Growth Mixture Modeling for Sequential Growth Processes

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Abstract

We re-visit the issue of "compensatory growth hypothesis". The main idea is that some infants who experience substandard growth due to nutrition deficiency may grow faster than other children at a later age, and eventually catch up. We test this hypothesis using the data from the Cebu longitudinal study that records two developmental phases for each individual: the first developmental phase includes 12 bi-monthly records from age zero to age two, and the second developmental phase includes three records measured around age 7, 10 and 14. To test the compensatory growth hypothesis is to identify a subgroup in the sample that grows slower than others from age 0-2, but catches up from age 7-14. Being able to simultaneously identify the optimal number of subgroups that has qualitatively different growth trajectories and the growth trajectory within each subgroup based on empirical data is the major strength of growth mixture modeling technique.

Introduction

"Catch-up growth" refers to a period of faster growth following a period of growth disruption at early childhood. The biological foundation of catch-up growth is the self-adjusting mechanism of human body (Boersma and Wit 1997). Clear evidence for catch-up growth has been shown in controlled clinical settings; however, evidence for catch-up growth in general population is much less clear.

Controlled clinical studies and population-based studies have different goals: controlled clinical studies try to find out what *will happen* under certain condition, population-based studies aim to show what *have happened* in a particular population. The present research belongs to the latter category. In an experimental setting, random assignment can be used to put respondents into "treatment group" and "control group" to make sure the results are comparable. Different treatment will be given to different groups and results can be readily interpreted. Such a clear distinction between treatment group and control group does not exist in most sample surveys, which makes subsequent analysis and comparison rather difficult. Researchers have proposed various *ad hoc* methods to group respondents in sample survey data to emulate the treatment vs. control group distinction: based on some cut-off points using standardized Z score, based on percentiles of standardized Z scores, or based on percentiles of the difference between two sequential standardized Z scores (Adair 1999; Cameron, Preece and Cole 2005; Eckhardt, Gordon-Larsen and Adair 2005; Mei et al. 2004).

There are several problems with *ad hoc* methods. First of all, *ad hoc* methods utilize data from two observation points, even when high quality longitudinal data is available. Second, the classification is based on *a priori* criteria as opposed to either theoretically-guide or based on rigorous statistical criteria. The results are likely to be sensitive to different choice of cut-off points.

We adopt a different approach. Instead of relying on difference score at two arbitrarily selected time points, we focus on the complete growth process, trying to identify one or more subgroups in the population that demonstrate growth trajectories similar to Figure 1. Building on the recent development in growth mixture modeling methodology (Muthen 2001a; Muthen 2004), we utilize each respondent's complete growth information to simultaneously identify the presence of qualitatively different growth trajectories and the (unobserved) subgroups that show the particular growth trajectory. The optimal number of latent subgroups will be decided based on rigorous statistical criteria. We choose to use data from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a large prospective study of a cohort of more than 3,000 Filipino children in Cebu metropolitan area that has been going on for more than 20 years. This data set has been used for the study of catch-up growth, which provides good baseline reference against which we can compare our results.

Identifying Catch-Up Growth in Population-Based Study: Issues and Difficulties

The concept of catch-up growth is often illustrated by diagrams like the one shown in Figure 1. The growth trajectory shown in Figure one can be divided into four spells where spell A represents a period of normal development, spell B represents a period of growth retardation, spell C represents a period of catch-up growth, and spell D represents another period of normal growth. In a controlled clinical setting, respondents' group memberships (treatment vs. control), the content and the intensity of the treatment, and the onset and the duration of each growth spell can be manipulated according to research plan to achieve maximum analytical clarity.

In a population-based study, since we do not know who are at the risk of growth retardation and who is eligible for catch-up growth, we do not know the onset of each growth spell as shown in Figure 1, and there is no distinction between treat vs. control group, the simple pre- post-treatment comparison is no longer applicable. Some argue the international growth reference can be treated as the “normal” growth trajectory against which catch-up can be assessed (Cameron, Preece and Cole 2005). The problem is in many developing countries children are universally much shorter than the international growth reference (as in the case of the CLHNS), majority of the sample will be under the stunting cut-off point. As results, the analysis will be driven by the contrast between two populations instead of between different sub-groups within the same population. It is much more difficult to convince somebody to believe that the Filipino children can grow as tall as American children than to convince them to believe that shorter Filipino children can grow as tall as taller Filipino children.

The real challenge with regard to catch-up growth in a population-based research is to find growth trajectories with specific shapes (similar to Figure 1) and to identify subgroups of individuals who demonstrate that specific growth trajectories. Since the subgroup membership is unobserved and has to be estimated from empirical data, high quality longitudinal growth data with as many as possible waves and innovative growth modeling statistical techniques that handle both continuous and categorical latent variables are required.

Review of *Ad Hoc* Methods

The unique nature of population-based study has not been fully appreciated in the past research regarding catch-up growth. Various *ad hoc* methods that treat catch-up growth as comparison of height measurements at two time points have been used in the past. Research attention has been devoted to issues like the choice between raw difference score or standardized difference Z score, which international growth reference should be used for standardization, or which two age groups should be compared. The real conceptual issues that matter most in population-based research regarding catch-up growth have been largely missing in the discussion.

From a methodological perspective, making inference about catch-up growth based on the comparison of two time points is problematic, for several reasons. First of all, without knowing the onset of each growth spell as illustrated in Figure 1, the choice of which two time points to compare is inevitably arbitrary, and little has been known about the extent to which substantive conclusions are influenced by difference choices of time points. Second, making inference about *change* based on only two measurements (a.k.a. “change score” or “difference score” approach) suffers from measurement error problem (Willett 1997).

Classification of individuals is also done in *ad hoc* fashion. These methods include: 1) standardize height measurement using international growth reference and classify respondents into groups based on some Z score cut-off points, e.g. $Z \leq -2$ (stunted) vs. to $Z > -2$ (not stunted) (Adair 1999); 2) classify respondents based on quantile using either raw score or standardized score (Mei et al. 2004); 3) classify respondents based on quantile of difference scores between two time points (Eckhardt, Gordon-Larsen and Adair 2005). One *ad hoc* method may perform better than another in a particular situation, depending on the data structure and characteristics of the study population. But there is no theoretical basis to decide which one is the clear winner. A common weakness shard by all *ad hoc* methods is that the classification of individuals is neither based on information of their growth trajectories, nor based on rigorous statistical criteria. In other words, *ad hoc* methods may put individuals with distinctively different growth trajectories into the same group as well as put individual with similar growth trajectories into different groups, depending on the cut-off points of choice.

Growth Mixture Model for Sequential Processes

In the case of cross-sectional data or data from a two-wave design, *ad hoc* methods may be the only choices. When high quality longitudinal data are available, *ad hoc* methods should give way to growth model and it various extensions. [1]

Following Muthen (2001b; 2004), let y_{ijk} be the height measurement of individual i of subgroup k measured at time point t, where the group membership is not observed but to be inferred from the data; let x_t be the time at each measurement point; let w_{itk} be a time-varying covariate, and let w_{ik} be a time-constant covariate. A simple growth mixture model is written as:

$$y_{itk} = \eta_{0ik} + \eta_{1ik} x_t + k_{tk} w_{itk} + \varepsilon_{itk} \qquad (1)$$

[1] Growth modeling methodology has been developed in two different traditions. "Individual growth model" is a special type of multilevel model while "latent growth model" is structural equation model with mean structure. It has been demonstrated that they can be perfectly mapped to each other and yields exactly the same results (Curran 2003; Willett and Sayer 1994).

$$\eta_{0ik} = \alpha_{0k} + \gamma_{0k} w_{ik} + \zeta_{0ik} \tag{2}$$

$$\eta_{1ik} = \alpha_{1k} + \gamma_{1k} w_{ik} + \zeta_{1ik} \tag{3}$$

$$P(c_{ik} = 1 | z_{ik}) = \frac{e^{\alpha_{ck} + \gamma_{ck} z_{ik}}}{\sum_{k=1}^{K} e^{\alpha_{ck} + \gamma_{ck} z_{ik}}} \tag{4}$$

Equation (1) specifies that individuals' height as function of their age and a time-varying covariate. Each individual's growth trajectory is determined by two growth factors: η_{0ik} the intercept factor and η_{1ik} the slope factor. This is the level-1 model in a multilevel model and a measurement model in a structural equation model. Equation (2) and (3) explains between-individual variation in growth factors using a time-constant covariate. They constitute level-2 models in a multilevel model and structure model in a structural equation model. Equation (4) predicts latent class membership c, which is a multinomial logistic regression. Equation (1)-(4) can be jointly estimated using maximum likelihood and the *EM* algorithm by treating the latent class variable c as missing data. Optimal number of latent classes can be decided based on Lo-Mendell-Rubin likelihood ratio test (Lo, Mendell and Rubin 2001) or bootstrap likelihood ratio test (McLachlan and Peel 2000).

The growth mixture model represented by Equation (1) to (4) makes it possible to simultaneously 1) determine the optimal number of latent subgroups based on rigorous statistical tests, 2) stochastically determine each respondent's latent subgroup membership and, 3) estimate distinctive growth trajectory for each latent subgroup. This unique feature of growth mixture model makes it an ideal analytical tool to study catch-up growth in population-based settings.

Data and Measurement

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) was conducted by the Carolina Population Center at the University of North Carolina at Chapel Hill, the Nutrition Center of the Philippines, the Office of Population Studies at the University of San Carlos, and the Nutrition Center of the Philippines. A baseline survey (1983-1984) was conducted among 3,327 women during their 6th or 7th month of pregnancy living in 33 randomly-selected communities from the Metropolitan Cebu area so that all impending births could be identified. Subsequent surveys took place immediately after birth, then at bimonthly intervals for 24 months; the baseline sample included 3,080 non-twin live births. Three follow-up surveys were conducted; in 1991-1992 (mean age 8 years, 74% of original sample), 1994-1995 (mean age 11.5 years, 71% of original sample), and 1998 (mean age 15.5 years, 68% of original sample). The CLHNS collected individual, household, and community information.

Our analysis utilizes the following variables: child's height is measured in centimeter measured at each interview; child's gender is measured as a binary variable in which boy is coded "1" and girl is coded "0"; mother's height is measured as logarithm of mother's height raw score measured in centimeter.

Figure 2 shows the structure of the CLHNS data. Four clusters of observations are discernable in the figure. The cluster on the left contains a total number of 13 bimonthly observations while each of the other three clusters contains only one observation. This unique data structure provides a good opportunity to tackle the issue of catch-up growth. A reasonable way to handle this unique data structure is to treat the first 13 waves as the first growth spell and the other 3 waves as a second growth spell, each having its own growth function.

This means that instead of having one set of Equation (1), (2) and (3) for the complete growth process, we will have two. This can be demonstrated more clearly in a path diagram like Figure 3.

As we mentioned earlier, one of the problems of *ad hoc* methods is measurement error that is intrinsic to two-wave design. Our growth mixture model can produce predicted height that is free of measurement error for any age group by properly centering the data. We center the first growth spell in the way that the intercept factor for the first growth spell I_1 represents predicted height at age 2 and the intercept factor for the second growth spell I_2 represents predicted height at age 8. We can do two types of comparisons: *ad hoc* methods vs. growth mixture model, and *ad hoc* methods using raw data vs. *ad hoc* methods using measurement error-free predicted values.

The CLHNS data has been used in previous research to study catch-up growth (Adair 1999; Eckhardt, Gordon-Larsen and Adair 2005). Our results can be compared against these previous studies to see whether we have made any new discoveries.

Analysis

The first step for growth mixture modeling is to decide the optimal number of latent classes. Our strategy is to begin with a single-class model, then a two-class model. If the two-class model improves model fit over the single-class, then we estimate a three-class model, and so on. Based on Lo-Mendell-Rubin likelihood ratio test, the best fitted model is the 4-class growth mixture model.

Table 1 shows some results of the best-fitted 4-class growth mixture model. At age two, class 2, which includes 148 children, is clearly the most disadvantageous group with regard to physical growth, mainly due to the relative low growth rate (1.00 cm/two months as opposed to around 1.40 cm/two months for other children) during that period of time. Other three groups do not show much between-group heterogeneity at this age. If we only include this growth spell in the model, the best fitted model is probably a 2-class model. The inclusion of the second growth spell makes the picture more complicated. At age eight, class 2 is still the most disadvantageous group. However, the mean difference between class 2 and class 3 has decreased from 8.45cm to 4.31cm, and the mean difference between class 2 and class 4 has decreased from 6.49cm to 3.33cm. Overall, class 1 is the most advantageous group. The growth advantage of this group over class 3 and class 4 is not clear at the first growth spell, but it grows much faster than the other two groups between age 2-8. As results, at age 8, members of class 1 are not only significantly taller than members of class 2, but also significantly taller than members of class 3 and 4.

How do these results speak to the issue of catch-up growth? Class 2, the least advantageous group, clearly fits the profile of suffering form growth retardation during the first growth spell, from birth to age two, thus is eligible for catch-up growth during the period of age 2-8. Catch-up growth did occur on this small group of children in the sense that difference in mean height between this small group and the majority of the sample (class 3 and 4, which constitute about 90% of the total sample) decreased significantly. However, even with catch-up growth, class 2 remains the least advantageous group during the whole growth process. This leads to the following conclusions.

Conclusion 1: Catch-up growth did occur among the Filipino children during age 2-8, but it was not enough to offset the negative influence of growth retardation during the first two years of life.

Catch-up growth does not seem to be limited between age 2-8. As Figure 4 shows, during age 8-16, the growth trajectory for latent class 3 clearly qualifies the definition of catch-up growth. What is interesting about this phenomenon is that class 3 is not the least advantageous group. From multinomial logistic regression that predicts latent class membership in Table 2, it can be seen that boys are much more likely to be in class 3 while girls are much more likely to be in class 4. This type of catch-up growth may not be as interesting as the one between age 2-8 because what it says is:

Conclusion 2: Boys will catch-up and overgrow girls during adolescence, even though there seems to be more tall girls than tall boys at age 8.

To have better intuitive sense of the distribution of the four latent classes, Figure 6 shows bivariate scatter plot of the predicted height at age 2 and age 8, with different colors representing different latent groups.

As the last step of our analysis, we compare our results with results from one of the *ad hoc* methods. We first standardize height measurement at the 24th month and at 1991 using the US CDC growth reference; then we generate a new variable indicating whether one was stunted at age 2; then we generate another new variable indicating whether one remained stunted at age 8. Then we tabulate this “catch-up” growth indicator variable with our latent class indicator variable to see how well they agree with each other. As shown in Table 3, the two methods yield drastically different results. While growth mixture model implies that children in class 2 are the only group who has experienced catch-up growth between age 2-8, 92% of children with catch-up growth identified by *ad hoc* method belong to the other three latent classes.

Discussion

Growth mixture model provides a powerful new analytical tool to deal with complicated research questions that involve identifying latent group membership based on the presence of qualitatively different growth trajectories. We demonstrate in this research how this new method can help reaching a better understanding of a difficult question in human biology and health research. We also compare our results with results from ad hoc methods. Based on our comparison, one needs to be cautious about major conclusions regarding catch-up growth based on *ad hoc* methods.

Our next step is to extend the analysis into two directions. First of all, we will include more covariates in the model, especially those can reflect changes in children's economic wellbeing. Second, we will try to incorporate new data wave into the analysis, which will be available in the next six months.

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Table 1: Growth Mixture Model Results

	Class 1	Class 2	Class 3	Class 4
Intercept at Age 2	79.69	71.99	80.44	78.47
	(.86)	(.86)	(.16)	(.15)
Growth Rate for 1st spell	1.40	1.00	1.40	1.36
	(.05)	(.04)	(.03)	(.03)
Intercept at Age 8	122.70	110.92	115.23	114.25
	(2.42)	(.97)	(.21)	(.27)
Growth Rate for 2nd spell	4.26	5.16	5.38	5.07
	(.12)	(.15)	(.03)	(.04)
Class Probability	.05	.05	.48	.42
Class Count	147	148	1460	1296

Table 2: Multinomial Logit Regression Predicting Latent Class Membership (Using Class 2 as the Reference Category)

	Class 1	Class3	Class4
Boy	-.84	3.53	-1.51
	(.59)	(.62)	(.66)
Mother's Height	-.09	-.43	.26
	(.28)	(.23)	(.18)
Intercept	1.28	4.65	-.45
	(3.07)	(2.49)	(2.06)

Table 3: Comparing Results from Growth Mixture Model and from *Ad Hoc* Methods

Ad Hoc Method	Latent Class Membership			
	Class 1	Class 2	Class 3	Class 4
No Catch-up Growth	60	102	1,499	1,272
Catch-up Growth	17	9	55	38

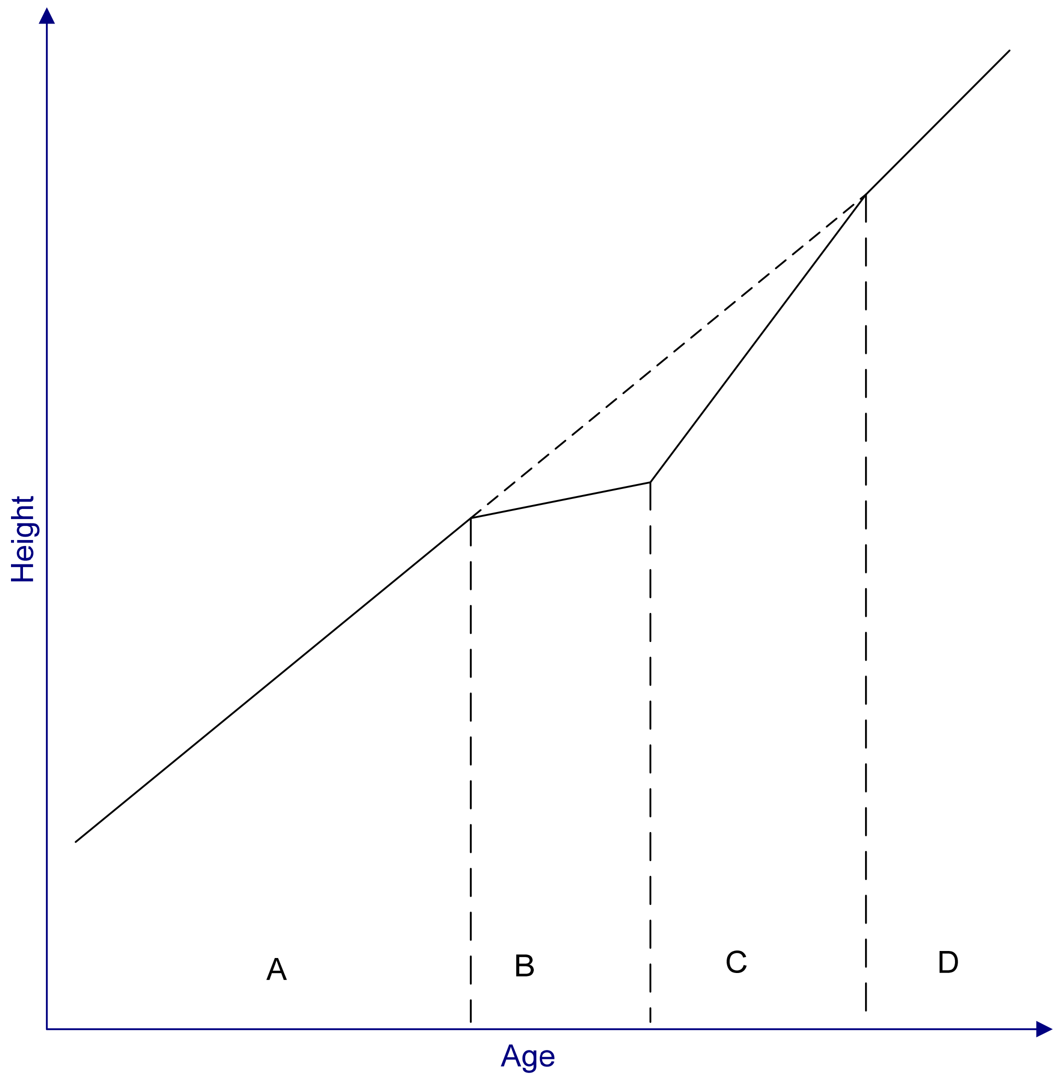

Figure 1: Diagram Illustrating Catch-Up Growth

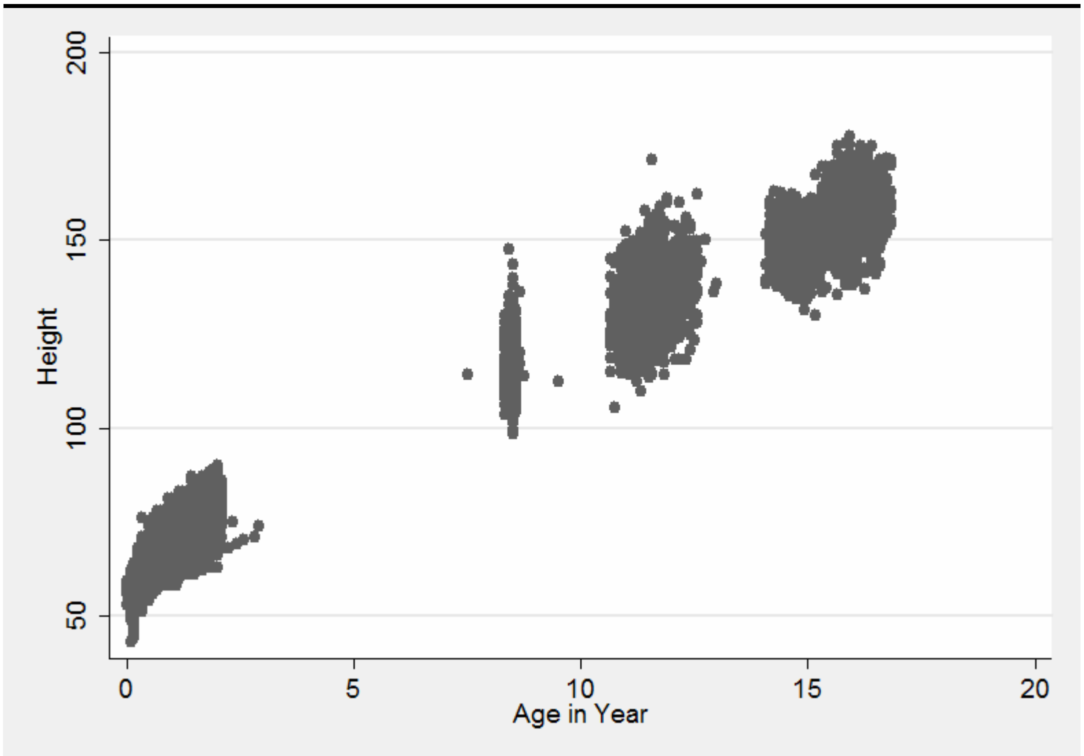

Figure 2: Scatter Plot of Children's Height by Age in the Cebu Longitudinal Health and Nutrition Survey

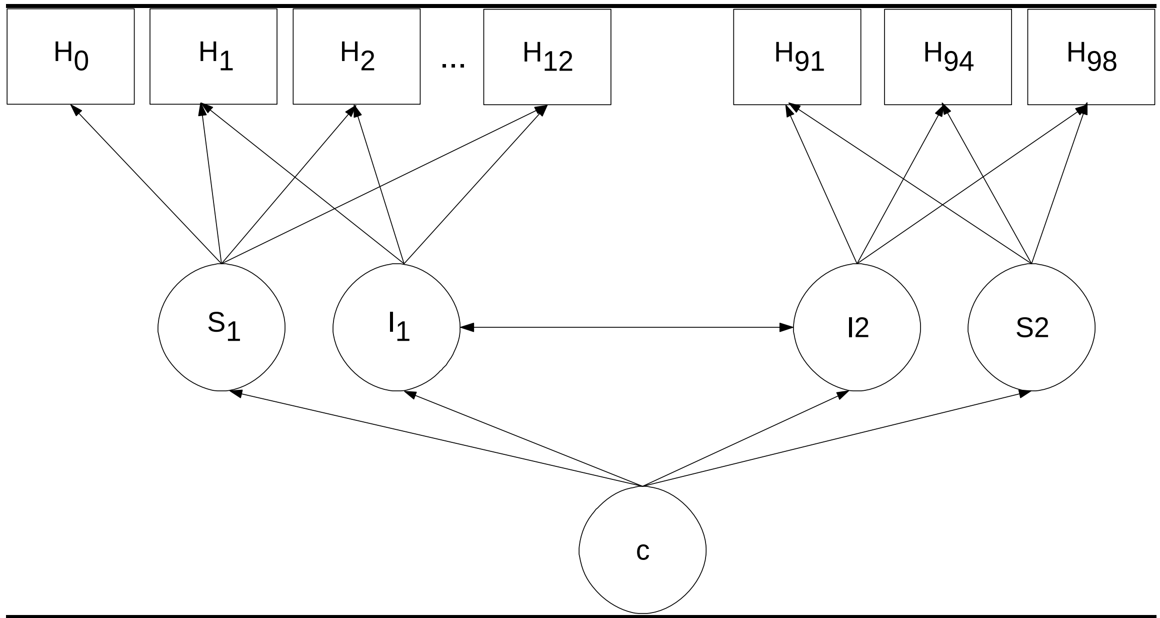

Figure 3: Diagram of the Growth Mixture Model for Two Sequential Growth Processes

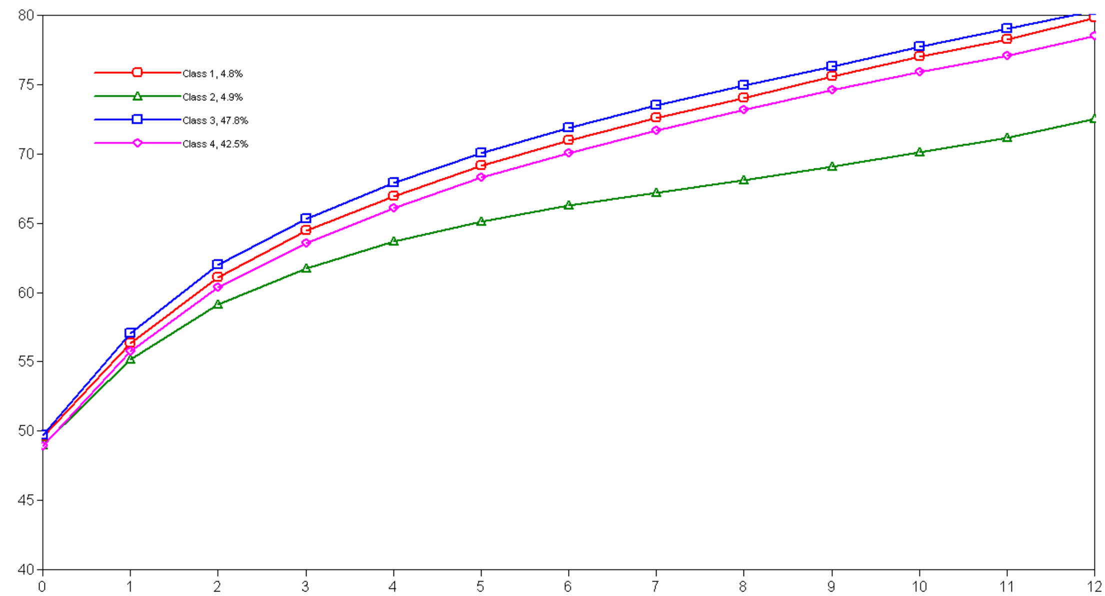

Figure 4: Growth Trajectories for the First Growth Spell (the First Two Years) from the Best Fitted Growth Mixture Model

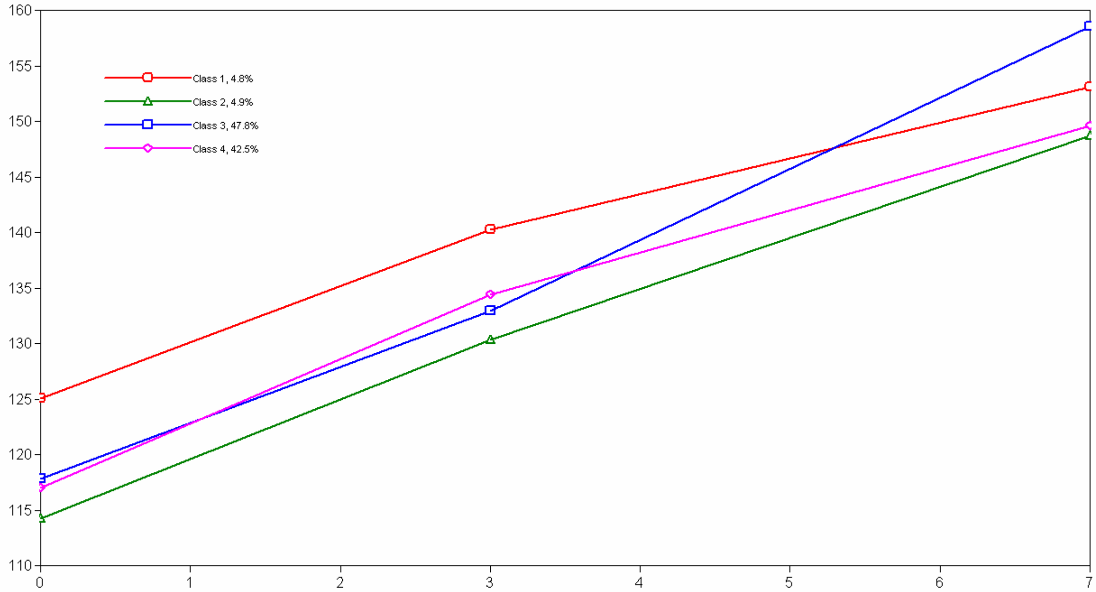

Figure 5: Growth Trajectories for the Second Growth Spell (from Age 8-17) from the Best Fitted Growth Mixture Model

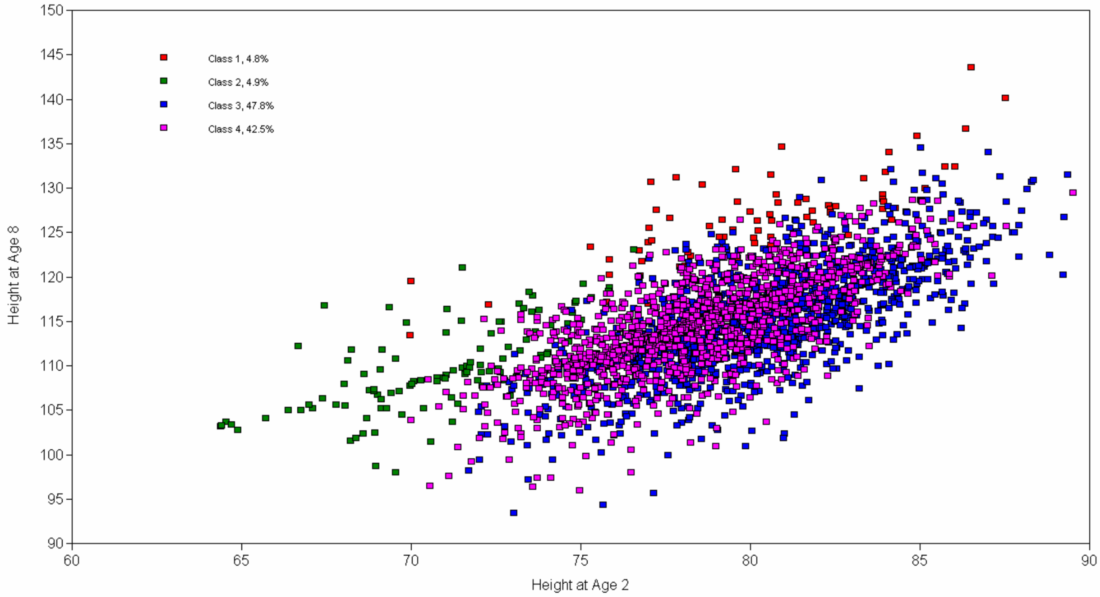

Figure 6: Bivariate Distribution of Predicted Height at Age Two and Predicted Height at Age Eight