An Analysis of Development of Dementia through the Extended Trajectory Grade of Membership Model

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Alzheimer’s disease is the most frequent form of dementia in the elderly, and age is its most powerful risk factor. One idea is to model the probability of being diagnosed with dementia at different ages in order to construct trajectories for different categories of people. Mixed membership models constitute the most promising method for this problem. We develop a few ideas of Manrique-Vallier (2010) to extend the basic TGoM model. In particular, we propose a parametric dependence between the distribution of the membership vectors and a few time-invariant covariates that allows us to interpret their effect on the individual trajectories.

10.1 Introduction

The previous chapter by Manrique (Manrique-Vallier, 2013) introduced a family of mixed membership models, the Trajectory Grade of Membership models (TGoM), useful in analyzing longitudinal data, i.e., sequences of responses obtained from the same individuals at various points in time. Each of the \( N \) individuals in the analysis is represented by a trajectory, which describes the evolution of the probability of particular values of the response variables over time. The individual trajectories are modeled as weighted combinations of a small number \( K \) of typical trajectories, corresponding to \( K \) ideal types of individuals or extreme profiles. Considering only one response variable \( Y \), an
individual trajectory at time $t$ can be written as

$$p(y_t|(g_1, \ldots, g_K), x_t, \theta) = \sum_{k=1}^{K} g_k f_{\theta_k}(y_t|x_t).$$

The membership vector $g = (g_1, \ldots, g_K)$ describes the degree of closeness of an individual to each extreme profile; $x_t$ is the value of a time-dependent covariate (e.g., age), and $f_{\theta_k}(y_t|x_t)$ is a function of time with parameter $\theta_k$ describing the trajectory of an individual of extreme profile $k$.

In this chapter we develop a few ideas of Manrique-Vallier (2010) to extend the basic TGoM in two directions. First, we include the survival outcomes as a response: the presence of dementia is correlated with mortality in elderly years (Bowen et al., 1996; Brodaty et al., 2012; Mölsä et al., 1995) and information about survival times can help to explain disability patterns. Second, we add time-invariant covariates in the model. We propose a particular parametric dependence between the membership distribution $G_\alpha$ and time-invariant covariates that allows us to interpret their effect on the membership vector in a way that is similar to the effect of covariates in a simple logistic regression.

10.1.1 Application: The Cardiovascular Health Study—Cognition Study

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly, and age is the most important risk factor for the development of clinical dementia. The prevalence of AD increases exponentially between the ages of 65 and 85, approaching 50% in the oldest segment of the population (Evans et al., 1989; Fitzpatrick et al., 2004). After 90 years of age, the incidence of AD increases dramatically, from 12.7%/year in the 90–94 age group, to 21.2%/year in the 95–99 age group, and to 40.7%/year in those over 100 years old (Corrada et al., 2010). This risk of AD is further affected by the presence of the APOE*4 allele, male sex, lower education, and having a family history of dementia (Fitzpatrick et al., 2004; Launer et al., 1999; Tang et al., 1996). Medical risks include the presence of systemic hypertension, diabetes mellitus, cardiovascular disease, and cerebrovascular disease (Irie et al., 2005; Kuller et al., 2003; Luchsinger et al., 2001; Matsuzaki et al., 2010; Ohara et al., 2011; Skoog et al., 1996). Lifestyle factors affecting risk include physical and cognitive activity and diet (Erickson et al., 2010; Scarmeas et al., 2006; Verghese et al., 2003). It is the interactions among these risk factors and the pathobiological cascade of AD that determines the likelihood of a clinical expression of AD—either as dementia or Mild Cognitive Impairment (MCI) (Lopez et al., 2012).

The Cardiovascular Health Study—Cognition Study (CHS-CS) is a rich database of multiple metabolic, cardiovascular, cerebrovascular, and neuroimaging variables obtained over the past 20 years, as well as detailed cognitive assessments beginning in 1990–91 (Saxton et al., 2004), 1998–99 (Lopez et al., 2003), 2002–03 (Lopez et al., 2007), and annually thereafter.

In 1992–94, 924 of the CHS participants in Pittsburgh underwent a structural MRI scan of the brain, and these individuals constitute the initial cohort of the Pittsburgh CHS-CS (Kuller et al., 2003). In our analysis we use data from the 652 individuals who were alive in 1998 and who agreed to genetic testing for APOE*4. We consider a single response variable $Y$ that codes diagnosis for each individual at different ages:

$$Y = \begin{cases} 
1 & \text{if dementia} \\
2 & \text{if MCI} \\
3 & \text{if normal}
\end{cases}$$

Age is the time dependent variable that defines the trajectories. In other words, we are interested in the probability of being diagnosed with MCI or dementia at different ages. We will also consider four time-invariant binary predictors: $X_1 = \text{Race (White)}$, $X_2 = \text{Education (Beyond High School)}$, $X_3 = \text{Hypertension (Present)}$, and $X_4 = \text{APOE*4 (Present)}$. 
There are a variety of pathways or trajectories that individuals can take as part of the natural history of AD. In order to try to capture these different pathways, we adapt the work of Manrique-Vallier (2010) on modeling trajectories toward disability (Manrique-Vallier and Fienberg, 2009) that combines features of a version of the cross-sectional Grade of Membership model (Erosheva et al., 2007) with those of a longitudinal multivariate latent trajectory model (Connor, 2006). This technique allows our data to identify a small number of theoretically appealing ‘canonical’ trajectories to dementia or MCI and then express each individual’s trajectory as a weighted combination of these canonical trajectories.

### 10.2 The Extended TGoM Model

In this section we present two extensions of the Trajectory Grade of Membership model. We start by recalling the basics of mixed membership models then gradually include survival outcomes and time-invariant predictors in our analysis.

Mixed membership models assume the existence of a small number of “typical classes” of individuals and model their evolution over time. They regard individuals as belonging to all of these classes in different degree by considering them as weighted combinations of the typical classes. It is possible to describe distinct general tendencies (the typical cases) while accounting for the individual variability.

Following the strategy described in the previous chapter, we start by assuming the existence of a specific number, $K$, of “typical classes” or “typical profiles” and we associate each individual, $i$, for $i \in \{1, \ldots, I\}$ (in our application $I = 652$), with its own membership vector $g_i = (g_{i1}, \ldots, g_{iK})$, representing the different degrees of closeness to each typical profile. Membership scores are restricted so that $g_{ik} > 0$ and $\sum_{k=1}^{K} g_{ik} = 1$ for any $i$. An individual with membership vector $g_i = (0, \ldots, 0, 1, 0, \ldots, 0)$, where 1 is in the $k$th position, is called an “ideal” (or extreme) individual of class $k$.

For any individual that is an ideal member of the $k$th typical class, we specify the distribution of the outcome variable $Y_i$ to form a trajectory for the response variable. Therefore,

$$f_{\theta_k}(y_i|\text{Age}_i) = P(Y_i = y_i|\text{Age}_i, \text{ith individual in } k\text{th class})$$

indicates the probability of outcome $y_i$ for an ideal individual of the $k$th class at a particular age.

We introduce the idea of mixed membership by setting the distribution of the outcome variable $Y_i$ for each individual $i$ as the convex combination

$$P(Y_i = y_i|(g_1, \ldots, g_K), \text{Age}_i) = \sum_{k=1}^{K} g_{ik} f_{\theta_k}(y_i|\text{Age}_i).$$  \hspace{1cm} (10.1)

Then we assume that for a single individual, conditional on the age at time $t$, $\text{Age}_{it}$, and its membership vector, the responses at $T$ measurement times are independent of each other:

$$P(Y_i = y_i|(g_1, \ldots, g_K), (\text{Age}_1, \ldots, \text{Age}_T)) = \prod_{t=1}^{T} \sum_{k=1}^{K} g_{ik} f_{\theta_k}(y_{it}|\text{Age}_{it}).$$

We further assume that the individuals are randomly sampled from the population and that the membership vectors are i.i.d. sampled from a common distribution $G_\alpha$, with support $\Delta_{K-1}$ to obtain the unconditional expression

$$P(Y = y|\text{Age}) = \prod_{i=1}^{N} \int_{\Delta} \prod_{t=1}^{T} \sum_{k=1}^{K} g_{ik} f_{\theta_k}(y_{it}|\text{Age}_{it}) G(dg).$$
10.2.1 Specifying the Trajectory Function

We must also specify a model for \( f_{Y_i}(y_i|\text{Age}) \). Since in our application the outcome variable is diagnosis has three ordered outcomes, we consider an ordered multinomial logit model (Gelman, 2007), described by the two following logistic regressions, for \( k = 1, \ldots, K \):

\[
\begin{align*}
P(Y > 1|\text{Age}, \text{individual in } k\text{th class}) &= \logit^{-1}(\beta_{0k} + \beta_{1k}\text{Age}) \\
P(Y > 2|\text{Age}, \text{individual in } k\text{th class}) &= \logit^{-1}(\beta_{0k} + \beta_{1k}\text{Age} - c_k).
\end{align*}
\] (10.2)

We then compute the probabilities of individual outcomes using the formulas:

\[
\begin{align*}
P(Y = 1) &= 1 - P(Y > 1) \\
P(Y = 2) &= P(Y > 1) - P(Y > 2) \\
P(Y = 3) &= P(Y > 2).
\end{align*}
\] (10.3)

Therefore, the expression in (10.1) implicitly contains \( \theta_k = (\beta_{0k}, \beta_{1k}, c_k) \), for \( k = 1, \ldots, K \). The parameters \( c_k \), which are called thresholds or cutpoints, are constrained to be positive, because the probabilities in (10.2) are strictly decreasing.

10.2.2 First Extension: Specifying the Dependency of Membership Vectors on Additional Covariates

Instead of attributing all variation over time to aging, we could place additional predictors in two different parts of the model. The first alternative is to place them at the level of the extreme profiles, as we have done for the variable Age. The second alternative is to model a dependency between the membership vectors and the new predictors. This is the strategy that we use, since it does not change the interpretation of the extreme profiles given in the previous chapter.

Suppose that, for each of the \( N \) individuals in our analysis, we have information about \( M \) binary time-invariant predictors \( X_1, \ldots, X_M \). We evaluate the effect of these predictors on the proximity of individuals to the three trajectories by allowing the distribution of the membership vectors \( g_i = (g_{i1}, g_{i2}, g_{i3}) \) to depend on the predictors:

\[
g_i|\alpha(x_i) \sim \text{Dirichlet}(\alpha(x_i)) \quad \text{for } i = 1, \ldots, I,
\] (10.4)

where

\[
\alpha(x) = \left\{ \begin{array}{l}
\exp(a_{01} + a_{11}x_1 + \cdots + a_{M1}x_M), \\
\exp(a_{02} + a_{12}x_1 + \cdots + a_{M2}x_M), \\
\ldots \\
\exp(a_{0k} + a_{1k}x_1 + \cdots + a_{Mk}x_M) \end{array} \right\}.
\] (10.5)

Then by (10.5) and the properties of the Dirichlet distribution, we can see that

\[
\log \frac{E(g_{i1}|a, x)}{E(g_{i2}|a, x)} = (a_{01} - a_{02}) + (a_{11} - a_{12})x_1 + \cdots + (a_{M1} - a_{M2})x_M,
\]

\[
\log \frac{E(g_{i1}|a, x)}{E(g_{i3}|a, x)} = (a_{01} - a_{03}) + (a_{11} - a_{13})x_1 + \cdots + (a_{M1} - a_{M3})x_M,
\]

\[
\log \frac{E(g_{i2}|a, x)}{E(g_{i3}|a, x)} = (a_{02} - a_{03}) + (a_{12} - a_{13})x_1 + \cdots + (a_{M2} - a_{M3})x_M,
\]

so that we can interpret the difference \( a_{mk} - a_{mh} \) as the effect of variable \( X_m \) on the population.
log odds of the event “individual \( i \) has a trajectory near profile \( k \)” versus the event “individual \( i \) has a trajectory near profile \( h \).” Other specifications for the dependency of the distribution of the membership vectors on the time-invariant predictors are possible. See Manrique-Vallier (2010) for another parametric function of the covariates \( \alpha(X) \) and Blei and Lafferty (2007); Galyardt (2012) for a logistic-normal prior that replaces the Dirichlet in (10.4).

10.2.3 Second Extension: Modeling Mortality

The presence of dementia is correlated with mortality. Patients with dementia are more likely to die than individuals of the same age without dementia (Bowen et al., 1996; Brodaty et al., 2012; Mölsä et al., 1995). Information about survival times can help to reconstruct certain regions of some trajectory patterns for which information about diagnoses is not sufficient. By design, all subjects in the CHS-CS are older than 65 years, therefore any reference to the distribution of survival time refers to the conditional version, given that the subjects have already lived more than 65 years. Within each canonical profile, we model the random survival time variable \( s \) in excess of 65 years using the Weibull distribution with inverse scale parameter \( \lambda_k \) and shape parameter \( \delta_k \), for \( k = 1, \ldots, K \):

\[
\begin{align*}
    w(s; \lambda_k, \delta_k) &= \delta_k \lambda_k^{\delta_k} s^{\delta_k-1} e^{-(s\lambda_k)^{\delta_k}}.
\end{align*}
\]

Our objective is to understand the survival patterns and their effects on the trajectories to dementia. Following Manrique-Vallier (2010), we make the following assumptions: 1) the canonical profiles specify both trajectories to dementia and mortality distributions; and 2) given the membership vector \( g_i \), the survival time \( s \) and the Diagnosis \( Y \) are independent. Therefore, the joint model for dementia and mortality can be written as:

\[
p(y_i, s_i | g_i, \text{Age}) = \left[ \prod_{t=1}^{T} \sum_{k=1}^{K} g_{ikt} f_{\theta_k}(y_{it} | \text{Age}_{it}) \right] \left[ \sum_{k=1}^{K} g_{ik} w(s_i; \lambda_k, \delta_k) \right],
\]

where the first factor defines the trajectories for MCI and dementia, as described in the previous sections, and the second factor models the individual mortality patterns using the same number \( K \) of extreme profiles and membership vector \( g_i \).

10.2.4 Full Bayesian Specification

We complete the Bayesian specification of the model by specifying uninformative priors for the trajectory parameters \( \beta_{0k}, \beta_{1k}, c_k \) and the parameters \( a_{jk} \) of the membership distribution \( G_\alpha \):

\[
\begin{align*}
    \beta_{0k} &\sim N(0, 100) \quad \text{for} \ k = 1, 2, \ldots, K \\
    c_k &\sim N(0, 100) \quad \text{for} \ k = 1, 2, \ldots, K \\
    a_{jk} &\sim N(0, 100) \quad \text{for} \ j = 0, 1, \ldots, M \text{ and } k = 1, 2, \ldots, K.
\end{align*}
\]

We also specify the following priors for the parameters of the Weibull distribution used to model the survival outcomes

\[
\begin{align*}
    \delta_k &\sim \text{Gamma}(1, 1) \quad \text{for} \ k = 1, 2, \ldots, K \\
    \lambda_k &\sim \text{Gamma}(1, 0.1) \quad \text{for} \ k = 1, 2, \ldots, K,
\end{align*}
\]

which are considered diffuse, but realistic to model human survival times in excess of 65 years.
10.3 Application to the CHS Data: Results

We fit the model described in the previous section to the CHS data using BUGS, a software package for Bayesian inference using Gibbs sampling (Lunn et al., 2009). The interested reader is referred to Manrique-Vallier (2010) for more details on an MCMC algorithm used in a similar setting. We report here primarily on a model with $K = 3$ canonical profiles (we discuss the selection of the number of profiles in Section 10.3.4 below). As described in Section 10.1.1 we recall that we consider the single outcome variable diagnoses (three levels: dementia, MCI, normal), the time-varying predictor Age, and four binary time-invariant predictors: $X_1 =$ Race (White), $X_2 =$ Education (Beyond High School), $X_3 =$ Hypertension (Present), and $X_4 =$ APOE*4 (Present).

10.3.1 The Trajectories Toward MCI and Dementia

Figure 10.1 shows the trajectories of the three canonical profiles, determined by the parameters, whose estimated posterior means and standard deviations are shown in Table 10.1. The probability of dementia as a function of age is shown in the left-hand panel, and the probability of MCI is shown in the right-hand panel. The bands around the three profiles are pointwise posterior 95% credible bands and describe the uncertainty related to the estimation of these trajectories. They are constructed using the MCMC draws of the parameters $\beta_{0k}$, $\beta_{1k}$, and $c_k$.

![Figure 10.1](image)

**FIGURE 10.1**  
$K = 3$ typical trajectories for dementia and MCI with pointwise posterior 95% credible bands.

Profile 1 (continuous green curve), the ‘healthy’ profile, shows the typical or canonical trajectory of individuals whose peak probability of transitioning to MCI occurs between 95 and 100 years of age. This group has only a 50% probability of progressing to dementia by age 100. Profile 2 (dotted red curve), or ‘unhealthy’ profile, shows the typical or canonical trajectory of individuals who have a peak probability of progressing to MCI between the ages of 75 and 80, and a peak probability of progressing to dementia between the ages of 80 and 85. Finally, Profile 3 (dotted black curve), the ‘intermediate’ profile, shows the typical or canonical trajectory of individuals having a peak probability of progressing to MCI between 85 and 90 years of age, with a peak probability of progressing to dementia between 90 and 95 years. Figure 10.2 shows two individual trajectories as convex combinations of the canonical profiles as described by Equation (10.1). The trajectory closer to the unhealthy profile belongs to an individual with the following characteristics: non-white, less
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<table>
<thead>
<tr>
<th>Extreme: trajectory’s parameter</th>
<th>Estimate (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>k=1 (healthy)</td>
<td>k=2 (unhealthy)</td>
</tr>
<tr>
<td>β₀</td>
<td>38.011 (0.521)</td>
</tr>
<tr>
<td>β₁</td>
<td>-0.388 (0.054)</td>
</tr>
<tr>
<td>c</td>
<td>1.799 (0.334)</td>
</tr>
</tbody>
</table>

**TABLE 10.1**
Posterior means and standard deviations for the parameters defining the three typical trajectories for dementia and MCI.

Educated, hypertensive, ApoE4 present. The trajectory closer to the ‘healthy’ profile belongs to an individual with the opposite characteristics: white, education beyond high school, non-hypertensive, no-ApoE4.

**FIGURE 10.2**
Two individual trajectories as weighted combinations of the three typical profiles. The trajectory closer to the ‘unhealthy’ profile belongs to an individual with the following characteristics: non-white, less educated, hypertensive, ApoE4 present. The trajectory closer to the ‘healthy’ profile belongs to an individual with the opposite characteristics: white, education beyond high school, non-hypertensive, no-ApoE4.

### 10.3.2 The Effect of Additional Covariates on the Membership Vectors

In order to understand the effects of the four time-invariant covariates on the closeness of an individual to each of the three canonical trajectories, it is necessary to examine the results in Table 10.2. The first three rows of the table show the effect of race on trajectory membership, and we see that for the comparison of Profiles 1 and 2, having race coded as white results in an increased probability of being near the healthy profile relative to being near the unhealthy profile (i.e., mean \(a_{11} - a_{12} = 1.21\) with posterior 95% credible interval \([0.82, 1.62]\)). In addition, race significantly increases the probability of being in the healthy profile relative to the intermediate profile. With regard to education, having more than a high school education resulted in increased closeness to the healthy profile relative to the unhealthy profile. However, education has no impact on the relative
closeness of the intermediate profile to either the healthy or unhealthy profiles. Hypertension is associated with greater closeness to the unhealthy profile relative to the intermediate profile, while the presence of even a single copy of the APOE*4 allele increases the closeness of individuals to the unhealthy profile.

<table>
<thead>
<tr>
<th>Effect of</th>
<th>Parameter: Estimate [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td>$a_{11} - a_{12}$ 1.21 [0.82, 1.62] $a_{11} - a_{13}$ 0.39 [-0.15, 0.84] $a_{12} - a_{13}$ -0.83 [-1.26, -0.47]</td>
</tr>
<tr>
<td>Education</td>
<td>$a_{21} - a_{22}$ 0.50 [0.10, 0.92] $a_{21} - a_{23}$ 0.26 [-0.15, 0.81] $a_{22} - a_{23}$ -0.24 [-0.66, 0.17]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$a_{31} - a_{32}$ -0.26 [-0.60, 0.07] $a_{31} - a_{33}$ 0.18 [-0.22, 0.62] $a_{32} - a_{33}$ 0.43 [0.13, 0.79]</td>
</tr>
<tr>
<td>ApoE4</td>
<td>$a_{41} - a_{42}$ -0.71 [-1.12, -0.26] $a_{41} - a_{43}$ 0.12 [-0.31, 0.60] $a_{42} - a_{43}$ 0.83 [0.40, 1.23]</td>
</tr>
</tbody>
</table>

**TABLE 10.2**

Posterior means and 95% credible intervals for the parameters representing the effects of time-invariant predictors on the closeness of individual trajectories to the typical profiles.

**10.3.3 The Survival Trajectories**

We also estimated survival trajectories, shown in Figure 10.3, based on the results of Table 10.3. For Profiles 1 and 3 the survival curves are almost overlapping, indicating that for individuals close to these profiles, the probability of being alive is below 50% only after the age of 90. By contrast for individuals that are close to the unhealthy profile, the probability of being alive is below 50% before the age of 90. The difference in the age for a 50% probability of survival is approximately 5 years between the unhealthy profile, and the healthy and intermediate profiles. By contrast, the difference in the age at which the different profiles reach a 50% probability of dementia is approximately 10 years between each trajectory, and at least 20 years between the unhealthy and healthy profiles (See Figure 10.1).

<table>
<thead>
<tr>
<th>Weibull’s parameter:</th>
<th>Estimate (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>k=1 (healthy)</td>
<td>$\lambda_1$ 3.887 (0.376) $\delta_1$ 0.034 (0.001)</td>
</tr>
<tr>
<td>k=2 (unhealthy)</td>
<td>$\lambda_2$ 4.050 (0.256) $\delta_2$ 0.040 (0.001)</td>
</tr>
<tr>
<td>k=3 (intermediate)</td>
<td>$\lambda_3$ 5.397 (0.616) $\delta_3$ 0.034 (0.001)</td>
</tr>
</tbody>
</table>

**TABLE 10.3**

Posterior means and standard deviations for the parameters defining the three typical survival trajectories.

**10.3.4 Discussion: The Number of Typical Profiles**

Finally, in order to evaluate our decision to include only three canonical trajectories in our model, we used the method of posterior predictive testing (Gelman, 2007) to compare the models with
K = 3 and K = 2 canonical profiles; we found that there were systematic differences between the model with K = 2 canonical profiles and the data. Using the estimated posterior distribution of the parameters, we replicated the original diagnoses, obtaining 1000 different simulated datasets. The model with two canonical profiles systematically overestimates the number of individuals that are diagnosed with MCI at least once in their life. The histograms in Figure 10.4 show this test statistic for 1000 simulated datasets for the model with K = 2 canonical profiles and the model with K = 3 canonical profiles. The vertical bars indicate the true value of the test statistic: 338 individuals have been diagnosed with MCI at least once. Then we compared the original and simulated diagnoses using the proportions of individuals affected by MCI at every age. In Figure 10.5 the black lines represent the true proportion of individuals affected by MCI between the ages of 71 and 105, and the red lines represent the same proportions for 30 simulated datasets. There are some discrepancies between the true proportions and those that were replicated using the model with K = 2 canonical profiles, while the proportions simulated through the model with K = 3 canonical profiles show no apparent discrepancies. We also attempted a model with four canonical profiles, but the estimation process was very slow to converge, and produced a fourth additional canonical profile that essentially duplicated the healthier one. Based on these results we conclude that the model with K = 3 canonical profiles best fits the data.

10.4 Conclusion and Remarks

We reported here the results of an MMTM analysis of the natural history of the development of dementia among individuals over the age of 65. We investigated the relative merits of three separate trajectories, and then identified the effects of four time-invariant covariates on the nearness of individuals to each of these profiles. The results provide new insights into the natural history of AD and
related dementias, and may also provide evidence for a potential difference in the pathophysiology of the development of dementia as a function of age.

One of the important characteristics of MMTMs is that individual subjects are assumed to have weighted membership in each of the three canonical trajectories. Thus, while it is theoretically possible for an individual to be an ideal or perfect member of one trajectory, in fact, as shown in Figure 10.2, individuals actually share characteristics of all three profiles to varying degrees. The main extension of the TGoM presented in this chapter involves a particular dependency between the distribution of the membership vectors and the time-invariant predictors added in the model. Particular values of the new covariates help to explain the closeness of individuals to one or another of the ideal trajectories.

Our decision to include three canonical trajectories in our model was based on three separate factors: MCMC convergence time and cost, the model fit, and the interpretability of the trajectories. The three profiles’ models not only provided us with a good cost-benefit ratio in terms of processing time and model fit (as assessed by posterior predictive model checking), but also provided interpretable trajectories—an unhealthy trajectory proceeding very rapidly through MCI to dementia, a slow trajectory that does not become apparent until after the age of 90, and an
intermediate trajectory through MCI to dementia with a peak probability of a clinical syndrome in the late 80s. We can view the results of the analysis of survivorship as a kind of validation of the three profile model. Thus, the fact that the individuals with an ‘unhealthy’ trajectory are also the ones most likely to die sooner is consistent with the observation that demented individuals have a higher risk of death (Bowen et al., 1996; Mölsä et al., 1995).

If the use of MMTMs were extended to larger databases with appropriate follow-up and assessment schedules, we might be able to evaluate the relative contributions of other genetic factors, treatment history, and biomarkers on the natural history of dementia.

References


