Quantify spatial inhomogeneity and anisotropy in the peripheral nerve cross-sections

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Contents

What are we doing?

We are demonstrating a pipeline that represents the segmented unmyelinated axons in several vagus and pelvic nerve cross-sections as spatial point patterns, and computes Sinkhorn distance between certain spatial features of the point patterns and their corresponding images, to quantify spatial inhomogeneity and anisotropy in the peripheral nerve cross-sections.

Data

The directory **spatial-neuro/quantifyVagusNerve/Data/** contains the following subdirectories:

- **U-Net predictions:** This subdirectory contains images (*.png*) of the segmented unmyelinated axons in the vagus and pelvic nerve cross-sections under consideration. Plebani et al. (2022) describes the segmentation process.
- **Inputs:** There are *.csv* and *.rds* files in this subdirectory. The *.csv* files contain several morphometric characteristics of the segmented unmyelinated axons in each nerve cross-section, along with their centroid locations, which we use in particular to construct the spatial point patterns. The morphometric characteristics are extracted using an open source image processing package Fiji (Schindelin et al. (2012)). The *.rds* files, drawn using R graphics tools, store the outer boundary and inner holes of the cross-sections that are used for spatial point pattern construction also. These are the main input files for the analysis.
- **Demo Inputs:** This subdirectory contains a small subset of the inputs for quick demonstration purpose.

- **Supporting Files:** Some additional information of the nerve samples, such as sample ID, nerve location and sex, are saved in this subdirectory. The pair-wise orientation of the cross-sections are computed at a certain stage of the pipeline. Those orientations are also stored inside this subdirectory.

Codes

The directory **spatial-neuro/quantifyVagusNerve/Codes/** contains the R code files. We utilize the R packages *spatstat* for spatial point pattern analysis, *T4transport* and *Barycenter* for optimal transportation problems extensively, along with the others. The R files can be run using RStudio terminal or Linux terminal. Here we demonstrate with the RStudio terminal commands. The changes required (if any) to run the codes from Linux terminal are mentioned inside the code files.

Configuration of the interaction distance

Code: LfunctAnova2.R

The nerve cross-sections under consideration can vary a lot size, resulting into quite different ranges of interaction in the constructed point patterns even after scaling. We find out a range of interaction distance which is common in all the point patterns by investigating their inhomogeneous L-function characteristics. We also figure out a particular interaction distance, to be used for computations related to *local* inhomogeneity and anisotropy, using analysis of variance that can moderately separate the inhomogeneous L-function characteristics between the vagus and pelvic samples.

This R file requires no command-line argument, the last line of the outputs shows the configured interaction distance.

```
> Rscript --no-save LfunctAnova2.R
```

Note: This pre-processing step is completely dependent on the set of nerve cross-sections under consideration. In case of addition or removal of any cross-section, the interaction distance needs to be recomputed.

Modification for local inhomogeneity and anisotropy

Code: Kinhomsector.R, LocalKSector.R

The R *spatstat* package provides several separate functions to compute the inhomogeneous, anisotropic and local versions of the K- and L-functions. We combine several of them to meet our requirement of analysis. These R files are sourced during subsequent computations.

Computation of Sinkhorn distance

The R code files for the computation of the Sinkhorn distance between nerve cross-sections require the command line arguments to be passed in the following order:

```
> Rscript --no-save code_file_name analysis_type scaling lambda version intr_dist
```

- **analysis_type:** We analyze the spatial point patterns in terms of basic spatial intensity (*"basic_density"*) , local inhomogeneous L-function (*"local_linhom"*), local inhomogeneous L-function with horizontal sector (*"local_linhom_sector_horizontal"*) and local inhomogeneous L-function with vertical sector (*"local_linhom_sector_vertical"*). The horizontal and vertical sectors covers 15 degree around the horizontal and vertical axes respectively.
- **scaling:** *0* - if the spatial point patterns are not to be scaled, *1* - if the spatial point patterns are to be scaled. We use the scaled point patterns.
- **lambda:** The tunable entropic regularizer parameter for Sinkhorn distance computation.
- **version:** *"complete"* - to use the complete input set, *"demo"* - to use the small subset of input for quick demonstration.

- **intr_dist:** The interaction distance computed in LfunctAnova2.R

Computation based on spatial point patterns

Code: T4transportSpatialIntensity.R, T4transportSpatialFeature.R

The R package *T4transport* is used for computing Sinkhorn distance based on the spatial point patterns directly. At first, the Sinkhorn distance between every pair of point patterns for basic spatial intensity is computed, assuming each point in the point pattern carry an uniform weight. While computing distance between a pair of point patterns, one pattern is kept fixed and the other one is rotated by every 45 degree. The orientation that gives the smallest Sinkhorn distance is recorded as the orientation to be used for computations of other spatial features.

```
> Rscript --no-save T4transportSpatialIntensity.R "basic_density" 1 1.0 "demo" 0.0352
```

The Sinkhorn distance between every pair of point pattern for every orientation, their minimum, maximum, mean and variance and the Sinkhorn distance matrix - everything is saved as *.xlsx* file, along with the plots of the point patterns and their corresponding density maps, inside **spatial-neuro/quantifyVagusNerve/Plots/** directory. The optimal orientations are saved in **spatial-neuro/quantifyVagusNerve/Data/Supporting Files/Angle of Rotation/** directory as *.xlsx* file.

Then, the Sinkhorn distance for other spatial features can be computed using the pre-computed orientations, where each point in the point pattern carries weight equal to the value of the spatial feature. The results are recorded in **spatial-neuro/quantifyVagusNerve/Plots/** directory in a similar way.

```
> Rscript --no-save T4transportSpatialFeature.R "local_linhom" 1 1.0 "demo"  0.0352
> Rscript --no-save T4transportSpatialFeature.R "local_linhom_sector_horizontal" 1 1.0 "demo"  0.0352
> Rscript --no-save T4transportSpatialFeature.R "local_linhom_sector_vertical" 1 1.0 "demo"  0.0352
```

Computation based on images of the spatial features

Code: BarycenterSpatialIntensity.R, BarycenterSpatialFeature.R

The R package *Barycenter* is used for computing Sinkhorn distance based on the images of the spatial features of the point patterns, rather than the point patterns themselves. The codes are run and the results are stored as before.

```
> Rscript --no-save BarycenterSpatialIntensity.R "basic_density" 1 0.5 "demo"  0.0352

> Rscript --no-save BarycenterSpatialFeature.R "local_linhom" 1 0.5 "demo"  0.0352
> Rscript --no-save BarycenterSpatialFeature.R "local_linhom_sector_horizontal" 1 0.5 "demo"  0.0352
> Rscript --no-save BarycenterSpatialFeature.R "local_linhom_sector_vertical" 1 0.5 "demo"  0.0352
```

Output and visualization

Code: VisualizeMDS.R

The directory **spatial-neuro/quantifyVagusNerve/Plots/** will contain the output plots and files in separate subdirectories. The *.xlsx* files saved here contains the Sinkhorn distance matrices and we can visualize the nerve samples in the Sinkhorn space of the corresponding spatial features by applying multi-dimensional scaling on them.

```
> Rscript --no-save VisualizeMDS.R
```

References

Cuturi, Marco. 2013. "Sinkhorn Distances: Lightspeed Computation of Optimal Transport." *Advances in Neural Information Processing Systems* 26.

Plebani, Emanuele, Natalia P Biscola, Leif A Havton, Bartek Rajwa, Abida Sanjana Shemonti, Deborah Jaffey, Terry Powley, Janet R Keast, Kun-Han Lu, and M Murat Dundar. 2022. “High-Throughput Segmentation of Unmyelinated Axons by Deep Learning.” *Scientific Reports* 12 (1): 1–16.

Schindelin, Johannes, Ignacio Arganda-Carreras, Erwin Frise, Verena Kaynig, Mark Longair, Tobias Pietzsch, Stephan Preibisch, et al. 2012. “Fiji: An Open-Source Platform for Biological-Image Analysis.” *Nature Methods* 9 (7): 676–82.