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SITAR—a useful instrument for growth curve analysis

Tim J Cole,[1]* Malcolm D C Donaldson[2] and Yoav Ben-Shlomo[3]

[1]MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London, UK, [2]University of Glasgow Department of Child Health, Royal Hospital for Sick Children, Glasgow, UK and [3]Department of Social Medicine, University of Bristol, Bristol, UK

*Corresponding author. MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK. E-mail: tim.cole@ich.ucl.ac.uk

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Background Growth curve analysis is a statistical issue in life course epidemiology. Height in puberty involves a growth spurt, the timing and intensity of which varies between individuals. Such data can be summarized with individual Preece–Baines (PB) curves, and their five parameters then related to earlier exposures or later outcomes. But it involves fitting many curves.

Methods We present an alternative SuperImposition by Translation And Rotation (SITAR) model, a shape invariant model with a single fitted curve. Curves for individuals are matched to the mean curve by shifting their curve up–down (representing differences in mean size) and left–right (for differences in growth tempo), and the age scale is also shrunk or stretched to indicate how fast time passes in the individual (i.e. velocity). These three parameters per individual are estimated as random effects while fitting the curve. The outcome is a mean curve plus triplets of parameters per individual (size, tempo and velocity) that summarize the individual growth patterns. The data are heights for Christ's Hospital School (CHS) boys aged 9–19 years ($N = 3245$, $n = 129\,508$), and girls with Turner syndrome (TS) aged 9–18 years from the UK Turner Study ($N = 105$, $n = 1321$).

Results The SITAR model explained 99% of the variance in both datasets [residual standard deviation (RSD) 6–7 mm], matching the fit of individually-fitted PB curves. In CHS, growth tempo was associated with insulin-like growth factor-1 measured 50 years later ($P = 0.01$, $N = 1009$). For the girls with TS randomized to receive oxandrolone from 9 years, velocity was substantially increased compared with placebo ($P = 10^{-8}$).

Conclusions The SITAR growth curve model is a useful epidemiological instrument for the analysis of height in puberty.

Keywords Height, puberty, Turner syndrome, growth curve, random effects

Introduction

A child's growth curve contains considerable information about their genetic make-up and environmental exposure.[1] It can be useful to characterize the nature of the curve and relate it both to previous or current exposures and putative later outcomes.[2] Thus, the characterization of the growth curve is an important

first stage in the life course study of early growth and later outcome.

By its nature the growth curve consists of a series of highly correlated measurements, and it is important to reduce the dimensionality of the data to simplify comparisons between individual children. The traditional approach is to identify a suitable parametric model for the given measurement and age range, for example the Jenss–Bayley curve[3] for weight in early life or the Preece–Baines (PB) curve[4] for height in puberty. The growth curve is then entirely characterized by the fitted parameters of the model, which can be used instead of the raw data to test for associations with exposure and/or outcome.

This article focuses on height in puberty, where the PB curve with its five estimated parameters fits individual growth curves extremely well, with a residual standard deviation (SD) of 6–7 mm.[4,5] However, as a summary of the underlying curve its five parameters are relatively high-dimensional for many purposes.

The ideal approach would be to fit a form of curve to all subjects simultaneously, and to estimate the subject-specific parameter values as subject random effects. Such an approach could in principle be applied to the PB curve. However, Beath[6] introduced a considerable simplification to the analysis of growth curves by describing a *shape invariant model* of infant weight. This consists of a single growth curve, which can be applied to all subjects by applying just three subject-specific translations and rotations of the curve to fit the individual subject growth curves.

The aim here is to fit the model described by Beath[6] and show how effectively it summarizes height growth around the time of puberty. The second aim is to show how the estimated subject-specific parameters can be related to earlier exposures and later outcomes.

Methods

Data sets

Two data sets are used as examples, both of height in puberty. The first, the Christ's Hospital School (CHS) cohort, consisted of a sample of 3245 boys, who attended the school at some stage between 1939 and 1968 and were measured twice a term between the ages of 9 and 19 years [median 42 measurements per boy, inter-quartile (IQR) range 35–47, range 1–63], a total of 129 508 heights. These were linked to follow-up data on 1520 adults, some 50 years later, when inter alia height and insulin-like growth factor 1 (IGF-1) levels were measured. The cohort has been described in detail previously,[7–9] and an inverse association between age at peak height velocity (APHV) and later IGF-1 has been reported.[9] This was based on estimates of APHV for each child derived from spline curves fitted to each child's data.

The second data set came from a randomized clinical trial of oxandrolone to increase final height in girls with Turner syndrome (TS). This is a chromosomal disorder where the second X chromosome is missing or malformed, leading to short stature and primary ovarian failure. A total of 106 girls with TS already on a standard dose of growth hormone were randomized to receive either oxandrolone or placebo from the age of 9 years (or the age at recruitment if later) until final height was reached. One girl dropped out immediately and 13 more later on, whereas 92 girls remained in the study and 82 had reached final height before the time of analysis. A total of 1321 heights were included in the analysis (median 12 per child, IQR 9–17, range 1–23). The trial, which also included a second randomization to early or late oestrogen for induction of puberty, is reported in detail elsewhere (EJ Gault *et al.*, submitted for publication).

The SITAR model

The method used to summarize the individual growth curves followed that of Beath,[6] and was also an extension of the model developed independently by the first author and colleagues.[7] This is a shape invariant model[10,11] that involves fitting the following random effects model to the set of height growth curves:

$$y_{it} = \alpha_i + h\left(\frac{t-\beta_i}{\exp(-\gamma_i)}\right) \quad (1)$$

where y_{it} is height for subject i at age t, $h(t)$ is a natural cubic spline curve of height vs age, and α_i, β_i and γ_i are subject-specific random effects. The aim is to choose the values of α_i, β_i and γ_i to make the individual growth curves as similar as possible, i.e. the mean spline curve $h(t)$. Their interpretations are as follows:

- α_i is a random height intercept that adjusts for differences in mean height—here it is termed *size*. Geometrically it can be thought of as a subject-specific shift up or down or *translation* in the spline curve, with α_i smaller for shorter children.
- β_i is a random age intercept to adjust for differences in the timing of the pubertal growth spurt in individuals i.e. the APHV, and it is here called *tempo* following Tanner's usage. Geometrically it corresponds to a subject-specific left–right shift or translation in the spline curve, with β_i negative for early puberty and positive for late.
- γ_i is a random age scaling that adjusts for the duration of the growth spurt in individuals. Its parameterization as $\exp(-\gamma_i)$ ensures that both positive and negative values are permissible, with zero corresponding to average velocity, and the minus sign means that it measures velocity rather than its inverse. (This minus sign is the reverse of Beath's notation.) Geometrically it corresponds to a shrinking or stretching of the age scale. Thus for a child

with a relatively short spurt and a steep growth curve, γ_i is positive to stretch the age scale and reduce the slope (i.e. peak velocity). Conversely, if γ_i is negative the age scale is shrunk and the curve slope increased. For this reason the parameter is termed *velocity*. Note that its effect is to make growth curves steeper or shallower, so it effectively *rotates* each curve (this terminology makes clear its similarity to a random slope effect, though strictly it is a scale change rather than a rotation).

Figure 1 illustrates the meanings of the three parameters geometrically, i.e. the three ways in which the mean growth curve (black solid line) can be transformed to match an individual's growth curve. Size is an up–down shift on the height axis (red dashed lines) and tempo is a right-left shift on the age axis (blue long dashed lines), while velocity is a shrinking–stretching of the age axis (green dot-dashed lines). The pairs of lines represent 95% of the population variation (i.e. ±2 SD). The principle is that by suitable choice of these subject-specific parameters, smoothed estimates of each individual growth curve can be obtained by transformation of the mean curve. This leads to a particularly simple way of assessing goodness of fit. If the model fits well, each individual curve can be back-transformed using the subject's triplet of estimated parameters, and all the curves should then sit on top of the mean curve. Expressed in words, the model allows individual curves to be super-imposed by translation and rotation, leading to the happy acronym SITAR (SuperImposition by Translation And Rotation). This is the SITAR model for growth curve analysis.

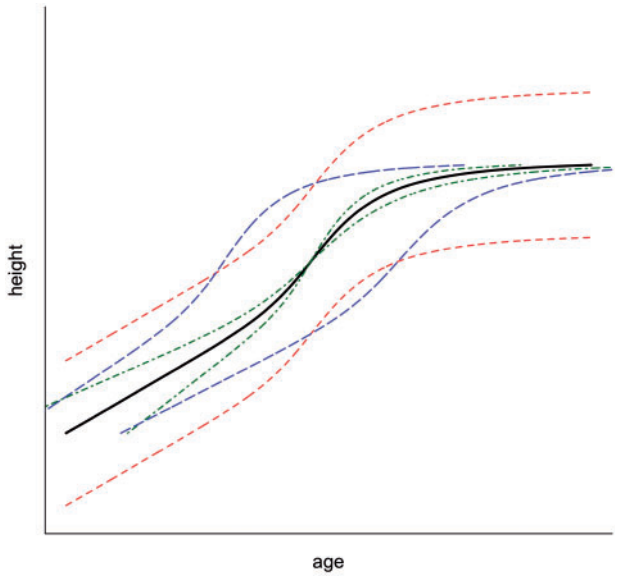

Figure 1 Illustration of the SITAR model for height in puberty. The solid line is the mean growth curve; the short dashed lines indicate a vertical or height shift in the curve corresponding to size (α); the long dashed lines indicates a horizontal or age shift corresponding to tempo (β) and the dot-dashed lines represent a shrinking–stretching of the age scale reflecting velocity (γ)

The model was fitted using the `nlme` function[12] in `R`,[13] with the age term centred to mean zero, the three parameters fitted as random effects and size and velocity also as fixed effects, and $h(t)$ a natural cubic spline curve with 6 degrees of freedom (df) fitted as fixed effects. Height and age were fitted both untransformed and log transformed, to identify the optimal underlying scales.

Growth related to exposure and outcome

In the CHS cohort, the relationships between the SITAR parameters and the outcome measures of height and IGF-1 at follow-up 50 years later were investigated using correlation and regression.

The analysis of the TS clinical trial data involved comparing the SITAR parameters in individuals in the two trial arms. This was done in three ways.

(i) Comparing the mean values of each growth parameter in the two arms using *t*-tests.
(ii) Extending the SITAR model to include fixed effects for each parameter by trial arm.
(iii) Fitting the SITAR model to the data for each trial arm separately, to demonstrate differences in the two mean curves.

The first two approaches test the effect of the oxandrolone intervention on the parameters, while the third shows its effect on the mean growth curve.

Results

The SITAR model

The SITAR model fitted the CHS data best on the scales of height and log age. Table 1 shows the deviances and residual standard deviations (RSDs) for the alternative models in the CHS and TS datasets, confirming that for CHS log age provided a far better fit than age (deviance 1460 units smaller), and height was better than log height. Despite this, the effect on the RSD was small. For the TS data, height and age were slightly better than height and log age by 19 units of deviance.

In general, a shift on the log scale translates to a scaling on the original scale. So a left–right shift on the log age scale corresponds to a shrinking–stretching on the age scale. Thus for the log age model the age scale can be viewed as elastic and fixed at zero, with the scale shrunk for early puberty and stretched for later puberty.

Figure 2 shows the raw data for the CHS cohort, a series of superimposed growth curves colour-coded to identify individuals. The RSD about the fitted spline curve is 6.6 cm (data not shown). Figure 3 shows the incremental effect of adjusting for each of the SITAR parameters in turn, where each subject's growth curve

Table 1 Comparison of SITAR models of height on age with and without log transformation

	Christ's Hospital		Turner Study	
Model	Deviance	Residual (cm)	Deviance	Residual (cm)
Height vs log age	***359 450***	***0.786***	3973.4	0.634
Height vs age	360 910	0.791	***3954.6***	***0.627***
Log height vs log age	361 150	0.792[a]	4057.8	0.660[a]
Log height vs age	362 810	0.797[a]	4039.8	0.653[a]

Deviances and RSDs for the two cohorts under the four models, ranked by size for CHS, with the minima shown in bold italic font.
[a]RSD obtained by multiplying by the geometric mean of height.

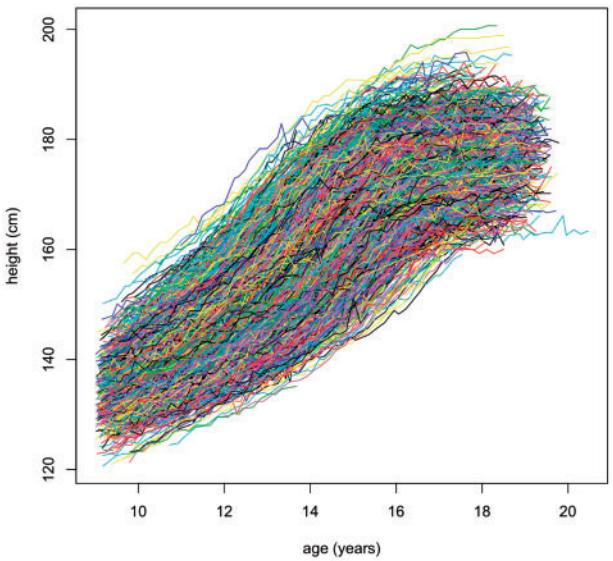

Figure 2 CHS data—3245 height growth curves and 129 508 heights from 9 to 19 years

is plotted using the individually adjusted height and age scales. In Figure 3a, a random height offset (i.e. the size parameter α) is adjusted for, so that individual curves are shifted up or down to minimize the RSD, which is reduced to 2.3 cm. In Figure 3b, a random age offset is added (the tempo parameter β), which shifts individual curves left–right and reduces the RSD to 1.2 cm. Finally, in Figure 3c the age scaling is added (the velocity parameter γ), which shrinks–stretches individual curves and reduces the RSD to 0.8 cm. The three graphs show increasingly obvious spiky outliers above and below the main body of data, corresponding to height recording errors at the time of measurement. To adjust for this, Figure 3d trims residuals exceeding 2.4 cm in absolute value ($n = 952$ or 0.74%) so as to remove the spikes but retain the main body of data. This reduces the RSD to 0.7 cm.

Thus the estimation of, and adjustment for, the SITAR parameters reduces the RSD from 6.6 to 0.7 cm, a reduction in variance of 98.9%. The final RSD is similar to the median RSD for PB curves fitted to each individual.[4,5]

Table 2 gives the standard deviations and correlations of the growth parameter random effects for the model in Figure 3c. Size is in units of cm, tempo is fractional due to the log age scale and velocity is a fractional multiplier (the latter two can be multiplied by 100 and viewed as percentages). Multiplying tempo by mean APHV (14.3 years) converts it to years, giving an SD of 0.97 years. The three growth parameters correlate with each other at around +0.3, indicating that boys entering puberty later (positive tempo β) tend to be taller (larger size α) and have a larger peak velocity (γ).

Figure 4 shows the individual raw and SITAR-adjusted growth curves for the TS cohort, colour coded by trial arm. The raw RSD is 5.9 cm, which shrinks to 0.6 cm on adjustment for the three parameters. Thus again 99% of the variance is explained by the SITAR model, and the remaining variability matches that of the PB curve. On this basis it can be argued that the three SITAR parameters explain *all* the differences in growth between individuals, so that they constitute a parsimonious summary of the individual growth curves.

Table 3 summarizes the growth parameter random effects for the model in Figure 4. Size is in units of cm and tempo in years, while again velocity is fractional. The tempo–velocity correlation of –0.46 differs from the +0.26 for the Christ's Hospital data, and shows that girls entering puberty early tend to have the largest height velocity. (Endocrinological note—most of the girls with TS did not enter puberty spontaneously, it was induced artificially, so tempo here relates more to the later fall in velocity than the earlier rise.)

Growth related to exposure and outcome

Table 4 relates the CHS pubertal height parameters to the clinical outcomes 50 years later. It shows summary statistics and correlations with the three SITAR parameters of age, height and IGF-1 as measured at mean age 63 years.[9] In addition, it gives APHV as derived individually for each child.[9]

Size and height are very strongly correlated ($r = 0.86$), though tempo and velocity also correlate with height to some extent. To clarify their relative contributions, Table 5 shows the multiple regression of later height on the three parameters, where the standardized coefficients indicate the effect on height of a 1-SD increase in each parameter. This confirms that size is by far the strongest predictor (+5.5 cm per SD), though both tempo and velocity are also predictive in opposite directions (−0.6 and +0.5 cm per SD, respectively).

Table 4 also shows a strong correlation between tempo and APHV (0.83). So tempo is closely related

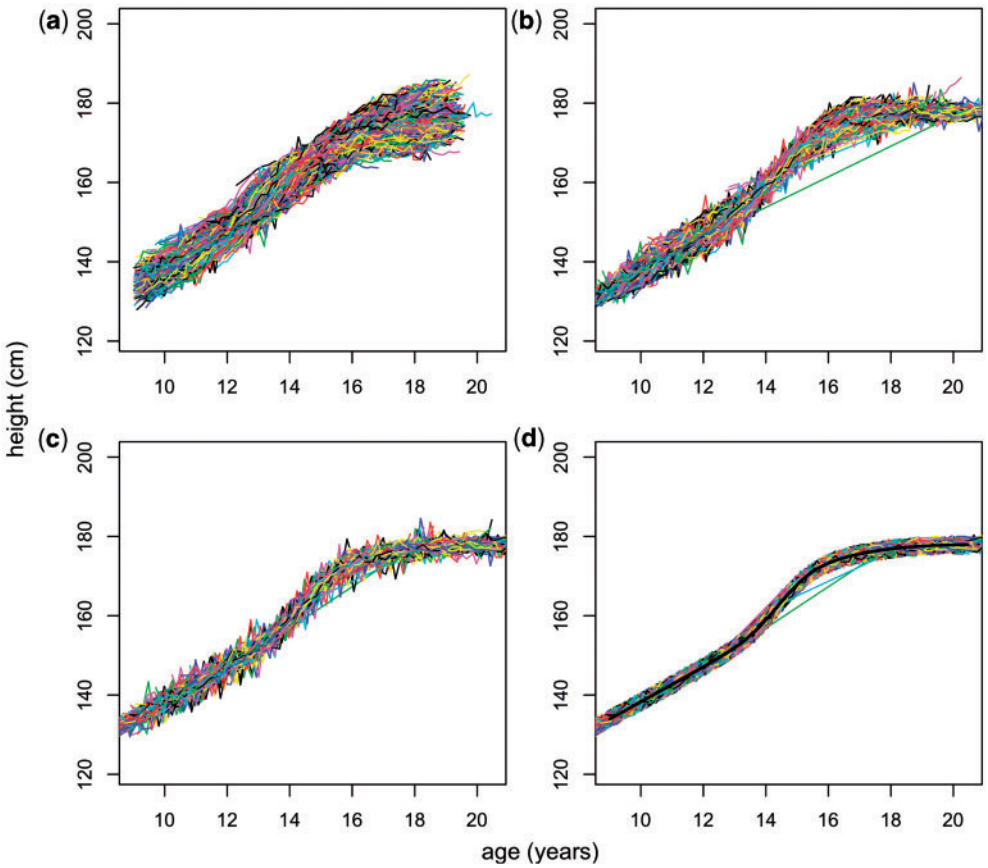

Figure 3 The effect on Figure 2 of adjusting in turn for (a) size α (shifting curves vertically), (b) tempo β (shifting curves horizontally), (c) velocity γ (shrinking–stretching age scales), and (d) extreme outliers

Table 2 CHS data: summary statistics of SITAR pubertal growth parameter random effects for 3245 subjects and 129 508 measurements

	SD	Correlations	
Size (cm)	6.1	Size	Tempo
Tempo (fractional)	0.068	0.33	
Velocity (fractional)	0.15	0.36	0.28
Residual (cm)	0.79		

to APHV though their SDs differ—1.6 cm for APHV vs 0.97 cm for scaled tempo.

The next strongest correlations (0.20–0.22) are for age with tempo, APHV and IGF-1. These represent secular trends over the period of data collection (1939–68), with puberty becoming earlier and IGF-1 higher. Finally there are smaller correlations of tempo and APHV with IGF-1 (−0.12 and −0.13, respectively, $P < 0.0002$). Thus the tempo of puberty (but not size or velocity) is strongly correlated with IGF-1 50 years later, and tempo and APHV are equally predictive.

As tempo and IGF-1 are both correlated with age, the tempo vs IGF-1 association could be due to the secular trend. Adjusting for age confirms this, the correlation of IGF-1 with tempo or APHV falling to −0.08 ($P = 0.01$, $N = 1009$).

Turning to the TS cohort, Figure 5 compares the individual growth parameter values by trial arm. There are small oxandrolone effects for size [+2.6 cm, 95% confidence interval (CI) 0.4–4.7, $P = 0.02$] and tempo (−0.3 years, –0.7 to +0.1, $P = 0.1$), but velocity is dramatically larger in the oxandrolone arm (+23%, 16–30%, $P = 10^{-8}$). Refitting the SITAR model with fixed parameter effects for differences between trial arms confirms this pattern (results not shown). Figure 6 shows the summary spline curves, each with 4 df, obtained for the two trial arms separately, and they demonstrate the steeper velocity in the oxandrolone arm. Analysis of the final height data confirms that oxandrolone increases final height by 4.5 cm (1.9–7.2, $P = 0.001$) (EJ Gault *et al.*, submitted for publication).

Discussion

The findings show that Beath's shape invariant model is useful for analysing the pubertal height growth curve, both in boys and girls. As well as providing the mean growth curve, it summarizes the departure

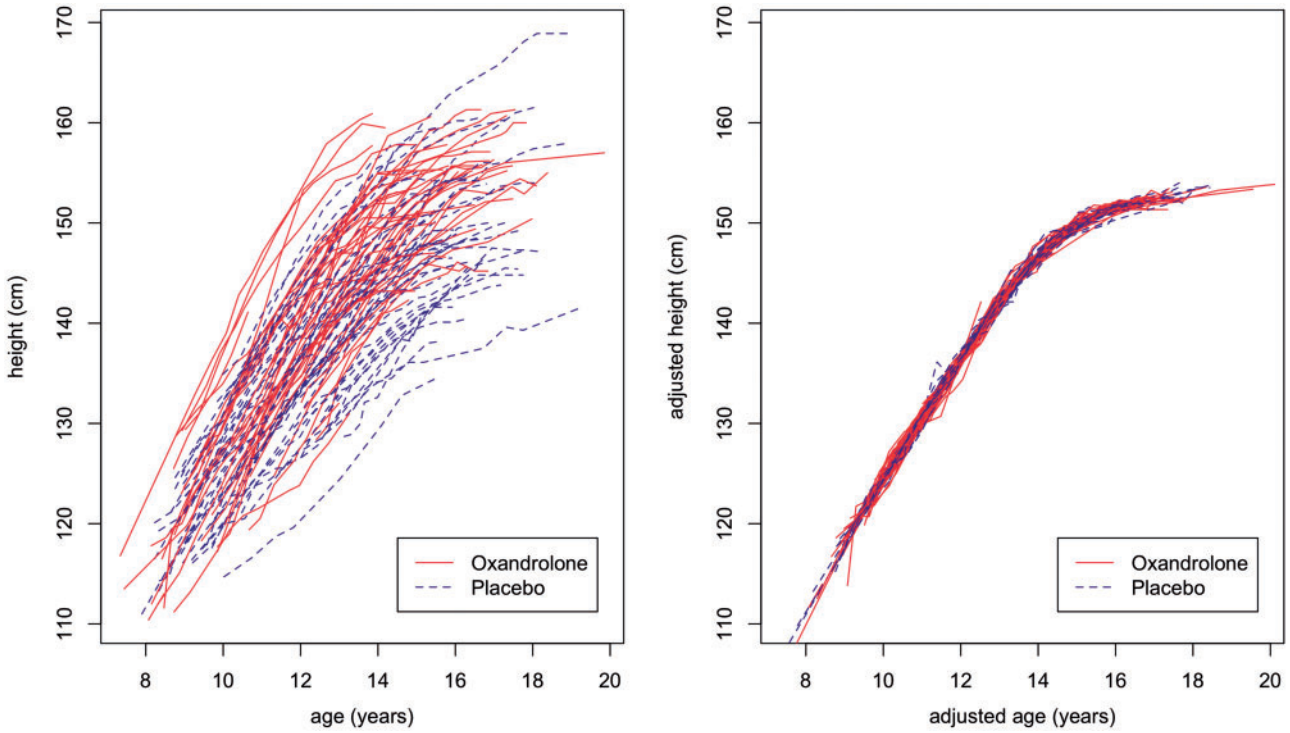

Figure 4 Turner Study data. Left: 105 height growth curves and 1321 heights from 9 to 19 years as randomized (oxandrolone red solid lines, placebo blue dashed lines). Right: the same curves after SITAR adjustment

Table 3 Turner Study data: summary statistics of SITAR pubertal growth parameter random effects for 105 subjects and 1321 measurements

	SD	Correlations	
Size (cm)	5.9	Size	Tempo
Tempo (years)	1.04	0.29	
Velocity (fractional)	0.23	0.28	−0.46
Residual (cm)	0.63		

of each individual curve from the mean in terms of three biologically meaningful parameters: size, tempo and velocity. Furthermore, the model explains effectively all the heterogeneity in growth between individuals, as the residual variability about the fitted curves is no greater than that obtained by fitting individual PB curves.[4,5] The name SITAR is proposed for the model as it superimposes by translation and rotation.

The SITAR model has some similarities with the random intercept–random slope model, in that size is a random intercept and velocity can be viewed as a random slope. However, where the two differ is that SITAR expects a nonlinear mean curve, and this allows the tempo random effect to be estimated—if the mean curve were linear the size and tempo effects would be indistinguishable. Thus, the most innovative aspect of SITAR is its random shift on the age scale.

The SITAR model should also be useful for endocrinologists in that it clarifies the nature of growth in puberty. The substantial population heterogeneity in pubertal height velocity shows itself as variability in PHV and APHV. However, these two quantities are effectively the same as the SITAR parameters velocity and tempo, and the present analysis makes clear that these parameters explain *all* the differences in growth velocity in both the CHS and TS cohorts. Note that the size parameter, which defines mean height and hence is important to set the relative position of the height distance curve, has no effect on the height velocity curve. The SITAR parameterization shows that differences in height velocity between individuals are entirely explained by differences in their internal 'growth body clock'.

The correlations between the three growth parameters indicate that CHS boys entering puberty later tend to be taller and have a larger peak velocity (Table 2). Girls with TS show similar correlations except that tempo and velocity are inversely related, with early puberty associated with greater velocity (Table 3). This accords with the fact that only a minority of girls with TS enter puberty spontaneously—the others have puberty induced artificially with oestrogen therapy, and their growth spurt is much smaller.

The positive correlation between size and tempo appears to contradict the previously reported negative correlation between height at school entry and APHV.[9] Clearly, the correlations of the growth parameters with height at any particular age depend on the values of the other parameters, as seen in Table 5 for

Table 4 CHS data: summary statistics and correlations of APHV and clinic measurements in later life[9] with SITAR pubertal growth parameter random effects

				Correlations					
	N	Mean	SD	Size	Tempo	Velocity	APHV	Age	Height
APHV (years)	1485	14.3	1.6	0.18	0.83	0.06	1		
Age (years)	1028	63.3	6.7	–0.02	0.20	0.00	0.21	1	
Height (cm)	1022	178.2	6.4	0.86	0.15	0.34	0.05	–0.15	1
IGF-1 (ng/ml)	1024	125	42	–0.02	–0.12	–0.03	–0.13	–0.22	0.03

Table 5 CHS data: multiple regression of height (cm) in later life on SITAR random effects, adjusted for age of measurement

	Standardized regression coefficient	Standard error	*t*	95% CI
(Intercept)	178.2	0.10	1860	178.0 to 178.4
Size	5.5	0.10	53.1	5.3 to 5.7
Tempo	–0.59	0.10	–5.7	–0.79 to –0.39
Velocity	0.54	0.10	5.3	0.34 to 0.74

Residual SD 3.0 cm, $R^2 = 0.77$.

later height. Repeating this analysis for height at different ages in puberty shows that for size, a 1-SD increase predicts an ~6-cm increase in height at all ages (which fits with the SD of ~6 cm for size in Tables 2 and 3). For tempo, a 1-SD increase is associated consistently with a reduction in predicted height, peaking at –7 cm at age 14. Thus around APHV the tempo effect eclipses the size effect. For velocity the effect is smaller, ranging from –2 to +1 cm. So conditional on the other parameters, tempo is consistently inversely associated with height at any particular age, which accords with the earlier finding.[9]

The SITAR model is useful for relating individual growth parameters to previous exposures and/or later outcomes. The TS example shows how SITAR provides a parsimonious analysis of the growth clinical trial, where the oxandrolone intervention is not only highly effective, but also is seen to operate primarily by increasing growth velocity (γ) rather than tempo (β) or size (α). The strength of the oxandrolone effect ($P = 10^{-8}$) is remarkable given the modest number of growth curves involved ($N = 105$). Its effect on the size parameter of +2.6 cm is less than on final height (+4.5 cm) as it reflects mean height throughout the study. In fact the Turner Study design was more complex than described here, with two separate randomizations in a factorial design, and the net effect of oxandrolone on final height exceeded 7 cm (EJ Gault *et al*., submitted for publication).

The CHS analysis relates the growth parameters to IGF-1 50 years later, and again finds just one of the three parameters to be important, this time tempo. Hence, earlier puberty is associated with higher IGF-1 after a lag of 50 years. The association is exaggerated by secular trends in tempo and IGF-1, but it remains after adjusting for age.

APHV measured from individual growth curves gives the same results as tempo. The high correlation of 0.83 between the two suggests that they are measuring essentially the same quantity, albeit on different measurement scales. However, tempo is much easier to estimate, being a random effect from a single analysis, whereas APHV involves analysing each individual growth curve.

Discussion of findings

The fact that the model fits well both in boys and girls, even growth disordered girls with TS, highlights its generality. The fit in the CHS boys was far better with a log age scale, where a left–right shift on the log age scale corresponds to a shrinking–stretching on the age scale anchored at birth. This elasticity of the growth curve affects the curve's slope (i.e. velocity), so that it is steeper for individuals with an early puberty and shallower for those reaching puberty later (see Figure 7 of Cole *et al*.[7]). This provides a statistical explanation for the clinical observation that PHV (velocity) is inversely correlated with APHV (tempo).[14] Thus log age provides a better fit for CHS because it models this correlation. Indeed, it over-compensates, as the negative correlation of −0.19 between tempo and velocity on the age scale (result not shown) switches to +0.28 on the log age scale (Table 2).

The log age scale did not provide a better fit for the girls with TS, which may be due to their mean velocity curve lacking a clear peak, due to most of them failing to enter puberty spontaneously. Thus there was less opportunity for an association between PHV and APHV.

Strengths and weaknesses

The strengths of the study are the two substantial and contrasting datasets that provide a useful test of the generality of the SITAR approach. In addition, they include examples of both exposure–growth and growth–outcome associations, which highlight respectively the velocity and tempo parameters of the model.

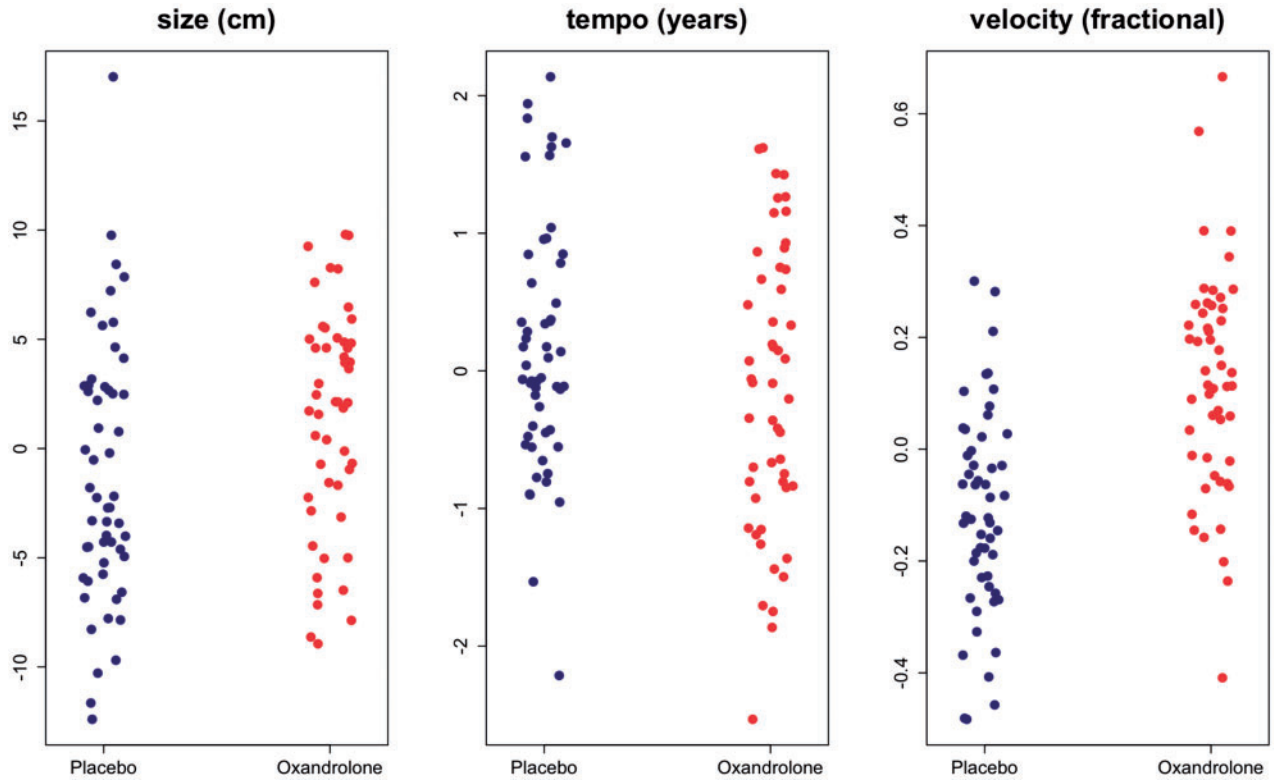

Figure 5 Turner Study. Comparison of the SITAR growth parameters by trial arm. Velocity is far greater for oxandrolone ($P = 10^{-8}$)

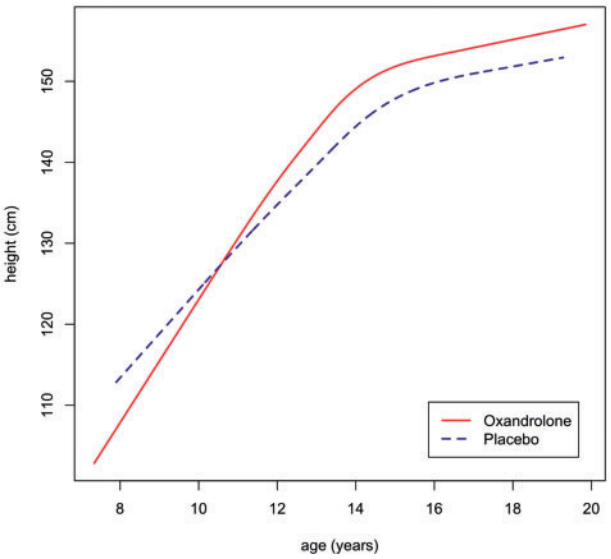

Figure 6 Turner Study. The mean growth curves for the two arms, indicating the greater velocity for oxandrolone

A weakness of the study is that the results apply only to height in puberty. Their relevance to height at other ages, e.g. pre-school, or to other measurements, e.g. weight, is not known. That said, Beath's article describing the method[6] applied it to weight from 0 to 2 years, where it appeared to fit well, though the goodness of fit of the model was not examined in the same way as here.

There is a need for future work to test the generality of the SITAR model, particularly in puberty where the heterogeneity of height growth, which appears to depend on the individual's time clock, may be related to the timing of changes in sex hormone status. The SITAR approach would be useful to examine hormone status in the same way as for height.

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Conflict of interest: None declared.

KEY MESSAGES

- SITAR is a shape-invariant growth curve model that summarizes individual growth curves with a single summary curve and subject-specific random effects.
- The random effects reflect each subject's size, growth tempo and growth velocity.
- Two examples demonstrate that the model explains virtually all inter-individual variability in height growth during puberty.
- This suggests that height growth variability arises from differences in subjects' internal body clocks.
- The random effects are useful to relate growth to preceding exposures and later outcomes.

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