# Latent class modeling using matrix-valued covariates with application to identifying early placebo responders based on EEG signals

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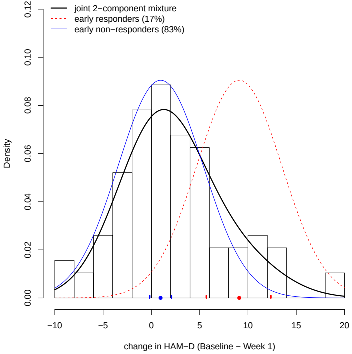
# Motivating study: placebo response

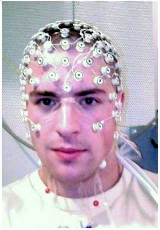
- Placebo response, i.e., *a positive medical response due to placebo effect, as if there were an active medication*, to antidepressant treatment is highly prevalent.
- For example, 96 placebo or drug treated depression patients

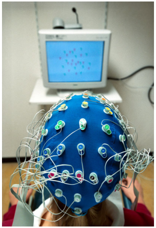



- Hamilton Depression (HAM-D) scale is a clinical measure to rate severity of depression
- Higher HAM-D scores indicate more severe depression
- An antidepressant takes more than 2 weeks to show real drug effect
- Subjects may cluster into two clinically relevant subgroups: early responder vs. non-responder.

# Motivating study: scientific goals

- Interest has focused on studying patient's characteristics that could contribute to placebo response
- However, typically measured clinical phenotypes, e.g. symptom severity and treatment history, have shown low predictive power.
- Now explore predictive ability of neuroimaging phenotypes, e.g, the electrical brain activity under certain tasks measured through Electroencephalography (EEG)





https://en.wikipedia.org/wiki/Electroencephalography
http://www.lsa.umich.edu/psych/danielweissmanlab/whatiseeg.htm

# Motivating study: statistical goals

- For clinical outcome HAM-D scores, formulate a latent class model
  - take into account uncertainty of latent class membership
- EEG covariate to predict latent class membership
  - $14 \times 45$ matrix (order-2 tensor)
  - captures brain activity measured at 14 electrodes, crossed with 45 frequencies within the theta (4 - 7 hz) and alpha (7 - 15 hz) bands.

# Motivating study: statistical goals

- Our approach: extend latent class models to incorporate matrix-valued EEG covariate
  - utilizes low rank CANDECOMP/PARAFAC (CP) decomposition (Kolda and Bader 2009) to represent the target coefficient matrix
    - reduce model dimensionality
    - explicitly capture bilinear structure
  - CP decomposition was previously considered by Hung and Wang (2013); Zhou et al. (2014) (penalized maximum likelihood approach)
  - In contrast, we adopt a hierarchical approach in formulating the CP decomposition and a Bayesian method for estimation (next)
    - provides a flexible way to incorporate prior knowledge on the patterns of covariate effect heterogeneity
    - provides a data-driven method of regularization
    - associated measures of uncertainty can be quantified through credible intervals

# The proposed methodology

- The manifest model for clinical outcome $y_i$

$$y_i = \eta_0 + \eta_1 \gamma_i + \epsilon_i, \ \epsilon_i \overset{iid}{\sim} N(0, \sigma^2)$$

  - $\gamma_i = 1$ indicates a placebo responder; $\gamma_i = 0$ a non-responder;
  - Constrain $\eta_0 + \eta_1 > 0$: placebo responders are expected to experience improved mood and hence positive clinical outcome values.

# The proposed methodology

- The low rank probit model:

$$\begin{aligned}\Phi^{-1}[p\{\gamma_i = 1\}] &= \boldsymbol{\theta}^T \boldsymbol{z}_i + \langle \boldsymbol{\Theta}, \boldsymbol{x}_i \rangle, \\ &= \boldsymbol{\theta}^T \boldsymbol{z}_i + \left\langle \sum_{r=1}^{R} \boldsymbol{\alpha}_r \boldsymbol{\beta}_r^T, \boldsymbol{x}_i \right\rangle, \\ &= \boldsymbol{\theta}^T \boldsymbol{z}_i + \left\langle \boldsymbol{A}\boldsymbol{B}^T, \boldsymbol{x}_i \right\rangle,\end{aligned}$$

  - $\boldsymbol{x}_i$ is $p \times q$ matrix covariate
  - $\boldsymbol{z}_i$ is a vector of scalar covariates
  - $\boldsymbol{\Theta} \in \mathbb{R}^{p \times q}$ denotes the target coefficient matrix
  - $\langle \boldsymbol{\Theta}, \boldsymbol{x}_i \rangle = \langle vec(\boldsymbol{\Theta}), vec(\boldsymbol{x}_i) \rangle$
  - CP decomposition: express $\boldsymbol{\Theta} = \sum_{r=1}^{R} \boldsymbol{\alpha}_r \boldsymbol{\beta}_r^T$, where $\boldsymbol{\alpha}_r \in \mathbb{R}^p$ and $\boldsymbol{\beta}_r \in \mathbb{R}^q$, $r = 1, \cdots, R < \min(p, q)$
  - let $\boldsymbol{A} = [\boldsymbol{\alpha}_1, \cdots, \boldsymbol{\alpha}_R] \in \mathbb{R}^{p \times R}$ and $\boldsymbol{B} = [\boldsymbol{\beta}_1, \cdots, \boldsymbol{\beta}_R] \in \mathbb{R}^{q \times R}$, we can re-write $\boldsymbol{\Theta} = \boldsymbol{A}\boldsymbol{B}^T$
  - Now reduced to estimating $\boldsymbol{A}$ and $\boldsymbol{B}$: a total of $R(p+q)$ parameters

# The proposed methodology

- Alternatively: re-express $\boldsymbol{A}$ and $\boldsymbol{B}$ w.r.t. their row vectors
  - $\boldsymbol{A} = [\tilde{\boldsymbol{\alpha}}_1, \cdots, \tilde{\boldsymbol{\alpha}}_p]^T$, $\boldsymbol{B} = [\tilde{\boldsymbol{\beta}}_1, \cdots, \tilde{\boldsymbol{\beta}}_q]^T$
  - $\tilde{\boldsymbol{\alpha}}_j \in \mathbb{R}^R$ and $\tilde{\boldsymbol{\beta}}_k \in \mathbb{R}^R$ can be interpreted as representing the effects due to the row and column components of the matrix covariate
  - $\boldsymbol{\Theta}_{j,k} = \langle \tilde{\boldsymbol{\alpha}}_j, \tilde{\boldsymbol{\beta}}_k \rangle$ is equivalent to modeling the two-way interaction effects
  - next we propose hierarchical priors on $\{\tilde{\alpha}_j\}_{j=1}^p$ and $\{\tilde{\beta}_k\}_{k=1}^q$

# The hierarchical formulation of CP decomposition

- For the row and column effect vectors in the CP decomposition, we consider the following hierarchical priors,

$$\tilde{\boldsymbol{\alpha}}_1, \cdots, \tilde{\boldsymbol{\alpha}}_p \overset{iid}{\sim} \text{MVN}(\boldsymbol{\mu}_\alpha, \boldsymbol{\Sigma}_\alpha); \text{ and } \tilde{\boldsymbol{\beta}}_1, \cdots, \tilde{\boldsymbol{\beta}}_q \overset{iid}{\sim} \text{MVN}(\boldsymbol{\mu}_\beta, \boldsymbol{\Sigma}_\beta)$$

  - $\tilde{\boldsymbol{\alpha}}_j^T$ is the $j^{th}$ row of $\boldsymbol{A}$ and $\tilde{\boldsymbol{\beta}}_k^T$ is the $k^{th}$ row of $\boldsymbol{B}$
  - allows borrowing information and also provides a data-driven method of regularization.
- To complete the specification of these hierarchical priors, we define the following hyper-priors,

$$\boldsymbol{\mu}_\alpha, \boldsymbol{\mu}_\beta \sim \text{MVN}(\mathbf{0}, \boldsymbol{\Sigma}_0); \text{ and } \boldsymbol{\Sigma}_\alpha, \boldsymbol{\Sigma}_\beta \sim \text{inverse Wishart}(\boldsymbol{S}_0, s_0)$$

  - let $\boldsymbol{\Sigma}_0 = 9/4\boldsymbol{I}$ to bound $\Pr(\gamma_i = 1)$ to be away from 0 and 1
  - a diffuse prior for $\boldsymbol{\Sigma}_\alpha$ and $\boldsymbol{\Sigma}_\beta$ with $\boldsymbol{S}_0 = 10\boldsymbol{I}$, and $s_0 = R + 1$.

# The hierarchical formulation of CP decomposition

- The CP decomposition of $\boldsymbol{\Theta}$ suffers from non-identifiability of $\boldsymbol{A}$ and $\boldsymbol{B}$ separately, since $\boldsymbol{A}\boldsymbol{B}^T = \boldsymbol{A}\boldsymbol{\Lambda}\boldsymbol{\Lambda}^{-1}\boldsymbol{B}^T$, for any $R \times R$ non-singular matrix $\boldsymbol{\Lambda}$.
- A consequence of this complication is that $\boldsymbol{\mu}_\alpha, \boldsymbol{\mu}_\beta, \boldsymbol{\Sigma}_\alpha, \boldsymbol{\Sigma}_\beta$ are not individually identifiable either.
- However, from a Bayesian perspective, good mixing and convergence can be achieved for all parameters in the identifiable $\boldsymbol{\Theta} = \boldsymbol{A}\boldsymbol{B}^T$.

# priors for other model parameters

- In the manifest model, we assume diffuse priors: $\eta_0 \sim N(0, \tau_0^2)$, $\eta_1 \sim N(0, \tau_0^2)\mathrm{I}(-\eta_0, \infty)$ with $\tau_0^2 = 100$ and $\sigma^2 \sim$ inverse gamma$(a_0, b_0)$ with $a_0 = b_0 = 0.01$.
- For covariate effect parameters in the probit model, we let $\boldsymbol{\theta} \sim N(\mathbf{0}, \boldsymbol{V}_0)$, where $\boldsymbol{V}_0 = (9/4)\boldsymbol{I}$ would bound the probability to be away from 0 and 1.

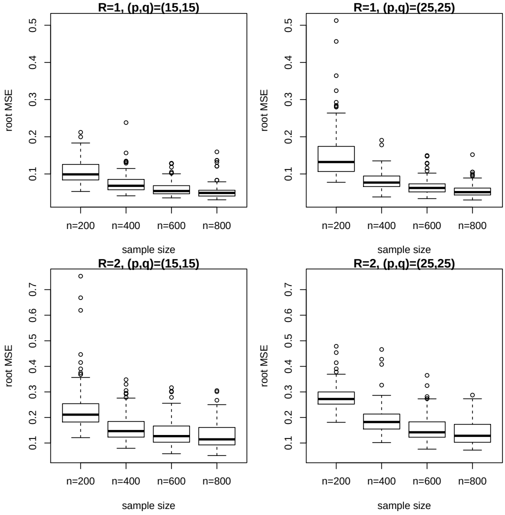
# Posterior computation

- note that $\left\langle \boldsymbol{A}\boldsymbol{B}^T, \boldsymbol{x}_i \right\rangle$ in the probit model can be rewritten as a linear function with respect to $\tilde{\alpha}_1, \cdots, \tilde{\alpha}_p$ or $\tilde{\boldsymbol{\beta}}_1, \cdots, \tilde{\boldsymbol{\beta}}_q$ as follows,

$$\left\langle \boldsymbol{A}\boldsymbol{B}^T, \boldsymbol{x}_i \right\rangle = \sum_{j=1}^{p} \tilde{\alpha}_j^T \boldsymbol{u}_{ij} = \sum_{k=1}^{q} \tilde{\boldsymbol{\beta}}_k^T \boldsymbol{v}_{ik}$$

  - $\boldsymbol{u}_{ij}$ denotes the $j^{th}$ row of $\boldsymbol{x}_i^T \boldsymbol{B} \in \mathbb{R}^{p \times R}$, $j = 1, \cdots, p$;
  - $\boldsymbol{v}_{ik}$ denotes the $k^{th}$ row of $\boldsymbol{x}_i^T \boldsymbol{A} \in \mathbb{R}^{q \times R}$, $k = 1, \cdots, q$.
- We introduce a latent variable $w_i$ such that $\gamma_i = \mathrm{I}(w_i > 0)$ and $w_i \sim \mathrm{N}(\boldsymbol{\theta}^T \boldsymbol{z}_i + \langle \boldsymbol{A}\boldsymbol{B}^T, \boldsymbol{x}_i \rangle, 1)$ (Albert and Chib,1993).
- $\{\tilde{\alpha}_j\}_{j=1}^{p}$ and $\{\tilde{\boldsymbol{\beta}}_k^T\}_{k=1}^{q}$ can be updated iteratively in a similar fashion as in a regular regression model

# Simulation study I: known rank



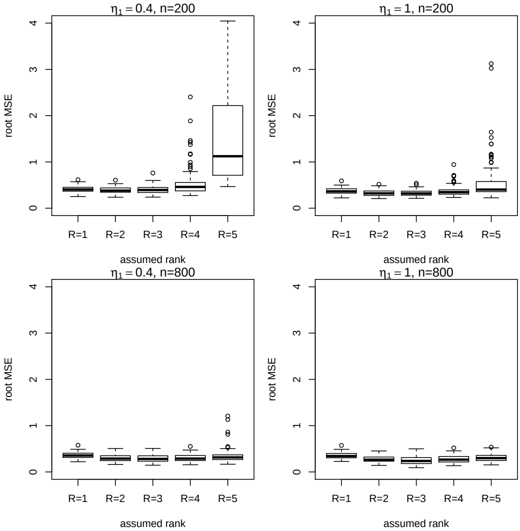

- the degree of overlapping in latent classes is fixed: $\eta_0 = 0$, $\eta_1 = 1.0$ & $\sigma^2 = 0.2^2$ (well separated).
- true values for $R$, $(p, q)$, and $n$ vary under different simulation scenarios.
- $\text{MSE} = \frac{1}{S}\sum_{s=1}^{S}\left\{\frac{1}{pq}\|\hat{\boldsymbol{\Theta}}^{(s)} - \boldsymbol{\Theta}^{(s)}_{\text{true}}\|_F^2\right\}$

# Simulation study I: known rank

Table: AUC for prediction of binary latent class indicator.

| | true rank $R = 1$ | | | | true rank $R = 2$ | | | |
|---|---|---|---|---|---|---|---|---|
| | $n = 200$ | $n = 400$ | $n = 600$ | n=800 | $n = 200$ | $n = 400$ | $n = 600$ | n=800 |
| **within sample AUC** | | | | | | | | |
| $(p, q) = (15, 15)$ | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| $(p, q) = (25, 25)$ | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| **out of sample AUC** | | | | | | | | |
| $(p, q) = (15, 15)$ | 0.86 | 0.90 | 0.90 | 0.91 | 0.80 | 0.88 | 0.91 | 0.92 |
| $(p, q) = (25, 25)$ | 0.87 | 0.93 | 0.94 | 0.95 | 0.74 | 0.88 | 0.92 | 0.94 |

# Simulation study II: misspecified rank




- true rank $R = 3$, $(p, q) = (15, 15)$; $n = 200$ or 800.
- $\eta_1 = 0.4$ and $\eta_1 = 1.0$ indicate high and low degrees of overlapping.
- the models are fit with varying assumed rank values

# Simulation study II: misspecified rank

Table: AUC for prediction of binary latent class indicator.

| | **high degree overlapping** | | | | | **low degree overlapping** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| assumed rank | R=1 | R=2 | R=3 | R=4 | R=5 | R=1 | R=2 | R=3 | R=4 | R=5 |
| | | | | | **within sample AUC** | | | | | |
| | 0.94 | 0.96 | 0.96 | 0.95 | 0.93 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| | | | | | **out of sample AUC** | | | | | |
| | 0.80 | 0.84 | 0.84 | 0.81 | 0.79 | 0.82 | 0.88 | 0.88 | 0.86 | 0.84 |

# Application to identify placebo responder subgroup using EEG data

- let $y_i$ denote the change in HAM-D (baseline - week 1)
- let $\boldsymbol{x}_i^* \in \mathbb{R}^{14 \times 45}$ denote Current Source Density amplitude spectrum values ($\mu V/m^2$) (Keyser and Tenke, 2006) at 14 electrodes in brain's posterior region, crossed with 45 frequency bands within the theta (4 - 7 hz) and alpha (7 - 15 hz) frequency waves
  - Multilinear Principal Component Analysis (MPCA) to reduce the original dimension of EEG data from $(p, q)$ to $(p_0, q_0)$.
  - The dimension $(p_0, q_0)$ and rank $R$ are determined by the widely applicable information criterion (WAIC) proposed by Watanabe (2010).
- let $\boldsymbol{z}_i$ denote gender and depression chronicity

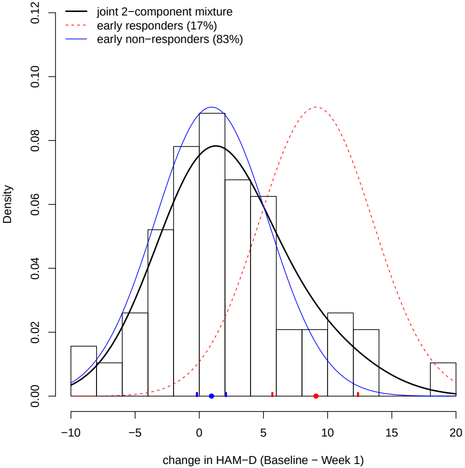
# Application to identify placebo responder subgroup using EEG data

Table: WAIC from fitting different models for the prediction of the placebo responder subgroup using EEG data.

| | rank R=1 | | | | | rank R=2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| $p_0$ / $q_0$ | 2 | 3 | 4 | 5 | 6 | 2 | 3 | 4 | 5 | 6 |
| 2 | 603.4 | 605.5 | 601.3 | 600.2 | 601.9 | 604.4 | 604.6 | 601.0 | 601.3 | 599.1 |
| 3 | 602.8 | 601.2 | 594.2 | 593.9 | 594.8 | 604.0 | 599.2 | 596.2 | 596.5 | 603.8 |
| 4 | 602.7 | 603.9 | 583.7 | 590.2 | 595.1 | 604.1 | 601.7 | 595.1 | 596.0 | 602.0 |
| 5 | 601.1 | 602.4 | 591.6 | 598.0 | 598.1 | 603.5 | 602.3 | 598.5 | 597.8 | 598.0 |
| 6 | 598.1 | 600.1 | 577.3 | 577.9 | 582.1 | 600.6 | 601.7 | 589.9 | 588.6 | 588.7 |
| 7 | 582.9 | 591.1 | 571.9 | 578.7 | 578.7 | 599.2 | 595.4 | 588.1 | 593.9 | 596.2 |
| 8 | 584.7 | 589.4 | 573.3 | 574.7 | 575.0 | 599.3 | 597.3 | 590.1 | 589.8 | 594.0 |
| 9 | 587.1 | 594.4 | **568.8** | 573.1 | 573.5 | 602.3 | 600.6 | 591.8 | 594.4 | 592.8 |
| 10 | 588.4 | 594.2 | 571.1 | 574.1 | 583.8 | 600.5 | 600.0 | 590.6 | 588.8 | 590.3 |

Note: WAIC for no-mixture model is 845.6.

# Application to identify placebo responder subgroup using EEG data




- the proportion of placebo responders for the placebo arm and drug arm: 9/50=18% and 7/46=15% respectively.
- a chi-square test indicates no significant difference

# Application to identify placebo responder subgroup using EEG data

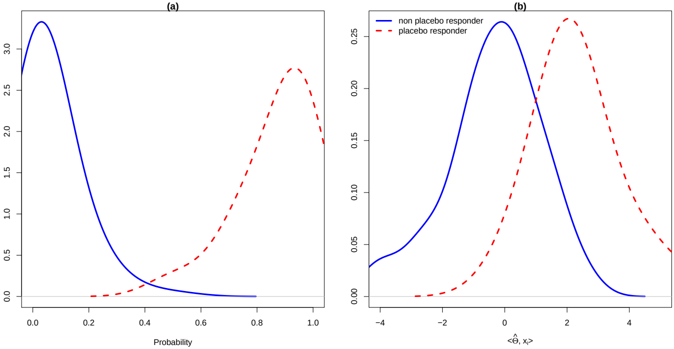
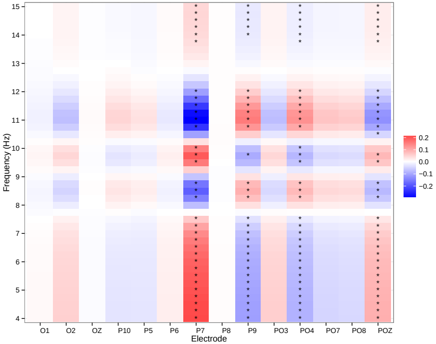



Figure: left: posterior density estimate of the probability of being in the placebo responder subgroup; right: posterior density estimate of $< \boldsymbol{\Theta}, \boldsymbol{x}_i >$.

# Application to identify placebo responder subgroup using EEG data

- Heatmap of the estimated coefficient matrix (* indicates significance at the 0.05 level)




- being chronically depressed is less likely for placebo response ($\hat{\theta}_2 = -1.65$ (95% CI: -3.59, -0.12)), while gender is not a contributing factor ($\hat{\theta}_1 = -1.34$ (95% CI: -3.14, 0.02)).

# Summary

- We consider a low rank hierarchical latent class model to incorporate matrix-valued covariates.
- The proposed approach readily extends to incorporate the covariates that are multi-dimensional arrays in general regression settings.
- Our simulation studies have shown that our proposed hierarchical approach is robust against rank misspecification.
- The findings in the application raise hope for utilizing EEG measures to differentiate potential placebo responders from non-responders in clinical practice to further guide the selection of effective treatment for depression patients.

# Simulation study: setup

- For all simulation scenarios, $(y_i, \boldsymbol{x}_i, \boldsymbol{z}_i, \gamma_i)$ are generated as follows,
  1. each element in $\boldsymbol{x}_i$, $\{\boldsymbol{x}_i\}_{j,k} \overset{iid}{\sim} \text{uniform}(-1, 1)$;
  2. let $\boldsymbol{z}_i = (1, z_{i1})^T$ with $z_{i1} \sim \text{uniform}(0, 1)$;
  3. let $\boldsymbol{\theta} = (0, 1)^T$, generate $\gamma_i$ given $\boldsymbol{x}_i$ and $\boldsymbol{z}_i$, with $\boldsymbol{\Theta}$ generated from: When rank $R > 1$,
     - 3.1 let $\boldsymbol{\mu}_\alpha = \boldsymbol{\mu}_\beta = (0, \cdots, 0)^T$ and $\boldsymbol{\Sigma}_\alpha = \boldsymbol{\Sigma}_\beta$ be diagonal with all diagonal elements equal to $0.5^2$; generate $\tilde{\boldsymbol{\alpha}}_j \overset{iid}{\sim} N(\boldsymbol{\mu}_\alpha, \boldsymbol{\Sigma}_\alpha)$, $j = 1, \cdots, p$ and $\tilde{\boldsymbol{\beta}}_k \overset{iid}{\sim} N(\boldsymbol{\mu}_\beta, \boldsymbol{\Sigma}_\beta)$, $k = 1, \cdots, q$;
     - 3.2 set $\boldsymbol{A} = [\tilde{\boldsymbol{\alpha}}_1, \cdots, \tilde{\boldsymbol{\alpha}}_p]^T$ and $\boldsymbol{B} = [\tilde{\boldsymbol{\beta}}_1, \cdots, \tilde{\boldsymbol{\beta}}_q]^T$, then $\boldsymbol{\Theta} = \boldsymbol{A}\boldsymbol{B}^T$.

     When rank $R = 1$,
     - 3.1 let $\mu_\alpha = \mu_\beta = 0$ and $\sigma_\alpha^2 = \sigma_\beta^2 = 0.5^2$; generate $\tilde{\alpha}_j \overset{iid}{\sim} N(\mu_\alpha, \sigma_\alpha^2)$, $j = 1, \cdots, p$ and $\tilde{\beta}_k \overset{iid}{\sim} N(\mu_\beta, \sigma_\beta^2)$, $k = 1, \cdots, q$;
     - 3.2 set $\boldsymbol{\alpha}_1 = (\tilde{\alpha}_1, \cdots, \tilde{\alpha}_p)^T$ and $\boldsymbol{\beta}_1 = (\tilde{\beta}_1, \cdots, \tilde{\beta}_q)^T$, then $\boldsymbol{\Theta} = \boldsymbol{\alpha}_1 \boldsymbol{\beta}_1^T$.
  4. We generate $y_i$ given $\gamma_i$, where we fix $\eta_0 = 0$ and $\sigma = 0.2$, but we vary the value of $\eta_1$ in different scenarios.