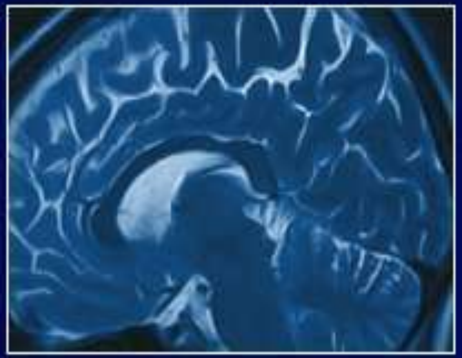

The Waisman Laboratory
for Brain Imaging and Behavior

University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH

Persistent homological brain network analysis

Moo K. Chung

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www.stat.wisc.edu/~mchung

November 24, 2017, Juan-les-Pins, France Winter Workshop

http://nbiasite.wordpress.com

NONSTANDARD BRAIN IMAGE ANALYSIS

Satellite Meeting of 2018
OHBM Singapore

June 22-23, 2018

Plenary Talks

Peter Bandettini, Jean-Baptiste Poline

Session on Deep Learning

Dinggang Shen, Daniel Alexander, Jong Chul Ye, Jong-Hwan Lee

Session on Imaging Genetics

Anqi Qiu, Li Shen, Hongtu Zhu, Tomas Nichols

Session on Nonstandard EEG Analysis

Hernando Ombao, Hakmook Kang, Mak Fiecas, Tim Johnson

Session on Nonstandard fMRI Analysis

Martin Lindquist, Alex D. Leow, Bharat Biswal, Christian F. Beckmann

Session on Nonstandard Brain Connectomics

Moo K. Chung, Andrew Zalesky, James C. Gee, Carl-Fredrik Westin

Poster Session

Abstract

Persistent homology, a branch of recently popular computational topology, provides a coherent mathematical framework for quantifying the topological structures of brain networks. Instead of looking at networks at a fixed scale, as usually done in many standard brain network analysis, persistent homology observes the changes of topological features of the network over multiple resolutions and scales. In doing so, it reveals the most persistent topological features that are robust under noise perturbations. This robustness in performance under different scales is needed for obtaining more stable quantification of the network. For the first half of the talk, we will review the basics of persistent homology. The remaining half of the talk will be focused on its applications in EEG and dMRI based brain network analysis. The talk is based on doi.org/10.1109/TMI.2012.2219590.

Acknowledgement

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Victorial Villalta-Gil, David Zald Vanderbilt University

Jae Jun Woo, Jong Chul Ye *KAIST, Korea*

Hernando Ombao *KAUST, Saudi Arabia*
Guorong Wu *University of North Carolina – Chapel Hill*

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P30 HD003352, U54 HD09025

Rips Filtration

Carlsson & de Silva, 2010
Edelsbrunner & Harer, 2009

What is filtration?

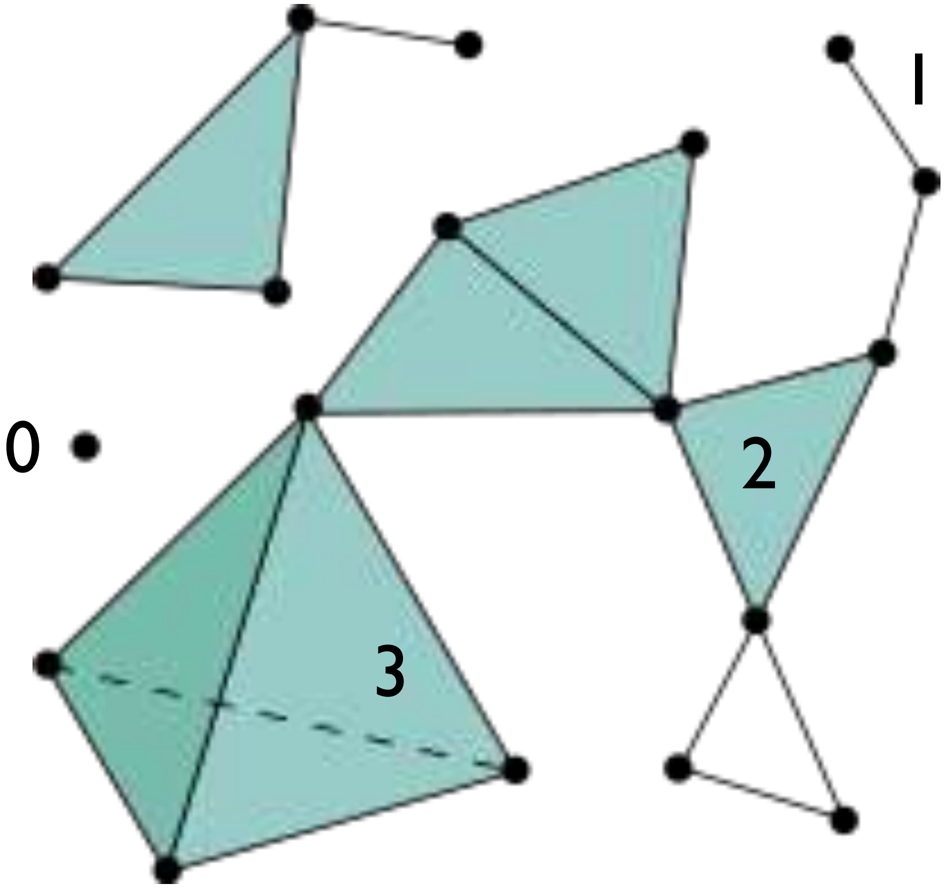
$$\mathcal{G}_1 \subset \mathcal{G}_2 \subset \mathcal{G}_3 \subset \cdots$$

Sequence of nested objects or vector spaces

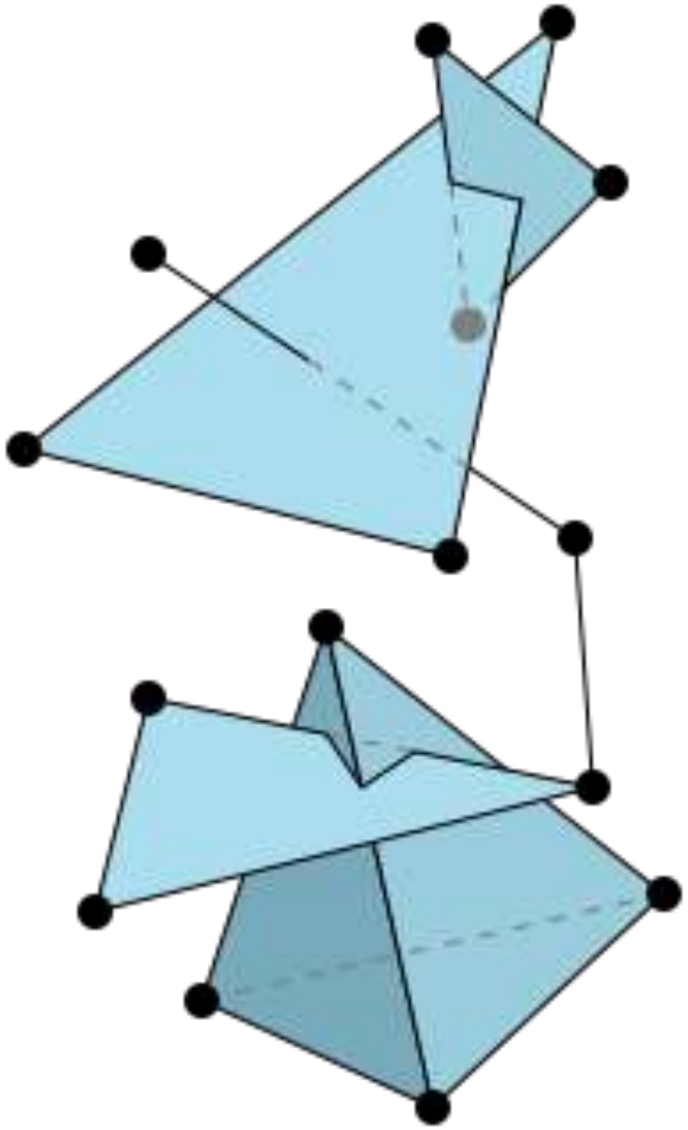
Monotonic feature function

$$\beta_i(\mathcal{G}_1) < \beta_i(\mathcal{G}_2) < \beta_i(\mathcal{G}_3) < \cdots$$

Simplicial complex

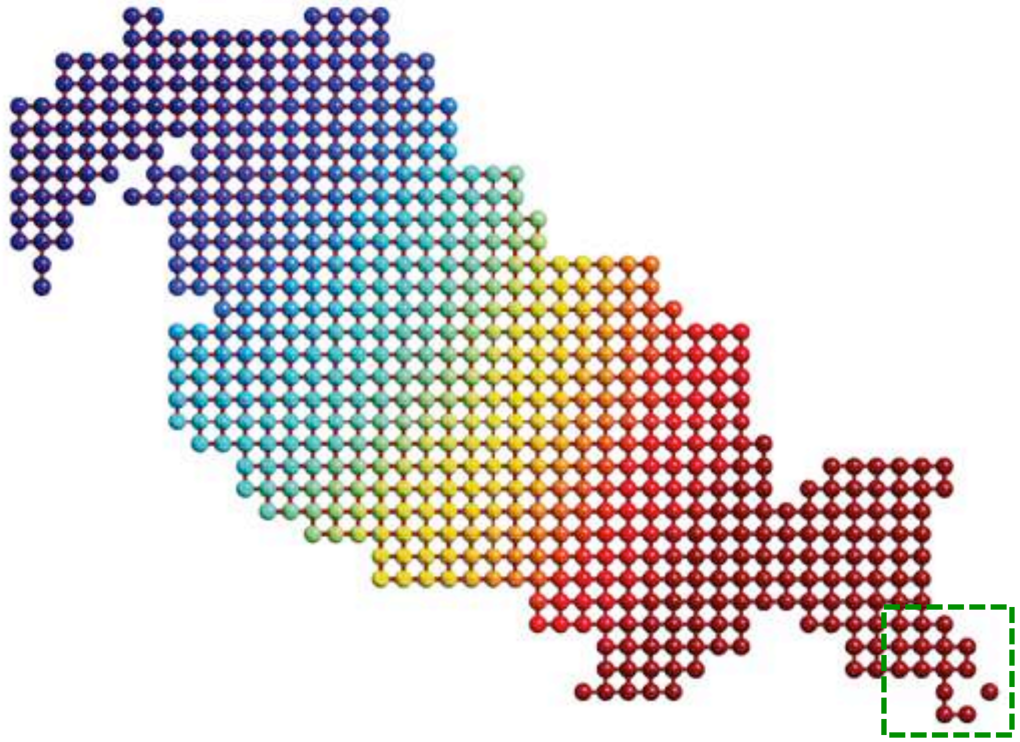


Simplicial complex

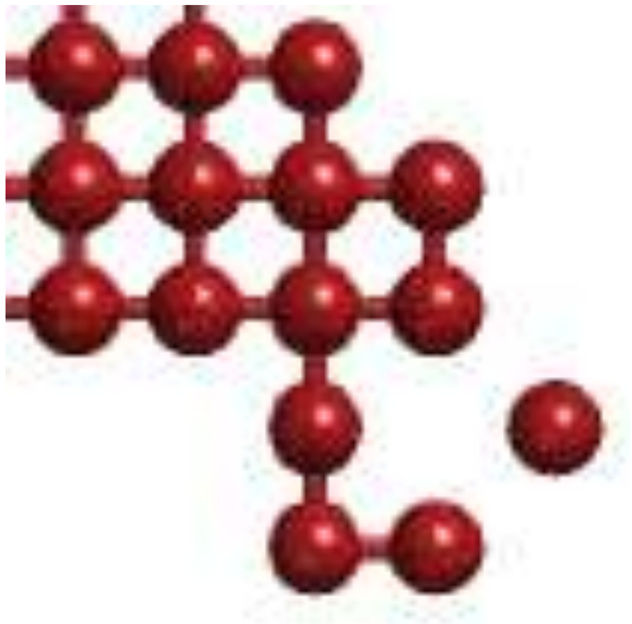


Not a valid simplicial complex

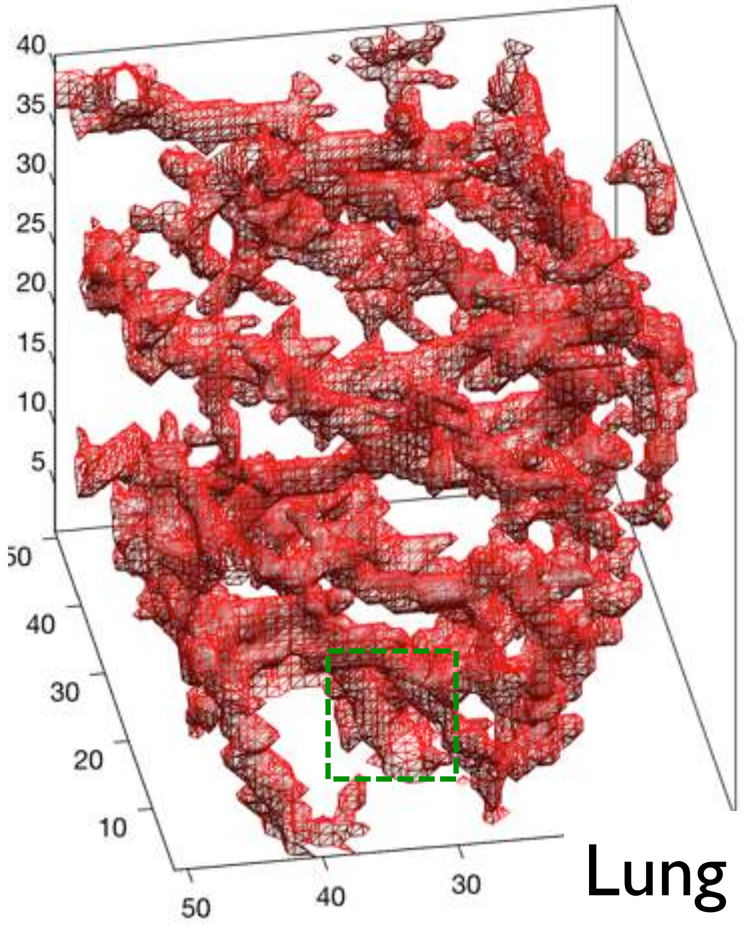
Cubical complex



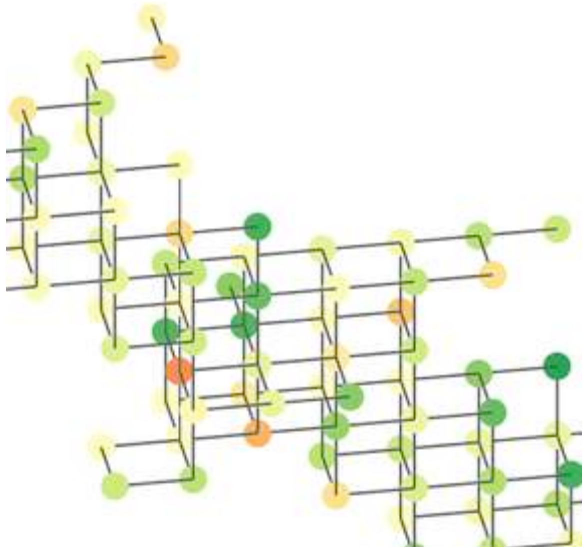
Left central gyrus



4-neighbor connectivity



Lung blood vessel

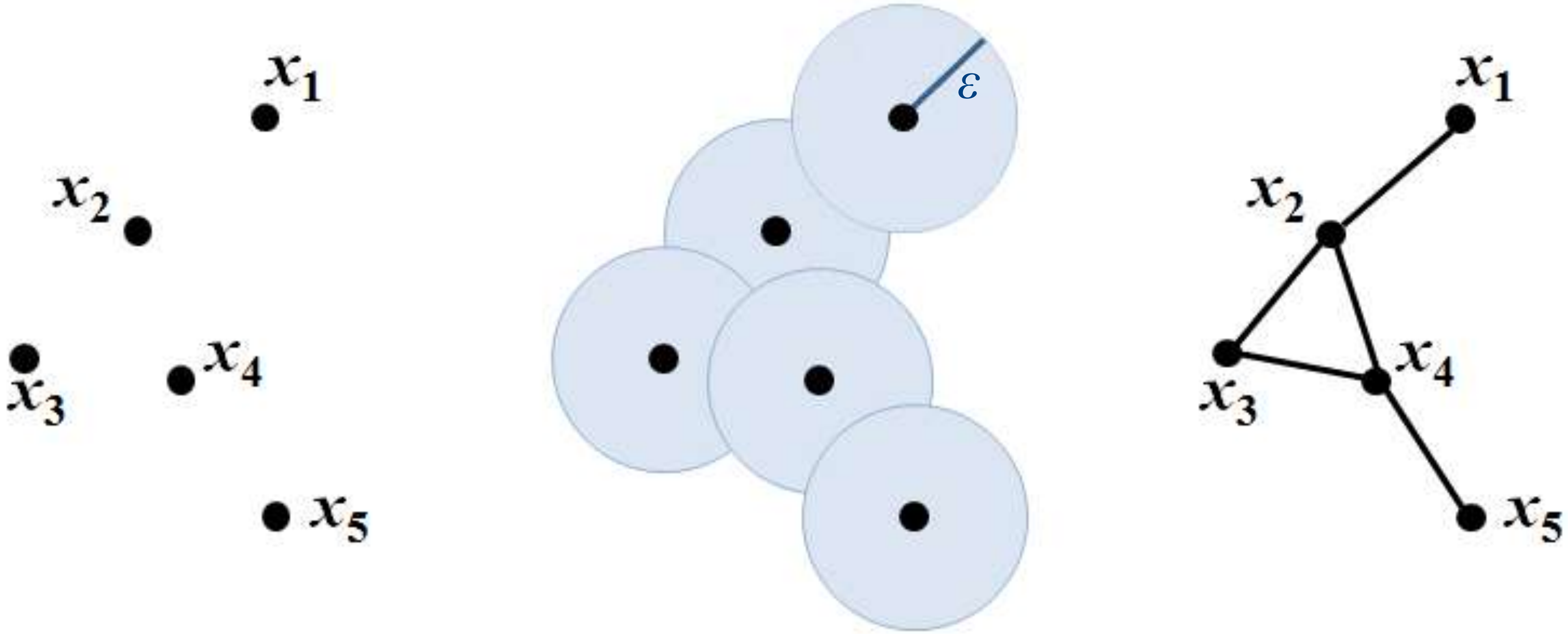


6-neighbor connectivity

Chung et al. 2018 arXiv:1710.07849

Rips complex of point cloud data

Rips complex approximates the topology of the point cloud data by connecting two point cloud data, x_i and x_j, if $d(x_\mathrm{i}, x_\mathrm{j}) < \varepsilon$.

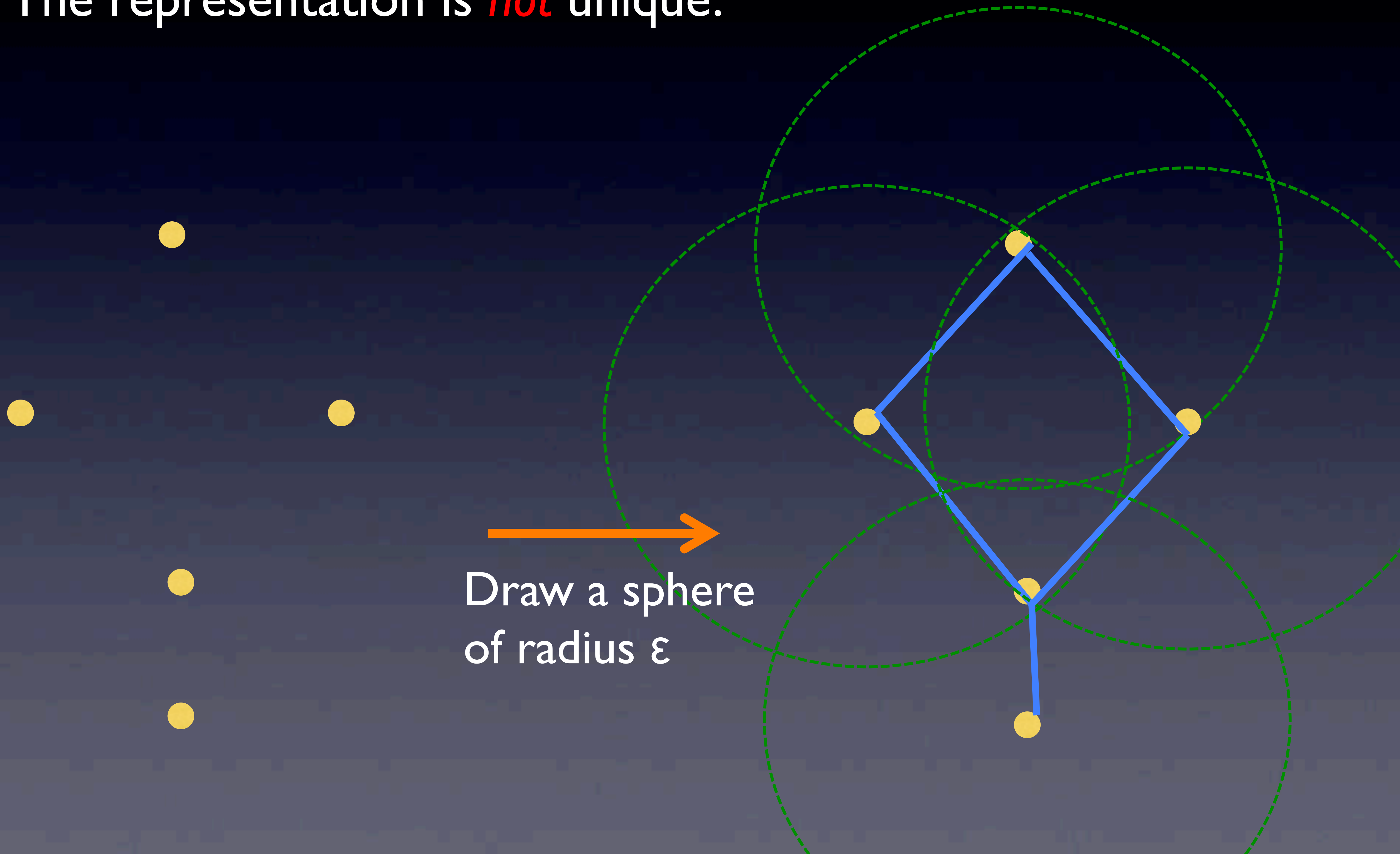


Rips Filtration of cloud point data

Computationally expensive:

For *n*-nodes, $O(n^{3k+3})$ for the *k*-th Betti number

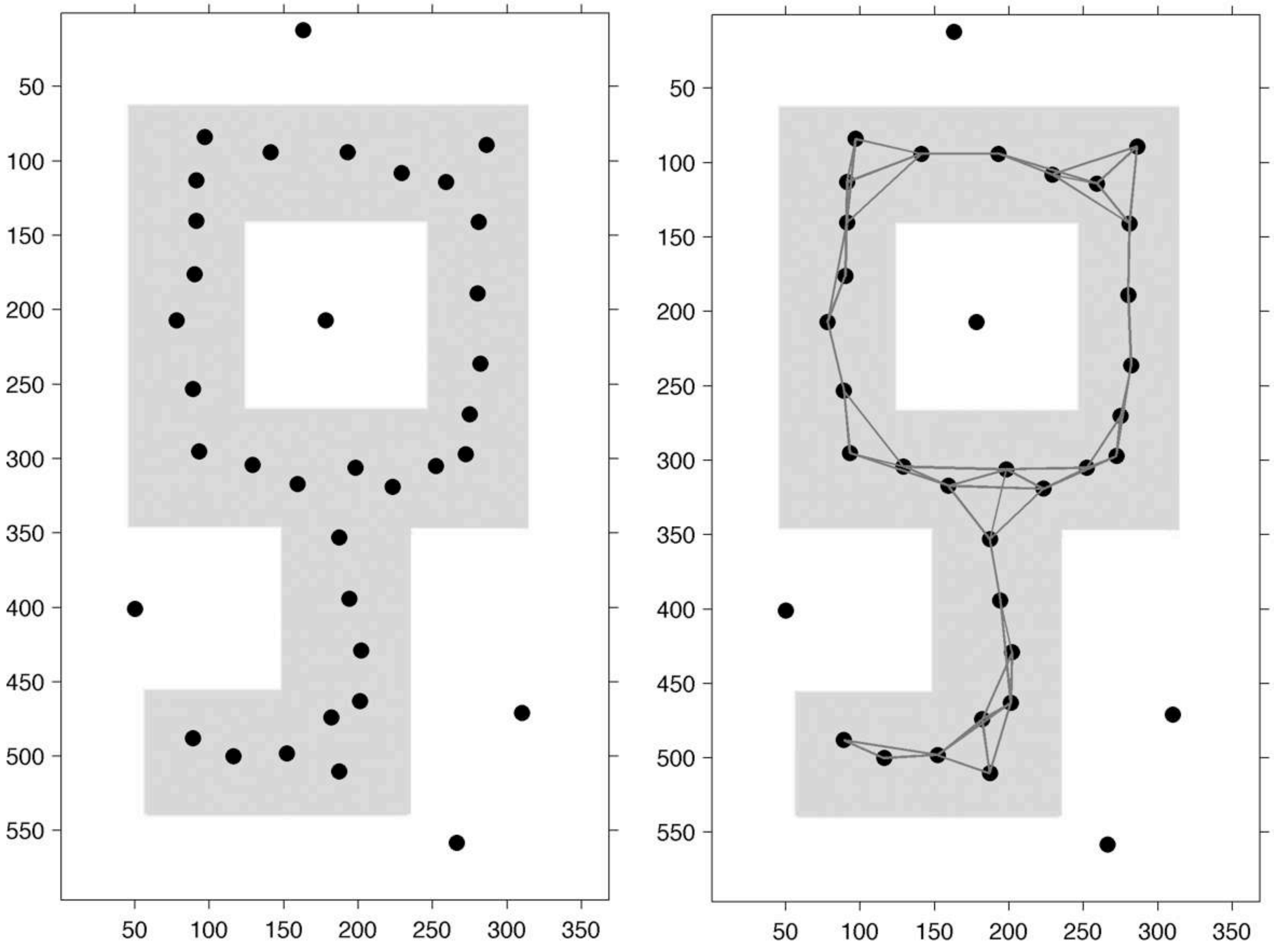
The representation is *not* unique.



Draw a sphere of radius ε

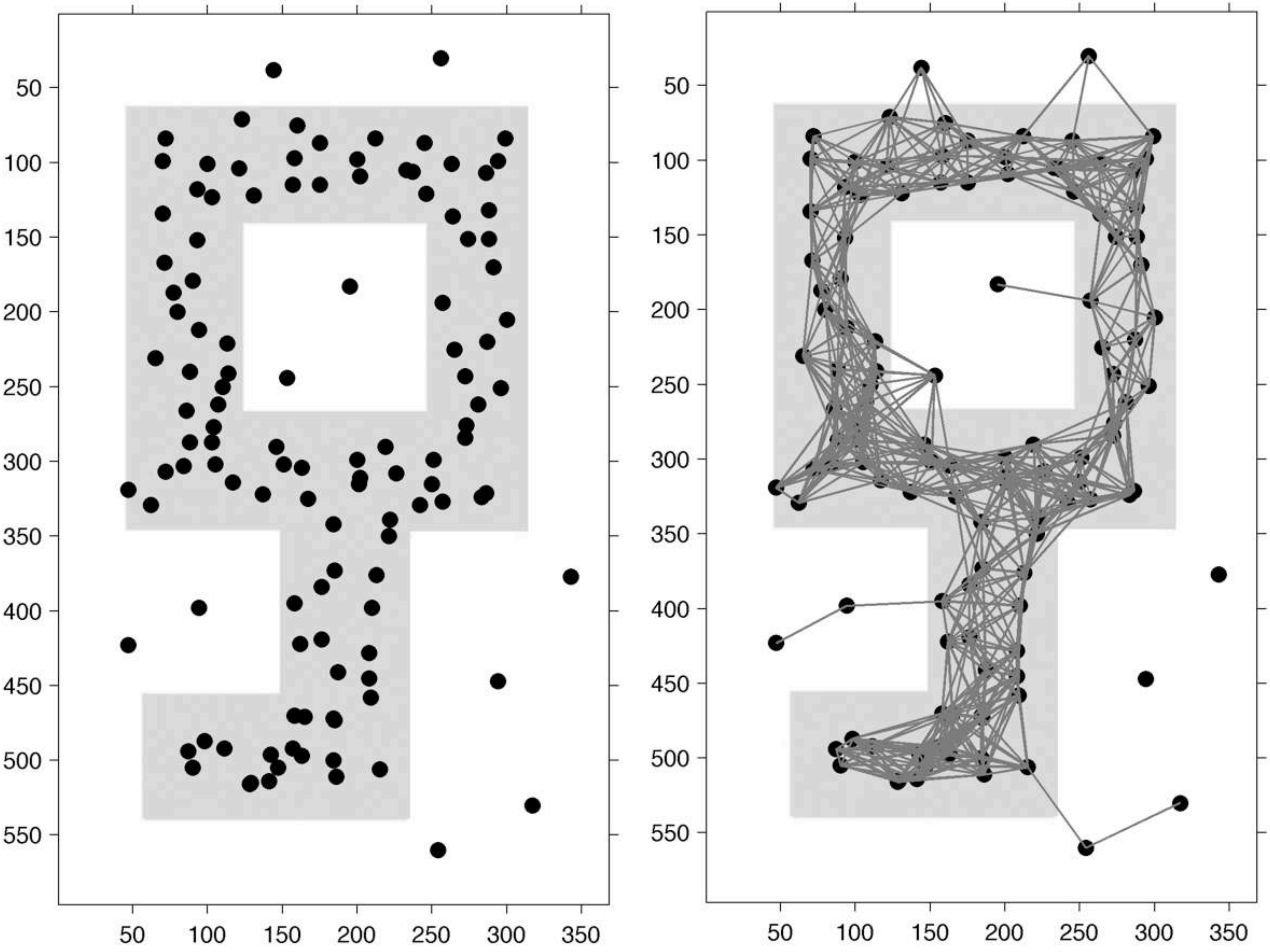
Rips complex of point cloud data

ε = 70mm



Rips complex of point cloud data

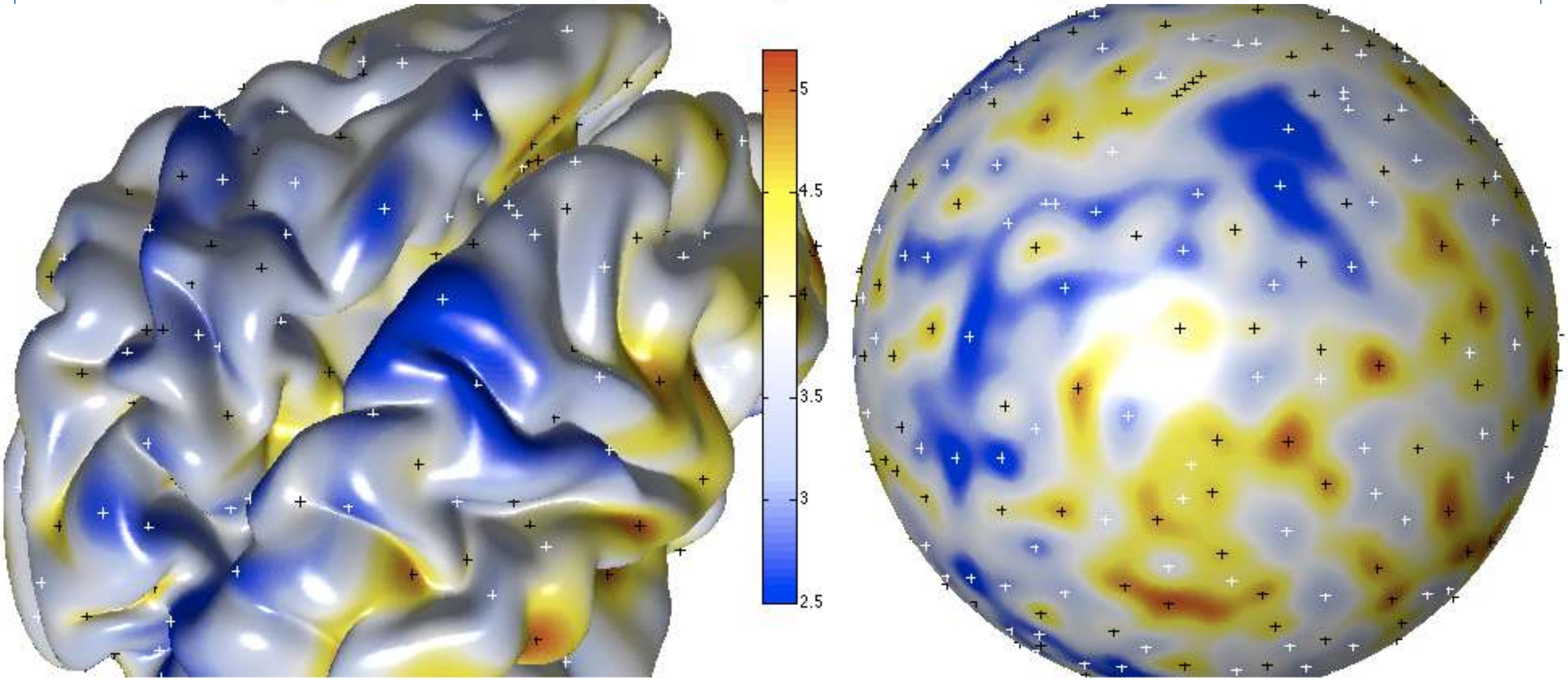
ε = 70mm



Morse Filtration

Persistence Diagrams of Cortical Surface Data

Moo K. Chung[1,2], Peter Bubenik[3], and Peter T. Kim[4]

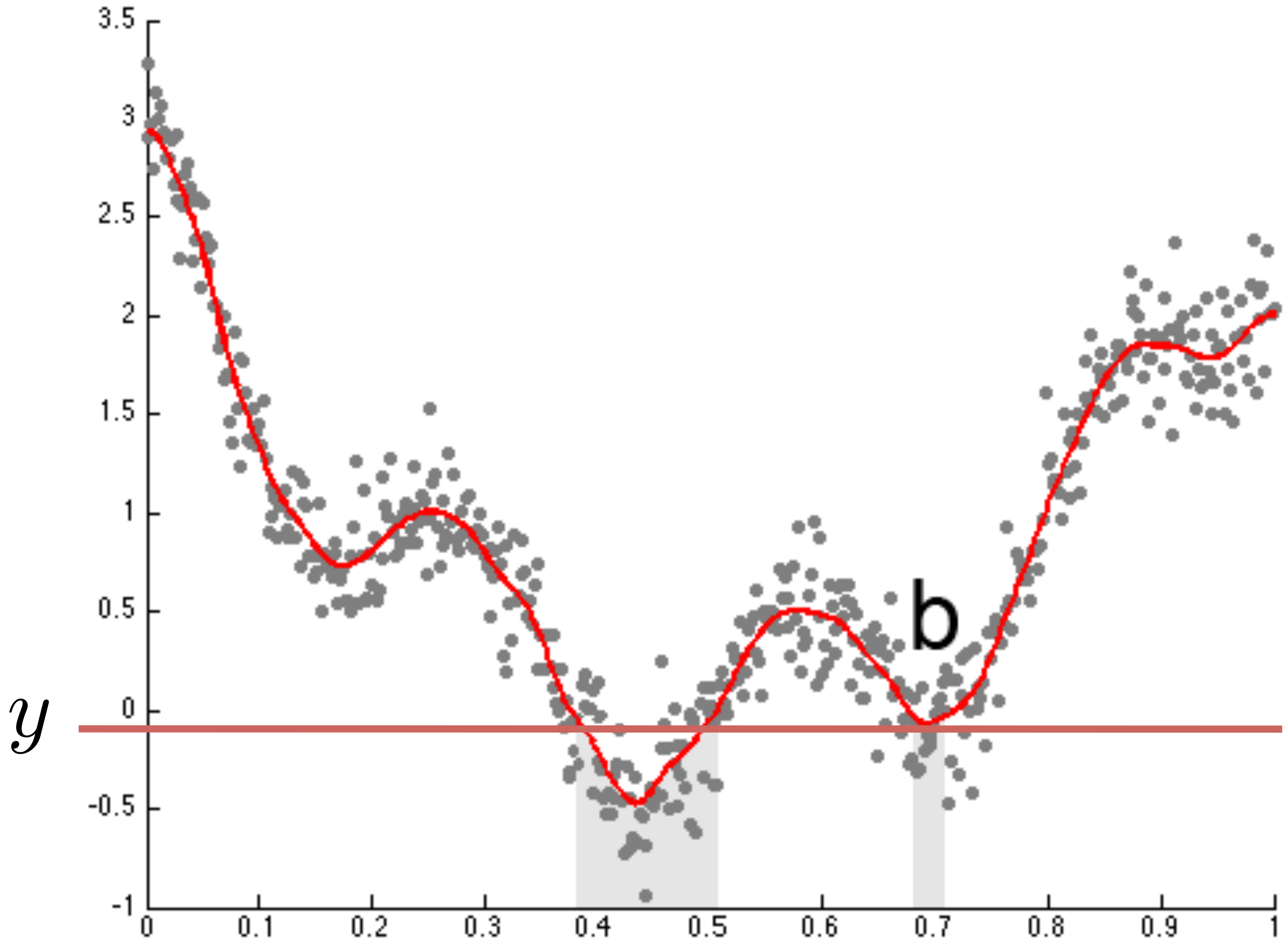


Chung et al., 2009 Information Processing in Medical Imaging (IPMI) 5636:386-397.
Pachauri et al., 2011 IEEE Transactions on Medical Imaging 30:1760-1770

Morse theory in signal processing

$$Y = \mu + \epsilon$$

Unknown signal μ is assumed to be a Morse function: all critical values are unique.



Sublevel set

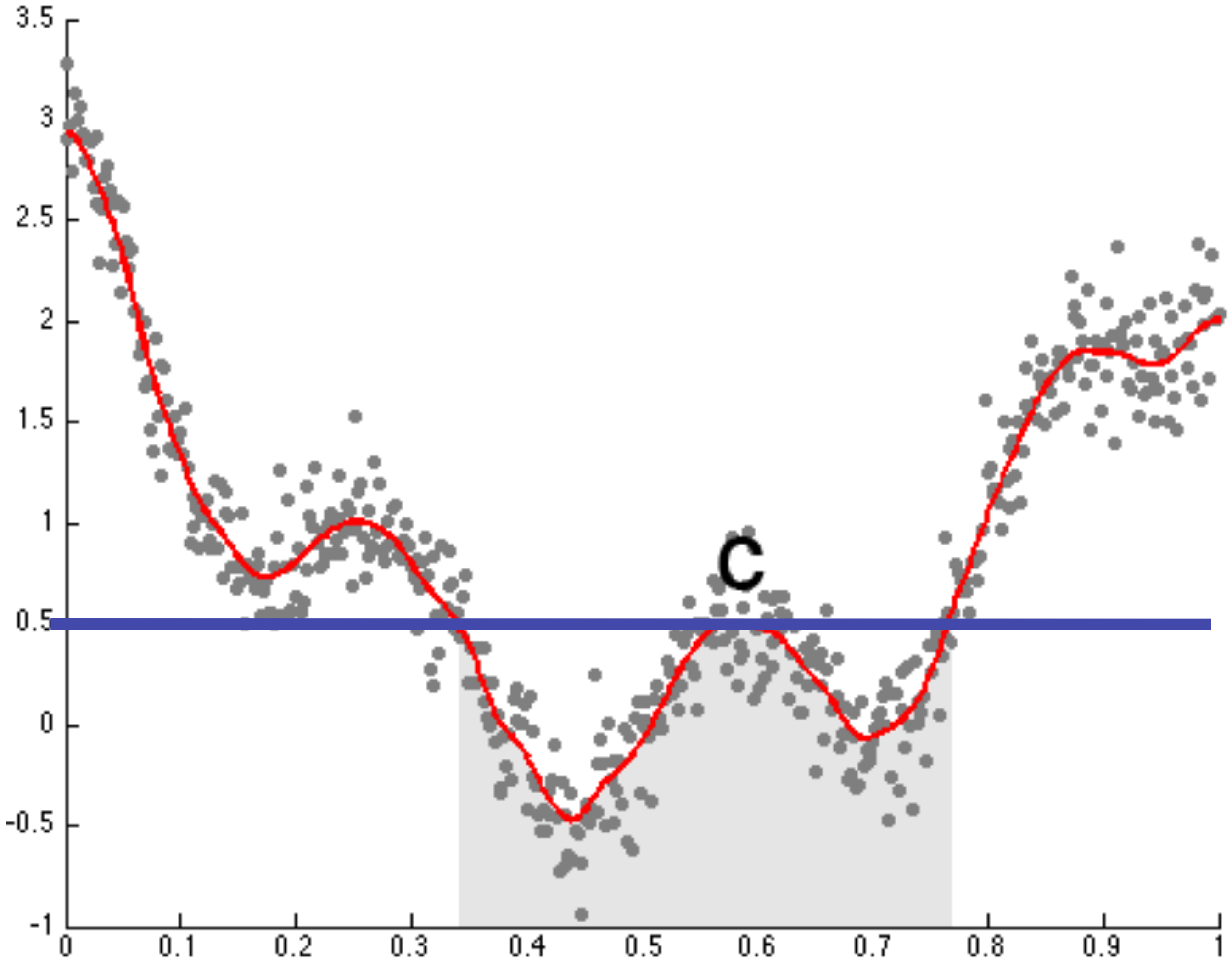
$$R(y) = \mu^{-1}(-\infty, y]$$

Number of connected components $\#R(y)$

Morse filtration

Consider a sublevel set

$$R(y) = \mu^{-1}(-\infty, y]$$



For critical values

$$b < c$$

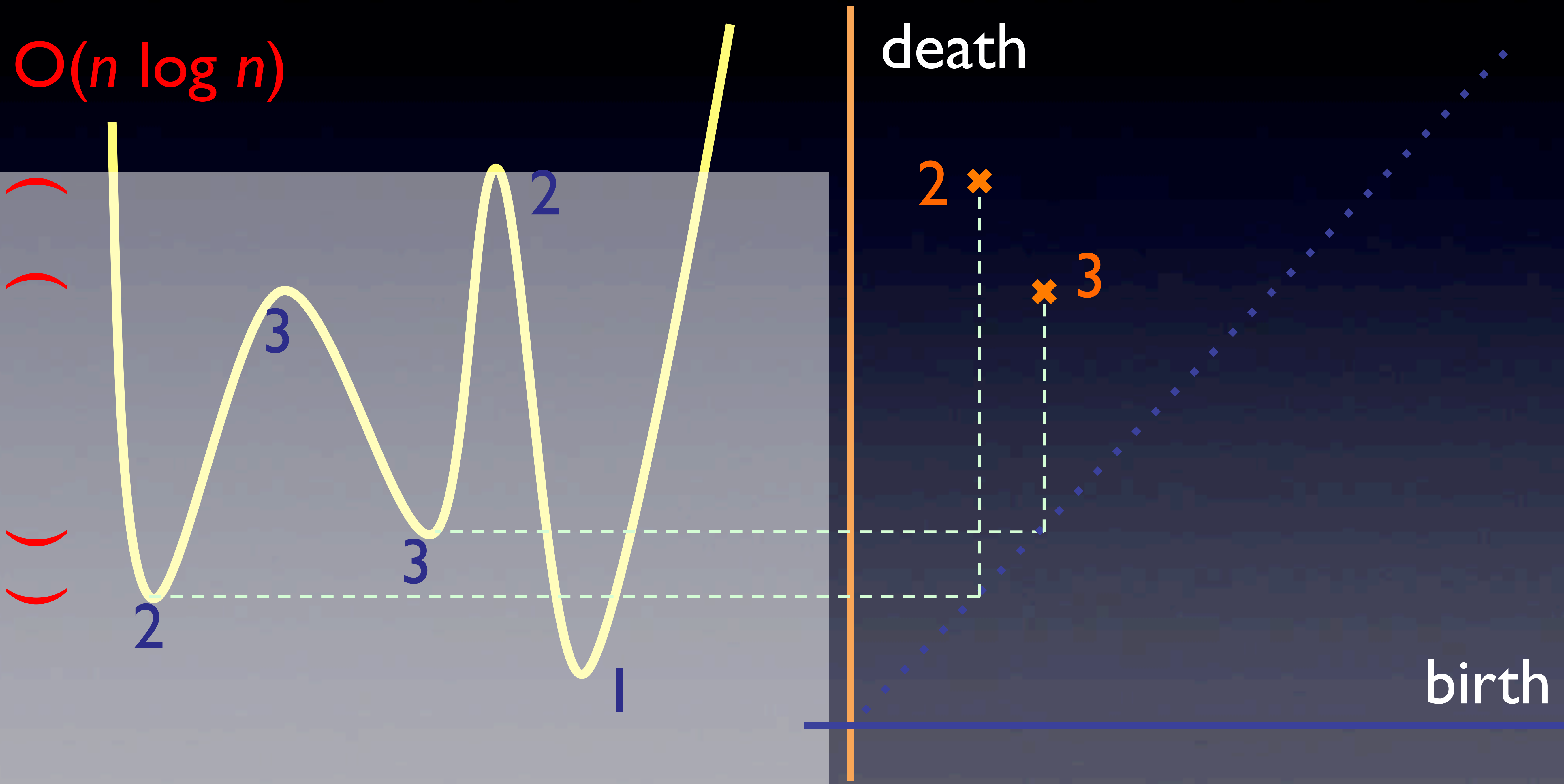
$$R(b) \subset R(c)$$

For all critical values $y_1 < y_2 < \cdots$,

$$R(y_1) \subset R(y_2) \subset \cdots$$

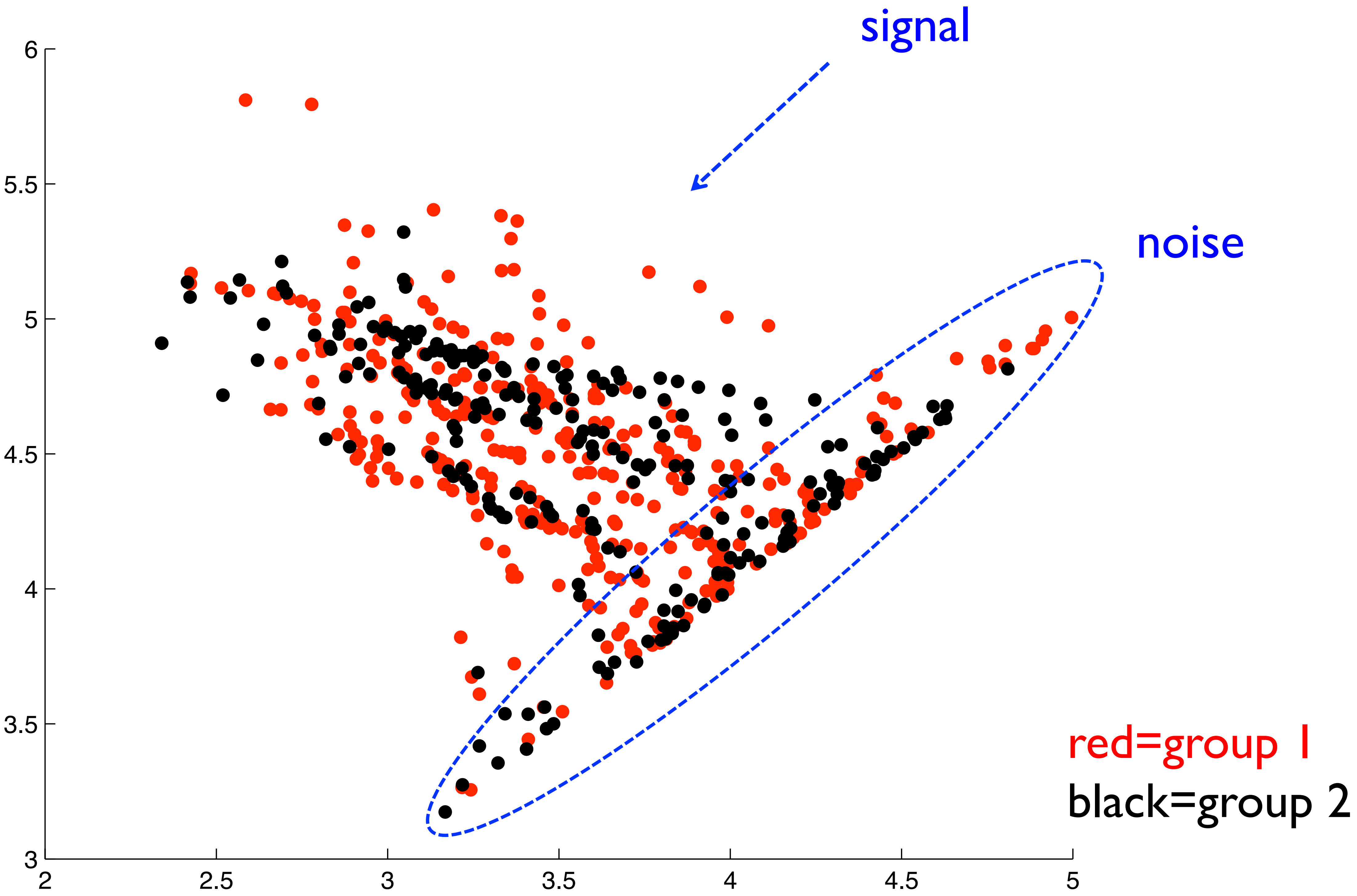
Persistent Diagrams

Persistence Diagram (PD)



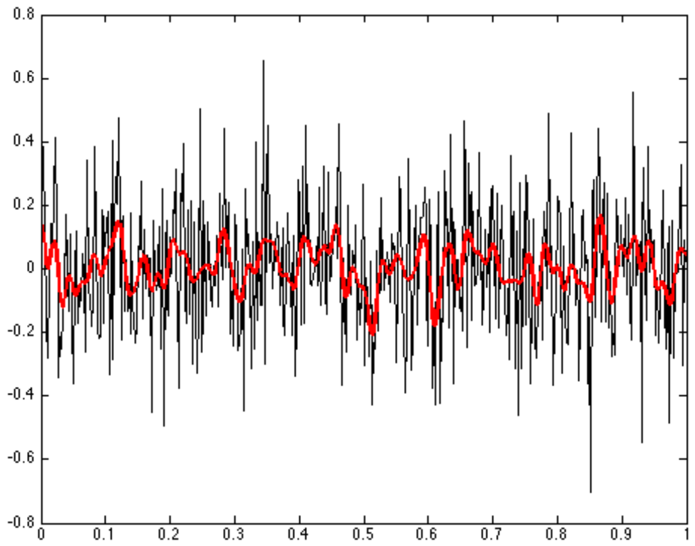
Pair the time of death with the time of the closest earlier birth

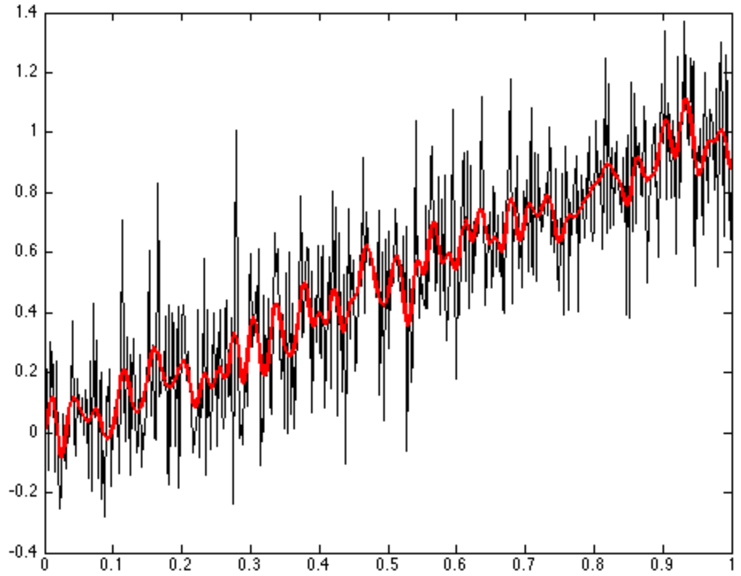
Signal in persistent diagrams

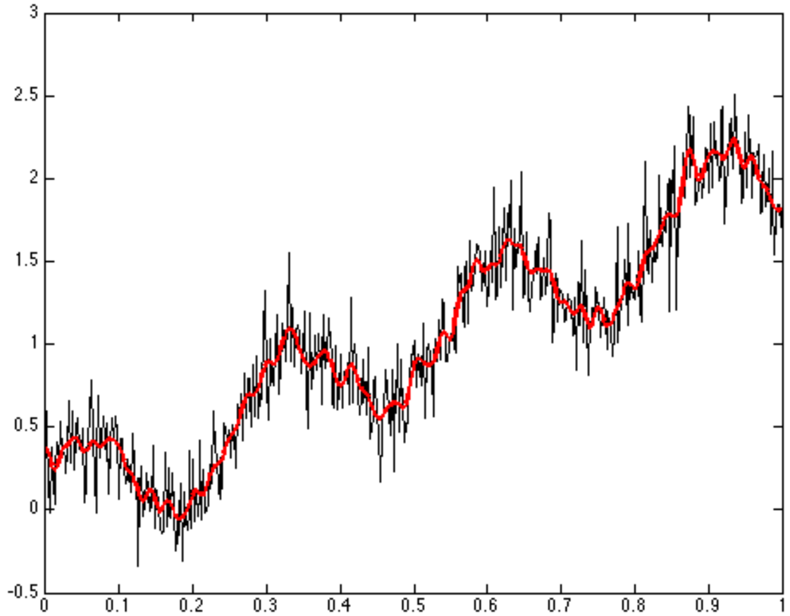


How do we analyze a collection of PDs?

Critical values capture the pattern of signal changes

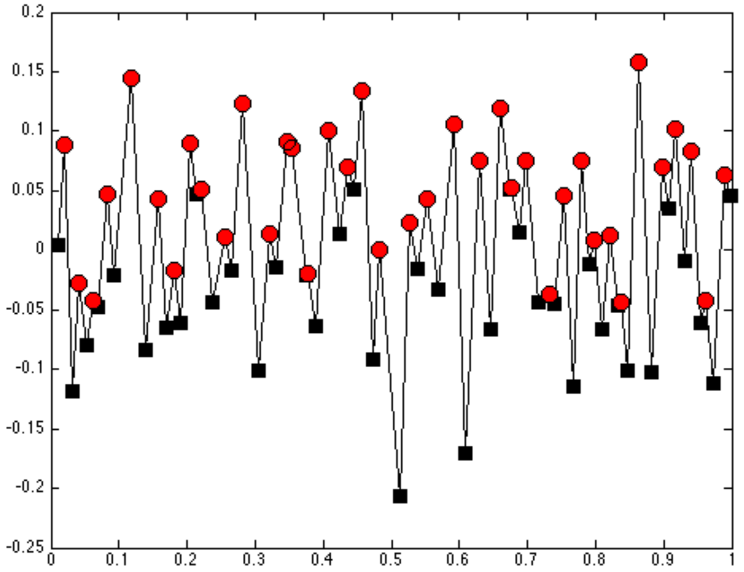


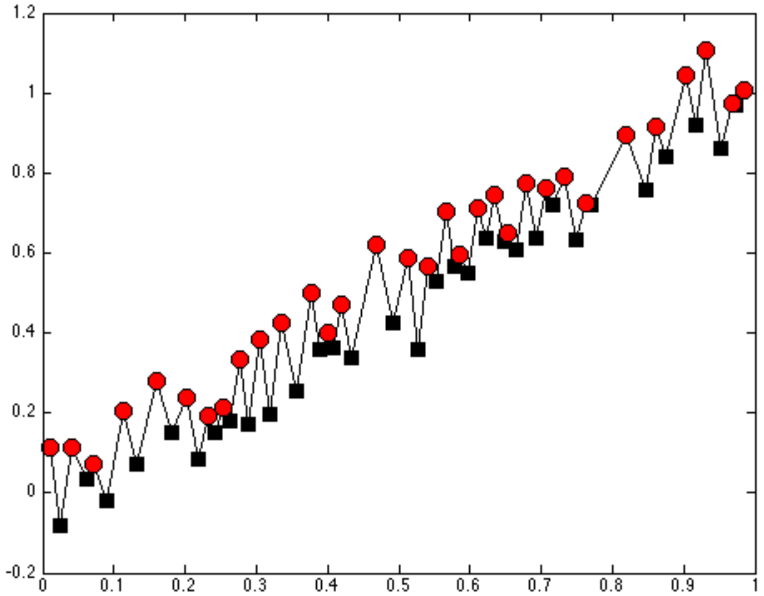


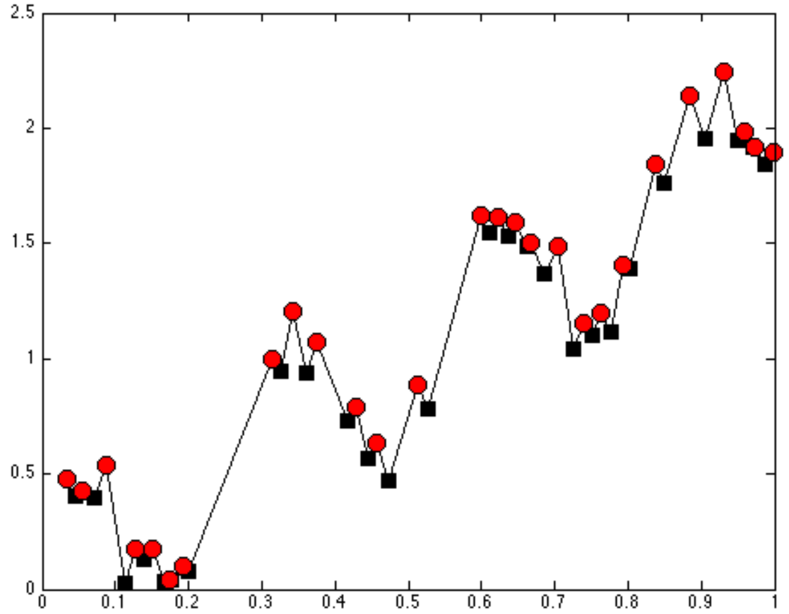


$$f(t) = e(t)$$

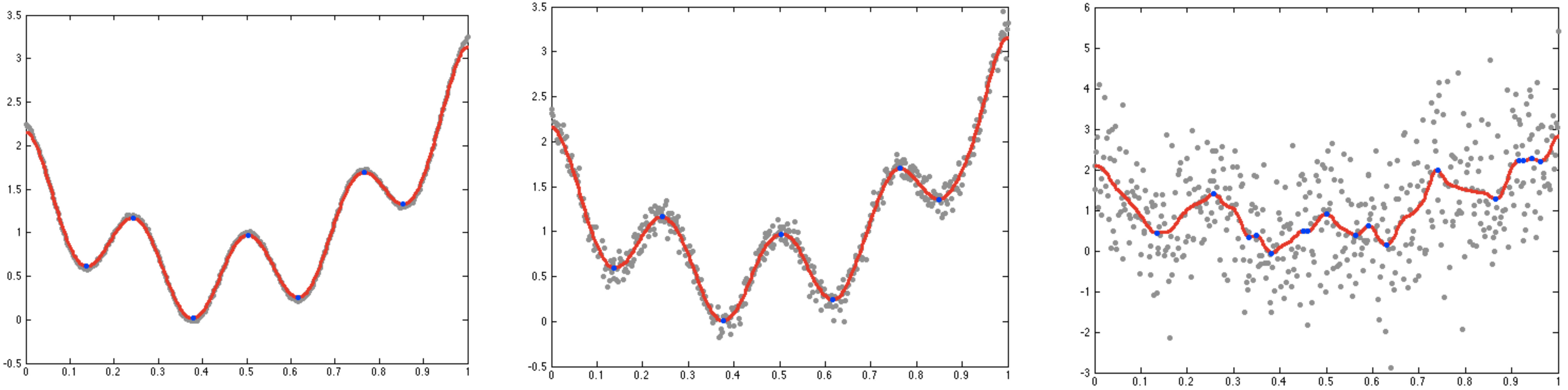
$$f(t) = t + e(t)$$



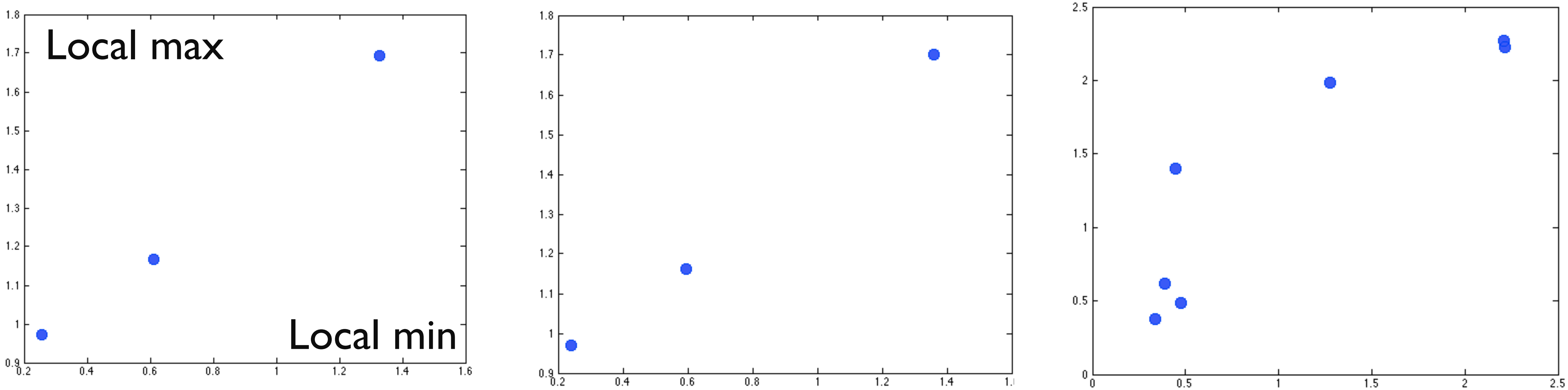




Example: $f(x) = x + 7(x - \frac{1}{2})^2 + \frac{1}{2}\cos(8\pi x) + \epsilon$

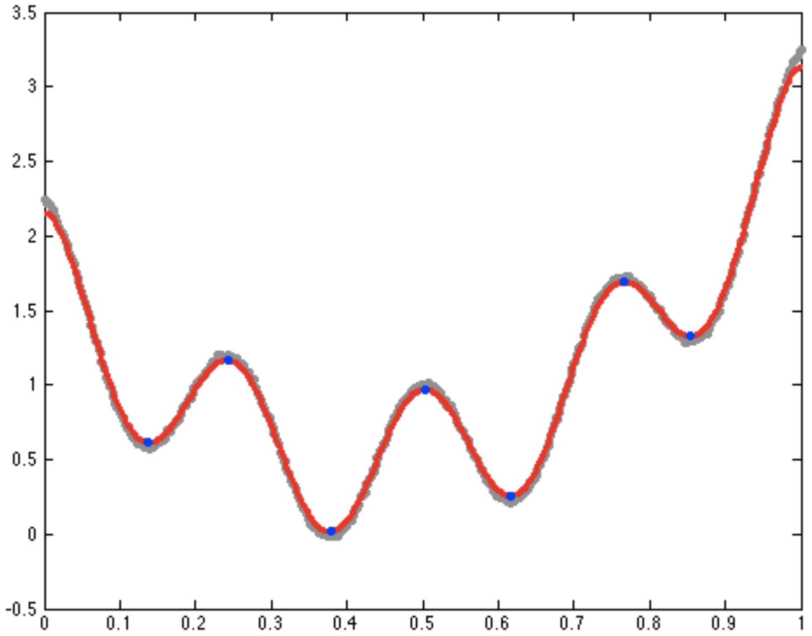


$\epsilon \sim N(0, 0.01^2)$ $\epsilon \sim N(0, 0.1^2)$ $\epsilon \sim N(0, 1^2)$

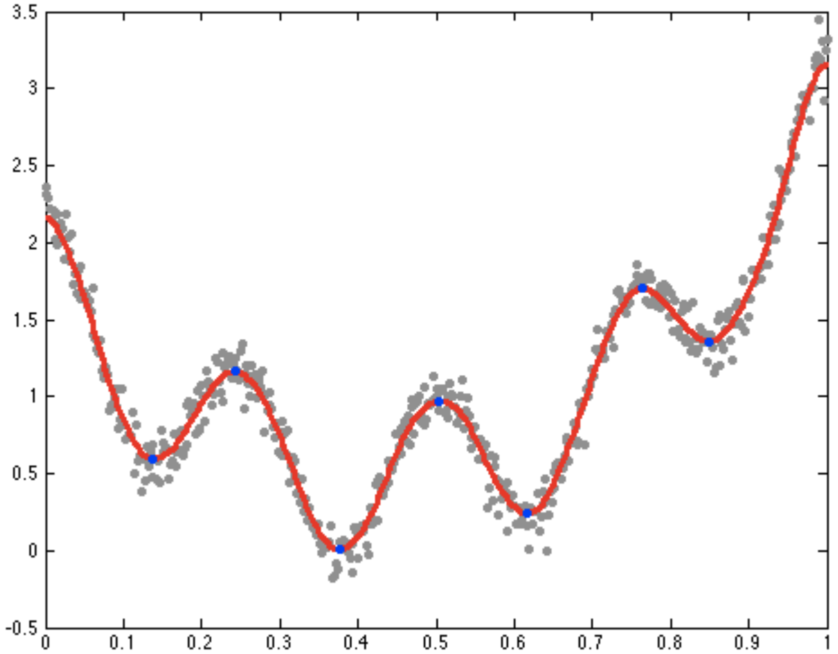


Stability of persistence diagram

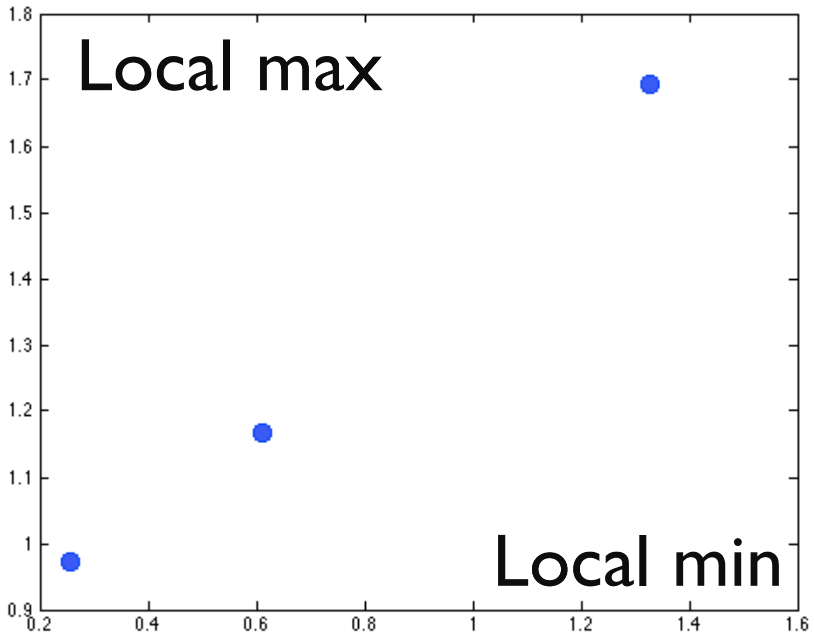
$$d(D(f), D(g)) \leq \|f - g\|_\infty$$

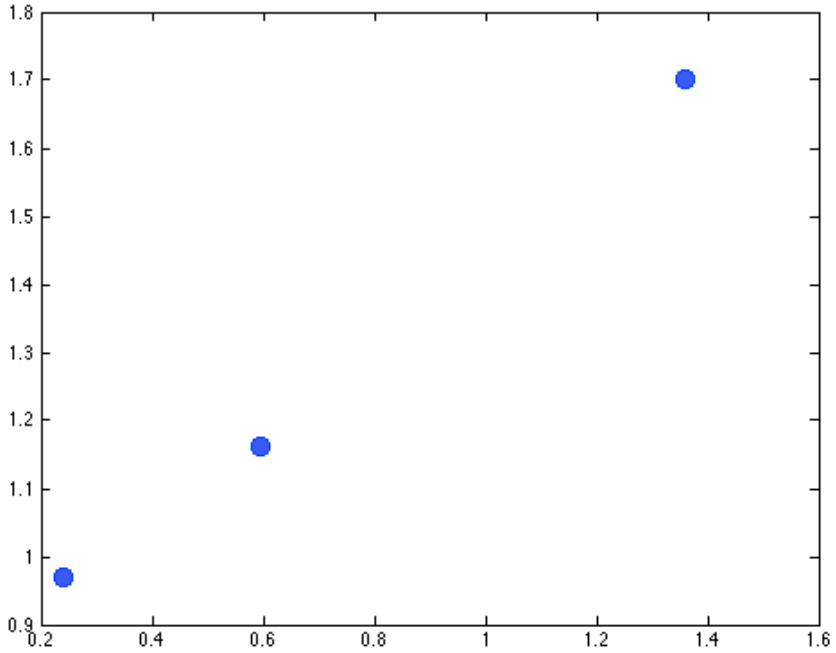


$$\epsilon \sim N(0, 0.01^2)$$

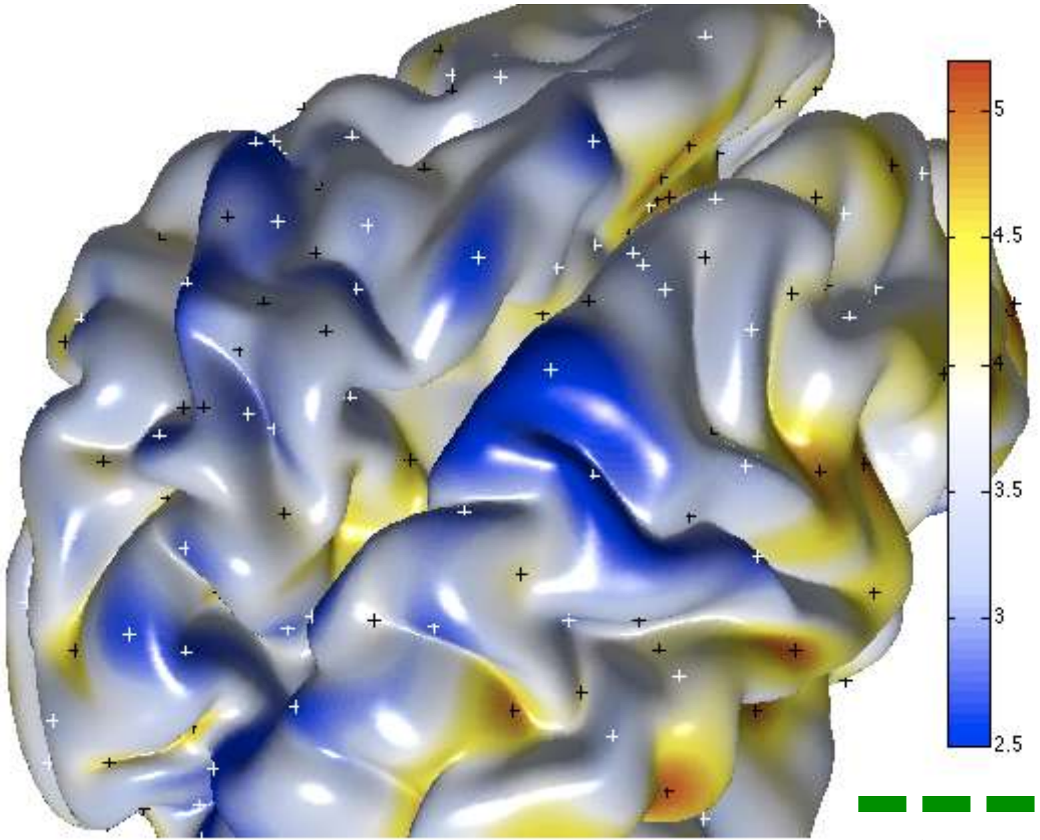


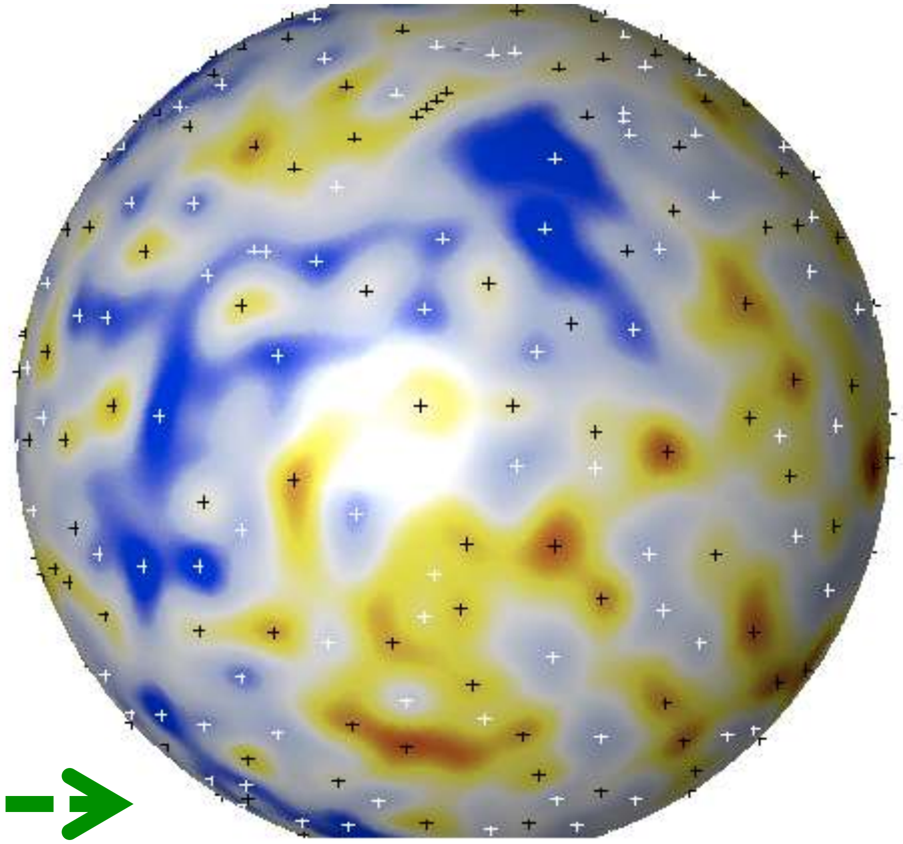
$$\epsilon \sim N(0, 0.1^2)$$





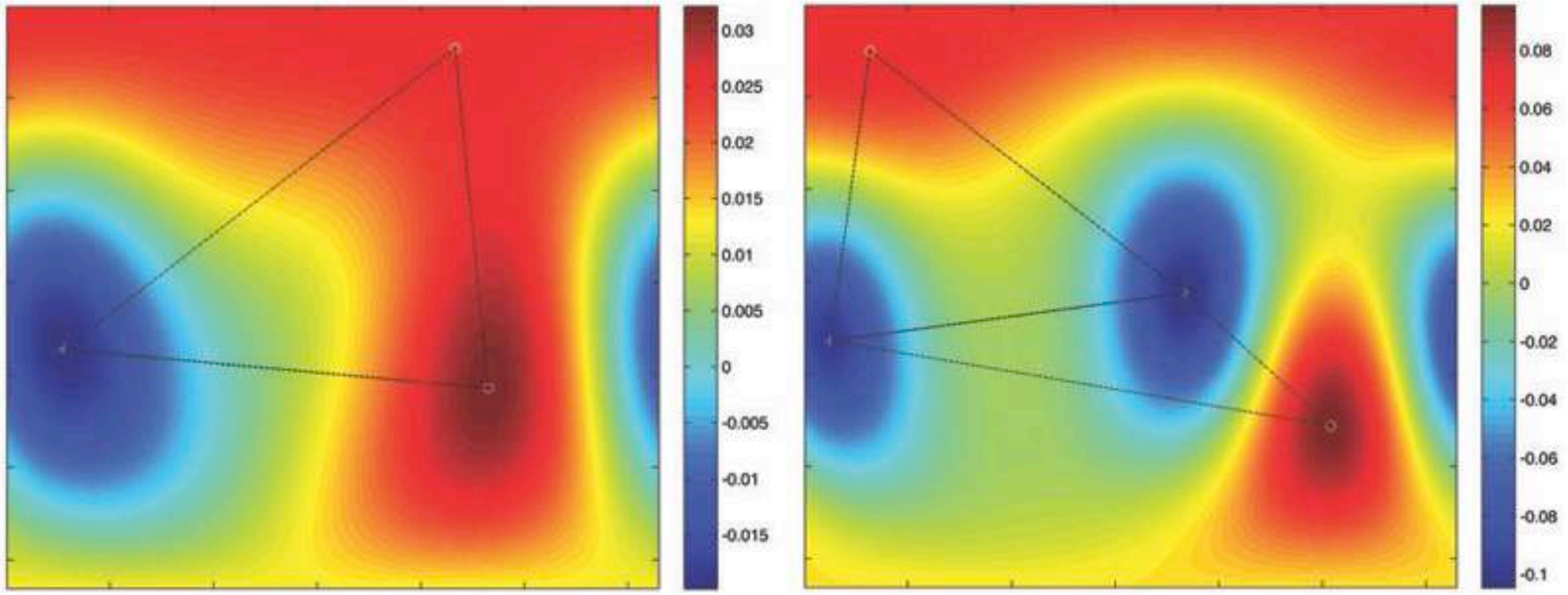
Persistent homology on cortical thickness



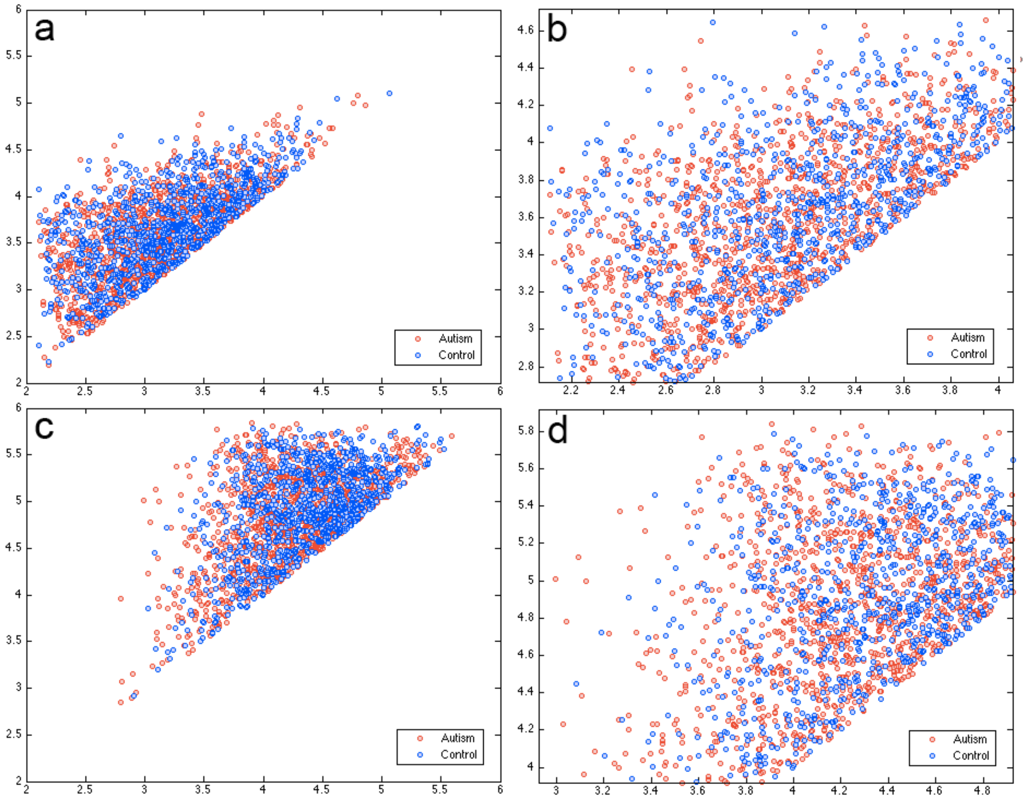


Deformation

Simplex construction



Persistent Diagram



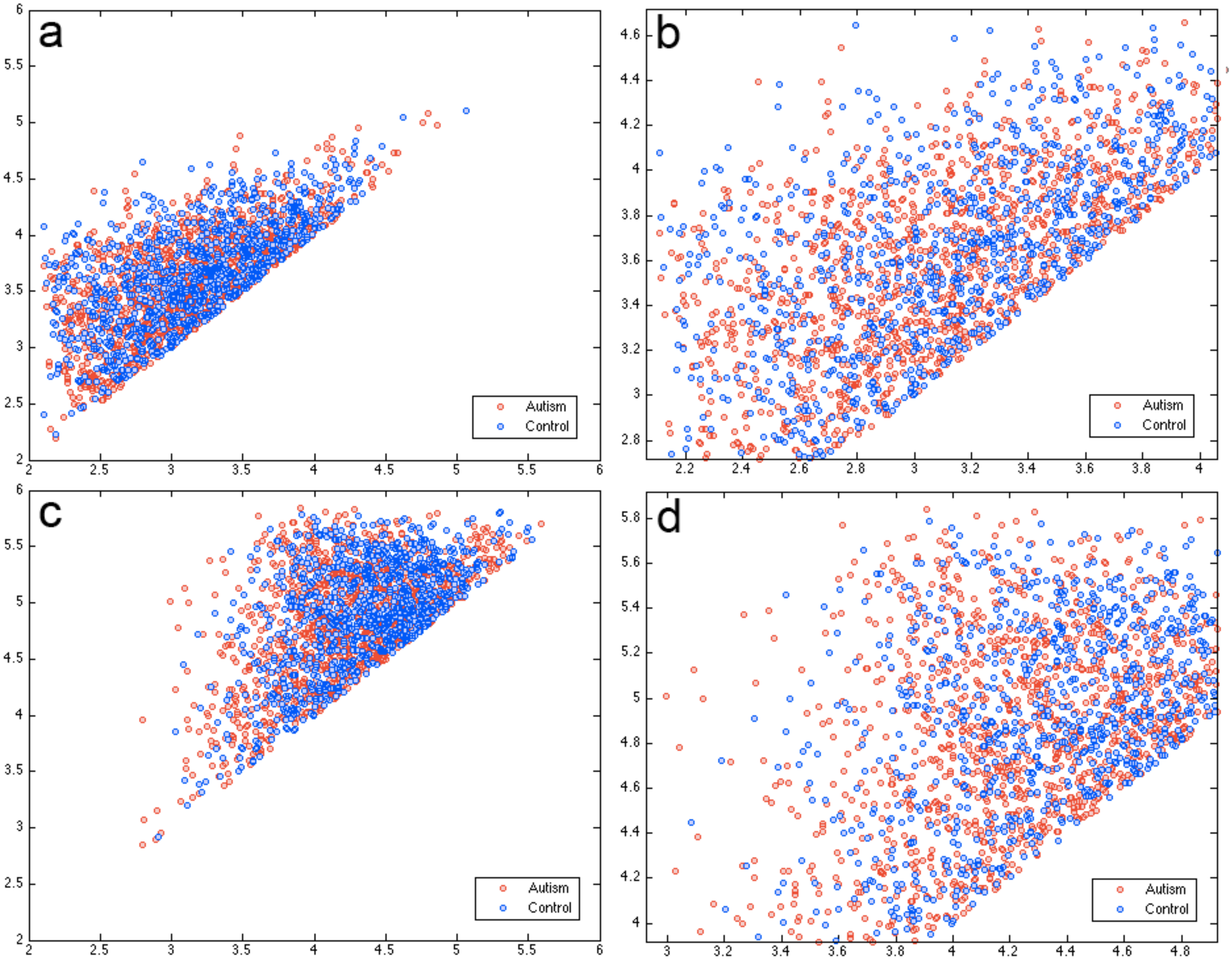
blue= control (n=11)   red= autism (n=16)

degree 0

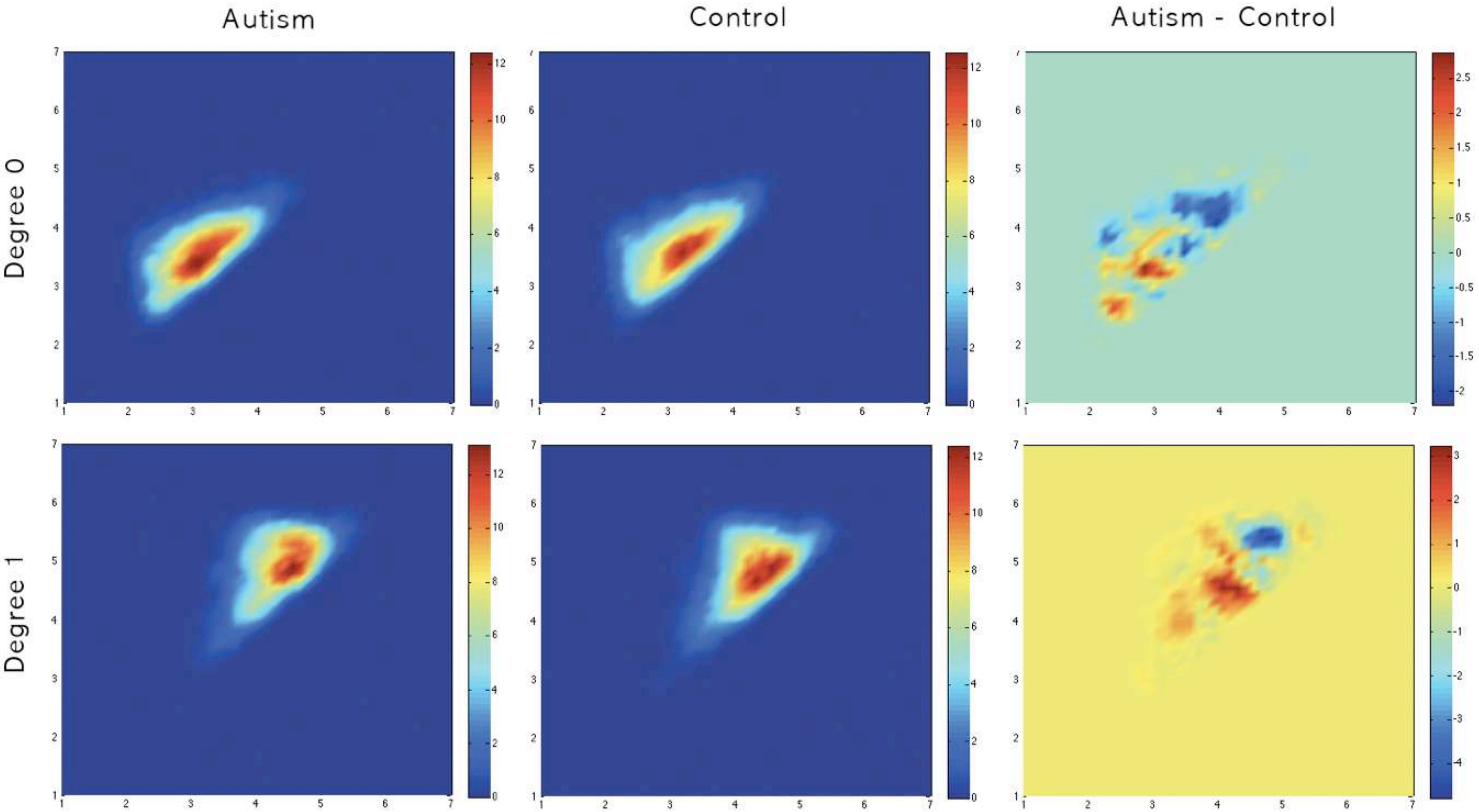
pairing of
saddle points
to minimums

degree 1

pairing of
saddle points
to maximums

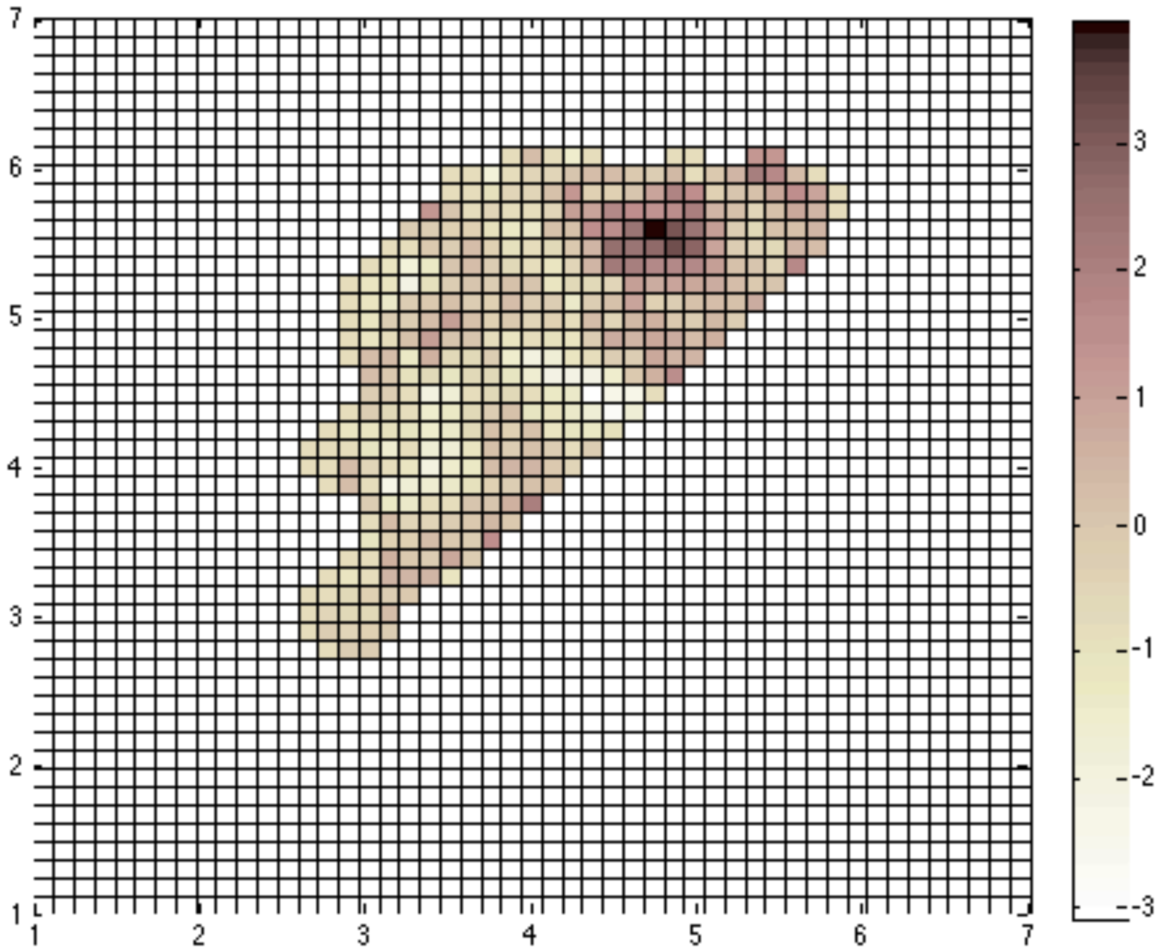


Kernel density (uniform kernel) in persistent diagram



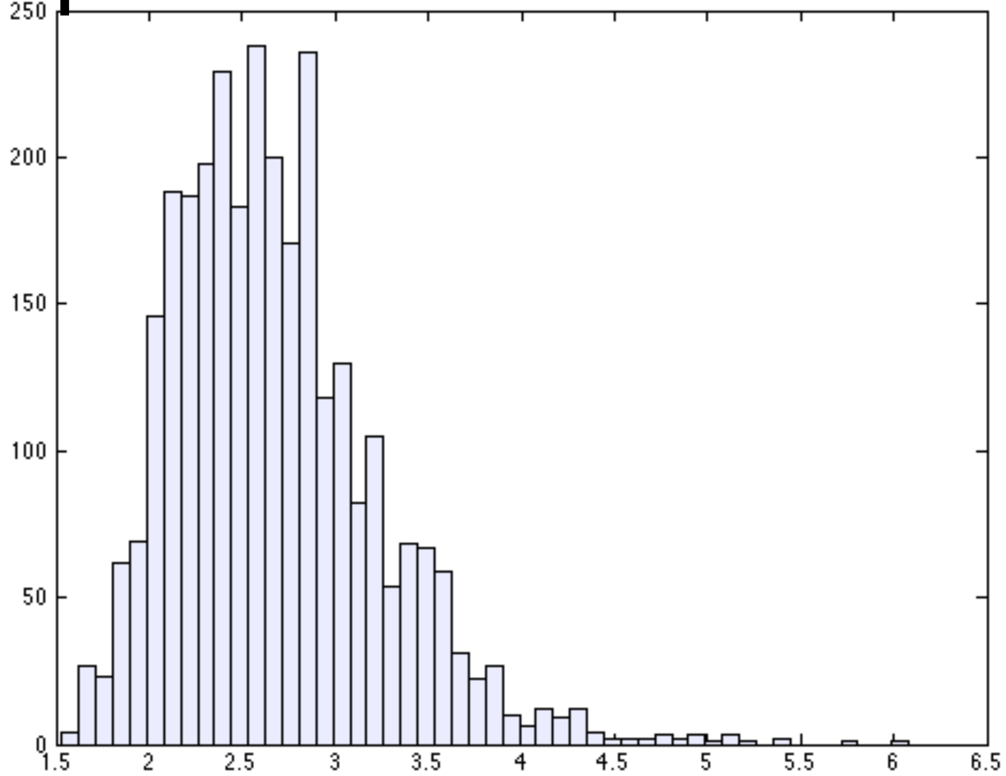
Statistical significance ?

Degree-1 distribution



Max t = 3.9507
Min t = -3.0961

Permutation test based on 5000 random permutations



95 percentile = 3.6432
5 percentile = -4.0237

More pairings for the control subjects
= More cortical folding

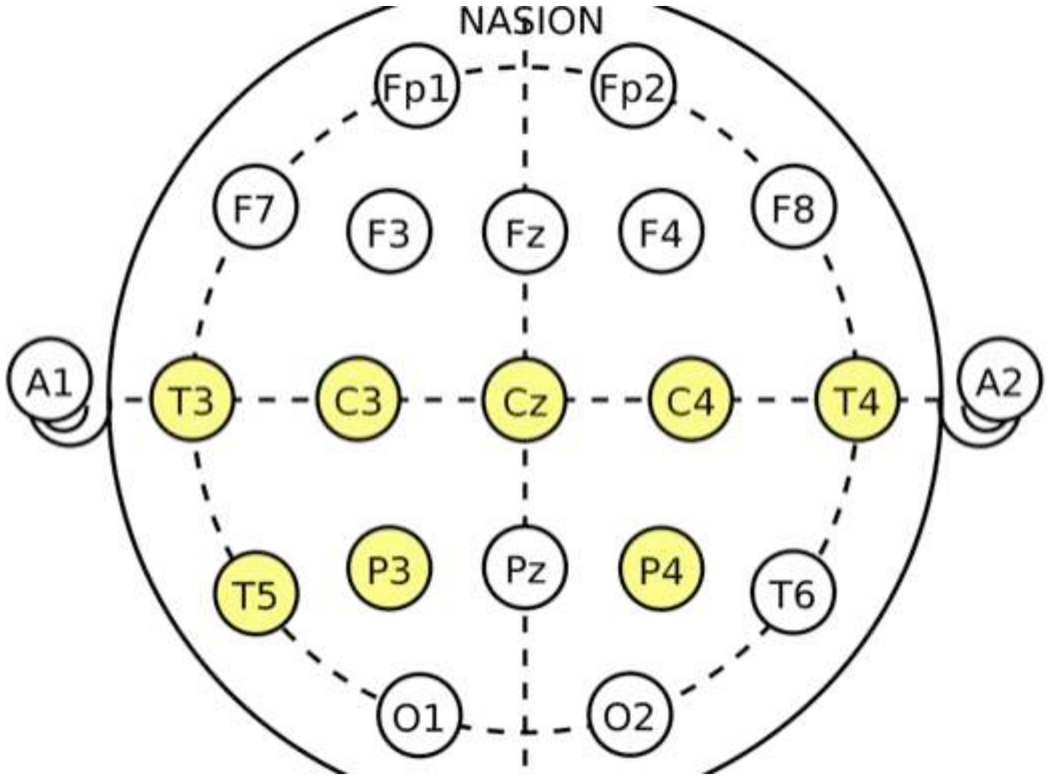
Persistent Landscape

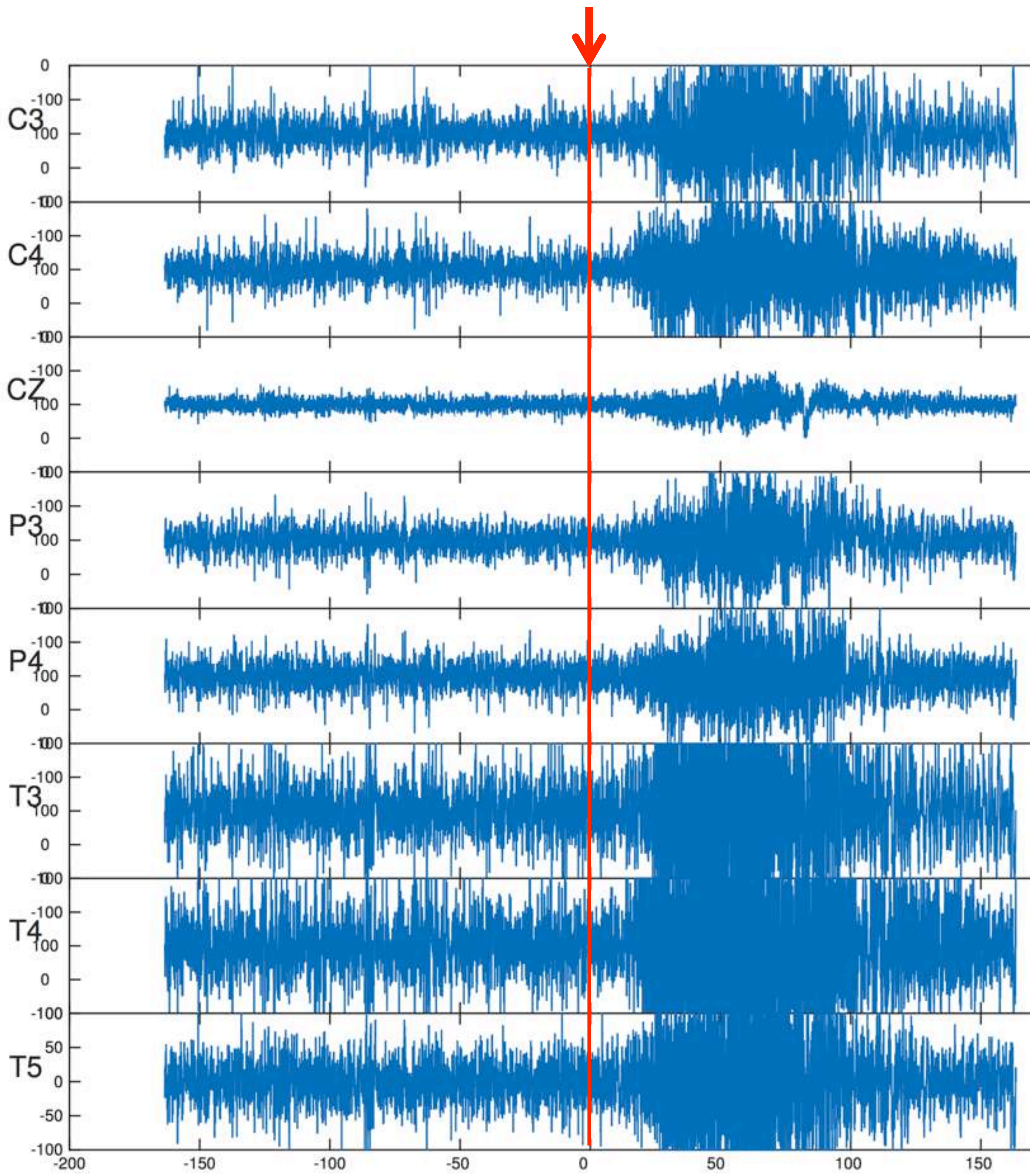
Bubenik, 2015 Journal of Machine Learning Research

Wang et al. 2014 Distinguished Paper Award in ENAR

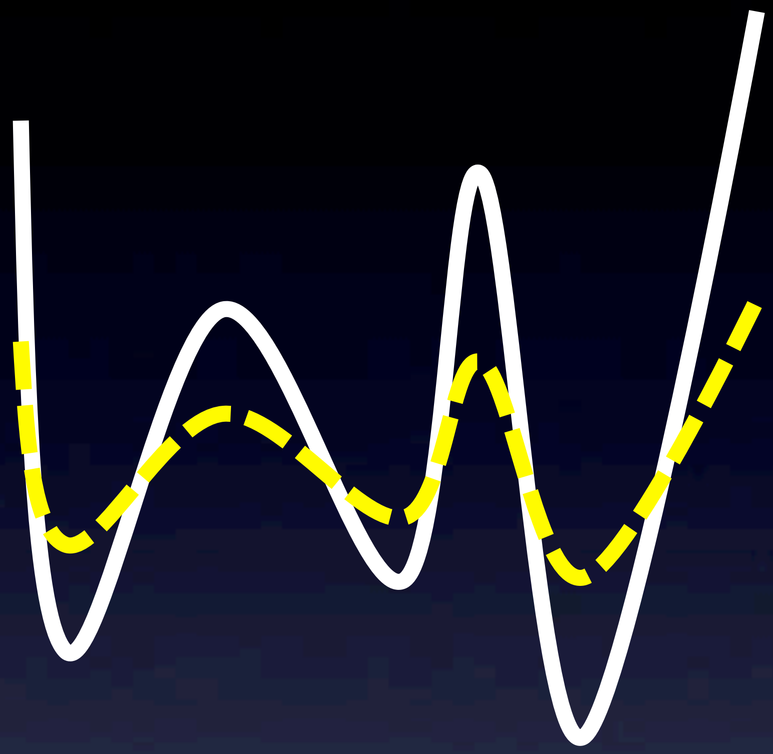
Wang et al. 2018 Annals of Applied Statistics, in press

Temporal epilepsy EEG

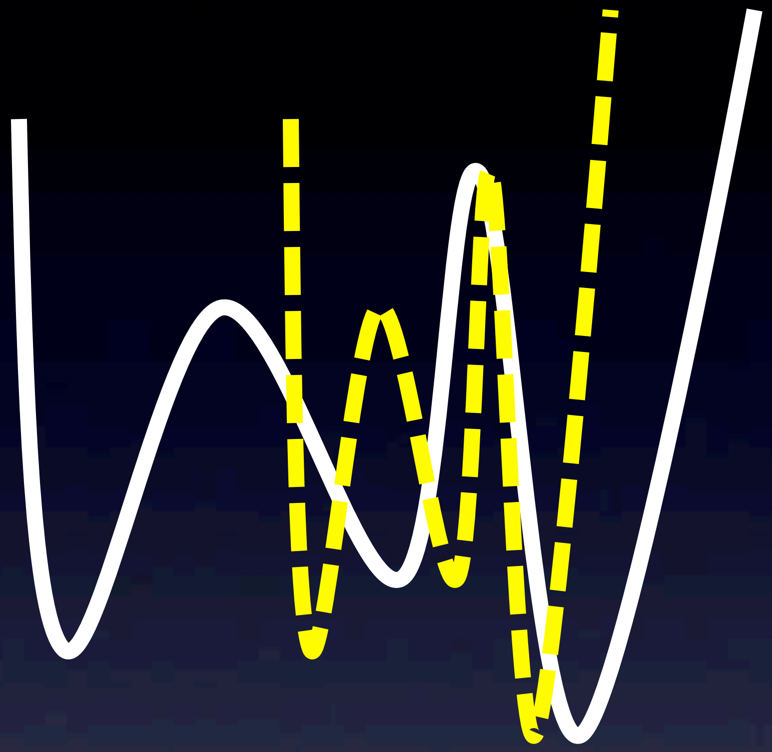



Seizure starts

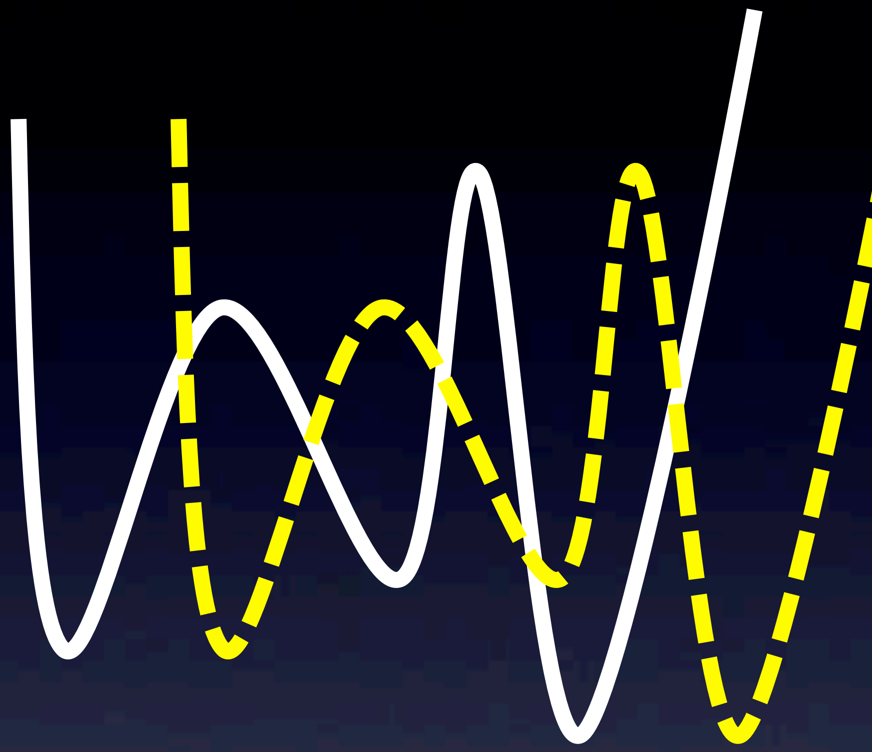
Existing methods are too sensitive



Scaling



Frequency change



Translation

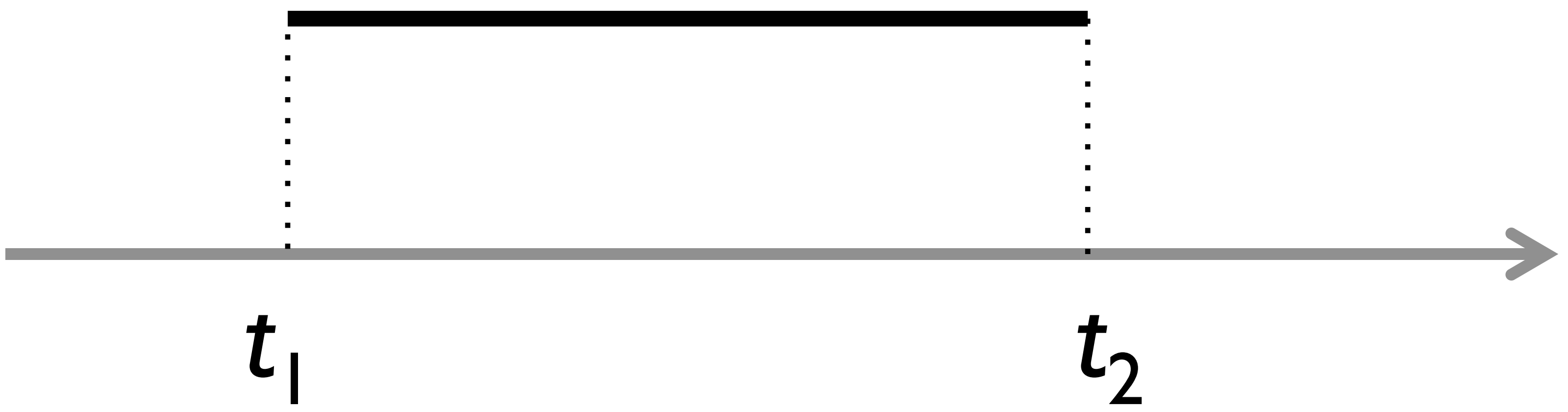
What method will *not* detect
the deforation of signal

Barcodes & persistent landscapes

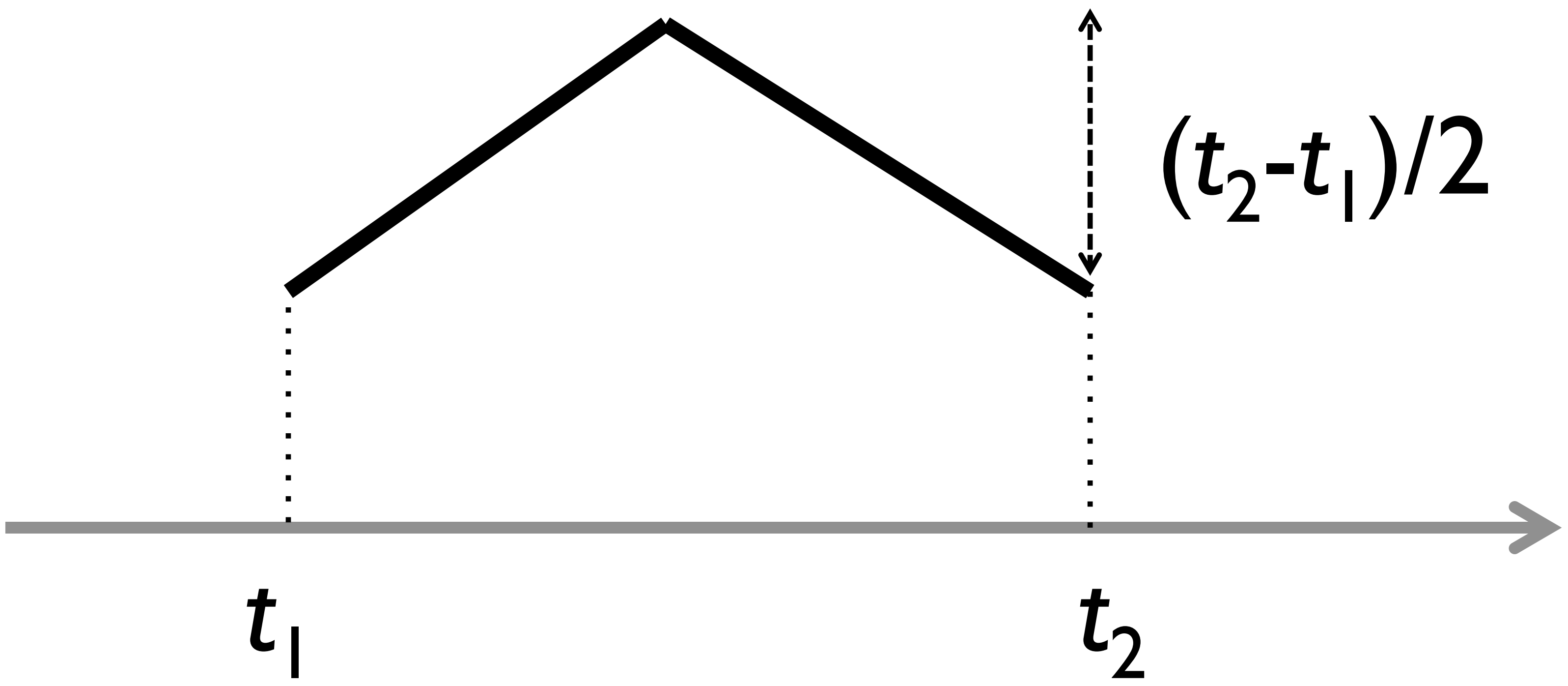
Barcode

Birth of a component

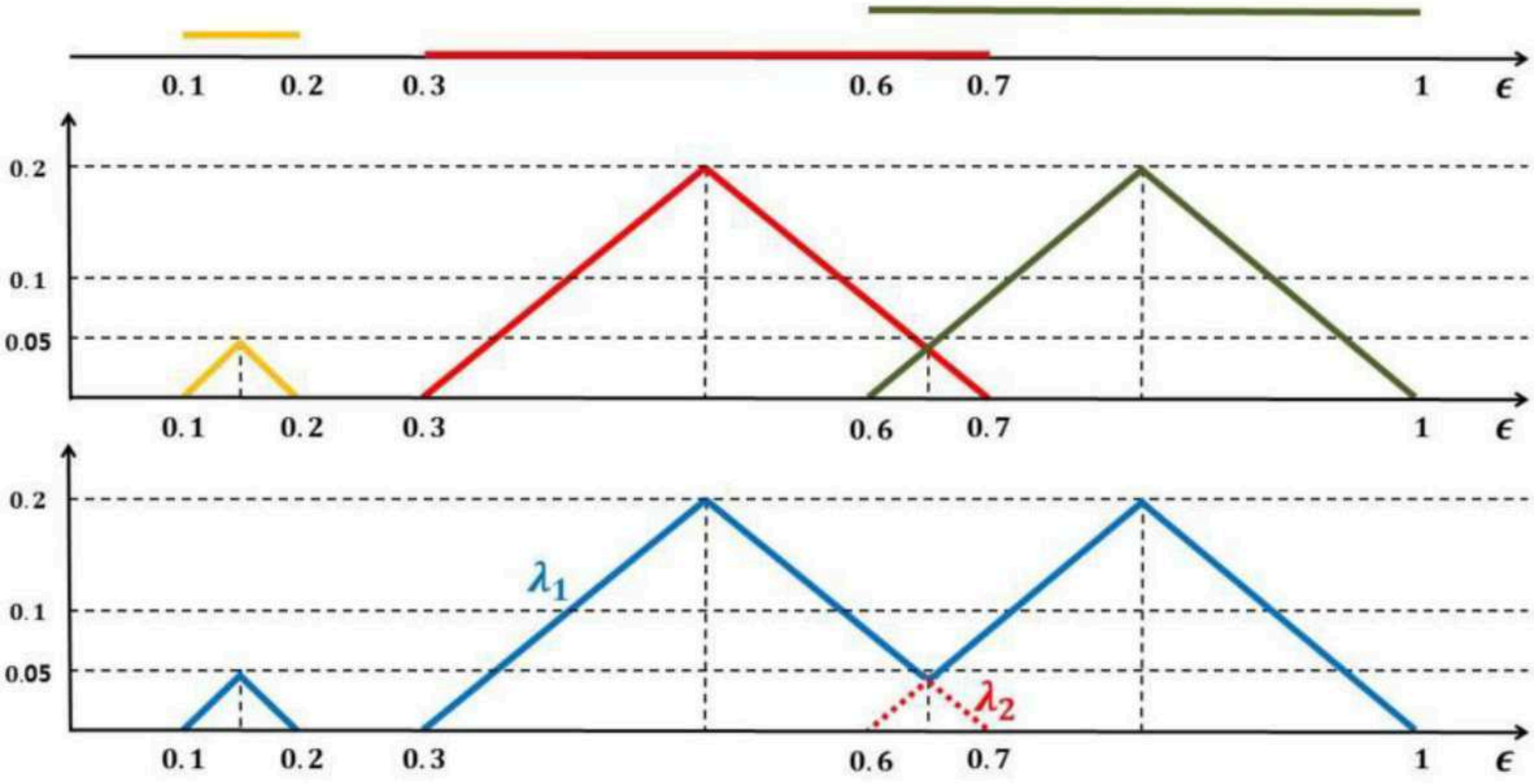
Death of a component



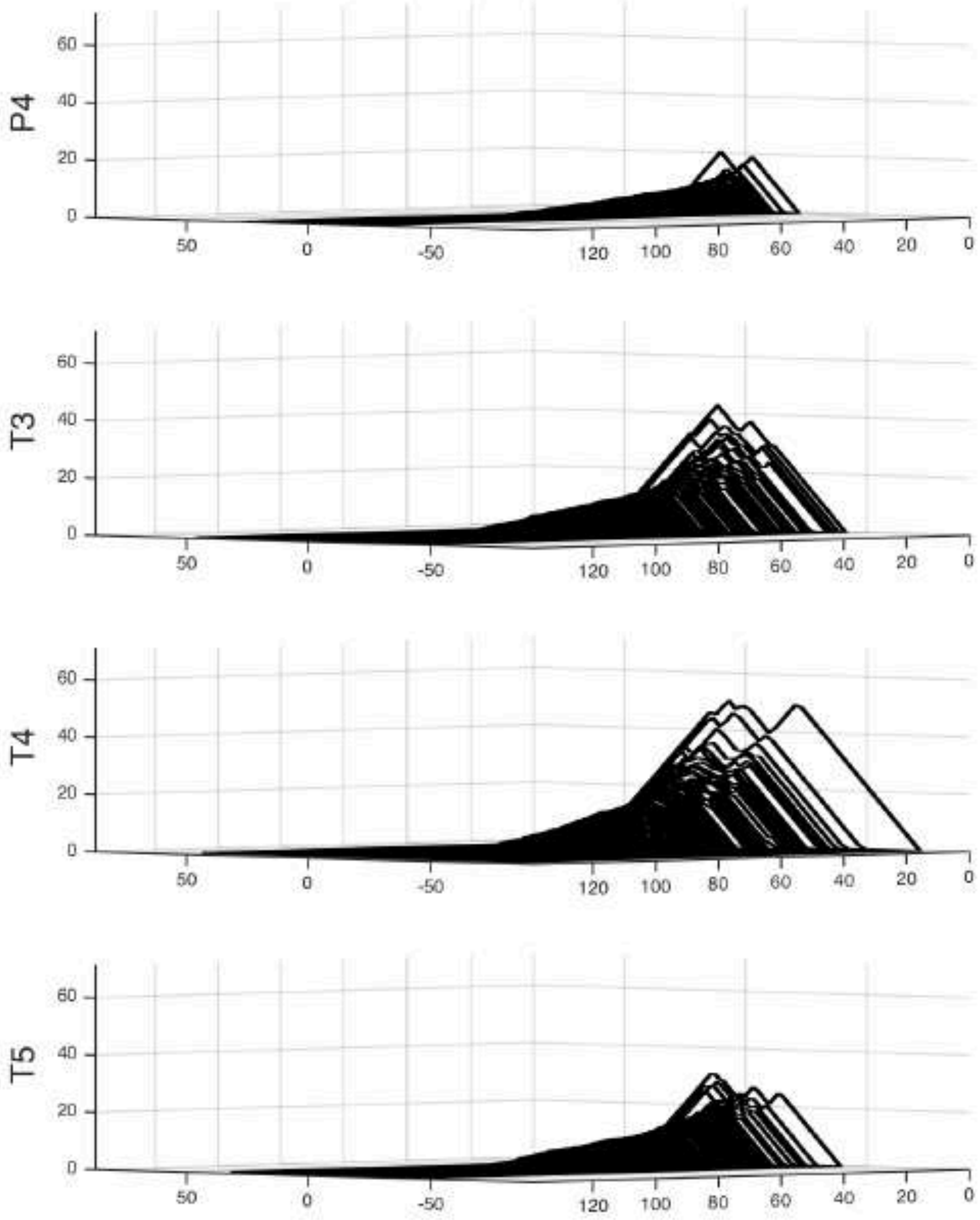
Persistent landscape



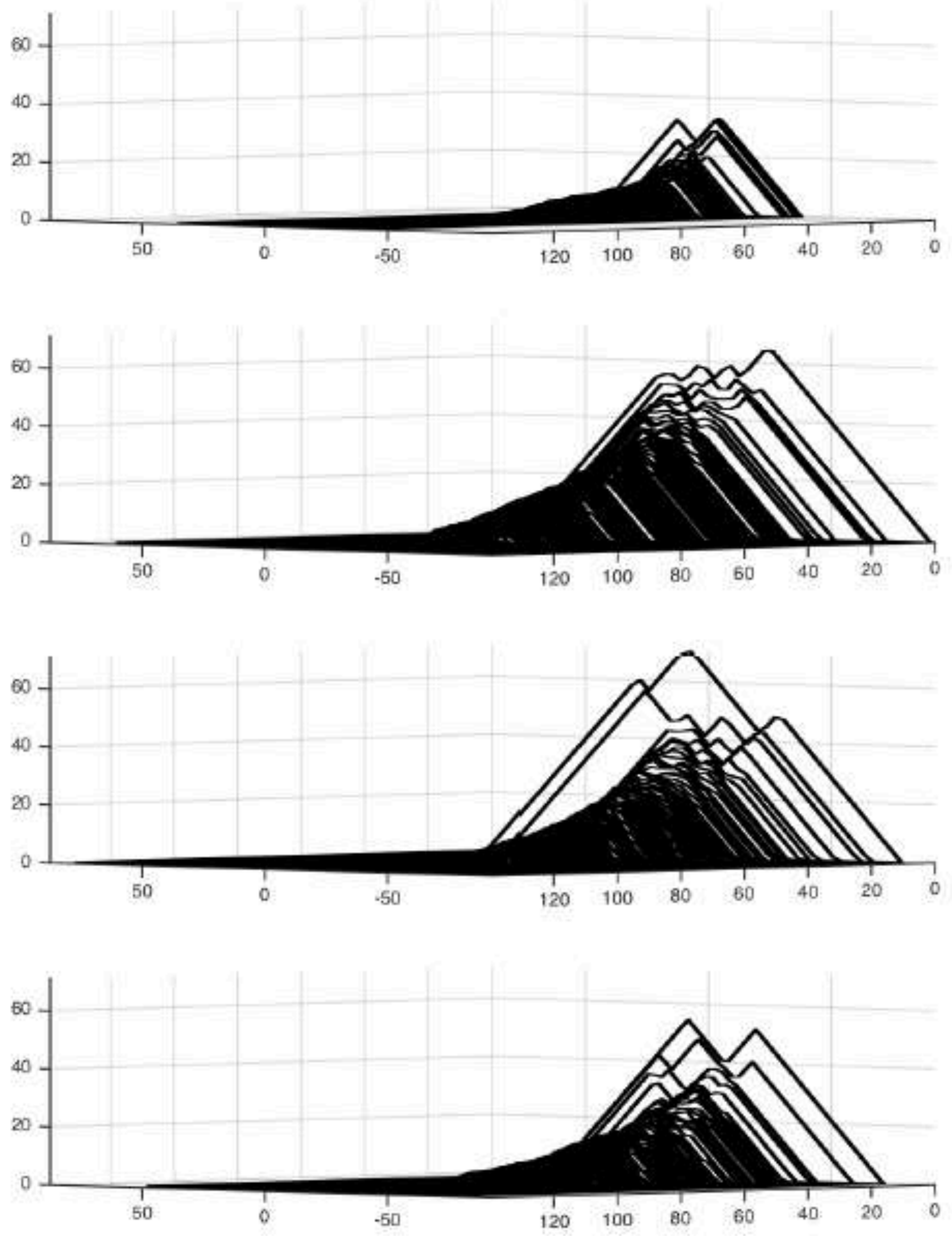
Barcodes & persistent landscapes



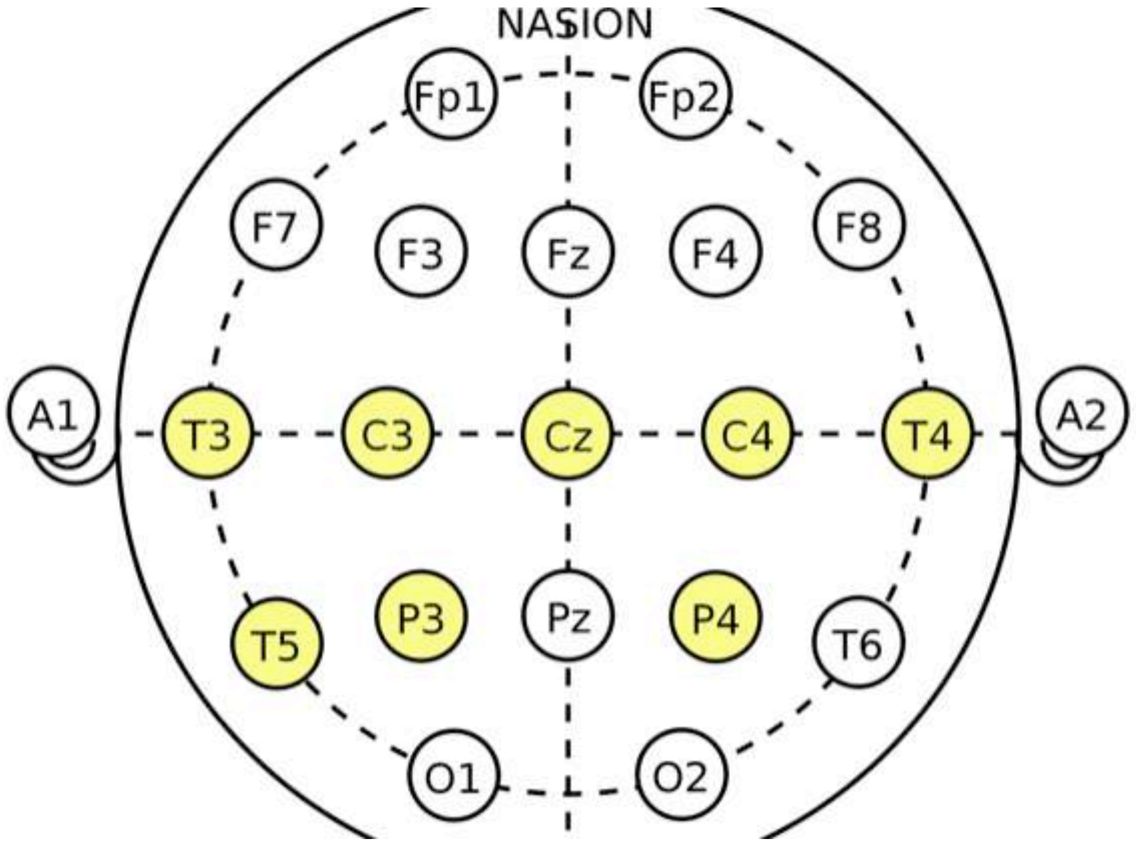
Persistent landscapes



before seizure



during seizure



Corrected p-value

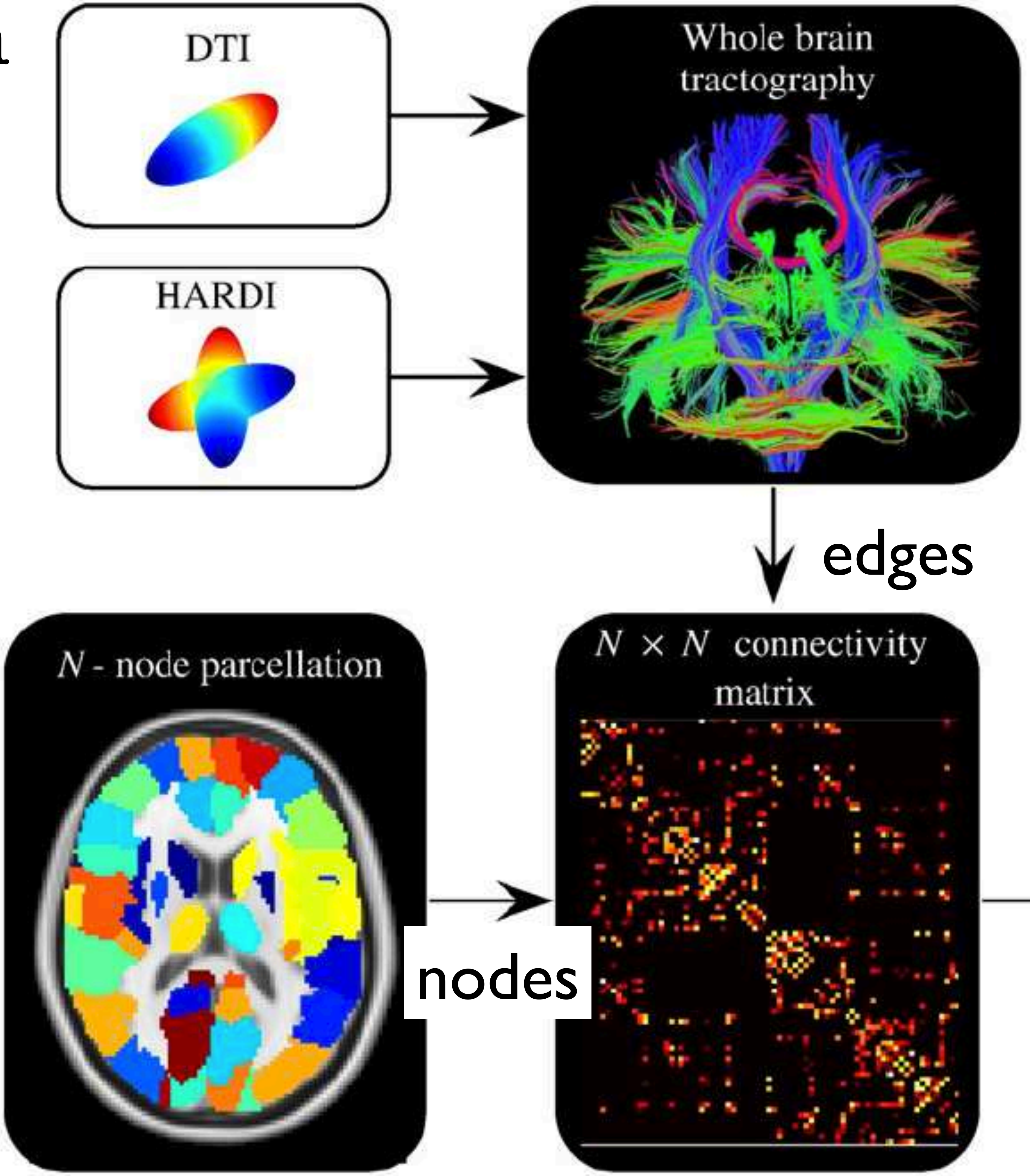
	Our method	Local variance
C3	0.0057	0.0001 $\times 10^{-45}$
C4	0.0054	0.0001
Cz	0.0001	0.0001
P3	0.0029	0.0001
P4	0.0001	0.0001
T3	0.0661	0.6721
T4	0.0162	0.0001
T5	0.1044	0.0001

No signal is signal!

Topological invariance → seizure origin

Standard brain network analysis

Standard brain connectivity analysis framework

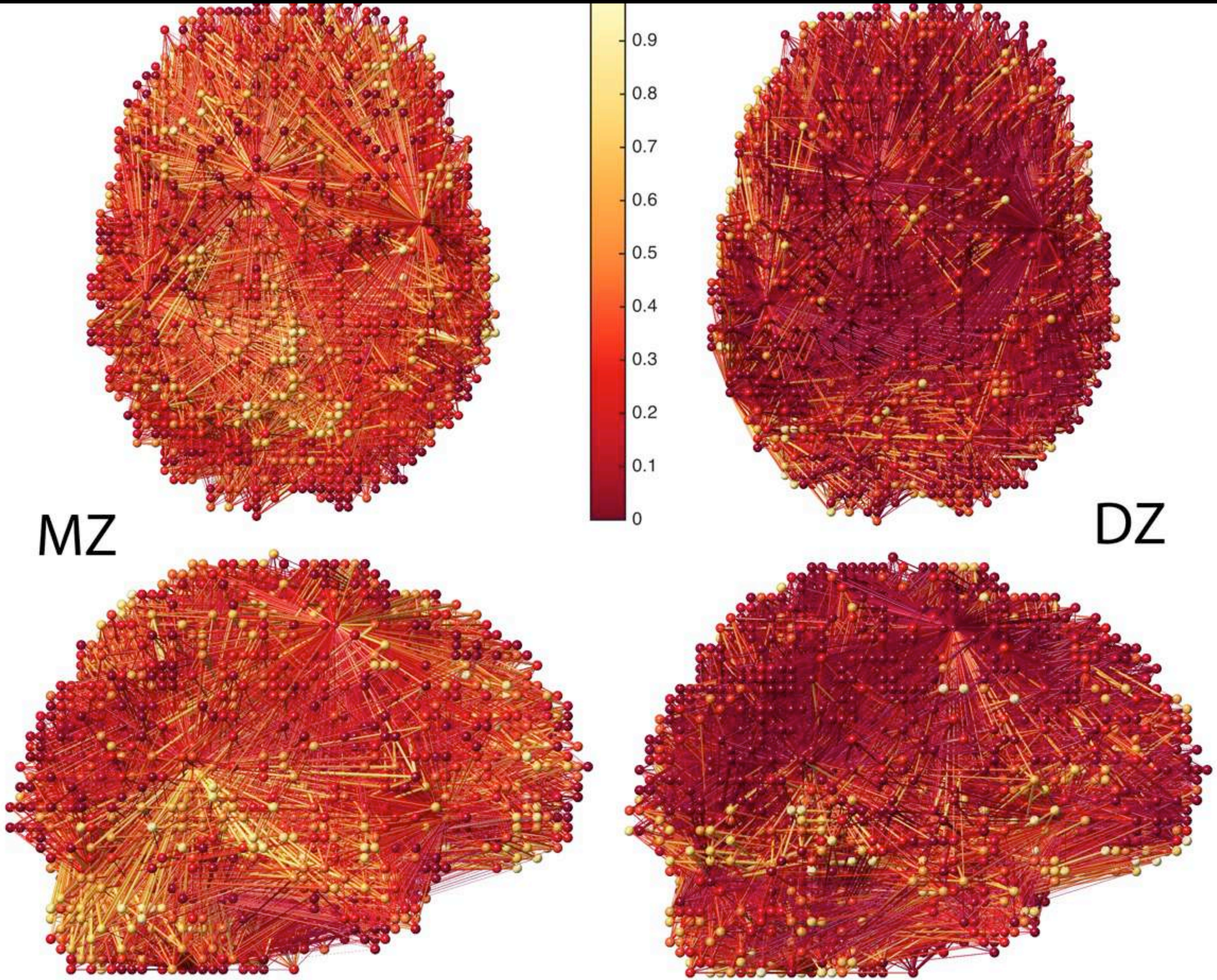


edges

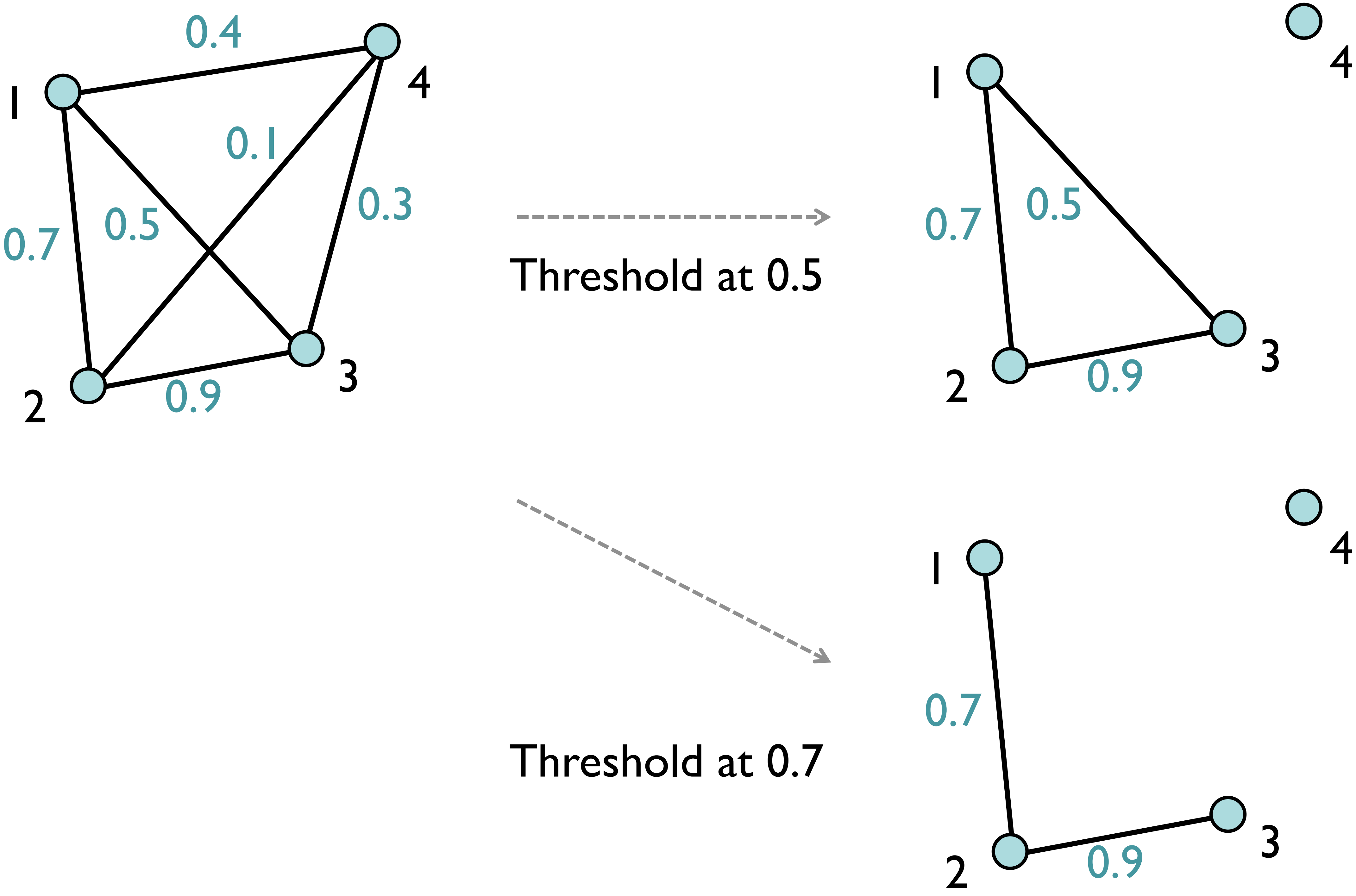
nodes

Zalesky et al. 2010 NeuroImage

Dense fMRI cross-correlation networks

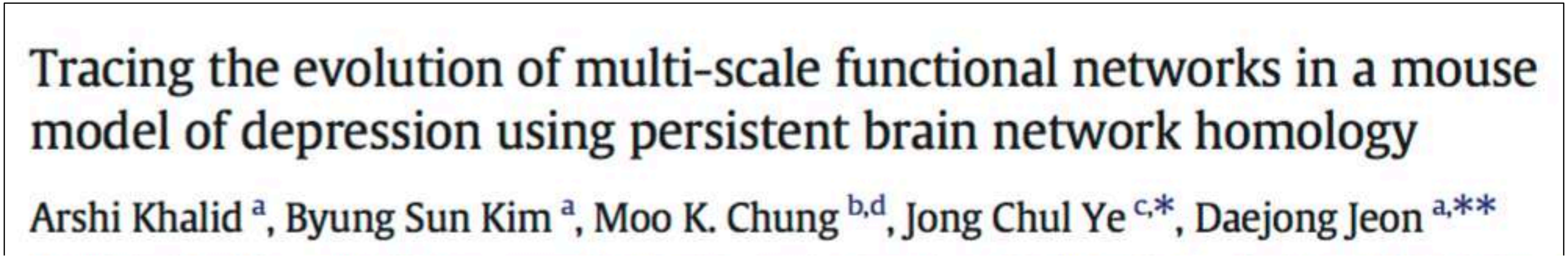


Topology changes depend on thresholds



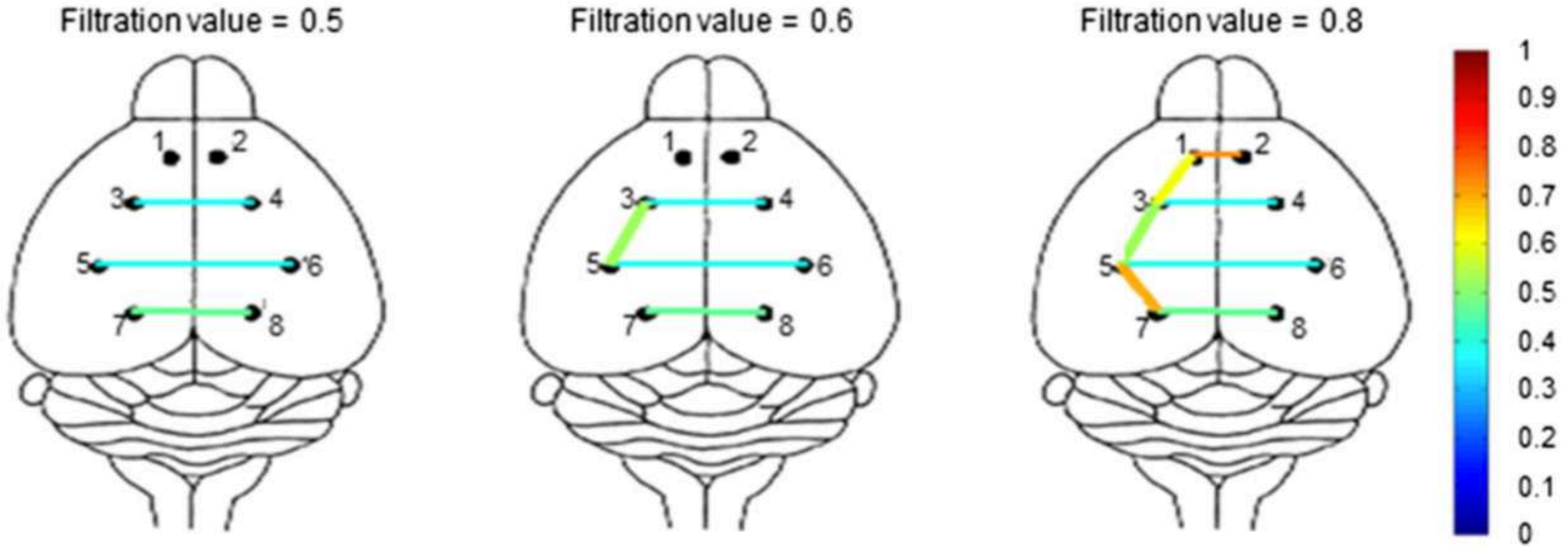
Threshold at 0.5

Threshold at 0.7

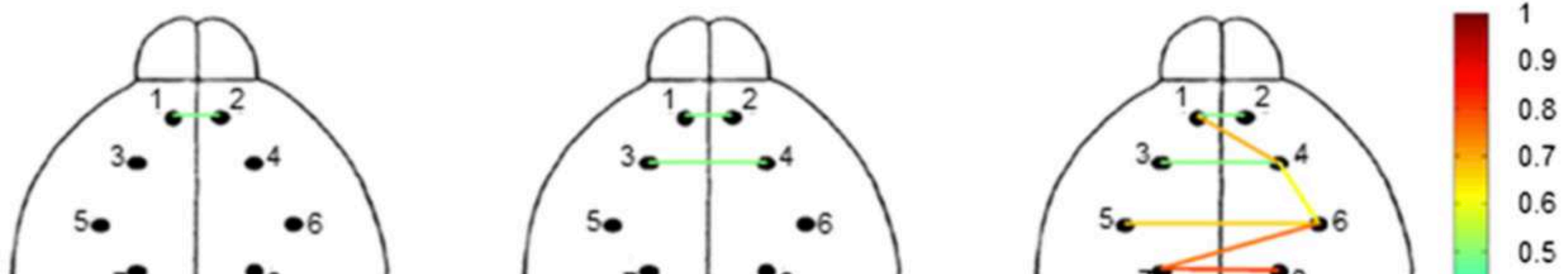


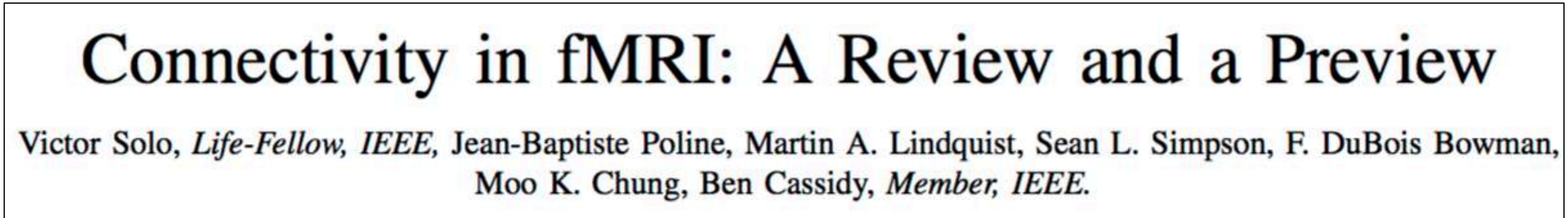
Tracing the evolution of multi-scale functional networks in a mouse model of depression using persistent brain network homology

Arshi Khalid [a], Byung Sun Kim [a], Moo K. Chung [b,d], Jong Chul Ye [c,*], Daejong Jeon [a,**]



Khalid et al. 2014 NeuoImage 101:351-363

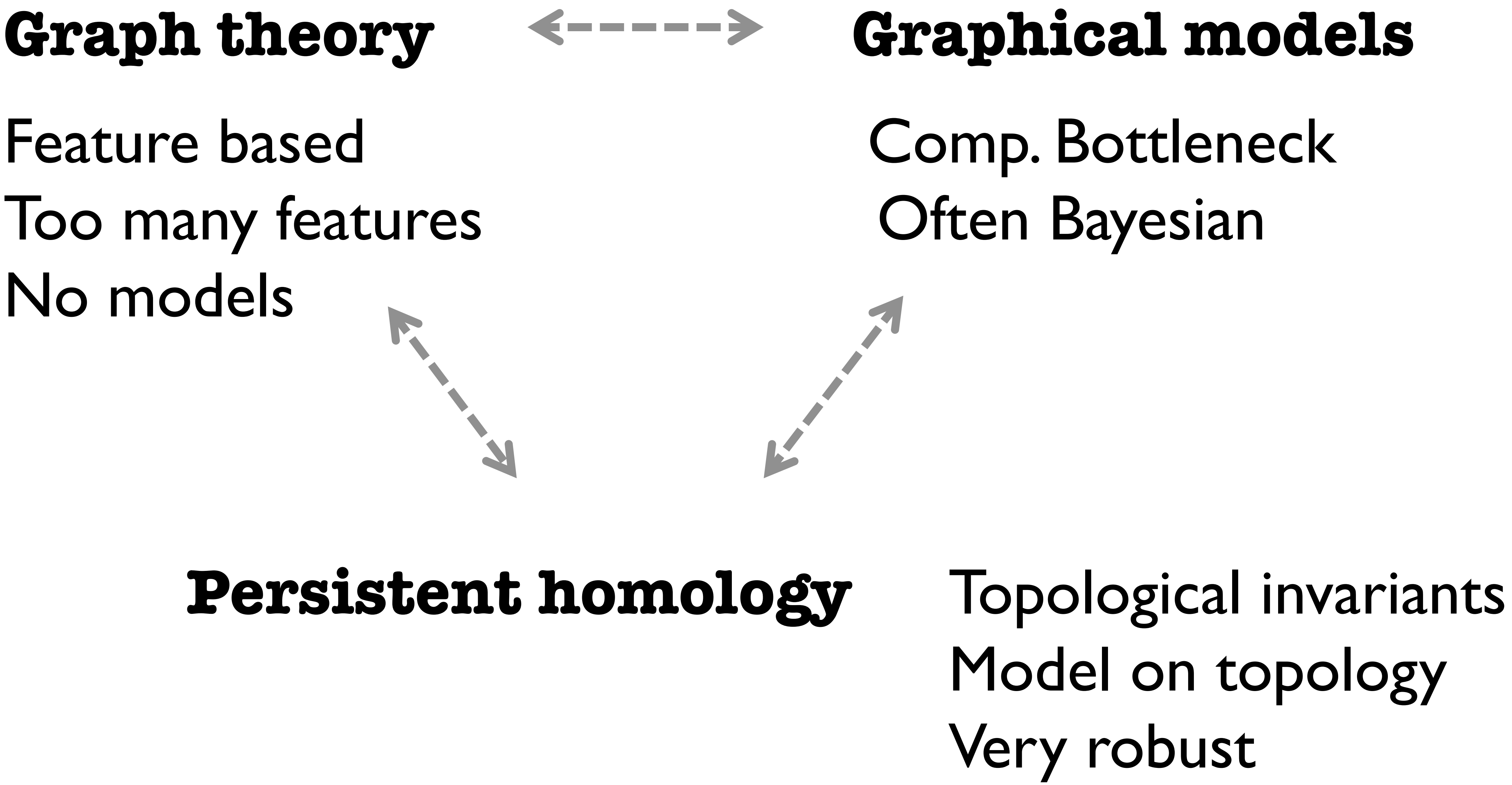




Connectivity in fMRI: A Review and a Preview

Victor Solo, *Life-Fellow, IEEE,* Jean-Baptiste Poline, Martin A. Lindquist, Sean L. Simpson, F. DuBois Bowman,
Moo K. Chung, Ben Cassidy, *Member, IEEE.*

Solo et al. 2018 IEEE Transactions on Medical Imaging



Graph theory

Feature based
Too many features
No models

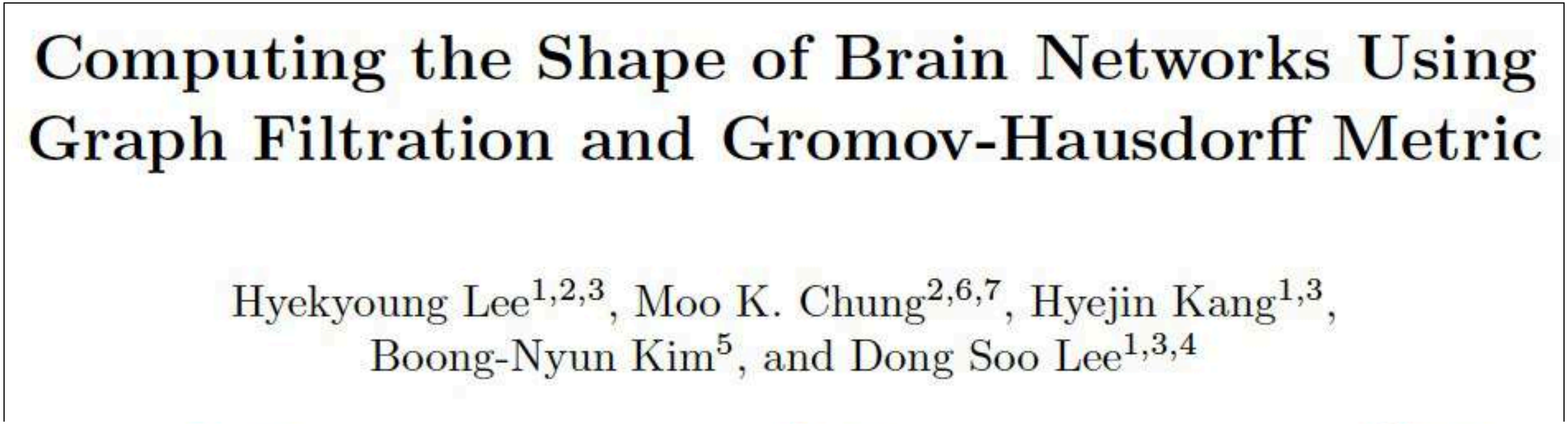
Graphical models

Comp. Bottleneck
Often Bayesian

Persistent homology

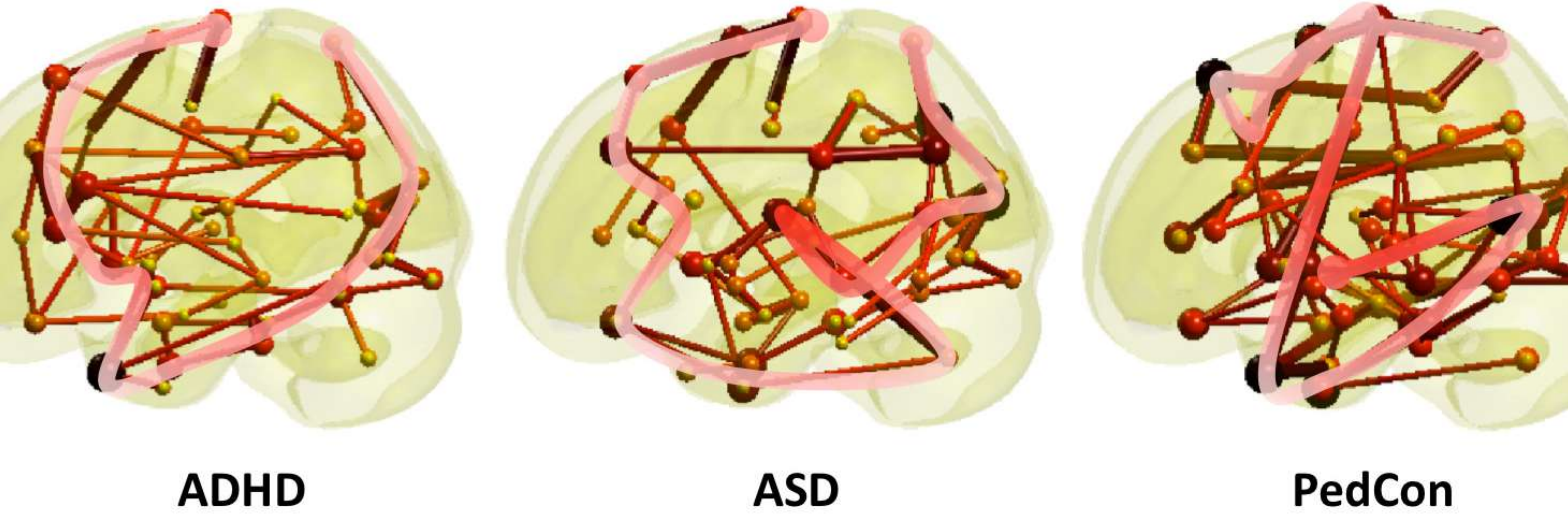
Topological invariants
Model on topology
Very robust

Graph Filtration



Computing the Shape of Brain Networks Using Graph Filtration and Gromov-Hausdorff Metric

Hyekyoung Lee[1,2,3], Moo K. Chung[2,6,7], Hyejin Kang[1,3],
Boong-Nyun Kim[5], and Dong Soo Lee[1,3,4]



Lee et al. 2011 MICCAI 302-309

Lee et al. 2012 IEEE Transactions on Medical Image 31:2267-2277

Network as a metric space

Nodes: $V = \{1, 2, \cdots, p\}$

Edge weights: $w = (w_{ij})$

$$w_{i,j} \geq 0, \;\; w_{ii} = 0, \;\; w_{ij} = w_{ji}$$

$$w_{ij} \leq w_{ik} + w_{kj}$$

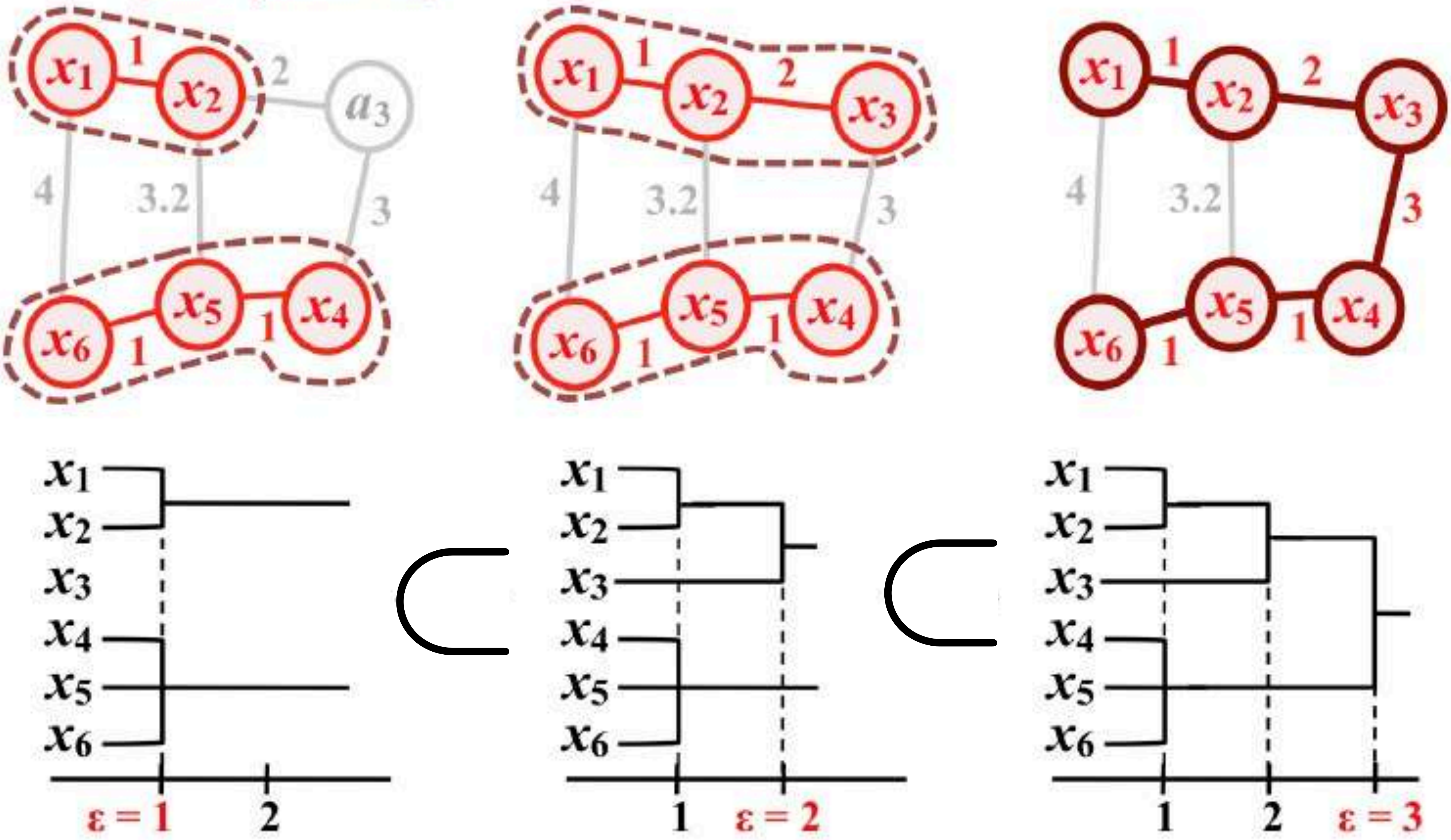
$\mathcal{X} = (V, w)$ is a metric space

Correlation metric

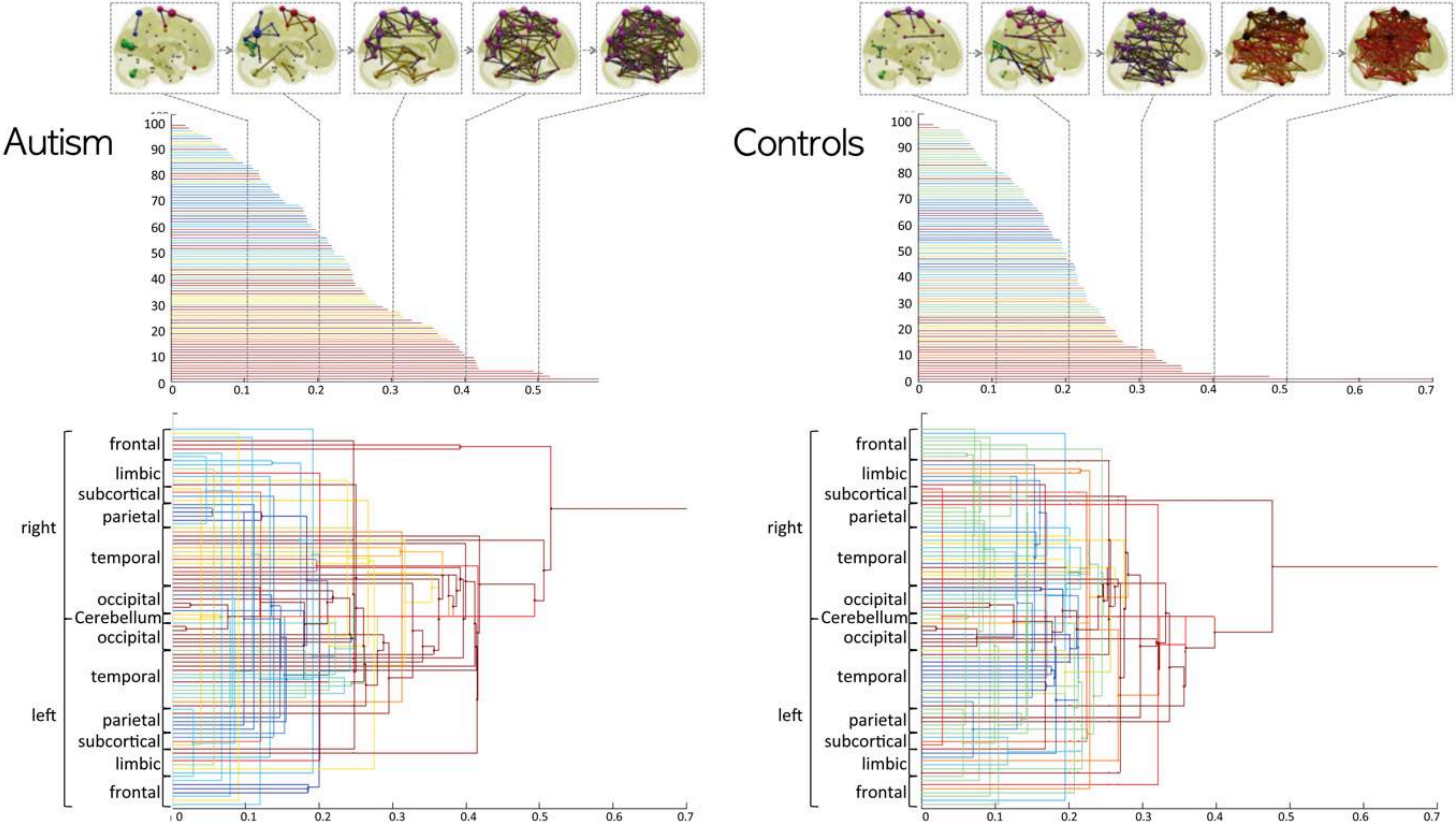
$1 - \mathrm{corr}(\mathbf{x}_i, \mathbf{x}_j)$ is not a metric

$\sqrt{1 - \mathrm{corr}(\mathbf{x}_i, \mathbf{x}_j)}$ is a metric

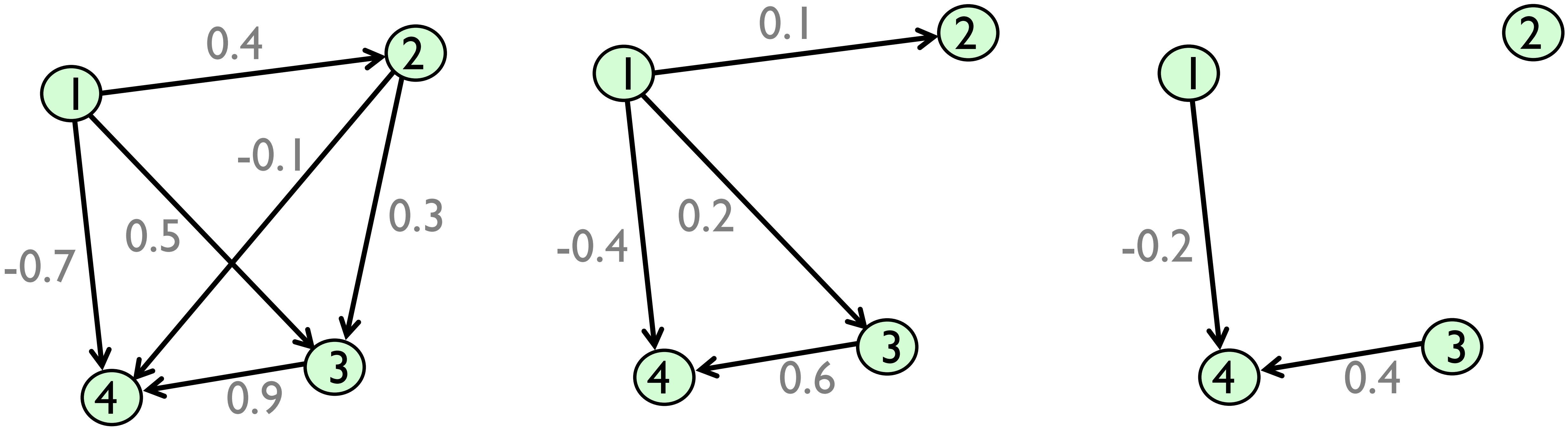
Graph filtration=single linkage dendrogram



Brain network as dendrogram

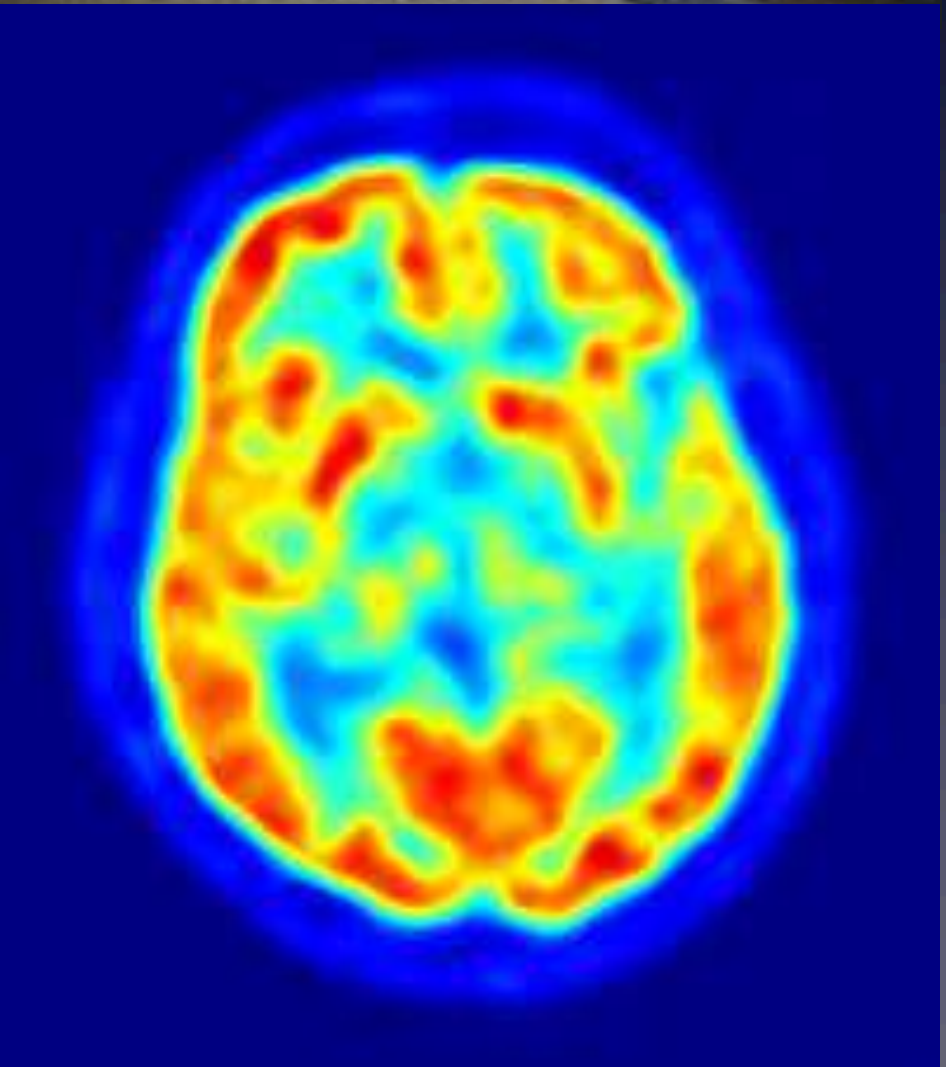


Graph filtration on directed graphs



$$G(0) \quad \supset \quad G(0.3) \quad \supset \quad G(0.5)$$

PET metabolic connectivity

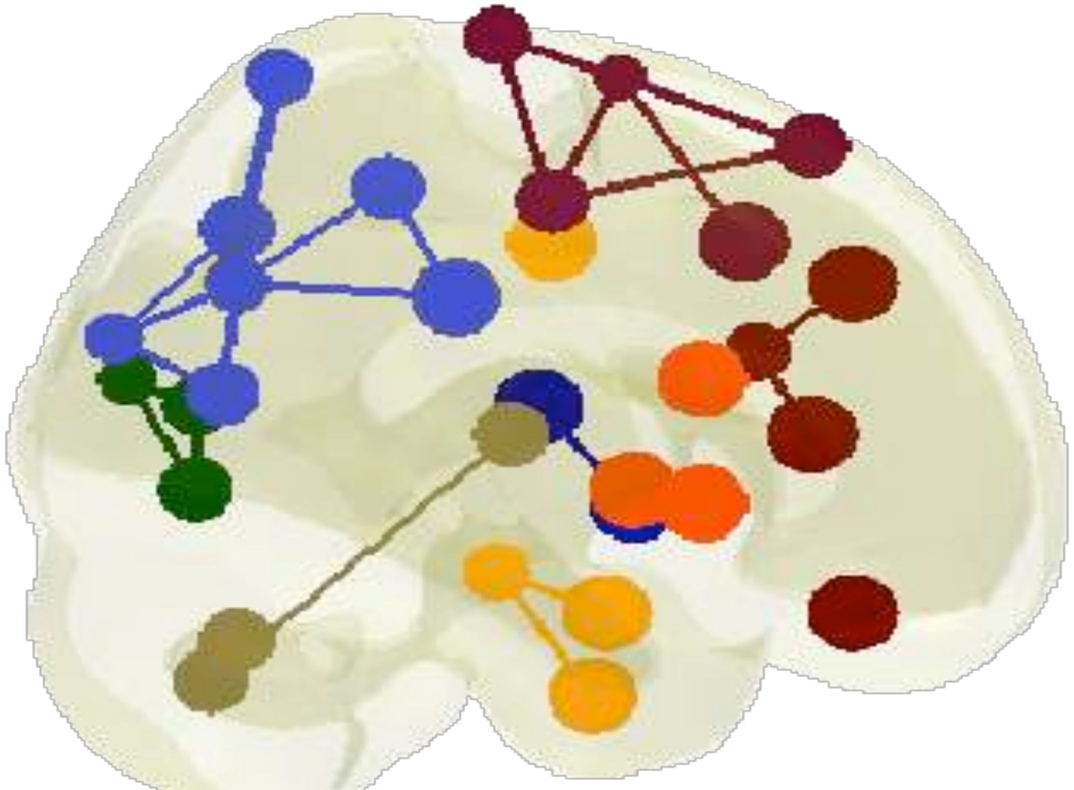


24 attention deficit hyperactivity disorder (ADHD) children

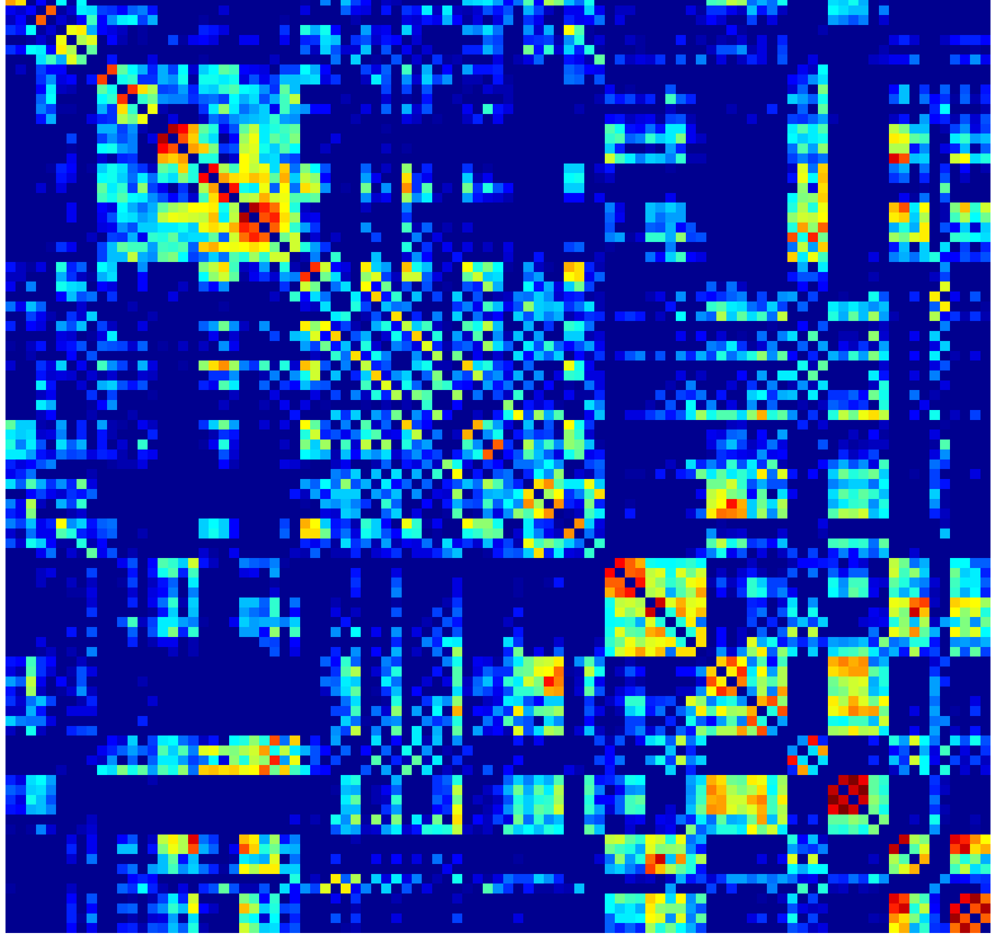
26 autism spectrum disorder (ASD) children

11 pediatric control subjects

Pet metabolic connectivity

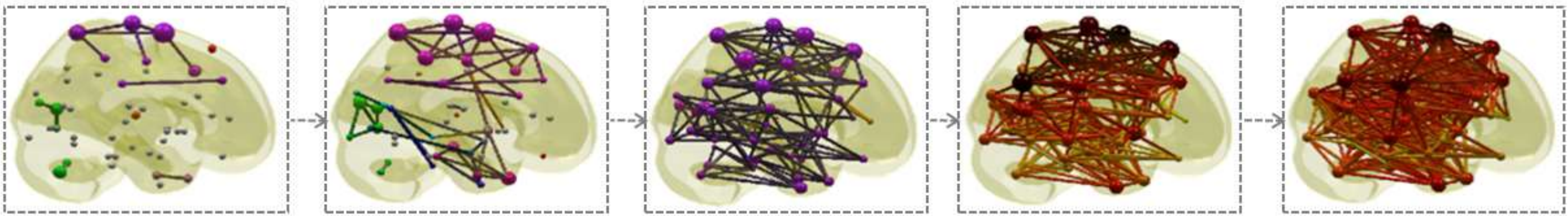


PET measures on 90 nodes



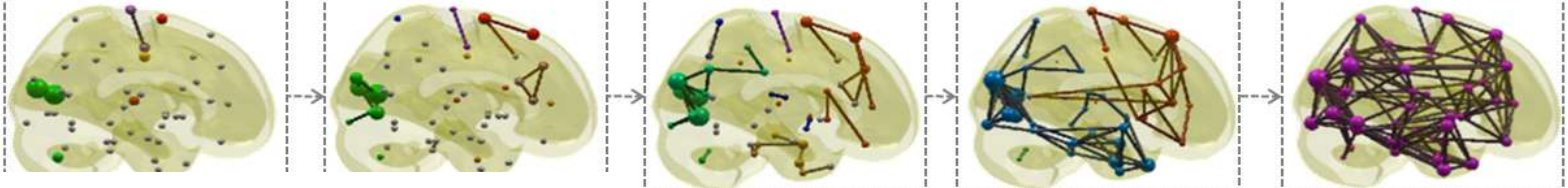
90 x 90 correlation map

Rips filtration on 1- correlation

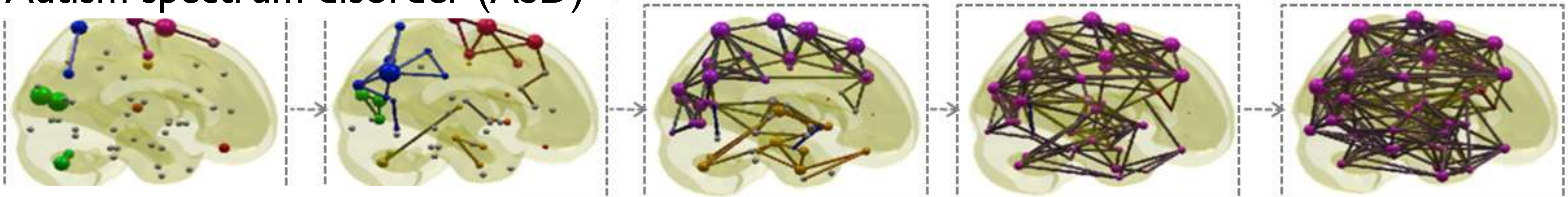


Graph filtrations

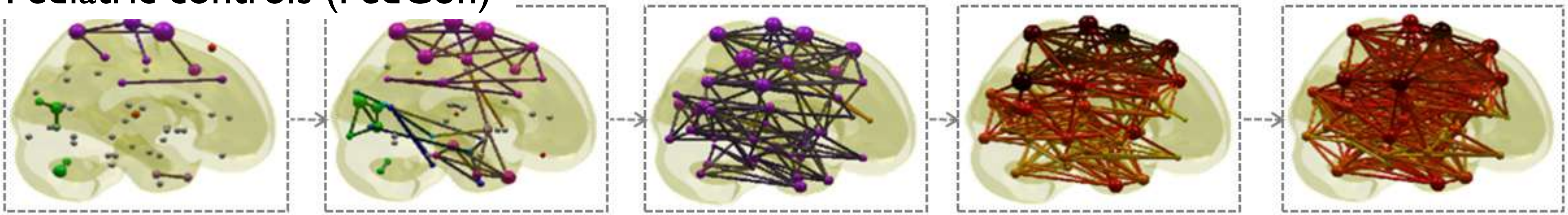
Attention deficit hyperactivity disorder (ADHD)



Autism spectrum disorder (ASD)



Pediatric controls (PedCon)



0.1 0.2 0.3 0.4 0.5

1-correlation

Maltreated multimodal study

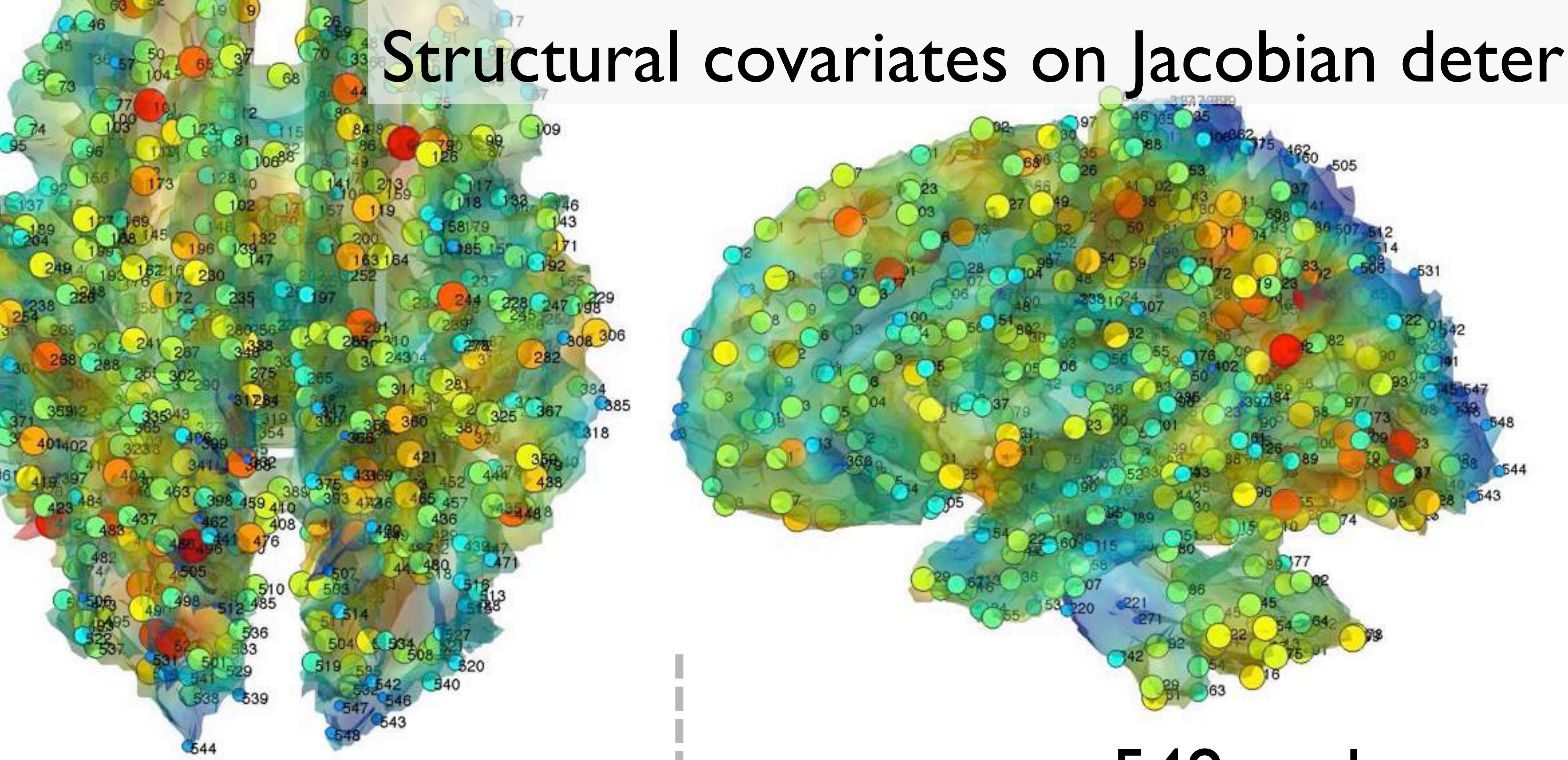
31 normal controls (12 ± 2 yrs.)

23 maltreated while living in post-institutional settings (2.5±1.4 yrs.) before adopted (11 ± 2 yrs.)

MRI → Jacobian determinant

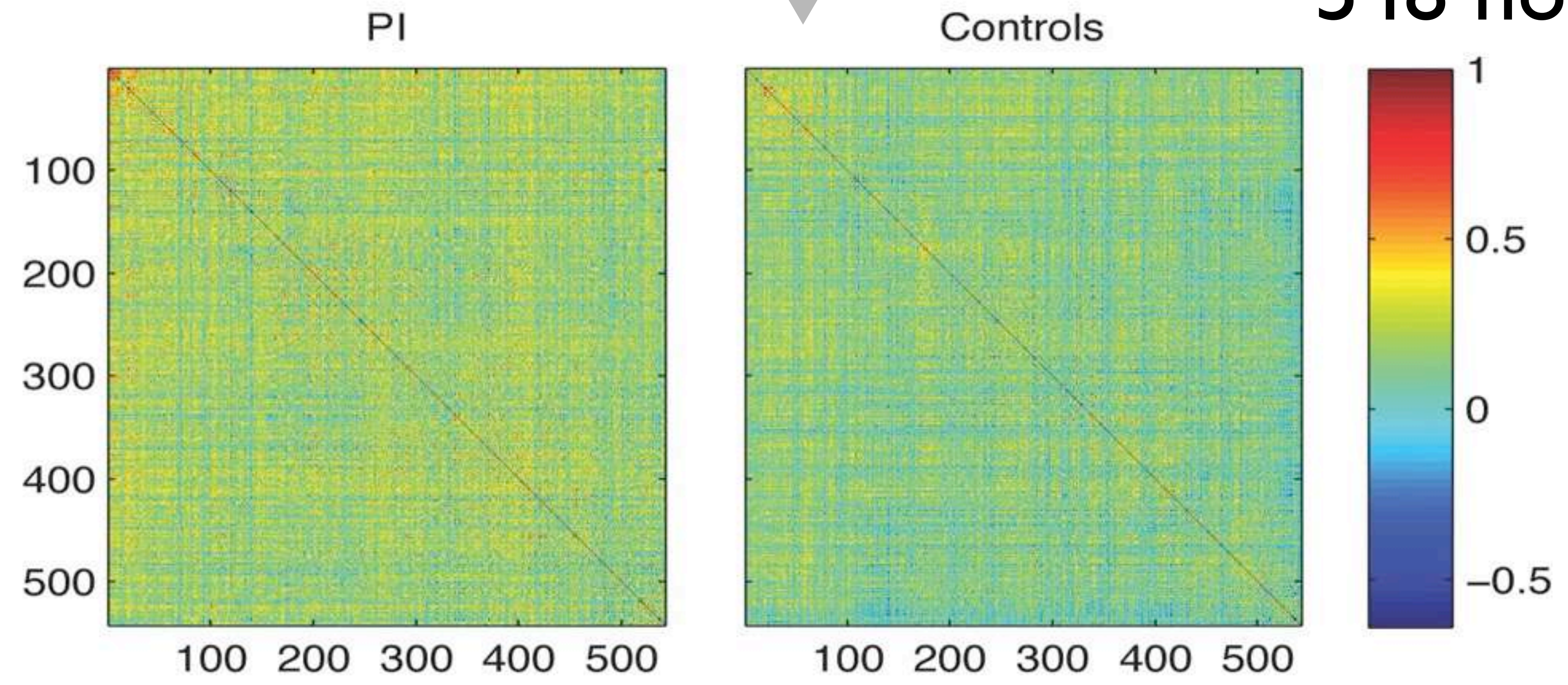
DTI → FA-values

Structural covariates on Jacobian determinants

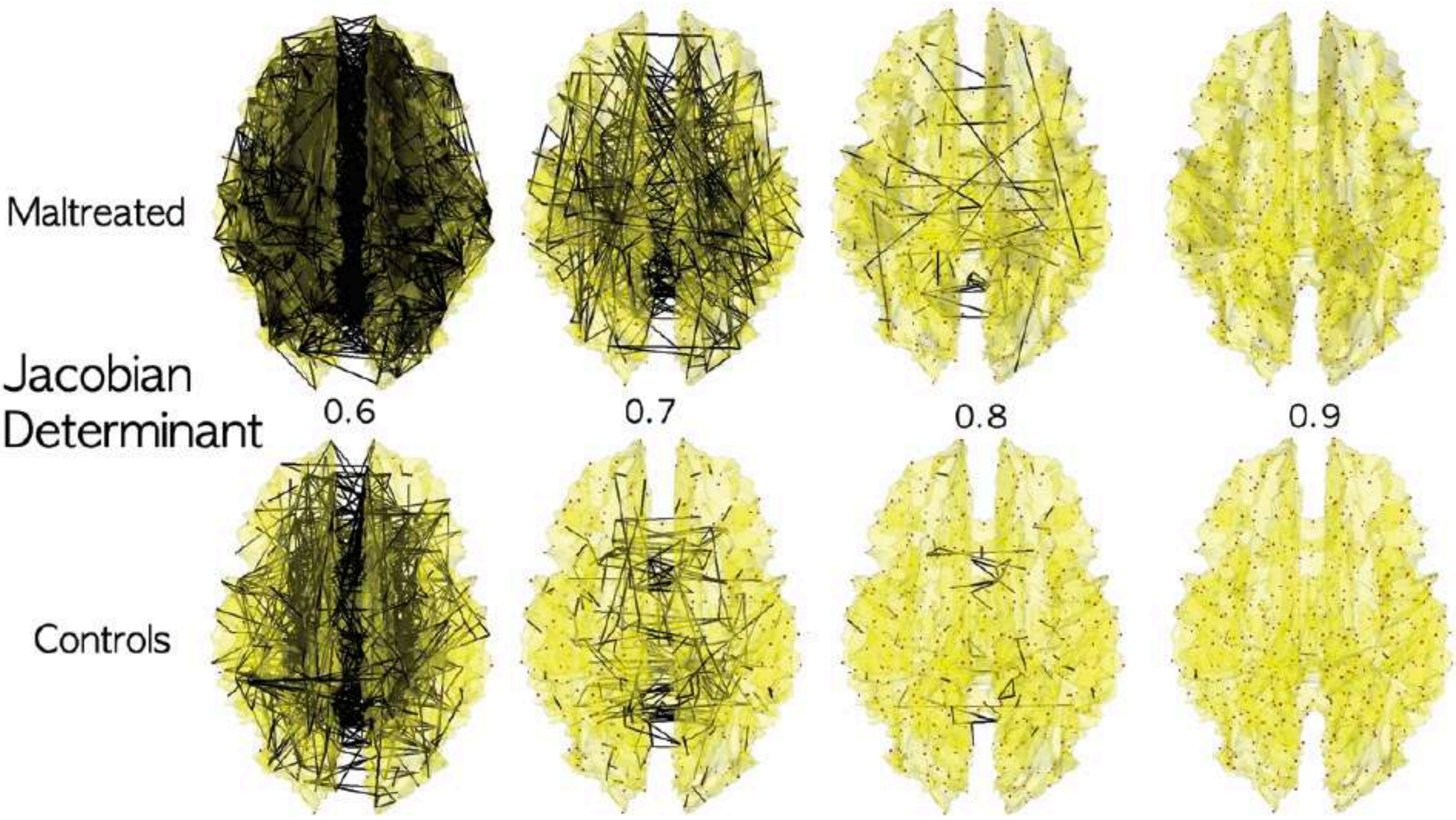


15.7mm
internodal
distance

548 nodes correlation

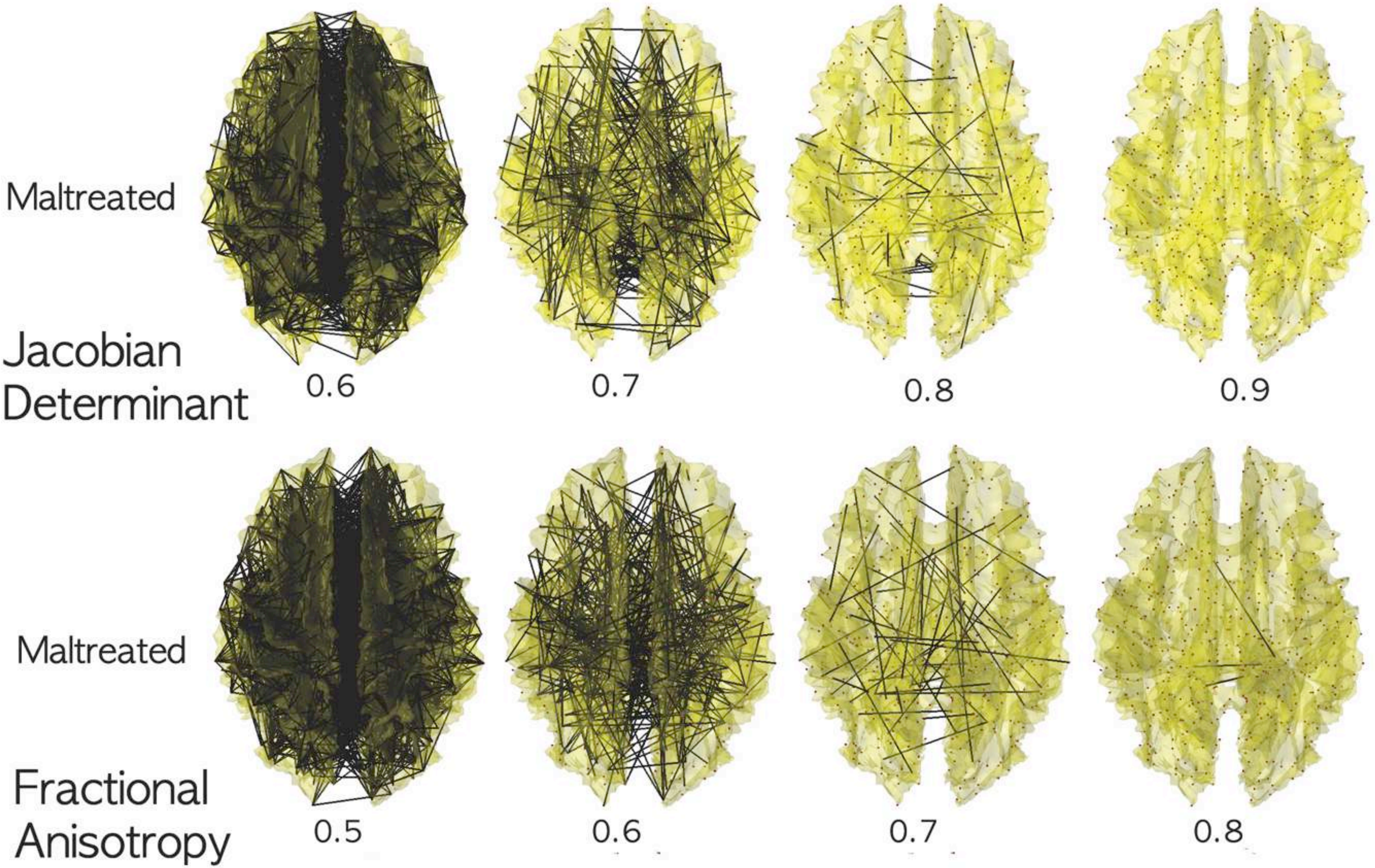


Graph filtrations on Jacobian determinant



Maltreated children are anatomically more homogenous

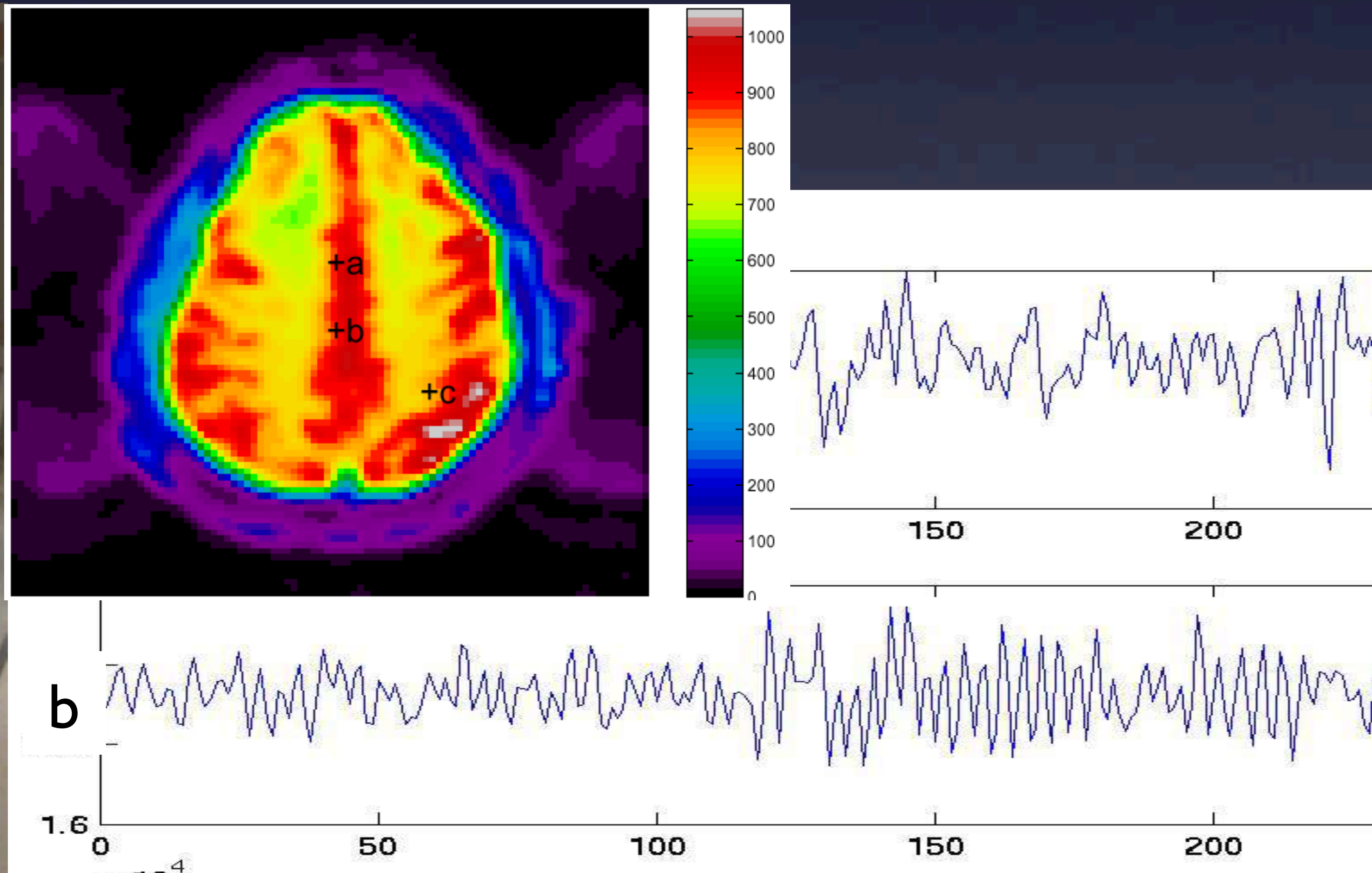
Graph filtrations on FA-values



Tennessee twin fMRI study

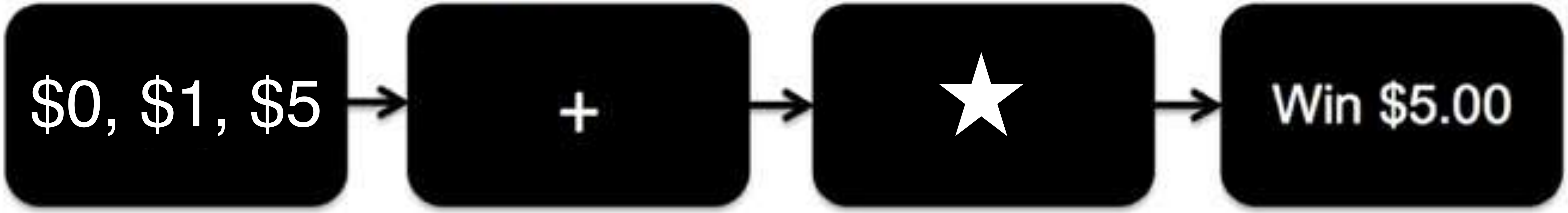
11 monozygotic (MZ) twins

14 dizygotic (DZ) twins
- 9 same-sex DZ pairs (5 male, 4 female)
- 5 different-sex DZ pairs



Paired statistical contrast images

Monetary incentive delay task



$0, $1, $5 → + → ★ → Win $5.00

3 runs of 40 trials

General Linear Model

$$W(v_i) = Zb(v_i) + \varepsilon(v_i)$$

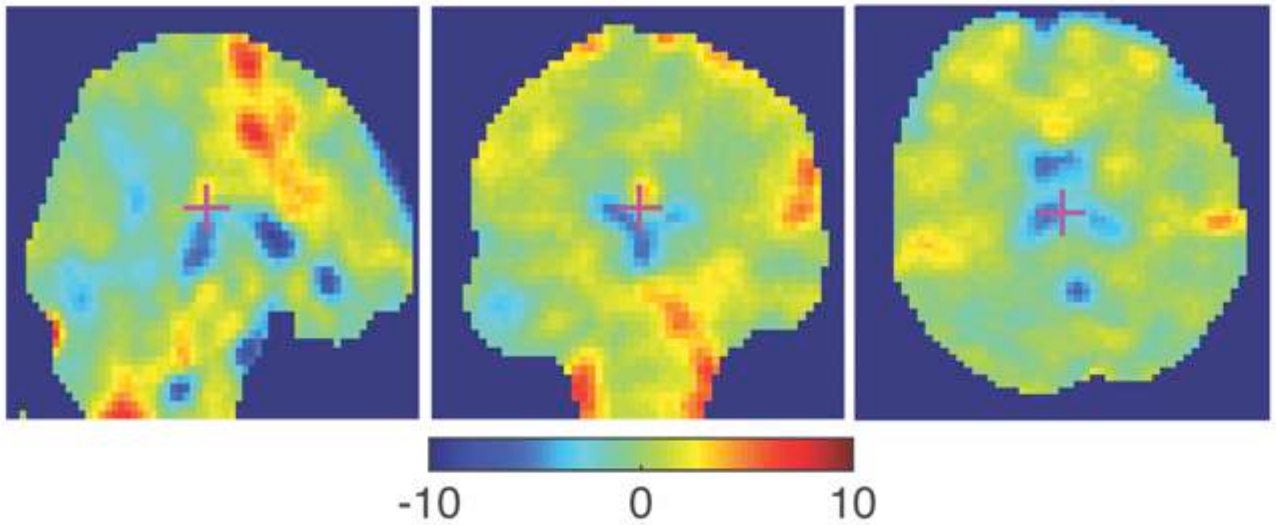
delay for $0 trials

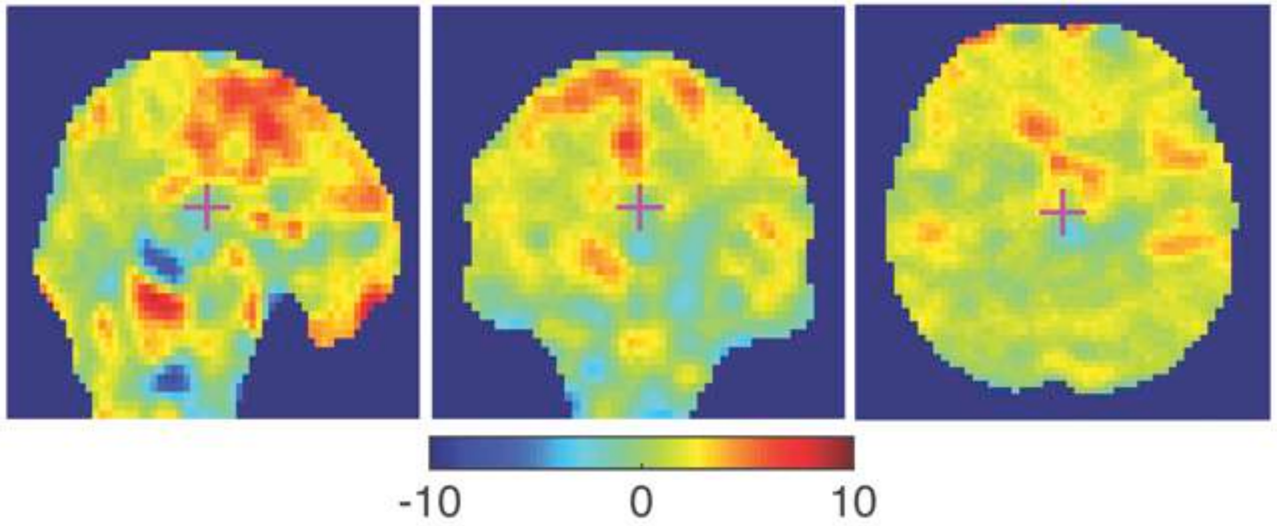
delay for $1 trials

delay for $5 trials

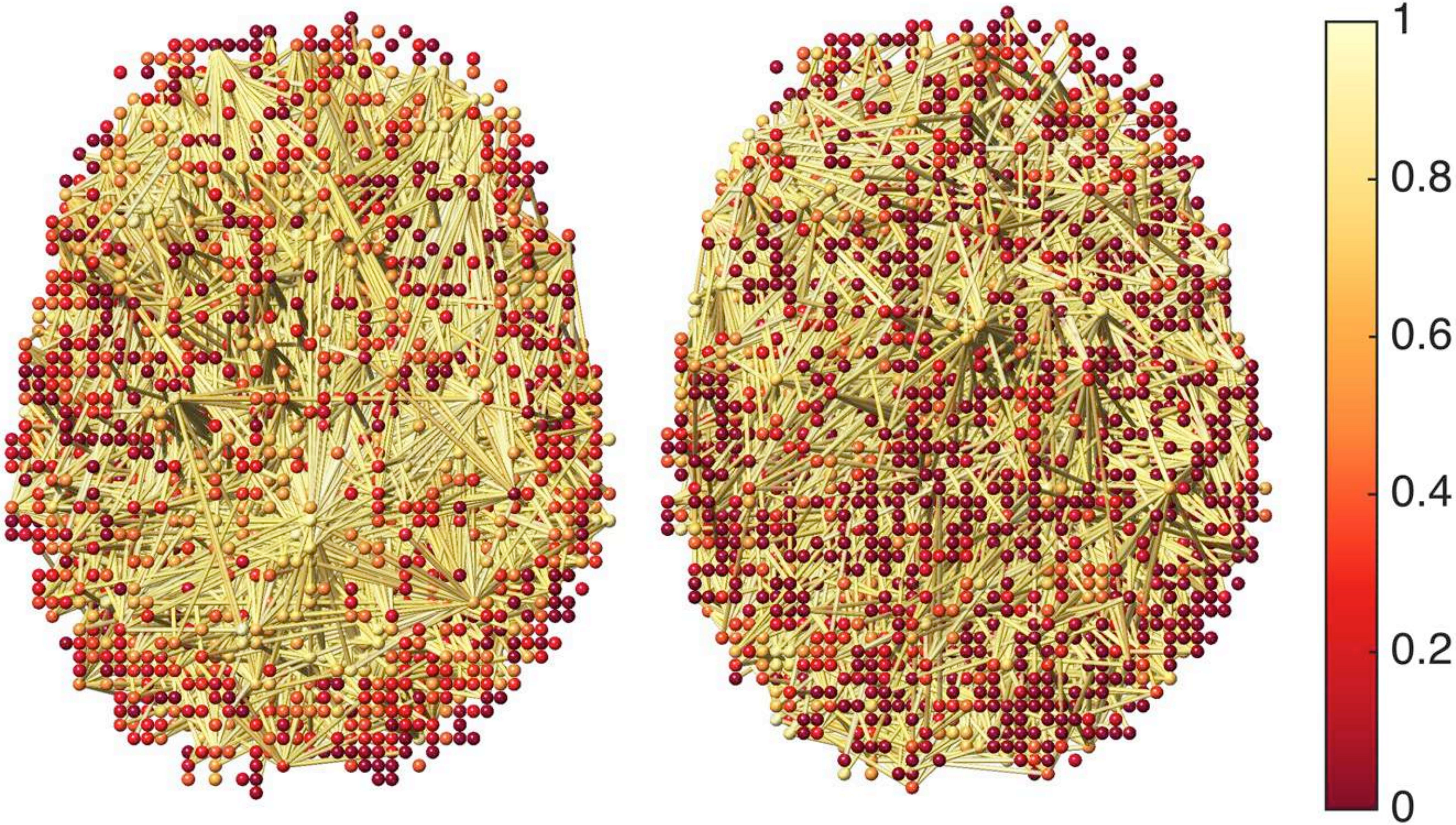
c

$c^T b(v_i)$ Contrast map



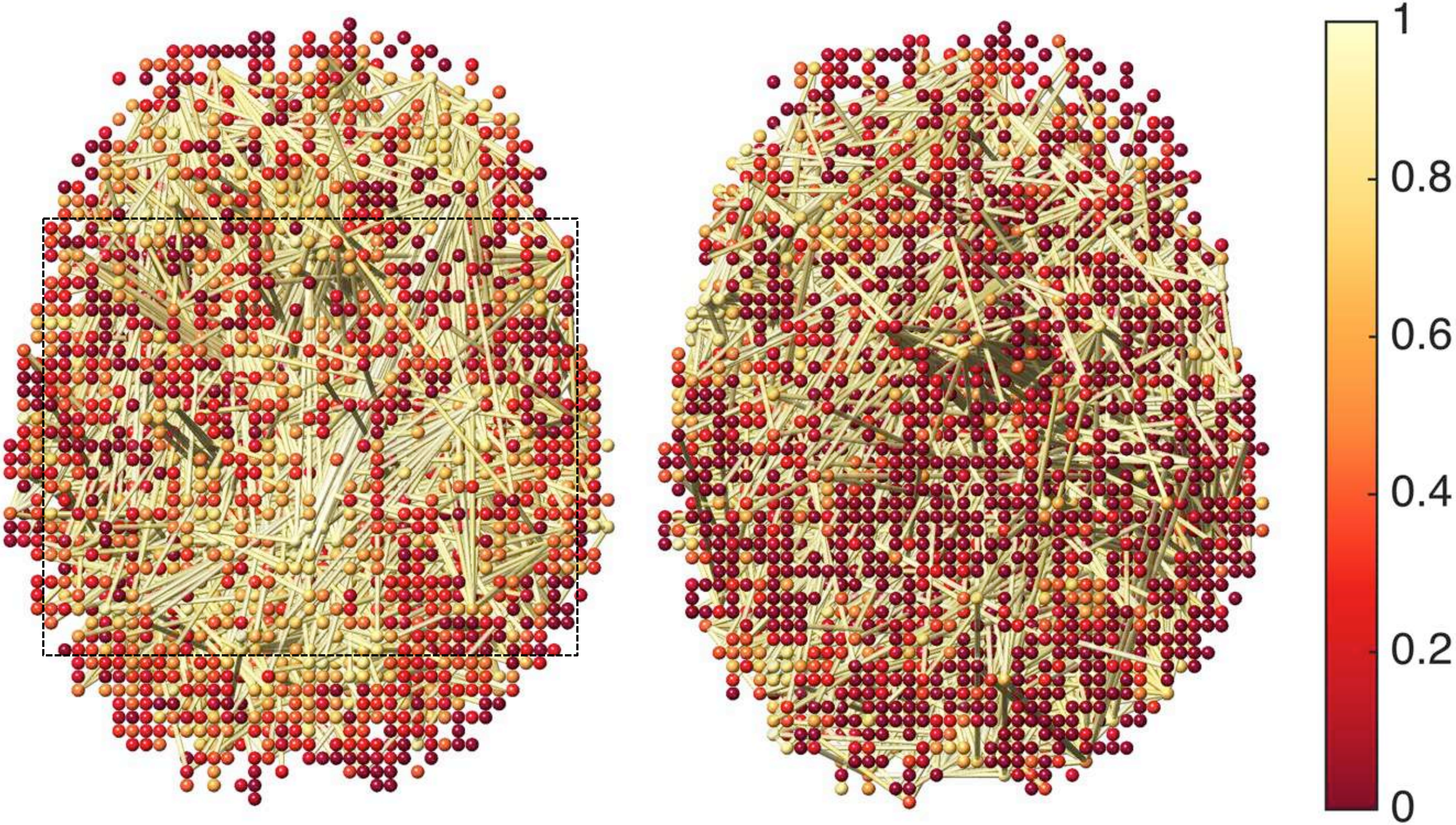


Networks at filtration value 0.7



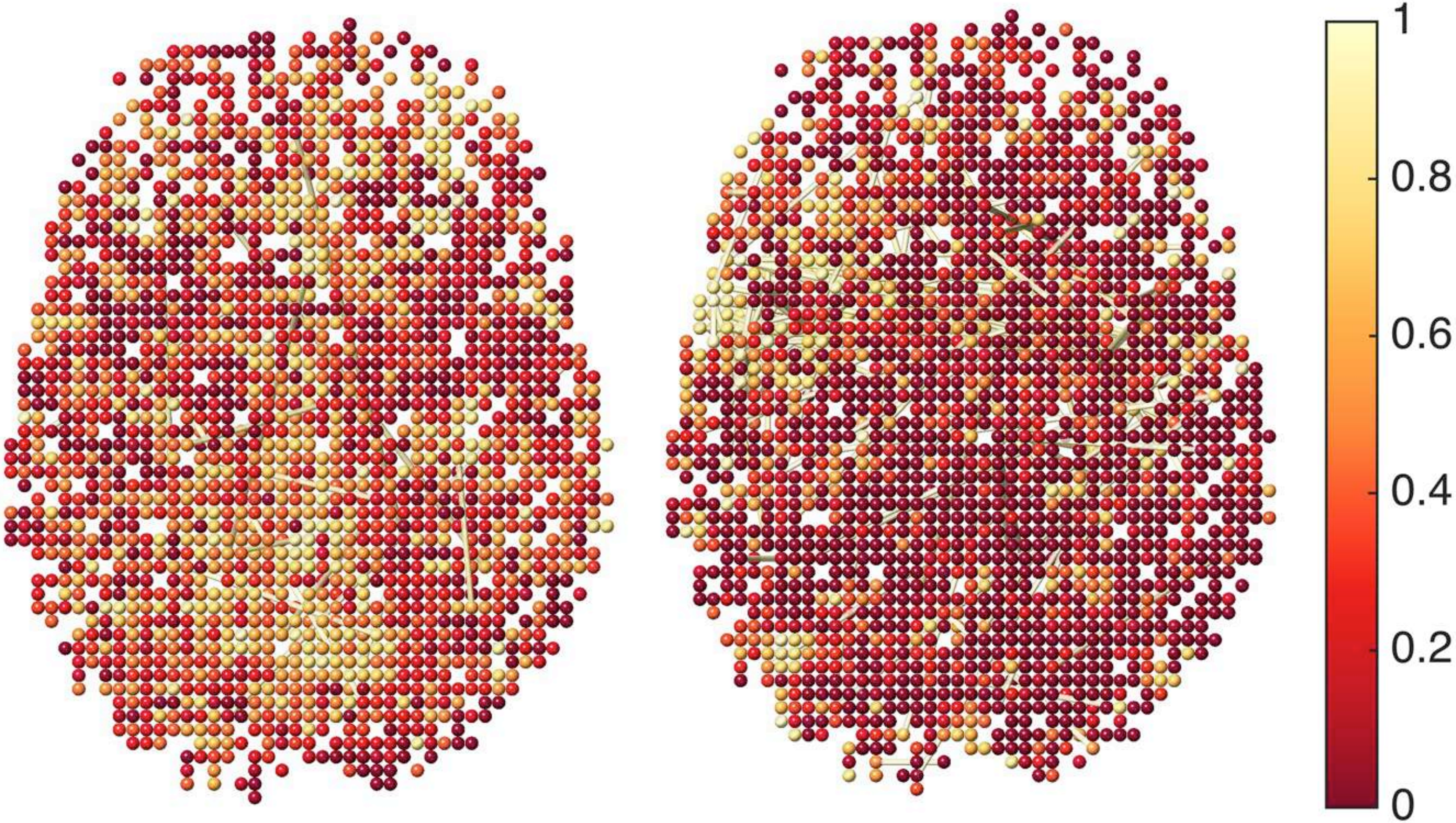
MZ-twins DZ-twins

Networks at filtration value 0.8



MZ-twins DZ-twins

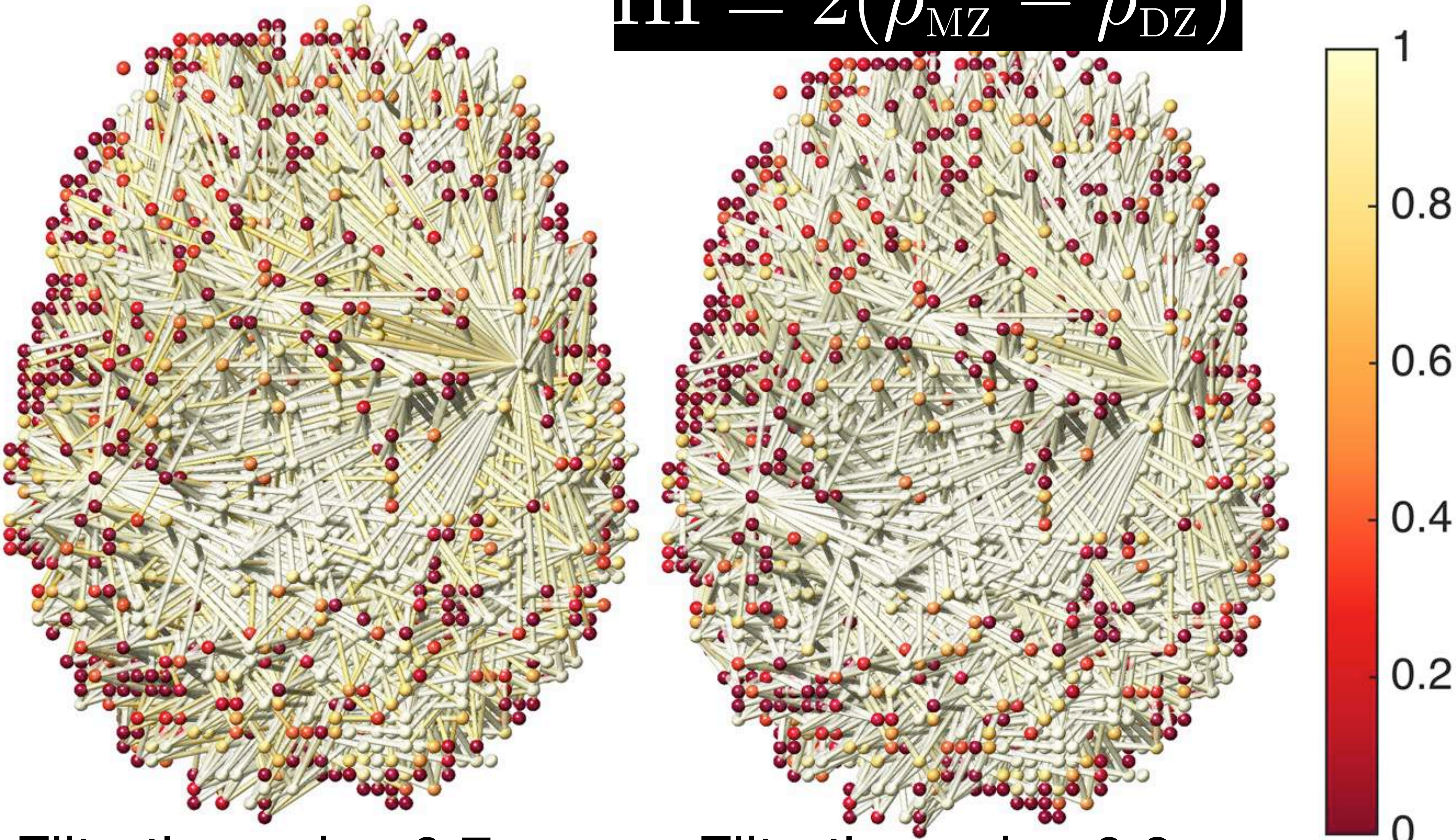
Networks at filtration value 0.9



MZ-twins DZ-twins

Heritability Index (at both nodes and edges)

$$\mathrm{HI} = 2(\rho_{\mathrm{MZ}} - \rho_{\mathrm{DZ}})$$

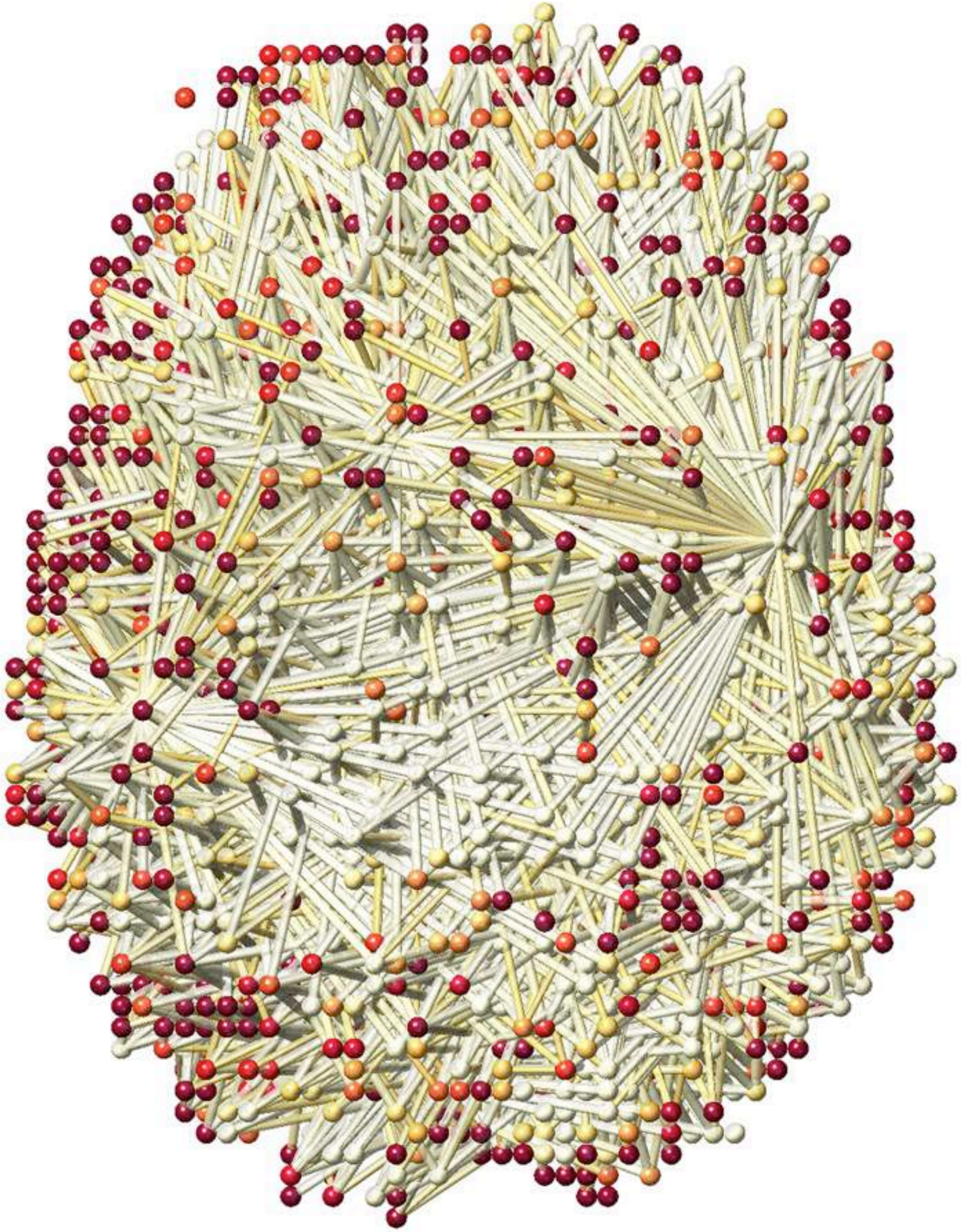


Filtration value 0.7

Filtration value 0.9

p-value < 0.0002

Heritability index map



+25000 nodes

+0.6 billion connections

Voxel-level functional network

Chung et al. 2017 IPMI

Betti Numbers

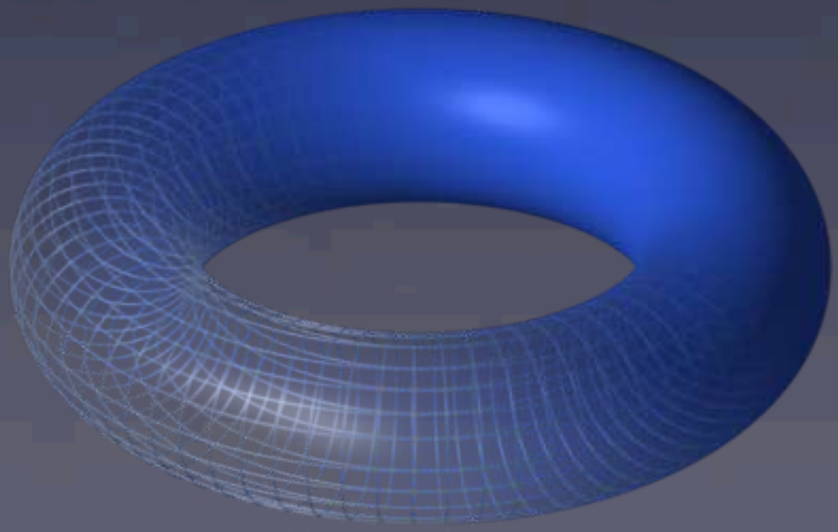
Betti numbers β_i # of i-dimensional holes/loops

β_0 = # of connected components = 3

β_1 = # of 1D holes = 1

β_2 = # of 2D cavities =0

Representation: (3,1,0,0,...)

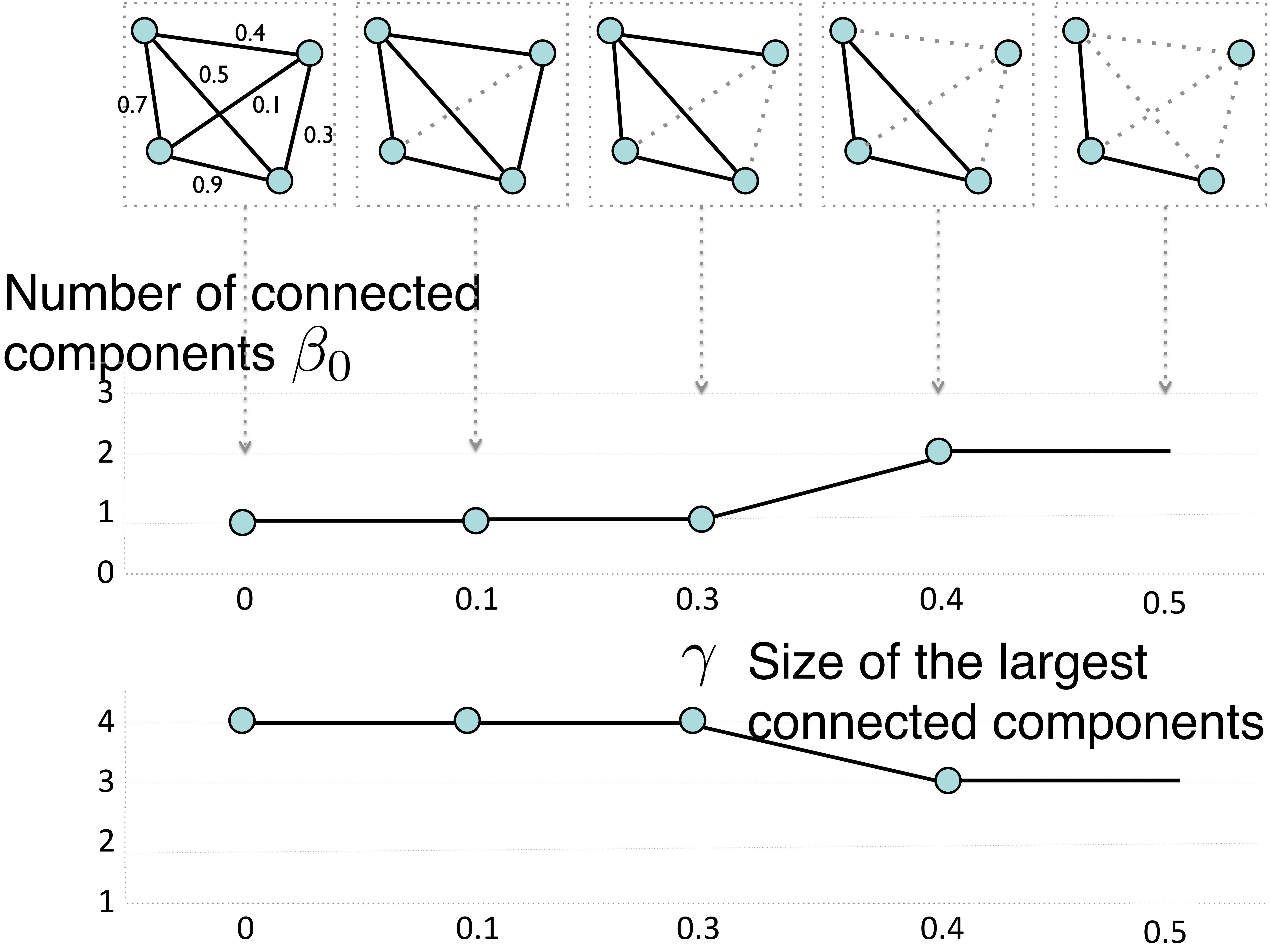


Euler characteristic:

$$\chi = \beta_0 - \beta_1 = 2$$

$$\beta_0 = 1, \beta_1 = 2, \beta_2 = 1$$

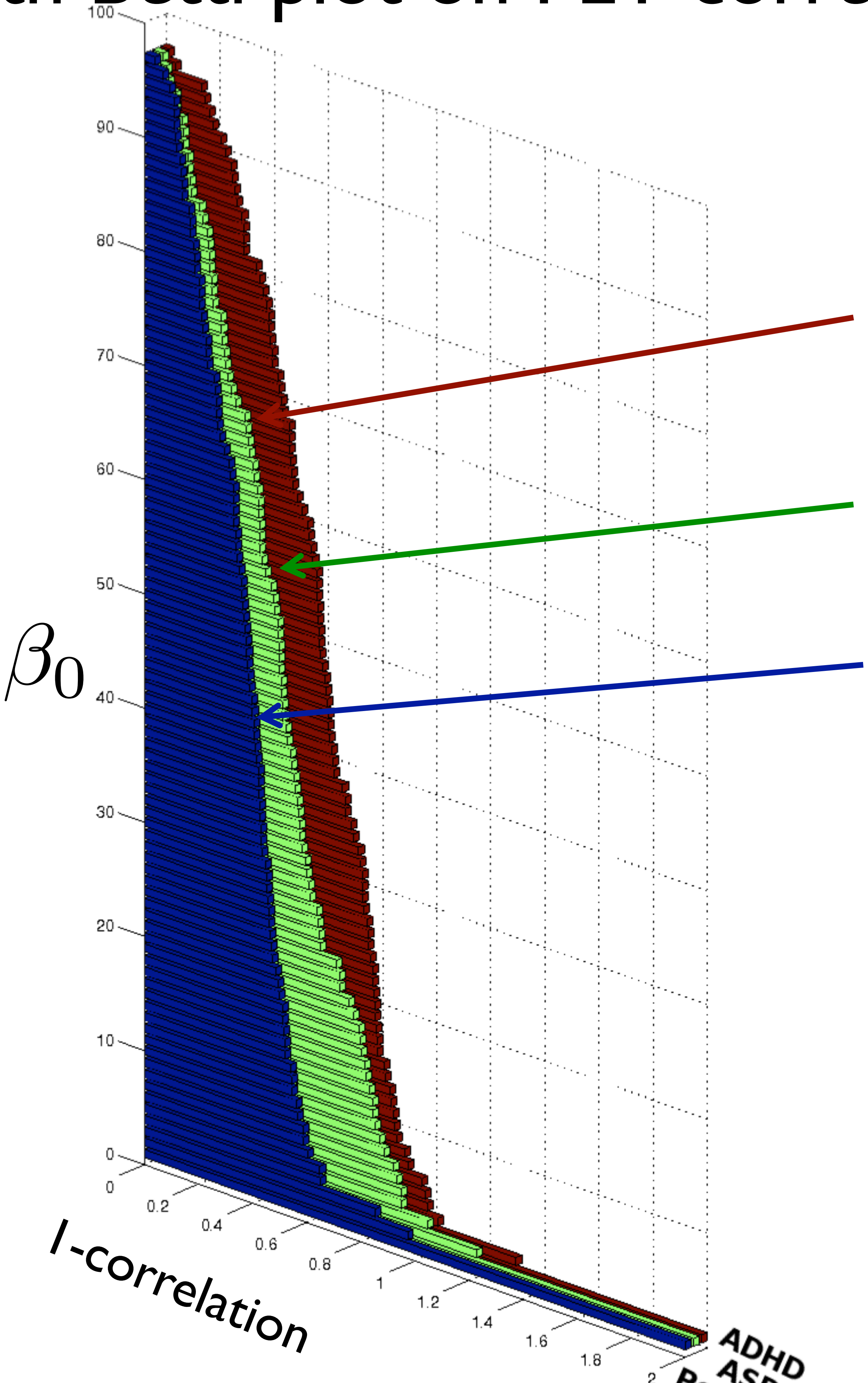
Representation: (1,2,1,0,0,...)



Number of connected components β_0

γ Size of the largest connected components

0-th Betti plot on PET correlation network



24 attention deficit hyperactivity disorder (ADHD) children

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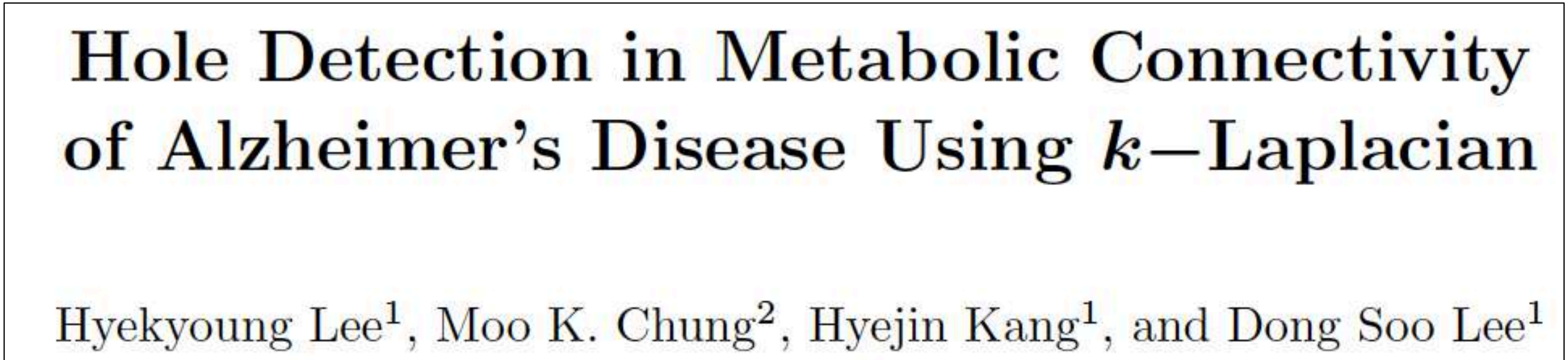
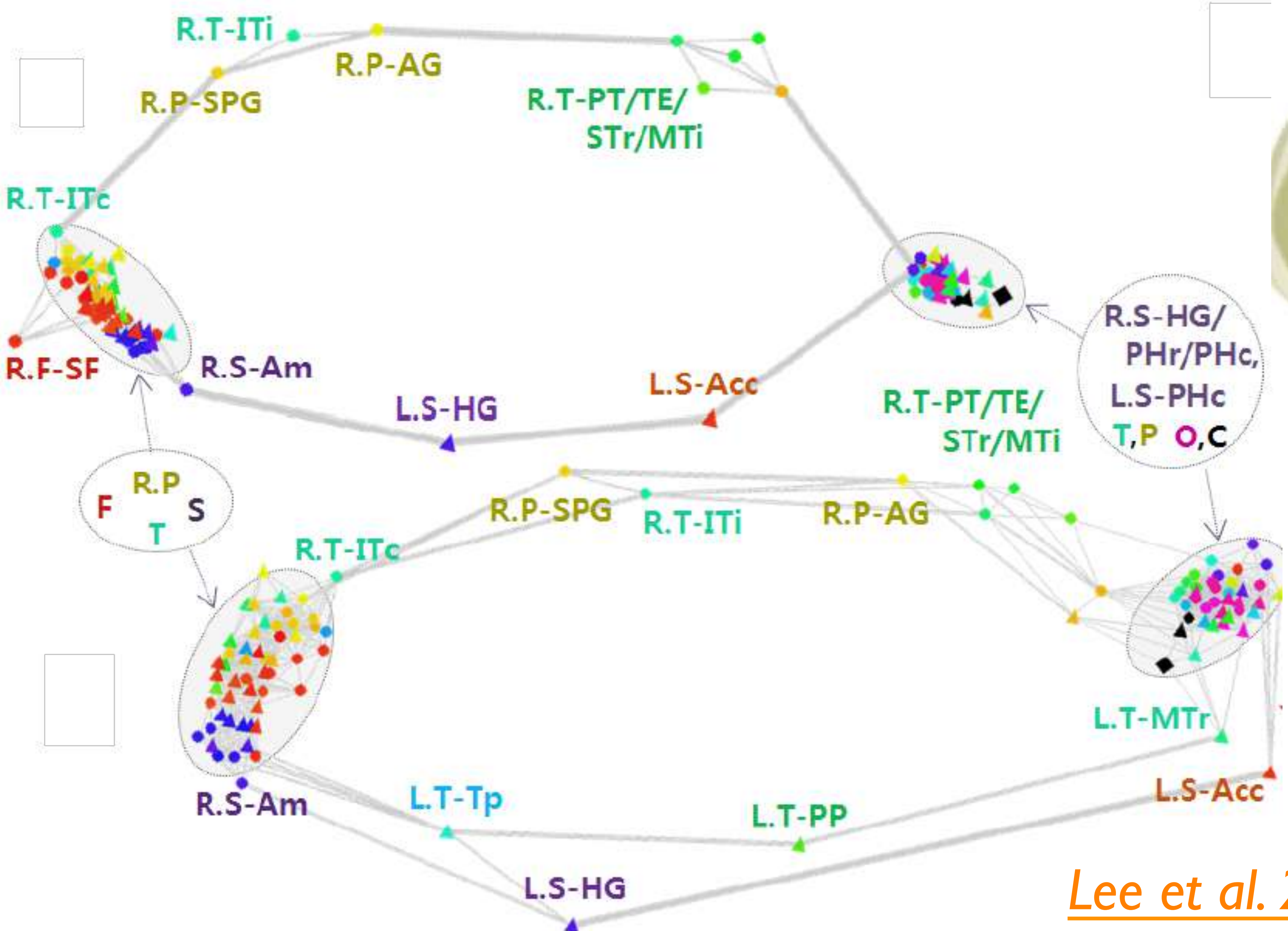
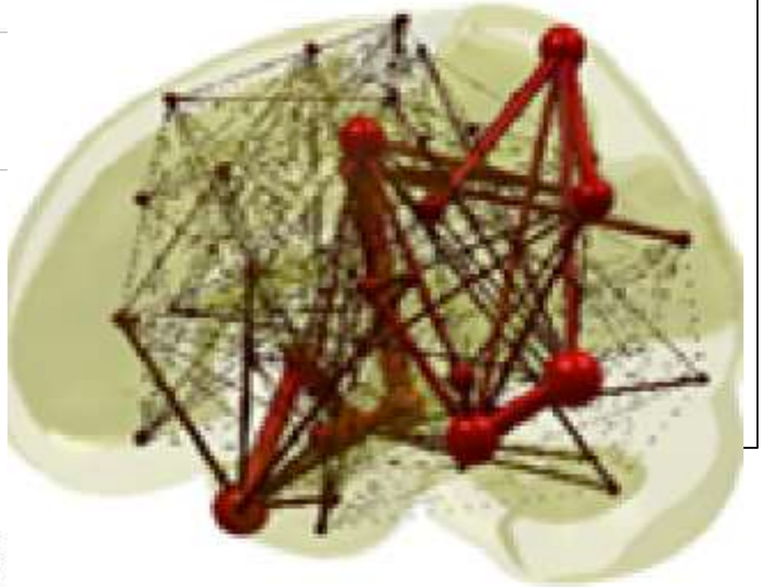


Hole Detection in Metabolic Connectivity of Alzheimer's Disease Using $k-$Laplacian

Hyekyoung Lee[1], Moo K. Chung[2], Hyejin Kang[1], and Dong Soo Lee[1]





Lee et al. 2014 MICCAI 297-304

Persistent homology on hierarchical connectivity

Chung et al. 2017 BioRxiv 209635

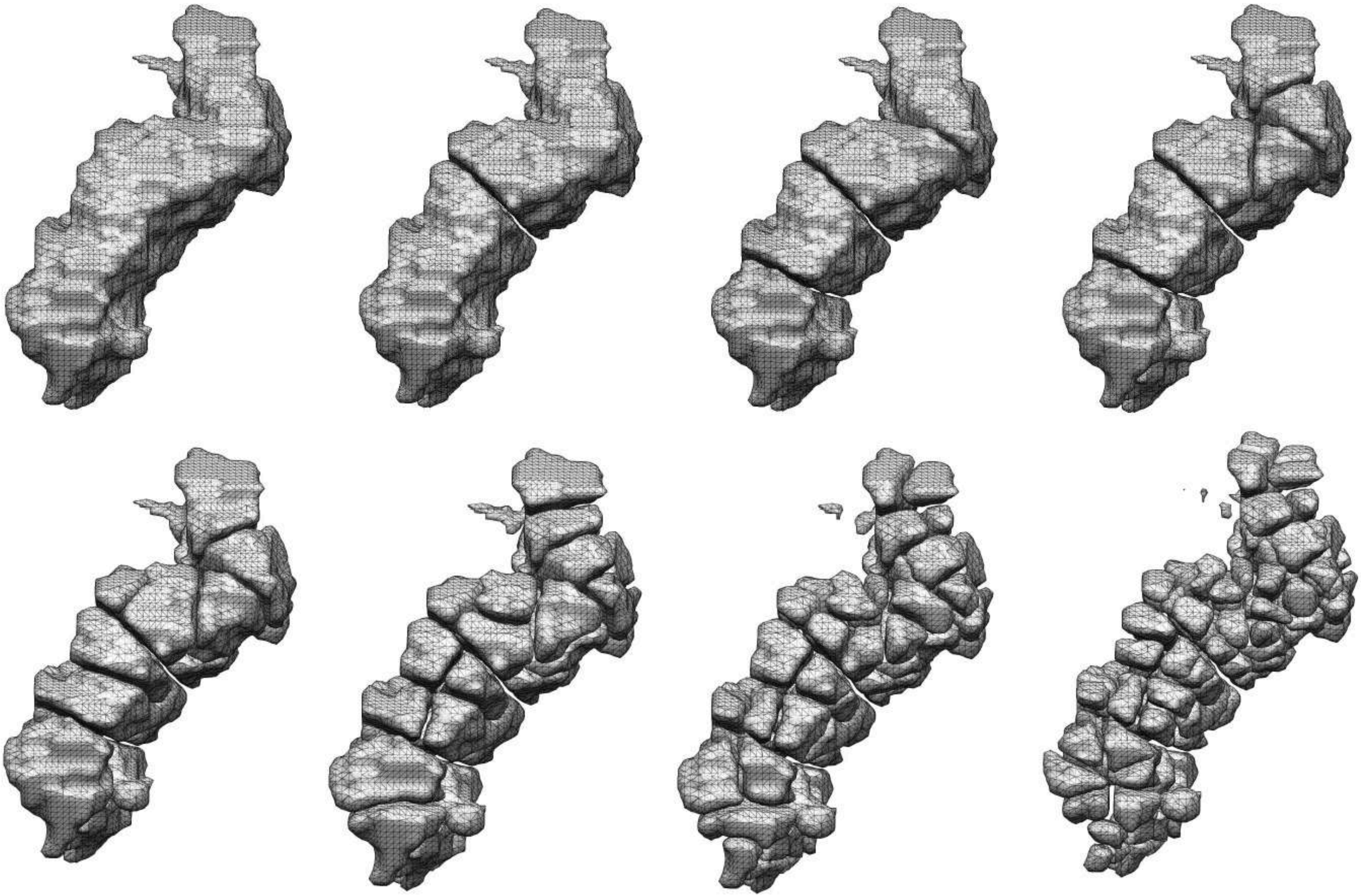
Winsconsin Twin Project

58 Monozygontic (MZ) twin pairs
53 same-sex dizygotic (DZ) twin pairs

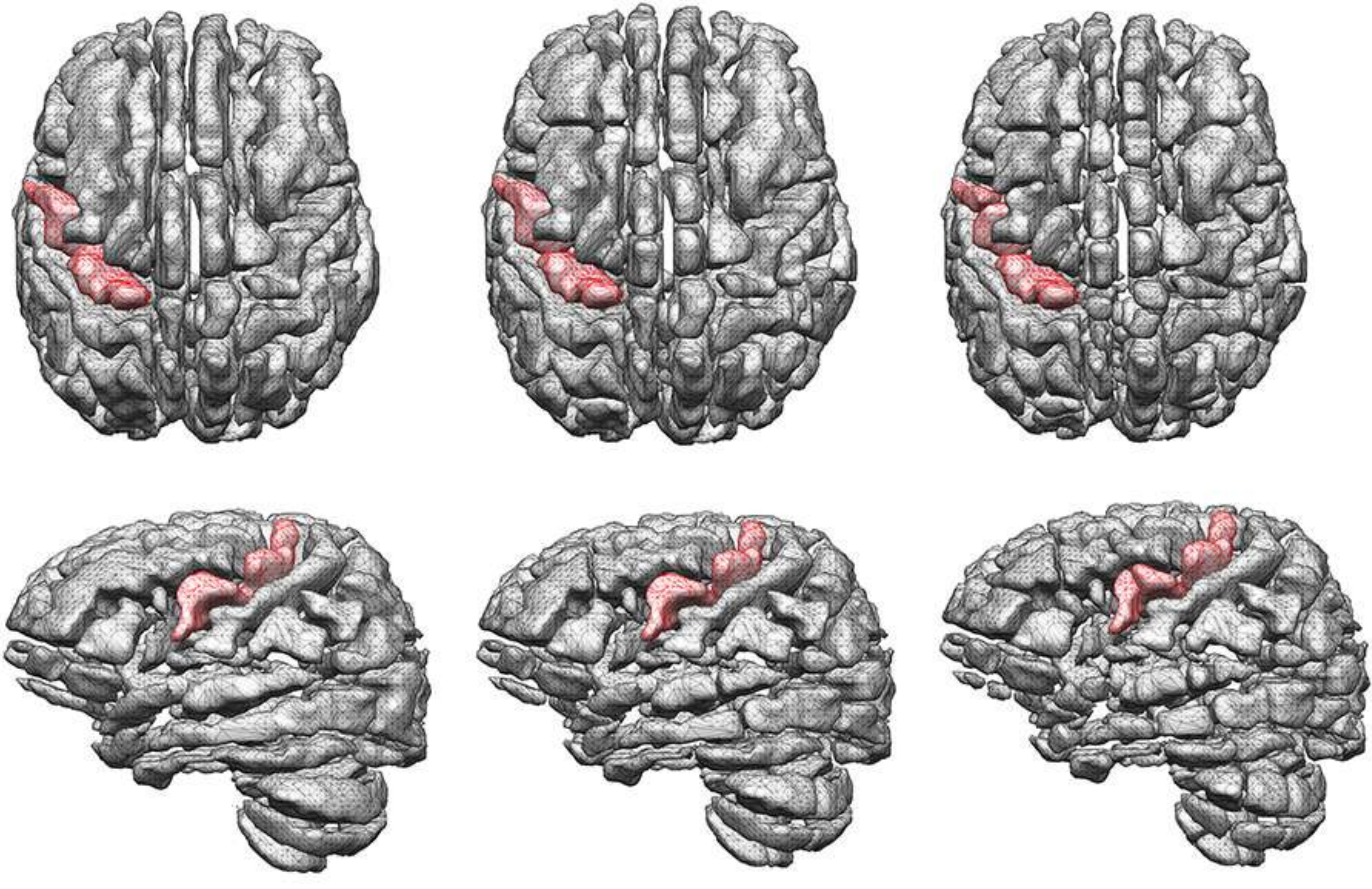
111 pairs = 222 subjects

6 non-DWI: b=0
63 DWI: b=500 (9 dir.), 800 (18 dir.) , 2000 (36 dir.)
Isotropic 2mm resolution

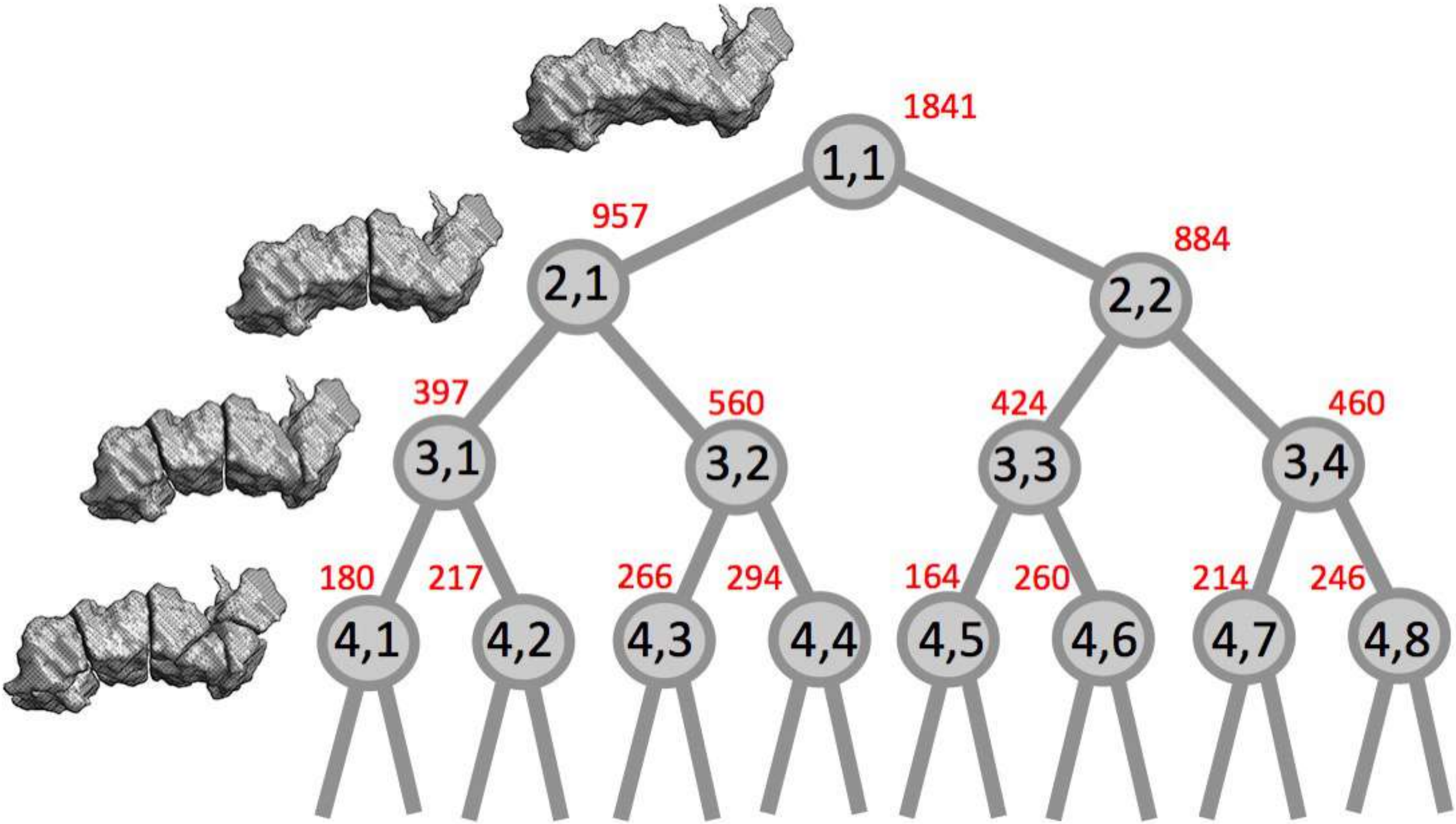
20-layer hierarchical parcellation



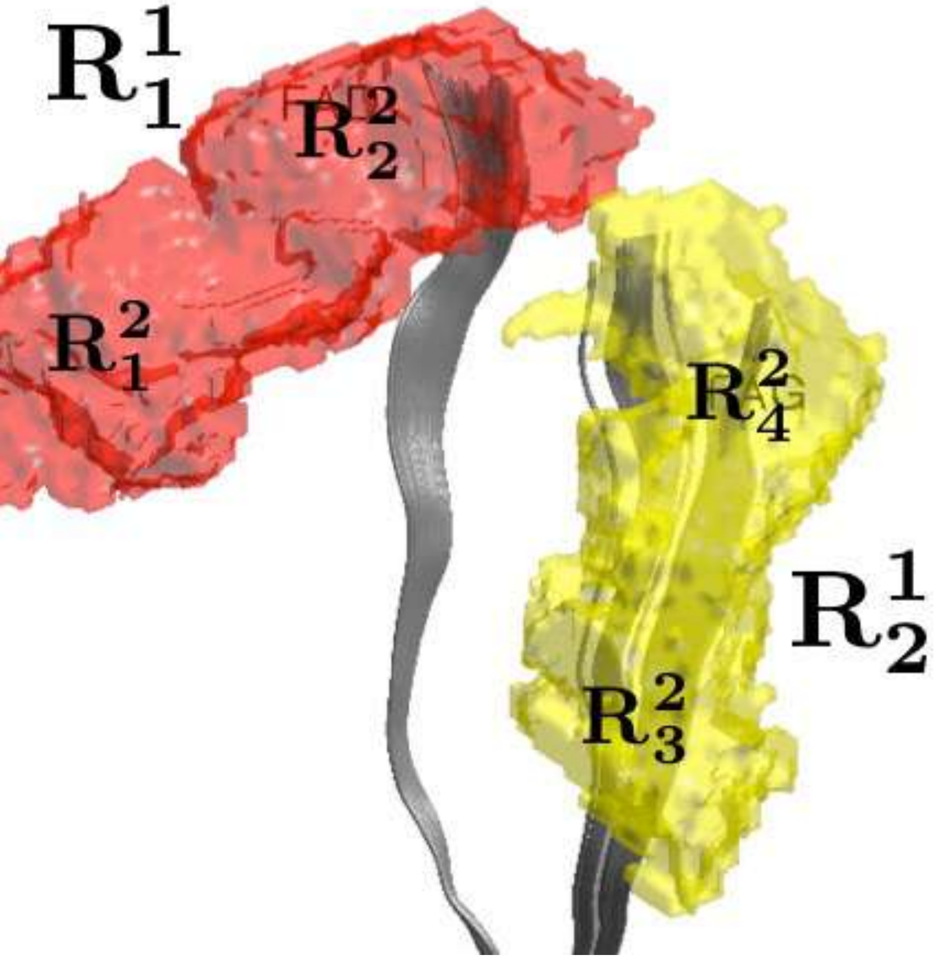
20-layer hierarchical parcellation

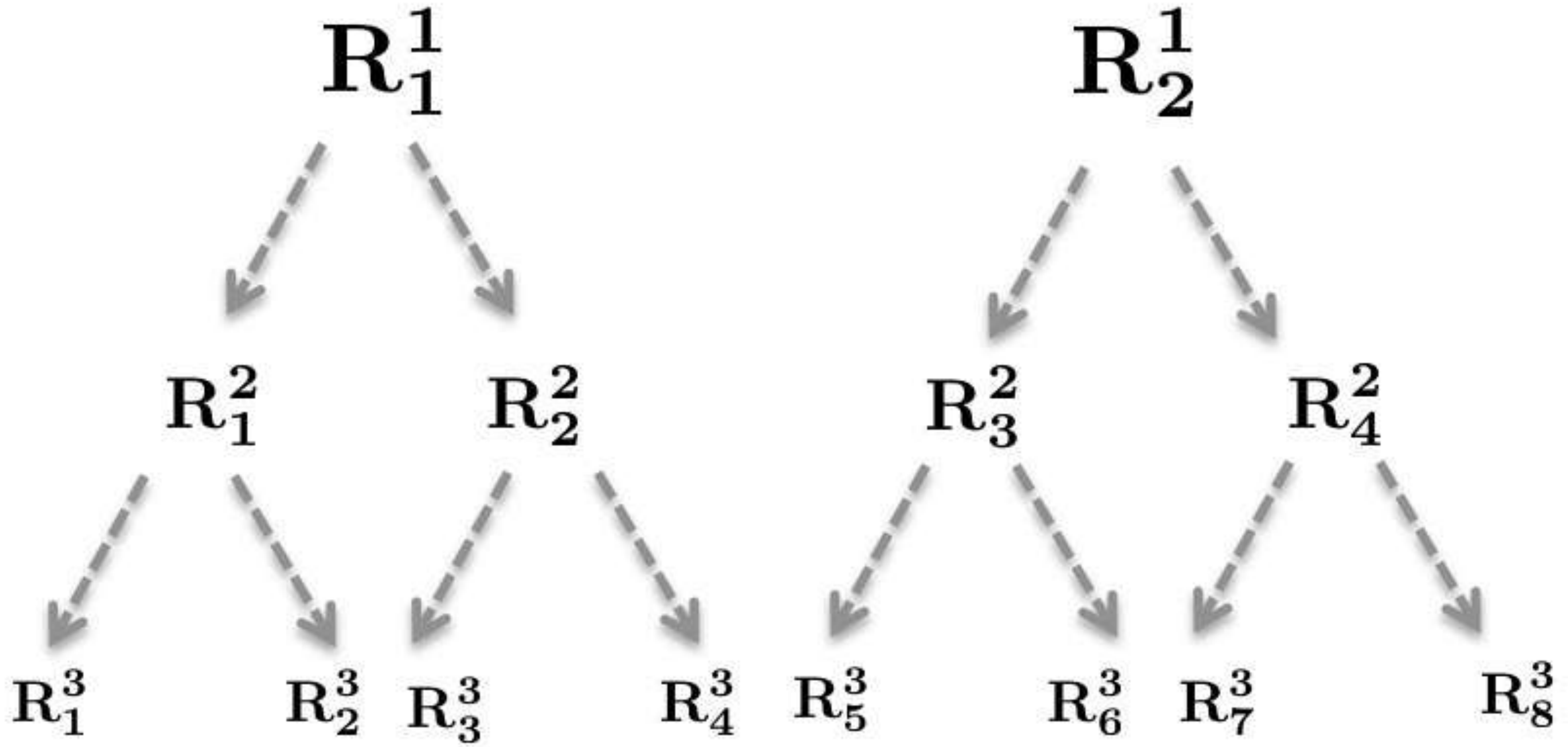


Number of voxels in each layer



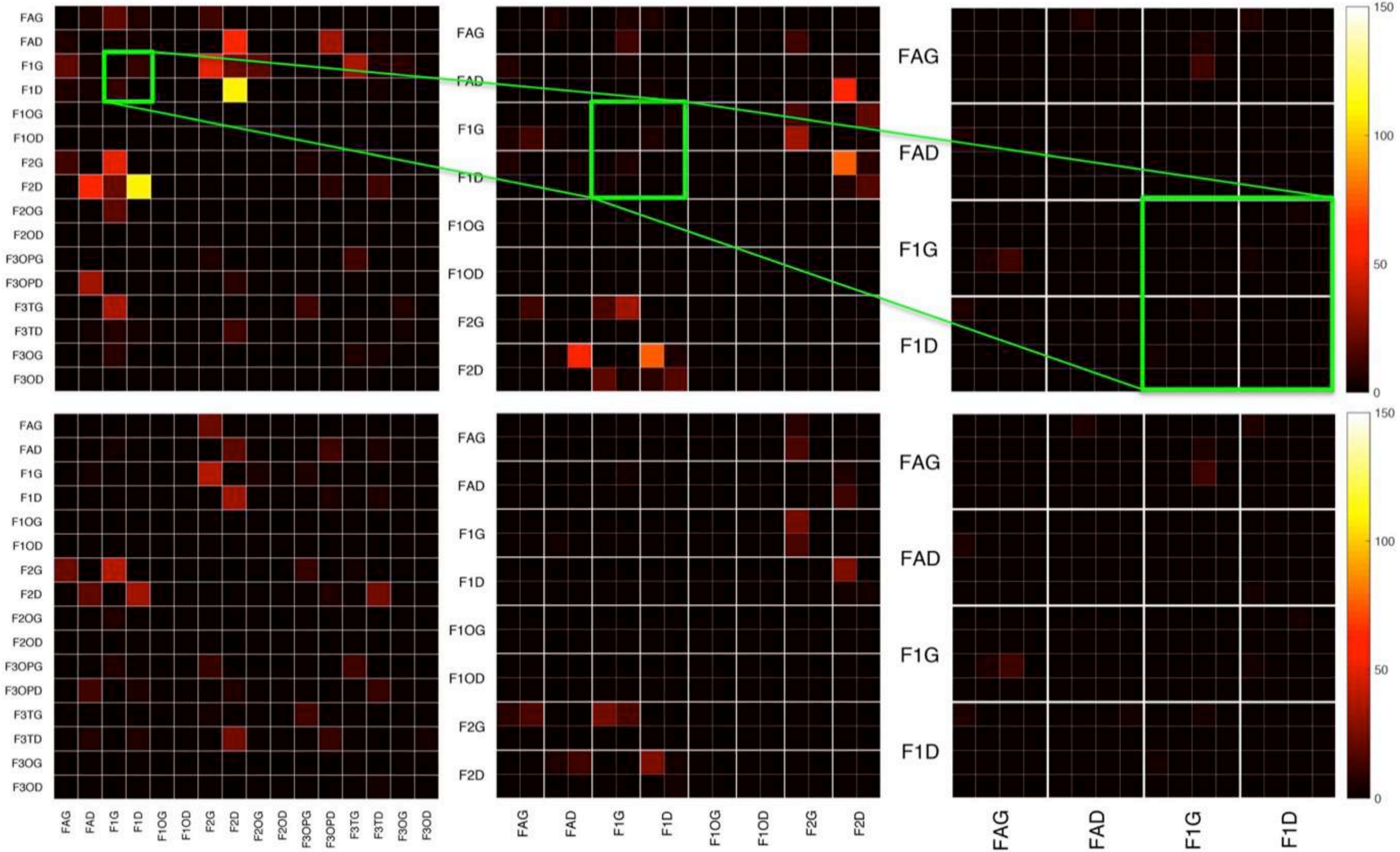
Hierarchical connectivity S^{i}_{jk}



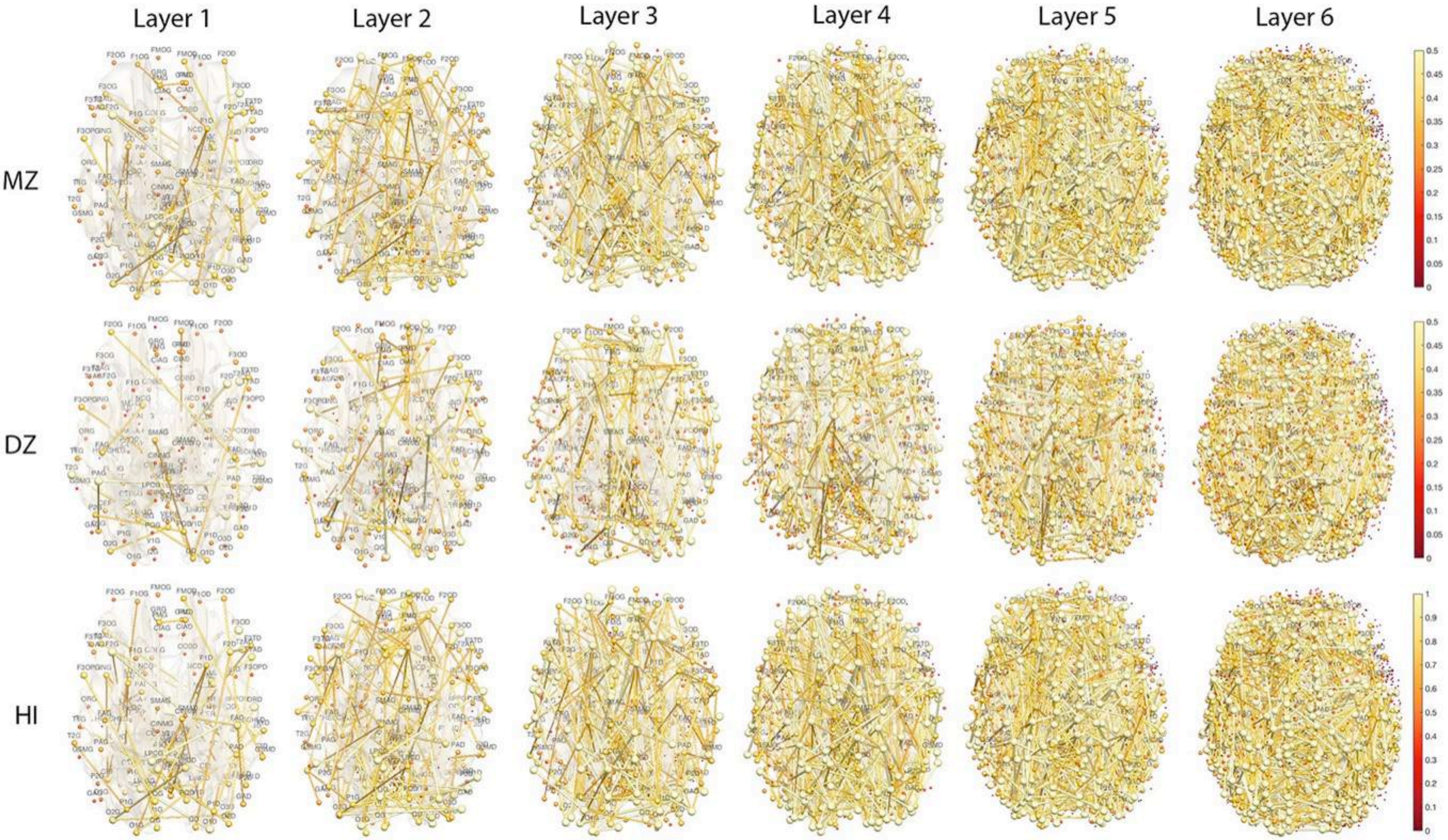


$$S^{i}_{jk} = \sum_{\mathbf{R}^{i+1}_{l} \subset \mathbf{R}^{i}_{j}} \; \sum_{\mathbf{R}^{i+1}_{m} \subset \mathbf{R}^{i}_{k}} S^{i+1}_{lm}$$

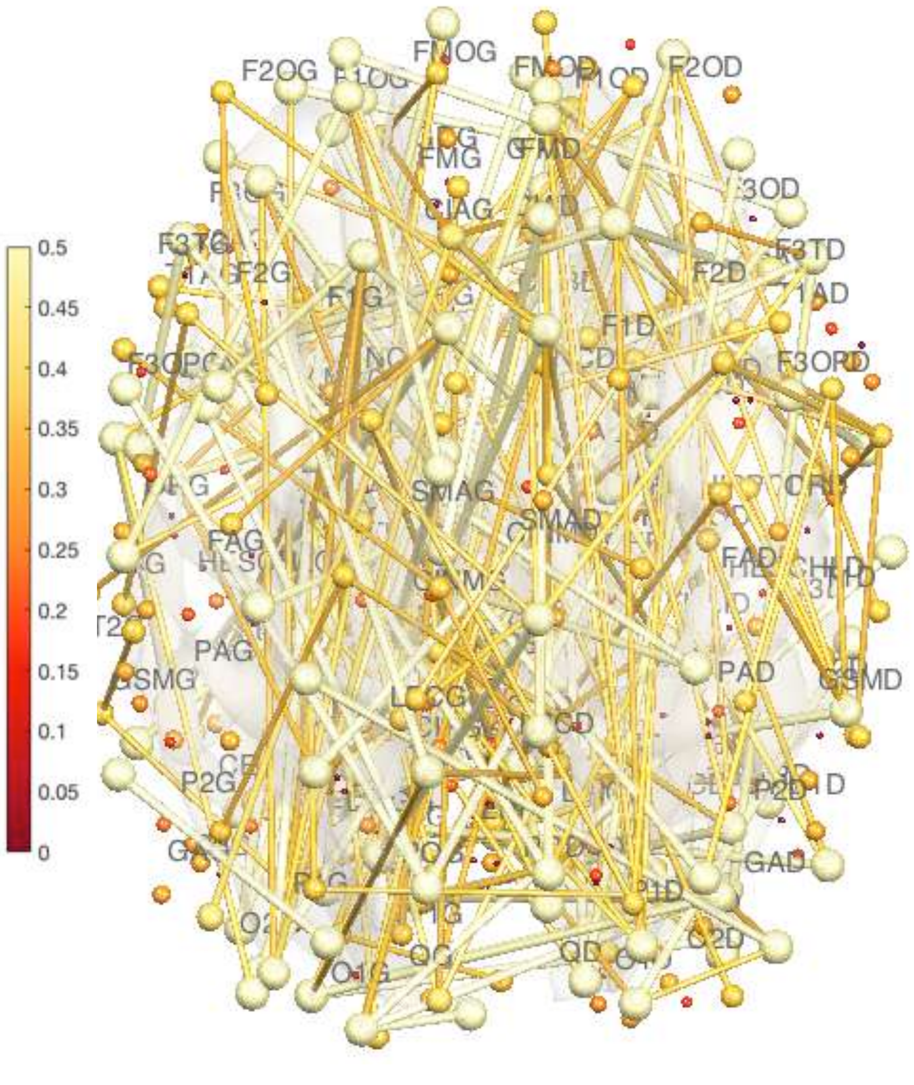
Hierarchical connectivity matrix



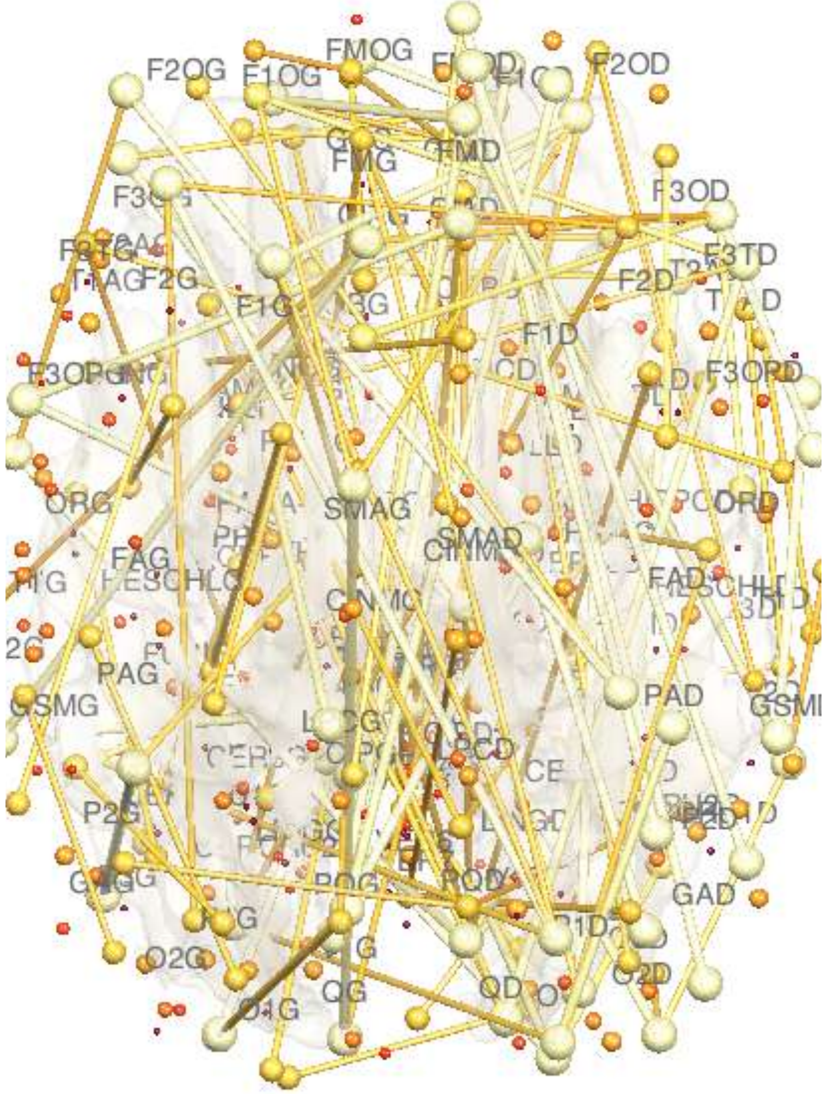
Twin correlations & heritability index



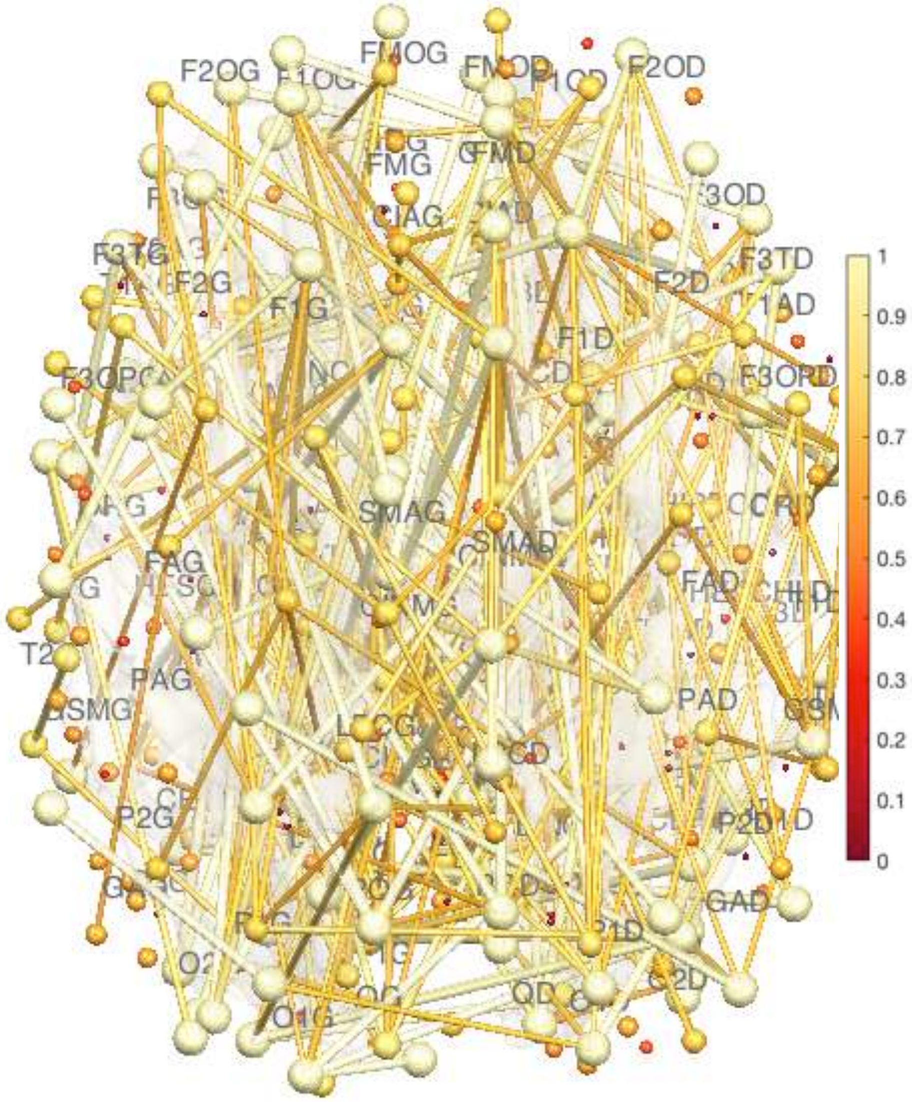
Twin correlations & heritability index (layer 3)



MZ

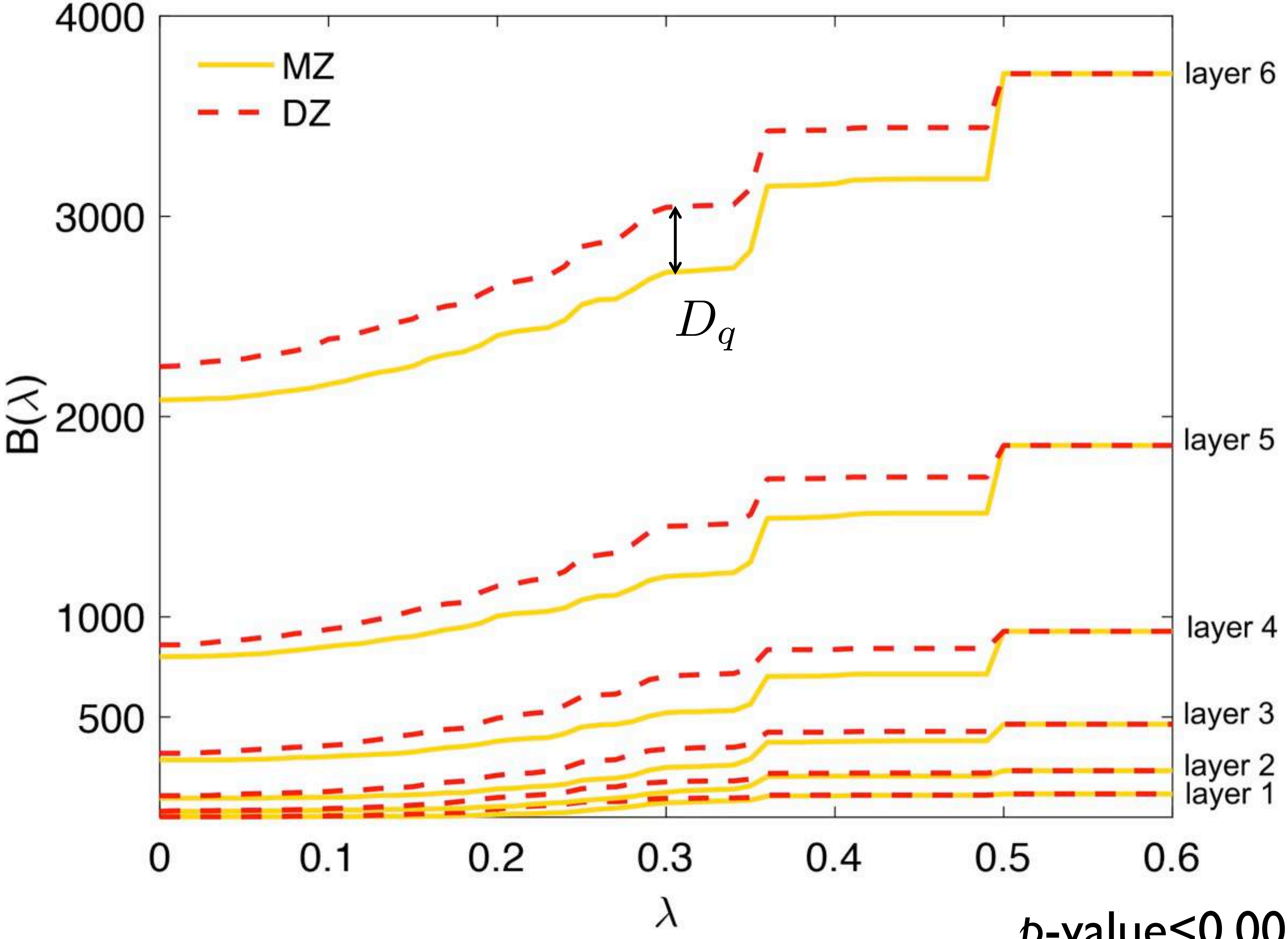


DZ



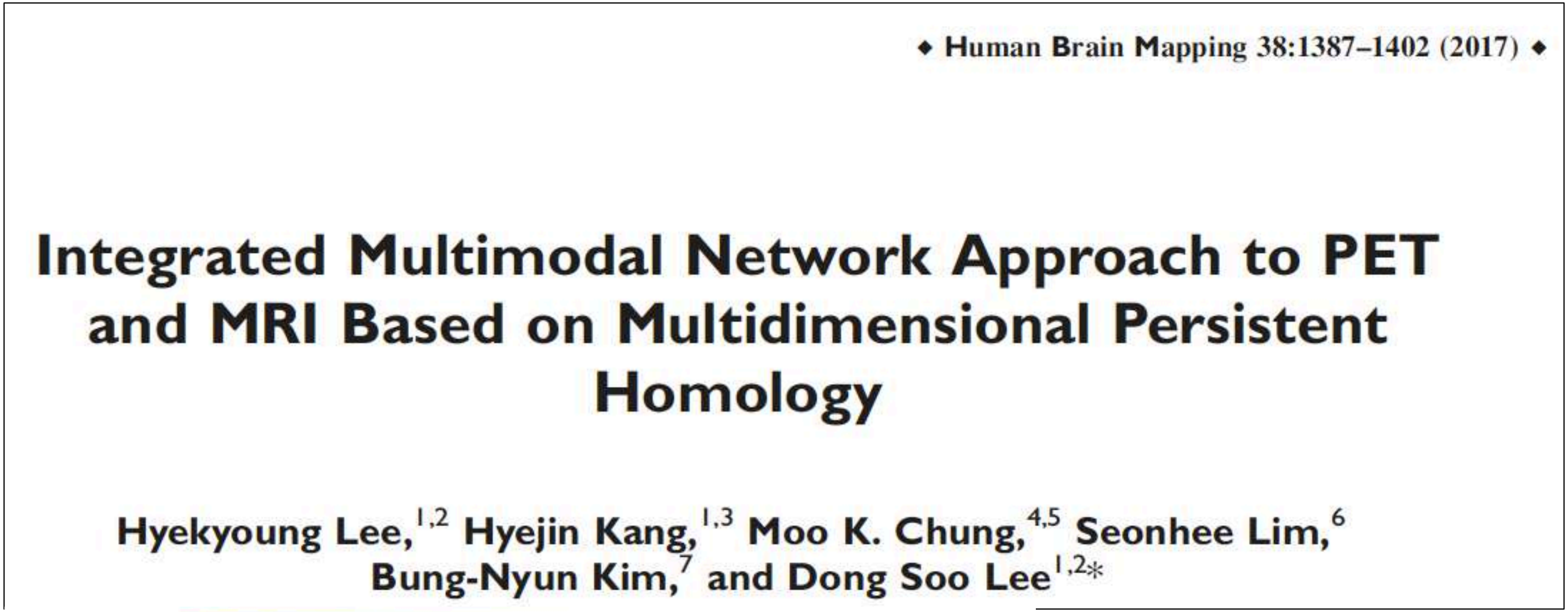
HI

Betti-0 plot (# of connected components)



p-value<0.00001

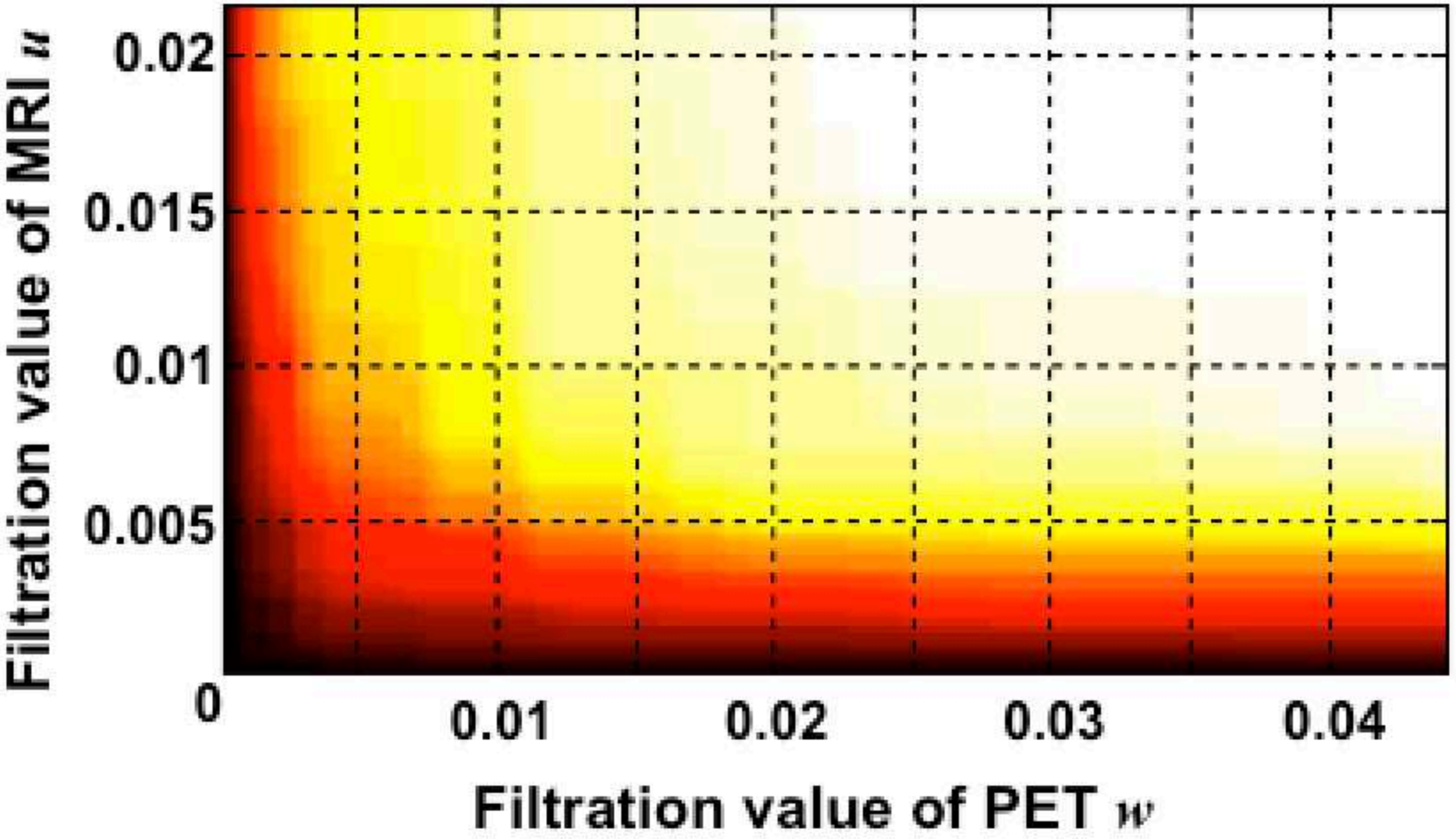
More complex graph filtrations



◆ Human Brain Mapping 38:1387–1402 (2017) ◆

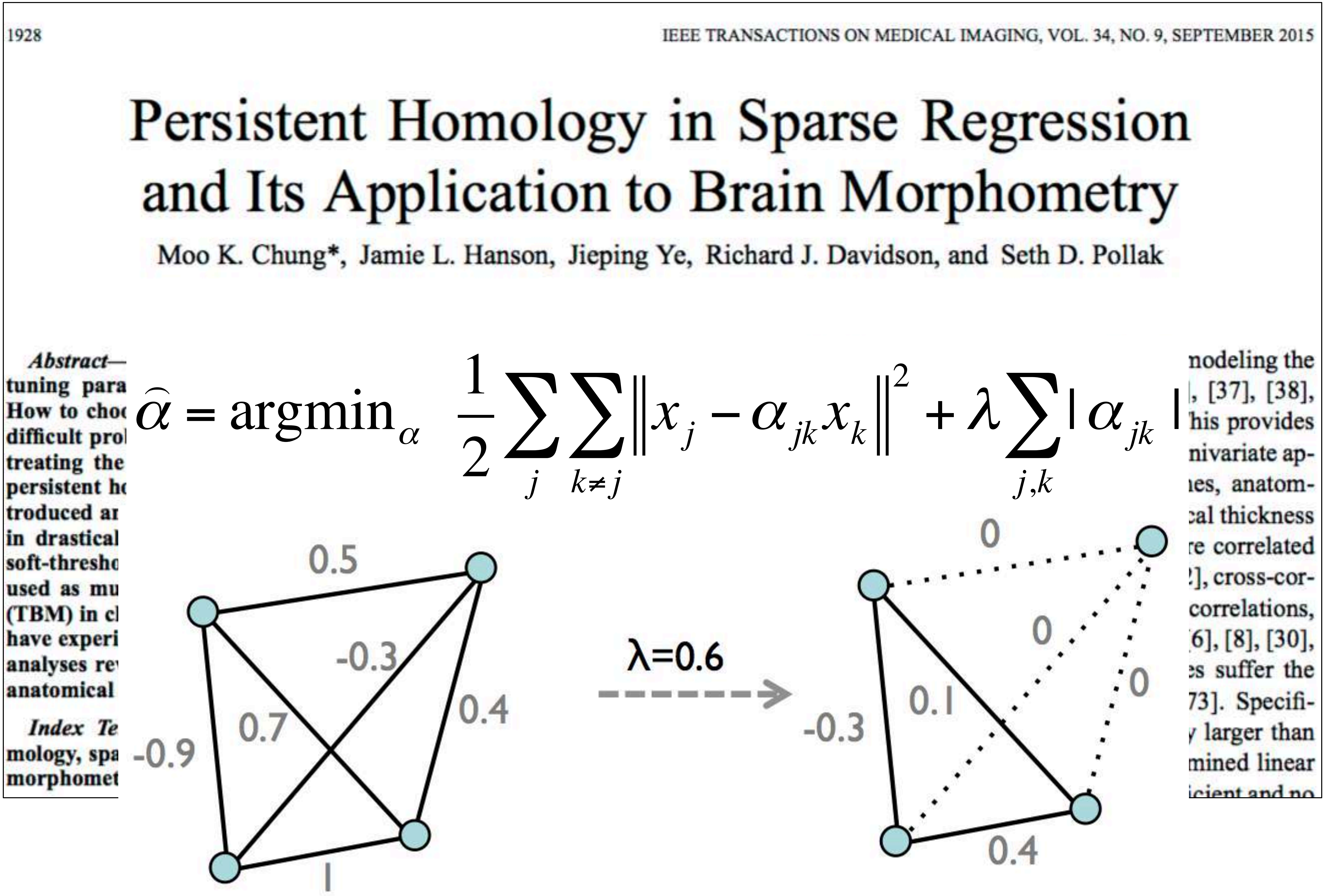
Integrated Multimodal Network Approach to PET and MRI Based on Multidimensional Persistent Homology

Hyekyoung Lee,[1,2] Hyejin Kang,[1,3] Moo K. Chung,[4,5] Seonhee Lim,[6]
Bung-Nyun Kim,[7] and Dong Soo Lee[1,2]*



β_0 surface plot

Lee et al. 2017
HBM 38:1387-1402



1928 IEEE TRANSACTIONS ON MEDICAL IMAGING, VOL. 34, NO. 9, SEPTEMBER 2015

Persistent Homology in Sparse Regression
and Its Application to Brain Morphometry

Moo K. Chung*, Jamie L. Hanson, Jieping Ye, Richard J. Davidson, and Seth D. Pollak

Abstract—
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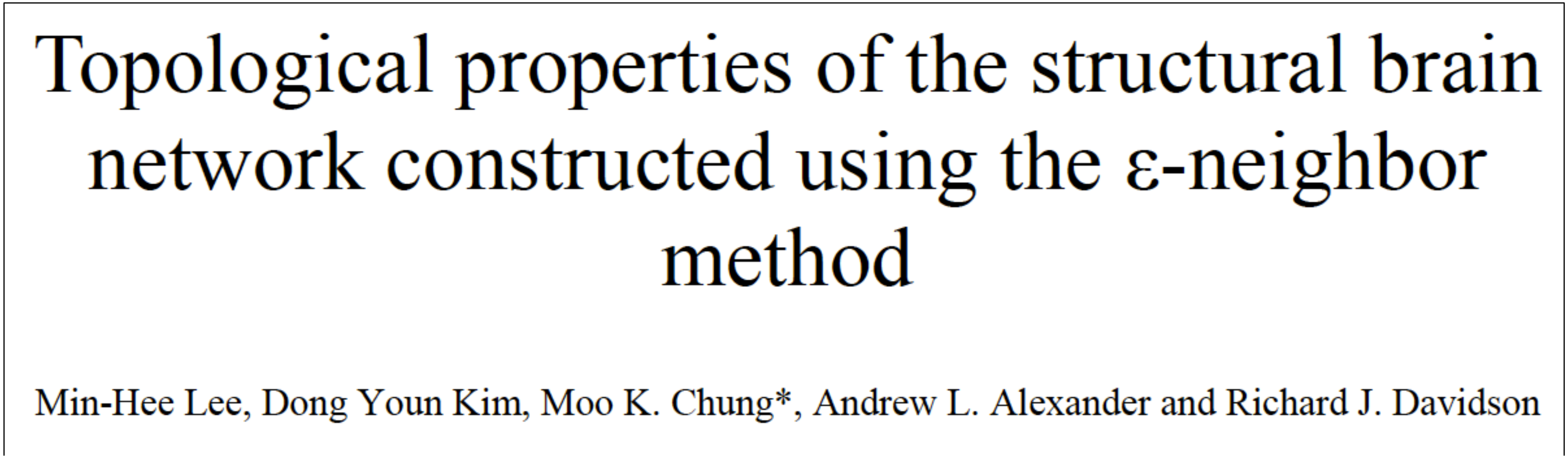
$$\widehat{\alpha} = \operatorname{argmin}_{\alpha} \ \frac{1}{2}\sum_{j}\sum_{k\neq j}\left\| x_j - \alpha_{jk}x_k \right\|^2 + \lambda\sum_{j,k}|\alpha_{jk}|$$

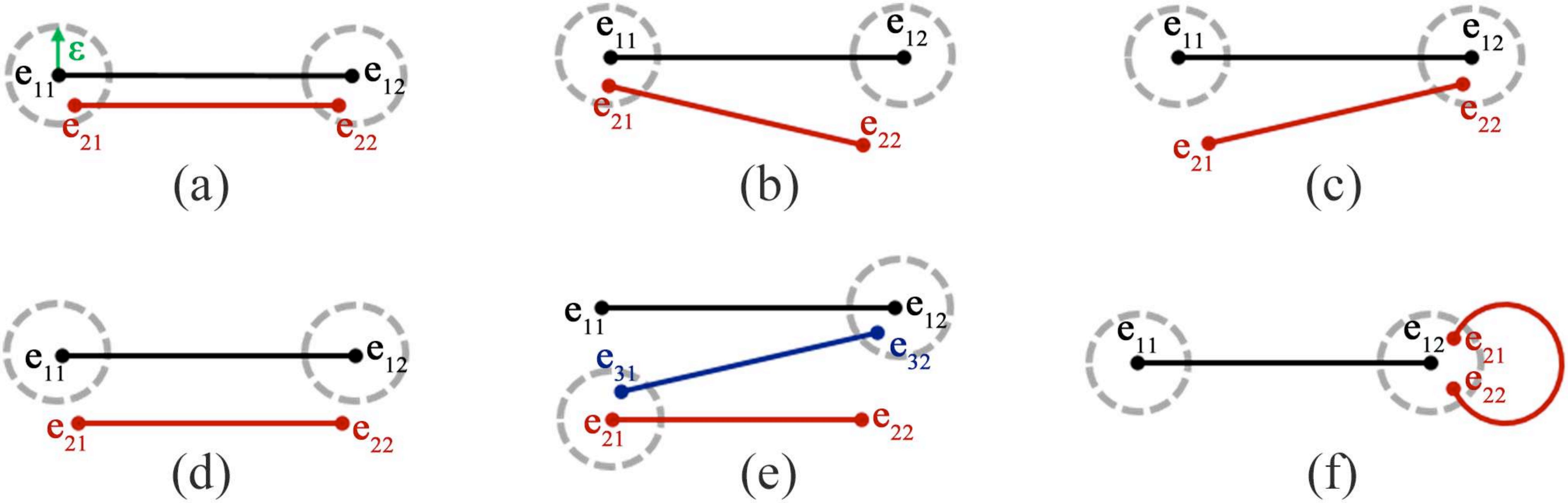
Chung et al. 2013 MICCAI 300-307

Chung et al. 2015 IEEE Transactions on Medical Imaging 34:1928-1939



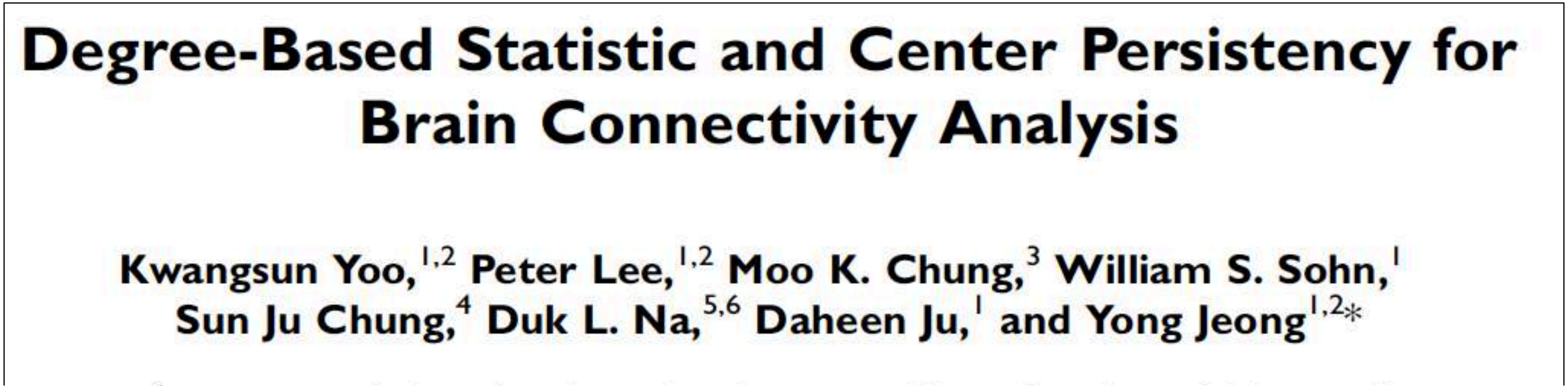
Topological properties of the structural brain network constructed using the ε-neighbor method

Min-Hee Lee, Dong Youn Kim, Moo K. Chung*, Andrew L. Alexander and Richard J. Davidson



Chung et al. 2011 SPIE 79624G

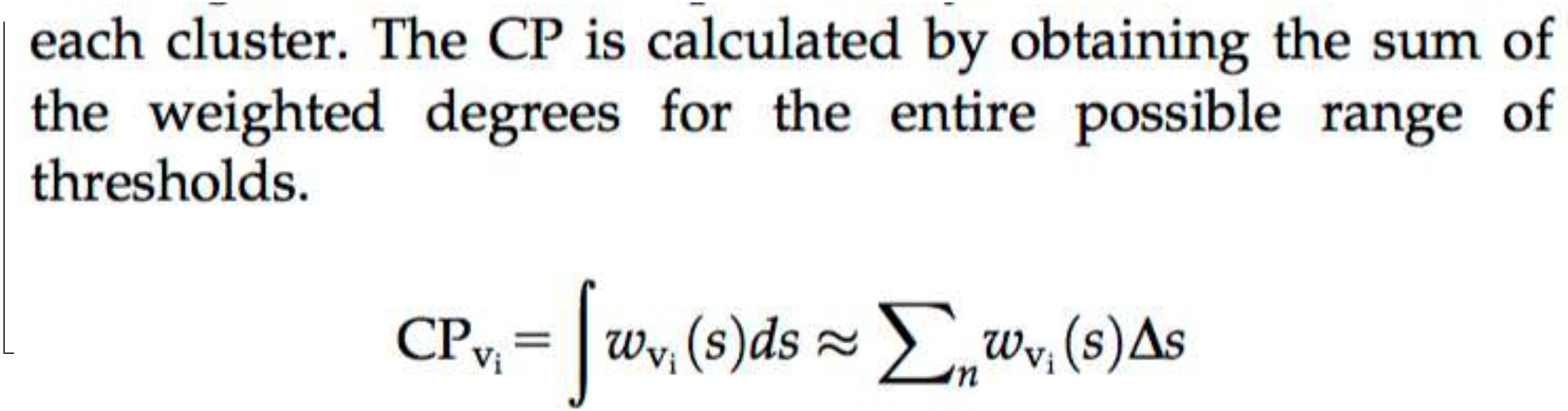
Lee et al. 2018 IEEE Biomedical Engineering



Degree-Based Statistic and Center Persistency for Brain Connectivity Analysis

Kwangsun Yoo,[1,2] Peter Lee,[1,2] Moo K. Chung,[3] William S. Sohn,[1]
Sun Ju Chung,[4] Duk L. Na,[5,6] Daheen Ju,[1] and Yong Jeong[1,2]*

Center persistency (CP)



each cluster. The CP is calculated by obtaining the sum of the weighted degrees for the entire possible range of thresholds.

$$\mathrm{CP}_{\mathrm{v_i}} = \int w_{\mathrm{v_i}}(s)ds \approx \sum_{n} w_{\mathrm{v_i}}(s)\Delta s$$

Yoo et al. 2017 Human Brain Mapping 38:165-181

Persistent homological network distances

Chung et al. 2017
Topological distances beweeen brain networks,
Connectomics in NeuroImaging (CNI) 10511:161-170

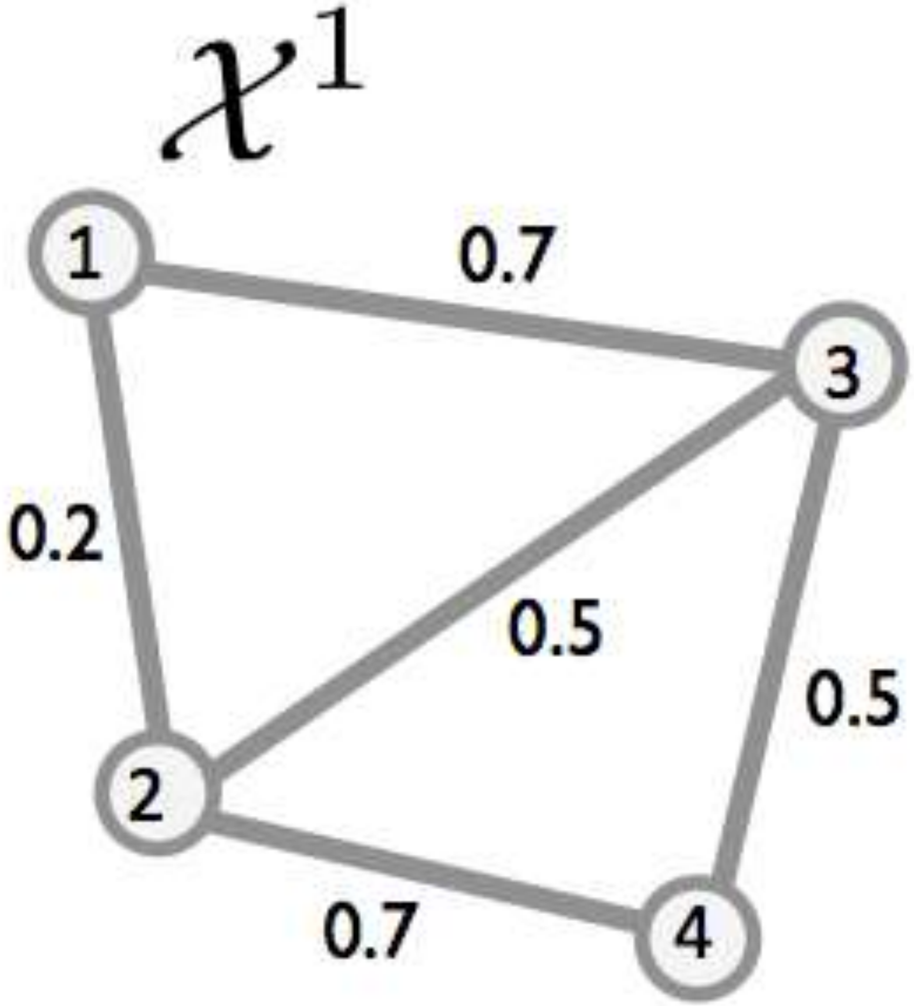
Matrix norm based distances

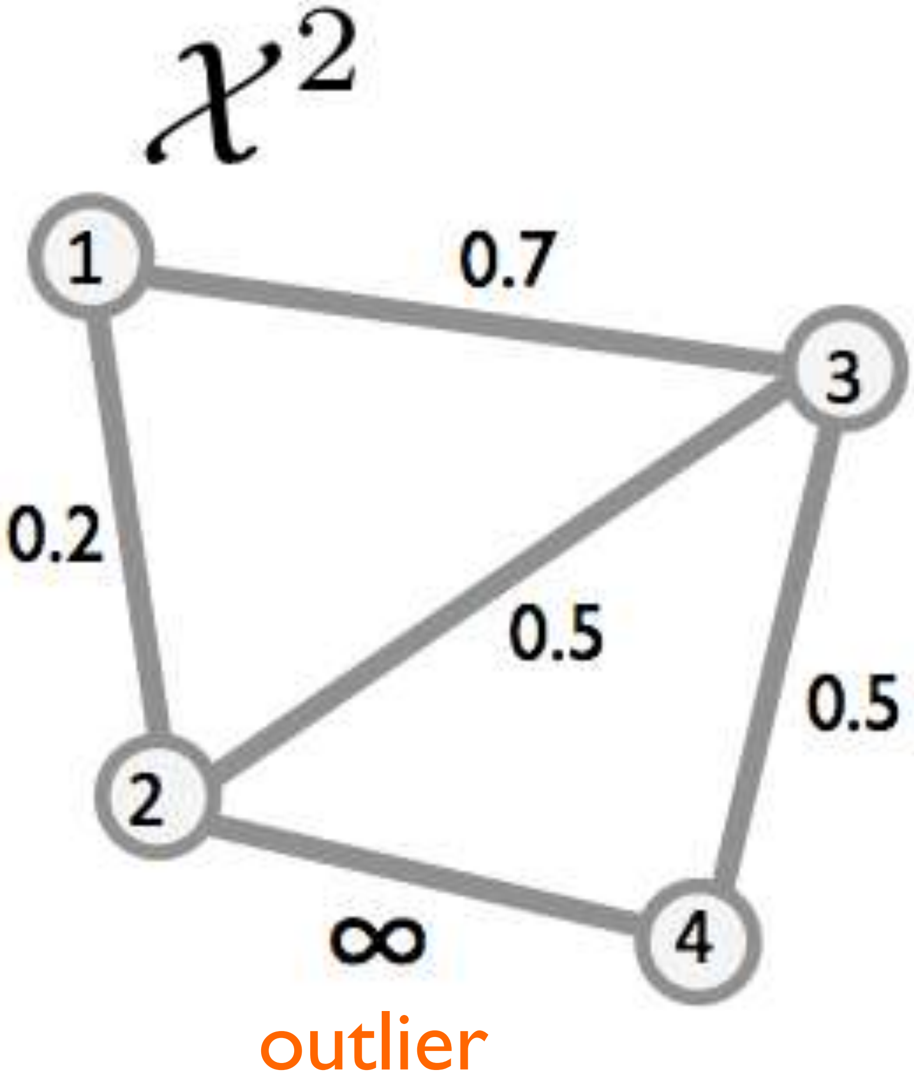
$$\mathcal{X}^1 = (V, w^1) \qquad \mathcal{X}^2 = (V, w^2)$$

$$D_l(\mathcal{X}^1, \mathcal{X}^2) = \Big(\sum_{i,j} |w^1_{ij} - w^2_{ij}|^l \Big)^{1/l}$$

$$D_\infty(\mathcal{X}^1, \mathcal{X}^2) = \max_{\forall i,j} |w^1_{ij} - w^2_{ij}|$$

Matrix norm fails!



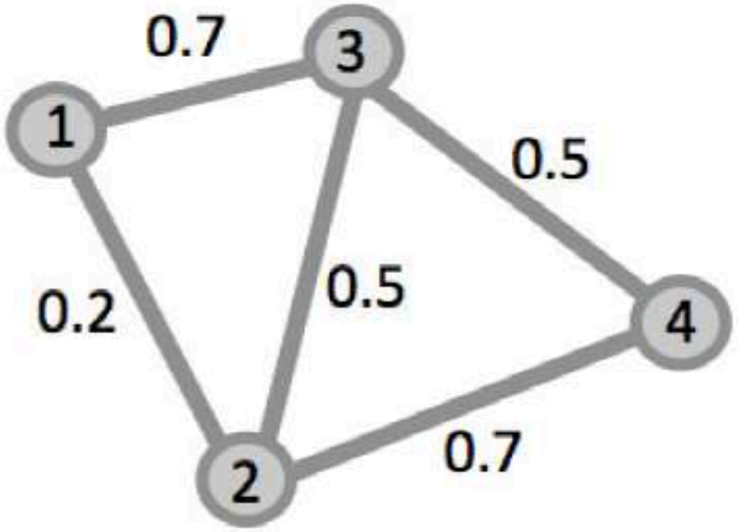


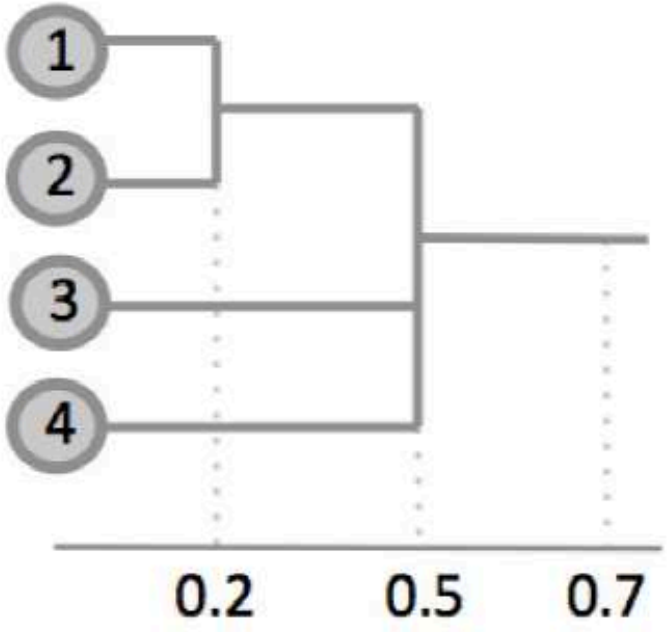
$$D_l(\mathcal{X}^1, \mathcal{X}^2) = \infty \qquad D_\infty(\mathcal{X}^1, \mathcal{X}^2) = \infty$$

Gromov-Hausdorff distance

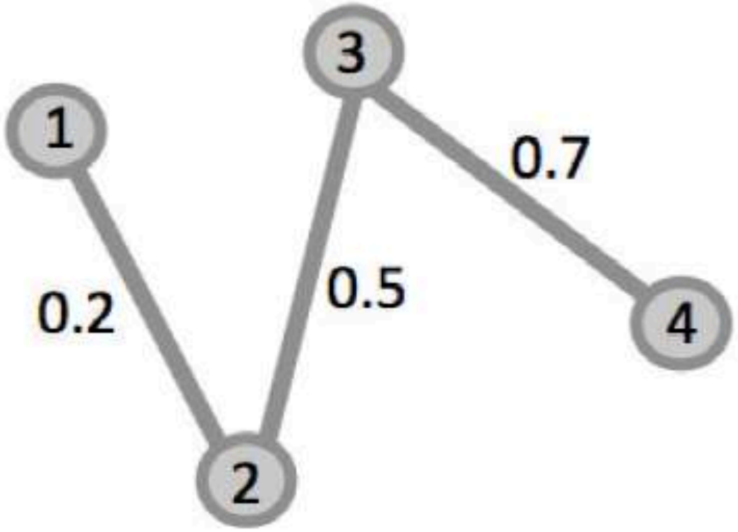
Lee et al., 2011 MICCAI 6892:302-309
Lee et al. 2012 IEEE Transactions on Medical Image 31:2267-2277

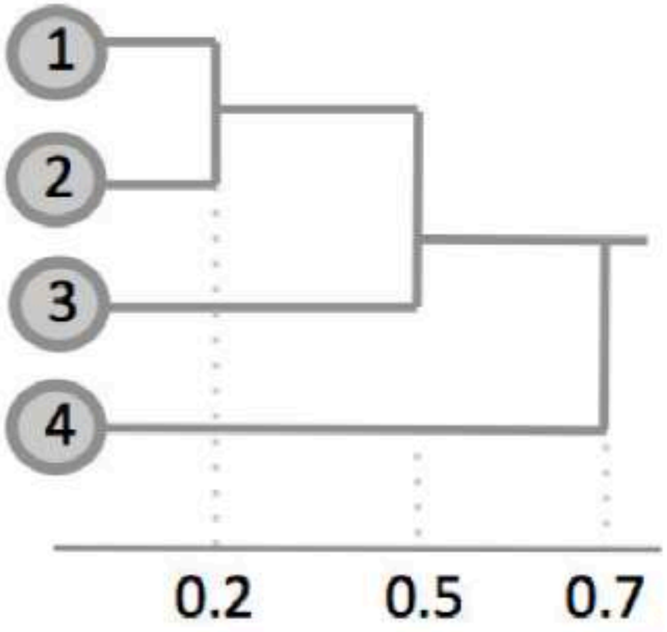
Single linkage distance (SLD)





$$\begin{matrix} 0 & 0.2 & 0.5 & 0.5 \\ 0.2 & 0 & 0.5 & 0.5 \\ 0.5 & 0.5 & 0 & 0.5 \\ 0.5 & 0.5 & 0.5 & 0 \end{matrix}$$





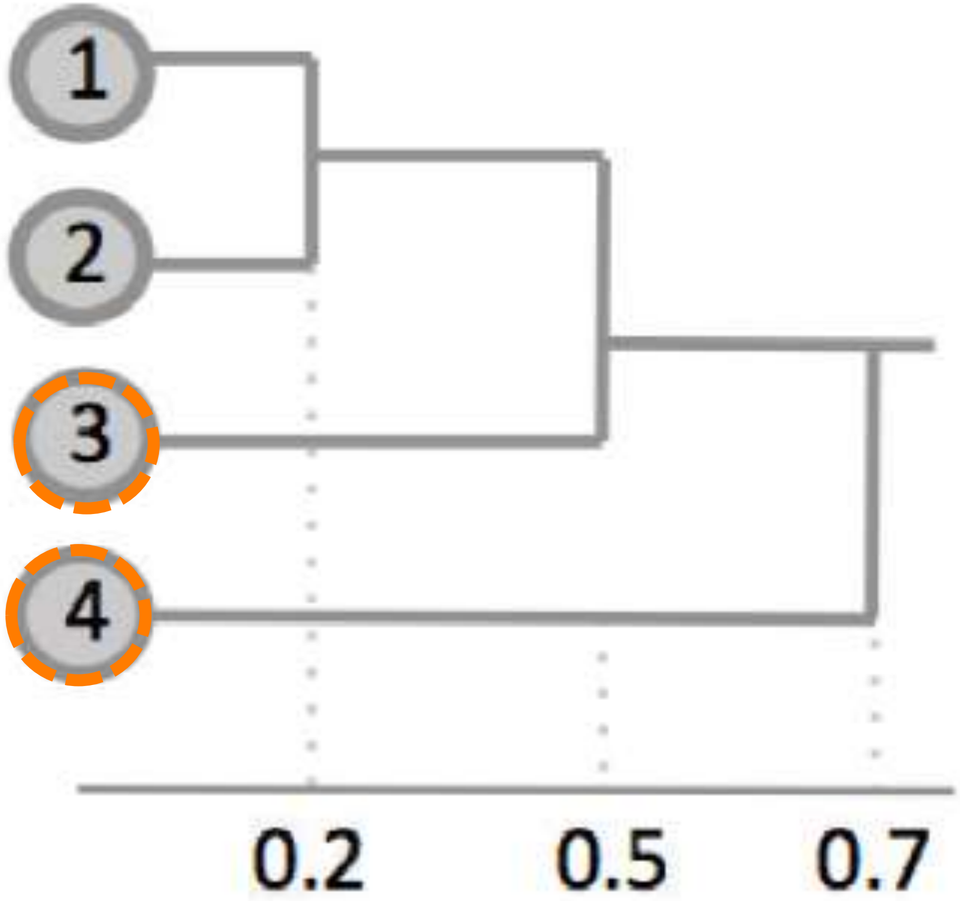
$$\begin{matrix} 0 & 0.2 & 0.5 & 0.7 \\ 0.2 & 0 & 0.5 & 0.7 \\ 0.5 & 0.5 & 0 & 0.7 \\ 0.7 & 0.7 & 0.7 & 0 \end{matrix}$$

dendrogram

SLD $s = (s_{ij})$

Single linkage distance (SLD)

ultrametric $s_{ij} \leq \max(s_{ik}, s_{kj})$



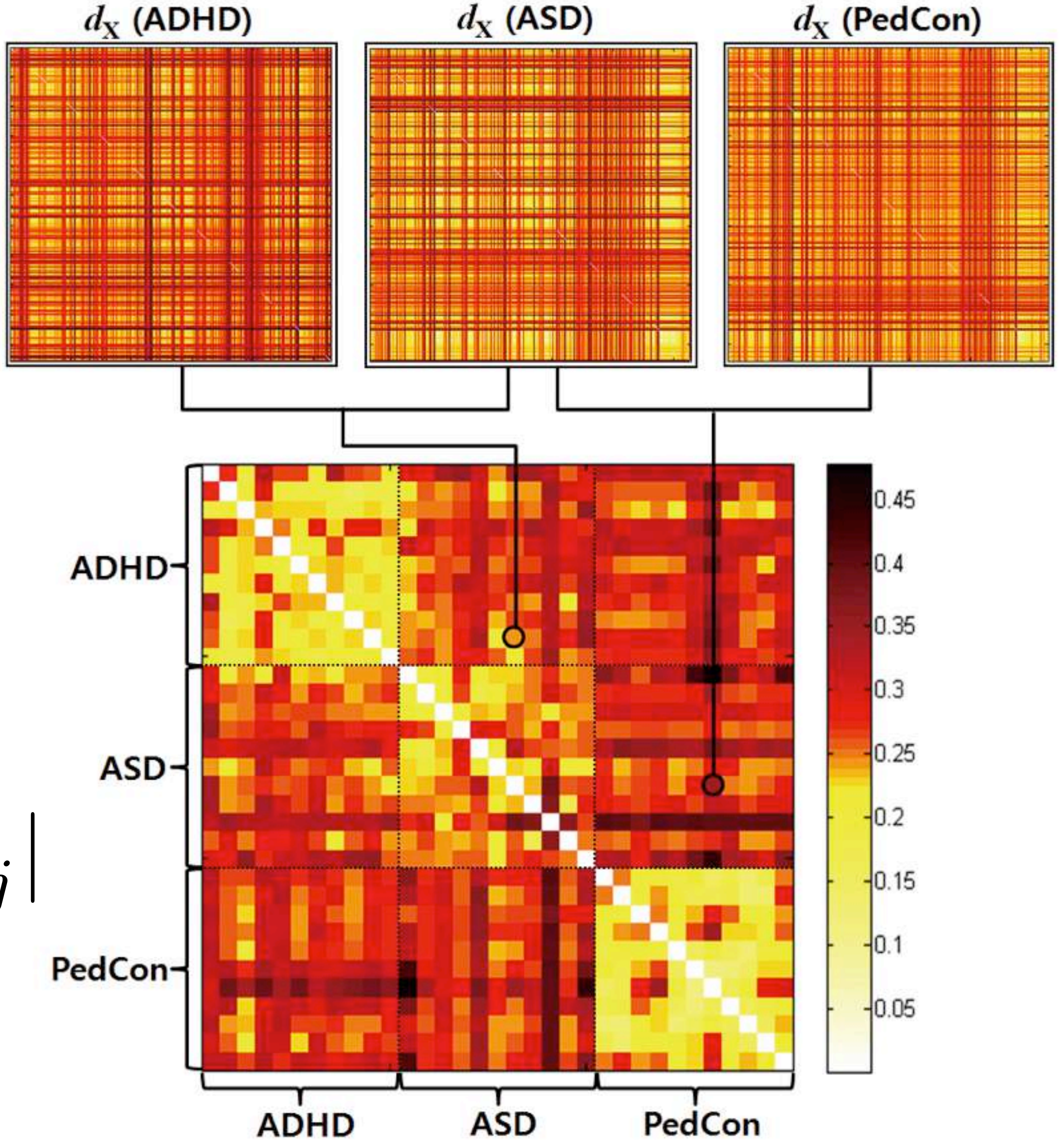
$$\begin{matrix} 0 & 0.2 & 0.5 & 0.7 \\ 0.2 & 0 & 0.5 & 0.7 \\ 0.5 & 0.5 & 0 & 0.7 \\ 0.7 & 0.7 & 0.7 & 0 \end{matrix}$$

Gromov-Hausdorff distance between networks

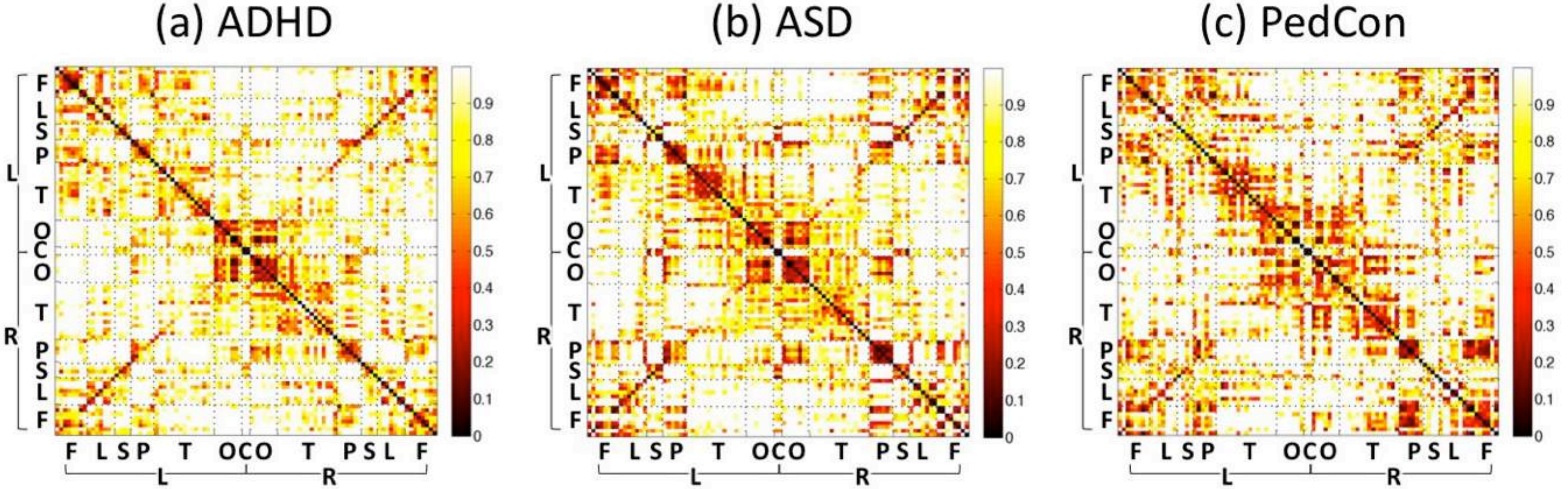
Single linkage distance

$$D_{GH}(\mathcal{D}^1, \mathcal{D}^2)$$

$$= \quad \frac{1}{2} \max_{\forall i,j} |s^1_{ij} - s^2_{ij}|$$



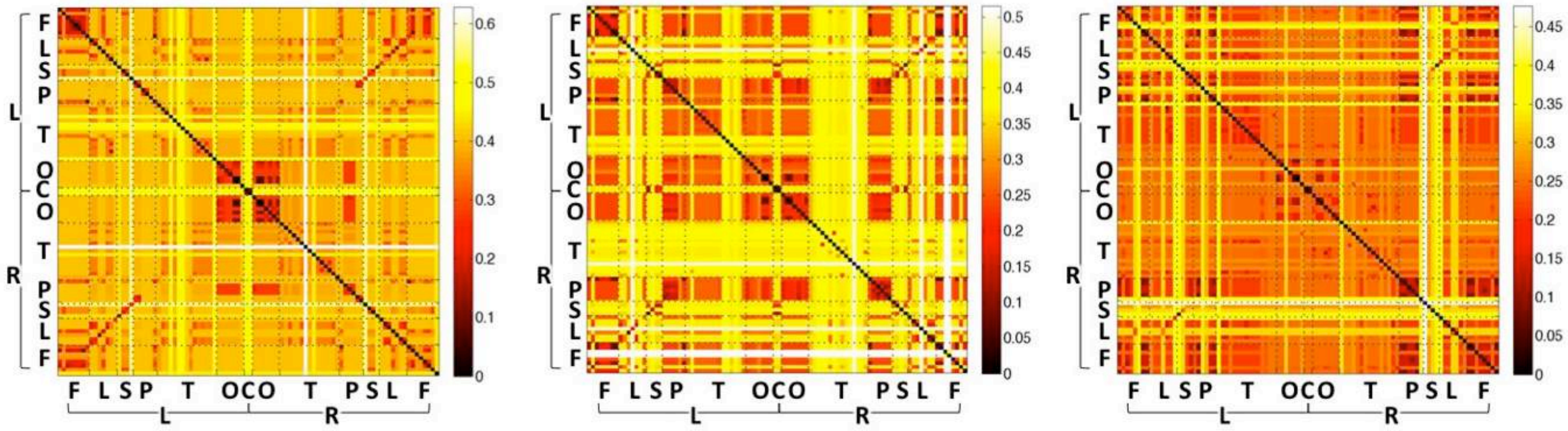
Connectivity matrix of brain network


(a) ADHD

(b) ASD

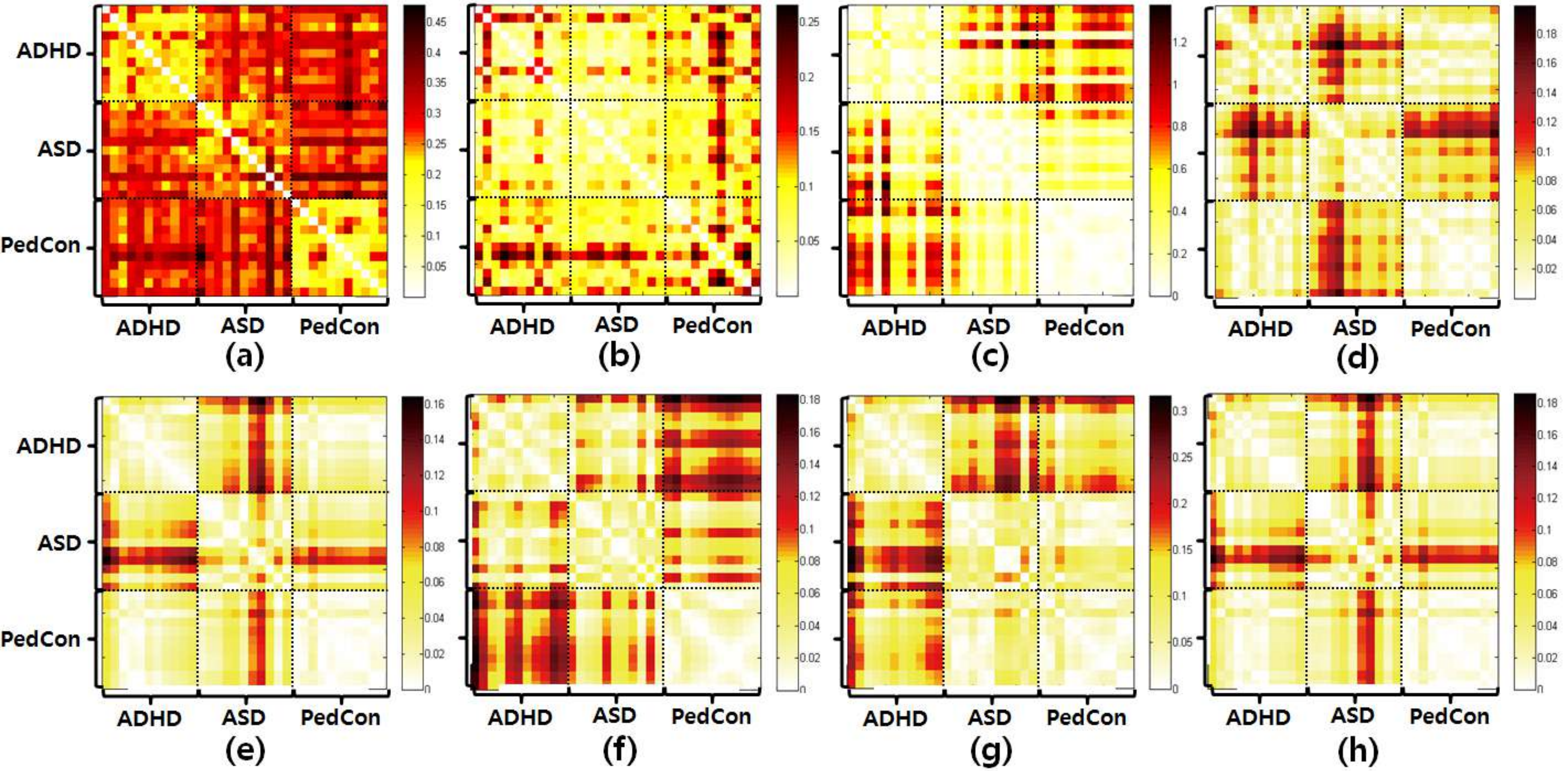
(c) PedCon

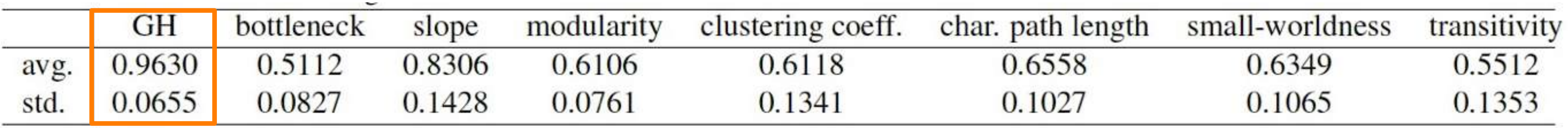
(d) Pairwise Distance Matrix = 1 - correlation



(e) Single Linkage

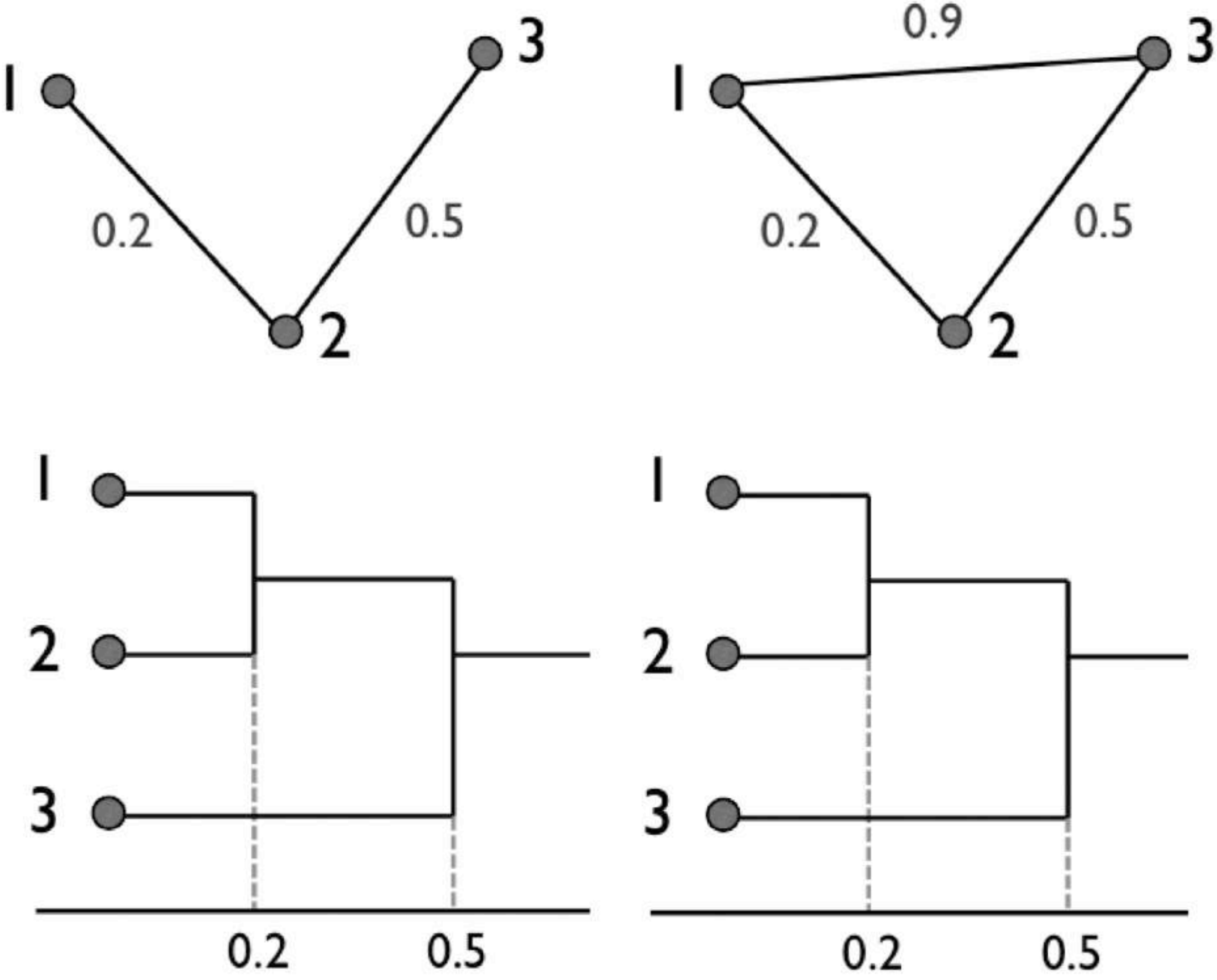
Clustering accuracy on PET correlation network





	GH	bottleneck	slope	modularity	clustering coeff.	char. path length	small-worldness	transitivity
avg.	0.9630	0.5112	0.8306	0.6106	0.6118	0.6558	0.6349	0.5512
std.	0.0655	0.0827	0.1428	0.0761	0.1341	0.1027	0.1065	0.1353

Limitation of GH-distance

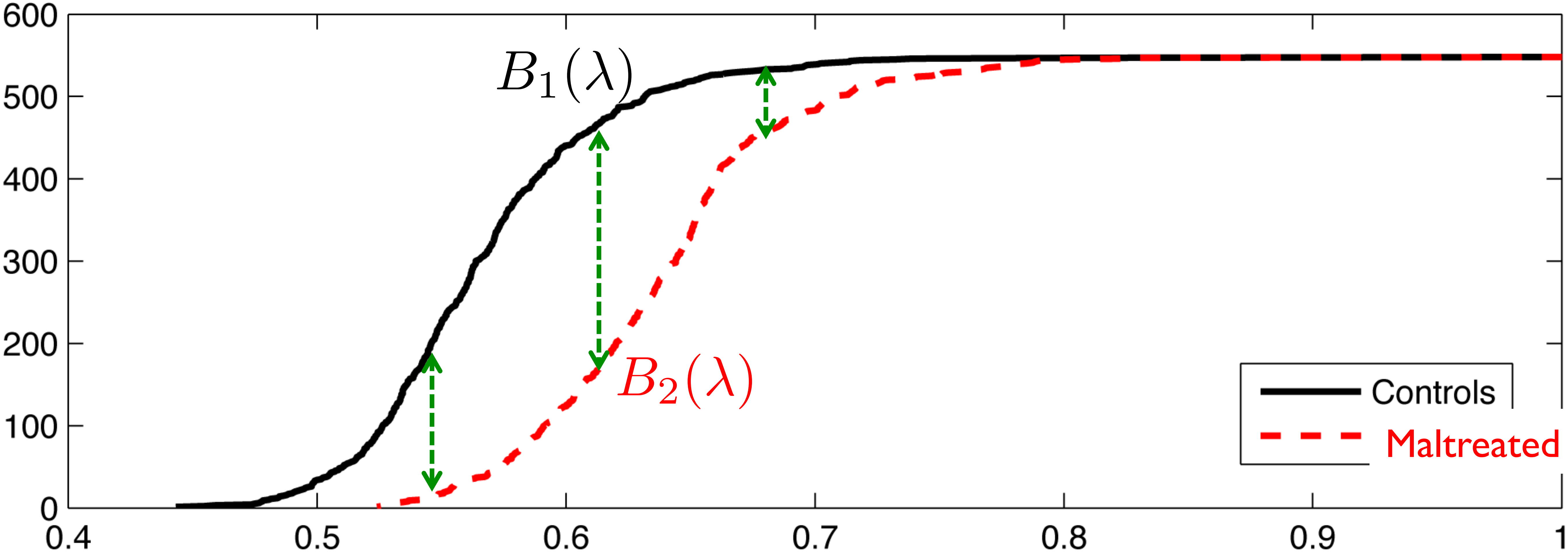


Need to design new topological distances

Kolmogorov-Smirnov (KS) distance

Chung, M.K. et al. 2017
Exact topological inference for paired brain networks via persistent homology. Information Processing in Medical Imaging (IPMI) 10265:299-310

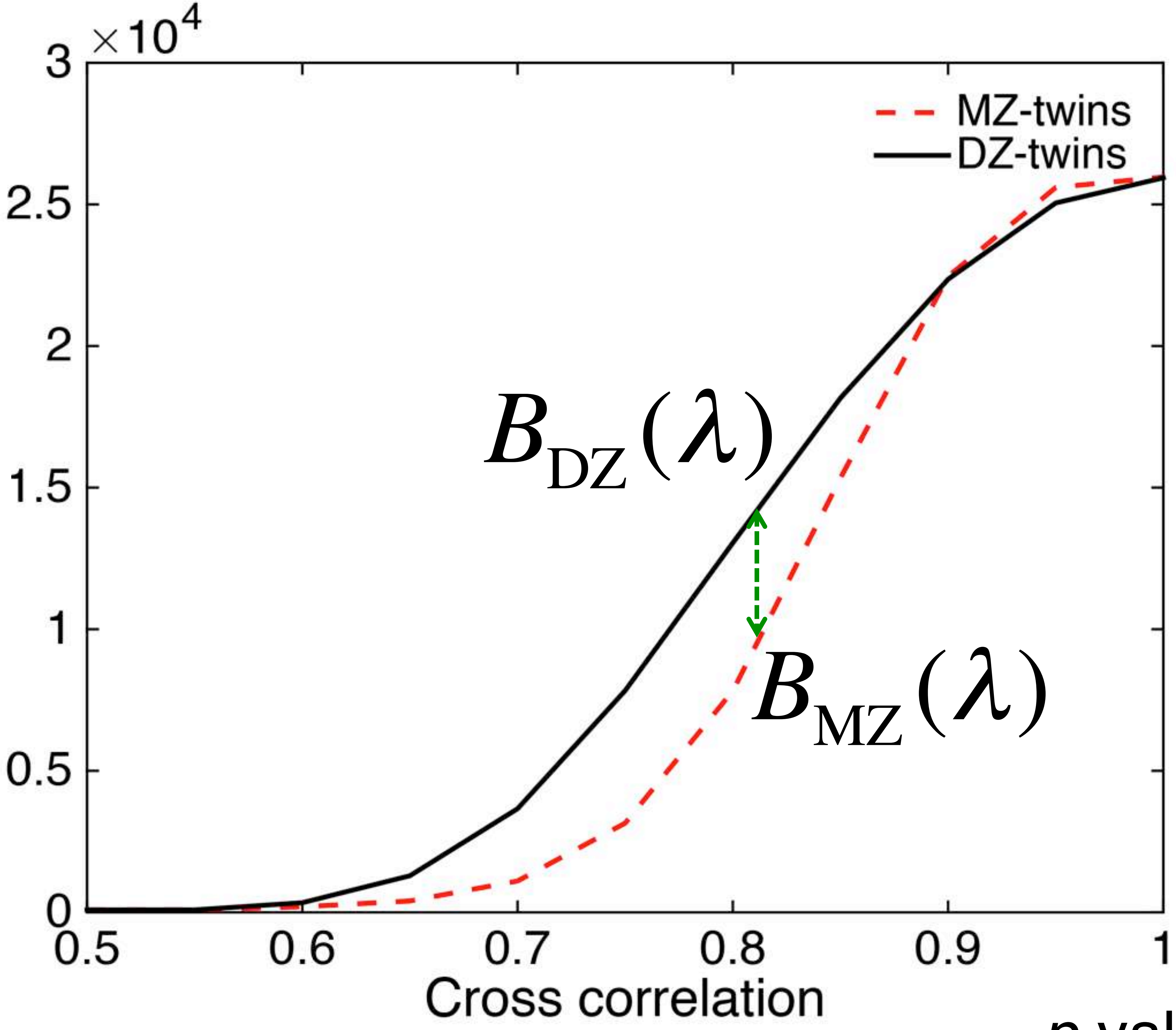
Betti-0 plot on FA correlations



KS-distance: $\max_{\lambda} |B_1(\lambda) - B_2(\lambda)|$

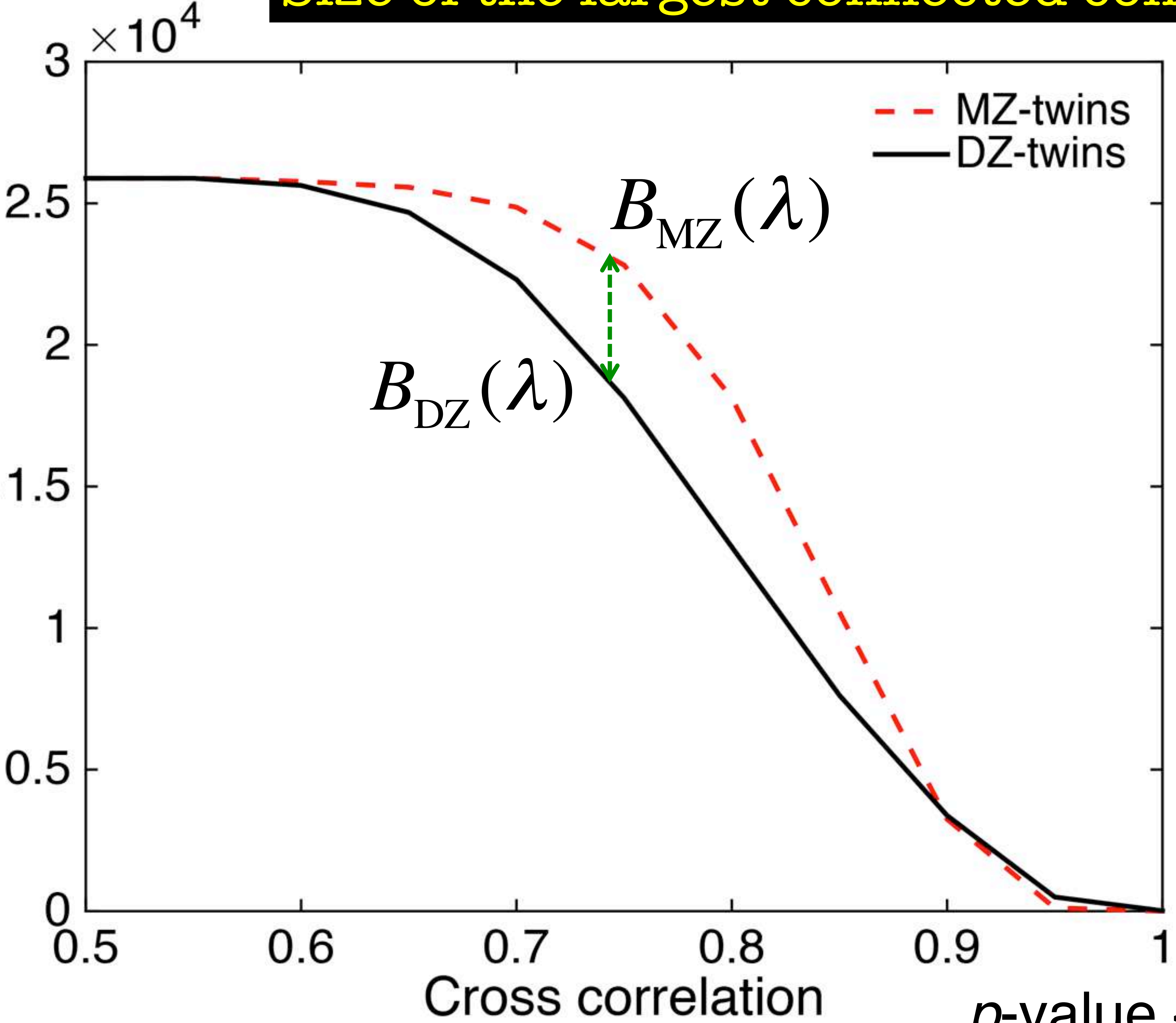
p-value <0.0001

Number of connected components



p-value < 0.0002

Size of the largest connected component



p-value < 0.0001

Exact permutation test

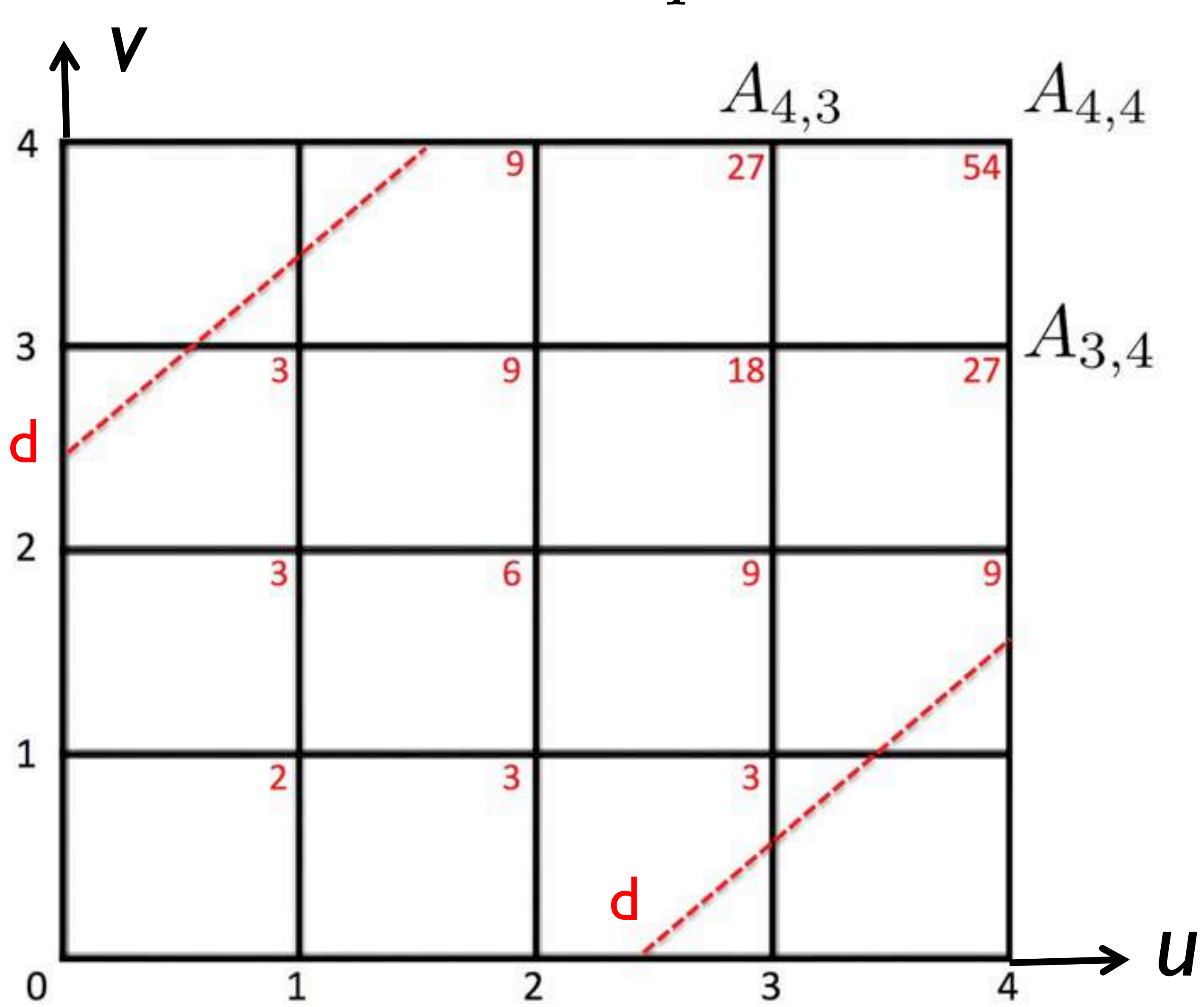
Theorem 1.

$$D_q = \sup_{1 \le j \le q} \left| B(G^1_{\lambda_j}) - B(G^2_{\lambda_j}) \right|$$

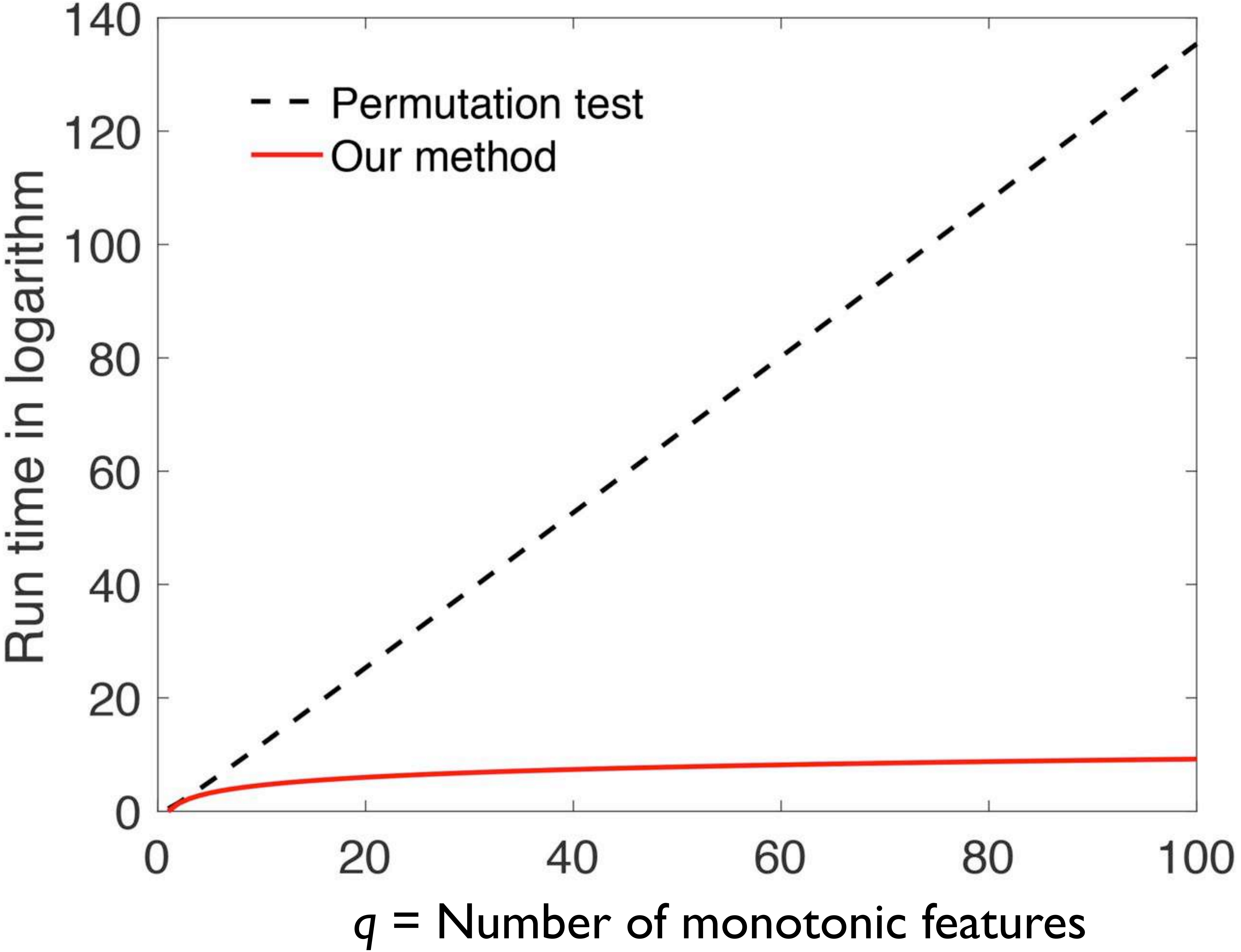
$$P(D_q \ge d) = 1 - \frac{A_{q,q}}{\binom{2q}{q}}$$

$$A_{u,v} = A_{u-1,v} + A_{u,v-1}$$

$$|u - v| < d$$

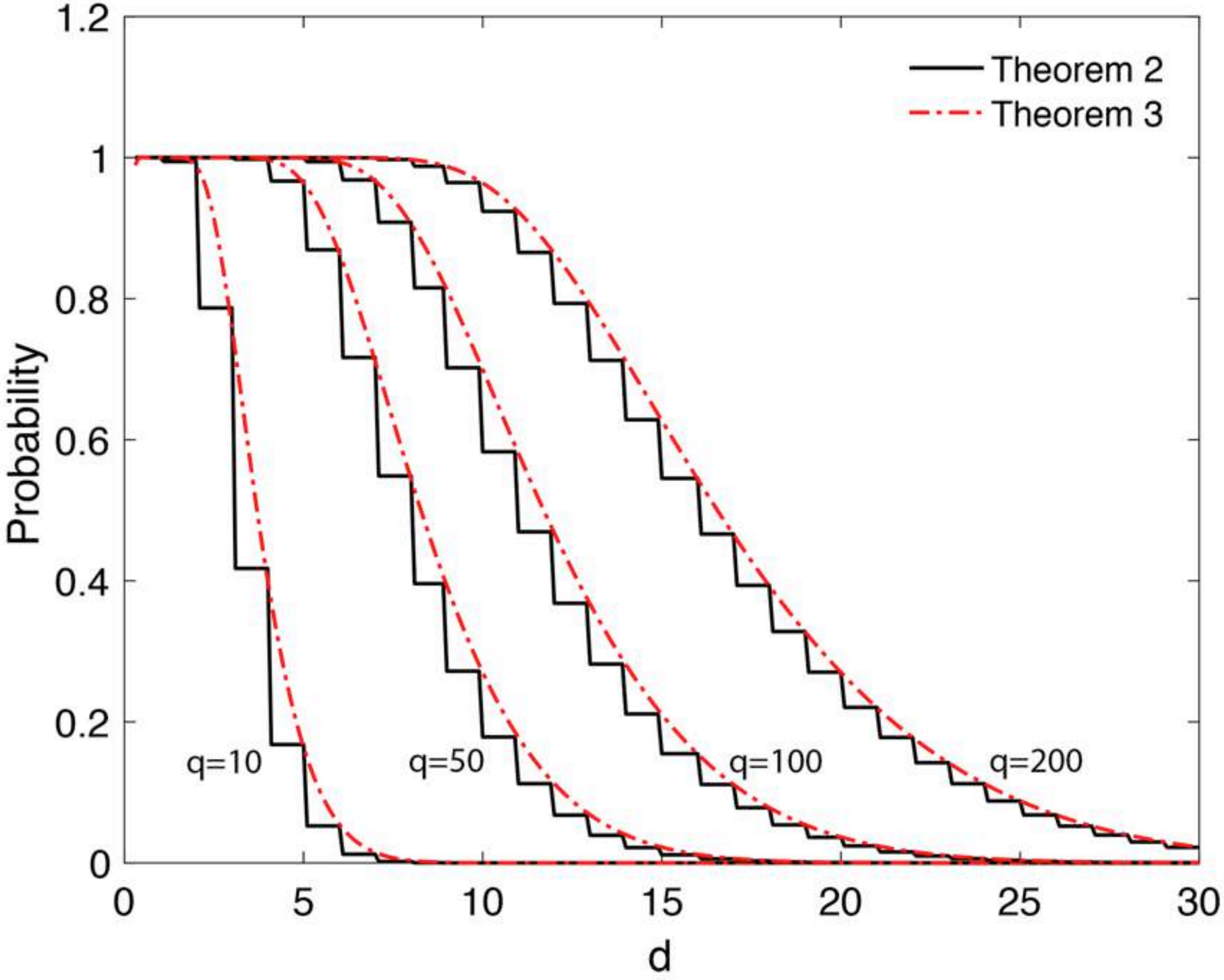


MATLAB codes:
www.stat.wisc.edu/~mchung/twins


Permutation test
Our method
Run time in logarithm
140
120
100
80
60
40
20
0
0
20
40
60
80
100
q = Number of monotonic features

Theorem 2.

$$\lim_{q\to\infty} P\left(D_q/\sqrt{2q} \geq d\right) = 2\sum_{i=1}^{\infty}(-1)^{i-1}e^{-2i^2d^2}$$



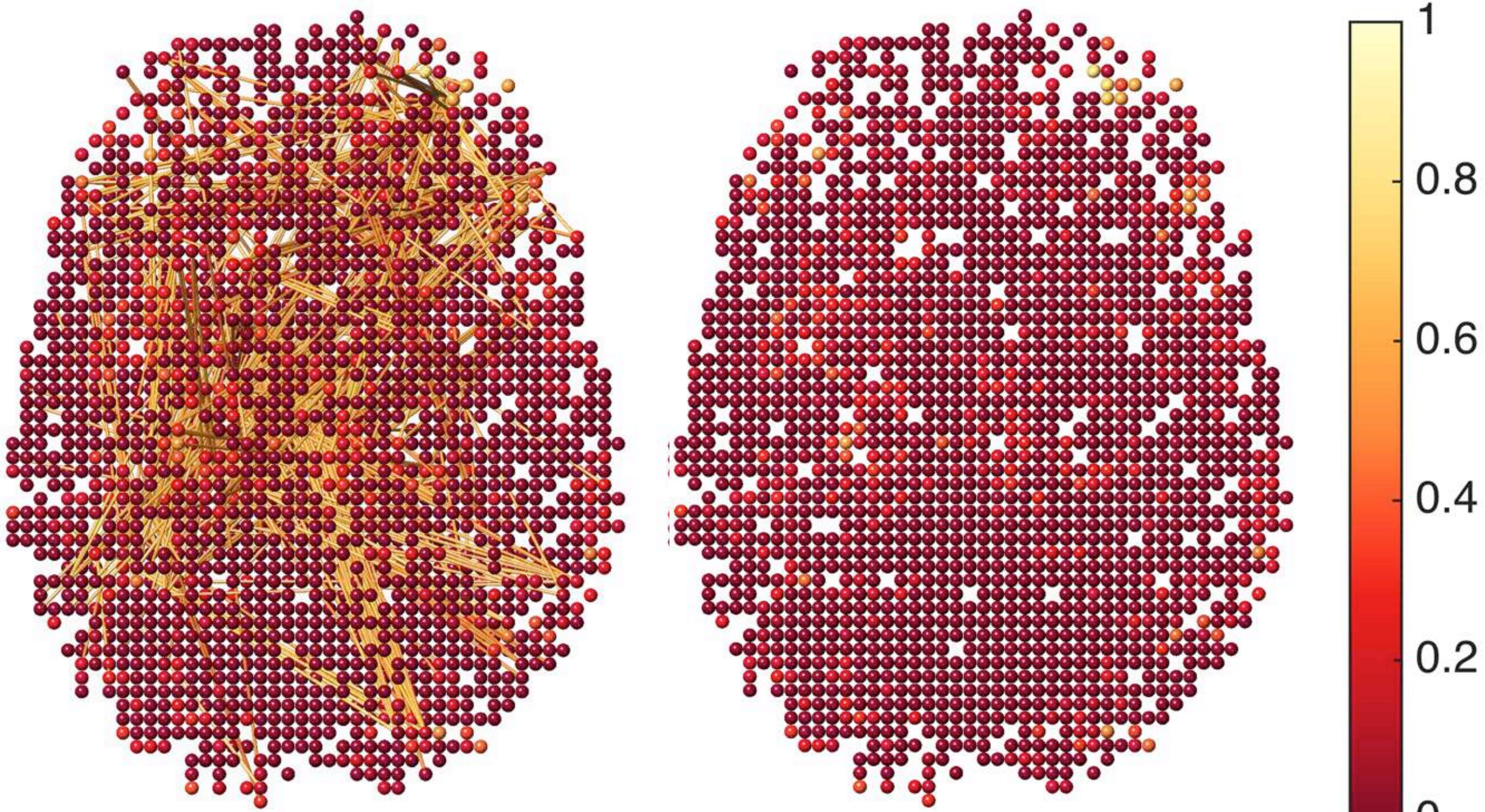
MATLAB codes:

www.stat.wisc.edu/~mchung/twins

Validations

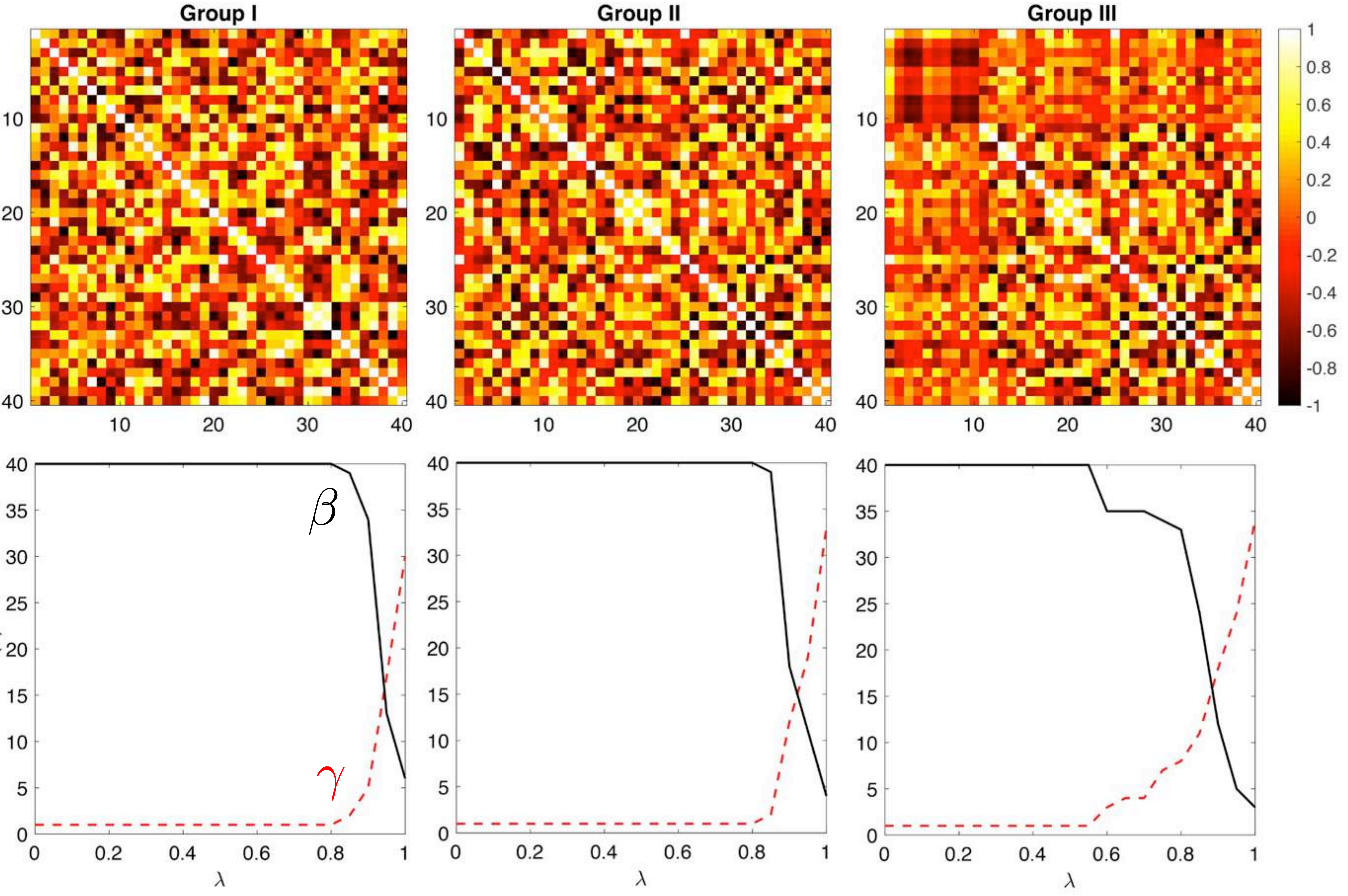
Null data check:

Network of random pairs in two group comparison



parameter 0.5 parameter 0.7

Random graph simulations



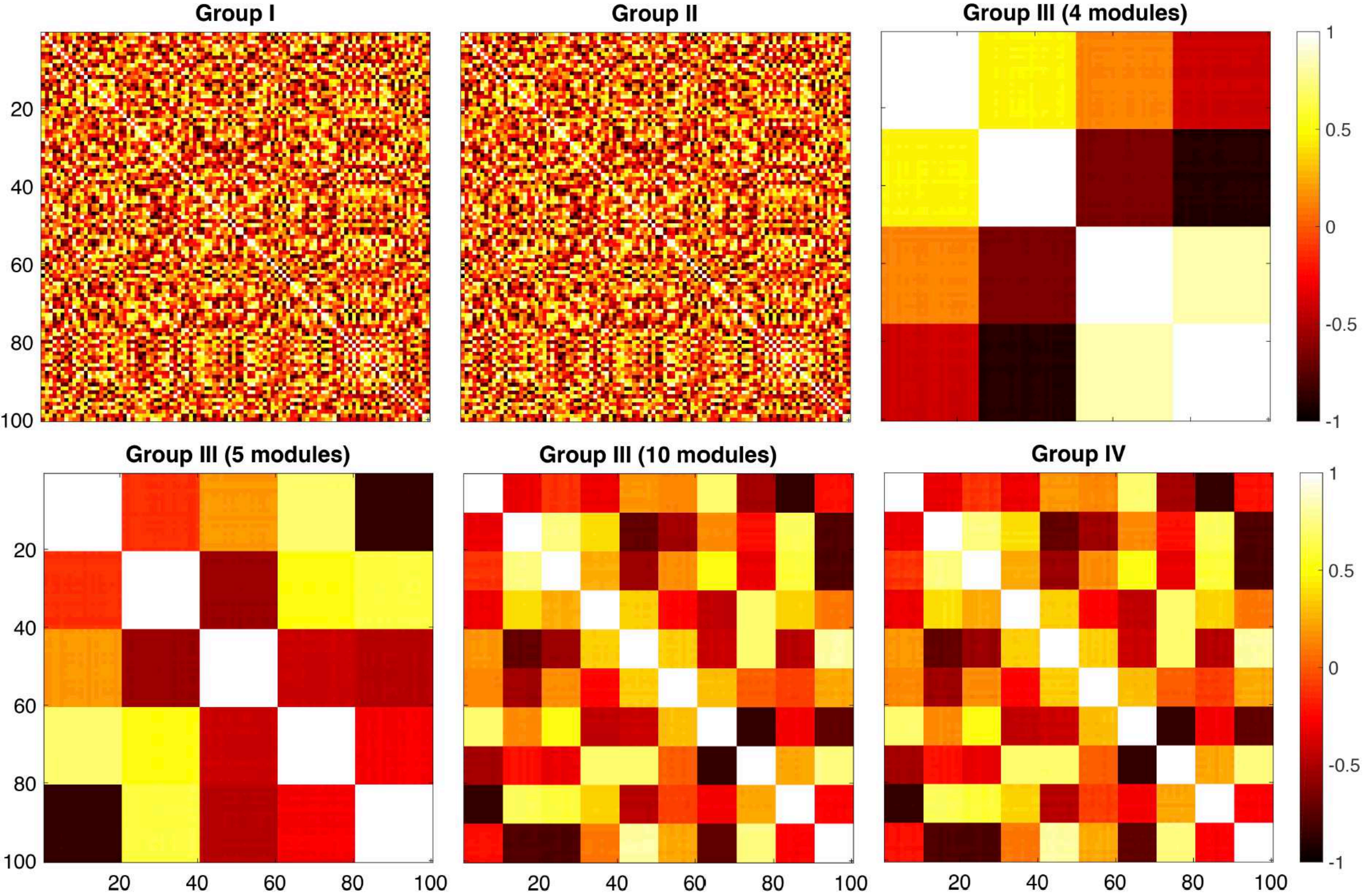
Simulating modular structure

$$\mathbf{x}_i = N(0, I)$$

$$\mathbf{y}_i = 0.5\mathbf{x}_{ci+1} + N(0, \sigma^2 I)$$

module size:
c number of nodes

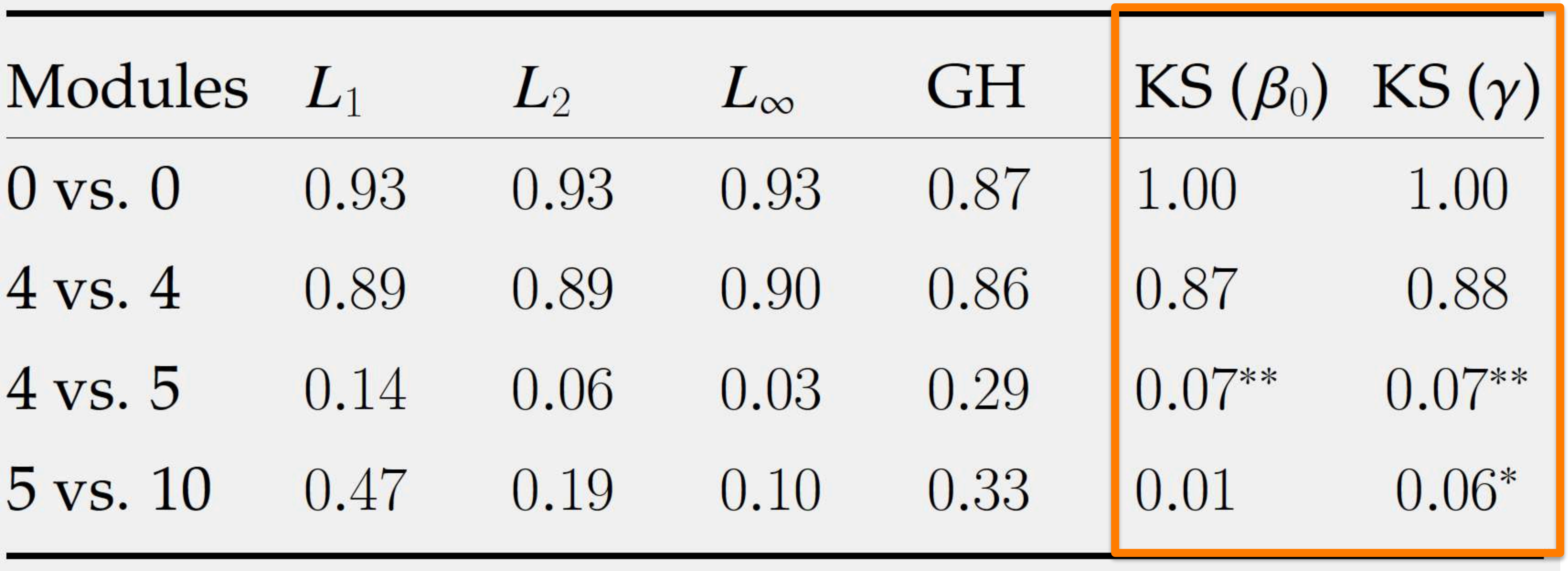
Simulations on modular structures



p-values on network distances

No diff.

Diff.



Modules	L_1	L_2	L_∞	GH	KS (β_0)	KS (γ)
0 vs. 0	0.93	0.93	0.93	0.87	1.00	1.00
4 vs. 4	0.89	0.89	0.90	0.86	0.87	0.88
4 vs. 5	0.14	0.06	0.03	0.29	0.07^{**}	0.07^{**}
5 vs. 10	0.47	0.19	0.10	0.33	0.01	0.06^{*}

$* = \text{x}10^{-3}$

$** = \text{x}10^{-4}$