University of BRISTOL

Model-Based Network Meta-Analysis

A collaboration between Bristol University and Pfizer

H. Pedder, M. Bennetts, S. Dias, M. Boucher, N. Welton

MRC Medical Research Council

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Hugo Pedder

Contents

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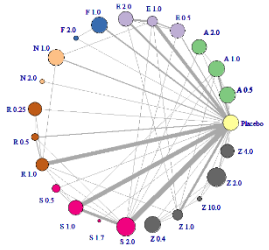
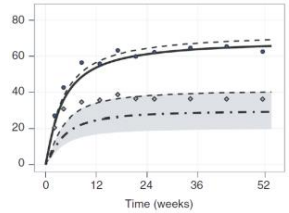
- How is it useful?
- Time-course MBNMA
  - Illustrative example: Pain in osteoarthritis
- Ongoing work



NMA

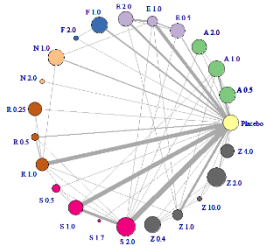
MBNMA



Model
Based
Network
Meta
Analysis

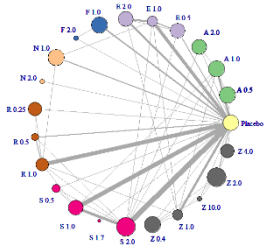
Dose-response MBNMA

Time-course MBNMA

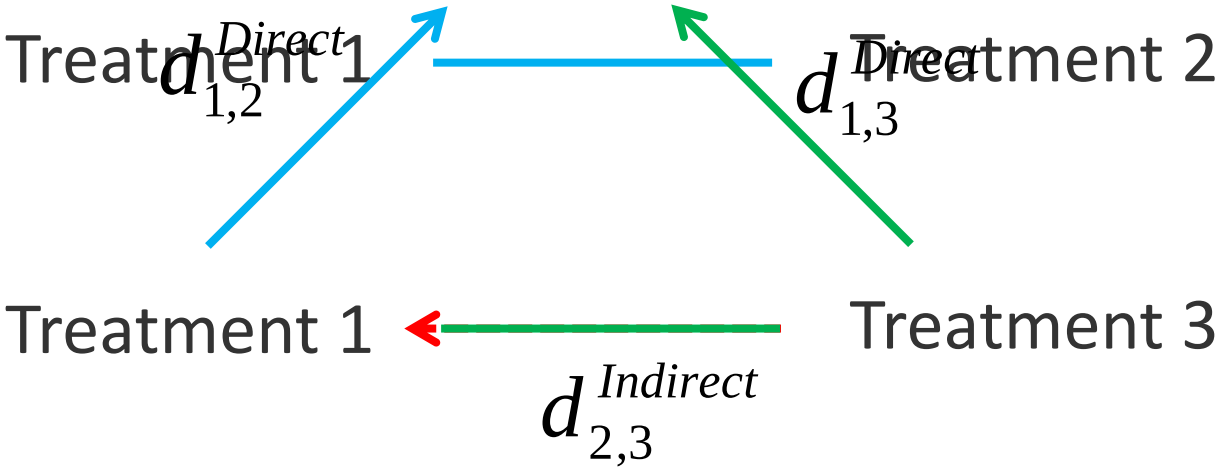


NMA - Background

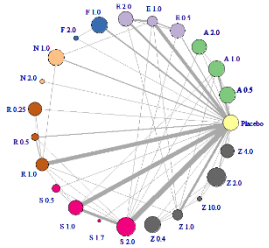
- Synthesises relative effects on multiple treatments
- Used in HTAs and guideline development to support decision-making



NMA - Background



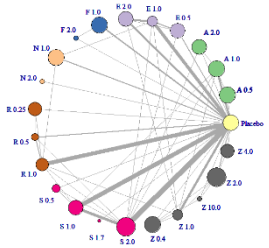
Consistency assumption: $d_{2,3}^{Indirect} = d_{1,3}^{Direct} - d_{1,2}^{Direct}$



NMA - Background

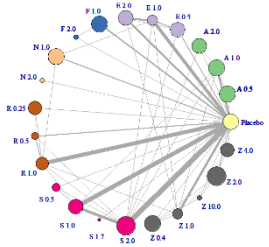
Limitations

- Doses/time points must be either:
  - “lumped”
  - “split”
  - …discarded



NMA - Background

	Follow-up (weeks)						
	0	2	4	6	8	10	12
Study 1							
Study 2							
Study 3							
Study 4							



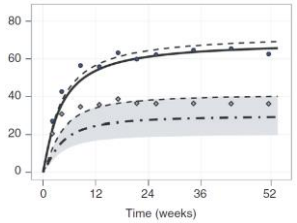
NMA - Background

	Follow-up (weeks)						
	0	2	4	6	8	10	12
Study 1							
Study 2							
Study 3							
Study 4							

“Lumping” time points ⇒ Heterogeneity / inconsistency

Discarding time points ⇒ Throwing away evidence

Discarding studies ⇒ Disconnected networks



MBNMA - Background

- Synthesises evidence on dose-response and time-course characteristics across multiple treatments
- Used in drug development to inform study design and make go / no go decisions

Limitations

- Pooling of arms rather than relative effects
  - violates randomisation
  - does not allow for testing of consistency

Model-Based Network Meta-Analysis **(MBNMA)**

- Synthesises evidence on dose-response and time-course characteristics
- Makes use of direct and indirect information
- Respects randomisation by pooling relative effects
- Allows for testing of consistency

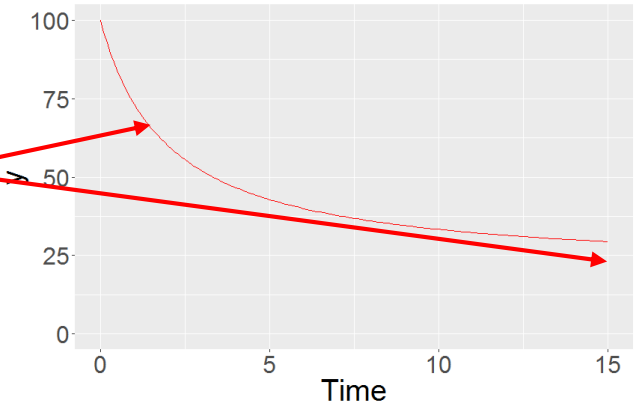
Time-Course MBNMA

Time-Course MBNMA

Normal likelihood: $y_{i,k,m} \sim N(\theta_{i,k,m}, se_{i,k,m})$

$i = study$
$k = arm$
$m = observation$

$$\theta_{i,k,m} = E_{0,i,k} + \frac{E_{\max,i,k} \times time_{i,m}}{ET_{50,i,k} + time_{i,m}}$$



Time-Course MBNMA

Normal likelihood: $y_{i,k,m} \sim N(\theta_{i,k,m}, se_{i,k,m})$

$i = study$
$k = arm$
$m = observation$

Consistency relationships on time-course parameters:

$$\theta_{i,k,m} = E_{0,i,k} + \frac{E_{\max,i,k} \times time_{i,m}}{ET_{50,i,k} + time_{i,m}}$$

$\mu_{E_{\max},i} + \delta_{E_{\max},i,k}$

$\mu_{ET_{50},i} + \delta_{ET_{50},i,k}$

Time-Course MBNMA

Normal likelihood: $y_{i,k,m} \sim N(\theta_{i,k,m}, se_{i,k,m})$

$i = study$
$k = arm$
$m = observation$

Consistency relationships on time-course parameters:

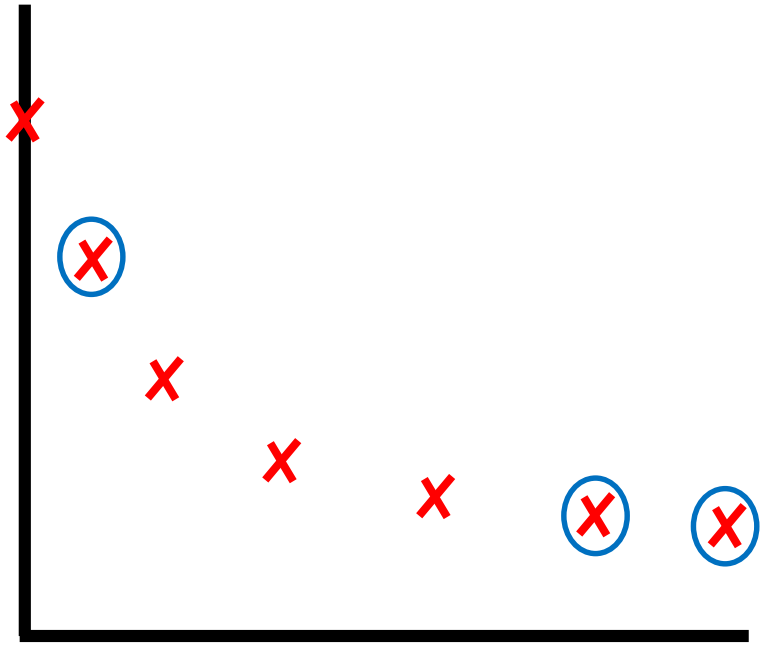
$$\mu_{E_{\max},i} + \delta_{E_{\max},i,k} \rightarrow \delta_{E_{\max},i,k} \sim N(d_{E_{\max},1,t_{i,k}} - d_{E_{\max},1,t_{i,1}}, \tau_{E_{\max}}{}^2)$$

$$\theta_{i,k,m} = E_{0,i,k} + \frac{E_{\max,i,k} \times time_{i,m}}{ET_{50,i,k} + time_{i,m}}$$

$$\mu_{ET_{50},i} + \delta_{ET_{50},i,k} \rightarrow \delta_{ET_{50},i,k} \sim N(d_{ET_{50},1,t_{i,k}} - d_{ET_{50},1,t_{i,1}}, \tau_{ET_{50}}{}^2)$$

Time-course MBNMA

Correlated observations



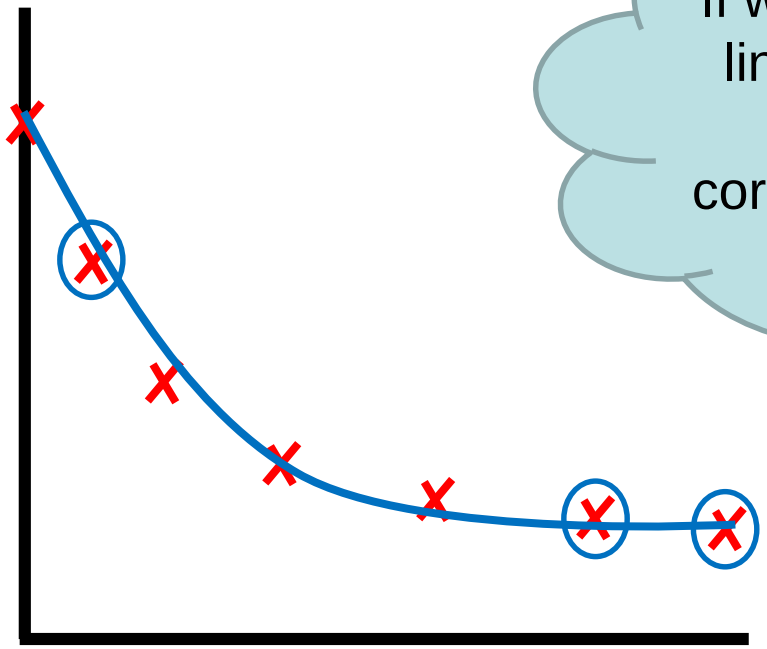
Multivariate Normal likelihood:

$$y_{i,k,m} \sim MVN(\theta_{i,k}, \Sigma_{i,k})$$

$\Sigma_{i,k}$ can be given an appropriate covariance structure

Time-course MBNMA

Correlated observations



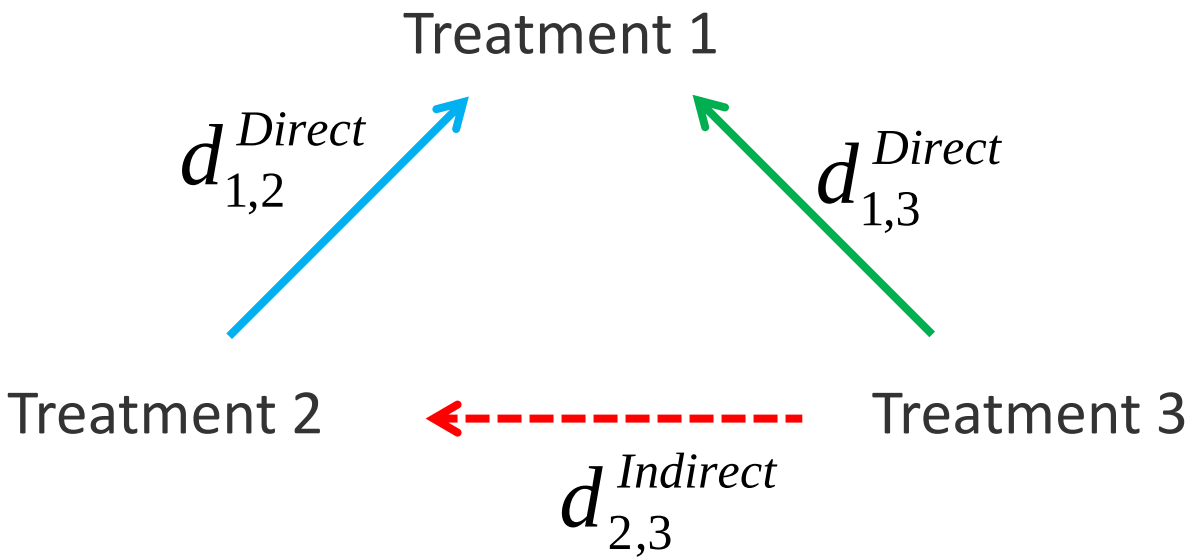
If we correctly identify the non-linear relationship we should have accounted for any correlation between time points

$$\Sigma_{i,k}$$ can be given an appro
covariance structu

Inconsistency

Inconsistency

A difference between direct and indirect evidence



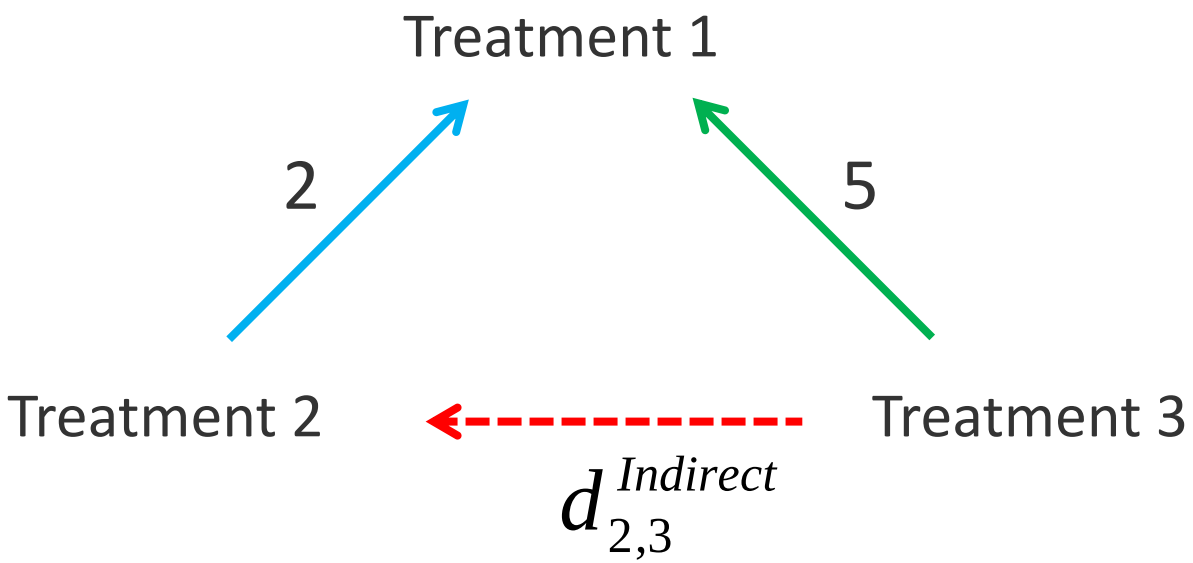
Indirect evidence

$$d_{2,3}^{Indirect} = d_{1,3}^{Direct} - d_{1,2}^{Direct}$$

Inconsistency

Inconsistency

A difference between direct and indirect evidence



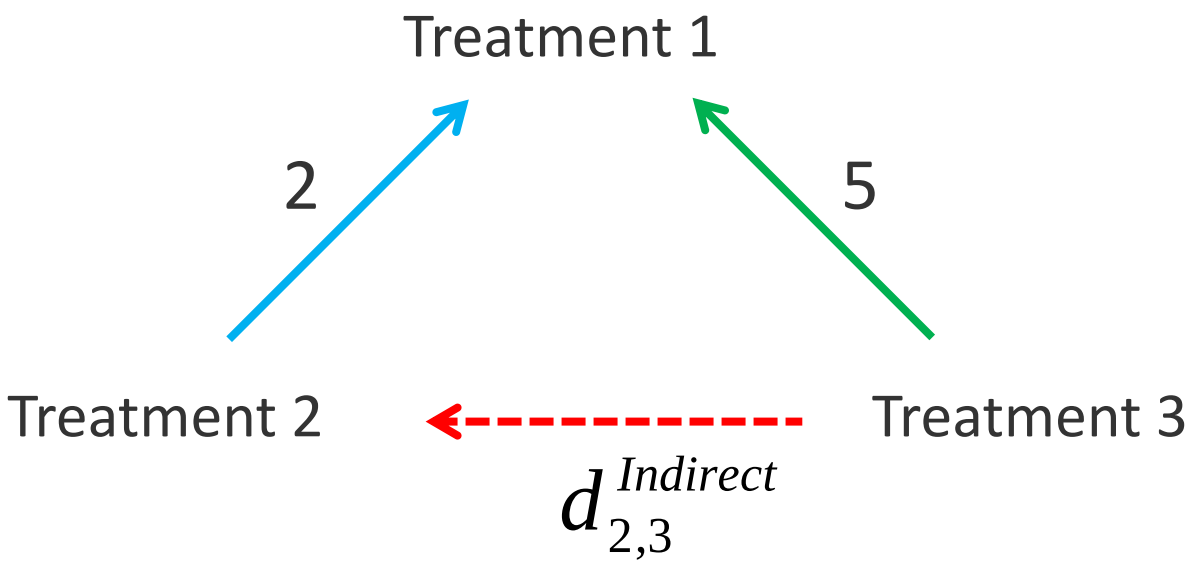
Indirect evidence

$$d_{2,3}^{Indirect} = 5 - 2$$

Inconsistency

Inconsistency

A difference between direct and indirect evidence



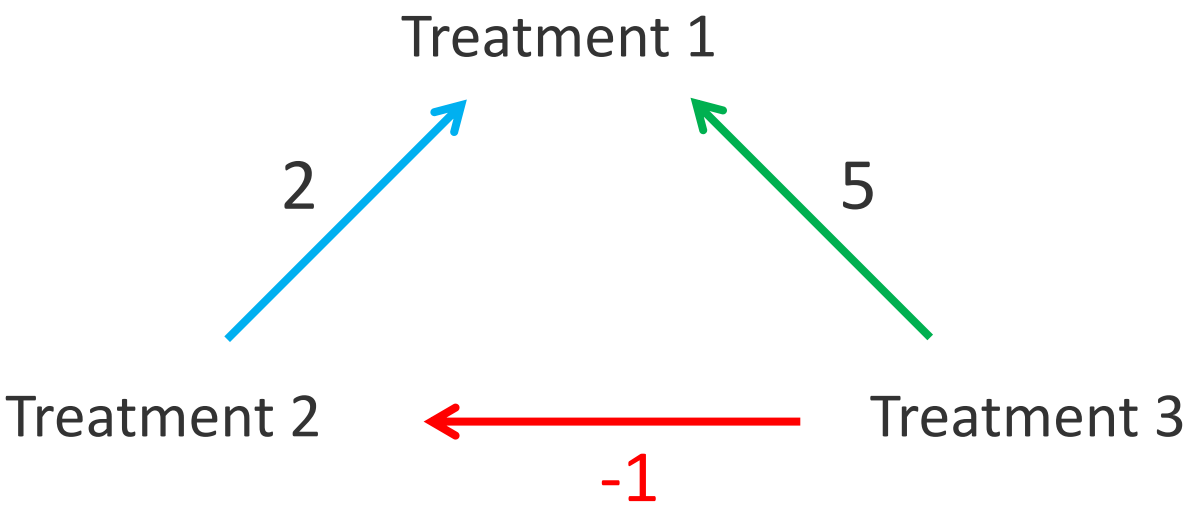
Indirect evidence

$$d_{2,3}^{Indirect} = 5 - 2 = 3$$

Inconsistency

Inconsistency

A difference between direct and indirect evidence



Indirect evidence

$$d_{2,3}^{Indirect} = 5 - 2 = 3$$

Direct evidence

RCT = -1

Time-course MBNMA

Testing for consistency

Global inconsistency	**For specific connected loops of treatments**
Unrelated mean effects model	Node-splitting

Time-course MBNMA

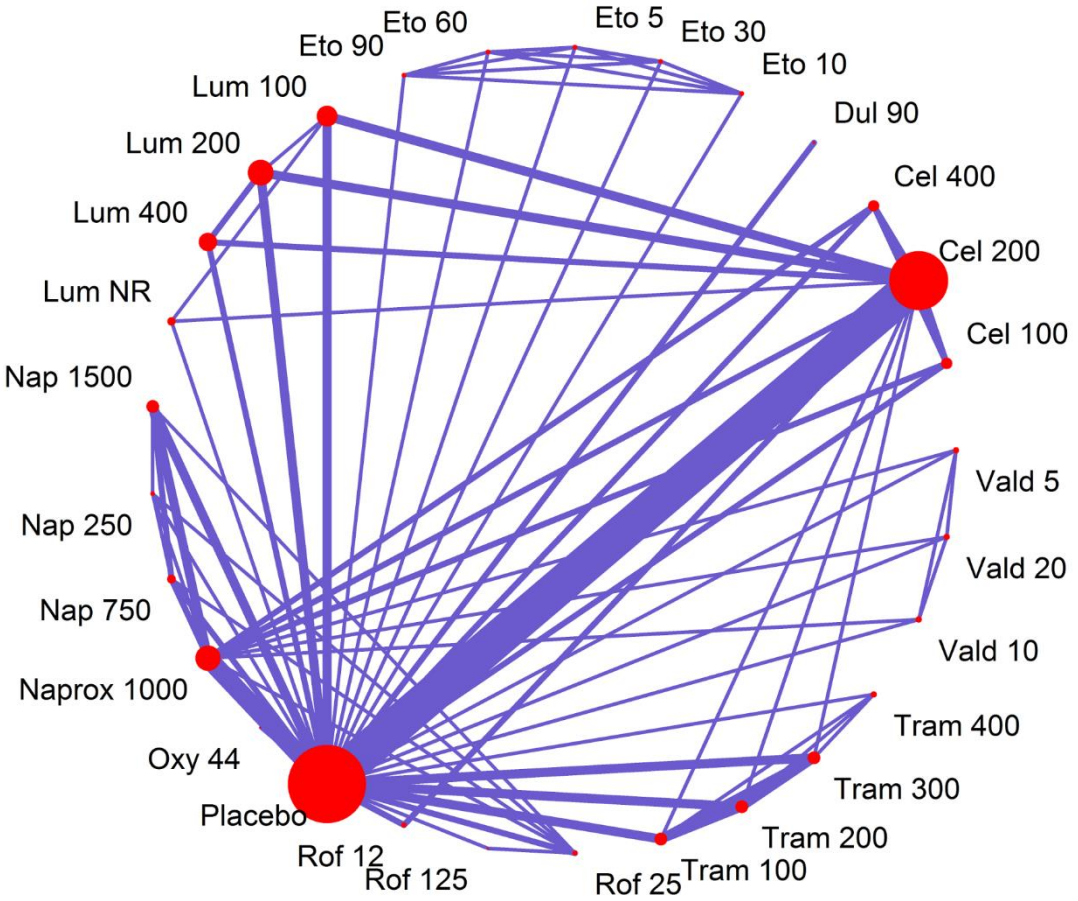
Modelling Strategy

- Inspect data (study means over time)
- Fit candidate time course functions (fixed treatment effects)
- Fit selected time course with random treatment effects
- Fit selected model with multivariate likelihood
- Check consistency in final model

Time-Course MBNMA Illustrative example

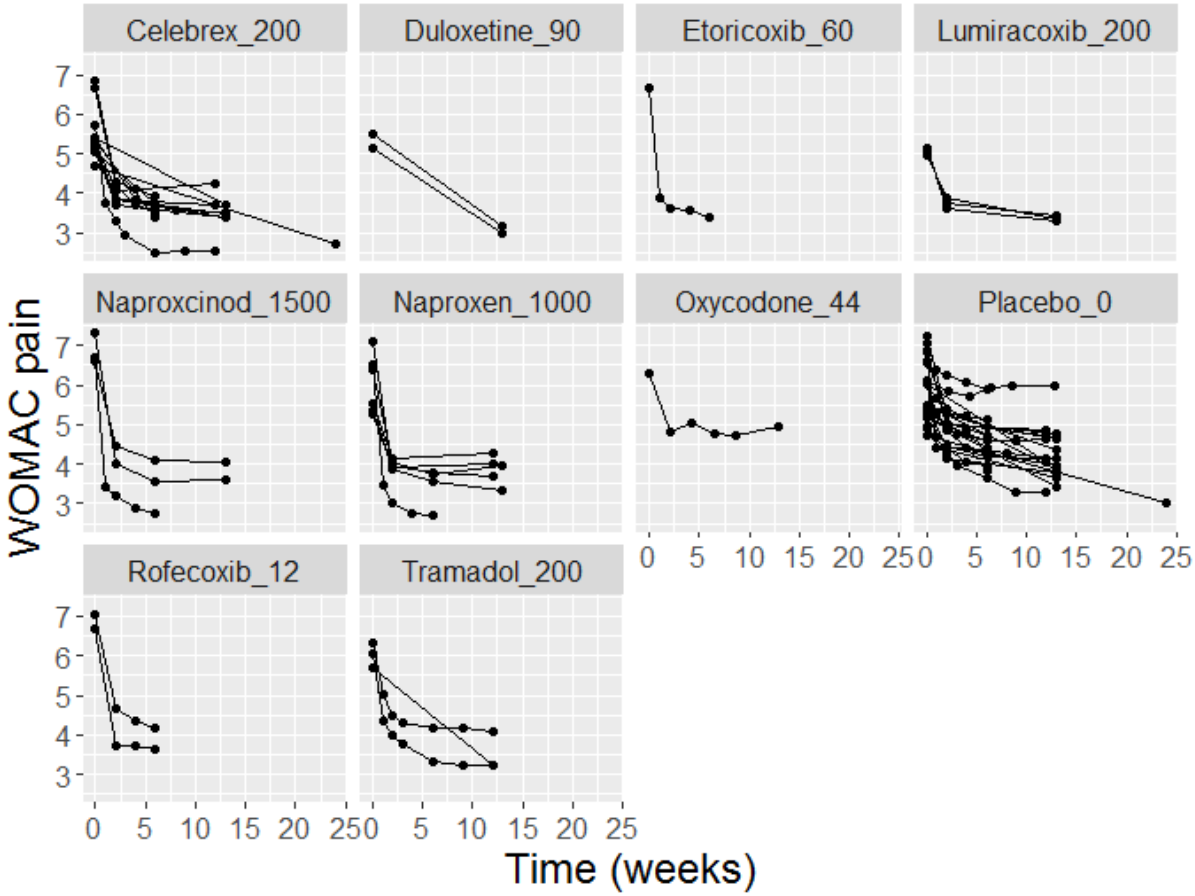
Example Dataset: Pain in osteoarthritis

- N studies: 24
- N treatments: 29
- Follow-up times reported per study: 3.5 (2-7)
- Arms per study: 4 (2-6)



Modelling Strategy

Inspect Data



Modelling Strategy

Compare univariate vs multivariate likelihood

Linear	Fixed E_{max}, Fixed ET_{50}	Univariate
Exponential	Random E_{max}, Fixed ET_{50}	Multivariate (compound symmetry)
Piecewise linear	Fixed E_{max}, Random ET_{50}	Multivariate (AR1)
E_{max}	Random E_{max}, Random ET_{50}	

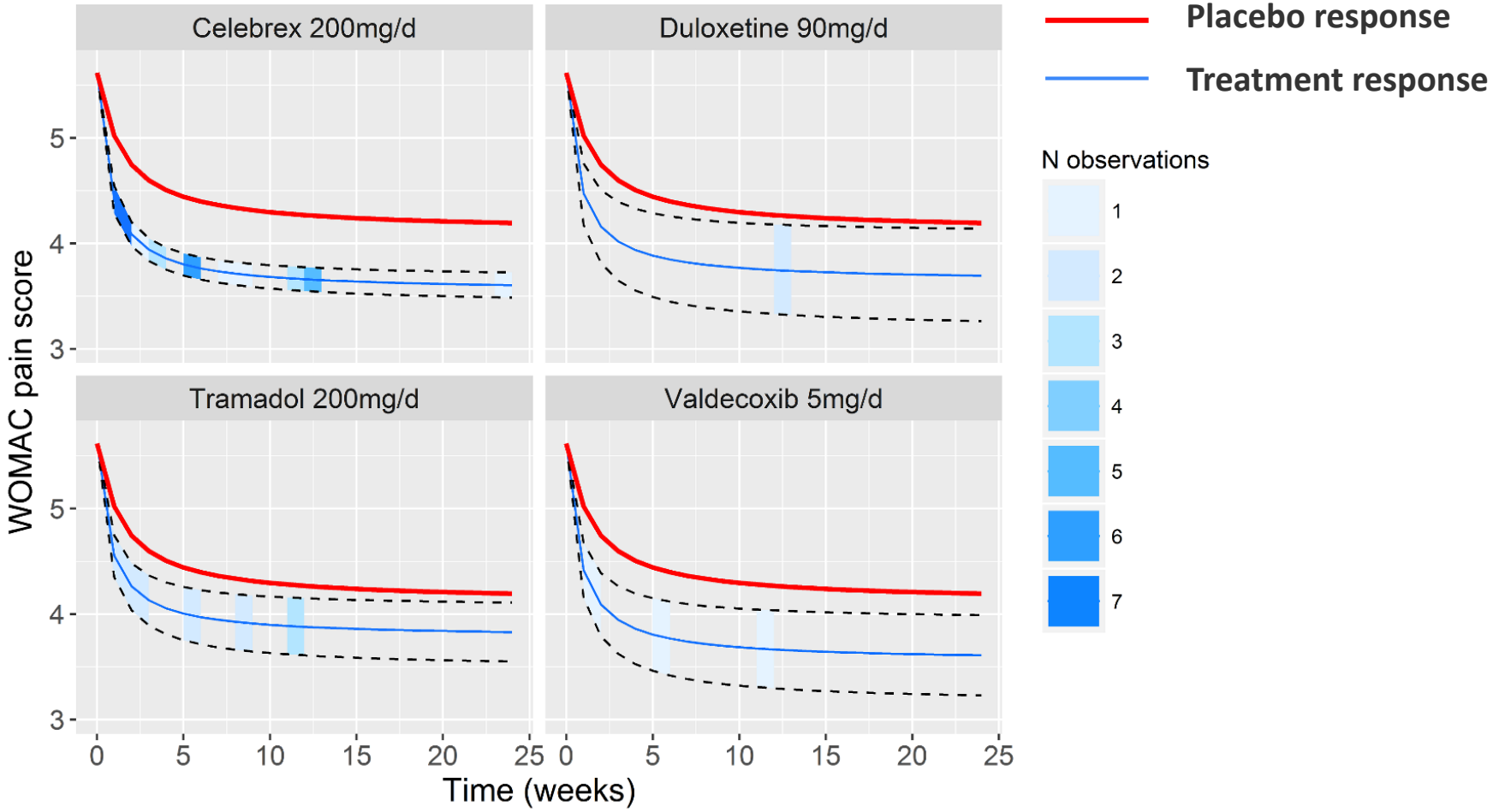
Final Model:

Time-course	Treatment effects	Univariate / Multivariate

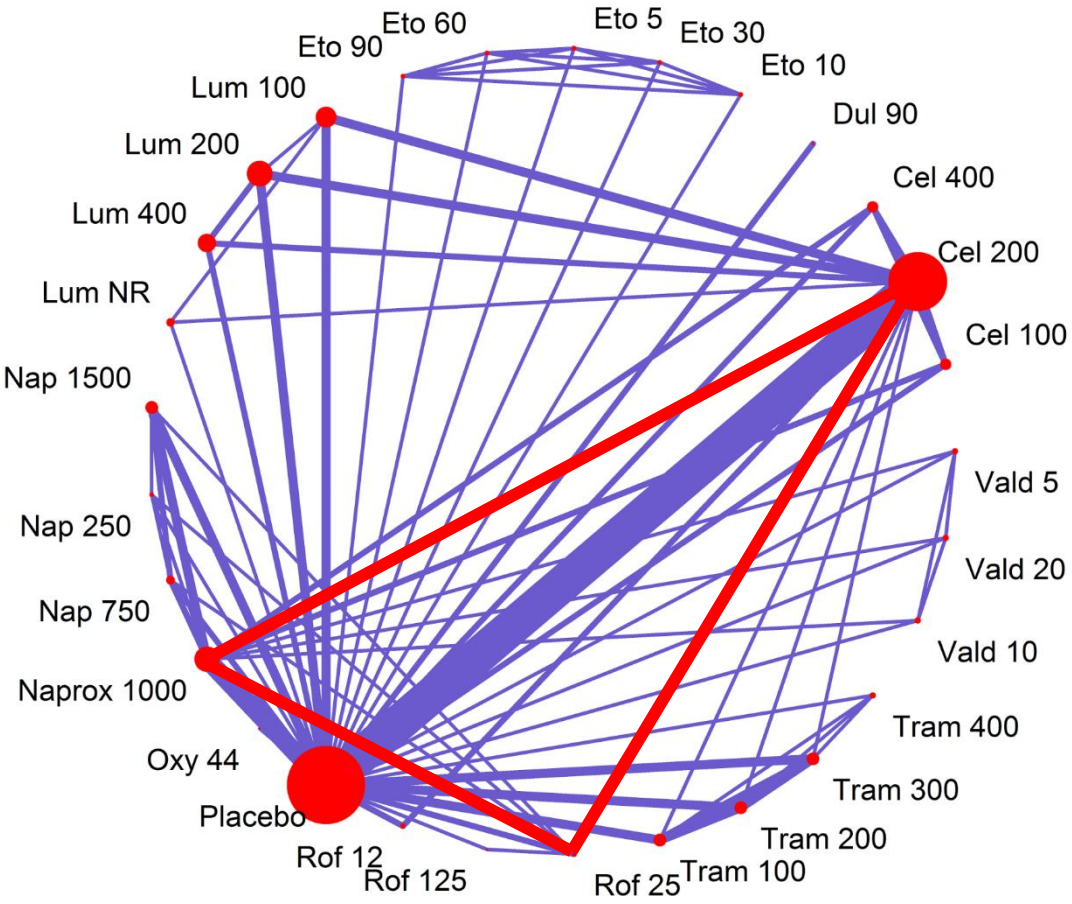
(+ simplifying assumptions)

Total residual deviance: 292 (compared to 345 data points)

Predicted mean effect

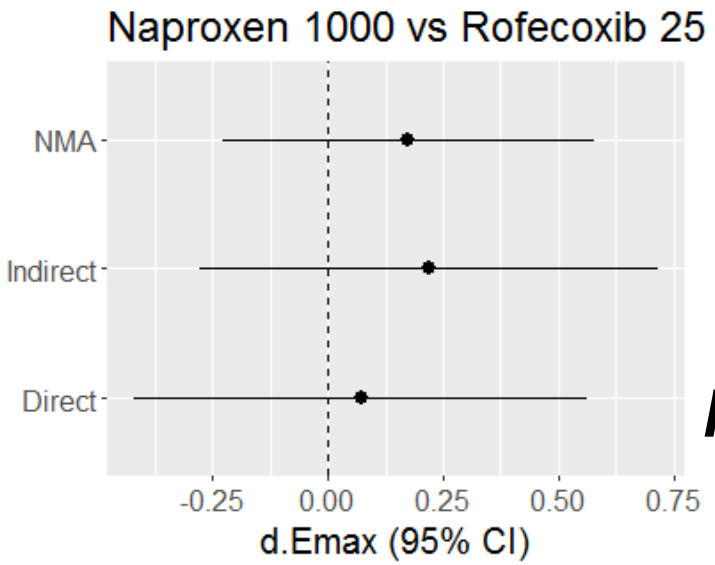


Testing for Consistency

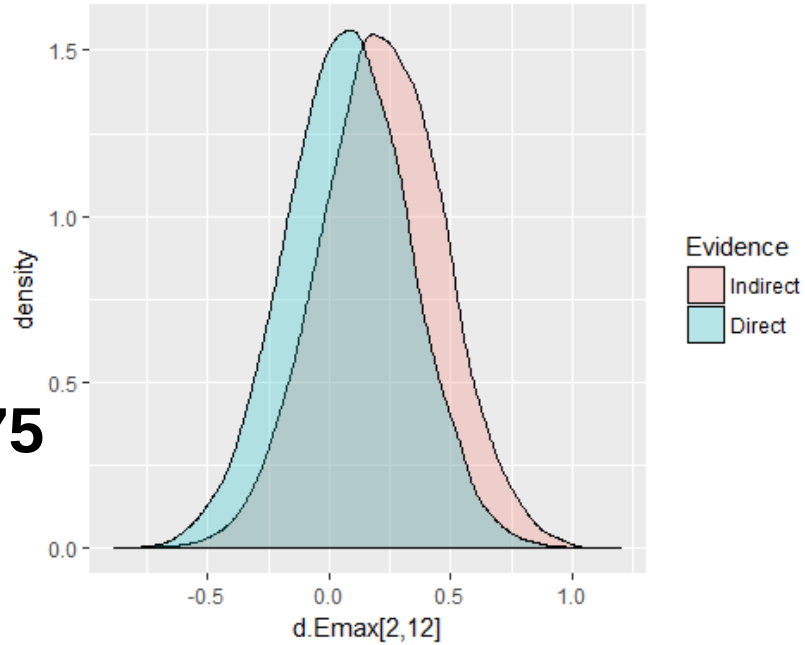


Node Splitting

- Splits evidence into “direct” and “indirect” for given comparison



***p* = 0.75**



Ongoing work

- MBNMA R package
- Simulation studies
  - Time-course
  - Dose-response
- Develop models for dose-response and time-course simultaneously

Summary

- MBNMA takes strengths from both NMA and MBMA
  - Synthesises evidence on dose-response and time-course characteristics
  - Makes use of direct and indirect information
  - Respects randomisation by pooling relative effects
  - Allows for testing of consistency
- We have demonstrated how it can be applied to a real-world dataset

Collaborators

University of Bristol

- Nicky Welton
- Sofia Dias

Pfizer

- Meg Bennetts
- Martin Boucher

Publications

Dose-Response MBNMA

Model-Based Network Meta-Analysis: A Framework for Evidence Synthesis of Clinical Trial Data (2016)

Mawdsley D., Bennetts M., Dias S., Boucher M., Welton N.J. *CPT Pharmacometrics Syst. Pharmacol. 5, 393-401*

Time-Course MBNMA

Modelling Time-Course Relationships with Multiple Treatments: Model-Based Network Meta-Analysis for Continuous Summary Outcomes *(in review)*

Pedder H., Dias S., Bennetts M., Boucher M., Welton N.J. *Research Synthesis Methods.*

Thank you for listening

For any further information, please get in touch:

hugo.pedder@bristol.ac.uk