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Phase Variation in Child and Adolescent Growth

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Abstract

Child growth is characterised by increases in height, and increases in maturational status. Functional data analysis provides a tool to separate these two sources of variation (registration) and differentiates between the variation in maturational tempo (temporal, or “phase” variation) and the variation in height (amplitude variation). We extended this concept by combining Principal Component Analysis (PCA) and the Maximum Likelihood Principle. Longitudinal data on height were obtained from two large growth studies from Lublin, Poland, and Zurich, Switzerland, with altogether 361 children. Variation in amplitude monotonically rises with age; variation in phase peaks during puberty. During mid-puberty, phase variation is large and explains up to 40 percent of total height variance in girls, and up to 50 percent in boys. Eight amplitude and 4 phase components appeared biologically significant. The largest amplitude component explained 91% of the amplitude variance and is characterised by an almost horizontal pattern. The largest phase component explained 66% (boys) and 63% (girls) of phase variance, rises throughout childhood and reaches up to 0.85 years in adolescent boys, and up to 0.75 years in adolescent girls. Phase components significantly correlated with the clinical signs of puberty. The combination of PCA and the Maximum Likelihood Principle provides a new, powerful and automatic tool for growth modelling that includes estimates of future growth, adult stature and developmental tempo. Preliminary results indicate that this approach can be used for automatised screening purposes.

KEYWORDS: variation, principal component analysis, PCA, growth, height prediction

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Erratum

The original citation for this article published on May 17th was as follows:

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Introduction

Modelling child and adolescent growth has a long history. Several of the more recent approaches have been summarised by Ledford and Cole (8), and Milani (10). Conventional modelling of human growth usually requires equidistant measurements from birth to maturity. Yet, everyday life is not that simple. “Natural” documents of child growth seldom consist of data that are obtained at regular annual or semi-annual intervals.

Many of these problems have been overcome using the concept of *growth tracks*. The term *tracking* has been used to denote an individual’s maintenance of relative rank of some longitudinally measured characteristic over a given time span (14). *Growth tracks* are insensitive to the timing of the measurements, and denote areas of probability within which subsequent measurements will predominantly be found. The more frequently an individual is measured, the better can his or her *growth track* be characterised. *Growth tracks* may be viewed as bunches of individual developmental canals (6). Yet growth tracks only spanned a few years as it proved difficult to obtain complete tracking of an individual throughout the total period of maturity.

Recent progress in longitudinal growth analysis has been made using the methods of functional data analysis (13). Functional data analysis was developed to analyse observations which are curves. Principal Component Analysis has been used for modelling individual growth from birth to adulthood (12).

Child growth is characterised by increases in height, and increases in maturational status. Variation in growth thus results both from variation in height, and from variation in the tempo at which the maturational status advances. In other words, some children may develop fast, appear tall at a young age, but may only reach medium height though at an early age, whereas others may develop slowly, appear short at a young age, but reach an appropriate adult stature later. Variation in maturational tempo may result in temporary variation in height, but does not usually imply equivalent variation in adult stature.

Functional data analysis provides a tool to clearly separate these two sources of variation (registration) and differentiates between the variation in maturational tempo (temporal, or “phase” variation) and the variation in stature (amplitude variation). Principal Component Analysis (PCA) can then be used to separately determine phase and amplitude variation.

Material and methods

Longitudinal data on height were obtained from two large national growth studies, performed at Lublin, Poland (4), and Zurich, Switzerland (11) with 232 healthy Swiss and 129 healthy Polish children. Of all measurements, we selected

measurements at the 23 standard ages: at birth, at the age of 0.25 y, 0.5 y, 0.75 y, 1.0 y, 1.5 y, 2.0 y, and at annual intervals thereafter up to 18 years. In the children of the Zurich study, stages of pubertal development (17), and skeletal maturation (1,5) were also documented.

A small pilot study showed that Swiss children grew more homogeneously than Polish children (data not shown in detail as we did not want to distract from the main point made in this paper). i.e., if we had based the present investigation solely on the Swiss population, we would have underestimated possible intra-population variation of children of other than Swiss origin.

This resulted in four groups of vectors of length 23 each, namely y_{ijs} , consisting of the height measurements obtained at the 23 standard ages from birth to maturity. Here $i=1, 2$ denotes the study, $s=1, 2$ denotes the sex (1 for male, 2 for female) and j denotes the number of the child.

A. Calculating the reference model

First, the groups of vectors were analyzed separately. Separation of temporal (phase) variation from amplitude variation (registration (13)) was done for each child. This was done in several steps. Initially, we calculated the mean vector y_{is}^* of the vectors in the actual group. For each of the vectors y_{ijs} in the actual group, we then shifted the values of each age point by an amount a_{jk} , $k=1, \dots, 23$, while keeping the associated height values. Using linear interpolation, we evaluated the resulting curve at the 23 original age points, obtaining vectors y'_{ijs} . The shifting was done so that the difference between the resulting vector and the mean becomes minimal, $|y'_{ijs} - y_{is}^*| \rightarrow \min$. This leads to a new mean vector y_{is}^* of the vectors y'_{ijs} . This procedure can be repeated, but since height development is monotone, it actually converges after the first step. The resulting vectors y'_{ijs} are – separately for each group – transformed into SD-scores z_{ijs} by subtracting the pointwise mean and dividing by the pointwise standard deviation.

This resulted in a 361×23 matrix Z of the SD-scores - whose rows are the vectors z - and a 361×23 matrix A of the age transformations, where $A_{ik} = a_{ik}$. We then grouped only by sex and performed PCA four times, both for the SD scores and the age transformations, and separately for both sexes.

The aim of PCA is to obtain loadings of the components that are uncorrelated. Although this is never perfectly the case, a scatterplot that shows a non-noise structure in some areas reveals small deficits in the approach, rather than showing interesting features of the data (not shown in detail).

We restricted the maximum number of components to the number that appeared “biologically significant”. i.e. we only allowed for components that explained a meaningful amount of height variance, and we ignored components

that explained less than the measurement error. Twelve components remained “biologically significant”, 8 amplitude, and 4 phase components.

The coefficients of these components are a model for growth from birth to maturity, since for each set of parameters one can construct a set of z-scores (which can be transformed into height values, using the appropriate mean and standard deviation), and a set of age points which correspond to these height values. So, as a result of the calculations so far, we get a reference growth model with 12 parameters, and we get the information on how these parameters are distributed in the two sexes of the study populations.

B. Applying the reference model to estimate individual growth curves

The reference model and the information about the distribution of the parameters can now be used to address a different goal: given an arbitrary set of height measurements of an individual child – that is, a vector h_i , $i=1..n$ of height values and a vector a_i , $i=1..n$ of age points – we ask: how can we estimate the most likely growth curve for this individual child? Obviously, given the true – but unknown – growth curve $h(a)$, all differences $h_i-h(a_i)$ must be measurement errors. We know the standard error of height measurements, and we assume that measurement errors are normally distributed. Under the assumption that the curve $h(a)$ represents the true growth curve of this child, we can associate the curve with a likelihood that it yields the observed measurements. The curve, in turn, is described by the 12 parameters for the principal components we calculated. This is the classical setting for applying the Maximum Likelihood principle. The Maximum Likelihood principle provides us with the most likely parameters that fit the given measurements.

Since the distribution of the parameters in the population is known, the parameters themselves can be assigned a likelihood. These likelihoods can be included in the optimization process to find the most likely parameters, thereby punishing unlikely curves even if they fit the measurements well. So, for each set of measurements, we end up with a 12 parameter optimization problem. We used the Hooke-Jeeves-Algorithm to find an approximation to the optimum. The resulting parameters allow us to decide whether the growth curve is within the normal range. Because we have more than one parameter, we used the False Discovery Rate procedure (2) to adjust for multiple testing.

To summarise, the approach involves two steps:

- A. Principal components for phase and amplitude variation are obtained from a reference population, resulting in a reference growth model.
- B. This model is used to
 - find the most likely growth curve, given an arbitrary set of measurements for an individual child

- decide whether the growth curve of this child is normal given the reference population.

Results

Both phase and amplitude contribute to the variance in height (Fig 1). Variation in amplitude monotonically rises with age; variation in phase peaks during puberty. This is plausible: tall and short children may become tall and short adults, but the tempo of maturation can affect growth only when children grow. During mid-puberty, phase variation is large and explains up to 40 percent of total height variance in girls, and up to 50 percent in boys. When adult height is achieved, phase variation can no longer affect height.

Eight amplitude and 4 phase components appeared biologically significant. The percentage of variance explained by each of these components however, differed markedly (Table 1). The largest amplitude component explained 91% of the amplitude variance (Table 1) and is characterised by an almost horizontal pattern around -1 SD after the first year of life (Fig 2) indicating that after this age, the main source of amplitude variance is simply being permanently tall or average or short. Amplitude component 2 explains some of the remaining variance in infancy and early childhood. It approaches 0 SD at mid-childhood and apparently, does not affect growth after this age. The remaining amplitudes components were relatively small. The largest phase component explained 66% (boys), and 63% (girls), the second largest 18% (boys), and 16% (girls) of the phase variance. Phase component 1 steadily rises and reaches up to 0.85 years in adolescent boys, and up to 0.75 years in adolescent girls. This simply indicates that the major source of temporal variance is a continuous increase in the inter-individual variability of tempo. Phase component 2 explains some remaining tempo variation during puberty. The remaining phase components were small.

Split-half reliability

Split-half reliability was tested in order to examine the stability of the amplitude and phase component estimates. After splitting the Swiss and Polish samples into two ethnically mixed cohorts (cohort A and B) that were analysed by reference components obtained from the opposite cohorts, 165 out of the 180 children of cohort A, showed “average” growth curves, 6 “abnormal” (outside the 5% limit of confidence), and 8 showed “very abnormal” growth curves (outside the 1% limit of confidence). One growth curve was outside the 0.1 % limit of confidence. For cohort B, 167 of the 181 children, showed “average” growth curves, 9 “abnormal”, 4 “very abnormal” growth curves, and we found one growth curve outside the 0.1 % limit of confidence. i.e., the distribution of children into the

categories normal, abnormal, and very abnormal growth, did not significantly differ from random ($p > 0.5$ using a chi-square test).

Validity

Left hand and wrist X-rays (“bone age determination”) (1,5) can be used to assess a child’s state of maturation and help characterise his or her developmental tempo. PCA-derived phase components also provide estimates of tempo. Using the Swiss children of split cohorts A and B, we correlated “bone age” and PCA-derived phase components, and two clinical signs of pubertal maturation (menarche and Tanner stage III of male genitalia (17), Table 2). Both “bone age” and PCA-derived phase components significantly correlated with the clinical signs of puberty. Surprisingly, the correlation between phase and menarche ($r_A = 0.76$, resp. $r_B = 0.88$) and phase and male genitalia III ($r_A = 0.72$, $p_A < 0.01$, resp. $r_B = 0.69$, $p_B < 0.01$) were higher than the correlation between bone age and menarche ($r_A = 0.64$, $p_A < 0.01$, resp. $r_B = 0.76$, $p_B < 0.01$) and bone age and male genitalia III ($r_A = 0.53$, $p_A < 0.01$, resp. $r_B = 0.52$, $p_B < 0.01$), i.e. estimates of PCA-derived phase components appeared to better coincide with pubertal signs than estimates of skeletal maturity.

PCA describes growth from the age of 0 to 18 years, thus PCA can also be used for predicting future growth and adult stature. We tested the validity of PCA derived growth prediction for every Swiss child. To do this, we calculated components based on all Swiss children except the one selected (step A: Calculating the reference model). We then used the measurements of the selected child up to various ages, and at each age, we calculated the most probable growth curve (step B: Applying the reference model to estimate individual growth curves). Predicted final height was defined as the value of this curve at age 18. Fig 3 demonstrates final height prediction by conventional left hand X-ray (1,5) and PCA. Except for bone age-derived height predictions in pre-pubertal boys, height predictions from X-ray and PCA appear to be equivalent.

Discussion

The terms “tall” and “short” usually compare children to an appropriate reference standard of height. But though the differential pattern of early and late maturing children has long been recognised (15), height measurements are often insufficient to precisely estimate developmental tempo. Additional information, such as indicators of pubertal maturation and X-rays of the left hand and wrist are usually considered essential for estimating a child’s state of maturation.

Obtaining additional information for estimating the state of maturation however, is often tiresome, and as it certainly needs additional professional

expertise, can rarely be performed at large scale, e.g., for surveillance, screening and preventive care purposes.

Recent progress in modelling individual growth with appropriate reference to temporal variation in child growth was made using Principal Component Analysis (PCA, (13)). Ramsay and Bock (12) separated temporal variation (variation in maturational tempo, “phase” variation) from amplitude variation (variation in height, i.e., being tall or short), and developed a most promising technique for further analysing, simplifying and eventually automatising the analysis of serial height data.

The present analysis relies on the Ramsay-Bock approach, but it adds a stochastic approach (the Maximum Likelihood Principle) and corrects for the effect of multiple testing using the False Discovery Rate procedure (2). This combination is new. It not only separates phase and amplitude variation in standard series of height measurements as suggested by Ramsay and Bock, it also allows the completion of rudimentary data by adding information that was previously obtained from a reference population. PCA of a reference population yields reference components. Reference components characterised by curves and standard deviations can be used to replace the principal components of a particular “unknown” child by z-scores.

The second step includes a stochastic approach. We use the Maximum Likelihood Principle and Hooke-Jeeves algorithm (3). We start with the (possibly incomplete series of) height z-scores of the “unknown” child, but we do not follow the usual Ramsay-Bock procedure. Instead, we optimise the “most likely profile of components” that are now re-written as z-scored principal components, and we end up with a z-score profile that is characteristic for this particular “unknown” child, i.e. we describe the individual pattern of height increment with an individual profile of z-scored principal components. As principal components range from birth to maturity, the new curve – consisting of z-scored principal components – also ranges from birth to maturity regardless of whether the height data of the unknown child were complete or incomplete. The new process includes estimates of final height (height value at maturity), and estimates of phase for all ages from birth to maturity.

The combination of PCA and the Maximum Likelihood Principle is a strictly mathematical tool. Yet, the mathematical term “phase” significantly correlates with bone age and clinical signs of puberty indicating that the mathematical approach provides a valid description of clinical markers.

Component 1 coincides with the clinical impression that a *correlation exists between adult height and heights of the same individuals as children and adolescents* (16). Component 2 explains height variation located in infancy and early childhood, and coincides with the impression of an *adjustment of size early*

in life when the prenatal maternal influence on body size switches towards an equilibrated maternal and paternal control of size after some 2 years of age (16).

Phase variance predominantly affects body stature during puberty where it explains up to 40% of height variance in girls, and up to 50% of height variance in boys. Phase component 1 steadily increases and coincides with the clinical impression that some children develop faster or slower than others.

One may speculate upon the biological significance of mathematical tools. PCA is a tool with *a priori* no biological significance. But the present analysis resulted in a mathematical description that appeared biologically meaningful: it coincides with clinical aspects of growth and development – with variation in amplitude, and variation in tempo.

The present study provides a new, powerful and automatic tool for growth modelling that includes estimates of future growth, final height and developmental tempo. Preliminary results (www.willi-will-wachsen.com (9)) indicate that the combination of PCA and the Maximum Likelihood Principle can be used for automatised screening purposes. Parents may enter data for their children; doctors may use such data for medical surveillance and research. The combination is particularly helpful for early detection of children with growth disorders, and may be a useful supplement to regional or nation-wide growth screening projects such as CrescNet (6).

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Legend to Figures

Fig 1 Total height and amplitude variance in Swiss children and adolescents. The difference between the two results from phase variation. During mid-puberty, phase variation is large and explains up to 40 percent of total height variance in girls, and up to 50 percent in boys.

Fig 2 Pattern of the two largest amplitude (Am 1, Am2, given in height SD) and the two largest phase components (Ph1, Ph2, given in years).

Am 1 is characterised by an almost horizontal pattern around -1 SD after the first year of life indicating that after this age, the main source of amplitude variance is simply: being permanently tall or average or short. Am 2 explains some of the remaining height variance in infancy and early childhood. Am 2 approaches 0 SD at mid-childhood and apparently, does not affect growth thereafter.

The largest phase component Ph 1 steadily rises and reaches up to 0.85 years in adolescent boys, and up to 0.75 years in adolescent girls. This simply indicates that the major source of temporal variance is a continuous increase in the inter-individual variability of tempo. Ph 2 explains some remaining tempo variation during puberty.

Fig 3 Standard deviations (SD) of final height predictions by conventional left hand X-ray (“bone age”) and by PCA. Except for bone age-derived height predictions in pre-pubertal boys, height predictions from X-ray and PCA appear to be equivalent.

Table 1

Percentage of variance, and cumulative proportion of amplitude and phase components

Amplitude components

Boys								
Component	1	2	3	4	5	6	7	8
% Variance	0.911	0.048	0.014	0.006	0.004	0.004	0.002	0.002
Cumul. Proportion	0.911	0.956	0.972	0.978	0.983	0.986	0.989	0.991
Girls								
Component	1	2	3	4	5	6	7	8
% Variance	0.911	0.050	0.011	0.006	0.004	0.004	0.003	0.003
Cumul. Proportion	0.911	0.961	0.972	0.978	0.982	0.986	0.989	0.991

Phase components

Boys				
Component	1	2	3	4
% Variance	0.659	0.185	0.068	0.033
Cumul. Proportion	0.659	0.844	0.912	0.945
Girls				
Component	1	2	3	4
% Variance	0.630	0.161	0.072	0.058
Cumul. Proportion	0.630	0.791	0.863	0.921

Table 2

Correlations between two clinical signs of pubertal development (Menarche and Tanner stadium III of male genitalia) and bone age, and PCA derived phase.

	Menarche	Genitalia III
Correlation (r) with bone age		
Cohort A	-0.64 (n= 51)	-0.53 (n=55)
Cohort B	-0.76 (n=55)	-0.52 (n=55)
Correlation (r) with Phase		
Cohort A	-0.76 (n=53)	-0.72 (n=58)
Cohort B	-0.88 (n=56)	-0.69 (n=55)

Figure 1

Figure 2

Figure 3