

Part 7

# Kernel estimation, shape-invariant modeling and structural analysis

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# 1 Introduction

There are a multitude of reasons for studying human growth, but two main areas of interest can be distinguished. First, one is interested in obtaining age-dependent reference curves for various somatic variables, usually based on cross-sectional data (see chapters 2, 3 and 10 for details). The clinical value is evident, but reference curves are also needed for clinical research to obtain comparable values at different ages. A second motivation is mainly scientific and relates to an understanding of the growth process over certain phases, or, more ambitiously, from birth to adulthood (compare chapters 1 and 2). Such studies are usually longitudinal and they are central in this chapter. In addition to the scientific interest, there are also clinical implications, e.g. for a qualitative understanding of growth disorders. The aim is to get a clear quantitative picture of prepubertal and pubertal growth. Further, we want to assess differences in growth in different parts of the body, and between boys and girls. An assessment of interindividual variation of growth patterns is also needed. Whereas the distance curve is of utmost interest for reference curves, it does not offer detailed information about the dynamic and the intensity of the growth process (see also chapter 2). Thus, interest focuses on the velocity curve and to a much lesser extent on the acceleration curve (while it is appealing, it is difficult to estimate reliably).

The methods presented in this chapter have proved their value for analyzing growth longitudinally. From the viewpoint of statistics, regression methods based on an adequate parametric function are the methods of choice to analyze growth longitudinally. While polynomial models would be computationally convenient, they can only be used for short periods and are inadequate for longer periods or for periods including the pubertal growth spurt or other fast changes. Nonlinear models need more expertise from the data analyst; the main problem in their application is, however, the choice of an appropriate model function. While e.g. the logistic function proved to be adequate for fitting the pubertal spurt of height (Marubini et al. 1972), finding a good model for the growth process from birth to adulthood

proved to be a thorny problem, since the model should have at most 5 or 6 parameters: even the best models missed some of the many different facets of the entire growth process, leading to biased results. This spurred interest in nonparametric methods of function fitting (also called “smoothing methods”) which work without prescribing a parametric model. The idea is that they should bring out the shape of the growth curve which is hidden in the noisy data. The fact that derivatives rather than distance functions are of interest needs now special attention, since derivatives are from the point of view of mathematics more difficult to estimate. The recent statistical literature offers a variety of methods for nonparametric function fitting (splines, kernel estimators, etc.). Here, we concentrate on kernel estimators, but the concepts are rather similar for other approaches. This method does not only render a curve but allows also to determine the age of occurrence of different features, such as the pubertal spurt, and other features of interest (section 4).

A characteristic of growth studies is that we have a sample of individual longitudinal data sets. While different subjects are different in quantitative terms, their growth has a similar shape, and this common shape should give information about the underlying model. It would then be of interest to quantify this common shape, and at the same time the individual parameters which stand for interindividual differences. This can be achieved with a method called “shape-invariant modeling” (nonlinear semiparametric modeling in statistical terminology) to be presented here as the second method. The third method (“structural analysis”) is also based on the whole sample of growth curves. Our first goal is to determine a valid average velocity curve. A naive average at chronological ages is certainly not valid, due to the different maturational tempo in different subjects: one boy at age 14 might be at the peak of the pubertal spurt, another may have just passed the spurt, whereas a third boy might still experience prepubertal growth. Consequently, one has to align individual curves to an average tempo before averaging them. Determining this alignment function is based on particular features or milestones of the growth process. All three methods discussed in this chapter are of interest beyond growth

studies, since they are applicable to many types of noisy curves. In fact they have become, or are going to become, part of the statistical toolbox (references are given later).

## 2 The first Zurich longitudinal growth study

The examples are mainly drawn from the Zurich Study, which was part of an extensive multicenter growth study (Falkner 1960). The first visit of the participants was at 4 weeks, and the following at 1/4, 1/2, 1, 1-1/2 and 2 years. Then came early intervals up to age 9 for girls and age 10 for boys. Afterwards, measurements took place half-early until further growth became small. Yearly measurements were then continued at least until age 18, but mostly until 20 (for further details see Prader et al. 1989). In order to quantify infant growth more accurately, it proved to be beneficial to add a “measurement” with value 0 at  $-0.75$  years. We have almost complete data for 120 boys and 112 girls at our disposal (roughly 32 measurements per child).

Here, we will analyze primarily variables reflecting the growth of the skeleton: height, leg and trunk height, arm length, biiliac and bihumeral width. They are mainly genetically determined and their growth shows a similar pattern in normal children. The mixed variables arm and calf circumference and weight — which also reflect growth of muscle mass and fat — can be analyzed similarly. The development of skinfolds shows a variable pattern from subject to subject, due to a substantial nongenetic influence, and they may thus need a different strategy for analysis (section 7).

## 3 Modeling longitudinal growth

Assume that measurements of some variable  $y$  have been taken  $n$  times for some child at ages  $t_1, \dots, t_n$ . In the examples below  $t_1, \dots, t_n$  will cover the whole growth process. Determining the underlying true growth curve  $r$  of that particular child is

a standard regression problem:

$$y_i = r(t_i) + \varepsilon_i, \quad i = 1, \dots, n. \quad (1)$$

The so-called residuals  $\varepsilon_i$  are assumed to have mean zero and residual variance  $\sigma_\varepsilon^2$  which may or may not depend on age. For skeletal growth the residual variance does depend on age: it is high in infancy and decreases then continuously, interrupted by a transient increase in puberty (see section 4 for a statistical treatments). These residuals stand for measurement error but also for biological random variation due to illness, seasonal and other exogenous factors. The regression function  $r$  represents the true underlying growth curve following the genetic potential. Fitting a linear function for  $r$  is easy, but totally inadequate for growth. Fitting a polynomial would also be easy, but is still inadequate, except for short periods. Thus, we truly need nonlinear regression models, which are more difficult to treat statistically (see chapter 9).

Over the years, a lot of work has gone into the development of adequate growth models. Here, we mention only a few:

- Double logistic model (Bock et al. 1973):

$$r(t) = \frac{a_1}{1 + \exp(-b_1(t - c_1))} + \frac{AH - a_1}{1 + \exp(-b_2(t - c_2))},$$

where  $AH$  is adult height.

- Model by Preece & Baines (1978):

$$\begin{aligned} r(t) = & 4(a - H(c)) \times \\ & \{[b_1 \exp(b_1(t - c)) + b_2 \exp(b_2(t - c))]\{1 + \exp(b_3(t - c))\} + \\ & (\exp(b_1(t - c)) + \exp(b_2(t - c)))b_3 \exp(b_3(t - c))\} \div \\ & \{[\exp(b_1(t - c)) + \exp(b_2(t - c))]\{1 + \exp(b_3(t - c))\}\}^2, \end{aligned}$$

where  $H(c)$  is height at age  $c$  (treated as an independent parameter).

- IPC Model by Karlberg (1987):

$$r_1(t) = a_1 + b_1(1 - \exp(-c_1t)) \quad (\text{infancy, exponential}),$$

$$r_2(t) = a_2 + b_2t + c_2t^2 \quad (\text{childhood, quadratic}),$$

$$r_3(t) = a_3/\{1 + \exp(-b_3(t - c_3))\} \quad (\text{puberty, logistic}).$$

These submodels are fitted sequentially.

- Model by Jolicoeur et al. (1988):

$$r(t) = a_1[1 - 1/\{(t/b_1)^{c_1} + (t/b_2)^{c_2} + (t/b_3)^{c_3}\}].$$

Note that the first two models need 6 parameters, the third 9 and the fourth 7. The Preece–Baines model for  $r(t)$  is actually the derivative of that proposed in the article cited above, because the authors model the distance curve instead of the velocity. The parameters of these models are usually estimated by nonlinear least squares methods, which involve iterative algorithms.

This list is, of course, not exhaustive but covers some of the popular models. These models do not provide a theoretical justification of measurements as do many models in the physical sciences — they are largely descriptive. Often they may describe a number of children adequately, but show difficulties to catch somewhat unusual individual curves. This problem can be avoided by using nonparametric function fitting, to be described in section 4. Choosing models with more parameters allows more flexibility, but at the price of increased variability. For this reason it does not make sense to include more than 5 or 6 parameters, given the fact that we have about 30 to 34 measurements.

The main problem with these nonlinear models is model bias: they deviate systematically from the underlying biological growth pattern. One example is the lack of the mid–growth spurt in most models which may also affect modeling the pubertal spurt, in particular for girls (as shown in Gasser et al. 1984a). This is already a problem for height growth, where the mid–growth spurt is smallest, but much more so for other variables such as shoulder or trunk. The parametric models have been evaluated for height growth, which is easier to model than some other

somatic variables. Thus, more problems might arise when analyzing e.g. growth of the shoulder or the legs, both due to a relatively higher residual variance and more abrupt changes in the shape of the velocity curve. The general case does not present particular problems for the methods discussed in sections 4 to 6. Figure 1 illustrates the problem for the Preece–Baines model. This is a particularly regularly growing girl, and from the raw velocities one notes easily a pubertal spurt at about age 13, and a mid–growth spurt peaking around 8 years. The kernel–estimated velocity curve (see section 4) reflects this pattern nicely, while the Preece–Baines model intrinsically lacks a mid–growth spurt which leads to an inadequate fit in this period. The lack of a mid–growth spurt is not the only bias — another one is a too early take–off for the pubertal spurt, which is a consequence of the first bias (identified as a general phenomenon in Gasser et al. 1984a).

Some models may also show a bias for the pubertal spurt by enforcing a symmetric peak when it is, in fact, asymmetric. Models have typically also some difficulty to formalize the rapid transition from a steep decline in velocity in infancy to an almost constant or steadily decreasing velocity trend in childhood. The estimation is performed for the distance curve where, unfortunately, a poor fit is not easy to spot in comparison to the velocity or acceleration curve (thus, one should always inspect the goodness–of–fit in the velocity curve as well). Using the above models, the velocity curve is obtained by taking the first derivative of the model and plugging in the estimated individual parameters.

What are the peculiarities of analyzing growth data by some suitable regression method? In contrast to most applications of regression in various fields, we are mainly interested in the velocity curve (and maybe in the acceleration curve). Derivatives of a function are notoriously more difficult to determine from noisy data than the function itself. Then we have a sample of subjects — and two genders — for which the method should be valid (in many disciplines there is just one curve to model). On one hand this multitude of curves represents a challenge, but on the other hand it is an opportunity, since we might be able to pool information from

different subjects to obtain information on the “true shape” of growth velocity. In what follows we will illustrate how these problems can be dealt with.

## 4 Kernel estimation

### 4.1 Motivation and definition

As discussed in section 3, parametric nonlinear models often fail to capture the true shape of the regression function underlying the noisy data. This problem is not exclusive of the analysis of growth data. For this reason, methods of curve estimation that work without an a priori fixed parametric model have been developed in statistics. They are, therefore, called “nonparametric”. The most important nonparametric function estimators are splines, kernel estimators and local polynomials (for a review see e.g. Gasser, Engel & Seifert 1993, or the book by Fan & Gijbels 1996). The different methods are closely related: an estimate of the regression function  $r$  at age  $t_0$  is obtained by computing a local weighted average of the data  $y_i$  falling in an interval  $(t_0 - h, t_0 + h)$  around  $t_0$ . Such weight functions or kernels are called “compact” because they are null outside a given interval; non-compact kernels exist but for convenience we will use only compact ones (besides, the optimal kernels — in a sense explained below — are compact). Smoothing splines have been applied in growth studies quite early (Largo et al. 1978), but since kernel estimators have some advantages we will concentrate on these. The statistical theory has been presented in Gasser & Müller (1984) and Gasser, Müller & Mammitzsch (1985a), while aspects related to growth can be found in Gasser et al. (1984a) and Gasser et al. (1984b).

In what follows we will assume that  $0 \leq t_1 \leq t_2 \leq \dots \leq t_n \leq 1$  for ease of notation. A kernel estimator  $\hat{r}(t_0)$  for  $r(t_0)$  can be written as follows:

$$\hat{r}(t_0) = \sum_{i=1}^n w_i(t_0; t_1, \dots, t_n; h) y_i \quad (2)$$

where the weights  $w_i$  are given by

$$w_i(t_0; t_1, \dots, t_n; h) = \frac{1}{h} \int_{s_{i-1}}^{s_i} K\left(\frac{t_0 - u}{h}\right) du, \quad s_i = \frac{t_i + t_{i+1}}{2}, \quad s_0 = 0, \quad s_n = 1. \quad (3)$$



While the sum goes from 1 to  $n$ , only those  $y_i$  lying in the interval  $(t_0 - h, t_0 + h)$  contribute to  $\hat{r}(t_0)$ . The above weighting scheme automatically accounts for unequal spacings between subsequent ages  $t_i$ , by giving more weight when the interval between two measurements is large. When applying this estimator, the decisive questions are how to choose the kernel (or weight function)  $K$  and how to choose the bandwidth (or smoothing parameter)  $h$ . This will be the central theme of this section.

The velocity curve  $r'(t_0)$  or the acceleration curve  $r''(t_0)$  (in general, the  $\nu$ -th derivative  $r^{(\nu)}(t_0)$ ) can be estimated using a formula similar to (2) with modified weights. The modifications needed in (3) are: first, the factor  $h^{-1}$  has to be replaced by  $h^{-\nu-1}$ , which implicitly produces a larger bandwidth for derivatives; second, a kernel  $K_\nu$  with specific properties (see below) has to be used. For numerical reasons the data should be interpolated to an equally spaced dense grid before estimating derivatives. (For our growth data we have used simple linear interpolation between measurements based on 200 interpolated points.) It is important to remark that bandwidth selection (see section 4.3) has to be performed on the original data, not on the interpolated one.

While parametric methods — in the ideal case where the model is true — have null or negligible bias, kernel estimators, as all smoothing methods, lead to bias. Intuitively it is clear that strong smoothing incurs in a strong bias and low variability, while little smoothing leads to little bias and strong variability; in between there should be a compromise balancing the two types of error. To make these intuitive arguments more precise, consider the following approximate (or asymptotic) expressions for bias and variance of the estimator of  $r(t_0)$ , for equally spaced data:

$$\begin{aligned} \text{Bias}(\hat{r}(t_0)) &= h^2 r''(t_0) \int K(u) u^2 du, \\ \text{Var}(\hat{r}(t_0)) &= \frac{\sigma_\varepsilon^2}{2nh} \int K(u)^2 du. \end{aligned}$$

The assumption of equal spacing is made for simplicity and can be relaxed, and similar expressions can be obtained for the estimators of the derivatives (Gasser & Müller 1984). Observe that while the bias increases as a square of the bandwidth

$h$ , the variance decreases hyperbolically with  $h$ . Moreover, the variance depends on the data only via the residual variance  $\sigma_\varepsilon^2$ , and the bias only on the second derivative of the underlying regression function  $r$  (or on  $r^{(\nu+2)}$  when estimating the  $\nu$ -th derivative). Qualitatively, then, bias leads to a flattening of peaks and valleys (where  $|r''(t_0)|$  is large), and little distortion in flat parts of the curve (where  $|r''(t_0)|$  is small). Thus the bias is “conservative” in so far it dampens true structure but does not generate artificial structure.

Ideally from a statistical perspective, the optimal choices of  $K$  (or  $K_\nu$  for derivatives) and  $h$  should lead simultaneously to low bias and low variability. The following two subsections explain how to achieve this.

## 4.2 Choice of kernel

To find a compromise between bias and variance one usually minimizes the mean square error MSE:  $MSE = Bias^2 + Variance$ . Minimizing the MSE leads to different optimal kernels for  $\nu = 0, 1, 2$ , which do not depend on the data or on  $h$ . Certain conditions for  $K$ ,  $K_1$  and  $K_2$  are necessary to guarantee that appropriately normalized sums (for  $K$ ) and appropriately normalized differences (for  $K_1$  and  $K_2$ ) are formed so that  $r$ ,  $r'$  and  $r''$  are estimated correctly. For  $\nu = 0$  one has to postulate that

$$\int K(u)du = 1, \quad K(u) = K(-u) \text{ (symmetric)}, \quad K(u) \geq 0.$$

For  $\nu = 1$  we require that

$$\int K_1(u)du = 0, \quad \int K_1(u)udu = -1, \quad K_1(u) = -K_1(-u),$$

and for  $\nu = 2$ :

$$\int K_2(u)du = 0, \quad \int K_2(u)udu = 0, \quad \int K_2(u)u^2 = 1, \quad K_2(u) = K_2(-u).$$

By non-elementary mathematical arguments, it is possible to explicitly construct optimal kernels  $K$ ,  $K_1$  and  $K_2$  which minimize the MSE for estimating  $r$ ,  $r'$  and  $r''$  respectively (Gasser et al. 1985a). The shape of these optimal kernels is depicted in figure 2. These kernels are simple polynomials of degree 2, 3 and 4, respectively. As

a consequence, the integral in (3) can be computed analytically and does not need to be computed numerically.

A little thinking shows that problems arise when these kernels are naively used at the boundary (e.g. to compute the velocity at birth, when data start at birth — truly a difficult problem). Special “boundary kernels” have been constructed to solve those problems. In growth studies, one can also alleviate boundary problems by introducing “data points” at age  $-0.75$  years with value zero (representing height at conception).

### 4.3 Choice of bandwidth

It is a nice feature that the same kernels can be used irrespective of the dataset at hand. Unfortunately this is not true for the optimal bandwidth, which depends heavily on the data. Figure 3 shows, for simulated data, the effect of misspecifying the bandwidth: it results in under- or over-smoothing. Too small a bandwidth leads to a rough appearance of the estimated curve, with many random wiggles — sign of undersmoothing. Choosing too large a bandwidth leads to a very smooth appearance, but a distortion of the curve at peaks. The optimal bandwidth is a compromise tolerating some bias for an overall smooth estimated curve.

Formulae for an approximately optimal bandwidth can be obtained by mathematical means both locally (at one point  $t_0$ ) and globally (the same bandwidth for all  $t$ ). They are given here for the estimator of the regression function  $r$  (similar expressions hold for  $r'$  and  $r''$ ):

- Local bandwidth:

$$h_{\text{opt}}(t_0) = \left( \frac{\sigma_\varepsilon^2}{c \cdot n \cdot r''(t_0)^2} \right)^{1/5} .$$

- Global bandwidth:

$$h_{\text{opt}} = \left( \frac{\sigma_\varepsilon^2}{c \cdot n \int r''(u)^2 du} \right)^{1/5} .$$

Here  $c$  is a known constant that depends on the kernel function. These optimal bandwidths result from minimizing the MSE. They, therefore, achieve a compromise

between bias and variability. The optimal local bandwidth adapts to the curvature in various regions of the regression function: it is large in flat parts (with little bias) and small at peaks (thus avoiding a large bias). The optimal global bandwidth is used in all regions and thus makes a compromise between different aspects of the curve. Note also that both optimal bandwidths increase as the noise variance  $\sigma_\varepsilon^2$  increases.

Unfortunately, these formulae cannot be applied to real data as they stand, since neither the residual variance  $\sigma_\varepsilon^2$  nor the second derivative of  $r$  are known (for estimating  $r^{(\nu)}$  we would even need knowledge of  $r^{(\nu+2)}$ ). Since  $r''(t)$  is much more difficult to estimate than  $r(t)$ , it seems unrealistic to use the above result to determine  $h_{\text{opt}}$  or  $h_{\text{opt}}(t_0)$  from the data in an adaptive way. However, there are algorithms that successfully solve these problems. In general, we can say that it is easier to approximate the integral  $\int r''(u)^2 du$  than to estimate  $r''(t_0)^2$ ; a solution for the first problem has been proposed by Gasser, Kneip & Köhler (1991a) and for the second by Brockmann, Gasser & Herrmann (1993). As for the estimation of  $\sigma_\varepsilon^2$ , there is a relatively simple nonparametric method proposed by Gasser, Sroka & Jennen-Steinmetz (1986). It consists in taking successive triplets of points, computing a linear function through the two outer points and taking the residual for the middle point; the estimate of  $\sigma_\varepsilon^2$  is obtained by adding the squares of these pseudo-residuals (appropriately scaled). Note that besides its role in the optimal bandwidth, the quantity  $\sigma_\varepsilon^2$  can also be of biological interest, giving information about the amount of random variation.

According to theory, simulations, and practical applications, these methods of bandwidth choice (called “plug-in” methods) work well. They lead to data-driven estimates of the global or the local optimal bandwidth and thus to rational rather than subjective smoothing. This is particularly relevant for derivatives, but also more difficult to achieve. There exist other methods for estimating the optimal bandwidth; a popular one is cross-validation, but it has been shown in the statistical literature that it is inferior to the plug-in method.

The question that comes up when we have a sample of curves as in growth studies, is whether we should use an optimal bandwidth for each curve or the same bandwidth for the whole sample. We favor the latter, and suggest taking as bandwidth the average of the individually estimated optimal bandwidths. This is advisable essentially for two reasons: first, because treating all subjects statistically in the same way leads to results which are comparable from subject to subject (for the same reason, the same bandwidth should be used for both genders); and second, because by averaging the individual bandwidths one gets a more reliable bandwidth, in particular for the local choice and for derivatives.

#### 4.4 Application to growth data

An illustration of kernel estimated velocities of trunk length is given in figure 4. The average optimal local bandwidth was used. While raw velocities are really noisy, estimated velocities based on kernel estimation show a smooth distinct pattern with a pubertal spurt and usually a discernible mid-growth spurt. One also notes visually two types of variability: the intensity of growth — for example the amplitude of the pubertal spurt — varies from child to child, and the timing of the spurt varies too, due to an individual maturational tempo. While the first type of variability is classical for statisticians and has been widely analyzed e.g. by analysis of variance or principal component analysis, the problem of time variability has largely been neglected. But it is time variability which makes many naive approaches — such as cross-sectional averaging of velocity curves — seriously flawed. Section 6, and partly also section 5, will deal with this problem.

The estimated velocity and acceleration curves can also be used to define individual features (or parameters) characterizing the individual growth process (see figure 5). The occurrence of these features is not always as clear-cut as it is for the child depicted in this figure; some rules to solve problems of non-uniqueness are discussed in section 6. The timing of the mid-growth spurt and of the pubertal spurt, and the tempo of transition through these spurts, can be assessed by the ages

of maximal and minimal velocity and acceleration. A statistical evaluation showed that the ages of maximal acceleration (T7) and in particular of minimal acceleration (T9) are surprisingly well defined, but age at take-off (T6) is often more ambiguous (Gasser, Sheehy & Largo 2001a). In the same spirit, we can determine maximal velocity and/or maximal acceleration to characterize the intensity of these spurts. The size of the velocity peak above prepubertal level is a more reliable indicator of intensity than maximal acceleration. Once such parameters are estimated for each individual, classical methods of statistics can be used to study various biomedical questions. In Sheehy et al. (1999), repeated measures analysis of variance was used to assess differences between boys and girls, and between different parts of the body, in the whole growth process. These parameters were also useful to investigate which aspects of the growth determine adult size, and in which way these influences act (Sheehy et al. 2000). Depending on the problem at hand, other sets of parameters might be useful: in Gasser et al. (2001a), various increments over the growth process have been suggested as an alternative, again using the timings of the pubertal spurt.

Based on these methods, the mid-growth spurt for height could be quantified for the first time (Gasser et al. 1985b); using acceleration was crucial, since the mid-growth spurt is often riding on a falling trend and then not necessarily a true maximum. It showed negligible differences for gender with respect to intensity and duration in all skeletal variables; the different parts of the body showed, however, large differences in intensity and partly also in timing (Sheehy et al. 1999). Height had the least intense mid-growth spurt, bihumeral width the most intense one. (Note that most of classical research was based on height, so that the mid-growth spurt was often overlooked). Both legs and trunk had a more intense mid-growth spurt than height, but since it was displaced in age, it became rather flat in the height velocity curve (see figure 9 of section 6). The pubertal spurt shows the differences in timing and intensity that are well known for gender, and partly known for different somatic variables. For boys, the pubertal spurt was not only more intense in absolute terms (except for iliac width) but also in relative terms when accounting for the

larger adult size of males. These are just a few results; further details are given in the papers cited above.

Software for kernel estimation, including choice of an optimal global or local bandwidth, can be downloaded from our homepage <http://www.unizh.ch/biostat>.

## 5 Shape-invariant modeling

While kernel estimation is an attractive method to explore individual dynamics and intensity of growth, the ultimate goal is to model growth, with the guidance of biomedical knowledge. (In contrast, the known parametric models are purely descriptive and the parameters have little biological relevance — meaningful parameters such as peak velocity and others, must be extracted from the fitted curves). Kernel estimation yields an individual velocity curve irrespective of the shape of all the other curves, and the individuals can be analyzed one by one. In reality, there are general mechanisms that regulate normal growth and result in a common shape for a sample of velocity curves. Fitting an adequate model which reflects this common shape, would lead to more consistent results across subjects by disregarding inconsistent, individual-specific features (formalized as random in (1)).

In those fields where one can get only one dataset to explore a relationship (e.g. in geophysics, where there is only one Earth), one can either guess at a parametric regression model or construct a model based on physical, chemical or biological knowledge. In growth studies, on the other hand, our present knowledge of endocrinological mechanism and of bone growth does not allow derivation of a functional growth model guided by basic biomedical principles, but we can obtain a multitude of individual realizations of some growth process, e.g. of height, which differ individually in quantitative but not in qualitative terms. Combining the information across subjects in a clever way might thus lead to a valid model.

A one-component shape-invariant model (SIM) is of the following form:

$$y_{ij} = a_i s\left(\frac{t_{ij} - b_i}{c_i}\right) + d_i + \varepsilon_{ij},$$

$$i = 1, \dots, m \quad (\text{subjects}); \quad j = 1, \dots, n_i \quad (\text{ages}).$$

The function  $s$  is called “shape function” and is common to all subjects, whereas  $a_i, b_i, c_i, d_i$  are individual parameters. Shape functions and parameters are both assumed unknown and have to be estimated from the data. Note that the logistic and the Gompertz models — often used for analyzing the pubertal spurt (Marubini et al. 1972) — can be seen as parametric versions of the SIM where  $s$  is fixed:

- Logistic model:  $s(x) = 1/(1 + \exp(-x))$ .
- Gompertz model:  $s(x) = \exp(-\exp(-x))$ .

Stützle et al. (1980) suggested the following 2–component SIMs for raw height velocity data  $v_i(t_{ij})$ :

- Additive 2–component SIM:

$$v_i(t_{ij}) = a_{1i} s_1\left(\frac{t_{ij} - b_{1i}}{c_{1i}}\right) + a_{2i} s_2\left(\frac{t_{ij} - b_{2i}}{c_{2i}}\right) + \varepsilon_{ij}.$$

- Switch–off 2–component SIM:

$$v_i(t_{ij}) = a_{1i} s_1\left(\frac{t_{ij} - b_{1i}}{c_{1i}}\right) \varphi\left(\frac{t_{ij} - b_{2i}}{c_{2i}}\right) + a_{2i} s_2\left(\frac{t_{ij} - b_{2i}}{c_{2i}}\right) + \varepsilon_{ij},$$

where

$$\varphi(y) = 1 - \frac{\int_{-\infty}^y \exp(-u^2) du}{\int_{-\infty}^{+\infty} \exp(-u^2) du}.$$

The switch–off function  $\varphi$  is not determined from the data but fixed a priori. It is required that  $\varphi$  descend smoothly from 1 to 0. An evaluation of different switch–off functions showed that the particular choice is not crucial, and that the above choice is plausible. The idea for both models is that the first component represents prepubertal growth and the second component represents pubertal growth. The introduction of a switch–off function, which stops further growth of the prepubertal component when pubertal growth climaxes, is based on biomedical knowledge about normal and pathological growth.

Figure 6 shows the resulting height velocity curve for the median boy, using the switch–off model (“median boy” means that the median of the estimated parameters



have been used). The pubertal spurt is clearly asymmetric, with stopping being faster than accelerating growth. A small mid-growth spurt around age 7 is clearly identifiable (compare also figure 9). The switch-off function provides a visually plausible separation into a prepubertal and a pubertal component. Figure 7 allows a comparison between the shape-invariant model, the Preece-Baines model and the kernel method for height growth of a girl. The Preece-Baines model leads to a substantially different fit compared to the other two methods.

What highlights about growth have emerged when using SIMs for analyzing height growth? These:

- Growth is qualitatively similar in boys and girls, since the same shape functions apply (quantitatively, growth is of course significantly dissimilar, e.g. the pubertal spurt is earlier and smaller in girls).
- The switch-off model is much more plausible than the additive model as shown e.g. by goodness-of-fit criteria.
- A distinct mid-growth spurt around 7 years appears in the first component.

That the two sexes grow similarly in qualitative terms cannot easily be deduced by other statistical methods. Based on Kneip & Gasser (1988), the switch-off 2-component SIM also holds for other somatic variables, and the above findings generalize. The success of the switch-off model demonstrates that the introduction of biological knowledge in the modeling process is a good strategy. The double-logistic model (Bock et al. 1973), which performs badly in goodness-of-fit criteria, is a special case of an additive model and would as such also profit from the introduction of a switch-off function.

To estimate the shape functions  $s_1$  and  $s_2$ , and at the same time the individual parameters  $a_{1i}, b_{1i}, c_{1i}$  and  $a_{2i}, b_{2i}, c_{2i}$  based on the estimated  $s_1$  and  $s_2$ , a relatively sophisticated algorithm is needed. The major steps are as follows:

1. Select approximate models  $s_1^{(0)}$  and  $s_2^{(0)}$  as starting points. These could be e.g. logistic or exponential functions, or pieces of the structural average (to be

defined in section 6). Put  $k = 0$ .

2. Determine parameters  $a_1^{(k)}, \dots, c_2^{(k)}$  for  $s_1^{(k)}$  and  $s_2^{(k)}$  by nonlinear least squares.
3. Compute residuals

$$\Delta y_{ij} = y_{ij} - a_{1i}^{(k)} s_1^{(k)} \left( \frac{t_{ij} - b_{1i}^{(k)}}{c_{1i}^{(k)}} \right) \varphi \left( \frac{t_{ij} - b_{2i}^{(k)}}{c_{2i}^{(k)}} \right) - a_{2i}^{(k)} s_2^{(k)} \left( \frac{t_{ij} - b_{2i}^{(k)}}{c_{2i}^{(k)}} \right).$$

4. Improve the model by fitting regression splines to the  $\Delta y_{ij}$  ( $i = 1, \dots, m; j = 1, \dots, n_i$ ) resulting in functions  $\Delta s_1^{(k)}$  and  $\Delta s_2^{(k)}$ .
5. Compute  $s_l^{(k)} = s_l^{(k)} + \Delta s_l^{(k)}$  for  $l = 1, 2$  as updated shape functions. Put  $k = k + 1$  and go to (2), or stop, if convergence is reached.

Note that for the model improvement stage (step 4) all measurements for all subjects are used, which leads to powerful results. Under suitable conditions, it can be mathematically shown that the method does what it is expected to do. The regression splines method used in this step is a well-known and convenient statistical tool for flexible function approximation. Regression splines consist of smooth piecewise polynomials; that is, they are polynomials on each of the several intervals in which the age range is divided, and each polynomial is smoothly connected to the adjacent ones. The demarcation of these intervals are called knots. In our case we used cubic polynomials, which is the standard choice. Due to the many measurements available (more than 6000), the placement and the number of knots is not critical. For further details on the algorithm see Stützle et al. (1980). A more general statistical foundation is given in Kneip & Gasser (1988). At present (year 2002) our software implementing the algorithm described above is not offered on the Web but can be requested from the authors.

As mentioned earlier, an advantage of modeling via SIM is that one can bring in a priori knowledge, e.g. biomedical knowledge. A further advantage is that one gets a parametric model without the need of prescribing from the onset a rather arbitrary regression function (as in the logistic or the Gompertz models, or the parametric models mentioned in section 3). Disadvantages are that the method is

quite sophisticated — more than those of Sections 4 and 6 — and thus not so easy to implement, and that it still can lead to some misspecification due to the postulated model structure.

## 6 Structural analysis

What we discuss in this section is conceptually related to shape-invariant modeling: again, we use the information from the whole sample of growth velocity curves to determine a consistent growth pattern free of individual fluctuations. Methodologically, the approach of structural analysis is based on kernel estimation (or some other nonparametric function estimator), particularly for the extraction of time of occurrence of some events (e.g. the timings of the pubertal spurt). These timings are often called landmarks or milestones and serve to align individual data to an average growth tempo.

In any context, estimation of the mean of an object of interest is a natural first step in data analysis. As already noted by Shuttleworth (1937), a naive cross-sectional mean curve does not provide a valid picture of growth: a cross-sectional average of velocity curves would e.g. render a “smeared” appearance of the pubertal spurt due to the variability in the timing of the spurt. To make curves comparable before averaging, some correction has to be made for the differences in timing. We chose a continuous transformation of the age axis to synchronize similar events (Gasser et al. 1990) at an average age (see below for details). Figure 8 illustrates this for a small sample of velocity curves of sitting height. Visually and from the average curves obtained, one notes the improvement achieved by the age transformation. The size of the pubertal velocity peak in particular would be severely underestimated without aligning to an average tempo.

Since the need for curve alignment arises in various fields — a technical example being analysis of speech — various data-analytic methods have been devised. The one described in this section is often called “landmark registration”, but we prefer to call it “structural analysis” since it relies on a common structure underlying

most growth curves. Here, we give an algorithmic description of how the alignment procedure works; a mathematically sound formalization can be found in Kneip & Gasser (1992). The procedure is as follows:

1. Structural points  $\tau_1, \dots, \tau_p$  are defined which occur in all or most curves: these can be ages when a minimum or a maximum of velocity or acceleration occurs during the pubertal spurt and during the mid-growth spurt. A structural point could also be the age where a percentage decrease has been realized, e.g., for the velocity curve in infancy.
2. The structural points  $\tau_1, \dots, \tau_p$  are determined via kernel estimation from individual velocity or acceleration curves, rendering  $\tau_{1i}, \dots, \tau_{pi}$  for subject  $i$ . Usually, some plausible rules are needed in addition; for example, an age range is known where a peak is expected. When a structural point cannot be safely determined in a subject, it is put to missing. Often the bandwidth  $h$  can be chosen a bit larger than for the curve itself.
3. Based on  $\tau_{1i}, \dots, \tau_{pi}$  the alignment functions  $h_i(t)$  are constructed in the following way:
  - $h(\bar{\tau}_s) = \tau_{si}$  for  $s = 1, \dots, p$ , where  $\bar{\tau}_s = \sum_{i=1}^m \tau_{si}/m$  (characterizing average tempo). This defines the transformation at structural points.
  - Between structural points, linear interpolation (or a more refined monotone interpolation as in Kneip & Gasser, 1992) is used. The resulting function  $h_i(t)$  is smooth and monotone increasing (a normal requirement for time transformations).
4. Before aligning individual data to an average tempo, a continuous velocity curve  $v_i(t)$  is constructed out of the raw velocities, for example by simple linear interpolation. The aligned individual velocity curve is then  $v_i(h_i(t))$  and the aligned average curve (the “structural average”) is:

$$\bar{v}(t) = \frac{1}{m} \sum_{i=1}^m v_i(h_i(t)).$$

5. Due to averaging,  $\bar{v}(t)$  will be much smoother than the interpolated and aligned individual raw velocities  $v_i(t)$ . If  $\bar{v}(t)$  is not smooth enough, some smoothing by kernel estimation is appropriate.

At present (year 2002) the authors' software implementing this algorithm is not available on the Web but will be provided at request. Related software, that parallels the book by Ramsay & Silverman (1997), can be found at the homepage of Jim Ramsay (<http://www.psych.mcgill.ca/faculty/ramsay/ramsay.html>).

The structural average has little or negligible bias compared to smoothed individual curves, since little smoothing (if at all) is involved. Due to the averaging process, it has also little variability, thus rendering a very accurate quantification of average growth. When determining e.g. peak velocity of the pubertal spurt from the structural average  $\bar{v}(t)$ , the result is much more accurate than the mean of individually determined peak velocities (following e.g. individual smoothing as in section 4). It can also be shown that the resulting structural average is closer to the underlying growth model. For mathematical details see Kneip & Gasser (1992). Since two types of variability are involved in this process (amplitude and time), it is mathematically not easy to give a standard deviation for the resulting structural average curve. One possibility is to take subsamples from the total sample, compute structural averages and assess variability visually.

Structural average curves are ideal for comparing growth of different groups, e.g. of boys and girls. They can also highlight, in a lucid way, differences in growth between various parts of the body (Gasser et al. 1991b, Gasser et al. 1991c). For instance, clear-cut results about differences in growth of trunk and legs could be obtained. While legs are relatively small at birth, they have a more intense growth after about 1-1/2 years until the advent of the pubertal spurt. The mid-growth spurt occurs earlier in the trunk than in the legs, while the pubertal spurt occurs later in the trunk. The pubertal spurt of the trunk is more intense compared to the legs and has also a different shape: while legs stop growth rather abruptly, the spurt of the trunk fades away slowly and is thus responsible for late growth and

further changes of body proportions. Similarly detailed results could be obtained for other somatic variables. Figure 9 gives an illustration for growth of height, trunk and legs (in relative velocity, % increase per year). Legs show a low velocity in infancy, an elevated one thereafter until the pubertal spurt, and an early and not too impressive spurt, followed by a rapid stopping of growth. The trunk has a high velocity in infancy (continuing the intra-uterine pattern) followed by a relatively low velocity until the pubertal spurt (which is relatively late and strong) and then slowly decreasing after the maximum. Height growth is sort of a compromise between leg and trunk growth. Interestingly, the mid-growth spurt is displaced for trunk and legs, and consequently it is weak for height. Biologically, then, it makes more sense to study trunk and legs separately, with their unique patterns.

Differences between groups were assessed by Schäfer et al. (1990) by comparing height growth in normal children with height growth in children with nephropathy. Ratcliffe, Pan & McKie (1992) obtained clear-cut results about growth of normal men compared with men with an XYY chromosomal disposition. The higher stature of XYY men is both due to a higher prepubertal velocity level and to a more intense pubertal spurt.

Interesting results could also be obtained by comparing the structural average curves of subjects with small or large adult sizes, leading to insights into the biological mechanisms responsible for these differences (Gasser et al. 2001b). For sitting height and biiliac width, an increased prepubertal velocity level is responsible for a large adult size; for legs this is also an important factor, but a delay in the pubertal spurt — and thus a longer growth period — is a further factor. For bihumeral width, the size of the pubertal peak is the decisive factor for adult size reached. The differences in growth of early and late maturers was also compared in this way (Gasser et al. 2001c). Except for legs, adult size was very similar. The shorter growth period of early maturers was mainly compensated by a higher prepubertal velocity level; only for boys a slightly higher pubertal peak was found.

## 7 Concluding remarks

We have discussed in this chapter three statistical approaches which proved to be useful for analyzing longitudinal data of growth of skeletal variables: kernel estimation for nonparametric function fitting (including first and second derivatives), shape-invariant modeling for determining shape functions (i.e. the regression model) as well as individual parameters, and an alignment procedure to synchronize curves before further analysis (e.g. before averaging curves). All three methods are of interest beyond applications to growth data and are in fact applied in fields as diverse as econometrics and engineering. Closer to auxology, kernel estimators might be useful for analyzing longitudinal hormonal data, while shape-invariant modeling has a potential for analyzing circadian rhythms in a sample of subjects.

The growth of skeletal variables is almost exclusively genetically determined, at least in developed countries. For variables involving soft tissue, exogenous factors come into play, and cause a more variable shape of growth from subject to subject. In our experience, kernel estimation and structural analysis still work for weight, BMI and circumferences. Determining milestones can become more problematic sometimes. We have not tried shape-invariant modeling for these variables. Skinfolds are different, since they are mainly influenced by exogeneous factors. One can, of course, apply kernel estimation to individual data, but the curves show a highly variable pattern from subject to subject. This makes further analysis difficult. One approach that was fruitful is the following: we used the alignment functions of height to align interpolated raw distances and velocities of skinfolds. The pattern of the resulting structural average curves was more relevant than the one obtained from the cross-sectional average. The biomedically relevant results can be found in a series of papers (Gasser et al. 1993b, Gasser et al. 1994a, Gasser et al. 1994b, Gasser et al. 1994c, Gasser et al. 1995).

Among the three nonparametric methods discussed in this article, kernel estimation is the most mature one scientifically (and the same applies to alternative methods of nonparametric function fitting such as splines and local polynomials).

In practice, it is advisable to start a data analysis with kernel estimators of the individual curves and to have a close look at the graphics obtained, in order to get an understanding of the process being studied. In a second step one might wish to extract features (meaningful parameters) from the individually estimated curves (be it distance, velocity or acceleration curves). They can be used for further statistical analysis. Often one will stop at this point. A natural next step would be the estimation of structural average curves to obtain a valid picture across somatic variables and for comparison of the two genders. Typically, these average curves are much more informative than the individual curves. Often the analysis of subgroups – e.g. subjects with a small or large size in some somatic variable, or early and late maturers – lead to substantial medical insight, not easy to obtain by other means. Shape-invariant modeling, on the other hand, is advisable at a later stage of research, and if sufficient statistical resources are available.

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## Figure captions

- Figure 1: Height velocity of a girl from 0 to 20 years: stars = raw velocity, solid line = kernel fit, dashed line = Preece–Baines fit.
- Figure 2: Optimal kernels for estimating  $r$  (left), for  $r'$  (middle), for  $r''$  (right).
- Figure 3: Kernel smoothing with various bandwidths for synthetic data ( $n = 50$ , above left, stars = data, dashed = true function), undersmoothing (below left), oversmoothing (below right), optimal smoothing (above right).
- Figure 4: Velocities of trunk length for 5 boys (above) and 5 girls (below). Left = raw velocities, right = kernel estimated velocities.
- Figure 5: Velocity (above) and acceleration (below) curves obtained by kernel estimation, together with features or landmarks.
- Figure 6: Height velocity of the median boy according to the switch–off 2–component shape–invariant model (solid curve). Growth due to first component (dash–dot), for second component (dashed).
- Figure 7: Height velocity curves of a girl based on shape–invariant modeling (solid curve), Preece–Baines fitting (dashed) and kernel fitting (dash–dot).
- Figure 8: Above: 6 velocity curves of the trunk (kernel fitting). Middle: after alignment procedure. Below: cross–sectional average curve (dashed), aligned or structural average curve (solid line).
- Figure 9: Structural average velocity curves of height (solid), trunk (dashed) and legs (dash–dot) for boys. Left: first 3 years on a different scale.



















