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A new approach to evaluating loop inconsistency in network meta-analysis

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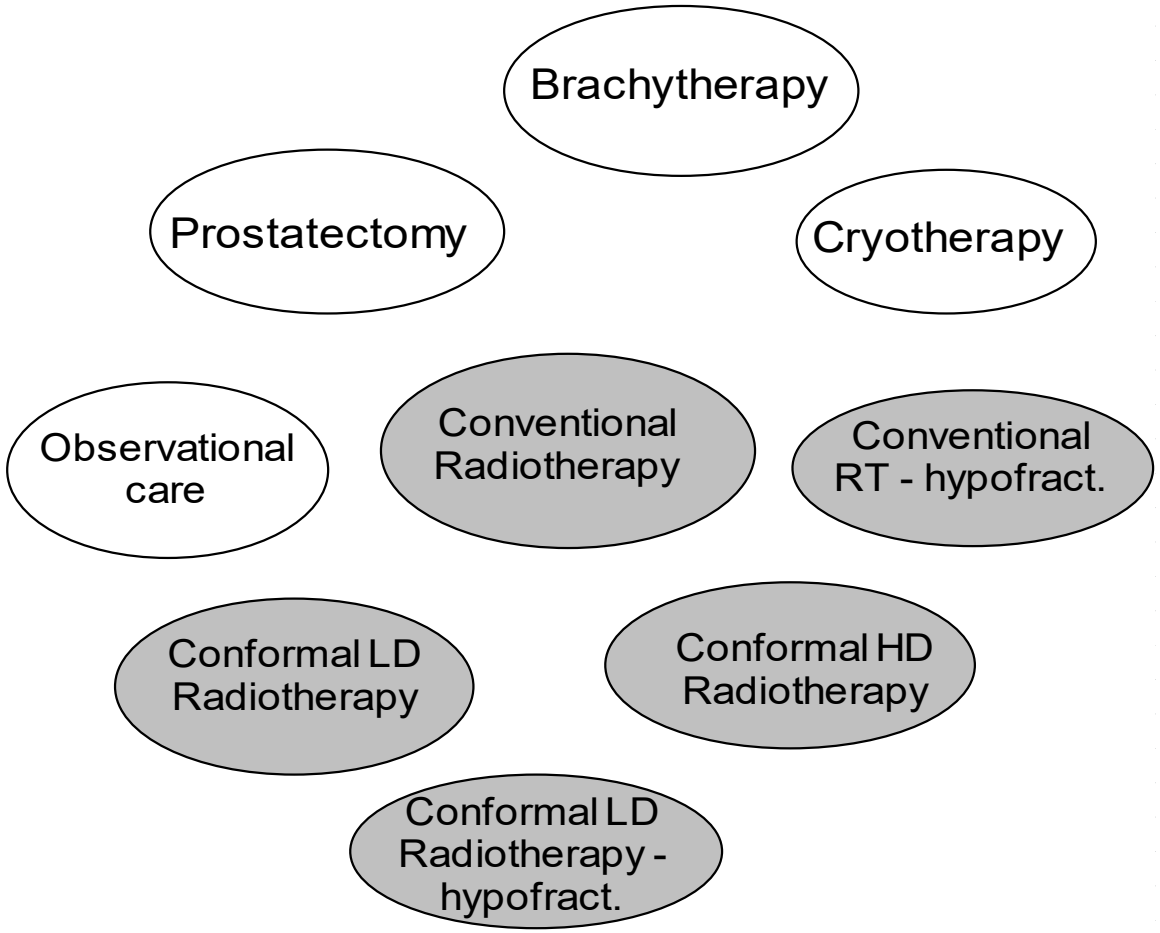
Example: multiple treatments for localised prostate cancer



Traditional approach:

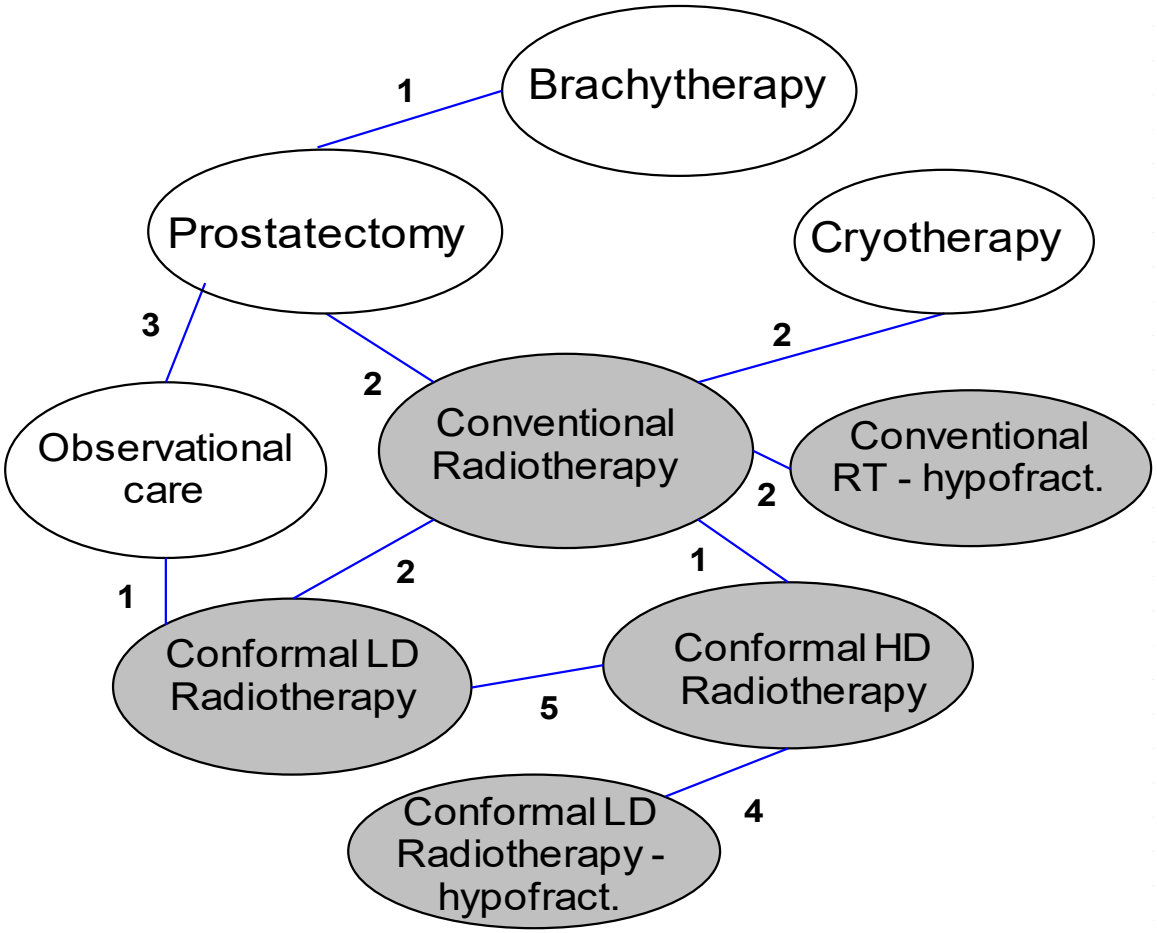
Carry out a series of standard meta-analyses to compare each pair of treatments.

Report multiple meta-analyses in a systematic review.

LD: low dose

HD: high dose

Example: multiple treatments for localised prostate cancer



LD: low dose

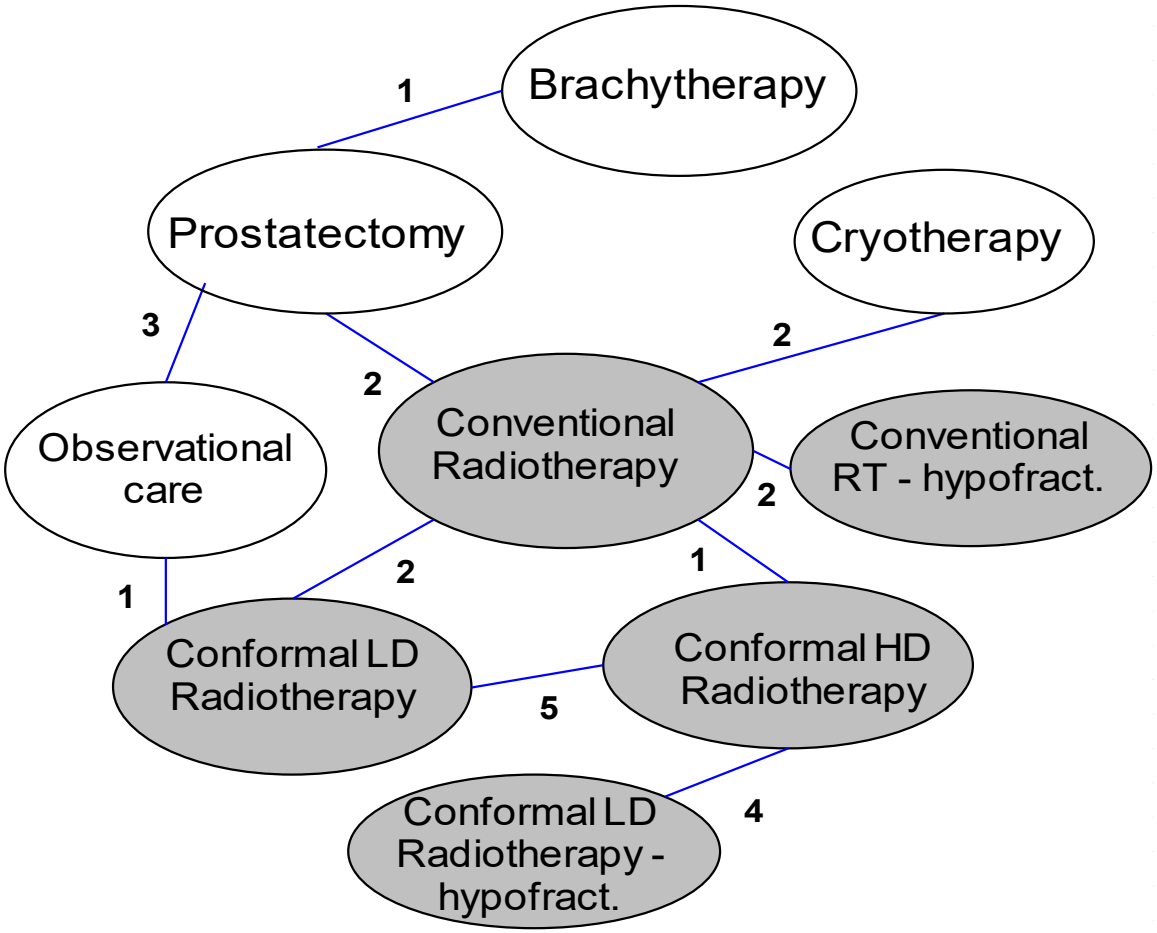
HD: high dose

Network meta-analysis:

Collect data from eligible trials comparing any of these treatments.

Perform a combined analysis, comparing all treatments simultaneously.

Motivation for network meta-analysis

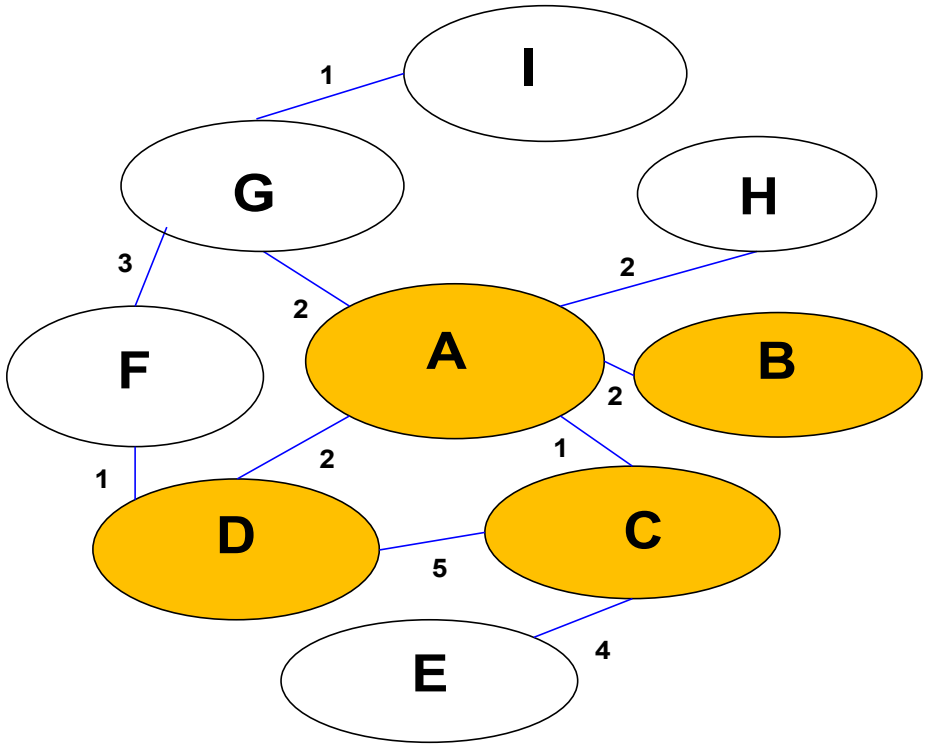


LD: low dose

HD: high dose

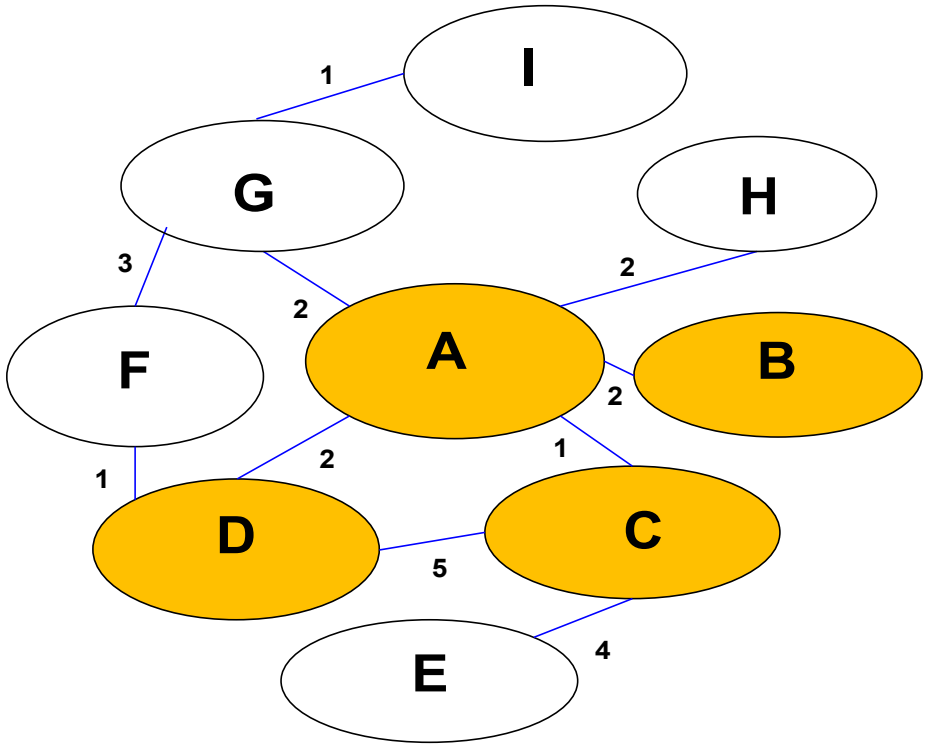
- Which treatment is most effective?
- How are treatments ranked with respect to effectiveness/safety?
- Which treatment is better: brachytherapy or cryotherapy? (no trial data available)
- Use of indirect as well as direct evidence

Indirect comparisons



- A vs. B comparison informed by direct evidence from trial data
- B vs. C comparison informed by indirect evidence, using A vs. B and A vs. C trial data
- A vs. C informed by both direct evidence and indirect evidence

Using direct and indirect evidence



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Standard models rely on an assumption of consistency, meaning direct and indirect evidence agree for each comparison.

Why might consistency not hold?

Example reasons (for loop ACD)

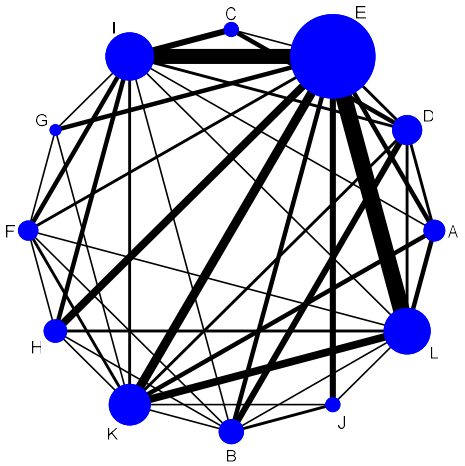
- Patients in AC trials are systematically different from those in AD and CD trials (e.g. because they are ineligible for treatment D)
- Treatment A was differently implemented (e.g. different doses) when used in AC trials than when used in AD trials
- Trials of different treatment comparisons were carried out in different time periods or different settings (e.g. AC trials are recent, while CD trials are older)

Testing for inconsistency

- Local tests are performed within a single loop, e.g. node-splitting approach (Dias et al., 2010)
- Global tests summarise evidence across whole network: design-by-treatment interactions model (Higgins et al., 2012)
- Existing global tests lack power, because degrees of freedom can be much larger than number of loops

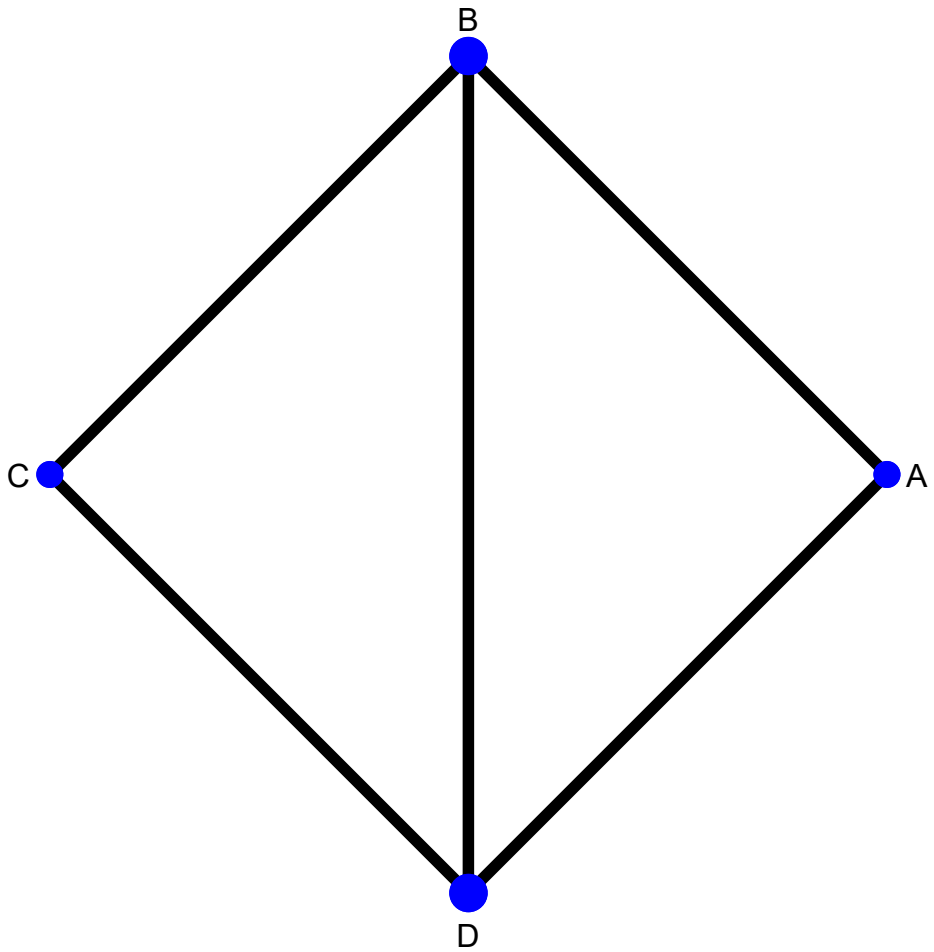
Objectives of current research project

- Define a local inconsistency model that handles treatments symmetrically within a loop
- Extend model to a global model for inconsistency across the network
- Develop an algorithm for identifying a set of independent loops within a network (for inclusion in global model)



Counting the independent loops in a network

Count how many edges need to be removed in order that no loops remain in the network



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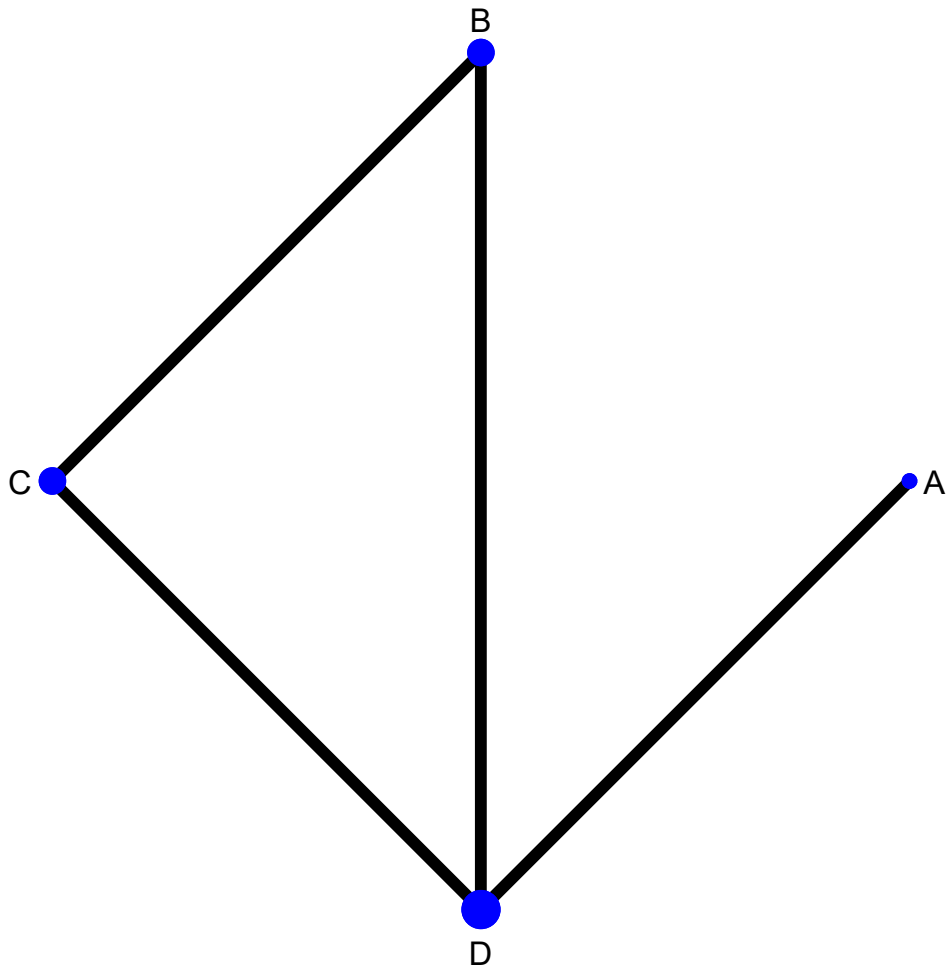

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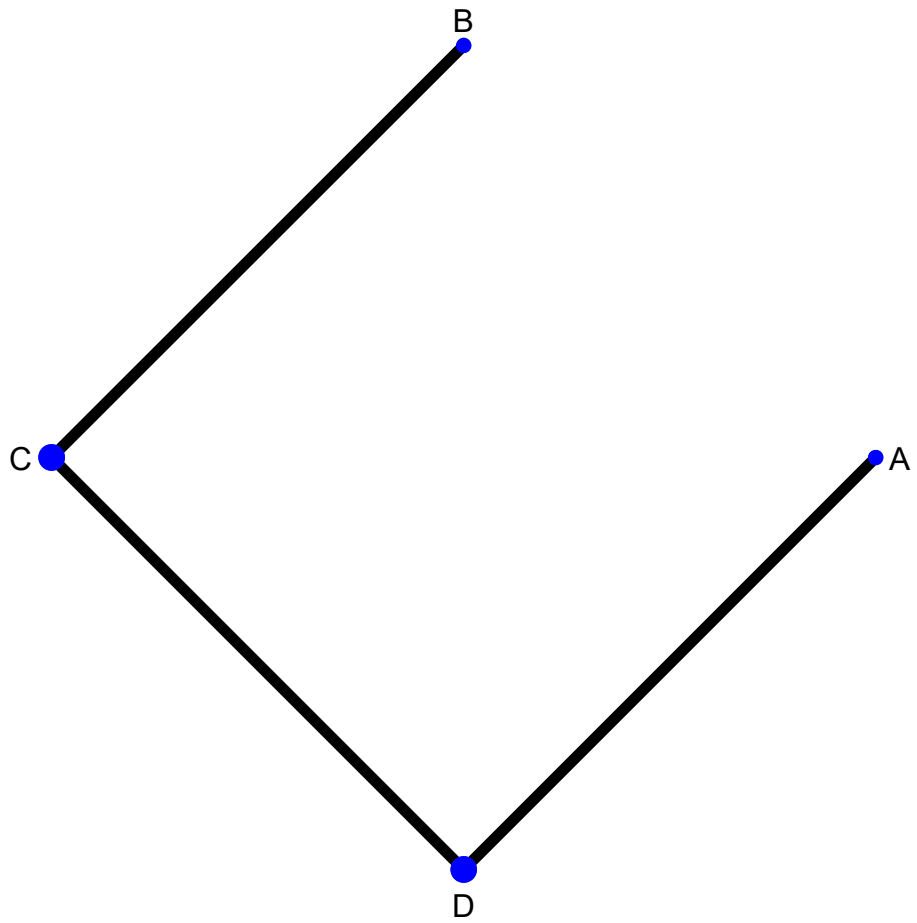
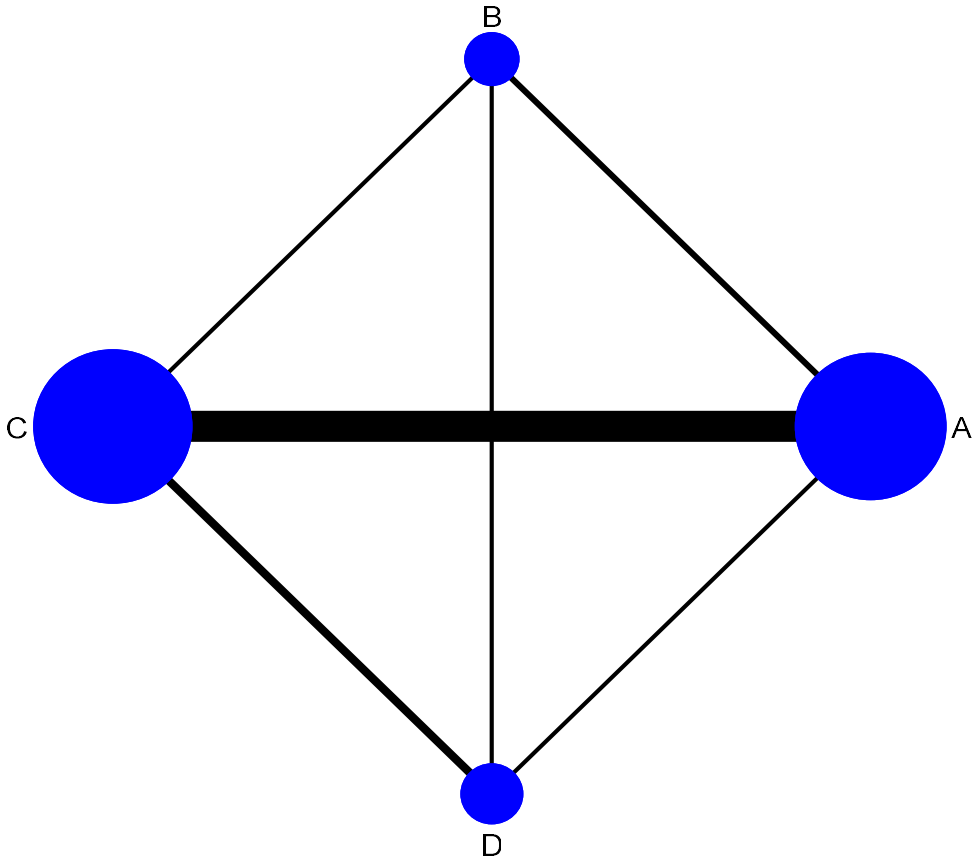
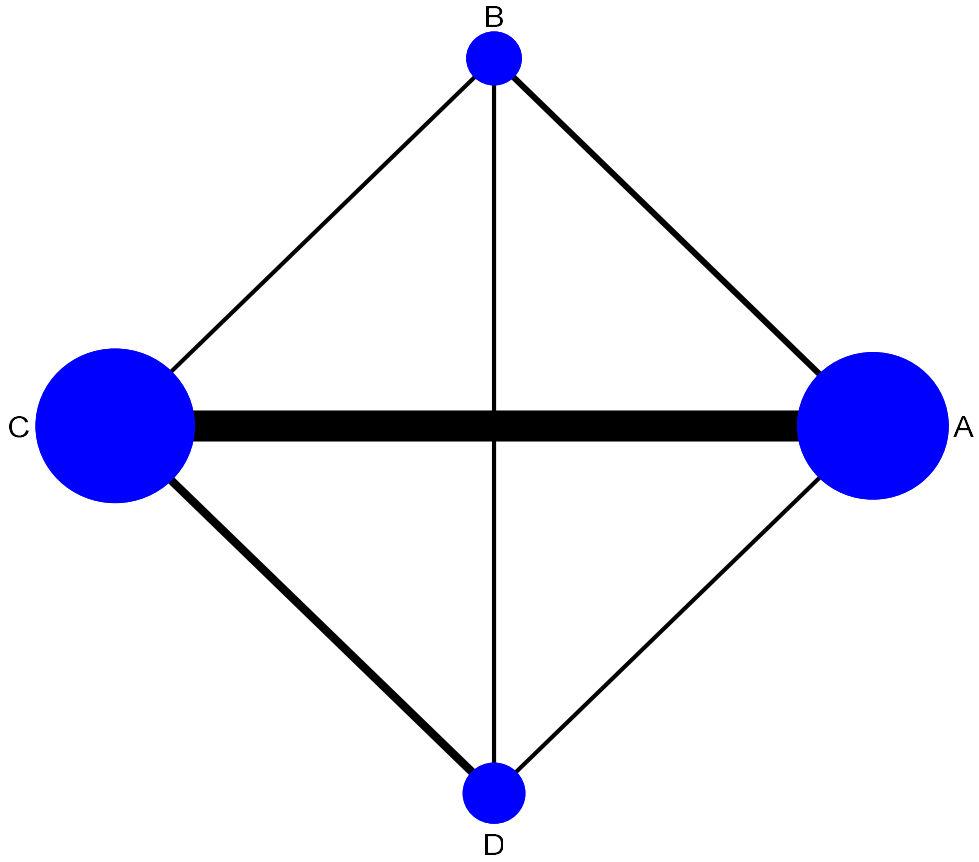
Count how many edges need to be removed in order that no loops remain in the network



Example 1: How many independent loops?



Example 1: How many independent loops?

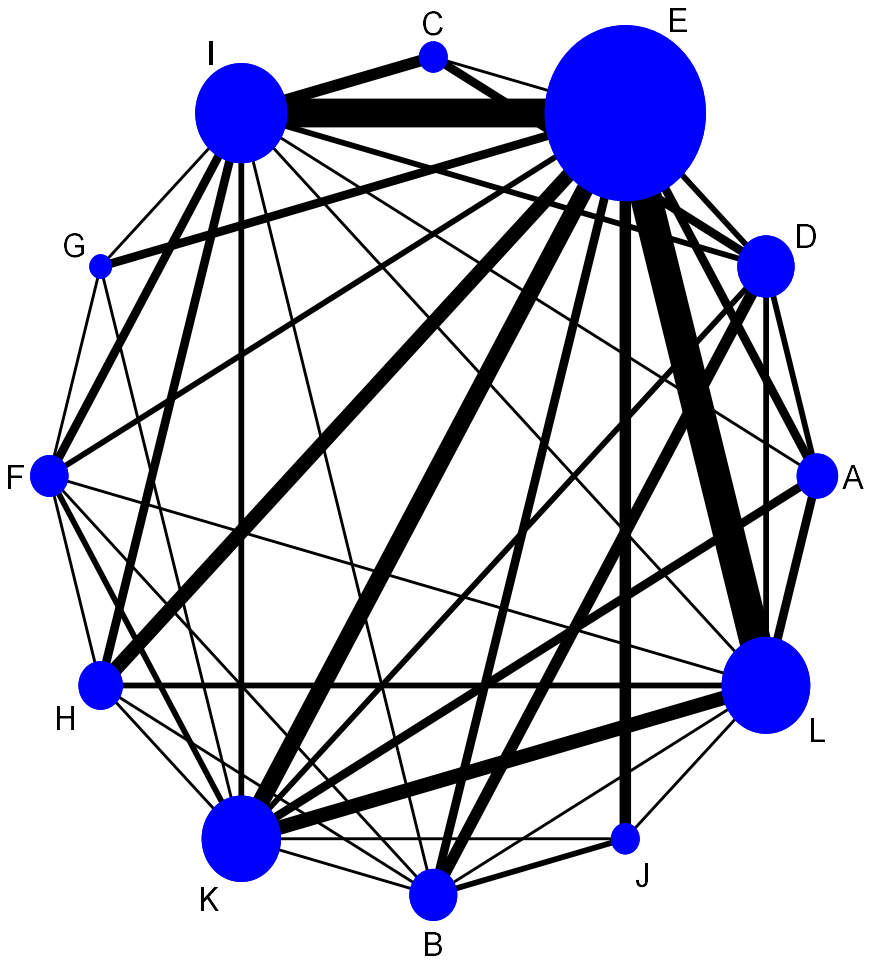


There are seven different possible loops in the network:

ABC, ABD, ACD, BCD, ABCD, ABDC, ACBD

But there are only three independent loops, for example ABC, ABD, ACD

Example 2: How many independent loops?

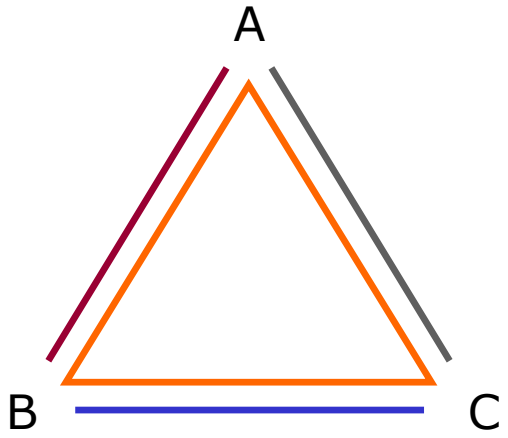


Counting the independent loops in a network

- In a network including only pairwise trials, the number of independent loops is *n-k+1* (for *n* contrasts, *k* treatments)
- Equivalent to counting the number of edges that need to be removed in order that no loops remain in the network
- But if the network includes multi-arm trials, counting the number of loops becomes more complicated

Consistency model

Network including trials with designs AB, AC, BC, ABC:



Trial design	B vs. A	C vs. A	C vs. B
AB	δ_{AB}	-	-
AC	-	δ_{AC}	-
BC	-	-	δ_{BC}
ABC	δ_{AB}	δ_{AC}	δ_{BC}

- Direct and indirect evidence are assumed to agree

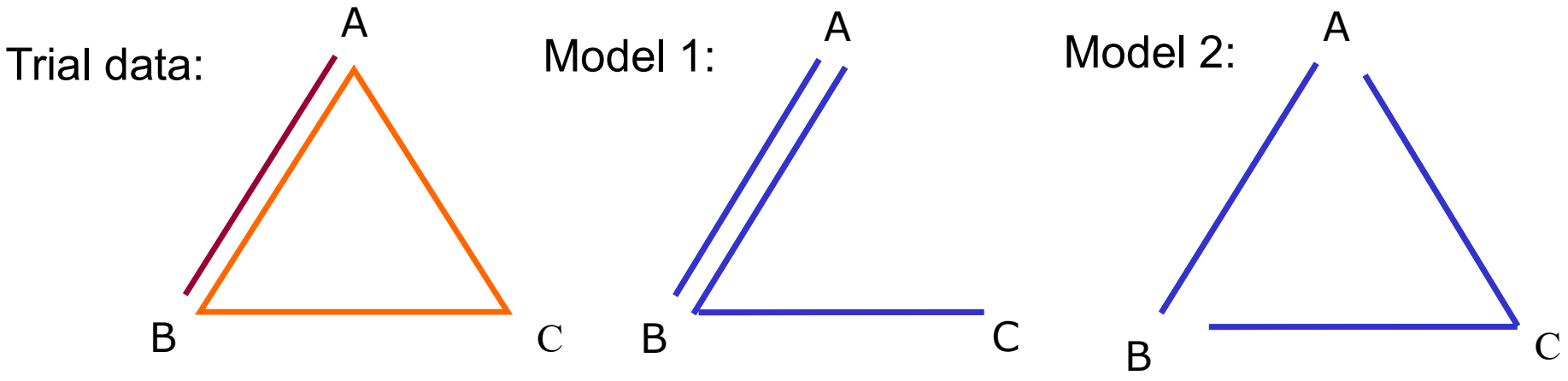
Proposed inconsistency model

Trial design	A vs. B	B vs. C	C vs. A
AB	$\delta_{AB} + \omega/3$	-	-
AC	-	$\delta_{AC} + \omega/3$	-
BC	-	-	$\delta_{BC} + \omega/3$
ABC	δ_{AB}	δ_{AC}	δ_{BC}

- Handles treatments symmetrically by adding equal amounts of inconsistency to each contrast
- Previous models handle treatments asymmetrically, e.g. by adding ω term to A vs. B contrast only
- Reversing sign of inconsistency terms results in the same model

Global model: how many independent loops?

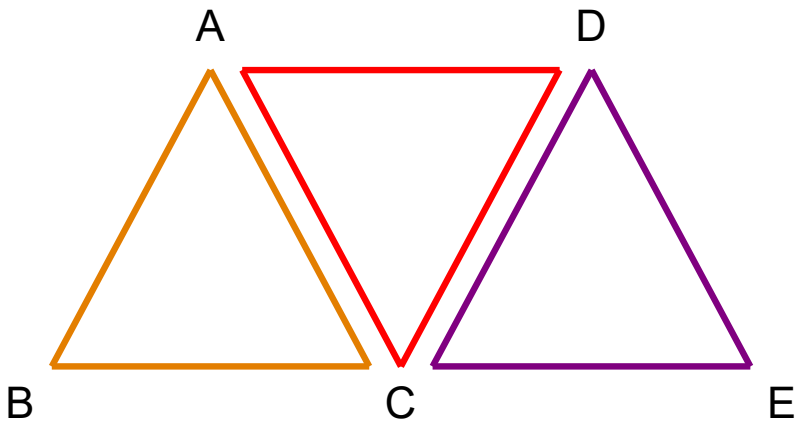
- In a network including only pairwise trials, number of independent loops is *n-k+1* (for *n* contrasts, *k* treatments)
- If multi-arm trials are included, different model parameterisations may produce different numbers of loops



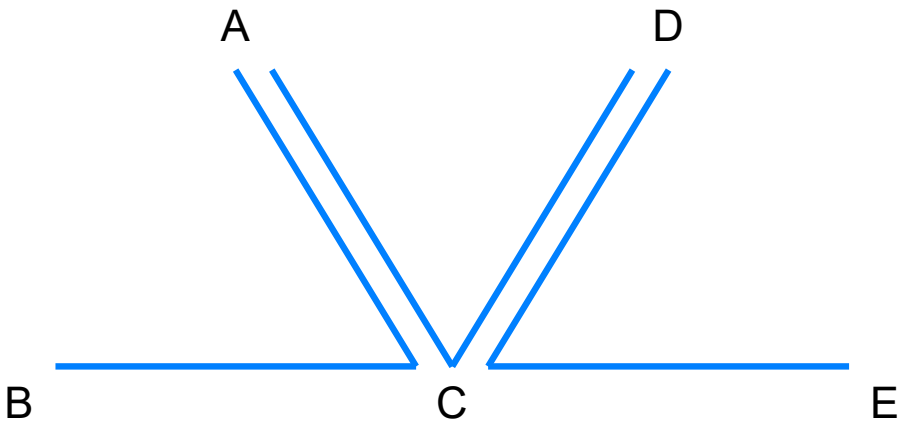
Example network: AB and ABC trials

How many independent loops?

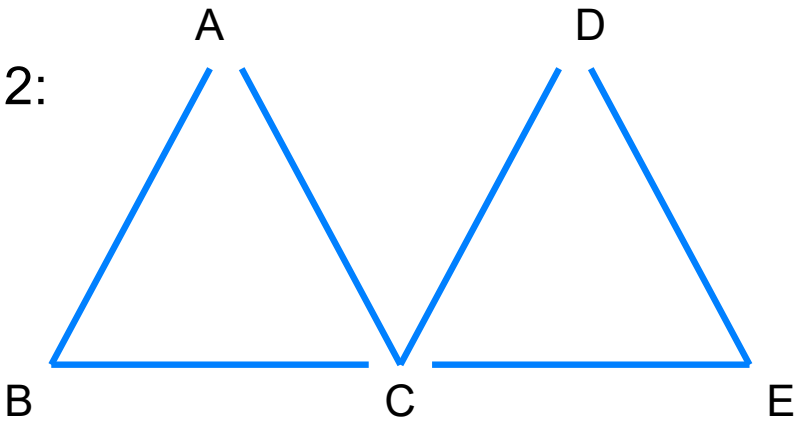
Trial data:



Model 1:



Model 2:



Example network: ABC, ACD and CDE trials

Identifying multiple loops

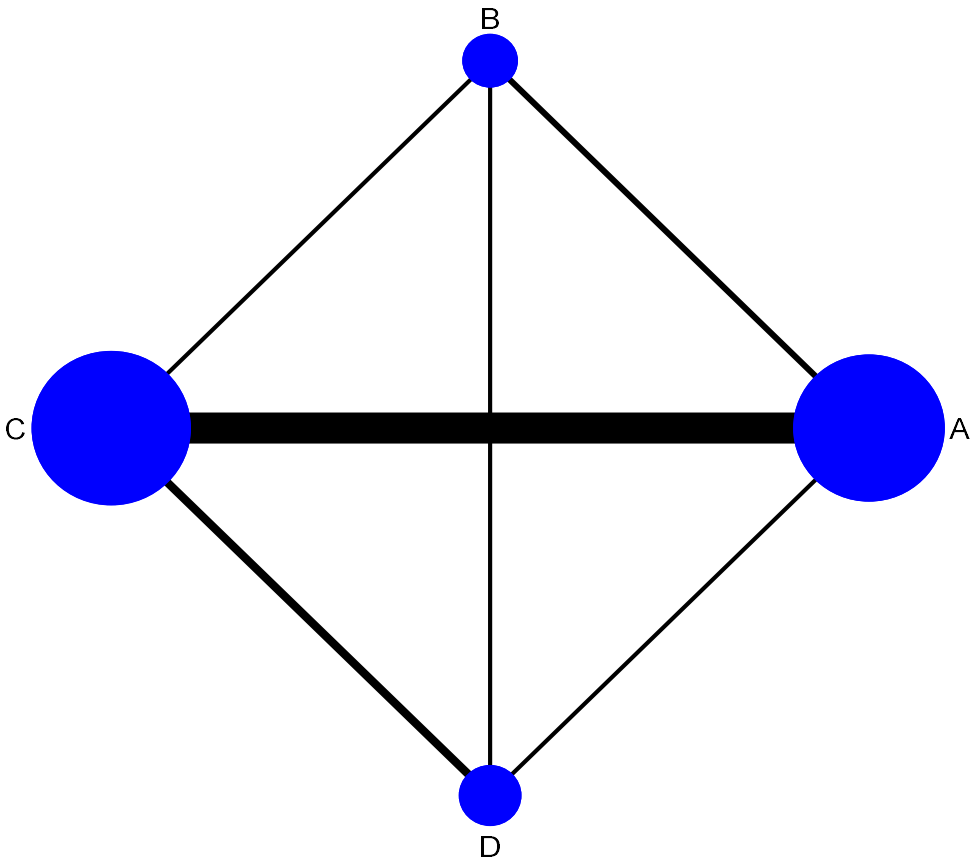
- Previous authors have chosen to maximise the number of loops (Lu and Ades 2006, van Valkenhoef et al. 2012)
- We choose to minimise the total number of loops
- This means between-trial variation is modelled as heterogeneity rather than inconsistency wherever possible
- Heterogeneity usually assumed equal across comparisons, so the model will include fewer parameters in total
- We have developed an algorithm to find an appropriate model parameterisation and identify independent loops

Smoking cessation network

- Network meta-analysis compared four treatments:
  - No intervention (A)
  - Self-help (B)
  - Individual counselling (C)
  - Group counselling (D)
- Outcome measured was successful cessation of smoking at 6-12 months
- Direct evidence available on all six pairwise comparisons
- Two three-arm trials with designs ACD and BCD

Hasselblad et al., 1998

Smoking cessation network



- All comparisons in multi-arm trials also appear in one or more pairwise trials
- Global model therefore includes a fixed number of independent loops
- Independent loops: 6-4+1=3 (6 contrasts, 4 treatments)

Results: smoking cessation network

Loop split	Inconsistency parameter(s) (SE)	p-value
ABC	-0.34 (0.75)	0.65
ABD	0.06 (1.01)	0.96
ACD	-0.34 (1.03)	0.74
BCD	-1.44 (1.18)	0.22
ABCD	-1.16 (1.28)	0.37
ABDC	0.24 (0.91)	0.80
ACBD	0.76 (1.21)	0.53

Global model: smoking cessation network

- By applying our algorithm, we find that ABC, ABD and ACD are independent loops
- We fit a global inconsistency model to split these three loops simultaneously

Loops split	Inconsistency parameter(s) (SE)	p-value
ABC, ABD, ACD simultaneously	-1.65 (1.37) 1.19 (1.42) -1.67 (1.52)	0.67

Multiple global models: smoking cessation network

Loops split	Inconsistency parameter(s) (SE)	p-value
ABC, ABD, ACD simultaneously	-1.65 (1.37) 1.19 (1.42) -1.67 (1.52)	0.67
ABD, ACD, ABC simultaneously	1.19 (1.42) -1.67 (1.51) -1.65 (1.37)	0.67
ABD, BCD, ABDC simultaneously	0.48 (1.56) -1.65 (1.37) 0.03 (1.45)	0.67

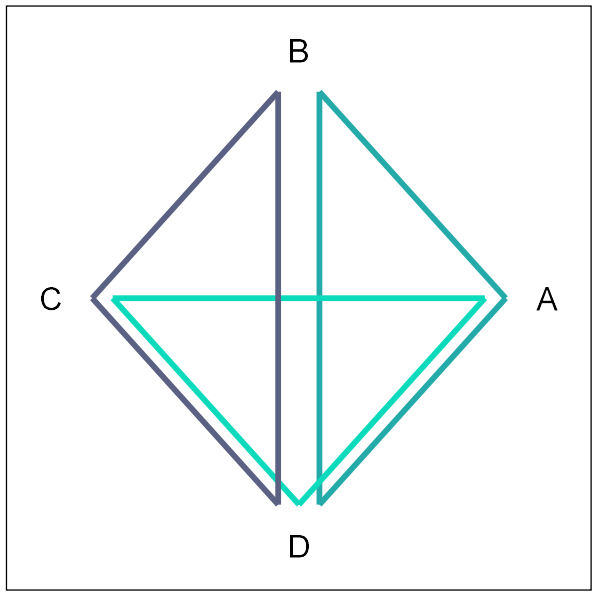
Graphical methods for visualising inconsistency

- We explored how to visualise the estimated inconsistencies within multiple loops in a network
- Propose plotting set of independent loops split in model
- Use colours to represent degree of significance of local inconsistency estimate
- Aim is to help meta-analysts identify which treatment loops to investigate for causes of inconsistency
- Because global model is not unique, plotting just one set of loops could lead to overinterpretation

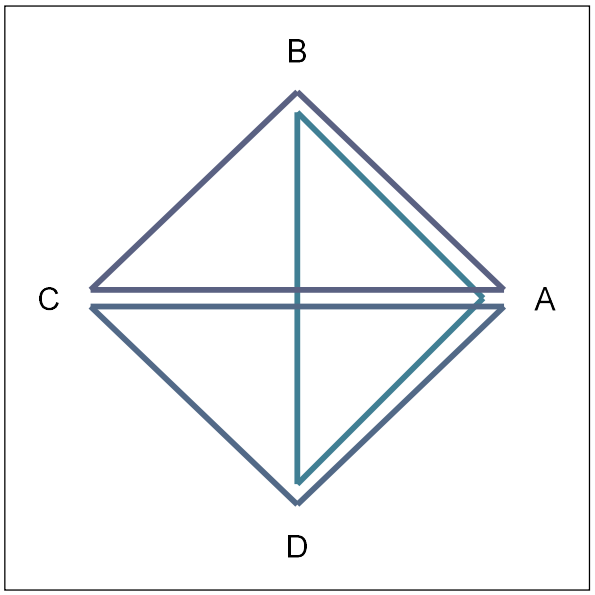
Visualising inconsistency in smoking network

Smoking cessation network

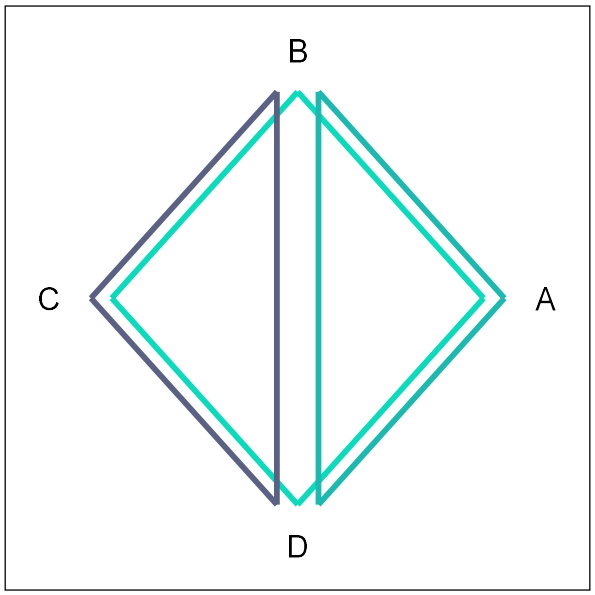
Model 1



Model 2



Model 3

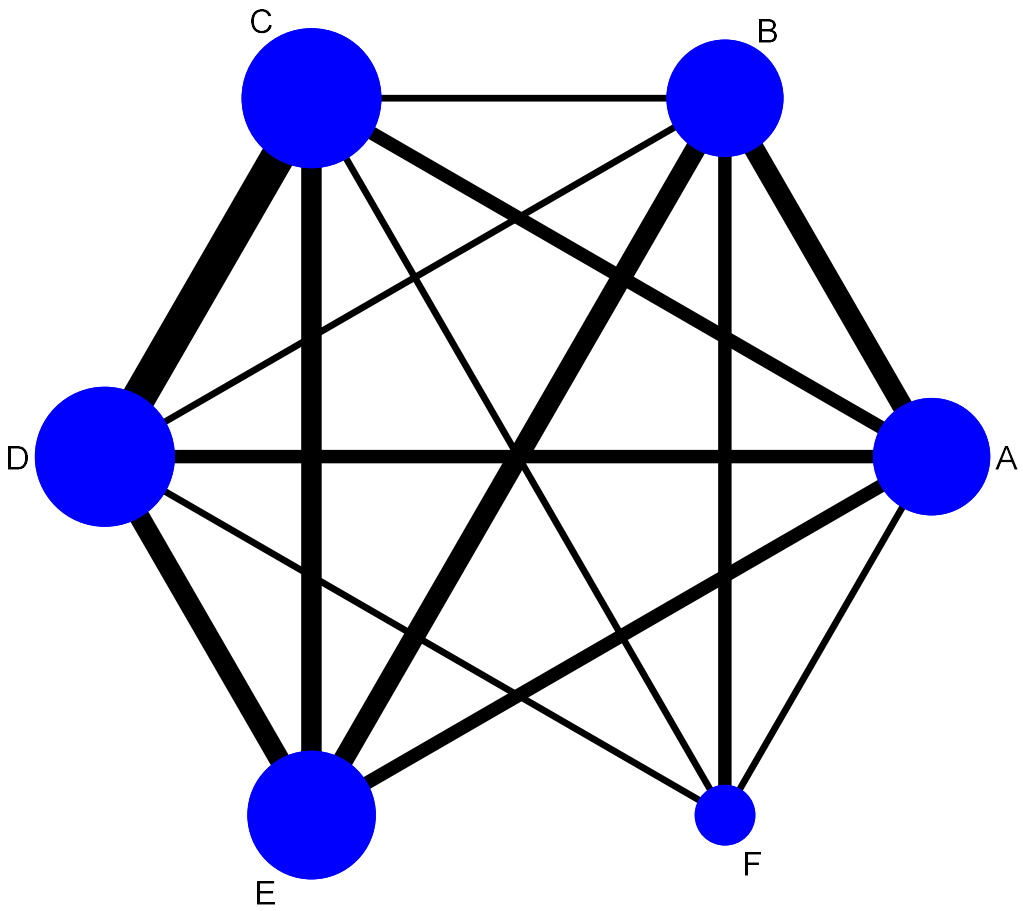


Diabetes prevention network

- Network meta-analysis compared six treatments:
  - Diuretic (A)
  - Placebo (B)
  - Beta blockers (C)
  - Calcium-channel blockers(D)
  - Angiotensin-converting-enzyme inhibitors (E)
  - Angiotensin-receptor blockers (F)
- Outcome measured was new cases of diabetes
- Four three-arm trials with designs ABC, ADE, CDE

Elliott et al., 2007

Diabetes prevention network



- Comparisons BC and DE are present in multi-arm trials but no pairwise trials
- There are multiple ways to parameterise the global model

Global model: diabetes prevention network

- By applying our algorithm, we find a parameterisation that minimises the number of loops in the model
- We find that ABD, ACD, ABE, ACE, ABF, ACF and ADF are independent loops

Loops split	Wald χ^2	Degrees of freedom	p-value
ABD,ACD,ABE,ACE,ABF, ACF,ADF simultaneously	6.49	7	0.48

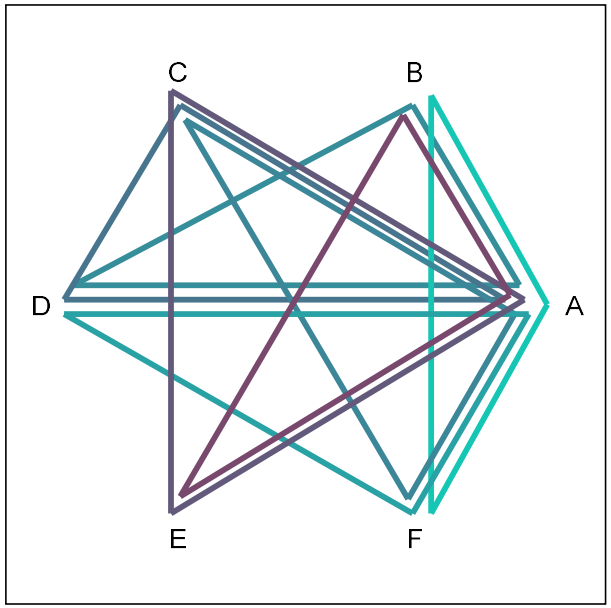
Multiple global models: diabetes network

Loops split	Wald χ^2	Degrees of freedom	p-value
ABD,ACD,ABE,ACE,ABF, ACF,ADF simultaneously	6.49	7	0.48
ABD,ACD,ADF,BDF,CDF, AEBD,AECD simultaneously	6.49	7	0.48
ABF,ACF,ADF,BDF,CDF,AFBE,AFCE simultaneously	6.49	7	0.48

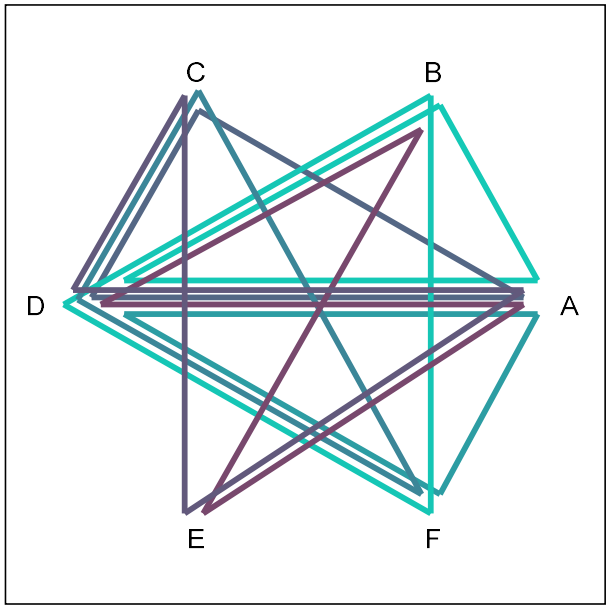
Visualising inconsistency in diabetes network

Diabetes prevention network

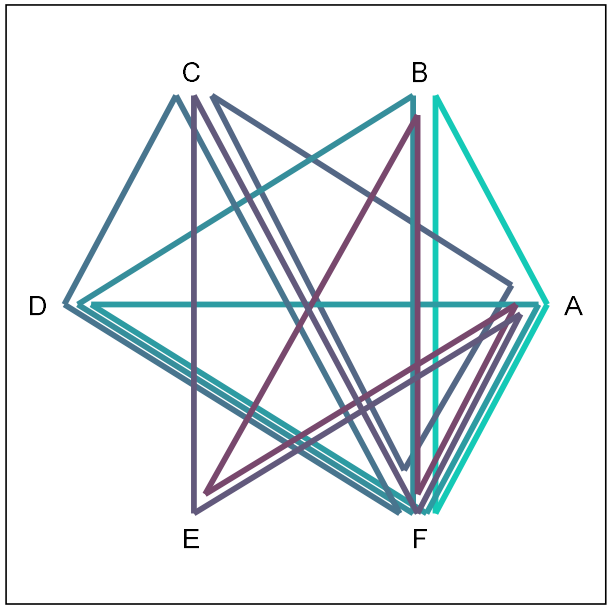
Model 1



Model 2



Model 3

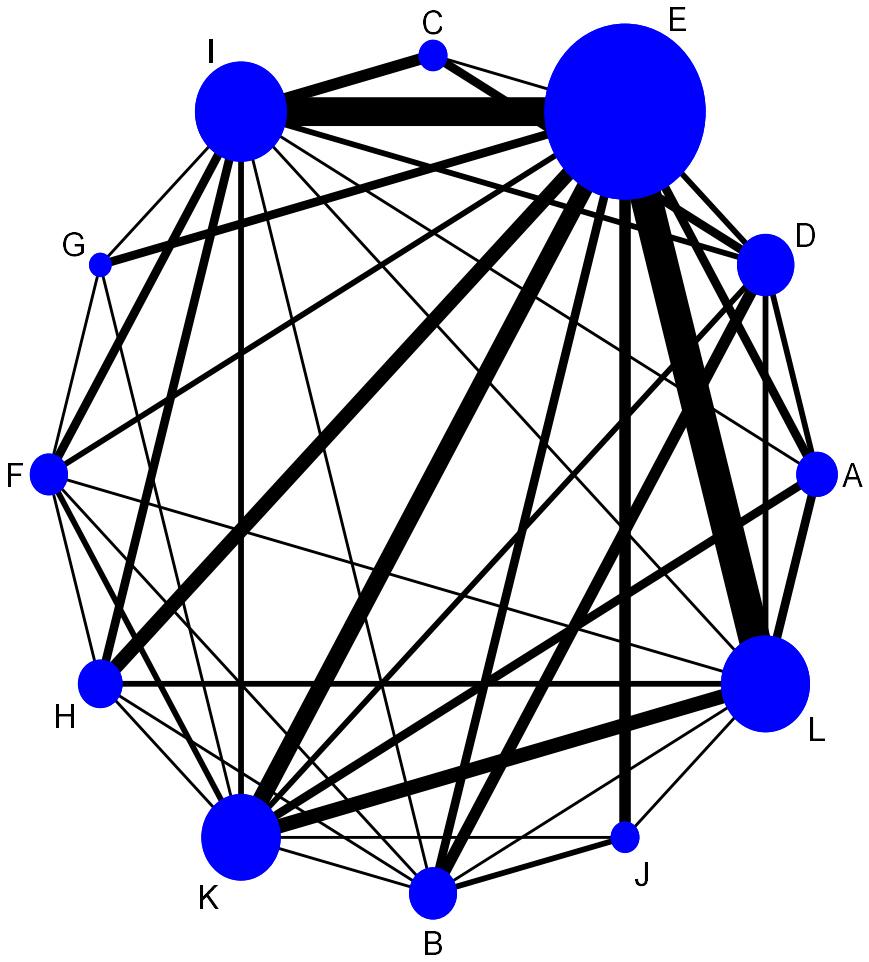


MANGA network

- Network meta-analysis compared 12 antidepressant drugs for treating adults with major depressive disorder:
  bupropion (A), citalopram (B), duloxetine (C), escitalopram (D), fluoxetine (E), fluvoxamine (F), milnacipran (G), mirtazapine (H), paroxetine (I), reboxetine (J), sertraline (K) and venlafaxine (L)
- Outcome for efficacy was response rate at 8 weeks
- Network includes two three-arm trials with design EIK

Cipriani et al., 2009

MANGA network



- All comparisons in multi-arm trials also appear in one or more pairwise trials
- Global model therefore includes a fixed number of independent loops
- Independent loops: 42-12+1=31 (42 contrasts, 12 treatments)

Global models: MANGA network

Loops split simultaneously	p-value
ADE, ADI, ADK, ADL, BDE, BDEF, BDEH, BDI, BDEJ, BDK, BDL, CDE, CDI, DEI, DEFI, DEGI, DEHI, DEK, DEFK, DEGK, DEHK, DIK, DEJK, DEL, DEFL, DEHL, DIL, DEJL, DKL, EFG, EFH	0.51
ADCE, ADCI, ADK, ADL, BDCE, BDCEF, BDCEH, BDCI, BDCEJ, BDK, BDL, CDE, EFG, EFH, CDI, CEI, CEFI, CEGI, CEHI, CEKD, CEFKD, CEGKD, CEHKD, CIKD, CEJKD, CELD, CEFLD, CEHLD, CILD, CEJLD, DKL	0.51

- Test for global inconsistency gives identical results for any set of 31 independent loops

Visualising inconsistency in MANGA network

- We have not attempted to create visualisation plots for loop inconsistencies across the MANGA network
- The complexity of the network means that many loops overlap and cross each other
- Inconsistency visualisation plots would not help with interpretation of the results

Summary

- Our proposed models handle treatments symmetrically and locate inconsistency in loops (not nodes or contrasts)
- The global model is invariant to choice of independent loops and we have shown how to identify these
- We chose to assign as much variation as possible to heterogeneity rather than inconsistency
- Our preference was based on choosing a model with fewer parameters in total and a simpler interpretation
- Implementation less straightforward than some previous approaches, but we aim to improve this

Summary

- In complex networks including multiple loops, multiple different sets of loops produce the same global model
- Practical exploration of potential causes of inconsistency for any one set of loops therefore seems less meaningful
- Visualisation plots can help by showing which part of the network shows the strongest evidence for inconsistency
- In comparison with the existing global model (design-by-treatment interactions model), our model uses fewer degrees of freedom and should improve power
- In future work, we plan to evaluate this approach in a simulation study

References (examples)

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We would like to thank Andrea Cipriani for providing the MANGA data set.

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