

## Analysis of Response Profiles of Clinical Trial Data

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### Abstract

Majority of clinical trial data analyses focus only on the last response of a patient and paying little attention to the responses before that. However, analysis of the response profile longitudinally can help to understand how the treatment works during the course of the treatments. In medical research with dynamic treatment allocation designs, patients' responses are tracked at every cycle or visit so that the proper treatment can be assigned for the next cycle of the trial. Therefore, it is crucial to extend the conventional data analysis to cover a broader scope so that the analytical results can be more informative to the clinical communities and the patients. We provide a case study of clinical trial data examining the whole response profile of each patient and trying to investigate the potential linkage of the responses with clinical factors and patient's background data.

**Keywords:** Profile Analysis, GEE, Multidimensional Scaling.

## 1 Introduction

Majority of clinical trial data analyses focus only on the last response of a patient and paying little attention to the responses before that. However, analysis of the response profile longitudinally can help to understand how the treatment works during the course of the treatments. In medical research with dynamic treatment allocation designs, patients' responses are tracked at every cycle or visit so that the proper treatment can be assigned for the next cycle of the trial. Therefore, it is crucial to extend the conventional data analysis to cover a broader scope so that the analytical results can be more informative to the clinical communities and the patients.

In this article, we provide a case study of clinical trial data examining the whole response profile of each patient instead of just the last observation and trying to investigate the potential linkage of the responses with clinical factors and patient's background. Using data from a recent clinical trial, we demonstrate the treatment effects longitudinally by graphical methods, we also estimate the probability of changing disease status during the study, and the similarity of response profiles so that patients can be segmented into subgroups or clusters. We further investigate the difference between the clusters by examining the baseline data and the data collected during the course of the study. The longitudinal response

profiles are also analyzed using generalized estimating equation to identify the treatment effects as well as the effects of covariates.

## 2 Data Example

Following are the response profiles from a sample of patients in a clinical trial with chemotherapy. The responses can be either stable disease (SD), progressive disease (PD), partial response (PR), nearly complete response (CP), or complete response (CR). The number of treatment cycles ranged from 1 cycle to more than 20 cycles. We only analyze the data from the first 22 cycles due to the sparseness of the patient population beyond that. According to the study protocol, whenever a patient had progression disease, the patient's treatment was terminated.

	pt	trt	rv3	rv5	rv7	rv8	rv9	rv10	rv11	rv12	rv13	rv14	rv15	rv16	rv17	rv18	rv19	rv20	rv21	rv22
1	1014021	A	SD	SD	SD	SD	SD	PR	PR	PR	PR	PR	PR	PR						
2	1014838	A	SD	SD	SD	SD	PR	PR												
4	1025268	B	SD																	
5	1034019	A	NE	NE	SD	PR	PR	PR	PR	PR	PR	PR	PR	PR			PR	PR	PD	PD
6	1034426	B	SD																	
7	1034430	A	SD	SD	PD															
8	1034812	A	PD																	
9	1034815	B	SD	SD	SD	SD	PD	PD												
10	1034822	A	SD	SD	SD	PR	PR	PR	CP	CP	NE	PD								
11	1034831	A	SD	SD	PR	PR	PR	PR	PR	PR	PR	PR								

One can also present the response profiles graphically (Figure 1), which gives an easier visualization to examine the responses. One can also display the cumulative responses longitudinally according to the duration of the study (Figure 2). As one can easily see that lots of patients with SD status at the beginning of the study, and toward the end of the study, many patients had dropped from the study (green area) and substantially number of patients had PR, CP, or CR. A graphical comparison between treatments can help to evaluate the efficacy of the treatment as shown in Figures 3 and 4.

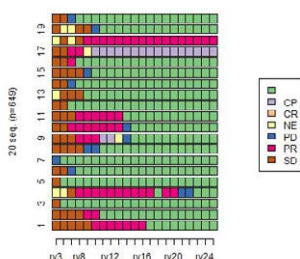


Figure 1: 20 Response Profiles

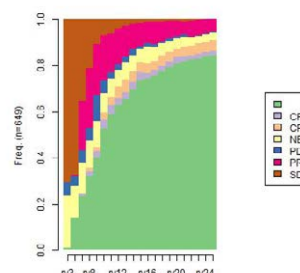


Figure 2: Cumulative Profiles

Similar to the analysis of discrete data, one can also create the frequency table to demonstrate the frequencies of each type of response profile as shown below.

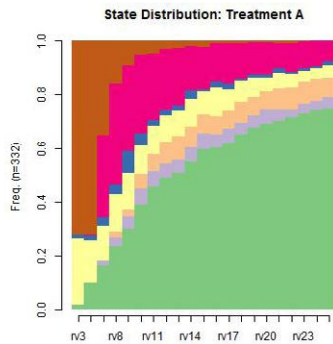


Figure 3: Group A

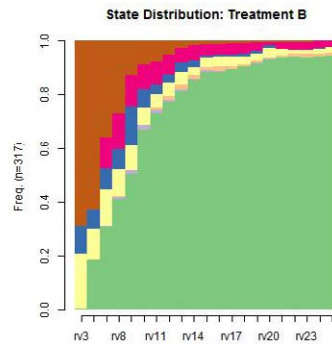


Figure 4: Group B

[>] 656 sequences with 5 distinct events/states including missing value as additional state  
 [>] 243 distinct sequences. min/max sequence length: 1/21

	Freq	Percent
PD/1-/20	37	5.70
SD/1-/20	37	5.70
SD/4-PD/1-/16	30	4.62
SD/2-/19	25	3.85
SD/1-PD/1-/19	24	3.70
SD/2-PD/1-/18	22	3.39
SD/3-PD/1-/17	14	2.16
SD/2-PR/2-PD/1-/16	13	2.00
NE/1-/20	10	1.54
SD/3-/18	10	1.54
SD/5-PD/1-/15	9	1.39
NE/1-SD/1-PD/1-/18	8	1.23
SD/2-PR/1-PD/1-/17	8	1.23
NE/2-/19	6	0.92
SD/2-PR/19	5	0.77
SD/3-PR/1-PD/1-/16	5	0.77
SD/3-PR/2-PD/1-/15	5	0.77
SD/6-PD/1-/14	5	0.77
NE/1-PD/1-/19	4	0.62
SD/1-NE/1-/19	4	0.62

One can also display the average duration of response for each response category either for the whole group (Figure 5) or by treatment groups, which will provide visual comparison of the treatment effects. As one can see from Figure 6, treatment A had longer durations for the better responses and shorter duration for progression disease.

### 3 Transition of Response States

An important information about response profiles is the transition rate between each pair of states  $(s_i, s_j)$ , i.e., the probability to switch at a given time position from state  $s_i$  to state  $s_j$ .

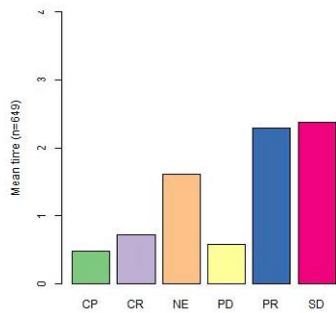


Figure 5: All Groups

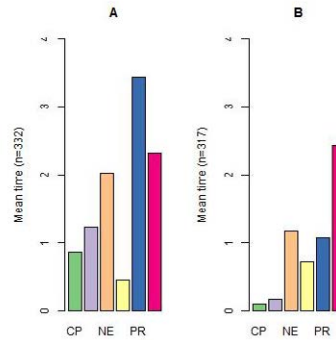


Figure 6: By Group

Let  $n_t(s_i)$  be the number of sequences that do not end in time position  $t$  and with state  $s_i$  at time position  $t$ , and let  $n_{t,t+1}(s_i, s_j)$  be the number of sequences with state  $s_i$  at time position  $t$  and state  $s_j$  at time position  $t + 1$ . The 1-step transition rate  $p(s_j|s_i)$  between states  $s_i$  and  $s_j$  is defined as

$$p(s_j|s_i) = \frac{\sum_{t=1}^{L-1} n_{t,t+1}(s_i, s_j)}{\sum_{t=1}^{L-1} n_t(s_i)}$$

with  $L$  the maximal observed sequence length.

The rates are assumed time position-independent and the outcome is a stochastic Markov process matrix where each row  $i$  gives a transition distribution from the originating state  $s_i$  in  $t$  to the states in  $t + 1$ . Transition rates provide information about the state changes observed in the data together with, on the diagonal, an assessment of the stability of each state. Similar transition matrix can be constructed for multiple time steps.

Following are the transition matrices for Treatments A and B. One can clearly see the difference of treatment effect which indicates the superiority of Treatment A to B.

computing transition rates for states CP/CR/NE/PD/PR/SD ...  
(Treatment A)

	[-> CP]	[-> CR]	[-> NE]	[-> PD]	[-> PR]	[-> SD]
[CP ->]	0.82	0.04	0.10	0.03	0.00	0.00
[CR ->]	0.00	0.86	0.11	0.03	0.00	0.00
[NE ->]	0.05	0.07	0.52	0.03	0.19	0.13
[PD ->]	0.00	0.00	0.00	1.00	0.00	0.00
[PR ->]	0.02	0.02	0.11	0.06	0.78	0.00
[SD ->]	0.01	0.00	0.10	0.05	0.22	0.61

computing transition rates for states CP/CR/NE/PD/PR/SD ...  
(Treatment B)

	[-> CP]	[-> CR]	[-> NE]	[-> PD]	[-> PR]	[-> SD]
[CP ->]	0.76	0.07	0.10	0.07	0.00	0.00
[CR ->]	0.00	0.76	0.18	0.06	0.00	0.00
[NE ->]	0.01	0.02	0.47	0.08	0.16	0.25
[PD ->]	0.00	0.00	0.00	1.00	0.00	0.00
[PR ->]	0.00	0.01	0.16	0.12	0.71	0.00
[SD ->]	0.01	0.00	0.11	0.16	0.07	0.64

## 4 Classification of Response Profiles

It is always of special interest in medical research to segment the patient population based on their responses so that the relationship between the responses and background data can be further investigated for each subgroup. For profile analysis, we need to define the similarities of response profiles via some appropriate metrics so that further analysis can be conducted.

### 4.1 Dissimilarities Between Response Profiles

Similar to the calculation of distance between two data points, one can define the distance between two response profiles. Let  $A(x, y)$  be a count of common states between sequences  $x$  and  $y$ . Define a dissimilarity measure through the following general formula

$$d(x, y) = A(x, x) + A(y, y) - 2A(x, y) \quad (1)$$

where  $d(x, y)$  is the distance between sequences  $x$  and  $y$ . The dissimilarity is maximal when  $A(x, y) = 0$ . It is zero when the sequences are identical.

One commonly used method is, among others, the simple Hamming distance (Hamming 1950), which is the number of time positions at which two sequences of equal length differ. It can be defined as

$$HD(x, y) = l - A_H(x, y),$$

where  $l = |x| = |y|$  is the common length of  $x$  and  $y$ , and  $A_H(x, y)$  is the number of matching time positions. The Hamming distance with equation (1) by using  $d(x, y)/2$  as proximity measure.

With the defined distance between response profiles, cluster analysis was performed to aggregate the responses which have close proximity. The cluster dendrogram is graphically shown in Figure 7. Four clusters are formed by cutting the dendrogram with height of 100. One can further visualize the data distributions of these clusters with the multivariate methods such as multidimensional scaling.

### 4.2 Visualizing Clusters via Multidimensional Scaling

The determination of coordinates of multidimensional scaling can be briefly described as following. Let  $\{x_1, x_2, \dots, x_n\} \in R^d$  and the inter-point distance be

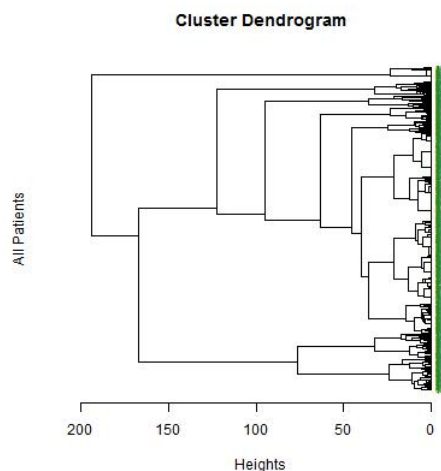


Figure 7: Clustering Response Profiles

$\delta_{rs} = \|x_r - x_s\|$ . Denote the dissimilarity matrix by  $D = [(\delta_{rs})]$  and define matrix  $A = [(a_{rs})]$  with  $a_{rs} = -\delta_{rs}^2/2$ .

Define the matrix

$$B = [(b_{rs})] = (I_n - 1_n 1_n'/n)A(I_n - 1_n 1_n'/n),$$

where  $b_{rs} = a_{rs} - \bar{a}_{r.} - \bar{a}_{.s} + \bar{a}_{..}$ . One can extract the  $k$  largest positive eigenvalues  $\gamma_1 > \gamma_2 > \dots > \gamma_k$  of  $B$  with corresponding eigenvectors  $Y_k = (y^{(1)}, y^{(2)}, \dots, y^{(k)})$  that are normalized by  $\|y^{(j)}\|^2 = \gamma_j$  for  $j = 1, 2, \dots, k$ . The  $n$  rows of  $Y_k$  are the principal coordinates in  $k$  dimensions and can be plotted pairwise to visualize the data distributions.

The coordinates of the responses are plotted in Figures 8 to 11. Each cluster is highlighted in red color. One can easily see the different data distributions of these responses. Cluster 1 mostly aggregates at the upper-left corner of the plot and cluster-2 mostly aggregates around the center of the plot, while clusters 3 and 4 represent the responses not confirming with these two bigger groups. Since clusters 3 and 4 represent a small subgroup of patients in the analysis, we will focus our following discussions on clusters 1 and 2.

### 4.3 Response Profile Differences Among Clusters

With further examination of the response profiles corresponding to the members of these clusters, interesting patterns of responses can be clearly revealed as shown in Figures 12, 13, and 14. Cluster 1 consists of the patients who had disease status improved from Stable Disease to Partial Response or stayed at the same disease status. Cluster 2 consists of all the patients who had their disease status worsen from Stable Disease to Progressive Disease. It also includes

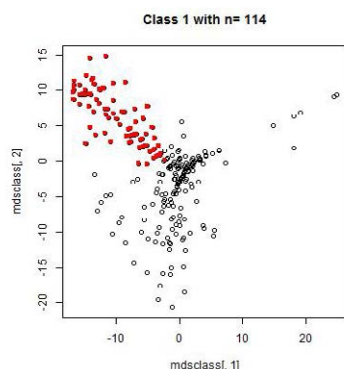


Figure 8: Cluster 1

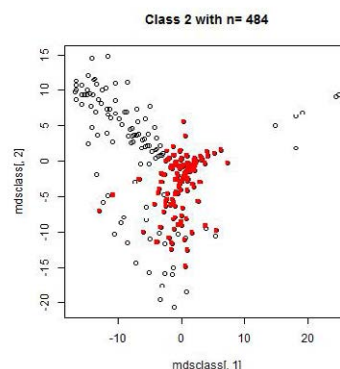


Figure 9: Cluster 2

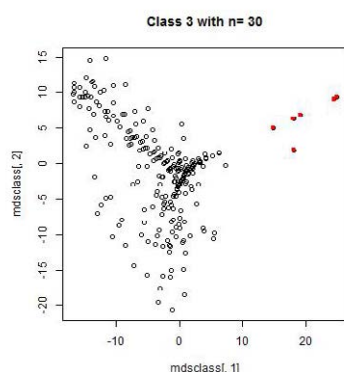


Figure 10: Cluster 3

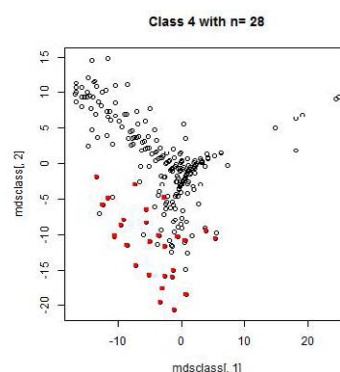


Figure 11: Cluster 4

the patients with disease status improved to Partial Response, nearly Complete Response, or Complete Response. Clusters 3 and 4 consist of patients who had improved disease status and none of the members in these clusters had any disease progression. Since any clustering method will be accompanied with different degrees of misclassification errors, it is likely some of the response profiles could have been better classified.

#### 4.4 Significant Clinical Variables for Each Cluster

To further investigate the significant covariates which underlying the clusters, the patients' baseline covariates, the treatment received, and the laboratory data during the study are carefully examined. A regression analysis was conducted with the covariates which was showing some degrees of significance after pre-screening. The results are shown below for clusters 1 and 2. Several laboratory tests and the abnormal serum protein levels show statistical significance in the model in addition to a few baseline covariates such as prior therapies received

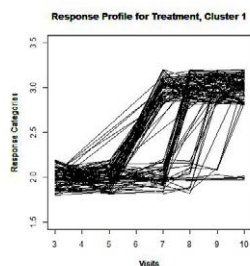


Figure 12: Cluster 1

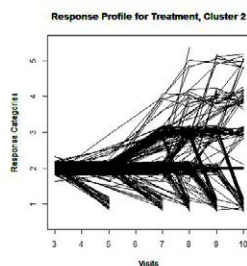


Figure 13: Cluster 2

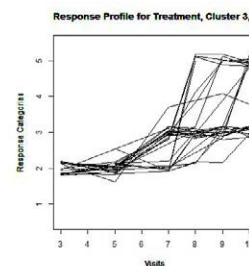


Figure 14: Clusters 3&amp;4

before the trial. Different sets of covariates appear in each cluster.

#### Analytical results for cluster 1:

```
Call: glm(formula = clustdata1[, 2] ~ n_prt + mmdur + strlab2 + AlbuminL +
  NeutrophilL + PlateletsH + RBCL + SerumIgAL + SerumIgAH +
  SerumIgGL + SerumIgGH + TotalProteinH, family = quasibinomial, data = clustdata1)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	0.54234	0.35424	1.531	0.126264
n_prt	0.32146	0.09976	3.222	0.001335 **
mmdur	0.05649	0.03242	1.742	0.081933 .
strlab2	-0.90648	0.22449	-4.038	6.04e-05 ***
AlbuminL	-1.80328	0.54017	-3.338	0.000891 ***
NeutrophilL	2.00171	0.39783	5.032	6.32e-07 ***
PlateletsH	3.03917	1.31229	2.316	0.020876 *
RBCL	-0.95070	0.32570	-2.919	0.003635 **
SerumIgAL	-0.78516	0.28668	-2.739	0.006337 **
SerumIgAH	-0.88987	0.43682	-2.037	0.042045 *
SerumIgGL	-1.14937	0.34321	-3.349	0.000859 ***
SerumIgGH	-1.68069	0.54402	-3.089	0.002092 **
TotalProteinH	-3.86644	1.24619	-3.103	0.002002 **

---

Signif. codes: 0 \*\*\* 0.001 \*\* 0.01 \* 0.05 . 0.1 1

(Dispersion parameter for quasibinomial family taken to be 0.7413571)

#### Analytical results for cluster 2:

```
Call: glm(formula = clustdata2[, 2] ~ trtgrp + prmel + AlbuminL + MonocytesH +
  RBCL + SerumIgAL + SerumIgAH + SerumIgGH, family = quasibinomial, data = clustdata2)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	-1.5632	0.5387	-2.902	0.003837 **
trtgrp	0.7503	0.2818	2.662	0.007950 **
prmel	-0.8368	0.2506	-3.339	0.000888 ***
AlbuminL	1.5906	0.4943	3.218	0.001357 **
MonocytesH	-1.2791	0.6236	-2.051	0.040649 *
RBCL	1.0554	0.3597	2.934	0.003465 **
SerumIgAL	1.1015	0.3260	3.379	0.000772 ***
SerumIgAH	1.9697	0.4869	4.046	5.85e-05 ***
SerumIgGH	1.0588	0.3961	2.673	0.007707 **

---

Signif. codes: 0 \*\*\* 0.001 \*\* 0.01 \* 0.05 . 0.1 1

(Dispersion parameter for quasibinomial family taken to be 1.350058)



## 5 Modeling of Response Profiles via GEE

Let  $Y_{it} \in \{1, 2, \dots, I > 2\}$  be the multinomial response for patient  $i$  ( $i = 1, \dots, N$ ) at time  $t$  ( $t = 1, \dots, T_i$ ) and assume missing data are missing completely at random (MCAR) as defined in Rubin (1976). Define  $Y_{itj} = I(Y_{it} = j)$  for  $j = 1, \dots, I$ , where  $I(A)$  denotes the indicator function of the event  $A$ , and  $Y_{it} = (Y_{it1}, \dots, Y_{it(I-1)})'$  with the response category  $I$  omitted. Denote response vector by

$$Y_i = (Y'_{i1}, \dots, Y'_{iT_i})'$$

and  $(T_{i(I-1)} \times p)$  covariate matrix for patient  $i$  by

$$x_i = (x_{i1}, \dots, x_{iT_i})'$$

Let

$$\pi_{itj} = E(Y_{itj}|x_i) = Pr(Y_{itj} = 1|x_i),$$

$$\pi_{it} = (\pi_{it1}, \dots, \pi_{it(I-1)})'$$

and

$$\pi_i = E(Y_i|x_i) = (\pi'_{i1}, \dots, \pi'_{iT_i})'$$

In addition, denote the link function by  $g$  and, for patient  $i$  at time  $t$ , is defined as

$$g[E(Y_{it}|x_i)] = g(\mu_{it}) = x_{it}\beta,$$

where  $\beta$  is the  $p$ -variate regression vector of interest.

### 5.1 Marginal models

The choice of the link function  $g$ , hence, the marginal model depends on the nature of the response scale. For ordinal multinomial responses, the family of cumulative link models

$$F^{-1}[P(Y_{it} \leq j|x_i)] = \beta_{0j} + \beta'_*x_{it}$$

or the adjacent categories logit model

$$\log(\pi_{itj}/\pi_{it(j+1)}) = \beta_{0j} + \beta'_*x_{it},$$

where  $F$  is the CDF of a continuous distribution and  $\{\beta_{0j}, j = 1, 2, \dots, J - 1\}$  are the category specific intercepts.

For nominal multinomial responses, the baseline category logit model can be used

$$\log(\pi_{itj}/\pi_{itJ}) = \beta_{0j} + \beta'_jx_{it},$$

where  $\beta_j$  is the  $j$ th category specific parameter vector. Note that the category specific intercepts need to satisfy a monotonicity condition

$$\beta_{01} \leq \beta_{02}, \dots, \leq \beta_{0(J-1)}$$

only when the family of cumulative link models is employed, and the regression parameter coefficients of the covariates  $x_{it}$  are category specific only in the marginal baseline category logit model.

## 5.2 Estimation of marginal regression parameters

Let  $\beta$  be the  $p$ -variate parameter vector that includes all the regression parameters. Let the general estimating equations be

$$U(\beta, \hat{\alpha}) = (1/N) \sum_{i=1}^N D_i V_i^{-1} (Y_i - \pi_i) = 0, \quad (2)$$

where  $D_i = \partial \pi_i / \partial \beta$ ,  $V_i(\beta, \hat{\alpha})$  is a  $T(J-1) \times T(J-1)$  weight matrix, and  $\alpha$  is the local odds ratio define below.

## 5.3 Local Odds Ratio

Consider the time-pairs  $\{(1, 2), (1, 3), \dots, (T-1, T)\}$ . For each time-pair  $(t, t')$ , form an  $J \times J$  contingency table such that the row totals correspond to the observed totals at time  $t$  and the column totals to the observed totals at time  $t'$ . Let  $\theta_{tjt'j'}$  be the expected local odds ratio at cut point  $(j, j')$ , and  $f_{tjt'j'}$  be the observed frequencies. Becker and Clogg (JASA, 1989) showed that

$$\log(f_{tjt'j'}) = (\text{row, column, interaction effects}) + \phi^{(t,t')} \mu_j^{(t,t')} \mu_{j'}^{(t,t')},$$

and

$$\log(\theta_{tjt'j'}) = \phi^{(t,t')} (\mu_j^{(t,t')} - \mu_{j+1}^{(t,t')}) (\mu_{j'}^{(t,t')} - \mu_{j'+1}^{(t,t')}).$$

Touloumis, Agresti, and Kateri (Biometrics, 2013) defined the parameter vector that contains the marginalized local odds ratios structure as

$$\alpha = (\theta_{1121}, \dots, \theta_{1(J-1)2(J-1)}, \dots, \theta_{(T-1)1T1}, \dots, \theta_{(T-1)(J-1)T(J-1)})'$$

which can be estimated by MLE. For practical purpose, the score functions  $\mu_j^{(t,t')}$  are simplified and let  $\mu_j^{(t,t')} = j$ , and the general association parameter  $\phi^{(t,t')} = \phi$ .

Conditional on  $\hat{\alpha}$  and the marginal model specification at times  $t$  and  $t'$  the probability

$$\{P(Y_{it} = j, Y_{it'} = j' | x_i) : t < t', j, j' = 1, \dots, J-1\}$$

and  $V_i$  can be calculated, hence  $\beta$  can be estimated via the GEE (2).

## 5.4 Results of Modeling

Data from cluster 1 was analyzed using the method discussed above using programs in R and the results are shown below. Similar analysis was also conducted for other clusters but are not shown here. The data beyond visit 10 was not included in the analysis.

The beta level at baseline and the age both show significant effects, but the treatment only offers moderate effect as patients from this cluster mostly only improved their disease status from SD to PR at the best. However, similar

analysis for cluster 2 shows significant treatment effect. Many patients in cluster 2 had improved their disease status from SD to PR, CP and even CR.

*Model and the parameter estimates:*

```
GEE FOR ORDINAL MULTINOMIAL RESPONSES
Link : Cumulative logit

call: ordLORgee(formula = Resp ~ factor(vis_num) + factor(trtgrp) +
  age + beta + n_psct, data = xdat, id = pt, link = "logit", LORstr = "category.exch")

Coefficients:
      Estimate   san.se   san.z Pr(>|san.z|)
beta01         1.35026  0.93392  1.4458    0.14824
beta02         3.77986  0.92989  4.0648    5e-05 ***
factor(vis_num)5 -0.18590  0.12986 -1.4315    0.15228
factor(vis_num)7 -1.67880  0.19489 -8.6143 < 2e-16 ***
factor(vis_num)8 -1.94960  0.30028 -6.4926 < 2e-16 ***
factor(vis_num)9 -2.65717  0.33162 -8.0128 < 2e-16 ***
factor(vis_num)10 -3.14579  0.36401 -8.6420 < 2e-16 ***
factor(trtgrp)2  -0.01723  0.24606 -0.0700    0.94418
age            -0.03010  0.01399 -2.1513    0.03145 *
beta          -0.05015  0.05593 -0.8967    0.36986
n_psct        -0.25766  0.17849 -1.4435    0.14887
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1 1
```

*The odds ratio of the effect for each covariate:*

	Est. Coefficients	Odds Ratio of Better Responses
beta01	1.35025563	0.25917400
beta02	3.77985846	0.02282592
factor(vis_num)5	-0.18590278	1.20430517
factor(vis_num)7	-1.67880421	5.35914371
factor(vis_num)8	-1.94960456	7.02590874
factor(vis_num)9	-2.65716906	14.25587441
factor(vis_num)10	-3.14579299	23.23809566
factor(trtgrp)2	-0.01722873	1.01737800
age	-0.03010472	1.03056244
beta	-0.05015157	1.05143045
n_psct	-0.25765765	1.29389577

*The correlation matrix of the parameters estimated in the final model:*

	beta01	beta02	(vis_5)	(vis_7)	(vis_8)	(vis_9)	(vis_10)	(trtgrp)2	age	beta	n_psct
beta01	0.87	0.85	0.00	0.00	0.00	0.01	-0.01	-0.03	-0.01	0	-0.09
beta02	0.85	0.86	0.00	-0.01	-0.04	-0.04	-0.06	-0.03	-0.01	0	-0.10
factor(vis_num)5	0.00	0.00	0.02	0.01	0.02	0.01	0.01	0.00	0.00	0	0.00
factor(vis_num)7	0.00	-0.01	0.01	0.04	0.03	0.03	0.03	0.00	0.00	0	0.00
factor(vis_num)8	0.00	-0.04	0.02	0.03	0.09	0.06	0.06	0.01	0.00	0	0.00
factor(vis_num)9	0.01	-0.04	0.01	0.03	0.06	0.11	0.07	0.00	0.00	0	0.01
factor(vis_num)10	-0.01	-0.06	0.01	0.03	0.06	0.07	0.13	0.01	0.00	0	0.02
factor(trtgrp)2	-0.03	-0.03	0.00	0.00	0.01	0.00	0.01	0.06	0.00	0	0.00
age	-0.01	-0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
beta	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0	0.00
n_psct	-0.09	-0.10	0.00	0.00	0.00	0.01	0.02	0.00	0.00	0	0.03

*The estimated local odds ratios:*

The local odds ratio matrix indicates the disease status improved from visit 3 to visit 5 is about 3.5 times, and it continued to improve for visit 7, but the effects started to decline after that.

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]	[,9]	[,10]	[,11]	[,12]
[1,]	0.000	0.000	3.525	3.525	4.534	4.534	1.437	1.437	1.250	1.250	0.887	0.887
[2,]	0.000	0.000	3.525	3.525	4.534	4.534	1.437	1.437	1.250	1.250	0.887	0.887
[3,]	3.525	3.525	0.000	0.000	2.512	2.512	3.422	3.422	1.982	1.982	1.424	1.424
[4,]	3.525	3.525	0.000	0.000	2.512	2.512	3.422	3.422	1.982	1.982	1.424	1.424
[5,]	4.534	4.534	2.512	2.512	0.000	0.000	1.383	1.383	1.347	1.347	1.062	1.062
[6,]	4.534	4.534	2.512	2.512	0.000	0.000	1.383	1.383	1.347	1.347	1.062	1.062
[7,]	1.437	1.437	3.422	3.422	1.383	1.383	0.000	0.000	1.591	1.591	1.375	1.375
[8,]	1.437	1.437	3.422	3.422	1.383	1.383	0.000	0.000	1.591	1.591	1.375	1.375
[9,]	1.250	1.250	1.982	1.982	1.347	1.347	1.591	1.591	0.000	0.000	1.604	1.604
[10,]	1.250	1.250	1.982	1.982	1.347	1.347	1.591	1.591	0.000	0.000	1.604	1.604
[11,]	0.887	0.887	1.424	1.424	1.062	1.062	1.375	1.375	1.604	1.604	0.000	0.000
[12,]	0.887	0.887	1.424	1.424	1.062	1.062	1.375	1.375	1.604	1.604	0.000	0.000

## 6 Summary

In this article, we conduct a case study of data from a good size clinical trial by studying the entire efficacy response profile of each patient and to explore the relationship between response profiles with covariates which were collected either before or during the trial. Many graphical tools are used to visualize the data and make it easier for researchers to understand the data distribution and to compare the efficacy of treatments. Various analytical tools for multivariate data are also used to segment the patient population into subgroups so that the treatment effects can be further analyzed in each subgroup and possibly to discover better personalized treatments.

Medical research with dynamic treatment allocation designs is gaining popularity especially for the early phase of drug discovery. Patients' responses are usually tracked at every cycle or visit in this type of study so that the proper treatment can be assigned for the next cycle of the trial to maximize the treatment benefit. Therefore, it is crucial to extend the conventional clinical data analysis which mostly only emphasizes the end results to a broader scope covering more extended observations so that the analytical results can be more informative to both the clinical communities and the patients.

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