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A Numerical Method for Estimating the Variance of Age at Maximum Growth Rate in Growth Models

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Abstract

Studies on maturation and body composition mention age at peak height velocity (PHV) as an important measure that could predict adulthood outcome. The age at PHV is often derived from growth models such as the triple logistic fitted to the stature (height) data. Theoretically, for a well behaved growth function, age at PHV could be obtained by setting the second derivative of the growth function to zero and solving for age. Such a solution obviously depends on the parameters of the growth function. Therefore, the uncertainty in the estimation of age at PHV resulting from the uncertainty in the estimation of the growth model, need to be accounted for in the models in which it is used as a predictor. Explicit expressions for the age at PHV and consequently the variance of the estimate of the age at PHV do not exist for some of the commonly used non-linear growth functions, such as the triple logistic function. Once an estimate of this variance is obtained, it could be incorporated in subsequent modeling either through measurement error models or by using the variances as weights. A numerical method for estimating the variance is implemented. The accuracy of this method is demonstrated through comparisons in models where explicit solution for the variance exists. The method of estimating the variance is illustrated by applying to growth data from the Fels study and subsequently used as weights in modeling two adulthood outcomes from the same study.

Keywords

Age at PHV; Fels Data; Numerical Derivative; Growth Functions; Growth Velocity

1. Introduction

In modeling growth of children, physical maturation has been considered an important factor for predicting the status of overall adulthood markers. Clinicians use stature at different phases of growth to detect and monitor wide variety of health problems (Berkey, 1993). One of the characteristics of growth that seems to predict adulthood markers is age at peak height velocity (PHV), which is defined as the age at which the maximum rate of growth occurs during the adolescent growth spurt. In situations where the adolescent growth spurt could be modeled by a well defined mathematical function, the age at PHV could be explicitly

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obtained by setting the second derivative of the growth function to zero and solving for the maximum in the desired age range. There is a plethora of growth functions that accommodate adolescent growth spurt. These include the Preece-Baines model (1978), extended Jolicoeur (1985), Shohoji and Sasaki (1987) along with the double and triple logistic functions (Bock and Thissen (1973, 1976)). Other classic growth functions such as the Richard's, the logistic and the Gompertz, have a maximum velocity (MV) at a very early age but do not provide another maximum in the adolescent range. Therefore, they are not useful for estimating the age at PHV.

Once an estimate of the age at PHV is obtained, in subsequent analyses of adulthood outcome measures, it could be used as a continuous covariate or as an ordinal covariate by characterizing a child into early, moderate or late maturer. In such analyses the estimate of the age at PHV is assumed to be free of error. This assumption, in general holds true when the covariate is predetermined or fixed in an experimental setting. However, the estimate of the age at PHV itself is a function of the estimates of parameters in the non-linear model and therefore is prone to uncertainties (Ratkowsky, 1983). Therefore, the measurement error in the estimates of age at PHV should be incorporated in the analyses of adulthood measures. One way to account for this is to fit measurement error models in which the estimate of the variance of age at PHV from the growth model is incorporated in the residual variance of the models for the adulthood outcome. As an alternative, the inverse of the standard errors (s.e.) of the estimates of age at PHV could be used as weights in the analyses of the adulthood outcome.

Estimating the asymptotic s.e. is straight forward when explicit expressions for the age at the maximum growth velocity are available. For example, consider the logistic growth function model

$$y=\frac{k}{1+\alpha e^{-\beta t}}, \quad (1)$$

where, y may be the stature in centimeters and t, age in years. The logistic function has asymptotes at $y = 0$ as t approaches $-\infty$ and $y = k$ as t approaches ∞. Thus, the initial growth is zero and the maturity in stature is attained at k.

In Figure 1, examples of important features of growth under the logistic model are shown. Figure 1a) shows the growth function. Figure 1b) shows the corresponding velocity curve, which is essentially the first derivative of the growth curve plotted against age. In Figure 1c) the acceleration curve, which is the second derivative of the growth curve plotted against age, is shown. The age at maximum velocity (MV) is where the maximum rate of growth occurs. A single peak is indicative of an initial growth followed by a period of deceleration. (Notice that the peak velocity occurs at an early age and that there are no peaks in the adolescent range.) In Figure 1c), the age at which the acceleration is zero corresponds to the age at MV.

To compute the age at MV, the logistic function is differentiated twice, equated to zero and solved for *t*. Solving the second derivative produces the age which optimizes the velocity curve and it is given by.

$$t_{\max}=\frac{-\ln\left(1/\alpha\right)}{\beta}. \quad (2)$$

A maximum likelihood estimate (mle) of t_{max} could be obtained by substituting the mles of the model parameters, α and β, respectively. Then the asymptotic variance of the estimate of t_{max} could be obtained using the Taylor's series approximation (Delta method). It can be shown that the expression for the variance is,

$$V(\widehat{t}_{\max})=\frac{1}{\alpha\beta}\left(\frac{\sigma_{\alpha}^{2}}{\alpha\beta}+\frac{\sigma_{\alpha\beta}\ln(1/\alpha)}{\beta^{2}}\right)+\frac{\ln(1/\alpha)}{\beta^{2}}\left(\frac{\sigma_{\alpha\beta}}{\alpha\beta}+\frac{\sigma_{\beta}^{2}\ln(1/\alpha)}{\beta^{2}}\right), \quad (3)$$

where σ_{α}^{2} and σ_{β}^{2} are the variances of the estimates of α and β, respectively and $\sigma\alpha\beta$ is the covariance between the estimates of α and β. Similar expressions could be obtained for the Gompertz model as well. The Gompertz growth function, the corresponding age at MV and its variance are shown below in equations (4), (5) and (6), respectively.

$$y=\alpha\exp\left\{-\exp(\beta-\gamma t)\right\}, \quad (4)$$

$$t_{\max}=\frac{\beta}{\gamma}, \quad (5)$$

$$V(t_{\max})=\frac{1}{\gamma^{4}}(\beta^{2}\sigma_{\gamma}^{2}-2\beta\gamma\sigma_{\beta\gamma}+\gamma^{2}\sigma_{\beta}^{2}). \quad (6)$$

For more complex models that allow for the estimation of adolescent growth spurts, such as the Preece-Bairnes, Jolicoeur, Shohoji and Sasaki, the double logistic and the triple logistic models, an explicit expression for the age at PHV (or the MV) does not exist. Consider the basic triple logistic model by Bock and Thissen (Thissen et al., 1976),

$$y=\frac{k_{1}(1-D)}{1+e^{-\alpha_{1}(t-\beta_{1})}}+\frac{k_{1}D}{1+e^{-\alpha_{2}(t-\beta_{2})}}+\frac{k_{2}}{1+e^{-\alpha_{3}(t-\beta_{3})}}, \quad (7)$$

where D represents contribution of the mid-childhood growth to the total overall growth. The parameters β_1, β_2 and β_3 are timing parameters that control the location of early-childhood, mid-childhood and adolescent components along the age axis. The parameters k_1 and k_2 represent the amount of growth contributed when an individual passes from pre-adolescent to adolescent stage, respectively. The growth function, the velocity curve and the acceleration curve are shown in figure 2. Unlike the logistic and Gompertz models, the growth velocity curve for the triple logistic function shows two maxima one of which is in the adolescent range.

Simple calculus could be used to show that the second derivative of the triple logistic function is complex non-linear and is given in equation (8) below (Semhar, 2010). An explicit solution for the age at PHV in this case does not exist.

$$
\begin{aligned}
\frac{\partial^2 y}{\partial t^2} = {} & \frac{-k_1\alpha_1^2(1-D)e^{-\alpha_1(t-\beta_1)}(1+e^{-\alpha_1(t-\beta_1)})+2k_1\alpha_1^2(1-D)e^{-2\alpha_1(t-\beta_1)}}{(1+e^{-\alpha_1(t-\beta_1)})^3}+ \\
& \frac{-k_1\alpha_2^2De^{-\alpha_2(t-\beta_2)}(1+e^{-\alpha_2(t-\beta_2)})+2k_1\alpha_2^2De^{-2\alpha_2(t-\beta_2)}}{(1+e^{-\alpha_2(t-\beta_2)})^3}+ \\
& \frac{-k_2\alpha_3^2e^{-\alpha_3(t-\beta_3)}(1+e^{-\alpha_3(t-\beta_3)})+2k_2\alpha_3^2e^{-2\alpha_3(t-\beta_3)}}{(1+e^{-\alpha_3(t-\beta_3)})^3}
\end{aligned} \qquad (8)
$$

Since the age at PHV itself has to be obtained numerically, expressions for the derivatives of the age at PHV, with respect to the model parameters, also are not tractable. Therefore, explicit expressions for the variance of age at PHV are also not available. The main focus of this article is to propose a numerical method for estimating the variance using approximate derivatives. As an alternative one could also consider re-sampling methods such as the Bootstrap. However, when the growth data are sparse the model fitting is often tedious and therefore repeating this process many times in a re-sampling method becomes computationally horrendous. The numerical method proposed here is less cumbersome and produces accurate estimates of the variance.

The method is illustrated using the data from the Fels Longitudinal Study (Roche, 1992). The data from Fels study is rich, consisting of growth of children from birth to 18 years, their demographics, such as birth weight, gender, etc. between the calendar years of 1929 and 2007. For a subset of children, the database also includes data on their adulthood outcomes such as insulin and glucose levels. The database consists of a total of 1923 subjects, 930 of whom were boys and 993 were girls. The subset for which the adulthood outcomes are available contains 632 children, of which 313 are males and 319 are females.

The remainder of the article is organized as follows. In the next section, the numerical approach for estimating the variance of the age at PHV for models that do not have explicit solutions for age at PHV is presented. Also in this section the applicability of the method is evaluated by applying the numerical method to the FELS data for estimating the age at MV in the case of logistic and Gompertz models and compared with the exact solutions presented earlier in this section. In the illustration section the method is applied to the FELS data for estimating variance of the estimate of the age at PHV under the triple logistic model. Then this estimate is used as a weight in a model for analyzing adulthood measures in which the age at PHV is included as a covariate. In the discussion section limitations and future problems are discussed.

2. A general approach for approximating the variance

Suppose $\mathbf{g}$ is a set of d (linear or nonlinear) functions of the elements of the p x 1 parameter vector θ and suppose the mle of $\mathbf{g}$ is $\hat{\mathbf{g}} = \mathbf{g}(\hat{\theta})$, where $\hat{\theta}$ is the mle of θ. Then the large sample variance of $\hat{\mathbf{g}}$ obtained through Taylor series approximation (Delta method) is as follows (Bickel, 2001).

$$\mathbf{V}(\mathbf{g}(\hat{\boldsymbol{\theta}}))=\left(\frac{\partial \mathbf{g}}{\partial \boldsymbol{\theta}}\right)\mathbf{V}(\hat{\boldsymbol{\theta}})\left(\frac{\partial \mathbf{g}}{\partial \boldsymbol{\theta}}\right)', \quad (9)$$

where $\left(\frac{\partial \mathbf{g}}{\partial \boldsymbol{\theta}}\right)$ is the d x p matrix of partial derivatives of the elements of **g** with respect to the elements of $\boldsymbol{\theta}$ and $\mathbf{V}(\hat{\boldsymbol{\theta}})$ is the variance covariance matrix of $\hat{\boldsymbol{\theta}}$. The estimates of age at PHV (or MV, where PHV is not plausible) are functions of the model parameters and therefore, to obtain the variance, the above approximation could be applied. In the case of logistic and the Gompertz growth functions explicit expressions for the age at MV are available and therefore an exact expression could be obtained. For many growth functions, such as the double and triple logistic, an explicit expression for the age at PHV itself is not available and consequently there is no explicit expression for its variance as well. The method proposed here, is based on a numerical computation of the derivative matrix $\left(\frac{\partial \mathbf{g}}{\partial \boldsymbol{\theta}}\right)$ using the fundamental definition of a derivative.

In calculus the derivative at any point corresponds to the slope of the tangent at that point. The slope of a nonlinear function varies at different points along the curve. Here, the objective is to find the slope of the nonlinear **g** with respect to each of the parameter estimates in $\boldsymbol{\theta}$. By definition, the slope of the tangent of the function g at the mle of a scalar (i.e., $\frac{\partial g}{\partial \theta}$) could be approximated,

$$\frac{\partial g}{\partial \theta} \approx \frac{g(\theta+h)-g(\theta)}{h}, \quad (10)$$

where h is a very small number in the neighborhood of the mle $\hat{\theta}$. Here, the choice of h is crucial. The rule of thumb is to choose h such that the graph of $g(\theta)$ vs θ is nearly linear in the interval $(\theta, \theta + h)$. For the multiparameter case, where **g** is also a vector, equation (10) has to be repeated for each parameter and each element of **g**.

To apply the approximation in (10) for the estimate of the variance of age at PHV (MV) the steps could be summarized as follows.

Step 1. Fit the growth function to each individual's growth and obtain the mles of the parameters, $\hat{\boldsymbol{\theta}}$, along with the estimate of the variance covariance matrix, $\mathbf{V}(\hat{\boldsymbol{\theta}})$. There are several software available for fitting non-linear models. For example, PROC NLIN in SAS could be used (SAS, 2008).

Step 2. Estimate the age at PHV (MV), $\hat{t}_{max}$, by equating the second derivative of the growth function with respect to time t to zero and solving. If this equation is non-linear a numerical method may have to be implemented. For example, PROC NLP in SAS could be used (Ratkowsky, 1983). This procedure allows constrained optimization, which could be utilized to estimate the age at PHV by specifying a range for the age.

Step 3. For each element, $\hat{\theta}_j$ in $\hat{\theta}$, substitute $\hat{\theta}_j + h_j$, repeat step 2 and obtain a new estimate of age at PHV, $\hat{t}_{\max}$ (j h $_j$;). Compute the approximate derivative with respect to θ_j at $\hat{\theta}_j$ as,

$$dt_j = \frac{\hat{t}_{\max}(j;h_j) - \hat{t}_{\max}}{h}.$$

Step 4. Repeat step 3 for j =1, 2, …, p and obtain the vector of derivatives, $\mathbf{dt} = (dt_1, dt_2, \ldots, dt_p)$.

Step 5. Compute the variance of age at PHV (MV) by substituting **dt** for $\left(\frac{\partial \mathbf{g}}{\partial \boldsymbol{\theta}}\right)$ and V $(\hat{\theta})$ for V $(\hat{\theta})$ in equation (9).

3. Comparison of the exact method versus the proposed approximation

To examine how well the 5-step method proposed in section 2 performs, the method was applied to the logistic and Gompertz models using the Fels data. Recall, for these two models explicit solutions as well as the exact form of the asymptotic variance of the estimate of age at MV is available. For the illustration purposes a subset of the Fels data for which there was adequate observations to fit the logistic or the Gompertz model was selected. An individual's data was deemed adequate if the non-linear fit produced estimates within the parameter space. Under this constraint, a sample of 446 children was used for the logistic case and a sample of 525 cases was used for the Gompertz case. In all 441 children from the logistic case were among the 525 in the Gompertz case. The maximum age range of the children was 0 to 18 years. (For some children their infant data are in terms of recumbent length, namely the height measured while lying face-up.) The PROC NLIN procedure in SAS was used to obtain the estimates of the model parameters $(\hat{\boldsymbol{\theta}})$ and the corresponding estimate of the variance, $\mathbf{V}(\hat{\boldsymbol{\theta}})$. The exact estimates of the age at MV and the corresponding variance estimates were obtained using the equations (2) and (3) for the logistic and (5) and (6) for the Gompertz models. For the comparisons, the estimates of the age at MV were numerically obtained using PROC NLP procedure in SAS. Then the 5-step method described in section 2 was applied to numerically estimate the variance of the age at MV.

The distribution of the estimates of age at MV is shown in Figure 3. The bold line represents the logistic model; the dotted bold line represents the Gompertz model.

Table 1 below shows the average age at MV, average variance computed using the exact method as well as the numerical method proposed in the paper. Clearly, the numerical method produces quite accurate estimates of the variance of age at MV. Notice, the correlation between the two methods is almost 1 in both logistic and Gompertz models. Although the two models differ in the estimate of the age at MV (3.537 and 1.046, respectively), the exact variance of these estimates and the approximate variances obtained by the 5-step procedure are identical up to 2 decimals. The difference in the means underscores the importance of the right choice of a model to fit growth, which should be primarily based on the underlying biological mechanism. As we show in the next illustration, in fact the best fitting model is a higher order model such as the triple logistic. Here the purpose of choosing the two models is to establish that the accuracy of the variance estimates is not specific to a model.

4. Application of the 5-step method for Triple logistic model

Because of the inherent human growth characteristics, the growth trajectories cannot be easily explained using the simple logistic or Gompertz models (Lozy, 1987; Thissen et al., 1976). Mechanistically, the triple logistic curve displays points of most interest such as the maximum or minimum rates of growth associated with the pre-pubertal and adolescent ages that appear naturally if a person sustains a normal growth. Therefore, the triple logistic curve can capture the ages at early-childhood, mid-childhood and adolescent stages and hence for estimating the age at PHV the triple logistic is most appropriate. The concept could be extended to other popular growth functions such as the Preece-Baines, Jolicoeur, and Shohoji and Sasaki models as well. In order to capture all aspects of the growth frequent data during the first two years and enough data during the next 16 years of a child's growth must be available. This includes recumbent length for both boys and girls. In the FELS data a smaller subset of 54 children had sufficient data in these years.

The PROC NLIN was applied to these children and the age at PHV was subsequently obtained using the PROC NLP for each child. The distribution of the ages at PHV is shown in Figure 4 for boys and girls separately along with the best fitting normal distribution. Notice that the distribution of the age at PHV fits the normal distribution better than the age at MV under the logistic and Gompertz models (Figure 3), which do not fit the growth as well as the triple logistic. In general the triple logistic model fitted well for most children. In Table 2 the mean age at PHV along with the variance estimated using the 5-step procedure, separately for the Boys and Girls, are shown.

5. Use of variance of age at PHV as weights in modeling adulthood measures

One of the main purposes of estimating the age at PHV is to use it as a predictor in modeling adulthood outcomes. Specifically, in the Fels data, the interest is in modeling adulthood levels of glucose and insulin in terms of the age at PHV and other covariates, such as the adulthood BMI measured at the same time. For instance, a study by Sun and Schubert (Sun et al., 2009) shows significant difference in mean levels of glucose and insulin between those whose age at PHV is higher (maturing late) versus those that are lower (maturing early). In general, in fitting least squares regression models the variance of the residual errors is assumed constant for all values of the independent variables. Since the age at PHV is an estimate based on a non-linear model, the inherent uncertainty may make this assumption inappropriate. The unequal variances of the estimates of age at PHV could lead to unstable estimates of regression coefficients. As a result the power of significance tests for all variables in the model may be reduced. There is vast amount of literature under measurement error models (Carroll et al., 1995; Fuller, 1987), to accommodate the error in estimation of PHV. Here, in order to illustrate the use of the variance of the estimate of age at PHV a simple alternative through weighted least square (WLS) regression, where the weights are given by the inverse of the square root of the variance estimates, is applied (Carroll, 1998). Thus, the observations whose value of glucose and insulin levels (dependent variables) that correspond to large variances of the estimate of the age at PHV would contribute less to the regression model.

The spaghetti plots of the growth data is presented in Figure 5. Notice from the figure that these data clearly indicate two growth spurts. The number of observations available varied from 11 to 44. The summary statistics, and the estimated mean age at PHV of the 54 children are presented in Table 3. One thing to notice here is that inclusion of recumbent length has led to an under estimate of the boys age at PHV compared to what is reported in some literature. This may be due to the fact that the individual is longer when lying down than when standing erect and during the infant years the difference between the boys and the girls is minimal. The recumbent length was included based on recommendations in the literature (Roche, 1992; Sun et al., 2009) for predicting adulthood outcome.

As described in section 2 and 3, for these children growth curves were fitted and the estimates of age at PHV and the corresponding variances were obtained. An analyses of the adulthood outcomes, Glucose and Insulin levels, were performed using a GLM approach. The independent variables included the Sex, BMI and the estimated age at PHV. The inverse of the square root of the variance estimates obtained from the 5-step procedure were included as weights. For comparison purpose, the analyses without the weights, which is the current standard, were also performed. In Table 4 the significance (p-values) of the various covariates, are presented for both the weighted (WLS) and unweighted (OLS) analyses. Notice that the inclusion of the weights changes the results in both directions. While for insulin the p-value reduced, for glucose it increased. This suggests that the application of the variance as weights provide more accurate results, but do not necessarily add to the power.

6. Discussion

In this article, a method for estimating the variances of the estimate of age at PHV in nonlinear models, where there are no explicit expressions for the estimate of the age at PHV are available, was presented. This method was based on an approximation of the derivatives using the fundamental definition of the derivatives. The proposed method was validated by comparing the results in models where exact expressions for the variance of the estimate of age at MV are available. An alternative to the proposed method might be through a bootstrap algorithm. However, non-linear model fitting is often time consuming and therefore obtaining 100’s (or 1000’s) of bootstrap samples might not be practical in most situations. As mentioned in the last section, the number of observations available varies considerably. This makes it difficult to apply computer intensive methods such as the bootstrap or random effects splines models (Tim et al., 2010) for estimating the variance of age at PHV or incorporating the variance simultaneously in a single analysis. For the SITAR model, it involves fitting individual cubic spline curves, but it is known that fitting splines with insufficient data leads to a fit that is erratic and a very high variability near the boundaries. For the bootstrap method, sampling within individuals on the growth part of the data could often lead to inadequate fit of the data. Although the proposed method requires three applications of a numerical method for estimating the age at PHV for each of the parameter in the model, it does not require more than one nonlinear model fitting for each individual.

The application of the method to Fels data, in which a triple logistic model was fitted to the children's growth data to estimate the age at PHV, demonstrated the importance of incorporating the corresponding variances as weights. The current standard is to assume that the estimated age at PHV used as covariates in the analyses of outcomes is a constant (Demerath, 2004). The results section demonstrated that appropriately weighting the outcomes with respect to how good the estimate of the age at PHV is, through their variances, in the analysis could substantially alter the conclusions. In some analyses the age at PHV is grouped into discrete categories and used as covariates. The variance estimates could be used as weights in these analyses as well.

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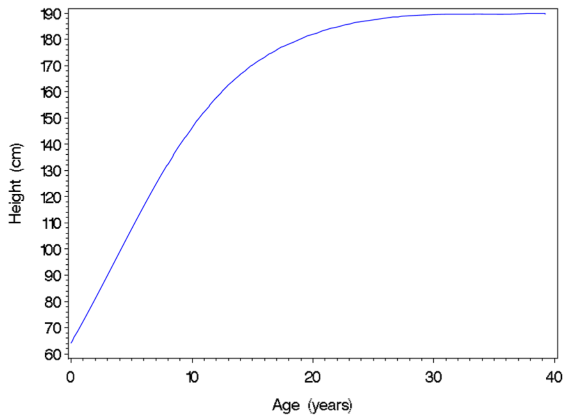
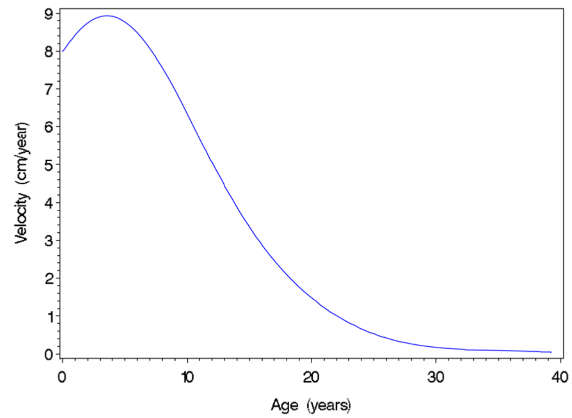
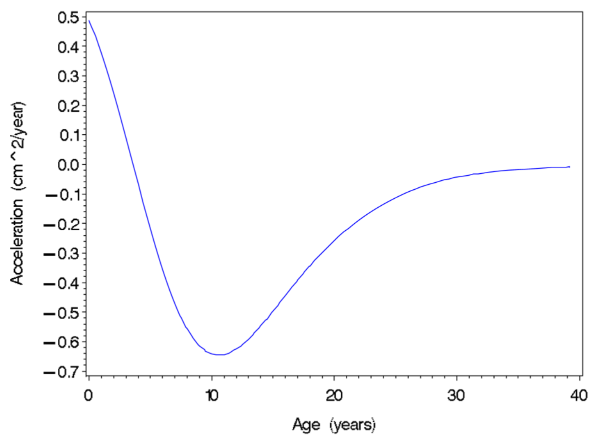


a) Growth Curve



b) Growth Velocity Curve



c) Growth Acceleration Curve

Figure 1.
Logistic Growth Model.

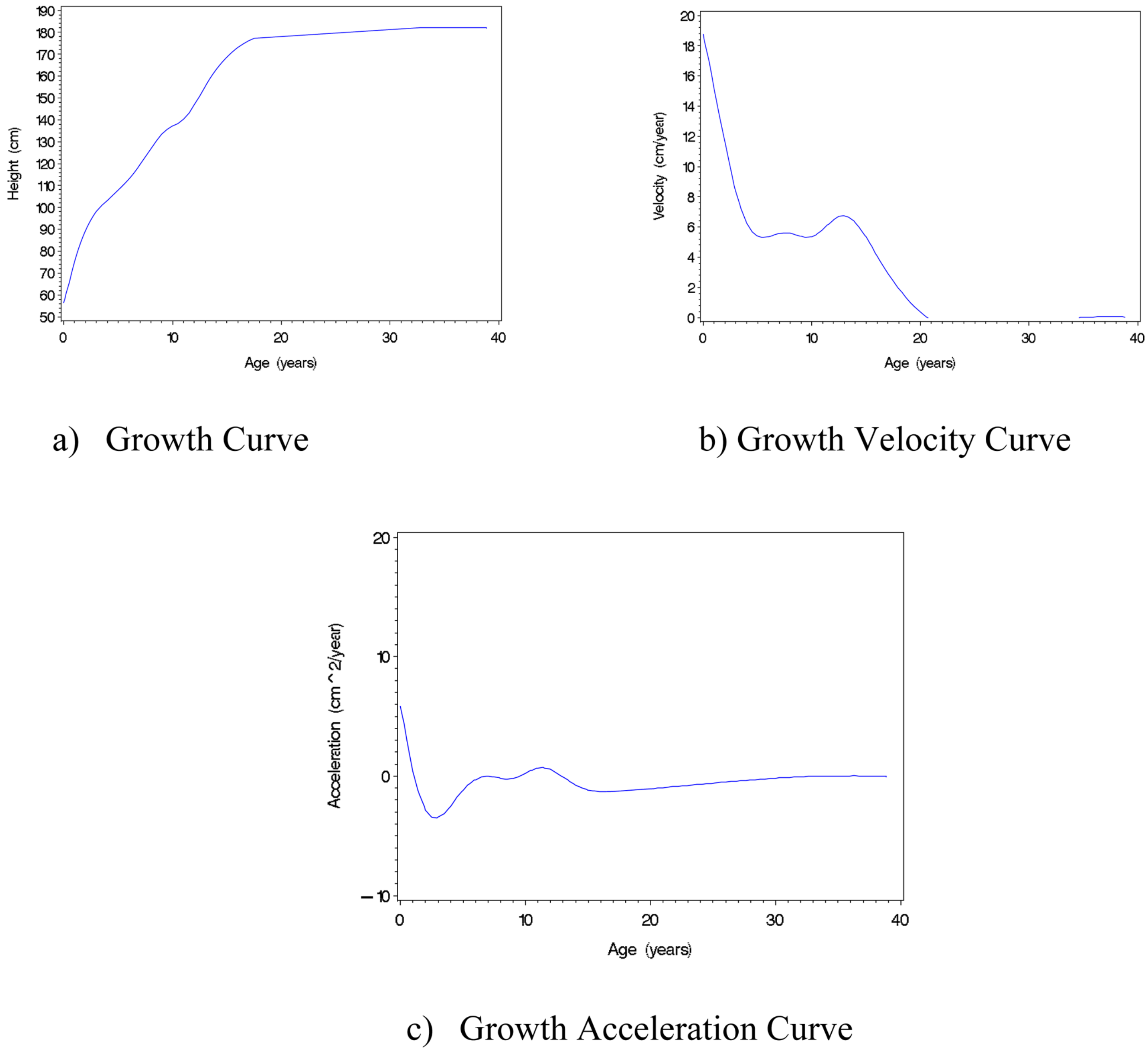


Figure 2.
Triple Logistic Model.

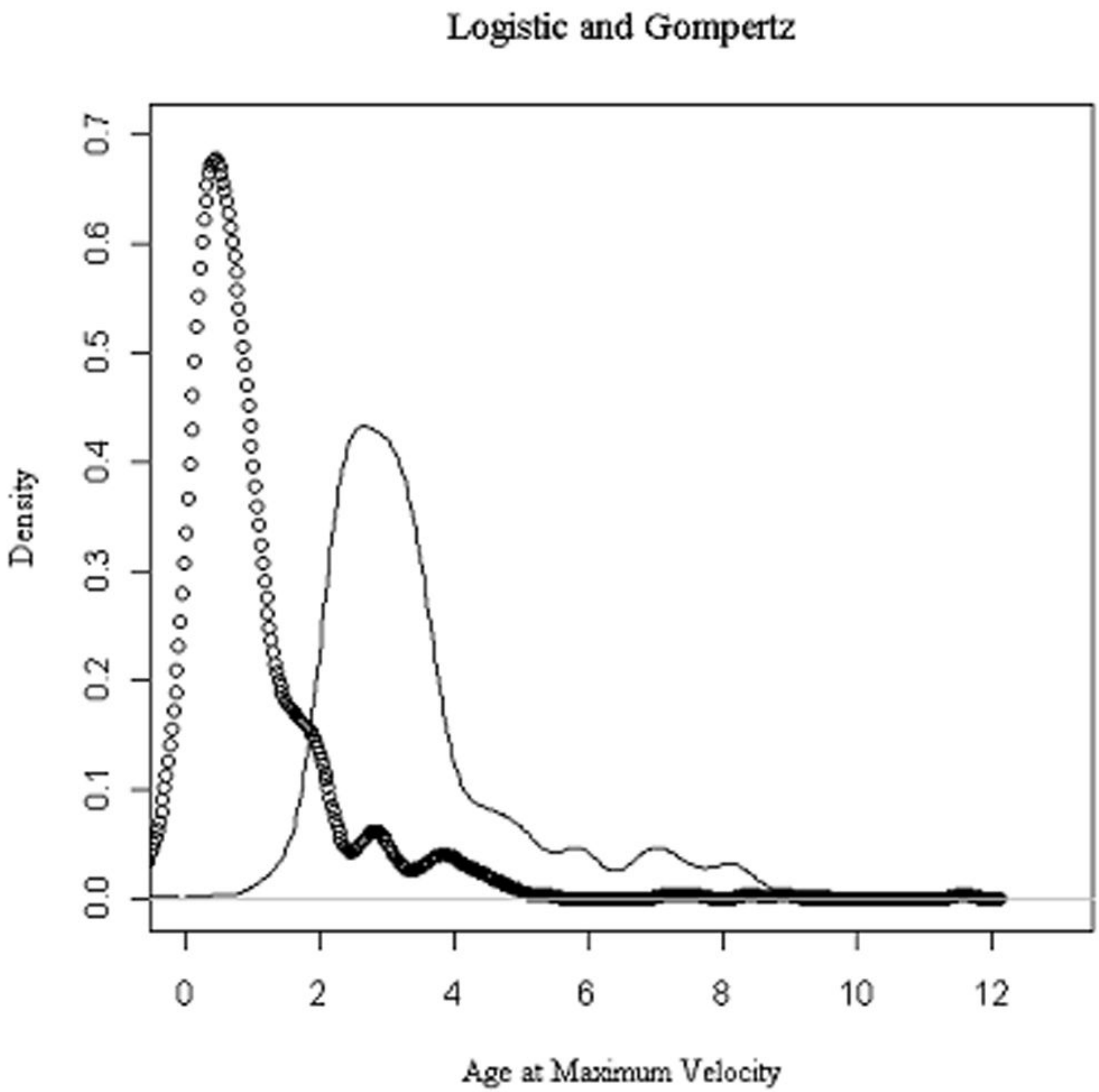


Figure 3.
Distribution plot for Age at MV for Logistic and Gompertz.

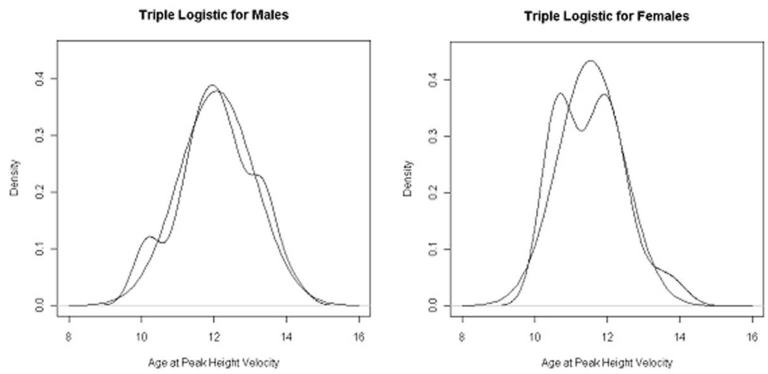


Figure 4.
Distribution plot for Age at PHV for Triple Logistic by Gender

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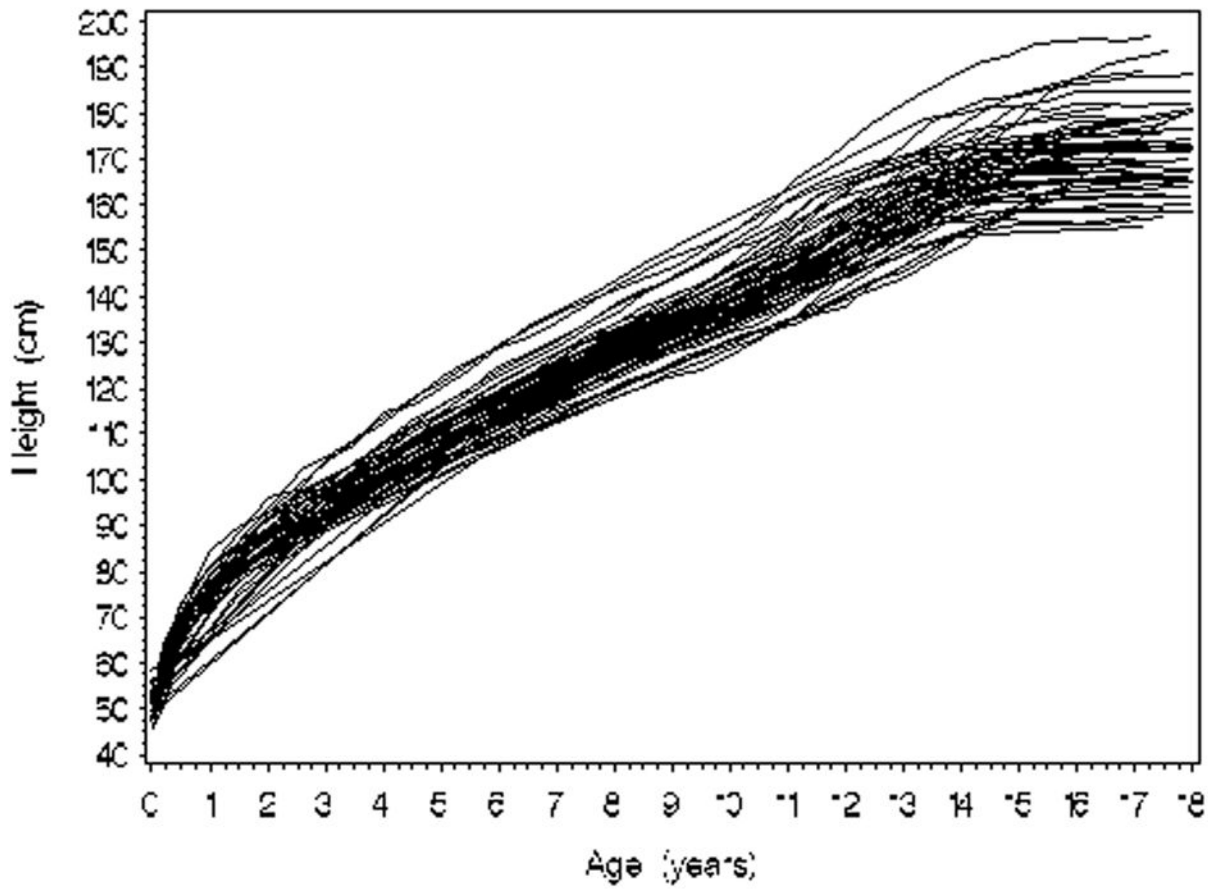

Figure 5.
The spaghetti plot of the growth data for Triple Logistic.

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Table 1

Means of Age at MV, Estimated and Exact Variances

	Logistic (N=446)		Gompertz (N=525)	
Variables	**Mean**	**SD**	**Mean**	**SD**
t (Age at MV)	3.537	1.635	1.046	1.270
Exact Variance of age at MV	0.430	1.175	0.195	0.612
Computed Variance of age at MV	0.431	1.176	0.195	0.612
Correlation between the methods	0.999 (<0.0001)		1 (<0.0001)	

Table 2

Means of Age at PHV, Estimated Variances for Triple Logistic

	Triple Logistic		
Variables	**N**	**Mean**	**SD**
Age at PHV (Girls)	28	11.55	0.92
Variance of age at PHV (Girls)	28	0.53	1.15
Age at PHV (Boys)	26	12.08	1.05
Variance of age at PHV (Boys)	26	0.46	0.65

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Table 3

Summary statistics

Variables	Boys			Girls		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**
Age at PHV	26	12.08	1.05	28	11.55	0.92
BMI	26	25.53	4.43	28	24.80	6.38
Glucose	26	88.81	14.461	28	84.21	9.81
Insulin	26	8.11	3.72	28	8.70	6.11
Weight	26	81.60	16.15	28	69.10	18.81

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Table 4

Significance (p-values) of predictors[†]

Variables	Insulin				Glucose			
	OLS		WLS		OLS		WLS	
	p-value	estimate	p-value	estimate	p-value	estimate	p-value	estimate
Sex	0.5987	6.8578	0.6538	1.814	0.1084	349.4606	0.6523	11.5467
Age at PHV	0.8964	0.4187	0.0021[†]	93.8694	0.1533	275.0112	0.3116	58.7111
BMI	0.0271[†]	126.7737	0.0384[†]	40.291	0.0127[†]	874.7248	0.0173[†]	340.3941

[†] Statistically significant at 5% significance level