Multiphasic Analysis of Growth Curve of Body Weight in Mice

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ABSTRACT : The present study describes the analysis of the multiphasic growth function (MGF) to body weight in laboratory and wild mice. Three genetic groups of laboratory mice (*Mus musculus domesticus*) designated $CF_{\#1}$, C3H/HeNCrj and C57BL/6NCrj, and a genetic group of Yonakuni wild mice (*Mus musculus molossinus yonakuni*, Yk) were used. Mean body weights of each genetic group-sex subclass from birth to 69 days of age taken at 3-day intervals were analyzed by a monophasic, diphasic and triphasic functions for describing growth patterns. A comparison among the three functions of the MGF was based on the goodness-of-fit criteria: residual standard deviation (RSD), adjusted R-square (Adj R^2) and Akaike's information criterion (AIC). Result of this study indicated that body weight averaged heavier for males than for females. Among the four genetic groups within both sexes, $CF_{\#1}$ showed the highest, subsequent followed by C3H/HeNCrj, C57BL/6NCrj and Yk. Comparison among the three functions revealed that the triphasic function was the best fit to growth data, with the lowest RSD, the highest Adj R^2 and the lowest AIC, for the four genetic groups. For the triphasic function, RSD within each genetic group-sex subclass was similar for males and females. Adj R^2 was 0.999 for all genetic group-sex subclasses. AIC for laboratory mice males and females ranged from -70.48 to 66.50 and from -92.81 to -68.64, respectively; whereas for Yk wild mice males was -74.29 and females -78.42. (*Asian-Aus. J. Anim. Sci. 1999. Vol. 12, No. 3 : 331-335*)

Key Words : Multiphasic Growth Function, Goodness-of-fit Criteria, Body Weight, Mice

INTRODUCTION

Several mathematical equations have been used as growth functions. Mathmatical functions of growth is needed because they present information on a lifetime sequence of body measurement.

Several functions for growth data have been developed over a long period of time and applied to animal species (Brody, 1945; Richards, 1959; Eisen et al., 1969; Obata and Mukai, 1982). Nonlinear growth functions, such as Gompertz, Brody, Richards, Logistic and von Bertalanffy describe a single-phase growth in S-shaped form. Recently, a nonlinear growth function which can be applied to fit more than one growth phase, called multiphasic growth function (MGF), proposed by Koops (1986) is used commonly. The MGF has been used to analyse the growth of laboratory mice (Koops et al., 1987), the growth of chickens (Grossman and Koops, 1988a; Kwakkel et al., 1993) and the lactation curve of dairy cattle (Grossman and Koops, 1988b).

As far as we know, until now no experiment has been conducted to fit a multiphasic function to body weight in different subspecies of mice. Following this reasoning, this study was conducted to describe the growth curve of laboratory and wild mice by a multiphasic growth function. We also propose to use several criteria of goodness-of-fit to determine which function gives the best description of given set of observed data.

MATERIALS AND METHODS

Data

Three genetic groups of domesticated laboratory mice (*Mus musculus domesticus*) designated $CF_{\#1}$, C3H/HeNCrj, and C57BL/6NCrj and a genetic group of Yonakuni wild mice (*Mus musculus molossinus yonakuni*, Yk) were used as materials in this study. Mating system and handling animal have been described elsewhere (Kurnianto et al., 1997; Kurnianto et al., 1998).

Body weights of mice were recorded individually at 3-day intervals from birth (0) to 69 days of age. The number of mice used at each genetic group as follows; $CF_{\#1}$, 21 and 21; C3H/HeNCrj, 15 and 15; C57BL/6NCrj, 12 and 12; Yk, 12 and 12 for males and females, respectively.

Data analysis

Mean body weight of the genetic group-sex subclass were used in the analysis of the multiphasic growth function (MGF). The MGF used to describe growth curve was proposed by Koops (1986), it is based on the summation of several sigmoid curves; each curve represents one growth phase described by a logistic curve. The MGF is written as:

$$Y_t = \sum_{i=1}^{n} \{a_i[1+\tanh(b_i(t-c_i))]\}$$

where Y_t is obervation of body weight at age t, n is number of growth phases, tanh is the hyperbolic tangent; and for each phase i: a_i is half asymptotic value (grams), b_i is growth rate relative to a_i (days^{-1}), and c_i is age at point of inflection (days).

Three functions were applied in this study. The number of parameters depends on number of phase possessed by a function. A monophasic, diphasic and triphasic function has 3, 6 and 9 parameters, respectively.

For each function, curve was fitted separately using nonlinear regression (PROC NLIN, Method DUD; SAS, 1990). Goodness-of-fit was checked on three criteria: 1) residual standard deviation RSD), 2) adjusted R-square

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Table 1. Parameter estimates for multiphasic analysis of growth at the four genetic groups[1]

		Laboratory mice						Yonakuni wild mice, Yk	
Function	Parameter	CF$_{\#1}$		C3H/HeNCrj		C57BL/6Ncrj			
		M	F	M	F	M	F	M	F
Monophasic	a_1	19.352	14.400	12.352	10.625	11.250	9.312	8.260	7.870
	b_1	0.057	0.059	0.051	0.049	0.050	0.045	0.040	0.043
	c_1	24.902	21.719	24.243	22.625	21.550	20.797	25.824	23.719
Diphsic	a_1	15.355	11.367	10.401	9.605	9.512	8.810	8.029	7.501
	b_1	0.042	0.049	0.042	0.045	0.044	0.500	0.041	0.046
	c_1	25.504	19.934	23.721	21.884	20.044	19.237	24.917	22.346
	a_2	4.462	3.030	2.072	1.031	1.736	0.877	0.293	0.381
	b_2	0.275	0.277	0.347	0.421	0.319	0.177	0.242	0.142
	c_2	25.527	25.843	26.877	27.150	26.551	30.753	61.515	54.759
Triphasic	a_1	2.973	4.208	2.771	3.614	3.364	3.064	2.697	2.394
	b_1	0.179	0.137	0.169	0.143	0.179	0.171	0.102	0.126
	c_1	5.451	5.569	5.827	5.981	3.797	4.135	5.586	4.223
	a_2	8.300	8.134	4.802	5.424	6.151	3.672	2.884	3.440
	b_2	0.176	0.148	0.189	0.134	0.129	0.170	0.121	0.123
	c_2	25.545	25.624	26.463	27.111	25.715	24.308	28.062	25.098
	a_3	9.250	5.596	5.501	2.361	3.101	4.119	2.959	1.992
	b_3	0.036	0.028	0.035	0.060	0.038	0.033	0.047	0.079
	c_3	37.277	63.413	39.523	58.497	62.209	56.058	49.489	47.161

[1] M: Male, F: Female; Parameters a_i in grams, b_i in day^{-1} and c_i in days.

Table 2. Residual standard deviation (RSD), adjusted R-square (Adj R^2) and Akaike's information criterion (AIC) as measures of goodness-of-fit for multiphasic analysis of growth at the four genetic groups

		Laboratory mice						Yonakuni wild mice, Yk	
Function	Goodness-of-fit[1]	CF$_{\#1}$		C3H/HeNCrj		C57BL/6Ncrj			
		M	F	M	F	M	F	M	F
Monophasic	RSD	0.999	0.844	0.685	0.581	0.669	0.592	0.284	0.283
	Adj R^2	0.994	0.992	0.992	0.992	0.991	0.988	0.996	0.996
	AIC	5.02	-3.14	-13.18	-21.09	-14.30	-20.15	-55.38	-55.56
Diphsic	RSD	0.485	0.531	0.449	0.504	0.499	0.486	0.265	0.261
	Adj R^2	0.998	0.996	0.996	0.993	0.989	0.991	0.996	0.996
	AIC	-23.69	-19.38	-27.29	-21.87	-22.36	-23.66	-52.82	-53.42
Triphasic	RSD	0.162	0.145	0.168	0.163	0.176	0.168	0.149	0.137
	Adj R^2	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
	AIC	-70.48	-75.75	-70.11	-92.81	-66.50	-68.64	-74.29	-78.42

[1] The criteria adopted from SAS (1990).

(Adj R^2), and 3) Akaike's information criterion (AIC). A function which shows lower RSD, higher adj R^2 and lower AIC indicates a better fit to observed data.

RESULTS

Parameter estimates of growth

Parameter estimates for asymptotic weight, growth rate and point of inflection for monophasic, diphasic and triphasic functions are presented in table 1. For the monophasic function, the asymptotic weight ($2a_i$) for CF$_{\#1}$ was 38.7 and 28.8 g, for C3H/HeNCrj 24.7 and 21.3 g, for C57BL/6NCrj 22.5 and 18.6 g, and for Yk 16.5 and 15.7 g for males and females, respectively. Age at point of inflection (c_i) was slightly older for males than for females; for CF$_{\#1}$ 25 and 22 days, for C3H/HeNCrj 24 and 23 days, for C57BL/6NCrj 22 and 21 days, and for Yk 26 and 24 days for males and females, respectiuely.

For the diphasic function, the total asymptotic weights ($taw_{di}=2a_1+2a_2$) for CF$_{\#1}$ were 39.6 and 28.8 g, for C3H/HeNCrj 25.0 and 21.3 g, for C57BL/6NCrj 22.5 and 19.4 g, and for Yk 16.6 and 15.8 g for males and females, respectively. It can be seen that the first phase showed a higher contribution to total asymptotic weight compared to the second phase. Contributions of the first phase to the total asymptotic weight was calculated as $(2a_1/taw_{di})\times100\%$; for CF$_{\#1}$ were about

77.5% and 79.0% for males and females, respectively. Meanwhile, for C3H/HeNCrj about 83.4 and 90.3%, for C57BL/6NCrj about 85.3 and 91.0%, and for Yk about 96.5 and 95.2%. Contributions of the second phase to the total asymptotic weight $((2a_2/taw_{di})\times 100\%)$ for $CF_{\#1}$ were about 22.5 and 21.1%, for C3H/HeNCrj about 16.6 and 9.7%. for C57BL/6NCrj about 15.6 and 9.1% and for Yk about 3.5 and 4.8% for males and females, respectively. At the first and the second phases of the diphasic function for the three laboratory mice, the age at point of inflection between both phases (c_1 aud c_2) tended to close to each another, c_1 ranged from 19～26 days and c_2 from 26～31 days. These conditions differed from that for Yk, for which age at point of inflection at the first phase was around 24 days of age, whereas the second phase was around 58 days of age.

For the triphasic function, the total asymptotic weights $(taw_{tri}=2a_1+2a_2+2a_3)$ for $CF_{\#1}$ were 41.1 and 35.9g, for C3H/HeNCrj 26.2 and 22.8g, for C57BL/6NCrj 25.2 and 21.7 g, and for Yk 17.1 and 15.6 g for males and females, respectively. Contribution of each phase was calculated as $(2a_i/taw_{tri})\times 100\%$. For these three laboratory mice males and females, contributions of the first phase to the total asymptotic weight $((2a_1/taw_{tri})\times 100\%)$ were 14.5～26.7 and 23.7～31.7%, of the second phase $((2a_2/taw_{tri})\times 100\%)$ were 36.7～48.8% and 33.8～47.6%, and of the third phase $((2a_3/taw_{tri})\times 100\%)$ were 24.6～45.1% and 20.7～38.0%, respectively. Meanwhile for Yk, about 31.9 and 30.6% of the total asymptotic weight were contributed by the first phase, about 33.8 and 44.0% by the second phase, and about 34.7 and 25.55% by the third phase for males and females, respectively. Age at point of inflection for the first and the second phase of this function for all genetic group-sex subclass tended to be same, around 5 days and 26 days, respectively; while age at point of inflection for the third phase vary more after 37 days, depending on the subspecies of mice.

Fit of growth functions

From the results of parameter estimates (table 1), fitting growth curves by the three functions were done and illustrated in figures 1 to 3. As shown in the figures, the four genetic groups suggested that body weight averaged heavier for males than for females. Furthermore, among the four genetic groups within both sexes, $CF_{\#1}$ showed the highest, subsequent followed by C3H/HeNCrj, C57BL/6NCrj and Yk as indicated by a total asymptotic weight (see also table 1).

Goodness-of- fit for multiphasic analysis of growth are presented in table 2. Of the three functions, the triphasic function showed the lowest residual standard deviation (RSD), the highest adjusted R-square (Adj R^2) and the lowest Akaike's information criterion (AIC) among the three phase functions for all genetic groups. The diphasic function showed better fit compared with monophasic function according to goodness-of-fit criteria. As shown for the triphasic function, RSD for $CF_{\#1}$ was 0.16 and 0.15 g, for C3H/HeNCrj 0.17 and 0.16 g, for C57BL/6NCrj 0.18 and 0.17 g, and for Yk 0.15 and 0.14 g for males and females, respectively.

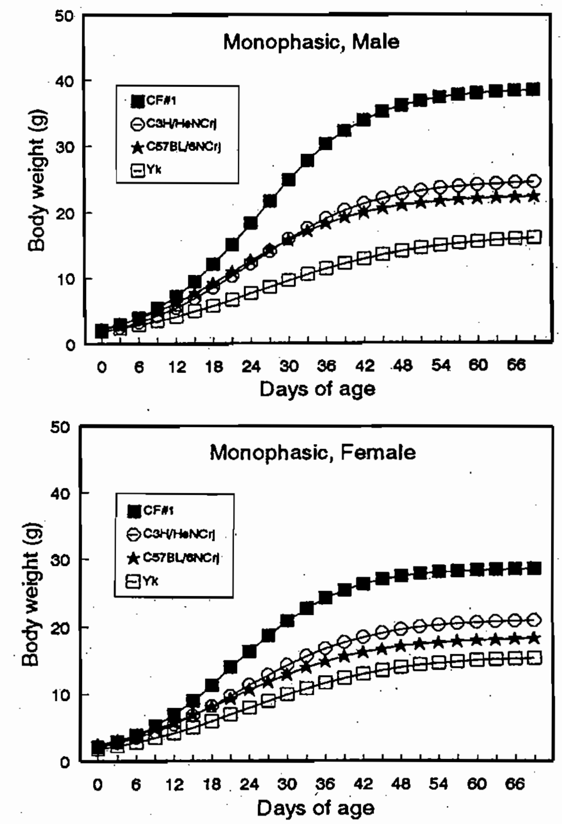

Figure 1. Fitted monophasic growth curve for the four genetic groups

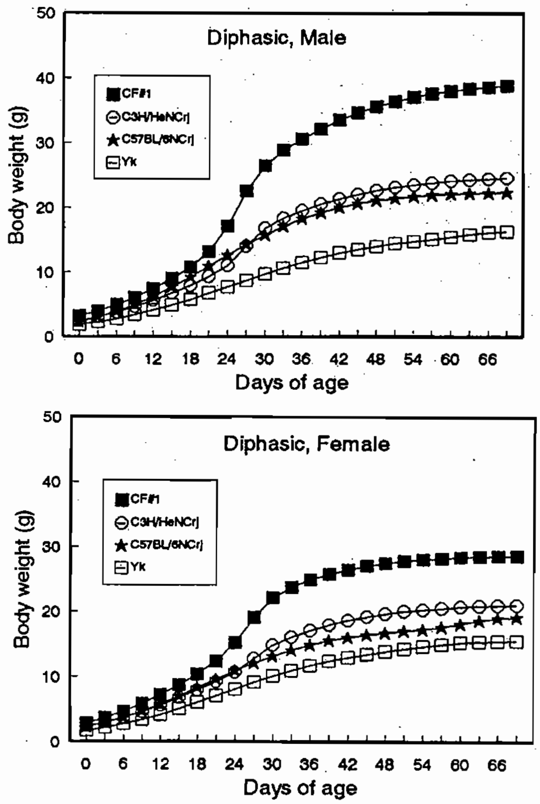

Figure 2. Fitted diphasic growth curve for the four genetic groups

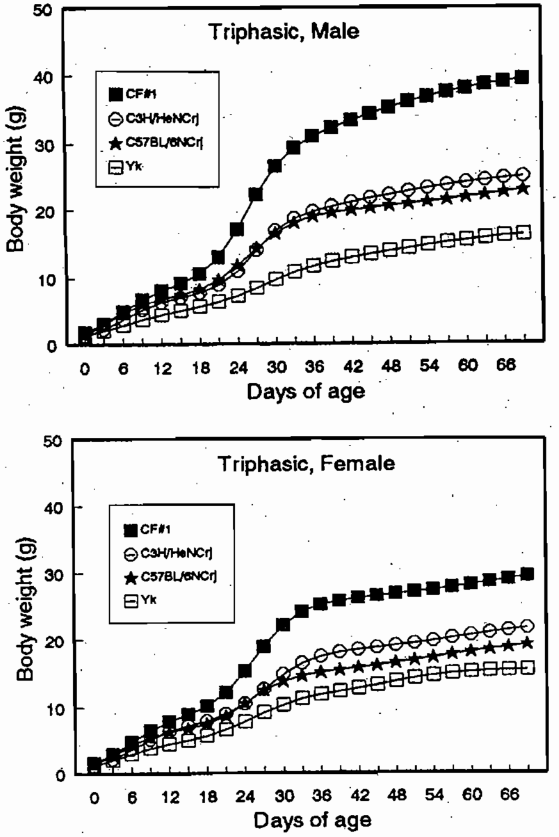

Figure 3. Fitted triphasic frowth curve for the four genetic groups

Adj R^2 was 0.999 for all genetic group-sex subclasses. AIC for CF#1 was -70.48 an4 -75.75, for CH3H/HeNCrj -70.11 aud -92.81, for C57BL/6NCrj -66.50 and -68.64, and for Yk -74.29 and -78.42 for males and females, respectively.

DISCUSSION

The term of growth usually evokes the images a sigmoid curves depicting a lifetime sequence of measure of body weight (Fitzhugh, 1976). Summation of many small sigmoid curve at any stage of development results in total growth curves, and this is the basis of multiphasic analysis. The phenomenon of multiphasic growth in mice was described by Gall and Kyle (1968) and Lang and Legates (1969). They observed two phases in growth curve and called these phases as the diphasic nature of growth.

Analysis of growth curve parameters in this study (table 1) showed a similarity in value of the total asymptotic weight attained by each function. The degree of this value, however, differed depend on the subspecies or genetic group. It is important to note, this does not imply that the total asymptotic weight is the heaviest weight attained by the individual, but it indicates the average weight of mature individual. The asymtotic weight of each phase were smaller for Yk wild mice than for laboratory mice for both sexes. This is not surprising because of lighter body weight of Yk compared to laboratory mice (Kurnianto et al., 1997: Kurnianto et al., 1998).

Results for age at point of inflection indicate a maximum growth rate reached by individual. For the monophasic function, age at point of inflection attained by both laboratory and wild mice tended to be same. Age at point of inflection in this phase was closely to the age of weanlng. For the diphasic function, the difference in age at point of inflection was in the second phase in which for Yk was later than for laboratory mice. Furthermore, there were no specific characteristics relating to age at point of inflection at the third phase of the triphasic function, indicating that a growth rate is different between one and other subspecies especially at the maturity phase.

The biological meaning of growth has been described by Hammond (1960), and for the triphasic function by Koops (1986). The most essential parts of the body, such as organs, brain and nerve system, develop in the first phase. Muscle and bone growth will be an important part in the second phase. Fat disposition most associates to growth in the third phase.

Fitted growth curve showed that although the four genetic groups differed in their body weight at a specific age, but they showed an identical growth patterns (figures 1 to 3). It is interest to note in both males and females that C3H/HeNCrj were smaller than C57BL/ 6NCrj from birth to 3 or 4 weeks of age. This was probably due to the poorer postnatal maternal ability of the C3H/HeNCrj dams than C57BL/6NCrj dams.

Eisen et al. (1969) pointed out that objective criteria are necessary in choosing the proper growth function for specific data. Based on the goodness-of-fit criteria used in this study, the triphasic function revealed the best fit to growth data compared with both the monophasic and the diphasic functions. This result was in agreement with those of Koops (1986) who applied the MGF to mean body weight of mice and Koops et al. (1987) to individual body weights of mice to describe the pattern of growth. They used residual variance, R-square and Durbin-Watson statistic for judging goodness-of-fit, and concluded that triphasic function was better than the monophasic function in describing the growth of mice. In the present study, criteria used were residual standard deviation, adjusted R-square and Akaike's information criteria. Residual standard deviation was used to evaluate the closeness between estimated and observed weight. Meanwhile, adjusted R-square and Akaike's information criterion were used to eliminate the effect of number of growth parameter for each function.

It is important to know the fit of single-phase growth functions to the mice weight data as reported previously. Eisen et al. (1969) made a general comparison of the three growth functions, namely logistic, Gompertz and Bertalanffy, based on the differences in residual variances of the respective function fitted to the growth data of individual mice.

The results indicated that logistic function gave the best fit for both sexes of the H_6 and C_l lines, the Bertalanffy function would be flavored only for females of the L_6 line, while the Gompertz function was intermediate between these two functions. Timon and Eisen (1969) used the Richards and logistic functions to describe the changes in the growth pattern of mice which have resulted from selection for increased postweaning weight gain, and observed that both the Richards sad logistics functions fitted the data equally well and the plotted trajectories coincided over most the growth curves. Kurnianto et al. (1997) compared the logistic, Gompertz and Asymptotic models (functions) for describing the growth patterns in wild and laboratory mice based on coefficient of determination (R^2), and concluded that the Gompertz model was the best fit to the body weight data.

It is generally well known that between two phases in the sigmoid curve are joined by a point inflection and joined during sexual maturity in animal (Brody, 1945). On the basis of that statement, it seemed that the second phase of the triphasic function was more consistent. The points of inflection at that phase were attained at around 26 days with somewhat earlier for females of Yk wild mice. Koops (1986) observed that age at point of inflection for the second phase of the triphasic function was 28.5 days, regardless sex of mice.

In conclusion, there was evidence that growth in mice was consisted of more than one growth phase. The MGF applied in this study demonstrated that triphasic function was the best fitted to growth data from birth to 69 days of age, according to the residual standard deviation, adjusted R-square and Akaike's information criterion.

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