

## Automating network meta-analysis

Gert van Valkenhoef

Department of Epidemiology, University Medical Center Groningen (NL),  
Faculty of Economics and Business, University of Groningen (NL)

18 Apr. 2011  
Bristol, United Kingdom

# Outline

- 1 Introduction
- 2 MTC models
- 3 Problem definition
- 4 Solution & evaluation
- 5 Discussion

# Mini-CV

- Born July 1985, The Netherlands
- MSc in Artificial Intelligence (focus on formal aspects)
- Several years experience in software development
- Current: PhD student (medical informatics/statistics)
  - Interests: the intersection between statistics and information technology applied to evidence-based medical decision making.

# PhD project

- Part of TI Pharma project Escher
  - “science-driven drug regulation”
- ADDIS decision support system
  - evidence-based decision support
  - for benefit-risk decision making
  - based on a database of clinical trials
  - using evidence synthesis
- **Network meta-analysis** highly relevant
  - but model specification difficult manual step

# Network meta-analysis in ADDIS

Please select the drugs to be included

Create Network meta-analysis

**Overview**

1. Select Indication
2. Select Outcome
3. Select Drugs
4. Select Studies
5. Select Arms
6. Overview

**Select Drugs**

Select the drugs to be used for the network meta-analysis. Click to select (green) or deselect (gray). To continue, (1) at least two drugs must be selected, and (2) all selected drugs must be

Network diagram showing connections between various drugs. Selected drugs (green) include Fluoxetine, Paroxetine, Placebo, Sertraline, and Venlafaxine. Deselected drugs (gray) include Bupropion, Duloxetine, Mirtazapine, Fluvoxami..., Escitalopr..., and Venlafaxine. The network shows connections between these drugs with associated weights.

Navigation buttons: Previous, Next, Last, Finish, Cancel

# Network meta-analysis in ADDIS

Please select the studies to be included

**Overview**

1. Select Indication
2. Select Outcome
3. Select Drugs
4. Select Studies
5. Select Arms
6. Overview

**Select Studies**

Select the studies to be used for meta analysis. At least one study must be selected to continue.

Studies measuring 310497006 Severe depression on HAM-D Responders

| <input type="checkbox"/>            | Study ID              | Title                     | Group allocation | Blinding     | Study size | In |
|-------------------------------------|-----------------------|---------------------------|------------------|--------------|------------|----|
| <input checked="" type="checkbox"/> | Chouinard et al, 1999 | A Canadian multicen...    | Randomized       | Double blind | 203        | 3  |
| <input checked="" type="checkbox"/> | Coleman et al, 1999   | Sexual dysfunction a...   | Randomized       | Double blind | 364        | 3  |
| <input checked="" type="checkbox"/> | Coleman et al, 2001   | A placebo-controlled ...  | Randomized       | Double blind | 456        | 3  |
| <input checked="" type="checkbox"/> | Croft et al, 1999     | A placebo-controlled ...  | Randomized       | Double blind | 360        | 3  |
| <input checked="" type="checkbox"/> | De Nayer et al, 2002  | Venlafaxine compare...    | Randomized       | Double blind | 146        | 3  |
| <input checked="" type="checkbox"/> | De Wilde et al, 1993  | A double-blind, comp...   | Randomized       | Double blind | 78         | 3  |
| <input checked="" type="checkbox"/> | Detke et al, 2004     | Duloxetine in the acc...  | Randomized       | Double blind | 367        | 3  |
| <input checked="" type="checkbox"/> | Dierck et al, 1996    | A double-blind comp...    | Randomized       | Double blind | 314        | 3  |
| <input checked="" type="checkbox"/> | Fava et al, 1998      | A double-blind study ...  | Randomized       | Double blind | 128        | 3  |
| <input checked="" type="checkbox"/> | Fava et al, 2002      | Accute efficacy of flu... | Randomized       | Double blind | 284        | 3  |
| <input checked="" type="checkbox"/> | Gagliano 1993         | A double blind comp...    | Randomized       | Double blind | 90         | 3  |
| <input checked="" type="checkbox"/> | Goldstein et al, 2002 | Duloxetine in the tre...  | Randomized       | Double blind | 173        | 3  |
| <input checked="" type="checkbox"/> | McPartin et al, 1998  | A comparison of onc...    | Randomized       | Double blind | 361        | 3  |
| <input checked="" type="checkbox"/> | Mehtonen et al, 2000  | Randomized, double...     | Randomized       | Double blind | 147        | 3  |
| <input checked="" type="checkbox"/> | Neufuss et al, 2000   | A double-blind, com...    | Randomized       | Double blind | 226        | 3  |

◀ Previous   Next ▶   Last   Finish   Cancel

# Network meta-analysis in ADDIS

Now please write down the model for us...

```
test.inco.model X
}

# Random effects in study Alves et al, 1999
re[1, 1] ~ dnorm(d.Fluoxetine.Paroxetine + d.Paroxetine.Sertraline + d.Sertraline.Venlafaxine +
w.Fluoxetine.Paroxetine.Sertraline.Venlafaxine, tau.d)
delta[1, 1, 1] <- 0
delta[1, 1, 5] <- re[1, 1]
# Random effects in study Ballus et al, 2000
re[2, 1] ~ dnorm(d.Paroxetine.Sertraline + d.Sertraline.Venlafaxine + -w.Paroxetine.Sertraline.Venlafaxine, tau.d)
delta[2, 2, 2] <- 0
delta[2, 2, 5] <- re[2, 1]
# Random effects in study Bennie et al, 1995
re[3, 1] ~ dnorm(d.Fluoxetine.Paroxetine + d.Paroxetine.Sertraline + -w.Fluoxetine.Paroxetine.Sertraline, tau.d)
delta[3, 1, 1] <- 0
delta[3, 1, 4] <- re[3, 1]
# Random effects in study Boyer et al, 1998
re[4, 1] ~ dnorm(d.Fluoxetine.Paroxetine + d.Paroxetine.Sertraline + -w.Fluoxetine.Paroxetine.Sertraline, tau.d)
delta[4, 1, 1] <- 0
delta[4, 1, 4] <- re[4, 1]
# Random effects in study Chouinard et al, 1999
re[5, 1] ~ dnorm(d.Fluoxetine.Paroxetine, tau.d)
delta[5, 1, 1] <- 0
delta[5, 1, 2] <- re[5, 1]
# Random effects in study Coleman et al, 1999
re[6, 1] ~ dnorm(-d.Sertraline.Venlafaxine + -d.Venlafaxine.Placebo + w.Placebo.Sertraline.Venlafaxine, tau.d)
delta[6, 3, 3] <- 0
delta[6, 3, 4] <- re[6, 1]
# Random effects in study Coleman et al, 2001
re[7, 1] ~ dnorm(d.Venlafaxine.Placebo + d.Sertraline.Venlafaxine +
w.Fluoxetine.Paroxetine.Sertraline.Venlafaxine.Placebo + d.Paroxetine.Sertraline + d.Fluoxetine.Paroxetine, tau.d)
delta[7, 1, 1] <- 0
delta[7, 1, 3] <- re[7, 1]
# Random effects in study Croft et al, 1999
re[8, 1] ~ dnorm(-d.Sertraline.Venlafaxine + -d.Venlafaxine.Placebo + w.Placebo.Sertraline.Venlafaxine, tau.d)
delta[8, 3, 3] <- 0
delta[8, 3, 4] <- re[8, 1]
```

# Network meta-analysis in ADDIS

This would not be feasible for most users!

- So we set out to automate this step

# Automating network meta-analysis

- The model has to be manually specified for each analysis
- Difficult step
  - Especially inconsistency models (Lu & Ades, 2006)
  - Problems have no bearing on interpreting the results
- An algorithm to generate the model would enable
  - network meta-analysis for a broader audience
  - network meta-analysis for (semi-)automated decision support



# Model generation: open problems

- ① How to choose the 'basic parameters'
  - Lu & Ades (2006) identified this as 'determining the ICDF'
- ② How to choose study baselines
  - (the model is in terms of relative effects, so a study is parametrized relative to some baseline)
- ③ How to specify priors
- ④ How to draw starting values for the markov chains

We solved (1-4), but I will discuss (1)

# Agenda

- Goal: determine ICDF in inconsistency models
- Approach:
  - ① Understand & formalize the problem
  - ② Apply existing algorithms → solution
  - ③ Evaluate running time on published evidence networks
- Conclusions: the problems are subtle, and the solution is (theoretically) inefficient, but very fast on published networks

# MTC models

Mixed Treatment Comparison (MTC) – Lu & Ades, 2004; 2006

- is an extension of (Bayesian) pair-wise meta-analysis
- combines direct and indirect evidence
- to summarize evidence from a network of trials
- using a Bayesian Hierarchical Model (BHM)
- estimated using Markov Chain Monte Carlo (MCMC)

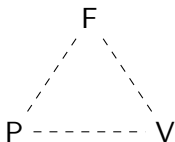
Main assumption:

- *consistency* between direct and indirect evidence
- can be tested using *inconsistency* models

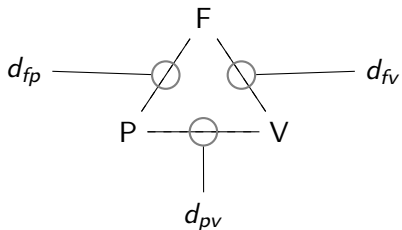
# Example MTC (1): data

| Study                           | Fluox  | Parox   | Venla   |
|---------------------------------|--------|---------|---------|
| Chouinard et al, 1999           | 67/101 | 67/102  |         |
| De Wilde et al, 1993            | 25/41  | 24/37   |         |
| Fava et al, 1998                | 31/54  | 32/55   |         |
| Fava et al, 2002                | 57/92  | 64/96   |         |
| Gagliano, 1993                  | 27/45  | 30/45   |         |
| Schone and Ludwig, 1993         | 9/52   | 20/54   |         |
| Alves et al, 1999               | 30/47  |         | 25/40   |
| De Nayer et al, 2002            | 27/73  |         | 37/73   |
| Dierick et al, 1996             | 95/161 |         | 107/153 |
| Rudolph and Feiger, 1999        | 52/103 |         | 57/100  |
| Silverstone and Ravindran, 1999 | 77/121 |         | 84/128  |
| Tylee et al, 1997               | 58/170 |         | 67/171  |
| Ballus et al, 2000              |        | 23/43   | 25/41   |
| McPartlin et al, 1998           |        | 128/178 | 137/183 |

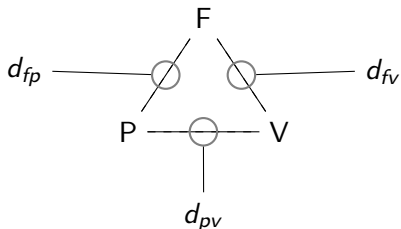
## Example MTC (2): consistency



## Example MTC (2): consistency

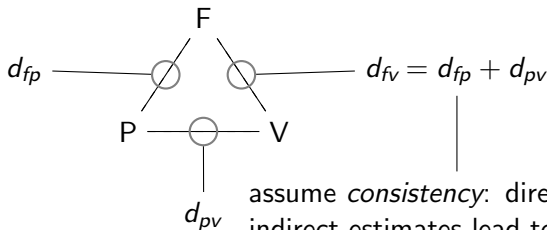


## Example MTC (2): consistency



|                | <b>pair-wise OR</b> | <b>network OR</b> |
|----------------|---------------------|-------------------|
| $\exp(d_{fp})$ | 1.24 (0.92, 1.67)   |                   |
| $\exp(d_{fv})$ | 1.30 (1.03, 1.65)   |                   |
| $\exp(d_{pv})$ | 1.20 (0.80, 1.82)   |                   |

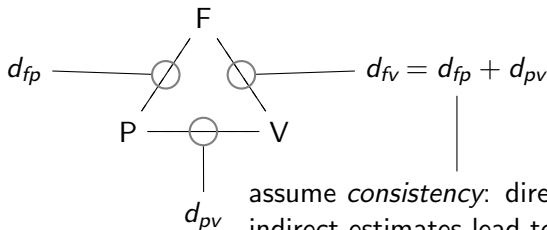
## Example MTC (2): consistency



assume *consistency*: direct and indirect estimates lead to the same conclusions.

|                | pair-wise OR      | network OR |
|----------------|-------------------|------------|
| $\exp(d_{fp})$ | 1.24 (0.92, 1.67) |            |
| $\exp(d_{fv})$ | 1.30 (1.03, 1.65) |            |
| $\exp(d_{pv})$ | 1.20 (0.80, 1.82) |            |

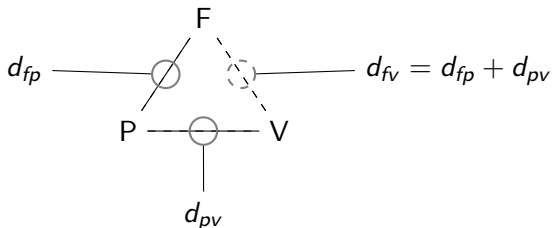
## Example MTC (2): consistency



assume *consistency*: direct and indirect estimates lead to the same conclusions.

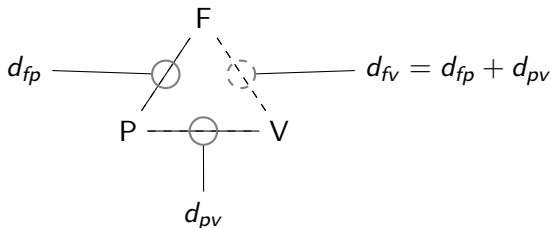
|                | <b>pair-wise OR</b> | <b>network OR</b> |
|----------------|---------------------|-------------------|
| $\exp(d_{fp})$ | 1.24 (0.92, 1.67)   | 1.22 (0.92, 1.61) |
| $\exp(d_{fv})$ | 1.30 (1.03, 1.65)   | 1.34 (1.08, 1.67) |
| $\exp(d_{pv})$ | 1.20 (0.80, 1.82)   | 1.11 (0.82, 1.50) |

## Example MTC (3): functional parameter



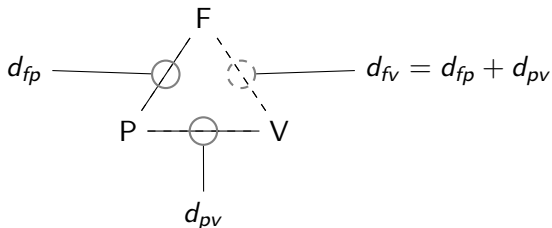
- $d_{fv}$  is fully determined by  $d_{fp} + d_{pv}$

## Example MTC (3): functional parameter



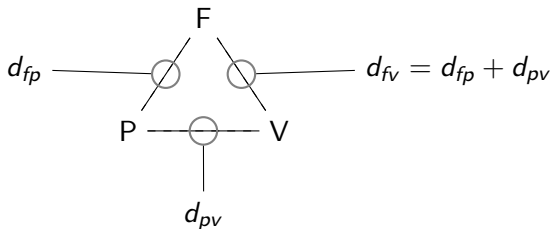
- $d_{fv}$  is fully determined by  $d_{fp} + d_{pv}$
- Call  $d_{fv}$  a **functional** parameter (can be eliminated)

## Example MTC (3): functional parameter

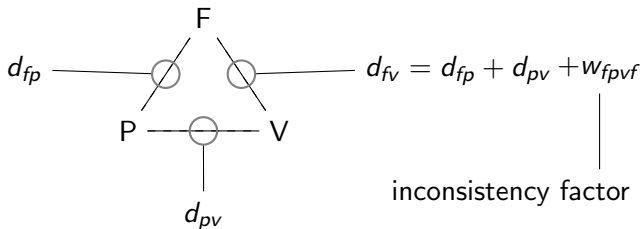


- $d_{fv}$  is fully determined by  $d_{fp} + d_{pv}$
- Call  $d_{fv}$  a **functional** parameter (can be eliminated)
- And  $d_{fp}, d_{pv}$  **basic** parameters ( $\sim \mathcal{N}(\cdot, \cdot)$ )

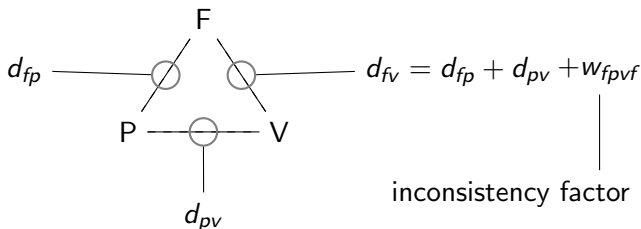
# Example MTC (4): inconsistency



## Example MTC (4): inconsistency



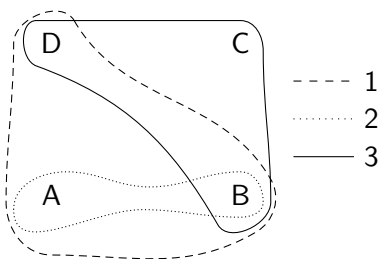
## Example MTC (4): inconsistency



Now we have an *inconsistency model*:

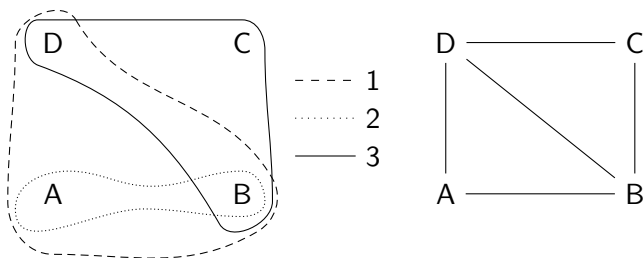
- The estimate of  $w_{fpvf}$  is an indicator for (in)consistency
- Basically it 'restores' the dimensionality of the model

# Evidence structure



- A set of studies  $S = \{S_1, \dots, S_n\}$
- Each study has a set of treatments  $T(S_i)$
- Fully connected comparison graph  $G(S_i) = (T(S_i), E(S_i))$
- The evidence structure is the collection of the  $G(S_i)$

# Evidence graph



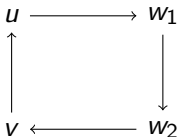
- Evidence graph  $G(S) = (T(S), E(S))$
- The graph of all comparisons made in at least one trial
- We assume that  $G(S)$  is connected
  - otherwise MTC is not possible

# Effect parameters

$$\begin{array}{ccc} & d((A, B)) = d_{AB} & \\ A & \xrightarrow{\hspace{10em}} & B \\ & \xleftarrow{\hspace{10em}} & \\ & d((B, A)) = -d_{AB} & \end{array}$$

# Consistency (general formulation)

Given a (simple, directed) cycle  $\mathbf{C} = ((u, w_1), \dots, (w_n, v), (v, u))$ .

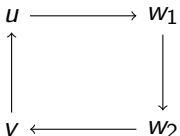


# Consistency (general formulation)

Given a (simple, directed) cycle  $\mathbf{C} = ((u, w_1), \dots, (w_n, v), (v, u))$ .

Then consistency dictates:

$$w_{\mathbf{C}} = \sum_{e \in \mathbf{C}} d(e) = 0$$



# Consistency (general formulation)

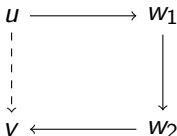
Given a (simple, directed) cycle  $\mathbf{C} = ((u, w_1), \dots, (w_n, v), (v, u))$ .

Then consistency dictates:

$$w_{\mathbf{C}} = \sum_{e \in \mathbf{C}} d(e) = 0$$

or, if  $\mathbf{p} = ((u, w_1), \dots, (w_n, v))$ :

$$d((u, v)) = \sum_{e \in \mathbf{p}} d(e)$$



# Basic and functional parameters

Consistency:

$$d((u, v)) = \sum_{e \in \mathbf{p}} d(e)$$

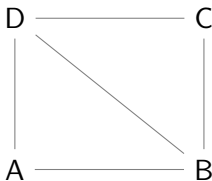
- The functional parameter  $d((u, v))$ 
  - is defined in terms of the basic parameters (right hand side)
  - so we can eliminate it from the BHM
- Each cycle has at least one functional parameter
  - Less, and we don't assume full consistency
- Each functional parameter is the only one in at least one cycle
  - Otherwise the definition becomes circular

## Basic parameters: spanning tree

Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .

## Basic parameters: spanning tree

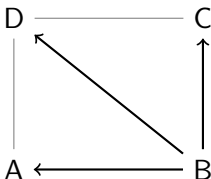
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



So choosing a spanning tree determines basic/functional parameters

## Basic parameters: spanning tree

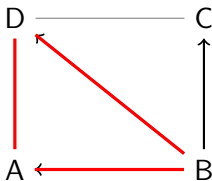
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



So choosing a spanning tree determines basic/functional parameters

## Basic parameters: spanning tree

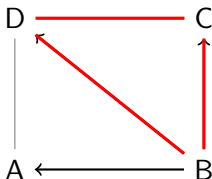
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



$$d((A, D)) = d((A, B)) + d((B, D))$$

## Basic parameters: spanning tree

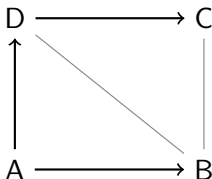
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



$$d((C, D)) = d((C, B)) + d((B, D))$$

## Basic parameters: spanning tree

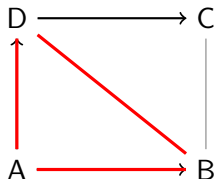
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



So choosing a spanning tree determines basic/functional parameters

## Basic parameters: spanning tree

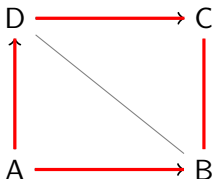
Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



$$d((B, D)) = d((B, A)) + d((A, D))$$

## Basic parameters: spanning tree

Proposition: if we partition the edges  $E(S)$  into basic and functional ones, such that  $E_b \cup E_f = E(S)$ , then  $G_b = (T_b, E_b)$  is a spanning tree of  $G(S)$ .



$$d((B, C)) = d((B, A)) + d((A, D)) + d((D, C))$$

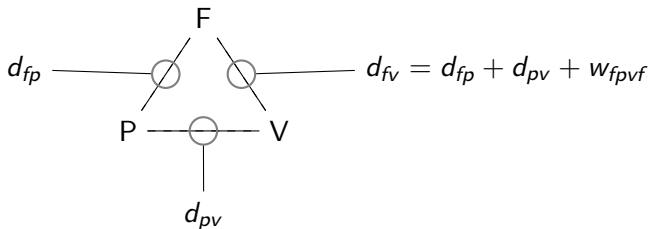
# Summary

- Consistency is a natural assumption in MTC
- Basic and functional parameters emerge from consistency
- It turns out that the basic parameters are a spanning tree

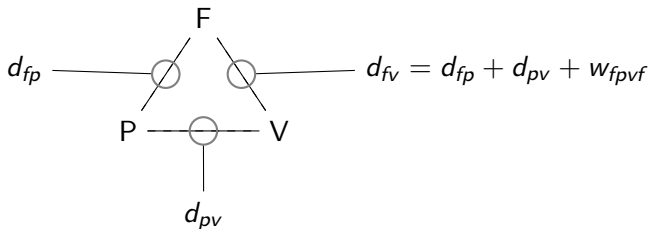
## Problem definition

- How should the spanning tree  $G_b$  be chosen?
- Examples will show that 'any will do' is not the answer

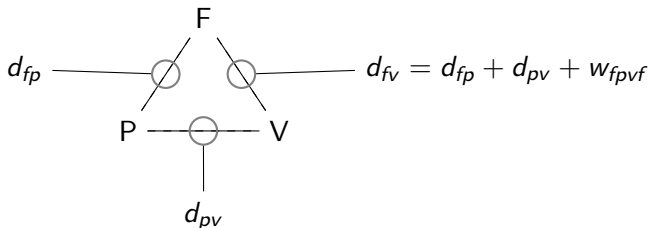
# Cycles that cannot be inconsistent (1)



# Cycles that cannot be inconsistent (1)



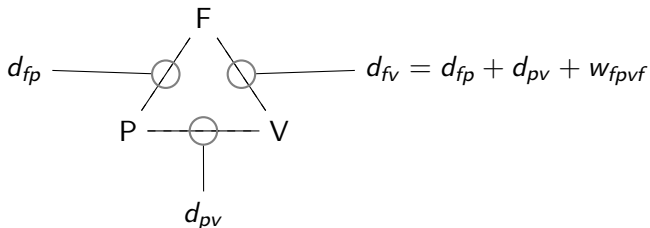
# Cycles that cannot be inconsistent (1)



Now imagine that there are only 3-arm trials in this structure.

- Clearly  $w_{fpvf} = 0 \rightarrow$  the model is under constrained

## Cycles that cannot be inconsistent (1)



Now imagine that there are only 3-arm trials in this structure.

- Clearly  $w_{fpvf} = 0 \rightarrow$  the model is under constrained
- So we should exclude  $w_{fpvf}$ , i.e. ICDF = 0.
  - ICDF = InConsistency Degrees of Freedom

## Cycles that cannot be inconsistent (2)

Definition: let  $f((u, v), S')$  be the distribution we estimate for  $d((u, v))$  based on the studies  $S' \subset S$ .

## Cycles that cannot be inconsistent (2)

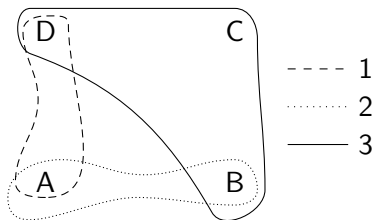
Definition: let  $f((u, v), S')$  be the distribution we estimate for  $d((u, v))$  based on the studies  $S' \subset S$ .

Conjecture (internal consistency): the estimate of  $d((u, v))$  will be the same regardless of the path we choose:

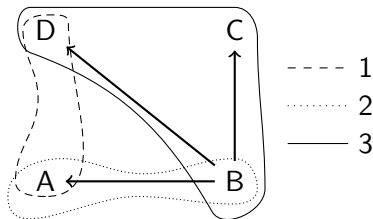
$$f((u, v), S') = f((u, w), S') + f((w, v), S')$$

Supposing that  $u, w, v \in T(S_i)$  for all  $S_i \in S'$ .

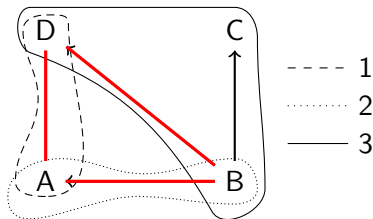
# Cycles that cannot be inconsistent (3)



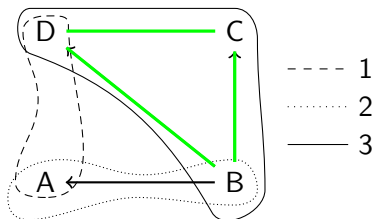
# Cycles that cannot be inconsistent (3)



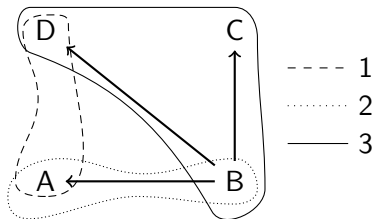
# Cycles that cannot be inconsistent (3)



# Cycles that cannot be inconsistent (3)

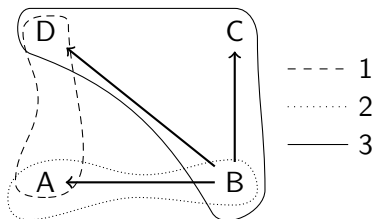


# Cycles that cannot be inconsistent (3)



$$\text{ICD} = 1 \quad (|E_f| = 2)$$

## Cycles that cannot be inconsistent (3)



$$\text{ICD} = 1 \quad (|E_f| = 2)$$

- ICD = number of  $w$ 's to be added for a specific  $G_b$
- ICDF = evidence structure 'degrees of freedom' (inherent)

## Cycles that cannot be inconsistent (4)

The conjecture gives an idea when to expect the same results from distinct paths.

The next slides have definitions and a theorem to generalize this to any cycle:

- Partition: subdivision into edges with supporting studies
- Reduction: dependent adjacent edges can be reduced to one
- Cycle with  $\geq 3$  independent adjacent edges can be inconsistent

## Elementary partition of a cycle

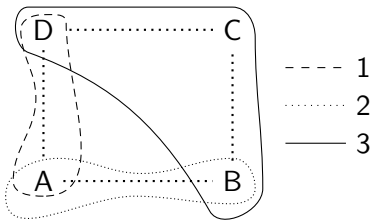
Definition: Let  $C$  be a (simple) cycle in  $G(S)$ , and fix a direction.  
The *elementary partition* of  $C$  is  $(P, r)$ , where:

- $P$  the set of edges of  $C$  (in the chosen direction)
- $r(e) = \{S_i \in S : e \in E(S_i)\}$

# Elementary partition of a cycle

Definition: Let  $C$  be a (simple) cycle in  $G(S)$ , and fix a direction. The *elementary partition* of  $C$  is  $(P, r)$ , where:

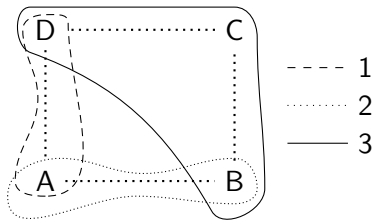
- $P$  the set of edges of  $C$  (in the chosen direction)
- $r(e) = \{S_i \in S : e \in E(S_i)\}$



# Elementary partition of a cycle

Definition: Let  $C$  be a (simple) cycle in  $G(S)$ , and fix a direction. The *elementary partition* of  $C$  is  $(P, r)$ , where:

- $P$  the set of edges of  $C$  (in the chosen direction)
- $r(e) = \{S_i \in S : e \in E(S_i)\}$

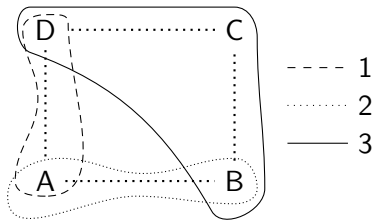


$$P = \{(A, B), (B, C), (C, D), (D, A)\}$$

# Elementary partition of a cycle

Definition: Let  $C$  be a (simple) cycle in  $G(S)$ , and fix a direction.  
The *elementary partition* of  $C$  is  $(P, r)$ , where:

- $P$  the set of edges of  $C$  (in the chosen direction)
- $r(e) = \{S_i \in S : e \in E(S_i)\}$



$$P = \{(A, B), (B, C), (C, D), (D, A)\}$$

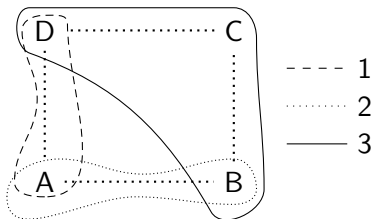
$$r((A, B)) = \{2\}$$

$$r((B, C)) = \{3\}$$

$$r((C, D)) = \{3\}$$

$$r((D, A)) = \{1\}$$

# Reduction of a partition



$$P = \{(A, B), (B, C), (C, D), (D, A)\}$$

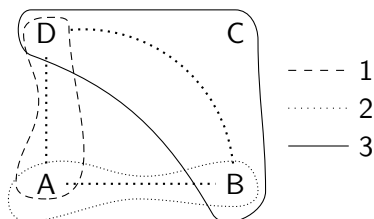
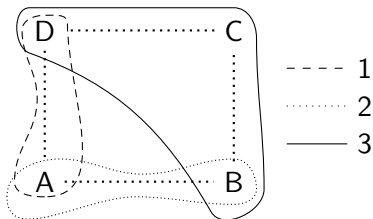
$$r((A, B)) = \{2\}$$

$$r((B, C)) = \{3\}$$

$$r((C, D)) = \{3\}$$

$$r((D, A)) = \{1\}$$

# Reduction of a partition



$$P = \{(A, B), (B, C), (C, D), (D, A)\}$$

$$r((A, B)) = \{2\}$$

$$r((B, C)) = \{3\}$$

$$r((C, D)) = \{3\}$$

$$r((D, A)) = \{1\}$$

$$P' = \{(A, B), (B, D), (D, A)\}$$

$$r'((A, B)) = \{2\}$$

$$r'((B, D)) = \{3\}$$

$$r'((D, A)) = \{1\}$$

## Reduction preserves estimates

Let  $(P, r)$  be the elementary partition of some cycle  $C$ . Then the (in)consistency equation can be written as:

$$F(P, r) = \sum_{e \in P} f(e, r(e)) = w_C$$

Lemma: if  $(P', r')$  is obtained from  $(P, r)$  in a single reduction step, then  $F(P', r') = F(P, r)$ .

Proof: by induction using internal consistency.

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

Proof ( $m < 3$ ):

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

Proof ( $m < 3$ ):

- if  $m = 0$ ,  $F(P, r) = 0$  due to internal consistency

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

Proof ( $m < 3$ ):

- if  $m = 0$ ,  $F(P, r) = 0$  due to internal consistency
- $m = 1$  would imply that  $C$  is not a cycle

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

Proof ( $m < 3$ ):

- if  $m = 0$ ,  $F(P, r) = 0$  due to internal consistency
- $m = 1$  would imply that  $C$  is not a cycle
- $m = 2$ : using reduction,  $F(P, r) \neq 0$  implies that

$$f((u, v), R_1) + f((v, u), R_2) \neq 0$$
$$f((u, v), R_1) \neq f((u, v), R_2)$$

Which is just heterogeneity on  $(u, v)$ .

# Inconsistency cycle

Theorem: let  $C$  be a cycle in  $G(S)$ . Suppose the elementary partition of  $C$  has  $m$  independent pairs of adjacent edges. Then,  $C$  is *potentially inconsistent* iff  $m \geq 3$ .

Proof ( $m \geq 3$ ): (Intuition) we can always choose the data such that  $w_C \neq 0$ .

## Inconsistency degree (not there yet)

- Now we know when a cycle is *potentially* inconsistent
  - *actually* inconsistent depends on data

## Inconsistency degree (not there yet)

- Now we know when a cycle is *potentially* inconsistent
  - *actually* inconsistent depends on data
- Seems like we can now define the Inconsistency Degree (ICD)
  - just count the potentially inconsistent cycles
  - (for a spanning tree)

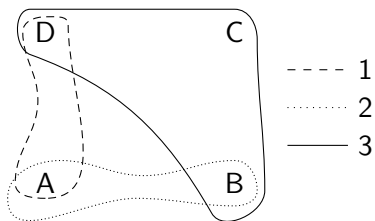
## Inconsistency degree (not there yet)

- Now we know when a cycle is *potentially* inconsistent
  - *actually* inconsistent depends on data
- Seems like we can now define the Inconsistency Degree (ICD)
  - just count the potentially inconsistent cycles
  - (for a spanning tree)
- But...

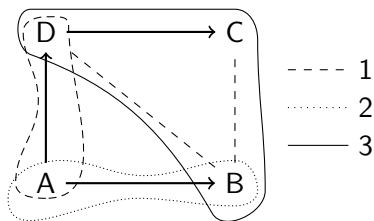
## Inconsistency degree (not there yet)

- Now we know when a cycle is *potentially* inconsistent
  - *actually* inconsistent depends on data
- Seems like we can now define the Inconsistency Degree (ICD)
  - just count the potentially inconsistent cycles
  - (for a spanning tree)
- But... there is one more problem to solve

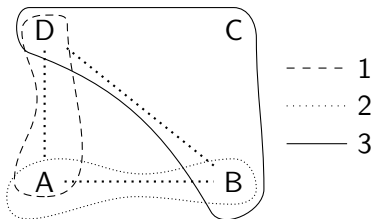
# Equivalent reductions



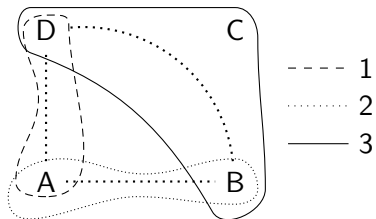
(a) Evidence structure



(b) Spanning tree



(c) Cycle 1



(d) Cycle 2

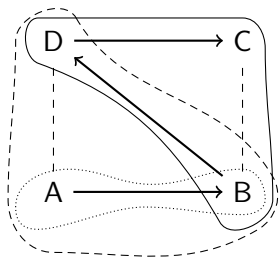
## Inconsistency degree

Definition: the cycles  $C_1$  and  $C_2$  are equivalent in  $S$  ( $C_1 \sim_S C_2$ ) if their maximally reduced elementary partitions in  $S$  are equivalent.

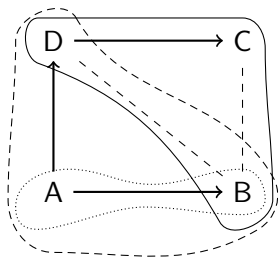
Definition: let  $G_b$  be a spanning tree of  $G(S)$ , and  $\mathbf{C}$  the set of cycles induced by  $G_b$ . Then  $\mathbf{C}/\sim_S$  are the equivalence classes under  $\sim_S$  in  $\mathbf{C}$ .

- If one cycle in a class is potentially inconsistent, so are the others (since they have the 'same' reduction)
- The inconsistency degree  $\text{icd}(S, G_b)$  is the number of classes in  $\mathbf{C}/\sim_S$  that are potentially inconsistent

# Spanning trees with different ICD



(a) ICD = 1



(b) ICD = 2

Figure:

# Spanning tree selection problem

The spanning tree selection problem is, given an evidence structure  $S$ , to choose the spanning tree  $G_b$  that maximizes  $\text{icd}(S, G_b)$ .

$$\text{icdf}(S) = \max\{\text{icd}(S, G_b) : G_b \text{ spanning tree of } G(S)\}$$

- One set of ICFs  $\mathbf{w}$  can be linearly transformed to another set  $\mathbf{w}'$  (Lu & Ades, 2006), given equal ICD.
- So it matters only that we maximize the ICD.

# Algorithm

The algorithm is very easy:

- ① Generate spanning trees (Gabow & Myers, 1978)
- ② Until we find one that maximizes  $\text{icd}(S, G_b)$ 
  - Which we can now calculate easily

# Algorithm

The algorithm is very easy:

- 1 Generate spanning trees (Gabow & Myers, 1978)
- 2 Until we find one that maximizes  $\text{icd}(S, G_b)$ 
  - Which we can now calculate easily
- 3 (there are some additional subtleties related to baseline selection)

# Evaluation

- We extracted the evidence structures from a review of 18 networks (Salanti et al., 2008).
- The 15 non-trivial ones were analyzed using the algorithm.
- All problems were solved in  $< 4$  seconds.
- (In some cases choosing the study baselines is problematic)

# Network meta-analysis in ADDIS

The screenshot displays the 'Create Network meta-analysis' window in the ADDIS software. On the left, an 'Overview' sidebar lists six steps: 1. Select Indication, 2. Select Outcome, 3. Select Drugs, 4. Select Studies, 5. Select Arms, and 6. Overview (which is currently selected). The main area shows a network diagram with three nodes: 'Fluoxetine' at the top, 'Paroxetine' in the middle, and 'Placebo' at the bottom. Edges connect the nodes with numerical weights: Fluoxetine to Paroxetine (6), Fluoxetine to Placebo (5), Paroxetine to Placebo (2), and a self-loop on Placebo (1). A 'Save analysis' dialog box is overlaid on the diagram, containing a question mark icon, the text 'Input name for new analysis', a text input field with 'Efficacy network' entered, and 'Cancel' and 'OK' buttons. At the bottom of the main window, there are navigation buttons: 'Previous', 'Next', 'Last', 'Finish', and 'Cancel'.

# Network meta-analysis in ADDIS

ADDIS v1.6 - Example Data\*

File Edit Add Help

New Study New Pair-wise meta-analysis New Network meta-analysis New Benefit-risk analysis

Indications  
310497006 Severe depr

Drugs  
Bupropion  
Citalopram  
Duloxetine  
Escitalopram  
Fluoxetine  
Fluvoxamine  
Mirtazapine  
Paroxetine  
Placebo  
Sertraline  
Venlafaxine

Endpoints  
CGI Severity Change  
Dropouts  
HAM-D Responders  
MADRS Responders

Adverse events  
Abdominal Pain  
Abnormal Ejaculation  
Accommodation Disturb  
Agitation  
Anorexia  
Anxiety  
Appetite Increased  
Asthenia  
Back Pain  
Blurred Vision  
Bronchitis  
Chest Pain  
Concentration Difficulties  
Constipation  
Depersonalization  
Diarrhea

Overview Consistency Inconsistency Node Split Memory Usage

there are closed loops in the evidence structure. For more information about assessing inconsistency, see G. Lu and A. E. Ades (2006), *Assessing evidence inconsistency in mixed treatment comparisons*, *Journal of the American Statistical Association*, 101(474): 447-459. doi:10.1198/016214505000001302.

Network Meta-Analysis (Inconsistency Model)

|                   |                   |                   |                   |                   |
|-------------------|-------------------|-------------------|-------------------|-------------------|
| Fluoxetine        | 1.27 (0.98, 1.64) | 0.62 (0.49, 0.80) | 1.24 (0.98, 1.58) | 1.40 (1.12, 1.74) |
| 0.79 (0.61, 1.02) | Paroxetine        | 0.44 (0.28, 0.69) | 0.99 (0.69, 1.41) | 1.14 (0.82, 1.58) |
| 1.60 (1.25, 2.05) | 2.27 (1.45, 3.56) | Placebo           | 1.90 (1.38, 2.61) | 2.26 (1.63, 3.12) |
| 0.81 (0.63, 1.02) | 1.01 (0.71, 1.45) | 0.53 (0.38, 0.72) | Sertraline        | 1.14 (0.81, 1.61) |
| 0.71 (0.57, 0.89) | 0.88 (0.63, 1.22) | 0.44 (0.32, 0.61) | 0.87 (0.62, 1.23) | Venlafaxine       |

Inconsistency Factors

| Cycle   | Confidence Interval |
|---|---------------------|
| Fluoxetine, Paroxetine, Sertraline                | 0.01 (-0.28, 0.29)  |
| Fluoxetine, Paroxetine, Sertraline, Venlafaxine   | 0.02 (-0.26, 0.30)  |
| Fluoxetine, Paroxetine, Sertraline, Venlafaxin... | -0.01 (-0.27, 0.30) |
| Paroxetine, Placebo, Venlafaxine, Sertraline      | -0.13 (-0.58, 0.32) |
| Paroxetine, Sertraline, Venlafaxine               | -0.01 (-0.29, 0.28) |
| Placebo, Sertraline, Venlafaxine                  | -0.04 (-0.35, 0.27) |

Variance Calculation

| Parameter               | Median (95% CrI)  |
|-------------------------|-------------------|
| Random Effects Variance | 0.09 (0.01, 0.28) |
| Inconsistency Variance  | 0.12 (0.00, 0.62) |

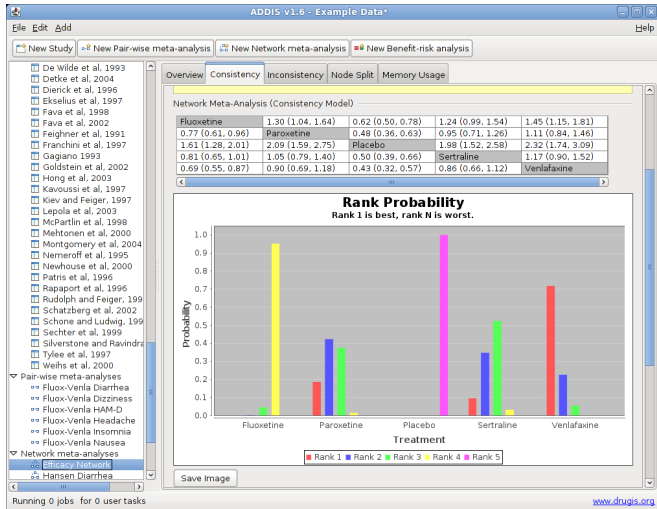
Convergence

Convergence is assessed using the Brooks-Gelman-Rubin method. This method compares within-chain and between-chain variance to calculate the Potential Scale Reduction Factor (PSRF). A PSRF close to one

Running 0 jobs for 0 user tasks

[www.drugs.org](http://www.drugs.org)

# Network meta-analysis in ADDIS



# Discussion

- MTC models can be **generated** (automatically)
  - instead of **specified** (manually)
- In some cases, the algorithm could be very inefficient
  - But we have not encountered this in practice

## Additional remarks

- To complete automation
  - Assign baselines using search
  - Guess sensible priors and starting values, using heuristics
- This has been implemented in working software
  - ① Tool to generate BUGS/JAGS models
  - ② R package for MTC analysis
  - ③ ADDIS software for storing and analyzing clinical trials
- Download @ <http://drugis.org>

## Future work

- Relax the baseline selection problem
- Solve the parametrization problem for node-splitting models
- Find a more efficient algorithm

## Future work

- Relax the baseline selection problem
- Solve the parametrization problem for node-splitting models
- Find a more efficient algorithm

All of these require a deeper understanding of the statistics

## Future work

- Relax the baseline selection problem
- Solve the parametrization problem for node-splitting models
- Find a more efficient algorithm

All of these require a deeper understanding of the statistics

- Which is why I'm here!

# Acknowledgements

## Co-authors

- Tommi Tervonen (Erasmus University Rotterdam)
- Bert de Brock (University of Groningen)
- Hans Hillege (University Medical Center Groningen)

## Funding

- Project Escher (TI Pharma, Netherlands)