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MULTI-LEVEL REPEATED MEASURES GROWTH MODELLING USING EXTENDED SPLINE FUNCTIONS

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SUMMARY

This paper explores the fitting of multi-level models to growth data over a wide age range using a new class of extended spline models. These extend conventional splines based on a ' + ' function representation by allowing variable order functions and by including fractional polynomial terms. The work focuses on modelling human growth in height and head circumference with example data sets. The procedures can be used with covariates and for comparing population parameters. © 1998 John Wiley & Sons, Ltd.

1. INTRODUCTION

In longitudinal studies, growth patterns are often summarized by certain linear or non-linear growth models so that a small number of parameters, or functions, of them, can be used to make group comparisons or to relate to other measurements. Historically, statistical methods for analysis of longitudinal data can be described in two broad categories: fitting a family of curves to a population with a between-individual structure, and fitting curves individually to each individual. In this paper we shall give examples from human growth but the same general principles will apply to animal and other forms of growth.

To analyse individual data, growth models are fitted to each individual. The resulting parameters that describe events such as the timing, magnitude and duration of the growth, may be used to compare groups etc. The effects of variables other than age, such as gender and social background, may also be included as covariates (Guo *et al.*,[1] Ratcliffe *et al.*[2]).

Alternatively, a model may treat an individual as a member of a population from the outset to that we are able to model directly the variations in growth parameters among individuals. Recently, efficient likelihood based methods have been devised which can handle unbalanced data, in which the number and time intervals of measurement can vary from individual to individual. The general multi-level model incorporates this class of methods as a special case and descriptions can be found in Goldstein,[3] Bryk and Raudenbush[4] and Longford.[5]

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Models fitted separately to individual subjects have tended to be non-linear in form (for example Jolicoeur *et al.*[6]) whereas the population based models have tended to be linear in the parameters. More recently, however, population based non-linear models have been studied (Berkey and Laird,[7] Bock *et al.*[8]).

In this paper we restrict discussion to linear models. The linear multi-level growth model[9] has important advantages; it can accommodate covariates which change over time, and within-subject residual terms which have a complex covariance. While this methodology can be extended in principle to non-linear models,[3] linear models are easier to interpret, are flexible and computationally relatively straightforward.[10] A non-linear curve typically requires a large number of parameters which makes estimation difficult, or else may introduce fixed relationships between growth events which are unrealistic.[12] Berkey[13] has pointed to problems of convergence and non-uniqueness of solutions for non-linear models.

In published population studies there is little which can handle longitudinal growth data with covariates involving a wide age range, for example, from birth to adulthood. This can be ascribed to two problems. First is the fact that the large variation in growth between individuals, especially in adolescence, makes it difficult to find adequate growth functions. Secondly, the structure of the underlying form of growth curve changes with age and the most flexible curves proposed, polynomials, cannot be used directly.[11]

The only linear model proposed to fitting height to both early childhood and adolescence is the general eight-parameter Reed model by Reed and Berkey.[14] The model combines a five-parameter model for early childhood and a separate five-parameter model for adolescence. The model for childhood is smoothly joined to one for the adolescent period in such a way that the curve is continuous in distance and velocity at the age where the two models are joined, resulting in eight effective separate parameters.

A major disadvantage of this approach lies in the requirement that the separate ‘piecewise’ polynomials join smoothly. When fitted to a sample from a population it also requires that the between- and within-individual variations at the joins are the same for both segments. This is often difficult to achieve (see discussion). A more flexible approach which guarantees the correct degree of smoothness for both the mean growth curve and the variation is to use the spline functions known as ‘grafted polynomials’ or ‘ + ’ functions.

Spline functions in general are piecewise polynomials of degree n whose function values and first $n-1$ derivatives agree at the points where they join (Wold,[15] Wegman and Wright[16]). The abscissae of these join points are called knots. The ‘ + ’ functions with fixed knots which we use is defined as

$$\begin{aligned} u_+ &= u \quad \textit{if} \quad u > 0 \\ &\ 0 \quad \textit{if} \quad u \leqslant 0. \end{aligned}$$

Smith[17] provided a framework for a unified statistical theory of spline regression with fixed knots and using the ‘ + ’ function representation. In general, with $m-1$ knots, $\xi_1 < \dots \xi_{m-1}$, and m polynomial pieces each of degree n, the spline is expressed as

$$f(x) = \sum_{i=0}^{n} \phi_{i0} x^i + \sum_{j=1}^{m-1} \phi_{nj} (x - \xi_j)_+^n . \tag{1}$$

We shall refer to this as a conventional + function spline, or simply as a *conventional spline.* In this case, f and its first $n-1$ derivatives will be continuous. Splines with $n = 3$ are cubic splines and are commonly used.

In fitting growth curves to populations experience suggests that fixed join points are important. Variable knot cubic splines were explored by Berkey *et al.*[18] for fitting height curves to long-term longitudinal data with satisfactory results for the period of the function less than age 11 years but were found inadequate for the adolescent portion where there were systematic biases. Variable knot cubic splines lead to non-linear estimation. Allowing joint points to vary across individuals in a quite general way would entail the equivalent of the estimation of a large number of nuisance parameters and interpretation may be difficult. An interesting alternative is to have a common set of join points but allow individual random variation around the ages at which these are fixed. We shall not consider this possibility in the present paper.

Expression (1) can be extended by including polynomial pieces of different degrees. The construction of spline models with polynomial pieces of different degrees has been illustrated by an example of a cubic-quadratic-linear spline[17] and there are other examples.[19] These functions can be written as

$$f(x)=\sum_{i}\phi_{i0}x^{i}+\sum_{j}\sum_{r}\phi_{rj}(x-\xi_{j})^{r}_{+} \tag{2}$$

where r is typically at most 2 or 3. If no value of r is less than 2, then f has continuous derivatives with respect to either ξ_j or x of order 0, 1, … $r-1$. Another form of ' + ' function which can be used to structure the model is $(\xi_j - x)^r_+$ which can be incorporated as an additional term.[11] We can introduce further flexibility while retaining linearity by also including fractional polynomial terms such as logarithms or non-positive-integer terms.[20] An example is the following expression:

$$f(x)=\sum_{i}\phi_{i0}x^{i}+\sum_{j}\sum_{r}\phi_{rj}(x-\xi_{j})^{r}_{+}+\sum_{j}\sum_{r}\theta_{rj}(\zeta_{j}-x)^{r}_{+}+\gamma_{1}\ln(\alpha x+\beta)+\gamma_{2}x^{-1}. \tag{3}$$

The location of ζ and ξ and the orders of the polynomials can be determined by the overall behaviour of the data assisted by the adoption of the rules of thumb suggested by Wold.[15] We allow the model (3) to have both terms of the form $(x-\xi_j)^r_+$, $(\zeta_j - x)^r_+$ if they do not overlap so that the model is neither restricted by non-increasing or non-decreasing degrees of polynomials in each phase of the model. These models are referred to as *extended splines*.

Little is known about using conventional or extended splines for fitting growth data. This paper will explore the use of these splines to describe a wide variety of growth patterns, and will incorporate the models into a more general multi-level structure with covariates.

2. TWO-LEVEL GROWTH MODELS

This section introduces the two-level model using measurements from early age to adulthood. Early in infancy there is a rapid increase in head circumference while after infancy it increases slowly at least until 18 years.[21] This suggests a more complex pattern of head circumference growth curve in early childhood than at other ages.

Let y_{ij} denote the ith head circumference measurement of person j at time t_{ij} (in years). We propose the following two-level model for growth in head circumference:

$$y_{ij}=\beta_{0j}+\beta_{1j}t_{ij}+\beta_{2j}t_{ij}^{2}+\beta_{3j}\ln(12t_{ij}+1)+\beta_{4j}(\zeta-t_{ij})^{3}_{+}+\beta_{5j}(t_{ij}-\xi)^{3}_{+}+e_{ij}. \tag{4}$$

Note that we are assuming simple within-individual variation with $e_{ij} \sim \mathrm{N}(0, \sigma_e^2)$ and all the coefficients in (4) varying across individuals (level 2), with the vector of coefficients β_j distributed as $\mathrm{N}(\beta, \Omega_u)$ and

$$\Omega_u = \begin{pmatrix} \sigma_{u0}^2 & & & & \\ \sigma_{u01} & \sigma_{u1}^2 & & & \\ \cdot & \cdot & \cdot & & \\ \cdot & \cdot & \cdot & \cdot & \\ \cdot & \cdot & \cdot & \cdot & \sigma_{u5}^2 \end{pmatrix}.$$

This is often known as a *random coefficient* model.[3]

This curve has three segments, each of which is continuous with continuous first and second derivatives at the knots. In the present case the final form of the curve and knots have been chosen after extensive preliminary investigations and are at 2 and 10 years. In this sense we may prefer to regard the knots as being estimated rather than fixed. In other applications and data sets these choices may vary.

We propose the following random coefficient model for height:

$$y_{ij} = \beta_{0ij} + \beta_{1j} t_{ij} + \beta_{2j} \ln(t_{ij}) + \sum_{k=1}^{m-1} \beta_{2+k} (\xi_k - t_{ij})_+^3 + u_{3j}(t_{ij} - 9)_+^2 + u_{4j}(t_{ij} - 11)_+^2$$

$$\beta_{0ij} = \beta_{0j} + e_{ij}, \quad \beta_{hj} = \beta_h + u_{hj}, \qquad h = 0, \ldots 2 \tag{5}$$

with $e_{ij} \sim \mathrm{N}(0, \sigma_e^2)$ and where the u_{kj} are assumed multivariate normal with 5×5 covariance matrix Ω_u. In this model there are $m = 6$ segments for the 'descending' cubic ' + ' function with 5 knots, at 9, 11, 13, 15 and 17 years of girls and 9, 11, 13, 15 and 17·5 years for boys. As far as possible we have attempted to maintain the same join points for males and females, but the earlier cessation of growth for females required an earlier final join point. We also assume an 'ascending' quadratic' + 'function with knots at 9 and 11 years.

3. MODELLING HEIGHT

In this section the extended splines are applied to our longitudinal data sets: first modelling height for males and females separately.

3.1. Preliminary separate-subject models for height

The subjects studied are 89 males with 3044 measurements and 67 females with 2134 measurements from the control group (99 males and 74 females) of the Edinburgh Longitudinal Study, initiated in 1972 and known to be chromosomally normal; they were born at a time when the Medical Research Council was conducting a new-born cytogenetic survey.[22] The inclusion criteria were that they had been followed up to at least 16 years of age for males and 15 years for females in 1992 when this study started. The children were measured 3-monthly during the first year of life and twice-yearly thereafter. The data used in this section cover ages from 0·25 to 18·5 years. Gross errors have been eliminated. Supine length was measured before two years of age.

First, model (5) is investigated by fitting curves for each individual using ordinary least squares (OLS) with the specified knots. In males the average residual standard deviation is 0·55 cm with

Table I. Model (5) of height (cm) for 89 males

Fixed coefficient

	Estimate	SE
Intercept	149·0	1·7
$\ln(t)$	6·27	0·22
$(t-9)$	0·17	0·01
$(11-t)_+^3$	−0·62	0·02
$(13-t)_+^3$	0·66	0·01
$(15-t)_+^3$	−0·22	0·01
$(17{\cdot}5-t)_+^3$	1·23	0·21

Level 2 covariance matrix (correlations in brackets)

	Intercept	$\ln(t)$	$t-9$	$(t-9)_+^2$	$(t-11)_+^2$
Intercept	25·69				
$\ln(t)$	−0·94 (−0·13)	2·03			
$t-9$	2·24 (0·89)	−0·30 (−0·43)	0·25		
$(t-9)_+^2$	−0·32 (−0·18)	0·08 (0·16)	−0·05 (−0·28)	0·13	
$(t-11)_+^2$	0·10 (0·03)	−0·14 (−0·16)	0·04 (0·15)	−0·12 (−0·97)	0·38

Level 1 variance = 1·03 (SE = 0·03) number of subjects = 89, number of measurements = 3044

a range from 0·29 cm to 0·91 cm. In females the average residual standard deviation is 0·49 cm with a range from 0·23 cm to 0·80 cm. These results are close to expectation.[23]

3.2. Random coefficient spline models

Using the chosen knots we fit models separately for males and females. The random coefficient model is that given by (5). Table I gives the estimates of the parameters. Examining fixed coefficient contrasts shows that all the fixed coefficients are significantly different from zero ($P < 0{\cdot}01$).

A likelihood ratio test[3] comparing the model in Table I with a corresponding variance component model where only the intercept term varies randomly at level 2 is highly significant ($P < 0{\cdot}001$) as expected. For a check of this model, a plot of standardized residuals by predicted values is given in Figure 1. It appears that the residuals are less variable in the middle of the age range. The only outliers are for measurements after 18 years where the data are sparse and Figures 1 and 2 use only measurements at ages less than or equal to 18 years. We have looked at models allowing the level 1 variance to be a function of age but none of these has been found to fit well. Figure 2 shows an approximately Normal distribution, again with a few outliers.

The estimated mean population curve of the model in Table I together with the cross-sectional means is shown in Figure 3. The cross-sectional means are derived from varying numbers of observations within narrow age intervals (± 2 weeks about target ages). The mean curve estimated by the multi-level model uses the precise age at which the measurement was taken.

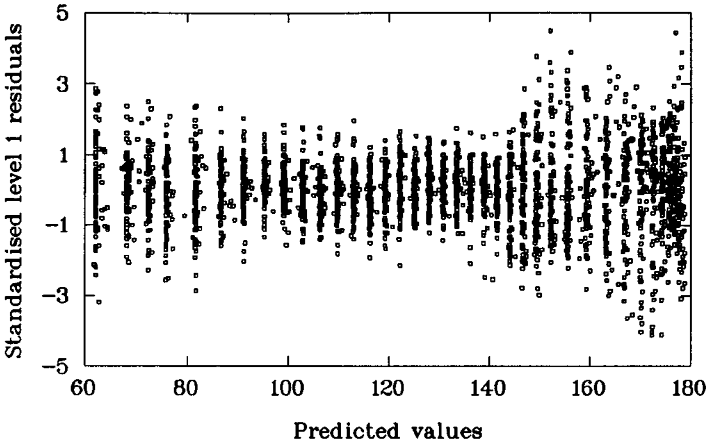

Figure 1. Plot of standardized level 1 residual by predicted values for height of males

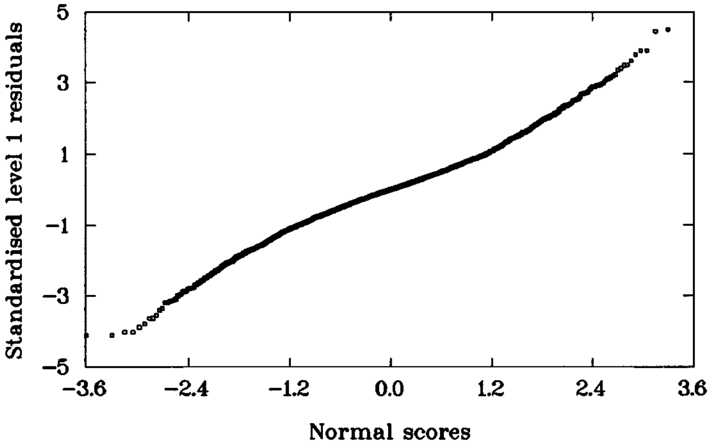

Figure 2. Plot of standardized level 1 residuals by Normal equivalent scores for height of males

Figure 4 shows the estimated velocity curve which is the first derivative of the multi-level model based on the estimated fixed parameters.

Table II gives the estimates of parameters for the females using model (5). As with males we have a highly significant likelihood ratio statistic for testing this model against a variance components model. A plot of standardized residuals by predicted values is given in Figure 5 and the Normal plot of standardized level 1 residuals is displayed in Figure 6, showing similar results as for males but with less extreme outliers.

Figure 7 shows the estimated mean population curve of the random coefficient model of Table II together with the cross-sectional means. Figure 8 presents the estimated velocity curves from the model using the first derivative of the model based on the estimated fixed parameters.

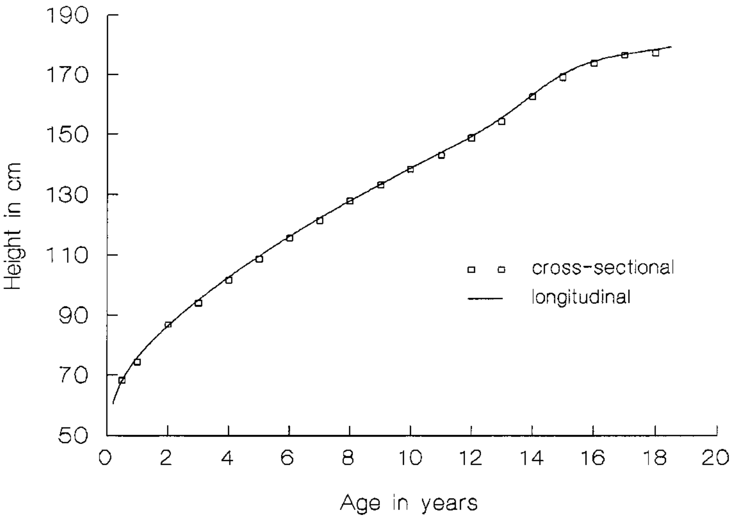

Figure 3. Longitudinally estimated mean curve (line) of height for males with the cross-sectional means (points)

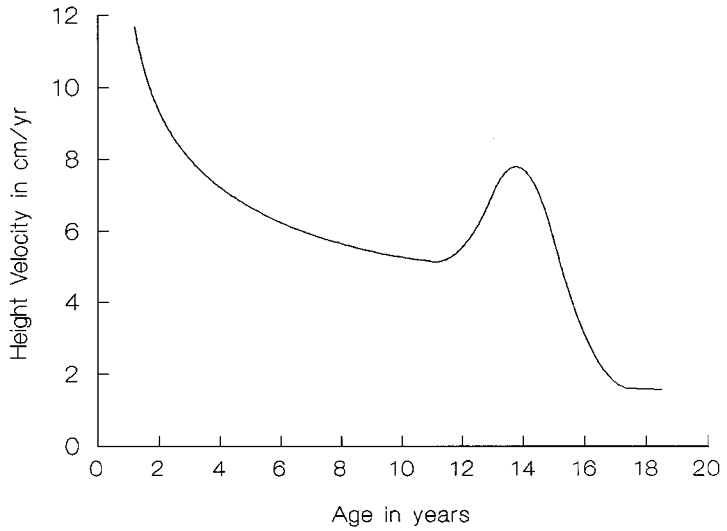

Figure 4. Estimated velocity curve of height for males

3.3. Estimating growth parameters

We use the estimated parameters to calculate the velocity curves for males and females (see Figures 4 and 5). We can also use the estimated parameters to calculate other growth parameters, such as the age of pre-pubertal 'take-off' or peak height velocity (PHV).[24]

Table II. Model (5) of height (cm) for 67 females

Fixed coefficient

	Estimate	SE
Intercept	146·3	1·8
$\ln(t)$	5·71	0·29
$(t-9)$	0·05	0·01
$(9-t)_+^3$	− 0·30	0·02
$(11-t)_+^3$	0·32	0·02
$(13-t)_+^3$	− 0·22	0·01
$(17-t)_+^3$	− 0·09	0·003

Level 2 covariance matrix (correlations in brackets)

	Intercept	$\ln(t)$	$t-9$	$(t-11)_+^2$	$(t-13)_+^2$
Intercept	42·82				
$\ln(t)$	− 4·80 (− 0·47)	2·42			
$t-9$	4·51 (0·94)	− 0·74 (− 0·65)	0·54		
$(t-11)_+^2$	− 2·56 (− 0·69)	0·33 (0·38)	− 0·31 (− 0·74)	0·32	
$(t-13)_+^2$	2·58 (0·47)	− 0·22 (− 0·17)	0·32 (0·52)	− 0·45 (− 0·94)	0·70

Level 1 variance = 0·94 (SE = 0·03) number of subjects = 67, number of measurements = 2134

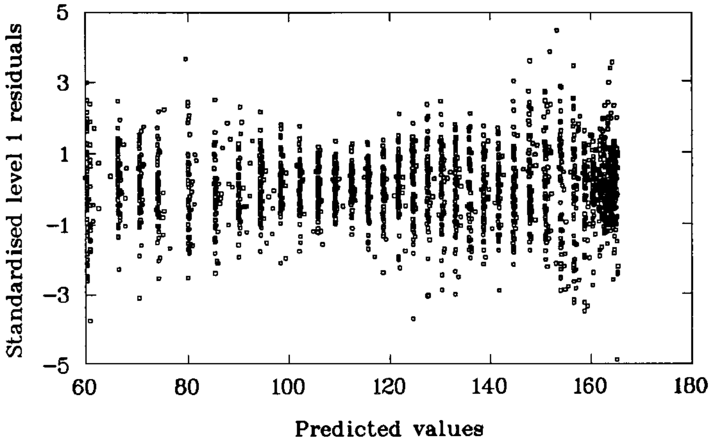

Figure 5. Plot of standardized level 1 residual by predicted values for height of females

If we use the model for females as an example, then the ages of minimum or maximum velocity are given by the solution to the following equation:

$$-(\beta_2+u_{2j})/t^2+6\beta_3(9-t)_+ +6\beta_4(11-t)_+ +6\beta_5(13-t)_+ +6\beta_6(17-t)_+ +2u_{3j}+2u_{4j}=0. \qquad (6)$$

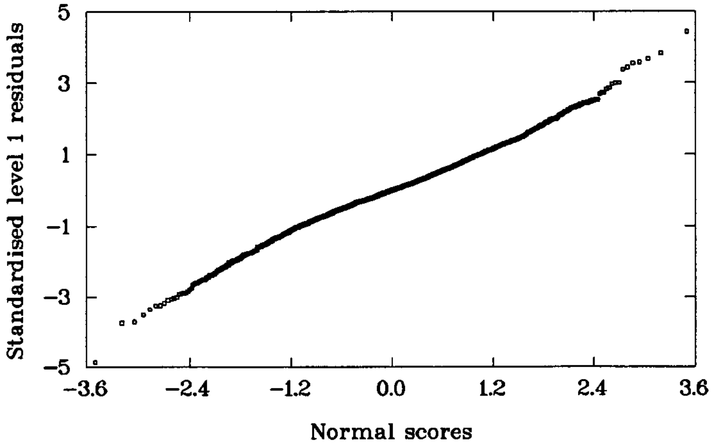

Figure 6. Plot of standardized level 1 residuals by Normal equivalent scores for height of females

Figure 7. Longitudinally estimated mean curve (line) of height for females with the cross-sectional means (points)

If we assume that the u_{hj} have a multivariate Normal distribution we can estimate the distribution of t, for example by simulation,[25] with the βs replaced by their estimates. This expression requires at least one random coefficient to be multiplied by a positive power of t in order to estimate the distribution of the growth parameters. However, it has not been possible to include random coefficients higher than the quadratic with the relatively small sample size.

Table III gives the mean values of the growth parameters. The means under the column 'overall' are obtained simply using the estimates from the fixed part of Table I for males and

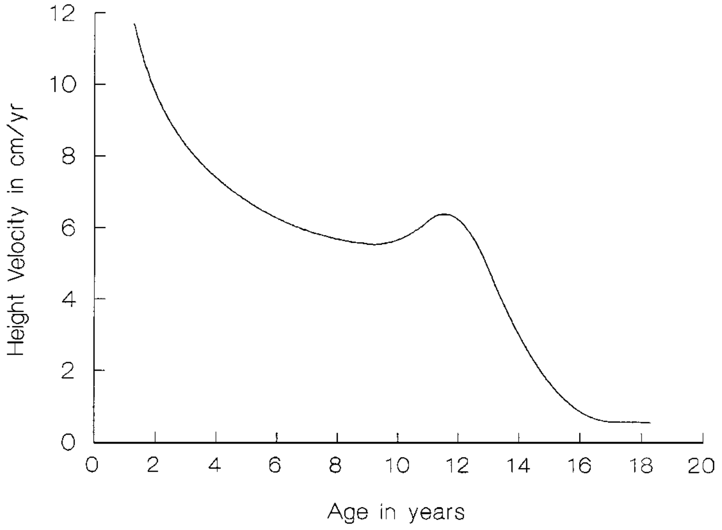

Figure 8. Estimated velocity curve of height for females

Table III. Average growth parameters for 89 males and 67 females

Growth parameters	Overall		Simulation	
	Males	Females	Males	Females
Age at take-off (years)	11·1	9·2	11·2	9·3
Velocity at take-off (cm/year)	5·1	5·5	4·9	5·6
Height at take-off (cm)	144·4	134·1	145·5	135·5
Age at PHV (years)	13·8	11·5	13·8	11·6
PHV (cm/year)	7·8	6·4	7·8	6·7
Height at PHV (cm)	161·4	147·6	161·6	149·2
Height at 18 years (cm)	178·1	165·1	178·9	165·5

Table II for females. Those under the column 'Simulation' are from a simulation sample of 100 individuals using the estimates and assuming multivariate normality. The two sets of estimates are similar. We could also use simulation to derive quantiles for the between-individual distribution of these growth parameters.

Our results are very close to those obtained by other methods. For males, these estimates are close to the results of Ratcliffe *et al.*[26] for the 16 earliest born boys of this data set using kernel estimation.[27,18] For females, the estimates are close to the results of Ratcliffe *et al.*[29] by using the same kernel estimation for the 16 earliest born girls from this data set.

In contrast to the model of Reed and Berkey,[14] the velocity curves of Figures 4 and 8 represent the main features of the pubertal spurt well and are, by definition, smooth at the joins.

The height mean curves in Figures 3 and 7 asymptote for feamles but not for males. There may be two reasons for this: one is that females stop growing earlier than males and by 18·5 years some

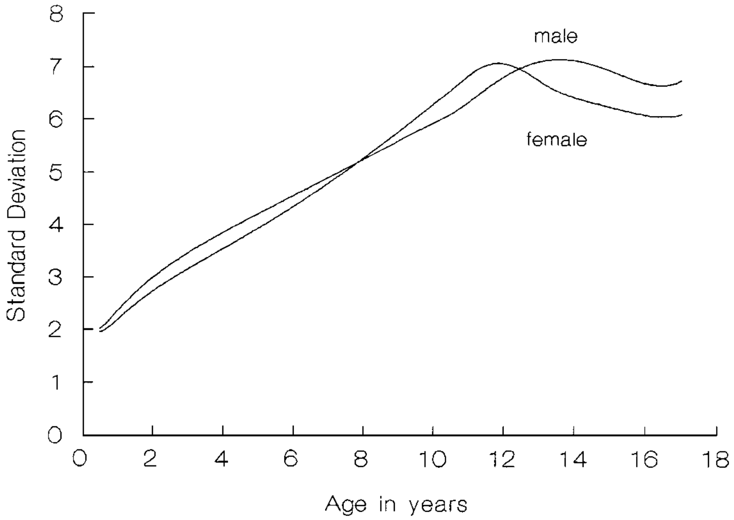

Figure 9. Between-individual standard deviation calculated from Tables II and III

boys in late development are still growing; another is that relatively small numbers in the final age group might lead to an average curve being unstable at that age, as discussed by Cole and Green.[30] In order to check the predicted mean value for males of 178·9 cm at 18·5 years using our model, we applied the BTT model to the data using the AUXAL program of Bock *et al.*[31] The BTT model is a non-linear model which explicitly includes an upper asymptote and is an extension to the triple logistic model of Bock and Thissen.[32] The predicted value is 178·8 cm, which is very close to our results.

3.4. Between-individual variation

Figure 9 shows the estimated between-individual standard deviation by age for each gender of the models in Tables I and II. For most ages, from early childhood to 16 years, these are close to those found by Tanner *et al.*[33] The standard deviation increases with age gradually at the pre-pubertal stage and faster at the pubertal stage. The difference in timing between the two genders is also clear and is reasonably consistent with the timing difference of the pubertal stages. The results are displayed only up to age 17 years due to small numbers after that age.

4. MODELLING HEAD CIRCUMFERENCE

Head circumference is an important part of growth monitoring. For example, in studying children with sex chromosomal aneuploidy, head circumference is a predictor of later cognitive ability.[2]

Using data from the Fels Longitudinal Study, Guo *et al.*[34] fitted a three-parameter linear model to the head circumference data for each individual. Roche *et al.*[21] presented a four-parameter non-linear model for head circumference from birth to 18 years. More recently,

Table IV. Number of measures of head circumference by karyotype

Karyotype	Individuals	Total number of measures
XY	83	2522
XX	60	1781
XYY	10	261
XXY	11	306
XXX	10	285

Ratcliffe *et al.*[2] studied the effect of karyotype on head circumference in the Edinburgh Longitudinal Study. Extended splines were used to fit data for each individual and the estimates were used to calculate means and standard deviations for several age groups of controls and chromosomally abnormal children. In the next section we describe the fitting of our extended spline models to these head circumference data using karyotype as a covariate.

4.1. Data

The subjects are 31 children with sex chromosome abnormalities (10 XYY, 11 XXY and 10 XXX) and 143 controls (83 XY and 60 XX), who had been identified by cytogenetic screening of consecutive liveborn infants between 1967 and 1979. Chromosomally normal male and female infants were recruited as controls between 1972 and 1976 from the two hospitals in which the cytogenetic survey was being carried out.[22]

Twins and low birth weight children were not included in this study. Details can be found in Ratcliffe *et al.*[2] Table IV shows the number of measurements.

As with height we first fitted each individual separately using ordinary least squares. For males, the average residual standard deviation is 0·21 cm with the range from 0·10 cm to 0·39 cm. For females, the average residual standard deviation is 0·24 cm with the range from 0·12 cm to 0·44 cm. This amount of residual variation is close to that reported by Roche *et al.*[21] and generally considered acceptable.

4.2. Random coefficient models

We fitted model (4) to the data together with four dummy variables for the karyotypes XX, XYY, XXY and XXX, with the normal male karyotype XY, as the base category. Thus in this model we jointly fit males and females. We shall allow just an overall difference between the karyotypes.

Table V shows the results from the basic two-level model (4) with the four karyotype dummy variables. We see that normal females are smaller by 0·94 cm, the mean head circumference of the XXX group is smaller than that of normal males by 2·22 cm and the mean for XXY is smaller than that of normal males by 1·32 cm.

We have also fitted models including interactions between some of the age terms and karyotype. These results are summarized in Table VI in terms of fixed part differences, and Figure 10 shows these graphically.

Table V. Model (4) of head circumference with covariate of karyotype

Fixed coefficient

	Estimate	SE
Intercept	39·95	0·26
t	– 0·20	0·04
t^2	0·008	0·002
$\ln(12t+1)$	3·31	0·10
$(2-t)^3_+$	– 0·54	0·03
$(t-10)^3_+$	0·003	0·001
XX–XY	– 0·94	0·17
XYY–XY	– 0·43	0·34
XXY–XY	– 1·32	0·33
XXX–XY	– 2·22	0·34

Level 2 covariance matrix (correlations in brackets)

	Intercept	t	t^2	$\ln(12t+1)$	$(2-t)^3_+$	$(t-10)^3_+$
Intercept	7·87					
t	1·07 (0·80)	0·23				
t^2	– 0·04 (– 0·73)	– 0·01 (– 0·97)	0·0004			
$\ln(12t+1)$	– 2·87 (– 0·89)	– 0·51 (– 0·93)	0·02 (0·84)	1·32		
$(2-t)^3_+$	– 0·90 (– 0·93)	– 0·13 (– 0·80)	0·01 (072)	0·36 (0·90)	0·12	
$(t-10)^3_+$	0·01 (0·45)	0·002 (0·61)	– 0·0001 (– 0·73)	– 0·005 (– 0·47)	– 0·001 (– 0·44)	0·00007

Level 1 variance = 0·07 (0·02)
Number of subjects = 174
Number of measurements = 5178

Table VI. Mean parameters (SE) and the karyotype (dummy varible) effects

Parameter	XY	XX–XY	XYY–XY	XXY–XY	XXX–XY
Intercept	39·83 (0·34)	– 0·62 (0·53)	– 2·27 (1·08)	– 1·33 (1·01)	– 0·39 (1·07)
t	– 0·25 (0·06)	0·11 (0·09)	– 0·16 (0·18)	0·02 (0·17)	0·38 (0·17)
t^2	0·01 (0·002)	– 0·002 (0·004)	0·002 (0·008)	0·02 (0·007)	– 0·12 (0·01)
$\ln(12t+1)$	3·42 (0·14)	– 0·27 (0·21)	0·75 (0·43)	– 0·10 (0·40)	– 0·95 (0·43)
$(2-t)^3_+$	– 0·53 (0·04)	– 0·03 (0·06)	0·24 (0·13)	0·01 (0·12)	– 0·21 (0·13)
$(t-10)^3_+$	0·005 (0·001)	– 0·005 (0·002)	0·001 (0·003)	– 0·001 (0·003)	0·003 (0·003)

5. DISCUSSION

Multi-level linear models with extended spline terms provide a flexible tool for fitting growth data. The use of ‘ + ’ functions and fractional polynomials allows for the local smoothing of data, including an upper asymptote, as well as the ability to model random coefficients across individuals. In addition, covariates are easily introduced as are further levels of nesting, for example by area.

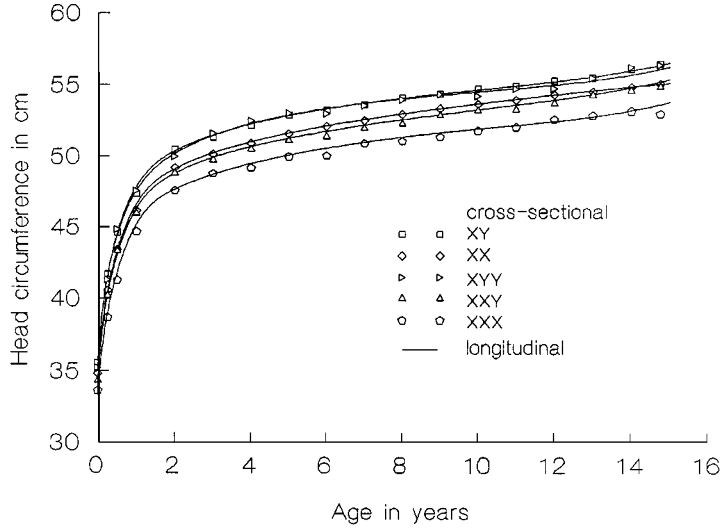

Figure 10. Estimated mean curves of head circumference by karyotype (line) with the cross-sectional means (points)

Although we have used long-term complete longitudinal data sets for purposes of comparison with existing methods, this is not necessary. Using a multi-level model we can utilize any mixed longitudinal data set, including purely cross-sectional data, so long as there are adequate numbers of measurements spanning the occasions of interest in the model. By comparing our results with those from other methods it seems that there is no particular advantage in the use of non-linear models, especially as these tend to require long-term data.

The important work of Royston and Altman[20] on fractional polynomials provides a valuable contribution to modelling growth data and these models are useful for some kinds of data. In general, however, the combination of fractional polynomials with spline functions allows greater flexibility. The computational burden of finding suitable fractional powers is often heavy and it would be useful to see whether the use of splines in additional to fractional polynomials provided a good alternative for the data analysed by Royston and Altman.

An alternative to the ' + ' function is to use constraints to combine segments smoothly at the joins.[11,14,35] Goldstein and Pan[36] illustrate the use of constraints in a two-level model. Unfortunately, it appears difficult in general to make the iterative algorithm converge when three or more segments are included or when covariates other than age are considered because of the need for smooth constraints at joints both for the fixed and the random parts of the model.

Similar problems may occur when the model of Reed and Berkey[14] is incorporated into a multi-level model. The Reed and Berkey model is composed of two fractional polynomials, for the pre-pubertal stage and the pubertal stage. In principle it can be estimated by a multi-level model with smoothness constraints. We need at least five constraints, three for the fixed part and two for the random part, and this leads to computational difficulties. In contrast, the constraints are implicit in the use of ' + ' functions so that these estimation problems do not arise.

The presence of end or edge effects is common in curve fitting and smoothing techniques.[30] This problem has been observed in our data and we would suggest including measurements up to 20 years, if possible, to obtain better results.

We have focused on human growth in length and head circumference not only because of their inherent interest but also because of their growth regularity. Not all measurements have an approximately Normal distribution,[37] however, and it may be necessary to transform data to approximate Normality. The procedure of Cole and Green[30] based upon smoothed Box–Cox transformations may be useful for this purpose.

We feel that it is reasonable to assume uncorrelated level 1 residuals in our model. Most of the data used in this study were collected at about 6 month intervals. A runs test on residuals, for each individual, was significant in 6 of 89 boys and 5 of 67 girls in height; in head circumference it was significant in 10 of 83 boys and 7 of 60 girls. We can explicitly extend our multi-level models to incorporate a time series structure on the level 1 residuals using the methods of Goldstein *et al.*[38] They point out that if measurements are taken close enough together then their deviations from the fitted smooth curve are bound to be correlated. For height measurements on children prior to adolescence the point at which this 'autocorrelation' becomes apparent is for measurements made about 3 months apart in the immediate pre-adolescent years.

We have chosen the precise form of model to fit, including join points, after preliminary data manipulation and modelling. Our analysis has an important exploratory component and we would hope that further replications of our procedures can be carried out.

Finally, all the methods of this paper can be extended readily to the multivariate case where several measurements are analysed jointly so that their interrelationships across time can be studied.

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REFERENCES

1. Guo, S., Siervogel, R. M., Roche, A. F. and Chumlea, W. M. C. 'Mathematical modelling of human growth: a comparative study', *American Journal of Human Biology*, **4**, 93–104 (1992).
2. Ratcliffe, S. G., Masera, N., Pan, H. and McKie, M. 'Head circumference and IQ of children with sex chromosome abnormalities', *Developmental Medicine and Child Neurology*, **36**, 533–544 (1994).
3. Goldstein, H. *Multilevel Statistical Models*, Arnold; London, and Wiley, New York, 1995.
4. Bryk, A. S. and Raudenbush, S. W. 'Application of hierarchical linear models to assessing change', *Psychological Bulletin*, **101**, 147–158 (1987).
5. Longford, N. T. 'A fast scoring algorithm for maximum likelihood estimation in unbalanced mixed models with nested random effects', *Biometrika*, **74**, 817–827 (1987).
6. Jolicoeur, P., Pontier, J. and Abidi, H. 'Asymptotic models for the longitudinal growth of human stature', *American Journal of Human Biology*, **4**, 461–468 (1992).
7. Berkey, C. and Laird, N. M. 'Nonlinear growth curve analysis: estimating the population parameters', *Annals of Human Biology*, **13**, 111–128 (1986).
8. Bock, R. D., Toit, S. H. C. and Thissen, D. *AUXAL*: *Auxological Analysis of Longitudinal Measurements of Human Stature*, Scientific Software International, Chicago, 1994.
9. Goldstein, H. 'Multilevel mixed linear model analysis using iterative generalised least squares', *Biometrika*, **73**, 43–56 (1986).
10. Healy, M. J. R. 'Growth curves and growth standards-the state of the art', *in* Tanner, J. M. (ed.), *Auxology* 88. *Perspectives in the Science of Growth and Development*, Smith-Gordon, London, 1989, pp. 13–21.
11. Seber, G. A. F. and Wild, C. J. *Nonlinear Regression*, Wiley, New York, 1989, pp. 433–459.
12. Goldstein, H. *The Design and Analysis of Longitudinal Studies*, Academic Press, London, 1979.

13. Berkey, C. S. 'Bayesian approach for a nonlinear growth model', *Biometrics*, **38**, 953–961 (1982).
14. Reed, R. B. and Berkey, C. S. 'Linear statistical model for growth in stature from birth to maturity', *American Journal of Human Biology*, **1**, 257–262 (1989).
15. Wold, S. 'Spline functions in data analysis', *Technometrics*, **16**, 1–11 (1974).
16. Wegman, E. J. and Wright, I. W. 'Splines in statistics', *Journal of the American Statisticl Association*, **78**, 351–365 (1983).
17. Smith, P. L. 'Splines as a useful and convenient statistical tool', *American Statistician*, **33**, 57–62 (1979).
18. Berkey, C. S., Reed, R. B. and Valadian, I. 'Midgrowth spurt in height of Boston children', *Annals of Human Biology*, **10**, 25–30 (1983).
19. Gallant, A. R. and Fuller, W. A. 'Fitting segmented polynomial regression model whose join points have to be estimated', *Journal of the American Statistical Association*, **68**, 144–147 (1973).
20. Royston, P. and Altman, D. G. 'Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling (with discussion)', *Applied Statistics*, **43**, 429–467 (1994).
21. Roche, A. F., Mukherjee, D. and Guo, S. 'Head circumference growth patterns: birth to 18 years', *Human Biology*, **58**, 893–906 (1986).
22. Ratcliffe, S. G. and Paul, N. *Prospective studies in children with sex chromosome aneuploidy*, Alan, R. Liss, New York, 1986.
23. Bock, R. D., Wainer, H., Peterson, A., Thissen, D., Murray, J. and Roche, A. 'A parameterisation for individual human growth curves', *Human Biology*, **45**, 63–80 (1973).
24. Tanner, J. M., Whitehouse, R. H., Marubini, E. and Resele, L. F. 'The adolescent growth spurt of boys and girls of the Harpenden Growth Study', *Annals of Human Biology*, **3**, 109–126 (1976).
25. Goldstein, H. 'Models for multilevel response variables with an application to growth curves', *in* Bock, D. (ed.), *Multilevel Analysis of Educational Data*, Academic Press, New York, 1989, pp. 108–125.
26. Ratcliffe, S. G., Pan, H. and McKie, M. 'Growth during puberty in XYY boy', *Annals of Human Biology*, **19**, 579–587 (1992).
27. Gasser, T., Kohler, W., Muller, H-G., Kneip, A., Largo, R., Molinari, L. and Prader, A. 'Velocity and acceleration of height growth using kernel estimation', *Annals of Human Biology*, **11**, 397–411 (1984).
28. Gasser, T., Kneip, A., Ziegler, P., Largo, R. and Prader, A. 'A method for determining the dynamics and intensity of average growth', *Annals of Human Biology*, **17**, 459–474 (1990).
29. Ratcliffe, S. G., Pan, H. and McKie, M. 'The growth of XXX females: population-based studies', *Annals of Human Biology*, **21**, 57–66 (1994).
30. Cole, T. J. and Green, P. J. 'Smoothing reference centile curves: the LMS method and penalized likelihood', *Statistics in Medicine*, **11**, 1305–1319 (1992).
31. Bock, R. D., Toit, S. H. C. and Thissen, D. *AUXAL*: *Auxological Analysis of Longitudinal Measurements of Human Stature*, Scientific Software International, Chicago, 1994.
32. Bock, R. D. and Thissen, D. 'Fitting multicomponent models for growth in stature', Proceedings of the 9th International Biometrics Conference (Boston), **1**, 431–442 (1976).
33. Tanner, J. M., Whitehouse, R. H. and Takaishi, M. 'Standard from birth to maturity for height, weight, height velocity, and weight velocity: British Children, 1965, Part I and II', *Archives of Disease in Childhood*, **41**, 454–471, 613–635 (1966).
34. Guo, S., Roche, A. F. and Moore, W. M. 'Reference data for head circumference and 1-month increments from 1 to 12 months of age', *Journal of Pediatrics*, **113**, 490–494 (1988).
35. Cox, M. G. 'Curve fitting with piecewise polynomials', *Journal of the Institute of Mathematics and its Applications*, **8**, 36–52 (1971).
36. Goldstein, H. and Pan, H. 'Percentile smoothing using piecewise polynomials with covariates', *Biometrics*, **48**, 1057–1068 (1992).
37. Healy, M. J. R., Rasbash, J. and Yang, M. 'Distribution-free estimation of age-related centiles', *Annals of Human Biology*, **15**, 17–22 (1988).
38. Goldstein, H., Healy, M. J. R. and Rasbash, J. 'Multilevel time series models with applications to repeated measures data', *Statistics in Medicine*, **13**, 1643–1655 (1994).