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NONPARAMETRIC REGRESSION ANALYSIS OF GROWTH CURVES[1]

By Theo Gasser, Hans-Georg Müller, Walter Köhler, Luciano Molinari and Andrea Prader

Zentralinstitut für Seelische Gesundheit, Universität Heidelberg, Universität Heidelberg, Universität Zürich and Universität Zürich

In recent years, nonparametric curve estimates have been extensively explored in theoretical work. There has, however, been a certain lack of convincing applications, in particular involving comparisons with parametric techniques. The present investigation deals with the analysis of human height growth, where longitudinal measurements were collected for a sample of boys and a sample of girls. Evidence is presented that kernel estimates of acceleration and velocity of height, and of height itself, might offer advantages over a parametric fitting via functional models recently introduced. For the specific problem considered, both approaches are biased, but the parametric one shows qualitative and quantitative distortion which both are not easily predictable. Data-analytic problems involved with kernel estimation concern the choice of kernels, the choice of the smoothing parameter, and also whether the smoothing parameter should be chosen uniformly for all subjects or individually.

1. Introduction. How somatic growth proceeds during childhood and adolescence, and whether it stays within normal limits, is of interest to pediatricians, the clothing industry, and many others. Cross-culturally, growth standards are an indicator of the adequacy of the provision of food, medical services etc. Most needs arising can be answered by collecting and analyzing cross-sectional data. However, dynamic features of growth, as e.g. the adolescent spurt occurring in various parts of the body and in height itself, can only be investigated via longitudinal measurements (the many facets of human growth are treated in detail in Falkner and Tanner, 1978). An understanding of the dynamics of normal growth has practical implications in the diagnosis and treatment of disorders of growth (Prader, 1978) and is of interest for understanding the basic mechanisms of growth, as a phenomenological correlate of endocrinological regulation (Sizonenko, 1978).

Fortunately, some human biologists and pediatricians planned and began several ambitious longitudinal studies of growth and development in 1954/1955 (Falkner, 1960), internationally coordinated by the International Children's Centre in Paris. The longitudinal study of growth and development, initiated at the pediatric clinic of the University of Zürich, on which our analysis of height

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growth is based, benefitted from favourable geographic and social circumstances and, due to this, it is rather complete and in good shape.

The analysis of growth curves is a classical theme in statistics (Wishart, 1938; Potthoff and Roy, 1964; Rao, 1965; Grizzle and Allen, 1969; Ghosh, Grizzle and Sen, 1973; Reinsel, 1982) where emphasis has been on using polynomial fitting and MANOVA techniques. This approach was, however, pursued only in the statistical literature and not in the field of application (for reasons outlined in Marubini, 1978). There, nonlinear regression was, with few exceptions, the method of choice for determining a small number of parameters per individual growth curve. The functional models used were descriptive rather than interpretative and were compared via goodness-of-fit criteria (Marubini et al., 1971, Preece and Baines, 1978). The by-now classical parametric models account for only part of the growth process (H = height, t = age): the Count model (Count, 1943) $H(t) = (a + bt) + c \log t$ and the Jenss model (Jenss and Bayley, 1937) $H(t) = (a + bt) - \exp(c - dt)$ both for the first few years and the logistic $H(t) = a + b/(1 + \exp(-c(t - d)))$ or the Gompertz function $H(t) = a + b \exp(-\exp(-c(t - d)))$ for the pubertal growth spurt (compared by Marubini et al., 1971, and Berkey, 1982). A verbal association of such a local fitting with a "growth cycle" cannot hide the fact that methodological problems and not biological reasoning are at the back of this local approach; problems, anyhow, arise when pasting together the local fits. An attempt at a global fitting was made by Bock et al. (1973) by adding two logistic functions ("double logistic model") for modeling height growth from birth to adulthood. It rendered a high residual mean square error and average parameters which disagreed substantially with previous findings. These discrepancies can be attributed to a serious bias of the double logistic model, since it proved to be much inferior to 5- and 6-parameter models suggested by Preece and Baines (1978):

model 1 PB: $$H(t) = a - \frac{2(a - H(b))}{\exp(c(t - b)) + \exp(d(t - b))}$$

model 3 PB:

$$H(t) = a - \frac{4(a - H(b))}{(\exp(c(t - b)) + \exp(d(t - b)))\,(1 + \exp(e(t - b)))}.$$

The above models are the best fixed models proposed so far for a global fitting of human height growth, which makes them fair candidates for a comparison with the nonparametric estimates introduced later on. (Let us note that self-modeling nonlinear regression (Stützle et al., 1980) is a promising approach from the statistical side and for human biology: the model estimated proved to be the same for boys and girls, and interesting features as e.g. a small pre-adolescent spurt in the velocity curve at about age 7 ("mid-growth spurt") could be identified).

A smoothing technique by eye applied to empirical difference quotients of height observed was used by Tanner et al. (1966a, b). In Largo et al. (1978), smoothing difference quotients of height by cubic splines was proposed in order to estimate velocity of height nonparametrically; following Wahba and Wold (1975), cross-validation was used to estimate individually the degree of smoothing. In the present investigation, a nonparametric estimate based on kernels (Gasser and Müller, 1979a, b) is introduced for estimating velocity and acceleration of height directly from height measured. Nonparametric curve estimates are known to have asymptotic efficiency zero compared to parametric techniques based on the true model. Evidence will be presented that there may be compelling reasons for the use of nonparametric curve estimates in order to promote our understanding of the dynamics of growth.

2. Some biomedical aspects. The most prominent feature of human growth is the pubertal spurt (PS), rising with the advent of puberty. The velocity of the PS peaks on the average at approximately 12 years for girls and 14 years for boys (compare Figures 2–5 of Section 7). Puberty does not only initiate a growth spurt (associated with a higher rate of proliferation of cells at the epiphyses) but it also essentially stops growth (with a certain time lag) due to an ossification of the epiphyses of the long bones. It is of interest to quantify onset, age of peaking, intensity, and duration of the spurt and also to study sex differences in these parameters. A substantial number of papers contribute to our understanding of the PS (Tanner et al., 1966; Tanner et al., 1976; Largo et al., 1978; to mention a few). A consistent result is that boys have a more intense and a later PS. The difference in intensity is tentatively ascribed to the higher concentration of androgenes in the puberty of boys than of girls. Further questions which arise are: Does the intensity or duration of the PS influence adult height? Or is it compensating for the height reached at the onset of the PS? Somewhat puzzlingly, the PS did not relate at all to adult height in previous research, and the importance of a compensating mechanism remained somewhat dubious. These, and other problems, made us look for different statistical approaches.

For most children, there is a small but distinct velocity peak at about age 7 (Figures 2–5), the so-called mid-growth spurt (MS), which has an interesting history: some older studies reported on the MS (Backman, 1934; Count, 1943; Grubb, 1942) based on the development of some extreme subjects. Interestingly enough, the MS—not being part of the parametric models—disappeared from the literature when statistics and computing came into common use in growth studies. Recently, it was identified as part of the model via self-modeling nonlinear regression for height (Stützle et al., 1980) and the existence of the MS was formally confirmed for a number of somatic quantities (Molinari, et al., 1980). A quantification of timing, intensity and duration of the MS was, however, still lacking; nothing was, therefore, known about sex differences and about relationships between the MS and the PS. The quantification of this often small phenomenon—almost drowned in the noise—was a further goal of our investigation.

Whereas height is measured, parameters and graphs in terms of velocity of height have attracted more interest. Accelerations have not been estimated so far in growth studies, but they might lead to additional information regarding the PS and there is hope that the MS is easier to quantify from accelerations. Estimating derivatives will, of course, blow up the noise, and a further difficulty is that no residuals can be defined.

Parameters defined in terms of maxima and minima of velocity have traditionally been used, sometimes called "biological" parameters to distinguish them from the model parameters, but "longitudinal" parameters is suggested as a neutral alternative. The longitudinal parameters of greatest interest so far were the age of minimal velocity before the PS, $T6$ ("onset of the PS"), and of maximal velocity during the PS, $T8$ ("timing of the PS"), and the height (H) and velocity (V) at these ages. Longitudinal parameters have the advantage of having a uniform interpretation across subjects and of offering some intuitive insight. Accelerations lead to additional longitudinal timings (e.g. the ages of maximal and minimal acceleration during the PS).

3. Subjects, design, and computing. Out of 412 children included in a prospective longitudinal study in 1955 at the Kinderspital Zürich, a random sample of 45 boys and 45 girls was selected for data analysis according to the following criteria: measurements had to be complete up to 3 years, and later no 2 consecutive and not more than 3 observations should be missing. Children suffering from a disease which hampers growth or who were treated with hormones known to affect growth were excluded. Height was measured as described in Falkner (1960), using gentle upward pressure under the mastoid process (and this by the same trained anthropometrist after the age of 8 years). Children were measured at 4, 13, 26, and 39 weeks, at 1 and 1½ years and afterwards yearly at birthday ± 14 days. From 9 onwards for girls (10 for boys), measurements were done at intervals of 6 months until the annual increment was less than .5 cm/year. Thereafter, measurements were continued at yearly intervals until the increment was less than .5 cm in 2 years. Missing observations were completed using an iterative procedure which assured that the filled-in pseudo observation had approximately zero residual (as described in Largo et al., 1978), resulting in a data vector of length $T = 34$. While there is no need for this procedure for the present investigation, it was considered more practical to use the same data base as previously.

Computations were done on the IBM 370/168 at the Computer Center of the University of Heidelberg. Software for kernel estimation, parameterization, and graphical analysis was developed, fitting of model 3 by Preece and Baines (1978) is based on an algorithm by Deuflhard and Apostolescu (1980). When for some curves an absolute minimum was reached which was not reasonable in terms of parameters, a marginally suboptimal minimum with more reasonable parameters was chosen as a solution. For the further statistical analysis of the individual parameters, the program package SAS was primarily used, and in a few instances BMDP.

Age (T) is given in years, velocity (V) in cm/y, and acceleration (A) in cm/y^2.

4. Kernel estimates. The basic model postulated is the following:

$$H_i^*(t_j) = H_i(t_j) + \varepsilon_{ij} \quad i = 1, \ldots, n, \qquad j = 1, \ldots, T \tag{1}$$

where:

$$H_i^*(t_j) = \text{height measured of individual } i \text{ at age } t_j.$$
$$H_i(t_j) = \text{true height}$$
$$\varepsilon_{ij} = \text{random variation, i.i.d. } \forall i, j,$$
$$E(\varepsilon_{ij}) = 0,\ E(\varepsilon_{ij}^2) = \sigma_i^2 < \infty.$$

The random term comprises measurement error, seasonal and diurnal variation, and might also be influenced by illness and adverse psychological conditions. Replicating measurements yielded a standard deviation of .18 cm for the measurement error (Whitehouse et al., 1974); local polynomial regression as well as cross-validation lead to a residual standard deviation of .5 cm from 2–8 years and of .3 cm from 15–18 years. This intuitively plausible time trend in the residual variance is neglected in the present model. Parametric estimation starts by postulating a functional class $H_i(t) = F(t, \underset{\sim}{\alpha}_i)$ ($\underset{\sim}{\alpha}_i$ = vector of individual parameter) and, for this crucial step, statisticians tend to rely on human biologists, and vice versa, introducing some circularity in the scientific process. Unfortunately, goodness-of-fit criteria do not necessarily lead to a wise choice among functional models, as will be shown in Section 7. Regression analysis has grown out of applications in engineering and physics (Draper and Smith, 1981; Daniel and Wood, 1980), where in contrast to biomedicine only one curve has usually to be fitted, and where the state of science gives firmer ground for model building.

A priori, it is not even clear whether all subjects develop in a homogeneous manner so that they can be fitted by the same class of functions. Such an assumption is not necessary when using nonparametric techniques, which might, therefore, also be used for identifying subgroups qualitatively different in development. The estimate proposed for the νth derivative of $H(t)$ is:

$$\hat{H}_\nu(t) = \frac{1}{b(T)^{\nu+1}} \sum_{j=1}^{T} H^*(t_j) \int_{s_{j-1}}^{s_j} W_\nu\left(\frac{t-u}{b(T)}\right) du. \tag{2}$$

Here, $\{s_j\}$ is any interpolating sequence $t_j \le s_j \le t_{j+1}$ (our choice was $s_j = (t_j + t_{j+1})/2)$) and $b(T)$ is the bandwidth or smoothing parameter. The kernel W_ν for estimating the νth derivative is called a kernel of order (ν, k) when it satisfies the following moment conditions:

$$\int_{-\tau}^{\tau} W_\nu(x) x^j dx = \begin{cases} 0 & j = 0, \ldots, \nu-1, \nu+1, \ldots, k-1 \\ (-1)^\nu \nu! & j = \nu \\ \beta \neq 0 & j = k \end{cases} \tag{3}$$

support $W_\nu = [-\tau, \tau]$ for some $\tau > 0$, W_ν Lipschitz continuous on $[-\tau, \tau]$. The most important underlying assumption is that $H(t)$ satisfies some smoothness conditions: given that H is k-times continuously differentiable ($k \ge \nu + 2$), the bias of $\hat{H}_\nu$ is of the form:

$$\frac{1}{k!} b(T)^{(k-\nu)} H^{(k)}(t) \int_{-\tau}^{\tau} W_\nu(x) x^k dx + o(b(T)^{(k-\nu)}). \tag{4}$$

The asymptotics assume $b(T) \to 0$, $T\,b(T)^{2\nu+1} \to \infty$ as $T \to \infty$. The variance is:

$$\frac{\sigma^2}{T\,b(T)^{2\nu+1}} \int_{-\tau}^{\tau} W_\nu(x)^2 dx + o\left(\frac{1}{T\,b(T)^{2\nu+1}}\right). \tag{5}$$

For data-analytic needs and in order to obtain the global rate of convergence $O(T^{-2(k-\nu)/(2k+1)})$ of the asymptotically optimal integrated mean square error (IMSE) and also the analytic form of the IMSE, "boundary kernels" with asymmetric support were introduced for estimating at the extremities of the data (i.e. for $t \in [t_1, t_1 + b)$, $t \in (t_T - b, t_T]$). The expression obtained for the IMSE (7) and for the asymptotic variance (5) allow then the definition of the classes of "optimal" and of "minimum variance" kernels, obtained by minimizing the respective functionals. Figure 1 shows optimal kernels for estimating derivatives $\nu = 0, 1, 2$ used in Section 6. Due to the nonequidistance of the design, the finite sample variance of $\hat{H}_\nu(t)$ will vary with t, and, as a consequence, minima and maxima and other properties of the estimated curve would have to be judged with a varying degree of subjective confidence. To avoid this effect, an algorithm has been constructed (see Section 6) to stabilize the variance finitely.

Details and derivations of these results, as well as results regarding weak and strong consistency and asymptotic normality, may be found in Gasser and Müller (1979a, b). A different kernel estimate (for $\nu = 0$) for fixed design regression had been proposed in Priestley and Chao (1972), and has been further investigated by Benedetti (1977) and by Schuster and Yakowitz (1979); an estimate for $\nu = 0$ closely related to ours has been studied by Cheng and Lin (1981). For a bibliog-

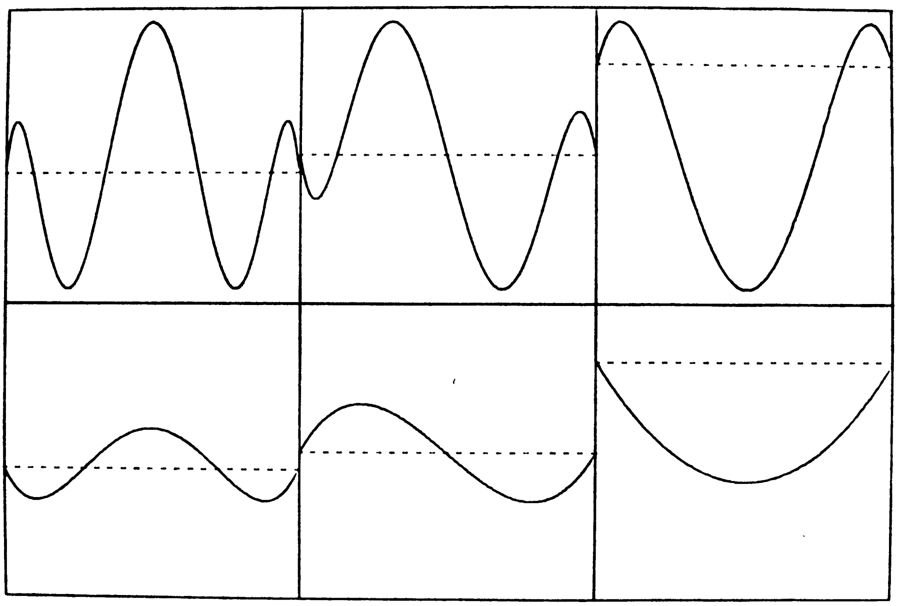

FIG. 1. *Optimal kernels for estimating a regression function and its derivatives of order $\nu = 1, 2$ (from left to right); below kernels of order $k = \nu + 4$, above $k = \nu + 2$. Minimum-maximum scale for kernels of order $(\nu + 4)$, kernels of order $(\nu + 2)$, scaled accordingly.*

raphy, the reader may consult Collomb (1981). Problems arising when estimating at the extremities of the data have recently been studied by Hall (1981) and by Rice and Rosenblatt (1981, 1983).

Smoothing splines, well supported by generally available software, have gained popularity among practitioners; their performance will therefore be compared with that of kernel estimates. The cubic smoothing spline $\hat{H}_s(t)$ for the measurements $H^*(t_j)(j = 1, \ldots, T)$ is the solution to the following minimization problem (λ plays a role similar to b for kernel estimates):

$$(6) \qquad \frac{1}{T} \sum_{j=1}^{T} (H^*(t_j) - \hat{H}_s(t_j))^2 + \lambda \int \hat{H}_s^{(2)}(t)^2 \, dt = \min.$$

Smoothing splines have their roots in numerics (Schoenberg, 1964; Reinsch, 1967); their statistical properties have been investigated by Wahba (1975) and by Rice and Rosenblatt (1981). The minimization problem arising makes the derivation of statistical properties more tedious (compared to (2)), and is also a factor in computer time.

5. Considerations for the choice of the smoothing parameter. Practical experience and asymptotic theory indicate that the choice of the smoothing parameter is crucial when estimating $H^{(\nu)}(t)$. In principle, one might suspect that qualitatively different empirical conclusions can be reached when arbitrarily varying the degree of smoothing; in our experience, conclusions remain stable within a reasonably wide range of b. In the present data analysis, the sample of children represents some sort of replication; features which are reproducible across the sample or a subsample merit interpretation.

In the smoothing case ($\nu = 0$), cross-validation has been suggested for determining a good smoothing parameter w.r. to IMSE (Craven and Wahba, 1979; Rice, 1982), instead of a visual adjustment. Due to the lack of residuals, neither a one-hold-out technique nor a visual analysis are feasible when estimating derivatives. We have, however, fundamental objections against using any individually optimized smoothing parameter when dealing with a sample of regression functions. They will be substantiated by an argument based on asymptotics; the leading term of the IMSE for child i is of the following form:

$$(7) \qquad \begin{aligned} \mathrm{IMSE}(H_i, \sigma_i^2, b) &= \frac{\sigma_i^2}{T\, b(T)^{2\nu+1}} \int W_\nu(x)^2 \, dx \\ &\quad + \frac{1}{k!^2} b(T)^{2(k-\nu)} \left(\int W_\nu(x) x^k \, dx \right)^2 \int H_i^{(k)}(t)^2 \, dt \end{aligned}$$

which yields as the individually optimal bandwidth (if $\int H_i^{(k)}(t)^2 \, dt \neq 0$)

$$(8) \qquad b_{i,\mathrm{opt}} = \left[\frac{2\nu + 1}{2(k - \nu)} \cdot \frac{k!^2 \sigma_i^2 \int W_\nu(x)^2 \, dx}{\left(\int W_\nu(x) x^k dx \right)^2 \int H_i^{(k)}(t)^2 \, dt} \cdot \frac{1}{T} \right]^{1/(2k+1)}$$

It is easy to see that the integrated squared bias is up to a factor $2(k-\nu)/(2\nu+1)$ equal to the integrated variance when using $b_{i,\mathrm{opt}}$:

$$\int \mathrm{Var}_i(t)\,dt = \frac{2(k-\nu)}{2\nu+1}\int \mathrm{Bias}_i(t)^2\,dt$$

$$(9)\qquad = n^{-(2(k-\nu)/(2k+1))} \cdot \left[c(k,\nu)\left(\sigma_i^2 \int W_\nu(x)^2\,dx\right)^{2(k-\nu)/(2k+1)} \cdot \left(\int H_i^{(k)}(t)^2\,dt\left(\int W_\nu(x)x^k\,dx\right)^2\right)^{(2\nu+1)/(2k+1)} + o(1)\right].$$

As a consequence, the individual variance of the estimate does not depend on the residual variance σ_i^2 only (as in (5)), but also on the kth derivative of the growth curve (compare (4)), and the same holds for the bias. This confounding of residual variance and bias may have somewhat absurd consequences in an interindividual analysis: a sample of identical true curves with unequal residual variances is by (8) treated with unequal individual bandwidths. The curves estimated will then also show a systematic interindividual variation due to differences in the bias (another example would be a sample where $\int H_i^{(k)}(t)^2\,dt$ is negatively correlated with σ_i^2). These objections against an individually optimized choice of bandwidth do not relieve us of the necessity of choosing a bandwidth (separately for $\nu = 0, 1, 2$) for the group of children in some rational way.

6. A finite sample evaluation for the choice of kernels and bandwidths and a comparison with splines. The kernel is a free quantity in the definition of the estimate. For derivatives there is no published material regarding the merits of different kernels; for $\nu = 0$ it has repeatedly been argued (compare e.g. Rosenblatt, 1971) that the choice of a suboptimal kernel incurs a small loss in asymptotic IMSE. Since this statement applied to positive and symmetric kernels (of order $k = 2$ in our notation), it is an open problem whether higher order kernels which asymptotically achieve a better rate of convergence are also superior for a realistic sample size. To answer such questions, simulation has traditionally been the method of choice, postulating some functional model and a residual distribution. For the nonparametric regression estimates considered here, exact finite sample results with respect to bias, variance and mean squared error can be obtained by just one replication (i.e. at low cost) as follows:

(i) a regression function $H(t)$ and a residual variance σ^2 have to be postulated as well as a measurement design $\{t_1, \ldots, t_T\}$ and an estimation design $\{\tau_1, \ldots, \tau_N\}$.

(ii) for some kernel W_ν and some bandwidth b the bias at τ_k is obtained by applying the estimate (2) to $H(t)$ yielding $\tilde{H}^{(\nu)}(t)$ and bias $(\tau_k) = \tilde{H}^{(\nu)}(\tau_k) - H^{(\nu)}(\tau_k)$; by summation of bias squared, one obtains an approximation of the integrated squared bias.

(iii) the variance at τ_k is obtained by multiplying the sum of squared weights by the residual variance:

$$\operatorname{Var}(\hat{H}_\nu(\tau_k)) = \sigma^2 \sum_{j=1}^{T} \left(\frac{1}{b(T)^{\nu+1}} \int_{s_{j-1}}^{s_j} W_\nu\left(\frac{\tau_k - u}{b(T)}\right) du \right)^2$$

(iv) for any kernel W_ν, the finite sample IMSE(b) can then easily be computed as a function of bandwidth; we computed the IMSE(b) at 20 bandwidths around its minimum and determined then the abscissa of the minimum more exactly by doing spline interpolation at 100 abscissae ($= b_{\text{opt}}$).

(v) This b_{opt} was then entered again into (ii) and (iii) to allow for a fair comparison between kernels and also with cubic smoothing splines with respect to integrated mean squared error, bias squared and variance (the same procedure can be applied to splines since they are linear smoothers; this was done separately for $\nu = 0, 1, 2$ using the derivative of the smoothing spline).

To stay close to the real problem, the published average growth model 3 for boys of Preece and Baines (1978) has served as the regression function $H(t)$; residual variances were $\sigma^2 = .4$, .3, and .2 cm^2. The measurement design assumed is the one given in Section 3 ($T = 34$) and the estimation design was chosen equidistant

TABLE 1

Evaluation (for $\nu = 0$) of splines, optimal kernels of minimal order and minimal order +2, and variance stabilization ("stab") for modeling average development of a boy according to Preece and Baines (1978) (results at empirically optimal smoothing parameter)

	$\sigma^2 = .4$			$\sigma^2 = .3$			$\sigma^2 = .2$		
	Bias^2	**Var.**	**IMSE**	**Bias^2**	**Var.**	**IMSE**	**Bias^2**	**Var.**	**IMSE**
Spline	4.8	16.9	21.7	3.9	13.4	17.4	3.1	9.6	12.7
***k* = 2 (stab)**	4.2	19.2	23.4	4.2	14.4	18.6	4.2	9.6	13.8
***k* = 2 (no)**	6.5	19.1	25.6	5.8	14.9	20.7	2.4	12.7	15.5
***k* = 4 (stab)**	0.6	19.4	20.0	0.6	14.4	15.0	0.6	9.5	10.1

TABLE 2

Same as Table 1, $\nu = 1$.

	$\sigma^2 = .4$			$\sigma^2 = .3$			$\sigma^2 = .2$		
	Bias^2	**Var.**	**IMSE**	**Bias^2**	**Var.**	**IMSE**	**Bias^2**	**Var.**	**IMSE**
Spline	8.9	13.6	22.5	7.3	11.6	18.9	5.6	9.1	14.7
***k* = 3 (stab)**	16.0	11.1	27.1	11.8	11.0	22.8	11.6	7.7	19.3
***k* = 3 (no)**	13.9	16.4	30.3	11.0	14.7	25.8	9.8	10.8	20.6
***k* = 5 (stab)**	6.8	13.5	20.3	7.1	10.2	17.3	6.0	7.5	13.4

with $N = 201$. Bias, variance, and MSE were inspected dependent on age; global results integrated from 4 to 18 years are given in Tables 1–3 (period of highest interest longitudinally). Minimum variance kernels were consistently inferior to the optimal ones and have been omitted. For $\nu = 0, 1$, and 2, variance stabilization (to be defined below) makes a profit in IMSE, kernels of minimal order $k = \nu + 2$ are definitely inferior to higher order kernels $k = \nu + 4$ and the spline is lying between kernels of order $\nu + 2$ and $\nu + 4$ (the kernel of order 2 for $\nu = 0$ is the Epanechnikov kernel, Epanechnikov, 1969; Rosenblatt, 1971). It came as a surprise to us that the higher order kernels are strikingly superior for this relatively small sample size: for $\nu = 1, 2$, the higher order kernel is for a residual variance of 0.4 cm^2 almost as good as the kernel of order $(\nu + 2)$ for a residual variance of 0.2 cm^2. Notable is also the small bias of the kernel of order (0, 4), introduced in Gasser and Müller (1979a). A decrease in residual variance leads to a relatively small decrease in bandwidth, which is followed primarily by a decrease in variance.

Splines, which are not much below higher order kernels in performance, need more computer time, in particular for $\nu = 0$ (Table 4).

The algorithm for the finite sample variance stabilization of the kernel estimate (2) is based essentially on step (iii), as defined above for the finite sample evaluation technique, and uses also the asymptotic relation (5):

(α) for some τ_i of the estimation design, say τ_1, a bandwidth b_1 has to be postulated;

(β) using (iii), the finite sample variance V_1 at τ_1 is computed with respect to b_1

TABLE 3
Same as Table 1, $\nu = 2$.

	$\sigma^2 = .4$			$\sigma^2 = .3$			$\sigma^2 = .2$		
	Bias²	**Var.**	**IMSE**	**Bias²**	**Var.**	**IMSE**	**Bias²**	**Var.**	**IMSE**
Spline	35.8	21.3	57.0	29.7	20.9	50.6	22.9	19.8	42.7
$k = 4$ (stab)	42.1	20.4	62.5	41.4	15.7	57.1	38.8	11.7	50.6
$k = 4$ (no)	45.0	21.2	66.2	41.6	18.5	60.1	39.5	14.1	53.6
$k = 6$ (stab)	26.3	24.8	51.1	26.1	18.8	44.9	22.3	15.7	37.9

TABLE 4
CPU *time (sec.) for one realization (at optimal smoothing parameter), averaged over* 20 *realizations; estimated at* 201 *abscissae.*

ν	**Kernel** $\nu + 2$	**Kernel** $\nu + 4$	**Spline**
0	.04	.10	.34
1	.08	.20	.32
2	.12	.27	.30

(γ) for τ_i, a bandwidth b_i is determined iteratively such that it yields a variance $V_i \in (V_1 \pm .05 \cdot V_1)$: starting with $b_i^{(0)} = b_{i-1}$, the variance $V_i^{(0)}$ is determined; if $V_i^{(0)}$ is not within the above limits, a new bandwidth $b_i^{(1)}$ is computed based on (5) and using $V_i^{(0)}$, the target variance V_1 and $b_i^{(0)}$ (etc).

The same algorithm can by (iii) adjust to an a priori known heteroscedasticity, and it also allows for systematic changes in the variance across the estimation design. Variance stabilization leads for $\nu = 0$ to an approximate doubling of the bandwidth for yearly measurements compared to half-yearly measurements, as to be expected; for $\nu = 1, 2$ this factor is substantially below 2 (asymptotically, the factor is 1.25 for $\nu = 1$ and 1.11 for $\nu = 2$). Variance stabilization was not applied to the extremities of the data.

After deciding in favour of variance stabilization and optimal kernels of order $(\nu + 4)$, the problem remained to find one "good" bandwidth, defined as the abscissa of the minimum of the sample mean of the individual $\text{IMSE}_i(b)$ $(i = 1, \ldots, n)$. This search relied on the finite sample evaluation technique (i)–(v), described above, and proceeded as follows:

(a) model 3 of Preece and Baines (1978) fitted to the data of subject i was used as an approximation for the individual regression function $H_i(t)$ in step (i); for all subjects a residual variance of 0.3 cm^2 was assumed.

(b) for $\nu = 0, 1, 2$ separately, and for optimal kernels of order $(\nu + 4)$ and using the variance stabilization technique, the individual finite sample integrated mean squared error $\text{IMSE}_i(b)$ was computed on a fixed equidistant grid at 10 bandwidths around the presumed optimal b.

(c) the average $\text{IMSE}(b) = 1/n \sum_{i=1}^{n} \text{IMSE}_i(b)$ was formed over all $n = 90$ subjects and this sample criterion was minimized after spline interpolation at 100 points to yield b_{opt}, used then in the data analysis.

The resulting bandwidths were for $\nu = 0$ 3.4 years (maximal) in the preadolescent and 1.8 years (minimal) in the adolescent period and for $\nu = 1$ these bandwidths were 3.8 and 3.1 years and for $\nu = 2$ 4.0 and 3.6 years (the transitions being regulated by the requirement of variance stabilization). Keeping in mind that measurements falling in the interval $(t \pm b)$ are used for the kernel estimates, these bandwidths are surprisingly large. When performing (c) separately for $n =$ 45 boys and girls, a substantially higher optimal bandwidth arose for girls due to their less accentuated pubertal spurt (PS). Using the two bandwidths separately would have artificially enlarged existing sex differences of growth dynamics due to a differential bias (this gives further support to the argumenation of Section 5 of using one and the same bandwidth for all subjects).

7. Nonparametric versus parametric fitting. Nonparametric curve estimates are a priori biased (4); basically, the bias leads to a leveling off of peaks and troughs in the curve. The bias of their location is usually less of a problem: it is negligible with symmetric peaks, and in the asymmetric case, the bias is directed towards the less steeply rising side of a peak. It is reassuring to know qualitatively the form and direction of the bias when inspecting an estimate, but it would be desirable to know the approximate size of the bias (see below).

Regarding parametric fitting, the situation is more complicated:

A. Qualitative distortion: certain structures are not taken into account at all in the model.
B. Quantitative distortion: all essential features are characterized by the model, but due to discrepancies between true and postulated function, quantitative differences arise.

Figures 2–5, displaying nonparametric and parametric estimates of velocity and acceleration of height for 4 children, illustrate the first point: in addition to the pronounced PS, a second peak arises at about 7 years (the mid-growth spurt, MS). The parametric model 3 of Preece and Baines (1978) ignores this phenomenon which is not part of the model (velocity and acceleration were obtained by differentiating parametrically fitted height, as is customary in growth studies). Moreover, gross discrepancies arise below 3–4 years of age (Preece and Baines, 1978, evaluated their model from 4 years upwards). The residual analysis undertaken by Preece and Baines (1978) was not able to pinpoint the deficiency with respect to the MS. The analysis of growth offers another interesting case of qualitative problems in fitting: the velocity peak of the PS is definitely asymmetric, with a slower rising than falling; the peak of the logistic function is symmetric, that of the Gompertz function asymmetric. Its asymmetry, however,

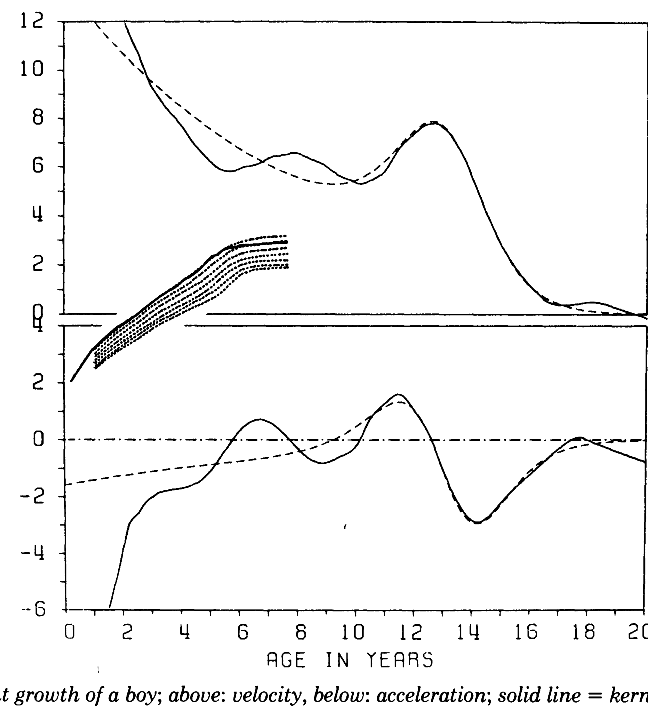

FIG. 2. *Height growth of a boy; above: velocity, below: acceleration; solid line = kernel estimate, dotted line = parametric estimate; small graph gives height measured with cross-sectional quantiles* (.03, .10, .25, .50, .75, .90, .97); *individual T*6 (*onset of* PS) *at* 10.2 *y* (*with velocity* 5.3 *cm*/*y*) *and individual T*8 (*peaking of* PS) *at* 12.6 *y* (*with velocity* 7.8 *cm*/*y*).

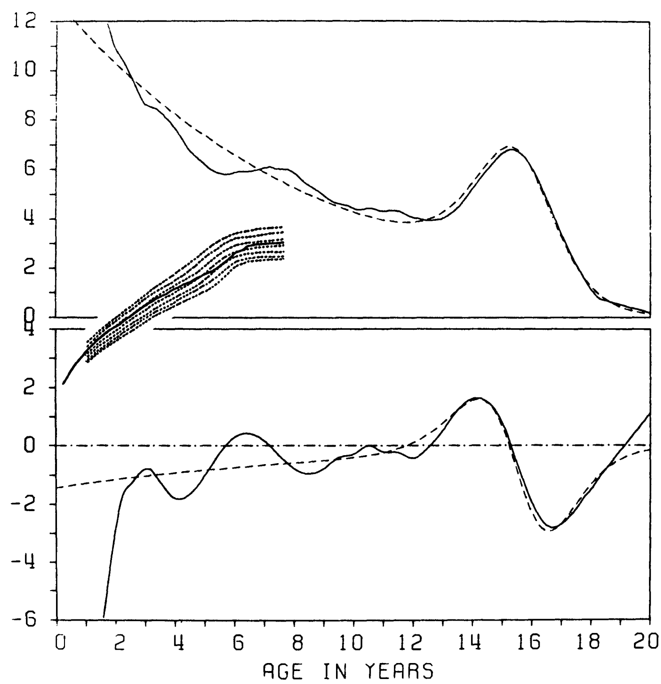

FIG. 3. *As in Fig.* 1, *for data of another boy; individual T6 at* 12.6 *y* (*with velocity* 3.9 *cm/y*) *and individual T8 at* 15.3 *y* (*with velocity* 6.8 *cm/y*).

goes in the wrong direction with a faster increasing than decreasing velocity. The fact that height is measured and fitted, whereas velocity (and acceleration) is of major interest (compare e.g. El Lozy, 1978) contributes to these problems. Figures 2–5 contain a small graph of individual height observed, illustrating the point that height is graphically rather uninformative compared to velocity or acceleration; this might also be reflected in the power of goodness-of-fit tests applied to height.

Problem B, the possible quantitative distortion of the PS (which is part both of the parametric and the nonparametric fit), remains to be investigated:

B1. A priori, we expect that the lack of structure (no fitting of the MS) might also lead to problems in quantifying the PS for the PB model (Preece and Baines, 1978).

B2. The maximum of velocity in the PS will have a downward bias for the kernel estimates, in particular for boys with their more accentuated spurt.

In the examples of Figure 2 and 3, there is a good overall agreement in modeling the PS, except for a slower and earlier rising of the parametric fit (more accentuated in accelerations). Figure 4 shows a case of a more severe discrepancy, probably attributable to the lack of an MS in the PB model. The smaller velocity peak of the kernel estimate in Figure 5 is interpreted as a bias of the nonparametric technique. For a more thorough investigation of bias, the longitudinal parameters introduced in Section 3 will be used (onset of the PS = *T*6, and

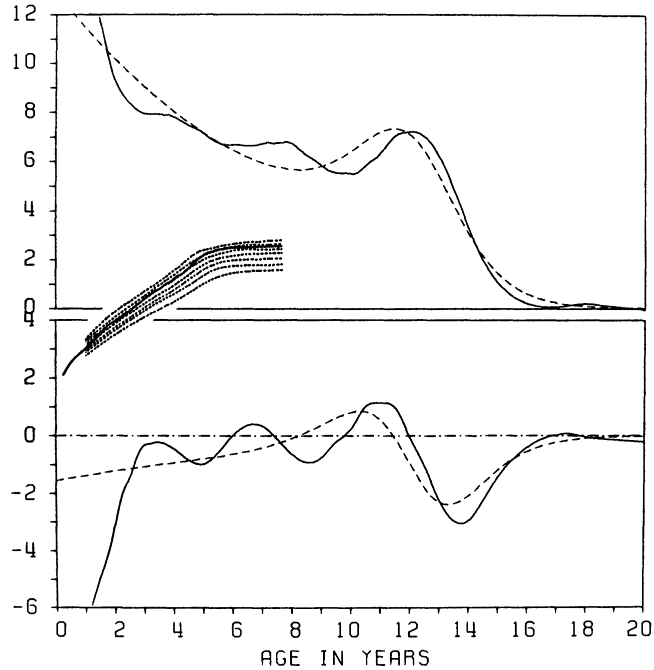

FIG. 4. *As in Fig. 1, for data of a girl: individual T6 at* 9.7 *y* (*with velocity* 5.5 *cm/y*) *and individual T8 at* 12.0 *y* (*with velocity* 7.2 *cm/y*).

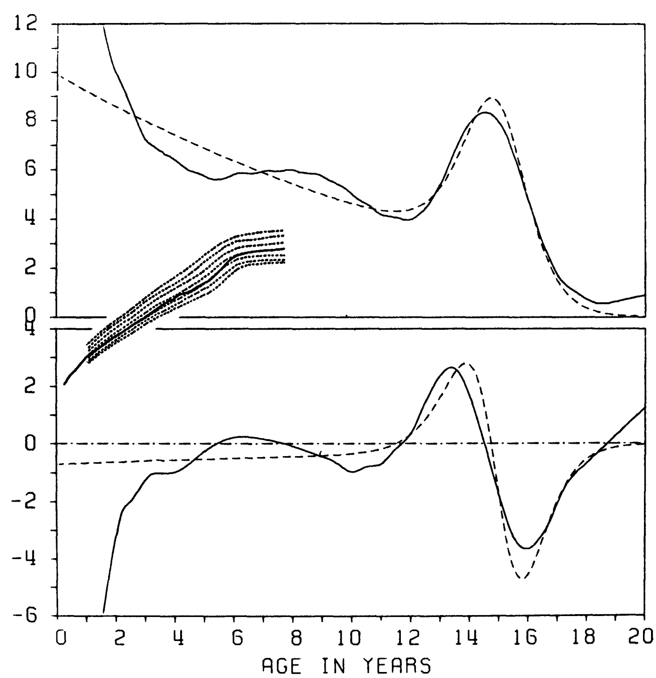

FIG. 5. *As in Fig. 1, for data of a boy; individual T6 at* 11.7 *y* (*with velocity* 4.0 *cm/y*) *and individual T8 at* 14.5 *y* (*with velocity* 8.3 *cm/y*).

timing of the PS = $T8$, and velocity V and height H at these ages). The discrepancy between the parametric and the nonparametric method in the average age of onset (Table 5) is substantial for boys and particularly large for girls (and, as a consequence, differences also arise for height and for velocity at onset). These methodological differences, as well as their differential effect for sex, are significant with low error probabilities (often $<10^{-4}$ by paired and by two-sample Wilcoxon tests, respectively). In view of this, empirical conclusions will be affected by the fitting method used. The positive average difference ($T6$-$T6$PB) is interpreted as a bias effect of the PB model since the bias of the kernel estimate is also negative if there is one. It is rather natural to associate the bias of $T6$PB with the qualitative distortion of the PB model due to the lacking MS, and this interpretation explains the larger bias for girls (their MS and PS are closer together). In order to check this conjecture, a stepwise regression was computed with y = $T6$-$T6$PB and with 6 longitudinal parameters as candidates for predicting this bias: for boys and girls the timing of the offset of the MS is the most influential variable for explaining y, and, as expected, it explains a larger proportion of the variance for girls ($R^2 = .35$). To further clarify causes of overall bad fitting by the PB model, a stepwise regression was computed with y = estimated residual variance (for PB model) and with 5 parameters characterizing the MS and the PS as possible predictors: for boys, the intensity of the MS—not part of the PB model—is the only variable retained for explaining interindividual variation in estimated residual variance. For girls, three variables are retained, two of them characterizing the MS and one characterizing the intensity of the PS. The conclusions are that the onset of the PS is systematically distorted (due to the lack of the MS) when doing parametric fitting by model 3 of Preece and Baines (1978) and that the sum of squared residuals of parametric fitting depends on individual characteristics of height growth $H_i(t)$.

There is a good overall agreement between parametric and nonparametric fitting (Table 6) regarding the timing of the velocity peak ($T8$ and $T8$PB) of the PS and height reached, whereas the average value for the velocity peak ($VT8$ and $VT8$PB) is smaller by almost 0.4 cm/y for boys when using kernel estimates. A stepwise regression with y = ($VT8$-$VT8$PB) showed that this difference is indeed negatively related to the intensity of the PS and that it can be interpreted as part of the bias of the kernel estimate. The following approach was used to

TABLE 5

*Comparison of estimates of age of minimal pre-*PS *velocity* ($T6$, $T6$PB) *and height* (H) *and velocity* (V) *at that age; determined by kernel estimates and by Preece and Baines model* 3 (PB); r = *rank correlations (between methods).*

	Sex	**T6**	**T6PB**	**HT6**	**HT6PB**	**VT6**	**VT6PB**
$\bar{x}$	boys	10.90	10.62	143.6	142.1	4.331	4.482
	girls	9.762	9.013	136.3	132.3	4.846	4.895
s	boys	1.065	.8291	6.793	6.490	.5042	.4744
	girls	.9557	.7123	7.312	6.185	.5837	.4617
r	boys	.790		.825		.818	
	girls	.815		.891		.817	

TABLE 6
Comparison of estimates of age of PS *peak height Velocity* (*T8*, *T8*PB) *and height* (*H*) *and velocity* (*V*) *at that age; determined by Preece and Baines model* 3 (PB); *r* = *rank correlation.*

	Sex	*T8*	*T8*PB	*HT8*	*HT8*PB	*VT8*	*VT8*PB
$\bar{x}$	boys	13.91	14.00	161.4	162.6	8.313	8.697
	girls	12.22	12.09	150.4	150.2	6.996	7.090
s	boys	.9505	.8861	6.629	6.337	.8218	1.034
	girls	.8066	.7771	5.968	5.856	.9519	1.039
r	boys	.971		.942		.911	
	girls	.873		.888		.974	

approximately determine the average bias of peak height velocity (*VT8*) of the kernel estimate:

(i) The raw measurements of the $n = 45$ boys and the $n = 45$ girls were aligned separately to the average *T8* by shifting them with respect to individual *T8*.
(ii) An individual constant was added such that height at *T8* would be identical for all boys (or girls respectively)
(iii) The resulting "super curve" of 45 children was smoothed with a visually determined small bandwidth (and thus a small bias, see (4)).

For boys, we obtained then an average peak velocity of 9.77 cm/y (compared to 8.31 cm/y for the individual kernel estimates and to 8.70 cm/y for the PB model) and of 7.85 cm/y for girls (instead of 7.00 cm/y for the individual kernel estimates and to 7.09 cm/y for the PB model). It came as a surprise to find a large portion of the average bias of the kernel estimate—which was a priori to be expected—also in the parametric fit, indicating that this model does not adequately incorporate the intensity of the PS.

8. Biological progress. We will now summarize some biological results (more detailed reports are available from the first author.). The mid-growth spurt (MS) was hitherto unquantified, and the newly introduced estimate for acceleration proved to be crucial for this step: the timing (6.4 years for maximal acceleration) and the intensity of the MS (maximal acceleration = .21 cm/y^2) were on the average exactly equal for the two sexes, whereas boys had a marginally longer lasting MS. This finding is in marked contrast to the known sex differences for the PS and makes a different regulation for the MS plausible. Figure 6 illustrates this point displaying probability densities (obtained by kernel estimates) for the timing of the MS and of the PS for the two sexes. The local mode on the l.h.s. is produced by a few children with a very long lasting MS (whether they represent the nucleus of a subgroup will be checked in subsequent work). As to the PS, there is in general a good agreement with published results, where they are comparable. Accelerations lead, however, to a more differentiated subdivision of the PS; judged from our results, the PS is not a global phenomenon: the phase from onset to maximal acceleration is in many aspects independent from the longer lasting phase from maximal acceleration to maximal deceleration, and sex differences of the PS are attributable more to the first phase. In view of the difficulties in modeling the PS, and also for investigating its dynamics, it is interesting to find a much more accentuated asymmetry of the pubertal peak for girls. The MS and the PS are for both sexes in most respects unrelated. A multivariate condensation of all longitudinal parameters was obtained for the combined sample of boys and girls (Figure 7) by multidimensional scaling, using the program MINISSA from Coxon et al. (1977). In order to characterize the

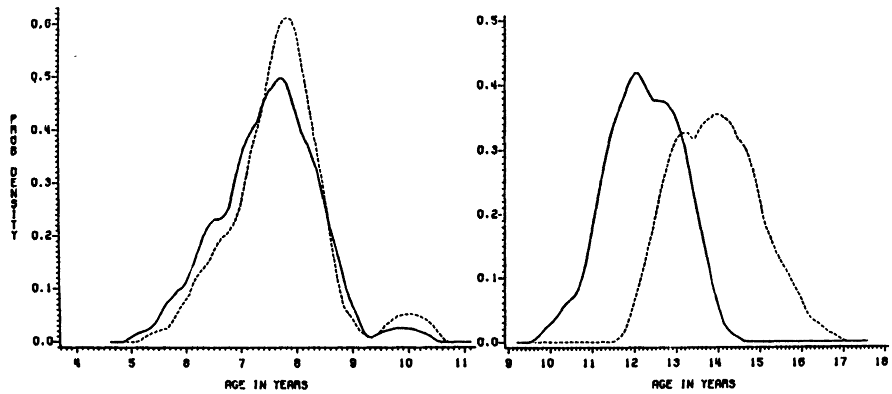

FIG. 6. *Probability densities (kernel estimates) of timings of midspurt for boys (dotted) and for girls (solid) left, and for timings of the pubertal spurt, right.*

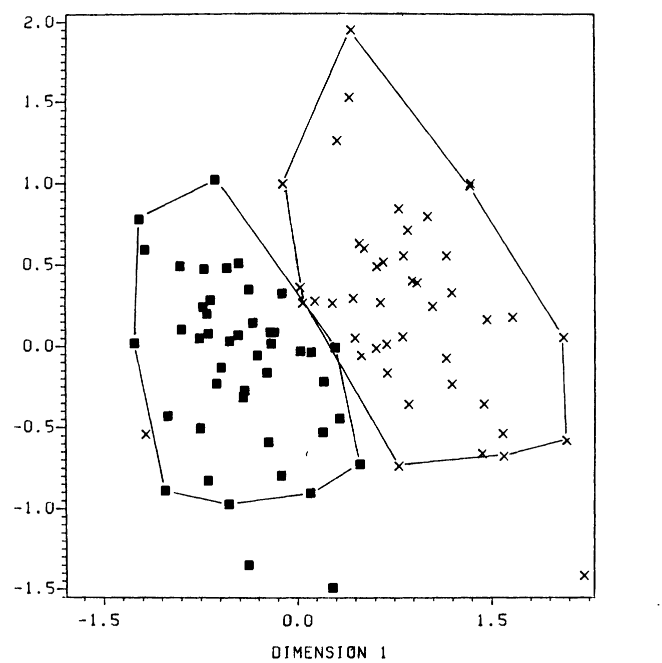

FIG. 7. *Two-dimensional* MDS *representation for combined groups of boys and girls based on all parameters of height growth extracted by kernel estimates* (■ = *boys,* × = *girls*); *straight lines* = 43/45 *convex hulls for the two sexes separately.*

region occupied by the two sexes, 43/45 convex hulls have been additionally introduced (by eliminating $2/45 \approx 5\%$ of the most extreme subjects as described in Gasser and Möcks, 1983): the two sexes are then almost distinct, which is remarkable since height measurements only are the basis of this representation.

9. Concluding remarks. When scrutinizing the Preece-Baines model for height, the aim was not to convince the reader of its disadvantages (it belongs to the best functions suggested for this purpose). The difficulties outlined are somewhat surprising, since a lot of work has been done in modeling and analyzing growth curves. While within a formal statistical point of view some can be attributed to the biomedical field (considered responsible for model building), the difficulties in diagnosing the lack of fit are statistical in nature (residual analysis based on the runs test, on the residual mean squared error and on graphics was not able to provide adequate information in this respect). It is also somewhat discomforting that asymptotic results for nonlinear regression assume the true model to be known (Jennrich, 1969; Wu, 1981). Some potential dangers of parametric fitting became verified: relevant structure—the MS—is not part of the model; the lack of the MS in the model also affects the quantification of the PS (too early an onset), and this bias is dependent on sex; the intensity of the PS is not adequately modeled; the fit below 4 years—not part of the original evaluation—is close to useless. Nonparametric regression estimates circumvent a number of the problems discussed:

- no functional model has to be postulated (the method can, therefore, be easily applied to other somatic variables), and there is indeed not even the assumption that all children (for example boys and girls) obey the same law of development;
- the bias is easier to understand since the method operates locally and since the estimate itself contains information about the bias;
- computation is fast and it does not lead to problems with local minima as in nonlinear regression.

It is an asset that finer details can be obtained reliably via the first and second derivative in a nonparametric way, even for such a sparse design. Cubic smoothing splines are, for our problems, lagging slightly behind higher order kernel estimates and they are computationally not competitive.

Further methodological work needs to be done: we would like to see the bias decreased, perhaps by using an adaptive smoothing scheme (less smoothing where the structure, and therefore the bias, occurs). It might also be worthwhile to investigate whether individual integrated mean square error is an appropriate criterion when later on analyzing longitudinal parameters across a sample of subjects, and to further substantiate the reasoning against an individually optimized smoothing parameter.

Problems like those encountered might be paradigmatic for other fields: the "interdisciplinary vacuum", where statisticians are asking for a functional model to perform a parametric fitting, and colleagues in the field of application are asking for the properties of the model and its quantification, arise quite frequently. Nonparametric techniques, and this applies also to derivatives, might then be a good starting point for data analysis.

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THEO GASSER
ZENTRALINSTITUT FÜR SEELISCHE GESUNDHEIT
P.O.B. 5970
6800 MANNHEIM 1
FRG

HANS-GEORG MÜLLER
WALTER KÖHLER
INSTITUT FÜR ANGEWANDTE MATHEMATIK
UNIVERSITÄT HEIDELBERG
IM NEUENHEIMER FELD 294
6900 HEIDELBERG 1
FRG

LUCIANO MOLINARI
ANDREA PRADER
KINDERSPITAL
UNIVERSITÄT ZÜRICH
STEINWIESSTR. 75
CH-8032 ZÜRICH
SWITZERLAND