Automated generation of node-split models for the assessment of inconsistency in mixed treatment comparisons

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Mixed treatment comparisons [2]

- Extension of pair-wise meta-analysis
- Enables *consistent* estimation on a network of trials
- Assumption: trials are exchangeable
- Assumption needs to be verified
  - Primarily: epidemiological judgment – trial characteristics
  - **Secondarily: statistical models to detect**
    - heterogeneity
    - inconsistency

Consistency models (random effects) [2, 3, 5]

- Likelihood for study i in terms of random effects $\boldsymbol{\delta}_i$:

$$\mathbf{data}_i \sim f_i(\boldsymbol{\delta}_i, \dots) \ .$$

- Random effects assumed normal:

$$\delta_{i,b,x} \sim \mathcal{N}(d_{b,x}, \sigma^2) \ ; \ \begin{pmatrix} \delta_{i,b,x} \\ \vdots \\ \delta_{i,b,z} \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} d_{b,x} \\ \vdots \\ d_{b,z} \end{pmatrix}, \Sigma \right)$$

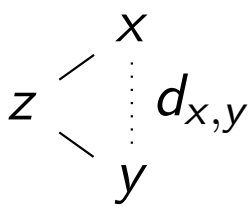
- And the relative effects $d_{x,y}$ are assumed consistent:

$$d_{x,y} = d_{x,z} + d_{z,y}$$

(follows from exchangeability assumption)

Consistency / inconsistency

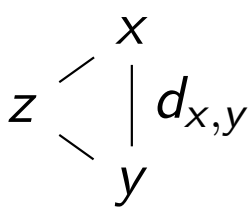
- Use consistency assumption to fill in missing comparisons:



Could be problematic/inconsistent

Can NOT be detected

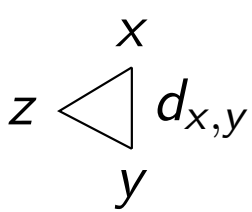
- Consistent synthesis of existing comparisons:



Could be inconsistent

Can be detected

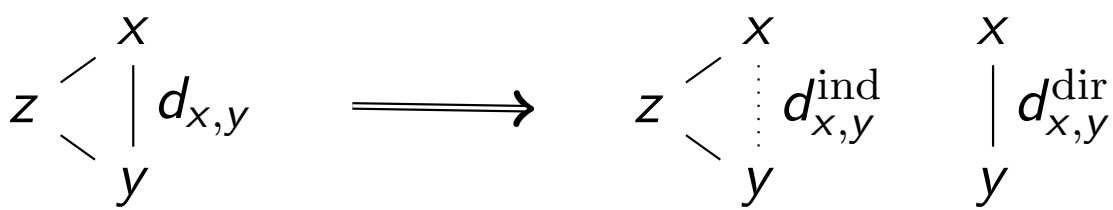
- Synthesis with only three-arm trials:



Can NOT be inconsistent

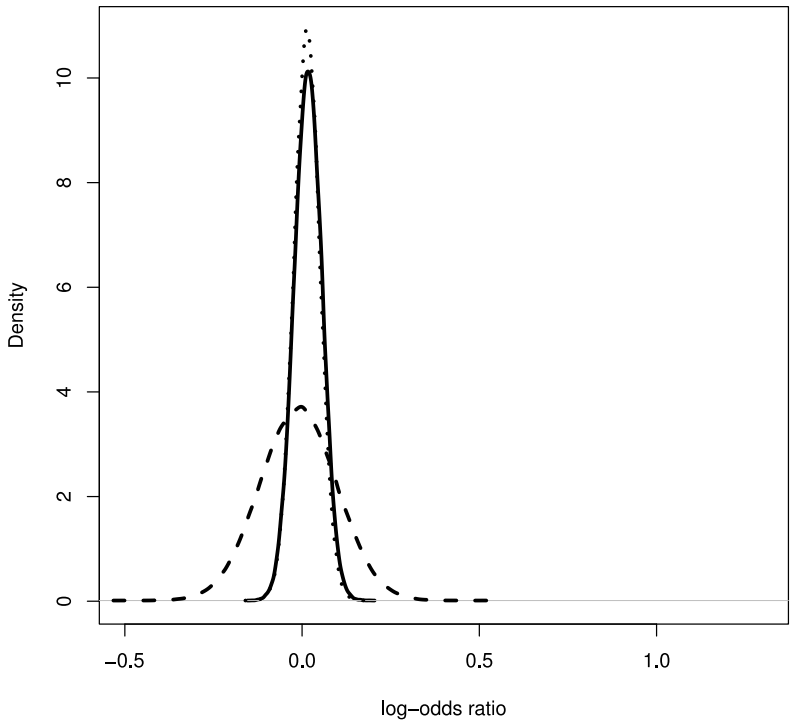
Node-splitting models [1]

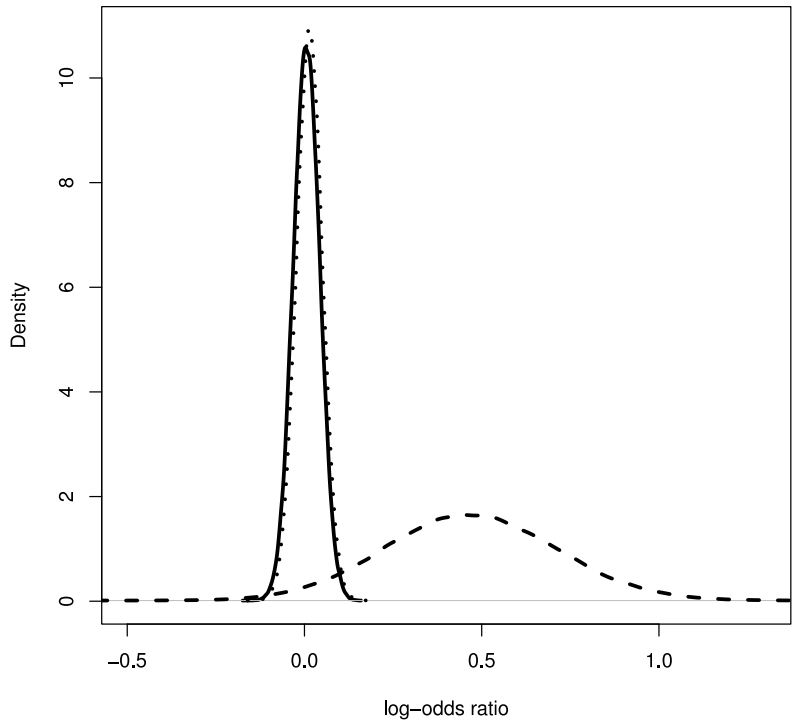
- Node-split models: split comparison $d_{x,y}$
  - Pair-wise meta-analysis of direct evidence $\rightarrow d^{\text{dir}}_{x,y}$
  - Consistency model of all other evidence $\rightarrow d^{\text{ind}}_{x,y}$
  - Under exchangeability, expect $d^{\text{ind}}_{x,y} = d^{\text{dir}}_{x,y}$



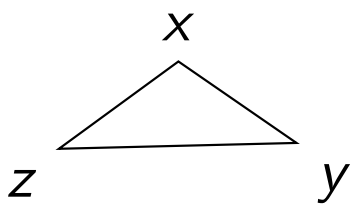
- Requires one model *per split node*

Node-splitting: example results





Node-splitting models: multi-arm trials



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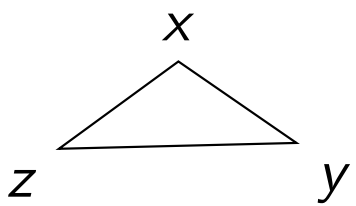

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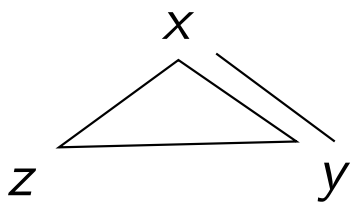

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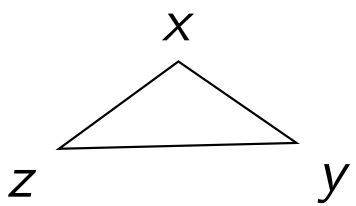

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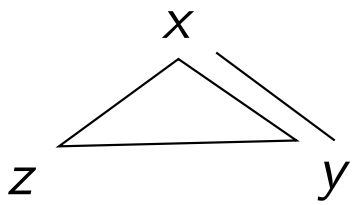

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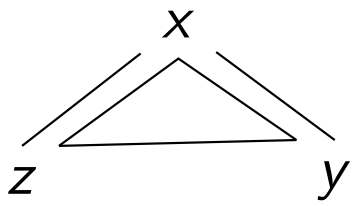
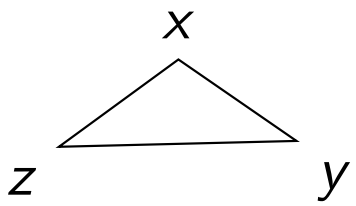


Potentially inconsistent?

Node-splitting models: multi-arm trials



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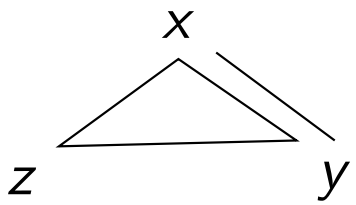

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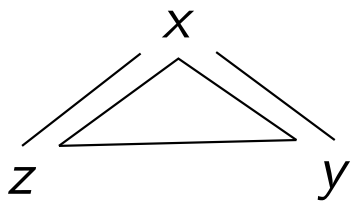

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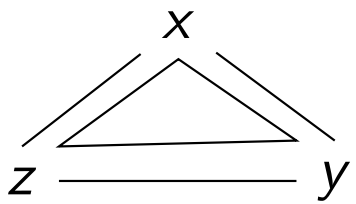

Potentially inconsistent!

Node-splitting: open problems

- What nodes should be split?
  - Easy for simple cases
  - But has to work for *any* network
- How to generate model structure?
  - Already solved for consistency models [6]
  - Strategy: choose split nodes carefully
    $\rightarrow$ apply method for consistency models

Choosing split nodes

- Ideally: split 'minimal set' of comparisons
  - But: that is very difficult to determine [4, 7]
- Practical compromise: simple (local) decision rule:
  - efficiently computable
  - splits all potential inconsistencies
  - splits only potential inconsistencies

Choosing split nodes: basic rule ($\leq$ 3-arm trials)

Given an evidence network, split $d_{a,b}$ iff:

- a and b are connected in the reduced network,
- consisting of the studies that *do not* include both a and b.

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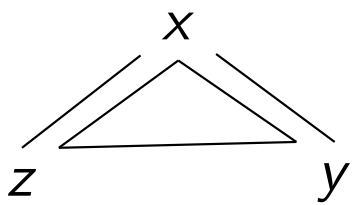

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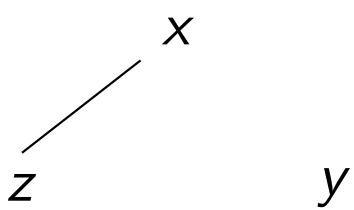

Split $d_{x,y}$?

Remove studies with x and y. $\rightarrow$ NO.

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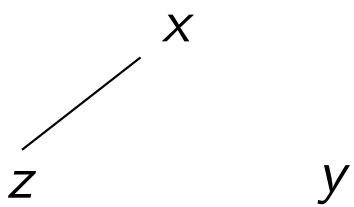

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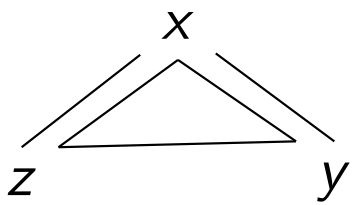

Split $d_{y,z}$?

Choosing split nodes: basic rule ($\leq$ 3-arm trials)

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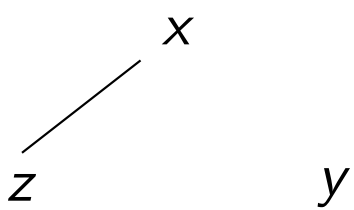

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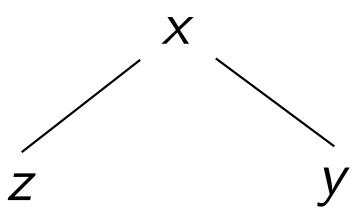
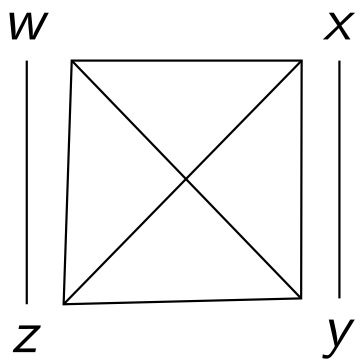


Split $d_{y,z}$?

Remove studies with y and z. $\rightarrow$ YES.

Choosing split nodes: basic rule (fails for 4-arm trials)



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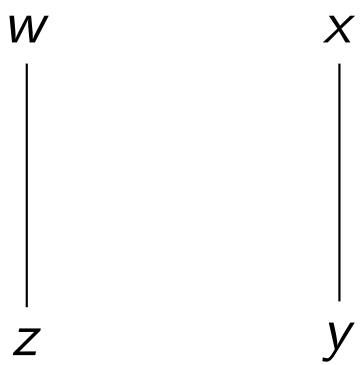

Split $d_{y,z}$?

Remove studies with y and z. $\rightarrow$???

Choosing split nodes: full rule (n-arm trials)

Given an evidence network, split $d_{a,b}$ iff:

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- by removing the a and b arms from studies including both.

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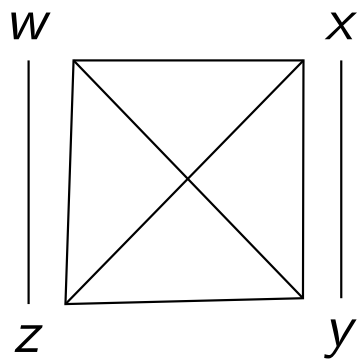

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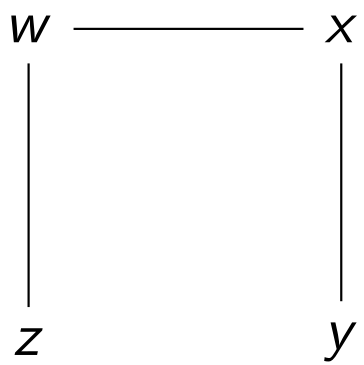

Split $d_{y,z}$?

Apply rule $\rightarrow$ YES.

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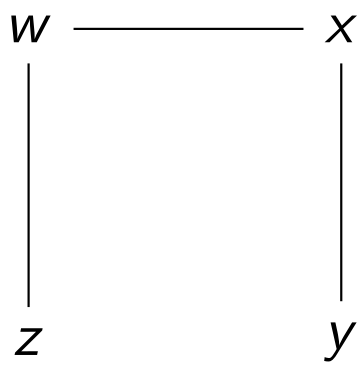


Split $d_{y,z}$?

Apply rule $\rightarrow$ YES.

The full rule:

- Works in general (for n-arm trials)
  - Because trials are fully connected graphs

Results: rule is appropriate

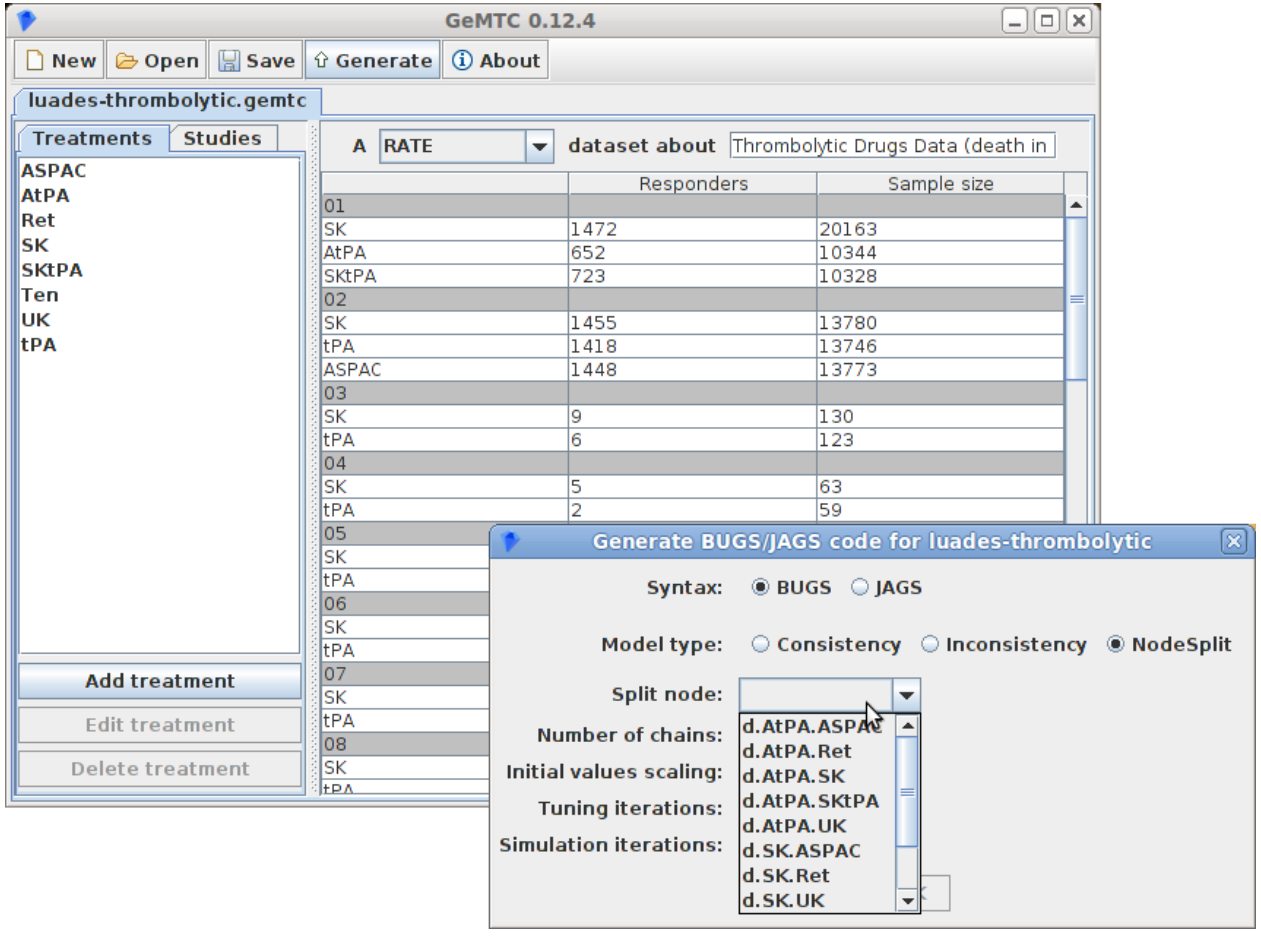
- Only splits nodes that are potentially inconsistent
  - Network of evidence independent of direct is connected
  - Equivalent to '3 independent sources'
- Splits a node for all independent potential inconsistencies
  - And probably more (redundancies)
- Will not bore you with the proofs!

Model generation is trivial

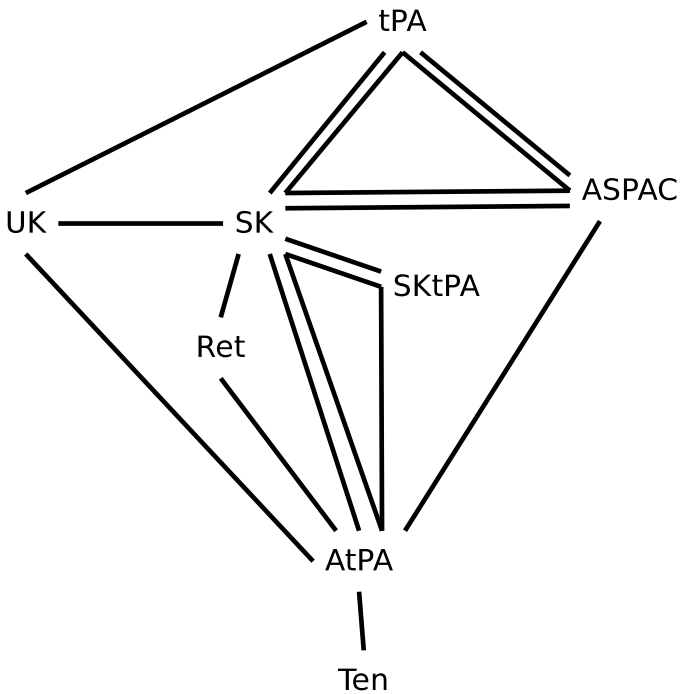
- Model generation for consistency models is trivial [6]
- The indirect evidence are just a consistency model
  - Assured by careful formulation of decision rule
- The direct evidence are just a pair-wise model
- More arbitrariness than for consistency models
  - $d_{x,y}$ is split, and occurs in a multi-arm trial
  - Which arm do we include in the $d_{x,y}^{\text{ind}}$ model?
    - Arm x?
    - Arm y?
    - Neither?

Implementation: GeMTC Software

- Methods implemented in free / open source software
- Available from `http://drugis.org/`



Example network



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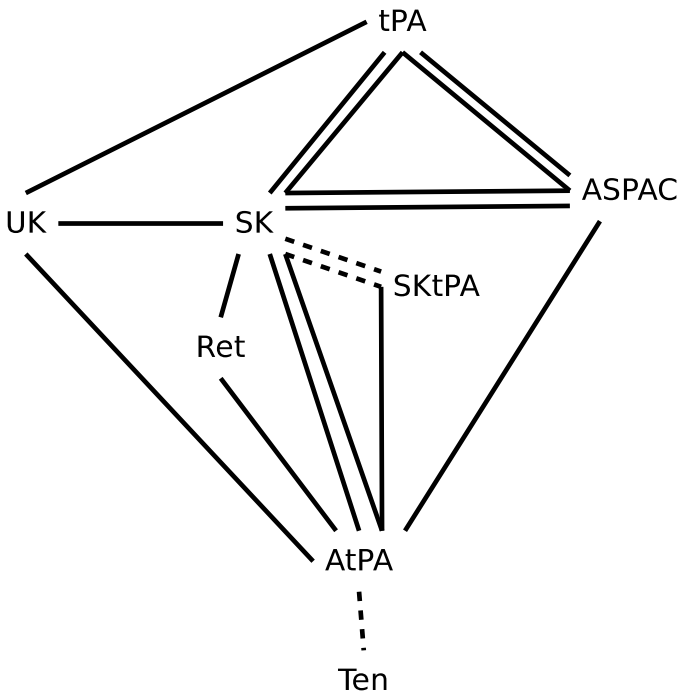

Discussion

- Proposed a decision rule for which nodes to split
- Model generation identical to consistency models
  - NOT true in general (depends on decision rule)
- Automated method + free / open source software
  - Choosing nodes to split by hand can be difficult
  - Remove tedium: specify many models for complex networks
  - Less opportunity to make small mistakes
  - Heuristically generated defaults preferable to static ones

References I


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G. van Valkenhoef, T. Tervonen, B. de Brock, and H. Hillege. Algorithmic parametrization of mixed treatment comparisons. *Stat Comput*, 2011. (in press).

Thank you!

Questions?

Slides available at `http://drugis.org`

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