A Double Spectral Approach to Disease Module Identification

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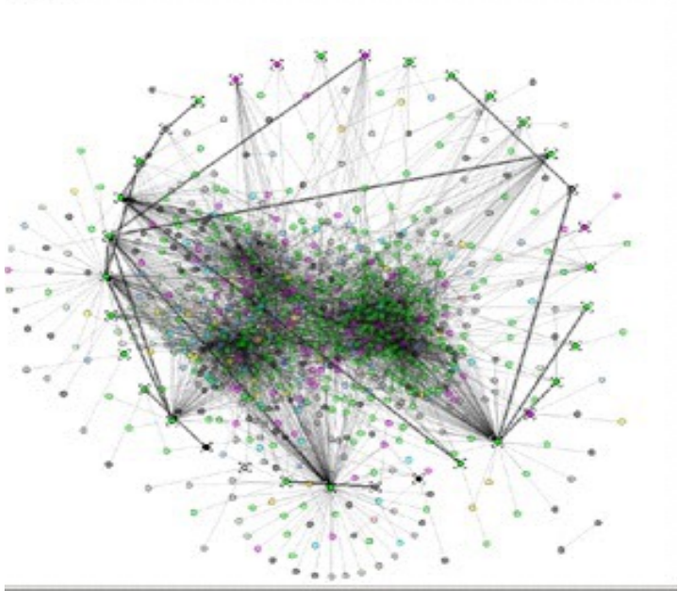
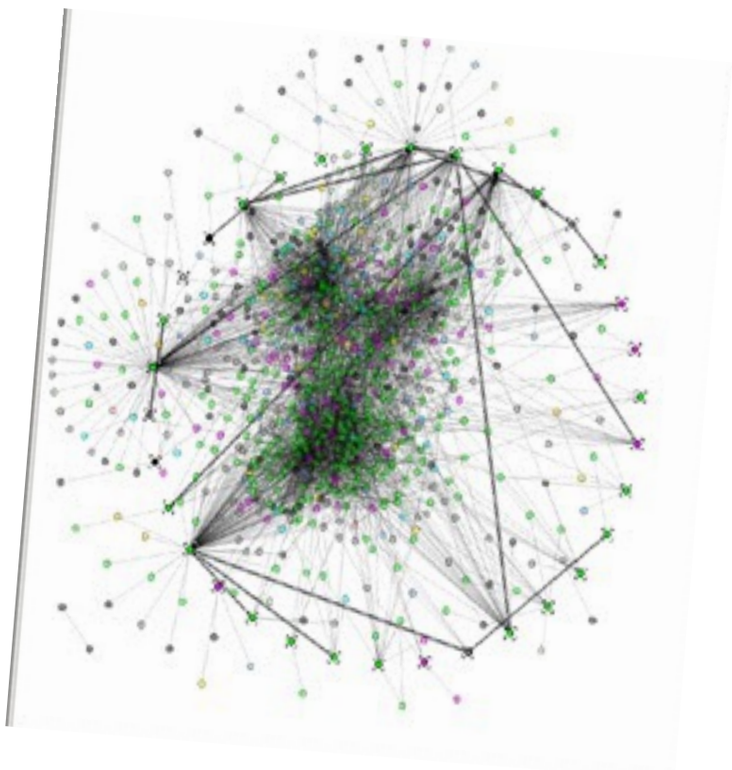
Tufts University

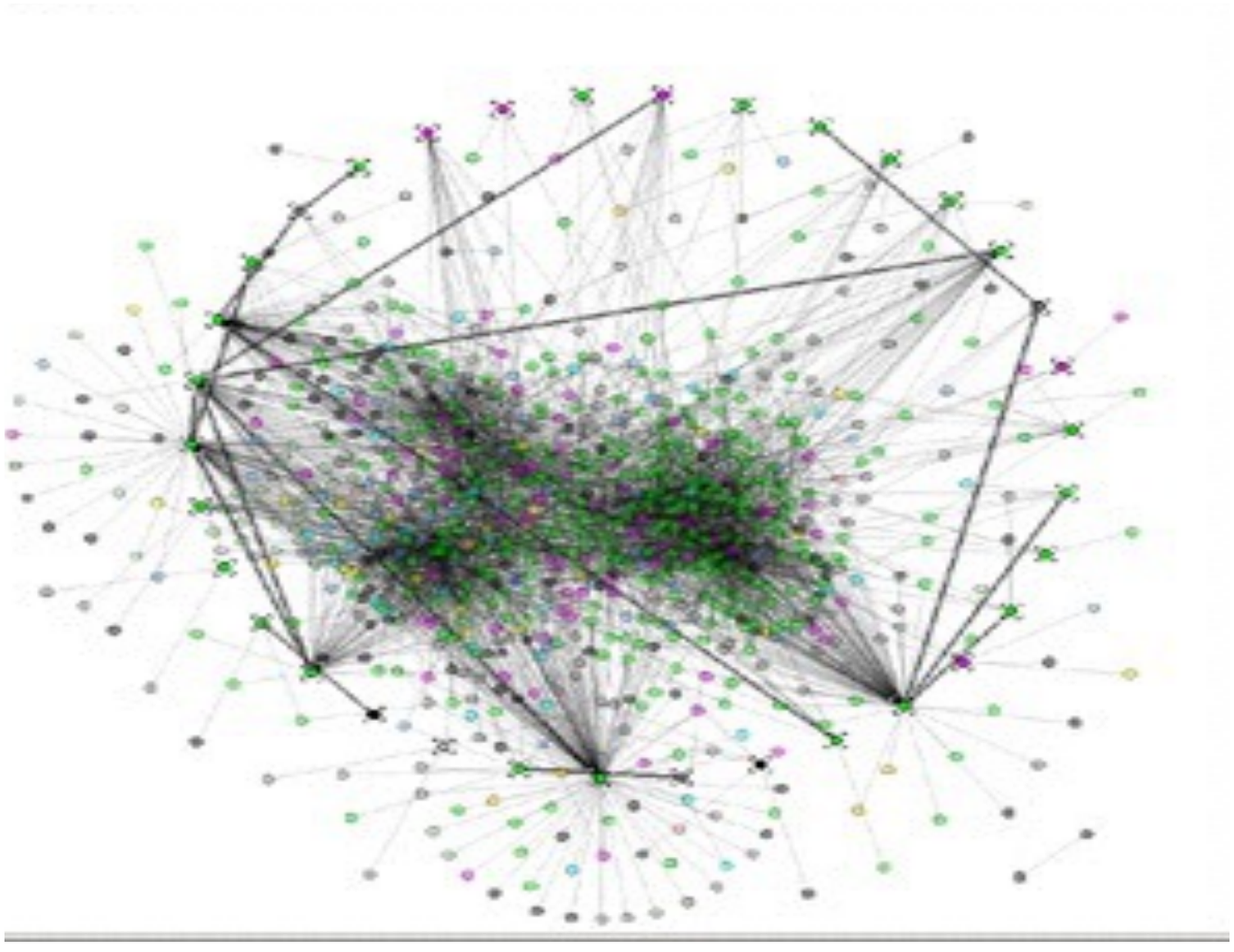
Our Goal

- Identify module structure in biological networks, enriched for a collection of disease gene sets.

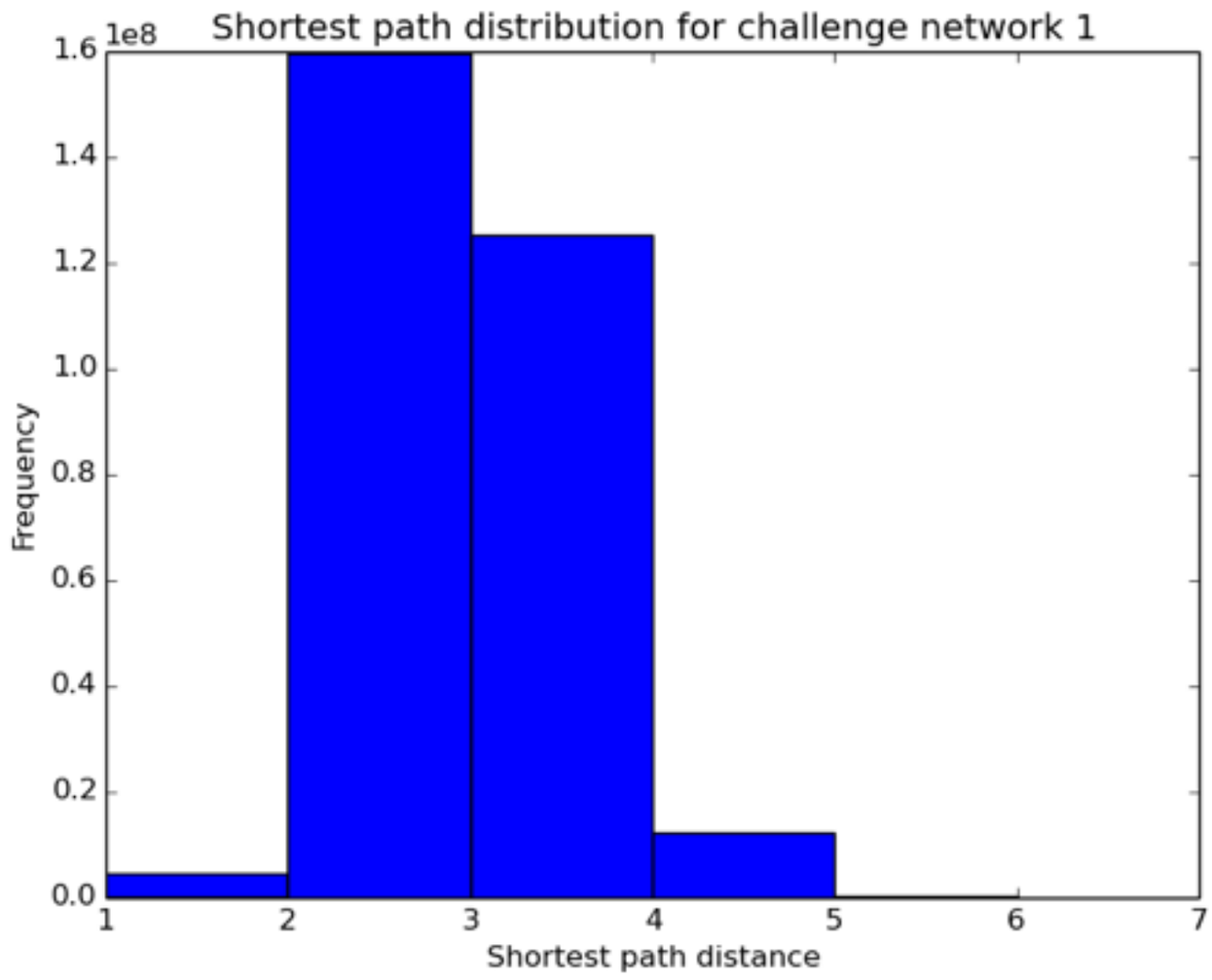




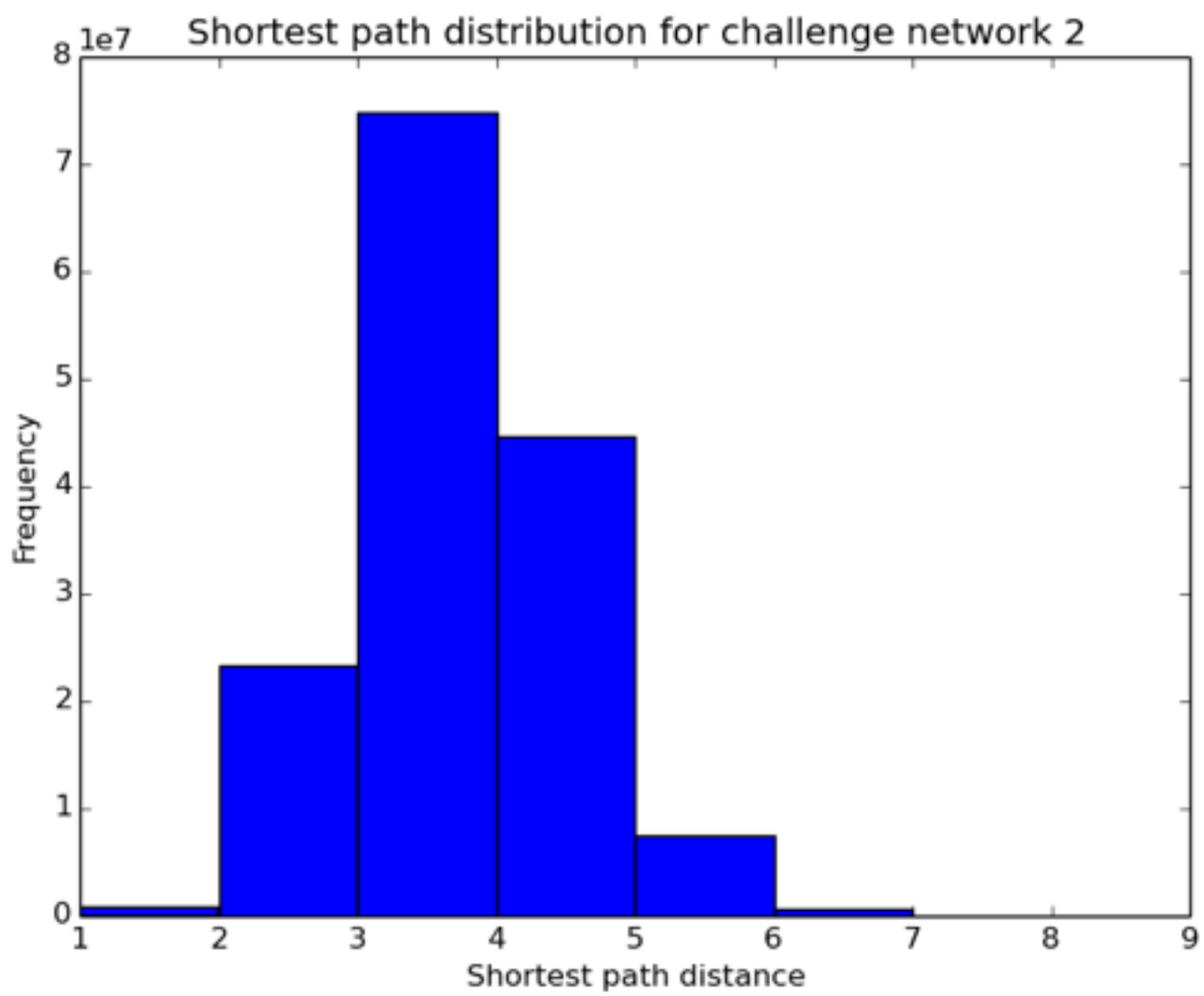
PPI network: issue with defining local neighborhoods: “small-world” network where everything is nearby!



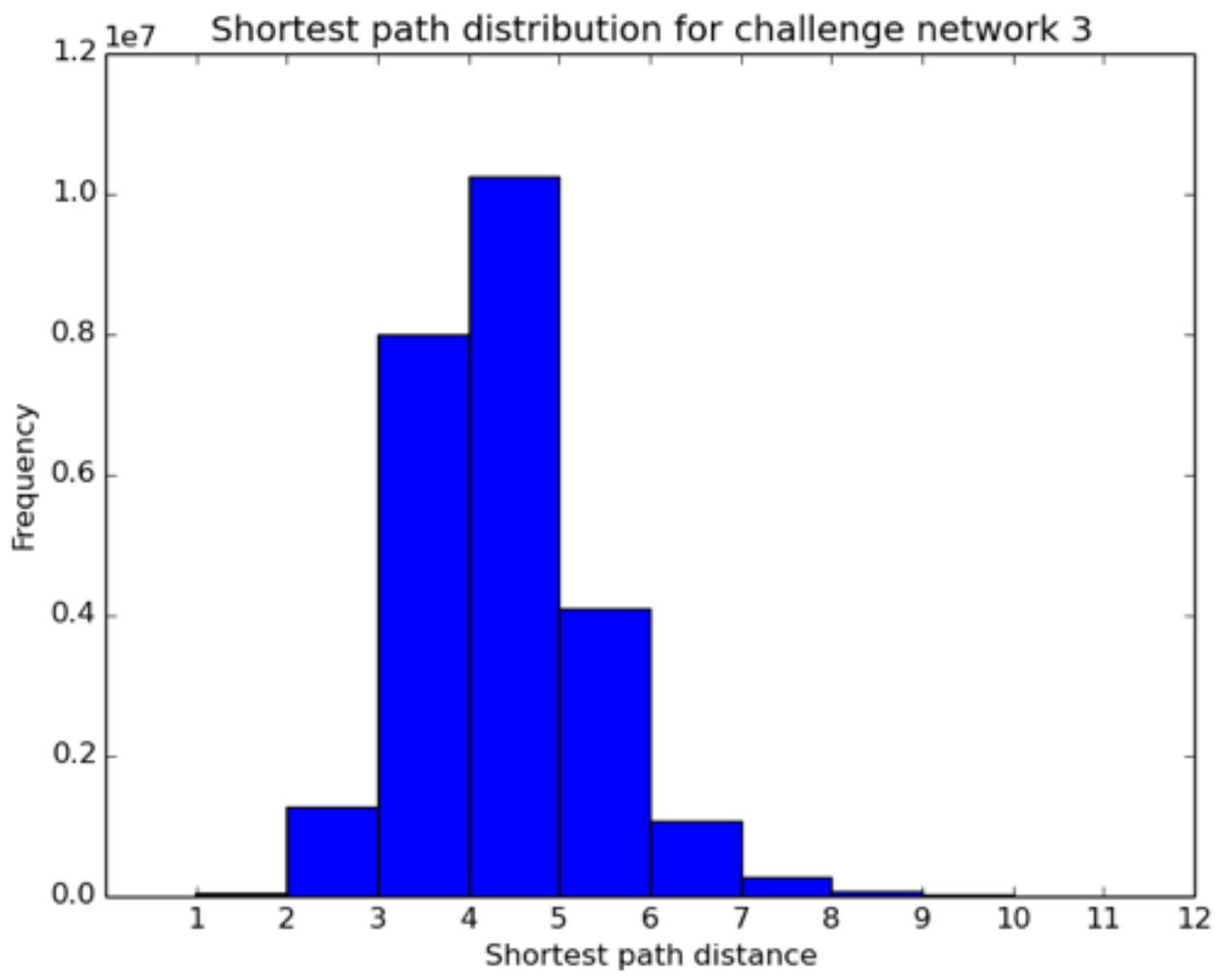
Dream Network 1



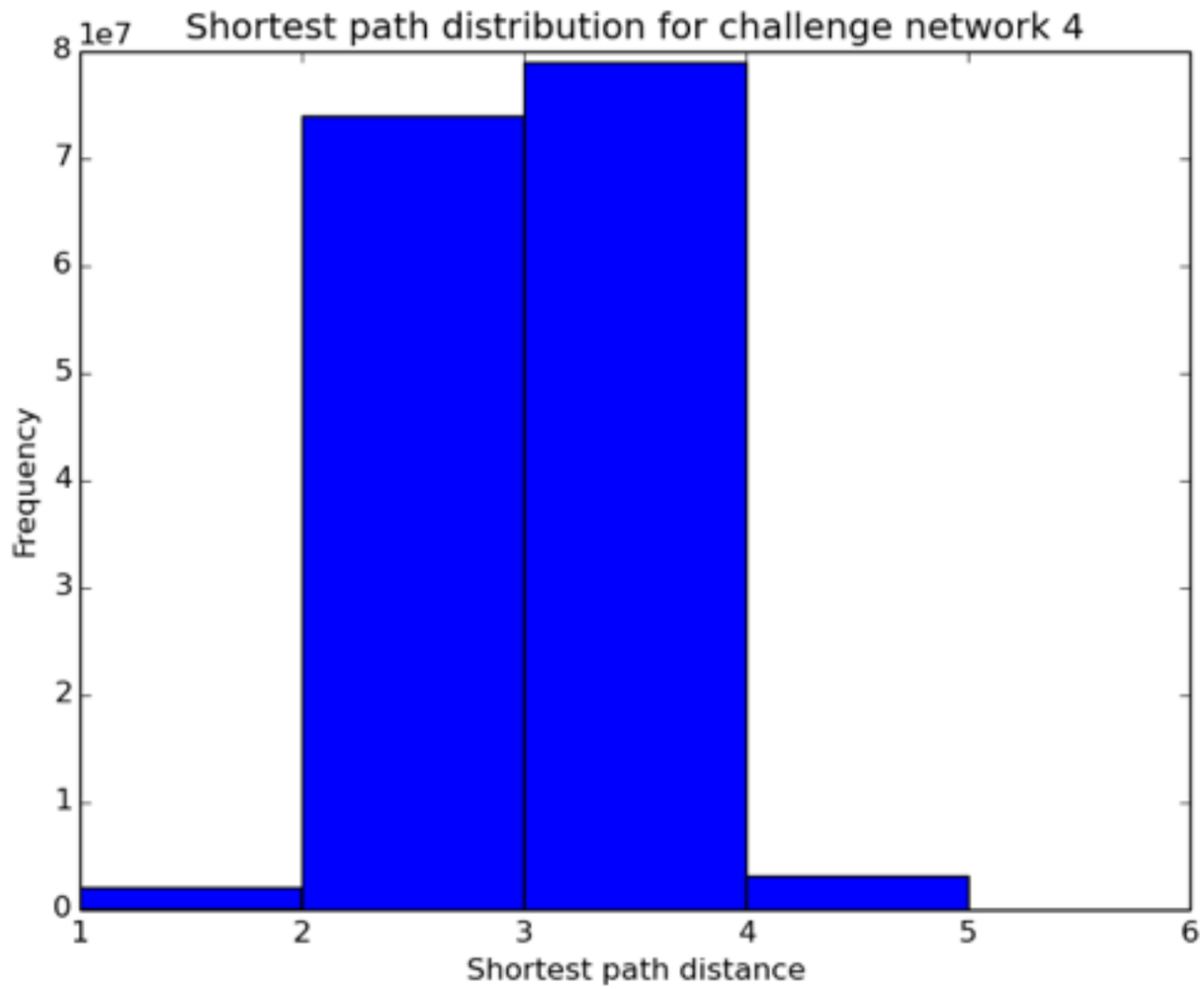
Dream Network 2



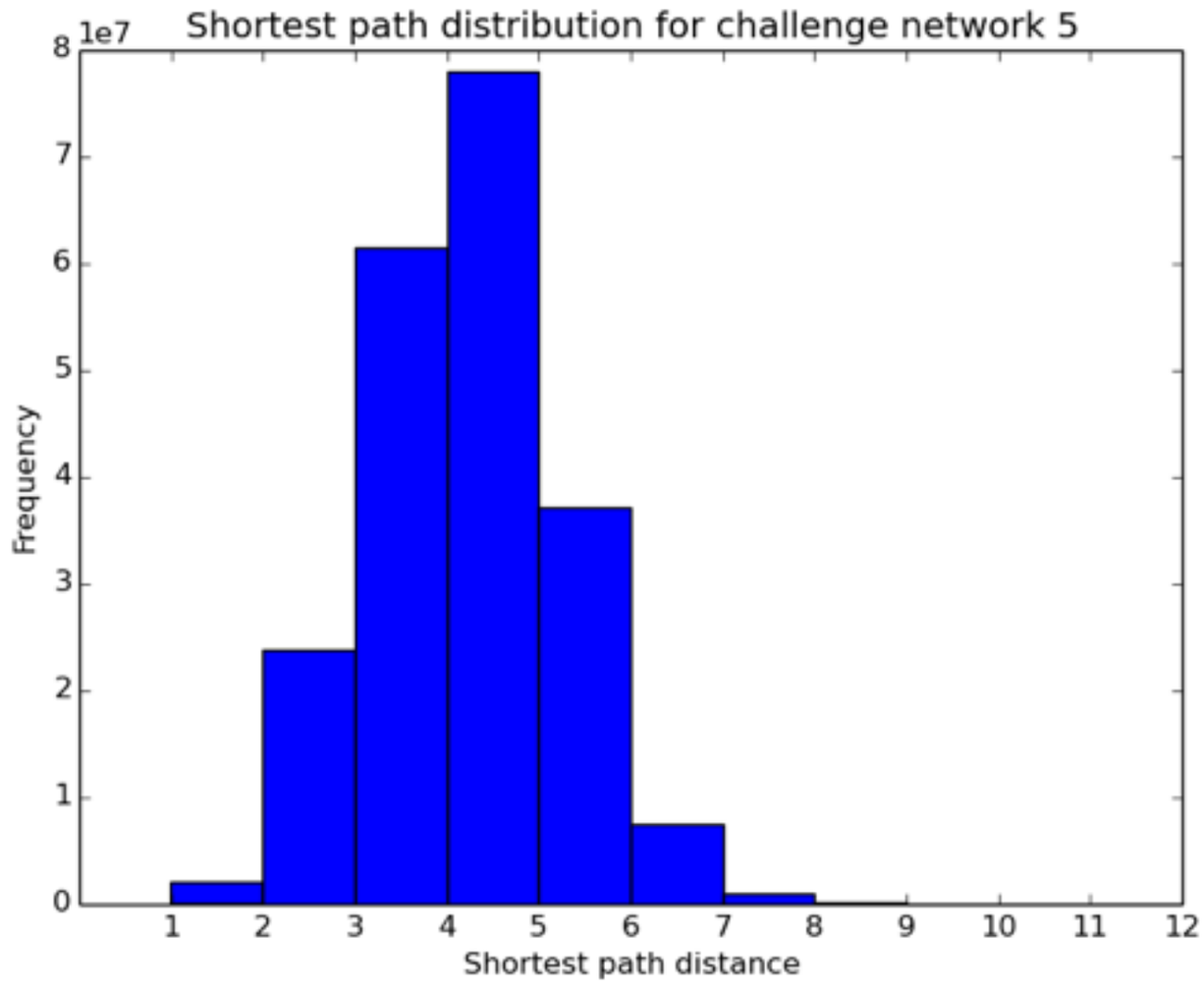
Dream Network 3



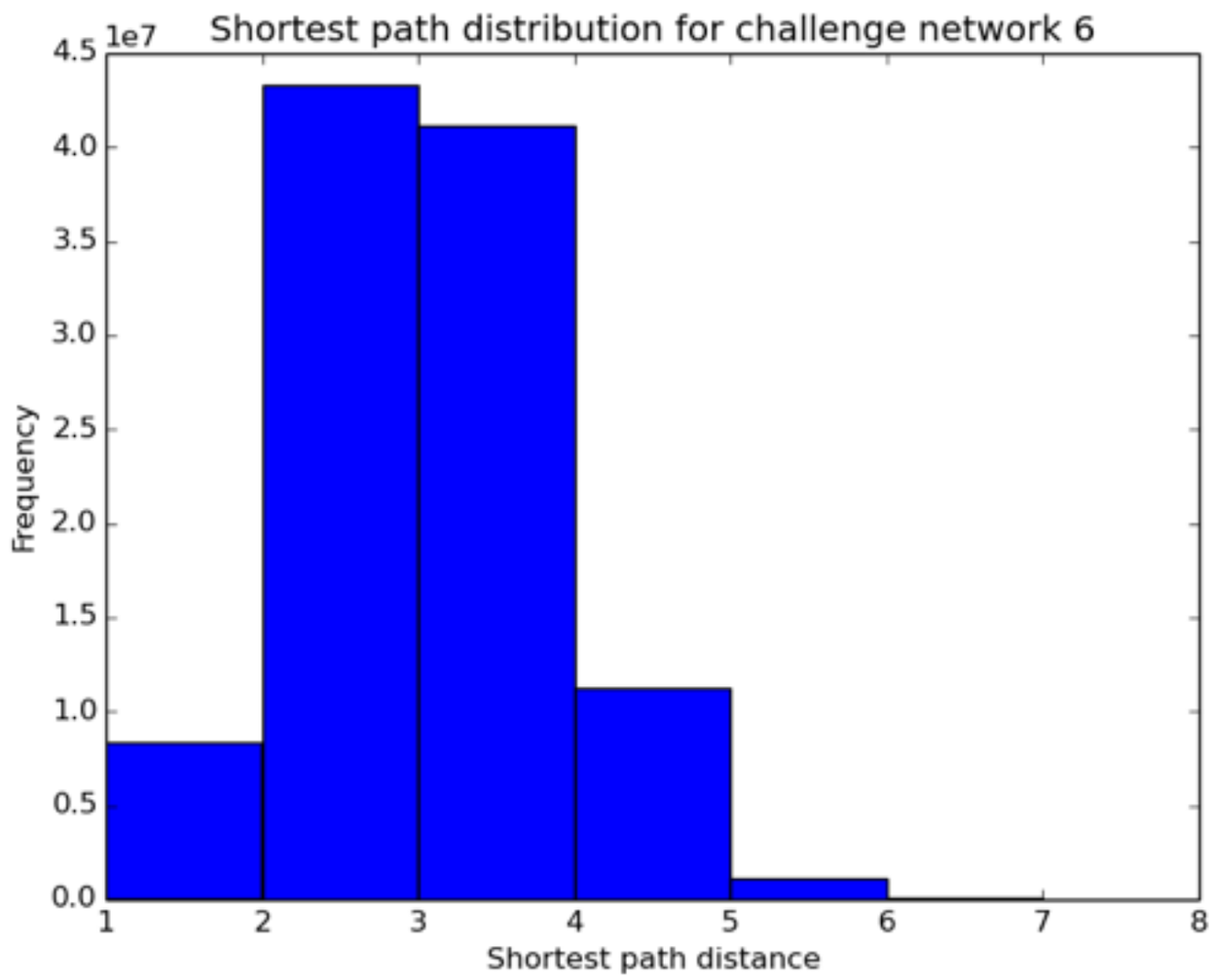
Dream Network 4



Dream Network 5



Dream Network 6



Our Approach

DSD

Diffusion State Distance

Cluster the resulting distance matrix

Correct cluster sizes

Look for bipartite subgraphs

Return valid clusters

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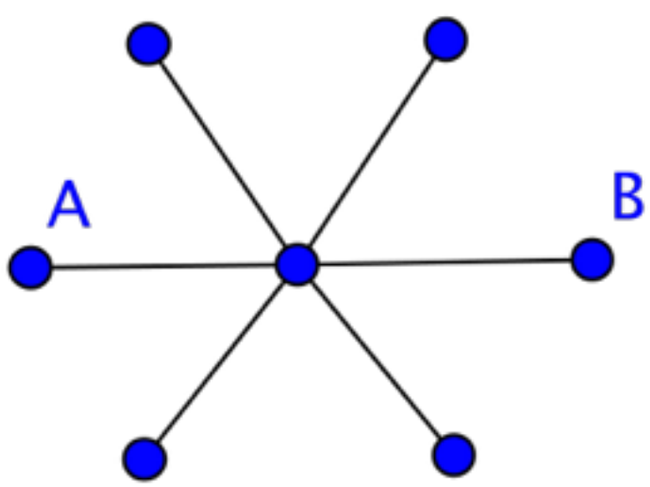
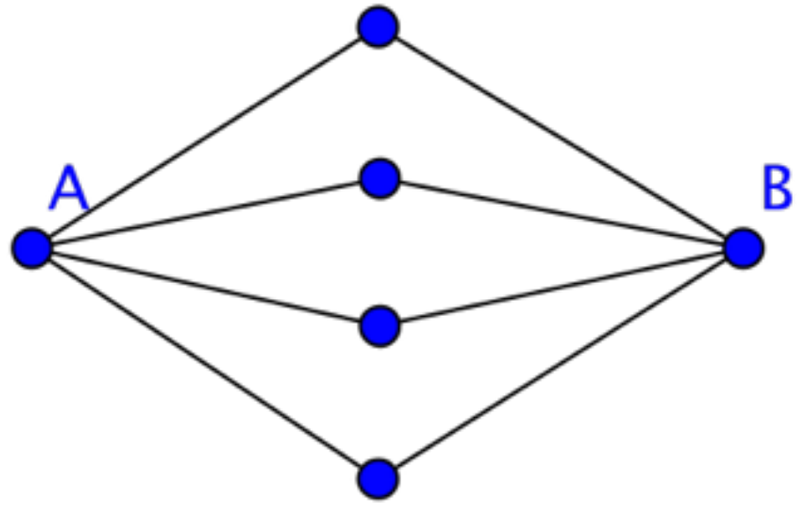
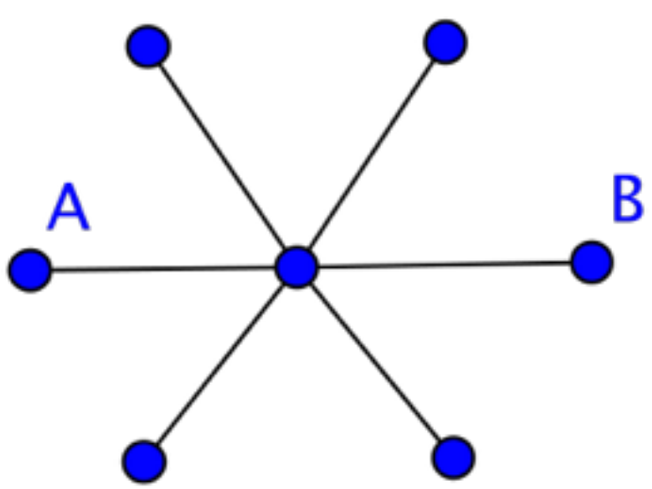
Our insight: not all short paths give equal indications of similarity

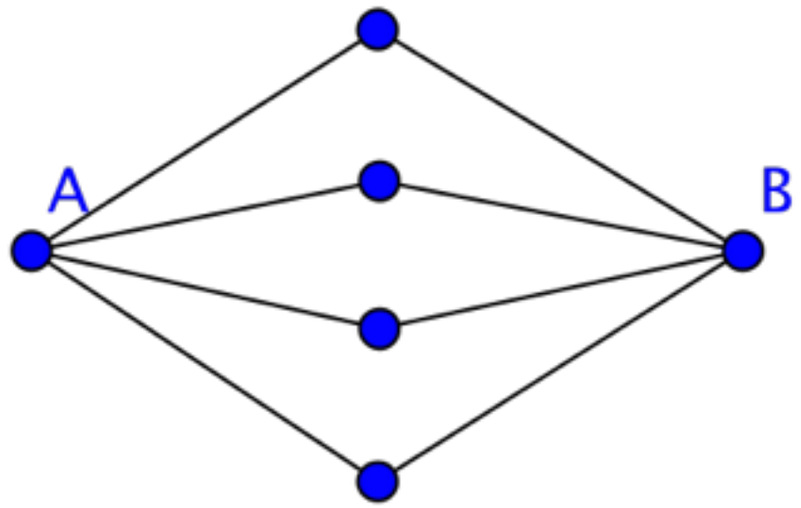




Define He (A,B) to be the expected number of times a k-step random walk starting at A reaches B (including 0-length walk)

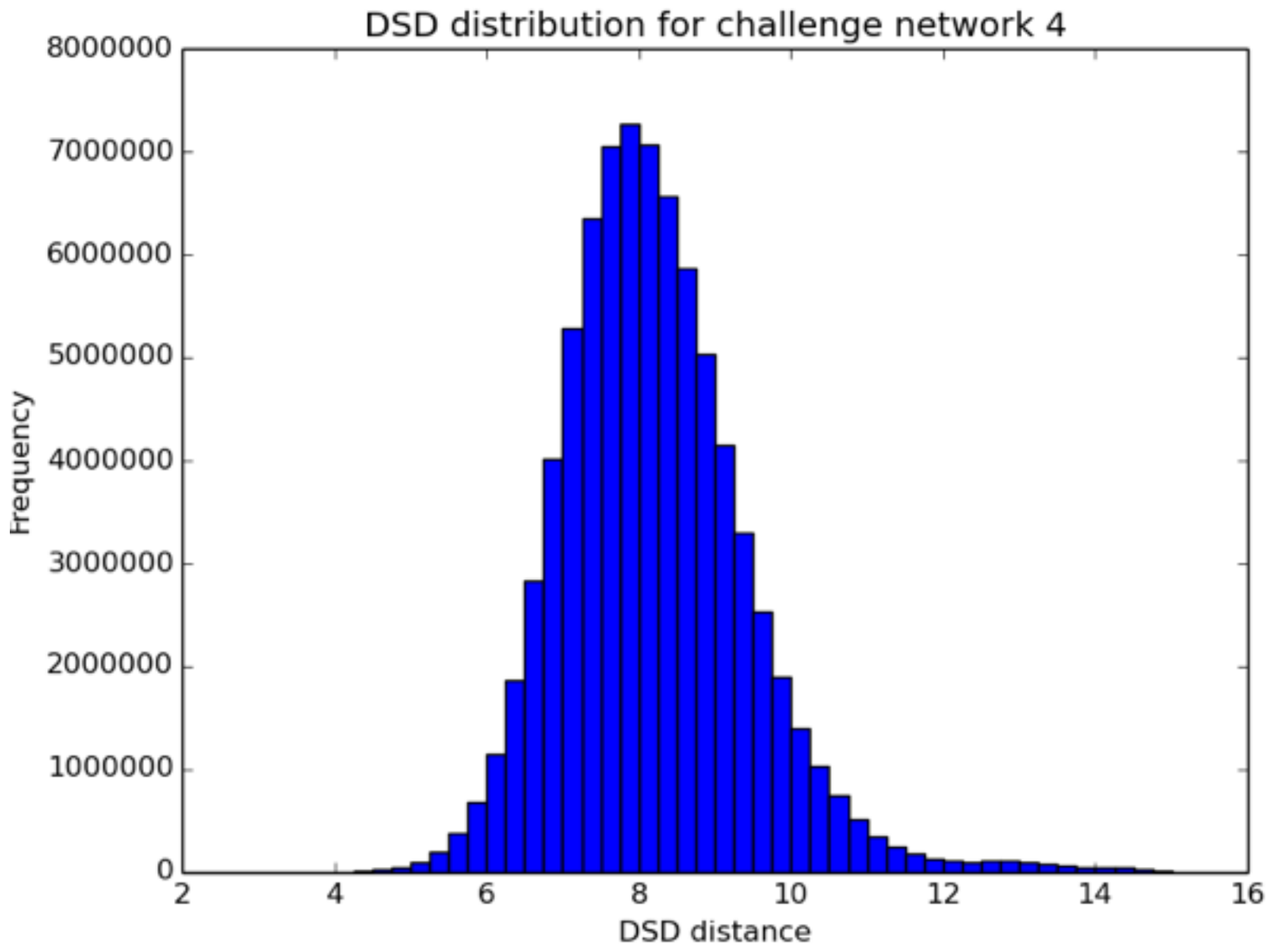
DSD: A Spectral Distance Metric





- $He^k(A) = (He^k(A, v_1), He^k(A, v_2), \ldots, He^k(A, v_n))$
- $DSD^k(A, B) = | He^k(A) - He^k(B) |_1$
- We prove DSD is a metric, and converges as $k \to \infty$: call the converged version DSD (A, B) .

DSD spreads out distances



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Speeding Up DSD

For an ergodic network, the DSD distance between two nodes u and v can also be written as

$$\mathrm{DSD}(u,v) = ||(\boldsymbol{b}_u^T - \boldsymbol{b}_v^T)(\boldsymbol{I} - \boldsymbol{P} + \boldsymbol{W})^{-1}||_1$$

where $\mathbf{b_i}$ is the i^{th} basis vector, **I** is the identity matrix, **P** is the transition matrix of the network, and **W** is a matrix where each row is a copy of $\boldsymbol{\pi}^{\mathbf{T}}$ = the steady state distribution of the network.

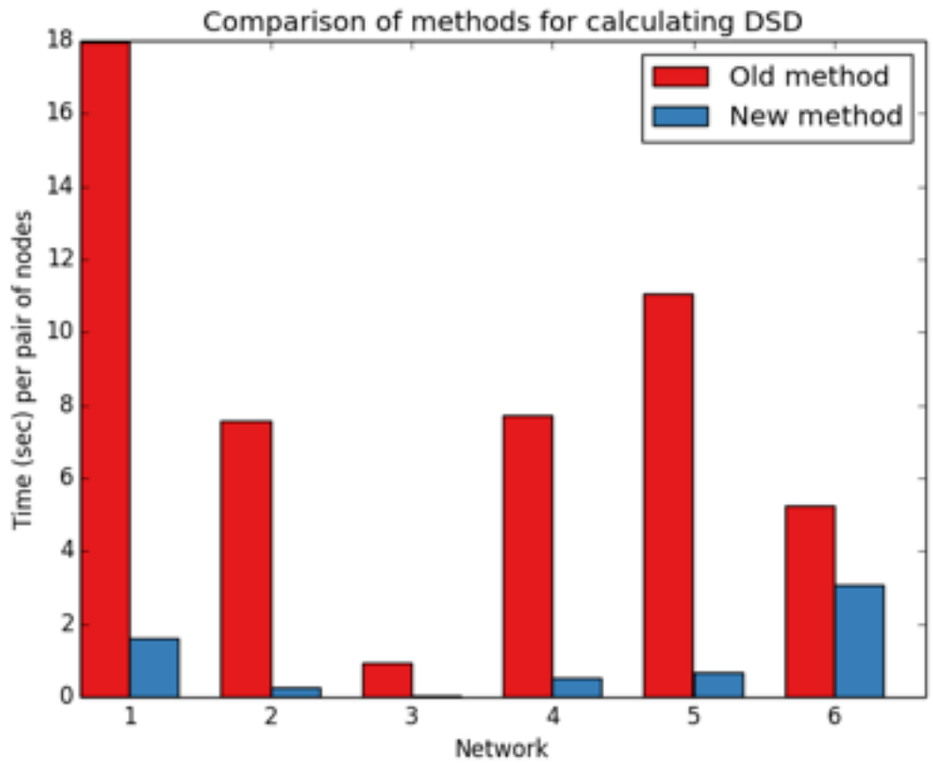
(proof of this in Cao et al. 2013)

Speeding Up DSD

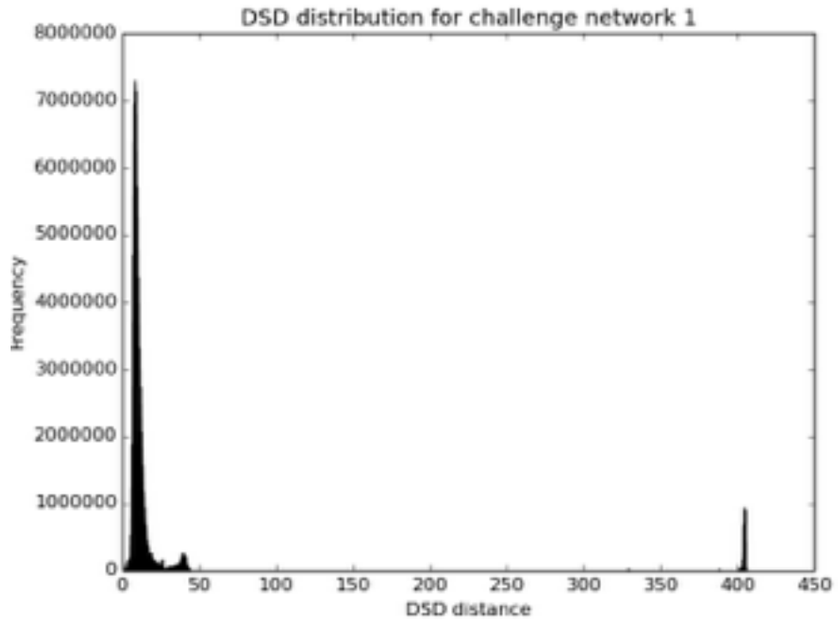
$$\mathrm{DSD}(u, v) = ||(\boldsymbol{b}_u^T - \boldsymbol{b}_v^T)(\boldsymbol{I} - \boldsymbol{P} + \boldsymbol{W})^{-1}||_1$$

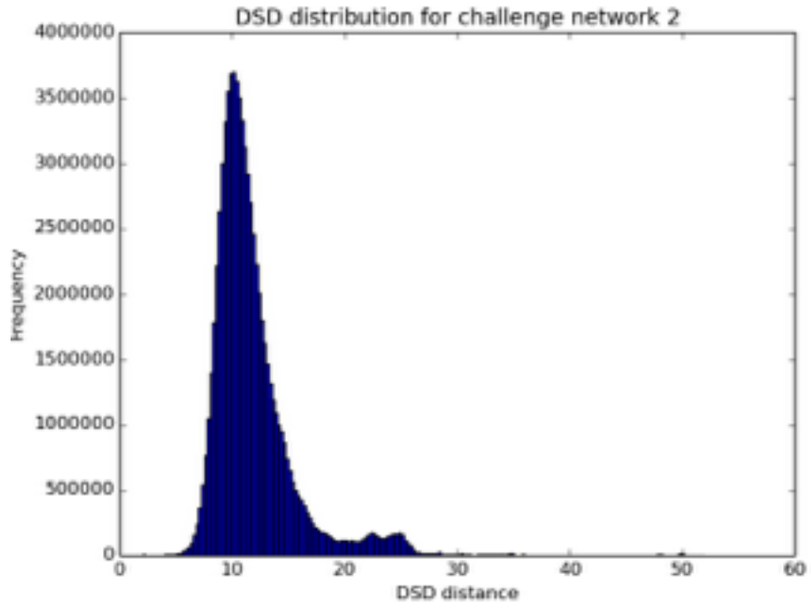
- Computing the matrix inverse $(\mathbf{I - P + W})^{-1}$ is the most computationally expensive part

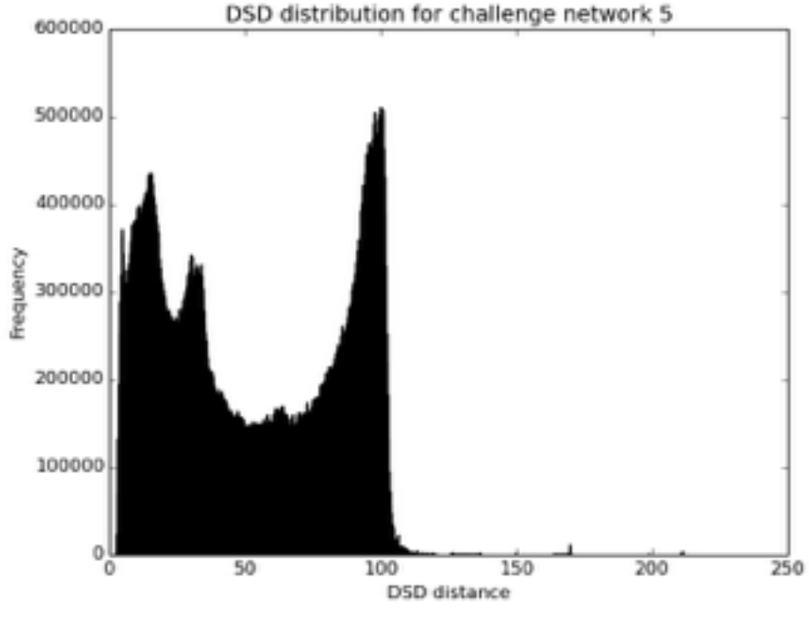
- We developed an efficient algorithm to reduce the amortized time for sparse networks, using algebraic multigrid methods

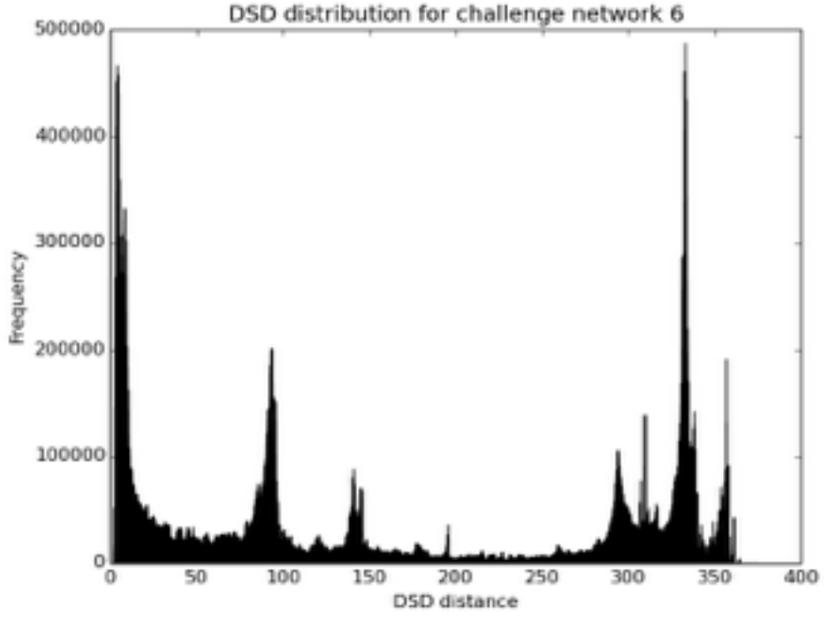


The method only computes approximate DSD; some artifacts, good enough









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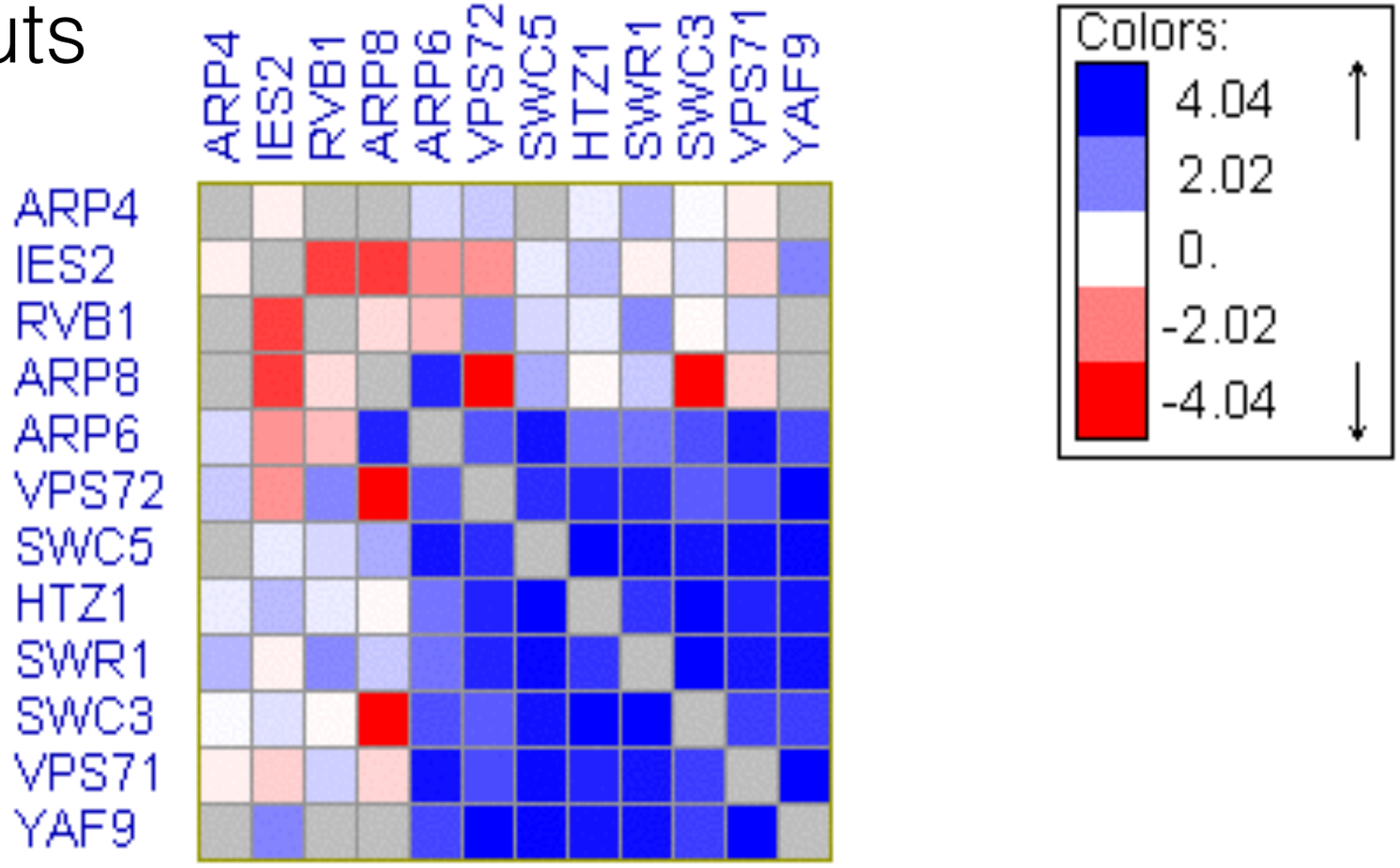
Genetic interactions (epistasis)

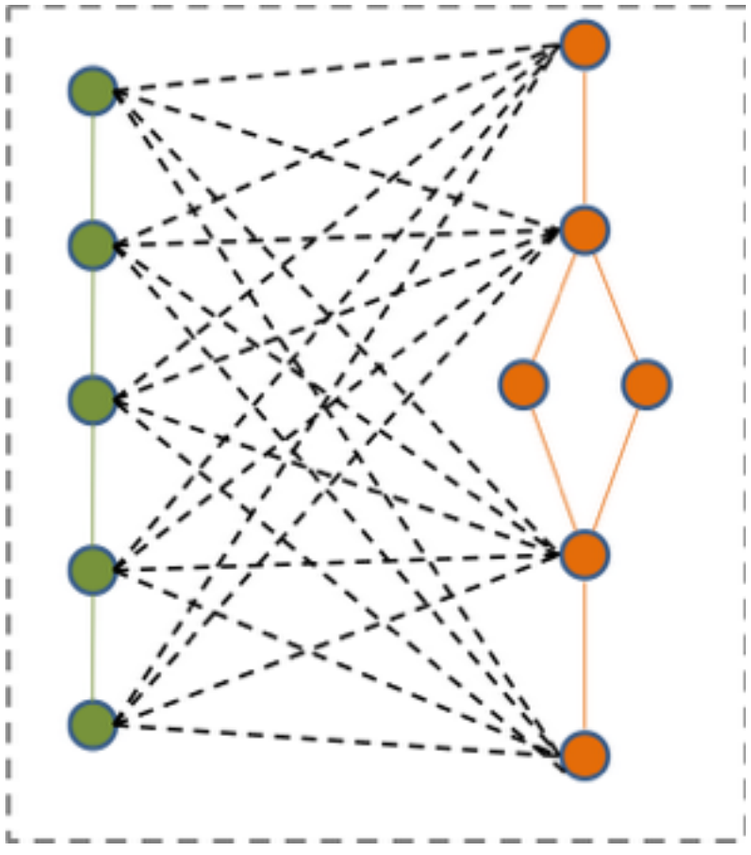
- For non-essential genes, we can compare the growth of the double knockout to its component single knockouts



Picture: Ulitsky

Finding Bipartite Subgraphs

- “Between Pathway Model” (Kelley and Ideker, 2005)
- Regions having many negative genetic interactions between them (and physical interactions within regions)
- May indicate compensatory biological pathways
- Use Brady et. al 2009 definition; based only on negative genetic interactions (ignore physical interactions)



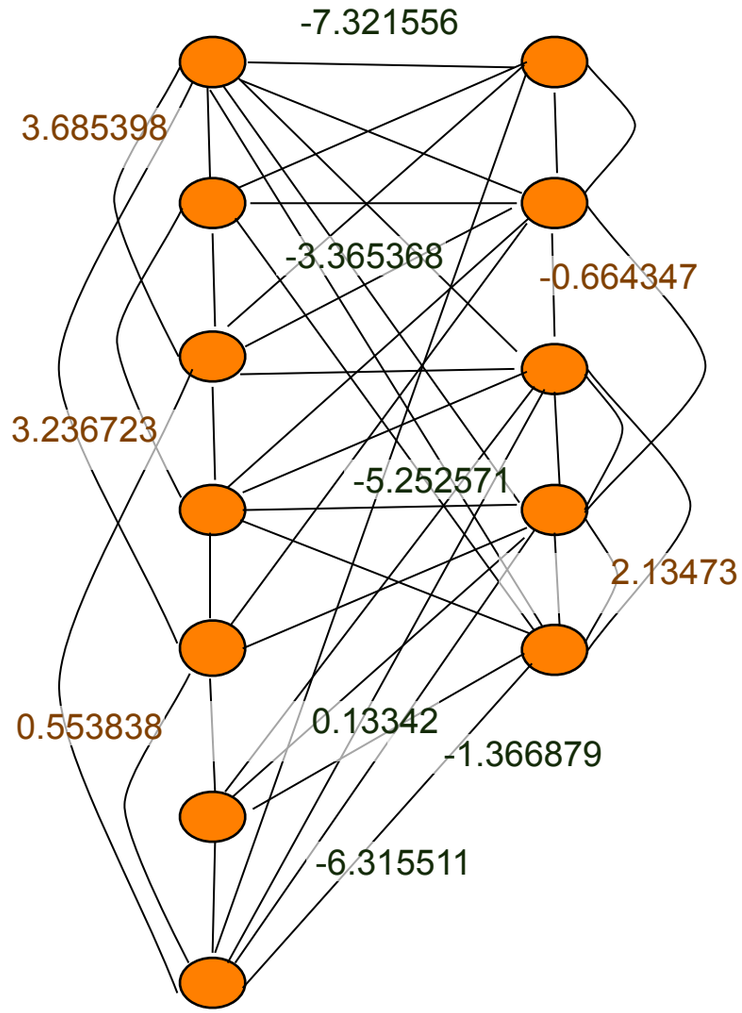
What is the Quality of a BPM?

Once we obtain a candidate BPM we can score it using interaction data.

Sum interactions within

Sum interactions between

Take the difference and normalize to create an interaction score



Look for a collection of BPMs in half the networks

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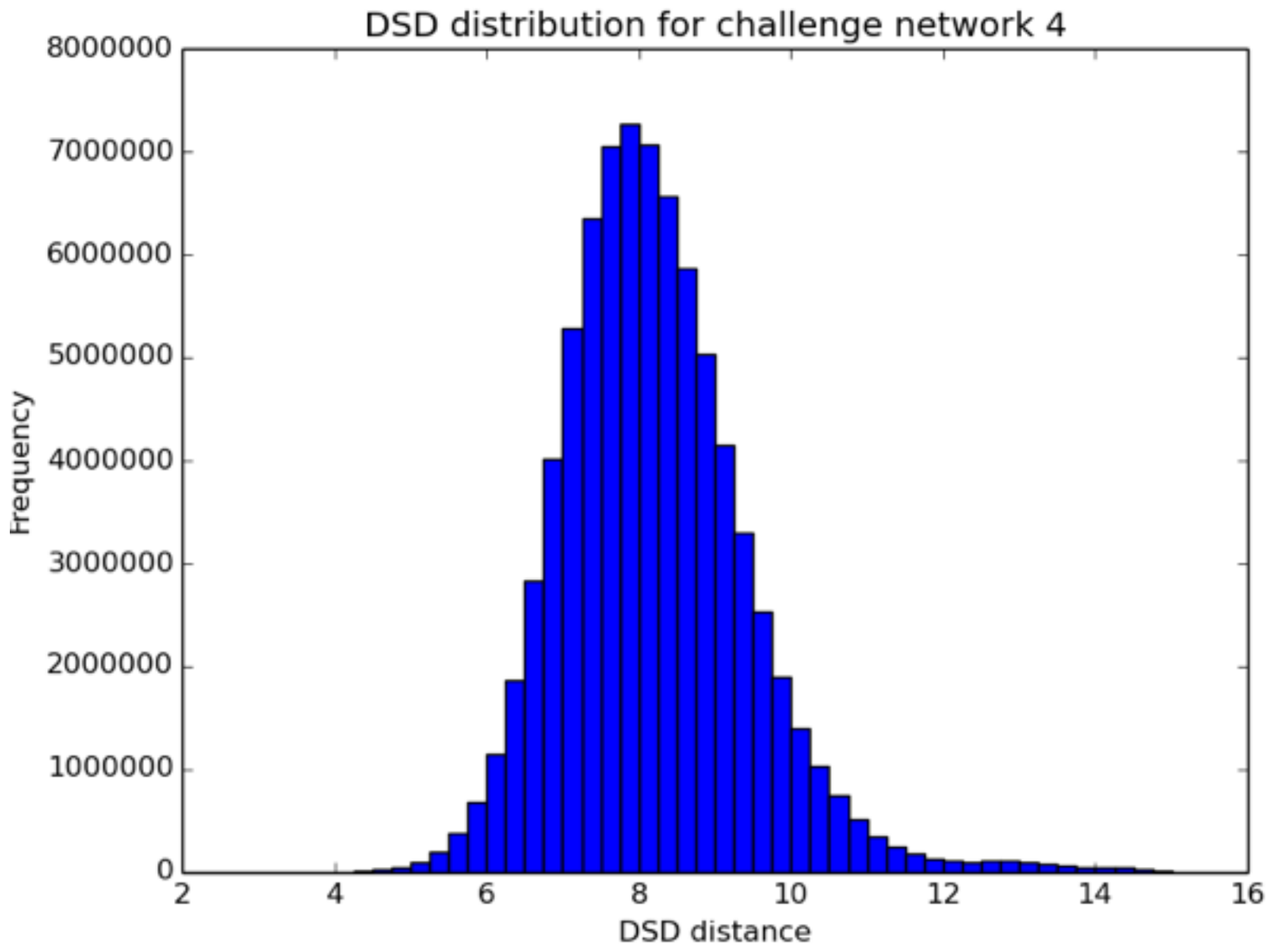
Subchallenge 1, Step 1: Get the DSD matrix for each network

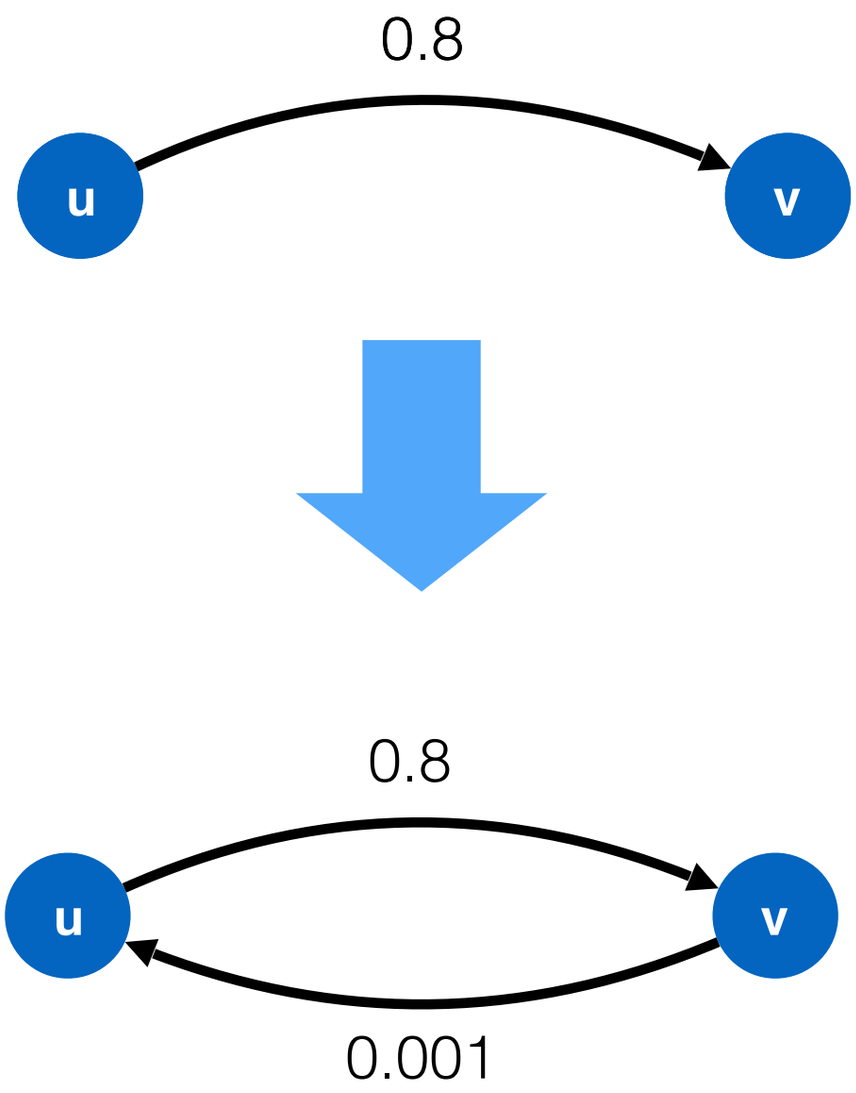


What about the directed network?

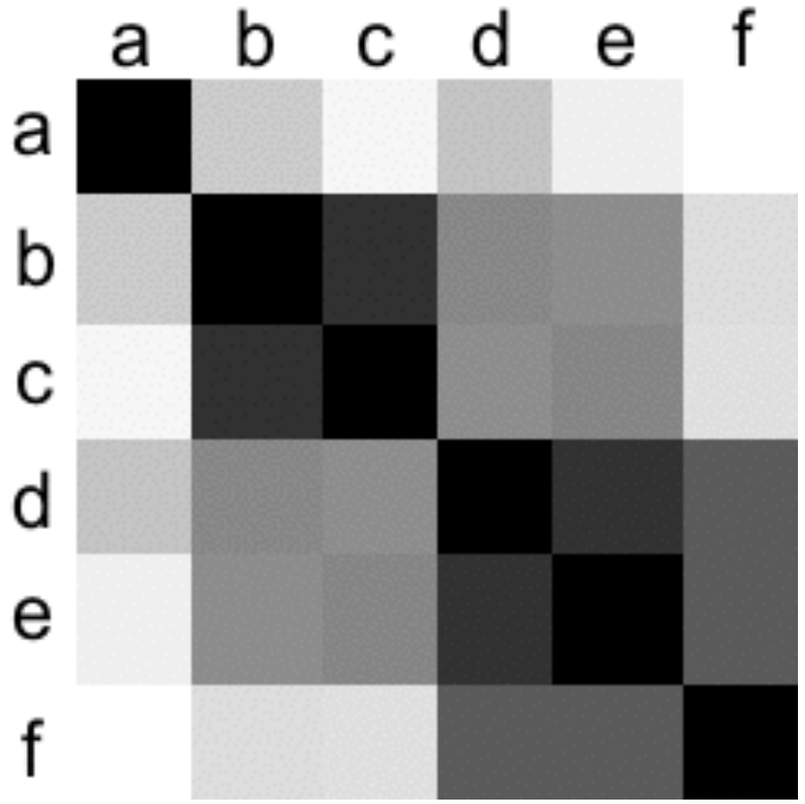
- We wanted to preserve edge direction, but keep the network (strongly) connected to run DSD in a sensible way

- Add low-weight back edges if none exists already

- Gave better results than treating all edges as undirected



We have a distance matrix. Now what?



- Many pre-existing methods to cluster a pairwise distance (or similarity) matrix
- Spectral clustering performed the best in the leaderboard rounds

Spectral Clustering

- Convert distance matrix to similarity matrix using radial basis function (RBF) kernel (high distance -> low similarity and vice-versa)
- Dimension reduction + k-means clustering (used default scikit-learn implementation)
- Tested different values of k in the training rounds

Pedregosa et al, JMLR 12:2825-2830 (2011)

Network 1 - Choosing k

Submission	NS (train)	NS for different FDR (1%, 2.5%, 10%)	NS (test)
k = 1000	14	(8, 10, 22)	16
k = 1200	14	(3, 7, 19)	N/A
k = 500, altered weighting scheme	14	(5, 9, 23)	N/A
k = 500	12	(3, 7, 20)	N/A

Network 5 - Choosing k

Submission	NS (train)	NS for different FDR (1%, 2.5%, 10%)	NS (test)
GC and k=100 overlap	6	(1, 2, 8)	N/A
GC and k=200 overlap	5	(3, 3, 7)	5
k=100	5	(1, 3, 6)	N/A

So far we have:

DSD

Diffusion State Distance

Cluster the resulting distance matrix

Correct cluster sizes

Look for bipartite subgraphs

Return valid clusters

Correcting Cluster Sizes

- Small clusters (size < 3): throw out
- Large clusters (size > 100): partition recursively (again using spectral clustering on the DSD matrix), until all clusters are of size < 100
- In practice, splitting large clusters improved most of the results we tested, and only hurt one result (out of ~15 comparisons)

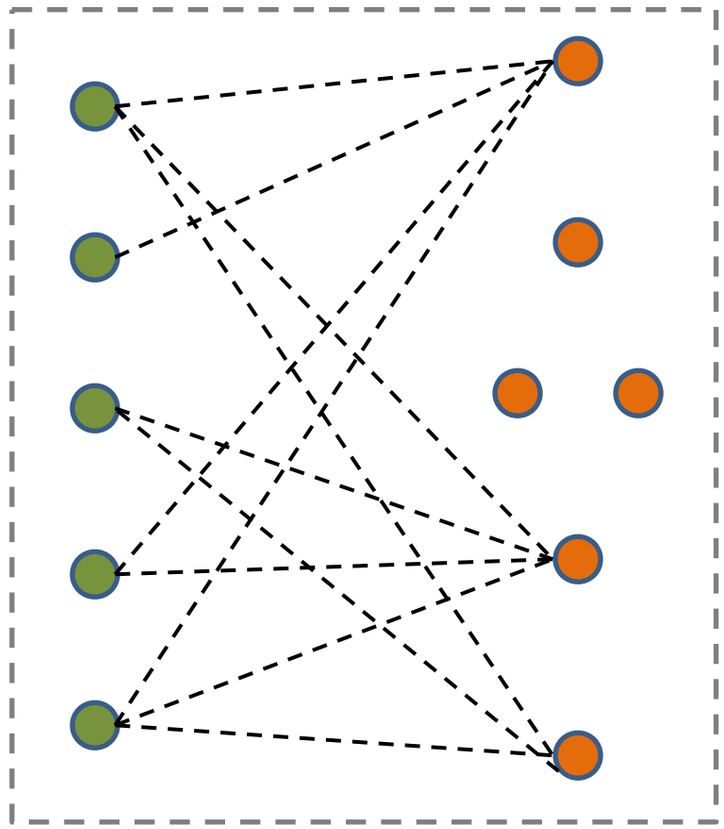
- For networks 1, 4, and 6, we're done.
- For networks 2, 3, and 5, we tried one more trick… looking for BPMs!

Finding Bipartite Subgraphs

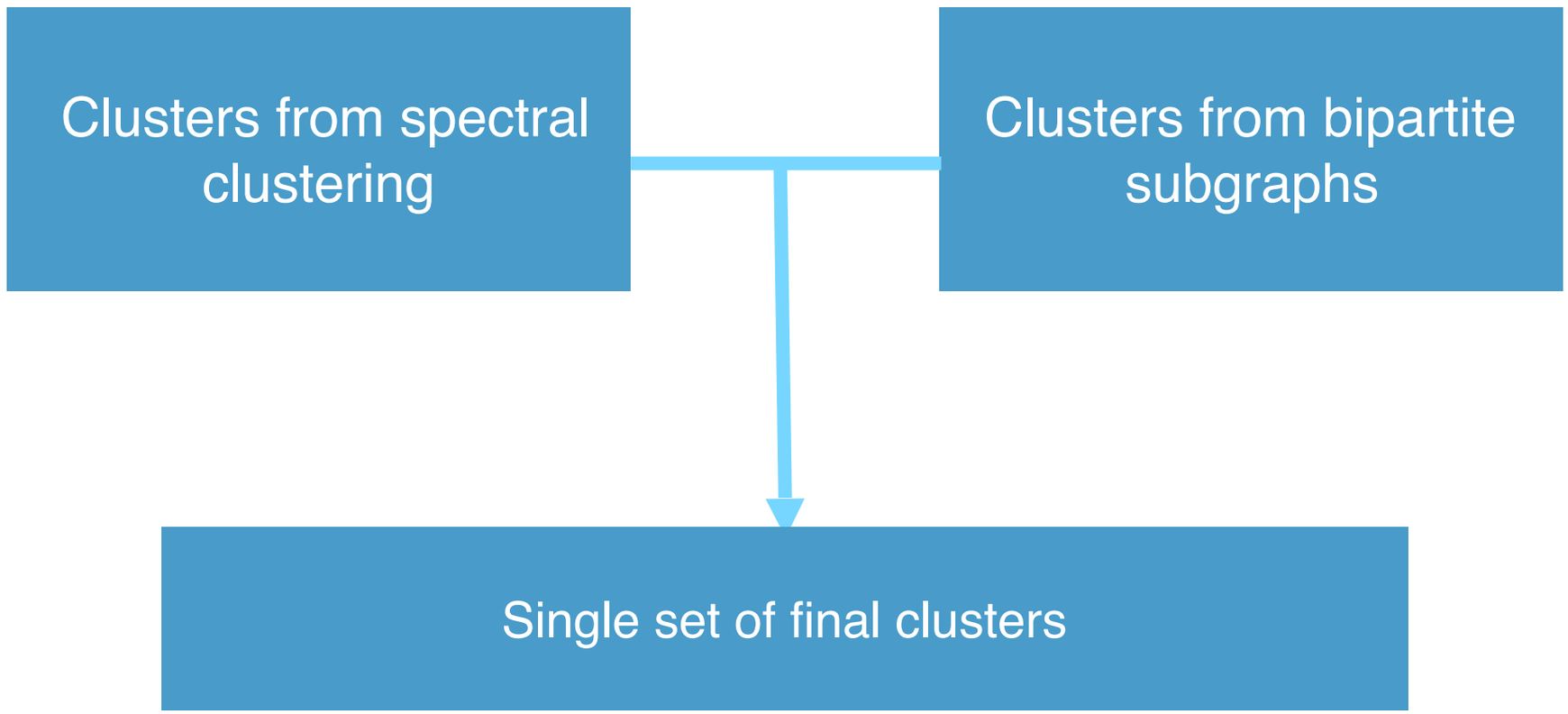
- We can identify many candidates by looking only at negative genetic interactions (Brady et al., 2009)

- We suspected there might be bipartite subgraphs in networks 2, 3, and 5

- We used the Genecentric software package to identify bipartite substructure

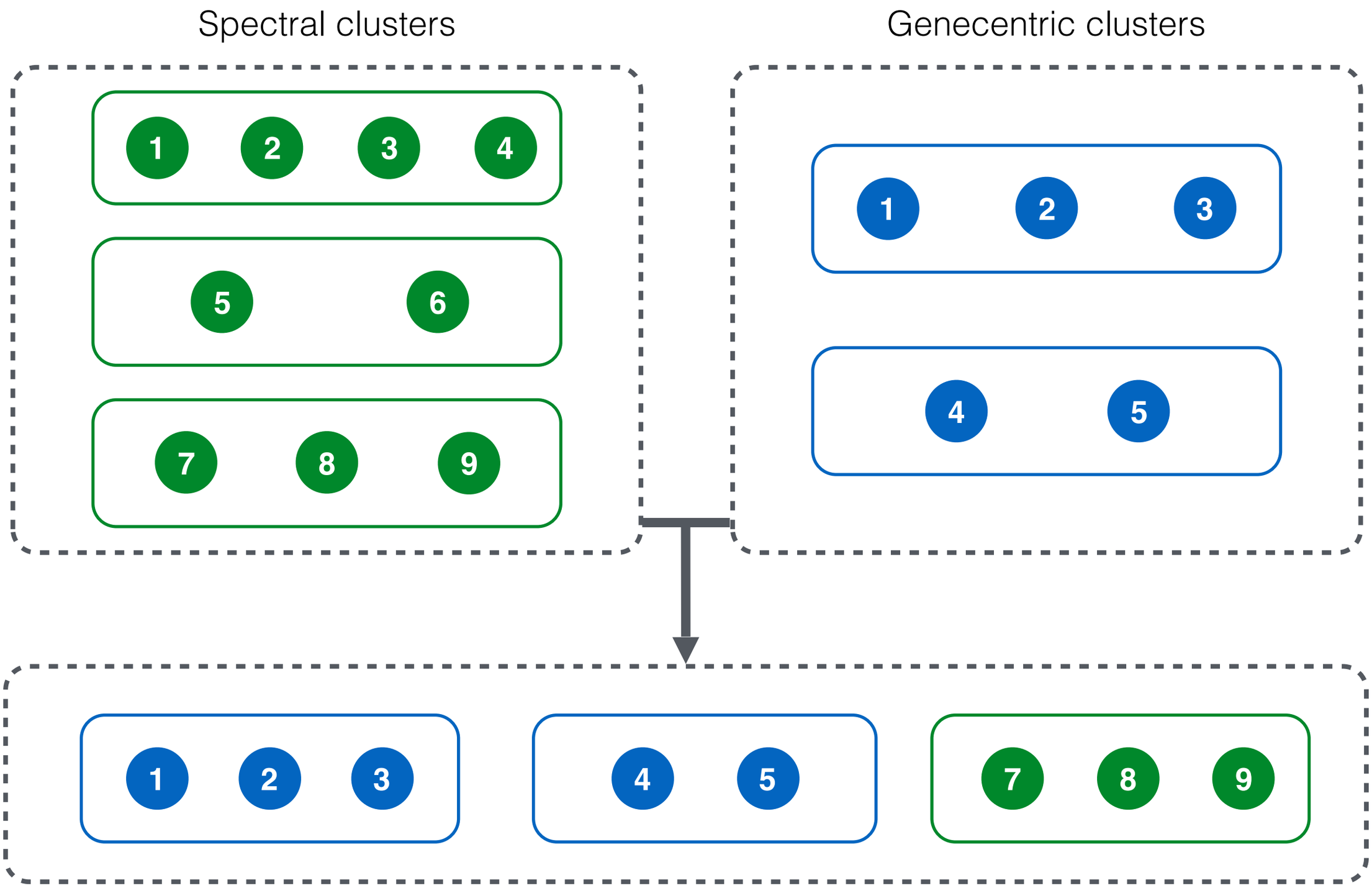


But, we're not quite finished

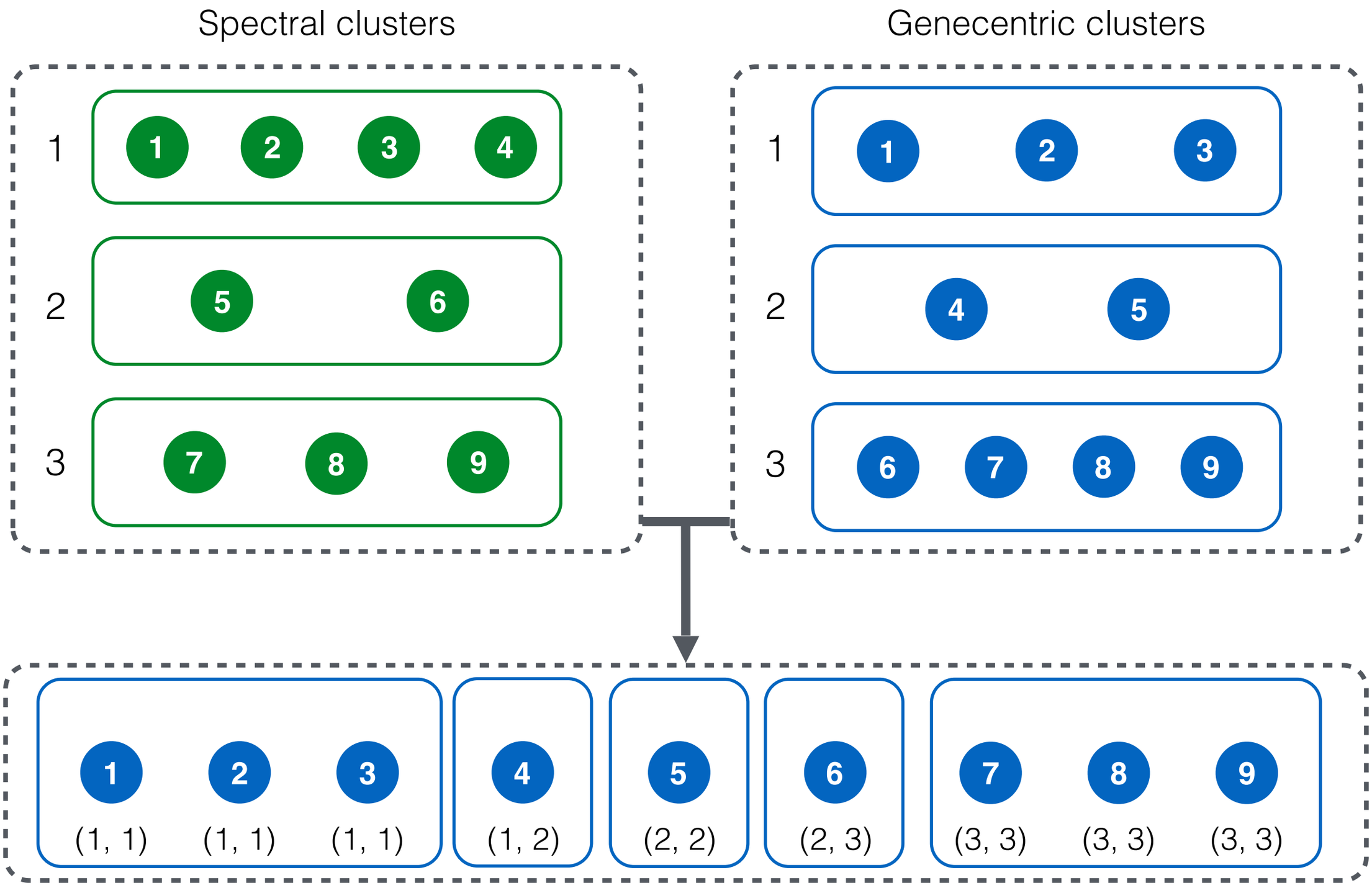


(for networks 2, 3, and 5)

Merging Clusters: Approach 1 (greedy)



Merging Clusters: Approach 2 (overlap)



Looking back:

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Diffusion State Distance

Cluster the resulting distance matrix

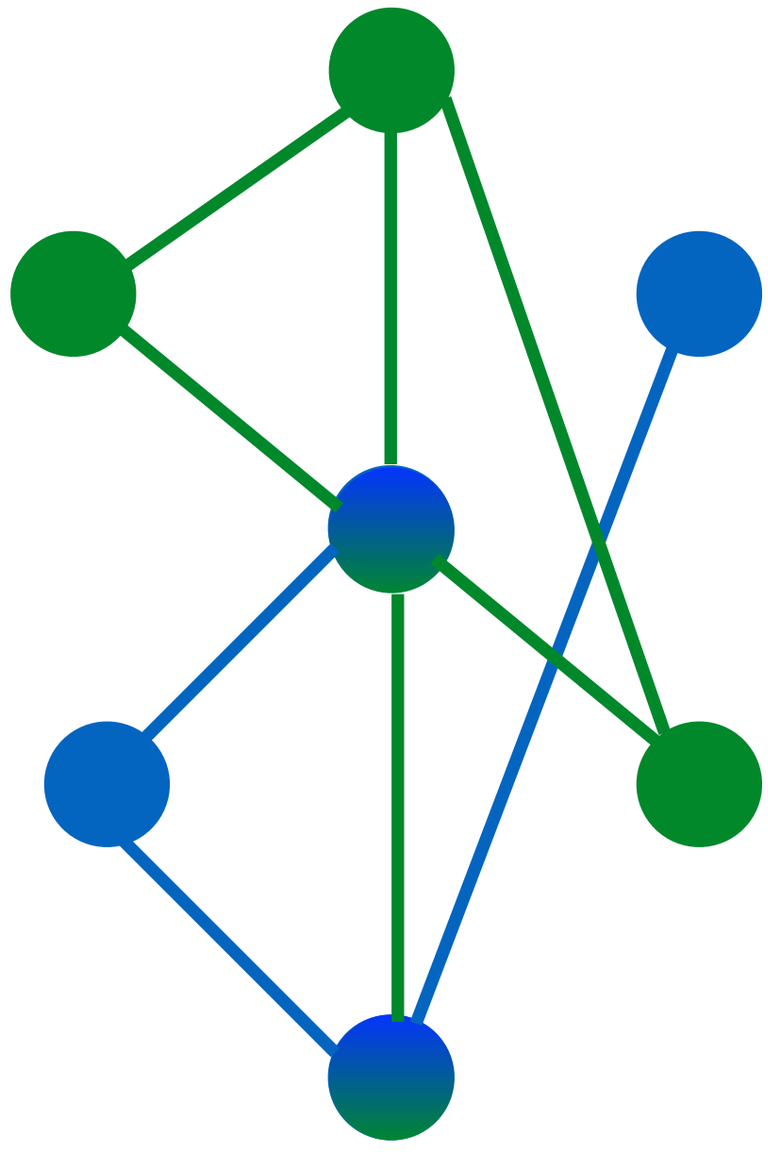
Correct cluster sizes

Look for bipartite subgraphs

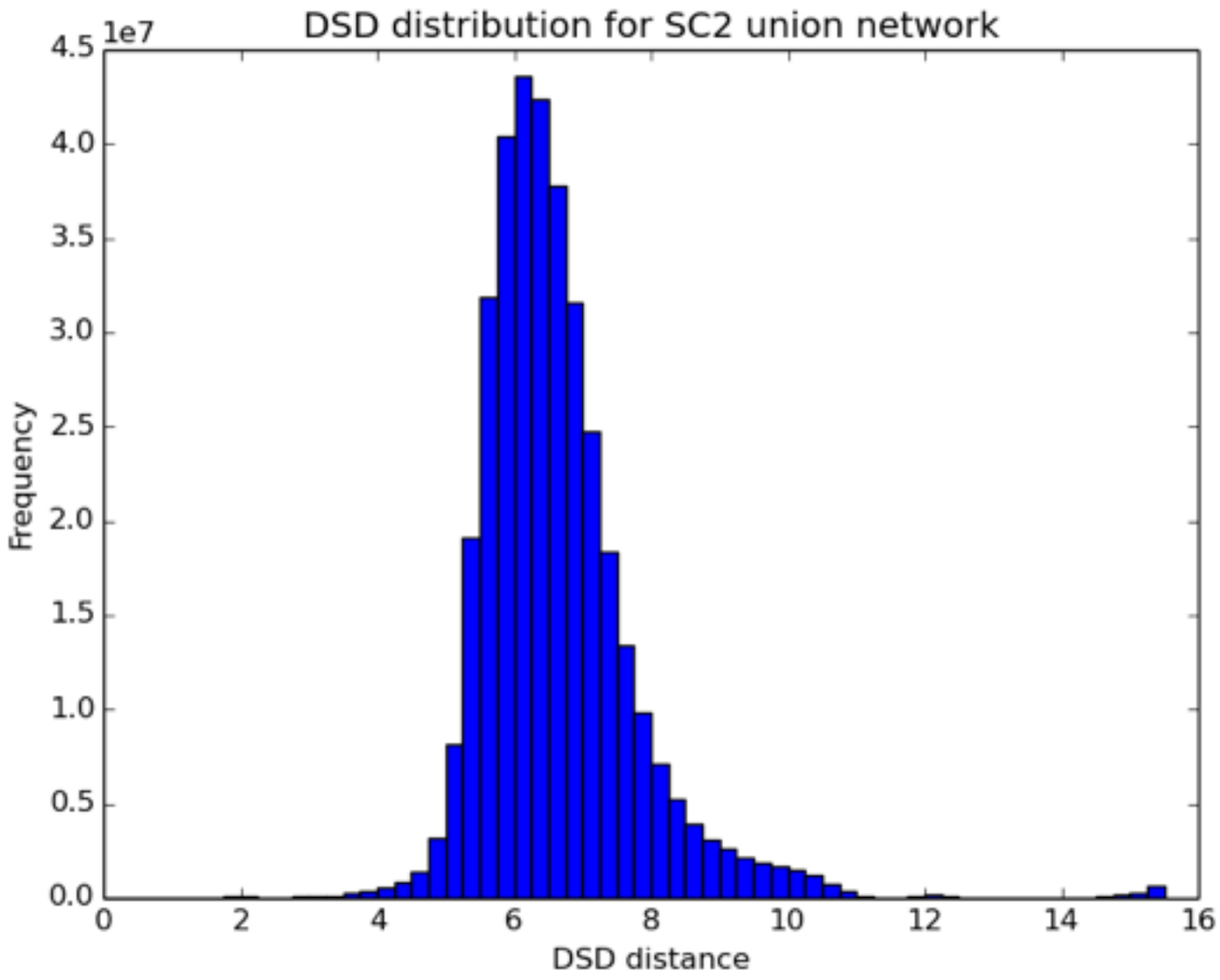
Return valid clusters

Subchallenge 2

- Took union of networks
- For overlapping edges with weights w_1, w_2, create edge with weight **max(w_1, w_2) + 0.05**
- Same DSD + spectral clustering approach as before
- Union of networks **1, 2, and 4** performed the best across FDR levels



Subchallenge 2:
Step 0: Superimpose networks 1,2 and 4
Step 1: Get the DSD matrix for the combined network



Future Directions

- Test modifications to edge weights
- Modify other clustering algorithms to run on top of DSD, there are many possible alternatives
- We could also test additional methods of combining edges (or adding networks) for Subchallenge 2

Acknowledgements

Thanks to the Tufts Bioinformatics and Computational Biology group for helpful ideas and critiques

BCBG

Bioinformatics and Computational Biology Group

Looking back