

Automating network meta-analysis

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Context: my research

- Development of ADDIS
 - Aggregate Data Drug Information System
- Decision support for evidence-based health policy decisions
 - So far focussed on drug benefit-risk assessment

ADDIS: core idea

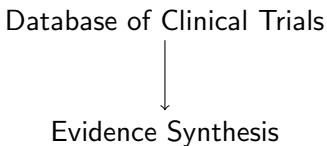
[van Valkenhoef et al., 2012c]

ADDIS: core idea

Database of Clinical Trials

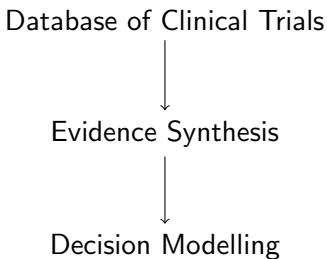
[van Valkenhoef et al., 2012c]

ADDIS: core idea



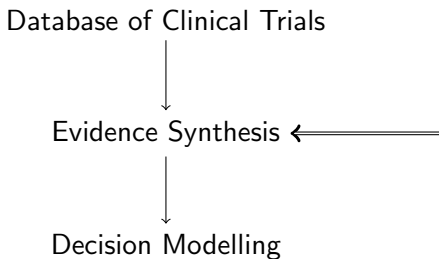
[van Valkenhoef et al., 2012c]

ADDIS: core idea



[van Valkenhoef et al., 2012c]

ADDIS: core idea



[van Valkenhoef et al., 2012c]

Network meta-analysis in ADDIS

- Pair-wise meta-analysis not suited for decision modelling
 - Often > 2 alternatives to be considered
 - *Consistent* use must be made of evidence
- Network meta-analysis solves this
 - Compare > 2 alternatives using network of trials
 - A.K.A.:
 - MTC: Mixed/Multiple treatment comparison
 - MTM: Mixed/Multiple treatment model/meta-analysis
- [van Valkenhoef et al., 2012b]

Consistency in network meta-analysis

- *Consistency* is the basic assumption:
 - $d_{x,z} = d_{x,y} + d_{y,z}$
- Intuitively: direct and indirect evidence 'compatible'
- Fundamentally: all studies are exchangeable
 - Inconsistency related to heterogeneity
- **Without consistency, there is no basis for decision!**

Testing for inconsistency

- Node-splitting [Dias et al., 2010]
 - Assess comparisons one-by-one
 - Comparing direct and indirect estimates
- Inconsistency models [Lu and Ades, 2006]
 - Identify sufficient set of 'inconsistency factors'
 - Under consistency, inconsistency factors = 0

Why automate?

- Writing BUGS code by hand: tedious, time-consuming, difficult, error-prone
- Most issues irrelevant to analysis
 - Exception: prior distributions
- Specialized frontend for network meta-analysis
 - Can save a lot of time
 - Prevents mistakes in BUGS code
 - Can draw attention to the *important* issues

Interest in automation

Lots of interest recently:

- My work with Tony Ades' group (Bristol U.)
- Alex Sutton / Nicola Cooper (U. of Leicester)
- Chris Schmidt (Tufts U.)
- Ian White – mvmeta (Cambridge)
- Petros Pechlivanoglou (next pres.)

The automation problem

For network meta-analysis in a Bayesian / MCMC framework:

- Generate model structure
- Choose prior distributions
- Specify data
- Generate starting values (for MCMC estimation)

[van Valkenhoef et al., 2012a]

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[van Valkenhoef et al., 2012a]

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[van Valkenhoef et al., 2012a]

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[van Valkenhoef et al., 2012a]

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 - Mostly trivial, but can be specified in various ways
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- Generate starting values (for MCMC estimation)
 - Should be 'over-dispersed' relative to posterior

[van Valkenhoef et al., 2012a]

GeMTC: generate MTC models

- GUI for data entry / management
- Generates models for WinBUGS or JAGS
 - Consistency models: 100% implemented
 - Inconsistency models: works, but needs theoretical work
 - Node-split models: next version (0.12)
- Limited to (absolute) data on continuous / dichotomous scale
 - Relative effect data planned (0.14)
 - Other scales unplanned future work

[van Valkenhoef et al., 2011, 2012a]

Screenshots!

GeMTC GUI 0.10

New Open Save Generate About

cipriani-efficacy.gemtc

Treatments Studies

bupropion
citalopram
duloxetine
escitalopram
fluoxetine
fluvoxamine
milnacipran
mirtazapine
paroxetine
reboxetine
sertraline
venlafaxine

Add treatment
Edit treatment
Delete treatment

A dichotomous dataset about ???

	Responders	Sample size
venlafaxine	80	153
Eker2005		
reboxetine	16	25
sertraline	17	24
Ekselius1997		
citalopram	136	200
sertraline	139	200
Fava1998		
fluoxetine	31	54
paroxetine	32	55
Fava2000		
fluoxetine	26	35
paroxetine		23 30
sertraline	37	43
Fava2002		
fluoxetine	57	92
paroxetine	64	96
sertraline	70	96
Feighner1991		
bupropion	37	61
fluoxetine	35	62
Gagiano1993		
fluoxetine	27	45
paroxetine	30	45
Geretsegger MY1021/BRC		
fluoxetine	8	52

Screenshots!

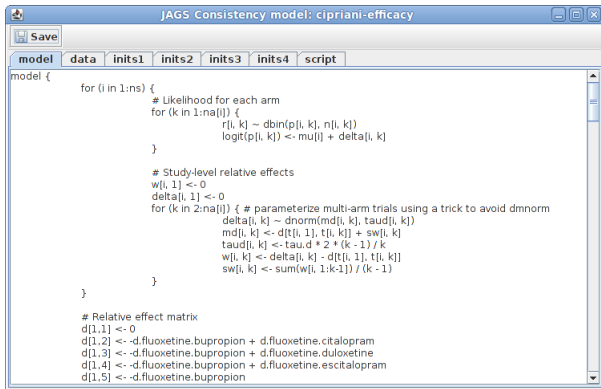
The screenshot shows the GeMTC 0.10 software interface. The main window displays a list of treatments on the left and a table of study data on the right. A dialog box titled "Generate BUGS/JAGS code for cipriani-efficacy" is open in the foreground. The dialog box contains the following options and fields:

- Syntax: BUGS JAGS
- Model type: Consistency Inconsistency NodeSplit
- Number of chains:
- Initial values scaling:
- Tuning iterations:
- Simulation iterations:

Below the dialog box, a table of study data is visible:

Study	Rebexetine	Venlafaxine
Akkaya2003	32	57
reboxetine	32	57
venlafaxine	37	50
Allard2004	50	75
citalopram	49	76
venlafaxine	49	76
Alyes1999	35	47
fluoxetine	35	47

Screenshots!



```
model {
  for (i in 1:ns) {
    # Likelihood for each arm
    for (k in 1:na[i]) {
      r[i, k] ~ dbin(p[i, k], n[i, k])
      logit(p[i, k]) <- mu[i] + delta[i, k]
    }

    # Study-level relative effects
    w[i, 1] <- 0
    delta[i, 1] <- 0
    for (k in 2:na[i]) { # parameterize multi-arm trials using a trick to avoid dnorm
      delta[i, k] ~ dnorm(md[i, k], taud[i, k])
      md[i, k] <- d[t[i, 1], t[i, k]] + sw[i, k]
      taud[i, k] <- tau.d * 2 * (k - 1) / k
      w[i, k] <- delta[i, k] - d[t[i, 1], t[i, k]]
      sw[i, k] <- sum(w[i, 1:k-1]) / (k - 1)
    }

    # Relative effect matrix
    d[1,1] <- 0
    d[1,2] <- -d.fluoxetine.bupropion + d.fluoxetine.citalopram
    d[1,3] <- -d.fluoxetine.bupropion + d.fluoxetine.duloxetine
    d[1,4] <- -d.fluoxetine.bupropion + d.fluoxetine.escitalopram
    d[1,5] <- -d.fluoxetine.bupropion
  }
}
```

Other software

- ADDIS: also runs the MTC and makes graphs, tables
 - But: less flexible, transparent
- GeMTC CLI (command-line interface)
 - Good if you have *lots* of MTC to run
 - Or in 'reproducible research'
- GeMTC R package
 - Ties GeMTC model generation and JAGS together
 - Still work-in-progress / experimental

Discussion

- GeMTC generates MTC models
 - In very general, theoretically sound way
 - Free / open source: <http://drugis.org/>
- There is still much work to do
 - Implement additional methods
 - Improvements to GUI (e.g. customize priors)
 - Integrate analysis into GUI
 - Better / more complete R package
- Automating reveals interesting theoretical questions
 - E.g. how should inconsistency be defined?

- S. Dias, N. J. Welton, D. M. Caldwell, and A. E. Ades. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*, 29(7-8, Sp. Iss. SI): 932–944, 2010. doi: 10.1002/sim.3767.
- G. Lu and A. E. Ades. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc*, 101(474):447–459, 2006. doi: 10.1198/016214505000001302.
- G. van Valkenhoef, T. Tervonen, B. de Brock, and H. Hillege. Algorithmic parametrization of mixed treatment comparisons. *Stat Comput*, 2011. doi: 10.1007/s11222-011-9281-9. (in press).
- G. van Valkenhoef, G. Lu, B. de Brock, H. Hillege, A. E. Ades, and N. J. Welton. Automating network meta-analysis. *Submitted manuscript*, 2012a.
- G. van Valkenhoef, T. Tervonen, J. Zhao, B. de Brock, H. L. Hillege, and D. Postmus. Multi-criteria benefit-risk assessment using network meta-analysis. *J Clin Epidemiol*, 65(4):394–403, 2012b. doi: 10.1016/j.jclinepi.2011.09.005.
- G. van Valkenhoef, T. Tervonen, T. Zwinkels, B. de Brock, and H. Hillege. ADDIS: a decision support system for evidence-based medicine. *Decision Support Systems*, 2012c. (in press).