

# Latent Space Modeling for Human Disease Network with Temporal Variations: Analysis of Medicare Data

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# Outline

- 1 Introduction
  - Background
  - Motivation
- 2 Method
  - Methodology
  - Statistical Properties
- 3 Experiments
  - Simulation Studies
  - Real Data Analysis

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- Background
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## 2 Method

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# Background: Human Disease Network

In the HDN analysis, the concept of network analysis is adopted. One node corresponds to a disease, and two diseases are connected with a network edge if they are “interconnected”.

- gene-centric HDN [Goh et al., 2007]
- phenotypic HDN [Zhou et al., 2014, 2022]
- **clinical outcome** HDN [Yang et al., 2022, Mei et al., 2025]
  - Two diseases are defined as interconnected if their clinical treatments and/or outcomes – such as inpatient length-of-stay (LOS), number of outpatient visits, and treatment costs – are “correlated”.

# Background: Latent Space Model

Our literature review suggests that one family of techniques, which has been widely adopted and shown as powerful in other contexts [Liu et al., 2024, Zhang et al., 2024a] but **limitedly examined for HDNs**, is latent space modeling [Hoff et al., 2002].

- Single layer network [Hoff et al., 2002, Ma et al., 2020]
- Multi-layer networks [Zhang et al., 2020]
- **Time-varying** networks [Sarkar and Moore, 2005, Liu et al., 2024]

# Background: Latent Space Model

Our literature review suggests that one family of techniques, which has been widely adopted and shown as powerful in other contexts [Liu et al., 2024, Zhang et al., 2024a] but **limitedly examined for HDNs**, is latent space modeling [Hoff et al., 2002].

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- **Time-varying** networks [Sarkar and Moore, 2005, Liu et al., 2024]

## **Limitation: Difficult to analyze the following sensible temporal structure**

- There are time intervals within which network structures remain **constant** – they correspond to small and slow changes in disease diagnosis, treatment.
- Between those intervals, network structures are assumed to **change smoothly**.

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# Data Exploration: Motivation

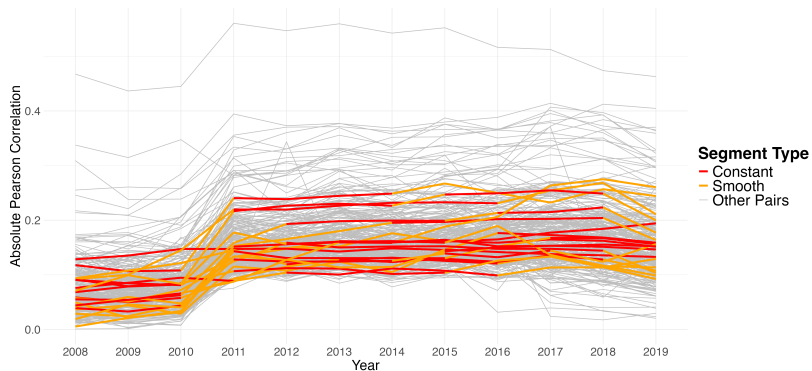


Figure: Pairwise interconnections: Pearson correlation

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# Data and Modeling Framework

- $p$ : number of diseases
- $T$ : number of time periods
- $n$ : number of subjects
- $\{y_{ij}^{(t)}\}_{i \in [n], j \in [p], t \in [T]}$ : clinical treatment measurement

As noted in the literature and can be seen from Figure 1, the marginal distributions of disease-specific LOS are highly zero-inflated.



# Time-varying Latent Space Modeling

- We adopt a two-part modeling approach for the estimation of network adjacency matrices [Mei et al., 2025].
  - $\mathbf{A} = \left[ \left( A_{jk}^{(1)} \right)_{j,k=1}^p ; \cdots ; \left( A_{jk}^{(T)} \right)_{j,k=1}^p \right] \in \{0, 1\}^{T \times p \times p}$ : a tensor for the time-varying adjacency matrices.
- We develop the latent space modeling based on the estimated  $\mathbf{A}$ .

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- We develop the latent space modeling based on the estimated  $\mathbf{A}$ .
- Overall, the model is defined as:

$$A_{jk}^{(t)} \sim \text{Bernoulli} \left( P_{jk}^{(t)} \right), \text{logit} \left( P_{jk}^{(t)} \right) := \Theta_{jk}^{(t)} = \alpha_j^{(t)} + \alpha_k^{(t)} + \mathbf{z}_j^\top \mathbf{\Lambda}^{(t)} \mathbf{z}_k,$$

where  $\text{logit}(x) = \log[x/(1-x)]$ ,  $P_{jk}^{(t)}$  represents the connection probability between diseases  $j$  and  $k$ , and  $\alpha_j^{(t)}$  is disease  $j$ 's heterogeneity parameter for period  $t$ .

# Identifiability

## Proposition

Suppose that two sets of parameters  $\left(\{\alpha^{(t)}\}_{t=1}^T, \{\Lambda^{(t)}\}_{t=1}^T, \mathbf{Z}\right)$  and  $\left(\{\alpha_{\dagger}^{(t)}\}_{t=1}^T, \{\Lambda_{\dagger}^{(t)}\}_{t=1}^T, \mathbf{Z}_{\dagger}\right)$  satisfy the following conditions:

1.  $\mathbf{J}_p \mathbf{Z} = \mathbf{Z}, \mathbf{J}_p \mathbf{Z}_{\dagger} = \mathbf{Z}_{\dagger}$ , where  $\mathbf{J}_p = \mathbf{I}_p - \frac{1}{p} \mathbf{1}_p \mathbf{1}_p^{\top}$ ;
2.  $\mathbf{Z}^{\top} \mathbf{Z} = p \mathbf{I}_r$  and  $\mathbf{Z}_{\dagger}^{\top} \mathbf{Z}_{\dagger} = p \mathbf{I}_r$ ;
3. At least one of  $\Lambda^{(t)}$ 's,  $t = 1, 2, \dots, T$ , is full rank.

Then,

$$\alpha^{(t)} \mathbf{1}_p^{\top} + \mathbf{1}_p \alpha^{(t)\top} + \mathbf{Z} \Lambda^{(t)} \mathbf{Z}^{\top} = \alpha_{\dagger}^{(t)} \mathbf{1}_p^{\top} + \mathbf{1}_p \alpha_{\dagger}^{(t)\top} + \mathbf{Z}_{\dagger} \Lambda_{\dagger}^{(t)} \mathbf{Z}_{\dagger}^{\top},$$

for  $t = 1, \dots, T$ , which implies that there exists an orthonormal matrix  $\mathbf{O} \in \mathbb{R}^{r \times r}$  where  $\mathbf{O}^{\top} \mathbf{O} = \mathbf{O} \mathbf{O}^{\top} = \mathbf{I}_r$ , such that

$$\alpha_{\dagger}^{(t)} = \alpha^{(t)}, \mathbf{Z}_{\dagger} = \mathbf{Z} \mathbf{O}, \Lambda_{\dagger}^{(t)} = \mathbf{O}^{\top} \Lambda^{(t)} \mathbf{O}$$

for  $t = 1, \dots, T$ .

# Estimation

The negative log-likelihood is:

$$L_{\text{NLL}}(\mathbf{Z}, \boldsymbol{\alpha}, \boldsymbol{\Lambda}) = - \sum_{t=1}^T \sum_{j,k=1}^p \left\{ A_{jk}^{(t)} \Theta_{jk}^{(t)} + \log \left( 1 - \sigma \left( \Theta_{jk}^{(t)} \right) \right) \right\},$$

As discussed above, we consider the temporal structure with “**piecewise constant + smoothly varying**” properties. To achieve this, we propose a penalty built on the combination of  $\ell_1$  and  $\ell_2$  norms. Following Tibshirani [2014] and other literature, we refer it to as the **Mixed Trend Filter (MTF)** penalty, which has the form:

$$Q(\boldsymbol{\alpha}, \boldsymbol{\Lambda}) = \lambda_1 \left( \left\| \mathbf{D}^{(1)} \boldsymbol{\alpha} \right\|_{\ell_1} + \sum_{t=1}^{T-1} \left\| \left( \mathbf{D}^{(1)} \boldsymbol{\Lambda} \right)^{(t)} \right\|_F \right) + \frac{\lambda_2}{2} \left( \left\| \mathbf{D}^{(3)} \boldsymbol{\alpha} \right\|_F^2 + \left\| \mathbf{D}^{(3)} \boldsymbol{\Lambda} \right\|_F^2 \right),$$

where  $\lambda_1, \lambda_2$  are data-dependent tuning parameters, and  $\mathbf{D}^{(k)} \in \mathbb{R}^{(T-k) \times T}$  is the discrete difference operator of order  $k$ .

# Computation

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## Algorithm 1 Coordinate-Proximal-Projected Gradient Descent for MTF-LSM

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**Require:**  $A \in \mathbb{R}^{T \times p \times p}$ ; initial estimates:  $Z_0, \alpha_0, \Lambda_0$ ; step sizes  $\eta_z, \eta_\alpha, \eta_\lambda$ ; tunings:  $\lambda_1, \lambda_2$ ;

```

1: while not convergent do
2:   for  $t$  in  $1:T$  do
3:      $\Lambda^{(t)} \leftarrow \Lambda^{(t)} + \eta_\lambda Z^\top \left( A^{(t)} - \sigma \left( \Theta^{(t)} \right) \right) Z - \eta_\lambda \frac{\lambda_1}{2} \nabla_{\Lambda^{(t)}} \left\| D^{(3)} \Lambda \right\|_F^2$ 
4:      $\Lambda^{(t)} \leftarrow \text{Prox}(\Lambda^{(t)}) = \arg \min_{\beta} \frac{1}{2} \|\beta - \Lambda^{(t)}\|_F^2 + \frac{\lambda_1}{2} (\|\beta - \Lambda^{(t-1)}\|_F + \|\beta - \Lambda^{(t+1)}\|_F)$ 
5:   end for
6:   for  $t$  in  $1:T$  do
7:      $\alpha^{(t)} \leftarrow \alpha^{(t)} + 2\eta_\alpha \left( A^{(t)} - \sigma \left( \Theta^{(t)} \right) \right) \mathbf{1}_p - \eta_\alpha \frac{\lambda_2}{2} \nabla_{\alpha^{(t)}} \left\| D^{(3)} \alpha \right\|_F^2$ 
8:      $\alpha^{(t)} \leftarrow \text{Prox}(\alpha^{(t)}) = \arg \min_{\beta} \frac{1}{2} \|\beta - \alpha^{(t)}\|_2^2 + \frac{\lambda_1}{2} (\|\beta - \alpha^{(t-1)}\|_1 + \|\beta - \alpha^{(t+1)}\|_1)$ 
9:   end for
10:   $Z \leftarrow Z + 2\eta_z \sum_{t=1}^T \left( A^{(t)} - \sigma \left( \Theta^{(t)} \right) \right) Z \Lambda^{(t)}$ 
11:   $Z \leftarrow J_p Z, Z \leftarrow ZW$  for  $W \in \mathbb{R}^{r \times r}$  s.t.  $Z^\top Z = pI_r, \Lambda^{(t)} \leftarrow W^{-1} \Lambda^{(t)} \left( W^{-1} \right)^\top$ 
12: end while

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# Conditions and Assumptions

**Definition 1.** For  $p, T, r \in \mathbb{N}, \mu_1, \mu_2, \mu_3 \in \mathbb{R}_+$ , the feasible parameter space is defined as:

$$\begin{aligned}\mathcal{F} &= \mathcal{F}_{p,T,r}(\mu_1, \mu_2, \mu_3) \\ &= \left\{ \mathcal{T} = [\Theta^{(1)}; \Theta^{(2)}; \dots; \Theta^{(T)}] \in \mathbb{R}^{T \times p \times p} : \right. \\ &\quad \Theta^{(t)} = \alpha^{(t)} \mathbf{1}_p^\top + \mathbf{1}_p \alpha^{(t)\top} + \mathbf{Z} \Lambda^{(t)} \mathbf{Z}^\top; \\ &\quad \mathbf{Z} \in \mathbb{R}^{p \times r}, \mathbf{Z}^\top \mathbf{Z} = p \mathbf{I}_r, \mathbf{J}_p \mathbf{Z} = \mathbf{Z}, \alpha^{(t)} \in \mathbb{R}^p \\ &\quad \Lambda^{(t)} \in \mathbb{S}^{r \times r}, \left\| \Theta^{(t)} \right\|_{\max} \leq \mu_1, t = 1, 2, \dots, T \\ &\quad \left. \left\| \alpha \right\|_{\max} \leq \mu_2, \left\| \Lambda^{(t)} \right\|_{\max} \leq \mu_3, t = 1, 2, \dots, T \right\},\end{aligned}$$

where  $\mathbf{J}_p = \mathbf{I}_p - \frac{1}{p} \mathbf{1}_p \mathbf{1}_p^\top$ ,  $\mathbb{S}^{k \times k}$  includes all symmetric  $k \times k$  matrices, and  $\|\cdot\|_{\max}$  calculates the maximum absolute value of entries for a matrix. For the estimator  $\hat{\mathcal{T}} = \arg \min_{\mathcal{T} \in \mathcal{F}} L(\mathcal{T})$  and the true parameter  $\mathcal{T}_\star \in \mathcal{F}$  associated with  $\alpha_\star$  and  $\mathbf{Z}_\star$ . Theorem 1 establishes the error bound.

# Statistical Properties of $\hat{\mathcal{T}}$

## Theorem

Assume that  $\sigma_{\min}(\Lambda_{\star}^{(t)}) \geq \kappa$ ,  $t = 1, 2, \dots, T$ , for some constant  $\kappa > 0$ .

Further assume that  $\lambda_1 + 32\lambda_2\mu_3r \leq \frac{\kappa^2 p}{32\mu_3 r M_{\mu_1} \sqrt{T}}$ , where  $b(x) = \log(1 + \exp(x))$ ,  $M_{\mu_1} = \frac{2}{\min_{|v| < \mu_1} b''(v)}$ . Then, there exist constants  $c_1, c_2 > 0$ , such that with probability at least  $1 - T \exp(-c_1 p) - \exp(-c_2(2p + T))$ ,

$$\|\hat{\mathcal{T}} - \mathcal{T}_{\star}\|_F^2 \leq C_1 p T + C_2(2p + T) + C_3 T$$

where positive constants  $C_1$  and  $C_2$  depend solely on  $(\mu_1, \mu_2, \mu_3, r)$ , while positive constant  $C_3$  additionally depends on  $(\lambda_1, \lambda_2)$ .

- The term  $C_1 p T$  is induced by  $\{\alpha^{(t)}\}_{t=1}^T$ .
- The second term  $C_2(2p + T)$  is induced by  $\{\mathbf{Z}\Lambda^{(t)}\mathbf{Z}^{\top}\}_{t=1}^T$ .
- The third term  $C_3 T$  is induced by the mixed trend penalty.

# Statistical Properties of $\hat{\alpha}$

## Corollary

*Assume that the conditions of Theorem 1 are satisfied and there exists a constant  $\delta > 0$  such that  $T \leq \delta p$ . Then, there exist constants  $c_1, c_2 > 0$ , such that with probability at least  $1 - T \exp(-c_1 p) - \exp(-c_2(2p + T))$ ,*

$$\frac{1}{T} \|\hat{\alpha} - \alpha_{\star}\|_F^2 \leq \tilde{C}_1 + \tilde{C}_2 T^{-1}$$

*where positive constant  $\tilde{C}_1$  depends solely on  $(\mu_1, \mu_2, \mu_3, r)$ , while positive constant  $\tilde{C}_2$  additionally depends on  $(\lambda_1, \lambda_2)$ .*

- Even in the worst-case scenario (without any constant-smooth trends), the penalty does not significantly increase the error.
- Under general conditions, the penalty may further reduce the optimization error, although this effect is not considered in the theoretical analysis.

# Statistical Properties of $\hat{\mathbf{Z}}$

## Theorem

*Assume that the conditions of Theorem 1 are satisfied and there exists a constant  $\delta > 0$  such that  $T \leq \delta p$ . Then, there exist constants  $c_1, c_2 > 0$ , such that with probability at least  $1 - T \exp(-c_1 p) - \exp(-c_2(2p + T))$ ,*

$$\min_{\mathbf{O} \in \mathbb{S}^{r \times r}} \left\| \mathbf{Z}_* \mathbf{O} - \hat{\mathbf{Z}} \right\|_F^2 \leq C_4 + C_5 T^{-1} + C_6 p^{-1}$$

*where positive constants  $C_4$  and  $C_5$  depend solely on  $(\mu_1, \mu_2, \mu_3, r)$ , while positive constant  $C_6$  additionally depends on  $(\lambda_1, \lambda_2)$ .*

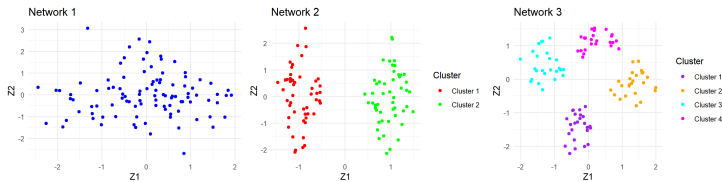
- Our approach maintains the same order of complexity as other relevant models [Ma et al., 2020, Zhang et al., 2020].

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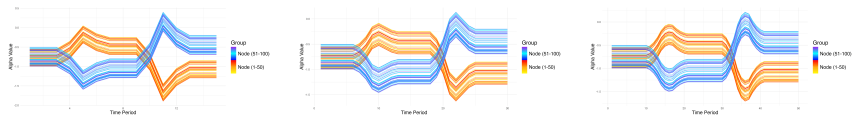
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# Data generation

We conduct simulations with three network structures and various parameter settings:  $p = 100, 200, T = 15, 30, 50$  and  $r = 2, 4$ .



(a) Latent space  $Z$  under different network structures ( $r = 2$ )



(b) Temporal trends of  $\alpha$  ( $T = 15$ ) (c) Temporal trends of  $\alpha$  ( $T = 30$ ) (d) Temporal trends of  $\alpha$  ( $T = 50$ )

Figure: Simulated Data Generation

# Alternative methods

- **LSM** [Ma et al., 2020]:  $\Theta^{(t)} = \alpha^{(t)} \mathbf{1}_p^\top + \mathbf{1}_p \alpha^{(t)\top} + \mathbf{Z}^{(t)} \mathbf{Z}^{(t)\top}$
- **TDCPD** [Zhang et al., 2024c]:  $\Theta^{(t)} = \mathbf{Z}^{(t)} \text{diag}(\beta^{(t)}) \mathbf{Z}^{(t)\top}$
- **LCSC-LSM** [Liu et al., 2024]:  $\Theta^{(t)} = \alpha^{(t)} \mathbf{1}_p^\top + \mathbf{1}_p \alpha^{(t)\top} + \mathbf{Z} \mathbf{Z}^\top$
- **KCN-LSM** [Zhang et al., 2024b]:  $\Theta^{(t)} = \alpha \mathbf{1}_p^\top + \mathbf{1}_p \alpha^\top + \mathbf{Z}^{(t)} \mathbf{Z}^{(t)\top}$
- **PLSM** [Zhang et al., 2024a]:

$$\Theta^{(t)} = \alpha \mathbf{1}_p^\top + \mathbf{1}_p \alpha^\top + \left( \text{diag}(\beta^{(t)}) \mathbf{Z} \right) \left( \text{diag}(\beta^{(t)}) \mathbf{Z} \right)^\top$$

- **FlexMn** [Zhang et al., 2020]: (Does not incorporate any penalty)

$$\Theta^{(t)} = \alpha^{(t)} \mathbf{1}_p^\top + \mathbf{1}_p \alpha^{(t)\top} + \mathbf{Z} \Lambda^{(t)} \mathbf{Z}^\top$$

- **Oracle**: Assume that the constant segments are known in advance for the proposed method.

# Evaluation metrics

When evaluating and comparing different methods, we first consider the relative errors defined as:

$$RE_{\Theta} := \frac{\sum_{t=1}^T \left\| \hat{\Theta}^{(t)} - \Theta_{\star}^{(t)} \right\|_F^2}{\sum_{t=1}^T \left\| \Theta_{\star}^{(t)} \right\|_F^2}, \quad RE_{\alpha} := \frac{\sum_{t=1}^T \left\| \hat{\alpha}^{(t)} - \alpha_{\star}^{(t)} \right\|_F^2}{\sum_{t=1}^T \left\| \alpha_{\star}^{(t)} \right\|_F^2}.$$

We also consider the special relative error of  $\mathbf{Z}$  based on the identifiability:

$$RE_{\mathbf{Z}} := \frac{\min_{\mathbf{O} \in \mathbb{S}^{r \times r}, \mathbf{O}\mathbf{O}^{\top} = \mathbf{I}_r} \left\| \hat{\mathbf{Z}} - \mathbf{Z}_{\star} \mathbf{O} \right\|_F^2}{\left\| \mathbf{Z}_{\star} \right\|_F^2}.$$

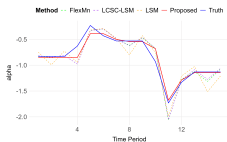
Finding the optimal  $\mathbf{O}$  is known as the orthogonal Procrustes problem, which can be solved by singular value decomposition (SVD). In particular, if we denote the SVD of  $\hat{\mathbf{Z}}^{\top} \mathbf{Z}_{\star}$  by  $\mathbf{S} \mathbf{\Sigma} \mathbf{V}^{\top}$ , then the optimal  $\mathbf{O}$  is given by  $\mathbf{V} \mathbf{S}^{\top}$ .

# Results: Tables

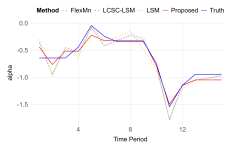
**Table:** Simulation results for **Network 3**,  $p = 200$ ,  $T = 50$  and  $r = 4$ . In each cell, mean (sd) based on 100 replicates. The bold and underlined values indicate the smallest and the second smallest, respectively.

| $T$ | Method          | $RE_{\Theta}$         | $RE_{\alpha}$         | $RE_Z$                |
|-----|-----------------|-----------------------|-----------------------|-----------------------|
| 50  | LSM             | 0.2133(0.0161)        | 0.1587(0.0113)        | 0.1156(0.0072)        |
|     | TDCPD           | 0.6141(0.0167)        | -                     | 0.8716(0.0005)        |
|     | LCSC-LSM        | 0.0348(0.0028)        | 0.0627(0.0019)        | 0.0194(0.0040)        |
|     | KCN-LSM         | 0.1502(0.0128)        | 8.1669(0.1833)        | 0.0953(0.0062)        |
|     | PLSM            | 0.0706(0.0027)        | 8.1836(0.2248)        | 0.2781(0.0029)        |
|     | FlexMn          | 0.0348(0.0028)        | 0.0627(0.0019)        | 0.0018(0.0001)        |
|     | <b>Proposed</b> | 0.0102(0.0004)        | <b>0.0253(0.0009)</b> | 0.0017(0.0001)        |
|     | <b>Oracle</b>   | <b>0.0100(0.0004)</b> | <u>0.0265(0.0008)</u> | <b>0.0016(0.0001)</b> |

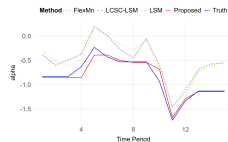
# Results: Figures of temporal trends



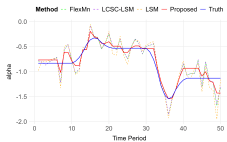
(a) Network 1,  $T = 15$



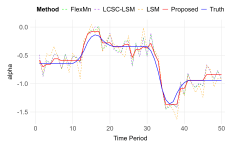
(b) Network 2,  $T = 15$



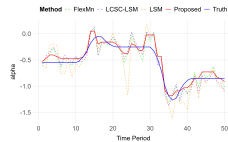
(c) Network 3,  $T = 15$



(d) Network 1,  $T = 50$



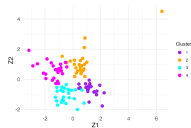
(e) Network 2,  $T = 50$



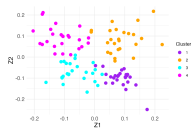
(f) Network 3,  $T = 50$

**Figure:** Simulation results: estimation of temporal trends ( $r = 2$  and  $p = 200$ ).

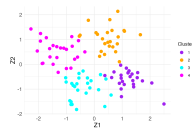
# Results: Figures of latent spaces



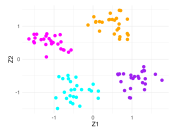
(a) LSM



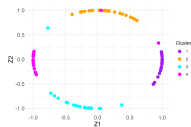
(b) TDCPD



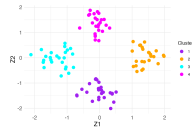
(c) KCN-LSM



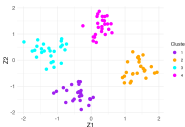
(d) LCSC-LSM



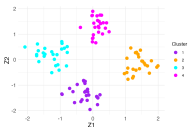
(e) PLSM



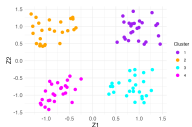
(f) FlexMn



(g) Proposed



(h) Oracle



(i) True

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# Medicare

- We first retrieve **133 million** Medicare inpatient records collected during the period from **January 2008 to December 2019**, representing service utilization of 35 million Medicare beneficiaries.
- As in the literature, we focus on subjects aged 65 years and above.
- Following the literature [Wei et al., 2017, Jiang et al., 2018], we extract the length-of-stay (LOS) information.
- The **final data** for analysis is a array containing the LOS measurements for each subject, each of the 108 diseases, and each of the 12 years.

Adopting the approach developed in Mei et al. [2023] to Medicare inpatient claims data from 2008 to 2019, **we first estimate the 12-year HDN adjacency matrices.**

# Analysis of shared latent space

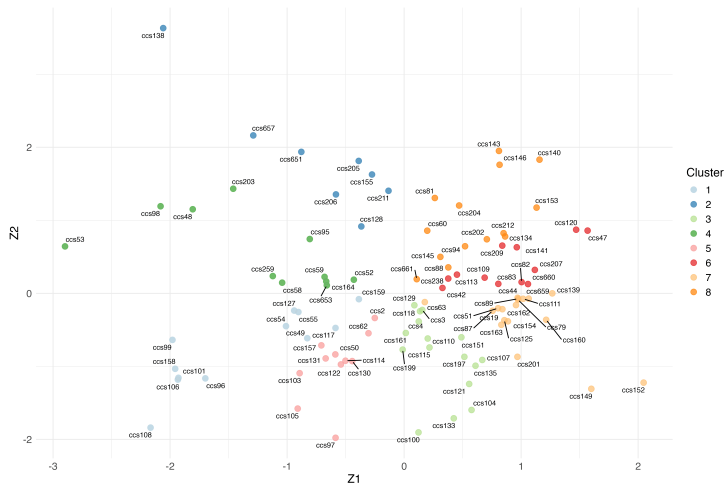
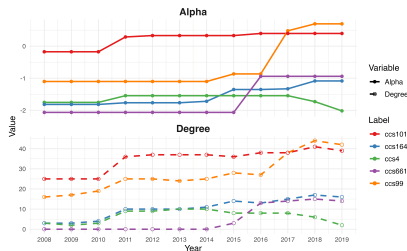
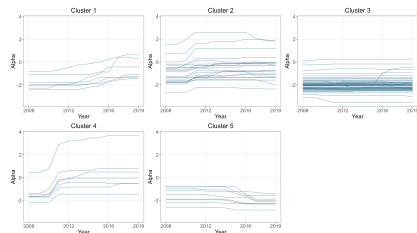


Figure: Clustering result of latent space ( $r = 2$ )

# Analysis of temporal trends



(a) Trends of alpha v.s. degree for selected nodes



(b) Clustering result of  $\{\alpha^{(t)}\}_{t=1}^T$  trends

## Analysis using the alternative methods (e.g. LCSC-LSM)

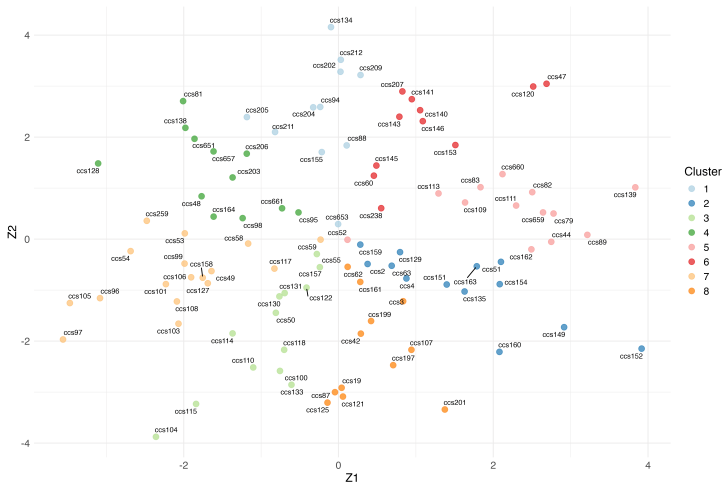
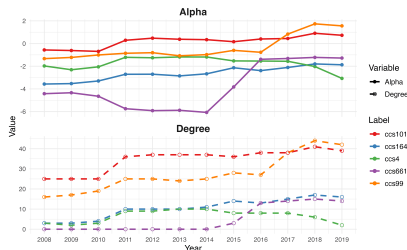
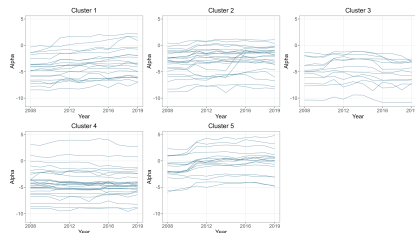


Figure: Clustering result of latent space ( $r = 2$ ) by LCSC-LSM

# Analysis using the alternative methods (e.g. LCSC-LSM)



(a) Trends of alpha v.s. degree for selected nodes by LCSC-LSM



(b) Clustering result of  $\{\alpha^{(t)}\}_{t=1}^T$  trends by LCSC-LSM

- This **instability** in temporal patterns not only complicates trend interpretation but also limits the utility of clustering analysis.

# THANKS!

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