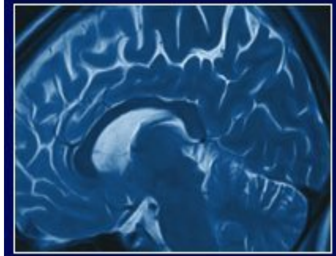
University of Wisconsin
SCHOOL OF MEDICINE
AND PUBLIC HEALTH



The Waisman Laboratory
for Brain Imaging and Behavior

Mapping Heritability of Large-Scale Brain Networks *via* Persistent Homology

Moo K. Chung

Dept. of Biostatistics and Medical Informatics
Waisman Lab. for Brain Imaging and Behavior
University of Wisconsin-Madison

www.stat.wisc.edu/~mchung

Collaborators

Paul J. Rathouz

Department of Biostatistics and Medical Informatics
University of Wisconsin-Madison

Victoria Vilalta-Gil, David H. Zald

Department of Psychology
Vanderbilt University

Benjamin B. Lahey

Department of Public Health Sciences
University of Chicago

Aims

1) Large-scale brain networks where all the voxels are network nodes

2) Heritability of the large-scale networks

3) Persistent homology

Large scale functional network

fMRI dataset

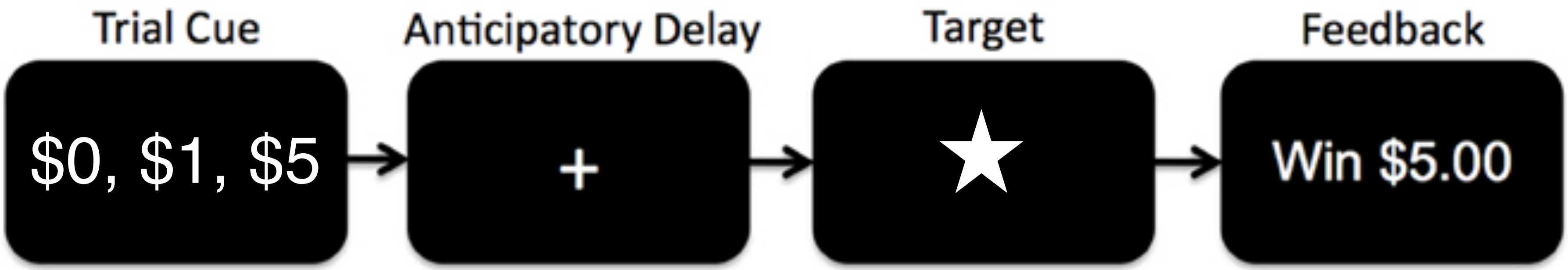
Subset of *Tennessee twin study* with 200 twins

11 monozygotic (MZ) twins

14 dizygotic (DZ) twins

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

Monetary incentive delay task



3 runs of 40 trials

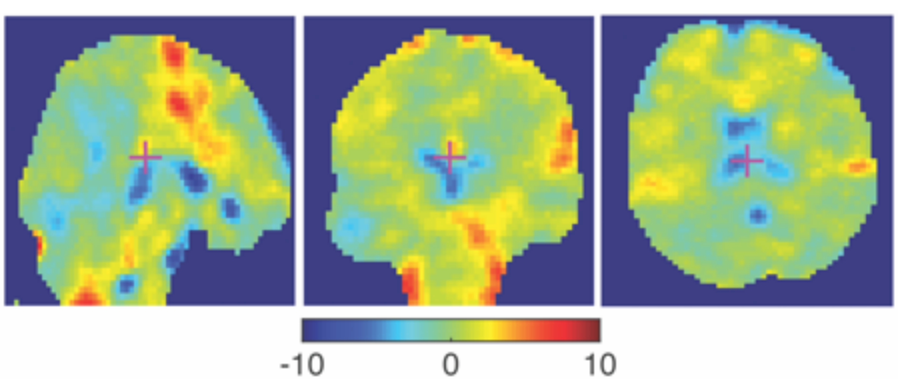
GLM

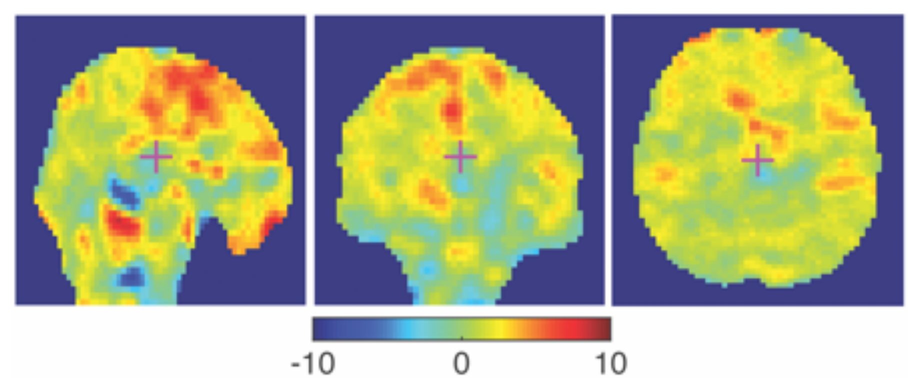
$$Y(v_i) = Xb(v_i) + \varepsilon(v_i)$$

delay for $0 trials
delay for $1 trials
delay for $5 trials

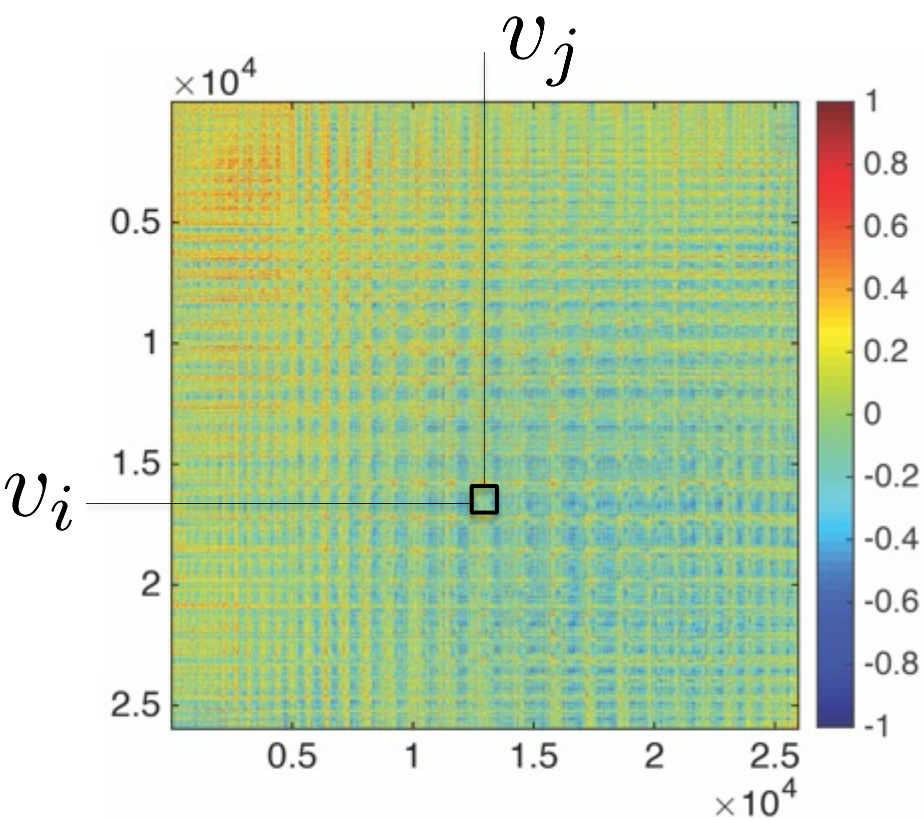
c

$c^T b(v_i)$ Contrast map





Small-*n* and large-*p* problem



0.67 billion connections
5.2GB memory
3min to save to hard drive

Our method:
18 sec. computation

p=25972 voxels in the template
25972 x 25972 = **0.67 billion connections**

Sparse networks

Existing sparse network models cannot construct networks with billion connections.

Center and scale data

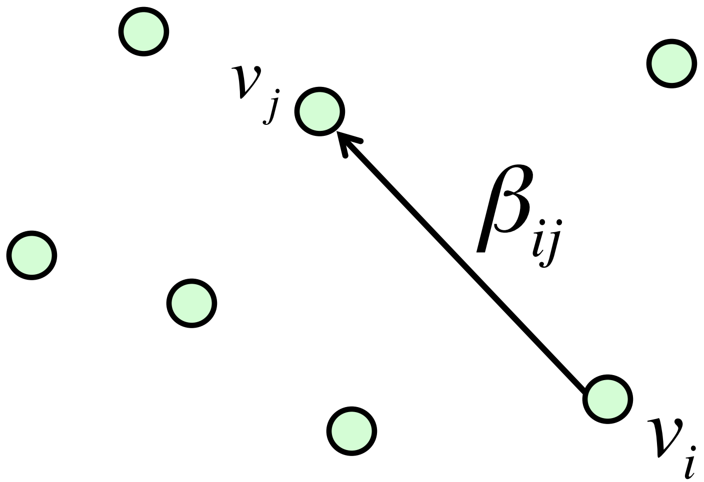
k-th paired images at voxel v_i : $x_k(v_i)$ $y_k(v_i)$

$$x = (x_1, x_2 \cdots, x_n)' \qquad y = (y_1, y_2, \cdots, y_n)'$$

$$\sum_{k=1}^{n} x_k(v_i) = \sum_{k=1}^{n} y_k(v_i) = 0$$

$$\|x\|^2 = x'x = \|y\|^2 = y'y = 1$$

Regression between voxels across twins



$$y(v_j) = \beta_{ij} x(v_i) + \varepsilon$$

Least-squares estimation:

$$\hat{\beta} = \operatorname{argmin}_{\beta} \sum_{i=1}^{p} \sum_{j=1}^{p} \left\| x(v_i) - \beta_{ij} y(v_j) \right\|^2$$

$$\hat{\beta}_{ij} = x'(v_i) y(v_j)$$

Sample cross-correlation

Sparse cross-correlation network

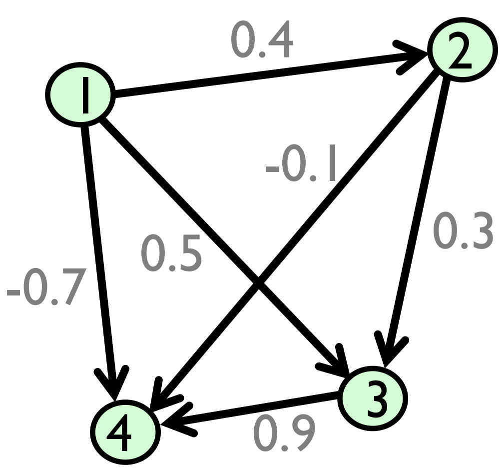
$$\hat{\beta} = \operatorname{argmin}_{\beta} \ \frac{1}{2}\sum_{i=1}^{p}\sum_{j=1}^{p}\left\| x(v_i) - \beta_{ij} y(v_j) \right\|^2 + \lambda \sum_{i,j} |\beta_{ij}|$$

Sample cross-correlation

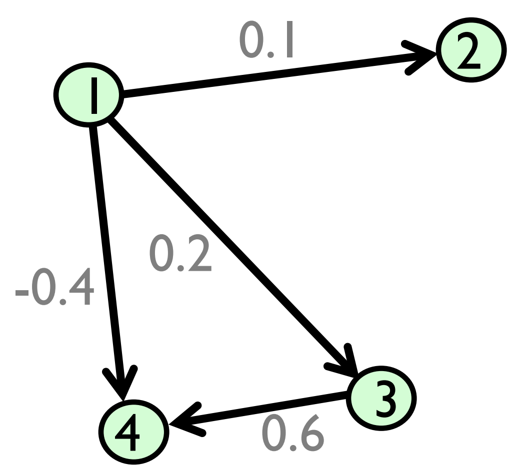
$$\begin{pmatrix} \times & 0.4 & 0.5 & -0.7 \\ \times & \times & 0.3 & -0.1 \\ \times & \times & \times & 0.9 \end{pmatrix}$$

Adjacency matrix

$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } \hat{\beta}_{ij} \neq 0 \\ 0 \text{ otherwise} \end{cases}$$



λ=0.3



Sparse network without optimization

Numerical optimization

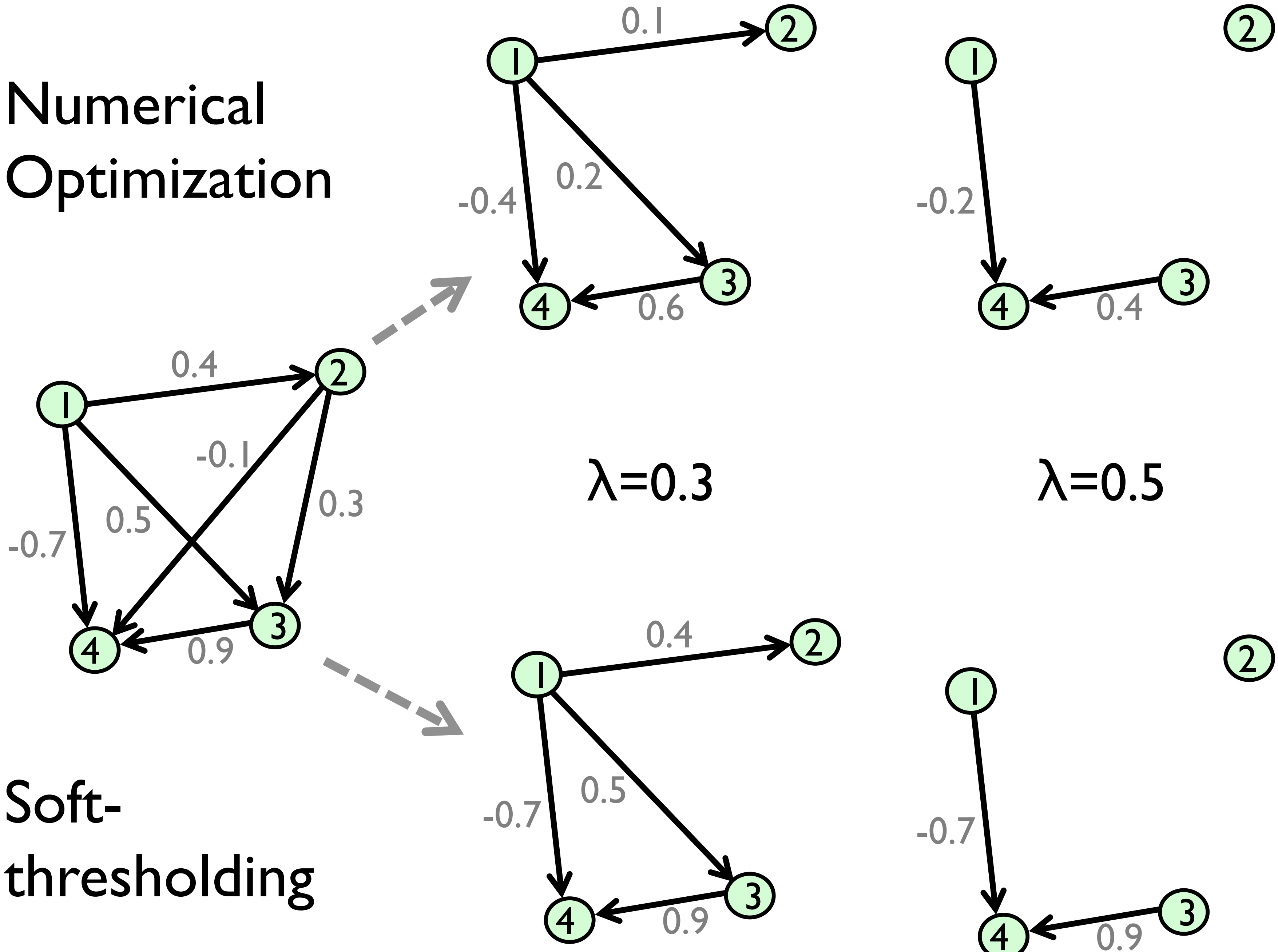
$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } \hat{\beta}_{ij}(\lambda) \neq 0 \\ 0 \text{ otherwise} \end{cases}$$

Soft-thresholding

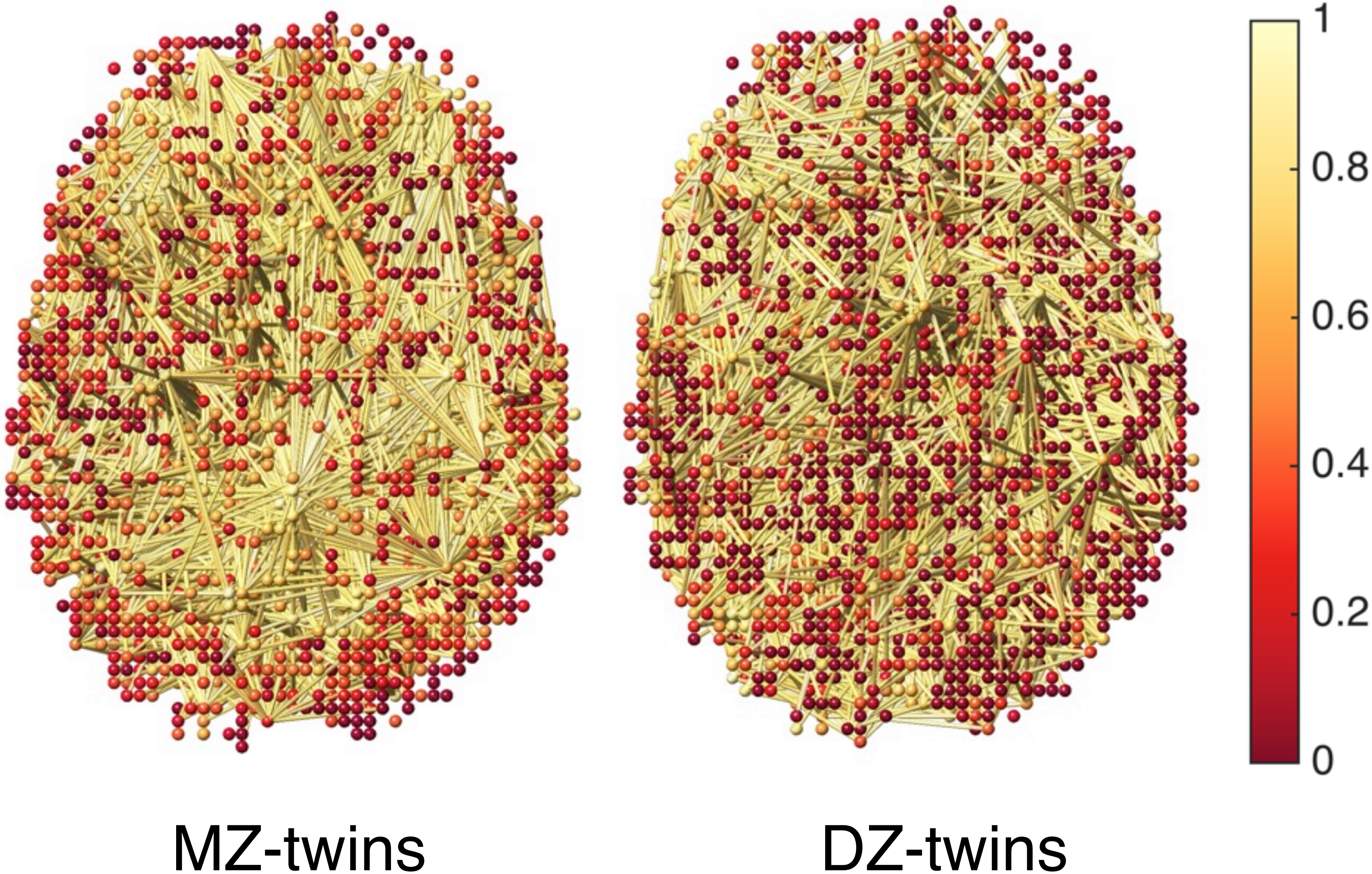
$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } \left| x'(v_i) y(v_j) \right| > \lambda \\ 0 \text{ otherwise} \end{cases}$$

10000 times faster!

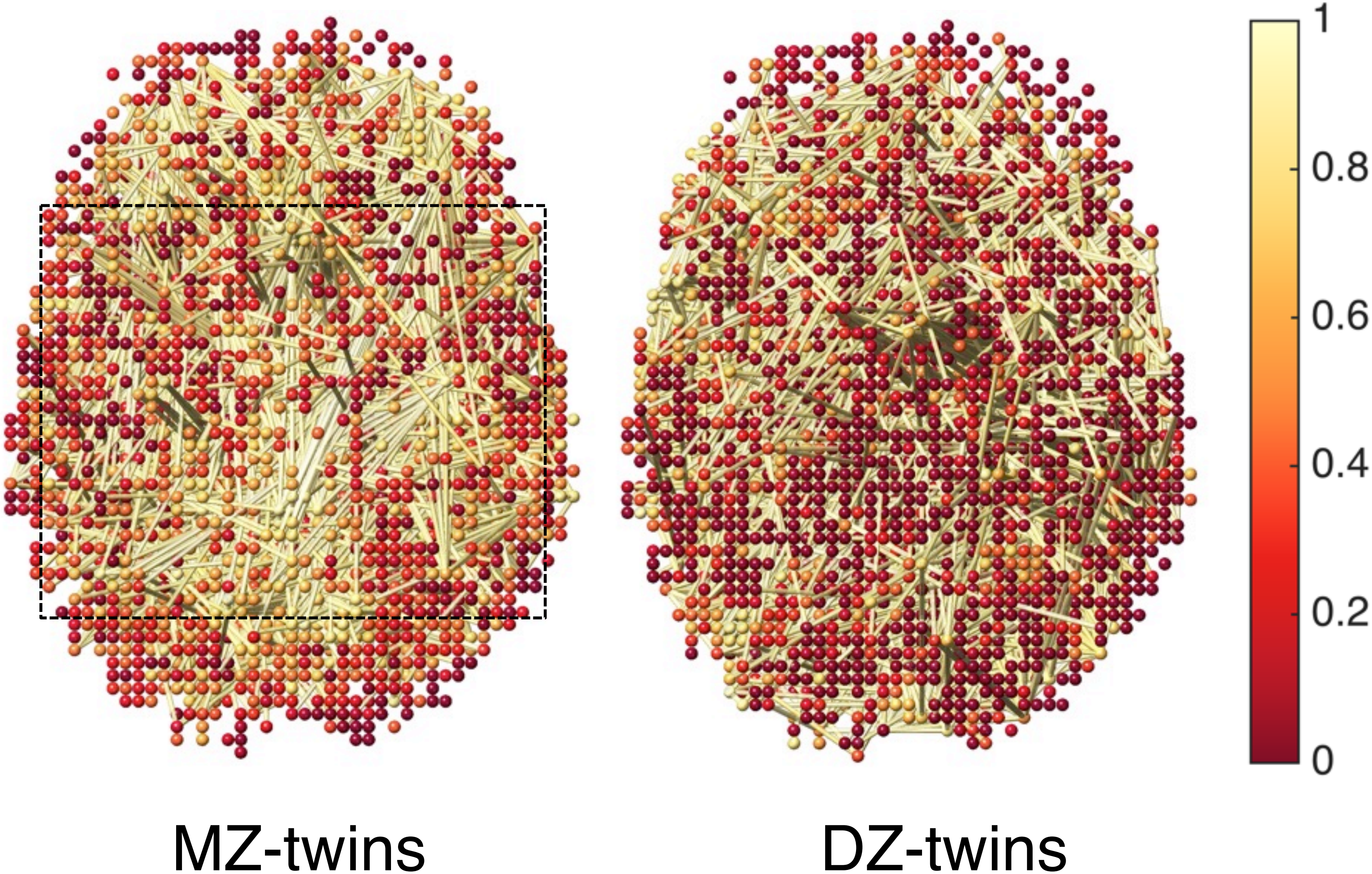
[*Chung et al. 2015 IEEE Transactions on Medical Imaging* 34:1928-1939]


Numerical
Optimization
Soft-
thresholding
λ=0.3
λ=0.5
0.4
-0.1
0.3
-0.7
0.5
0.9
0.1
0.2
-0.4
0.6
-0.2
0.4
0.4
0.5
-0.7
0.9
-0.7
0.9

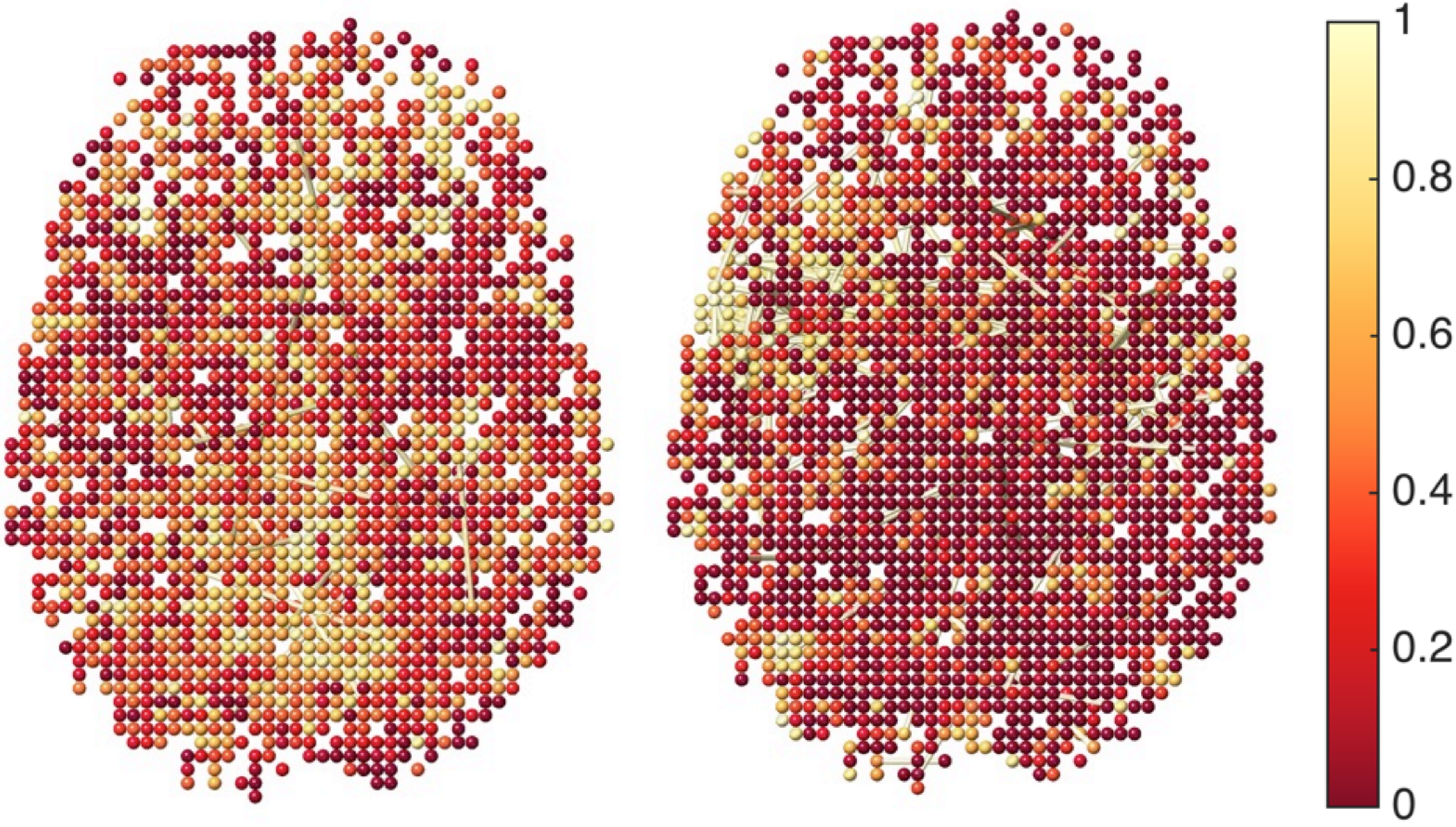
Network at sparse parameter 0.7



Network at sparse parameter 0.8

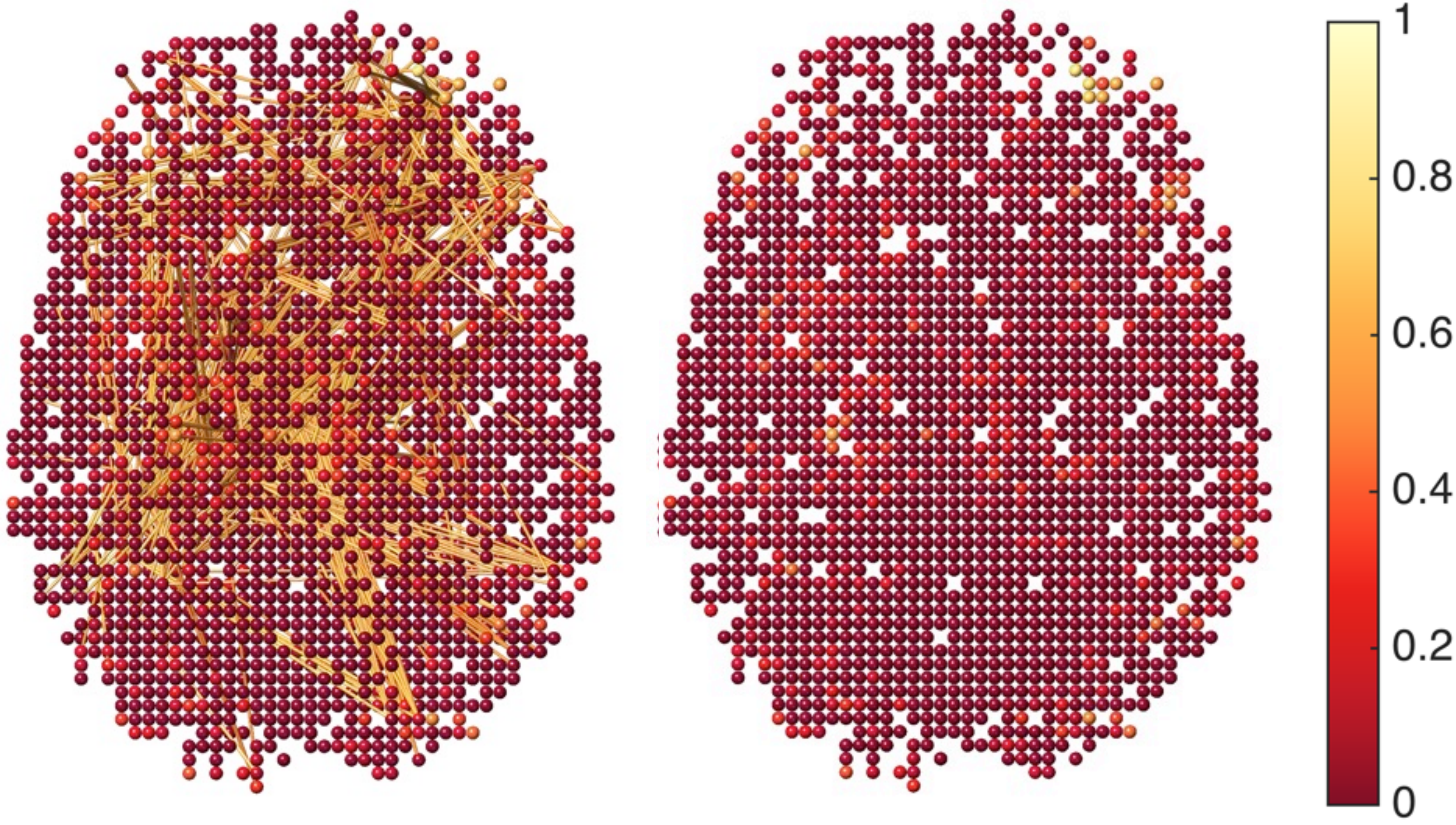


Network at sparse parameter 0.9



MZ-twins DZ-twins

Sanity check: Network of random pairs



parameter 0.5 parameter 0.7

Heritability graph index

ACE model

MZ-twins share 100% of genes
DZ-twins share 50% of genes

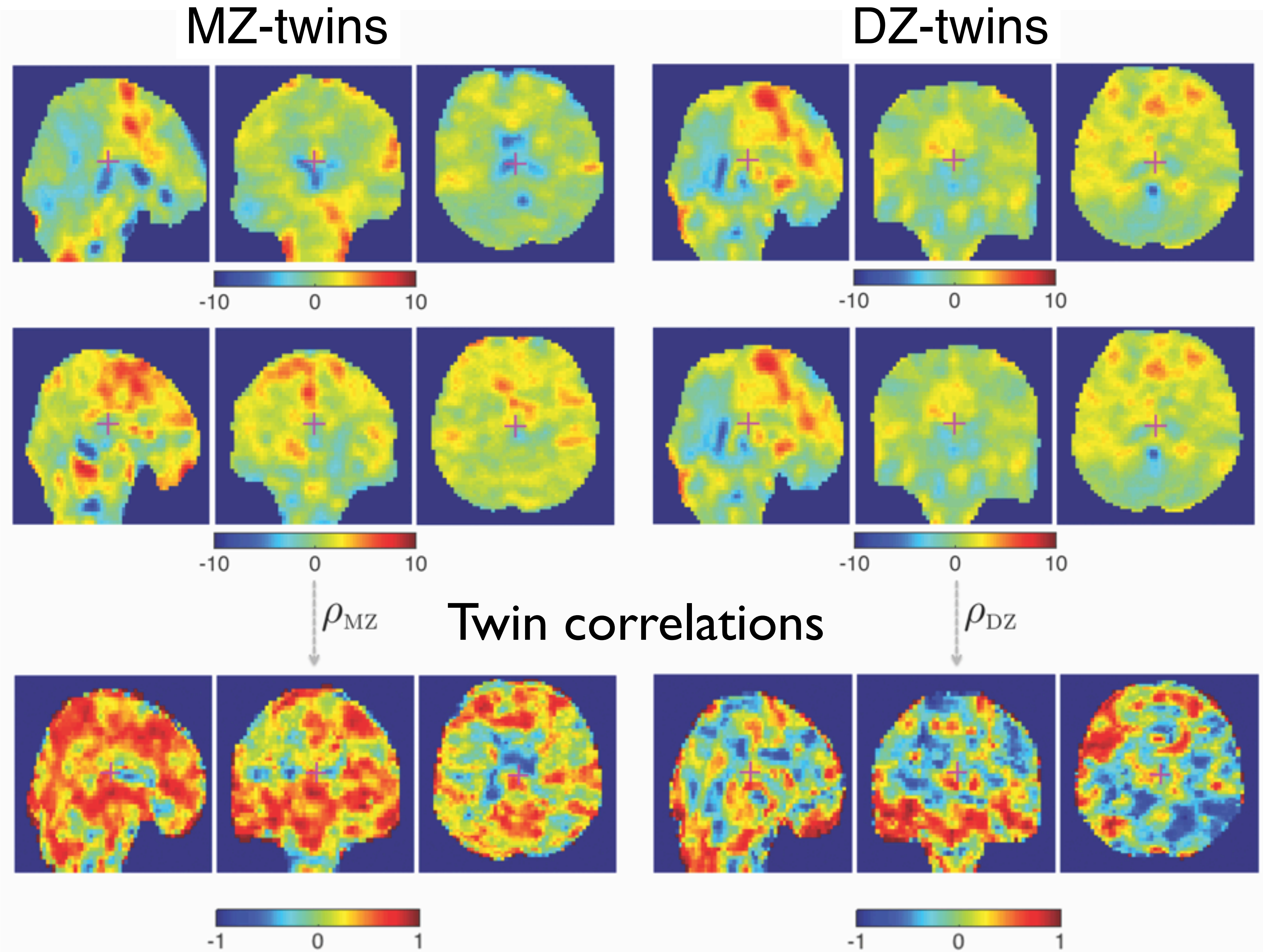
$$\rho_{MZ} = A + C$$

Additive genetics — Common environment

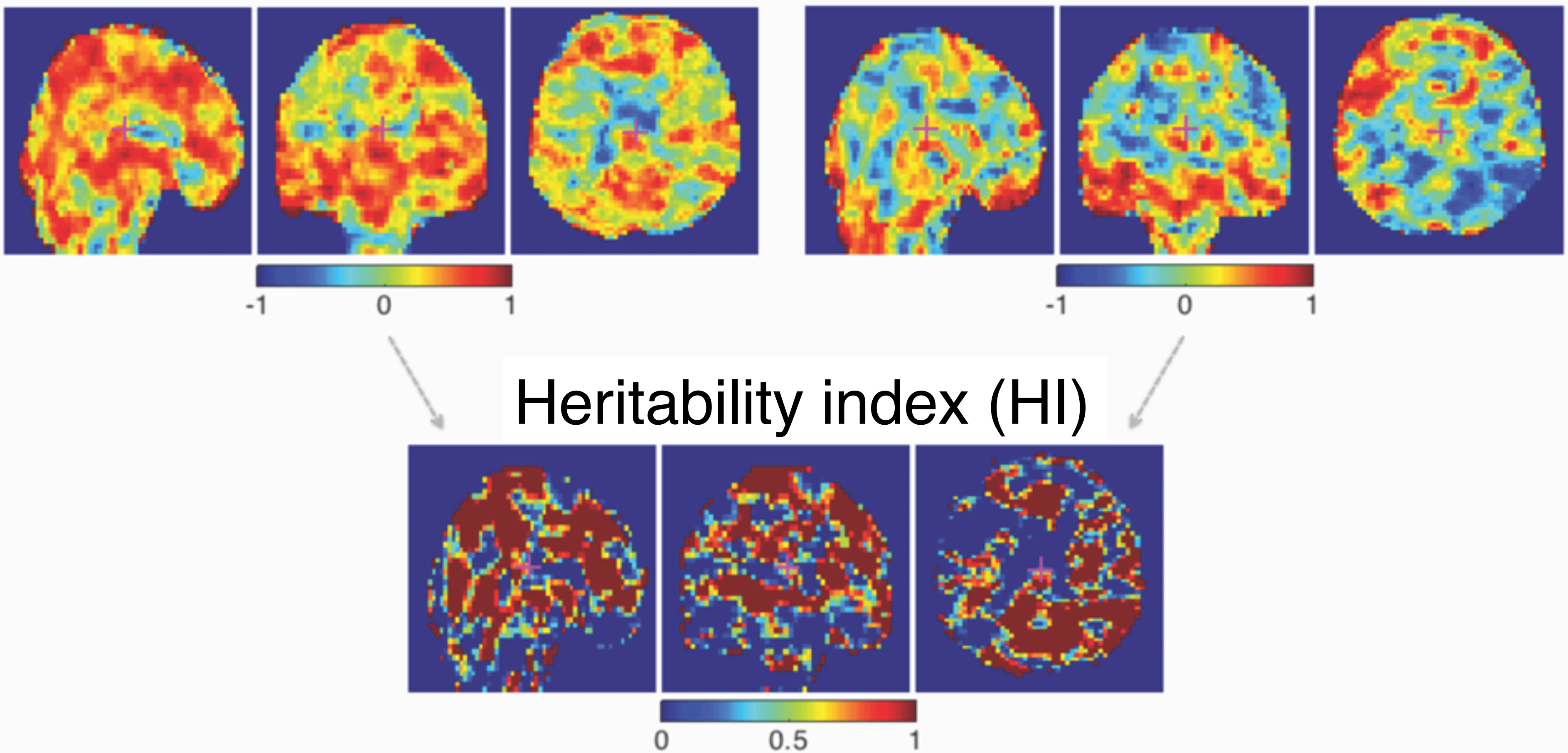
$$\rho_{DZ} = A/2 + C$$

Falconer's formula for heritability index (HI)

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


MZ-twins
DZ-twins
-10
0
10
ρ_{MZ}
Twin correlations
ρ_{DZ}
-1
0
1

Correlation of MZ-twins   Correlation of DZ-twins

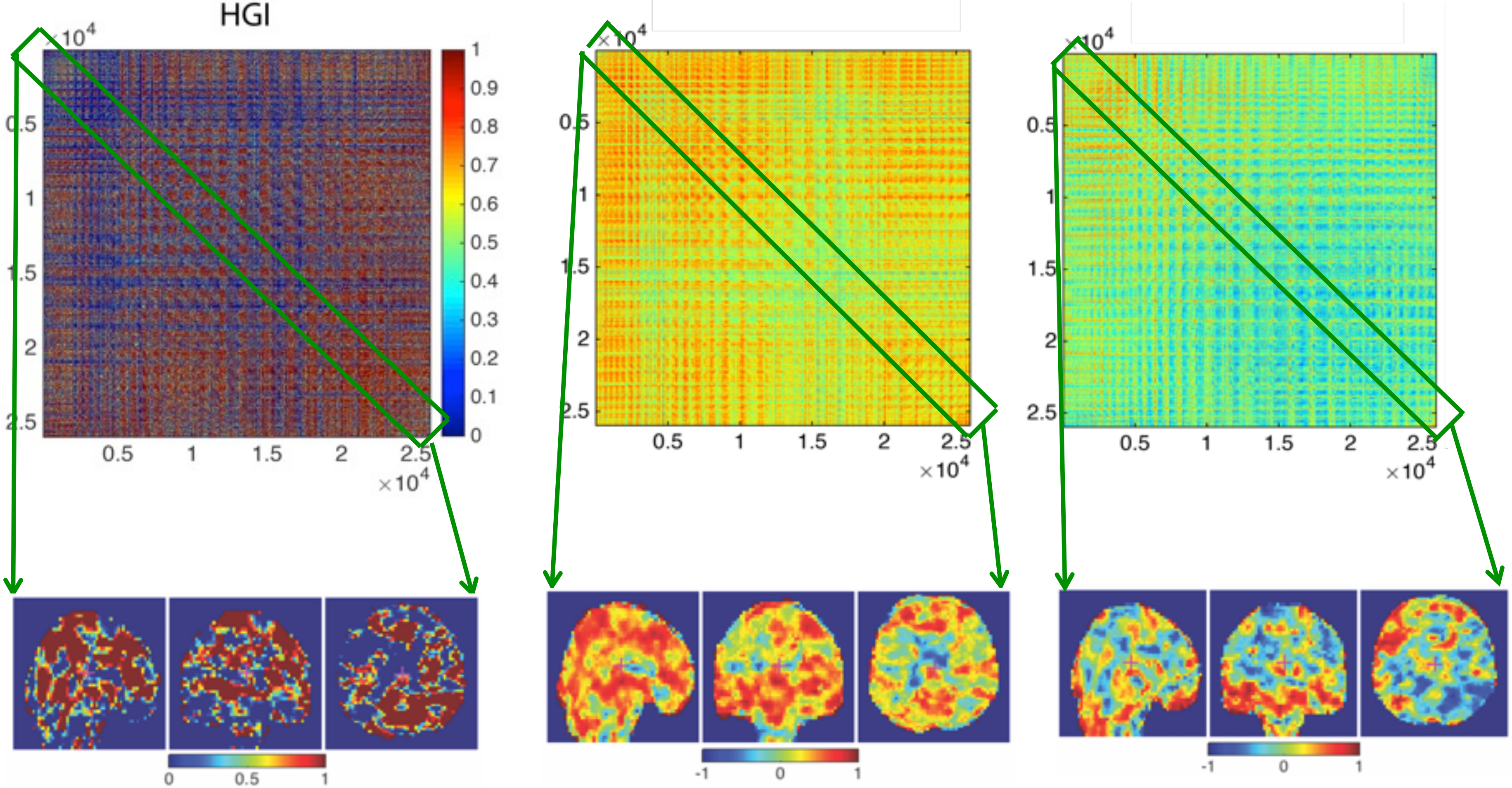


At voxel v_i, $\mathrm{HI}(v_i) = 2\left[\rho_{\mathrm{MZ}}(v_i) - \rho_{\mathrm{DZ}}(v_i)\right]$

HI = the proportion of statistical variation due to (additive) genetic influences.

Heritability graph index (HGI)

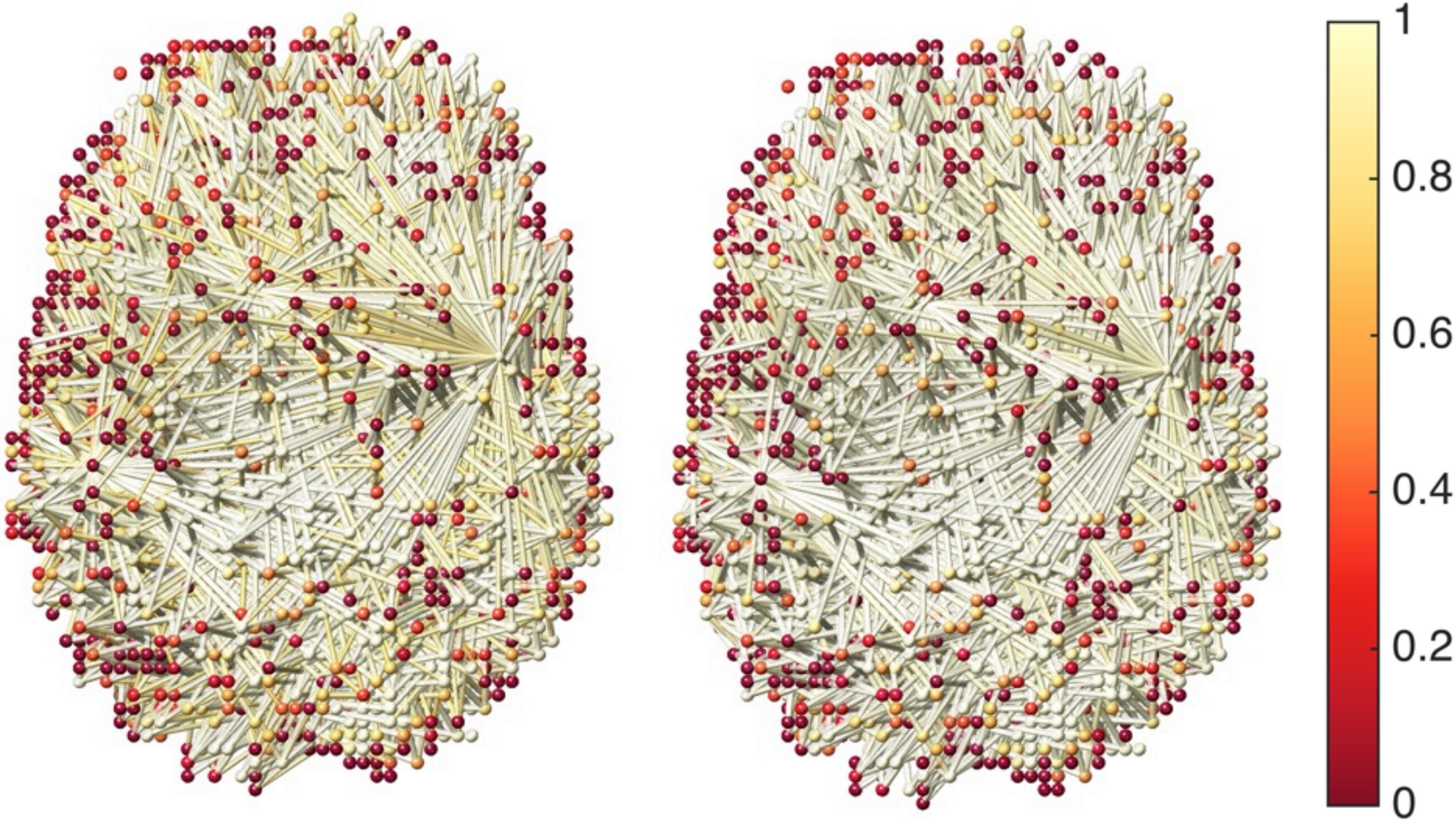
$$\text{HGI}(v_i, v_j) = 2\left[\rho_{\text{MZ}}(v_i, v_j) - \rho_{\text{DZ}}(v_i, v_j)\right]$$



HI

Twin correlations

Heritability graph Index



Sparse parameter 0.7

Sparse parameter 0.9

Persistent homology

Statistical significance of HGI?

Graph filtration

Infinite collection of networks at every possible parameter:

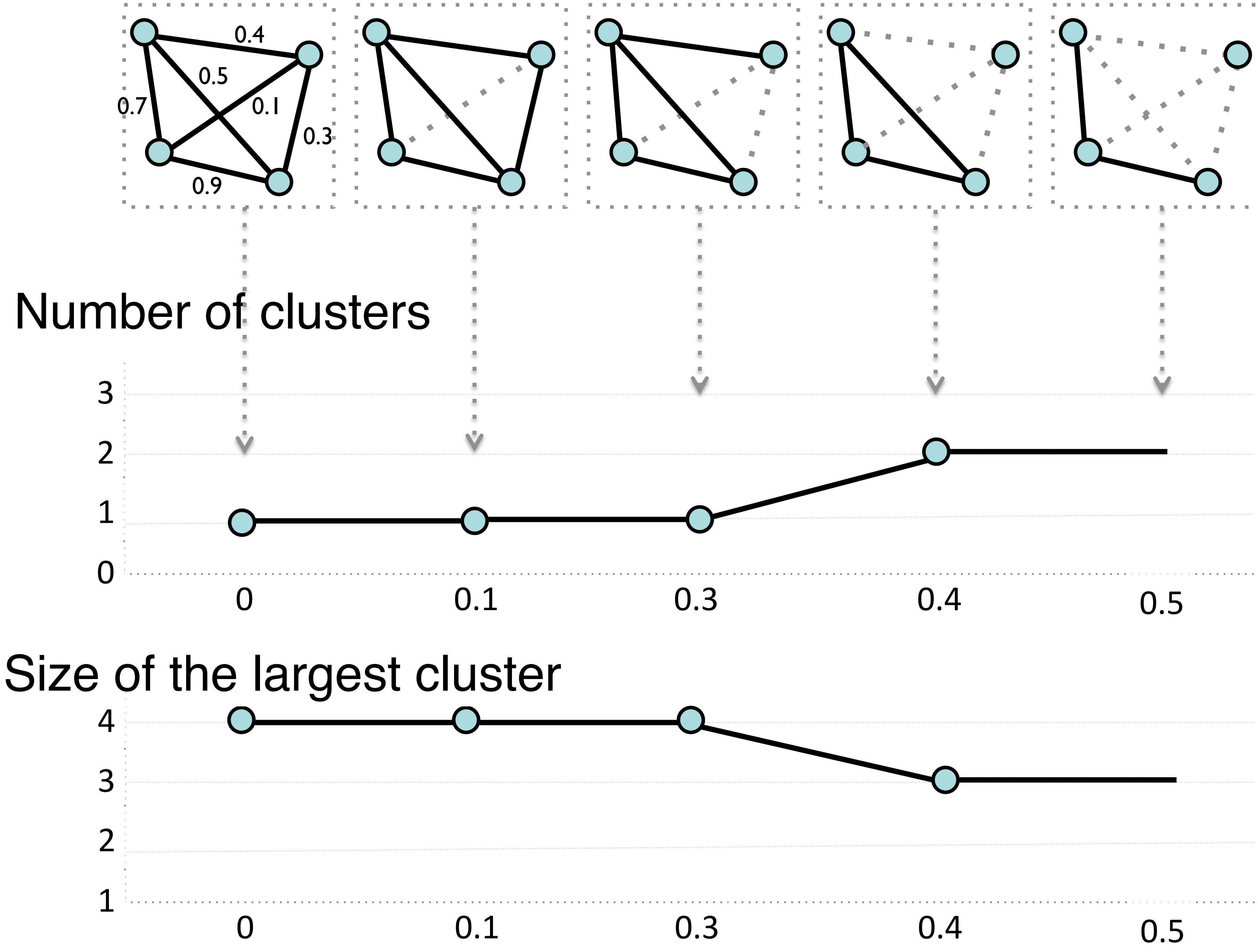
$$\{G(\lambda), \lambda \in \mathrm{R}^{+}\}$$

Monotonicity property

$$G(\lambda_1) \supset G(\lambda_2) \supset G(\lambda_3) \supset \cdots$$

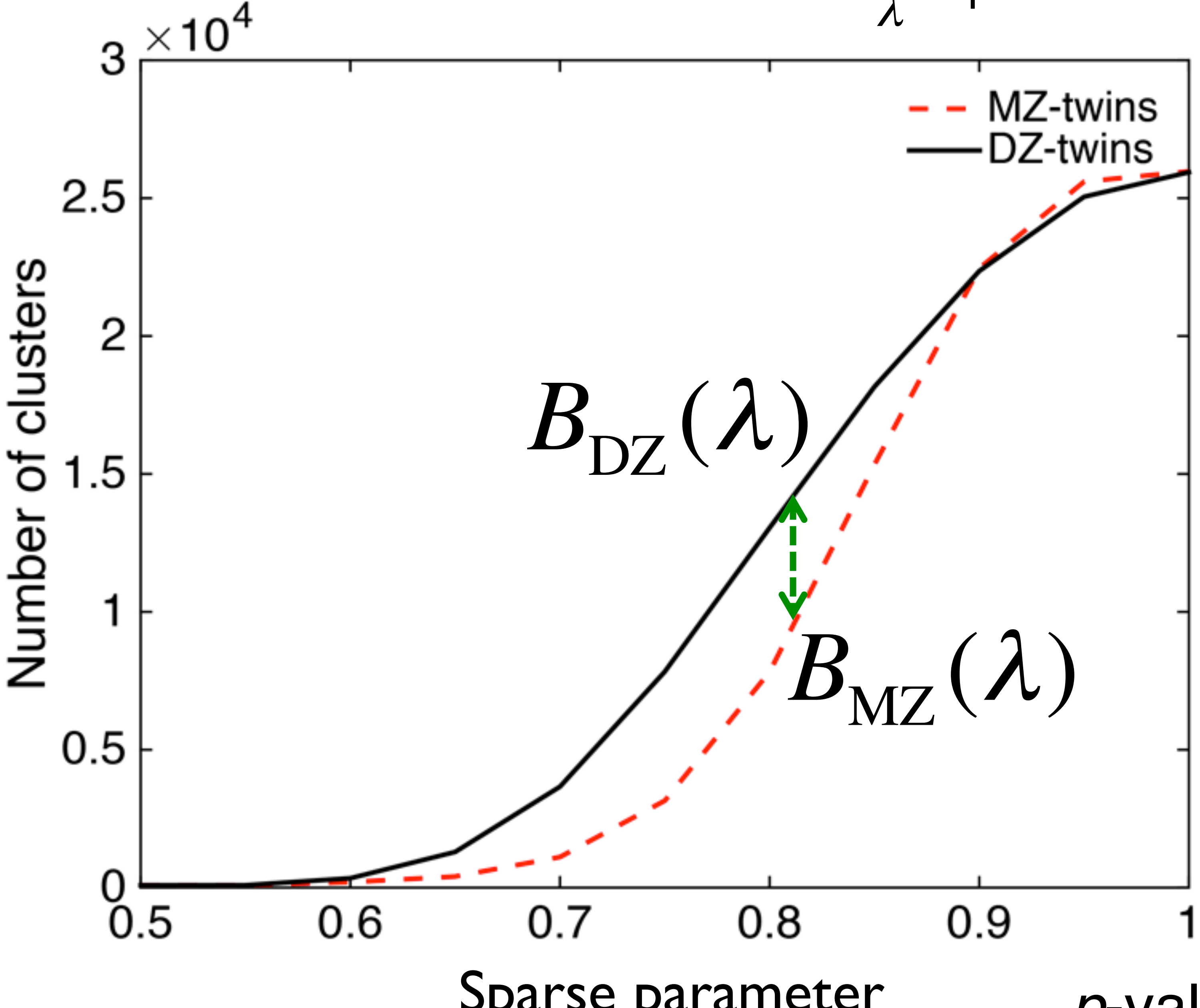
for $\lambda_1 \le \lambda_2 \le \lambda_3 \le \cdots$

Lee, H. et al. 2012. IEEE Transactions on Medical Imaging. 31:2267-2277

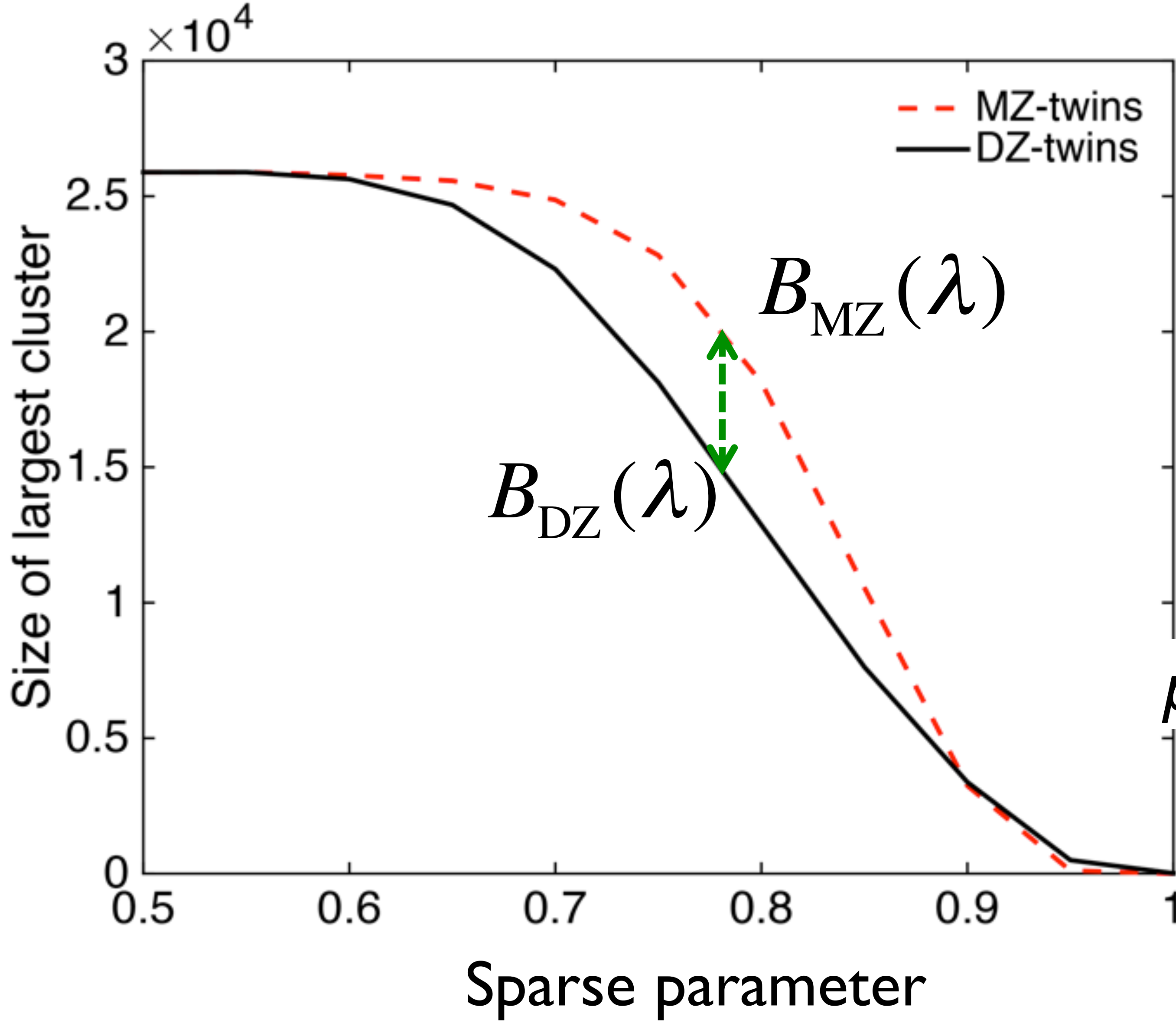

0.4
0.5
0.7
0.1
0.3
0.9
Number of clusters
3
2
1
0
0
0.1
0.3
0.4
0.5
Size of the largest cluster
4
3
2
1
0
0.1
0.3
0.4
0.5

Betti-0 plot

$$D = \max_{\lambda} \left| B_{\mathrm{MZ}}(\lambda) - B_{DZ}(\lambda) \right|$$



p-value < 0.0002



[Chung et al. 2016 arxiv:509.04771](#)

p-value < 0.0001

$$p\text{-value} = P\left(\max_{\lambda}\left|B_{\mathrm{MZ}}(\lambda) - B_{\mathrm{DZ}}(\lambda)\right| \geq \sqrt{2(p-1)}d\right) \approx 2e^{-2d^2} + \ldots$$

Discussion

Infinite-scale network models will always outperform multi-scale network models.

Thresholding edge weights is equivalent to sparse network modeling.

p-value for global network inference can be computed mathematically.

Thank you