Analysis of Growth in Intersubspecific Crossing of Mice Using Gompertz Model

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ABSTRACT : The aim of this study was to describe growth patterns of mice using Gompertz model. Two distinct types of mice, laboratory mouse $CF_{\#1}$ (*Mus musculus domesticus*) and Yonakuni wild mouse (Yk, *Mus musculus molossinus yonakuni*) were used. From all possible crosses, there were two parental types and two reciprocal F_1 crosses obtained. Individual body weights were measured weekly from birth to ten weeks of age on 321 mice. Standardization to six mice was conducted and only first litters were used. Growth curve parameters were estimated to fit growth data. The results showed that growth among genetic groups were significantly different ($p < 0.05$) for both sexes, in which parental type of $CF_{\#1}$ and Yk had the highest and the smallest values, respectively. Meanwhile, reciprocal F_1 crosses were intermediate between parental types. It was concluded that Gompertz model provided and excellent fit for the growth data with a high coefficient determination ($R^2 = 0.999$).
(**Key Words:** Growth Curve, Gompertz Model, Subspecific, Mice)

INTRODUCTION

In improving animal productivity, special attention must focus on traits of the greatest economic importance. Attention has been given to the body weight as a consequence of the growth.

Mathematical models used to illustrate growth are useful because they summarize information contained in such data into a few parameters with biological meaning (Fitzhugh, 1976). Many attempts have been conducted to fit the growth curve by mathematical model formulation (Richards, 1959), and nonlinear models have been used to describe growth patterns. One of these is the Gompertz model which has been extensively used in mice (Laird and Howard, 1967; Kidwell et al., 1969; Eisen et al., 1969).

Experiments describing growth patterns in a single laboratory mouse are common (Gall and Kyle, 1968; Timon and Eisen, 1969). However, studies on analysis of the growth diferences in two distinct types of mice are lacking. The objectives of this study were to estimate growth curve parameters and to fit growth data in mice of subspecies $CF_{\#1}$ and Yonakuni, and their reciprocal

crosses from birth to ten weeks of age using Gompertz model.

MATERIALS AND METHODS

Experimental procedures

Domesticated laboratory mouse (*Mus musculus domesticus*) and Yonakuni wild mouse (*Mus musculus molossinus yonakuni*) were used in this study. For convenience in keeping records, two subspecies used were designated $CF_{\#1}$ and Yk, respectively. Such symbols have been used exclusively in all tables and discussions. $CF_{\#1}$ is described as an albino mouse with pinkeye, and known as a European mouse. Yk is a wild mouse endemic to Ryukyu Islands (southern islands of Japan) and has gray skin. The mice of each subspecies had been reared and mated within a closed colony since 1994. They were mated randomly within subspecies when they reached nine to ten weeks of age, and sibs matings were avoided. The mating ratio was one male for two or three females. The offspring from this matings were used as parents for the following generation. The stock population size was maintained at approximately 20 males and 60 females per generation.

For growth analysis in this study, mice were randomly taken from the stock population. Matings were made within and between subspecies. Therefore there were four

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genetic groups resulting from all possible crosses of the two subspecies described, two groups of parental type and two groups of reciprocal F_1 crosses. The parental types were $CF_{\#1}$ and Yk, and the reciprocal F_1's CY and YC. C and Y represent of $CF_{\#1}$ and Yk, respectively, with the first symbol in the F_1 indicated the subspecies of dam, and the second symbol was the subspecies of sire. Mating ratio was one male for two or three females. Matings within subspecies avoided sibs mating.

Litters were weighed individually and standardized to six mice, by reduction and augmentation, using three mice of each sex where possible. The standardization to litter size was necessary to eliminate the effects of number of litters suckled. Possible effects due to the number of litters were eliminated by using only first litter.

Mice were weaned at three weeks of age. At weaning the mice were separated and caged based on sex with three mice per age. Body weights were taken weekly on individuals from birth (0) to ten weeks of age. The number of mice for each genetic groups was as follows: $CF_{\#1}$, 45 and 45; Yk, 44 and 45; CY, 45 and 45; and YC, 24 and 28 for males and females, respectively.

Mice were fed on the pellets (CE-2 Clea Japan Inc.) and tap water, both of which were provided at all times (*ad libitum*). The cage and other equipment were cleaned throughly twice per week to avoid contamination. Room temperature was maintained at 24°C.

Statistical analysis

Growth curve parameters were estimated from individual body weights using Gompertz model (Eisen et al., 1969) and analyzed useing Gauss-Newton method of SAS (1990). Gompertz model was chosen based on an earlier study suggesting this model provided a fit for weight data compared to logistic and asymptotic models (Kurnianto et al., 1997).

Growth curve parameters were used in fitting weight data within each genetic group-sex subclass. The Gompertz model formulated as:

$$y_t = A \ exp \ [\ -B \ exp \ (-kt) \ ]$$

where,

y_t : body weight (g) at age t (weeks)

A : asymptotic (mature) weigth

B : integration constant, time scale parameter of no specific biological significance

k : growth rate constant, which a logarithmic function of degree of maturity in body weight changes linearly per unit time

exp : base of natural logarithm (2.7183).

Other parameters derived from the model used were age and weight at the point of inflection designated as t_i and y_i, respectively.

$$t_i = \ln B / k \text{ and } y_i = A / exp$$

The differences in mean growth parameters between sexes within genetic groups and among genetic groups of the same sex were tested using t-test and Duncan's range-multiple test, respectively.

RESULTS AND DISCUSSION

Growth curve parameters

Means and standard deviations of growth curve parameters for each genetic group are presented in table 1. Results of t-test between sexes within genetic group are presented in table 2. The asymptotic weight (A) among the genetic groups were significantly different ($p < 0.05$) for both sexes. The highest A value was attained by genetic group $CF_{\#1}$, for males and females 44.52 g and 34.24 g, respectively. Meanwhile, the smallest A value was attained by genetic group Yk, 12.80 g for males and 12.44 g for females. The A values of reciprocal F_1 crosses were intermediate between parental types. When comparison between sexes within genetic group were taken into consideration, the A values for males were larger ($p < 0.01$) than females in all groups except in genetic group Yk (table 2).

The growth rate constant (k) of males were significantly different ($p < 0.05$) in each comparison of all possible pairs among the four genetic groups with exception between $CF_{\#1}$ and YC. In contrast, no significant differences were observed among the four genetic groups of females compared. It can be seen that the k values among females were vary more than males. The genetic group which had the highest and the smallest k values for both sexes were CY and $CF_{\#1}$, respectively. Table 2 shows that the k values of females were highly significant (negative sign, $p < 0.01$) larger than that of males for genetic group $CF_{\#1}$ and CY, while significant ($p < 0.05$) for YC, but non significant ($p > 0.05$) for Yk. The large k values indicate early maturing individuals and small k values indicate late maturing individuals. Following this indication, the results demonstrated that CY males matured earlier than other genetic groups. Furthermore, in the comparison between sexes, females had larger k value than males. These results indicated that females tended to mature earlier than males, in agreement

with the findings of previous studies (Laird, 1966; Laird and Howard, 1967) indicating a general tendency for females to pass through growth period faster and to mature earlier than males.

Table 1. Means and standard deviation of estimated growth curve parameters of Gompertz model (A, B, k, t_i, and y_i) for each genetic group

Estimated Parameter	Parental Types		Reciprocal F_1	
	$CF_{\#1}$	Yk	CY^1	YC^1
Male	$(45)^\#$	(44)	(45)	(24)
A	44.52 ± 1.83^a	12.80 ± 3.64^d	31.91 ± 2.85^b	29.46 ± 3.01^c
B	3.10 ± 0.10^a	2.69 ± 0.25^c	2.82 ± 0.14^b	2.74 ± 0.17^c
k	0.43 ± 0.04^c	0.46 ± 0.06^b	0.48 ± 0.05^a	0.44 ± 0.06^c
t_i	2.62 ± 0.26^a	2.21 ± 0.44^c	2.20 ± 0.33^c	2.40 ± 0.46^b
y_i	16.34 ± 0.75^a	4.93 ± 0.99^d	11.74 ± 1.05^b	10.84 ± 1.11^c
R^2	0.999	0.999	0.999	0.999
Female	(45)	(45)	(45)	(28)
A	34.24 ± 2.35^a	12.44 ± 1.69^d	21.35 ± 2.35^b	20.22 ± 1.86^c
B	2.88 ± 0.11^a	2.28 ± 0.23^d	2.48 ± 0.13^c	2.61 ± 0.15^b
k	0.49 ± 0.03^a	0.53 ± 0.65^a	0.63 ± 0.10^a	0.52 ± 0.39^a
t_i	2.20 ± 0.21^a	1.76 ± 0.40^c	1.46 ± 0.27^d	1.97 ± 0.39^b
y_i	12.60 ± 0.87^a	4.52 ± 0.67^d	7.85 ± 0.87^b	7.44 ± 0.68^c
R^2	0.999	0.999	0.999	0.999

[a,b,c,d] Means followed by different superscript in the same row of each growth curve parameter are significantly different at $p < 0.05$.
[1] CY is the genetic group of mice from $CF_{\#1}$ female mated with Yk male; YC is the genetic group from Yk female mated with $CF_{\#1}$ male.
[#] Number in the paranthesis represent the number of mice used.

Table 2. The t-test between sexes in the estimated growth curve parameters of Gompertz model (A, B, k, t_i and y_i) calculated for the four genetic groups[1]

Estimated Parameters	Parental Types		Reciprocal F_1	
	$CF_{\#1}$	Yk	CY	YC
A	23.14**	0.59^{NS}	19.14**	13.52**
B	9.89**	1.42^{NS}	12.17**	7.48**
k	$-7.02**$	-1.56^{NS}	$-9.27**$	$-1.70*$
t_i	8.46**	2.00*	11.70**	5.62**
y_i	21.88**	2.29**	19.17**	13.52**

[1] The t-test calculated to compare means parameters of females from males.
* Significant at $p < 0.05$.
** Significant at $p < 0.01$.
[NS] Non significant ($p > 0.05$).

The parameter which refers to the transition between two stages on the growth curve, autoacceleration and autoretardation, is the point of inflection. This point corresponds to two parameters, namely age at point of inflection (t_i) and weight at point of inflection (y_i). Comparison of all possible pairs of the four genetic

groups showed that $CF_{\#1}$ was the oldest and the largest at the point of inflection for both sexes which were shown by the highest t_i and y_i values, 2.62 weeks and 16.34 g, respectively. Animals reach a maximum growth rate at the point of inflection (Brody, 1945). In this study, males within genetic groups reached maximum growth rate later than females. As shown in table 1, ages at point of inflection ranged from 2.20 to 2.62 weeks for males, and from 1.46 to 2.20 weeks for females. These results indicated individuals were younger at the point of inflection than that of findings of Nagai et al. (1976), who used H6 and M16 populations selected for 36 and 73 generations for 6 weeks body weight and 3 to 6 weeks postweaning gain, and C_2 and ICR unselected mice. Nagai et al. (1976) found that without separating sexes, the mice had a maximal rate between 21 and 31 days of age (3 to 4 weeks of age). Differences between the results of Nagai et al. (1976) and the present one were probably due to differences in the mating design and the strains used.

There was a relationship between the k value and t_i. The genetic group with higher k values reached the t_i at a younger age. It was found CY had the largest k values for both males and females, followed by Yk, YC and $CF_{\#1}$.

Thus, CY reached the point inflection at the youngest age among the four genetic groups. For all genetic groups, males were significantly (p < 0.05-p < 0.01) older and larger at the point of inflection than females.

Fitting of growth model

Illustration of growth patterns of this study was based on a set of data by averaging individual estimated body weights. Mean of body weight was computed at each age for each genetic group.

Fitted Gompertz model to body weights were illustrated in figure 1 for male and figure 2 for female. As shown in the two figures, fitted growth model to weight data showed the same general characteristic with sigmoid form in all genetic groups. $CF_{\#1}$ had the largest body weight, followed by CY, YC and Yk. Differences between $CF_{\#1}$ and the other three genetic groups were more pronounce with increasing age. In fact, Yk wild mouse has a smaller body weight than $CF_{\#1}$ laboratory mouse. Crossing between these two subspecies resulted in offspring with means body weight intermediate between the parental types. Comparison of means body weight were significantly different (p < 0.05) between all possible pairs of the four genetic groups.
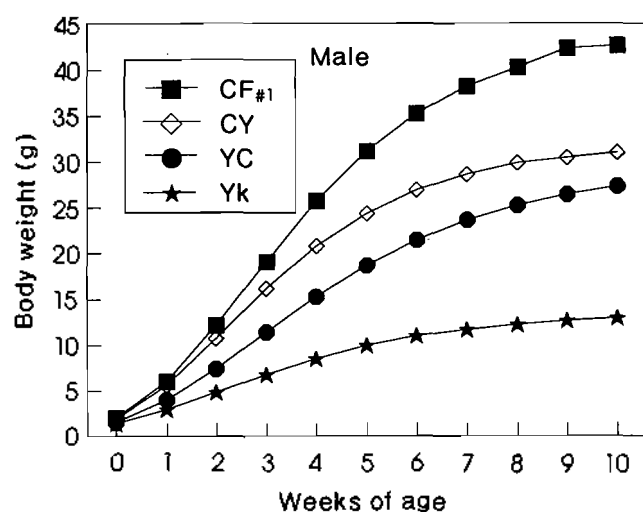

Figure 1. Gompertz growth curves fitted to body weight at male of each genetic group.
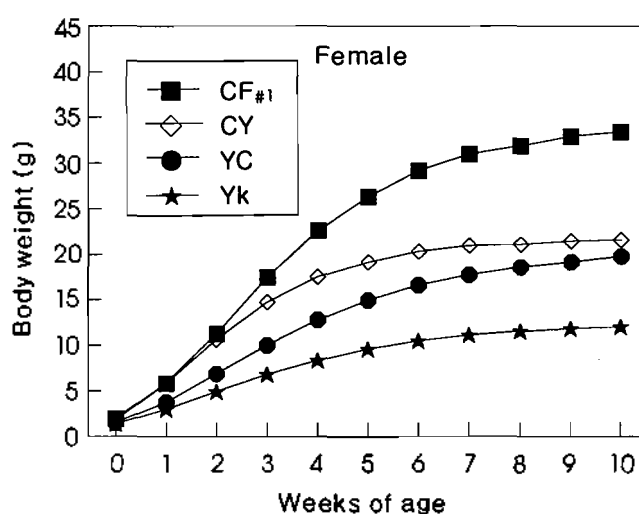

Figure 2. Gompertz growth curves fitted to body weight at female of each genetic group.

Table 3. Means residual of the estimated body weight from the observed body weight from birth to 10 weeks of age[1]

| Weeks of Age | Parental Types | | | | Reciprocals F_1 | | | |
| | $CF_{\#1}$ | | Yk | | CY | | YC | |
	Male	Female	Male	Female	Male	Female	Male	Female
	(45)*	(45)	(44)	(45)	(45)	(45)	(24)	(28)
0	−0.56	−0.05	−0.03	−0.03	−0.10	−0.06	0.03	0.04
1	0.89	0.84	0.33	0.24	1.12	0.77	0.26	0.11
2	−1.14	−0.83	−0.61	−0.44	−1.04	−0.96	−0.10	−0.75
3	−2.76	−1.71	−0.08	−0.34	−1.82	−1.01	−0.94	−0.24
4	3.11	2.02	0.84	0.45	1.00	0.29	2.43	1.93
5	3.47	1.75	0.16	0.69	1.45	0.45	1.96	1.02
6	1.09	−0.45	0.94	0.77	0.27	−0.40	0.96	0.02
7	0.14	−0.92	0.27	−0.33	−0.20	−0.05	−0.02	−0.48
8	−0.80	−0.47	0.11	−0.27	−0.20	0.14	−0.79	−0.57
9	−1.90	0.18	−0.20	−0.01	0.17	−0.01	−0.97	−0.42
10	−1.90	0.18	−0.20	−0.01	0.17	−0.01	−0.97	−0.97

[1] Residual = observed body weight - estimated body weight.
* Number in paranthesis represent the number of mice used.

Growth curves in figure 1 and figure 2 showed that CY mice were larger than YC mice at all age examined. It should be noted that this result indicates a differences in maternal effects between dams. In this study, maternal effects of $CF_{\#1}$ dams were larger than Yk dams. It was pointed out by Pattie et al. (1990), differences in growth of young animal can be caused by genetic differences between their dams in characteristics which are important for growth, such as milk production. The importance of maternal effects on body weight was reported in cross-fostering experiments in mice (Cox et al., 1959; Brandsch and Kadry, 1977). The cross-fostering studies indicated that maternal effect is a function of lactational output of the dam.

The means residual of estimated body weight from observed data illustrating the goodness of fit is presented in table 3. There was similarity in fit for the growth model in the four genetic groups for both males and females. Although the Gompertz model tended to overestimate between 2-3 weeks of age and to underestimate between 4-6 weeks of age, it provides an excellent fit for growth data, shown by the high coefficient of determination ($R^2 = 0.999$). As pointed out by Sall (1981), a higher R^2 indicates more perfect fit with smaller error, because R^2 is the portion of variability attributed to the model.

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REFERENCES

Brandsch, H. and A. E. H. Kadry. 1997. The relative importance of prenatal and prenatal maternal influence on growth in mice. Theor. Appl. Genet. 51:119-125.

Brody, S. 1945. Bioenergetics and Growth. Hafner Press, New York.

Cox, D. F., J. E. Legates and C. C. Cockerham. 1959. Maternal influence on body weight. J. Anim. Sci. 18:519-527.

Eisen, E. J., B. J. Lang and J. E. Legates. 1969. Comparison of growth functions within and between lines of mice selected for large and small body weight. Theor. Appl. Genet. 39:251-260.

Fitzhugh, H. A., Jr. 1976. Analysis of growth curves and strategies for altering their shape. J. Anim. Sci. 42:1036-1051.

Gall, G. A. E. and W. H. Kyle. 1968. Growth of the laboratory mouse. Theor. Appl. Genet. 38:304-308.

Kidwell, J. F., A. Howard and A. K. Laird. 1969. The inheritance of growth and form in the mouse. II. The Gompertz equation. Growth. 33:339-352.

Kurnianto, E., A. Shinjo and D. Suga. 1997. Comparison of three growth curve models for describing the growth patterns in wild and laboratory mice. J. Vet. Epidemiol. 1: (in press).

Laird, A. K. 1966. Postnatal growth of birds and mammals. Growth. 30;349-363.

Laird, A. K. and A. Howard. 1967. Growth curve in inbred mice. Nature. 25:786-788.

Nagai, J., Bakker, H. and E. J. Eisen. 1976. Partitioning and heterotic components of direct and maternal genetic effects on growth in mice using crossfostering techniques. Genetics. 84:113-124.

Pattie, W. A., H. Martojo, L. Iniques and S. S. Mansjoer. 1990. Second Workshop in Animal Breeding on Use of Computer Programs in Animal Breeding. IPB-Australia Project, Bogor, Indonesia.

Richards, F. J. 1959. A flexible growth function for empirical use. J. Exp. Bot. 10:290-300.

Sall, J. 1981. SAS Technical Report A-102, SAS Regression Applications. SAS Institute Inc. SAS Circle, Box 8000, Cary, NC 27512-8000.

SAS (Statistical Analysis System). 1990. SAS/STAT User's Guide. Volume 2, Version 6, Fourth Edition. SAS Institute Inc; SAS Campus Drive. Cary, NC 27513.

Timon, V. M. and E. J. Eisen. 1969. Comparison of growth curves of mice selected and unselected for postweaning gain. Theor. Appl. Genet. 39:345-351.