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Hypothesis testing of a change point during cognitive decline among Alzheimer's disease patients

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Abstract. 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 research.

Keywords: Alzheimer's disease, cognitive decline, change point, mixed effects model, hypothesis testing

1. Introduction

1.1. Background

Although cognitive decline is common in human aging, previous research shows that the processes of cognitive decline are different among normal aging people versus people who develop dementia. For those who develop dementia, it is believed that accelerated decline in cognitive function will occur at a certain time point during their course of cognitive decline [6]. A "change point" may be defined as the time when the baseline rate of cognitive decline accelerates and a more rapid rate of cognitive decline occurs. Because it is presumed that this acceleration in cognitive decline occurs before the diagnosis of dementia, it is of research interest to study whether and when it happens during the natural history of Alzheimer's disease. Determine whether a change point exists is important for selecting more accurate models for the complex pattern of cognitive decline among different patient populations. More accurate models of cognitive decline are valuable for designing clinical trials in AD. If a change point does exist long before AD diagnosis, then the estimation of its location is useful for early detection of the onset of AD.

Statistical models for longitudinal data are essential tools for modeling cognitive decline. General discussion of longitudinal modeling of the course of cognitive decline can be found in [3,15]. Applications of

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random effects models to evaluate longitudinal pattern of cognitive decline can be found in [11,13]. For the accelerated decline, longitudinal models with change points are good candidates for modeling purposes. The so-called trilinear model proposed in [15] has a built-in idea of change point(s) at different stages of cognitive decline. An application of the trilinear approach in an AD trial can be found in [4]. Several researchers have also introduced mixed effects models with change points. Hall [9] used linear mixed model to estimate the time point at which the rate of decline starts to accelerate in persons who developed dementia. Using a profile likelihood approach, Hall concluded that the average change point for the Buschke Selective Reminding test occurs about 5.1 years before a clinical diagnosis of dementia. Belisle [2] applied a hierarchical Bayesian model with a random change point for each individual and found that change point models are better fit than simple linear mixed models.

Although several authors have studied the problem of change point in cognitive decline, all the previous works assumed that a change point exists and focused on the estimation of the change point. In this paper, we answer the question whether there is indeed a change point by developing a statistical hypothesis test to detect a change point over the course of cognitive decline among AD patients before the diagnosis of AD. Then we propose an estimate of the change point location if its existence is confirmed by the hypothesis test. Our approach is based on general linear models which allow very flexible covariance structures for longitudinal observations. This model includes the linear mixed model as a special case. Our test does not assume that either a change point exists or its location is known. When the change point location is unknown, the test statistics is defined as the largest likelihood ratio statistics among those corresponding to all possible change point locations. However, due to the inherent complexity of the test statistics, it is not analytically tractable when the change point is unknown. Therefore parametric bootstrap method is applied to simulate the probability distribution of the test statistics. If the change point is confirmed, the estimation of its location is based on the Akaike's Information Criterion (AIC). We applied this method to a data set from the Neuropsychological Database Initiative (abbreviated as NDI) to demonstrate our testing and estimation procedures.

1.2. The NDI study

The Alzheimer's Disease Centers' Neuropsychological Database Initiative is a collaborative effort on the part of sixteen federally funded ADCS to merge the diagnostic and neuropsychological data obtained from normal and cognitively impaired individuals into a single large, multi-center database. The database is intended to serve as a resource for investigators planning clinical trials to prevent Alzheimer's disease (AD) and cognitive decline associated with aging. The assembled database contains clinical and neuropsychological data on commonly collected instruments from over 4,000 normal individuals and 800 patients with Mild Cognitive Impairment (MCI). Previous analyses have shown that in this cohort, approximately 2% of normals developed a diagnosis of AD after 4 years of follow-up whereas almost 10% developed MCI.

Within the NDI database, we located a subset of 92 patients with definitive diagnosis of AD. The mean age was 76.9 with standard deviation of 9.39. Number of years of education was 14.07 with a standard deviation of 3.24. The cognitive decline as measured by a battery of neuropsychological tests. In this paper, we will examine the Mini Mental Status Exam which is the most popular mental status test. Large amount of missing values is common for data from Alzheimer's disease patients. Among the 92 AD patients, we selected those who had at least three measurements of MMSE. There are 47 of these patients and their longitudinal measurements are presented in Fig. 1.

The origin is set at 0 where the diagnosis of AD is confirmed. The number of -1, -2, -3, ..., -12 are the number of years before AD. The maximum follow up time is 12 years in this subset of AD patients. As we can see, there is heavy missingness in the data. However, some individuals show accelerated decline to AD diagnosis.

2. Method

2.1. The model of the underlying cognitive decline processes

We assume that a sample of n individuals is observed annually for k years before the diagnosis of AD. We let 0 represent the time that AD is diagnosed. Let $t = -k, -(k-1), \ldots, -1.0$ be the number of years before AD. All individuals are observed at the same time points. The complete observation for the ith individual is $\mathbf{C}_i = (y_{i1}, y_{i2}, , \ldots, y_{i,k+1})^T$, i.e., y_{is} is observed $k + 1 - s$ years before the diagnosis of AD. Note that the superscript T means the transpose of a vector or a matrix. Assume that

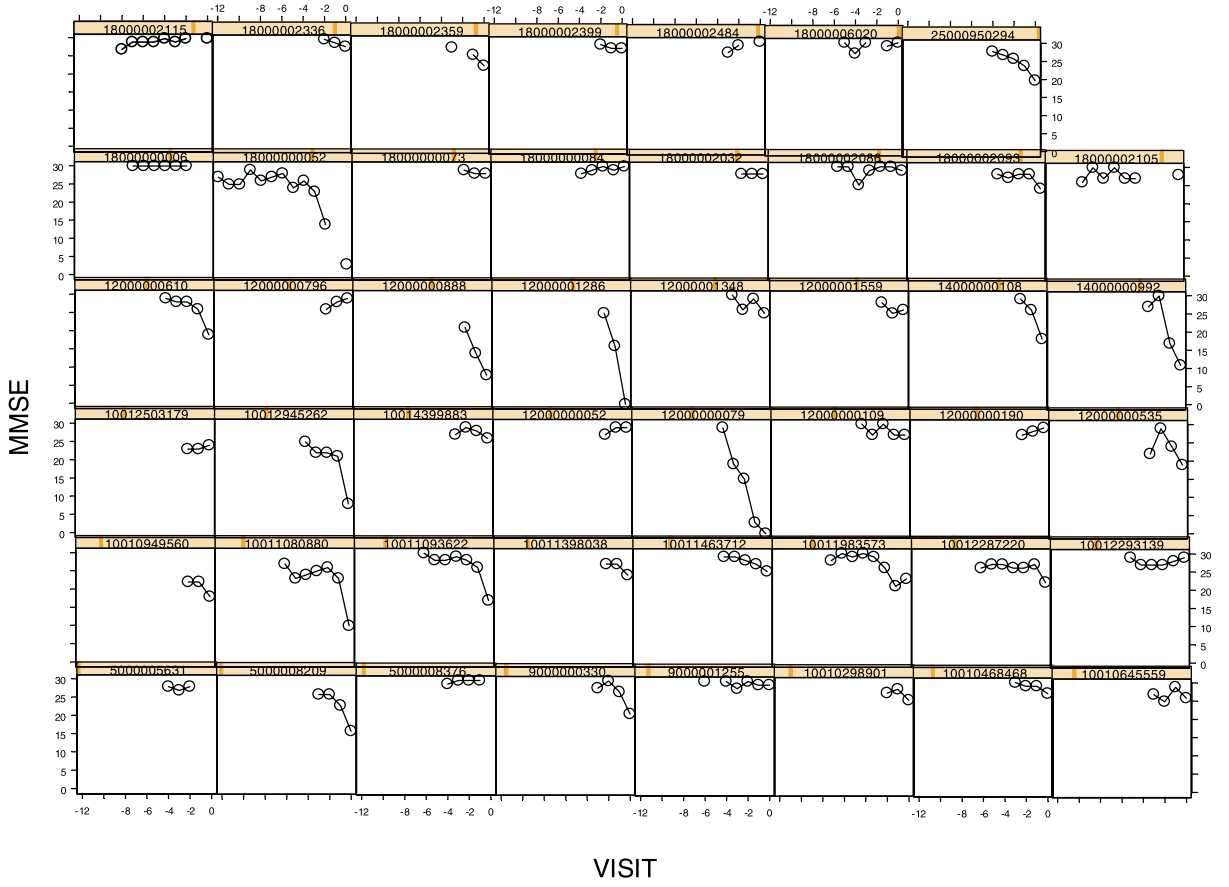

Fig. 1. Cognitive Decline on the Mini Mental Status Exam Score.

$\mathbf{C}_i \sim \mathbf{N}_{k+1}(\mu, \sum(\varphi))$, where φ is the vector of unknown parameters for the variance-covariance matrix. Also assume that for the ith individual only n_i observations are recorded: $\mathbf{Y}_i = (y_{it_1}, y_{it_2}, \ldots, y_{it_{nj}})^T$. Let $\mathbf{J}_i$ be a $n_i \times (k+1)$ matrix of 0's and 1's such that $\mathbf{Y}_i = \mathbf{J}_i\mathbf{C}_i$, then $\mathbf{Y}_i \sim N_{nj}(\mathbf{J}_i\mu, \sum_i)$, where $i = 1, 2, \ldots, n$ and $\sum_i = \mathbf{J}\sum(\varphi)\mathbf{J}_i^T$. Throughout the paper, we assume that the missing data are missing completely at random (MCAR) in the sense of Little and Rubin, see [12].

We assume that the progression of the $y_{it}^{'}s$ on time t follows a linear relationship. This assumption is reasonable since cognitive decline tends to be slow and can be approximated by linear trend. In particular, it has been well documented in the AD literature that decline in MMSE scores is nearly linear, apart from plateaus, see [1] and the references therein.

The null hypothesis $\mathbf{H}_0$ assumes that the rate of cognitive decline is constant over the time period from $-$k to 0 years. The alternative hypothesis $\mathbf{H}_1$ assumes that the rate of progression of the $y_{it}^{'}s$ accelerates somewhere between $-(k-1)$ and -1 years before AD. Mathematically, if we write $\mathbf{C}_i = \mu + \varepsilon_i$, then under $\mathbf{H}_0$: $\mu = \mathbf{T}\begin{pmatrix}\beta_0\\ \beta_1\end{pmatrix}$, where

$$\mathbf{T} = \begin{pmatrix} 1 & -k \\ 1 & -(k-1) \\ \ldots & \ldots \\ 1 & -1 \\ 1 & 0 \end{pmatrix} \text{ and } \varepsilon_i = \begin{pmatrix} \varepsilon_{i1} \\ \varepsilon_{i2} \\ \ldots \\ \varepsilon_{i,k+1} \end{pmatrix},$$

$i = 1, 2, \ldots, n$

We assume that the $\varepsilon_i^{'}$s are iid $N(0, \sum(\varphi))$. Under $\mathbf{H}_0$, the model for $\mathbf{Y}_i$ is

$$\mathbf{Y}_i = \mathbf{J}_i\mathbf{T}\begin{pmatrix}\beta_0\\ \beta_1\end{pmatrix} + \mathbf{e}_i \tag{1}$$

where $\mathbf{e}_i = \mathbf{J}_i\varepsilon_i \sim N_{n_i}(0, \mathbf{J}_i\sum(\varphi)\mathbf{J}_i^T)$.

The alternative hypothesis is that there is a change point in the rate of cognitive decline which indicates a bilinear model for expectation of $\mathbf{C}_i$. Assume that the

change point of rate of decline occurs τ years before the diagnosis of AD, where $0 < \tau < (k-1)$, the corresponding model for $\mathbf{C}_i$ is

$$\begin{aligned}\mathbf{C}_i &= \mathbf{T}_1 \begin{pmatrix}\theta_0\\ \theta_1\end{pmatrix} + \mathbf{T}_2 \begin{pmatrix}\gamma_0\\ \gamma_1\end{pmatrix} + \varepsilon_i \\ &= (\mathbf{T}_1\ \mathbf{T}_2) \begin{pmatrix}\theta_0\\ \theta_1\\ \gamma_0\\ \gamma_1\end{pmatrix} + \varepsilon_i\end{aligned} \tag{2}$$

where $\mathbf{T}_1 = \begin{pmatrix} q & -k \\ 1 & -(k-1) \\ & \ldots\ldots \\ 1 & -(\tau+1) \\ \mathbf{0} & \mathbf{0}\end{pmatrix}, \mathbf{T}_2 = \begin{pmatrix}\mathbf{0} & \mathbf{0} \\ 1 & -\tau \\ \ldots & \\ 1 & -1 \\ 1 & 0\end{pmatrix}$, and $\varepsilon_i = \begin{pmatrix}\varepsilon_{i1}\\ \varepsilon_{i2}\\ \ldots\\ \varepsilon_{i,k+1}\end{pmatrix}, i = 1, 2, \ldots, n$. Here, the bold **0**s in $\mathbf{T}_1$ and $\mathbf{T}_2$ are vectors of 0s with appropriate dimensions.

We assume that the ε_i's are iid $N(0, \sum(\varphi))$.

We restrict the parameters to satisfy $\theta_0 - \tau\theta_1 = \gamma_0 - \tau\gamma_1$ to guarantee that the mean of C is continuous over time. Therefore, we have under H_1,

$$\mathbf{C}_i \sim N\left(\mathbf{X}_\tau \begin{pmatrix}\theta_0\\ \theta_1\\ \gamma_1\end{pmatrix}, \sum(\varphi)\right)$$

where

$$\mathbf{X}_\tau = \begin{pmatrix} 1 & -k & 0 \\ 1 & -(k-1) & 0 \\ \ldots & & \\ 1 & -(\tau+1) & 0 \\ 1 & -\tau & 0 \\ 1 & -\tau & 1 \\ \ldots & & \\ 1 & -\tau & \tau \end{pmatrix}$$

The model for $\mathbf{Y}_i$ under $\mathbf{H}_1$ is

$$\mathbf{Y}_i = \mathbf{J}_i \mathbf{X}_\tau \begin{pmatrix}\theta_0\\ \theta_1\\ \gamma_1\end{pmatrix} + \mathbf{e}_i$$

where $\mathbf{e}_i = \mathbf{J}_i\varepsilon_i \sim N_{n_j}(0, \mathbf{J}_i \sum(\varphi)\mathbf{J}_i^T)$.

2.2. Hypothesis test when the location of the change point is known

When τ is known, both models under $\mathbf{H}_0$ and $\mathbf{H}_1$ can be estimated by maximum likelihood method. Since the linear model under $\mathbf{H}_0$ is nested in the bilinear model under $\mathbf{H}_1$, a likelihood ratio test can be used to test $\mathbf{H}_0$ against $\mathbf{H}_1$. The likelihood ratio statistics $W_\tau = -2\log\Lambda(\tau)$ can be computed, where $\Lambda(\tau)$ is the ratio of the two likelihoods corresponding to H_0 and H_1 respectively, evaluated at the MLEs of the parameters. More specifically, let L_0, L_1 be the likelihood function under H_0 and the likelihood function under H_1, respectively. Let $\begin{pmatrix}\hat\beta_0\\ \hat\beta_1\end{pmatrix}$ and $\hat{\sum}^0 = \sum(\hat\varphi_0)$ be the MLEs under H_0 with $\hat{\sum}_i^0 = J_i\hat{\sum}^0 J_i^t$ and $\begin{pmatrix}\hat\theta_0\\ \hat\theta_1\\ \hat\gamma_1\end{pmatrix}$ and $\hat{\sum}^1 = \sum(\hat\varphi_1)$ be the MLEs under H_1 with $\hat{\sum}_i^1 = J_i\hat{\sum}^1 J_i^T$, it can be shown that

$$\begin{aligned}\mathbf{W}_\tau &= -2\log\Lambda(\tau) \\ &= -\sum_{i=1}^{n}\left(Y_i - J_iX_\tau\begin{pmatrix}\hat\theta_0\\ \hat\theta_1\\ \hat\gamma_1\end{pmatrix}\right)^T \left(\hat{\sum}_i^1\right)^{-1} \\ &\quad \left(Y_i - J_iX_\tau\begin{pmatrix}\hat\theta_0\\ \hat\theta_1\\ \hat\gamma_1\end{pmatrix}\right) + \sum\nolimits_{i=1}^{n}(Y_i \\ &\quad - J_iT\begin{pmatrix}\hat\beta_0\\ \hat\beta_1\end{pmatrix}\Bigg)^T \hat{\sum}_i^0 \left(Y_i - J_iT\begin{pmatrix}\hat\beta_0\\ \hat\beta_1\end{pmatrix}\right) \\ &\quad + \sum\nolimits_{i=1}^{n}\left[\log\left|\hat{\sum}_i^0\right| - \log\left|\hat{\sum}_i^1\right|\right]\end{aligned} \tag{3}$$

Under H_0, W_τ has an asymptotic χ_1^2 distribution. Thus, a size α test rejects H_0 if $W_\tau > \chi_{1,a}^2$.

2.3. Hypothesis test when the location of the change point is unspecified

When τ is unknown, a size α test rejects H_0 if $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\} > c$ where c is a critical value such that $\Pr(\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\} > c|H_0) = \alpha$. In general, the distribution of the test statistic $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\}$ under H_0 has no closed form, and therefore has to be simulated. We propose to simulate its distribution by parametric bootstrap method. In the first step, we estimate the general linear model (1) under H_0 by maximum likelihood method using the original sample. Second, generate bootstrap samples using the general linear model (1) with the MLEs of the parameters as their true values. In the bootstrap samples, the missing data mechanism is simulated in this way: the missing data matrix 's $\mathbf{J}_i$'s was first obtained from

the original sample and then applied to each bootstrap samples to obtain the "observed" values. Third, for each bootstrap sample, calculate W_τ^* for all possible values of τ between 1 and $(k-1)$ using the bilinear model corresponding to H_1 and then compute $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\}$. Fourth, the empirical distribution of $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau^*\}$ under H_0 is an approximation to the distribution of $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\}$. For a specified α, the critical value c can be determined from that empirical distribution. The fifth step is to compute $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\}$ using the bilinear model under H_1 and the original sample and then compare it to c.

2.4. Estimation of the location of the change point when is accepted

When H_1 is accepted, we denote $\begin{pmatrix}\hat\theta_{0j}\\ \hat\theta_{1j}\\ \hat\gamma_{ij}\end{pmatrix}$ and $\hat{\sum}^{1j}=\hat{\sum}^{1}(\hat\varphi_{ij})$ as the MLEs of $\begin{pmatrix}\theta_0\\ \theta_1\\ \gamma_1\end{pmatrix}$ and $\sum^1$ when the change point is located at j. Let $\hat{\sum}_i^{1j}=J_i\hat{\sum}^{1j}J_i^T$, and for $1\leqslant j\leqslant k$, let

$$L\left(\hat\theta_{0j},\hat\theta_{1j},\hat\gamma_{1j},\hat{\sum}^{1j}\right)=-\sum_{i=1}^{n}\ln\left|\hat{\sum}_i^{1j}\right|$$
$$-\sum_{i=1}^{n}\left(Y_i-J_iX_j\begin{pmatrix}\hat\theta_{0j}\\ \hat\theta_{1j}\\ \hat\gamma_{1j}\end{pmatrix}\right)^T$$
$$\left(\hat{\sum}_i^{1j}\right)^{-1}\left(Y_i-J_iX_j\begin{pmatrix}\hat\theta_{0j}\\ \hat\theta_{1j}\\ \hat\gamma_{1j}\end{pmatrix}\right)$$

We propose to estimate the location of the unknown change point τ by $\hat\tau$ where is such that

$$L\left(\hat\theta_{0\hat\tau},\hat\theta_{1\hat\tau},\hat\gamma_{1\hat\tau},\hat{\sum}^{1\hat\tau}\right)= \tag{4}$$
$$\max_{1\leqslant\tau\leqslant k-1}L\left(\hat\theta_{0\tau},\hat\theta_{1\tau},\hat\gamma_{1\tau},\hat{\sum}^{1\tau}\right)$$

Our estimator is similar to the profile likelihood estimates proposed by Hall [5] under the mixed model framework although our model contains a more general family of variance-covariance matrices. The choice of our estimator is consistent with choosing the minimum AIC (Akaike's Information Criterion) since the number of unknown parameters are the same for different change point locations.

3. Implementation

Our proposed hypothesis test is valid for general linear models with arbitrary variance-covariance matrix $\sum(\varphi)$. For the actual implementation of this hypothesis testing method, we used a random intercept, random slope model with a bilinear fixed effect part containing an unknown change point τ. This model family is rich enough to capture the slow linear trend of cognitive decline and possible occurrence of accelerated decline as well as the heterogeneity in baseline measurements and rate of decline between and within individuals. The main advantage of this simplified approach is that the complicated likelihood ratio test statistics can be extracted directly from standard software for fitting mixed models such as SAS PROC MIXED or SPLUS *lme*. Note that all the model fitting must use ML (maximum likelihood estimation) instead of REML (restricted maximum likelihood estimation).

To be more specific, we use a random intercept and random slope model with a bilinear fixed effect part with a change point at τ. The model under H_1 can be written as

$$y_{is}=(\theta_0+\theta_1t)I(t\leqslant-\tau-1)+(\gamma_0+\gamma_1t)$$
$$I(t\geqslant-\tau)+a_i+b_it+\delta_{is}$$

where $t=-(k+1-s)$ and $I(A)$ is the an indicator function whose value is 1 if the event A is true and 0 if A is false. The vectors $(a_i,b_i)^T$ are random effects reflecting the heterogeneity of the intercepts and the slopes for individuals. We assume they have an arbitrary covariance structure, i.e.,

$$\begin{pmatrix}a_i\\ b_i\end{pmatrix}\sim N(0,\Pi)$$

Also, the serial correlation over time is modeled by assuming that $(\delta_{i1},\delta_{i2},\ldots,\delta_{ik+1})'$ follows another normal distribution with a zero mean vector and a first-order autoregressive covariance matrix Ω. All these assumptions give a specific case of model (2) in which $\varepsilon_{is}=a_i+b_it_s+\delta_{is}$ with

$$\sum(\varphi)=T\Pi T'+\Omega.$$

When τ is known, define another variable $X=I(t\leqslant-\tau-1)$, then the bilinear model becomes

$$y_{is}=\gamma_0+\gamma_1t+(\theta_0-\gamma_0)X+(\theta_1-\gamma_1)tX$$
$$+a_i+b_it+\delta_{is}$$

Note that under the constraint that the mean of the bilinear model is continuous over time, there are only

three free parameters among $(\theta_0, \theta_1, \gamma_0, \gamma_1)$ since they must follow the constraint of $\theta_0 - \theta_1\tau = \gamma_0 - \gamma_1\tau$. What is particularly important is that the null hypothesis H_0(no change point) is equivalent to $H_0 : \gamma_1 = \theta_1$, i.e., the regression coefficient corresponding to the interaction term of time t and X should be 0. Thus the hypothesis test for the existence of a change point is converted to testing a regression coefficient in a mixed effects model, which can be easily done by likelihood ratio test in SAS PROC MIXED or SPLUS function *lme*.

4. Results and discussion

4.1. Hypothesis testing on a unknown change point for MMSE

We applied our method on MMSE score to detect if a change point exists in the data. First we estimated the mean vector of MMSE starting from the diagnosis of AD back to 12 years prior to diagnosis using the linear model of no change point and the original sample. The estimated mean vector is

The first row is the number of years prior to diagnosis of AD, the second row is the raw mean MMSE from observed data and the third row is the estimated MMSE scores from the mixed model. The raw mean MMSE scores showed a change point at year 6 before AD. However, there were a lot of missing values which makes the raw means not reliable. From the estimated mean vector, it is obvious that the linear model of no change point does not fit the data well as the predicted mean of MMSE exceeds 30 starting from 6 years before AD.

In order to statistically test the hypothesis that there is no change point in the decline of MMSE score against the alternative that some unknown change point occurs before the diagnosis of AD, we use bootstrap method to approximate the test statistic , where W is given by (3). The description of the parametric bootstrap procedure is described in the METHOD section. Figure 2 shows the histogram of the bootstrap distribution of the likelihood ratio statistics based on 1000 bootstrap samples.

The critical value c is approximated by the 95% percentile of this bootstrap distribution and is found to be 6.70. The likelihood ratio statistics corresponding to the bilinear mixed models under H_1 over visit 1 to 11 is $\max_{1\leqslant\tau\leqslant 11}\{W_\tau\} = 31.96$. Since $\max_{1\leqslant\tau\leqslant 11}\{W_\tau\} > c$, the null hypothesis of no change point is rejected at approximately $\alpha = 0.05$. The likelihood reaches its maximum at the 5 years before AD. This is in agreement with the estimated mean vector of MMSE which has a component of 30.38 at the year 6.

5. Discussion

Our hypothesis testing approach shows that there is a change point in the mixed effects model for the longitudinal trajectories of MMSE scores, which is a widely used mental status screening test. We have detected this change point despite of the large amount of missing data, which indicates the effect of accelerated decline is quite significant. In this sense, our analyses provide statistical support for this widely held clinical belief that there is an accelerated cognitive decline during the course of Alzheimer's disease progression. Our hypothesis testing favors the bilinear model instead of the simple linear model also indicates that it is not appropriate to evaluate treatment effect based on linear rate of decline for Alzheimer's disease patients. Therefore, longitudinal modeling of cognitive decline in AD patients should incorporate change points.

The strength of our model include (a) it is a longitudinal model which is desirable for modeling changes in cognitive decline (b) it is more general than the trilinear model [3] because the slopes of the bilinear fixed effects are arbitrary other than flat during the initial and final stages of the trilinear model. (c) it does not assume the change point is known which is a contribution to the previous change point modeling of AD data (d) it partially addressed the missing data problem under small sample size.

There are several limitations of our method (a) to simplify notation, we assumed that the repeated measures are made at exactly same time points in our demonstration. The entire procedure, however, can be extended easily to accommodate unequally spaced patient visits with appropriate adjustments in design matrices T, T_1 and T_2 in model (1) and (2). (b) We are limited on the case of a unique change point of cognitive decline before the diagnosis of AD but the similar methodology should be explored for the situation of multiple change points (c) Another limitation of our method is the assumption of linear and bilinear model under H_0 and H_1. Although the linear and bilinear assumptions are always locally appropriate based on the theory of Taylor's expansion, their validity needs to be verified for the whole course of cognitive decline before

Table 1
Raw and Estimated Mean MMSE Scores

Time	0	−1	−2	−3	−4	−5	−6	−7	−8	−9	−10	−11	−12
Raw Mean MMSE	22.02	25.34	26.89	27.16	27.91	27.82	29.00	28.20	27.67	27.50	25.00	25.00	27.00
Estimated Mean MMSE	23.32	24.50	25.68	26.85	28.03	29.21	30.38	31.56	32.74	33.91	35.09	36.27	37.44

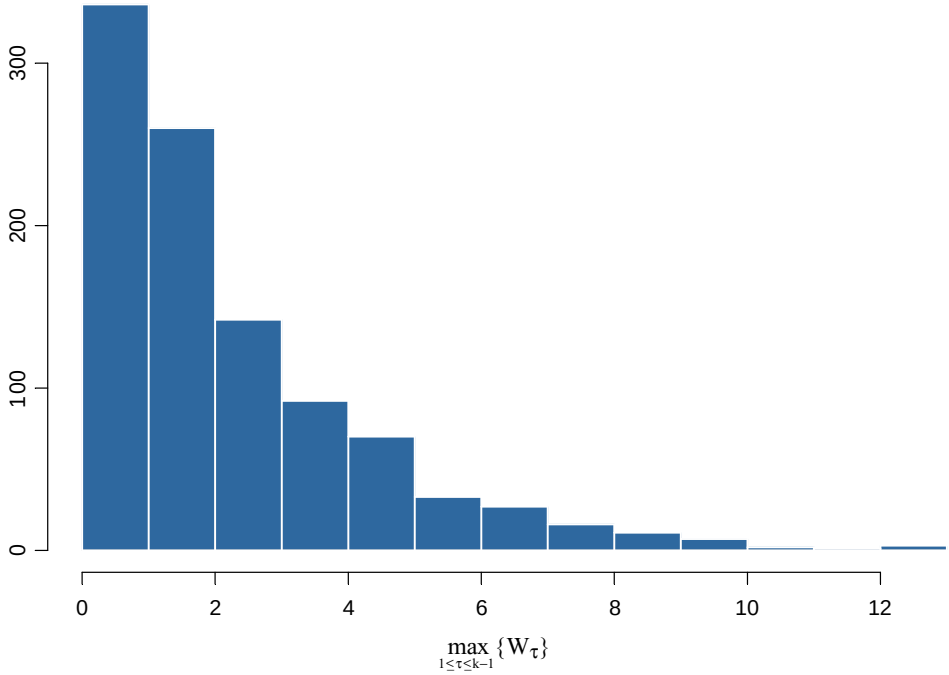

Fig. 2. Empirical distribution of $\max_{1\leqslant\tau\leqslant k-1}\{W_\tau\}$ for MMSE using 1000 bootstrap samples.

the diagnosis of AD which may be intrinsically nonlinear for some cognitive test scores. (d) The assumption of MCAR for the missing data is likely to be invalid for data in Alzheimer's disease research. We are only able to obtain consistency for the change point location estimate when the model is linear, the data is balanced and missing data are MCAR. On the other hand, there seems to be no consensus approach on the missing data issue in AD research in the literature. In general, missing data in AD research is a challenging problem that requires more investigations. (e) We assumed normal distributions for both the response and the random effects. Many cognitive test scores such as MMSE are on ordinal scales. Therefore, generalization of our results to more general type of response variables should be explored. The estimates on the fixed effects in random effects models, however, are not sensitive to departure of their random effects distributions from normality, Butler and Louis [5], Verbeke and Lesaffre [14] (f) A difficult problem with cognitive testing scores is the ceiling and floor effect [7,8]. Item response theory (IRT) can partially address the ceiling effect of MMSE. In practice, IRT has been incoporated into MMSE test for online screening, Ashford [1]. However, we have not seen work on incorporate IRT into mixed models of AD data. We defer such effort to future research.

Our test is useful for determining if a change point exists for the mean curve of an "average person" within a specified sample. It is sometimes also of interest to predict the location of a change point for each individual. Dementia of an individual change point can be determined by using a Bayesian approach, see [1, 6]. We point out that it is analytically difficult to develop hypothesis tests similar to ours for the problem of random change points. This is based on the fact that the distribution of the observed vector of cognitive function over time is mathematically intractable due to the nonlinear nature of the change point in model (2) when the location of the change point is assumed to be random. Therefore, the maximum likelihood estimation cannot be done. Although large-scale computer simulations can be used to approximate the distribution of the observed vector of cognitive function over time, we feel that a Bayesian approach is more appropriate.

Our future work include (a) carry out this hypothesis test on other neuropsychological tests to detect change points on different instruments and cognitive domains. From our preliminary findings, we believe that the change point can be detected on at least some of the cognitive test scores. Furthermore, the accelerated declines on different cognitive domains are different. Those cognitive tests with change points located at the early stage of AD are more useful for detecting the disease onset in AD trials (b) generalize our method to handle ceiling and floor effect, more general response variables, multiple change points, multivariate change points and more general missing data mechanism.

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