Uncovering cell type neighborhood changes in Alzheimer's disease

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Abstract

Neurons in the cerebral cortex are organized in a well-defined, layered structure, with distinct cell types positioned in specific locations. In the human brain, the six-layered cortex consists of excitatory cell groups, each localized to particular layers. In contrast, glial cells, which serve as support cells, are interspersed among neurons, performing various functions such as responding to pathological insults and maintaining synaptic balance. Recent research has mapped the spatial distribution of individual cell types in the middle temporal gyrus—a cortical area involved in language processing—using brain samples from the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD). This cohort includes donors across the full spectrum of the disease, providing an opportunity to investigate how cellular spatial neighborhoods change as the disease progresses. In this work, we developed a spatial point process framework to investigate interactions between different cell types. We incorporated a stochastic block latent model to capture layer-specific interactions and to track how these relationships evolve with increasing disease severity. Through simulation studies, we demonstrated the model's ability to accurately recover an underlying ground truth block structure and quantify the effects of disease, showcasing its potential as a powerful tool for understanding cell type interactions during disease progression.

Introduction

- This dataset includes 79 specimens from 34 distinct donors, with each specimen associated with both a donor-specific and specimen-specific pseudotime, representing a particular stage of Alzheimer's progression.
- For all supertypes in a given specimen, we classify them into layered and non-layered cell types through a comparison of the supertype window area to the specimen window area and quadrat count analysis afterwards.
- Neuronal cells are usually layered while non-neuronal cells are non-layered.

Figure 1. Visualization of neuronal and non-neuronal cell types from a selected specimen. The top three panels show subclasses of excitatory, inhibitory, and non-neuronal cell types, while the bottom panels display examples of supertypes within selected subclass categories.

Blockstructure of cell types

The block structure is imposed for layered cell types using segregation index, defined by Pielou (1977), $S = 1 - \frac{p_{12} + p_{21}}{p_1 p_{\cdot 2} + p_2 p_{\cdot 1}}$, where p_i denotes the probability of observing a point with mark i, p_{ij} denotes the probability that a typical point of mark i has its nearest neighbor with mark j, and $p_{\cdot i} = p_{1i} + p_{2i}$ for $i, j = 1,2$.

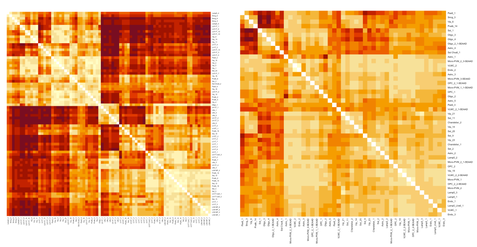


Figure 2. Average segregation index of layered and nonlayered supertypes

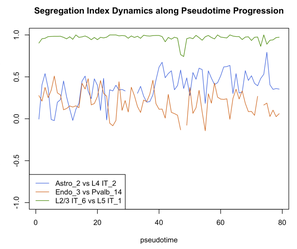


Figure 3. Examples of segregation index dynamics along specimen pseudotime

Spatial connectivity matrix

- We calculate the interaction between cell type pairs using the multitype L-function, which is a scaled version of the multitye K-function. It counts the expected number of points of type j within a given distance r of a point of type i. Mathematically, $L_{ij}(r) = \sqrt{K_{ij}(r)/\pi}$, where $K_{ij}(r) = 1/\lambda_j \mathbb{E}[\text{number of type } j \text{ points distance } r \text{ from a typical type } i \text{ point}]$.
- Here we show the connectivity matrices from 3 specimens, corresponding to the specimen-specific pseudotime at 2, 36, and 76 (range: 0-78).

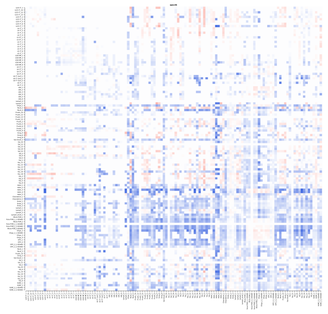


Figure 4. An example of the spatial connectivity matrix from a selected specimen (at specimen-pseudotime 36)

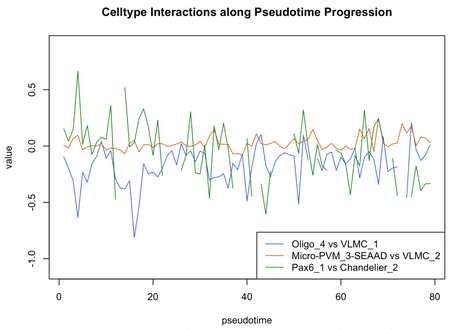


Figure 5. Examples of interaction strength changes between supertypes along specimen pseudotime

Latent Stochastic Blockmodel

We develop a latent Stochastic Blockmodel to capture layer interactions.
Firstly, assign a membership z_i to each cell type i,

$$z_i \sim \text{Cat}(\pi_i), \text{s.t. } \pi_i \sim \text{Dir}(\theta)$$

Then, define a latent block-level connectivity matrix that accounts for layer-wise interaction between cell types, independent of donor-specific attributes.

$$y_{ijd} \sim \text{Ber}(z_i^T B z_j), B \in \mathbb{R}^{K \times K} \text{ s.t.}$$
$$B_{ij} \sim N(0,1) \text{ if } i = j \quad B_{ij} \sim N(-2,1) \text{ otherwise}$$

Finally, we relate the latent level to the observation level.

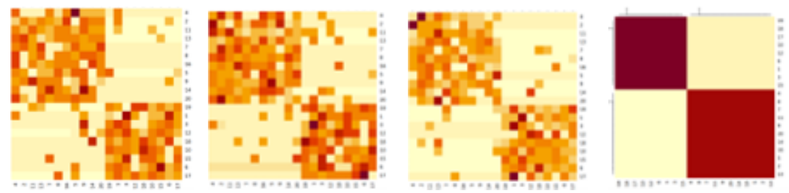
$$X_{ijk} \sim \text{Po}(\alpha + \beta_k \cdot y_{ijd_k} + t_{d_k} \cdot r_{ij}) \text{ s.t.}$$
$$\alpha \sim N(0,1), \beta \sim N(1,1), r_{ij} \sim N(0,1)$$

where d_k is the donor index for the specimen k. Note α is baseline rate, β_k is the block contribution and r_{ij} is the disease contribution.

Simulation results

Simulate the following block and disease effect:

- Take 20 nodes with two blocks.
- Simulate 60 connectivity matrices for 30 donors with disease pseudo-time equally distributed in $[0,0.9]$.
- Set $r_{ij} = 20$ for two pairs of nodes, $r_{ij} = 0$ for other pairs.



Connectivity matrices for the 1st, 15th, and 30th donor.
We successfully recovered the underlying blocks and disease effects.

Discussions

- Real dataset is noisy with many missing cell types due to cell die-out.
- We can have more pairs of cell types with disease effects. How to determine the significances of the disease effects?
- Subclasses are parent classes of supertypes. A natural extension could be a hierarchical model that characterizes the interactions at subclass level.

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