Identifying longitudinal treatment effect trajectories using flexible outcome modeling and clustering

MSR45

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Background and Objectives

Background

- Treatment response is a complex phenomenon that is influenced by a variety of factors, including patient characteristics.
- Identification of characteristics that potentially modify treatment effects can allow for improved trial planning, recruitment, and subsequent interpretation of results.
- Current approaches rely on patient observations collected at a single timepoint which may not fully capture the dynamic nature of treatment response.
- Longitudinal responses, on the other hand, afford the ability to consider full response trajectories, giving a more comprehensive understanding of treatment efficacy and patient subgroups.

Objectives

- Describe a process to explore patient characteristics that may be associated with different longitudinal patterns of response to the treatment.
- Use a longitudinal approach to consider full trajectories of response.

Methods

Data simulation

- Treatment effects were simulated from three multivariate normal distributions with different implied trajectories of treatment response and associated patient characteristics.

Component Analysis

- Patient characteristics of interest were first used to derive new factors using factor analysis of mixed data. The baseline characteristics used to create the factors were age, time since diagnosis of disease, and sex.

Modeling

- A mixed model for repeated measures (MMRM[1]) with unstructured covariance was then fit to model the treatment effects of the continuous outcome across time with an interaction effect between the treatment, time, and the resulting first principal components (PC1 + PC2). The model also adjusted for baseline outcome. Flexible splines were applied to the factors and time to capture non-linear trends in the trajectory of the response. Given the MMRM, the marginal means were estimated and used to predict individual treatment effects over time, based on their specific characteristics, and the change from baseline at each time point was obtained.

Clustering

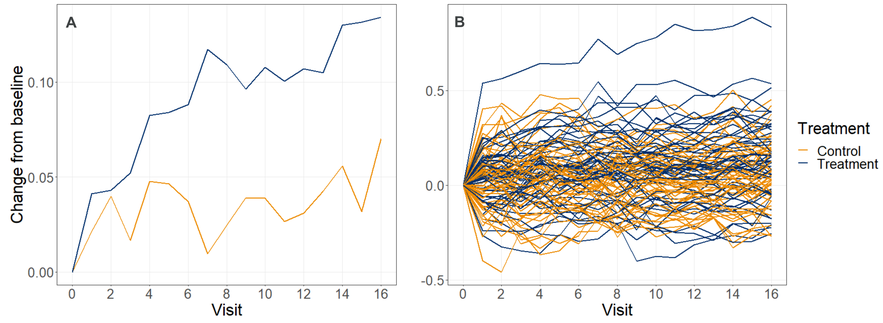
- The longitudinal changes in treatment effect were clustered using a longitudinal k-means method[2]. The number of clusters was determined by applying the elbow method to the log likelihood, BIC, and WMAE. Individual predicted responses and mean cluster responses were plotted and the patient characteristics from each cluster were summarized in order to identify key differences between clustered trajectories.

Results

Data Simulation

- 100 observations were generated.
- Mean treatment trajectories show the intervention group outperforming the group across all visits (Figure 1A).
- Individual trajectories show a wide range of treatment responses within each group (Figure 1B).

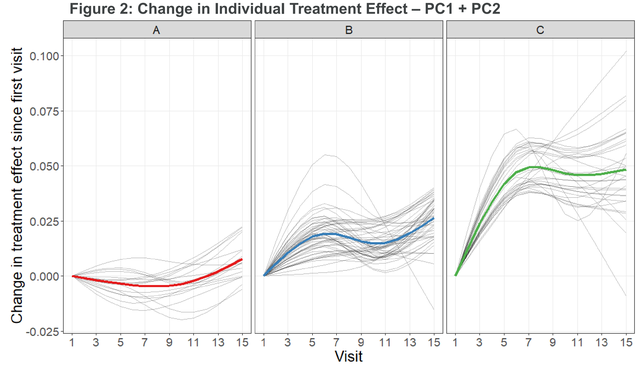
Figure 1: Simulated treatment response trajectories



Clustering

- After examining the log likelihood, BIC, and WMAE, the optimal number of clusters was determined to be three. After three clusters, the model performance does not improve as much.
- The three clusters of individuals predicted are shown in Figure 2. The mean trajectory for each cluster is also presented.
- The three trajectory clusters can be described as:
  - Cluster A: Minimal growth
  - Cluster B: Moderate growth
  - Cluster C: Fast Growth

Figure 2: Change in Individual Treatment Effect – PC1 + PC2



Cluster Characteristics

- Baseline characteristics were summarized for each cluster (Table 1).
- Cluster C (fast growth) is associated with younger individuals (mean = 39.7 years), male gender (90%).
- Conversely, cluster A (minimal growth) is associated with older individuals (mean = 80.5 years)
- The moderate growth cluster, cluster B, consists of individuals in middle age (mean = 50.2).

Table 1: Characteristics by cluster

Characteristics	Cluster		
	Minimal Growth Cluster A	Moderate Growth Cluster B	Fast Growth Cluster C
Cluster size	17	52	31
Mean age (SD)	80.5 (21.7)	50.2 (24.5)	39.7 (17.3)
Mean days since diagnosis (SD)	547 (218)	576 (288)	624 (354)
Female	76%	60%	10%

Discussion

The combination of data reduction, flexible outcome models, and longitudinal clustering may be a useful tool for model-based exploration of heterogeneity in longitudinal treatment effects

Abbreviations BIC = Bayesian information criterion; MMRM = mixed model for repeated measures; PC = principal component; SD = standard deviation; WMAE = weighted mean absolute error

References

1. Siddiqui, Ohidul. "MMRM versus MI in dealing with missing data—a comparison based on 25 NDA data sets." *Journal of biopharmaceutical statistics* 21.3 (2011): 423-436.

2. Genolini, Christophe, and Bruno Falissard. "KmL: k-means for longitudinal data." *Computational Statistics* 25.2 (2010): 317-328.

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