Growth charts and growth models for paediatrics and epidemiology
LMS and SITAR: modelling cross-sectional and longitudinal growth data

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Growth assessment

- The process of growth assessment involves *statistical summary*
- Here we focus on two scenarios
  - Single measurements, as summarised by growth centile charts
  - Serial measurements, as summarised by families of growth curves
Assessing single measurements

- Single measurements are compared with the population distribution
  - conditioned on age and sex
- Centile charts of height and weight *etc*
  - Júlíusson 2013
  - WHO 2006
  - British 1990
Assessing serial measurements

• Treat the measurements as growth curves for individuals
• Summarise the growth curves to obtain the population distribution
  • Question: how to summarise growth curves?
• Answer: assume all curves are the same basic shape, but differ in simple ways
Aim

• To illustrate statistical techniques for growth summary
  • The LMS method for constructing growth charts
  • The SITAR method for summarising growth curves

• Using boys height in puberty as main example
  • Other examples in puberty and infancy
Height in puberty

- Dramatic pubertal growth spurt
  - Intensity defined by peak height velocity (PHV)
- Wide variation in timing of spurt
  - Timing defined by age at PHV (APHV)
Age at peak height velocity

Early

Average

Late

APHV timing

PHV intensity
Christ’s Hospital School 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
  - Measured at start and end of term
  - Six times a year for median 7 years
Single measurements

First view data as cross-sectional, to construct centile curves

(it does not matter that the data are longitudinal)
Christ’s Hospital boys height

• 129 508 heights
Christ’s Hospital boys height

- 129 508 heights
- The median (or 50\textsuperscript{th} centile) splits the data into halves
Christ’s Hospital boys height

- 129,508 heights
- The median (or 50\textsuperscript{th} centile) splits the data into halves
- … and the quartiles (25\textsuperscript{th} and 75\textsuperscript{th} centiles) into quarters
Normal distribution

• Can assume normally distributed - summarise by mean and SD

• Assume mean and SD change smoothly with age
Statistics for growth references

- Need to summarise the population distribution of the measurement by age
  - Define distribution moments as *smooth functions of age*
- Three alternative approaches
  - Normal distribution (mean and SD)
    - Used for height and head circumference
  - Also adjust for skewness (LMS method)
    - Useful for weight, BMI and skinfolds etc
  - Also adjust for kurtosis (GAMLSS)
    - May improve fit for extreme centiles
GAMLSS

• All three alternatives can be fitted as special cases of GAMLSS

• Fitted using statistical language \( R \)
  • Normal distribution (NO)
  • LMS method adjusting for skewness
    • Box-Cox Cole-Green (BCCG)
  • Further kurtosis adjustment
    • Box-Cox Power Exponential (BCPE)
Normal distribution

• Mean and SD change smoothly with age
Normal distribution

- Mean and SD change smoothly with age
- Nine centiles, equally spaced on the z-score scale
LMS method

- Median, coefficient of variation and skewness change smoothly with age
  - $\lambda =$ skewness, $\mu =$ median, $\sigma =$ CV (hence LMS)
- Skewness positive before puberty and negative after
LMS method (BCCG)

- Median, coefficient of variation and skewness change smoothly with age
  - $\lambda =$ skewness, $\mu =$ median, $\sigma =$ CV (hence LMS)
- Skewness positive before puberty and negative after
- Skewness adjustment affects outer two centiles
Kurtosis adjustment (BCPE)

- Like LMS method but kurtosis also changes with age
Kurtosis adjustment

• Like LMS method but kurtosis also changes with age
• Note lighter tails near age at peak velocity (14.5 years)
• Affects only extreme centiles
Summary

• Need to adjust for skewness but not kurtosis
• LMS method achieves this

• LMS method does two things
  • It defines centile curves for given Z scores $z_\alpha$
    • (normal equivalent deviate)
  • And it converts measurements to Z scores
Convert Z score to measurement centile

\[ \text{Centile}_{100} = M(1 + LSz)^{1/L} \]

\(L, M\) and \(S\) are values read off the curves for given age and sex.
Convert measurement to Z score

\[ z = \frac{(\frac{\text{Measure}}{M})^L - 1}{LS} \]

L, M and S are values read off the curves for given age and sex.
LMS converts measurements to Z scores

**Boys weight reference**

- Weight (kg) vs. Age (years)
  - 98 kg at 7 years
  - 91 kg at 6 years
  - 75 kg at 5 years
  - 50 kg at 4 years
  - 25 kg at 3 years
  - 9 kg at 2 years
  - 2 kg at 1 year

**Boys weight Z score reference**

- Weight Z Score vs. Age (years)
  - Z Score 2.5 at 7 years
  - Z Score 2 at 6 years
  - Z Score 1.5 at 5 years
  - Z Score 1 at 4 years
  - Z Score 0.5 at 3 years
  - Z Score 0 at 2 years
  - Z Score -1 at 1 year
  - Z Score -1.5 at 0.5 years
  - Z Score -2 at 0 years
  - Z Score -2.5 at -0.5 years

- 98 kg at 7 years corresponds to Z Score 2.5
- 91 kg at 6 years corresponds to Z Score 2
- 75 kg at 5 years corresponds to Z Score 1.5
- 50 kg at 4 years corresponds to Z Score 1
- 25 kg at 3 years corresponds to Z Score 0.5
- 9 kg at 2 years corresponds to Z Score 0
- 2 kg at 1 year corresponds to Z Score -1
- 1.5 kg at 0.5 years corresponds to Z Score -1.5
- 1 kg at 0 years corresponds to Z Score -2
Multiple Z scores example

- Gambian infant during first year of life
- Z scores for length, weight, two skinfolds, arm circumference
- Cumulative effect of repeated infections on growth
- Yet length preserved
Summary – Centile chart construction

• GAMLSS a powerful tool for constructing centile charts
  • Easy to fit using R
• LMS method adjusts for age-varying skewness
  • Kurtosis adjustment makes little difference
• Converts measurements to / from Z scores
  • Useful for analysing growth data
Serial measurements

Now view same data as longitudinal growth curves
Christ’s Hospital School boys height

3,245 boys
129,508 heights

size
timing
intensity
Size, Timing and Intensity

- **Size** is the mean height of individuals, relative to others
- **Timing** is their age at peak height velocity, relative to others
- **Intensity** is their peak height velocity, relative to others

- Adjusting individual growth curves for S, T & I has the effect of superimposing the curves
Developmental age

- Timing and intensity reflect developmental age
  - Based on physical development
- Developmental age runs in parallel with chronological age
- Can plot the two ages against each other
Developmental age vs chronological age

- Assume linearly related
- Intercept and slope define each line
  - Advanced
  - Delayed
  - Getting more delayed
  - Getting more advanced
- Same developmental age, different chronological age
  - Timing of event
Developmental age vs chronological age

- Assume linearly related
- Intercept and slope define each line
  - Advanced
  - Delayed
  - Getting more delayed
  - Getting more advanced
- Same developmental age, different chronological age
  - Timing/tempo of event
  - Intensity/rate of event (inverse of duration)
Superimposing growth curves

- Adjust for size, timing and rate of puberty to superimpose individual curves
  - Size
  - Timing
  - Rate
- SuperImposition by Translation And Rotation (SITAR)

Cole, Ben Shlomo & Donaldson, IJE 2010
The geometry of SITAR
SITAR – superimposing growth curves

- Adjust for size, timing and rate of puberty to superimpose individual curves
  - Size
  - Timing
  - Rate
- SuperImposition by Translation And Rotation (SITAR)

Cole, Ben Shlomo & Donaldson, IJE 2010
CHS data

- RSD = 6.6 cm
- No random effects
CHS data

- RSD = 2.3 cm
- Size
CHS data

- RSD = 1.2 cm
- Size
- Timing
CHS data

- RSD = 0.8 cm
- Size
- Timing
- Rate
CHS data

- RSD = 0.7 cm
- Size
- Timing
- Rate
- Trim residuals >2.4 cm (0.7%)
CHS data

- RSD = 0.7 cm
- Size
- Timing
- Rate
- Trim residuals >2.4 cm (0.7%)
- Add mean curve
SITAR – superimposing growth curves

- Adjust for size, timing and rate of puberty to superimpose individual curves
  - Size
  - Timing
  - Rate
- SuperImposition by Translation And Rotation (SITAR)

Cole, Ben Shlomo & Donaldson, IJE 2010
Summary – CHS data

• SITAR model fits CHS data remarkably well
  • Explains 99% of the variance
• Effectively captures *all* inter-individual variability in pubertal height growth
• Can use the size-timing-intensity random effects to summarise individual growth
CHS mean curve

- Natural cubic B-spline with 6 d.f.
SITAR growth patterns

• SITAR converts growth curves:
  • to a mean curve
  • and a growth pattern for each individual:

• So SITAR can:
  • compare mean curves between groups
  • relate individual growth patterns to later health
SITAR

Anoushka Shankar
Compare LMS and SITAR

- **LMS**
  - Constructs growth centile charts
  - Cross-sectional data
  - Spline curves for
    - L - skewness
    - M - median
    - S - coefficient of variation
  - Centile curves are functions of L, M and S

- **SITAR**
  - Summarises growth curves
  - Longitudinal data
  - Mean spline curve and random effects for
    - Size
    - Timing
    - Intensity or Rate
  - Individual curves combine all four
Compare LMS and SITAR mean curves

- LMS median curve
Compare LMS and SITAR mean curves

- LMS median curve
- SITAR mean curve
  - SITAR curve steeper
    - Merrell (1931)
Compare LMS and SITAR mean curves

- LMS median curve
- SITAR mean curve
  - SITAR curve steeper
    - Merrell (1931)
- SITAR velocity curve
  - Clear age at take-off
  - Sharp peak
S I T A R growth curve analysis

- Model:
  \[
  T_{ij} = e^{i(t_{ij})}
  \]
  \[
  y_{ij} = i + h(T_{ij})
  \]

- Data
  - developmental age \( T_{ij} \)
  - chronological age \( t_{ij} \) for subject \( i \)
  - measurement \( y_{ij} \)

- Smooth curve
  - \( h(.) \) natural cubic B-spline with specified d.f.

- Random effects
  - \( \alpha_i \) size, \( \beta_i \) timing, \( \gamma_i \) rate for subject \( i \)
Example

Clinical trial of calcium supplement on height growth in The Gambia
Example – Clinical trial of calcium supplement on height in The Gambia

- Does a pre-pubertal calcium supplement affect height growth in Gambian boys and girls?
- **80/80** boys/girls; annual heights from 8-24 years
  - randomised at 8 years to receive
    - calcium (700 mg/d)
    - or placebo
  - for 1 year

Calcium Trial

- SITAR-adjusted mean curves by sex/trial arm
  - Ca supp — Placebo ---
- Boys
  - APHV 7 months earlier
    (p = 0.01)
  - Final height 2.6 cm less
    (p = 0.002)
- Girls - no Ca effect

Summary – Calcium Trial

- Pre-pubertal calcium supplement leads to earlier puberty and earlier growth cessation in boys
- Final height 2.6 cm less in supplemented group

Original aim – improve diet to improve growth

Be careful what you wish for…

Example

Clinical trial of oxandrolone on height growth in Turner Syndrome
Example – Clinical trial of oxandrolone

- Does oxandrolone increase final height in girls with Turner Syndrome?
- **105** girls with annual heights from 8-18 years
  - randomised at 9y to oxandrolone or placebo

Turner Trial

- Individual growth curves by trial arm

Turner Trial

- SITAR-adjusted growth curves by trial arm
- Clear differences in growth curves

Turner Trial

- SITAR-adjusted growth curves by trial arm
- Clear differences in mean growth curves
- Oxandrolone adds 4.5 cm to final height (P = 0.001)

Example

Role of IGF-1 in pubertal growth
Example – Role of IGF-1 in pubertal growth

• Insulin-like growth factor 1 (IGF-1) believed to be important in puberty, but role unclear

• Chard Growth Study (1981)

• 24/27 boys/girls followed from 9-16 years
  • 681 IGF-1 measurements
  • 321 testosterone / 326 estradiol
  • 1243 height (in 54/70)

Chard height

- SITAR modelling of height by sex
- Over 99% of variance explained
- Dotted lines indicate age at peak velocity

Chard IGF-1

- SITAR modelling of IGF-1 by sex
- 65% of variance explained
- IGF-1 rises then falls
- Consistent mean curve emerges from noisy raw data

Chard sex steroids

- SITAR modelling of testosterone/estradiol
- 86% of testosterone variance explained
  - But only 47% estradiol
- Both curves rise through puberty

Timing of puberty

- Does age at peak velocity for the different measurements correlate across subjects?
- Random effects for timing define subject-specific ages at peak velocity (APV)
- So can look at correlations between timing random effects across subjects, by sex

Correlations between timing random effects

Boys (n=24)

- Height: 0.92
- IGF-1: 0.85
- Testosterone

Girls (n=27)

- Height: 0.74
- IGF-1: 0.61
- Estradiol
Summary – IGF-1 in puberty

- Mean curve for IGF-1 shows that IGF-1 rises, peaks and then falls in individuals
- Age at IGF-1 peak velocity highly correlated with corresponding ages for height and sex steroids
- Evidence that IGF-1 plays an important role in puberty

Example

Life course: pubertal growth and later IGF-1
Example – Life course and CHS data

- CHS sample followed up in 2001
  - 1024 subjects, mean age 63 years
- IGF-1 measured
- Relate IGF-1 to pubertal growth
  - as measured by SITAR
  - SITAR timing adjusted for secular trend

SITAR and later IGF-1

- SITAR parameter correlations with IGF-1
  - Size uncorrelated
  - intensity uncorrelated
  - timing negatively correlated ($r = -0.08$, $p < 0.01$)

Summary – Life course

• Early puberty is associated with higher IGF-1 fifty years later

• Likely explanation: IGF-1 related to timing of puberty and also tracks into adult life

Example

Gemini Study of infant weight
Example – Gemini Study of infant weight

- **2340** twin pairs followed from birth
- Median gestation 37 weeks
- **21617** weights to 1 year
- Relate weight to postmenstrual age (twin 1)

Gemini Study – weight in infant twins

94.9%
Gemini Study

- SITAR mean curve shows peak weight velocity at 43 weeks
  - ~6 weeks postnatal age
Weight in infancy - Effects of size, timing and intensity

![Graphs showing weight and weight velocity over postmenstrual age for different scenarios.]

- **Big** and **Small** scenarios
- **Fast** and **Slow** scenarios
Summary – Gemini Study

- SITAR provides a good fit to infant weight
- Weight velocity peaks ~6 weeks after birth
  - i.e. earlier in preterm infants
- SITAR timing reflects early growth rate
  - Analogous to time to regain birthweight
SITAR growth and development

• “Development” relates to timing of developmental markers
  • Such as Tanner stage or bone maturity
• Early vs late development relates to timing
• Fast versus slow development relates to intensity
• Markers of development can be fitted in SITAR
  • Size not relevant, as value of marker depends only on developmental age (same measurement scale for all)
• Hence fit including SITAR timing and intensity
  • but omit SITAR size
Example

Bone maturation in South Africa
Example – Bone maturation in South Africa

- Birth to Twenty Study
- White/black boys/girls from Soweto aged 9-20 yr
- Annual hand-wrist x-rays
- Bone maturity score based on TW3 RUS
  - Scale 0 to 1000 (= adult)
- Subjects/measurements
  - 106/575  214/1803  101/615  186/1572
  - white boys  black boys  white girls  black girls

TW3 RUS bone maturity score by sex and ethnicity

Boys

Girls

[Graphs showing TW3 RUS bone maturity scores for boys and girls by ethnicity, with variance explained percentages for each group.]
Mean curves for bone maturity score by sex and ethnicity
Summary – Birth to Twenty Study

• Can fit SITAR to developmental measures as well as growth measures
  • Just need to omit SITAR size random effect
• Bone maturity score results striking
  • Complex curve shape, same for all groups
  • Black boys delayed 6 months vs white
  • Black girls not delayed
• Striking sex by environment interaction
Lots of examples

- CHS – LMS and SITAR model height
- Gambia – calcium supplement reduces height
- Turner Syndrome – oxandrolone increases height
- Chard – IGF-1 related to timing of puberty
- CHS – timing of puberty affects later IGF-1
- Gemini – infant weight velocity peaks at 6 weeks
- BTT – bone maturation varies by sex and ethnicity
Conclusions – single measurements

- GAMLSS a powerful tool for constructing centile charts
  - Allows conversion of measurements to Z-scores
- Easy to fit using R
- For height in puberty, clear evidence of age-varying skewness
- For weight, BMI etc skewness even more apparent
  - though little sign of kurtosis
Conclusions – serial measurements

- SITAR efficiently summarises growth curves as
  - a mean curve
  - and size-timing-intensity random effects by subject
- Easy to fit using $R$
- Very effective at modelling height during puberty
- Also works well in infancy
  - Subjects entirely characterised by SITAR parameters
  - Individual data redundant
- Applications in clinical trials and the life course
Conclusions – serial measurements

• Shape of velocity curve depends only on timing and intensity parameters

• **Hypothesis**: biological mechanism that generates between-subject variability operates on the age scale (not the height scale)

• Suggests that a body clock set early / late (APHV) and running fast / slow (PHV) explains pubertal growth variability

• SITAR is a useful instrument for growth curve analysis
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