Handout S9-L

Identifying and addressing inconsistency in network meta-analysis

Julian Higgins

Cochrane Comparing Multiple Interventions Methods Group
Oxford Training event, March 2013

Acknowledgements

- Georgia Salanti
- Anna Chaimani
- Argie Veroniki

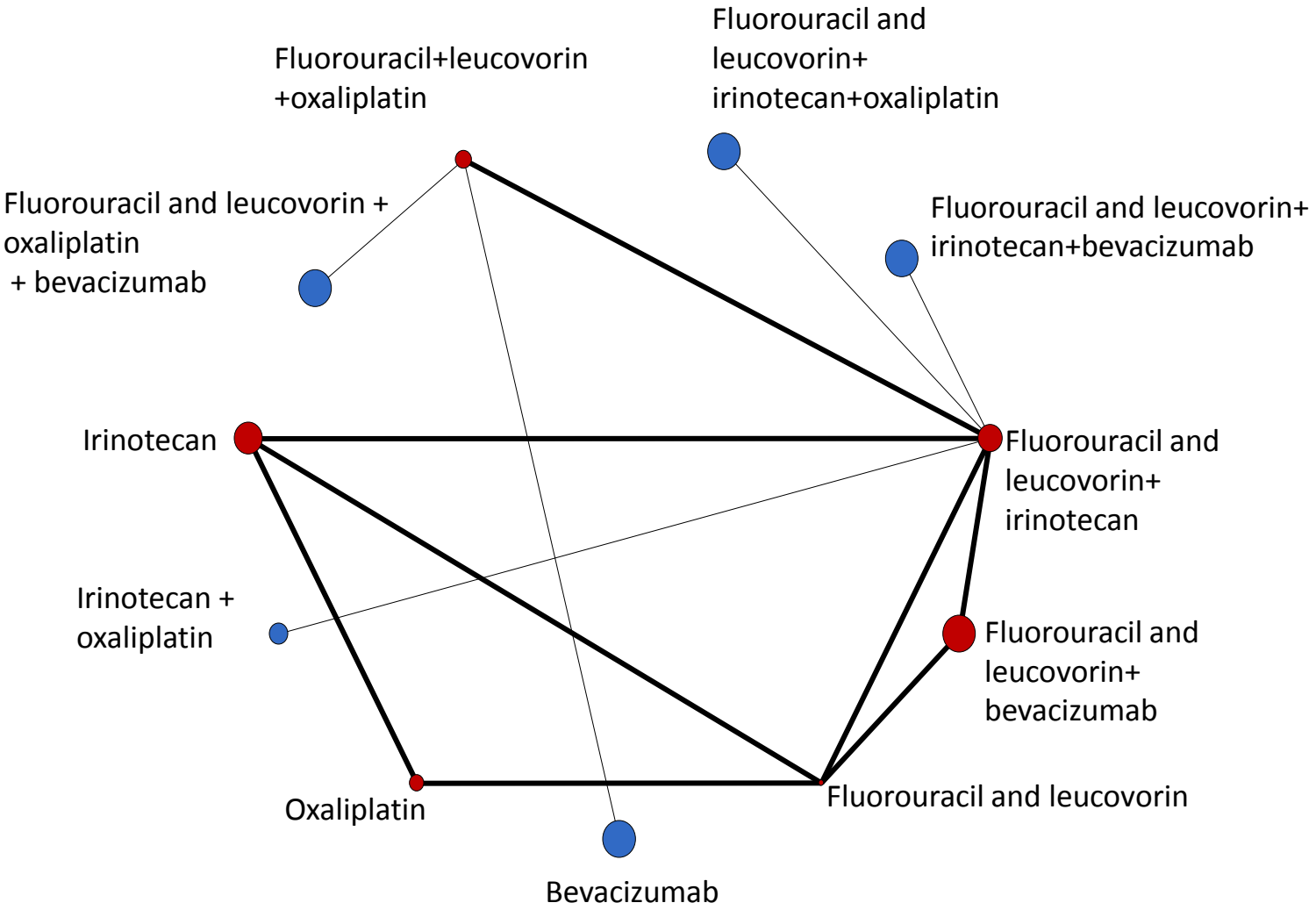
Transitivity and consistency in a network

- Standard network meta-analysis approaches are built on a consistency model
  - All pieces of evidence (direct and many indirect sources) are in agreement (or coherent)
- This assumes transitivity holds for any indirect comparison
- Across the network:
  - Every treatment in the network has a 'fixed' definition irrespective of the comparator
  - The 'missing' treatments in each trial may be viewed as missing at random
  - All sets of trials grouped by comparison are similar with respect to the distribution of effect modifiers
  - There are no differences between observed and unobserved effects for every comparison in the network beyond those attributed to heterogeneity

Transitivity and consistency in a network

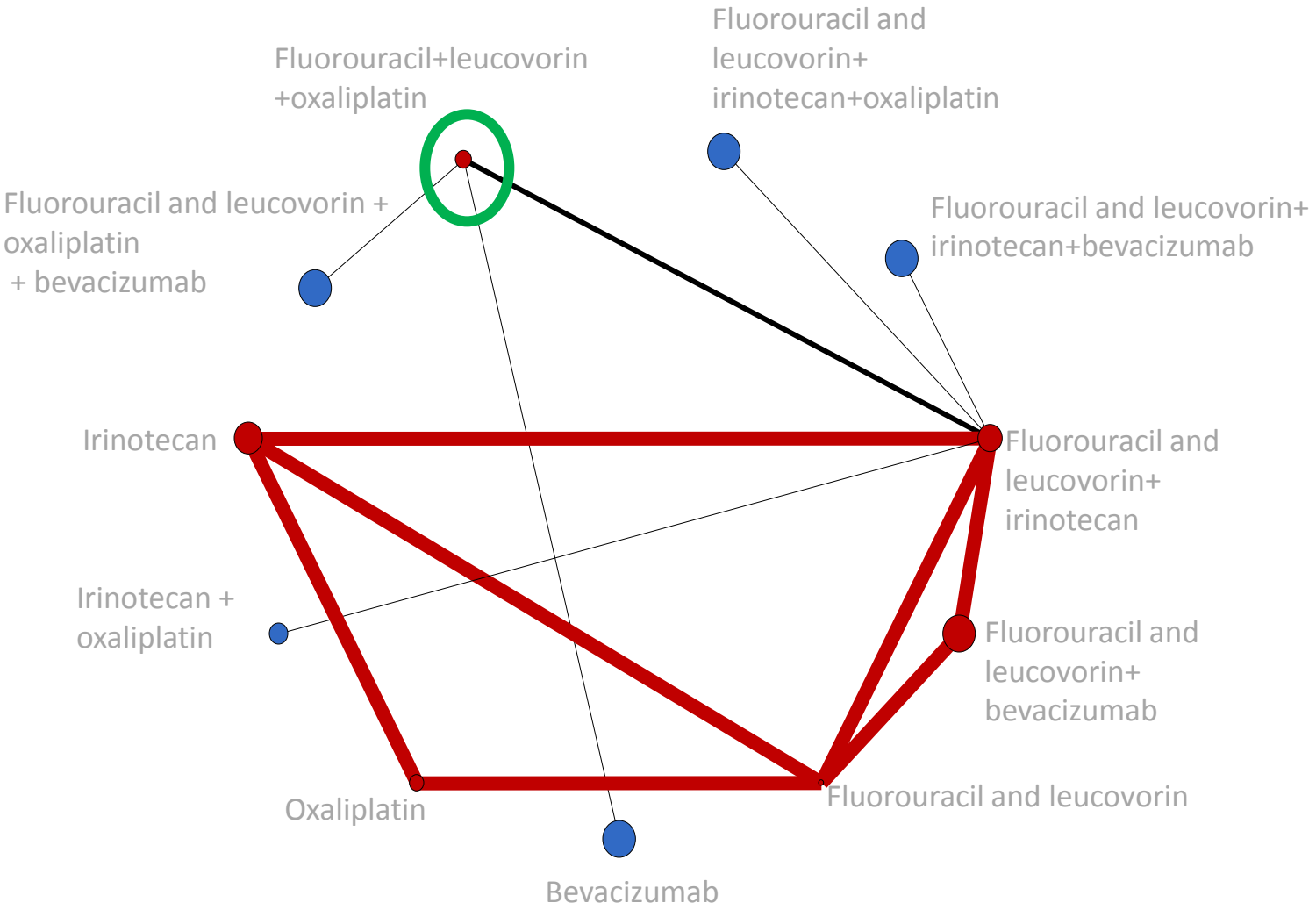
- We can only examine these things empirically when we have closed loops

Consistency and transitivity in a network



Golfinopoulos et al, 2007

Consistency and transitivity in a network



Are networks typically inconsistent?

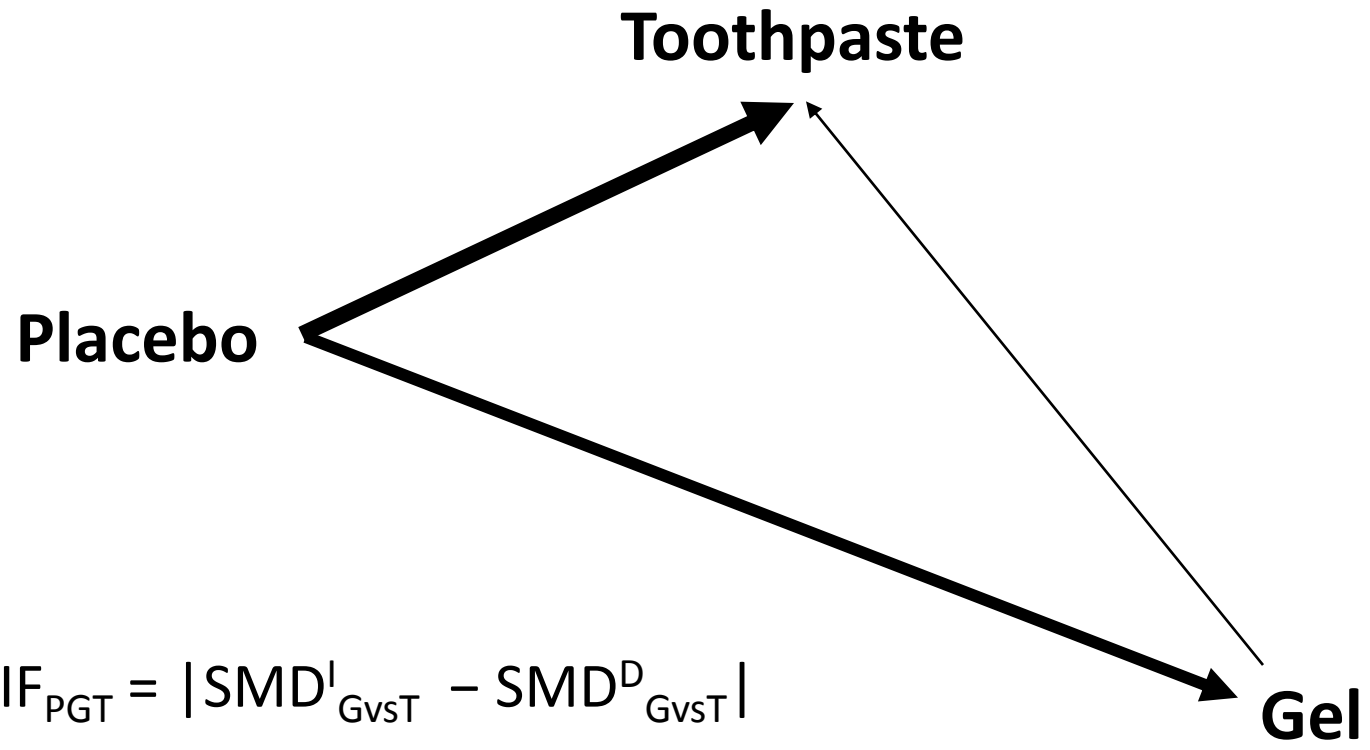
- In an empirical study of 40 networks, one in six networks had evidence of inconsistency Veroniki et al, 2013
  - using a 'design-by-treatment interaction' model (see later)

Statistical approaches for evaluating inconsistency in a network

- Compare direct with indirect evidence
  - Loop-specific approach
  - Node- splitting
- Use a model that allows for inconsistency
  - Relax consistency assumption completely
  - Add ‘inconsistency’ parameters
    - Random or fixed effects
    - Per loop, or per design
  - Either compare consistency and inconsistency models or draw conclusions from the inconsistency model

COMPARING DIRECT AND INDIRECT EVIDENCE

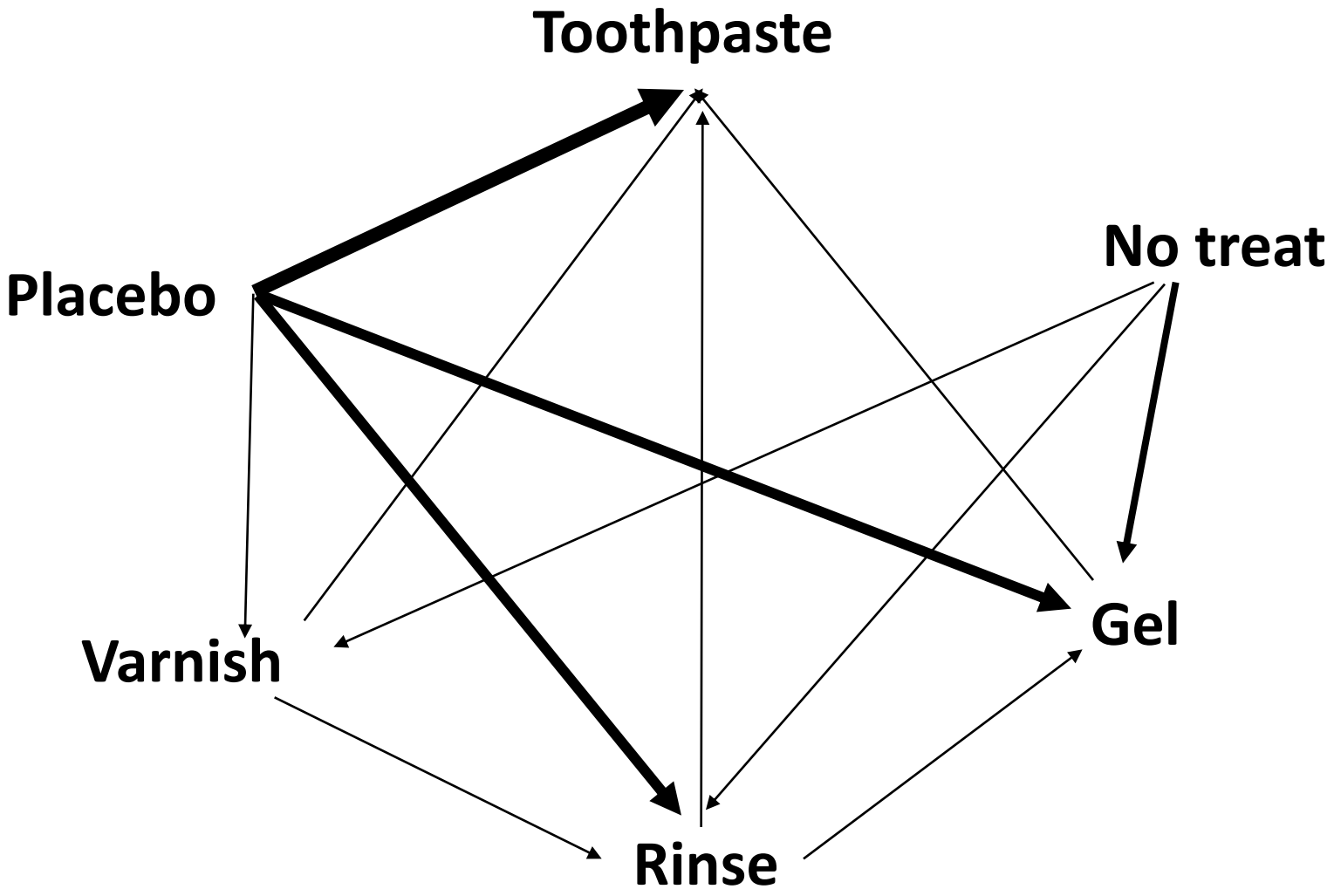
Comparing direct with indirect evidence within each loop



$IF_{PGT} = |SMD^{I}_{GvsT} - SMD^{D}_{GvsT}|$

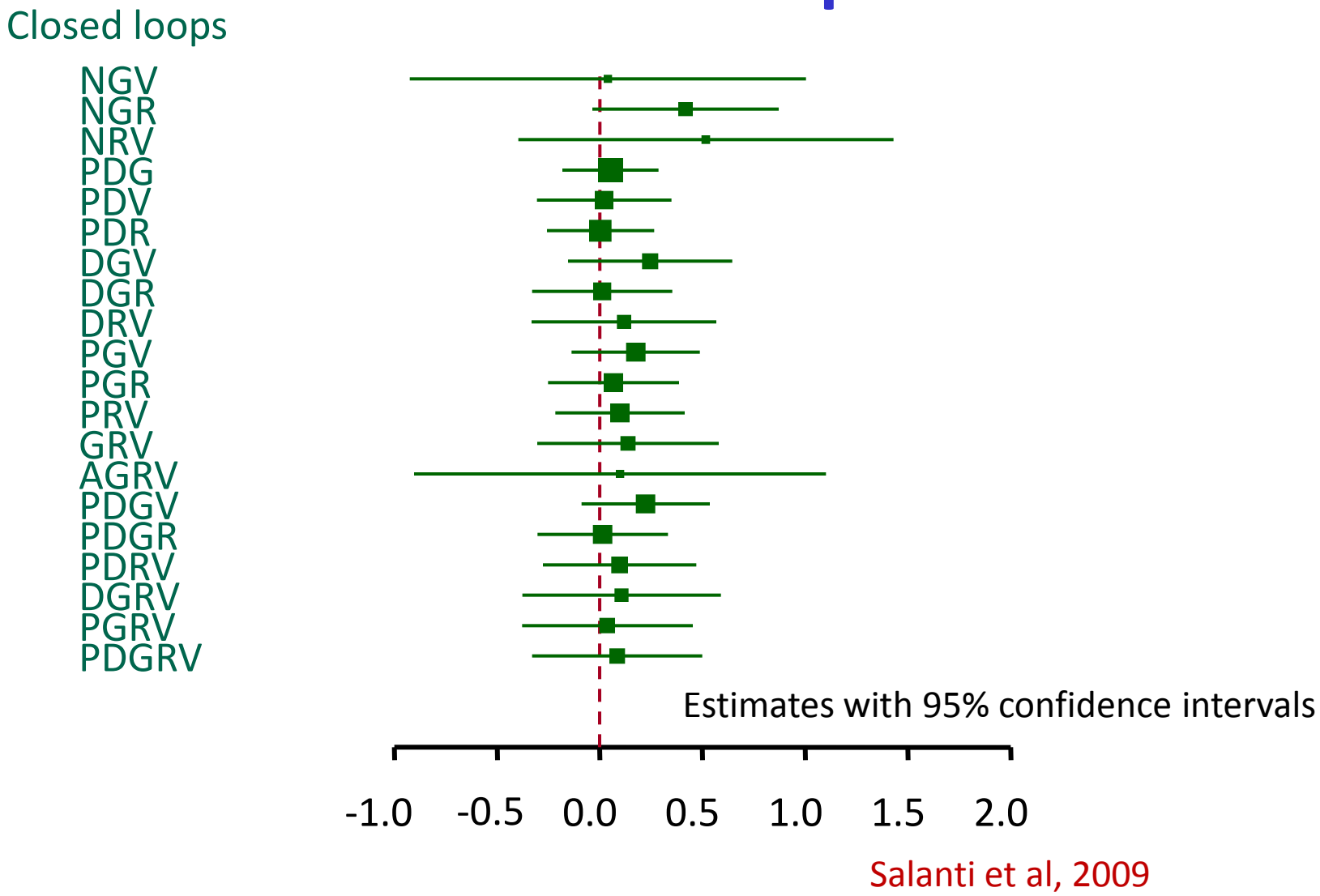
Is it statistically significant?
Calculate 95% CI for IF
Calculate z score, p-value....

Comparing direct with indirect evidence within each loop



Extend the idea to all closed loops assuming loop-specific heterogeneity parameters

Comparing direct with indirect evidence within each loop



Salanti et al, 2009

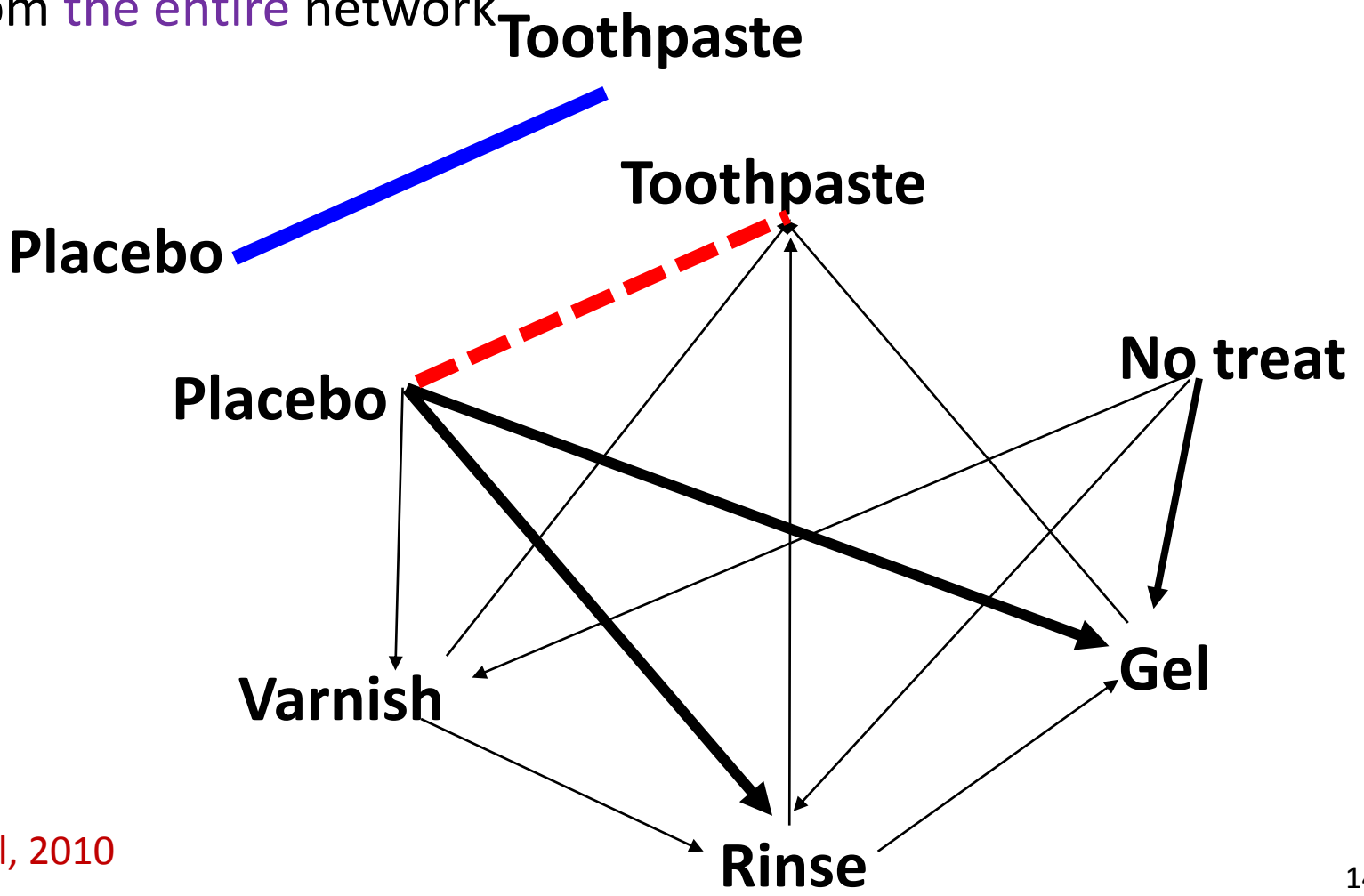
Comparing direct with indirect evidence within each loop

- Benefits
  - Simple and easy to apply
  - Can indicate loops with large inconsistency
- Limitations
  - Multiple, correlated tests which cannot be combined to infer about the consistency of the entire network
  - If a particular comparison is problematic (= does not fit with the rest of the evidence) this will show in all loops that include this comparison
  - Low power (but then all methods these do…)
  - We don't contrast direct vs ***all*** indirect evidence

Node splitting

or SIDE (Separating Indirect from Direct Evidence)-splitting

Contrast direct evidence with
indirect from the entire network



Dias et al, 2010

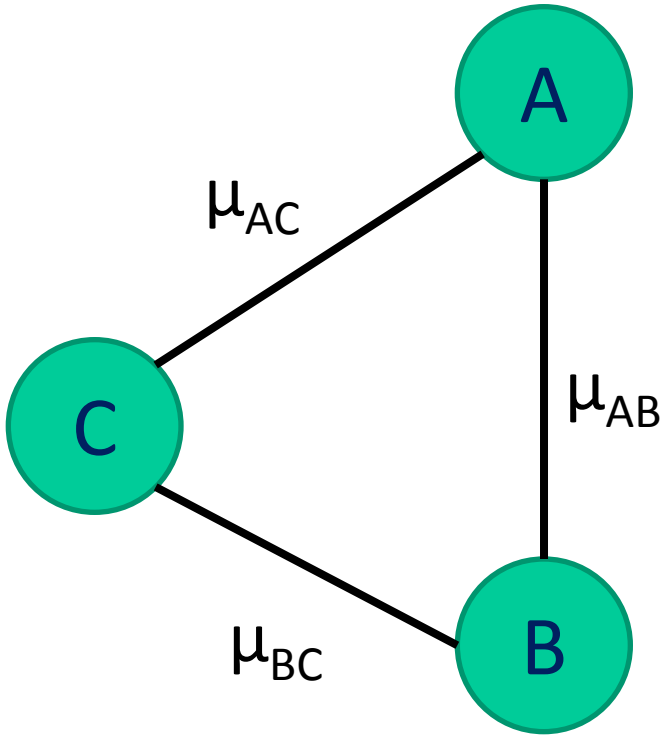
INCONSISTENCY MODELS

Dropping the consistency assumption

- An ‘inconsistency model’ can be obtained by omitting the consistency equations
  - so that it collapses into a series of independent meta-analyses
  - (might break up the comparisons in a multi-arm study)
- Compare the inconsistency model with the consistency model in terms of goodness of fit and trade-off between model fit and parsimony
- In a Bayesian framework use the deviance information criterion (DIC, similar to AIC)
  - model with lowest DIC more parsimonious (thus preferable)
- In a frequentist framework, we want a parametric form for the inconsistency model (with the consistency model nested)…

Modelling inconsistency

The consistency model

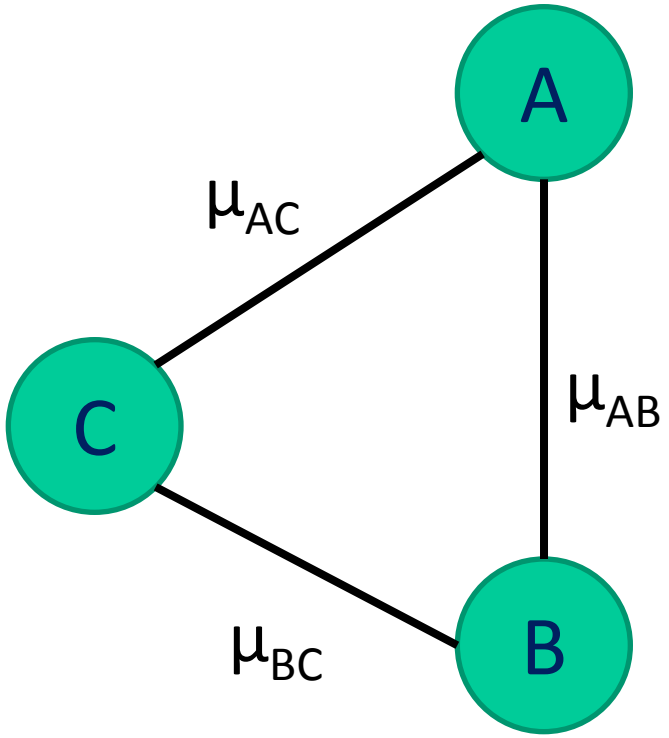


Consistency equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB}$$

Modelling inconsistency

The inconsistency model



Inconsistency equation

$$\mu_{BC} = \mu_{AC} - \mu_{AB} + w_{ABC}$$

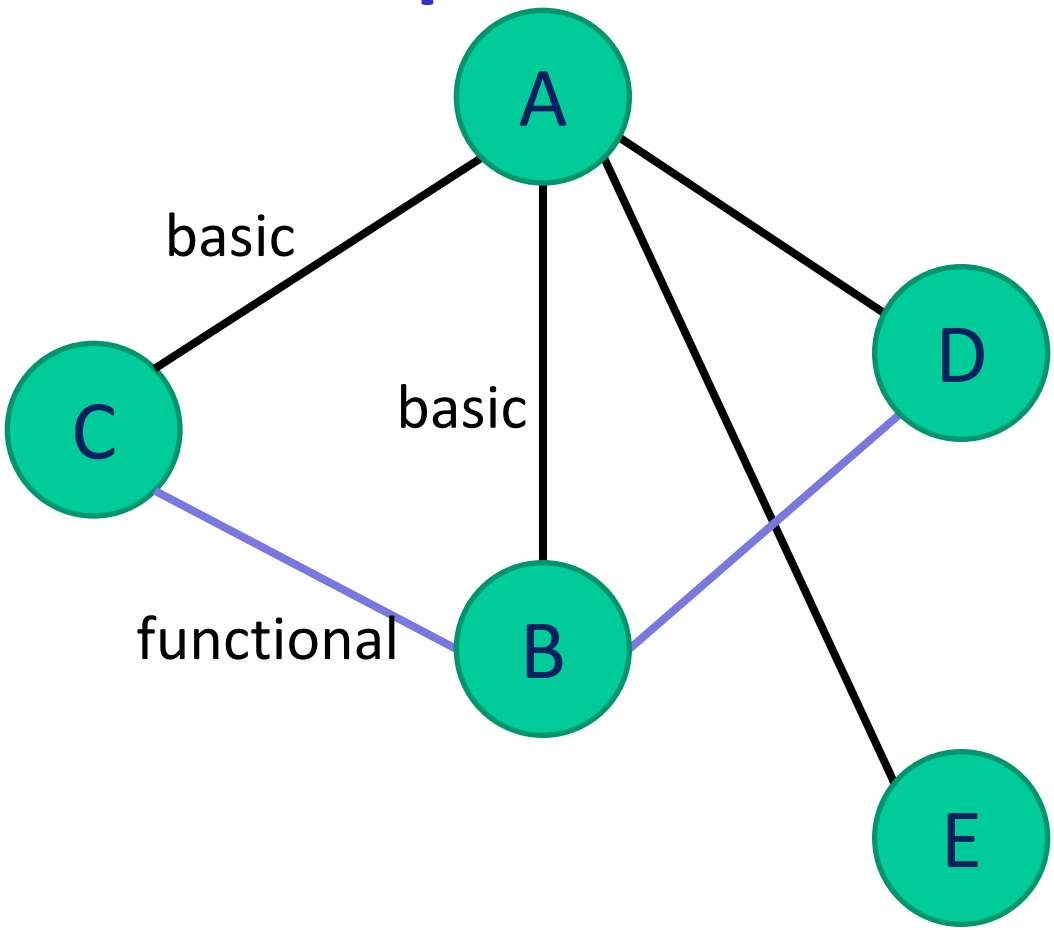
Model for consistency

Modelled effects (basic parameters μ_{AB} and μ_{AC}); δ_i is the study-specific random effect			
Comparison	A	B	C
AB	ref	$\mu_{AB} + \delta_i$	
AC	ref		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$

Model for inconsistency

Modelled effects (basic parameters μ_{AB} and μ_{AC}); δ_i is the study-specific random effect			
Comparison	A	B	C
AB	ref	$\mu_{AB} + \delta_i$	
AC	ref		$\mu_{AC} + \delta_i$
BC		$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w_{ABC}$

Lu & Ades inconsistency model: a parameter for each loop



Consistency equations:

$\mu_{BC} = \mu_{AC} - \mu_{AB} + w_{ABC}$

$\mu_{BD} = \mu_{AD} - \mu_{AB} + w_{ABD}$

$\mu_{DC} = \mu_{AC} - \mu_{AD}$

$\mu_{BE} = \mu_{AE} - \mu_{AB}$

$\mu_{DE} = \mu_{AE} - \mu_{AD}$

$\mu_{CE} = \mu_{AE} - \mu_{AC}$

Lu & Ades, 2006

How many new parameters? Inconsistency degrees of freedom

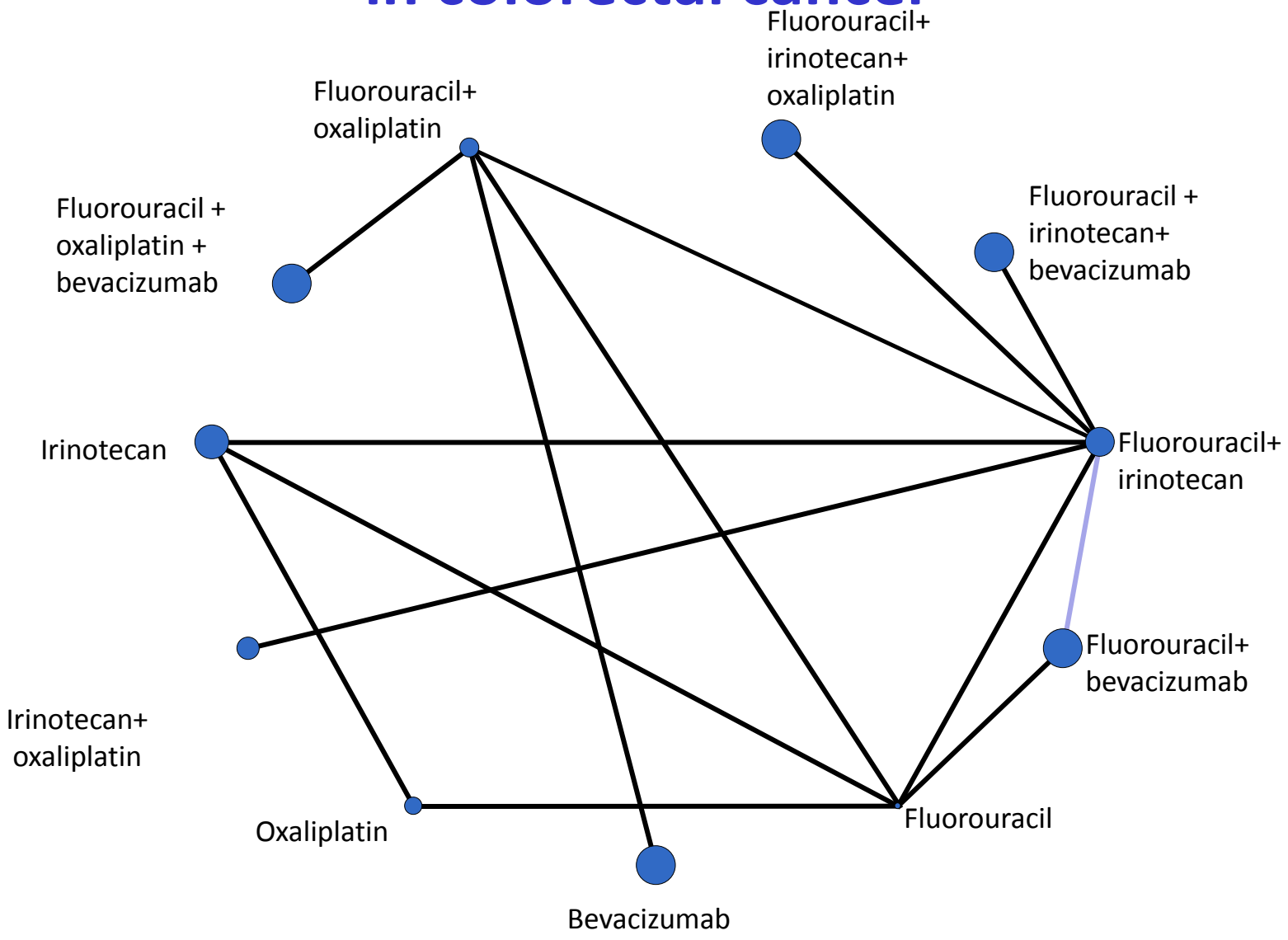
- How many inconsistency degrees of freedom are in the network?
- As many as the (supported*) functional parameters

$$Df = \#comparisons - (\#treatments - 1)$$

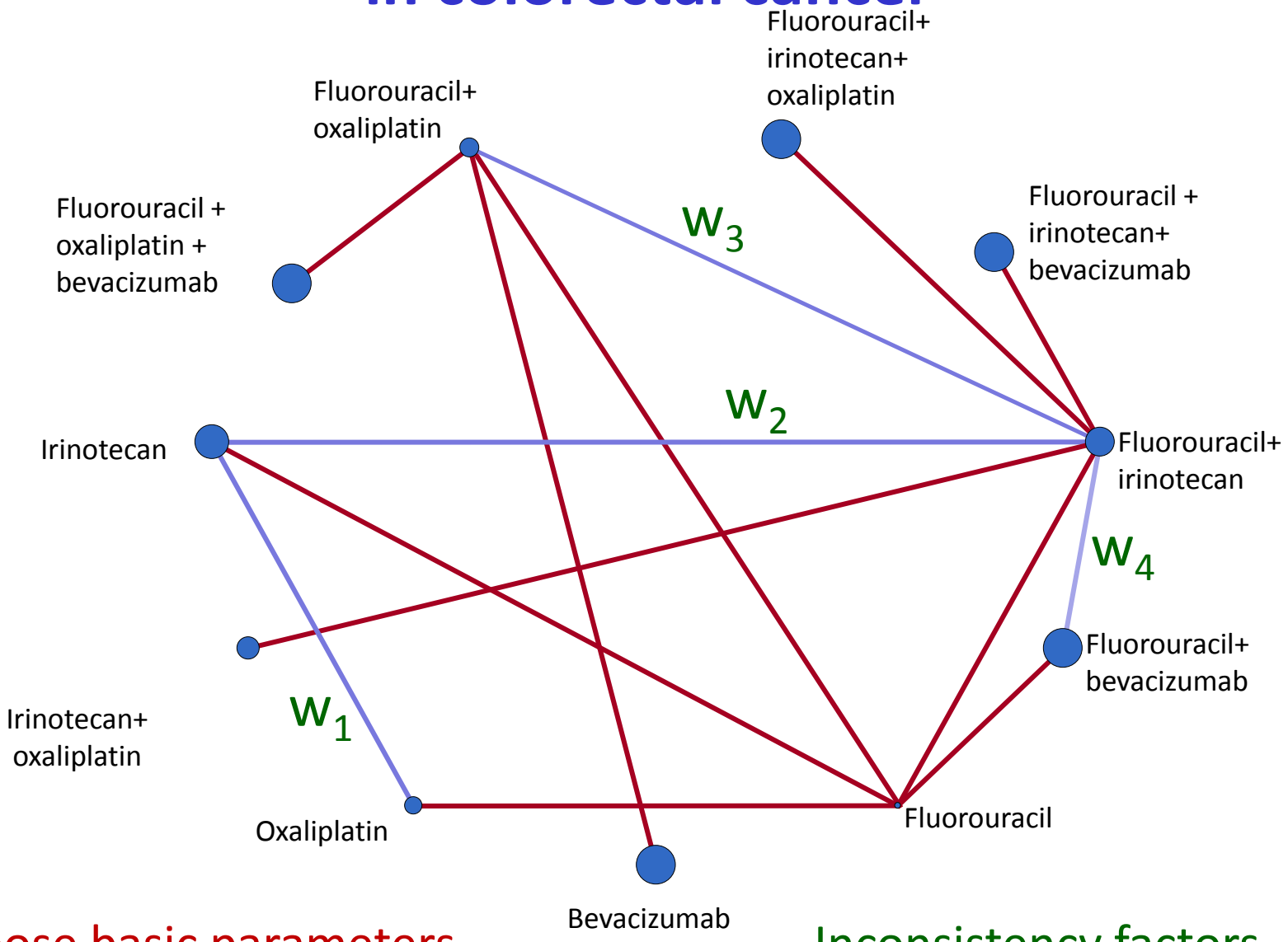
$$Df = N_{comp} - (T - 1)$$

*supported functional parameters = non-basic parameters for which there is direct evidence

Example: Survival with 11 chemotherapy regimens in colorectal cancer



Example: Survival with 11 chemotherapy regimens in colorectal cancer



Choose basic parameters

Inconsistency factors

Lu & Ades model

distributions of inconsistency factors

- Give the inconsistency parameters (*w*) a random-effects distribution across loops

$$w_j \sim N(0, \sigma^2)$$

- Compare σ^2 with τ^2 (heterogeneity) to infer about inconsistency
  - Relates to the definition of inconsistency as differences between direct and indirect affects beyond heterogeneity
  - Need many loops to estimate σ^2 well

- Alternative is to use fixed effects for the *w* parameters
  - Can interpret them individually

Results: colorectal cancer network

- $w_1 = -0.08$, $w_2 = -0.07$, $w_3 = -0.06$, $w_4 = -0.03$ (on logHR scale)
  - No loop is remarkably inconsistent

- $\sigma^2 = 0.11$ (SD 0.04), $\tau^2 = 0.19$ (SD 0.18)

- $P(\sigma^2 > \tau^2) = 0.41$
- No important changes in posterior HRs or fit of the model
- The assumption of consistency is reasonably supported by the data

Multi-arm trials: they need attention in parameterization

- Multi-arm trials are consistent by definition
- So, a loop which is informed by a multi-arm trial cannot be inconsistent
- This modifies the inconsistency degrees of freedom

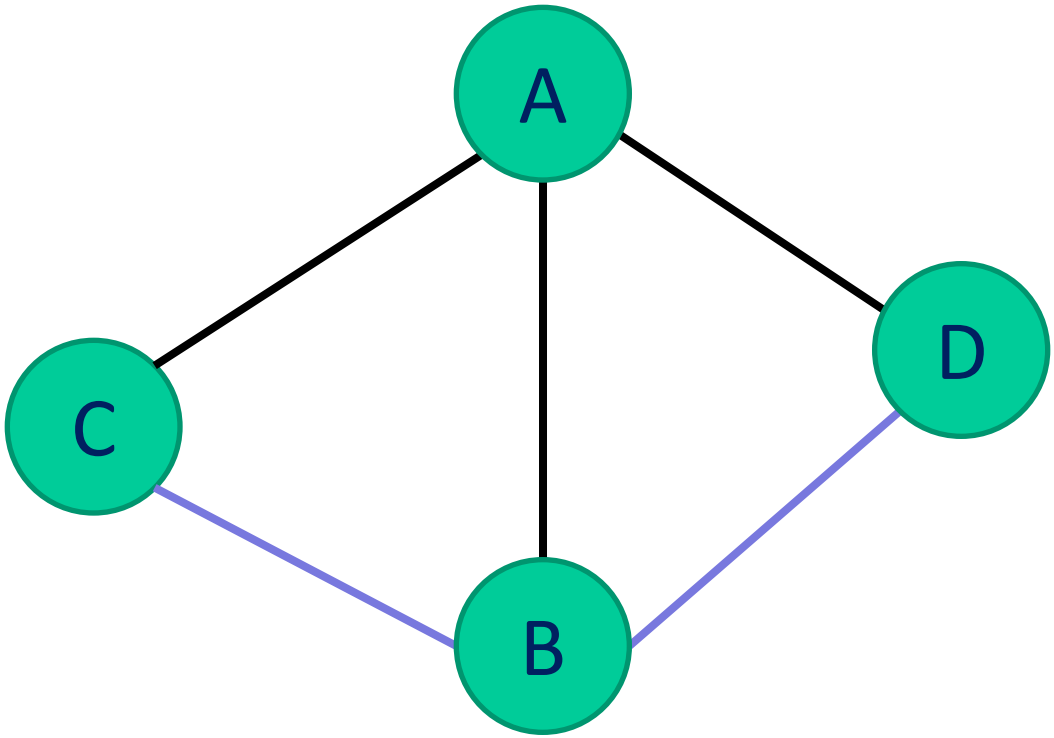
$$Df = N_{comp} - (T - 1) - S$$

Where **S** is the number of independent inconsistency relations in which the corresponding parameters are supported by no more than two independent sources of evidence

- Care is also needed when selecting the contrasts to include in the data

Lu & Ades inconsistency model

parameterization with pair-wise trials



Consistency equations:

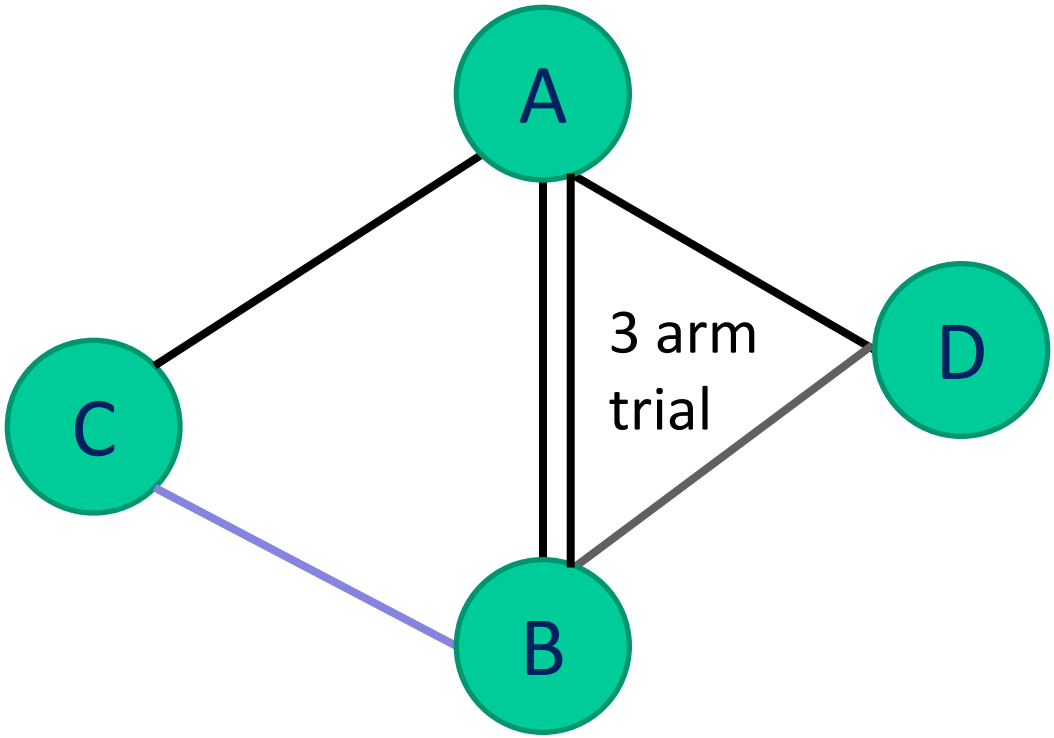
$\mu_{BC} = \mu_{AC} - \mu_{AB} + w_{ABC}$

$\mu_{BD} = \mu_{AD} - \mu_{AB} + w_{ABD}$

$\mu_{DC} = \mu_{AC} - \mu_{AD}$

Lu & Ades inconsistency model

parameterization with multi-arm trials



Consistency equations:

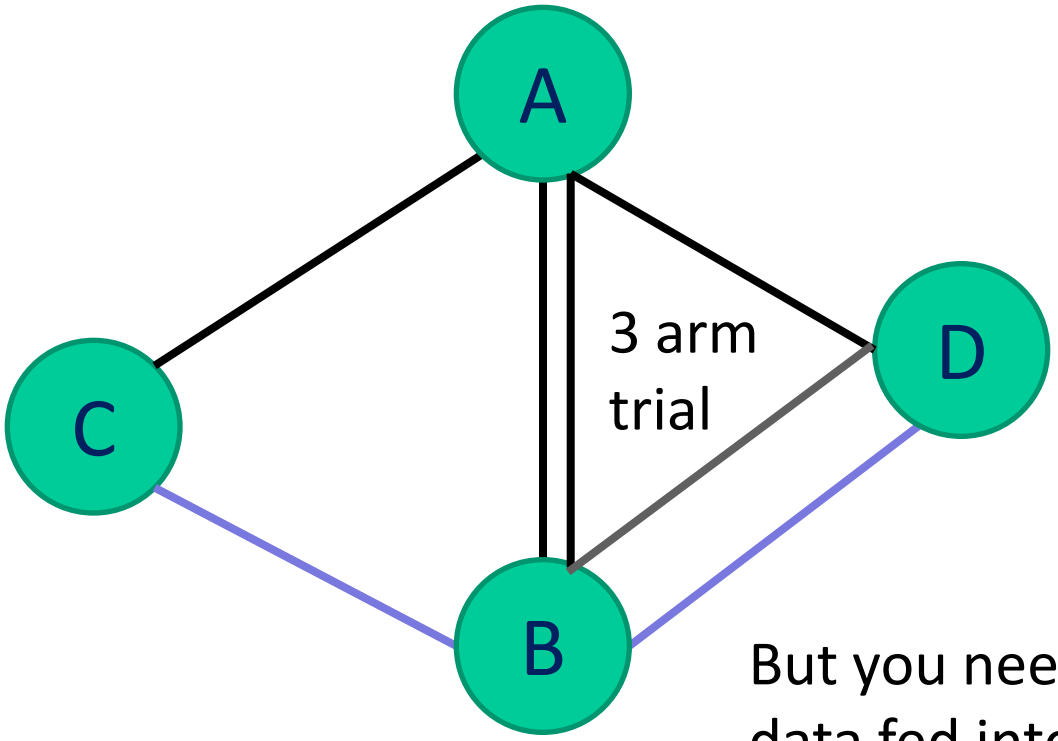
$\mu_{BC} = \mu_{AC} - \mu_{AB} + w_{ABC}$

$\mu_{BD} = \mu_{AD} - \mu_{AB} + w_{ABD}$

$\mu_{DC} = \mu_{AC} - \mu_{AD}$

Lu & Ades inconsistency model

parameterization with multi-arm trials



Consistency equations:

$\mu_{BC}=\mu_{AC}-\mu_{AB}+w_{ABC}$

$\mu_{BD}=\mu_{AD}-\mu_{AB}+w_{ABD}$

$\mu_{DC}=\mu_{AC}-\mu_{AD}$

But you need to make sure that the data fed into the analysis from the three arm trial includes contrast AD so that inconsistency in the loop ABD can be identified

Issues with the Lu and Ades model

- In the presence of multi-arm trials, the Lu and Ades inconsistency model is not uniquely defined
- Because multi-arm trials must be consistent, a network with multi-arm trials will have a mixture of consistent and inconsistent loops

Issues with the Lu and Ades model

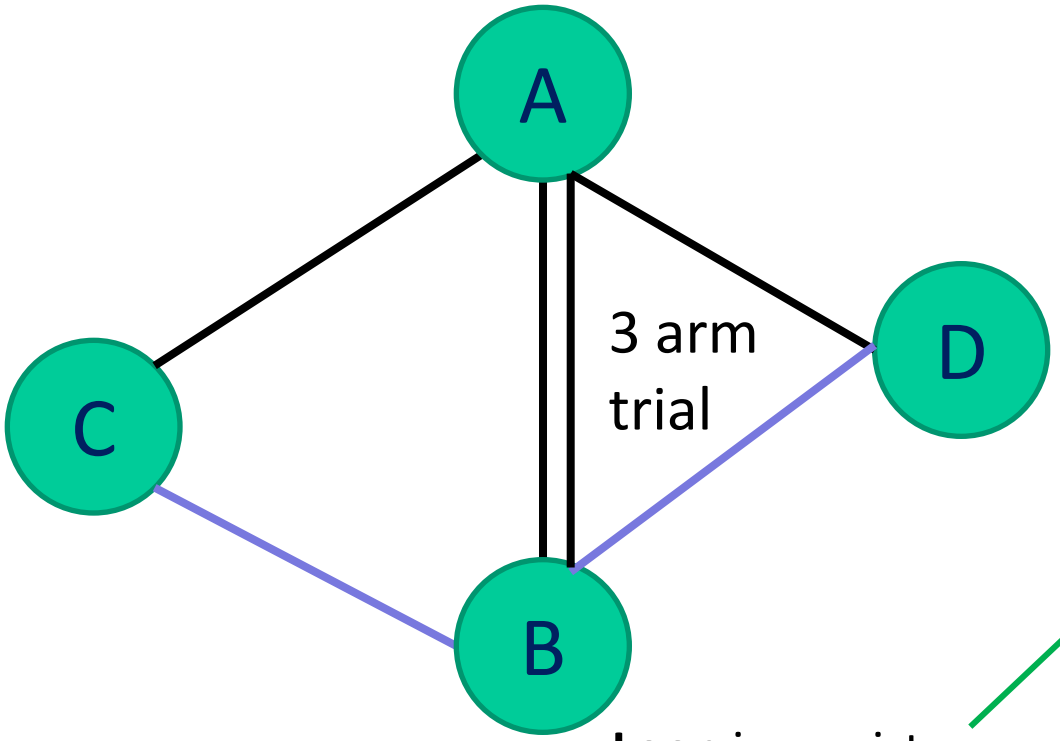
- In the presence of multi-arm trials, the Lu and Ades inconsistency model is not uniquely defined
- Because multi-arm trials must be consistent, a network with multi-arm trials will have a mixture of consistent and inconsistent loops
- A model that is completely general is one that allows for all types of inconsistency
  - inconsistency within loops made up of different trials
  - inconsistency between two-arm and three-arm trials
  - and beyond...
- Such a model has been termed a design-by-treatment interaction model

Inconsistency as 'design by treatment interaction'

- Goes 'beyond' loop inconsistency
- Design:= the treatments compared in a trial
  - ABC is a different design from AB or BC
- Design inconsistency: when the relative effectiveness of A versus B is different across designs
  - μ_{AB} is different when estimated in AB or ABC studies
- More degrees of freedom (more inconsistency factors)

Higgins et al, 2012, White et al, 2012

‘Design by treatment interaction’



Consistency equations:

$\mu_{BC}=\mu_{AC}-\mu_{AB}+w_{ABC}$

$\mu_{BD}=\mu_{AD}-\mu_{AB}+w_{AB}$

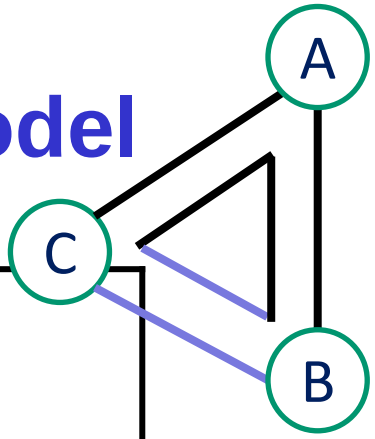
$\mu_{DC}=\mu_{AC}-\mu_{AD}$

Loop inconsistency

Design inconsistency for disagreement between the three arm ABC trial(s) and the AB trial(s)

Higgins et al, 2012, White et al, 2012

Loop inconsistency: Lu-Ades model



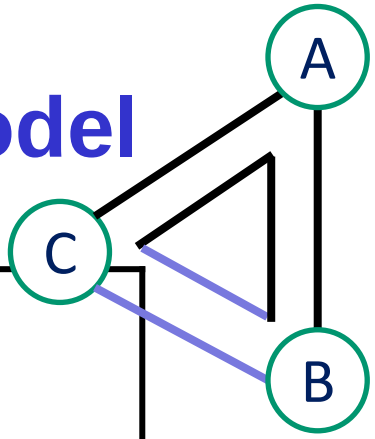
Modelled log odds ratios

(basic parameters μ_{AB} and μ_{AC});

δ_i is the heterogeneity random effect

Design	A	B	C
AB	ref	$\mu_{AB} + \delta_i$	
AC	ref		$\mu_{AC} + \delta_i$
BC	ref	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w_{ABC}$

Loop inconsistency: Lu-Ades model



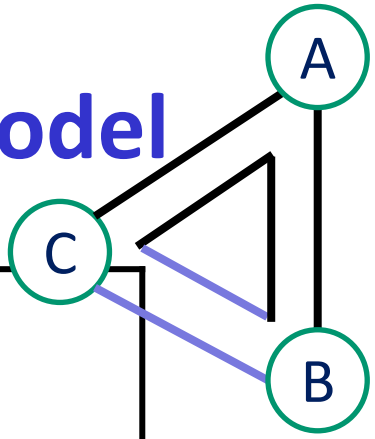
Modelled log odds ratios

(basic parameters μ_{AB} and μ_{AC})

δ_i is the heterogeneity random effect

Design	A	B	C
ABC	ref	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	ref	$\mu_{AB} + \delta_i$	
AC	ref		$\mu_{AC} + \delta_i$
BC	ref	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w_{ABC}$

‘Design by treatment interaction’ model



Modelled log odds ratios

(basic parameters μ_{AB} and μ_{AC})

δ_i is the heterogeneity random effect

Design	A	B	C
ABC	ref	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i$
AB	ref	$\mu_{AB} + \delta_i + w_{AB}$	
AC	ref		$\mu_{AC} + \delta_i + w_{AC}$
BC	ref	$\mu_{AB} + \delta_i$	$\mu_{AC} + \delta_i + w_{BC}$

Design-by-treatment interaction model

- Allows for inconsistency factors to represent
- loop inconsistency
- inconsistency between designs
- The inconsistency parameters can usually be interpreted in different ways

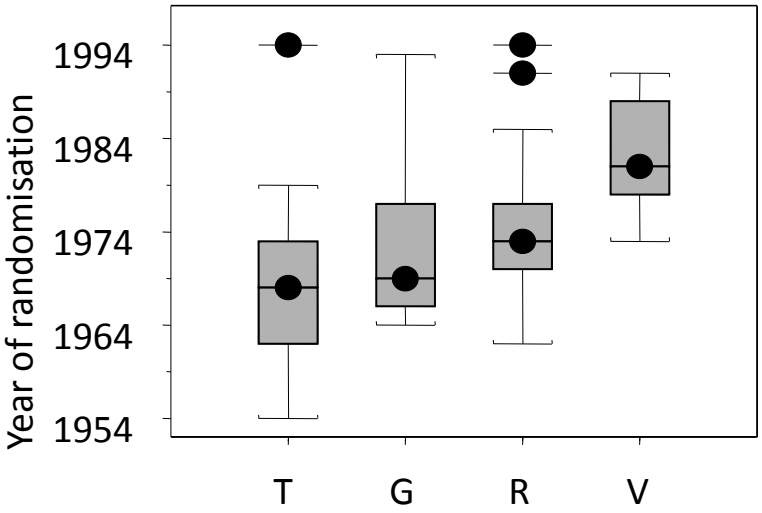
- Inconsistency parameters might be assumed to be fixed effects random-effects

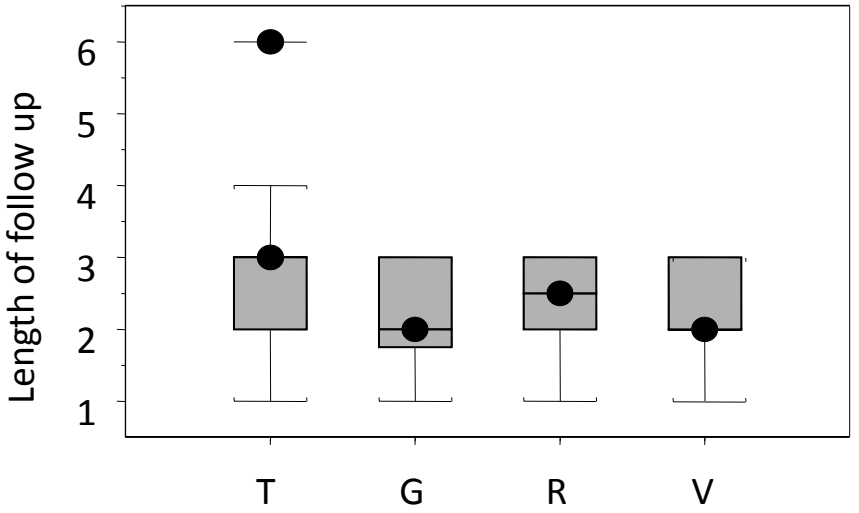
What if we don't find any inconsistency?

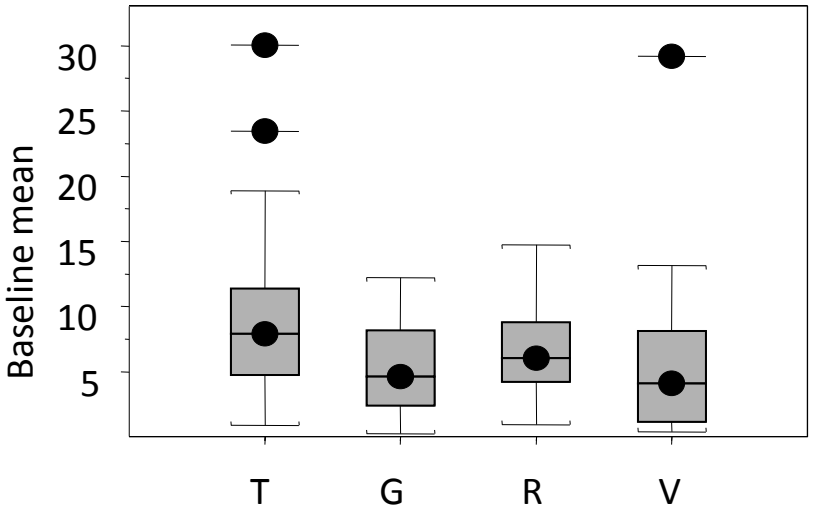
- The absence of statistically significant inconsistency does not mean there is consistency
  - Issues of power and the trade-off with heterogeneity may limit the usefulness of the tests of consistency

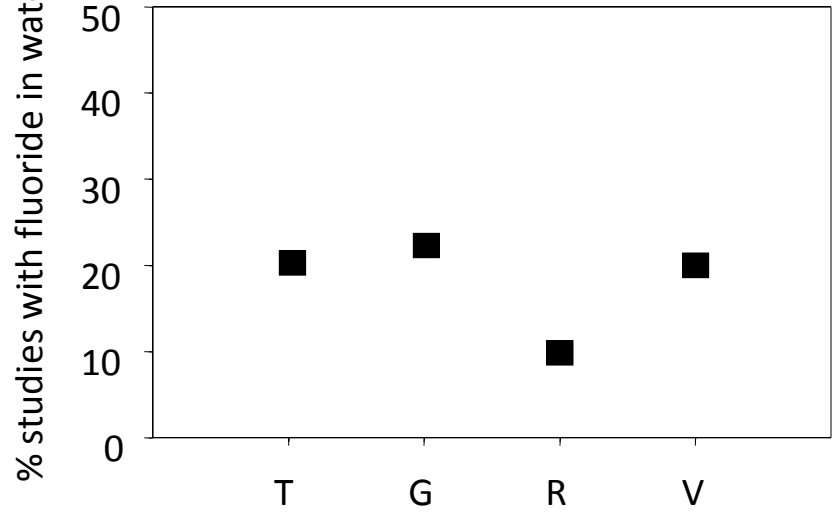
- Conceptual evaluation of the consistency assumption (i.e. the plausibility of transitivity) should always take place
  - Look at the distribution of effect modifiers across studies

Fluorides: characteristics of placebo-controlled trials







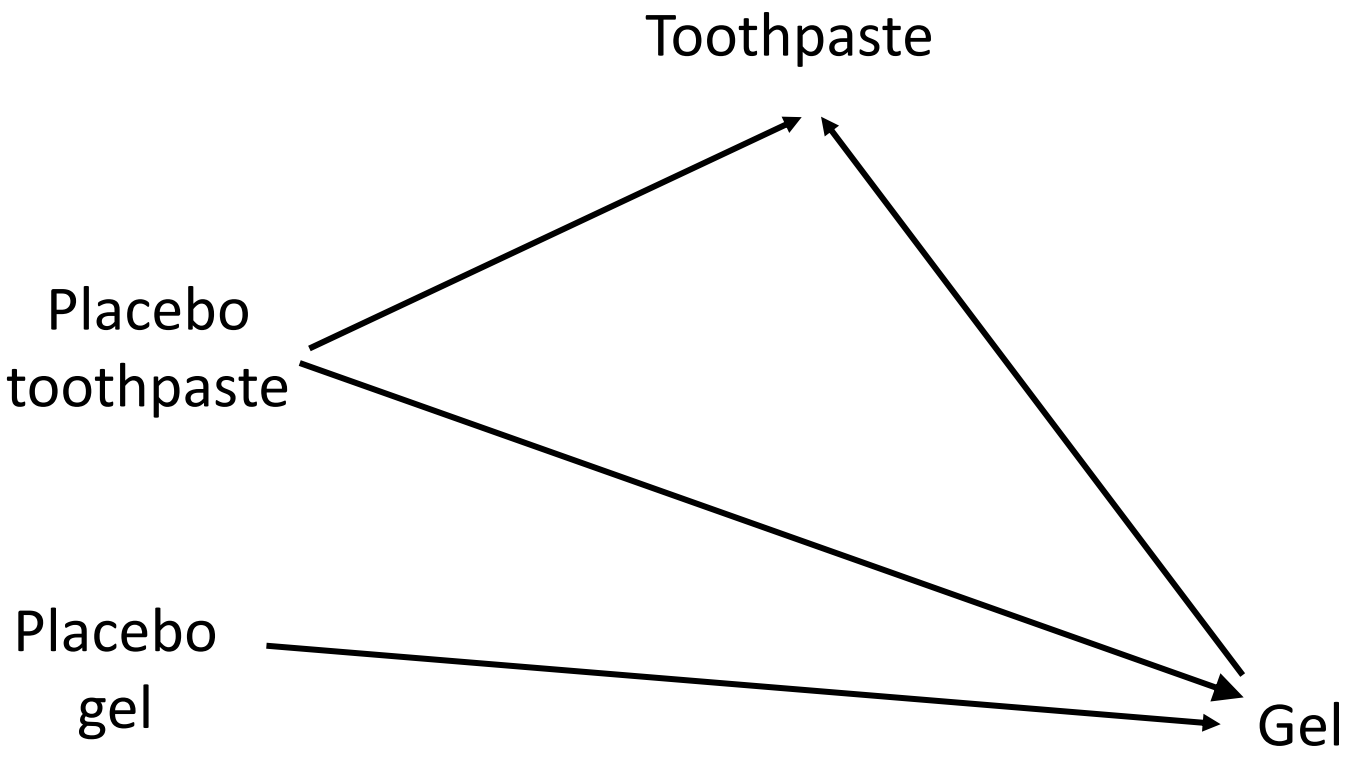


DEALING WITH INCONSISTENCY

What if we find inconsistency?

- Tricky!
- Might consider
  - splitting intervention nodes in the network
  - presenting results from an inconsistency model
  - presenting a variety of separate direct, indirect and mixed comparisons
    - care required: selective inclusion of evidence pieces might lead to bias
  - try to explain inconsistency
    - use network meta-regression

Dropping the consistency assumption



Fit models with different placebo effects (splitting vs lumping for the placebo node) and compare the model fit (e.g. DIC)

Network meta-regression

- Including covariates in the network meta-analysis
- Cooper *et al*, 2009 and Salanti et al 2009 describe a general framework

- Three types of assumption for the regression coefficients
  - different regression coefficients for different treatment effects
    - default mvmeta approach
  - exchangeable regression coefficients across treatment effects
    - not possible in mvmeta
  - common regression coefficient across treatment effects
    - mvmeta (latest version) with commonparm option

Network meta-regression

- Fit the models (adjusted and unadjusted) and examine
  - Improvement in fit
  - Changes in heterogeneity
  - The distribution of the effect of covariates

- It is expected that network meta-regression will have problems similar to those in regular meta-regression (low power, prone to bias)

Network meta-regression

Fluoride	No adjustment		Year of randomisation		Baseline mean caries level	
	Mean SMD	P(best)	Mean SMD adjusted to 1994 values	P(best)	Mean SMD adjusted to zero	P(best)
No treatment	reference		reference		reference	
Placebo	–0.22 (–0.34, –0.09)	0%	–0.23 (–0.36, –0.11)	0%	–0.17 (–0.29, –0.05)	0%
Toothpaste	–0.54 (–0.67, –0.40)	57%	–0.43 (–0.59, –0.26)	37%	–0.35 (–0.49, –0.20)	25%
Gel	–0.45 (–0.58, –0.34)	4%	–0.36 (–0.50, –0.21)	4%	–0.34 (–0.47, –0.22)	30%
Rinse	–0.50 (–0.63, –0.37)	14%	–0.41 (–0.56, –0.25)	16%	–0.35 (–0.49, –0.21)	24%
Varnish	–0.50 (–0.65, –0.34)	25%	–0.42 (–0.59, –0.26)	42%	–0.32 (–0.48, –0.17)	20%

Salanti et al, 2009

See also Cooper et al, 2009; Nixon et al, 2006

Network meta-regression

You can use them to account for

- Patient-level covariate (beware of ecological bias)
- Risk of bias assessments
  - e.g. Dias et al, 2010
- Small study effects
  - e.g. Chaimani & Salanti, 2012
- Sponsorship bias
  - e.g. Cipriani et al, 2009

References

- Chaimani A, Salanti G. Using network meta-analysis to evaluate the existence of small-study effects in a network of interventions. *Research Synthesis Methods* 2012; **3**: 161–176.
- Cipriani A, Furukawa TA, Salanti G et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; **373**: 746–758.
- Cooper NJ, Sutton AJ et al. Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation. *Statistics in Medicine* 2009; **28**: 1861–1881.
- Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010; **29**: 932–944
- Dias S, Welton NJ, Marinho VCC, Salanti G, Higgins JPT, Ades AE. Estimation and adjustment of bias in randomised evidence using mixed treatment comparison meta-analysis. *Journal of the Royal Statistical Society Series A* 2010; 173: 613–629.
- Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JPA. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. Lancet Oncology 2007; 8: 898-911.
- Higgins JPT, Jackson D, Barrett JK, Lu G, Ades, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies *Research Synthesis Methods* 2012; **3**: 98–110.
- Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006; **101**: 447–459.
- Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. *Statistics in Medicine* 2007; 26: 1237-54.
- Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods 2012; 3: 80–97.
- Salanti G, Marinho V, Higgins JPT. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *Journal of Clinical Epidemiology* 2009; **62**: 857-64
- Veroniki AA, Vasiliadis HS, Higgins JPT, Salanti G. Evaluation of inconsistency in networks of interventions. *International Journal of Epidemiology* (to appear)
- White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research Synthesis Methods* 2012; 3: 111-125