_0), kg	Final weight (W_f), kg	Parameter c	Age at half-maximal growth (K), wk	Age at inflection point (t^*), wk	Maximum growth rate (ΔW_{max}), kg/wk	Average growth rate during postnatal life ($\langle \Delta W \rangle$), kg/wk
Data set 1								
Fish (avg) ^a	14	23.4	77.5	2.39	7.6	5.2	7.51	4.43
(min.–max.)		6.3–45.8	32.9–120	1.22–3.71	2.9–14.9	.77–12.1	.811–15.4	.517–9.88
Data set 2								
Mice (avg)	3	.005	.035	1.52	5.1	1.6	.005	.002
(min.–max.)		.001–.010	.029–.039	1.09–2.17	2.7–7.7	.16–3.0	.003–.008	.002–.003
Hamster ^b	2	.002–.004	.021–.111	1.64–2.56	4.2–4.6	1.8–3.4	.003–.017	.002–.011
Rats (avg)	3	.022	.387	1.61	8.7	3.3	.027	.015
(min.–max.)		.004–.059	.254–.548	1.22–1.88	8.2–9.3	1.3–4.9	.019–.038	.011–.018
Data set 3								
Guinea pigs ^b	2	.088–.111	.814–1.11	1.31–1.52	15.0–18.0	3.9–5.3	.029–.035	.016–.018
Cats ^b	2	.195–.276	2.90–4.84	2.18–3.09	14.8–20.7	11.9–13.1	.152–.152	.093–.098
Rabbits ^b	2	.067–.089	4.03–4.67	2.02–2.23	9.1–10.3	5.9–6.1	.291–.298	.176–.184
Data set 4								
Broilers (avg)	3	.074	2.58	2.67	8.3	5.5	.259	.164
(min.–max.)		.059–.086	1.93–3.40	1.93–3.15	5.7–13.3	4.4–7.4	.160–.349	.096–.224
Turkeys ^b	2	.201–.242	4.22–7.02	3.29–3.45	16.2–18.5	13.6–15.3	.233–.331	.150–.214
Data set 5								
Dogs (avg)	16	.881	19.5	2.10	18.2	10.9	.667	.406
(min.–max.)		.153–3.13	2.57–60.9	1.67–2.56	15.9–23.6	7.0–14.5	.107–1.56	.067–.932
Data set 6								
Sheep (avg)	6	5.03	73.8	1.67	25.2	11.5	1.80	1.01
(min.–max.)		3.80–6.93	50.6–114	1.30–2.51	18.6–47.8	4.7–34.1	1.36–2.45	.693–1.37
Goats ^b	2	2.96–3.76	65.3–85.7	1.03–1.14	62.1–75.1	1.2–5.7	.712–.978	.318–.363
Pigs (avg)	3	2.34	327	2.09	38.27	22.1	5.68	3.45
(min.–max.)		.580–5.47	274–391	1.71–2.44	32.6–46.2	21.2–22.8	5.20–5.98	3.02–3.74
Horse ^b	1	85.5	731	1.39	56.7	15.5	7.03	3.73
Data set 7								
Holstein heifers (avg)	16	51.6	618	2.14	48.5	29.0	7.99	4.87
(min.–max.)		37.4–58.3	542–714	1.62–2.76	37.3–58.1	23.0–35.2	5.88–9.61	3.38–6.10
Cattle (avg)	6	45.6	738	1.62	65.6	24.4	6.97	3.98
(min.–max.)		20.1–75.4	501–1,184	1.19–1.98	53.9–80.5	10.0–31.3	3.87–11.6	2.09–6.88

^aFor fish species, units of size are in centimeters and age is in years.

^bFor these species $N \leq 2$, and therefore all the estimate values are given.

Ransnas (1987) was performed to check whether the improved fit was worth the cost (in lost degrees of freedom) of the additional parameter c , and the goodness-of-fit was significantly ($P < .05$) improved by the generalized model in 71 cases (out of 83, 85.5%).

Evaluation of the Generalized Model

The data fits obtained with the model derived in this study were compared statistically with those obtained with the Gompertz and Richards growth functions. The statistical evaluation was based on fitting behavior, examination of residuals, and statistics for goodness-of-fit.

The three models were fitted to all the growth data without problems, although in order to reach convergence within a reasonable number of iterations, the initial estimates of the parameters were different for each type of animal. If the values supplied as initial estimates were very different from the final solutions, the algorithm failed to converge in some cases. As the initial estimates were moved closer to the final solution, convergence was met in a fewer number of iterations. Uniqueness of the solution was checked by giving different initial estimates within a reasonable range of values. Growth curves were sigmoidal in most cases, because inflection points could be determined in 87% and 100% of the curves with the Richards and GMM models, respectively. A detailed inspection of the curves showing non-sigmoidal behavior when fitting the Richards model found that, although fitting always converged to a solution, in nine cases (growth data for two mice, one rat, one guinea pig, two sheep, two goats, and one cattle breed) the best solution could not be considered satisfactory because parameter n had a value smaller than -1 , which is physiologically unacceptable (France and Thornley, 1984). Therefore, the Richards was the only model showing some limitations to fitting all the growth data satisfactorily.

Examination of the residuals obtained for each curve when fitting the three models was based on analysis of systematic relationships between residuals and the explanatory variable (age). Clustering of residuals with the same sign and serial correlation may be indicative of inappropriate fitting of the model to experimental data. The distribution of number of runs of sign is shown in Figure 4. A small number of runs of sign is obtained when the residuals are not randomly distributed, so residuals of the same sign tend to cluster together on some parts of the curve. The number of cases with significantly ($P < .05$) too few runs according to the test of Draper and Smith (1981) was 38 (45.8%), 23 (27.7%), and 18 (21.7%) for the Gompertz, Richards, and GMM models, respectively. In contrast, only one (1.2%) curve fitted by the Gompertz and GMM models and two (2.4%) fitted by the Richards had ($P < .05$) too many runs (associated to negative serial correlation of the residuals).

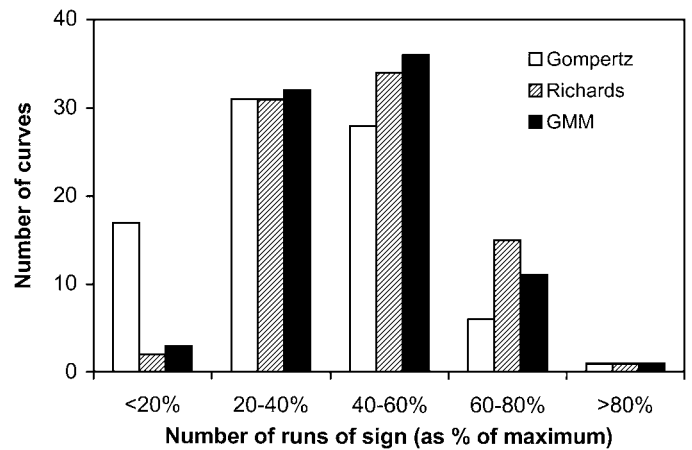


Figure 4. Parallel histogram of the distribution of the growth curves (total number = 83) according to the computed number of runs of sign observed in the fitted curves by the Gompertz, Richards, and generalized Michaelis-Menten (GMM) models.

Serial correlation of residuals was examined further with the Durbin-Watson statistic (DW) (Draper and Smith, 1981). The DW has been used to test whether a model has been successful in describing the underlying trend. The DW values obtained when fitting the three models to all growth data are summarized in Table 2. A DW value around 2 or statistically nonsignificant (test described by Draper and Smith, 1981) is obtained when the serial correlation is small and the residuals are distributed randomly around the zero line (when plotted against time). When the DW is significant (either its value or the difference $4 - DW$ approaches zero), the serial correlation is significant because of the presence of cycles in the residuals plot. Some serial correlation can be expected with growth data, because size at time $t - 1$ is very likely to be autocorrelated with size at time t when measurement intervals are short. With the GMM model there were fewer curves with a significant DW, and more with a nonsignificant DW.

The values of R^2 indicate that the proportion of variation explained was in general high for all the models;

Table 2. Durbin-Watson statistic (DW) values obtained by fitting the Gompertz, Richards, and generalized Michaelis-Menten (GMM) models to the growth data

Item	Gompertz	Richards	GMM
Average	1.512	1.935	1.763
Minimum	.273	.415	.433
Maximum	3.268	3.336	3.263
Median	1.362	2.068	1.723
Number of curves with significant ($P < .05$) DW	29	22	15
Number of curves with nonsignificant ($P > .05$) DW	39	51	59

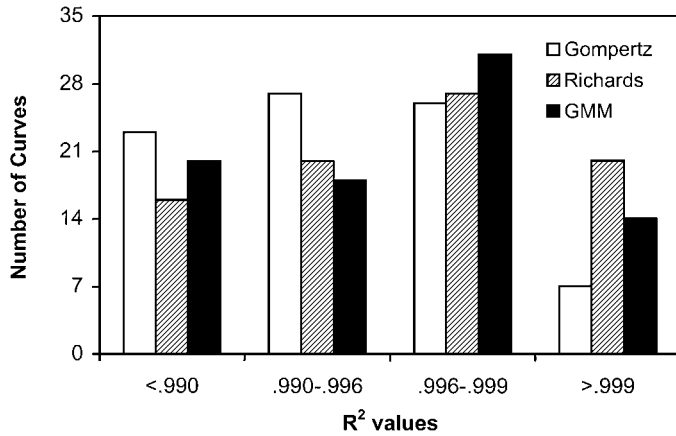


Figure 5. Parallel histogram of the distribution of the growth curves (total number = 83) according to the computed proportion of variation accounted for (R^2 values) by the Gompertz, Richards, and generalized Michaelis-Menten (GMM) models.

the average R^2 values across the 83 growth curves were .990, .993, and .992 and the medians .995, .997, and .997 for the Gompertz, Richards, and GMM models, respectively. The distribution of the growth curves according to the R^2 values obtained with the three models is shown in Figure 5. The R^2 values were in most cases close to unity (the variance ratio or F -test reached a high level of significance for all the curves and models) and could be used only as an overall measure of fit rather than as a basis for model comparison. Evaluation of goodness-of-fit, based on the residual variance, of the three models to the growth curves is summarized in Table 3, which shows the average, median, minimum,

and maximum residual sum of squares (RSS) observed for the three models across the 83 curves. A pairwise comparison between models is also given in Table 3, showing that in general Richards and GMM models were superior to the Gompertz model in terms of goodness-of-fit, whereas differences between Richards and GMM were small.

Estimation of Growth Parameters

The comparison between models in the estimated growth parameters was performed including all the animals for which growth traits could be computed for the three models (parameters could not be estimated with the Richards for nine curves), excluding the fish growth data because for these size was in units of length. Therefore, this comparison was based on the results for 60 animals. Ranges of values of the growth parameters estimated by the three models are shown in Table 4. Models can be compared from the pairwise differences between means (bias between models), deviation from unity of the slope when estimates obtained with a model are plotted against those obtained with another model, and correlation analyses. The MSPE between two models can be partitioned (Bibby and Toutenburg, 1977) into bias, slope, and random components.

Some differences existed among models with respect to some of the growth parameters studied. The Richards model gave lower estimates of the birth weight than the GMM model with nearly all curves fitted (95% of the curves), whereas final weights estimated with the GMM model were always greater than the estimates obtained with the other two models (the bias was on average 8.5%). Average postnatal growth rates computed from the GMM parameters were on average 6.3%

Table 3. Residual sum of squares (RSS) obtained when fitting the Gompertz, Richards, and generalized Michaelis-Menten (GMM) models to the growth data, and pairwise comparisons between models using an F -test (see text for details)

Item	Gompertz	Richards	GMM
Average	1,005.7	782.4	983.8
Median	35.4	20.4	21.0
Minimum	.0047	.0016	.0006
Maximum	9,468	6,246	8,517
Number of cases in which the model specified in the row gave a RSS smaller than the model specified in the column (total number of cases = 83)			
	Gompertz	Richards	GMM
Gompertz	—	0	29
Richards	83	—	52
GMM	54	31	—
Number of cases in which the model specified in the row was significantly ($P < .05$) superior to the model specified in the column (total number of cases = 83)			
	Gompertz	Richards	GMM
Gompertz	—	0	6
Richards	40	—	11
GMM	31	3	—

Table 4. Comparison of the growth parameter estimates^a obtained with the generalized Michaelis-Menten (GMM), Richards, and Gompertz models

Item	Avg	Range (min.–max.)	RMSPE ^b	Slope ^c	Correlation analysis ^d		
					r	ρ_s	r_c
Initial weight (W_0), kg							
GMM	18.03	(.0011–85.5)					
Richards	15.59	(.0000–80.7)	4.740	1.12 (.017)	.992	.964	.980
Gompertz	16.13	(.0015–93.6)	9.473	1.04 (.051)	.928	.937	.919
Final weight (W_p), kg							
GMM	246.1	(.021–1,184)					
Richards	226.6	(.019–1,090)	32.391	1.08 (.004)	.999	.999	.994
Gompertz	225.9	(.019–1,072)	35.688	1.09 (.007)	.999	.996	.993
Maximum growth rate (ΔW_{max}), kg/wk							
GMM	3.49	(.003–11.6)					
Richards	3.22	(.003–10.6)	.419	1.09 (.005)	.999	.999	.993
Gompertz	3.12	(.002–10.5)	.586	1.12 (.010)	.997	.997	.985
Average postnatal growth rate ($\langle \Delta W \rangle$), kg/wk							
GMM	2.10	(.0016–6.88)					
Richards	2.25	(.0018–7.34)	.235	.934 (.005)	.999	.999	.995
Gompertz	2.20	(.0018–7.42)	.223	.959 (.010)	.996	.997	.995
Time to grow to 50% of the asymptote (t_{50}), wk							
GMM	27.6	(3.8–63.6)					
Richards	25.9	(3.4–56.6)	2.69	1.09 (.012)	.996	.990	.987
Gompertz	25.8	(3.3–56.7)	4.61	1.14 (.024)	.985	.987	.966

^aComparison performed including all the growth curves for which growth traits could be computed for the three models, with the exception of those for fish growth ($n = 60$).

^bPairwise RMSPE = square root of the mean square prediction error between GMM and either Richards or Gompertz models.

^cPairwise regression coefficients between GMM and either Richards or Gompertz models.

^dPairwise correlation coefficients between GMM and either Richards or Gompertz models (r = Pearson linear correlation coefficient, ρ_s = Spearman rank correlation coefficient, and r_c = concordance correlation coefficient).

and 4.5% smaller than those estimated with the Richards and Gompertz, respectively. The average growth rates were smaller with the GMM than with the Richards model in 95% cases and smaller than with the Gompertz model in 77% cases. This was reflected in similar differences between models in the values of t_{50} , which were on average 6.8% longer with the GMM model than with the other two. By contrast, greater maximum growth rates were computed when the GMM model was fitted (on average 7.8% higher than with the Richards and 11.9% higher than with the Gompertz model), and the GMM model gave higher values of this parameter for 93% and 88% curves than the Richards and Gompertz models, respectively. These differences were due to the different fits obtained with the three models; the GMM model generally resulted in fits that were steeper at the point of inflection and flatter over the initial part of the curve and also as it reached the upper asymptote than those obtained with the other two models. The inflection point was also at an earlier age with the GMM model than with the other two (the average time to reach the point of inflection was 17.0, 18.5, and 19.5 wk for the GMM, Richards, and Gompertz models, respectively). In spite of these differences between models in the parameter values, the ranking of the 60 animals according to these parameters was

very similar regardless of the model used to estimate them, as indicated by the highly significant Spearman correlation coefficients obtained (Table 4). The high linear and concordance correlation coefficients obtained with all the parameters (close to unity in most cases) are associated with close relationships and significant reproducibilities among models in the parameter estimates, suggesting that the comparisons between animal species and breeds in their growth attributes will be very similar using parameters estimated with any of the three models.

Discussion

Nonlinear growth functions can be grouped into three categories: functions that only represent diminishing returns behavior (monomolecular [Spillman and Lang, 1924]), functions describing smooth (continuous) sigmoidal behavior with a fixed point of inflection (logistic [Robertson, 1923] and Gompertz equation [Davidson, 1928]), and functions representing sigmoidal behavior with a variable (flexible) point of inflection (Richards equation [Richards, 1959], Janoscheck equation [Janoscheck, 1957], and France model [France et al., 1996b]). In some instances, the flexible functions are generalized models that encompass simpler models for

particular values of an additional parameter. All these models are single-phase functions, in contrast to multiphasic approaches used for the analysis of growth data (Koops, 1986) that aim to interpret systematic deviations that might be obtained with the single-phase functions. Flexible sigmoidal models are an alternative to multiphasics provided the data do not exhibit discernible multiple inflection points (France et al., 1996b).

The model derived herein provides a robust, flexible growth function, capable of describing both diminishing returns and sigmoidal behavior. The main advantage of the new function is its flexibility, which is conferred by the variable point of inflection that can occur at any age between birth and K , i.e., at any weight between W_0 (birth weight) and $(W_f + W_0)/2$, as c varies over the range $1 < c < \infty$. Another advantage is that the point of inflection can be calculated using a simple algebraic expression.

The function is analogous to the equation form originally proposed by Hill (1913) to describe the kinetics of the binding of oxygen to hemoglobin in respiratory physiology. The equation form has been also used in allosteric enzyme kinetics (Segal, 1975), as a generalization of the Michaelis-Menten equation (Michaelis and Menten, 1913). Recently, this equation has been applied to describe disappearance curves obtained using the polyester bag technique for incubating feeds in the rumen (López et al., 1999). In its original application the equation was a static model, relating the velocity of reaction to the amount of substrate. The equation was also largely empirical, because it was not derived using the rate:state formalism (Eq. [1]), and even the biological interpretation of the parameters was empirical. Parameter c was introduced to obtain a sigmoidal curve when velocity is plotted against substrate concentration, characteristic of allosteric enzyme kinetics, in contrast to the hyperbolic plot that is expected of non-allosteric enzymes. The latter can be represented by the Michaelis-Menten equation, a special case of the Hill equation. The principal difference is the power c , which has been called the Hill coefficient. The value of the Hill coefficient is considered as a measure of the degree of positive substrate cooperativity, or as the number of binding sites for the substrate present in the protein or enzyme. An increasing value of c results in an increasing sigmoidal curve showing positive cooperativity for the substrate. A value less than one is associated with negative cooperativity.

The Hill equation was not applied in a growth context until Mercer et al. (1978) used it as a nutrient response model. Jolicoeur (1985) used the original Hill equation (a three-parameter form of Eq. [4]) by constraining the curve to pass through the origin ($W_0 = 0$). These applications are empirical in that they offer no derivation of the function used. The function proposed in this work is derived using rate:state principles, from a function relating growth rate to animal size (length or weight), with a time-dependent relative (or specific) growth rate (μ) that exhibits different behavior depending on the

value of parameter c (Figure 1). The relative growth rate is an interesting parameter because it is additive (Ricker, 1979) and allows for comparison of growth rates among animals of different weight (different species, breeds, or ages). The function used to represent μ is a rational polynomial in time for $c > 1$ that results in a sigmoidal growth function. The biological interpretation of parameter c given for the kinetics of allosteric enzymes and carrier proteins is not appropriate when the function is used to represent growth. Instead, the parameter c may be characterized as a slope term that determines the time to reach near-asymptotic size (Figure 2), and the proportion of the final size (W_f) at which the inflection (maximum growth rate) occurs, and hence is responsible for the differences in shape among growth curves. Thus, if we define degree of maturity at age t (u) as the proportion of the final size at that age (i.e., $u = W/W_f$), then using Eq. [6] it can be shown that:

$$c = (1 - u_0)/(1 + u_0 - 2u^*), \quad [13]$$

where u_0 and u^* are the degrees of maturity at birth and at the inflection point, respectively. Therefore, parameter c is related to the degree of maturity at the inflection point (u^*) depending on the degree of maturity at birth (u_0) characteristic of each species and breed. The possible range of u^* is u_0 (for $c = 1$) $\leq u^* \leq (u_0 + 1)/2$ (as $c \rightarrow \infty$). The upper limit occurs when the time of inflection point (t^*) equals K . With K being the time when the weight $W_0 + (W_f - W_0)/2$ is achieved, the parameters of the function are now readily interpretable. Taylor (1980b) showed that the growth curves of a wide variety of species were similar when scaled appropriately for mature size. The parameter c of the new function reflects the small differences between animal species in the steepness of the curve and in the position of the inflection point observed in the standardized growth curves.

In the equation proposed by Jolicoeur (1985), the parameter W_0 was omitted in order to get a flexible function with only three parameters. This function cannot be used to describe postnatal growth, so the author justified its use on the grounds that growth can be described by a curve passing through the origin provided time is measured from the moment at which the egg starts developing actively. So, the function was to fit growth data using total age, estimated in mammals by adding the average duration of gestation to postnatal age. But the periods of growth before and after birth can be categorized according to changes in nutrient supply, hormonal influences, and relative growth rates (Bell, 1992; Lawrence and Fowler, 1997). A major characteristic of fetal growth in late gestation is that it is constrained for a number of spatial and nutritional reasons, preventing the fetus from achieving its genetic capacity for growth (Bell, 1992), in contrast to the rapid acceleration in growth that occurs almost immediately after birth in well-fed animals. However, the difficulty of obtaining accurate measures of size during prenatal

growth may affect the estimation of the growth parameters, due to lack of records over an important part of the growth curve. Although the algebraic expression of Jolicoeur (1985) can be considered valid from the mathematical point of view, the model proposed in the present study seems to be more appropriate to describe postnatal growth, deserving the inclusion of an additional parameter (W_0).

The generalized model can generate special cases for particular values of the parameters, although the simpler models are not sigmoidal and seem to be generally inappropriate to describe animal growth. When fitted to a wide range of growth data, the generalized model was clearly superior to the Michaelis-Menten equation, mainly because animal growth curves generally follow a sigmoidal pattern. In the present analysis the estimate of parameter c was greater than one for most of the curves fitted, indicating the sigmoidal behavior of the growth data. This was confirmed when the Gompertz and Richards models were fitted to the growth data, because the conditions for the existence of a point of inflection for both models (France and Thornley, 1984) were satisfied for most growth curves. It is noteworthy that nonbiological estimates of the shape parameter of the Richards model (parameter n of Eq. [11]) were obtained for nine growth curves for which best fitting was achieved for n -values smaller than -1 . Those would be the only cases in which the Richards model would support nonsigmoidal growth, but the solutions achieved were biologically unacceptable.

Jolicoeur (1985) suggested that some growth curves are not sigmoidal, especially for species (many kinds of fishes and some mammals) that may show unlimited growth. The growth curves of these species seem to be hyperbolic, with no inflection point, and with a characteristic asymptotic phase in which growth slows down but never seems to stop completely until the individual dies. In these cases, the new function will find a solution in which $c \leq 1$. This demonstrates the capability of the new function to fit growth data with and without an inflection point, and with different behavior in the asymptotic phase. However, it is of interest to check whether a hyperbolic shape is the actual pattern of the growth curve, characteristic of that animal species, or the consequence of an inappropriate data set. The asymptote can be regarded as the mature body size but is not a stable value and varies considerably within individuals depending on the availability of feed, the demands of the reproductive cycle, and, in some cases, the season of the year (Lawrence and Fowler, 1997). It is therefore important to define the mature size characteristic of each animal species. Ricker (1979) stressed the question of how to determine the asymptotic size of fish that seem to show unlimited growth. Mature size is also difficult to define in animals that show important changes in weight and body composition after maturity, as for instance in humans or in dairy cows. The availability of observations in mature animals is critical to obtain accurate estimations of the final size, but this

requires that animals be kept beyond a typical market weight. This does not conform with meat animals raised under commercial conditions, whose growth curve may appear as a relatively flat slope. In the comparison among models, there seemed to be some bias between the estimates of final weight (W_f) obtained with the new function and with the Richards and Gompertz models (Table 4), with the new function tending to give slightly greater estimates. Estimates of mature weights obtained are a result of the fitting algorithm, and only if the mature size of each animal were precisely defined would it be possible to judge which function gives a more accurate estimate of the parameter. In general, the new function provided a way of slowing down the approach to the asymptotic weight and a slightly different fit in the early part of the curves, which may be useful in describing certain data sets.

The scarcity of observations in the segment of the curve around the inflection point may lead to inappropriate conclusions, because the curve shape seems to be the aspect of growth that is most sensitive to environmental factors. Some nonlinear models tend to underestimate the shape parameter (McCallum and Dixon, 1990), although this bias can be reduced by increasing the frequency of sampling during the period of rapid growth. A robust estimation of the point of inflection requires an adequate number of weight/length recordings, because with scarce observations the straight-line phase of growth in the fitted curve is extended, and the standard error of the inflection point is enlarged, because this point can be situated in any place on the straight line.

The new function is able to fit the growth data with a goodness-of-fit similar to that of the Richards model and, in general, superior in many cases to that obtained with the Gompertz. Although no model was better than the others in every respect, the overall statistical evaluation has shown that the new function and the Richards model provide a satisfactory fit to most data sets. Similar results were observed when other flexible and generalized models were evaluated for fitting growth data (Brown et al., 1976; Gille and Salomon, 1995; France et al., 1996b). In the present study, the new function seemed to have a better distribution of residuals than the Richards and showed a comparable overall goodness-of-fit (in terms of residual variance), justifying its use to fit growth data.

A model comparison based on the analysis of the estimates of important growth parameters was performed, to check whether models gave similar or different estimates of these parameters. In the case of discrepancies among models of important biological significance, the function giving the most reliable estimates of the analyzed growth traits should be chosen. Some of the equation constants (W_0 , W_f) are already important parameters to evaluate the growth potential of each type of animal. Other growth traits can be computed for each animal using the corresponding estimates of the equations parameters, such as the maxi-

mum growth rate, average growth rate during postnatal growth, or the time to half-final growth. These parameters are used to compare the genetic potential of animals and to understand the effects of genetic and environmental factors on growth. To compare growth curves and parameters, frequentist or Bayesian procedures can be used (Berkey, 1982; Laird, 1990; Blasco and Varona, 1999), but in any case it is important to choose a model that provides accurate estimates of those parameters. The comparison between models in terms of estimating growth parameters revealed that, in spite of small differences between the values obtained with each model, ranking of animals according to those parameters was similar with the three models, given the highly significant correlations observed (Table 4) between them. This is in agreement with other authors (Brown et al., 1976; Perotto et al., 1992). Therefore the new model seems to be suitable to fit growth data and to characterize the growth attributes of different animal species.

Implications

A new generalized Michaelis-Menten-type growth model was derived from rate:state principles, and by assuming that relative growth rate is time-dependent. The model is characterized by flexibility, the simplicity of the fitting procedure, and the biological interpretability of parameters. In contrast to some other models, the new function allows the inflection point to be determined for sigmoidal growth curves from a simple algebraic expression. The goodness-of-fit based on the pattern of distribution of the residuals and on the magnitude of the residual variance was similar to that achieved with the Richards model, with only minor differences between both equations with respect to their abilities to fit a wide range of fish, poultry, and farm and companion animal growth data. The new function also provides farm and companion animal growth data satisfactory estimates of growth traits to differentiate and characterize the growth attributes of each type of animal, underlining its viability as a suitable additional growth function.

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