Change Point Analysis of Cognitive Decline – a Review

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Outline

- Longitudinal profiling of cognitive decline in AD
- Change point analysis for cohort studies
- Change point analysis for cognitive decline
- Open Questions and Future Directions

Cognitive Decline

- Cognitive decline over time is closely related to the onset and conversion to AD
- Different measurement methods (neuropsychological, imaging, genetic, …) produce rich data for longitudinal profiling of cognitive decline
- A clinical belief is that accelerated cognitive decline is associated with AD, at least in some patients.

Research Question:

- Can longitudinal profiling that incorporates change point analysis provide insights in the early detection and monitoring of AD?
- If the answer is yes, then how to do it and how much can we do it?

Change Point Analysis

- The field of change point analysis is too large to be reviewed for this talk.
- We will focus on change point analysis for cohort studies, namely, longitudinal and survival data.
- A rough classification of the published papers related to change point analysis is shown in the next slide:

Change Point Analysis

- Statistical models (mixed models or/and Cox model).
- Single change point vs. multiple change points
- Population average change point vs. random change points
- Statistical methods (MLE, LRT, profile likelihood, Bayesian)

Change Point Analysis in Cognitive Profiling

- **Hall CB, Lipton RB, Sliwinski M, Stewart WF. *A change point model for estimating the onset of cognitive decline in preclinical Alzheimer's disease*.** *Statistics in Medicine*2000;19(11-12):1555-66.
- This study found that approximately 5 years before the diagnosis of dementia, memory function (as measured by Buschke Selective Reminding test) started accelerating in decline. (Sample: Bronx Aging Study)

Change Point Analysis in Cognitive Profiling

- **Blisle, P; Joseph L; Wolfson,DB. and Zhou, XJ(2002)** ***Bayesian estimation of cognitive decline in patients with Alzheimer's disease*** The Canadian Journal of Statistics / La Revue Canadienne de Statistique, 30, 37-54
- Recently, there has been great interest in estimating the decline in cognitive ability in patients with Alzheimer's disease. Measuring decline is not straightforward, since one must consider the choice of scale to measure cognitive ability, possible floor and ceiling effects, between-patient variability, and the unobserved age of onset. The authors demonstrate how to account for the above features by modeling decline in scores on the Mini-Mental State Exam in two different data sets. To this end, they use hierarchical Bayesian models with change points, for which posterior distributions are calculated using the Gibbs sampler. They make comparisons between several such models using both prior and posterior Bayes factors, and compare the results from the models suggested by these two model selection criteria.

Change Point Analysis in Cognitive Profiling

Hall CB, Ying J, Kuo L and Lipton RB. ***Bayesian and profile likelihood change point methods for modeling cognitive function over time*** Journal Computational Statistics & Data Analysis. Volume 42 Issue 1-2, 28 February 2003

- Change point models are often used to model longitudinal data. To estimate the change point, Bayesian (Biometrika 62 (1975) 407; Appl. Statist. 41 (1992) 389; Biometrics 51 (1995) 236) or profile likelihood (Statist. Med. 19 (2000) 1555) methods may be used.We compare and contrast the two methods in analyzing longitudinal cognitive data from the Bronx Aging Study. The Bayesian method has advantages over the profile likelihood method in that it does not require all subjects to have the same change point. Caution must be taken regarding sensitivity to choice of prior distribution, identifiability, and goodness of fit. Analyses show that decline in memory precedes diagnosis of dementia by 7.5-8 years, and individual change points are not needed to model heterogeneity across subjects.

Change Point Analysis in Cognitive Profiling

- **Ji M, Xiong CJ and Grundman M.** ***Hypothesis testing of a change point during cognitive decline among Alzheimer's disease patients*** Journal of Alzheimer's Disease Volume 5, Number 5/2003 375-382

  In this paper, we present a statistical hypothesis test for detecting a change point over the course of cognitive decline among Alzheimer's disease patients. The model under the null hypothesis assumes a constant rate of cognitive decline over time and the model under the alternative hypothesis is a general bilinear model with an unknown change point. When the change point is unknown, however, the null distribution of the test statistics is not analytically tractable and has to be simulated by parametric bootstrap. When the alternative hypothesis that a change point exists is accepted, we propose an estimate of its location based on the Akaike's Information Criterion. We applied our method to a data set from the Neuropsychological Database Initiative by implementing our hypothesis testing method to analyze Mini Mental Status Exam scores based on a random-slope and random-intercept model with a bilinear fixed effect. Our result shows that despite large amount of missing data, accelerated decline did occur for MMSE among AD patients. Our finding supports the clinical belief of the existence of a change point during cognitive decline among AD patients and suggests the use of change point models for the longitudinal modeling of cognitive decline in AD

Change Point Analysis in Cognitive Profiling

- **Yu B. Ghosh P Joint modeling for cognitive trajectory and risk of dementia in the presence of death.** Biometrics. 2010 Mar;66(1):294-300
- Dementia is characterized by accelerated cognitive decline before and after diagnosis as compared to normal aging. It has been known that cognitive impairment occurs long before the diagnosis of dementia. For individuals who develop dementia, it is important to determine the time when the rate of cognitive decline begins to accelerate and the subsequent gap time to dementia diagnosis. For normal aging individuals, it is also useful to understand the trajectory of cognitive function until their death. A Bayesian change-point model is proposed to fit the trajectory of cognitive function for individuals who develop dementia. In real life, people in older ages are subject to two competing risks, e.g., dementia and dementia-free death. Because the majority of people do not develop dementia, a mixture model is used for survival data with competing risks, which consists of dementia onset time after the change point of cognitive function decline for demented individuals and death time for nondemented individuals. The cognitive trajectories and the survival process are modeled jointly and the parameters are estimated using the Markov chain Monte Carlo method. Using data from the Honolulu Asia Aging Study, we show the trajectories of cognitive function and the effect of education, apolipoprotein E 4 genotype, and hypertension on cognitive decline and the risk of dementia.

Change Point Analysis in Cognitive Profiling

- **Hall CB, Ying J, Kuo L, Sliwinski M, Buschke H, Katz M, Lipton RB *Estimation of bivariate measurements having different change points, with application to cognitive ageing*** 20(24) pp 3695–3714, 30 December 2001

  Longitudinal studies of ageing make repeated observations of multiple measurements on each subject. Change point models are often used to model longitudinal data. We demonstrate the use of Bayesian and profile likelihood methods to simultaneously estimate different change points in the longitudinal course of two different measurements of cognitive function in subjects in the Bronx Aging Study who developed Alzheimer's disease (AD). Analyses show that accelerated memory decline, as measured by Buschke Selective Reminding, begins between seven and eight years before diagnosis of AD, while decline in performance on speeded tasks as measured by WAIS Performance IQ begins slightly more than two years before diagnosis, significantly after the decline in memory.

Change Point Analysis in Cognitive Profiling

- **Ardo van den Hout, Graciela Muniz-Terrera, Fiona E. Matthews.** ***Smooth random change point models***. Statistics in Medicine, 30(6), pp 599–610, 15 March 2011

  Change point models are used to describe processes over time that show a change in direction. An example of such a process is cognitive ability, where a decline a few years before death is sometimes observed. A *broken-stick* model consists of two linear parts and a breakpoint where the two lines intersect. Alternatively, models can be formulated that imply a smooth change between the two linear parts. Change point models can be extended by adding random effects to account for variability between subjects. A new smooth change point model is introduced and examples are presented that show how change point models can be estimated using functions in R for mixed-effects models. The Bayesian inference using WinBUGS is also discussed. The methods are illustrated using data from a population-based longitudinal study of ageing, the Cambridge City over 75 Cohort Study. The aim is to identify how many years before death individuals experience a change in the rate of decline of their cognitive ability.

Change Point Analysis in Cognitive Profiling

- **G. Muniz Terrera, A. van den Hout & F. E. Matthews**. ***Random change point models: investigating cognitive decline in the presence of missing data.*** Journal of Applied Statistics . 38(4) 2011 pages 705-716

With the aim of identifying the age of onset of change in the rate of cognitive decline while accounting for the missing observations, we considered a selection modelling framework. A random change point model was fitted to data from a population-based longitudinal study of ageing (the Cambridge City over 75 Cohort Study) to model the longitudinal process. A missing at random mechanism was modelled using logistic regression. Random effects such as initial cognitive status, rate of decline before and after the change point, and the age of onset of change in rate of decline were estimated after adjustment for risk factors for cognitive decline. Among other possible predictors, the last observed cognitive score was used to adjust the probability of death and dropout. Individuals who experienced less variability in their cognitive scores experienced a change in their rate of decline at older ages than individuals whose cognitive scores varied more.

Change Point Analysis in Cognitive Profiling

- **Tapsoba Jde D, Lee SM, Wang CY**. ***Joint modeling of survival time and longitudinal data with subject-specific change points in the covariates*.** Stat in Med. 2011 Feb 10;30(3):232-49

Joint models are frequently used in survival analysis to assess the relationship between time-to-event data and time-dependent covariates, which are measured longitudinally but often with errors. Routinely, a linear mixed-effects model is used to describe the longitudinal data process, while the survival times are assumed to follow the proportional hazards model. However, in some practical situations, individual covariate profiles may contain change points. In this article, we assume a two-phase polynomial random effects with subject-specific changepoint model for the longitudinal data process and the proportional hazards model for the survival times. Our main interest is in the estimation of the parameter in the hazards model. We incorporate a smooth transition function into the changepoint model for the longitudinal data and develop the corrected score and conditional score estimators, which do not require any assumption regarding the underlying distribution of the random effects or that of the change points. The estimators are shown to be asymptotically equivalent and their finite-sample performance is examined via simulations. The methods are applied to AIDS clinical trial data.

Open Questions

- Existence? (Mixture distribution)
- Missing data (nonignorable missing)
- Censoring
- Ceiling effects
- Different change points on different domains
- Joint modeling of longitudinal and survival end points
- Covariates to change points
- Clinical relevance

Bayesian Hierarchical Model with Change Point

- **Carlin BP, Gelfand AE and Smith AFM. *Hierarchical Bayesian Analysis of Change Point Problems.*** JRSSB 41(2) 1992
- A general approach to hierarchical Bayes changepoint models is presented. In particular, desired marginal posterior densities are obtained utilizing the Gibbs sampler, an iterative Monte Carlo method. This approach avoids sophisticated analytic and numerical high dimensional integration procedures. We include an application to changing regressions, changing Poisson processes and changing Markov chains. Within these contexts we handle several previously inaccessible problems.

Bayesian Hierarchical Model with Change Point

- **Wang, L; McArdle, JJ.** ***A Simulation Study Comparison of Bayesian Estimation with Conventional Methods for Estimating Unknown Change Points***. Structural Equation Modeling: A Multidisciplinary Journal, v15 n1 p52-74 Jan 2008
- The main purpose of this research is to evaluate the performance of a Bayesian approach for estimating unknown change points using Monte Carlo simulations. The univariate and bivariate unknown change point mixed models were presented and the basic idea of the Bayesian approach for estimating the models was discussed. The performance of Bayesian estimation was evaluated using simulation studies of longitudinal data with different sample sizes, varying change point values, different levels of Level-1 variances, and univariate versus bivariate outcomes. The numerical results compared the performance of the Bayesian methods with the first-order Taylor expansion method and the adaptive Gaussian quadrature method implemented in SAS PROC NLMIXED. These simulation results showed that the first-order Taylor expansion method and the adaptive Gaussian quadrature method were sensitive to the initial values, making the results somewhat unreliable. In contrast, these simulation results showed that Bayesian estimation was not sensitive to the initial values and the fixed-effects and Level-1 variance parameters can be accurately estimated in all of the conditions. One concern was that the estimates of the Level-2 covariance parameters were found to be biased when the Level-1 variance was large in the bivariate model. However, and in general, the new Bayesian approach to the estimation of turning points in longitudinal data proved to be quite robust and practically useful.

Bayesian Hierarchical Model with Change Point

- Bayesian Hierarchical Model with Change Points may be a plausible tool for investigating the complex challenge of modeling cognitive declines
- Can the change point analysis (past and future) of cognitive decline can play a role in AD detection, treatment and prevention ? There must be more interactions between statisticians and clinicians to understand the process of cognitive function change over time.