Analysis of Response Profiles of Clinical Trial Data

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Presentation at BASS XXII, 2015

November 2, 2015

Outline of Presentation

Research Rationale and Objectives

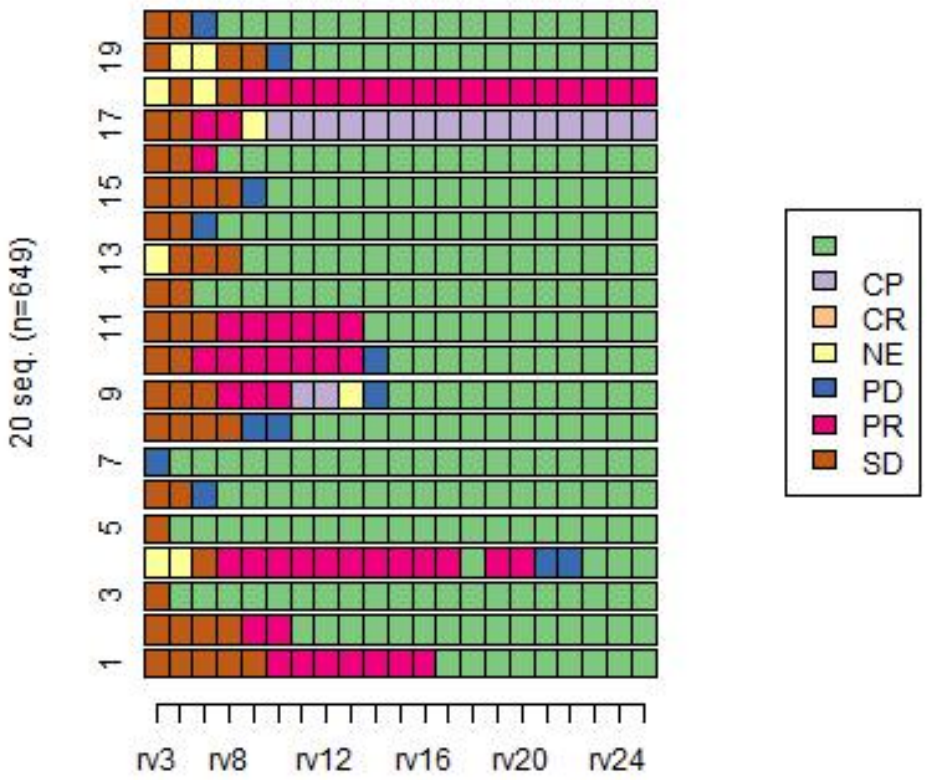
- Majority of the data analysis focus only on the last response of a subject and paying little attention to the responses before that.
- Analysis of the response profile longitudinally helps to understand how the treatment works during the course of treatment.
- In clinical research with dynamic treatment allocation designs, subject' responses are tracked at every cycle so that the proper next treatment can be selected.
- This research examines the entire response profile of each patient and tries to link the responses with clinical factors and patient's background.
- Data from a recent clinical trial is used to illustrate the analytical procedures.

Example of Patient Response Profiles

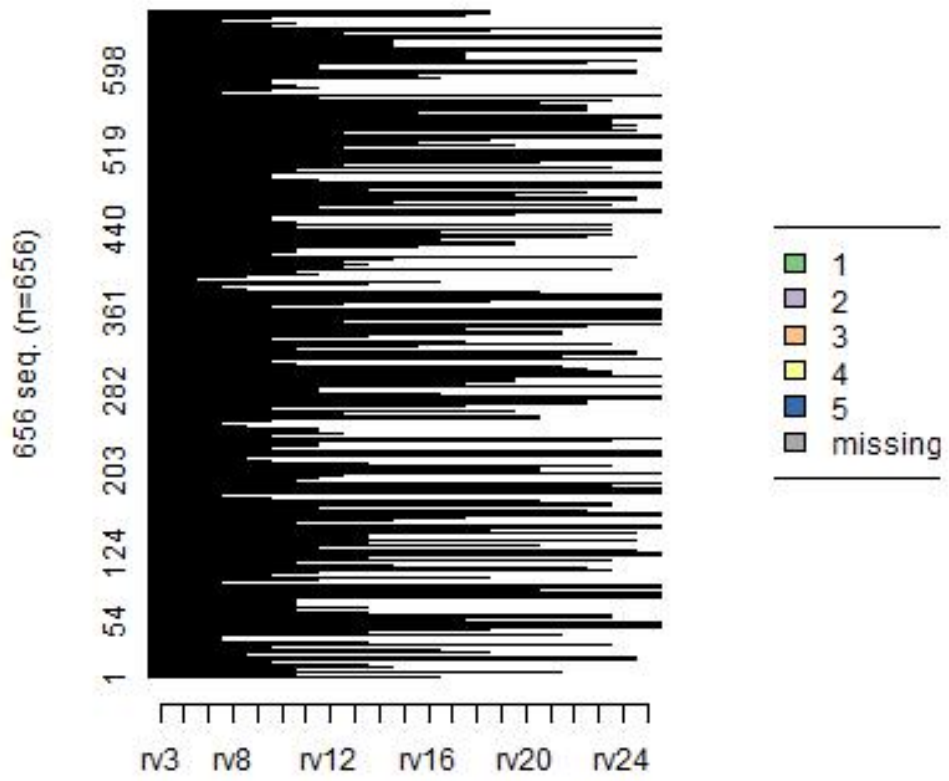
Example of response profiles of 10 subjects:

	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	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	PD								

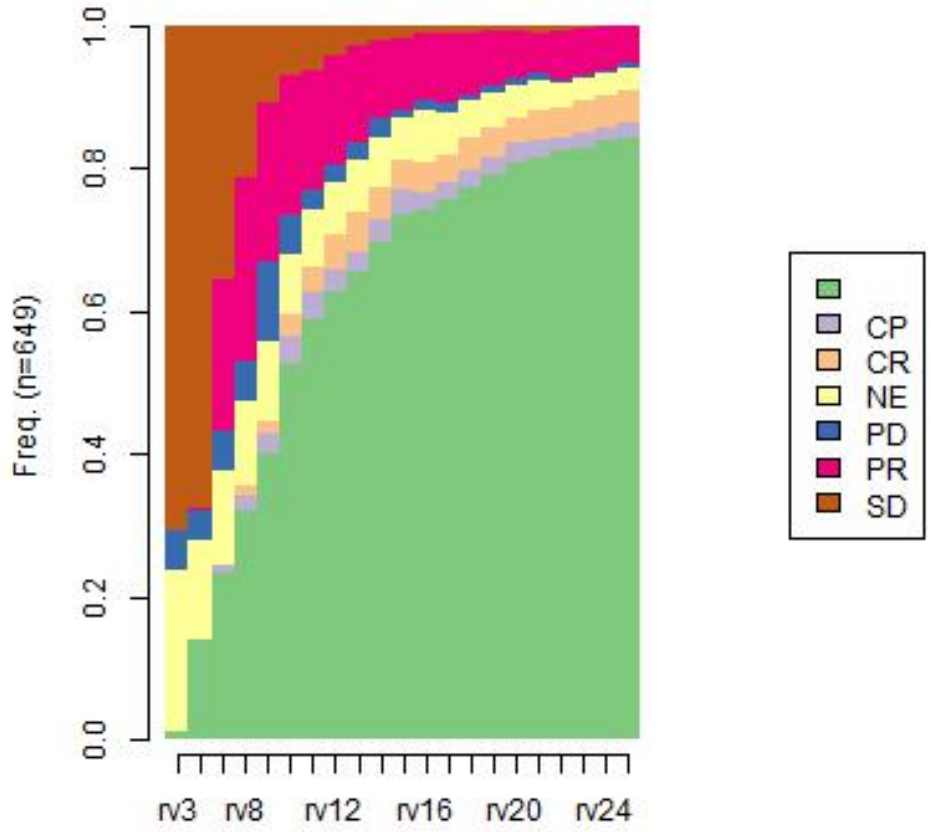
Graphical View of 20 Response Profiles



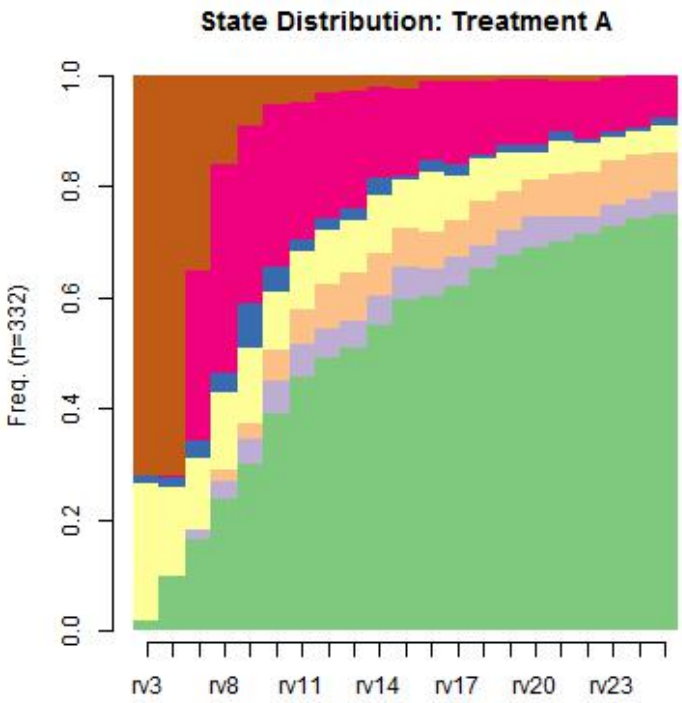
Response Profiles of all subjects (too ambitious!)

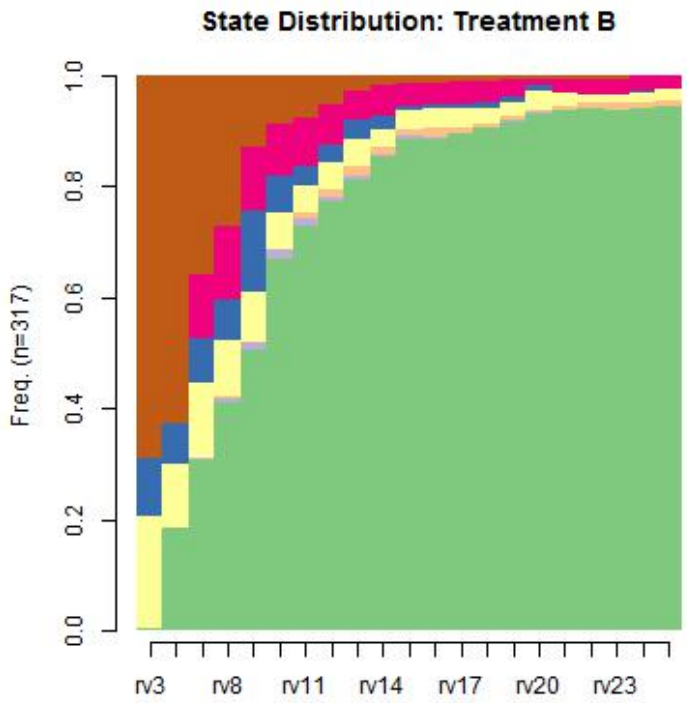


Longitudinal View of Cumulative Response Profiles



Cumulative Response Profiles by Group





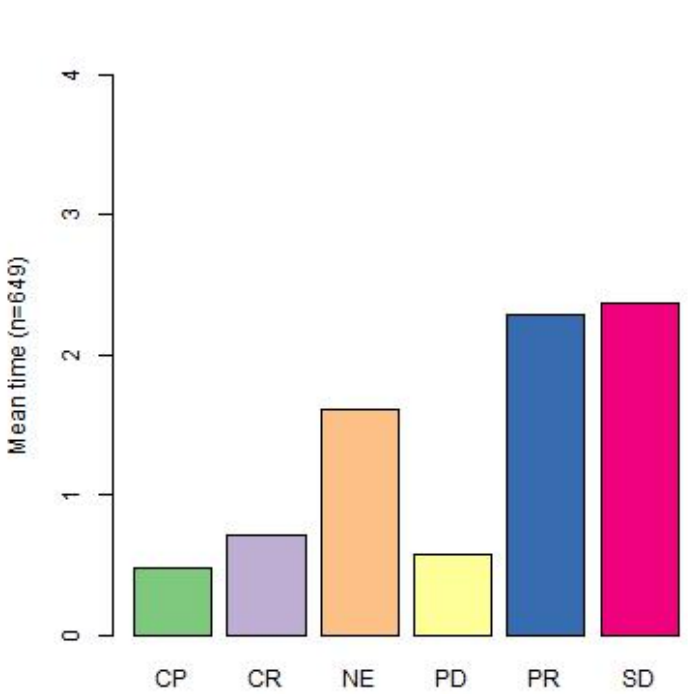
Frequencies of Patient Response Profiles

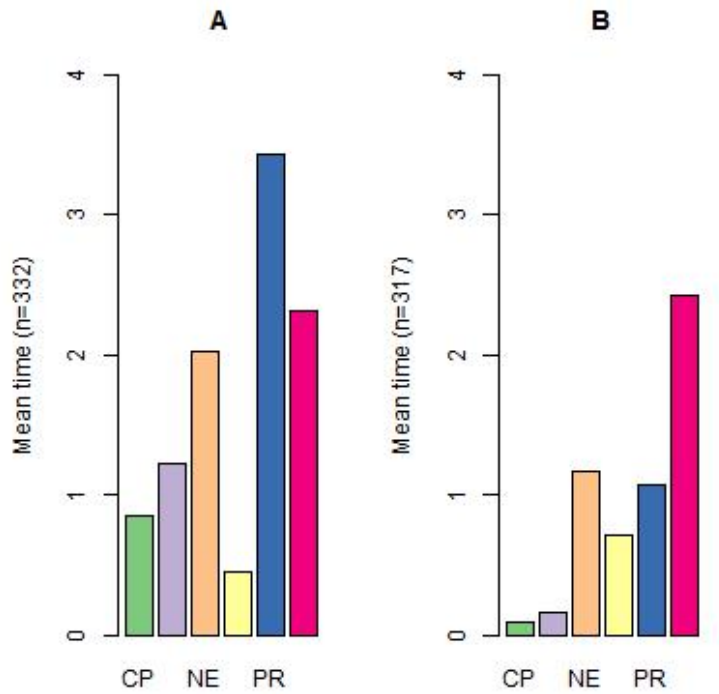
```
[>] 656 sequences with 5 distinct events/states
[>] including missing value as additional state
[>] 243 distinct sequences
[>] min/max sequence length: 1/21

First 20 profile patterns and frequencies:
```

	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

Mean Time Duration of Response States





toc

Response States Transition Matrix - 1

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

- Let $n_t(s_i)$ be the number of sequences that do not end at time t and with state s_i at time t.
- Let $n_{t,t+1}(s_i, s_j)$ be the number of sequences with state s_i at time t and state s_j at time $t+1$.
- 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.

Response States Transition Matrix - 2

- The rates are assumed to be time position-independent.
- 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 state s_j 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 k-step state transition.

Response States Transition Matrix - 3

```
649 sequences in the data set (min/max sequence length: 1/21)
computing transition rates for states CP/CR/NE/PD/PR/SD ...
```

	[-> CP]	[-> CR]	[-> NE]	[-> PD]	[-> PR]	[-> SD]
[CP ->]	0.82	0.05	0.10	0.03	0.00	0.00
[CR ->]	0.00	0.84	0.12	0.03	0.00	0.00
[NE ->]	0.04	0.05	0.51	0.05	0.18	0.18
[PD ->]	0.00	0.00	0.00	1.00	0.00	0.00
[PR ->]	0.02	0.02	0.12	0.08	0.77	0.00
[SD ->]	0.01	0.00	0.11	0.11	0.15	0.63

(Both Groups Combined)

Response States Transition Matrix - 4

```
computing complexity index for 332 sequences ...
computing transition rates for states CP/CR/NE/PD/PR/SD ...
```

	[-> 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

(Treatment A)

Response States Transition Matrix - 5

```
computing complexity index for 317 sequences ...
computing transition rates for states CP/CR/NE/PD/PR/SD ...
```

	[-> 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

(Treatment B)

Shannon's entropy (the entropy index) - 1

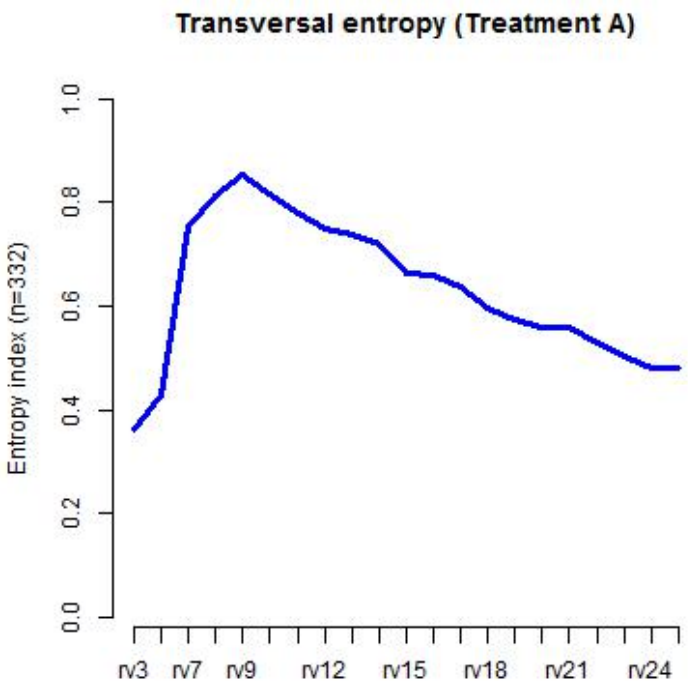
It is also of interest to know how active the states changed in time.

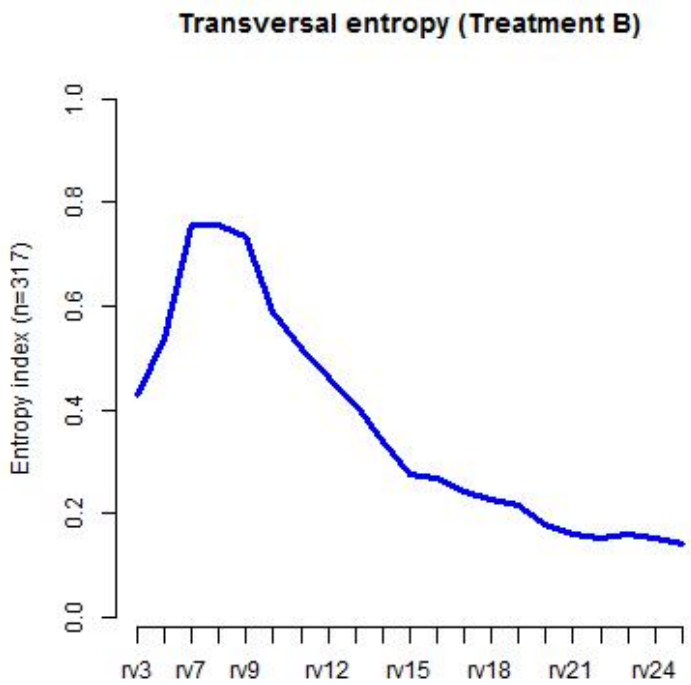
- Let p_i denote the proportion of cases in state i at the considered time position, the entropy is defined as

$$h(p_1, \cdots, p_a) = -\sum_{i=1}^{a} p_i \log(p_i) \tag{1}$$

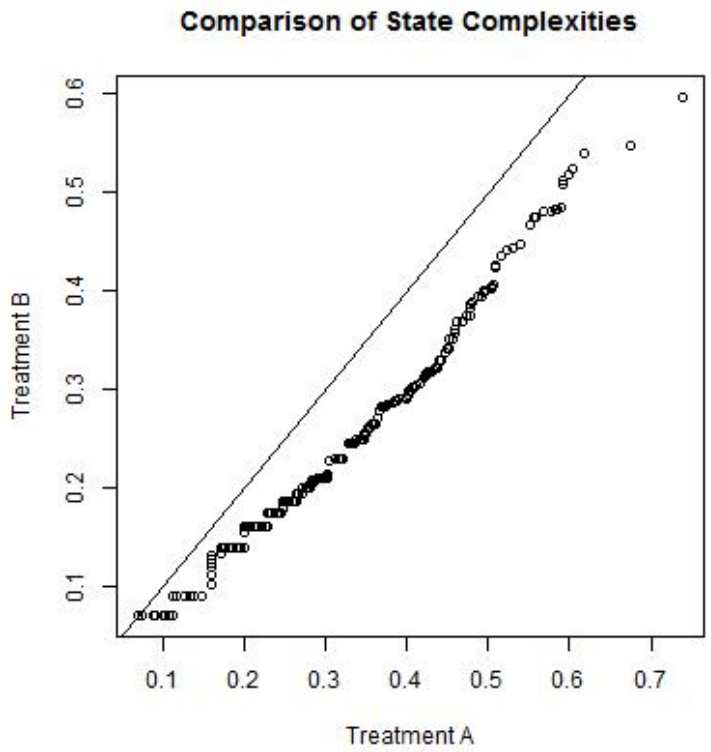
  where a is the number of the states.
- The entropy is 0 when all cases are in the same state and is maximal when we have the same proportion of cases in each state.
- The entropy is a convenient measure of the diversity of states observed at a given time position.

Shannon's entropy (the entropy index) by Group





Shannon's longitudinal entropy - Group comparison



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Dissimilarities Between Response Profiles - 1

- Let $A(x, y)$ be a count of common states between sequences x and y. Define a dissimilarity measure through the following general formula

$$d(x, y) = A(x, x) + A(y, y) - 2A(x, y) \tag{2}$$

  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.

Dissimilarities Between Response Profiles - 2

- The simple Hamming distance (Hamming 1950) is the number of time positions at which two sequences of equal length differ.
- It can be defined as

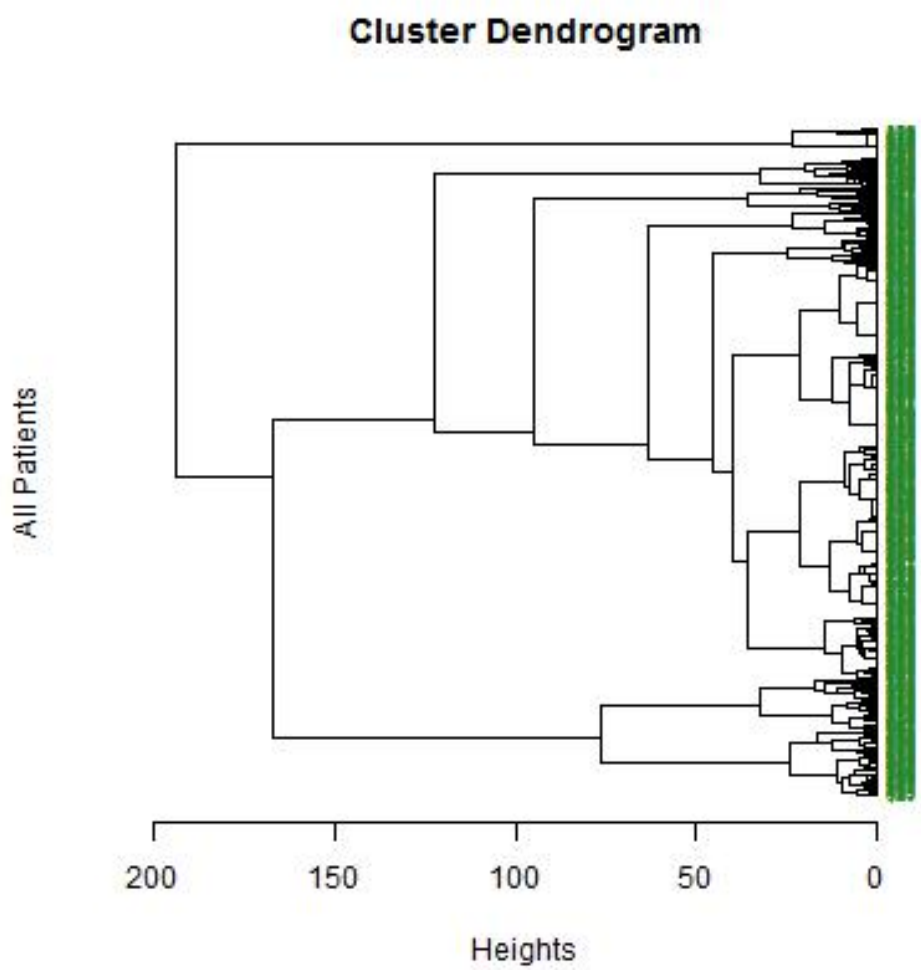
$$HD(x, y) = l - A_H(x, y),$$

where

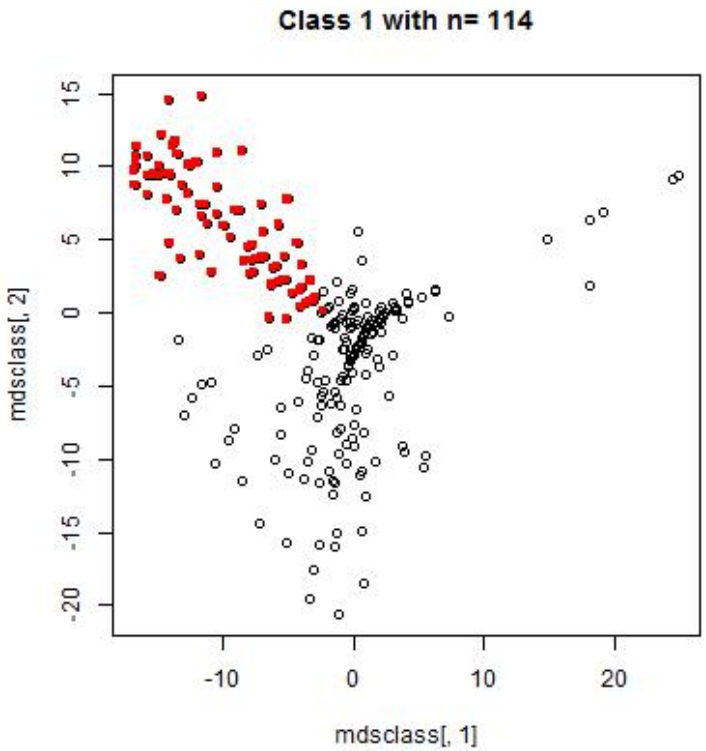
  - $l = |x| = |y|$ is the common length of x and y,
  - $A_H(x, y)$ is the number of matching time positions.

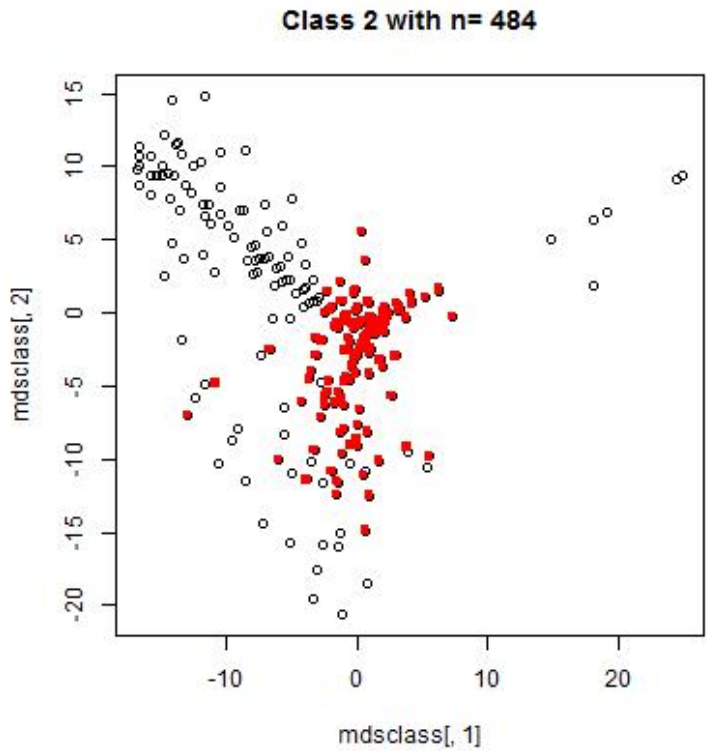
- The Hamming distance with equation (2) by using $d(x, y)/2$ as proximity measure.

Clustering Response Profiles

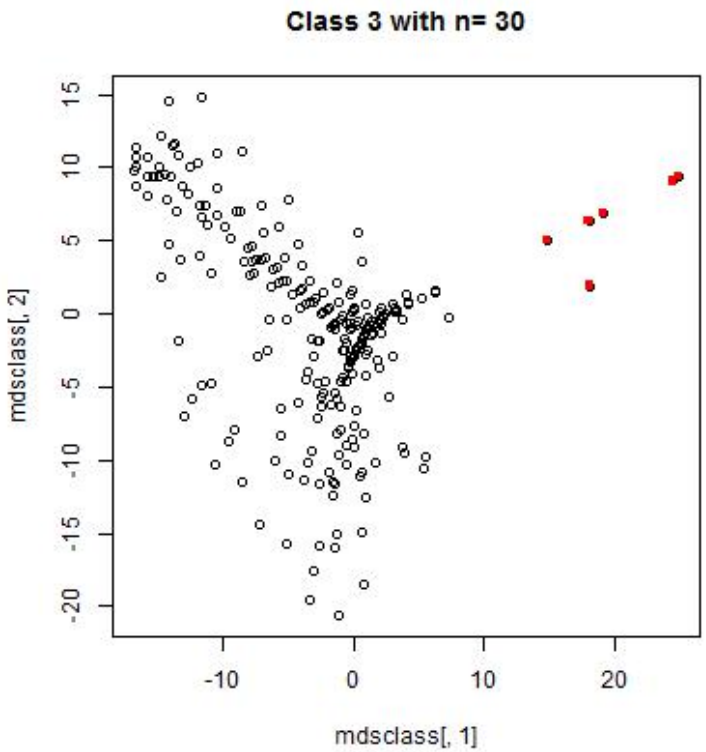


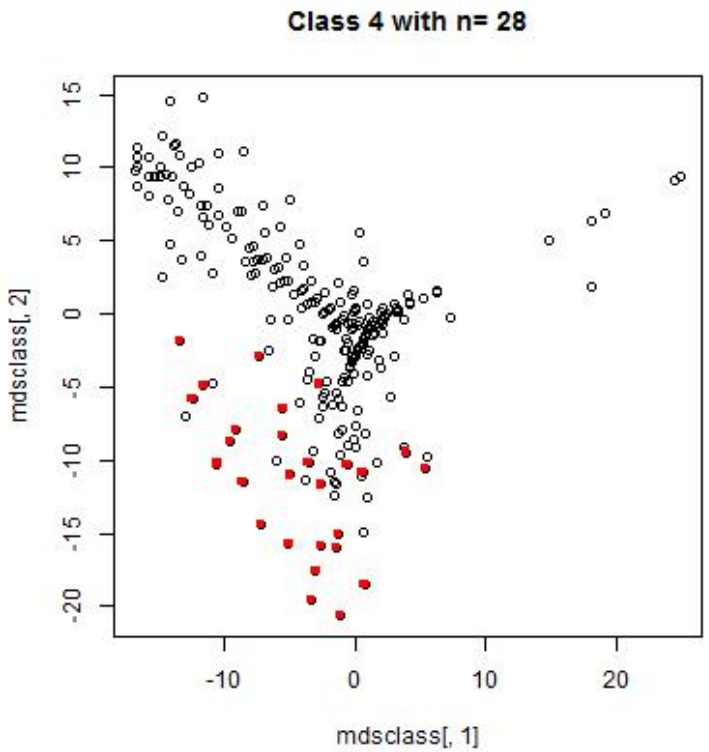
Visualizing Clusters via MDA Coordinates



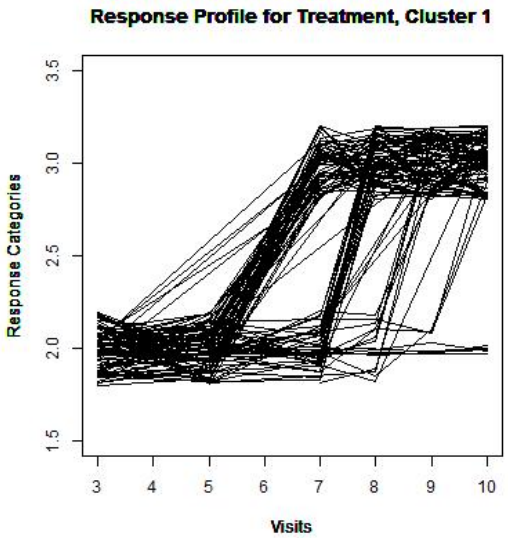


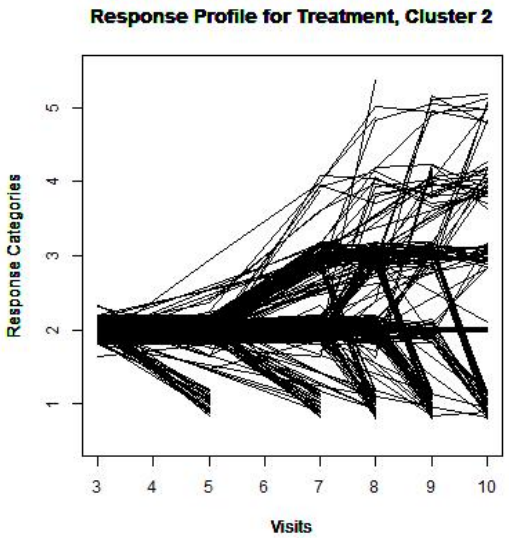
Visualizing Clusters via MDA Coordinates

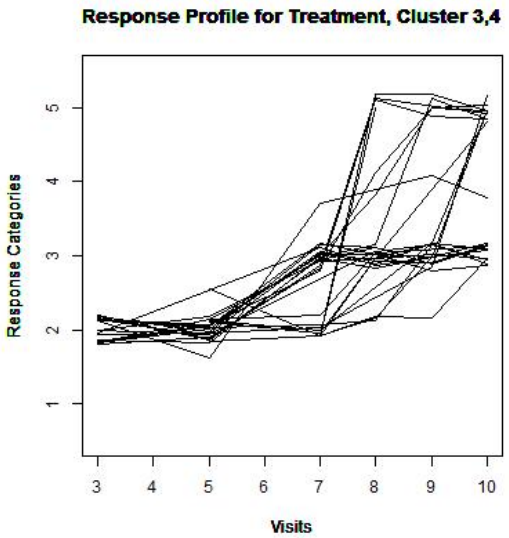




Response Profile Differences Among Clusters







Significant Clinical Variables for Each Cluster - 1

Cluster 1:

```
Call: glm(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)
```

Significant Clinical Variables for Each Cluster - 2

Cluster 2:

```
Call: glm(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)
```

Significant Clinical Variables for Each Cluster - 3

Cluster 3 (not very meaningful)

```
Call: glm(clustdata3[, 2] ~ trtgrp + wgtlbs + HemoglobinL + NeutrophilL +
      TotalProteinL + TotalProteinH + WBCL + WBCH,  family = quasibinomial, data = clustdata3)

Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)   -0.030766   1.212068  -0.025  0.97976
trtgrp        -0.909929   0.465616  -1.954  0.05112 .
wgtlbs        -0.010893   0.005695  -1.913  0.05623 .
HemoglobinL   -1.278757   0.553320  -2.311  0.02116 *
NeutrophilL   -3.982999   1.401341  -2.842  0.00463 **
TotalProteinL  1.699110   0.862776   1.969  0.04936 *
TotalProteinH  1.568914   0.602142   2.606  0.00939 **
WBCL           2.928279   1.098168   2.667  0.00786 **
WBCH           2.972175   1.266401   2.347  0.01924 *
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

(Dispersion parameter for quasibinomial family taken to be 0.8828353)
```

Significant Clinical Variables for Each Cluster - 4

Cluster 4 (not very meaningful)

```
Call: glm(clustdata4[, 2] ~ beta + trtgrp + n_pat + n_prt + wgtlbs + sex + prvel + PlateletsH +
      prmel + prdox + strlab2 + lbles + AlbuminL + LymphocytesH + MCVL + MonocytesH + NeutrophilsL +
      SerumIgAL + SerumIgAH + SerumIgGH + SerumIgML,  family = quasibinomial, data = clustdata4)

Coefficients:
              Estimate Std. Error t value Pr(>|t|)
(Intercept)  10.804782   2.067386   5.226 2.39e-07 ***
beta         -0.451664   0.128160  -3.524 0.000457 ***
trtgrp       -1.820682   0.498185  -3.655 0.000280 ***
n_pat        -0.485390   0.227962  -2.129 0.033641 *
n_prt        -1.344828   0.328923  -4.089 4.93e-05 ***
wgtlbs       -0.022980   0.006257  -3.673 0.000262 ***
sex          -0.966395   0.357699  -2.702 0.007095 **
prvel         1.719151   0.573021   3.000 0.002811 **
prmel         1.175529   0.405804   2.897 0.003908 **
prdox        -1.181259   0.364440  -3.241 0.001256 **
strlab2      -0.753699   0.435724  -1.730 0.084190 .
lbles        -0.748678   0.405826  -1.845 0.065558 .
AlbuminL     -4.520015   1.272080  -3.553 0.000411 ***
LymphocytesH -12.313233  3.135045  -3.928 9.58e-05 ***
MCVL          4.487353   1.860209   2.412 0.016153 *
MonocytesH    1.728668   0.735898   2.349 0.019146 *
NeutrophilsL 10.695509   2.379572   4.495 8.37e-06 ***
PlateletsH   -29.758485  9.062105  -3.284 0.001084 **
SerumIgAL     -2.128172   0.488473  -4.357 1.55e-05 ***
```

Significant Clinical Variables for Each Cluster - 5

```
SerumIgAH     -7.858927   1.790045  -4.390 1.34e-05 ***
SerumIgGH     -1.858542   0.688102  -2.701 0.007110 **
SerumIgML     -2.096981   0.472279  -4.440 1.07e-05 ***
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

(Dispersion parameter for quasibinomial family taken to be 0.3131812)
```

toc

Modeling Response Profiles via GEE - 1

Notations:

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

Modeling Response Profiles via GEE - 2

- Denote response vector by

$$Y_i = (Y_{i1}', \cdots, Y_{iT_i}')'$$

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

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

- Let

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

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

and

$$\pi_i = E(Y_i|x_i) = (\pi_{i1}', \cdots, \pi_{iT_i}')'.$$

Modeling Response Profiles via GEE - 3

- Denote the link function by g and, for subject i at time t, is defined as

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

  where β is the p-variate regression vector of interest.
- The choice of the link function g (hence the marginal model) should reflect the response scale.

Modeling Response Profiles via GEE - 4

- For **ordinal multinomial responses**, the family of cumulative link models

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

- or the adjacent categories logit model

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

  where F is the CDF of a continuous distribution and $\{\beta_{0j}, j = 1, 2, \cdots, J-1\}$ are the category specific intercepts.
- Note: the category specific intercepts need to satisfy a monotonicity condition

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

  when the family of cumulative link models is employed.

Modeling Response Profiles via GEE - 5

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

$$\log(\pi_{itj}/\pi_{itJ}) = \beta_{0j} + \boldsymbol{\beta_j' x_{it}},$$

  where β_j is the jth category specific parameter vector.
- Note: the regression parameter coefficients of the covariates x_{it} are category specific in the marginal baseline category logit model.

Modeling Response Profiles via GEE - 6

Estimation of the marginal regression parameter vector

- Let β be the p-variate parameter vector that includes all the regression parameters.
- Let the general estimating equation be

$$\boldsymbol{U}(\beta, \hat{\boldsymbol{\alpha}}) = (1/N) \sum_{i=1}^{N} \boldsymbol{D_i V_i^{-1}(Y_i - \pi_i)} = \mathbf{0}, \tag{3}$$

where

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

Modeling Response Profiles via GEE - 7

Local Odds Ratio

- Consider the time-pairs $\{(1,2),(1,3),\cdots,(T-1,T)\}$.
- 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 cutpoint (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

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

Modeling Response Profiles via GEE - 8

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

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

  which can be estimated by MLE.

- Note: for practical purpose, the score functions $\mu_j^{(t,t')}$ are simplified and let $\mu_j^{(t,t')} = j$, and the general association parameter $\phi^{(t,t')} = \phi$.

Modeling Response Profiles via GEE - 9

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

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

and $\boldsymbol{V_i}$ can be calculated, hence $\boldsymbol{\beta}$ can be estimated via the GEE (3).

Modeling Response Profiles via GEE - 10

Model Fitting for Cluster 1:

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

call: ordLORgee(Resp ~ factor(trtgrp) + age + beta + n_psct,
      data = xdat, id = pt, link = "logit", LORstr = "uniform")

Coefficients:
                 Estimate   san.se   san.z Pr(>|san.z|)
beta01           -0.02995  0.74876 -0.0400      0.96809
beta02            1.93939  0.73483  2.6392      0.00831 **
factor(trtgrp)2   0.03449  0.17693  0.1949      0.84544
age              -0.02518  0.01095 -2.3004      0.02143 *
beta             -0.02312  0.03718 -0.6218      0.53411
n_psct           -0.23305  0.12761 -1.8262      0.06781 .
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
```

Modeling Response Profiles via GEE - 11

Model Fitting for Cluster 1:

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

call: ordLORgee(Resp ~ 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          -0.02491  0.82330 -0.0302      0.97587
beta02           1.86298  0.79867  2.3326      0.01967 *
factor(trtgrp)2  0.08449  0.21544  0.3922      0.69492
age             -0.02923  0.01193 -2.4507      0.01426 *
beta            -0.03528  0.04723 -0.7468      0.45516
n_psct          -0.19395  0.15734 -1.2327      0.21771
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
```

Modeling Response Profiles via GEE - 12

- rxdiff1
- predict1

Modeling Response Profiles via GEE - 13

```
Local Odds Ratios Estimates (uniform):
          v3       v5       v7       v8       v9      v10
v3  0.000000 1.536842 1.536842 1.536842 1.536842 1.536842
v5  1.536842 0.000000 1.536842 1.536842 1.536842 1.536842
v7  1.536842 1.536842 0.000000 1.536842 1.536842 1.536842
v8  1.536842 1.536842 1.536842 0.000000 1.536842 1.536842
v9  1.536842 1.536842 1.536842 1.536842 0.000000 1.536842
v10 1.536842 1.536842 1.536842 1.536842 1.536842 0.000000

Local Odds Ratios Estimates (category-exch):
           v3       v5       v7       v8       v9        v10
v3  0.0000000 3.524637 4.533996 1.437081 1.250256 0.8870811
v5  3.5246371 0.000000 2.512431 3.422035 1.982073 1.4240733
v7  4.5339961 2.512431 0.000000 1.383113 1.347196 1.0620751
v8  1.4370814 3.422035 1.383113 0.000000 1.590531 1.3749597
v9  1.2502561 1.982073 1.347196 1.590531 0.000000 1.6036001
v10 0.8870811 1.424073 1.062075 1.374960 1.603600 0.0000000
```

Modeling Response Profiles via GEE - 14

Model Fitting for Cluster 2:

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

ordLORgee(Resp ~ 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          -1.13280  0.44856 -2.5254      0.01156 *
beta02          -0.37412  0.43864 -0.8529      0.39370
beta03           2.34313  0.44767  5.2341      < 2e-16 ***
beta04           3.84869  0.48232  7.9796      < 2e-16 ***
beta05           5.27519  0.56302  9.3694      < 2e-16 ***
factor(trtgrp)2  0.71292  0.10934  6.5200      < 2e-16 ***
age             -0.01476  0.00616 -2.3982      0.01648 *
beta             0.00900  0.01677  0.5365      0.59163
n_psct          -0.07882  0.09061 -0.8699      0.38436
```

Modeling Response Profiles via GEE - 15

- rxdiff3
- predict3

Modeling Response Profiles via GEE - 16

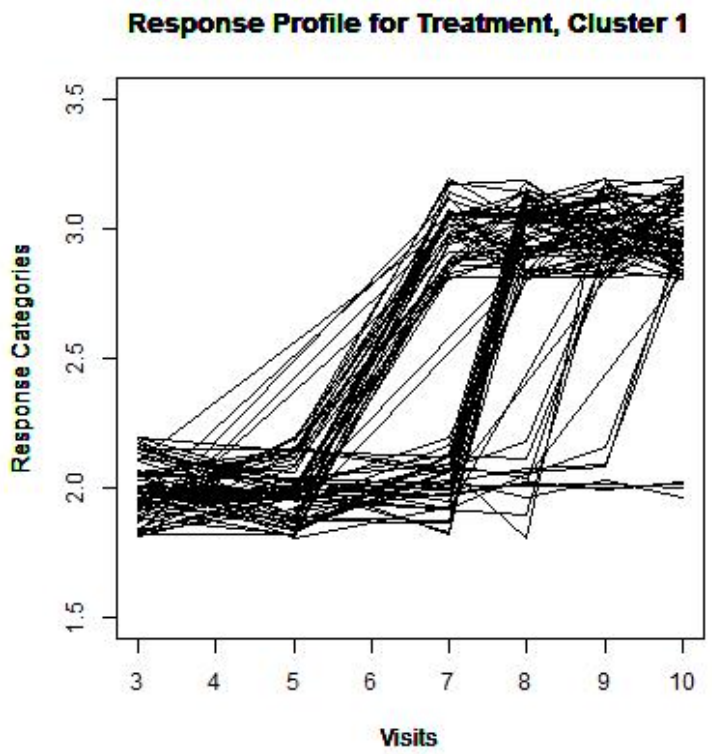
```
Local Odds Ratios Estimates (category-exch):
          v3       v5       v7       v8       v9      v10
v3  0.000000 1.267894 1.425216 1.090078 1.062992 1.110347
v5  1.267894 0.000000 1.369849 1.288635 1.126296 1.140510
v7  1.425216 1.369849 0.000000 1.289670 1.400998 1.400214
v8  1.090078 1.288635 1.289670 0.000000 1.162275 1.206059
v9  1.062992 1.126296 1.400998 1.162275 0.000000 1.336574
v10 1.110347 1.140510 1.400214 1.206059 1.336574 0.000000
```

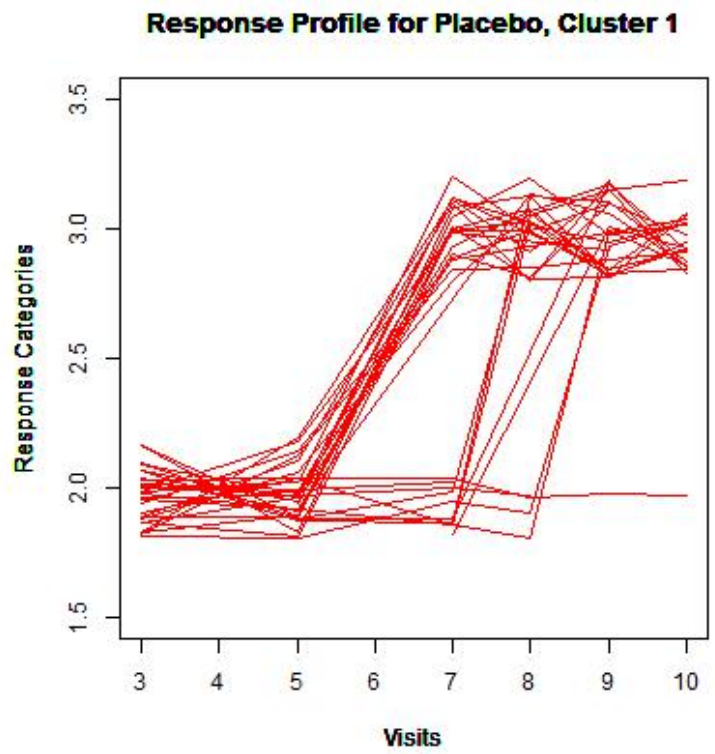
Summary

- Examining the entire response profiles can provide much more insight about the efficacy and safety of treatments.
- Most of the studies in pharmaceutical companies do not yet commonly implement this level of data analysis.
- In dynamic treatment allocation study designs and other more adaptive studies, subjects' responses are tracked at every cycle or visit so that the appropriate next treatment can be assigned.
- For better drug development success and more beneficial individualized medicine, examining the whole profile of responses has become an important methodology of advanced research for a more in-depth understanding of medical treatment effect.

Thank You for Your Attention!

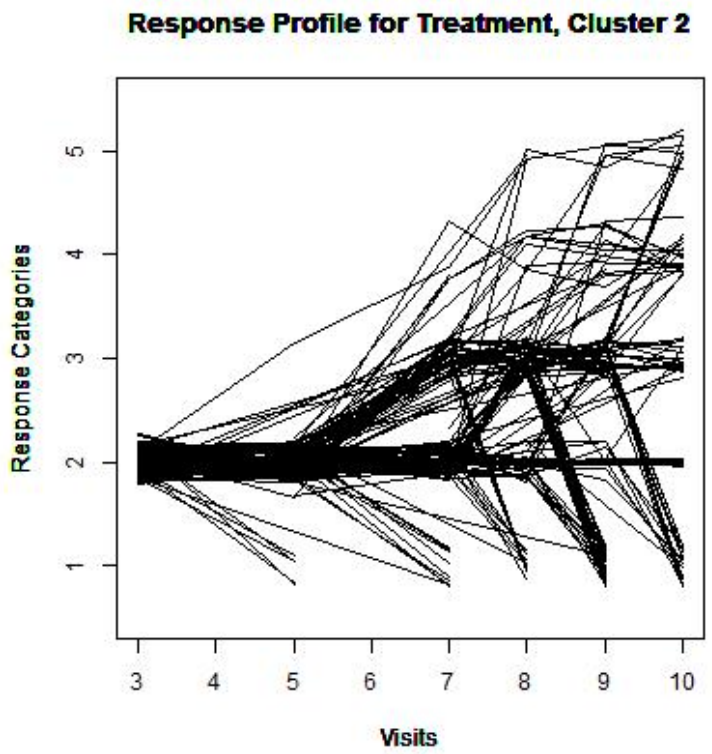
Treatment Effect on Response Profiles (Cluster 1)

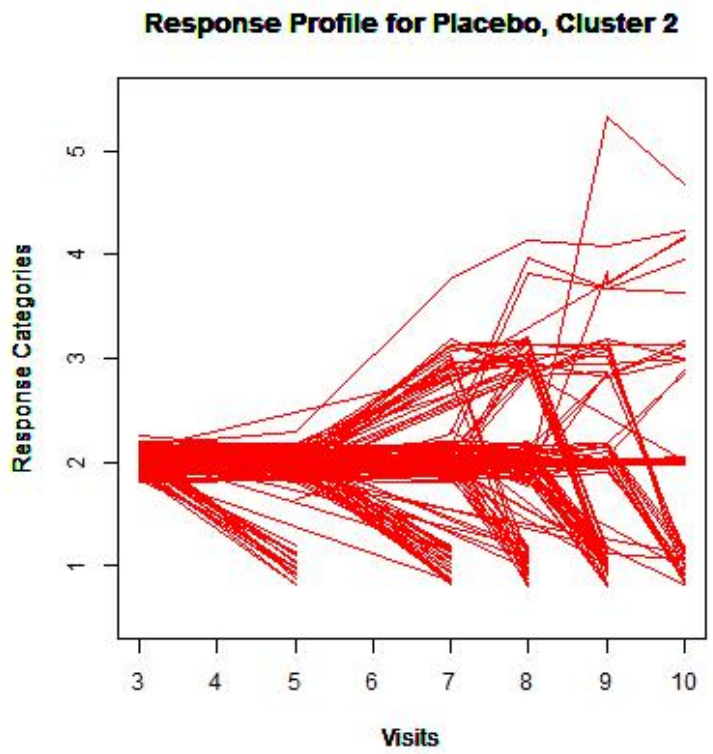




▸ rxdiff2

Treatment Effect on Response Profiles (Cluster 2)





▸ rxdiff4

Prediction Error of Multinomial GEE Model (Cluster 1)

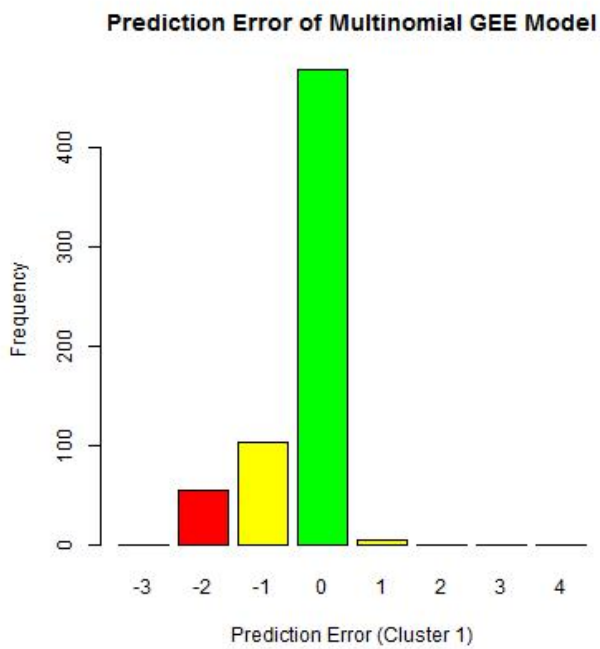


Figure 1: LOR = uniform

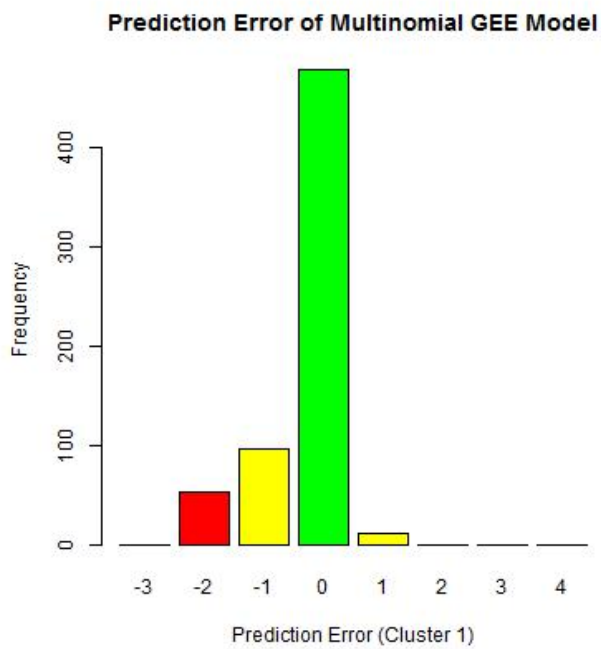
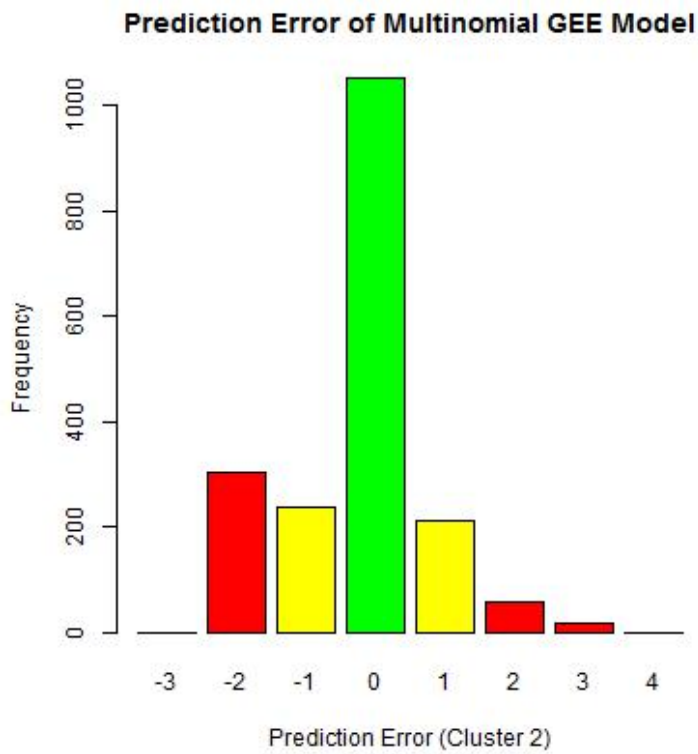


Figure 2: LOR = cat-exch

predict2

Prediction Error of Multinomial GEE Model (Cluster 2)



predict4