Methods for assessing consistency in Mixed Treatment Comparison Meta-analysis

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Overview

• Mixed Treatment Comparison Meta-analysis (MTC)
  • Consistency assumptions
• How many inconsistencies?
• Different methods to assess consistency
  • Model fit
  • Direct v indirect evidence
• Conclusion
Example: Thrombolytic

- Treatment for acute myocardial infarction
- 9 treatments, 50 trials
- Two 3-arm trials
- 16 direct comparisons (out of 36)
- Data is number of 30-day mortalities out of total number of patients
Thrombo: Treatment Network

<table>
<thead>
<tr>
<th></th>
<th>SK (1)</th>
<th>t-PA (2)</th>
<th>Acc t-PA (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t-PA (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acc t-PA (3)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK+t-PA (4)</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>r-PA (5)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TNK (6)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PTCA (7)</td>
<td>8</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>UK (8)</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>ASPAC (9)</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Introduction to MTC

1. Four treatments A, B, C, D
2. Take treatment A as the reference treatment
3. Then the treatment effects (eg. log odds ratios) of B, C, D relative to A are the basic parameters
4. Given them priors:

\[ d_{AB}, d_{AC}, d_{AD} \sim N(0, 100^2) \]
Functional parameters in MTC

The remaining contrasts are functional parameters

\[ d_{BC} = d_{AC} - d_{AB} \]
\[ d_{BD} = d_{AD} - d_{AB} \]
\[ d_{CD} = d_{AD} - d_{AC} \]

\{ CONSISTENCY assumption \}

- Any information on functional parameters tells us indirectly about basic parameters
- Either FE or RE model satisfying these conditions
**MTC Random effects model**

- The underlying model is

\[
\theta_{ik} = \mu_i + \delta_{ik} I_{k \neq 1}
\]

- Priors

\[
\tau \sim U(0,10)
\]

\[
d_{1,k} \sim N(0,100^2) \quad k = 2, \ldots, 9
\]

\[
\mu_i \sim N(0,100^2) \quad i = 1, \ldots, 50
\]
Consistency

- We assume that the treatment effect $d_{BC}$ estimated by BC trials, would be the same as the treatment effect estimated by the AC and AB trials if they had included B and C arms.
- Assume that trial arms are missing at random.
Inconsistencies

- In a pre-specified population...
- The **true** treatment effects **must be** consistent
- But there may be inconsistencies in the **EVIDENCE**
- How to check for this?
Main ideas for checking consistency

1. Compare posterior distributions obtained from direct and indirect evidence for each comparison (triangle structures)
   - P-values, plots

2. Model fit/comparison problem
   - Fit models with and without consistency assumptions
   - Compare model fit (residual deviance, DIC)

3. A mixture of both
Comparison of direct and indirect estimates

- Bucher’s method for triangles (JCE, 1997)
  - Separate Pairwise meta-analyses on all contrasts
  - Calculate indirect estimate (using consistency equations)
  - Ignores network
- Can be extended to whole networks*
  - Problems when three-arm trials included or when random effects models used.

*Dias et al. Submitted to Statistics in Medicine (2009)*
<table>
<thead>
<tr>
<th>Triangle</th>
<th>Node</th>
<th>Indirect</th>
<th>Direct</th>
<th>inconsistency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean</td>
<td>sd</td>
<td>mean</td>
</tr>
<tr>
<td>1,2,7</td>
<td>2,7</td>
<td>-0.66</td>
<td>0.19</td>
<td>-0.54</td>
</tr>
<tr>
<td>1,2,8</td>
<td>2,8</td>
<td>-0.37</td>
<td>0.52</td>
<td>-0.30</td>
</tr>
<tr>
<td>1,2,9</td>
<td>2,9</td>
<td>0.00</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>1,3,5</td>
<td>3,5</td>
<td>0.10</td>
<td>0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>1,3,7</td>
<td>3,7</td>
<td>-0.51</td>
<td>0.19</td>
<td>-0.22</td>
</tr>
<tr>
<td>1,3,8</td>
<td>3,8</td>
<td>-0.21</td>
<td>0.52</td>
<td>0.14</td>
</tr>
<tr>
<td>1,3,9</td>
<td>3,9</td>
<td>0.15</td>
<td>0.06</td>
<td>1.41</td>
</tr>
</tbody>
</table>
How many inconsistencies?

- Inconsistencies are properties of loops
- Inconsistency degrees of freedom (ICDF) is the maximum number of possible inconsistencies*
- Informally described as the number of independent 3-way loops in the evidence structure
- In this example the ICDF is seven
  - Count independent 3-way loops
  - discounting the loop formed only by the 3-arm trial (1,3,4), in blue.

* Lu and Ades, JASA 2006
Thrombo: Treatment Network

- ASPAC (9)
- PTCA (7)
- SK + t-PA (4)
- TNK (6)
- Acc t-PA (3)
- r-PA (5)
- SK (1)
- t-PA (2)
- UK (8)
Inconsistency models*

Consistency model
9 treatments,
8 basic parameters

\[ d_{1,2}, d_{1,3}, d_{1,4}, \ldots \sim N(0, 100^2) \]

\[ d_{2,3} = d_{1,3} - d_{1,2} \]

\[ \ldots \]

\[ d_{8,9} = d_{1,9} - d_{1,8} \]

Inconsistency model
Add 7 parameters
Compare model fit

\[ \omega_{1,x,y} \sim N(0, \sigma^2_{\text{Inconsistency}}) \]

\[ d_{2,7} = d_{1,7} - d_{1,2} + \omega_{1,2,7} \]

\[ d_{2,8} = d_{1,8} - d_{1,2} + \omega_{1,2,8} \]

\[ \ldots \]

\[ d_{3,9} = d_{1,9} - d_{1,3} + \omega_{1,3,9} \]

* Lu and Ades, JASA 2006
Box plot of inconsistency factors $\omega$
Node-splitting*

- Node splits on each contrast (node, eg. BC)
  - Studies which compare BC directly: *inform direct estimate*
  - Rest of data with BC removed: *inform indirect estimate*

- Draw plots of posterior distributions based on direct and indirect evidence
  - Bayesian p-value to check for consistency

- Compare model fit
  - Check between-trial heterogeneity parameters
  - residual deviance, DIC statistics

*Ohlsson & Spiegelhalter, Workshop (2006)
Marshall & Spiegelhalter, Bayesian Analysis (2007)
Dias et al. Submitted to Statistics in Medicine (2009)
Compare direct and indirect evidence

Consistent

Possibly inconsistent?
Inconsistent!

Node (3,9) is split
Direct evidence on (3,9) conflicts with indirect evidence
Bayesian p-value < 0.005
Independent mean effects model

Consistency model  
9 treatments,  
8 basic parameters

\[
d_{1,2}, d_{1,3}, d_{1,4}, \ldots, d_{1,9} \sim N(0, 100^2) \\
d_{2,3} = d_{1,3} - d_{1,2} \\
\ldots \\
d_{8,9} = d_{1,9} - d_{1,8}
\]

Independent mean effects model  
15 parameters (one for each pairwise contrast)

\[
d_{1,2}, d_{1,3}, d_{1,4}, \ldots, d_{3,7}, d_{3,8}, d_{3,9} \sim N(0, 100^2)
\]

No consistency assumptions
Compare residual deviance for each data point

Trials 44,45 compare treatments 3 and 9
## Compare model fit (RE model)

<table>
<thead>
<tr>
<th>Model</th>
<th>Residual deviance*</th>
<th>pD</th>
<th>DIC</th>
<th>Between-trial heterogeneity $\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTC</td>
<td>102.7</td>
<td>61.6</td>
<td>164.3</td>
<td>0.97</td>
</tr>
<tr>
<td>Independent mean effects</td>
<td>97.4</td>
<td>67.8</td>
<td>165.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Inconsistency ($\omega$-factors)</td>
<td>98.4</td>
<td>64.6</td>
<td>163.0</td>
<td>0.09 inconsistency variance = 0.40</td>
</tr>
<tr>
<td>Node (3,9) split</td>
<td>96.9</td>
<td>58.7</td>
<td>155.6</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* Compare to 102 data points
Conclusions

- Explore heterogeneity WITHIN contrasts before looking at inconsistency BETWEEN contrasts
- Different methods allow comparison of data in different ways
- Use global goodness of fit to justify choice of consistency model
- Node-splitting to explore how evidence is being combined
  - But splits each pairwise comparison
- How many inconsistencies?
- Independent mean effects model solves multiplicity issue
  - Extra parameters = max number of inconsistencies
- If inconsistency detected, reconsider entire dataset!
References

• Our website: https://www.bris.ac.uk/cobm/research/mpes
• Bucher HC, Guyatt GH, Griffith LE, Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Epidemiology* 1997; 50: 683-691.