SITAR growth curve analysis to evaluate interventions and life course outcomes

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Early growth and the life course

- Hypothesis that early growth influences the life course
- Need to model growth to relate it to later outcome
  - Summarise growth curve in very few parameters
- Different measurements at different ages
  - e.g. weight gain in infancy
  - BMI change in childhood
  - Height velocity in puberty
- Main example here: height velocity in puberty

Height in puberty

- Dramatic pubertal growth spurt
  - Intensity of spurt defined by peak height velocity (PHV)
    - Mean PHV - 10 and 8 cm/yr in boys and girls
- Wide variation in timing of spurt
  - Timing of spurt defined by age at PHV (APHV)
    - Mean APHV - 14 and 12 years in boys and girls
    - SD of APHV - 1 year
- Biologically important, with complex hormonal changes

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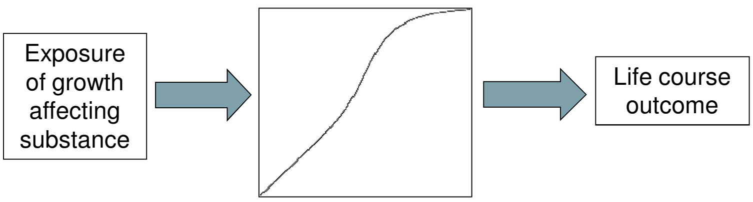
Exposure, growth and outcome



Pubertal growth curve

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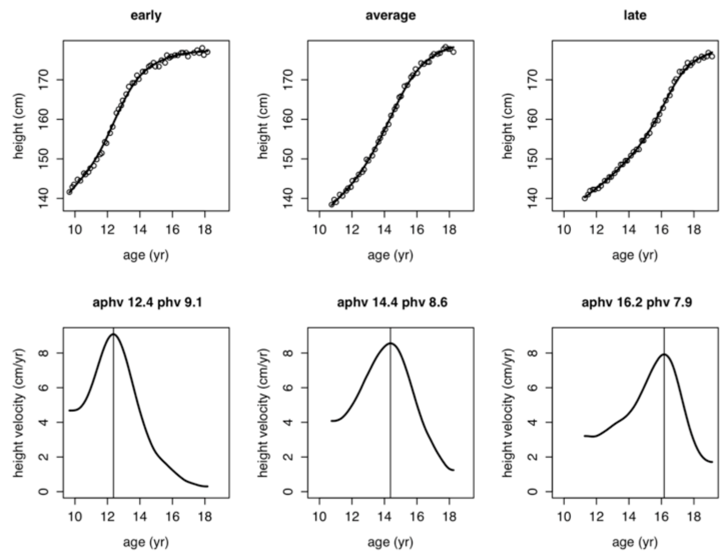
Height in puberty in boys

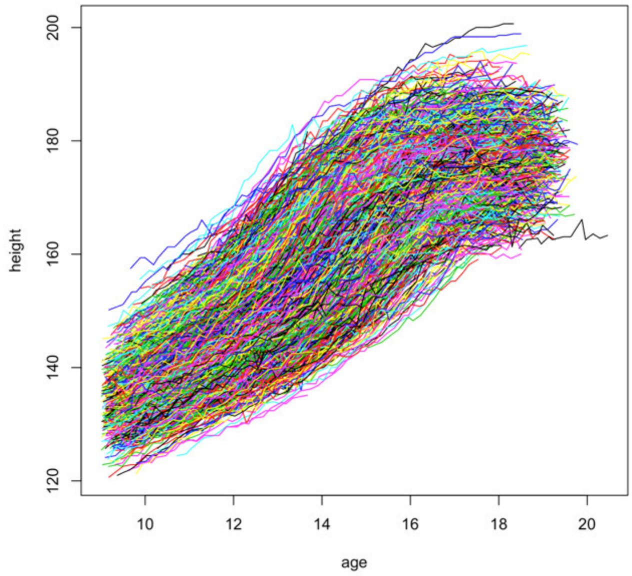


CHS data

- Height in 3245 boys aged 9-19 years
  - From Christ’s Hospital School, Sussex, UK
  - Data collected 1936-1969
- 129,508 measurements – median 42 per boy
  - Each child measured twice a term

CHS data

- N = 129,508 heights
- n = 3245 boys



Growth curve analysis

- Important form of analysis for longitudinal data
- Two aims
  - Model shape of average growth curve
  - Characterise differences in growth pattern between individuals
- One aim often of greater interest than the other

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Possible growth curve models

- Parametric curves fitted to individuals
- Example: Preece-Baines curve

Preece MA, Baines MJ. A new family of mathematical models describing the human growth curve. Ann Hum Biol 1978;5:1-24.

Preece Baines curve

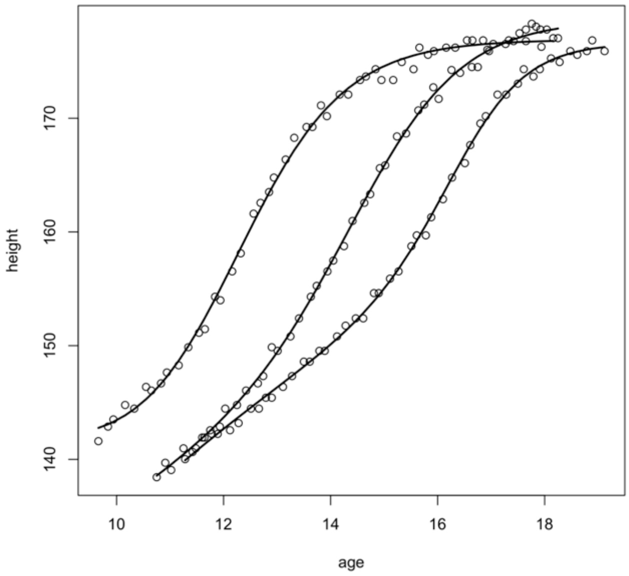
- Five parameter curve of height *h* versus age *t*

$$h = a - \frac{2(a-b)}{\exp[c(t-e)] + \exp[d(t-e)]}$$

  - a = adult height
  - b = height at take-off
  - c = rate constant 1
  - d = rate constant 2
  - e = age at peak height velocity
- Based on differential equation defining growth spurt
- Residual standard deviation ~ 0.6 cm

Preece Baines curves

- Data for three subjects
- Early, median, late puberty
- Fitted Preece-Baines curves



Preece-Baines curve

- Advantages
  - Individual curves and parameters for individuals
- Disadvantages
  - Requires ~complete data
  - Slow to fit
  - May not fit
  - No average curve

Random effects models

- Random intercept, random slope model
- Preece-Baines
  - Fit all individuals in single model with subject-specific parameter random effects
- Random spline curve models

Growth curve analysis

- Parametric curves
  - e.g. Preece-Baines
    - Too complex - needs 5 d.f. per subject
- Random effects models
  - Random intercept, random slope
    - Too simple - assumes linear growth curve
  - Preece-Baines
    - Too complex - needs 5 parameter random effects
  - Random spline curve models
    - Too complex - multiple curves

Growth curve analysis

- Need well-fitting model with average curve and simple subject effects
  - SITAR!

Aim

- To describe SITAR, a method of growth curve analysis that
  - efficiently summarises the average curve and
  - parsimoniously estimates individual departures from it
- So as to simplify the analysis of exposure-growth and growth-outcome studies

Three elements to SITAR

- Size
- Tempo
- Velocity

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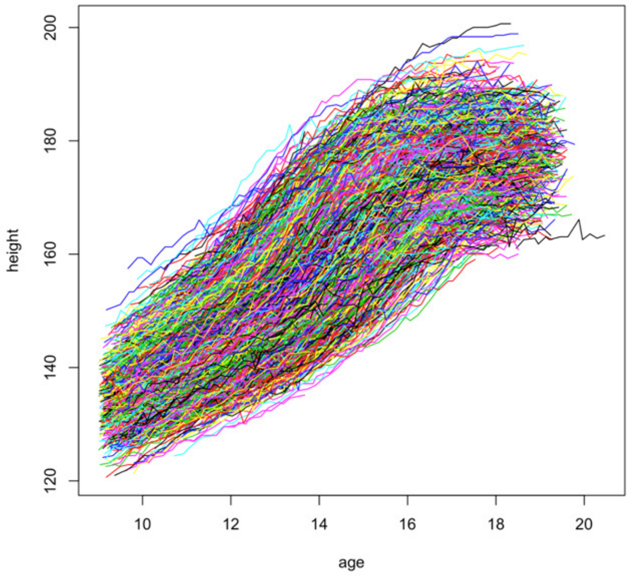
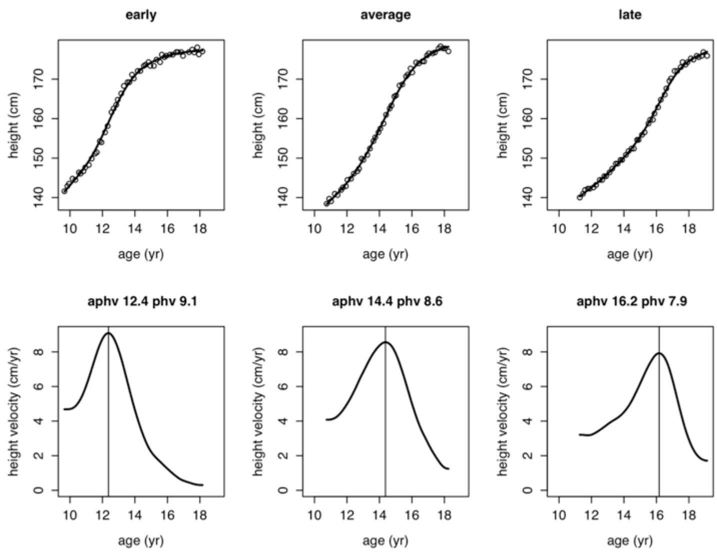
Size



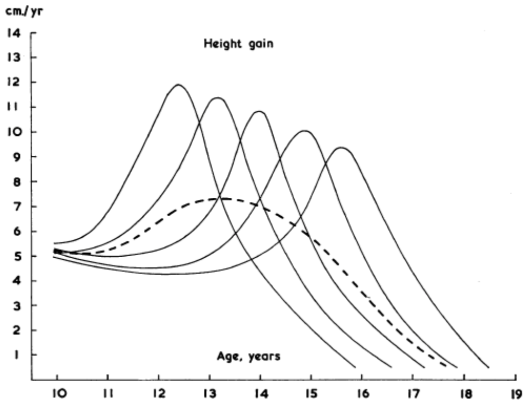
SITAR - Size

- *Size* is the mean height of individuals relative to others
- To adjust for it, need to *shift* height curve up-down
- Can be thought of as random intercept

Height and height velocity



Height velocity curves



- Timing or *tempo* of puberty shown by individual velocity curves
- Averaging the curves leads to serious bias
  - Merrell (1931)
  - Tanner et al (1966)

Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965 Parts I and II. Arch Dis Child 1966;41:454-71, 613-35.

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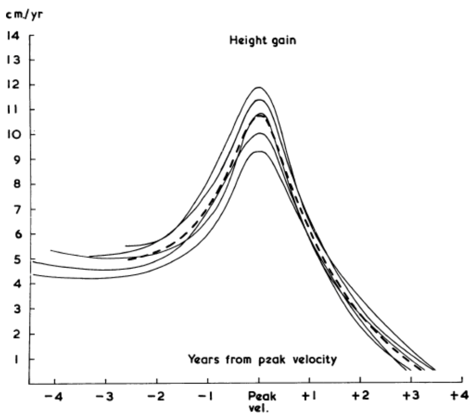
Height velocity curves



- Synchronise curves by centring on age at peak velocity
- Mean velocity curve now unbiased
- Need *tempo* adjustment to estimate mean curve

Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965 Parts I and II. Arch Dis Child 1966;41:454-71, 613-35.

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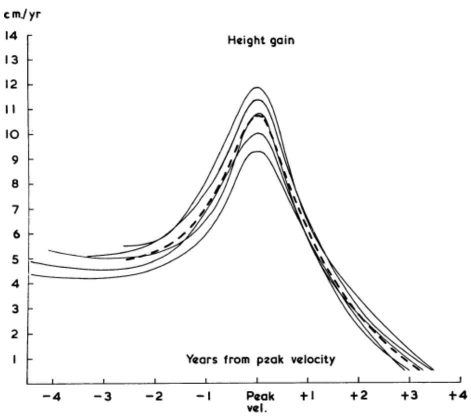
SITAR - Tempo

- *Tempo* is the timing of puberty in individuals
- To adjust for it, need to *shift* growth curve left-right on age scale
- Note difference from conventional regression
  - where age scale assumed fixed and only height scale modelled

Peak height velocity



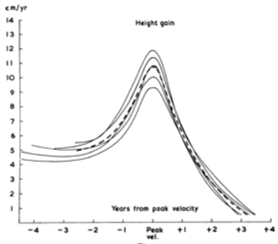
- Peak velocity differs between individuals
- Adjust for peak velocity - all curves then superimposed
- How to adjust?
  - By rescaling age

Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children, 1965 Parts I and II. Arch Dis Child 1966;41:454-71, 613-35.

UCL

SITAR - Velocity

- *Velocity* is the rate of passage through puberty in individuals
- To adjust for it, need to *shrink/stretch* age scale
- Makes growth curve steeper/shallower
  - Affects mean velocity including peak velocity
- Superimposes velocity curves



(B)

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Shape invariant model (SIM)

- Fit single growth curve: $y_t = h(t) + \varepsilon$
  - But with subject-specific age & height transformations
    - Height velocity from 1-20 years – Stutzle et al (1980)
    - Height from 0-20 years – Gasser et al (1990)
    - Weight from 0-2 years – Beath (2007)

Beath KJ. Infant growth modelling using a shape invariant model with random efffects. Stat Med 2007;26:2547-64.

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Family of growth curve models

1. Fit average growth curve (natural cubic spline)

   $y_t = h(t) + \varepsilon$

2. Add random height offsets by subject (size)

   $y_{ti} = \alpha_i + h(t) + \varepsilon$

3. Add random age offsets by subject (tempo)

   $y_{ti} = \alpha_i + h(t - \beta_i) + \varepsilon$

4. Add random age scalings by subject (velocity)

   $y_{ti} = \alpha_i + h\left(e^{\gamma_i}(t - \beta_i)\right) + \varepsilon$

Beath KJ. Infant growth modelling using a shape invariant model with random efffects. Stat Med 2007;26:2547-64.

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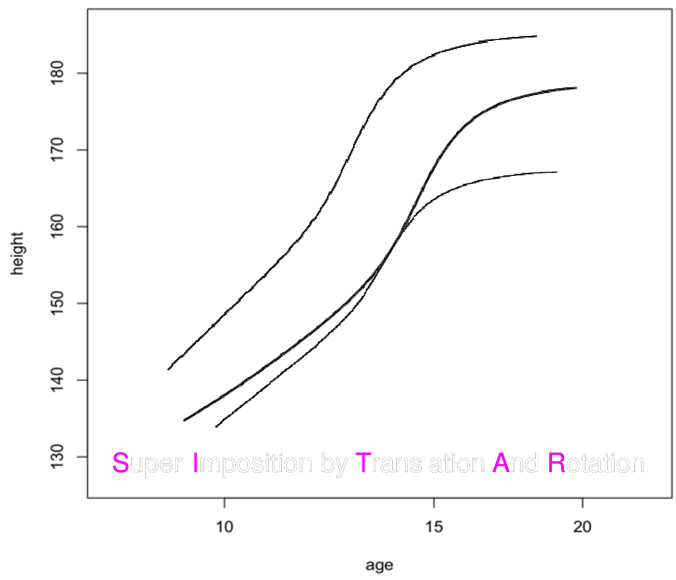
SITAR



Size α

Tempo β

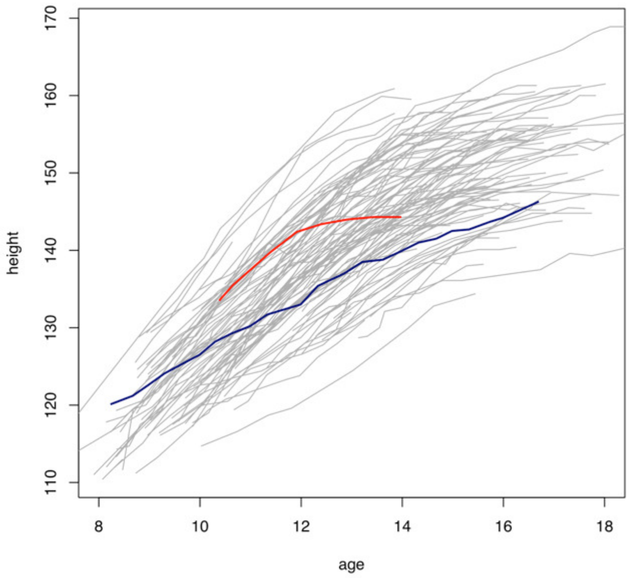
Velocity γ

Example 1

Example 2

SuperImposition by Translation And Rotation

- S I T A R
- Examples of
- Translation (red)
- Rotation (blue)



S I T A R

- Given $y_{ti} = \alpha_i + h\left(e^{\gamma_i}\left(t - \beta_i\right)\right) + \varepsilon$
  - The effect of α and β is *translation* (in height and age space)
  - The effect of γ is essentially *rotation*
- Taken together they effectively *superimpose* individual curves
- Hence *Super-Imposition by Translation And Rotation*
- or S I T A R

Anoushka Shankar

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Family of growth curve models

- Average curve – natural cubic spline with 6 d.f.
- Fit models using `nlme()` in `R`
- Consider log transforms for height and/or age

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Log age scale

- CHS data fit dramatically better on log age scale
  - Multiplicative age effect
- Subject differences in timing arise from
  - shrinking/stretching the age scale
  - *not* left/right shifting the age scale

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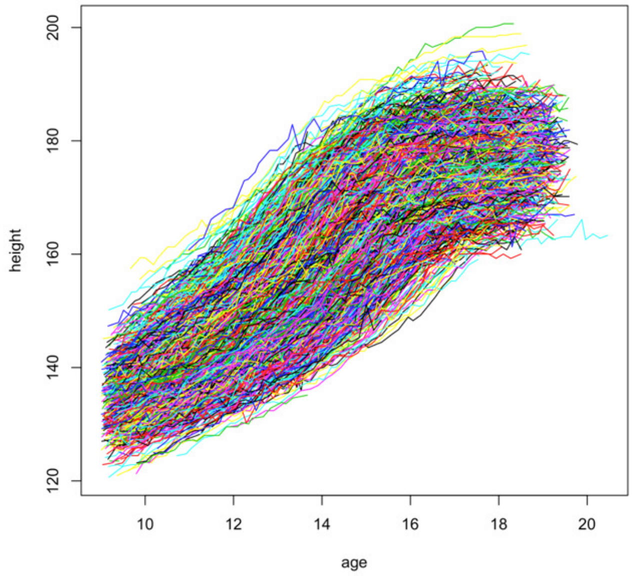
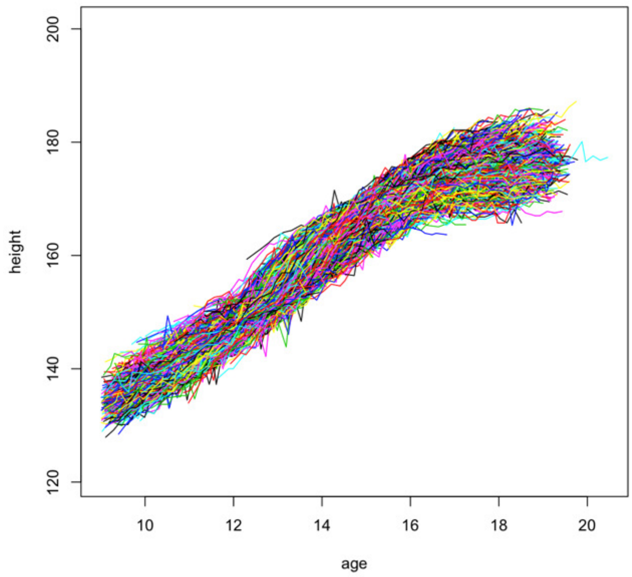
CHS data

- RSD = 6.6 cm
- No random effects



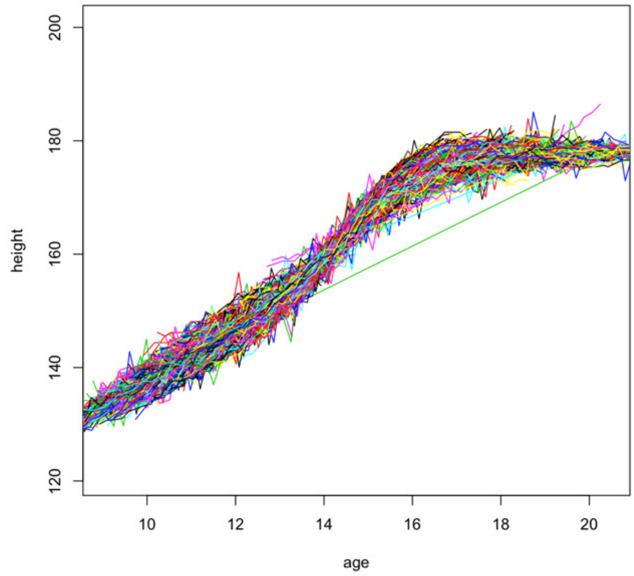
CHS data

- RSD = 2.3 cm
- Size 〈



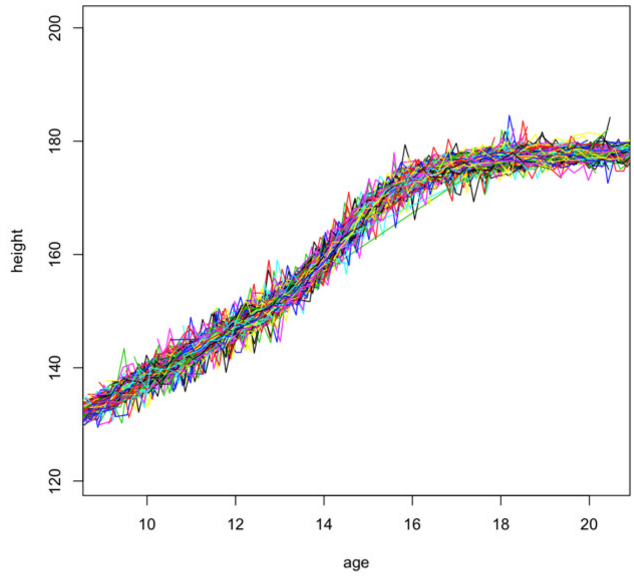
CHS data

- RSD = 1.2 cm
- Size 〈
- Tempo ®



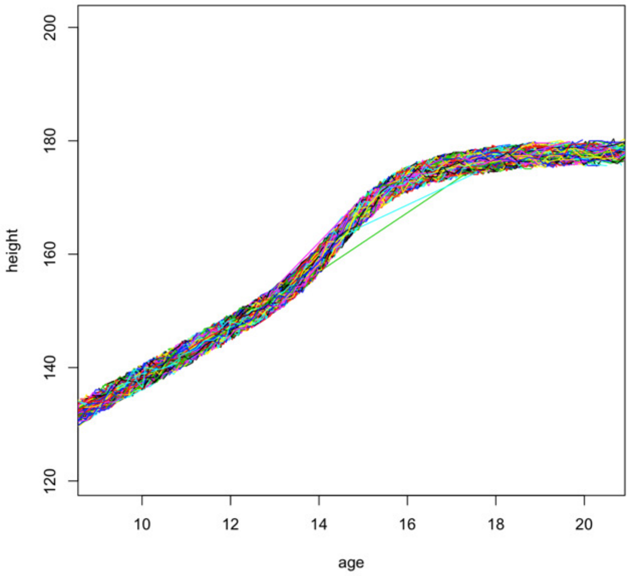
CHS data

- RSD = 0.8 cm
- Size 〈
- Tempo ®
- Velocity ©



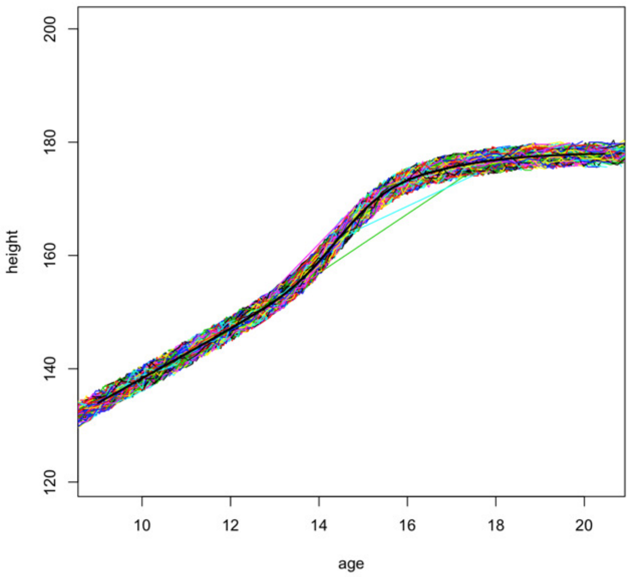
CHS data

- RSD = 0.7 cm
- Size 〈
- Tempo ®
- Velocity ©
- residuals >2.4 cm trimmed



CHS data

- RSD = 0.7 cm
- Size 〈
- Tempo ®
- Velocity ©
- residuals <2.4 cm trimmed
- average curve

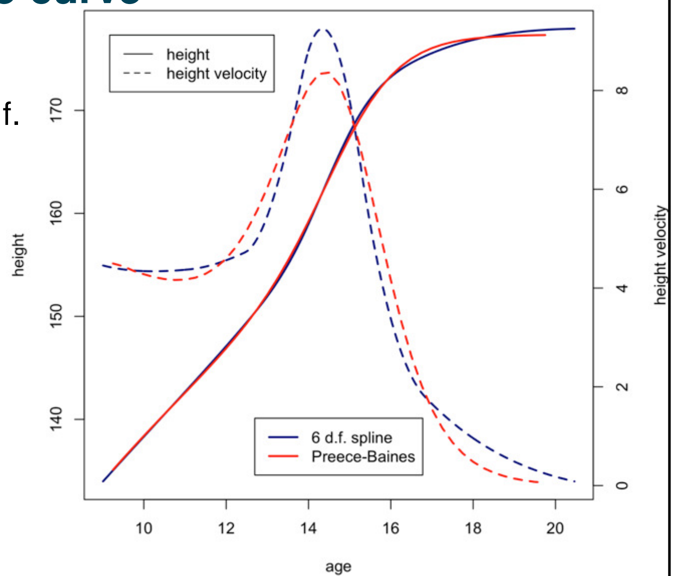


Summary 1

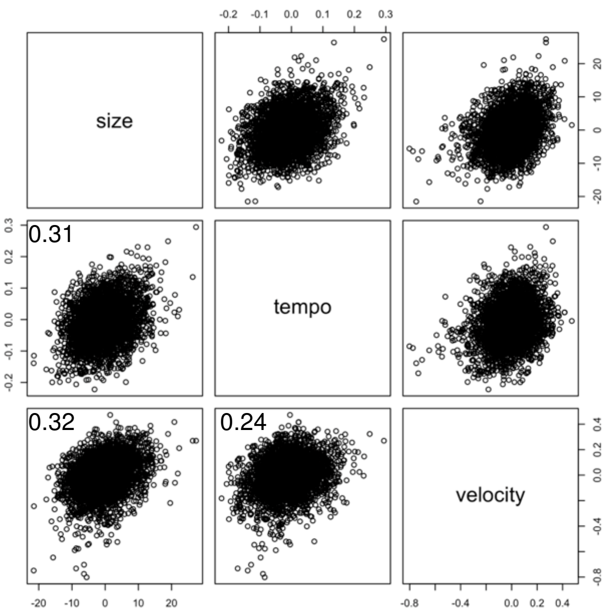
- SITAR model fits CHS data extraordinarily well
- RSD reduced from 6.6 cm to 0.7 cm
  - 98.9% of variance explained
  - RSD of 0.7 cm similar to mean RSD of 0.6 cm for individually fitted Preece-Baines curves
- Beath's model effectively captures *all* inter-individual variability in pubertal height growth
- We can ignore original data and focus on subject-specific parameter values

CHS average curve

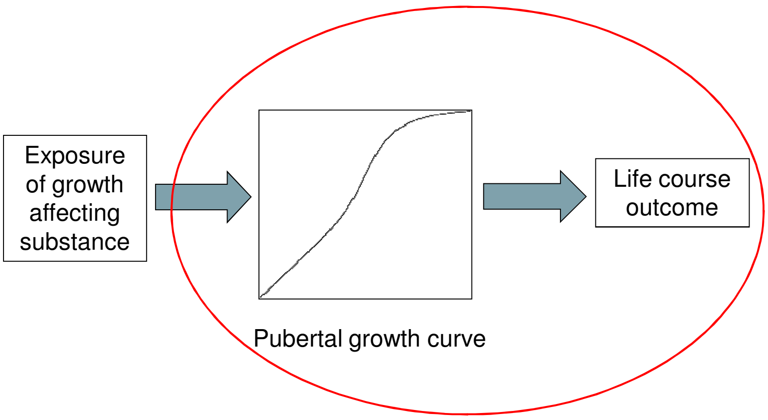
- Natural cubic spline with 6 d.f.
- Preece-Baines



Parameters for 3245 subjects



Exposure, growth and outcome



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Height in puberty and outcome 50 years on

- Christs Hospital School cohort followed up in 2001
- IGF-1 measured (insulin-like growth factor 1)
  - N = 1024, at mean age 63 (SD 6) years
- Correlate with SITAR size, tempo and velocity random effects

Tempo correlations with IGF-1 (n = 1024)

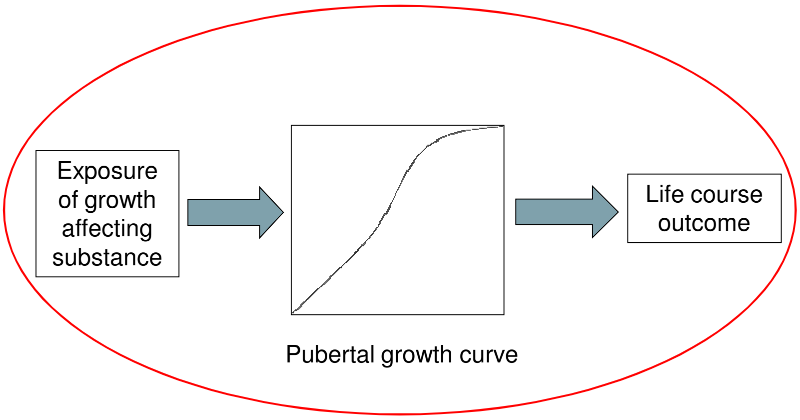
	IGF-1
Size	-0.02
Tempo	-0.12***
Velocity	-0.03

- IGF-1 negatively correlated with tempo (p = 0.0001)
- But tempo and IGF-1 related to age (date of birth)
- Adjusted for age, IGF-1 correlated with tempo (p = 0.01)
- But not correlated with size or velocity

Summary 2

- The tempo of pubertal growth is associated with IGF-1 fifty years later
  - Size and velocity are unrelated to IGF-1
- Likely explanation for association: IGF-1 related to timing of puberty and also tracks into adult life

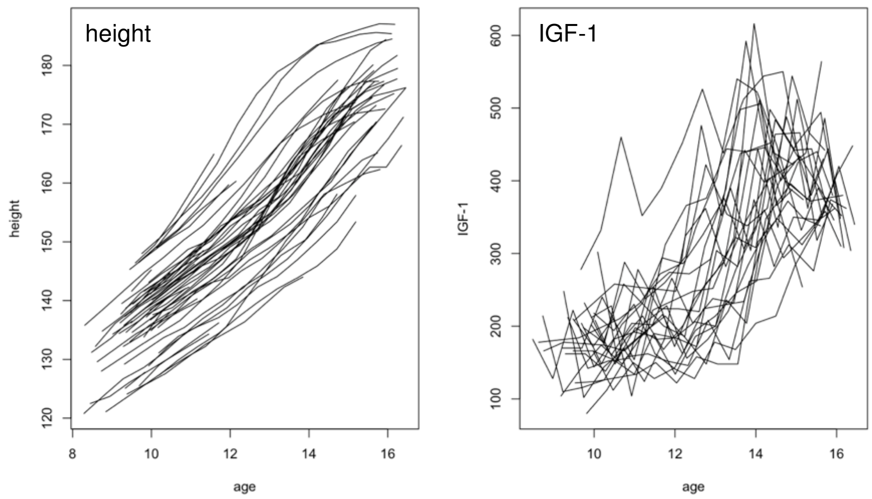
Exposure, growth and outcome



Chard data

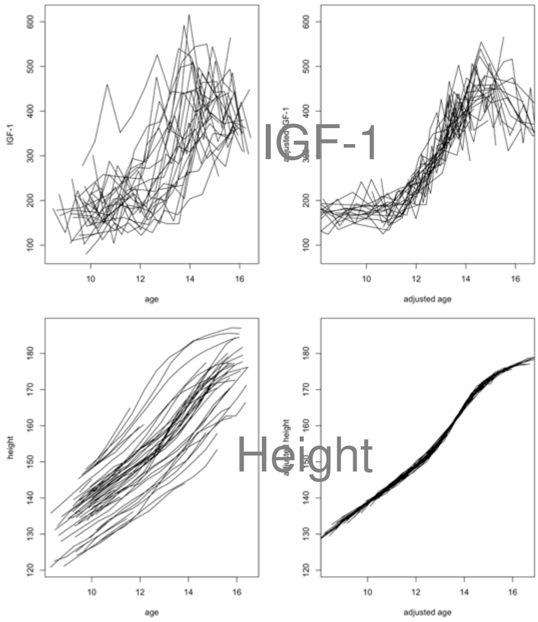
- Height and IGF-1 in boys aged 9-16 years
  - Recruited from school in Chard, Somerset, UK
- 510 height measurements (n=54)
  - Median 11.5 per subject
- 310 IGF-1 measurements (n=24)
  - Median 14 per subject

Chard data

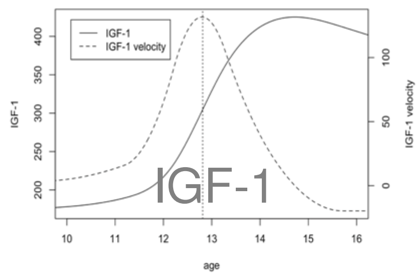


Chard

IGF-1, Height and SITAR



Peak velocity



Peak velocity for IGF-1 occurs earlier than peak height velocity

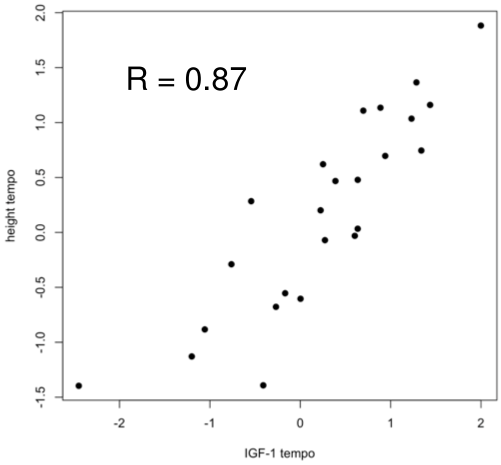
Does IGF-1 drive height spurt?

Is IGF-1 tempo correlated with height tempo?

Chard: correlation between height tempo and IGF-1 tempo

Q: is IGF-1 tempo correlated with height tempo?

A: Yes!



Summary 3

- The steep pubertal rise in IGF-1 precedes that for height
- The ages at peak velocity are strongly correlated (r = 0.87)
- Likely explanation: IGF-1 drives the timing of the pubertal height spurt
- … and also tracks into later adult life
  - With an earlier rise associated with a higher level later

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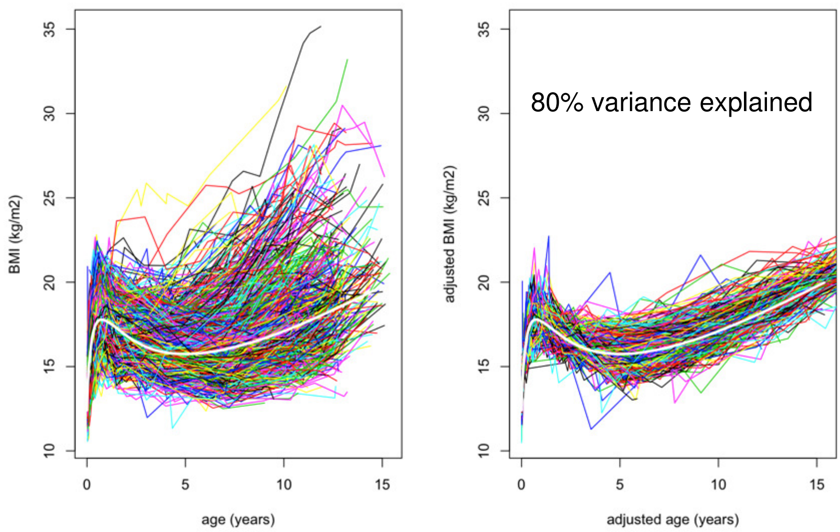
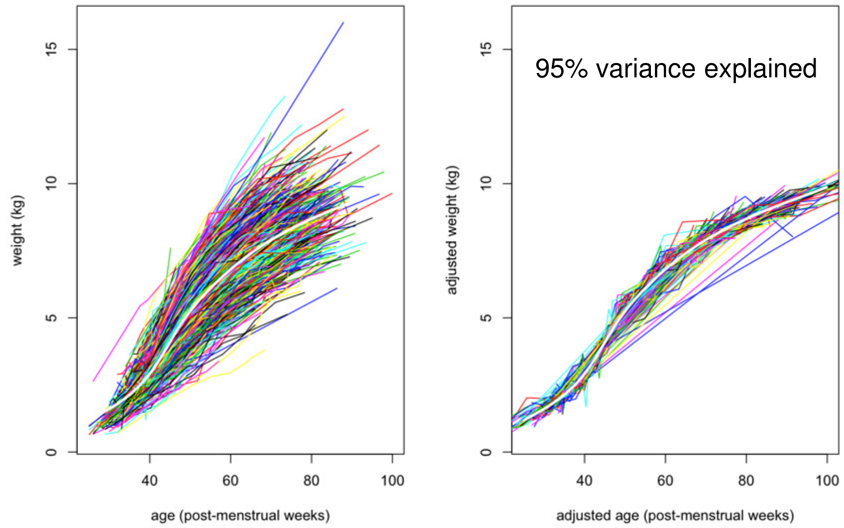
Other SITAR applications

- SITAR also works well for other measurements and ages
  - BMI in childhood
  - Weight in infancy
  - Weight in very preterm infants

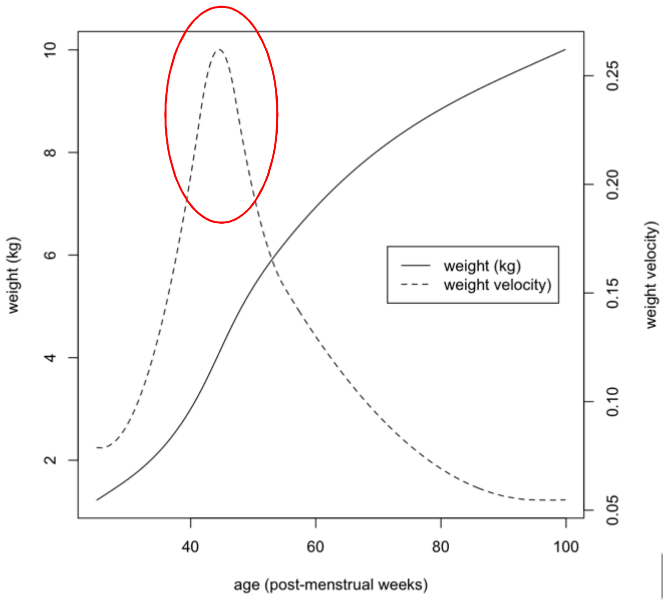
BMI in childhood - Uppsala Study



Weight in infant twins - Gemini Study



Weight in infancy - Gemini Study



SITAR and fixed effects

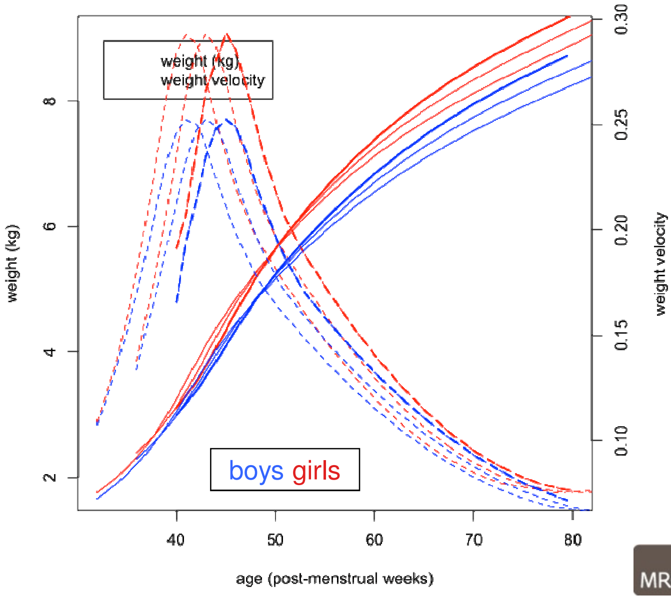
- Given $y_{ti} = \alpha_i + h\left(e^{\gamma_i}\left(t - \beta_i\right)\right)$
- Can add design fixed effects to random effects

- e.g. weight in infancy
  - Adjust SITAR parameters for sex and weeks premature
  - Leads to sex-gestation-specific mean growth curves

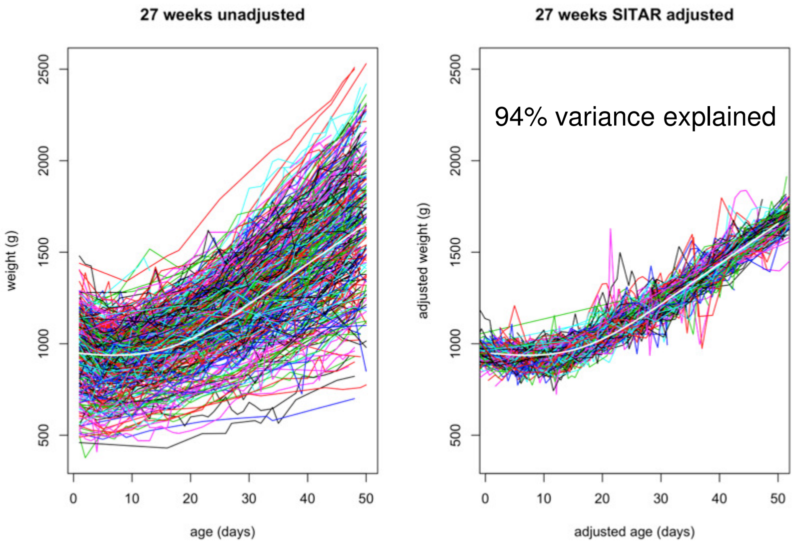
$$y_{ti} = (\alpha_i + sex + wkpt) + h\left(e^{(\gamma_i + sex + wkpt)}\left(t - (\beta_i + sex + wkpt)\right)\right)$$

$$y_{ti} = (\alpha_i + sex + wkpt) + h\left(e^{(\gamma_i + sex)}\left(t - (\beta_i + wkpt)\right)\right)$$

Weight by sex (boys red, girls blue) and gestation (32, 36 & 40 weeks)



Weight in very preterm infants



Summary 4

- SITAR explains most growth curve variability

Height in puberty	Weight in childhood	BMI in childhood	IGF-1 in puberty
99%	95%	80%	66%

- Suggests that translation and rotation make up large part of variability

Conclusions 1

- SITAR model fits data well, particularly height in puberty
- Height velocity curve depends only on tempo and velocity parameters

- **Hypothesis**: pubertal height growth varies on the age scale (and not the height scale)

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Conclusions 2

- Model useful for analysing growth curves
- Subjects entirely characterised by triplets of size, tempo and velocity
- Parameters efficiently estimated
- Individual data then redundant

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Conclusions 3

- Parameters can be related to differences in
  - later outcome (e.g. IGF-1 in later life)
  - past / current exposure (e.g. IGF-1 in puberty)
- Analysis shows not only associations with growth, but also *which* aspects of growth are relevant
  - IGF-1 relates to tempo
- SITAR is a useful instrument for growth curve analysis

Cole TJ, Donaldson MDC, Ben-Shlomo Y.
SITAR - a useful instrument for growth curve analysis.
Int J Epidemiol 2010;39:1558-66.

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Thanks to (in order of appearance)

- Yoav Ben-Shlomo for the CHS data
- Lynn Ahmed for the Chard data
- David Leon for the Uppsala data
- Laura Johnson for the Gemini data
- Neena Modi for the preterm data

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