A dynamic trajectory class model for intensive longitudinal categorical outcome

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This paper presents a novel dynamic latent class model for a longitudinal response that is frequently measured as in our prospective study of older adults with monthly data on activities of daily living for more than 10 years. The proposed method is especially useful when the longitudinal response is measured much more frequently than other relevant covariates. The trajectory classes are latent classes that represent distinct temporal patterns of the longitudinal response wherein an individual may remain in a trajectory class or switch to another as the class membership predictors are updated periodically over time. The identification of a common set of trajectory classes allows changes among the temporal patterns to be distinguished from local fluctuations in the response. Within a trajectory class, the longitudinal response is modeled by a class-specific generalized linear mixed model. An informative event such as death is jointly modeled by class-specific probability of the event through shared random effects with that for the longitudinal response. We do not impose the conditional independence assumption given the classes. We illustrate the method by analyzing the change over time in activities of daily living trajectory class among 754 older adults with 70,500 person-months of follow-up in the Precipitating Events Project. We also investigate the impact of jointly modeling the class-specific probability of the event on the parameter estimates in a simulation study. The primary contribution of our paper is the periodic updating of trajectory classes for a longitudinal categorical response without assuming conditional independence. Copyright © 2014 John Wiley & Sons, Ltd.

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1. Introduction

Many health studies involve conditions whereby individuals make transitions over time among different health states. In this paper, we use trajectory classes to represent the states describing patterns of a categorical disability measure over time. As an individual survives through successive periods of time, the trajectory classes may change as well and therefore afford the potential updating of the trajectory classes, which is a novel feature in this paper.

A longitudinal study of activities of daily living (ADL) among older persons motivated the methodological development in this article [1–3]. Many authors ascertained ADL status on a monthly basis by telephone interview and thus an intensively measured longitudinal response. They considered a person to be disabled in ADL if he or she needed help from another person or was unable to complete any of the basic ADL tasks of walking, bathing, dressing, and transferring. They labeled a person's ADL response as independent if he or she had no disability in any of the four tasks, as mild disability if one or two ADL tasks were disabled, and as severe disability if three or four ADL tasks were disabled. They obtained more comprehensive health measures such as physical frailty, cognitive status, depressive symptoms, and chronic diseases through in-home assessments that were conducted at baseline and every 18 months there after for more than 10 years.

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Individual ADL trajectories may segregate into distinct patterns within an 18-month interval, and these patterns may change in the next 18-month time interval. We can capture the evolution of these distinct patterns over time by our proposed dynamic latent class model that allows periodic updating of trajectory class membership within an individual. Studies describe a trajectory pattern within a time interval by a class-specific generalized linear mixed model within a general growth mixture modeling framework [4–6]. Within-individual correlation is accounted for by random effects. We model membership in a trajectory class as a polytomous response by using covariates that include baseline and time-dependent predictors. We update class membership each subsequent time interval as the time-dependent predictors for class are updated. Changes in trajectory class memberships over time signify corresponding changes in the state of the longitudinal response pattern across time intervals rather than localized fluctuation in the response itself within an time interval. We smooth out the fluctuation by using the class-specific regression model within a time interval. Because an event of interest such as death occurs during the follow-up and is informatively related to the longitudinal response [7], we account for the occurrence of the event through modeling trajectory class-specific probability of the event within each class. So the model for the event occurrence shares random effects with the longitudinal response through factor loadings, in addition to the shared latent classes. Conditioning on the person's trajectory class memberships, we do not assume independence between the longitudinal responses and the event occurrence, nor between the longitudinal responses in different time intervals, because of the shared random effects. Although not explored in this paper, we can alternatively model the event as time to event from baseline (instead of from the end of previous interval). However, it is not straightforward to model the class-specific time-to-event outcome because an individual changes his or her class membership over time.

We do not provide a comprehensive review of the literature on latent class models where class membership for an individual does not change over time. Instead we compare our dynamic latent class model with latent transition models (LTMs) [8–14] where class membership is dynamic and changes over time. Our proposed model estimates class membership for trajectory classes repeatedly over time based on updated predictors, whereas LTMs estimate the transition probabilities among latent classes over time.

The LTMs are sometimes termed as hidden Markov models in which a transition probability is dependent only on the latent class (hidden state) in the preceding time point. Reboussin, Liang, and Reboussin [8] studied multiple health indicators with LTMs using estimating equations, and Rijmen *et al.* [13] and Reboussin and IaLongo [14] estimated the model parameters using maximum likelihood (ML). Miglioretti [9] presented an LTM for multivariate longitudinal responses using a fully Bayesian approach. Chung, Park and Lanza [10] studied multiple indicators with two latent class variables, and Chung, Lanza, and Loken [12] compared estimates in LTMs on the basis of ML [11] and Bayesian inference. Altman [15] used Monte Carlo expectation–maximization algorithm [16] in estimating mixed hidden Markov models with random effects in generalized linear mixed models. LTMs estimate the baseline probability of class membership and transition probabilities at follow-up time points and typically assign class membership only at baseline. As a result, uncertainty in class membership increases with each subsequent time point. In contrast, our dynamic latent trajectory class model estimates trajectory class membership over all time intervals simultaneously and directly assigns class membership for each subsequent interval by incorporating information from time-dependent predictors that are updated in each time interval. The use of multiple indicators in LTMs does not accommodate missing data of one or more indicators at a given time point, whereas our proposed model incorporates all available response data.

Our model is similar to the latent class marginal model presented by Reboussin and Anthony [17], which also assigns class membership at all time points without modeling transition probabilities. However, our model differs from theirs in that we estimate the parameters through the method of ML that allows the number of classes to be chosen through an information criterion while they used estimating equations to reduce computational burden. In addition, we additionally incorporate random effects and jointly model the probability of informative event—death.

Finally, our approach does not rely on the assumption of local independence, serial independence, or conditional independence given latent classes. The local independence assumption implies that the responses (e.g., multiple indicators) at a given time point are independent given the latent classes. The series independence assumes that longitudinal responses at different time points are independent given the latent classes. Conditional independence assumes that responses of different types (e.g., among multiple indicators, among multivariate longitudinal responses, or between longitudinal response and the event of interest in case of joint modeling of longitudinal and event process) are independent given

the latent classes. LTMs typically assume local independence. The latent class models for multiple indicators ([8, 10], growth mixture models [6], and joint models of longitudinal response and risk of an event [18, 19] assume neither local independence nor serial independence by using the random effects within each latent class; however,these latent class models do assume conditional independence. The joint latent class models for simultaneous longitudinal response and risk of an event described by Beuckens *et al.*, Garre *et al.* and Proust-Lima *et al.* [20–22] do not assume conditional independence. Uebersax [23] discussed relaxing the conditional independence assumption by including shared random effects across different indicators in mixed latent trait model that is adopted in this paper. Jacqmin-Gadda *et al.* [24] have developed a post hoc score test for assessing the conditional independence assumption in a joint latent class model.

We organized our paper as follows. In Section 2, we describe our data structure and present our dynamic latent class model. In Section 3, we specify the ML method of estimation and the assignment of trajectory class membership. In Section 4, we present the results from the analysis of the ADL data set. We conduct a simulation study in Section 5, and we conclude with a discussion in Section 6.

2. Methods

2.1. Data structure

The data for our proposed dynamic latent class model typically consist of a frequently measured longitudinal response of interest and less frequent and more comprehensive measures of time-dependent covariates. Here we use the ADL example of the Precipitating Event Project (PEP) to describe the data structure.

We indicated the severity of ADL disability by the number of ADL tasks in walking, bathing, dressing, and transferring that the person was unable to carry out independently (from none to four). We considered a person with no disability in any of the four tasks independent, disability in one or two ADL tasks was considered mild, and disability in three or four ADL tasks was considered severe. The PEP data set that we consider in this article consists of 70,500 person-month follow-up interviews for 126 months on 754 individuals through June 2010 on the severity of ADL disability. We completed comprehensive home-based assessments of functional health measures (e.g., frailty, cognitive status, depression, and chronic diseases) completed at baseline and subsequently at 18-month intervals. We ascertained deaths by review of the local obituaries, from the next of kin or another knowledgeable person during a subsequent telephone interview or by both methods [1–3].

We hypothesize a total of C trajectory classes summarizing distinct patterns of the longitudinal response of ADL disability over all time intervals. We allow a person's trajectory class to change over different person intervals, which are defined by the 18-month period between two consecutive comprehensive in-home interviews when functional health measures were updated. Therefore, the proportion of each trajectory class can change over time, which reflects the evolution of the longitudinal response pattern rather than local fluctuation that is smoothed out by using model (2).

2.2. Specification for dynamic trajectory class model

We first introduce notation for the responses and covariates. Suppose there are n independent individuals indexed by $i = 1, \ldots n$. We let $Y_{ij(m)k}$ denote the indicator of the discrete longitudinal response falling into kth category ($k = 1, \ldots, K$) for person i at time point j nested within interval m ($m = 1, \ldots, M$) with $j = 1, \ldots, J_{im}$, and the time elapsed since the beginning of the interval is denoted by $t_{ij(m)}$. Let D_{im} denote the indicator of the event of interest for person i in interval m. For the example of ADL response, we have $k = 1, 2,$ and 3 for no, mild, and severe disabilities, respectively. An older person might die in an interval, so the minimum and the maximum values of J_{im} in our data set are 0 and 18, respectively. The minimum and the maximum values of M in our data set are 1 and 7, respectively.

We first specify the membership probability for trajectory class c ($c = 1, \ldots, C$) through a polytomous logistic regression model. The membership for a trajectory class can be influenced by covariates and time elapsed since baseline.

$$\log(\pi_{imc}/\pi_{im1}) = \mathbf{X}_{im}^{\mathrm{T}} \boldsymbol{\alpha}_c, \tag{1}$$

where π_{imc} denotes the probability of class c for individual i in interval m, $\mathbf{X}_{im}$ is the vector of predictors for trajectory class c for person i in interval m that can include baseline and interval-specific

covariates along with their interactions terms, as well as the terms of time as represented by the linear and quadratic terms of the interval index $(m-1)$ (see Table III for a listing of covariates). α_c is the corresponding vector of regression coefficients specific for class c where $c=1$ is the reference class so that $\alpha_1 = 0$. $\mathbf{X}_{im}$ is expressed as $(x_{im1}, x_{im2}, \ldots)^T$ and α_c as $(\alpha_{1c}, \alpha_{2c}, \ldots)^T$.

We then model the class-specific trajectory for a longitudinal categorical response within an interval m through a generalized linear mixed model for a polytomous response:

$$\log(\mu_{ij(m)kc}/\mu_{ij(m)1c}) = \boldsymbol{\beta}_{kc}^T \mathbf{t}_{ij(m)} + \boldsymbol{\rho}_{kc}^T \text{diag}(\mathbf{b}_i)\mathbf{t}_{ij(m)}. \tag{2}$$

In model (2), $\mu_{ij(m)kc}$ is the corresponding mean of $Y_{ij(m)k}$ at time j if individual i is in class c in interval m. $\beta_{kc} = (\beta_{0kc}, \beta_{1kc}, \beta_{2kc}, \ldots)^T$ is a vector of class c-specific fixed regression coefficients for the vector $\mathbf{t}_{ij(m)} = \left(1, t_{ij(m)}, t_{ij(m)}^2, \ldots\right)^T$, which contains the intercept and polynomial terms of time for the kth category of the polytomous response of Y. We can replace the polynomial terms of time can be replaced with splines. $\mathbf{b}_i = (b_{0i}, b_{1i}, b_{2i}, \ldots)^T$ is a vector of random effects for individual i that is assumed to be independent normal with mean zero and variance vector $\boldsymbol{\sigma}^2 = (\sigma_0^2, \sigma_1^2, \sigma_2^2, \ldots)$, and diag($\mathbf{b}_i$) denotes the diagonal matrix with the diagonal elements being $\mathbf{b}_i$. $\boldsymbol{\rho}_{kc} = (\rho_{0kc}, \rho_{1kc}, \rho_{2kc}, \ldots)^T$ is a vector of response category k-specific and class c-specific factor loadings for the corresponding random effects. Because the elements in the vectors $\boldsymbol{\beta}_{1c}$ and $\boldsymbol{\rho}_{1c}$ are set to zero for the reference category $k=1$ (no ADL disability) of the polytomous response, there are a total of $C \times (K-1)$ vectors for submodels in (2) with non-zero β's and ρ's. We set the factor loadings in $\boldsymbol{\rho}_{21}$ for the second response category $k=2$ in the reference class $c=1$ to one to ensure model identifiability.

For an ordinal response, Liu *et al.* (2010) [25] used Mplus software [26] to fit the growth mixture model with two random effects (intercept and slope). Our use of a model for nominal response allows the parameters of time trends and those of the predictors to vary across different ADL categories (i.e., mild or severe) and thereby avoid a strong and often unrealistic proportional odds assumption that would restrict the parameters (excepting the intercept) to be the same across different categories.

Given the trajectory classes for a given interval, the aforementioned specification is similar to that of the mixed effect logit model for a longitudinal nominal response described by Hedeker and Gibbon [5] in which the variance components of the random effects vary across the different response categories. We can handle measurements that are missing at random [27] by the mixed model through ML estimation. However, because the occurrence of an event of interest is regarded as informative, we explicitly model the class-specific probability of the event in (3). We do not consider the issue of intermittent missing longitudinal responses that are missing not at random as it is not a focus of this paper.

Finally, each class has its own probability for the occurrence of an event such as death. We jointly model the event with a class-specific logistic model with shared random effects and factor loadings:

$$\text{logit}(p_{imc}) = \delta_{0c} + \boldsymbol{\gamma}_c^T \mathbf{b}_i^S, \tag{3}$$

where p_{imc} is the probability of individual i in class c having the event in interval m and δ_{0c} and $\boldsymbol{\gamma}_c = (\gamma_{0c}, \gamma_{1c}, \gamma_{2c}, \ldots)^T$ are the class c-specific intercept and the vector of class c-specific factor loadings for the random effects $\mathbf{b}_i^S$ shared with the longitudinal model (2), respectively. Please note that the elements in $\mathbf{b}_i^S$ are either the same as or a subset of $\mathbf{b}_i$. For example, the event submodel may share the random intercepts but not the random slopes of time from the longitudinal submodel. Because an individual changes his or her class memberships over time, it is highly complex if indeed possible, to specify a class-specific time-to-death model from baseline. So we do not pursue this route in this paper. We do not assume conditional independence given the classes because the random effects are shared among different intervals and with the model for death.

A random effect represents a source of variability. It can have different variances by pairing it with different factor loadings. Together, the terms $\boldsymbol{\rho}_{kc}^T \mathbf{b}_i$ in (2) and $\boldsymbol{\gamma}_c^T \mathbf{b}_i^S$ in (3) can yield a total of $K \times C$ different sets of variabilities associated with the vector of random effects because there are $(K-1)$ longitudinal response categories within each class and one event that are associated with specific factor loadings. Further imposing a more complex serial correlation structure beyond compound symmetry as implied by the person-specific random effect would add further computational complexity in our dynamic latent class model.

3. Estimation

We use ML methods to simultaneously estimate the parameters in our model. We can write the likelihood of the observed data (all the longtiudinal ADL responses and the death) under our model as follows:

$$\prod_{i=1}^{n} \int_{\mathbf{b}_i} \prod_{m=1}^{M} \left[\sum_{c=1}^{C} \left\{ \pi_{imc} \prod_{j(m)=1}^{J_{im}} \left(\prod_{k=1}^{K} \mu_{ij(m)kc}^{Y_{ij(m)k}} \right) \right\} p_{imc}^{D_{im}} (1 - p_{imc})^{(1-D_{im})} \right] f(\mathbf{b}_i) \mathrm{d}\mathbf{b}_i, \qquad (4)$$

where $f(\mathbf{b}_i)$ is the density function of the random effects vector. The terms $\prod_{j(m)=1}^{J_{im}} \left(\prod_{k=1}^{K} \mu_{ij(m)kc}^{Y_{ij(m)k}} \right)$ and $p_{imc}^{D_{im}} (1 - p_{imc})^{(1-D_{im})}$ are the person i's likelihood of the longitudinal response and of death, respectively, within interval m conditional on class c and the random effects $\mathbf{b}_i$. Because the longitudinal response and death also depend on the random effects, they are not conditionally independent given the trajectory classes.

3.1. Estimating procedure and determining the number of trajectory classes

The likelihood function given in (4) does not have a closed form solution even though computation of the integral and the summation can be reduced using the expectation–maximization algorithm [16]. We numerically maximized the logarithm of the likelihood given in (4). We tried a combination of different optimization techniques and integration methods using SAS `proc nlmixed` [28] in order to obtain stable parameter estimates. ML estimates using the non–adaptive Gauss-Hermite quadrature with 40 fixed points for integration and the Newton–Raphson ridging optimization almost always converged for our models using the criteria for the quadratic form in the gradient and the inverse Hessian at gconv $= 10^{-6}$. We obtained standard errors of the parameter estimates by numerically inverting the negative Hessian matrix. SAS `IML Studio` can be used to invoke `proc nlmixed` as well. The SAS `proc nlmixed` code for estimating our models is given in the Appendix.

We started our estimation with one trajectory class model of $C = 1$, which can be regarded as a typical joint model of a longitudinal nominal response and a binary event. We used the estimates from one trajectory class model plus additional parameter values of $\boldsymbol{\alpha}$'s, $\boldsymbol{\beta}$'s, $\boldsymbol{\rho}$'s, $\boldsymbol{\delta}$'s, and $\boldsymbol{\gamma}$'s for a second class as the initial values for fitting two-class models; the additional set of parameters were set to several different combinations of zeros and ones to give different sets of initial values. Similarly, the estimates from the best of two trajectory-class models plus additional parameter values of $\boldsymbol{\alpha}$'s, $\boldsymbol{\beta}$'s, $\boldsymbol{\rho}$'s, $\boldsymbol{\delta}$'s and $\boldsymbol{\gamma}$ for a third class were then used as the initial values for three-class models, and so on. The purpose of multiple sets of initial values was to avoid local maxima. For a given C, we set the model with the largest log-likelihood value as the best and final model for that C.

To determine the optimal number of trajectory classes, C, we fit models with increasing C, and we declare C as our final number of trajectory classes when the BIC of the C-class model was smaller than the BIC for both the models with class number of $C - 1$ and $C + 1$, respectively. WE calculated the BIC on the basis of the number of person intervals, not the number of persons.

3.2. Determining membership for trajectory class

We assigned trajectory class membership for person i in interval m to the trajectory class that has the maximum of $\tilde{\pi}_{imc}$ for $c = 1, \ldots, C$, where $\tilde{\pi}_{imc}$ is the posterior probability of being in trajectory class c given the observed data of the longitudinal responses and the event outcome of death:

$$\begin{aligned} \tilde{\pi}_{imc} &= P(\text{Class}_{im} = c | \mathbf{Y}_{im}, D_{im}), \\ &= \frac{\pi_{imc} f(\mathbf{Y}_{im}, D_{im} | \text{Class}_{im} = c)}{\sum_{c=1}^{C} \pi_{imc} f(\mathbf{Y}_{im}, D_{im} | \text{Class}_{im} = c)}, \end{aligned} \qquad (5)$$

where Class_{im} is the class membership of person i in interval m and $\mathbf{Y}_{im}$ represents the longitudinal response for person i within interval m, that is, $\mathbf{Y}_{im} = (Y_{ij(m)k}, j = 1, \ldots, J_{im}; k = 1, \ldots, K)$. The term $f(\mathbf{Y}_{im}, D_{im} | \text{Class}_{im} = c)$ is the likelihood of person i's data within interval m conditional on class c only:

$$f(\mathbf{Y}_{im}, D_{im}|\text{Class}_{im} = c), = \int_{\mathbf{b}_i} \prod_{j(m)=1}^{J_{im}} \left(\prod_{k=1}^{K} \mu_{ij(m)kc}^{Y_{ij(m)k}} \right) p_{imc}^{D_{im}} (1 - p_{imc})^{(1-D_{im})} f(\mathbf{b}_i) \mathrm{d}\mathbf{b}_i. \quad (6)$$

Despite estimating in a likelihood framework using the Gauss–Hermite quadrature, we chose to compute the posterior probabilities using a Monte Carlo integration because SAS PROC NLMIXED does not output these probabilities. Specifically, we generated 10,000 random effects of $\mathbf{b}_i$ for person i from a joint normal distribution with mean 0 and the variance vector $\boldsymbol{\sigma}^2$. We calculated the expression within the integral without the $f(\mathbf{b}_i)$ by inserting the ML estimates of $\boldsymbol{\beta}$'s, $\boldsymbol{\rho}$'s, $\boldsymbol{\delta}$'s, and $\boldsymbol{\gamma}$'s for each generated random effect. We obtained the sample average over these 10,000 calculations as the estimated $f(\mathbf{Y}_{im}, D_{im}|\text{Class}_{im} = c)$. We estimated π_{imc} by inserting the ML estimates of the $\boldsymbol{\alpha}$'s. We thus obtained estimated $\tilde{\pi}_{imc}$'s for each person-interval, and the membership of the person-interval was then assigned to the trajectory class with maximum $\tilde{\pi}_{imc}$. We can use R software [29] or R code invoked within SAS IML Studio for calculating probabilities of the class memberships.

4. Results from analyzing the activities of daily living data

4.1. Description of response variables and covariates for trajectory class membership

The longitudinal categorical response variable is a discrete measure of severity in ADL disability with categories of 'no disability' ($k = 1$), 'mild' ($k = 2$), and 'severe' ($k = 3$) as defined in Section 2.1. The response variable $Y_{ij(m)k}$ at month j for person i during the interval m is coded as 1 if the response falls into the kth category of severity in ADL disability and as 0 otherwise. All participants in PEP were ADL independent at entry.

We recorded time-dependent covariates through comprehensive in-home assessments that were conducted at baseline and every 18 months. We include the following predictors in the polytomous logistic regression model for class membership in (1): Age85, indicating whether a person was 85 years or older; Gender, indicating female sex; LiveAlone, indicating whether a person was living alone; Frail, indicating whether a person was physically frail, on the basis of slow gait speed ([30]; Depression, indicating whether a person had a value ⩾ 20 for the Center for Epidemiological Studies Depression scale of depressive symptoms; Cognitive, indicating whether a person suffered any cognitive impairment indicated by < 24 on the Folstein mini-mental state examination (MMSE) score; and Chronic, indicating whether a person had two or more chronic conditions. We measured all the predictors at the beginning of an interval m, and they were time-varying except for Gender. We included all the predictors along with their two-way interactions with p-values less than 0.05 in predicting the probability of being in any of the C classes. The two-way interactions included Age85 by Frail, Age85 by Cognitive, Depression by Cognitive, and Cognitive by Chronic. Because we are interested in how trajectory class membership changes over successive time intervals, we included the linear and quadratic terms for the interval index $(m - 1)$ and $(m - 1)^2$ as time-dependent covariates for class membership.

4.2. Solution from fitting the dynamic trajectory class model to the ADL data

In PEP, 433 participants died after a median follow-up of 56.5 months, and 35 dropped out of the study after a median follow-up of 23.5 months. Data were otherwise available for 98.7% of the 70,500 monthly telephone interviews.

We first fit our dynamic trajectory class models with the fixed effects given in Table III and random intercept only with class-level-specific and ADL-level-specific factor loadings, that is, $\mathbf{b}_i = \mathbf{b}_i^S = b_{0i}$, $\boldsymbol{\rho}_{kc} = \rho_{0kc}$ (for $k \geqslant 2$ and all c's), and $\boldsymbol{\gamma}_c = \gamma_{0c}$ (for all c's) in the submodels (2) and (3). For this model, the five-class solution had the best (smallest) BIC of 37,870 with a total number of 106 parameters; the BIC values for the best four-class and the best six-class solutions were 38,866 and 38,272 with total numbers of 82 and 130 parameters, respectively. Cubic and higher order terms for $(m - 1)$ were not statistically significant in model (1) nor were the cubic and higher order terms for t in the longitudinal submodel (2). For the period-specific ADL trajectories, of all the quadratic time terms, we find that only those pertaining to the mild category in the developing and low classes were significant.

Upon a referee's suggestion that additional inclusion of random slope of time may impact the latent classes identified and give greater flexibility [31], we included individual-specific random slope to the aforementioned five-class random intercept model to account for more individual-specific variability.

We proceeded to fit five-class models with random slope under two settings: (i) the random slope in only the longitudinal submodel; and (ii) the random slope in both longitudinal and death submodels. In each setting, we included the associated factor loadings for the random slope as (a) class-common and ADL-level common where they are set to be one across different classes and different ADL levels; (b) class-common and ADL-level-specific where factor loadings are the same across different classes and different across ADL levels; and (c) class-specific and ADL-level-specific where factor loadings vary across both classes and ADL-levels. According to BIC, the best fitting five-class model is from setting (i) and configuration (c) with both class-level-specific and ADL-level-specific factor loadings for the random slope included only in the longitudinal submodel, that is, $\mathbf{b}_i = (b_{0i}, b_{1i})^T$, $\boldsymbol{\rho}_{kc} = (\rho_{0kc}, \rho_{1kc})^T$ (for $k \geqslant 2$ and all c's), $\mathbf{b}_i^S = b_{0i}$, and $\boldsymbol{\gamma}_c = \gamma_{0c}$ (for all c's). The individual random slope was not shared with the death submodel because models with the inclusion of shared random slope had worse BIC values. Also, the inclusion of a covariance between the random intercept and the slope resulted in non-significant improvement of log-likelihood and worse BIC. The BIC for the best four-class, five-class, and six-class models from setting (i) and configuration (c) are $38,060$, $37,719$, and $40,839$, respectively. The six-class solution that has a higher likelihood value than a four-class or five-class solution could not be obtained, which implies that the data do not support a six-class configuration. We therefore only present in this section results from the best fitting five-class model with shared random intercept and the random slope only in the longitudinal model.

We emphasize that class membership is assigned to each person-interval. Each person can contribute up to a maximum of seven intervals, each of which can potentially be assigned to a different latent class trajectory.

We obtain the model fitted ADL value at a time point in an interval for a class c trajectory by

$$\sum_{k=1}^{K} k \ P(Y_{ij(m)k} = 1 | \text{Class}_{im} = c),$$

$$= \sum_{k=1}^{K} k \int_{\mathbf{b}_i} \frac{\exp\left(\beta_{0kc} + \beta_{1kc}t_{ij(\cdot)} + \beta_{2kc}t_{ij(\cdot)}^2 + \rho_{0kc}b_{0i} + \rho_{1kc}b_{1i}\right)}{\sum_{l=1}^{K} \exp\left(\beta_{0lc} + \beta_{1lc}t_{ij(\cdot)} + \beta_{2lc}t_{ij(\cdot)}^2 + \rho_{0lc}b_{0i} + \rho_{1lc}b_{1i}\right)} f(\mathbf{b}_i)d\mathbf{b}_i,$$

where $\cdot$ represents m because the aforementioned calculation does not depend on the value of m. Because the integral has no closed form solution, we used the Monte Carlo integration technique as described in Section 3.2. We calculated the observed trajectories from the observed data on the basis of the determined class.

We showed the five fitted and observed ADL trajectories in Figure 1. We noted that the trajectories are very similar in shape whether we include zero, one, or two random effects. To plot the observed ADL trajectories, we first assigned each person-interval to a trajectory class according to Section 3.2 and then calculated the sample average of the observed ADL values for each time point by collapsing over all the intervals. The fitted ADL trajectories matched the observed ones rather well. The independent trajectory is nearly flat and has almost no ADL disability throughout an interval. The developing trajectory changes from no disability at the beginning of an interval towards mild ADL disability at its end. The low trajectory is also nearly flat and has an overall ADL disability between that of mild and no disability. The progressive trajectory changes from a disability level of the low class at the beginning toward that of the high class. The trajectory of the high class is relatively flat and has an overall ADL disability at the severe level.

4.3. Evolution of memberships for trajectory classes over time

Table I provides the overall prevalence of the five trajectory classes over all time intervals and their observed and estimated mortality in ascending order of overall severity of ADL disability. The independent trajectory class is the most prevalent class with an overall prevalence of 66.8%. The low and high trajectory classes have prevalences of around 6%, while the developing and progressive high classes have prevalences of about over 11%, respectively. Mortality rate is generally low in the independent, developing, and low classes (1.3%, 3.2%, and 0.4%, respectively). The progressive and high classes have very high mortality rate (60.7% and 44.3%, respectively). That the mortality rate of the developing class is higher than that of either the independent or low classes and the progressive class higher than high class indicates that as a person's disability deteriorates he or she is at higher risk of mortality than in adjacent stable disability classes.
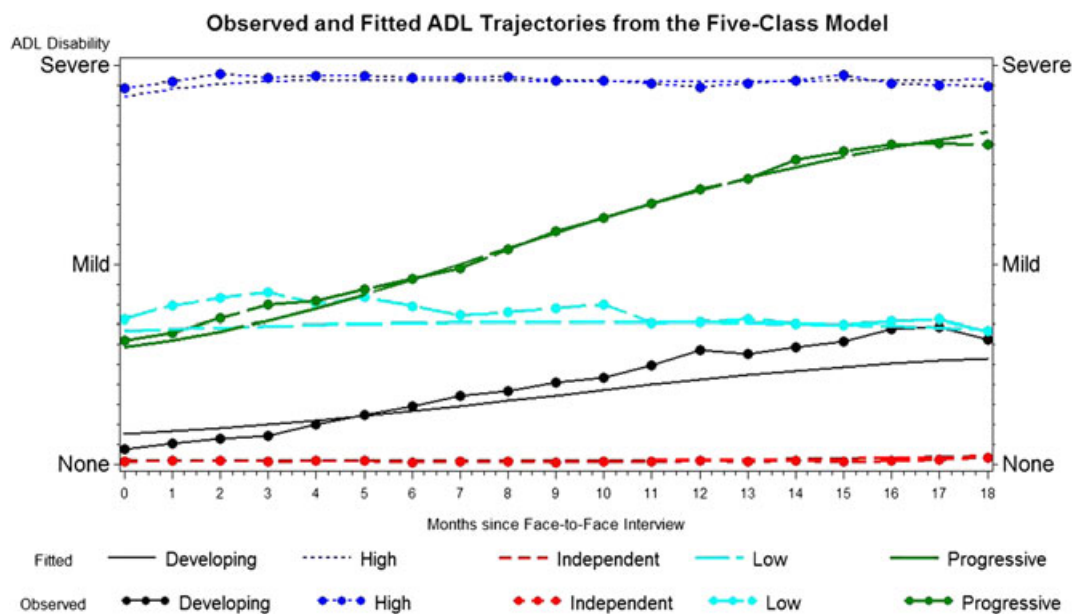
Figure 1. The five trajectory classes of activities of daily living.

Table I. Prevalence of trajectory class over time and mortality.									
	Person-interval	Mortality %		Prevalence % in interval m					
c Class	(Prevalence %)	Data	Estimated	1	2	3	4	5	6	7
1 Independent	2607 (66.83)	1.30	1.00	81.1	74.9	66.1	61.5	54.7	52.0	46.7
2 Developing	473 (11.76)	3.17	2.90	12.3	11.6	11.2	12.8	13.2	11.1	9.4
3 Low	246 (6.12)	0.41	0.80	2.3	4.8	6.9	6.8	9.0	7.3	8.4
4 Progressive	458 (11.39)	60.70	57.05	4.2	6.6	12.2	11.0	14.9	16.9	21.8
5 High	237 (5.90)	44.30	43.00	0.13	2.1	3.6	7.9	8.2	12.7	13.7

Table II. Class evolution over time.					
Class in	Class in $(m + 1)$th interval				
c mth interval	Independent (%)	Developing (%)	Low (%)	Progressive (%)	High (%)	Death (%)
1 Independent	79.3	10.4	2.1	6.4	0.5	1.3
2 Developing	15.6	23.3	20.8	31.7	5.4	3.2
3 Low	10.9	12.7	36.8	33.0	6.1	0.4
4 Progressive	0.3	0.3	2.3	13.9	83.5	60.7
5 High	0.0	0.5	1.0	7.7	46.5	44.3

The last seven columns of Table I present the change in class prevalence over time. The proportion of individuals in the independent class monotonically decreased over time, while the proportion of individuals in the developing class changed the least over time. The proportions of individuals in the low, progressive, and high classes generally increased over time. We captured these time trends in each of the four classes by using the terms of interval indexes as the predictors for the log-odds of being in each of the classes relative to the independent class in the model (1) for membership probabilities (Table I).

Table II shows the evolution of the trajectory classes over time in terms of person-interval. For a surviving member in a relatively stable trajectory class (independent, low, or high), he or she was more likely to remain in the same class in the next interval. In contrast, for a surviving member in a deteriorating class (developing or progressive), he or she was more likely to further deteriorate than to maintain their status, improve, or recover. If an individual in any class was to get worse in next interval, he or she was more likely to deteriorate to the class adjacent to her current class. We next describe the evolution of each class. Near 80% of the members in the independent trajectory class remained independent in the subsequent interval. The survivors of the low class who changed their disability status in the next

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interval were more likely to become worse than to improve or recover. For those who survived in the high class, the chance of improving to a lower disability class was very slim, and they had only a small chance (7.7%) to oscillate to the progressive class. Those who survived in the developing class were more likely to deteriorate to the low and the progressive classes than to recover or remain in the developing class in the next interval. Those who survived in the progressive class were more likely to deteriorate to more severe disability (high trajectory class) than to remain in the same class and had little chance of improvement or recovery.

4.4. Predictors of trajectory classes

The top panel of Table III reports the estimated log odds of the covariates effects on membership probabilities relative to the independent class. Female sex is associated with the low class whereas living alone is negatively associated with membership in all four classes. The rest of the main effects must be interpreted in the context of their significant two-way interactions and the distribution of the predictors. For example, the risk factor `Age85` (effect is for persons ≥ 85 years who are not frail and do not have cognitive impairment) shows significant positive association with membership in the developing class but not with the other classes. In the same interpretive framework, `Frail` and multiple `Chronic` conditions are each positively associated with all disability classes; `Depression` is positively associated with membership in the developing, progressive, and high classes; and `Cognitive` impairment is

Table III. Coefficients estimates from the five-class dynamic trajectory class model.

| | | Class index c | |
| | | 1 | 2 | 3 | 4 | 5 | |
$x_{im\cdot}$	Covariate or outcome	Independent	Developing	Low	Progressive	High	Coefficient
Estimated log-odds of the classes versus the independence class in model (1)
x_{im1}	Age85	0	0.63*	0.55	0.12	−3.72	α_{1c}
x_{im2}	Gender	0	−0.17	0.91*	−0.19	0.29	α_{2c}
x_{im3}	LiveAlone	0	−0.25	−0.70*	−0.38*	−2.76*	α_{3c}
x_{im4}	Frail	0	1.40*	2.64*	1.78*	4.52*	α_{4c}
x_{im5}	Depression	0	0.73*	0.34	0.99*	1.51*	α_{5c}
x_{im6}	Cognitive	0	0.64	−0.11	2.08*	3.21*	α_{6c}
x_{im7}	$\geqslant 2$ Chronic	0	0.62*	0.47*	1.08*	1.24*	α_{7c}
$x_{im1:4}$	Age85×Frail	0	−0.27	−0.20	1.09*	3.84	$\alpha_{1:4c}$
$x_{im1:6}$	Age85×Cognitive	0	1.06*	1.82*	0.62	1.53*	$\alpha_{1:6c}$
$x_{im5:6}$	Depression×Cognitive	0	0.05	0.41	−0.58	−0.41	$\alpha_{5:6c}$
$x_{im6:7}$	Cognitive×Chronic	0	−0.63	−0.44	−1.17*	−1.35*	$\alpha_{6:7c}$
x_{im0}	Intercept	0	−2.53*	−5.43*	−4.87*	−10.44*	α_{0c}
x_{imt^1}	$(m-1)$	0	0.06	0.81*	0.50*	1.40*	α_{t^1c}
x_{imt^2}	$(m-1)^2$	0	0.02	−0.07*	−0.021	−0.10*	α_{t^2c}
Estimated regression coefficients and factor loadings in the longitudinal model (2)
Mild	Intercept	−5.81*	−4.47*	−0.70*	−0.90*	1.06*	β_{01c}
	$t_{ij(m)}$	−0.14	3.56*	1.41*	2.78*	1.05	β_{11c}
	$t^2_{ij(m)}$	0.35	−0.66*	−1.02*	1.02	0.94	β_{21c}
	Loading (intercept)	1.93**	1.09*	1.59*	2.34*	0.38*	ρ_{02c}
	Loading (slope)	0.22**	2.80*	4.22*	6.05*	−4.76	ρ_{12c}
Severe	Intercept	−6.90*	−6.92**	−2.81*	−1.78*	3.30*	β_{02c}
	$t_{ij(m)}$	−2.07	5.39*	0.08	4.20*	4.68*	β_{12c}
	$t^2_{ij(m)}$	1.48	−1.39	−0.06	1.14	−0.71	β_{22c}
	Loading (intercept)	0.62*	0.85*	1.28*	2.09*	0.37*	ρ_{03c}
	Loading (slope)	1.75	3.42*	9.82*	16.62*	9.22	ρ_{13c}
Estimated coefficients and factor loadings in the death model (3)
	Intercept	−4.91*	−3.13*	−5.48*	0.35*	0.06*	δ_{0c}
	Loading (intercept)	0.41	0.14	0.65	−0.58*	−0.05	γ_{0c}

*Denotes statistically significant effect at 0.05.
**Denotes the square root of the variance estimates of σ_0 and σ_1 for the random intercept and random slope, respectively, with the factor loadings set to one.

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associated with the progressive and high classes. With the exception of the `Cognitive` impairment by multiple `Chronic` conditions interaction, the significant interactions of `Age85` by `Frail` and `Age85` by `Cognitive` impairment have a synergetic effect above the additive main effects with an increased likelihood of being in the ADL disability classes relative to the independent class. For example, summing the main effects of `Age85` and `Cognitive` impairment, and their statistically significant interactions show a synergetic effect of `Age85` and `Cognitive` impairment for the developing, low, and high ADL classes above those of the main effects of the two separate factors. The subadditive effect of the interaction between `Cognitive` impairment and multiple `Chronic` conditions interaction might be due to a selection effect due to the presence of other risk factors. The attenuation of the additive effects of the two main effects can be potentially explained by the distribution of the predictors in the sample. The majority (85%) of participants with `Cognitive` impairment and multiple `Chronic` conditions were also `Frail`, whose coefficient has a larger value than that of the interaction between `Cognitive` impairment and multiple `Chronic` conditions in all classes. The linear terms α_{t1_c} for the effects of the interval index were significantly associated with membership in the low, progressive, and high classes of disability, meaning that the odds of membership in these classes increases over time. In contrast, the quadratic terms α_{t2_c} have a negative sign meaning the linear effect is attenuated over time for these classes. The near-zero coefficients α_{t1_2} and α_{t2_2} in the developing class indicate that the odds of being in this class changed little over time, which is consistent with the observation that the proportion of person-intervals in the developing class changed the least (Table I). In contrast, the odds of being in the low, progressive, or high classes ($c = 3$, 4, or 5) increase over time. These trends in the log odds verify the findings presented in Table I.

Because interpretation of the predictors' effect on class membership is not straightforward, because of the presence of multiple interactions, we evaluated the covariate profiles by class (Table IV). As class increased in its overall disability level, the percentage of individuals older than 85 years generally increased. Female individuals predominated the low class, which was characterized by mild disability. The proportion of individuals who lived alone was dramatically lower in the high class than other classes. About 30% of individuals in the independent class were physically frail, while physical frailty predominated for all other classes with disability. The high class was dominated by cognitively impaired individuals. The percentage of depressed individuals was also much higher in all disability classes than in the independent class. Classes with disability had high percentages of individuals with multiple chronic conditions compared with the independent class. Regarding different levels for the two covariates interaction of the `Age85` and `Frail`, individuals older than 85 years were much more likely to be frail than those who were younger. For the high class, all the individuals older than 85 years in an interval were `Frail` (58.2%/58.2% = 100%); about 97% (48.8%/50.4%) and 95% (53.3%/55.9%) older individuals in the low and the progressive class were respectively `Frail`; and about 45% (8.2%/18.4%) and 80% (37.0%/46.3%) older individuals in the independent and the developing class were respectively `Frail`. This suggests that older individuals with any disability were most likely to be physically frail. About 86% (49.8%/58.2%) of the older individuals in the high class had cognitive impairment, while fewer than half of the older individuals in any other class had cognitive impairment. About 78% (33.3%/42.6%) of the

Table IV. Covariates profile by class.					
	Percentage of person-intervals with the binary covariate being one				
	Trajectory Classes				
Covariates	Independent	Developing	Low	Progressive	High
Age85	18.4	46.3	50.4	55.9	58.2
Gender	64.0	67.7	87.8	64.0	75.1
LiveAlone	41.6	48.0	35.4	40.6	5.1
Frail	30.0	77.8	95.5	84.9	99.8
Depression	12.3	32.4	28.9	29.1	42.6
Cognitive	8.6	29.2	22.8	41.7	78.5
⩾ 2 Chronic	59.7	68.9	70.7	76.2	73.0
Age85 & Frail	8.2	37.0	48.8	53.3	58.2
Age85 & Cognitive	1.4	18.0	18.3	26.4	49.8
Depression & Cognitive	1.3	11.4	8.5	10.9	33.3
⩾ 2 Chronic & Cognitive	5.5	18.6	12.3	28.6	53.6

Table V. Results from the simulation study.

	Independent class						
	PEP data		Simulated data				
			Including death model			No death model	
Parameter	ML estimate	Standard error	Sample average	Standard deviation	Coverage rate	Sample average	Standard deviation
α_{11}	0						
α_{21}	0						
α_{31}	0						
α_{41}	0						
α_{51}	0						
α_{61}	0						
$\alpha_{1:41}$	0						
$\alpha_{1:61}$	0						
$\alpha_{5:61}$	0						
α_{71}	0						
$\alpha_{6:71}$	0						
α_{01}	0						
α_{t^11}	0						
α_{t^21}	0						
β_{011}	0						
β_{111}	0						
β_{211}	0						
ρ_{11}	0						
β_{021}	−5.81	0.29	−5.81	0.19	90.0%	−5.82	0.21
β_{121}	−0.14	0.52	−0.16	0.35	95.8%	−0.15	0.36
β_{221}	0.35	0.35	0.36	0.23	96.8%	0.35	0.24
σ	2.00	0.21	1.94	0.14	81.4%	1.95	0.13
ρ_{21}	1	0					
β_{031}	−6.90	0.51	−6.93	0.45	94.6%	−6.97	0.42
β_{131}	−2.07	1.13	−2.06	1.16	95.0%	−2.02	1.10
β_{231}	1.48	1.14	1.38	0.87	95.2%	1.44	0.75
ρ_{31}	0.63	0.12	0.63	0.11	95.2%	0.64	0.11
δ_{01}	−5.39	0.72	−5.66	0.91	93.0%	0	
γ_{01}	0.21	0.37	0.18	0.33	97.4%	0	

PEP, Precipitating Event Project; ML, maximum likelihood.

depressed individuals in the high class had cognitive impairment, while fewer than 40% of the depressed individuals in any other class had cognitive impairment. More than 73% (53.6%/73.0%) of the individuals with multiple chronic conditions in the high class had cognitive impairment, while fewer than 40% of individuals with multiple chronic conditions in any other class had cognitive impairment.

4.5. Assessing random effects with factor loadings and fitting trajectory class model without death

The bottom two panels of Table III provide the estimates of the factor loadings from the five-class model. As expected, the variance in σ^2 for the random intercept and slope in $\mathbf{b}_i$ are 1.93 and 0.22, respectively, both highly significant, and all the factor loadings for the random intercept $\rho_{0 \cdot c}$ in ρ's in the longitudinal model (2) are highly significant. These results indicate that the participants are highly heterogeneous with respect to the odds of a response category with mild or severe ADL disability for all the trajectory classes. The variance of the random intercept and the variance of the random slope represent the degree of individual heterogeneity, respectively, for being mildly disabled and for its linear time trend in the independent class. Both variances serve respectively as the reference variance components. A factor loading serves as a scale to the corresponding variance.

Regarding the factor loadings of the random intercept in the longitudinal model, compared with the reference, the tendency of being mildly disabled in the developing class has a similar level of individual heterogeneity with the factor loading being 1.09. The tendency of being severely disabled in both

	PEP data		Simulated data				
			Including death model			No death model	
Parameter	ML estimate	Standard error	Sample average	Standard deviation	Coverage rate	Sample average	Standard deviation
α_{12}	0.67	0.26	0.65	0.26	96.2%	0.69	0.24
α_{22}	−0.39	0.16	−0.40	0.14	94.4%	−0.40	0.15
α_{32}	−0.053	0.15	−0.051	0.14	94.6%	−0.052	0.14
α_{42}	1.40	0.19	1.39	0.18	94.8%	1.43	0.17
α_{52}	0.73	0.19	0.73	0.17	96.0%	0.74	0.17
α_{62}	0.88	0.36	0.89	0.38	95.2%	0.87	0.37
$\alpha_{1:42}$	−0.26	0.30	−0.23	0.33	94.4%	−0.29	0.29
$\alpha_{1:62}$	0.76	0.51	0.77	0.51	95.0%	0.77	0.49
$\alpha_{5:62}$	0.025	0.41	0.019	0.45	96.2%	0.063	0.45
α_{72}	0.65	0.16	0.64	0.16	95.0%	0.64	0.15
$\alpha_{6:72}$	−0.98	0.36	−0.97	0.39	94.4%	−0.96	0.39
α_{02}	−2.55	0.23	−2.56	0.22	95.2%	−2.57	0.22
$\alpha_{t^1 2}$	−0.022	0.13	−0.020	0.12	94.4%	−0.024	0.11
$\alpha_{t^2 2}$	0.023	0.021	0.023	0.020	95.2%	0.023	0.019
β_{012}	0						
β_{112}	0						
β_{212}	0						
ρ_{12}	0						
β_{022}	−4.47	0.19	−4.44	0.24	89.0%	−4.45	0.22
β_{122}	3.56	0.42	3.55	0.37	96.0%	3.54	0.36
β_{222}	−0.66	0.27	−0.66	0.22	95.2%	−0.66	0.22
ρ_{22}	0.98	0.10	0.98	0.068	93.4%	0.97	0.062
β_{032}	−6.92	0.64	−6.94	0.45	96.0%	−6.98	0.49
β_{132}	5.39	0.70	5.40	0.74	95.2%	5.51	1.00
β_{232}	−1.40	0.43	−1.39	0.40	95.6%	−1.45	0.53
ρ_{32}	0.73	0.086	0.74	0.069	92.8%	0.73	0.066
δ_{02}	−2.14	0.41	−2.14	0.29	95.6%	0	
γ_{02}	−0.031	0.11	0.024	0.12	94.4%	0	

Table V. (Continued).

Developing class

of the independent (factor loading $= 0.62$) and the developing classes (factor loading $= 0.85$) and the tendency of being disabled in the high class (factor loading $= 0.38$ and 0.37) have less heterogeneity; the tendency of being mildly or severely disabled in both the low and progressive classes has greater heterogeneity. Regarding the factor loadings of the random slope, all the time trends for mild and severe disability in all the classes have a greater heterogeneity comparing with that for the mild disability in the independent class.

The factor loadings δ_{rc} in the joint model (3) for death are not significant except for the progressive class (δ_{r4}). These results indicate that the longitudinal ADL response and death are actually conditionally independent given the trajectory classes except for the progressive class. Using the individual tendency for mild disability in the independence class as the reference for the factor loadings, the negative sign for δ_{14} indicates that a higher tendency of being mildly disabled in the independence class is associated with a lower probability of dying in the progressive class and the lowered probability is mainly due to the lower tendency of evolving to the progressive class from the independence class.

We also fit the dynamic trajectory class model without using the death submodel (3) and found the same five trajectory classes. Also, the ADL trajectories, the memberships for the trajectory classes, and the changes in membership over time were similar to the results presented earlier. This is mainly due to the large amount of the dynamic ADL measures. In the next section, we present the results of simulation study to assess the influence of the death submodel.

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Table V. (Continued).							
			Low Class				
	PEP data		Simulated data				
			Including death model			No death model	
Parameter	ML estimate	Standard error	Sample average	Standard deviation	Coverage rate	Sample average	Standard deviation
α_{13}	0.40	0.41	0.40	0.40	95.2%	0.34	0.37
α_{23}	0.65	0.22	0.66	0.21	93.2%	0.66	0.20
α_{33}	−0.43	0.18	−0.44	0.16	94.8%	−0.43	0.15
α_{43}	2.39	0.27	2.43	0.24	95.6%	2.42	0.22
α_{53}	0.38	0.23	0.37	0.24	95.2%	0.38	0.21
α_{63}	0.42	0.46	0.38	0.52	95.6%	0.42	0.46
α_{73}	0.76	0.23	0.78	0.22	94.6%	0.78	0.20
$\alpha_{1:43}$	0.034	0.44	0.031	0.41	94.0%	0.068	0.41
$\alpha_{1:63}$	1.29	0.42	1.31	0.41	95.0%	1.33	0.44
$\alpha_{5:63}$	0.058	0.22	0.050	0.46	95.2%	0.062	0.46
$\alpha_{6:73}$	−0.72	0.22	−0.72	0.44	94.4%	−0.74	0.44
α_{03}	−5.30	0.38	−5.39	0.38	94.8%	−5.44	0.40
$\alpha_{t^1 3}$	0.69	0.15	0.71	0.17	94.0%	0.70	0.14
$\alpha_{t^2 3}$	−0.051	0.024	−0.053	0.028	94.4%	−0.051	0.021
β_{013}	0						
β_{113}	0						
β_{213}	0						
ρ_{13}	0						
β_{023}	−0.70	0.16	−0.66	0.26	85.7%	−0.65	0.28
β_{123}	1.41	0.38	1.42	0.36	96.0%	1.38	0.32
β_{223}	−1.02	0.25	−1.03	0.24	96.2%	−1.00	0.21
ρ_{23}	1.54	0.16	1.49	0.11	91.5%	1.47	0.11
β_{033}	−2.81	0.25	−2.81	0.32	86.1%	−2.79	0.30
β_{133}	0.076	0.74	0.12	0.70	96.8%	0.094	0.68
β_{233}	−0.056	0.50	−0.071	0.49	95.8%	−0.058	0.47
ρ_{33}	1.30	0.15	1.26	0.11	87.1%	1.23	0.11
δ_{03}	−3.10	0.42	−3.15	0.45	96.4%	0	
γ_{03}	0.25	0.22	0.23	0.22	93.4%	0	

5. Simulation studies

We conducted simulation studies using the parameter estimates from the best fitting five trajectory class model with random intercept and class–level-specific and ADL-level-specific factor loadings. We did not include random slope for the sake of reducing computational burden. We used the same set of covariates $\mathbf{X}$ as listed in Table III. We generated normally distributed b_{0i} for all individuals using the estimate of the variance component σ_0^2. To generate ADL responses and death, we first generated prior class membership c for a given i and m according to $(\pi_{imc}, c = 1, \ldots, 5)$ using model (1) with the fixed covariates from the data set. Once the c's were generated for each person interval, we then generated the vector of $(Y_{ij(m)k}, k = 1, 2, 3)$ for given i, j, m, and corresponding c according to model (2). Finally, we generated indicators for death according to p_{imc}. We generated 500 samples each with the original cohort size of 754 individuals, and we fit the dynamic trajectory class model with and without the submodel for death (3) using the ML estimates from the five class model as the initial parameter values. The ML estimates in all simulated samples converged. For each parameter in each simulated sample (total number of simulated samples = 500), we constructed the 95% confidence interval of the parameter estimate in the sample using the asymptotic standard error for the parameter estimate by inverting the negative Hessian matrix as described in Section 3.1. For each parameter, we calculated the coverage rate (column 6 in Table V) as the percentage of the confidence intervals in 500 simulated samples containing the ML parameter estimates (column 2 in Table V). While Altman [15] found some issues in estimating variance

Table V. (Continued).

	Progressive class						
	PEP data		Simulated data				
			Including death model			No death model	
Parameter	ML estimate	Standard error	Sample average	Standard deviation	Coverage rate	Sample average	Standard deviation
α_{14}	−0.019	0.38	−0.024	0.34	95.2%	−0.033	0.37
α_{24}	−0.10	0.16	−0.11	0.17	95.6%	−0.11	0.16
α_{34}	−0.33	0.16	−0.33	0.16	94.8%	−0.32	0.15
α_{44}	1.75	0.21	1.76	0.18	96.2%	1.77	0.20
α_{54}	0.91	0.21	0.93	0.21	93.8%	0.91	0.20
α_{64}	2.48	0.35	2.60	0.39	93.0%	2.50	0.34
α_{74}	1.16	0.22	1.18	0.21	95.0%	1.18	0.20
$\alpha_{1:44}$	1.11	0.41	1.12	0.39	96.2%	1.13	0.40
$\alpha_{1:64}$	0.35	0.35	0.35	0.35	95.4%	0.38	0.39
$\alpha_{5:64}$	−0.58	0.40	−0.56	0.36	95.8%	−0.56	0.40
$\alpha_{6:74}$	−1.50	0.37	−1.48	0.38	93.2%	−1.53	0.37
α_{04}	−5.25	0.35	−5.29	0.33	94.6%	−5.31	0.29
$\alpha_{t^1 4}$	0.56	0.14	0.57	0.15	95.0%	0.57	0.13
$\alpha_{t^2 4}$	−0.041	0.021	−0.045	0.023	94.8%	−0.042	0.021
β_{014}	0						
β_{114}	0						
β_{214}	0						
ρ_{14}	0						
β_{024}	−0.90	0.22	−0.89	0.32	87.3%	−0.86	0.33
β_{124}	2.78	0.66	2.77	0.52	95.8%	2.76	0.49
β_{224}	1.02	0.60	1.03	0.44	96.2%	1.02	0.38
ρ_{24}	1.85	0.21	1.82	0.15	91.0%	1.79	0.14
β_{034}	−1.78	0.23	−1.79	0.27	92.0%	−1.75	0.30
β_{134}	4.20	0.70	4.20	0.60	93.6%	4.18	0.52
β_{234}	1.14	0.61	1.13	0.38	92.8%	1.14	0.41
ρ_{34}	1.52	0.19	1.50	0.13	90.4%	1.46	0.12
δ_{04}	0.41	0.75	0.40	0.56	93.8%	0	
γ_{04}	−0.58	0.18	−0.59	0.12	92.0%	0	

component in her mixed hidden Markov models when sample size was small and the bias and asymptotic variance estimates of the variance component improved with increased sample size, we did not find any comparable bias or unstable asymptotic standard errors in our estimation of the variance component and the factor loadings in our simulation studies.

Because the ADL response was measured intensively over time in each person and thus contains much more information than the single incidence of death and because ADL and death were conditionally independent on the basis of the finding in Section 4.5 except for the progressive class, we speculated whether or not the death submodel (3) contributed to the derivation of the trajectory classes (α's in model (1)) and affected the estimates of the trajectory parameters (β's and ρ's in model (2)). Table V results show that the trajectory class model with (the second to last column block) and without the submodel for death (the last column block) had similar parameter estimates for the class membership model and the longitudinal ADL model. we can actually calculate the probabilities of death for each of the trajectory classes from the observed data after the class memberships are derived from the longitudinal model alone.

We also performed the simulation study where only up to two intervals were present (we have up to seven intervals in our data set); the trajectories were almost not affected. The lack of change could be mainly because the longitudinal ADL information was very rich compared with the information from death because a person-interval still contains up to 18 repeated measures. Similar to the point made by Dantan *et al.* [32], the latent classes exhibit much more heterogeneity than the information in the death.

Table V. (Continued).

	High class						
	PEP data		Simulated data				
			Including death model			No death model	
Parameter	ML estimate	Standard error	Sample average	Standard deviation	Coverage rate	Sample average	Standard deviation
α_{15}	−2.71	0.95	−2.7069	0.89	94.6%	−2.63	0.86
α_{25}	0.10	0.22	0.10	0.24	95.0%	0.095	0.20
α_{35}	−2.61	0.31	−2.63	0.28	96.4%	−2.62	0.30
α_{45}	4.29	0.68	4.47	0.76	98.0%	4.49	0.72
α_{55}	1.52	0.32	1.55	0.32	96.2%	1.53	0.34
α_{65}	3.30	0.54	3.35	0.64	93.4%	3.38	0.59
α_{75}	1.22	0.45	1.29	0.55	95.6%	1.28	0.48
$\alpha_{1:45}$	2.73	0.87	2.69	0.86	95.0%	2.65	0.87
$\alpha_{1:65}$	1.43	0.45	1.49	0.48	93.2%	1.48	0.48
$\alpha_{5:65}$	−0.55	0.47	−0.53	0.48	96.6%	−0.52	0.49
$\alpha_{6:75}$	−1.64	0.56	−1.66	0.65	93.6%	−1.71	0.59
α_{05}	−10.02	0.91	−10.33	0.79	96.0%	−10.37	0.90
$\alpha_{t^1 5}$	1.37	0.24	1.37	0.24	96.0%	1.40	0.23
$\alpha_{t^2 5}$	−0.10	0.034	−0.11	0.037	93.4%	−0.11	0.032
β_{015}	0						
β_{115}	0						
β_{215}	0						
ρ_{15}	0						
β_{025}	1.06	0.42	1.05	0.46	97.6%	1.07	0.33
β_{125}	1.05	1.44	1.17	1.32	96.4%	1.13	1.25
β_{225}	0.94	1.66	1.06	1.41	96.0%	1.15	1.34
ρ_{25}	0.48	0.16	0.49	0.17	97.0%	0.48	0.12
β_{035}	3.30	0.34	3.35	0.30	97.6%	3.33	0.29
β_{135}	4.68	1.35	4.69	1.19	96.0%	4.69	1.18
β_{235}	−0.71	1.61	−0.47	0.96	95.0%	−0.42	1.34
ρ_{35}	0.23	0.16	0.23	0.15	96.0%	0.24	0.11
δ_{05}	0.094	0.15	0.097	0.18	95.4%	0	
γ_{05}	−0.06	0.20	−0.06	0.12	94.2%	0	

6. Discussion

We presented a dynamic trajectory class model for an intensive longitudinal categorical response where an individual is assigned to possibly different trajectory classes over the time intervals when the predictors for class memberships are updated. Our model focuses on modeling the evolution of latent states over time as dynamic trajectory classes, whereas a traditional LTM focuses on modeling initial latent states and transition probabilities among those states over time. Our model directly assigns class membership to each time interval in each individual, whereas the LTM assigns only the baseline class membership for each individual. In contrast with LTMs where uncertainly in class assignment increases over time, the person-interval assignment is the major advantage of our dynamic latent class model.

Using our approach, we found five distinct ADL trajectories that conferred different mortality experiences. We used a modeling strategy where the trajectory classes did not change in nature but the proportion of individuals in each class changed over time. Specifically, we found that over time fewer individuals were independent and more evolved into trajectory classes with varying levels of disability. We also found that the likelihood of remaining in the same class for the three flat (or stable) trajectories, independence, low, and high, was much higher than for either of the deterioration classes, that is, developing or progressive. For these two classes, the likelihood of further deteriorating was much greater than staying in the same class or improving. For those in the high class, the chance of improving or recovery from disability was negligible, whereas tendency of death was dominant.

Because the longitudinal response was measured intensively over time and was an extremely rich source of information, simultaneously modeling probabilities of death pertaining to respective classes had little impact on the trajectory classes as shown in the simulation studies. To further examine the influence of death on the trajectories, we increased the values of the factor loadings by two folds for the death model in an additional simulation study, and still found the influence of death was negligible. This can be explained mathematically because the model for death using the latent classes and random effects with factor loadings is not identifiable by itself. It can only be identified through the joint model with the longitudinal response. In the absence of modeling the class-specific probability of death using model (3), trajectory-specific mortality rates could be obtained post hoc. As the referee pointed out, differential changes in the factor loadings among classes can be investigated in future work in order to increase the differences among classes. Furthermore, death can be modeled as time to event from the baseline. However because class membership changes over time, it is quite challenging to incorporate the class information into the time-to-event model. This is one of the topics for our future research.

There is an important limitation in the inclusion of additional random effects in our model that warrants mention. Our model fit required both linear and quadratic terms of time in the PEP data set (none of the cubic terms of time was statistically significant). The ideal solution would have been to include corresponding random effects for intercept, linear, and quadratic terms of time. Although our model converged with subject-specific random intercept and random linear terms of time, it would not converge with the addition of the random quadratic term of time at the current computational capacity in nonlinear growth mixture model for categorical response with latent classes and random effects. We acknowledge that future computational work, which will allow the simultaneous inclusion of the full complement of random terms to reflect the fixed temporal terms, will increase the capacity of our approach to improve model fit.

We also found that in our model the estimation convergence was better achieved using non-adaptive quadrature with 40 points or more rather than using adaptive quadrature where the placement of quadrature points changes from iteration to iteration. As computing power increases over time, future work may include fitting models with serial correlation (using bespoke program instead of implementation through SAS PROC NLMIXED), multiple random effects (we were able to fit two random effects at the current computational capacity for our dynamic latent class model but having difficulty to fit a model with three or more random effects), and nested random effects where person interval-specific random effects can be decomposed into the additive random effects of interval-specific random effects and person-specific random effects. The nested random effects model is analogous to the correlated frailty model in survival analysis.

Appendix

```
options ls=128 ps=56 ;
libname ord 'C:\Col\Aging\Codes';
data fcdh_rh; set ord.r01pep;

proc sort; by studyid fup_18m;
run;

data fcdh; set fcdh_rh; by studyid fup_18m;
        if last.studyid ne 1 then died_bth = 0;
        array fu[7] fu1-fu7;
        do i = 1 to 7;
                fu[i] = (fup_18m =i);
        end;
        keep studyid fup_18m iid fu1-fu7 AGE_FU85 FEMALE LIVALNFU
        fc3_walk scesd_20 MMSE_24r
CCSIFU_GE2 YM1-YM19 died_bth;
run;

data ini5; set ord.initialvalue5;
run;
```

```
proc nlmixed data=fcdh qpoints=40 noad maxiter=1000 tech=nrridg
gconv=1e-6 itdetails;

parms / data = ini5;

ARRAY X[19] YM1-YM19;
ARRAY PIA[19] PIA1-PIA19;
ARRAY PIB[19] PIB1-PIB19;
ARRAY PIC[19] PIC1-PIC19;
ARRAY PID[19] PID1-PID19;
ARRAY PIE[19] PIE1-PIE19;

* logistic regression for death;
        Apdeath = 1 / (1 + EXP(- (deltaA0 + letaA*u) ));
        Bpdeath = 1 / (1 + EXP(-(deltaB0 + letaB*u )));
        Cpdeath = 1 / (1 + EXP(-(deltaC0 + letaC*u)));
        Dpdeath = 1 / (1 + EXP(-(deltaD0 + letaD*u)));
        Epdeath = 1 / (1 + EXP(-(deltaE0 + letaE*u)));

* added for joint model with death;

DO I=1 TO 19;
 time = (I-1)/12;
 time2 = time**2;
 time3 = time**3;

beta01 = beta01C + beta01A*time + beta01B*time2 + rho4*u + gamma4*u1
*time;
beta02 = beta02C + beta02A*time + beta02B*time2 + rho5*u + gamma5*u1
*time;
betadeno3 = 1 + EXP(beta01) + EXP(beta02);

beta11 = beta11C + beta11A*time + beta11B*time2 + rho2*u + gamma2*u1
*time;
beta12 = beta12C + beta12A*time + beta12B*time2 + rho3*u + gamma3*u1
*time;
betadeno1 = 1 + EXP(beta11) + EXP(beta12);

beta21 = beta21C + beta21A*time + beta21B*time2 + u + u1*time;
beta22 = beta22C + beta22A*time + beta22B*time2 + rho*u + gamma*u1
*time;
betadeno2 = 1 + EXP(beta21) + EXP(beta22);

beta41 = beta41C + beta41A*time + beta41B*time2 +rho6*u + gamma6*u1
*time;
beta42 = beta42C + beta42A*time + beta42B*time2 +rho7*u + gamma7*u1
*time;
betadeno4 = 1 + EXP(beta41) + EXP(beta42);

beta51 = beta51C + beta51A*time + beta51B*time2 +rho8*u + gamma8*u1
*time;
beta52 = beta52C + beta52A*time + beta52B*time2 +rho9*u + gamma9*u1
*time;
betadeno5 = 1 + EXP(beta51) + EXP(beta52);

 IF X[I] =0 THEN DO;
```

```
    PIA[I] = 1/betadeno3;
    PIB[I] = 1/betadeno1;
    PIC[I] = 1/betadeno2;
    PID[I] = 1/betadeno4;
    PIE[I] = 1/betadeno5;
END;

 ELSE IF X[I] =1 THEN DO;
    PIA[I] = EXP(beta01)/betadeno3;
    PIB[I] = exp(beta11)/betadeno1;
    PIC[I] = exp(beta21)/betadeno2;
    PID[I] = exp(beta41)/betadeno4;
    PIE[I] = exp(beta51)/betadeno5;
          END;
 ELSE IF X[I] =2 THEN DO;
    PIA[I] = EXP(beta02)/betadeno3;
    PIB[I] = exp(beta12)/betadeno1;
    PIC[I] = exp(beta22)/betadeno2;
    PID[I] = exp(beta42)/betadeno4;
    PIE[I] = exp(beta52)/betadeno5;
          END;
 Else IF X[I] = . THEN DO;
    PIA[I] = 1; PIB[I] = 1; PIC[I] = 1; PID[I] = 1; PIE[I] = 1; END;

 END;


PRODA=PIA1*PIA2*PIA3*PIA4*PIA5*PIA6*PIA7*PIA8*PIA9*PIA10*PIA11*PIA12
  *PIA13*PIA14*PIA15*PIA16*PIA17*PIA18*PIA19;
PRODB=PIB1*PIB2*PIB3*PIB4*PIB5*PIB6*PIB7*PIB8*PIB9*PIB10*PIB11*PIB12
  *PIB13*PIB14*PIB15*PIB16*PIB17*PIB18*PIB19;
PRODC=PIC1*PIC2*PIC3*PIC4*PIC5*PIC6*PIC7*PIC8*PIC9*PIC10*PIC11*PIC12
  *PIC13*PIC14*PIC15*PIC16*PIC17*PIC18*PIC19;

prodd=PID1*PID2*PID3*PID4*PID5*PID6*PID7*PID8*PID9*PID10*PID11*PID12
   *PID13*PID14*PID15*PID16*PID17*PID18*PID19;
prode=PIE1*PIE2*PIE3*PIE4*PIE5*PIE6*PIE7*PIE8*PIE9*PIE10*PIE11*PIE12
   *PIE13*PIE14*PIE15* PIE16*PIE17*PIE18*PIE19;


    pinumerA = exp(alphaA0 + alphaA1*AGE_FU85 + alphaA2*FEMALE +
   alphaA3*LIVALNFU + alphaA4*fc3_walk + alphaA5*scesd_20 +
   alphaA6*MMSE_24r + alphaA7*CCSIFU_GE2 +
    alphaA14*age_fu85*fc3_walk+ ALPHAA16*AGE_FU85*MMSE_24r
        +alphaA56*MMSE_24r*scesd_20 +alphaA67*CCSIFU_GE2*MMSE_24r
        + alphaafu1*fup_18m + alphaafu2*fup_18m*fup_18m );

pinumerB = exp(alphaB0 + alphaB1*AGE_FU85 + alphaB2*FEMALE+
   alphaB3*LIVALNFU + alphaB4*fc3_walk + alphaB5*scesd_20 +
   alphaB6*MMSE_24r + alphaB7*CCSIFU_GE2+
    alphaB14*age_fu85*fc3_walk+ ALPHAB16*AGE_FU85*MMSE_24r
          +alphaB56*MMSE_24r*scesd_20 +alphaB67*CCSIFU_GE2*MMSE_24r
    + alphabfu1*fup_18m + alphabfu2*fup_18m*fup_18m );

pinumerD = exp(alphaD0 + alphaD1*AGE_FU85 + alphaD2*FEMALE+
   alphaD3*LIVALNFU + alphaD4*fc3_walk + alphaD5*scesd_20 +
   alphaD6*MMSE_24r + alphaD7*CCSIFU_GE2 +
    alphaD14*age_fu85*fc3_walk+ ALPHAD16*AGE_FU85*MMSE_24r
          +alphaD56*MMSE_24r*scesd_20+alphaD67*CCSIFU_GE2*MMSE_24r
```

```
+ alphadfu1*fup_18m + alphadfu2*fup_18m*fup_18m);

pinumerE = exp(alphaE0 + alphaE1*AGE_FU85 + alphaE2*FEMALE
      + alphaE3*LIVALNFU + alphaE4*fc3_walk + alphaE5*scesd_20
      + alphaE6*MMSE_24r + alphaE7*CCSIFU_GE2
      + alphaE14*age_fu85*fc3_walk+ ALPHAE16*AGE_FU85*MMSE_24r
                  +alphaE56*MMSE_24r*scesd_20 +alphaE67*CCSIFU_GE2
                  *MMSE_24r
      + alphaefu1*fup_18m + alphaefu2*fup_18m*fup_18m );

pideno = 1+ pinumerA + pinumerB + pinumerD+ pinumerE ;

pieA = pinumerA/pideno; pieB = pinumerB/pideno;
pieD = pinumerD/pideno; pieC = 1/pideno; pieE = pinumerE/pideno;

l_latclass = pieA*prodA*(Apdeath*died_bth+(1-Apdeath)*(1-died_bth))
+ pieB*prodB*(Bpdeath*died_bth+(1-Bpdeath)*(1-died_bth))
                  + pieC*prodC*(Cpdeath*died_bth + (1-Cpdeath)
                  *(1-died_bth)) +
pieD*prodD*(Dpdeath*died_bth+(1-Dpdeath)*(1-died_bth))
                  + pieE*prodE*(Epdeath*died_bth + (1-Epdeath)
                  *(1-died_bth)) ;

ll_latclass = log(l_latclass);

        model ll_latclass ~ general(ll_latclass);
        random u u1 ~ normal([0,0], [su*su, 0, su1*su1])
        subject=studyid ;
        ods output ParameterEstimates = pe5nobetafualphafu222;
run;
```

Acknowledgements

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