Network Meta-Analysis and Diffusion

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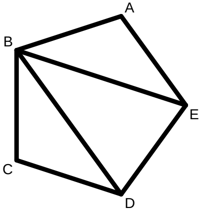
Outline

1. **Diffusion in network graphs**
   - Toy example: Simple diffusion
   - Toy example: Lazy diffusion
   - Toy example: Diffusion with an absorbing node
   - Star-shaped graph: Simple diffusion
   - Star-shaped graph: Lazy diffusion
   - Real-data example: Diffusion with an absorbing node
2. **A geometric series of diffusion matrices**
3. **Computing covariance and hat matrix via geometric series**
   - Finding NMA estimates iteratively
   - Examples
4. **Discussion**

Diffusion in network graphs: Simple diffusion



$\mathbf{A}$ (Weighted) adjacency matrix

$\mathbf{D}$ Diag.matrix of weighted degree

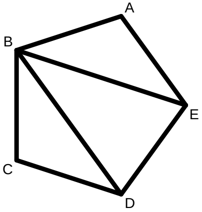
$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$ Diffusion (transition) matrix

Column = origin,

row = target point

$$\mathbf{A} = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 \end{pmatrix} \quad \mathbf{D} = \begin{pmatrix} 2 & 0 & 0 & 0 & 0 \\ 0 & 4 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 0 & 3 \end{pmatrix} \quad \mathbf{T} = \begin{pmatrix} \mathbf{0} & 0.25 & 0 & 0 & 0.333 \\ 0.5 & \mathbf{0} & 0.5 & 0.333 & 0.333 \\ 0 & 0.25 & \mathbf{0} & 0.333 & 0 \\ 0 & 0.25 & 0.5 & \mathbf{0} & 0.333 \\ 0.5 & 0.25 & 0 & 0.333 & \mathbf{0} \end{pmatrix}$$

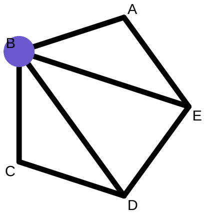
Diffusion in network graphs: Lazy diffusion



$\mathbf{A}$	Adjacency matrix
$\mathbf{D}$	Degree matrix
$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$	Diffusion (transition) matrix
$\tilde{\mathbf{T}} = (\mathbf{T} + \mathbf{I})/2$	Lazy diffusion matrix (half of the mass remains)

$$\mathbf{A} = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 \end{pmatrix} \quad \mathbf{D} = \begin{pmatrix} 2 & 0 & 0 & 0 & 0 \\ 0 & 4 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 0 & 3 \end{pmatrix} \quad \tilde{\mathbf{T}} = \begin{pmatrix} \mathbf{0.50} & 0.125 & 0 & 0 & 0.167 \\ 0.25 & \mathbf{0.50} & 0.25 & 0.167 & 0.167 \\ 0 & 0.125 & \mathbf{0.50} & 0.167 & 0 \\ 0 & 0.125 & 0.25 & \mathbf{0.50} & 0.167 \\ 0.25 & 0.125 & 0 & 0.167 & \mathbf{0.50} \end{pmatrix}$$

Diffusion in network graphs: Absorbing diffusion



$\mathbf{A}$	Weighted adjacency matrix
$\mathbf{D}$	Weighted degree matrix
$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$	Diffusion (transition) matrix
$\mathbf{T}_{-B}$	Diffusion matrix, here with absorbing node B (column B replaced with unit vector)

$$\mathbf{A} = \begin{pmatrix} 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 1 & 1 & 1 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 1 \\ 1 & 1 & 0 & 1 & 0 \end{pmatrix} \quad \mathbf{D} = \begin{pmatrix} 2 & 0 & 0 & 0 & 0 \\ 0 & 4 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 3 & 0 \\ 0 & 0 & 0 & 0 & 3 \end{pmatrix} \quad \mathbf{T}_{-B} = \begin{pmatrix} 0 & \mathbf{0} & 0 & 0 & 0.333 \\ 0.5 & \mathbf{1} & 0.5 & 0.333 & 0.333 \\ 0 & \mathbf{0} & 0 & 0.333 & 0 \\ 0 & \mathbf{0} & 0.5 & 0 & 0.333 \\ 0.5 & \mathbf{0} & 0 & 0.333 & 0 \end{pmatrix}$$

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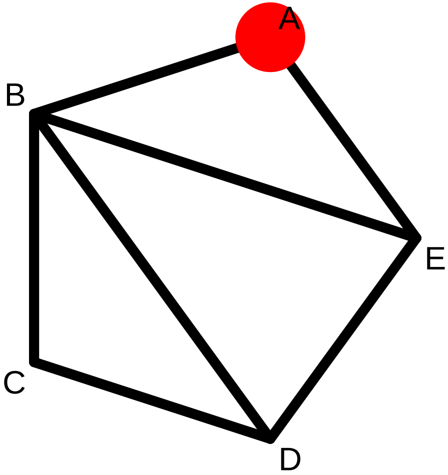
Simple diffusion, starting with all mass in A



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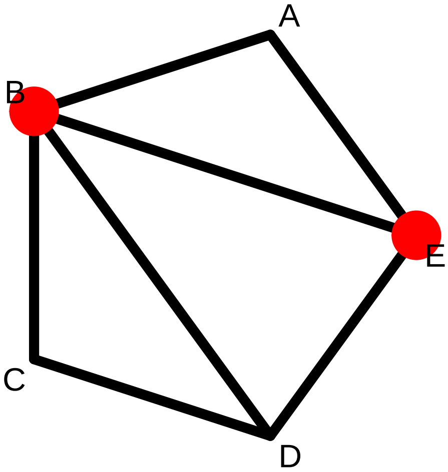

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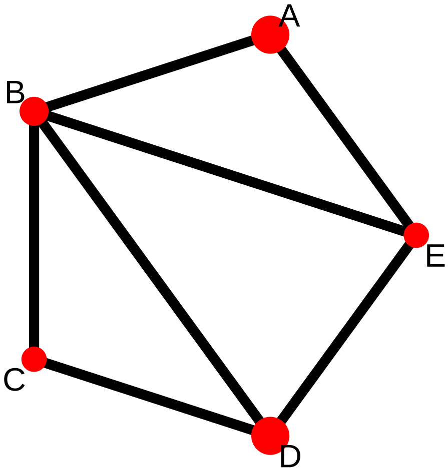

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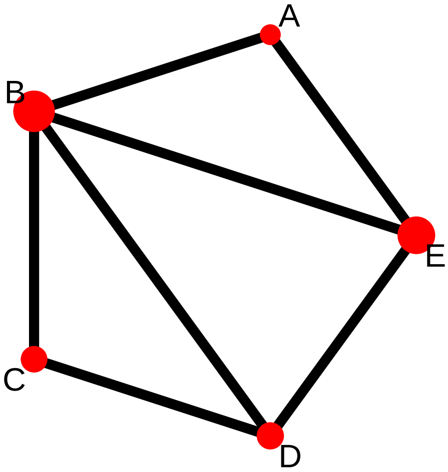

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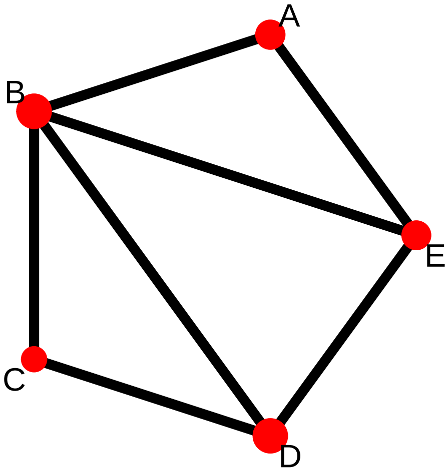

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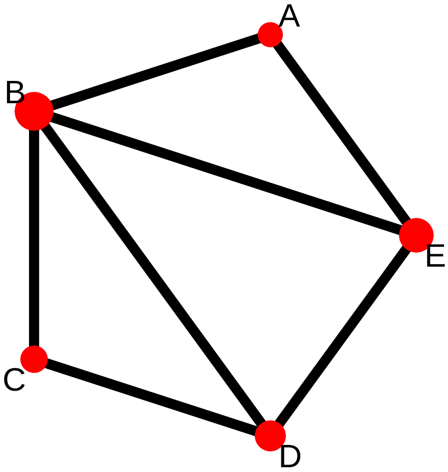

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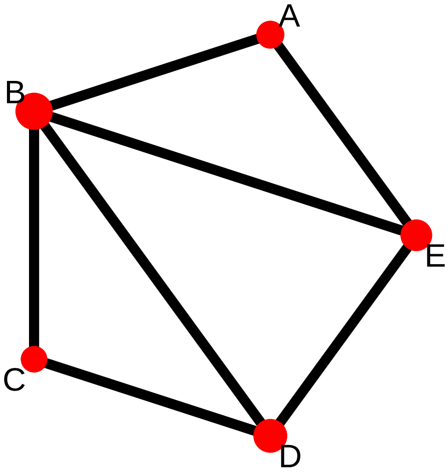

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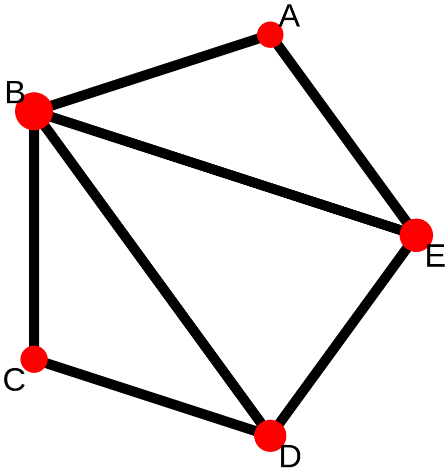

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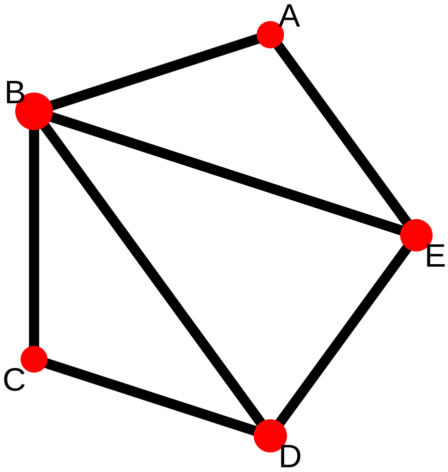

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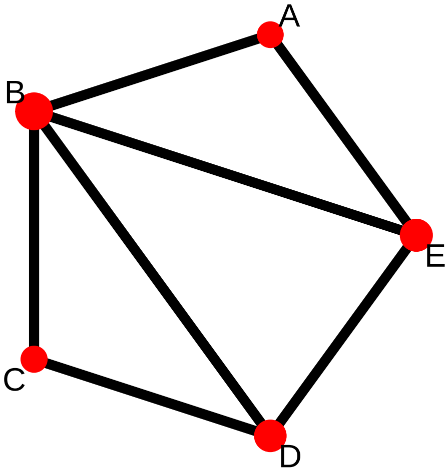

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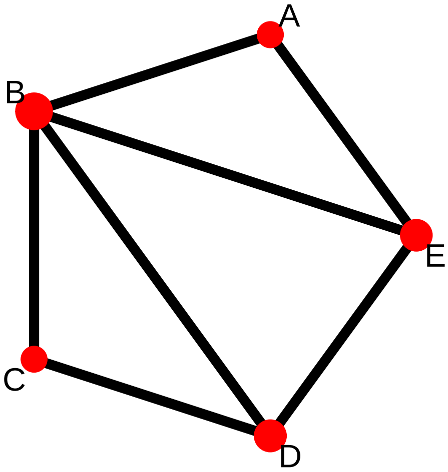

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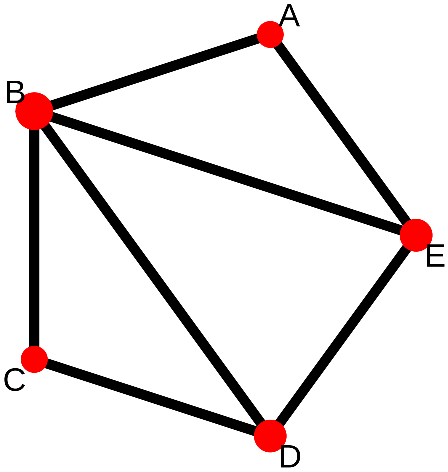

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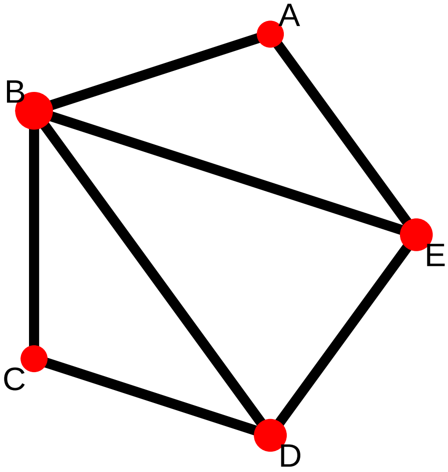
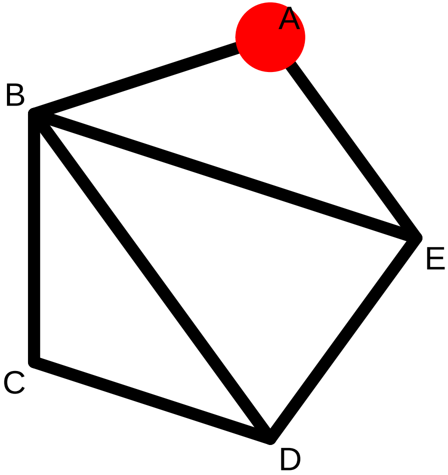


- After many iterations, distribution stabilizes proportional to the degrees
- Final distribution does not depend on the starting distribution:

Node	A	B	C	D	E
Weight	$\frac{2}{14}$	$\frac{4}{14}$	$\frac{2}{14}$	$\frac{3}{14}$	$\frac{3}{14}$

Lazy diffusion: half of the mass doesn't move



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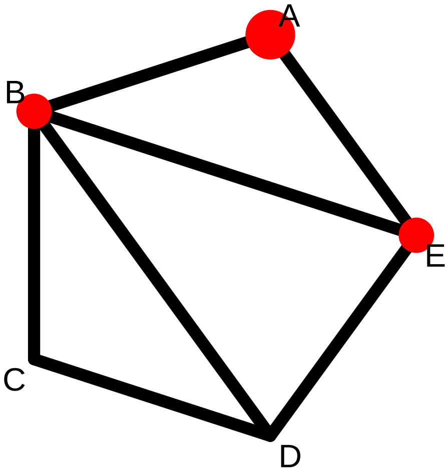

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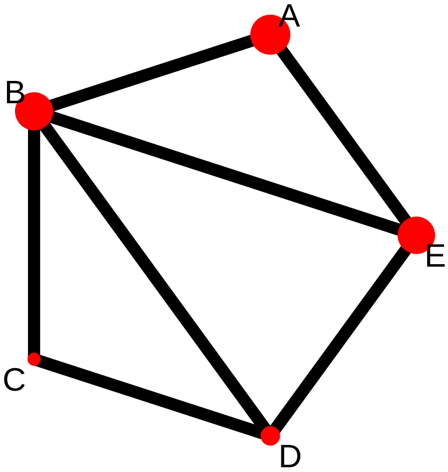

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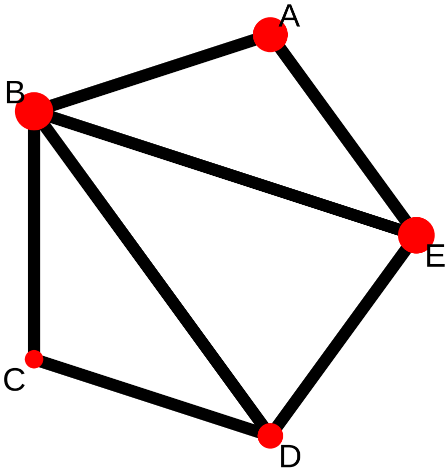

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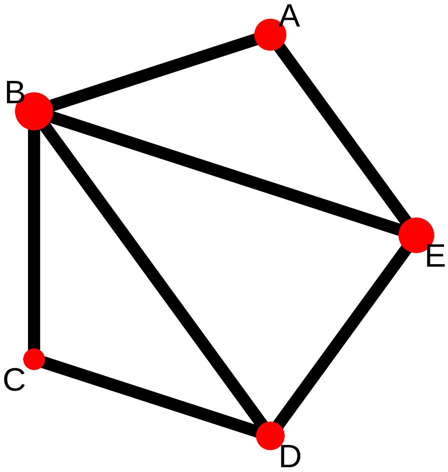

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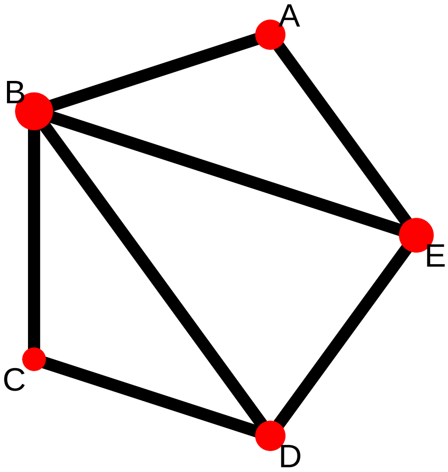

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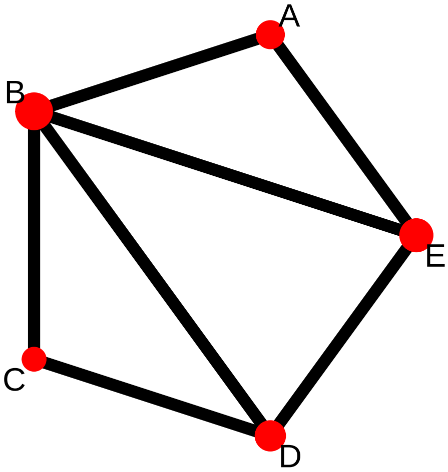

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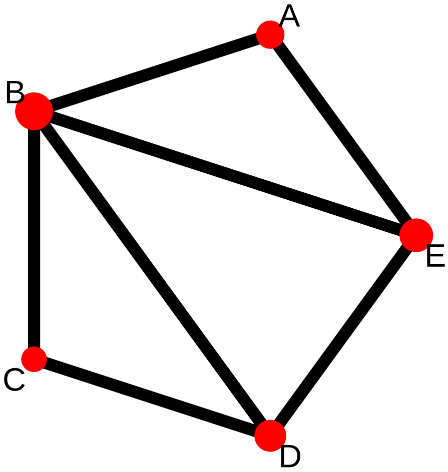

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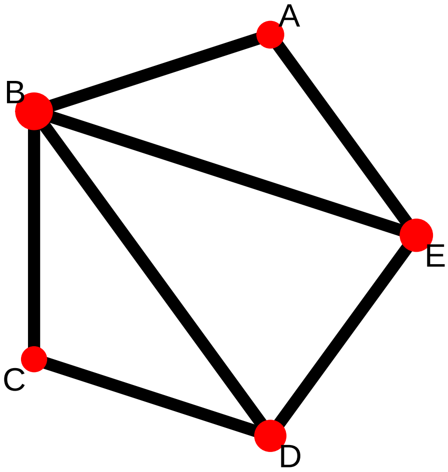

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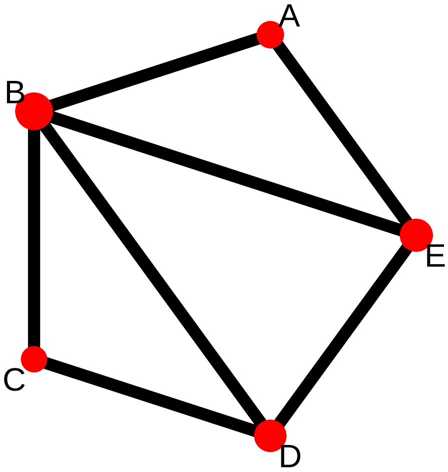

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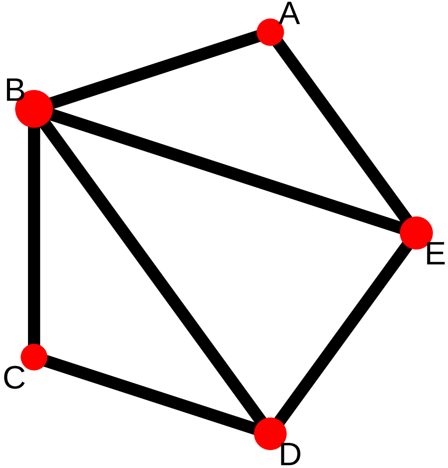

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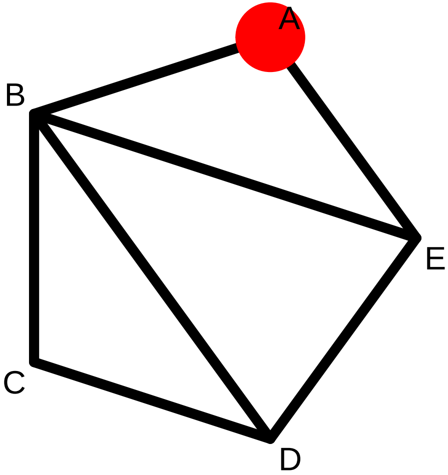
Diffusion with absorbing node B, starting in A



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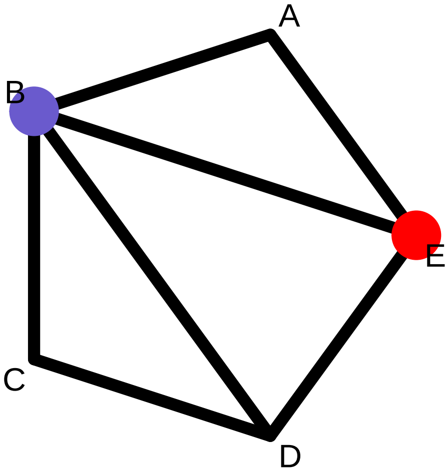

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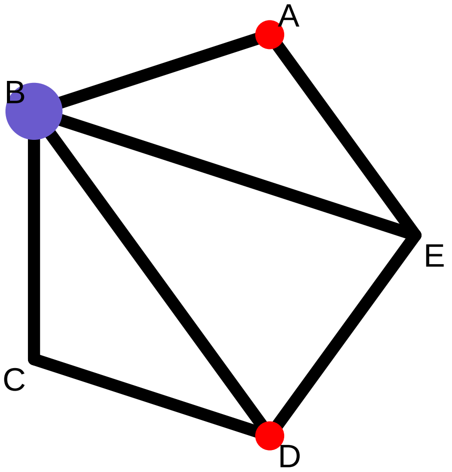

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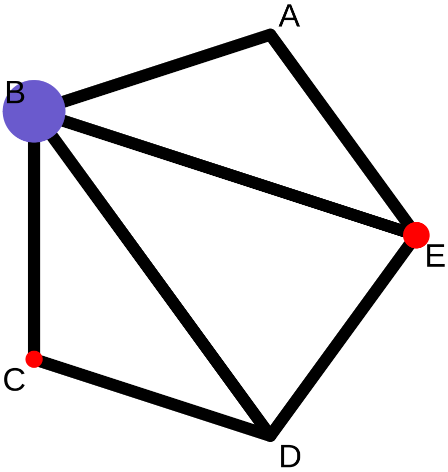

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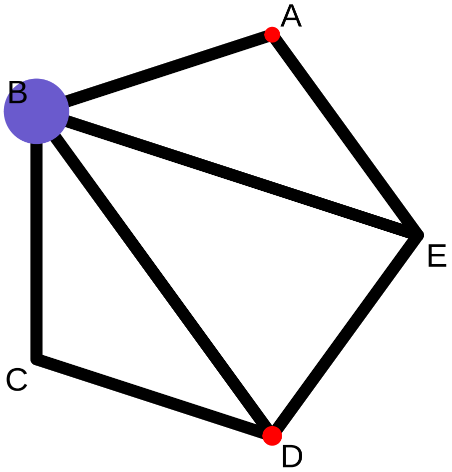

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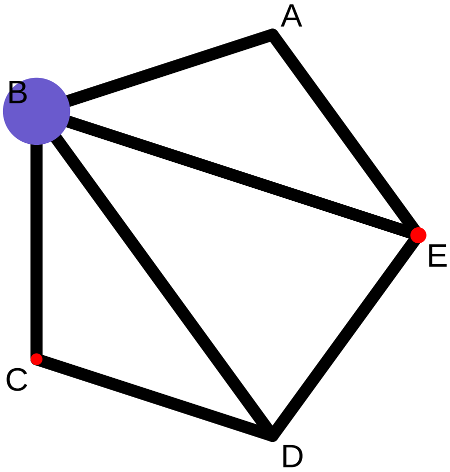

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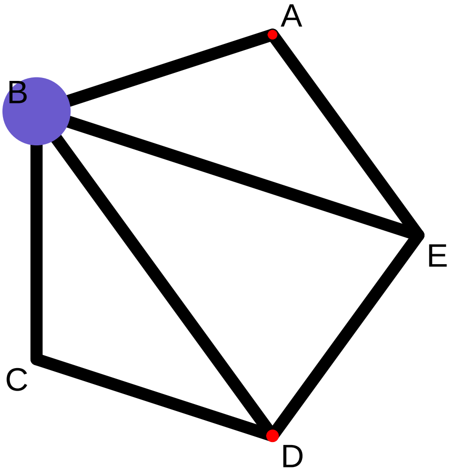

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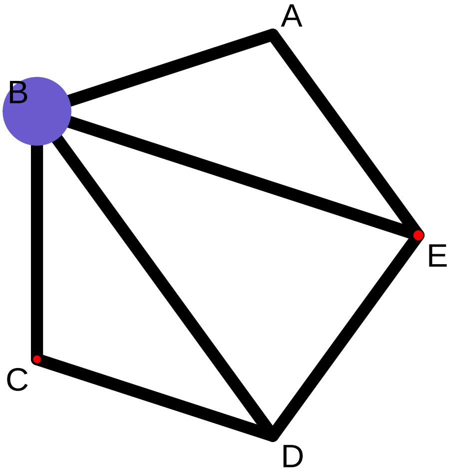

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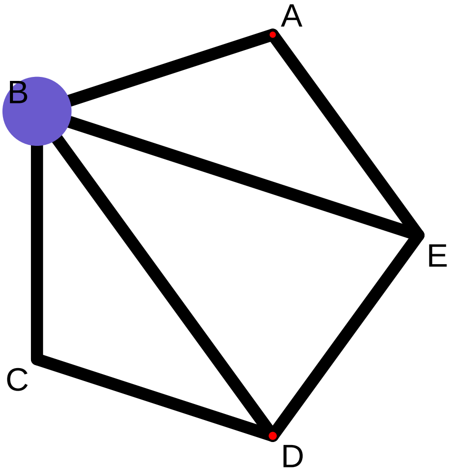

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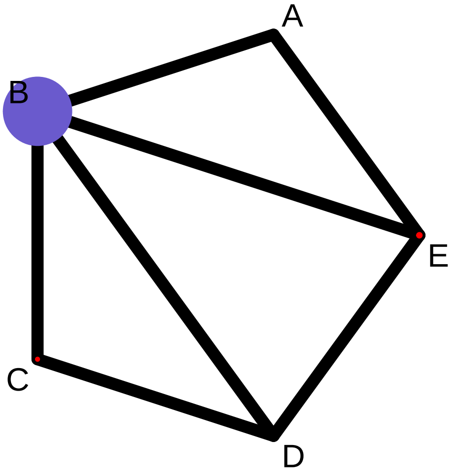

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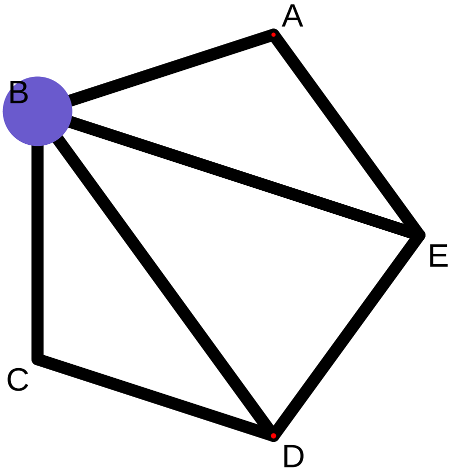
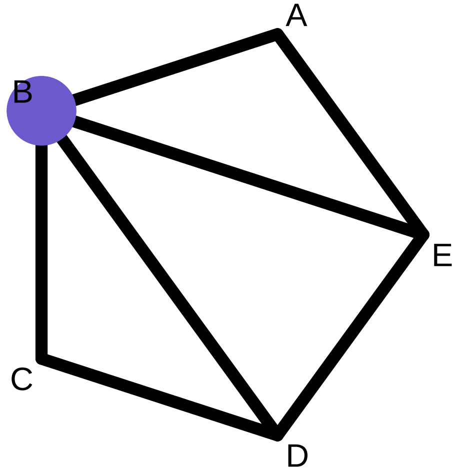


Diffusion with absorbing node B, starting in A



- After some iterations, all mass is concentrated in the absorbing node:

Node	A	B	C	D	E
Weight	0	1	0	0	0

Iterating diffusion

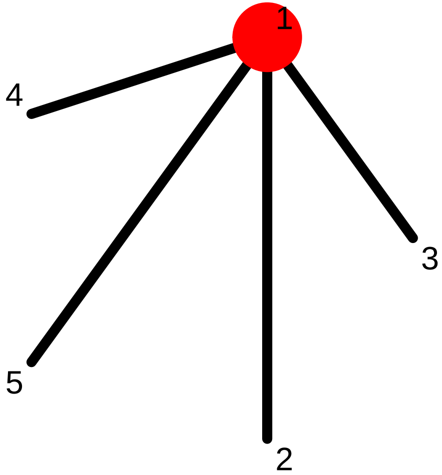
- Simple or lazy diffusion: Limit matrix has equal columns, proportional to the (weighted) degrees:

$$\mathbf{T}, \tilde{\mathbf{T}} \to \mathbf{T}^{\infty} = \frac{1}{14} \begin{pmatrix} 2 & 2 & 2 & 2 & 2 \\ 4 & 4 & 4 & 4 & 4 \\ 2 & 2 & 2 & 2 & 2 \\ 3 & 3 & 3 & 3 & 3 \\ 3 & 3 & 3 & 3 & 3 \end{pmatrix}$$

- Absorbing diffusion: Limit matrix has equal columns, all mass in the absorbing node:

$$\mathbf{T}_{-B} \to \mathbf{T}^{\infty}_{-B} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Iterating simple diffusion for a bipartite graph



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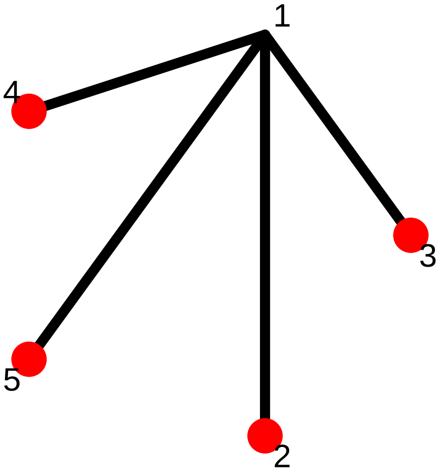

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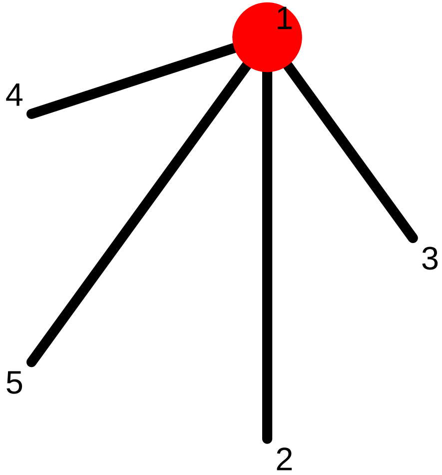

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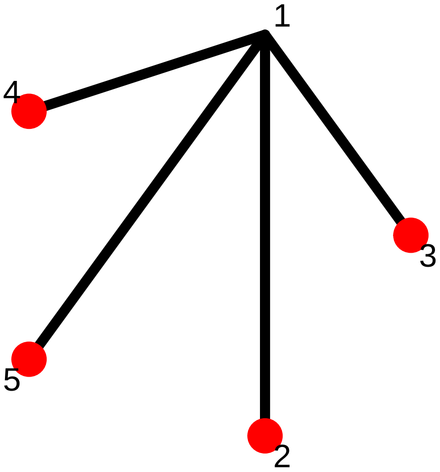

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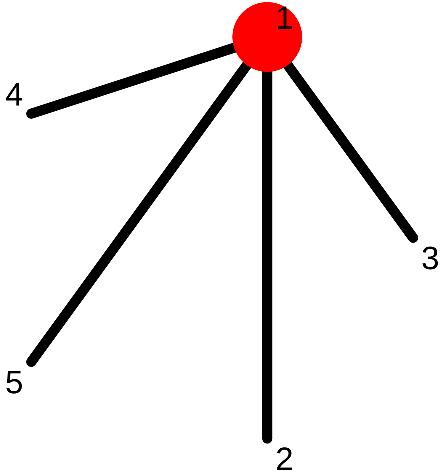

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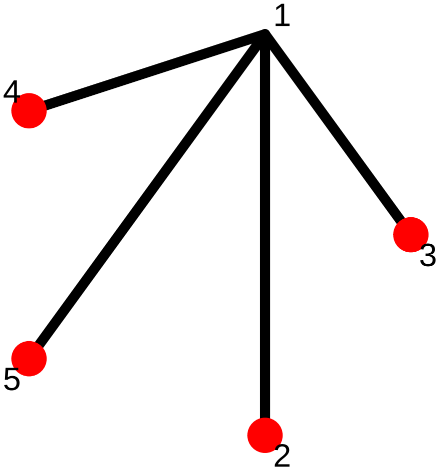
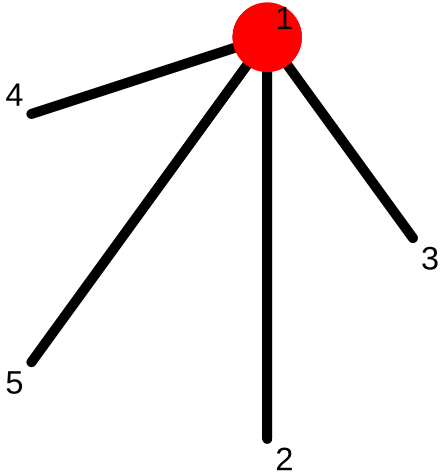


- Mass oscillates between two sets of nodes
- No convergence

Lazy diffusion: half of the mass doesn't move



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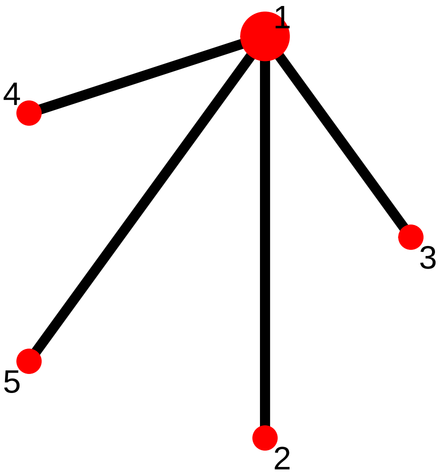
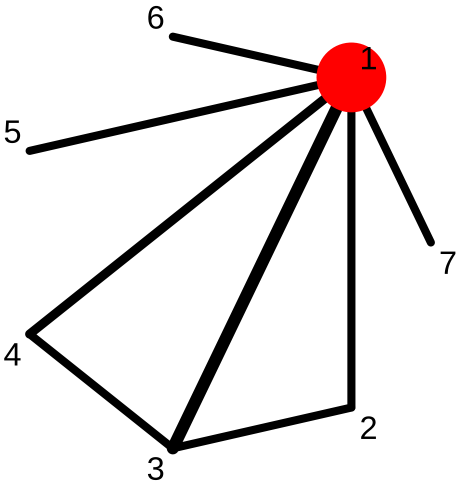


- After only one iteration, distribution stabilizes proportional to the degrees
- Final distribution does not depend on the starting distribution

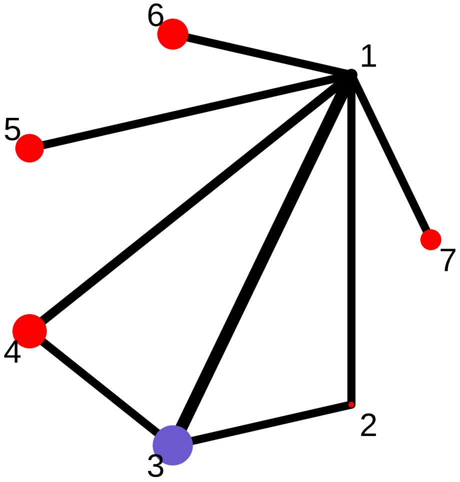
$$\mathbf{T}^{\infty} = \frac{1}{8} \begin{pmatrix} 4 & 4 & 4 & 4 & 4 \\ 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 \end{pmatrix}.$$

Absorbing diffusion for an almost bipartite graph [Jalota et al., 2011]



- 102 trials (including 3 three-arm trials) of 7 interventions

Absorbing diffusion for an almost bipartite graph (node 3 absorbing)



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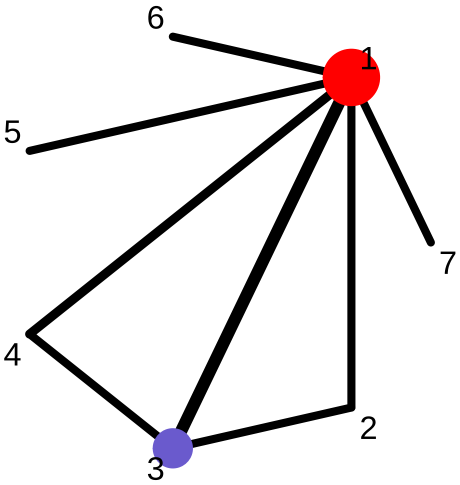

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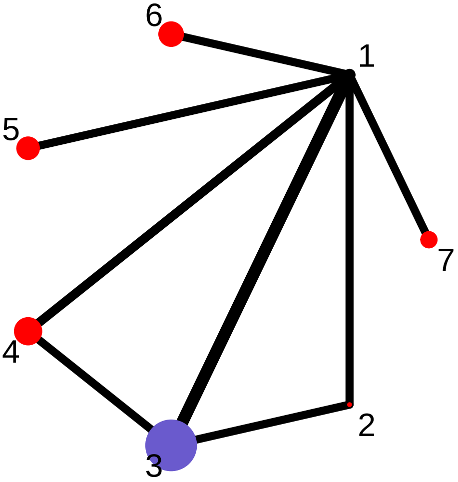

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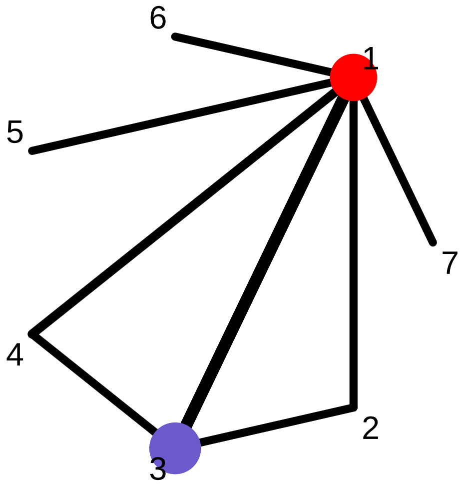

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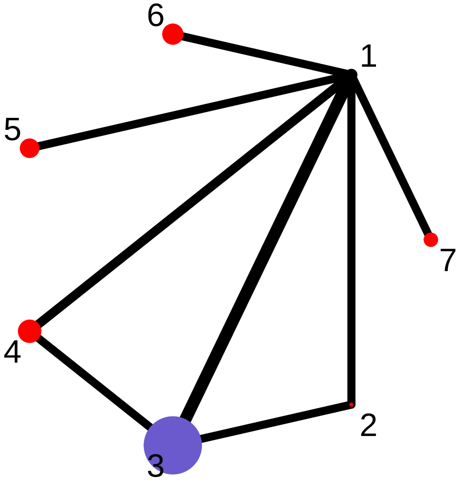

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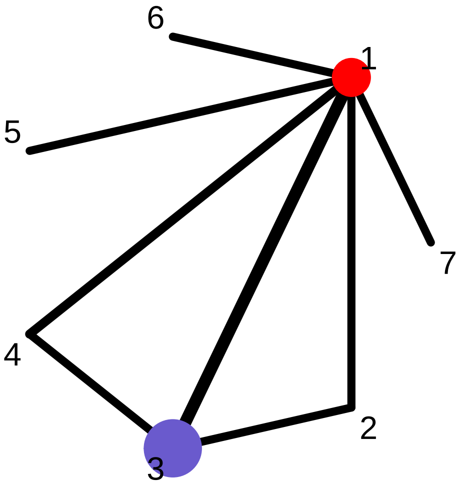

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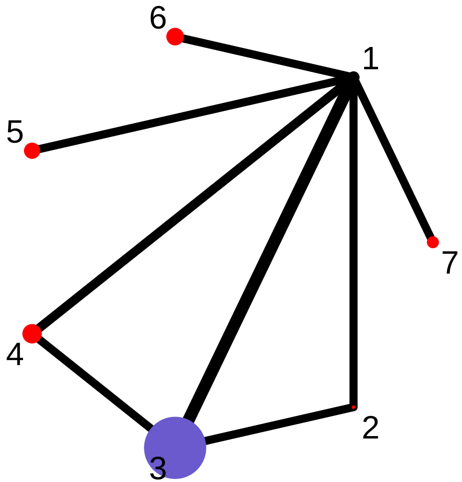
Absorbing diffusion for an almost bipartite graph (node 3 absorbing)



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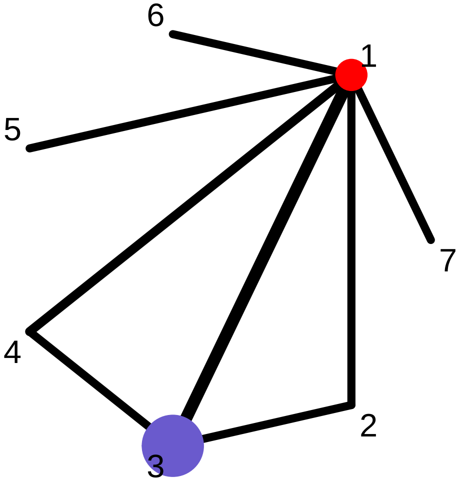

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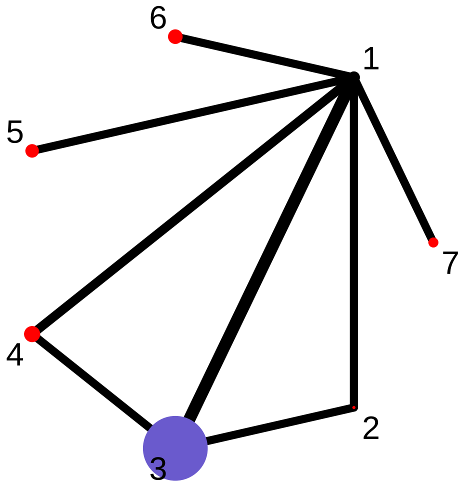

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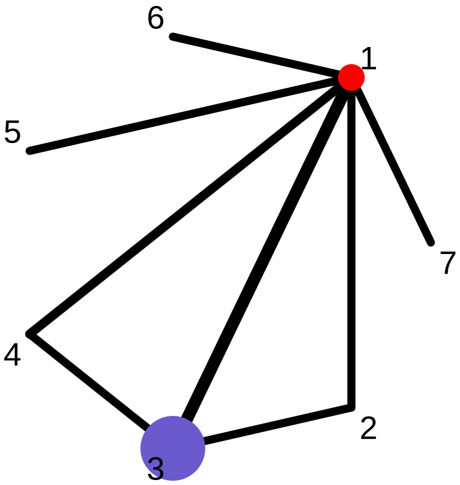

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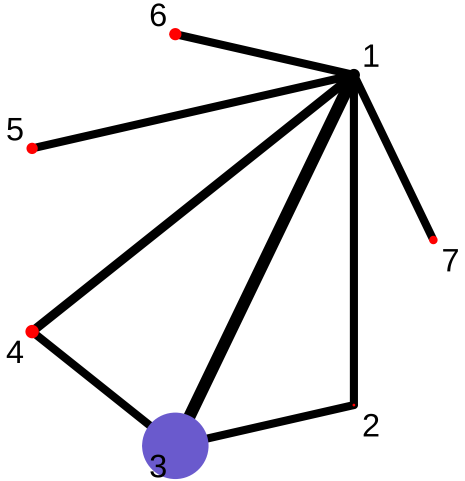

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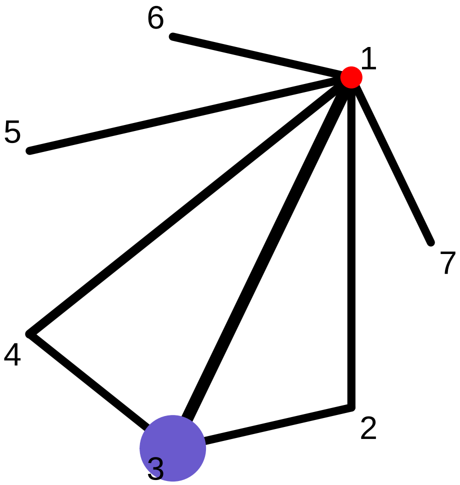

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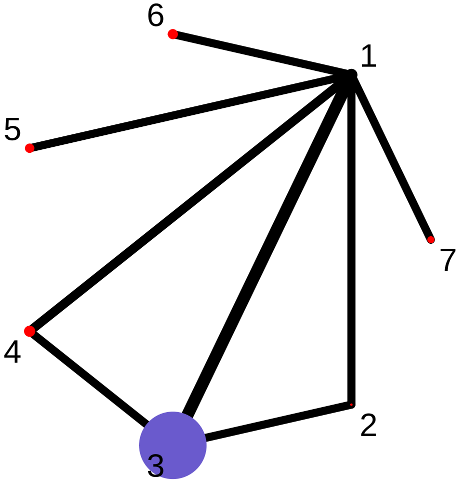

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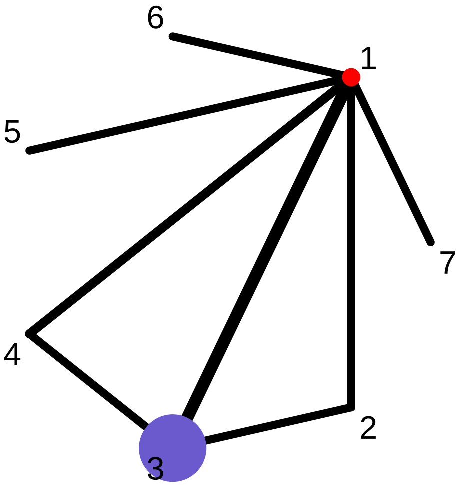

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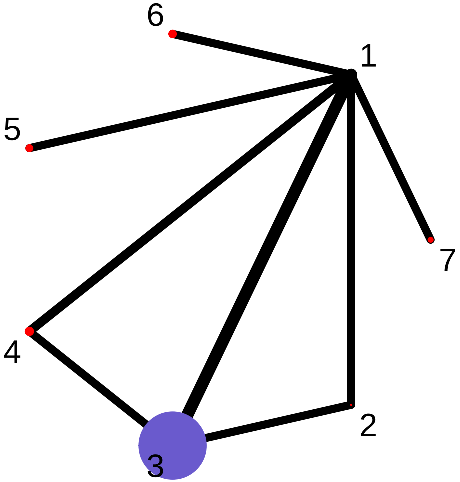

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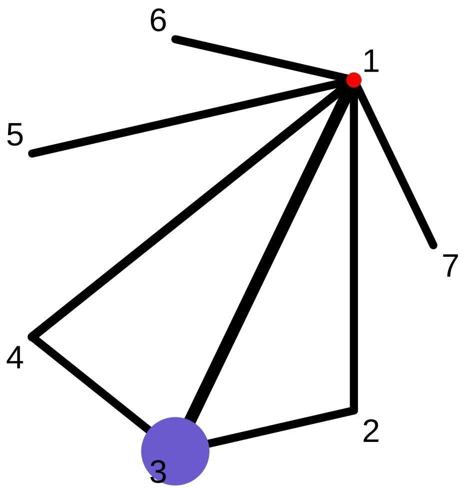

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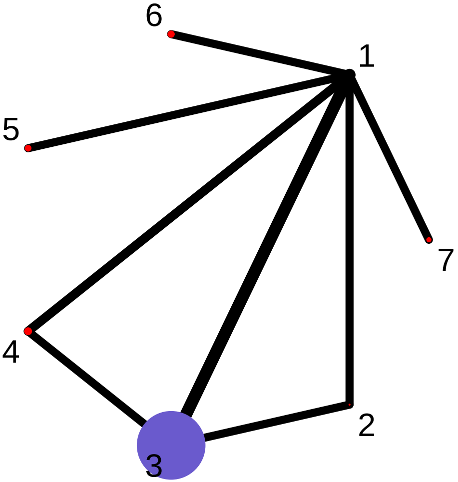

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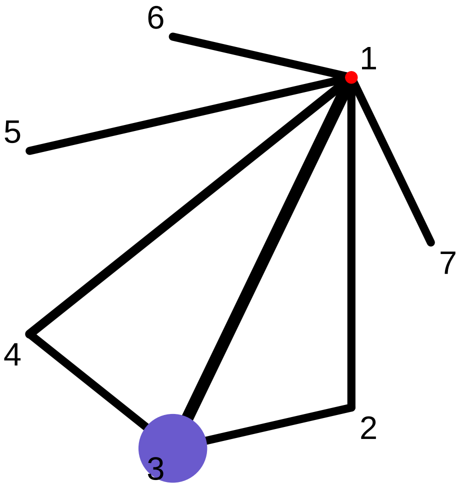

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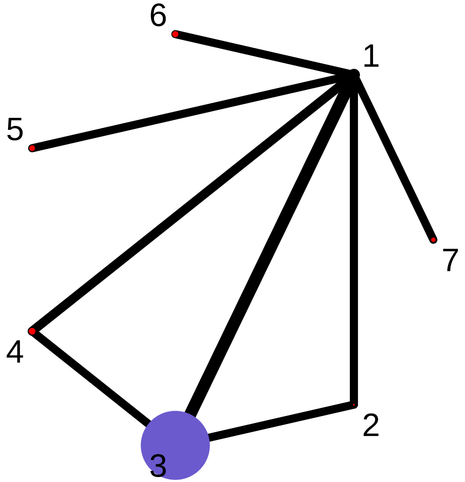

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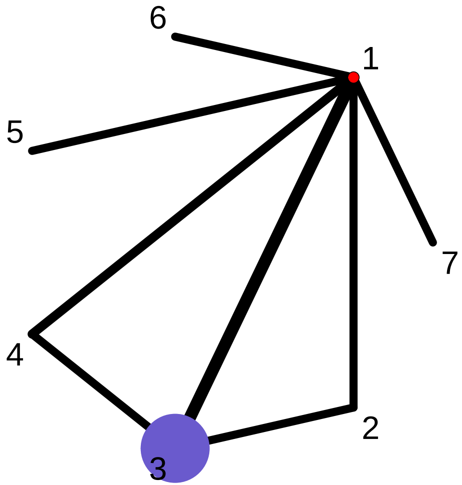

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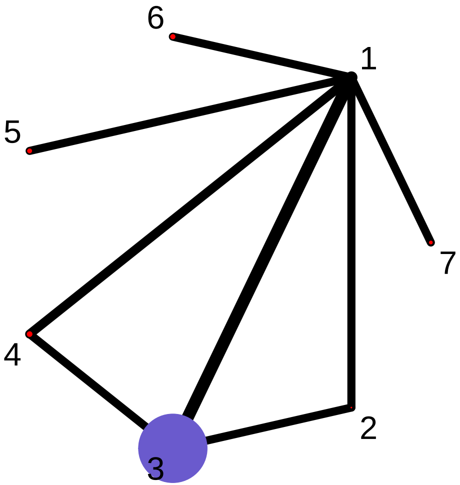

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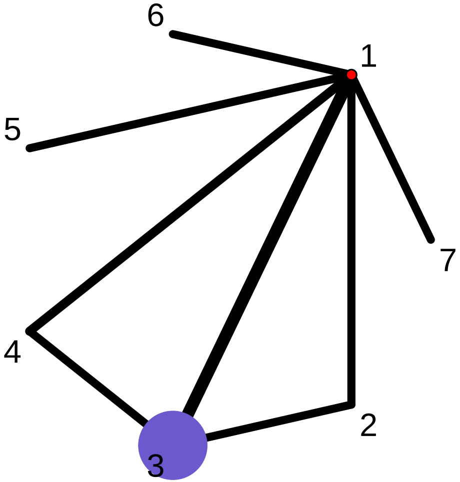

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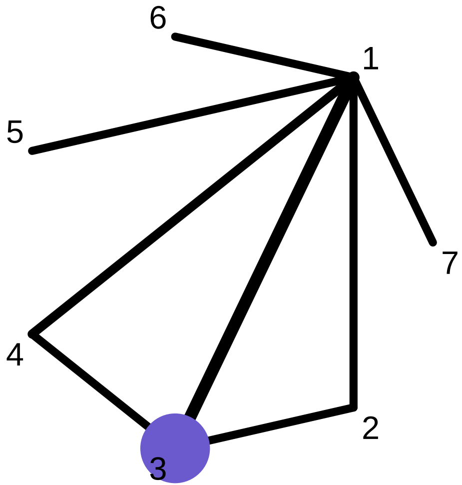

- 102 trials (including 3 three-arm trials) of 7 interventions
- After many iterations, all mass is concentrated in the absorbing node (here 3)

Covariance matrix and hat matrix

- $\mathbf{X}$ design matrix, $\mathbf{W}$ (diagonal) weight matrix
- Laplacian matrix

$$\mathbf{L} = \mathbf{X}^\top \mathbf{W} \mathbf{X}$$

- $\mathbf{L}^+$ pseudoinverse of Laplacian matrix
- Variance-covariance matrix of the NMA estimates

$$\mathbf{C} = \mathbf{X}\, \mathbf{L}^+ \mathbf{X}^\top$$

- Hat matrix

$$\mathbf{H} = \mathbf{C}\mathbf{W}$$

- Idea: Replace $\mathbf{L}^+$ with a geometric series of diffusion matrices!

Geometric series

For $x \in \mathbb{R}, |x| < 1$:

$$x^k \to 0$$

$$\sum_{k=0}^{\infty} x^k = 1 + x + x^2 + x^3 + \cdots = \frac{1}{1-x}$$

Geometric series

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$$\sum_{k=0}^{\infty} x^k = 1 + x + x^2 + x^3 + \cdots = \frac{1}{1-x}$$

If the series $\sum_{k=0}^{\infty} \mathbf{M}^k$ converges for a matrix $\mathbf{M}$, we have:

$$\mathbf{M}^k \to \mathbf{0}$$

$$\sum_{k=0}^{\infty} \mathbf{M}^k = \mathbf{I} + \mathbf{M} + \mathbf{M}^2 + \mathbf{M}^3 + \cdots = (\mathbf{I} - \mathbf{M})^{-1}$$

($\mathbf{0}$ is the null matrix, $\mathbf{I}$ is the identity matrix)

A geometric series of diffusion matrices – Rough idea

$\mathbf{A}$	Weighted adjacency matrix
$\mathbf{D}$	Weighted degree matrix
$\mathbf{L} = \mathbf{D} - \mathbf{A}$	Laplacian matrix
$\mathbf{L}^{+}$	Moore-Penrose pseudoinverse of $\mathbf{L}$
$\mathbf{I}$	Identity matrix
$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1} = (\mathbf{D} - \mathbf{L})\mathbf{D}^{-1} = \mathbf{I} - \mathbf{L}\mathbf{D}^{-1}$	Diffusion (transition) matrix

If $\mathbf{L}$ were regular:

$$\mathbf{L}^{-1} =$$

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However, $\mathbf{L}^{-1}$ does not exist …

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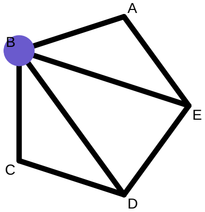
However, $\mathbf{L}^{-1}$ does not exist … but there are solutions!

Solution 1: Absorbing diffusion



$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$ Diffusion (transition) matrix

Choose a reference node

$\mathbf{T}_{-B}$ Diffusion matrix with absorbing node (B)

$$\mathbf{T}_{-B} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0.333 \\ 0.5 & 1 & 0.5 & 0.333 & 0.333 \\ 0 & 0 & 0 & 0.333 & 0 \\ 0 & 0 & 0.5 & 0 & 0.333 \\ 0.5 & 0 & 0 & 0.333 & 0 \end{pmatrix}$$

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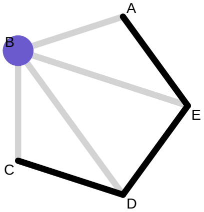

$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$ Diffusion (transition) matrix

Choose a reference node

$\mathbf{T}_{-B}$ Reduce diffusion matrix by row / column belonging to B

$$\mathbf{T}_{-B} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0.333 \\ 0.5 & 1 & 0.5 & 0.333 & 0.333 \\ 0 & 0 & 0 & 0.333 & 0 \\ 0 & 0 & 0.5 & 0 & 0.333 \\ 0.5 & 0 & 0 & 0.333 & 0 \end{pmatrix}$$

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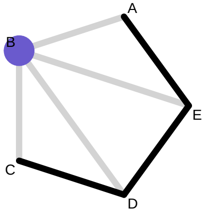

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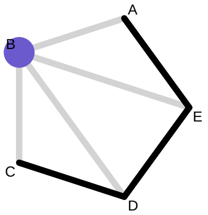
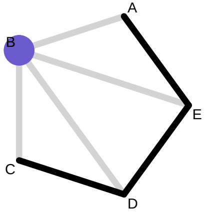


$\mathbf{T} = \mathbf{A}\mathbf{D}^{-1}$	Diffusion (transition) matrix
	Choose a reference node
$\mathbf{T}_{-B}$	Reduce diffusion matrix by row / column belonging to B
$(\mathbf{T}_{-B})^k \to \mathbf{0}$	Null matrix

$$\mathbf{T}_{-B} = \begin{pmatrix} 0 & 0 & 0 & 0.333 \\ 0 & 0 & 0.333 & 0 \\ 0 & 0.5 & 0 & 0.333 \\ 0.5 & 0 & 0.333 & 0 \end{pmatrix}$$

Sequence $(\mathbf{T}_{-B})^k$ converges against the null matrix, series $\sum_{k=0}^{\infty} (\mathbf{T}_{-B})^k$ converges

Covariance matrix and hat matrix



$\mathbf{T} = \mathbf{T}_{-B}$	Reduced diffusion matrix
$\mathbf{X} = \mathbf{X}_{-B}$	Reduced design matrix
$\mathbf{D} = \mathbf{D}_{-B}$	Reduced degree matrix
$\mathbf{W}$	Weight matrix

$$\mathbf{X} = \mathbf{X}_{-B} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & -1 \\ 0 & -1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$$

Covariance matrix and hat matrix written using a geometric series of absorbing diffusion matrices:

$$\mathbf{C} = \mathbf{X}\mathbf{D}^{-1} \sum_{k=0}^{\infty} \mathbf{T}^k \mathbf{X}^\top$$

$$\mathbf{H} = \mathbf{X}\mathbf{D}^{-1} \sum_{k=0}^{\infty} \mathbf{T}^k \mathbf{X}^\top \mathbf{W}$$

Solution 2: Lazy diffusion

$$(\tilde{\mathbf{T}})^k \to \mathbf{T}^\infty = \frac{1}{14}\begin{pmatrix} 2 & 2 & 2 & 2 & 2 \\ 4 & 4 & 4 & 4 & 4 \\ 2 & 2 & 2 & 2 & 2 \\ 3 & 3 & 3 & 3 & 3 \\ 3 & 3 & 3 & 3 & 3 \end{pmatrix}$$

$$\mathbf{X}^\top = \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 1 & 1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & -1 & 0 & -1 & 1 \\ 0 & -1 & 0 & 0 & -1 & 0 & -1 \end{pmatrix}$$

$$\Rightarrow \tilde{\mathbf{T}}^k \mathbf{X}^\top \to \mathbf{T}^\infty \mathbf{X}^\top = \mathbf{0}$$

$$\mathbf{C} = \frac{1}{2}\mathbf{X}\mathbf{D}^{-1} \sum_{i=0}^{\infty} \left(\tilde{\mathbf{T}}^k \mathbf{X}^\top\right)$$

$$\mathbf{H} = \frac{1}{2}\mathbf{X}\mathbf{D}^{-1} \sum_{i=0}^{\infty} \left(\tilde{\mathbf{T}}^k \mathbf{X}^\top\right) \mathbf{W}$$

- The sum $\sum_{i=0}^{\infty} \tilde{\mathbf{T}}^k$ does not converge.
- However, $\sum_{i=0}^{\infty} \left(\tilde{\mathbf{T}}^k \mathbf{X}^\top\right)$ converges!

What this means

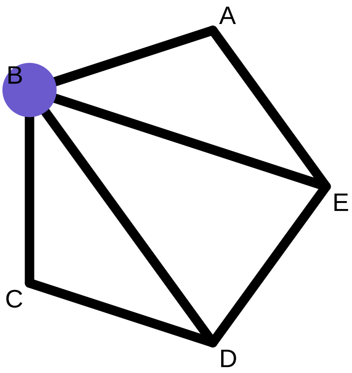
- Both methods (absorbing or lazy diffusion) work in general (also for bipartite networks)
- Instead of matrix (pseudo-)inversion, we use a geometric series
- The underlying idea is $\sum_{k=0}^{\infty} \mathbf{T}^k = (\mathbf{I} - \mathbf{T})^{-1}$
- Using the partial sums, we may define a matrix series approximating the hat matrix:

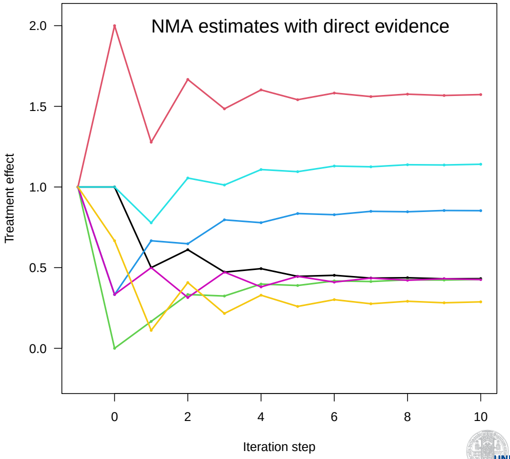
$$\mathbf{H}_N = \mathbf{X}\mathbf{D}^{-1} \sum_{k=0}^{N} \mathbf{T}^k \mathbf{X}^\top \mathbf{W} \quad \rightarrow \quad \mathbf{H}$$

- Based on $\mathbf{H}_0, \mathbf{H}_1, \mathbf{H}_2, \ldots$ we start with the observed treatment effects $\mathbf{y}$ and obtain a sequence of estimates approximating the network estimates:

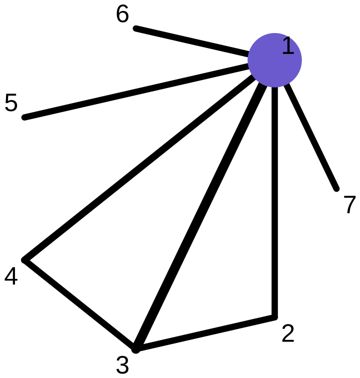
$$\hat{\mathbf{y}}_N = \mathbf{H}_N \mathbf{y} \quad \rightarrow \quad \hat{\mathbf{y}} = \mathbf{H}\mathbf{y}$$

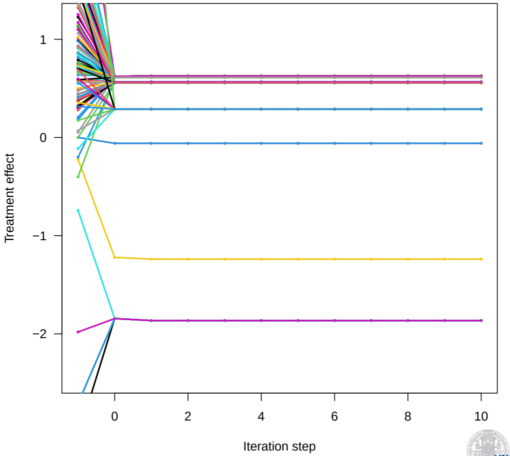
Finding NMA estimates iteratively, toy example (all observed treatments effects assumed to be 1)





Finding NMA estimates iteratively [Jalota et al., 2011]
Strong dependency on the choice of the absorbing node (blue)





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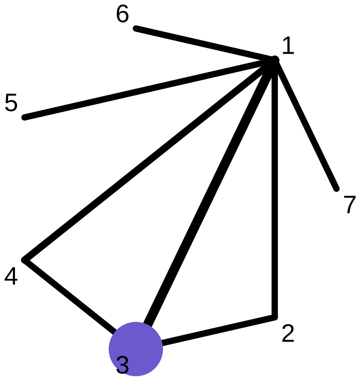

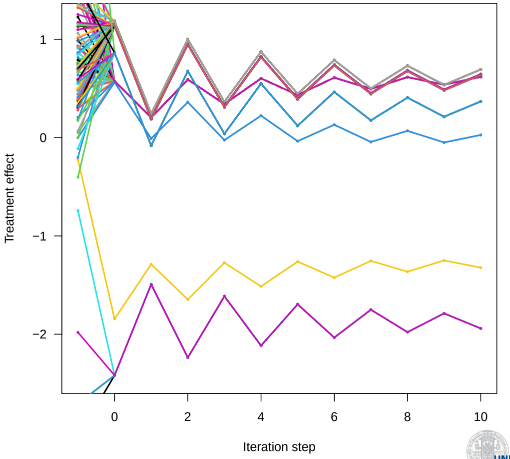

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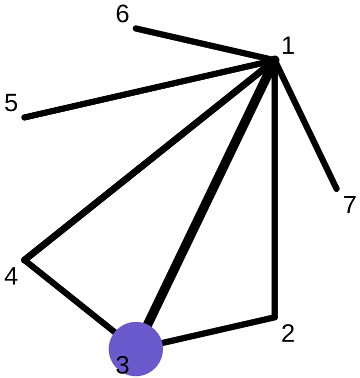

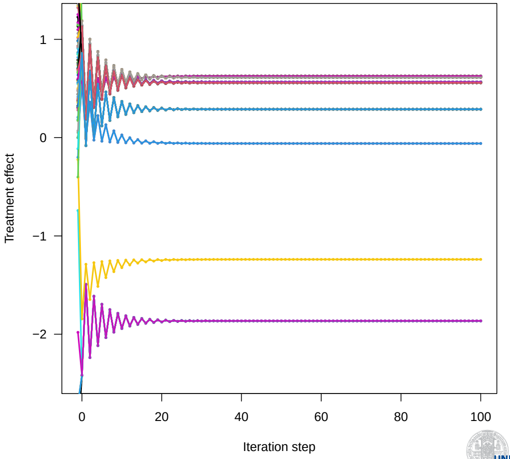

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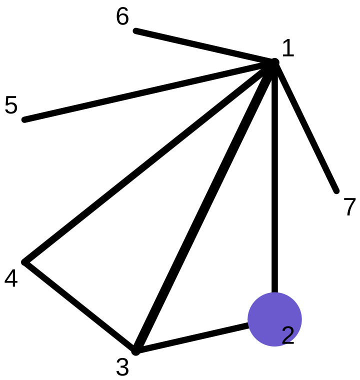
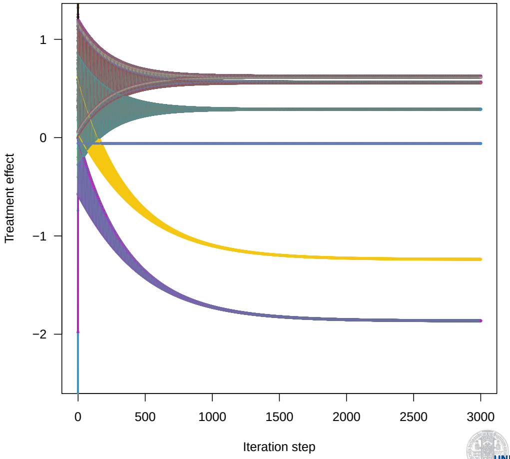
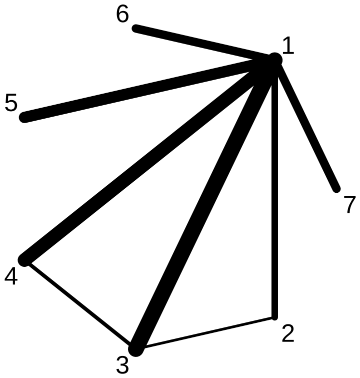
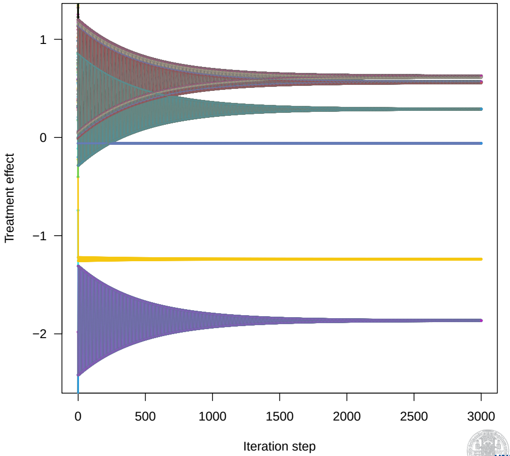




Finding NMA estimates iteratively [Jalota et al., 2011]

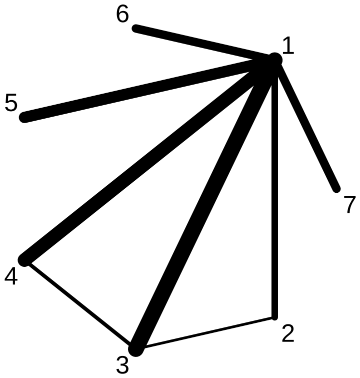
Simple diffusion

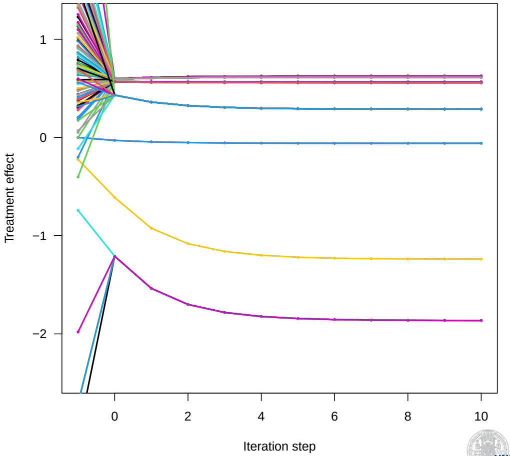




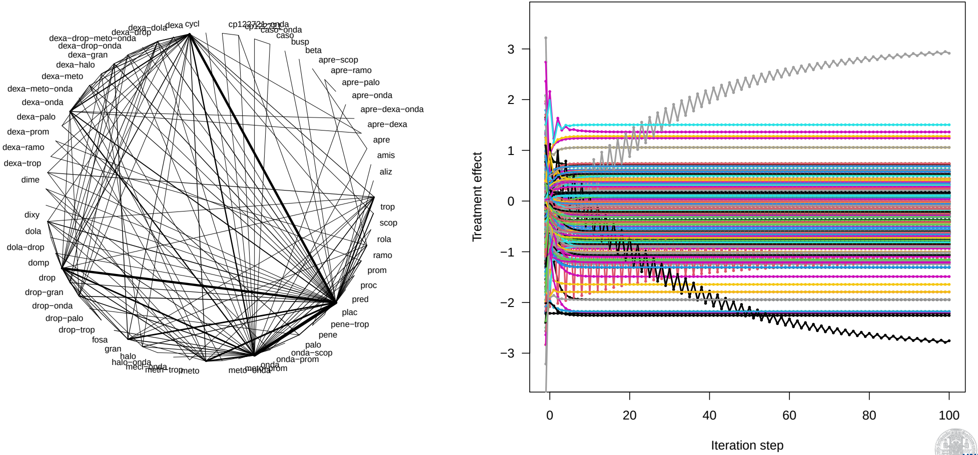
Finding NMA estimates iteratively [Jalota et al., 2011]

Lazy diffusion

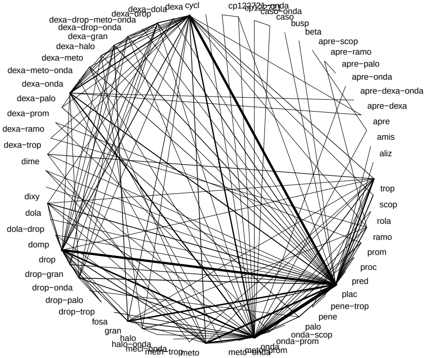


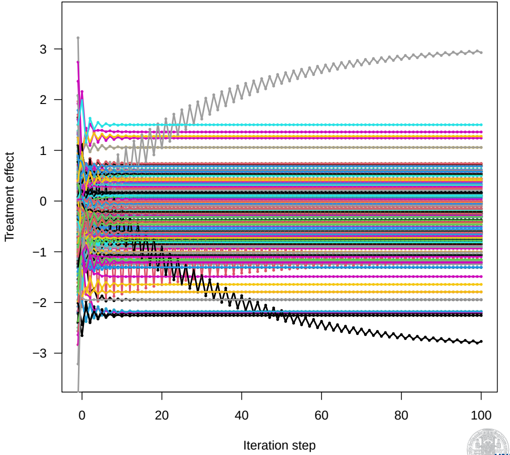


Finding NMA estimates iteratively - absorbing diffusion [Weibel et al., 2017]

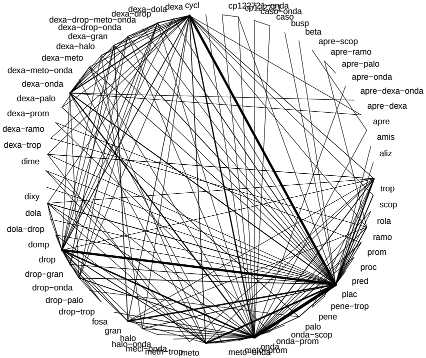


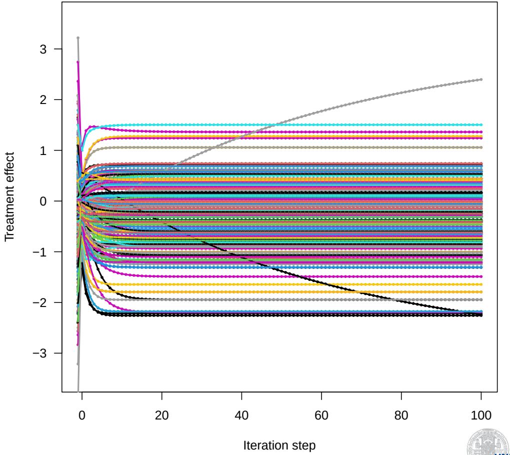
Finding NMA estimates iteratively - simple diffusion [Weibel et al., 2017]





Finding NMA estimates iteratively - lazy diffusion [Weibel et al., 2017]





Discussion

- Absorbing diffusion:
  - Speed of convergence strongly depends on the choice of the reference node
  - Best to choose a central node
- Lazy diffusion
  - Works for all networks, often fast
- Simple diffusion
  - Works only for non-bipartite networks
  - Can be very slow for networks that are “almost bipartite”

Conclusion

Yes, all this is not necessary in practice; however, it provides another connection between graph theory and statistics

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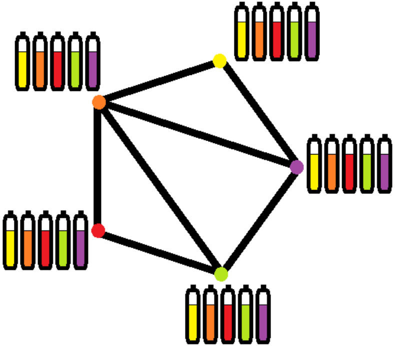
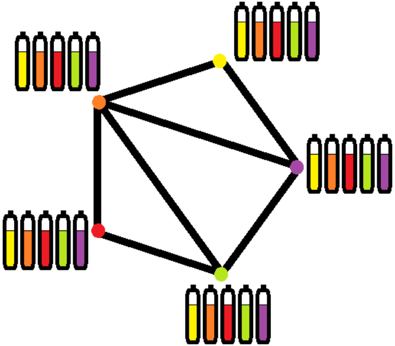
Interpretation: Walkers and drinks



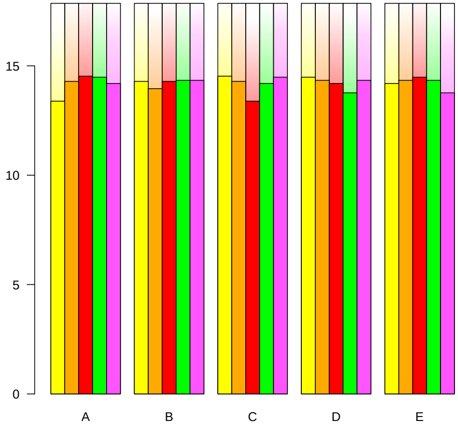
- Mark the n network nodes with different colors
- Also n drinks in the same colors available at each node
- Colored walkers are placed at the node with the same color
- Each walker takes a sip of “their own” drink at their starting node; for example, “yellow” walkers take a sip of lemon juice
- All walkers start stepwise dispersing through the network

Interpretation: Walkers and drinks



- Whenever arriving at a node, each walker takes another sip of “their own” drink from the bottle placed at that node
- Walk stops after large number of steps
- At each node, the remaining juice is reduced according to the node’s weighted degree
- For each node in the network, compare the remaining volume of juice between pairs of differently colored bottles at the same node
- Compare differences between nodes

Walkers and drinks



The “differences of differences” matrix is the covariance matrix:

$$\mathbf{C} = \mathbf{X}\mathbf{D}^{-1}\sum_{k=0}^{\infty}(\mathbf{T}^k\mathbf{X}^\top)$$

$$= \begin{pmatrix} 0.62 & 0.57 & 0.52 & 0.38 & \dots \\ 0.57 & 1.14 & 0.71 & 0.43 & \dots \\ 0.52 & 0.71 & 0.90 & 0.48 & \dots \\ 0.38 & 0.43 & 0.48 & 0.62 & \dots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$