Alignment of fMRI Time-series and Functional Connectivity

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December 5, 2020
Imaging Data Workshop

Outline

1. Introduction to Functional Data
2. Transforming High-dimensional Data to Functional Data
3. Numerical Illustrations
4. **Part II:** Stringing Object Data
5. Brain Efficiency and Community Detection of Brain Network
6. Data Analysis

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What is Functional Data?

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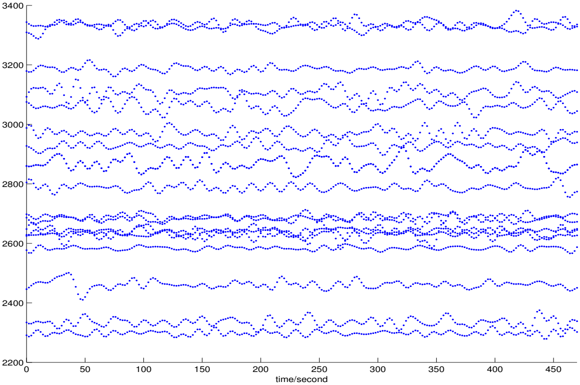
- The second part of the talk is for object data with focus on time-series data.

Examples of Functional Data

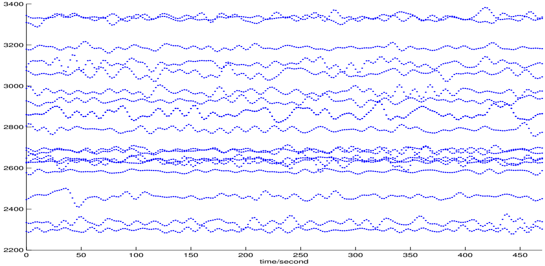
- fMRI data at a particular voxel for 20 subjects $\Longrightarrow n = 20.$



Real/Observed Functional Data

- In reality, functional data are recorded intensely on a time grid

  - The fMRI data were recorded every two seconds for about 10 minutes (300 time points) $\Longrightarrow$ 300 dimensional data.



$\Longrightarrow$ high-dimensional data.

- **Is there a curse of high dimensionality?**

High-dimensional vs. Functional Data

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- **How did functional data get away with the curse of large p and measurement errors?**

  Answer: We assume continuity and smoothness of the data, so information in a neighborhood can be shared.
  - We can do so because there is a natural ordering of the data.

High-dimensional vs. Functional Data

- **Question:** Can we order p-dim data so the ordered data represent a discretized version of functional data?

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- **Question:** Can we order p-dim data so the ordered data represent a discretized version of functional data?

- **Goal:** Convert high-dim multivariate data to functional data as a preprocessing step to perform further data analysis.

  * This makes sense only if the high-dim data are all measured on the same scale.

End of Introduction

Macchuipiccu, Peru

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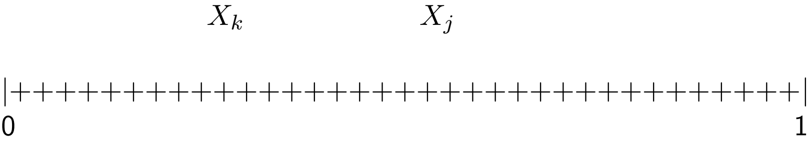
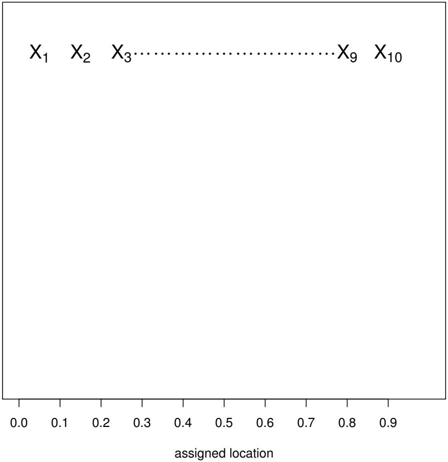


$\Longrightarrow$ string p features to new locations on $[0, 1]$.

Stringing Method



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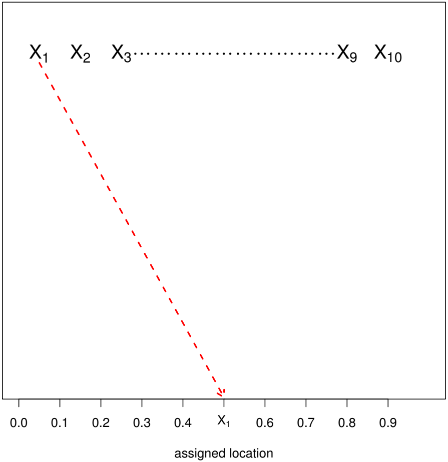

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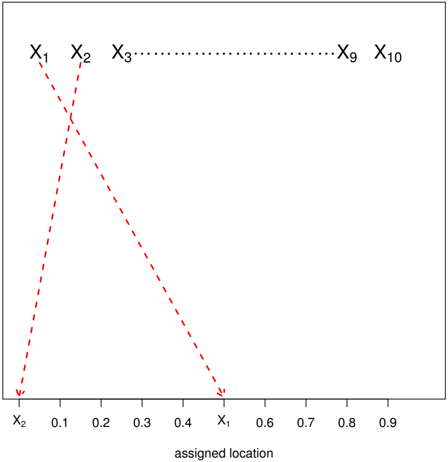

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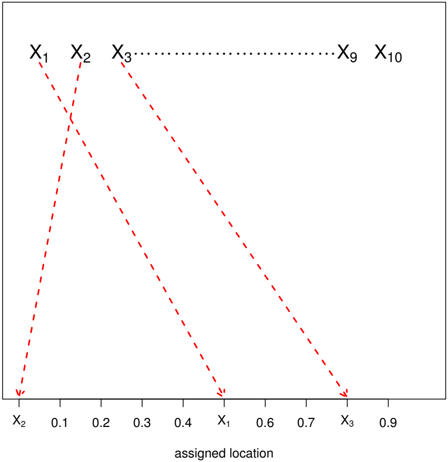

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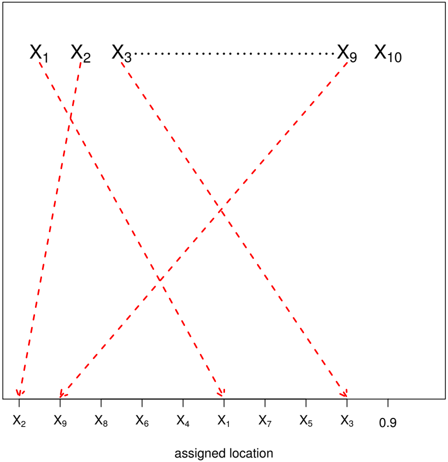

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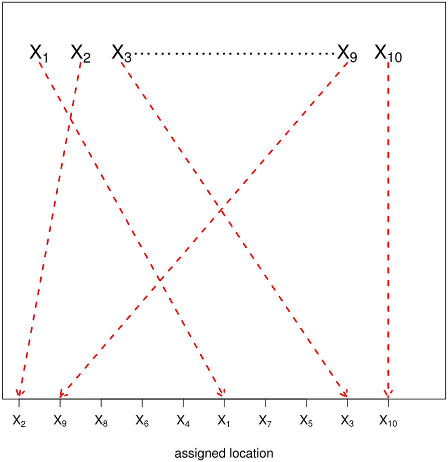
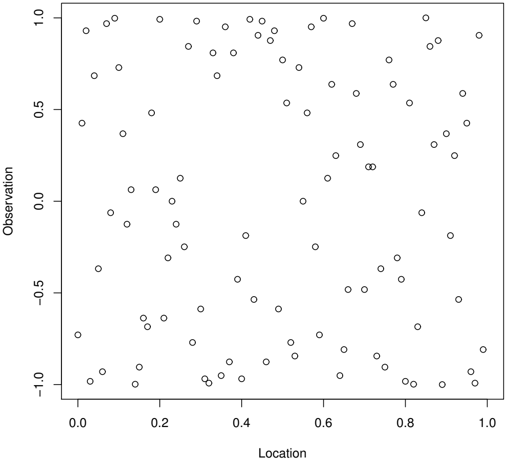


Stringing in Action



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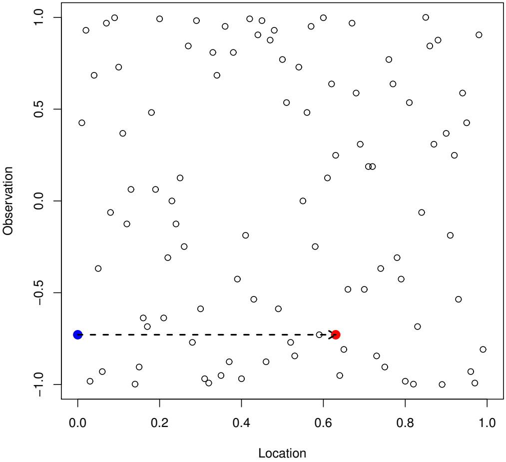

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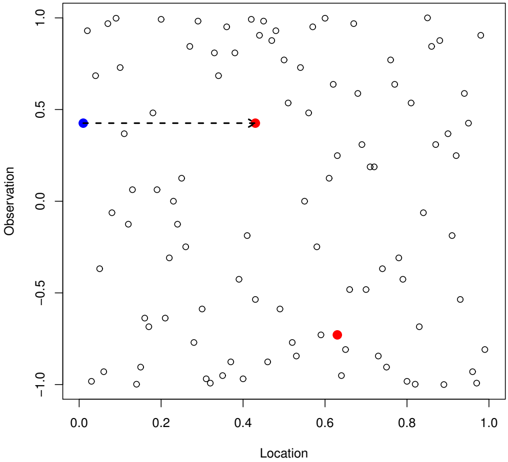

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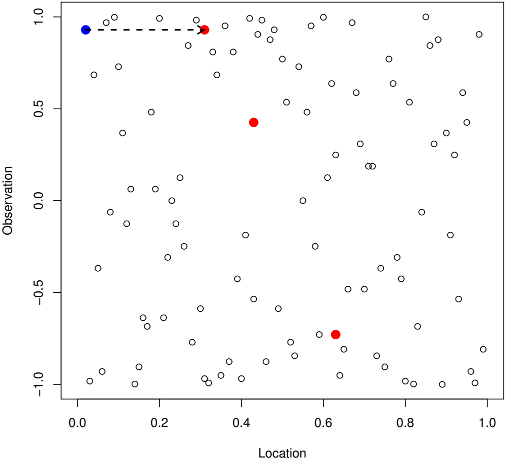

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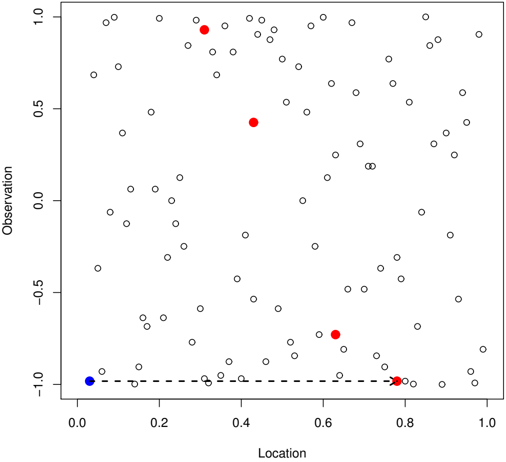

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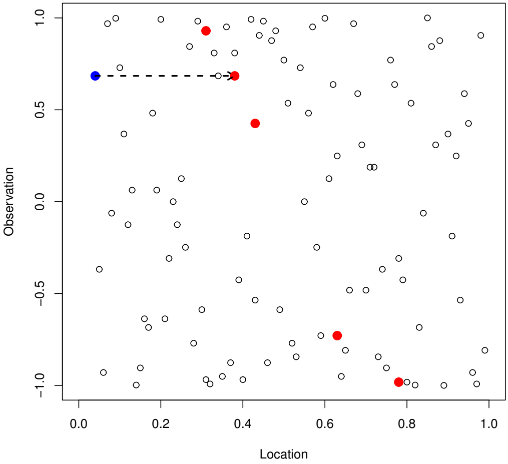

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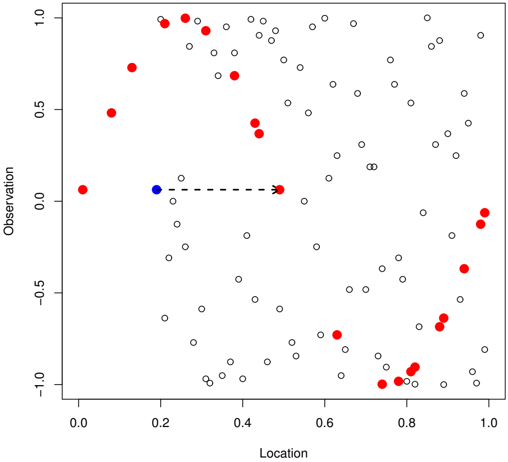

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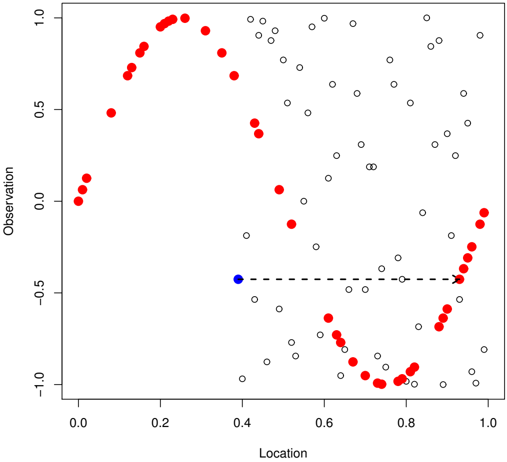

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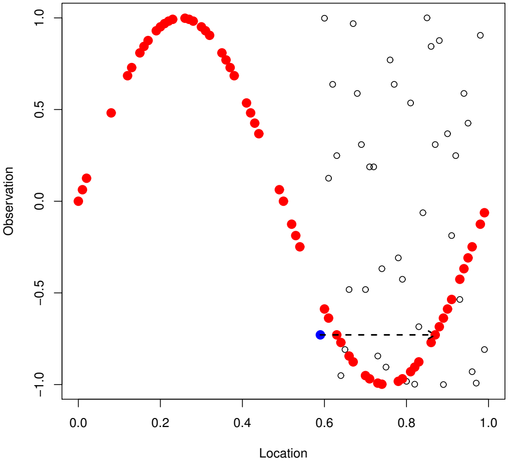

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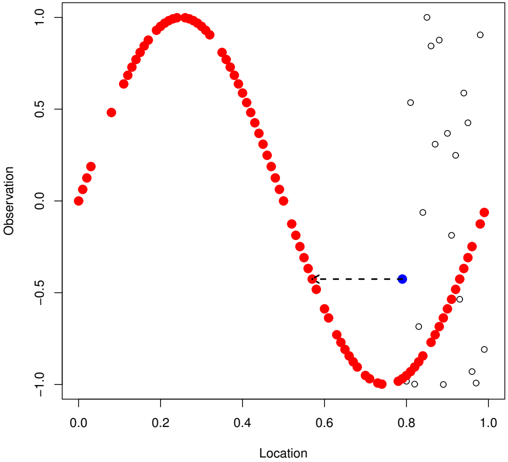

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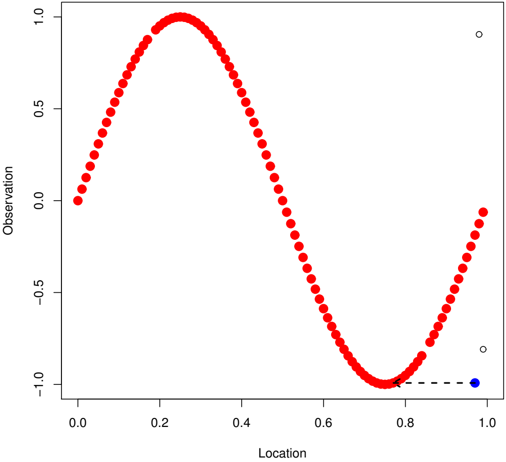

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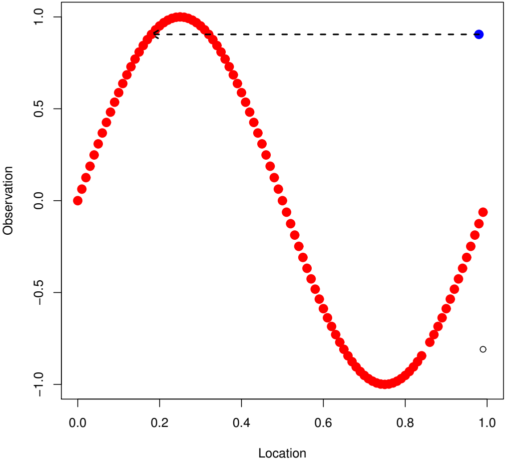

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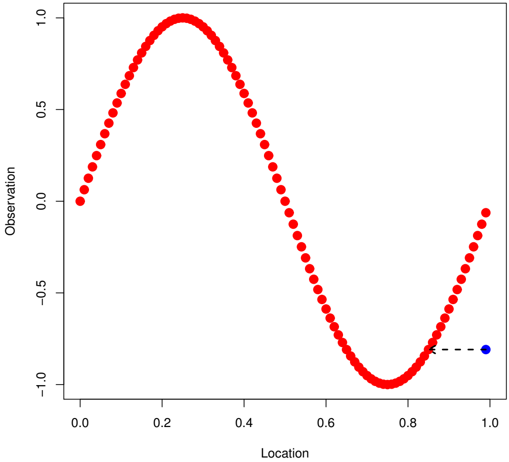

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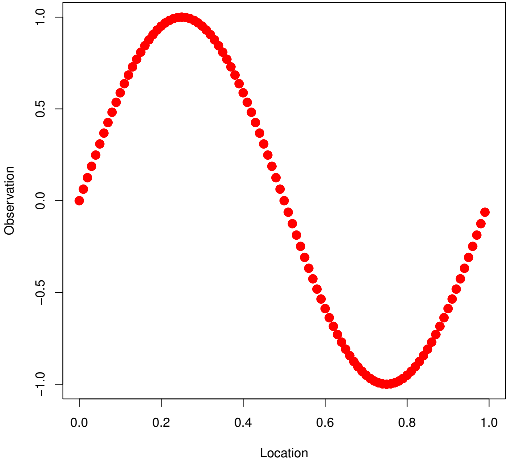
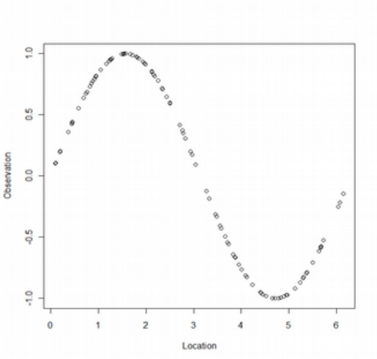


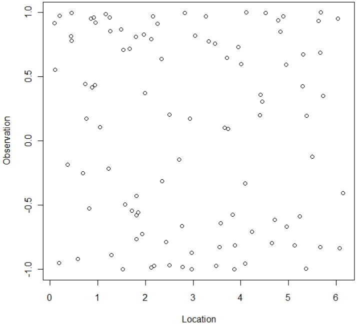
Key Assumption for the Stringing Method

- Assumption: There is a latent order which corresponds to a smooth process.



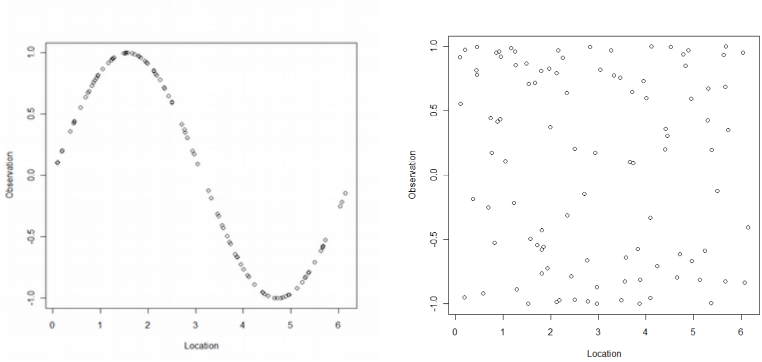
Key Assumption for the Stringing Method

- The latent order was scrambled.



Goal of the Stringing Method

- Stringing restores the latent order which corresponds to a smooth process.



How does stringing work?

Observe p-dim data $(X_1, \ldots, X_p)$ from n subject.

- Choose a distance d to measure proximity/similarity between features
  $\Rightarrow p \times p$ Distance matrix (D_{jk}), where $D_{jk} = d(X_j, X_k)$,
  for the components of the p-dim data.

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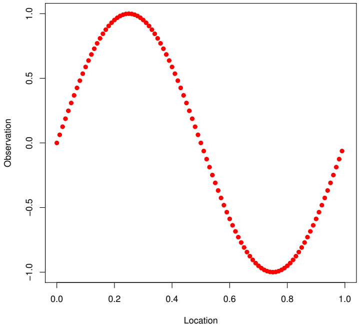
  for the components of the p-dim data.

- Apply multidimensional scaling (**MDS**) to assign a location, on the interval $[0, 1]$, to each variable in such a way that variables that are similar to each other are located close to each other on $[0, 1]$.

How does stringing work?

- Construct a new p-dim data for each subject based on the reconfiqured p data pairs, (new variable locations, level of variable),



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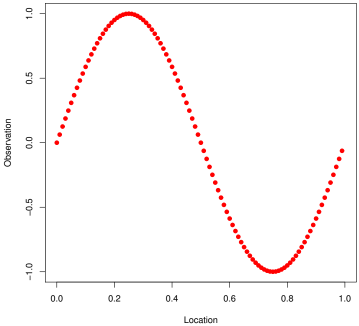

- Treat this new/transformed p-dim data as discretized observations of a latent smooth random function.

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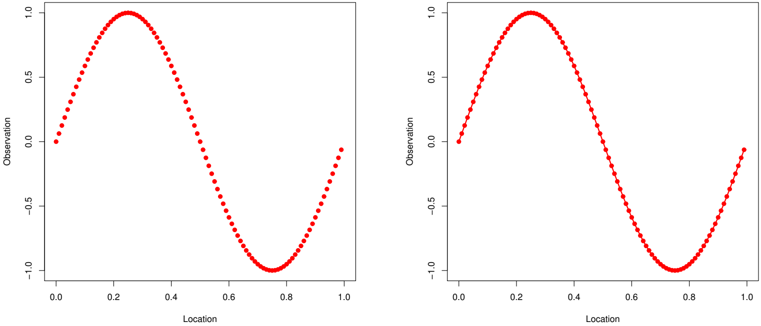

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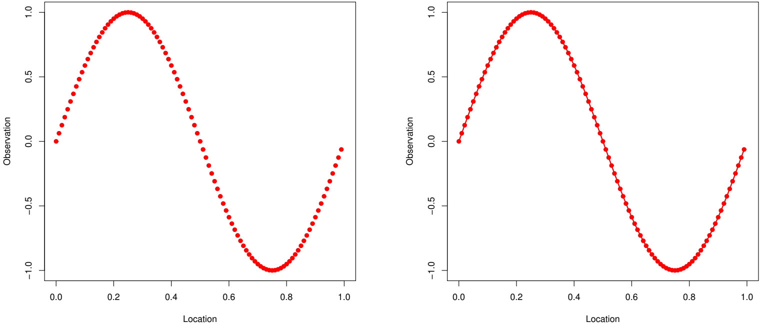

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* After stringing, one can use functional data approaches to represent the data and for further data analysis.

More about Stringing Method

- MDS maps p objects to p points in a target space $\mathcal{R}^d$.

  - When $d = 1$, this is called UDS (unidimensional scaling).

  - Stringing applies UDS to "string" the p variables onto p locations on $[0, 1]$ like peals on a string.

More about Stringing Algorithm

For variables X_j and X_k, let (x_{ij}, x_{ik}) be the observation from the ith subject.

We used both Euclidean distance and transformed Pearson correlation as the metric distance (or proximity measure).

- **Euclidean distance:** $\hat{D}_{jk} = [\frac{1}{n}\sum_i (x_{ij} - x_{ik})^2]^{1/2}$
- **Pearson distance:** $\hat{D}_{jk} = 2(1 - \hat{\rho}_{jk})$, where $\hat{\rho}_{jk} = \frac{1}{n-1}\sum_i (x_{ij} - \bar{x}_j)(x_{ik} - \bar{x}_k)/\{\hat{\sigma}_j \hat{\sigma}_k\}$, with $\bar{x}_j = \frac{1}{n}\sum_i x_{ij}$, $\hat{\sigma}_j = [\frac{1}{n-1}\sum_i (x_{ij} - \bar{x}_j)^2]^{1/2}$.

More about Stringing Algorithm

- **Stringing step:** Minimize the stress function $S_{\mathbf{D}}(s_1, \ldots, s_p) = \sum_{j<k}(|s_j - s_k| - D_{jk})^2$, where $s_j \in \mathbb{R}$ is the coordinate of the projected location of the jth variable in the one dimensional projection space.
- The resulting one-dimensional configuration
  - reflects the pairwise distances between variables
  - leads to an ordering of the features
  - provides support points for constructing a trajectory $Z(t)$ from the predictor levels for each subject

End of Stringing Methodology

Outline

Application 1: Stringing for Visulization

- Molecular classification problem to diagnose type of leukaemia based on gene expression array data (Golub et al. 1999).

  The gene expression data were obtained from Affymetrix chips, containing 7129 genes, reduced to **50** most significant genes by t-tests.

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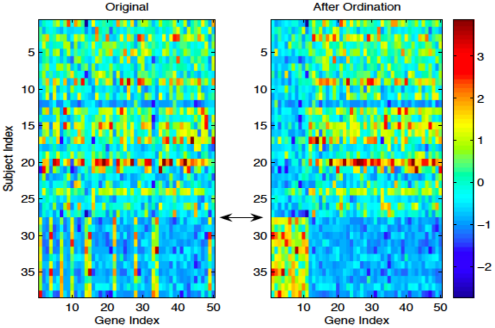
- Gene expression data (50 genes) for 38 patient

  - 27 with acute lymphoblastic leukaemia (ALL)
  - 11 with acute myeloid leukaemia (AML).

Stringing Gene Expression for Visualization

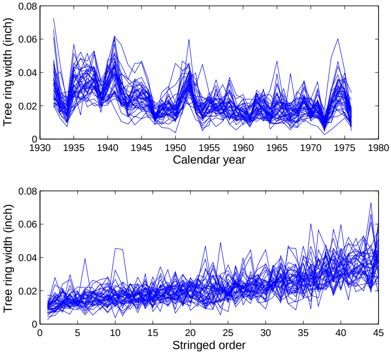


Leukaemia gene expressions for 50 significant genes
Left: Original order   Right: Stringed order

*** Stringing separates the leukaemia types based on patient's gene expression data.**

Application 2: Recovering the Latent Factor(s)

- Annual tree ring widths from 1932-1976 for 45 blue oak trees (Mary Ranch, Santa Clara, California), $p = n = 45$.



Top: Observed series of tree ring width data.
Bottom: Ordered tree ring series obtained by Stringing.

Tree Ring Data

- We implemented Stringing with Euclidean distances.
- **Results:** Stringing recover climatic variation, primarily annual precipitation.
- **Stringing** → Tree ring width as a smooth function of precipitation, with scrambled observations due to random precipitation levels per year.

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EVIDENCE ???

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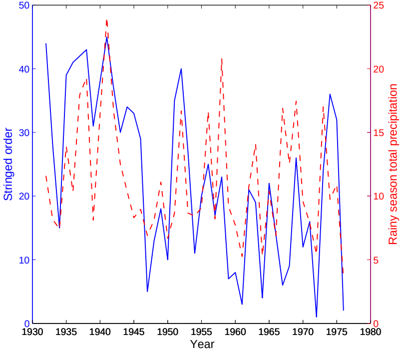

Comparison of the Stringing function (solid) for the tree ring width data with yearly rainy season precipitation (dashed).

Tree Ring Data

- Stringing Function Ψ is found to be significantly associated with (known) precipitation levels.

  (Confirmed by bootstrap test for association)

- **Stringing uncovers precipitation levels.**

Application 3: Stringing for Modeling

Alaska

Predicting Survival from Gene Expression Data

- $n = 240$ patients with diffuse large-B-cell type lymphoma (DLBCL), $p = 7399$ gene expression levels.
- **Goal:** Predict survival (possibly right censored) based on gene expression levels.
- Patients were randomly divided into training (160 subjects) and test (80 subjects) groups.
- Data were preprocessed following similar approach as in Bair and Tibshirani (2004), who proposed supervised PCA.
  - **80** genes were selected as input for stringing.
- After stringing we propose a functional Cox model using the expression levels $X(t)$ of these 80 stringed genes.

Functional Cox Model

- Censored lifetimes as responses: Proportional hazards

$$h(t|X_i) = h_0(t)\exp\left[\int_0^1 X_i(s)\beta(s)\,ds\right], \tag{1}$$

with baseline hazard function $h_0(t)$.

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with baseline hazard function $h_0(t)$.

- This model is different from the conventional Cox model with longitudinal covariates: $h(t|X_i) = h_0(t) \exp\left[X_i(t)\beta(t)\right]$.

Rather, it is a continuous approximation of

$$h(t|X_i) = h_0(t) \exp\left[X_i^T \beta\right], \tag{2}$$

where X_i and β are both 80-dim vectors.

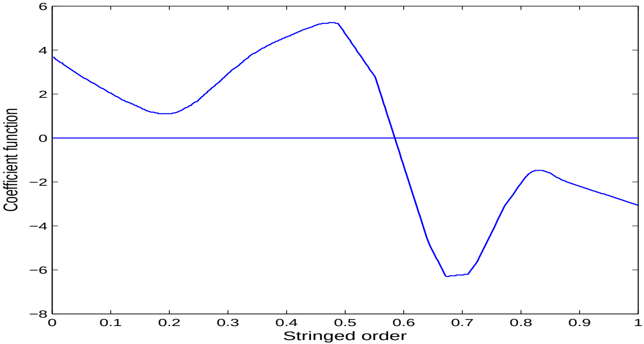
Functional Cox Model

- The Cox model in (2) involves high-dim covariates.

  The functional Cox model in (1) involves an infinite dimensional covariates.

  Which one is more evil?

Prediction for Large B-cell Lymphoma



Coefficient function for the stringed functional Cox regression model, as obtained for one random split of the DLBCL gene expression data.

Comparing Deviance

We use the deviance proposed by Bovelstad et al. (2007).

$$DEV = -2\{(l^{test}(\hat{\beta}) - l^{test}(0)\}.$$

Smaller deviance is better!

	PCR	Ridge	Lasso	Stringing
1st quartile	1	-6	-1.5	-11.5
median	-3	-8.5	-4.5	-18
3nd quartile	-6.5	-11	-7	-21

* Comparison of quartiles of deviances for survival prediction for four methods across test sets: Stringing; supervised principal component regression (PCR); ridge regression (Ridge); Lasso.

Functional Cox Models: Qu, W. and Wang (2016)

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- We allow vector covariates in addition to functional covariates.

$$h(t\,|X) = h_0(t)\exp\left\{\theta_0' Z + \int_{\mathcal{S}} X(s)\beta_0(s)ds\right\}, \tag{3}$$

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- We applied penalized partial likelihood to estimate θ_0 and $\beta_0(t)$, and developed the semiparametric efficiency of the parametric estimate and minimax property of the nonparametric estimate of $\beta_0(t)$.

End of Part I

Sinkhole in Lake Berryessa (near Davis).

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- So far in Part I, we stringed the **scalar** components of p-dim multivariate data.

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- In Part II, we replace the **scalar** by an **object**,
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- Our toy object is the fMRI time-series with the goal to study functional brain connectivity.

Functional Magnetic Resonance Imaging

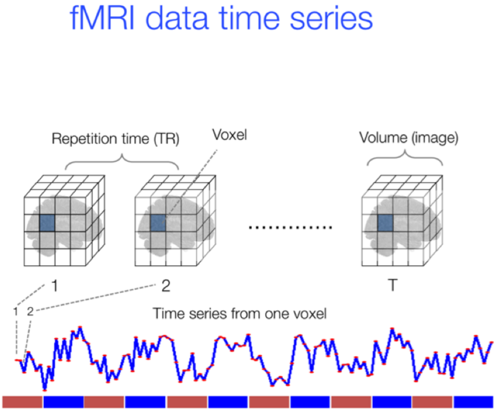
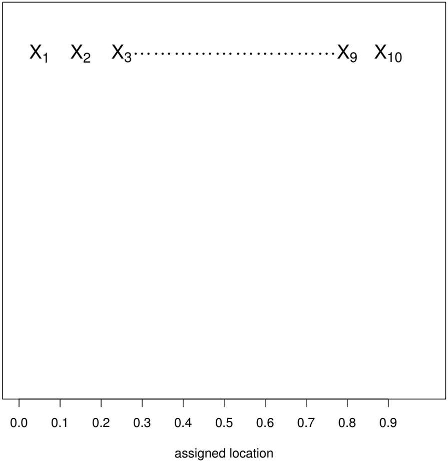


Figure 1: Time-varying Images

Stringing Method



Parcellation of Brain Regions: Automated Anatomical Labeling (AAL)

- We use the AAL template to partition the brain into 90 regions.

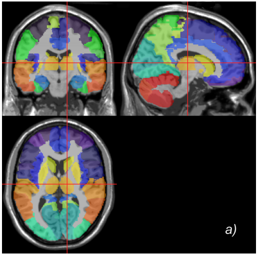


Figure 2: Parcellation of brain regions.

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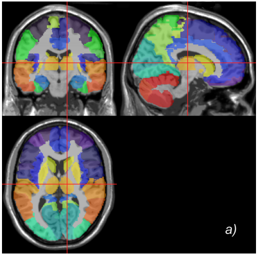


Figure 2: Parcellation of brain regions.

- Extract 90 time-series from these regions - region of interest (ROI) analysis.

ROI based fMRI Data: 90 Time Series

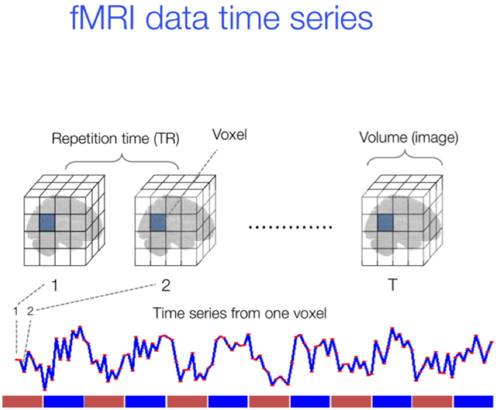
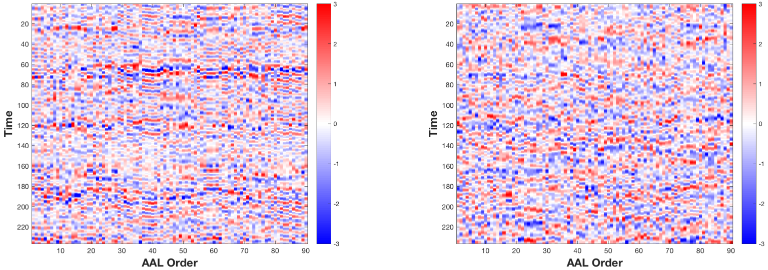


Figure 3: Time-varying Images

Alzheimer's Disease fMRI Data from UC Davis

- The dataset consists of 172 normal and 67 Alzheimer's disease subjects.
- For each subject, an image with spatial resolution 61x73x61 voxels and temporal resolution 236 time points is acquired.
- Use AAL template to partition a brain into 90 regions.
- Extract 90 time-series from these regions
  - We will apply stringing on these time-series.

Visualization of Brain Images



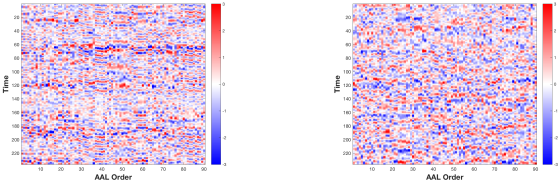
(a) AAL Order (Demented)

(b) AAL Order (Normal)

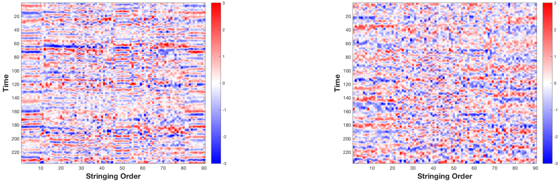
Figure 4: Brain image for a demented (a) and normal (b) subject.

Panels (a) and (b) show the 90 BOLD signals arranged horizontally according to the AAL ordering.

Alignment of fMRI Time Series



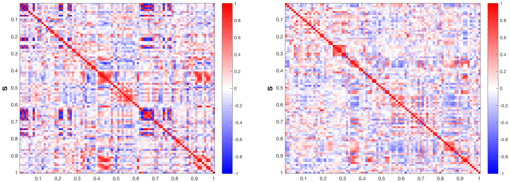
(a) AAL Order (Demented) (b) AAL Order (Normal)



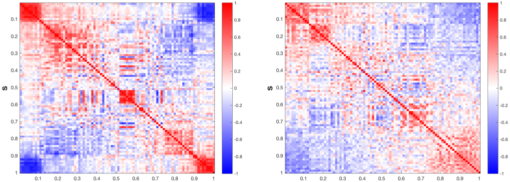
(c) Aligned Order (Demented) (d) Aligned Order (Normal)

Figure 5: Brain image for a representative demented (a and c) and normal (b and d) subject. Panels (c) and (d) show the aligned BOLD signals.

Brain Connectivity Map



(a) AAL Order (Demented) (b) AAL Order (Normal)



(c) Align Order (Demented) (d) Align Order (Normal)

Figure 6: Panels (a) and (b) show the correlation of 90 normalized BOLD signals arranged according to the AAL ordering, panels (c) and (d) show the correlations of the aligned normalized BOLD signals.

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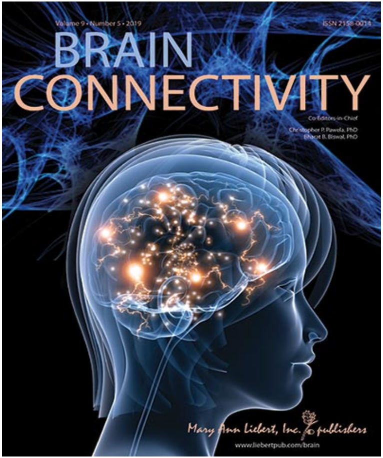
- What does similarity means?

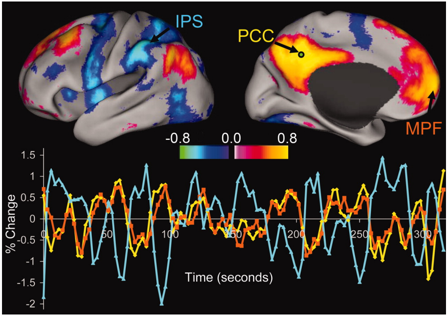
Stringing fMRI data for Brain Connectivity



Functional Connectivity: Our Primary Interest

Functional connectivity: Connectivity between brain regions that share functional properties - often defined as temporal correlation of fMRI time-series for anatomically separated brain regions (Friston et al., 1993) .

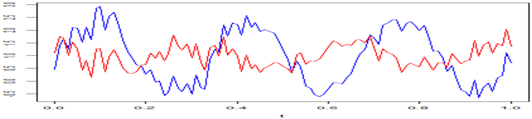
Intrinsic correlations between a seed region in the PCC and all other voxels in the brain for a single subject during resting fixation.



Michael D. Fox et al. PNAS 2005;102:9673-9678

Choice of the Similarity/Disparity Measure

- In neuroscience, Pearson correlation (PC) of two time series is used to measure their functional connectivity (temporal dependency).



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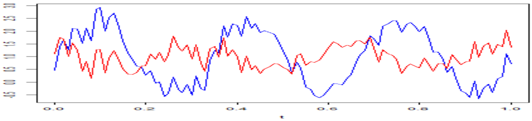

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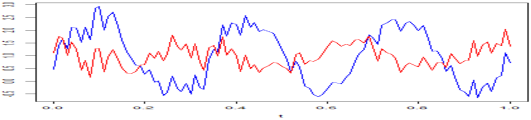

  - This is problematic since the temporal data are correlated.
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- **Functional Data View**: PC is the cosine angle of two standardized time series, which are the discretized realizations of two stochastic processes $X_j(t)$ and $X_k(t)$.

$$\rho_{jk} = \langle X_j(t), X_k(t) \rangle = \int X_j(t) X_k(t) dt.$$

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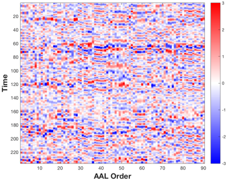
$$\rho_{jk} = \langle X_j(t), X_k(t) \rangle = \int X_j(t) X_k(t) dt.$$

- We thus use $d_{jk} = 2(1 - \rho_{jk})$ as a disparity measure.
  $\Rightarrow$ It is the L^2-norm of two normalized time series.

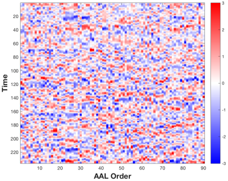
$$\begin{aligned} \int (X_j(t) - X_k(t))^2 dt &= \int X_j^2(t) dt + \int X_k^2(t) dt - 2 \int X_j(t) X_k(t) dt \\ &= 2 - 2\rho_{jk}. \end{aligned}$$

.

Alignment of fMRI Time Series

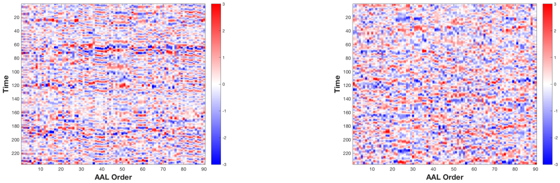


(a) AAL Order (Demented)



(b) AAL Order (Normal)

Alignment of fMRI Time Series



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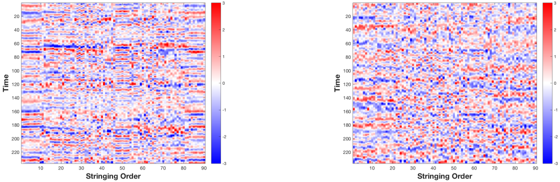

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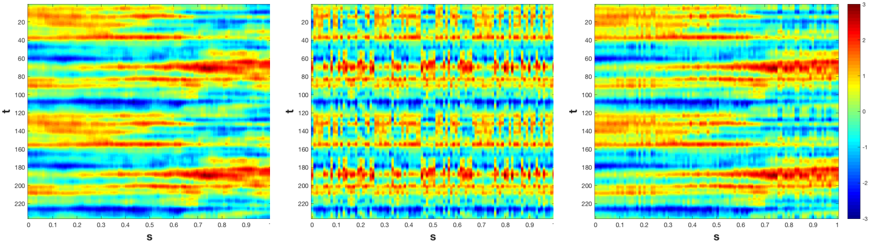
Figure 8: Brain image for a representative demented (a and c) and normal (b and d) subject. Panels (c) and (d) show the aligned BOLD signals.

Illustration of Object Stringing



(a) original data (b) permuted data (c) aligned data

Figure 9: (a) is a smooth stochastic process $Z(s,t)$, (b) is the randomly permuted stochastic process of (a), and (c) is the process recovered by the proposed alignment method.

Outline

1. Introduction to Functional Data
2. Transforming High-dimensional Data to Functional Data
3. Numerical Illustrations
4. **Part II:** Stringing Object Data
5. Brain Efficiency and Community Detection of Brain Network
6. Data Analysis

A Summary of Brain Efficiency

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- We propose a new path length L_A for the aligned objects.

  Let $\psi(1) \to \psi(2) \to \cdots \psi(p-1) \to \psi(p)$ be the ordered path, where $\psi(j)$ is the the subject index of the jth aligned object.

$$L_A = \sum_{j=1}^{p-1} d_{\psi(j)\psi(j+1)}.$$

$$|+++++++++++++++++++++++++++++++++++|$$

$\psi_1\psi_2\psi_3 \ \ldots$ $\psi_{p-1}\psi_p$

A New Community Detection Method

$$Q^w(B, b_1, \cdots, b_{B-1}) = \frac{1}{l_w} \sum_{j,k \in \{1,\cdots,p\}} \left(w_{jk} - \frac{w_{j\cdot} w_{k\cdot}}{l_w} \right) \times \sum_{h=1}^{B} \mathbf{1}_{\{b_{h-1} \le s_j^*, s_k^* < b_h\}}, \tag{4}$$

$w_{jk} = e^{\rho_{jk}}$, $w_{j\cdot} = \sum_{k \neq j} w_{jk}$, and $l_w = \sum_{j,k \in \{1,\cdots,p\}} w_{jk}$.

- B is the number of communities and b_h is used to defined boundary of a community.
  $\Rightarrow$ Objects whose aligned orders fall in $[b_{h-1}, b_h)$ form a community.

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- We apply the genetic algorithm to find the maximum of the weighted modularity criteria over all possible $(B, b_1, \cdots, b_{B-1})$.

Conventional Modularity (Newman, 2006)

- Conventional Modularity:

$$Q^w(B, C_1, \cdots, C_n) = \frac{1}{l_w} \sum_{j,k \in \{1,\cdots,n\}} \left(w_{jk} - \frac{w_{j\cdot} w_{k\cdot}}{l_w} \right) \times \delta(C_j, C_k), \tag{5}$$

Where C_j is the community to which object j is assigned;
$\delta(C_j, C_k) = 1$ if object j and k are in the same community, otherwise it is 0.

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- Complexity of solution space: $\mathcal{O}(B^p)$ vs. $\mathcal{O}(2^p)$ (our approach).

Data Analysis

Bear Valley (Near Davis)

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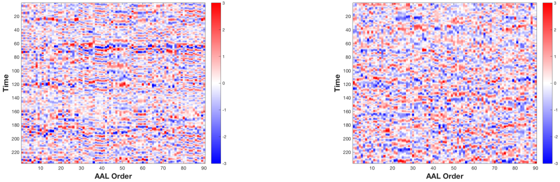

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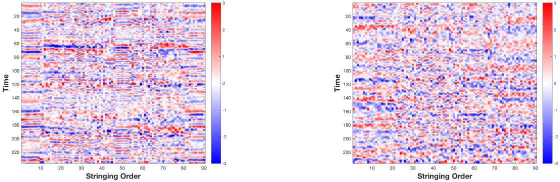
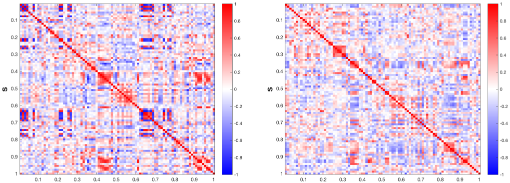


(c) Aligned Order (Demented) (d) Aligned Order (Normal)

Figure 10: Brain image for a representative demented (a and c) and normal (b and d) subject. Panels (c) and (d) show the aligned BOLD signals.

Brain Connectivity Map



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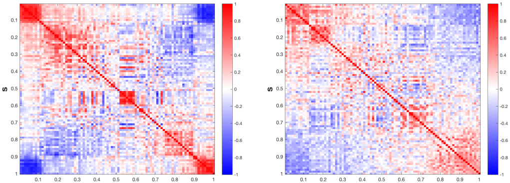

(c) Align Order (Demented)(d) Align Order (Normal)

Figure 11: Panels (a) and (b) show the correlation of 90 normalized BOLD signals arranged according to the AAL ordering, panels (c) and (d) show the correlations of the aligned normalized BOLD signals.

Comparison of Brain Efficiency

- H_0 : The brain efficiency of the normal and demented group is the same.

Type	Wilcoxon test	t test
Length of MST	0.1361	0.1673
Length of Path	0.0934	0.1198

Table 1: P value of the Wilcoxon test and t test

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- Comparison of our approach with another package: Brain Connectivity Toolbox (BCT). [1]

---

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	Rank sum test: Number of Communities				
	$\bar{X}_1$	$\bar{X}_2$	s_1	s_2	p-value
Align	4.2500	4.8955	1.7576	1.9473	0.0032
BCT	3.8198	4.0149	0.7391	0.7281	0.0625

Table 2: 1=normal group; 2=demented group.
The p values are from Wilcoxon rank sum test.

---

[1] M. Rubinov and O. Sporns. Complex network measures of brain connectivity: Uses and interpretations. NeuroImage, 52(3):1059 – 1069, 2010. Computational Models of the Brain.

Conclusion

- Results of the data analysis show that the alignment approach allows us to successfully reduce the complexity of the data structure.
- Further exploration reveals that the number of communities in normal and demeneted groups is significant different.
- More communities imply high wire cost for functional connectivity: energy inefficient

Post Alignment Analysis

- Consider aligned time-series as an images:
  Apply image classifiers to normal and Alzheimer's disease subjects.

  -To be done.

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  -To be done.

- Consider brain connectivity map for aligned data:
  Apply Convolutional Neural Networks to classify emotional EEG data.

  Moon, Chen, Hsieh, W. and Lee (2020).
  "Emotional EEG Classification using Connectivity Features and Convolutional Neural Networks"

Thank You !

References

- Part I:

  Chen, K., K. Chen, H.-G. Müller and J.-L. Wang (2011)
  Stringing High-Dimensional Data for Functional Analysis
  JASA

  Qu, S., J.-L. Wang and X. Wang (2016) Optimal estimation for the functional Cox model
  Annals of Statistics

- Part II:
  Chen, C.-J. and J.-L. Wang (2019)
  A New Approach for Functional Connectivity via Alignment of Blood Oxygen Level-Dependent Signals
  Brain Connectivity

Collaborators


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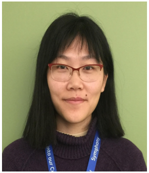
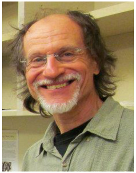
U. Pittsburgh


Kun Chen
GE Healthcare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