Shortest path or random walks? A framework for path weights in network meta-analysis

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This is joint work with

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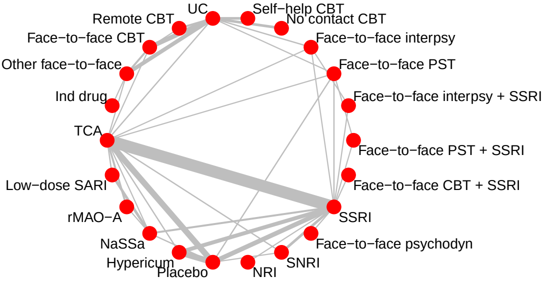
Annabel Davies, Bristol, UK

Outline

Network meta-analysis (NMA)

- A generalization of pairwise meta-analysis to more than two treatments
- Under certain assumptions of transitivity, allows estimating treatment effects for all comparisons in the network, even if not directly observed
- Bayesian and frequentist methods available
- Example: Depression in primary care [Linde et al., 2016]



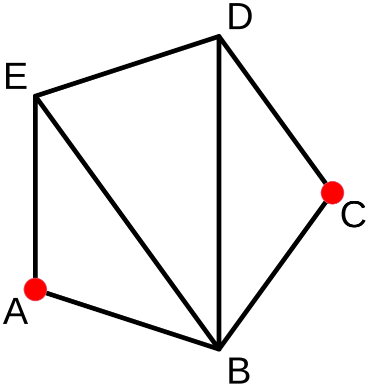
Percentage contributions of comparisons to network estimates

- Motivating question: How large is the contribution, measured as a percentage, of each observed direct comparison to a network estimate A:C?
- Percentage contributions implemented in web application CINeMA (Confidence in Network Meta-Analysis) [Nikolakopoulou et al., 2020, Papakonstantinou et al., 2018, Institute of Social and Preventive Medicine, 2017]
- Alternative approach, based on random walks [Davies et al., 2022]
- Both implemented in function `netcontrib()` of R package **netmeta**, methods `shortestpath` and `randomwalk` [Balduzzi et al., 2023]
- Both approaches are considering paths, based on the hat matrix
- **Today: Focus on paths and path weights!**

A small fictitious network

A network with 5 treatments and 7 direct comparisons

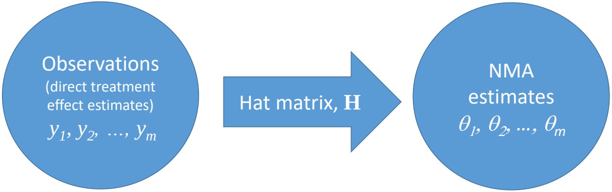
- All standard errors are assumed to be 1
- Focus on comparison A:C



Frequentist approach to NMA

- Estimation via weighted least squares
- Vector $\mathbf{y}$ of observed relative effects (i.e., mean differences) can be projected on network estimates via hat matrix $\mathbf{H}$
- The full hat matrix $\mathbf{H}$ of the aggregate model maps $\mathbf{y}$ to the vector of estimated NMA effects $\hat{\theta}^{nma}$:

$$\hat{\theta}^{nma} = \mathbf{H}\mathbf{y}$$



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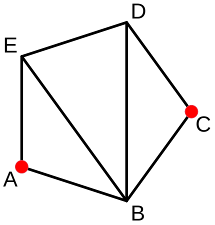
- For example, for comparison A:C we have

$$\hat{\theta}^{nma}_{A:C} = \mathbf{h}^{\top}_{A:C}\mathbf{y}$$

where $\mathbf{h}^{\top}_{A:C}$ is the A:C row of the hat matrix $\mathbf{H}$:

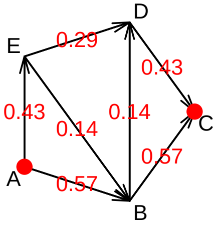
$$\hat{\theta}^{nma}_{A:C} = 0.57y_{AB} + 0.43y_{AE} + 0.57y_{BC} + 0.14y_{BD} - 0.14y_{BE} - 0.43y_{CD} - 0.29y_{DE}$$

Hat matrix for example



$$\mathbf{H} = \begin{pmatrix} AB & AC & AD & AE & BC & BD & BE & CD & CE & DE \\ 0.62 & 0 & 0 & 0.38 & -0.05 & -0.10 & -0.24 & -0.05 & 0 & -0.14 \\ 0.57 & 0 & 0 & 0.43 & 0.57 & 0.14 & -0.14 & -0.43 & 0 & -0.29 \\ 0.52 & 0 & 0 & 0.48 & 0.19 & 0.38 & -0.05 & 0.19 & 0 & -0.43 \\ 0.38 & 0 & 0 & 0.62 & 0.05 & 0.10 & 0.24 & 0.05 & 0 & 0.14 \\ -0.05 & 0 & 0 & 0.05 & 0.62 & 0.24 & 0.10 & -0.38 & 0 & -0.14 \\ -0.10 & 0 & 0 & 0.10 & 0.24 & 0.48 & 0.19 & 0.24 & 0 & -0.29 \\ -0.24 & 0 & 0 & 0.24 & 0.10 & 0.19 & 0.48 & 0.10 & 0 & 0.29 \\ -0.05 & 0 & 0 & 0.05 & -0.38 & 0.24 & 0.10 & 0.62 & 0 & -0.14 \\ -0.19 & 0 & 0 & 0.19 & -0.52 & -0.05 & 0.38 & 0.48 & 0 & 0.43 \\ -0.14 & 0 & 0 & 0.14 & -0.14 & -0.29 & 0.29 & -0.14 & 0 & 0.57 \end{pmatrix}$$

Idea: Interpret hat matrix row A:C as flow from A to C

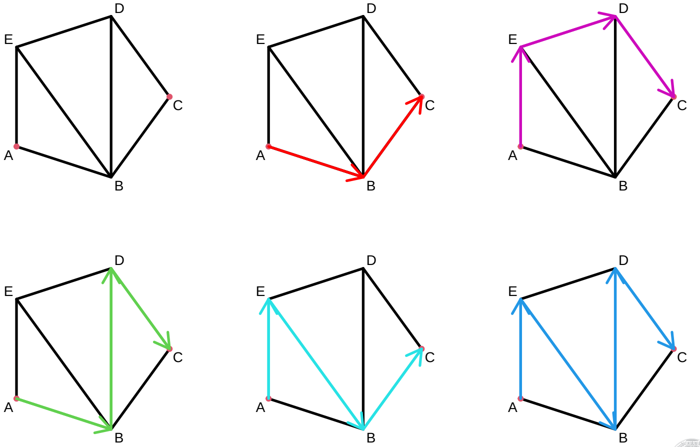


Signs indicate the direction [König et al., 2013]

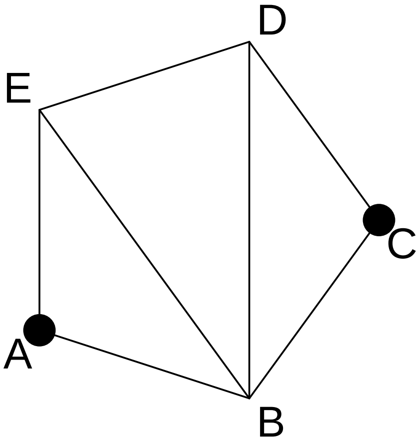
$$
\mathbf{H} = \left(\begin{array}{cccccccccc}
AB & AC & AD & AE & BC & BD & BE & CD & CE & DE \\
0.62 & 0 & 0 & 0.38 & -0.05 & -0.10 & -0.24 & -0.05 & 0 & -0.14 \\
0.57 & 0 & 0 & 0.43 & 0.57 & 0.14 & -0.14 & -0.43 & 0 & -0.29 \\
0.52 & 0 & 0 & 0.48 & 0.19 & 0.38 & -0.05 & 0.19 & 0 & -0.43 \\
0.38 & 0 & 0 & 0.62 & 0.05 & 0.10 & 0.24 & 0.05 & 0 & 0.14 \\
-0.05 & 0 & 0 & 0.05 & 0.62 & 0.24 & 0.10 & -0.38 & 0 & -0.14 \\
-0.10 & 0 & 0 & 0.10 & 0.24 & 0.48 & 0.19 & 0.24 & 0 & -0.29 \\
-0.24 & 0 & 0 & 0.24 & 0.10 & 0.19 & 0.48 & 0.10 & 0 & 0.29 \\
-0.05 & 0 & 0 & 0.05 & -0.38 & 0.24 & 0.10 & 0.62 & 0 & -0.14 \\
-0.19 & 0 & 0 & 0.19 & -0.52 & -0.05 & 0.38 & 0.48 & 0 & 0.43 \\
-0.14 & 0 & 0 & 0.14 & -0.14 & -0.29 & 0.29 & -0.14 & 0 & 0.57
\end{array} \right)
$$

Step 1: Look for all directed paths from A to C

Note: We consider only paths that are compatible with the hat matrix row with respect to sign/direction!



Idea: Partition the flow into streams across each of the directed paths [Papakonstantinou et al., 2018]



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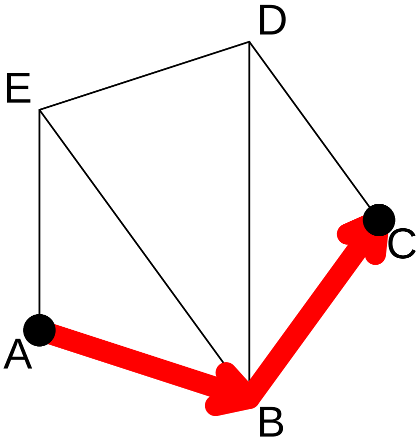

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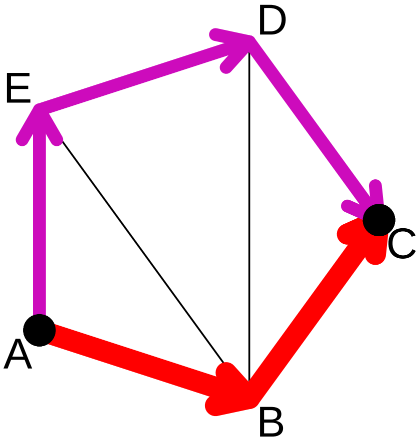

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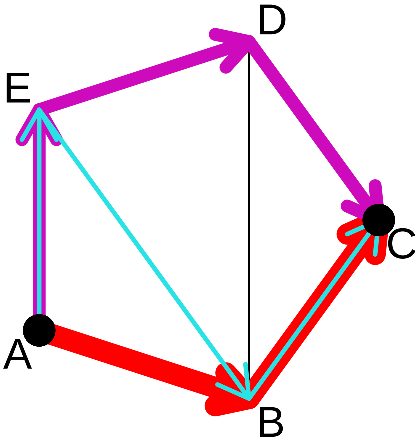

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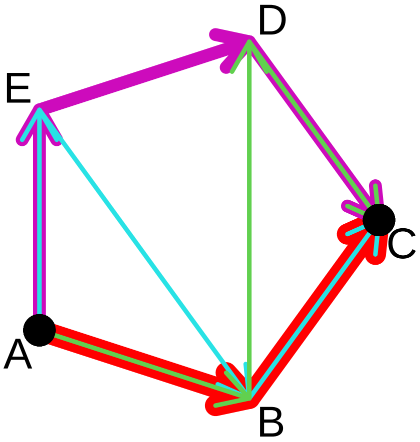

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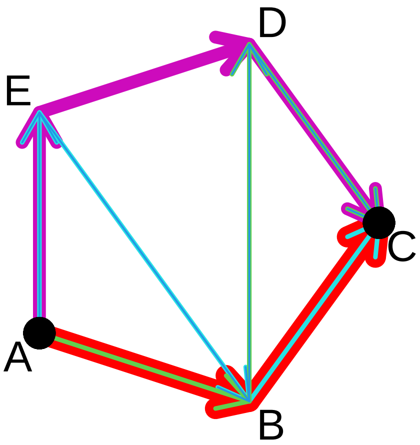
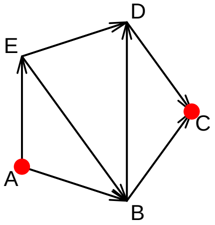


Step 2: Construct path-design matrix for comparison A:C



All paths from A to C that are compatible with the hat matrix row:

$A \to B \to C$
$A \to B \to D \to C$
$A \to E \to B \to C$
$A \to E \to B \to D \to C$
$A \to E \to D \to C$

$$\mathbf{Z}_{A:C} = \begin{pmatrix} A:B & A:C & A:D & A:E & B:C & B:D & B:E & C:D & C:E & D:E \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & -1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & -1 \end{pmatrix}$$

Step 3: Obtain path weights by solving a linear equation

Aim: Construct weights for each of the P (here $P = 5$) paths that contribute to the flow from A to C

- Looking for a vector of path weights ϕ of length P such that path p obtains weight $\phi_p (p = 1, \dots, P)$. Remember:

$$\hat{\theta}_{A:C}^{nma} = \mathbf{h}_{A:C}^{\top} \mathbf{y}$$

- Request

$$\mathbf{h}_{A:C}^{\top} \mathbf{y} = \phi^{\top} \mathbf{Z}_{A:C} \mathbf{y}$$

for all $\mathbf{y}$.

- We are looking for a solution ϕ of the linear equation system

$$\mathbf{h}_{A:C}^{\top} = \phi^{\top} \mathbf{Z}_{A:C}$$

Step 3: Obtain path weights by solving a linear equation

- Linear equation system for comparison A:C

$$\mathbf{h}_{A:C}^{\top} = \phi^{\top}\mathbf{Z}_{A:C}$$

- In general, the path-design matrix $\mathbf{Z}_{A:C}$ has no inverse
- `shortestpath` and `randomwalk` provide two solutions, often different
- Another solution is `pseudoinverse`:

$$\phi^{\top} = \mathbf{h}_{A:C}^{\top}\mathbf{Z}_{A:C}^{+}$$

($\mathbf{Z}_{A:C}^{+}$ Moore-Penrose pseudoinverse of $\mathbf{Z}_{A:C}$ [Albert, 1972])

Step 3: Obtain path weights by solving a linear equation

- General solution of the equation system [Albert, 1972, Theorem (3.12)]

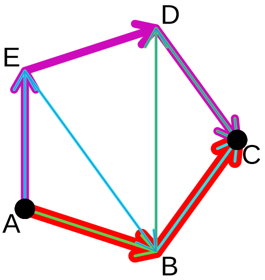
$$\phi^\top = \mathbf{h}_{A:C}^\top \mathbf{Z}_{A:C}^+ + \mathbf{x}^\top (\mathbf{I} - \mathbf{Z}_{A:C}\mathbf{Z}_{A:C}^+)$$

  where $\mathbf{I}$ is the $P \times P$ identity matrix and $\mathbf{x} \in \mathbb{R}^P$ an arbitrary vector of length P
- Unique if and only if $\mathbf{Z}_{A:C}\mathbf{Z}_{A:C}^+ = \mathbf{I}$
- `pseudoinverse` is the special case for $\mathbf{x} = \mathbf{0}$
- The sum of entries in each solution ϕ is 1 [Rücker et al., 2023]
- In general, there are infinitely many solutions!

Consider some particular solutions

- `shortestpath` [Papakonstantinou et al., 2018] - Starting from the shortest path from A to C, collect streams along further paths until the full flow is exhausted
- `randomwalk` [Davies et al., 2022] - Find all paths from A to C and use a random walk algorithm to define path weights and edge weights
- `pseudoinverse` [Rücker et al., 2023] - Find the least squares solution of the equation system - minimizes the L2 norm (sum of squares, ϕ^2)
- `cccp` - Use R package **cccp** [Pfaff, 2020] to find another solution that minimizes the L1 norm (sum of $|\phi|$ coefficients)
- `otherpath` - Similar to `shortestpath`, but start with another path

Path weights for comparison A:C for these solutions



Method	A-B-C	A-B-D-C	A-E-B-C	A-E-B-D-C	A-E-D-C
`shortestpath`	0.571	0	0	0.143	0.286
`randomwalk`	0.457	0.114	0.114	0.029	0.286
`cccp`	0.471	0.101	0.101	0.042	0.286
`pseudoinverse`	0.393	0.179	0.179	-0.036	0.286
`otherpath`	0.429	0.143	0.143	0	0.286

Shortest path order: ABC, AEDC, AEBDC; other path order: AEDC, AEBC, ABDC, ABC

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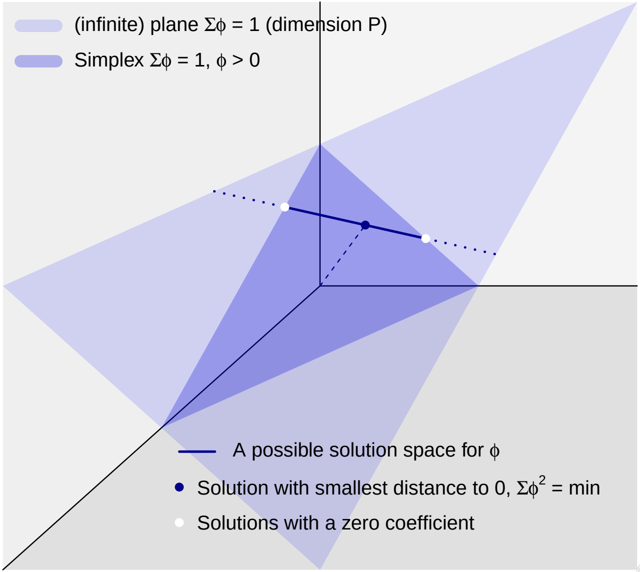
Properties of solutions for finding path weights

Method	Minimizes norm	Variance	Negative weights possible	Needs all-paths search
`shortestpath`	L1	large	no	no
`randomwalk`	L1	medium	no	yes
`cccp`	L1	medium	no	yes
`pseudoinverse`	L2	small	yes	yes

Geometric visualization of solutions



Summary I

- Contributions are not uniquely defined!
- Question: Which is the best solution, and what are the criteria?
- `pseudoinverse` minimizes L2 norm (Euklidean distance to origin) and thus the variance between path weights
- `shortestpath` , `randomwalk` and `cccp` minimize L1 norm (sum of absolute path weights)
- `shortestpath` often shows the largest variance between weights
- Sometimes another path order ”needs fewer paths”, i.e., attributes zero weight to more paths
  - Alternatively, start with the ”widest road” instead of the shortest?
- For further discussion, see [Rücker et al., 2023] (just submitted and on arXiv)

Summary II

- Path weights used to define edge weights (”contributions”)
- Implemented in function `netcontrib()`, argument `method` of R package **netmeta**
- Most similar: `randomwalk` and `cccp`
- Most different: `shortestpath` and `pseudoinverse`
- Run time: `shortestpath` is fastest (doesn’t need all-paths search, which can be VERY slow for large networks)
  - For example, `shortestpath` ignores paths $A \to B \to D \to C$ and $A \to E \to B \to C$

⇒ Current recommendation (and default in CINeMA and R package **netmeta**): `shortestpath`

Outlook

- So far, path weights mainly used to define edge weights ("contributions")
- Path weights may lead to a new definition of "path inconsistency" (current work in Freiburg)
- Interpreting hat matrix elements as flows may have applications also in more general regression theory

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How to obtain edge weights from path weights

- $|\mathbf{Z}_{A:C}|$ matrix derived from $\mathbf{Z}_{A:C}$ by taking elementwise absolute values
- λ vector of path lengths, given by the row sums of $|\mathbf{Z}_{A:C}|$
- Transform the entries of ϕ to weights $\mathbf{w}$ by setting

$$\mathbf{w} = (\phi/\lambda)^\top |\mathbf{Z}_{A:C}|$$

  where the division ϕ/λ is made elementwise
- The sum of weights is 1:

$$\mathbf{w}^\top \mathbf{1} = (\phi/\lambda)^\top |\mathbf{Z}_{A:C}| \mathbf{1} = (\phi/\lambda)^\top \lambda = \phi^\top \mathbf{1} = 1$$

Appendix: Frequentist approach

- Estimation via weighted least squares
- Vector $\mathbf{y}$ of observed relative effects (i.e., mean differences) can be projected on network estimates via hat matrix $\mathbf{H}$
- $\mathbf{H}$ is defined as

$$\mathbf{H} = \mathbf{B}(\mathbf{B}^\top\mathbf{W}\mathbf{B})^+\mathbf{B}^\top\mathbf{W}$$

  where
  - $\mathbf{B}$ is the edge-incidence matrix of the full aggregate network (dimension $m \times n$),
  - $\mathbf{W}$ is a diagonal matrix of inverse variance weights (dimension $m \times m$), assumed to be appropriately adjusted for multi-arm studies [Rücker and Schwarzer, 2014]
  - $(\mathbf{B}^\top\mathbf{W}\mathbf{B})^+$ is the Moore-Penrose pseudoinverse of the Laplacian matrix $\mathbf{L} = \mathbf{B}^\top\mathbf{W}\mathbf{B}$ [Rücker, 2012]
- $m \times m$ full hat matrix $\mathbf{H}$ of the aggregate model maps $\mathbf{y}$ to the vector of estimated NMA effects $\hat{\theta}^{nma}$:

$$\hat{\theta}^{nma} = \mathbf{H}\mathbf{y}$$