Clustering of Longitudinal Data: A Tutorial on a Variety of Approaches

A Preprint

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November 11, 2021

Abstract

During the past two decades, methods for identifying groups with different trends in longitudinal data have become of increasing interest across many areas of research. To support researchers, we summarize the guidance from the literature regarding longitudinal clustering. Moreover, we present a selection of methods for longitudinal clustering, including group-based trajectory modeling (GBTM), growth mixture modeling (GMM), and longitudinal k-means (KML). The methods are introduced at a basic level, and strengths, limitations, and model extensions are listed. Following the recent developments in data collection, attention is given to the applicability of these methods to intensive longitudinal data (ILD). We demonstrate the application of the methods on a synthetic dataset using packages available in R.

Keywords longitudinal clustering, growth mixture modeling, latent-class trajectory modeling, intensive longitudinal data, time series

1 Introduction

The analysis of longitudinal data is prominent in correlational studies that look for correspondence between observations of the same variables over extended period of time, such as substance use or mental health in psychology, recidivism behavior in sociology, and relapse or medication adherence in medicine. Longitudinal studies enable researchers to assess and study changes over time of the variables of interest. With the increasing capabilities of data collection and storage, more and more longitudinal studies are designed to involve a large number of repeated measurements of the same variable per subject over time. When a considerable number of observations are available, the data is commonly referred to as intensive longitudinal data (ILD) (Walls and Schafer, 2006). ILD has the advantage of allowing for a more granular assessment of change over time, especially at the subject level.

Analyzing longitudinal data requires models that take the structure of the data into account. The assessment of variability is key, as no two subjects are identical. In addition to the presence of measurement variability within each subject, models should account for differences (i.e., heterogeneity) between subjects. For example, in the analysis of medication adherence, subjects may exhibit considerably different levels of adherence over time. An example of such a modeling approach is multilevel modeling. Here, the model describes the mean trend (i.e., longitudinal pattern), and captures the differences between subjects by modeling the subject-specific deviations from the trend.

In studies with considerable between-subject variability or non-normal deviations from the trend, subjects may exhibit large deviations, to the point that the mean trend may not be representative of the longitudinal patterns of the subjects (Hamaker, 2012). An intuitive alternative approach is to represent the differences across subjects in terms of a set of common trends. This way, the subject-specific deviations are reduced to the nearest trend. This approach is generally referred to as longitudinal clustering, and involves the automatic discovery of groups of subjects with similar longitudinal characteristics. Longitudinal clustering is of interest, for example, in behavioral studies, where subjects can...
exhibit a range of behaviors that are due to various unobserved factors, resulting in structural deviations. We shall use the level of adherence of sleep apnea patients to positive airway pressure (PAP) therapy as the running example in this work. Factors such as perceived importance, self-efficacy, personality traits, claustrophobia, and many more have been shown to affect the level of adherence to PAP therapy [Cayanan et al. 2019], resulting in a spectrum of longitudinal patterns across patients.

In this tutorial, we present a review of the literature on methods for clustering longitudinal data. While there are several aspects to modeling longitudinal data, we focus on the discovery of subgroups with different forms of longitudinal variations. Moreover, we summarize the guidance from literature on how to conduct such a longitudinal cluster analysis. Several types of methods have been proposed over the past two decades for clustering longitudinal data. Our intent is to assist the reader in making an informed decision on which method to apply in their cluster analysis, and to acquaint the reader with the available methodologies for longitudinal clustering. We describe each method along with its assumptions, advantages, and practical limitations. Secondly, we cover the topic of model specification, with a focus on the number of clusters needed to best represent the data. We survey the commonly used metrics and approaches to identify the most appropriate number of subgroups. Lastly, the methods are demonstrated on a synthetic dataset inspired by a real-world example in the context of daily PAP therapy adherence of patients with sleep apnea [Aloia et al., 2008]. We will use this dataset to highlight differences in the assumptions of the methods and the estimation, as well as to show how to specify and apply each method.

The selection of methods has been based on prevalence and with the aim of creating a varied selection with different strengths and limitations. The variety of methods enables readers to select the most appropriate method for their case study. Moreover, we only considered methods that are applicable for identifying univariate longitudinal patterns of change, and have a publicly available implementation in R. Relevant papers were identified via keyword searches and the snowball method. While we present the methods for the purpose of analyzing ILD, each of the methods are applicable to repeated measures data to some degree. The application of longitudinal clustering is becoming more commonplace. Based on a conservative keyword search, we observe a considerable increase in the number of publications concerning longitudinal clustering in different fields over time, from 37 publications in the nineties, to 273 publications between 2000–2009, and 1,257 publications between 2010–2019.

**Terminology**  As the scope of this review is intended to be interdisciplinary, we describe the key terms used in this paper, and list the commonly used alternative terms. We explain the topic of longitudinal cluster analysis in the context of clustering subjects over time, but the methodology applies equally well to any application involving repeated measures data, e.g., modeling devices, animal growth, or accident rates.

At the subject level, the sequence of longitudinal observations are commonly referred to as a trajectory, a time series, a temporal pattern, a curve, a trend, or a dynamic. Due to the frequency of measurement in the case of ILD, measurements are not necessarily equidistant in time. Moreover, subjects can have different non-corresponding times of measurement, and the number of measurements may vary. With this in mind, we define the trajectory of a subject $i$ as a sequence of $n_i$ observations by

$$y_i = \{y_{i,1}, y_{i,2}, \ldots, y_{i,n_i}\},$$

(1.1)

where the observation $y_{i,j}$ is taken at time $t_{i,j} \in \mathbb{R}$.

By clustering, we refer to the definition of a cluster analysis from the field of machine learning, specifically that of unsupervised learning, where data is grouped (i.e., clustered) based on similarity, and the group definitions and assignments are not known in advance. In the field of statistics a distinction is made between known clusters and unobserved clusters. In the former case, subjects are stratified based on a known nominal factor, for example, by assigning subjects to subgroups based on age or sex. Unknown clusters are commonly referred to as latent (i.e., hidden) classes, groups, profiles, or clusters. In this paper, we use the term cluster as referring to the unobserved type.

Longitudinal clustering can be regarded as a specific area of time series clustering that is specifically concerned with the identification of common patterns of change or state changes throughout a longitudinal study. Whereas the scope of time series clustering extends to the modeling and assessment of any temporal similarity for any type of time series data [Aghabozorgi et al., 2015]. Moreover, it includes the identification of temporal subsequences within time series.

**Overview**  The paper is organized as follows. We begin by elaborating on the case study in Section 2. In Section 3 we first summarize the concept of multilevel modeling as a precursor to modeling subgroups. Furthermore, we explain the concept of clustering; both philosophically and practically. The selected methods are described and demonstrated

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1 A systematic search was performed per decade using Web of Science. Articles must contain the keyword “longitudinal”, and one of the keywords “mixture”, “latent-class”, “clustering”, or “group-based”.
in Section 4. We outline the recommended steps involving a longitudinal cluster analysis in Section 5. Lastly, Section 6 discusses the findings from the case study in addition to the general challenges, limitations, and future work of longitudinal clustering.

2 Case study

We use the case study in order to illustrate the longitudinal cluster methods, and to contrast the strengths and limitations of the methods in a practical setting. The longitudinal methods are applied to a synthetic dataset, which facilitates a more detailed comparison between methods, and enables a fully reproducible and transparent demonstration. The data is generated from the population characteristics and groups as reported by Aloia et al. (2008), who investigated patterns of daily time on therapy among 71 obstructive sleep apnea patients in their first year of therapy. The synthetic dataset and analysis code are provided in the supplementary materials.

Sleep apnea is a common chronic disorder. Patients suffer from frequent paused or diminished breathing during their sleep, resulting in fragmented sleep and overall poor sleep quality. Sleep apnea is commonly treated using positive-airway pressure (PAP) therapy. This involves a device that assists the patient in breathing during sleep by supplying positive air pressure through a mask worn by the patient. Patients are required to use the device every time they sleep. Considering the inconveniences and difficulties patients can face with the therapy, some patients struggle to comply with the therapy for longer periods of time, whereas others do well. The progression of the therapy is determined by many factors, e.g. the initial perception patients have of the therapy, the coping ability of the patient, and social support (Weaver and Grunstein, 2008; Cayanan et al., 2019). An effective treatment can only be ensured when patients are compliant to the therapy, where the threshold for therapy compliance is usually set at 4 hours of therapy per day, but PAP use for longer than 6 hours has been shown to have positive effects (Weaver and Grunstein, 2008). The patterns of change in usage hours are therefore of interest. Most past studies have treated the patient population as being homogeneous, whereas others have attempted to stratify the population in order to address the differences in therapy adherence over time between subjects (Aloia et al., 2008; Babbin et al., 2015).

Aloia et al. (2008) modeled the trajectories of daily hours on therapy of each patient in terms of an intercept, slope, variance, autocorrelation, and number of attempted days. Seven clusters were manually identified using two expert raters. The cluster of Good users (24%) have a high number of therapy days and a high average hours of usage (6.6 hours). Slow improvers (13%) have an initially low number of hours early in therapy but increased over time, whereas the Slow decliners (14%) exhibit the opposite pattern. Variable users (17%) have a lower average usage (5 hours), and showed fluctuations in adherence over time. Occasional attempters (8%) have low attempt probability and low hours of use (3.2 hours), but the patients did continue therapy. Lastly, a sizable proportion of patients prematurely stopped with therapy, as represented by the Early drop-outs (13%) and Non-users (11%).

We utilize the reported patient and cluster statistics to generate 500 patient trajectories, with each patient comprising at most 361 observations. The trajectories are generated according to the original cluster proportions, and each trajectory is assigned a random deviation in intercept and slope from its respective cluster. Considering the scope on identifying patterns of change, we introduce a second-order term in the cluster trajectory shapes to evaluate whether the methods are able to recover these shapes. The cluster coefficients used to generate the trajectories are reported in Table 1. Due to the considerable computation time of the mixture methods, we downsampled the generated data to a biweekly average, resulting in 26 observations per patient, with 13,000 observations in total. The cluster trajectories and downsampled individual trajectories are visualized in Figure 2.1. Overall, 21% of biweekly observations are zero, and the mean non-zero usage is 4.6 hours ($\sigma = 2.1$ hours).

2.1 Evaluation

All methods are evaluated in R 3.6.3 using freely available packages (R Core Team, 2020). Each method is evaluated for 1 to 8 clusters in order to assess the number of clusters that correspond to the most representative solution of each method. If available for the respective method, we use the Bayesian information criterion (BIC) in order to guide the identification of the most appropriate number of clusters per method. It is defined by $\text{BIC} = p \log n - 2 \log \hat{L}$, where $\hat{L}$ denotes the likelihood of the candidate model, $p$ is the number of model parameters, and $n$ are the number of observations. The BIC is one of the most widely used metrics in longitudinal clustering (Van de Schoot et al., 2017). A lower BIC indicates a more representative model for the data. The BIC includes a penalty factor for model complexity, resulting in a higher score for a model with more parameters. If the BIC values are similar between adjacent solutions, we base the final choice for the number of clusters on a subjective analysis of the variety in patterns identified by the methods (Nagin and Odgers, 2010).
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Table 1: Group coefficients for generating the trajectories. Values enclosed in parentheses denote the standard deviation of the random effects. The attempt probability is conditional on the patients still being on therapy. The early drop-outs and non-users are modeled to stop prematurely at day 80 (30) and day 20 (10), respectively.

| Cluster            | $\pi$ | $\beta_0$ | $\beta_1 \times 10^2$ | $\beta_2 \times 10^4$ | $\sigma^2$ | $P_{\text{attempt}}$ |
|--------------------|-------|-----------|------------------------|------------------------|------------|---------------------|
| Good users         | 24%   | 6.6 (.54) | 0.0 (.16)              | 0.0                    | 2.0 (.82)  | 97%                 |
| Slow improvers     | 13%   | 4.8 (1.0) | 1.7 (.16)              | -0.30                  | 3.6 (1.3)  | 94%                 |
| Slow decliners     | 14%   | 6.1 (.63) | -1.9 (.14)             | 0.30                   | 3.2 (.85)  | 77%                 |
| Variable users     | 17%   | 4.4 (.87) | 0.96 (0.0)             | -0.30                  | 3.4 (1.2)  | 82%                 |
| Occasional attempters | 8%   | 3.2 (1.1) | -0.30 (.91)            | 0.0                    | 3.6 (1.8)  | 29%                 |
| Early drop-outs    | 13%   | 4.0 (1.1) | -0.14 (1.0)            | -1.0                   | 5.0 (2.6)  | 69%                 |
| Non-users          | 11%   | 2.5 (.93) | 0.0 (.91)              | 0.0                    | 3.0 (1.7)  | 70%                 |

In case the BIC is not available for the respective longitudinal cluster method (i.e., there is no model likelihood), we apply the average silhouette width (ASW) ([Rousseeuw, 1987]). The ASW is a data-based measure of class separation. The silhouette value measures the similarity of an object to the objects in its assigned cluster, relative to the similarity of the other clusters. It is expressed as a score between -1 and 1, where a higher value indicates a greater similarity to the assigned cluster. The ASW is obtained by averaging the silhouette values of all trajectories. The topic of selecting the number of clusters is discussed in more detail in Section 4.5.

3 Background

Prior to performing an exploratory cluster analysis, it is worthwhile to consider the case where the data comprises no clusters, i.e., the case where there is only a single cluster ([Greenberg, 2016], [Bauer, 2007], [Sher et al., 2011]). We therefore begin by describing regression modeling, and how regression models can capture heterogeneity without the need for clusters.

Subjects can be considered as independent sources of variation, with each subject having, for example, their own mean response level, change over time, or measurement variability. Under this assumption, and given that subjects have a sufficient number of observations (as is typically the case with ILD), subjects can be modeled independently using established methods from the field of time series analysis ([Liu, 2017]). This is referred to as a two-step or bottom-up approach. The individual time series are commonly represented using linear regression or autoregressive models.

Aside from between-subject variability, there may be other sources of variation in the data. One can think of the measurement device used by the subject having a certain measurement error, which is shared across subjects using the same device. Another common source of variability are the different sites at which measurements are collected. Mixed modeling ([Hartley and Rao, 1967], [Laird, 1978]) enables researchers to assess subject-specific effects, and to decompose the variability in the data. It is also commonly referred to as hierarchical modeling, random effects modeling, random
coefficient modeling, and variance component modeling. The model describes the population-level effects, referred to as fixed effects, and describes a part of the subject-specific observations in terms of a structural deviation from the fixed effects. The subject-specific deviations are a source of variation as the deviations cannot be fully explained in terms of covariates, and therefore are treated as random variables, also referred to as random effects or latent variables.

A possible way of modeling longitudinal change is to incorporate time as a covariate into the model. First- or second-order polynomials are commonly used to describe change as a function of time. If more flexible curves are required, cubic splines or fractional polynomials can be used. Figure 3.1 illustrates a first-order linear mixed model describing the outcome of each individual over time by an intercept and slope, where the assessment represents time.

In linear mixed-effects modeling, the response is assumed to be normally distributed (although extensions exist (Fitzmaurice et al., 2011)), and the fixed and random effects are assumed to be a linear combination of covariates, giving

\[
y_{i,j} = x_{i,j} \beta + z_{i,j} u_i + \varepsilon_{i,j}
\]

\[
u_i \sim N(0, \Sigma)
\]

\[
\varepsilon_{i,j} \sim N(0, \sigma^2_e).
\]

Here, \(x_{i,j}\) denotes the patient-specific covariates at time \(t_{i,j}\), and \(\beta\) are the respective coefficients. The random effects design vector is denoted by \(z_{i,j}\), where the random effects \(u_i\) are jointly normally distributed with zero mean and variance-covariance matrix \(\Sigma\), and uncorrelated with \(\varepsilon_{i,j}\). The measurement error is denoted by \(\varepsilon_{i,j}\) and is assumed to be independently normally distributed with zero mean, a common variance \(\sigma^2_e\), and uncorrelated. Alternatively, the residuals can be modeled to be serially correlated (autocorrelated), but more complex correlation structures are often not possible with the inclusion of random effects due to identifiability problems.

Mixed modeling is advantageous over fitting individual regression models especially for datasets with a small number of measurements per trajectory, as the estimates of the subject-specific trajectory coefficients are more reliable due to the partial pooling of information across subjects. Mixed effects models can be estimated with maximum likelihood estimation. Alternatively, a Bayesian sampling approach can be taken. This has the advantage that researchers are able to incorporate domain knowledge in each model parameter, improving model estimation especially under small sample size due to the ability to include of prior knowledge (Spiegelhalter et al., 1994).

3.1 Meaning of clusters

A cluster analysis is generally exploratory in nature, meaning that the definitions of the clusters, or even the number of clusters, are unknown and need to be estimated from the data. There are two possible objectives to clustering, which determines how the resulting clusters are interpreted. In most cases, the motivation for clustering comes from the knowledge or expectation of considerable heterogeneity. In an indirect application of clustering, clustering is used as a tool for approximating a heterogeneous population in terms of a finite number of groups without any distributional assumption on the heterogeneity. The identified subgroups may help in accounting for correlations between longitudinal characteristics (e.g., the association between intercept and change over time). This is applicable when the population heterogeneity cannot be adequately modeled using a parametric approach such as multilevel modeling. Even in the case where a parametric model can represent the heterogeneity, clustering may be preferred as this representation of the heterogeneity can be easier to interpret (Sterba et al., 2012; Rights and Sterba, 2016).
Figure 3.2: Representation of a heterogeneous distribution using different approaches. The vertical gray lines in (b), (c) and (d) denote the class centers.

An alternative reason for clustering is to test or develop theories on subgroups (Moffitt, 2003), referred to as a direct application of clustering. Here, the resulting clusters are regarded as representing distinct population groups. Throughout the years however, the approach has been criticized for the lack of a formal test or validation of results (Bauer and Curran, 2003; Bauer, 2007). Overall, a direct application is only advisable under strong theoretic assumptions or highly distinct (i.e., separated) subgroups. Ideally, the clusters are defined from theory, where clustering is applied as a confirmatory analysis, serving as an empirical validation (Sher et al., 2011). In all other cases, an indirect application is a more practical and lenient interpretation, and is therefore generally preferred (Nagin and Odgers, 2010; Sher et al., 2011; Skardhamar, 2010).

The challenge of accounting for heterogeneity also applies to the cluster models. An intuitive approach to clustering involves describing the heterogeneity in terms of a number of homogeneous subgroups. In contrast, modeling heterogeneity within clusters allows for a more flexible representation of the overall heterogeneity. We illustrate the concept visually in Figure 3.2, depicting a heterogeneous population in which each subject is represented by a random variable. The parametric approach, assuming a normal distribution, is shown in Figure 3.2b. Applying a cluster algorithm that models homogeneous clusters produces non-overlapping bins (i.e., the clusters), represent a part of the heterogeneity, without any assumption on the variability within the cluster. This is illustrated in Figure 3.2c, where seven bins are used to represent the population density over the different values. Due to the lack of overlap between classes, this segmentation arbitrarily improves the approximation of the true distribution for an increasing number of bins.

Alternatively, a parametric model can be assumed for the heterogeneity within each cluster. Such a model represents a mixture of distributions, referred to as a finite mixture model (McLachlan and Peel, 2000). Figure 3.2d shows the density of the three normal distributions that make up the mixture model. In this example, this was the true model from which the data was generated. This approach has the advantage of requiring fewer classes due to the ability to model outliers, but these models are more challenging to specify and identify. Moreover, the overlap between classes increases as the number of classes increases.

4 Methods

We have organized the methods for longitudinal clustering into three approaches, with increasing model complexity. In the first approach, a cross-sectional cluster algorithm is directly applied to the observations. The second approach comprises feature-based estimation methods which model the trajectories independently, and cluster the trajectories by the model representation. The third approach involves the use of a mixture model to perform clustering using
parametric group models. The methods are described under the assumption that the number of clusters is part of the model specification.

4.1 Cross-sectional clustering

In a cross-sectional clustering approach, cluster algorithms or mixture methods that are ordinarily applied to cross-sectional data with different variables are applied directly to the longitudinal observations. Here, the trajectories (or objects, in a cross-sectional context) are represented by a sequence of observations measured at fixed times \( t_1, \ldots, t_n \), with \( y_i = (y_{i1}, \ldots, y_{in}) \). Thus, each assessment moment \( t_j \) represents a separate (random) variable. This representation requires individuals to be measured at (almost) identical assessment times across subjects, although the assessment times need not be equidistant.

Considering that cross-sectional methods do not model dependence between parameters, applying cross-sectional methods to longitudinal data carries the assumption that the observations are locally independent (i.e., the temporal ordering of the observations can be ignored). Although this assumption does not hold in a longitudinal setting, it results in a nonparametric trajectory model that can model sudden changes over time. The approach is therefore especially useful in an exploratory analysis in case where the shape of the cluster trajectories is unknown. Another reason why these methods are favorable for an initial exploration is that they are orders of magnitude faster to compute compared to more complex longitudinal models. The approach is also referred to as raw data-based approach (Liao, 2005). While the approach is versatile, its applicability is limited to complete data with identical assessment times across subjects, which are challenging requirements in case of ILD. We describe two commonly used methods for cross-sectional clustering of longitudinal data below. The methods are available in most statistical software packages (e.g., in SPSS, SAS, STATA, and R), and have been used in practice.

4.1.1 \( k \)-means clustering

The aim of \( k \)-means clustering is to represent a set of objects in terms of a predefined number of representative objects \([\text{MacQueen} 1967]\). It is essentially a quantization method, and it is used in many fields, including machine learning, image processing, and signal coding. In the analysis of longitudinal data, the methodology is referred to as \( k \)-means for longitudinal data (KML), or longitudinal \( k \)-means analysis (LKMA). An early example of this type of analysis can be found in the work of \([\text{Gude and Odd} 2000]\), who performed a thorough longitudinal cluster analysis on patients with personality disorders receiving treatment to identify groups of patients with different symptom distress over time. The trajectories comprised three assessments of global symptom distress. They assessed the cluster agreements between different random starting positions, and performed post-hoc analyses on the clusters which revealed correlations on other aspects of the patients. Their work has been replicated recently by \([\text{Jensen et al.} 2014]\), with similar results. KML has been used to identify adherence patterns in obstructive sleep apnea patients undergoing nasal CPAP therapy \([\text{Wang et al.} 2015]\). Furthermore they investigated the early prediction of the (ordered) adherence clusters using a cumulative logit model. ANOVA F-tests were used to identify predictor variables that could aid in predicting the adherence pattern. The KML methodology is implemented in the R package \textit{kml}\footnote{https://CRAN.R-project.org/package=kml} created by \([\text{Genolini et al.} 2015]\).

In \( k \)-means, clusters are assumed to be homogeneous, as each representative object defines the center of a cluster, referred to as the centroid. The cluster membership of objects is determined by their nearest centroid. An example of \( k \)-means on synthetic 2D data is given in Figure 4.1. Assuming that the total variance consists of a within-cluster and between-cluster variance component, minimizing the within-cluster variance ensures maximal separation of the clusters. Thus, the \( k \)-means algorithm searches for the clustering \( \{I_1, I_2, \ldots, I_G\} \) that minimizes the within-cluster sum of squares, with each cluster \( I_g \) having one or more objects. The objective function is described by

\[
\arg \min_{I_1, \ldots, I_G} \sum_{g=1}^{G} \sum_{i \in I_g} ||y_i - \hat{\mu}_g||^2, \tag{4.1}
\]

where \( \hat{\mu}_g \) denotes the centroid of cluster \( g \). Finding the optimal cluster assignments is computationally infeasible as it requires iterating over all possible assignment combinations for all objects. Instead, the algorithm uses a heuristic iterative approach. The solution is sensitive to the choice of the initial centroids. The centroids can be selected, for example, by selecting \( k \) objects at random as the centroids \([\text{MacQueen} 1967]\), or using the output from a cluster algorithm such as agglomerative hierarchical clustering (as seen in the analysis by \([\text{Axén et al.} 2011]\)). A method proposed by \([\text{Arthur and Vassilvitskii} 2007]\), named \( k \)-means++, generally provides better starting conditions by selecting a disperse set of centroids at random.
The $k$-means method assumes that the within-cluster variance is equal across clusters. When the subgroups in the data have different variation, the estimated cluster boundaries will likely be wrong, even when the centroids are estimated correctly. The challenge is that cluster assignments can be problematic if many objects are relatively distant from the respective cluster centroid (i.e., outliers), or being close to the cluster boundary in-between clusters. An adaptation of $k$-means, named fuzzy $c$-means, addresses this concern by using probabilistic cluster assignment based on the distance to the centroids (Dunn 1973; Bezdek 1981). Another challenge is the presence of subject outliers, as these are not represented by the cluster centroids. An example of this can be seen in Figure 3.2 on page 6 where the tails of the distribution fall outside any of the bins. In some cases, these outliers can affect the resulting cluster centers. This can be prevented by excluding these subjects from the data (referred to as trimmed $k$-means).

An advantage of $k$-means is that the algorithm scales well and converges to a solution relatively quickly. In some studies, the trajectories are stratified prior to clustering as a way to guide the clustering process. An example of this approach is seen in the work of Chen et al. (2007), where the authors evaluated patterns of change in self-reported back pain over one year of time. The change in pain intensity over time, as computed using linear regression, is used to stratify trajectories in three strata (decreasing, increasing, and constant pain intensity), and clustering is performed within the strata.

**Case study** We use the R package $kml$ (version 2.4.1) to cluster the trajectories (Genolini et al., 2015). For each number of clusters, we run the estimation procedure 20 times, and select the best solution from the repeated runs based on the BIC. The successive solutions for an increasing number of clusters consistently improve the model fit, suggesting a solution with a large number of clusters. The package computes the BIC corresponding to the best solutions for 2 to 8 clusters, as depicted in Figure 4.2(a). There is a balance to be found between the practical aspect of the number of clusters and the improvement in model fit. Arguably, the three-cluster solution may be preferred as the latter solutions add relatively little improvement. However, with the objective of identifying patterns of adherence and the improved model fit, we visually assessed the remaining solutions.

We selected the seven-cluster solution because from this solution onward, the occasional attempters were distinguished from the non-users. The identified cluster trajectories are shown in Figure 4.2(b). Although the number matches the true number of clusters, this is only incidental, as KML failed to identify two cluster trajectory shapes correctly, and this does not improve by introducing more clusters. Overall, the solution recovered most of the cluster trajectories, demonstrating the benefit of a nonparametric approach in an exploratory setting.

**4.1.2 Latent profile analysis**

Latent profile analysis (LPA) is a statistical approach in which subjects are modeled to belong to one of several unknown clusters (i.e., profiles). Lazarsfeld et al. (1968) and Vermunt and Magidson (2002), Furthermore, the measurement error is taken into account into the probability of belonging to a certain class. LPA describes a mixture of profiles represented by multivariate normal distributions, an approach also referred to as Gaussian mixture modeling, or model-based clustering (Aghabozorgi et al., 2015). The method is also commonly referred to as latent class analysis.
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Figure 4.2: KML case study analysis.

(a) BIC per solution (lower is better).

(b) The identified cluster trajectories.

Case study

We estimate the LPA models using the mclust package (version 5.4.5) in R [Scrucca et al. 2016] with cluster-specific diagonal covariance matrices. Ten repeated runs were found to be sufficient in identifying the best

(LCA), although in some fields this name specifically refers to a model involving categorical rather than continuous observations.

Similar to KML, LPA can be applied for the identification of longitudinal patterns without any assumption on the shape by modeling the observations as locally independent variables at the subject level (Feldman et al. 2009; Twisk and Hoekstra 2012). This type of application of LPA is sometimes specifically referred to as a longitudinal latent-profile analysis (LLPA). The expected value of an observation at time $t_j$ depends on the cluster membership. Given the cluster membership $g$, we have

$$y_{i,j} = \mu_{g,j} + \varepsilon_{g,i,j}, \quad i \in I_g,$$

where $\mu_{g,j}$ represents the cluster-specific mean at time $t_j$, $\varepsilon_{g,i,j} \sim N(0, \sigma_{g,j})$, and $\sigma_{g,j}$ is the cluster-specific standard deviation at time $t_j$. The probability density of the observations of subject $i$ is computed by marginalizing over all $G$ clusters, giving

$$f(y_i) = \sum_{g=1}^{G} \pi_g \prod_{j=1}^{n} \phi(y_{i,j}|\mu_{g,j},\sigma_{g,j}),$$

where $\phi(\cdot)$ denotes the probability density function of the normal distribution, and $\pi_g$ denotes the cluster proportion with $\pi_g > 0$ and $\sum_{g=1}^{G} \pi_g = 1$. In order to reduce the number of parameters, the variance is commonly assumed to be equal across measurements over time, i.e., $\sigma_{g,j} = \sigma_g$ (Peugh and Fan 2013).

The model is usually estimated through maximum likelihood estimation using the EM algorithm [McLachlan and Peel 2000]. Here, the data is sought to be explained in terms of the unknown observation model $\theta = (\pi_1, \ldots, \pi_{G-1}, \mu_1, \ldots, \mu_G, \sigma_1, \ldots, \sigma_G)$, and the unknown cluster membership matrix $z$, where $z_{i,g}$ is the probability of patient $i$ belonging to cluster $g$ conditional on $\theta$. The algorithm takes an iterative approach, involving an alternating estimation of $z$ and $\theta$, conditional on the other. In the E-step, the cluster assignment probabilities are estimated from the given parameters $\theta$ and $y$. In the M-step, the parameters $\theta$ are estimated given $z$. The iterations are repeated until the improvement in log-likelihood is sufficiently low. The estimation must be initialized with some values for $\theta$. Here, random values can be used, or preferably, the output of a less complex cluster model.

While LPA is more computationally expensive than KML, it allows for greater flexibility in fitting the data due to the ability to account for cluster-specific variances, and even time-specific variances (Magidson and Vermunt 2002).

LPA is available in many software packages, including in MPLUS [Muthén and Muthén 2012], LATENT GOLD [Vermunt and Magidson 2016], and the R package mclust [Scrucca et al. 2016].

Case study

We estimate the LPA models using the mclust package (version 5.4.5) in R [Scrucca et al. 2016] with cluster-specific diagonal covariance matrices. Ten repeated runs were found to be sufficient in identifying the best

[LCA], although in some fields this name specifically refers to a model involving categorical rather than continuous observations.

Similar to KML, LPA can be applied for the identification of longitudinal patterns without any assumption on the shape by modeling the observations as locally independent variables at the subject level (Feldman et al. 2009; Twisk and Hoekstra 2012). This type of application of LPA is sometimes specifically referred to as a longitudinal latent-profile analysis (LLPA). The expected value of an observation at time $t_j$ depends on the cluster membership. Given the cluster membership $g$, we have

$$y_{i,j} = \mu_{g,j} + \varepsilon_{g,i,j}, \quad i \in I_g,$$

where $\mu_{g,j}$ represents the cluster-specific mean at time $t_j$, $\varepsilon_{g,i,j} \sim N(0, \sigma_{g,j})$, and $\sigma_{g,j}$ is the cluster-specific standard deviation at time $t_j$. The probability density of the observations of subject $i$ is computed by marginalizing over all $G$ clusters, giving

$$f(y_i) = \sum_{g=1}^{G} \pi_g \prod_{j=1}^{n} \phi(y_{i,j}|\mu_{g,j},\sigma_{g,j}),$$

where $\phi(\cdot)$ denotes the probability density function of the normal distribution, and $\pi_g$ denote the cluster proportion with $\pi_g > 0$ and $\sum_{g=1}^{G} \pi_g = 1$. In order to reduce the number of parameters, the variance is commonly assumed to be equal across measurements over time, i.e., $\sigma_{g,j} = \sigma_g$ (Peugh and Fan 2013).

The model is usually estimated through maximum likelihood estimation using the EM algorithm [McLachlan and Peel 2000]. Here, the data is sought to be explained in terms of the unknown observation model $\theta = (\pi_1, \ldots, \pi_{G-1}, \mu_1, \ldots, \mu_G, \sigma_1, \ldots, \sigma_G)$, and the unknown cluster membership matrix $z$, where $z_{i,g}$ is the probability of patient $i$ belonging to cluster $g$ conditional on $\theta$. The algorithm takes an iterative approach, involving an alternating estimation of $z$ and $\theta$, conditional on the other. In the E-step, the cluster assignment probabilities are estimated from the given parameters $\theta$ and $y$. In the M-step, the parameters $\theta$ are estimated given $z$. The iterations are repeated until the improvement in log-likelihood is sufficiently low. The estimation must be initialized with some values for $\theta$. Here, random values can be used, or preferably, the output of a less complex cluster model.

While LPA is more computationally expensive than KML, it allows for greater flexibility in fitting the data due to the ability to account for cluster-specific variances, and even time-specific variances (Magidson and Vermunt 2002). LPA is available in many software packages, including in MPLUS [Muthén and Muthén 2012], LATENT GOLD [Vermunt and Magidson 2016], and the R package mclust [Scrucca et al. 2016].

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[https://www.statmodel.com/](https://www.statmodel.com/)
[http://www.statisticalinnovations.com/latent-gold-5-1/](http://www.statisticalinnovations.com/latent-gold-5-1/)
[https://CRAN.R-project.org/package=mclust](https://CRAN.R-project.org/package=mclust)
solution per number of clusters (determined by the BIC). The BIC per number of clusters is visualized in Figure 4.3a showing a considerable improvement up to four clusters. While the eight-cluster solution compares favorably, it comprises a small cluster of only ten patients, which would limit the power of a post-hoc analysis. Based on the BIC, one would ordinarily select the four-cluster solution. However, upon inspection of the successive solutions, the five-cluster solution distinguishes the early drop-outs from the non-users, which would be of added value in an exploratory analysis for patterns of adherence. Moreover, the solutions involving more than five clusters comprise spurious empty clusters, or clusters which are too small to be of practical use.

The cluster trajectories of the preferred five-cluster solution are shown in Figure 4.3b showing an emphasis on representing trajectories with lower usage due to the modeling of cluster-specific and time-varying variances, because these decline over time for the early drop-out and non-user groups.

4.2 Distance-based clustering

In a distance-based cluster approach, trajectories are clustered based on their pairwise similarity, as measured by a user-specified dissimilarity metric, i.e., distance measure. This approach comprises cluster methods for which the user can specify an arbitrary distance metric. This enables fast experimentation with different measures of similarity suitable to the application at hand. The distance between two trajectories $y_1$ and $y_2$ is defined by a distance measure $d(y_1, y_2)$. A commonly used measure is the Euclidean distance

$$d(y_1, y_2) = \sqrt{\sum_{j} (y_{1,j} - y_{2,j})^2}, \quad (4.4)$$

which essentially yields a raw-data based approach. However, the advantage of a distance-based approach is that domain knowledge can be taken into account in specifying the distance measure to capture the relevant properties of the trajectories. The Euclidean distance has been shown to be applicable to longitudinal data (Genolini and Falissard, 2010), resulting in cluster trajectories with arbitrary shapes, but conversely the measure is sensitive to temporal offsets between subjects, and noise. Many alternative distance measures have been suggested, including measures that account for temporal offsets (e.g., dynamic time warping), or reduce the complexity of the trajectory (e.g., piecewise-constant approximation) (Aghabozorgi et al., 2015; Wang et al., 2013). Another advantage is that the pairwise distances between trajectories yields a hierarchy which provides additional information on the heterogeneity.

4.2.1 Agglomerative hierarchical clustering

Hierarchical clustering is a type of cluster method that identifies a hierarchy in a set of objects based on a distance measure. The resulting hierarchy provides an ordering of the objects based on their similarities, which can be a useful tool in visualizing a spectrum of trajectories with different shapes. The number of clusters can be estimated from the distance between hierarchical clusters (Islam et al., 2013).

Agglomerative hierarchical clustering (AHC) uses a bottom-up approach to identify the hierarchical structure of the objects. Each of the objects start out as separate clusters. The AHC approach is commonly used in combination with a post-hoc analysis to identify factors that may differ between clusters. Babbin et al. (2015) investigated the daily
Figure 4.4: Example of a dendrogram computed from longitudinal data comprising three groups, each having three trajectories. The cluster trajectories are described by an intercept and slope, with coefficients $\beta_A = (3, -0.3)$, $\beta_B = (2, 0)$, and $\beta_C = (0, 0.2)$, respectively.

Time on CPAP therapy of patients with obstructive sleep apnea to identify clusters of patients with similar adherence trends. Other examples include the investigation of Hoepner et al. (2008) of daily smoking patterns after patients went through a reduction program, and patterns of alcohol use (Harrington et al., 2014).

In AHC, the hierarchy is identified using a greedy approach, where at each step the two most similar clusters are combined into a new cluster. This is repeated until a single cluster remains containing all objects. The resulting hierarchy can be visualized in a dendrogram. To illustrate, Figure 4.4 depicts the hierarchy of nine trajectories generated from three different linear models. Combining objects and clusters involves two distance measures. Firstly, a distance measure $d(y_i, y_j)$ is needed for determining the similarity of the trajectory of individual $i$ and individual $j$, with $i \neq j$. Secondly, a distance measure between clusters $I_r$ and $I_s$ is needed, where a cluster $I_g$ is the subset of individuals (out of all individuals $I$) that belong to cluster $g$. The distance $d(I_r, I_s)$ is referred to as the linkage criterion, with $r \neq s$.

An intuitive approach to measuring the distance between clusters is to measure the average pairwise distances between the clusters. This is referred to as the unweighted average linkage (UPGMA), and is computed by

$$d(I_r, I_s) = \frac{1}{|I_r| \cdot |I_s|} \sum_{i \in I_r} \sum_{j \in I_s} d(y_i, y_j).$$

Alternative linkage criteria which are commonly used include the minimum linkage, centroid linkage, and Ward’s minimum variance method.

AHC provides a good trade-off between finding a reasonable hierarchy quickly, and identifying the optimal hierarchy (i.e., the hierarchy that minimizes the overall distance). However, the computation time quickly grows with the number of trajectories, due to the pairwise distances that must be computed between all subjects.

Case study As all measurements across patients are aligned in the case study, we can apply the Euclidean distance to compute the pairwise similarity between patient trajectories. We then apply the agglomerative hierarchical cluster algorithm that is available in R using the average linkage. For each number of clusters, the trajectory assignments are obtained based on the identified hierarchy visualized in Figure 4.6a. The solutions are compared using the ASW. As can be seen in Figure 4.6b, the ASW is considerably lower for solutions with more than three clusters. A cluster solution with an ASW above 0.5 is generally considered to have some consistent structure. In an exploratory setting it may be worthwhile to forfeit this rule of thumb in favor of identifying additional meaningful temporal patterns, given that the clusters are of sufficient size. In this case however, the solutions with a larger number of clusters include clusters of outliers comprising only a single trajectory (as can be seen from the hierarchy), so the three-cluster solution is preferred.

The solution comprising three clusters is shown in Figure 4.6c. Here, the cluster trajectories are computed by averaging across all trajectories that are assigned to it. The solution provides a balanced representation of the seven groups, combined based on the respective mean level.
4.3 Feature-based clustering

In a feature-based clustering approach, individual trajectories are described in terms of a parametric model that captures the relevant characteristics. Here, each trajectory $y_i$ is reduced to a set of model parameters $b_i = (b_{i,1}, b_{i,2}, ..., b_{i,p})$ which can be regarded as the $p$ features of the trajectory. Clusters of trajectories with similar characteristics can then be identified by applying a cross-sectional cluster algorithm to the model parameters. The appeal of a feature-based clustering approach is that researchers can incorporate domain knowledge in defining the similarity between trajectories by using an appropriate model, or by computing several independent characteristics. The characteristics may better capture the differences between trajectories than a cross-sectional approach based on the shape alone, resulting in more well-separated clusters (Wang et al., 2006). The approach is also commonly referred to as a feature-based or model-based approach (Aghabozorgi et al., 2015).

The second step of clustering is easy to implement and available in most statistical software packages through the widespread availability of clustering algorithms such as $k$-means. There are several strengths to the approach; especially within the context of ILD. Firstly, the parametric representation of trajectories is naturally more robust to missing observations, as the computed characteristics tend to be based on multiple observations. Secondly, the approach can handle trajectories of varying lengths between individuals or measured at different intervals (Wang et al., 2006). Lastly, the method scales well with the amount of data, as the representation is of constant size independent of the number of observations. Moreover, the trajectory representations only need to be computed once, after which a cluster algorithm can be fitted to the feature data for varying settings as part of the model selection.

4.3.1 Individual time series representations

Trajectories can be represented in many ways. An intuitive approach to describing each trajectory is in terms of a linear model dependent on time (e.g., an intercept and slope), as seen in multilevel modeling, where the individual trajectory representations can be obtained from the estimated random effects, and are then clustered using a cluster algorithm (e.g., $k$-means (Twisk and Hoekstra, 2012)). While this is a useful approach when there are relatively few observations per trajectory, independently estimating the representation of each trajectory frees researchers of any assumptions on

---

The term “model-based clustering” appears to be used for both feature-based clustering of model parameters and mixture modeling.
the population heterogeneity, providing a better fit (Liu 2017). This approach is referred to as an individual time series (ITS) analysis (Bushway et al., 2009; Greenberg, 2016; Liu, 2017).

An example of the ITS approach to clustering is seen in a method named anchored \( k \)-medoids, created by Adepeju et al. (2019), where the trajectories are represented by time-dependent linear regression models. The trajectories are then clustered based on the coefficients using \( k \)-medoids. The \( k \)-medoids cluster algorithm is similar to \( k \)-means, but uses one of the observations (i.e., objects) as the cluster center instead of an average across observations. This is especially useful for ITS representations because the algorithm can handle arbitrary distance metrics, and does not require the computation of an average cluster representation, which may not be sensible for some model coefficients or distance metrics.

There are two advantages to the ITS approach. Firstly, the trajectory models can be estimated independently, allowing for a trivial parallelization of the estimation process. Secondly, the independent models do not need to account for any variability between trajectories, and are therefore easier to estimate than a multilevel approach. A disadvantage of modeling each trajectory independently is that there may be trajectories for which the model fit is poor, resulting in clusters primarily containing poorly fitted models of which the original trajectories may not be similar. A poor fit can be the result of a trajectory not meeting the model assumptions, or the number of data points being insufficient for the model. The possibility to combine multiple representations into a single model vector provides additional challenges similar to those seen in cross-sectional clustering involving high-dimensional data: The coefficients may need to be normalized to ensure that the distance function is not disproportionately affected by coefficients of a higher magnitude. On the other hand, a subset of coefficients may be deemed more important (Fulcher and Jones, 2014).

In its simplest form, trajectories can be represented by summary statistics such as the mean, standard deviation, skewness, range, degree of stationarity, periodicity, autocorrelation, or entropy (Fulcher et al., 2013; Aghabozorgi et al., 2015). Another practical approach is to categorize the response variable into a finite number of values (i.e., states). Kiwuwa-Muyingo et al. (2011) modeled the adherence behavior of patients undergoing medical treatment for HIV infection using a first-order Markov chain, modeling the transitional probabilities of the non-adherent and adherence states. They used AHC using Ward’s minimum variance method to cluster the transitional probability vectors. A limitation of many of the statistical measures proposed is that they are under the assumption that the statistical properties do not change over time. This can be resolved by correcting for longitudinal changes, by estimating the properties over multiple segments of the trajectory, or by fitting a linear model that represents the change over time.

In other cases, an abrupt change in the observations may be expected from domain knowledge. Change points are for example modeled in the work of Axén et al. (2011), who investigated patients diagnosed with non-specific low back pain. In this work, the trajectories were modeled using two linear models which describe the early and late trajectory, respectively, fitted using spline regression. The linear model coefficients, as well as the estimated intersection point of the two lines, were used as inputs for the second step clustering.

Wang et al. (2006) propose a set of nine statistical features for describing a trajectory: Firstly, a trajectory can be decomposed into several components (Kendall et al., 1983): a trend \( T_t \) (the long-term average level), a seasonal effect \( S_t \), and a cyclic effect \( C_t \) (also referred to as periodicity or frequency). Assuming that the components are not proportional, a time series can be described using an additive model

\[
y_t = T_t + C_t + S_t + \varepsilon_t,
\]

where \( \varepsilon_t \) denotes the irregular component (i.e., the residual). Secondly, Wang et al. suggest to describe aspects of the measurement distribution in terms of the skewness and kurtosis. Thirdly, the temporal structure of the data is expressed in terms of the autocorrelation and a test for non-linearity, e.g., through a nonparametric kernel test or neural network test. Lastly, the trajectory complexity is assessed using self-similarity (a measure of long-term dependence) and other methods commonly used in describing chaotic systems (e.g., the Lyapunov exponent, which is a measure of divergence in response to small perturbations). Especially, the latter metrics require a sizable number of observations per trajectory to be estimated reliably, so these are only suitable for ILD.

The irregular component \( \varepsilon_t \) describes the local changes of a trajectory. A straightforward way to describe the component is through a white noise process of zero mean and variance \( \sigma^2 \), assuming independent and identically distributed observations. When the local changes are assumed to correlate with past values, an autoregressive (AR) model is typically used. This model regresses past values using a \( p \)-th order polynomial. Alternatively, the model error may depend on previous errors, which can be described using a moving average (MA) model of the past \( q \) error terms. Combining these two models, we obtain an ARMA \((p, q)\) model describing a stochastic process

\[
y_t = c + \sum_{i=1}^{p} \phi_i y_{t-i} + \sum_{j=1}^{q} \theta_j \varepsilon_{t-j} + \varepsilon_t,
\]

(4.6)
with $c$ describing the model intercept, and $\phi_{1,\ldots,p}$ and $\theta_{1,\ldots,q}$ describing the parameters of the AR and MA models, respectively. The model residuals are denoted by $\epsilon_i$, and are assumed independent and follow a normal distribution with zero mean and variance $\sigma^2$. ARMA can be applied to non-stationary data by first applying one or more differencing steps $y_t = y_t - y_{t-1}$ to the data, in which case the approach is referred to as ARIMA (where the I stands for integrated). ARIMA is mostly used in the economical and financial domain for predicting future values, but it is also of use for process modeling (e.g., adaptive control), and descriptive modeling (Jebb et al., 2015; Aloia et al., 2008). Kalpakis et al. (2001) have proposed a distance measure for comparing ARIMA models, which are then clustered using $k$-medoids. This approach could be regarded as a hybrid of the feature-based and distance-based approaches to longitudinal clustering. Other useful methods for describing stochastic processes are autoregressive conditional heteroskedasticity (ARCH), Gaussian processes, and state space models (Fulcher et al., 2013).

Case study  We model each patient independently on several aspects. Each trajectory is represented in terms of an intercept $\beta_{i,0}$, an orthogonal polynomial of degree two with coefficients $\beta_{i,1},\beta_{i,2}$, a residual error $\sigma_{e,i}$, and the log-number of attempted days $\log N_i$. This yields the patient representation $b_i = (b_{i,1} = \beta_{i,0}, b_{i,2} = \beta_{i,1}, b_{i,3} = \beta_{i,2}, b_{i,3} = \sigma_{e,i}, b_{i,4} = \log N_i)$. The patient representation vectors $\mathbf{b}_i$ are scaled to ensure zero mean and unit variance across the features. We compute a distance matrix using the Euclidean distance, and then apply $k$-medoids using the cluster package[4] (version 2.1.0) (Maechler et al., 2019) in order to obtain clusters which are represented by one of the computed representation vectors. Similar to the AHC analysis, we evaluate cluster solutions using the ASW.

The inclusion of irrelevant features can negatively affect the cluster separation. It is therefore important to select the relevant aspects. Moreover, the approach is sensitive to spurious estimates of the patient-specific coefficients, as only a limited number of observations are available. These aspects reduce the separation between clusters, resulting in a lower ASW. We investigated different subsets of the patient representation vector by assessing the highest observed ASW. This revealed that the inclusion of $b_{i,3} = \sigma_{e,i}$ negatively affected cluster separation, and should be excluded. This is despite the fact that the data was generated with some degree of group-specific variance. It was found that the residual error is often underestimated, likely resulting from overfitting of the polynomial trajectory of some of the patients.

The ASW per number of clusters for the final model $b_i = (b_{i,1} = \beta_{i,0}, b_{i,2} = \beta_{i,1}, b_{i,3} = \beta_{i,2}, b_{i,3} = \log N_i)$ is displayed in Figure 4.6a. The highest ASW of 0.49 is obtained for the seven-cluster solution. The cluster trajectories visualized in Figure 4.6b were obtained by averaging across the respective trajectories. The solution matches the ground truth, demonstrating the ability to recover the underlying clusters when the relevant longitudinal aspects are used.

4.4 Mixture modeling

Mixture models describe a distribution in terms of a set of underlying distributions, under the assumption that the distribution comprises different data-generating processes or random variables. Usually, the submodels assume the same parametric distribution, but with different coefficients. An example of a mixture distribution comprising normals

\[ \text{https://CRAN.R-project.org/package=flexmix} \]
was shown in Figure 3.2A on page 6. In a statistical analysis setting, mixture models comprise a set of regression models. Here too, the submodels tend to have an identical specification.

The basic idea behind a longitudinal mixture model is to fit a mixture distribution to the longitudinal observations \( y_i \). Thus the mixture model density \( f(y_i | \theta) \) with model parameters \( \theta = (\pi, \theta_1, \ldots, \theta_G) \) is defined by

\[
f(y_i | \theta) = \sum_{g=1}^{G} \pi_g f(y_i | \theta_g).
\]

Here, \( f(y_i | \theta_g) \) denotes the conditional density of \( y_i \) given that \( i \) belongs to cluster \( g \). The cluster membership of individual trajectories is unknown and therefore treated as being probabilistic. The probability of a random subject belonging to cluster \( g \) is denoted by \( \pi_g \), where \( 0 \leq \pi_g \leq 1 \) and \( \sum_g \pi_g = 1 \). This can also be interpreted as the cluster proportion. The posterior probability of a subject belonging to a given cluster is computed by normalizing the respective cluster density over all clusters by

\[
\Pr(y_i | i \in I_g, \theta) = \frac{\pi_g f(y_i | \theta_g)}{\sum_{g'=1}^{G} \pi_{g'} f(y_i | \theta_{g'}).}
\]

While the cluster assignments are probabilistic, meaning that a subject can belong to any cluster with a certain probability, the subject is usually assumed to belong to the cluster with the highest posterior probability.

The effect of baseline covariates on the cluster membership can be explored by including a multinomial logistic regression component for \( \pi_g \). For a vector of covariates \( x_i \) of subject \( i \), the cluster membership probability is computed by

\[
\pi_g(x_i) = \frac{\exp(\eta_g x_i)}{\sum_{g'=1}^{G} \exp(\eta_{g'} x_i)},
\]

where \( \eta_g \) denotes the multinomial regression coefficients for cluster \( g \). For the purpose of model identifiability, the last cluster is used as the reference, with \( \eta_G = 0 \). In the remainder of the overview, we assume a model without cluster membership covariates for brevity.

The estimation of these mixture models follow the same approach as the EM algorithm described in subsection 4.1.2 on LPA, as this is a type of mixture model as well. The important distinction is that the mixture models presented in this section allow for an arbitrary number of measurements per trajectory, and at arbitrary moments in time.

### 4.4.1 Group-based trajectory modeling

Similar to the concept of methods such as k-means or LPA, group-based trajectory modeling (GBTM) describes the population heterogeneity via a set of homogeneous clusters, where subjects are only represented by their respective cluster trajectory.\(^8\)\(^9\) In contrast, GBTM represents the trajectories using a parametric model. It can be regarded as a multilevel model with nonparametric random effects (i.e., a finite number of random effect values, representing the clusters), which is especially useful when random effects are non-normal or correlated.\(^7\) The model is easy to interpret due to its distinct cluster trajectories. The method is also referred to as latent-class growth analysis or modeling (LCGA, LCGM), semi-parametric group-based modeling (SGBM), TRAJ,\(^7\) and sometimes as nonparametric multilevel mixture modeling (NPMM).

The method originates from the field of criminology. Two decades ago, Nagin and Land\(^1\) (1993) suggested a model for describing developmental trajectories in individuals for whom the number of yearly crimes was measured in relation to age. They proposed a longitudinal Poisson mixture model for separating the trajectories, comprising count data, into distinct clusters. In a later paper, Nagin\(^1\) (1999) presented GBTM as a flexible method for identifying distinct trajectories in a set of longitudinal measurements. Furthermore, models were proposed that assume (censored) normal data or binary data for the observations. Its applications extend further than the domain it was originally created for. GBTM has been applied in the field of psychology, medicine,\(^1\) ecology, among others.

A GBTM describes the trajectories using a linear model. The design vector at time \( t_{i,j} \) is denoted by \( x_{i,j} \). The cluster trajectories are often modeled using polynomials. As an example, \( x_{i,j} = (1, t_{i,j}, t_{i,j}^2) \) describes a second-order polynomial time trajectory. The trajectories as modeled by a GBTM, given membership to a specific cluster \( g \),
are described by
\[ y_{i,j} = x_{i,j}\beta_g + \varepsilon_{g,i,j}, \quad i \in I_g, \] (4.10)
where \( \beta_g \) denotes the cluster-specific regression coefficients, and the residual error \( \varepsilon_{g,i,j} \) is assumed to be independently normally distributed with zero mean and variance \( \sigma_g^2 \). The marginal mean is computed by
\[ \mathbb{E}(y_{i,j}) = \sum_{g=1}^{G} \pi_g x_{i,j}\beta_g. \] (4.11)

The GBTM parameters and clusters are estimated by maximizing the likelihood of the model for a given number of clusters \( G \) using the EM algorithm. Missing observations tend to be assumed missing at random and are therefore ignored. The model can be adapted to fit a wide variety of response distributions. It has also been used to model data under a censored normal, zero-inflated Poisson, logistic, or beta distribution (Jones and Nagin, 2007; Elmer et al., 2018).

Jones and Nagin (2007) proposed the estimation of confidence intervals on cluster membership probabilities and trajectories using Taylor-series expansion. Nielsen et al. (2014) proposed an alternative to model estimation and selection using a cross-validation error methodology. Nagin et al. (2018) extended the GBTM to account for multiple outcome trajectories, in which the outcomes are assumed to be conditionally independent. This is found to be favorable to the alternative of clustering each outcome separately and then combining the results.

There are a couple of disadvantages to modeling trajectories through polynomials. Firstly, the possible shapes a polynomial may represent is limited, so the model may not be able to fit the longitudinal shape. Secondly, higher-order polynomials tend to overfit the data or produce spurious shapes. Researchers should therefore be careful in interpreting the shapes in detail. As a more reliable alternative, Francis et al. (2016) proposed smoothing the cluster trajectories using a cubic B-spline. They observed an improved model fit while allowing for more flexible cluster trajectories.

Overall, GBTM is applicable to ILD in many aspects. The model can handle missing data, observations measured at different times, and estimation is relatively fast due to the low number of parameters involved. In addition, the probabilistic nature of the model has been shown to make it suitable for real-time prediction, where cluster membership and the expected trajectory can be computed as new observations become available (Elmer et al., 2019).

Implementations of GBTM are available in SAS (Jones et al., 2001), STATA (Jones and Nagin, 2013), MPLUS (Muthén and Muthén, 2012) and OPENMX (Boker et al., 2011), and in R via the lcmm (Proust-Lima et al., 2017), crimCV, flexmix (Grün and Leisch, 2008), or mixtools (Benaglia et al., 2009) package, among others.

**Case study** Prior to the GBTM analysis, we investigate the appropriate trajectory representation by evaluating mixed models with different polynomial degrees in the fixed and random effects. We normalize the 26 measurement times by scaling the range from [1, 351] to [0, 1] for numeric stability. The mixed models and GBTMs are estimated with the R package lcmm (version 1.7.8), developed by Proust-Lima et al. (2017). The model fit and variance components are reported in Table 2. The residual standard error and BIC indicate an improved fit with a higher order polynomial. While the model with polynomial representation of degree 3 achieves the best fit, the improvement over the second degree model is relatively small. In consideration of the linear increase in the number of model parameters with an increasing number of clusters, we settle for a quadratic representation.

We estimate the GBTM solutions using a grid search with 20 random starts in order to identify a good starting position during model optimization. As depicted in Figure 4.7a, the model fit improves with an increasing number of clusters. Judging from the change in improvement from one solution to the next, a three- or four-cluster solution is preferred. Upon visual inspection of both solutions, we opt for the four cluster solution due to the addition of the cluster trajectory similar to the Variable users group in the ground truth.

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The plugin is available at [http://www.andrew.cmu.edu/user/bjones](http://www.andrew.cmu.edu/user/bjones)

[1] https://www.statmodel.com

[2] http://openmx.psyc.virginia.edu

[3] https://CRAN.R-project.org/package=lcmm

[4] https://CRAN.R-project.org/package=crimCV

[5] https://CRAN.R-project.org/package=flexmix

[6] https://CRAN.R-project.org/package=mixtools
Table 2: Single-cluster analysis using mixed modeling with a normalized time covariate. Here, $\sigma_0, \ldots, \sigma_3$ represent the square root of the diagonal of the covariance matrix $\Sigma$.

| Model degree | $\sigma_0$ | $\sigma_1$ | $\sigma_2$ | $\sigma_3$ | $\sigma_\varepsilon$ | BIC    |
|--------------|-----------|-----------|-----------|-----------|----------------|--------|
| 0            | 2.5       | -         | -         | -         | 0.79           | 33,433 |
| 1            | 2.2       | 1.4       | -         | -         | 0.63           | 29,205 |
| 2            | 2.1       | 4.4       | 3.2       | -         | 0.58           | 27,375 |
| 3            | 2.0       | 8.7       | 6.3       | 4.1       | 0.57           | 27,146 |

Figure 4.7: GBTM case study analysis.

(a) BIC per solution (lower is better).
(b) The identified cluster trajectories.

The four cluster trajectories are shown in Figure 4.7b Overall this solution adequately captures the heterogeneity of the data. Cluster A (32%) represents the non-users, early drop-outs, and occasional attempters. Cluster B (35%) comprises the slow improvers and good users. The remaining clusters match the ground truth.

4.4.2 Growth mixture modeling

Growth mixture modeling (GMM) extends GBTM with the inclusion of parametric random effects, enabling a better fit to the data under the assumption of within-cluster variability (Verbeke and Lesaffre, 1996; Muthén and Shedden, 1999; Muthén et al., 2002; Muthén, 2004). The method is also described as a longitudinal latent-class mixed model, a multilevel mixture model, or a finite mixture of mixed models. GMM has been applied across many domains in the past decade.

Although GMM is commonly applied and described in a SEM framework, we present it in a mixed-modeling approach in order to be consistent with the notation of the previous sections. The longitudinal observations, conditional on belonging to cluster $g$, can be described by the linear mixed model specified in Equation 3.1 on page 5 with

\[ y_{i,j} = x_{i,j} \beta_g + z_{i,j} u_{g,i} + \varepsilon_{g,i,j}, \quad i \in I_g \]

\[ u_{g,i} \sim N(0, \Sigma_g) \]

\[ \varepsilon_{g,i,j} \sim N(0, \sigma^2_{\varepsilon,g}). \]  

(4.12)

where the symbols have the same meaning as defined for the mixed model, but are cluster-specific. The marginal mean of a GMM is thus given by

\[ \mathbb{E}(y_{i,j}|u_{g,i}) = \sum_{g=1}^{G} \pi_g \left[ x_{i,j} \beta_g + z_{i,j} u_{g,i} \right]. \]  

(4.13)

The model parameters are commonly estimated using Maximum Likelihood Estimation (MLE) via the expectation-maximization (EM) algorithm. Due to the large degrees of freedom, the iterative EM procedure is unlikely to find the optimal solution, and instead tends to converge towards suboptimal solutions. A better solution can be found by fitting the model many times from random starting points and selecting the best fit from these candidates. Alternatively, the solution of simpler models is used as a starting point, e.g., using a GBTM (Jung and Wickrama, 2008).
Although GMM is suitable for ILD much like GBTM, it is considerably slower to compute due to the number of model parameters growing drastically with the number of clusters. Consider that each cluster has a new set of parameters $\beta_g, \Sigma_g$, and $\sigma^2_{g,i}$, in addition to the cluster-specific random variables $u_{g,i}$ (Twisk and Hoekstra, 2012). The model complexity is typically reduced to speed-up estimation by assuming that certain parameters are identical across the different clusters (e.g. the residuals and variances). These challenges also inspired a different approach to performing a covariate analysis. While these could be included into the GMM, for larger datasets it is more practical to estimate an unconditional GMM, followed by a multinomial logistic regression of the covariates based on the subject cluster membership, referred to as a three-step approach (Asparouhov and Muthén, 2014). We address the three-step approach in a more general context in Section 5.

Bayesian estimation In a Bayesian approach, the model parameters $\theta$ of the GMM are treated as a random variable, whereas in MLE a point estimate is obtained (Gelman et al., 2013). The posterior distribution of the model parameters given the data can be computed using Bayes’ rule

$$Pr(\theta|Y) = \frac{Pr(Y|\theta)Pr(\theta)}{Pr(Y)},$$

(4.14)

where $Y$ denotes the dataset, $Pr(Y|\theta)$ denotes the likelihood of observing the data under the given model, $Pr(\theta)$ denotes the prior information about the model parameters, and $Pr(Y)$ denotes the evidence for the model. As $Pr(Y)$ is constant over $\theta$, it suffices to consider $Pr(\theta|Y) \propto Pr(Y|\theta) \cdot Pr(\theta)$ for statistical inference. Bayesian inference is most beneficial when informative priors can be provided, as the ability to incorporate domain knowledge into the parameter estimation through priors improves model estimation under low sample sizes (Gelman et al., 2013). However, specifying informative priors could be challenging in an exploratory cluster analysis setting, especially when a large number of clusters is sought out.

Compared to MLE, Bayesian inference allows for the estimation of more complex models involving a large number of parameters, for which numerical integration is infeasible (Ansari et al., 2000). In a comparison between MLE and Bayesian estimation, Depaoli (2013) found that the Bayesian approach resulted in an improved recovery of the model parameters. Serang et al. (2015) demonstrated the improved parameter recovery and smaller standard errors for estimating nonlinear trajectories, applied to reading development trajectories of children, although they noted an increase in convergence problems.

Due to the identical definition of the clusters in the mixture, the cluster ordering (i.e., labels) can change freely during sampling, referred to as the label switching problem. This presents a problem when attempting to interpret the cluster-specific posterior distribution samples. A possible solution to label switching is to add constraints to the model to ensure identifiability, such as enforcing an ordering on the cluster intercepts $\beta_{1,0} < \beta_{2,0} < ... < \beta_{G,0}$ (Sperrin et al., 2010).

Advanced applications Growth mixture modeling is a powerful and flexible statistical approach for exploratory analyses, which is likely why the method has been applied extensively by researchers throughout the past two decades. Moreover, the model is applicable to ILD for the same reasons as GBTM. An example of an ILD application is seen in the work of Shiyko et al. (2012), who proposed an approach to applying a Poisson-GMM to ILD to investigate patient’s daily number of smoked cigarettes. Many researchers have adapted GMM to meet their analysis needs. We highlight some of the proposed extensions here.

Type of response The method can be applied to different types of data such as binary, categorical, ordinal, count, and zero-inflated data, requiring different distributions for the response. Muthén and Asparouhov (2009), Proust-Lima et al. (2009) demonstrated a joint application of GMM in modeling multiple longitudinal outcomes with time-to-event data. While the response distribution can be determined from the data, the distribution of the random effects is more difficult to establish, as wrongly modeling the within-cluster heterogeneity simply results in additional clusters (Bauer, 2007). The assumption of normally distributed subgroups has been reconsidered in recent years. Alternative distributions such as a skewed-normal or skewed-t have been proposed in order to account for the skewness and thickness of the tails of the random effects distribution, resulting in a GMM which is more robust to non-normal groups and group outliers (Lu and Huang, 2014; Muthén and Asparouhov, 2015; Wei et al., 2017). A disadvantage of support for thicker tails is that it results in an even larger overlap between clusters than is already the case for a mixture of normals.

Trajectory representations Many researchers have explored different temporal shapes and structures. Grimm et al. (2010) investigated nonlinear trajectories in the reading development of children using specific functions. Nonlinear trajectories have also been estimated using regularized polynomials (Shedden and Zucker, 2008), fractional polynomials (Ryoo et al., 2017), and splines (Marcoulides and Khojasteh, 2018, Ding, 2019). Researchers have also accounted
for sudden changes over time using piecewise trajectory representations, referred to as a piecewise GMM (PGMM) (Li et al., 2001). PGMMs have also been proposed to handle multiple change points, change points determined by the model (Liu et al., 2018; Ning and Luo, 2018), and subject-specific change points (Lock et al., 2018). The intervals between change points can also be regarded as a possible state change. In a multiphase or sequential-process GMM (Kim and Kim, 2012; Reinecke et al., 2015), the latent class membership is estimated per interval. State change patterns can then be assessed using latent transition models (Collins and Lanza, 2010).

**Missing data** In most analyses, missing data is assumed to be missing at random. However, it is not uncommon for the missing data mechanism to affect the longitudinal data process, resulting in biased estimates if unaccounted for (Little, 1995). This type of missingness is referred to as non-ignorable. [Li et al., 2011] applied a Bayesian approach to modeling a GMM where the missing data mechanism was dependent on the cluster and observed covariates. A common source of non-ignorable missing data is the premature and permanent drop-out from observation. A detailed overview of adaptations to model these mechanisms is provided by [Enders, 2011] and [Muthén et al., 2011]. More recent approaches to missing data include a shared-parameter model (Gottfredson et al., 2014), [Cetin-Berber and Leite, 2018].

**Software** GMM is available through several modeling programs, e.g. **MPLUS** (Muthén and Muthén, 2012), **LATENT GOLD** (Vermunt and Magidson, 2016), and the R packages **OpenMx** (Boker et al., 2011), **lmem** (Proust-Lima et al., 2017), **mixAK** (Komárek and Komárková, 2014), **flexmix** (Grün and Leisch, 2008), and **mixtools** (Benaglia et al., 2009). GMM can be estimated using a Bayesian approach in several software packages, including OPENBUGS (Lunn et al., 2009), JAGS (Depaoli et al., 2016), and **STAN** (Carpenter et al., 2017), all of which have interfaces to R. In R, specific Bayesian models are implemented, for example, in **mixAK** (Komárek and Komárková, 2014), and **brms** (Bürkner, 2017).

**Case study** The GMM analysis follows the same steps as the GBTM analysis, and the same software is used to estimate the model. We therefore refer to Table 2 for the exploration of the trajectory shape using a single-cluster mixed model. We employ a quadratic GMM with cluster-specific random patient intercepts, and cluster-independent structured covariance matrices. We found that a grid search with 20 random starts was sufficient for consistently arriving at the best solution. The resulting model BICs are shown in Figure 4.8a, indicating that the best model fit is obtained at the seven-cluster solution. The cluster trajectories thereof are shown in Figure 4.8b, showing a close match with the ground truth insofar the cluster trajectories can be represented using second-order polynomials.

1. [https://CRAN.R-project.org/package=mixAK](https://CRAN.R-project.org/package=mixAK)
2. [http://openbugs.net](http://openbugs.net)
3. [http://mcmc-jags.sourceforge.net](http://mcmc-jags.sourceforge.net)
4. [http://mc-stan.org](http://mc-stan.org)
5. [https://CRAN.R-project.org/package=brms](https://CRAN.R-project.org/package=brms)
4.4.3 Time-varying effect mixture modeling

In regression analysis, the associations between the covariates and outcome are typically modeled as being constant over time. In practice however, associations may change over time, resulting in a lack of understanding of the true temporal association if this change is not accounted for. In a varying-coefficient model (VCM), the dynamic association between covariates is modeled using smooth functions [Hastie and Tibshirani, 1993]. VCM has been applied in longitudinal studies, in which covariates are modeled with one or more time-varying coefficient functions denoted by \( \beta(\cdot) \). In this form, the model is referred to as a time-varying coefficient model (TVCM), time-varying effect model (TVEM), or dynamic generalized linear model. The individual trajectory is described by

\[
y_{i,j} = \sum_{q=0}^{Q} x_{q,i,j} \beta_q(t_{i,j}) + \varepsilon_{i,j},
\]

where \( x_{q,i,j} = 1 \), \( \beta_0 \) denotes the time-varying intercept over time, and \( \beta_q \) denotes the temporal association between the covariate \( x_{q,i,j} \) and time. Furthermore, the residuals \( \varepsilon_{i,j} \) are assumed to be normally and independently distributed with zero mean and variance \( \sigma^2 \). The coefficient functions are described through smooth continuous functions (i.e. the first-order derivative is continuous), and are able to capture nonlinear longitudinal relations between the covariates and time. Note that in the absence of covariates, the model comprises a single coefficient function that captures the longitudinal trajectory. TVEM is a promising approach for ILD, as the large volume of data enables the identification of more complex dynamic associations (Tan et al., 2012).

Over the years, several approaches have been suggested for the estimation of the smoothing functions. Spline regression is used to describe the function by a piecewise polynomial (typically of order 2 or 3) over a given series of intervals (Liang et al., 2003; Hoover et al., 1998). The interval boundaries, referred to as knots, need to be selected carefully based on the data. An alternative approach named spline smoothing does not require selection of intervals, but is much more computationally intensive (Hoover et al., 1998; Hastie and Tibshirani, 1993). A more recent approach involving P-splines takes the middle ground, using a penalty factor to prevent overfitting while ensuring a smooth fit (Song and Lu, 2010; Tian et al., 2012). Splines are described through a linear model, and consequently, a TVEM describes a linear model of which the model parameters can be estimated using ordinary least-squares (OLS).

Mixtures of VCMs or TVEMs have been proposed for handling heterogeneity, where the different groups are represented through clusters-specific coefficient functions (Lu and Song, 2012; Dziak et al., 2015; Huang et al., 2018; Ye et al., 2019). Lu and Song (2012) used an approach similar to GMM, where a random intercept and slope are included in order to model within-cluster heterogeneity. However, the use of linear random effects in combination with non-linear cluster trajectories may be limiting, as the nonlinear changes remain homogeneous within cluster. Dziak et al. (2015) proposed an alternative model which they named MixTVEM, given by

\[
y_{i,j} = \sum_{q=0}^{Q} x_{q,i,j} \beta_{g,q}(t_{i,j}) + \varepsilon_{g,i,j}, \quad i \in I_g,
\]

The measured outcome \( y_{i,j} \) is assumed to be normally distributed when conditioned on the cluster variable. The model is similar to GBTM, but accounts for cluster heterogeneity using an AR-1 model with measurement error. Huang et al. (2018) proposed a mixture of VCMs with flexible mixing proportions and dispersion, enabling the modeling of these aspects over a covariate, e.g., time.

The parameters of the model can be estimated using the EM algorithm (Dziak et al., 2015) or a Bayesian approach (Lu and Song, 2012). The optimization procedure for MixTVEM is initialized by assigning random posterior probabilities to the classes. Dziak et al. (2015) recommend to run the procedure for at least 50 random starts as the optimization may converge on different solutions, or fail to converge altogether. Due to the needed repeated runs, the tuning of the penalty factor, and the relative complexity of the model, the method is highly computationally intensive to estimate, as noted by Yang et al. (2019).

Case study The MixTVEM models are estimated using the R code provided by Dziak et al. (2015) [version 1.2]. P-splines of a third degree polynomial order are used with six interior knots, spaced equally over time. The model is fitted from 20 random starts in order to obtain good starting conditions, although on a few occasions, a rerun was needed due to convergence problems. Moreover, the single-cluster estimation consistently failed due to observations with zero variability from the non-users, which we resolved by adding a negligible amount of perturbation to the measurements with zero hours. The BICs of the selected solutions are depicted in Figure 4.9a, showing different
levels of model fit to the data across the number of clusters. We select the solution involving five clusters as it best captures the different patterns of change over time.

The five cluster trajectories are visualized in Figure 4.9b. Cluster B (35%) comprises the good users and the slow improvers. Cluster A (17%) and D (16%) correctly identify the variable users and slow decliners, respectively, but the cluster trajectories do not match the true shapes that would be expected from the correct assignment. Cluster C (17%) and E (16%) comprise the non-users, early drop-outs, and occasional attempters. However, the presence of the occasional attempters appears to have affected both cluster trajectories, such that neither matches the ground truth.

4.5 Number of clusters

The determination of the number of clusters is a prominent topic in the field of cluster analysis, as the number of clusters is usually part of the model definition and can greatly affect the resulting solution. However, there is no consensus on how to identify the true number of clusters. This is largely attributable to the different types of cluster analyses; each having different purposes, expectations, and applications (Von Luxburg et al., 2012). The identification of the number of clusters is part of a broader search for the appropriate cluster model, which we shall refer to as model selection. Interestingly, considerable attention is given in the literature to the identification of the number of clusters, over the more general topic of ensuring the overall best model specification, referred to as model selection. This is arguably justifiable in a longitudinal context under the assumption that the trajectory models are sufficiently flexible. We summarize the many approaches and metrics used for identifying the number of clusters.

Model metrics Although no tests exist for the number of clusters or the presence of clusters, approximate likelihood ratio tests (LRT) enable researchers to test whether the model with \( G + 1 \) clusters describes the data statistically significantly better than the identically specified model with \( G \) clusters. Commonly used variants are the Vuong-Lo-Mendell-Rubin (VLMR) LRT (Lo et al., 2001), the adjusted Lo-Mendell-Rubin (aLMR) LRT (Lo et al., 2001), and the bootstrap LRT (BLRT) (McLachlan and Peel, 2000). These approaches are useful on smaller datasets for preventing overfitting. However, the tests tend to result in the identification of too many clusters (i.e., overextraction) on large datasets, where smaller changes between models are statistically but not practically significant (Grimm et al., 2017). A similar concept is seen in difference-like criteria, which measure the relative improvement between successive cluster solutions (Vendramin et al., 2010). Along similar lines, Grimm et al. (2017) have applied k-fold cross-validation for model selection based on how well the model represents previously unseen data (in terms of the likelihood).

The most commonly applied approach involves the estimation of a cluster model for a range of number of clusters. A metric is then used to identify which of the models provides the best fit. Information criteria strike a balance between model fit (the likelihood) and model complexity (the number of model parameters). These model metrics can also be used to compare across model specifications, selecting the model that minimizes the metric.

Metrics for identifying the number of clusters have been studied extensively for GMM and GBTM (Nylund et al., 2007; Feldman et al., 2009; Klijn et al., 2017; Totighi and Enders, 2008). Overall, the findings are mixed, likely due to the different settings (e.g., sample size, cluster separation, noise) under which these evaluations have been performed (Grimm et al., 2017). Overall, the BIC is commonly used for the class enumeration in GBTM and GMM. The BLRT has been demonstrated to be a reliable alternative (Nylund et al., 2007; McNeish and Harring, 2017).
Malsiner-Walli et al. (2016) proposed a metric based on the occurrence of empty clusters in a mixture model with many clusters, where the true number of clusters is determined based on the number of non-empty clusters. This approach has the advantage of only requiring a single model to be fitted. Nasserinejad et al. (2017) experimented with this metric for different thresholds for the number of trajectories that constitute a non-empty cluster. Another metric of interest is the entropy of the posterior probability matrix, as a measure of cluster separation (i.e., probabilities should be close to either zero or one).

Bayesian metrics Different criteria have been proposed for models estimated through Bayesian inference. They make use of the posterior distribution of the model coefficients. One of the more commonly used criteria is the deviance information criterion (DIC), introduced by Spiegelhalter et al. (2002). Its use has not been without criticism. For example, there exist multiple definitions of the DIC, each with a different interpretation (Celeux et al., 2006). Spiegelhalter et al. (2014) have summarized and addressed the concerns. Recent alternative criteria are the widely applicable AIC (WAIC), and Pareto-smoothed importance sampling using leave-one-out cross validation (PSIS-LOO) (Vehtari et al. 2017).

Cluster criteria Criteria for cluster algorithms tend to assess the solution based on the underlying data, and assume a hard partitioning of the data. The advantage of such an approach is that it is independent from the method that was used, making it possible to assess the model fit across cluster methods. The criteria tend to contrast the within-cluster variability against the between-cluster variability in order to assess the separation between clusters, as seen, e.g., the Calinski-Harabasz (CH) and Davies-Bouldin criteria. As an example, Todo and Usami (2016) found the CH criterion to perform better for model selection than BIC in a latent profile analysis. Another commonly used criterion is the ASW. A comprehensive overview of commonly used cluster criteria is provided by Vendramin et al. (2010).

Upper bound The upper bound on the largest number of clusters to be evaluated is based on multiple factors. Firstly, prior knowledge may give researchers reasons to expect the true number of clusters to be below a certain number. Computational factors are also at play (Nasserinejad et al., 2017), as the model computation time scales non-linearly with an increasing number of clusters for complex models, making the evaluation of a larger number of clusters impractical. Along similar lines, the increasing model complexity with an increasing number of clusters tends to result in more frequent occurrences of convergence issues. The largest number of clusters that can be estimated is also limited by the sample size, considering that all submodels must comprise a sufficient number of trajectories in order to obtain reliable estimates (Sterba et al., 2012). Studies involving a small sample size are therefore naturally limited to identifying a lower number of clusters. Similarly, having a large number of clusters limits the power of a post-hoc cluster comparison.

Subjective assessment Researchers have argued against the optimization of a sole metric for the identification of the number of clusters, as it is rather mechanical in nature, and disregards the domain-dependent aspect of the analysis (Nagin et al., 2018). Moreover, the commonly used metrics tend to focus on discerning a sufficiently improved model fit, however, a better model may fit aspects of the heterogeneity which are not of interest for the purpose of the analysis (Van Den Bergh and Vermunt, 2019). This issue can occur in datasets with considerable overlap between clusters, where the introduction of additional clusters may consistently improve the model fit, albeit with diminishing returns. Due to the non-linear nature of these diminishing improvements, there tends to be a point or region where the marginal improvement drops. The identification of this turning point, representing the preferred number of clusters, creates room for subjectivity into the decision. This approach, often assessed visually, is commonly referred to as the "elbow method". It is used, for example, by Dziak et al. (2015) in their MixTVEM analysis, to assess the relative improvement in terms of the BIC.

Arguably, the choice of metric or metrics involves a domain-dependent decision. As the choice of the best metric may not be clear-cut, taking into consideration multiple metrics can provide a more reliable result (Ram and Grimm, 2009). However, because fit metrics capture different aspects of the model fit, it is inevitable that some of the metrics are in disagreement on the optimal number of clusters.

Hierarchical models There is a practical limit to the number of clusters that can be used to approximate the heterogeneity, for it becomes increasingly difficult to produce unique labels for each of the clusters (Sterba et al., 2012). Instead of identifying an independent set of clusters, one can search for a cluster tree hierarchy using a hierarchical cluster algorithm, where each cluster is further explained in terms of subclusters. In this way, an arbitrary level of granularity can be obtained up to the subject level. This approach can be estimated through a cross-sectional or feature-based approach using an agglomerative hierarchical cluster algorithm. In recent years, Van Den Bergh and Vermunt (2017) proposed a top-down parametric approach based on GBTM, named latent-class growth trees (LCGT). They identified the root of the hierarchy using a standard GBTM analysis and metric, but subsequent clusters are fitted.
using a two-cluster GBTM until no more significant improvement is obtained. Another advantage of the approach is that the tree accounts for classification error, as opposed to the hard partitioning used in traditional hierarchical cluster algorithms. Furthermore, covariates can be included for comparison or cluster membership prediction through a three-step estimation approach (Van Den Bergh and Vermunt, 2019).

**Non-parametric mixture models** A promising alternative to the post-hoc identification of the number of clusters, or model selection in general, is seen in the area of nonparametric modeling, where only a single model is estimated. Here, the model complexity is grown as needed to represent the data in an infinite parameter space. In such a model, the number of clusters \( G \) is part of the model parameters to be estimated (Richardson and Green, 1997). Green and Richardson (2001). This model can be realized using a Bayesian approach by placing a Dirichlet process (DP) (Ferguson, 1973) prior on the number of clusters \( G \). The DP mixture model (DPMM) describes the observations as a function of the model parameters \( \theta \) provided by the DP (Lo, 1984). It has been applied to clustering gene expression data (Sun et al., 2017). [Heinzl and Tutz (2013)] demonstrated that a DPMM could also be estimated with an EM algorithm instead of MCMC, although they did not compare between estimation algorithms. DPMMs can be estimated in R for example via the DPpackage23 by Jara et al. (2011) or the BClustLonG24 package by Sun et al. (2017).

**5 Guidelines for conducting a longitudinal cluster analysis**

Many decisions are involved in a longitudinal cluster analysis. The need for guidelines comes not only from obtaining reliable results, but also comes from ensuring proper reporting to enable reproducible research. Unfortunately, the exploratory and domain-dependent nature of clustering inevitably means that there is no single formal process or method that covers all applications and purposes (Nagin and Odgers, 2010). Instead, the analysis should be adapted to the research questions or intended application of the model. Guidelines can still play a role here, as there are common themes to any longitudinal cluster analysis.

We broadly outline the typical aspects and approaches involved in a longitudinal cluster analysis. We focus on the guidance given by researchers on the topic of mixture modeling, as these typically parametric models tend to involve many decisions (Nagin and Odgers, 2010). We summarize the steps as follows:

1. **Analyzing the model variables.** The type of longitudinal response (e.g., categorical, ordinal, continuous) and the distribution thereof (e.g., normal, Poisson, zero-inflated, truncated) should be understood. In addition, the distribution of the covariates should be investigated, as outliers may skew the results.

2. **Investigating the missing data mechanism.** This step is crucial for ILD, where the varying continuous measurement times may be underlying to patterns of missingness. An advantage of clustering is that for a missing data mechanism related to the longitudinal outcome, this is handled by the clusters. Data is therefore usually assumed to be missing at random (MAR). Missing not at random (MNAR) data has been handled by using pattern mixture models.

3. **Single-cluster modeling.** Prior to the cluster analysis, it is good practice to understand the performance of the single-cluster case (Ram and Grimm, 2009; Van de Schoot et al., 2017). If the single-cluster model achieves a good fit, there may be little added value from complicating the analysis by introducing additional clusters. Alternatively, the heterogeneity could be assessed by comparing the coefficients obtained from separate models for each trajectory if the sample size allows for it. The single-cluster model may also be of use for identifying the approximate trajectory shape.

4. **Providing a rationale for clustering.** Ideally, the analysis is justified by theory or domain knowledge (e.g., previous studies) that strongly hint at the existence of clusters. This step also pertains to the way the clusters are interpreted, i.e., whether to use direct or indirect clustering.

5. **Identifying the best model.** This step is by far the most intricate, both in terms of number of decisions and computation time. In view of exploring the data heterogeneity, it is preferable to start with a model that does not account for covariates other than time (Vermunt, 2010), referred to as the unconditional model. An example of method and model selection is found in the analysis by Feldman et al. (2009). The choice of method, model specification, estimation method, and the selected number of clusters all affect the model fit to the data. As such, arriving at the final model may involve several iterations of the following substeps:

   (a) **Choosing the cluster method.** The methods have different strengths and limitations in terms of, e.g., flexibility in modeling trajectory shapes, capability to model heterogeneity, sample size requirements, and computational scalability. It is worthwhile to weigh these aspects in deciding on the method to use.

   (b) **Choosing the estimation approach and method.** Cluster models can be challenging to estimate, as estimation algorithms may be unable to identify the optimal solution in the vast parameter space. It is

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23 https://CRAN.R-project.org/package=DPpackage
24 https://CRAN.R-project.org/package=BClustLonG
therefore recommended to perform repeated runs with different random starting values, and to select the model with the best fit from the candidate models (Jung & Wickrama, 2008; Sher et al., 2011; McNeish & Harring, 2017). Moreover, it is worthwhile to experiment with different estimation methods for improved convergence (e.g., by increasing the number of iterations) and computational efficiency. The estimation algorithm may fail to converge, or the identified solution is invalid due to various reasons (e.g., out-of-bound coefficients, or empty clusters).

(c) Specifying and selecting the most appropriate model. This typically manual process involves many decisions, including the specification of the trajectory shape (e.g., polynomial, or spline), the distribution of the response variable, any covariates, the shared parameters between clusters (e.g., the covariance matrix), and cluster heterogeneity. These decisions can be guided by domain knowledge or by metrics for assessing the improved fit to the data. In particular, the trajectory shapes can be explored using a cluster model with a nonparametric representation of the cluster trajectory (Todo & Usami, 2016). Alternatively, the task of model specification and selection can be considerably simplified by using regularized or nonparametric models.

(d) Identifying the number of clusters. There are many approaches to identify the number of clusters, as described in 4.3. Typically a forward selection approach is used where a cluster model is fit and evaluated for an increasing number of clusters (Van de Schoot et al., 2017). One or more metrics, possibly taking into account domain knowledge, are used to gauge the best number of clusters.

(e) Assessing the model adequacy. The model fit can be assessed from the residual observation errors of the model, which may reveal structural deviations (Wang et al., 2005; Feldman et al., 2009; Lennon et al., 2018). Adequacy may also be considered in terms of model parsimony, as similar clusters or clusters representing only a small proportion of the trajectories add little value to the overall model fit. The separation between clusters can be evaluated through the cluster membership probability matrix (Nagin, 2005), or by comparing the cluster trajectories and the variability within clusters (either visually or by the means or coefficients) (Feldman et al., 2009; Nagin and Odgers, 2010; Lennon et al., 2018). It is also worthwhile to assess the standard errors or confidence interval of the model coefficients for meaningful effects.

(f) Validating the model. Longitudinal cluster models can involve many parameters as the number of parameters scales linearly with the number of classes, and thus the models are sensitive to overfitting (i.e., may not generalize well) on small datasets. If a model is estimated on random subsets of the data (e.g., via bootstrapping) and yields the same solution, this is indicative that the estimation of the model is robust. Preferably, the model is evaluated on a holdout (i.e., validation) sample (Frankfurt et al., 2016), or using a k-fold cross-validation approach. Here, the data is split into k folds, where k − 1 folds are used for training, and the remaining fold is used for testing. It is a useful approach for model evaluation or selection under a more limited sample size (Grimm et al., 2017). Overall, we observe few examples in literature where this step is performed, nevertheless, it is advisable to assess the robustness of the selected model, as an overspecification or overextraction of the number of clusters may result in a model that does not generalize well.

6. Analyzing covariates. In many analyses, the association of the longitudinal patterns with other variables is of interest. Covariates may be included to explain the cluster membership or the variability within and between clusters. There are different ways to go about analyzing these effects. In a one-step approach, the covariates are included in the model specification in step 5c. The inclusion of covariates into the model results in a more complex model which may be difficult to estimate, leading to convergence issues or long estimation times. Moreover, the interpretation of the identified longitudinal patterns becomes more difficult, as the clusters are based on more than the longitudinal change over time. In a standard three-step approach, the longitudinal cluster model is first estimated without covariates to establish the underlying latent groups. In the second step, individual trajectories are assigned to a cluster. In the third step, the covariates are analyzed. The last step can be approached in several ways. A post-hoc analysis for comparing covariates between clusters is commonly done either by comparing the means of covariates between clusters using ANOVA, or by predicting cluster membership using multinomial logistic regression. However, it is important to correct for the uncertainty in cluster assignments when comparing covariates between clusters (Vermunt, 2010; Bakk et al., 2013). A more detailed overview of the different estimation approaches is given by Van de Schoot et al. (2017).

7. Interpreting the findings. The implication of the identification of clusters depends on the type of cluster application. A substantial overlap between clusters may still yield meaningful findings in an indirect application, yet discredit the existence of truly distinct clusters for a direct application of clustering. Similarly, a predictive application of the model with high accuracy depends on a large separation between clusters. Most importantly, researchers should consider whether the identified clusters or differences between clusters are statistically and practically meaningful.
With so many decisions involved in the analysis, reporting these decisions is of the utmost importance. Van de Schoot et al. (2017) developed a comprehensive 21-item checklist based on the consensus of 27 experts, referred to as the guidelines for reporting on latent trajectory studies (GRoLTS), with the aim of improving the transparency and replicability of the analysis. Complementary to the guidelines summarized above, the checklist recommends to report the software and version that was used to perform the analysis, and to make the analysis source code available. While we will not repeat the other items, we encourage the reader to read the GRoLTS in full.

Van de Schoot et al. (2017) conducted a preliminary analysis of the state of reporting in the literature by applying GRoLTS to a selection of studies. They selected 38 papers that used latent-class trajectory modeling for identifying patterns of post-traumatic stress symptoms after a traumatic event. On average, the papers only met nine of the requirements, with the most complete paper meeting fifteen requirements. We believe these findings help to quantify the broader problem across domains of a lack of sufficient reporting. Guidelines such as GRoLTS are therefore valuable and practical tools towards achieving greater transparency, with more interpretable and reproducible findings.

6 Discussion

The case study highlights the differences and similarities between the evaluated approaches to longitudinal clustering. The most apparent contrast is the different number of clusters of the best solutions (either determined by a cluster metric or manual assessment). The discrepancy is largely attributable to the different trajectory representations and within- and between-cluster assumptions of the methods. All methods converged on a solution for each of the requested number of clusters. Moreover, the solutions for four clusters or less were highly similar across methods.

The synthetic case study data comprised considerable between- and within-patient variability. Despite this, the relatively straightforward KML and LLPA approaches yielded useful solutions. While LLPA uses the same non-parametric representational approach as KML, the identified cluster trajectories were different. LLPA does account for variability at each day allowing it to distinguish trend on the basis. In the case study that resulted into detecting drop outs from attempters. Both methods are fast to compute and involve a minimal number of modeling decisions, and are therefore practical approaches for quickly obtaining a sense of the variability in trajectory shapes in a heterogeneous dataset. There are similarities to the solutions of KML and GBTM, where KML is preferably for non-linear trajectories (Genolini and Falissard 2010). However, the ability to incorporate domain knowledge into a GBTM analysis makes it suitable to assess heterogeneity even under small sample size (Feldman et al. 2009; Twisk and Hoekstra 2012).

The solutions found by GBTM and MixTVEM were similar. However, MixTVEM is more flexible yet conservative in the trend shapes due to its regularization, which is generally preferable. The differences observed between the GBTM and GMM solutions demonstrate the importance of the model specification. Because of the large variation in intercept between patients, GBTM needs more clusters to represent the many different patient trajectory intercepts, whereas GMM can accommodate larger variability in intercepts into a single cluster, leaving more clusters to model other temporal differences (e.g., slope). However, this advantage comes at the cost of a more complex model, resulting in significantly longer computation times, and possibly convergence problems, as evident from the considerably longer computation time of GMM over GBTM (Feldman et al. 2009; Twisk and Hoekstra 2012). In a comparison between KML and GMM, it was found that GMM is preferred (Twisk and Hoekstra 2012); this was the case even for a small sample size (Martin and von Oertzen 2015). Overall, the feature-based approach and GMM most closely approximated the true group trajectories from which the data was generated.

With the relatively recent attention for ILD, the number of studies evaluating the methods on this type of data is limited however. This is unfortunate as ILD presents new challenges with respect to the volume of data, missing data, model complexity, and higher computational demands. Many methods scale poorly with an increasing number of clusters, placing practical limitations on the model complexity and volume of the data. In case of large sample size or large number of observations, this provides a serious practical limit on the maximum number of clusters that can be estimated. An almost inevitable problem associated with ILD is the missingness of data. Patterns of missingness. We only briefly touched upon this topic.

Due to the broad scope of this tutorial, we cannot possibly cover all areas of research on methods for longitudinal clustering. Nevertheless, we do wish to mention some of these unaddressed areas. We restricted the scope to a single outcome, whereas for example, KML, GBTM and GMM have extensions that support multivariable longitudinal outcomes, also referred to as joint trajectories. Furthermore, with the aim of presenting the commonly used approaches to longitudinal clustering, we may have omitted several alternative approaches. For example, we only briefly touched upon the field of functional data analysis. This is a class of methods that attempt to represent the data in terms of smooth functions, a method to which TVEM is related. There has been an increasing interest in further modeling sources of variation in the data by modeling subject-specific variability in addition the mean level, referred to as joint mean-variance modeling. As seen in the LLPA case study demonstration, this can have an impact on the identified
clusters. In other applications, trajectories may be expected to change cluster membership over time. Here, the clusters represent different unobserved states in which the subject resides over time. Here, a latent transition analysis can be used to model the transitions between clusters (Collins and Lanza[2010]).

7 Summary

The area of longitudinal clustering has gained much traction over the past two decades. We have attempted to present a comprehensive guide on how longitudinal cluster analyses can be conducted, with an emphasis on the different methods which are available for this purpose. Clustering is a powerful tool for exploratory purposes, but such analyses should be performed thoughtfully. We encourage researchers to experiment with different methods and model specifications in order to identify the most appropriate model for the data, and to report the steps and decisions that were part of the analysis in order to ensure interpretable results.

Acknowledgments

The authors thank the anonymous reviewers for their valuable feedback on this work.

Funding

This work was supported by Philips Research. Niek Den Teuling and Steffen Pauws are employees of Philips.

Supplementary materials

The dataset and R code used in each of the examples is available online at https://github.com/philips-labs/demo-clustering-longitudinal-data.

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Appendix

A Strengths and limitations per approach

Table 3: High-level comparison between approaches.

| Approach                  | Strengths                                                                 | Limitations                                                                 |
|---------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Cross-sectional clustering| • Fast to compute                                                          | • Observation moments must be aligned across trajectories                   |
|                           | • Algorithm implementations are widely available                          | • Requires complete data                                                     |
|                           | • Non-parametric cluster trajectory representation                        | • Sensitive to measurement noise                                             |
|                           |                                                                          | (Green, 2014)                                                               |
| Distance-based clustering | • Versatile; many available distance metrics, which could also be combined | • Only practical up to a limited number of trajectories, as the number of pairwise distances to compute grows quadratically with the number of trajectories |
|                           | • The distance matrix only needs to be computed once                      | • No robust cluster trajectory representation                               |
|                           | • Fast to evaluate for a large number of clusters                         | • Some distance metrics require aligned observations (e.g., Euclidean)       |
| Feature-based clustering  | • Versatile; longitudinal features can be arbitrarily combined into a trajectory model | • Generally requires ILD in order to ensure a reliable estimation of the features per trajectory |
|                           | • Fast to compute                                                          | • Feature estimates may be unreliable for trajectories that cannot be represented |
|                           | • Can incorporate domain knowledge                                         |                                                                             |
|                           | • Compact trajectory representation                                        |                                                                             |
| Mixture modeling          | • Parametric cluster trajectory representation                             | • Computationally intensive                                                 |
|                           | • Versatile; choice of latent-class model, trajectory model, latent-class membership model | • Number of parameters typically scales linearly with the number of clusters |
|                           | • Compact trajectory representation                                        | • The estimation procedure may not converge to a good solution; many random starts are needed |
|                           | • Relatively low sample size requirement, both in number of trajectories, and number of observations per trajectory |                                                                             |
|                           | • Domain knowledge can be incorporated                                     |                                                                             |
|                           | • Can assess the association of external variables or distant outcomes     |                                                                             |

(Martin and von Oertzen, 2015)
### B Strengths and limitations of mixture models

Table 4: High-level comparison between the described mixture models.

| Approach | Relative strengths | Relative limitations |
|----------|--------------------|----------------------|
| **GBTM** | • Fast to compute  | • Sensitive to outliers |
|          | • Few parameters   | • Poor fit, as individual trajectories are not modeled |
|          | • Easy to interpret| • Tends to overestimate the number of clusters (Twisk and Hoekstra, 2012) |
| **GMM**  | • Within-cluster heterogeneity | • Slow to compute (Twisk and Hoekstra, 2012) |
|          | • Fewer clusters needed to represent heterogeneity (Muthén and Asparouhov, 2015) | • Requires many random starts (McNeish and Harring, 2017) |
|          | • Random effects allow for cluster trajectories with a lower emphasis on, e.g., intercept. | • Convergence issues (Twisk and Hoekstra, 2012) |
|          | • Forecast individual trajectories | • Clusters can overlap considerably (Feldman et al., 2009) |
|          |                    | • Sensitive to the specified distribution of the random effects |
| **MixTVEM** | • Easy to interpret | • Slow to compute (Yang et al., 2019) |
|          | • Assess time-dependent association of external variables | • Requires tuning of penalization factor |
|          | • Penalized splines result in less spurious temporal patterns | • Convergence issues (Yang et al., 2019) |