Multiple-Treatments Meta-Analysis

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With thanks to Deborah Caldwell, Julian Higgins and Sofia Dias
Evidence Based Medicine

- **Backbone:** meta-analysis
- Rigorous statistical models
- Clinical practice guidelines
  - NICE, WHO, The Cochrane Collaboration, HuGENet

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Two interventions

Randomized Controlled trials (RCTs)

Meta-analysis of RCTs

Multiple-treatments meta-analysis

Many different intervention

Cohort studies, Case-control studies
```
12 new generation antidepressants
19 meta-analyses published in the last two years

“Although Mirtazapine is likely to have a faster onset of action than Sertraline and Paroxetine no significant differences were observed…”

“...statistically significant differences in terms of efficacy .... between Fluoxetine and Venlafaxine, but the clinical meaning of these differences is uncertain…”

“Venlafaxine tends to have a favorable trend in response rates compared with duloxetine”

“...meta-analysis highlighted a trend in favour of Sertraline over other Fluoxetine”

Fluoxetine: 28€    Venlafaxine:111€    Sertaline: 76 €
How to do it?

Models within a Bayesian Framework
Advantages of the methods
Presentation of results
MTM using meta-regression
Assumption of consistency

Maths Warning!
Why use Bayesian statistics for meta-analysis?

- **Natural approach for accumulating data**
- **Repeated updating of meta-analyses fine:** posterior should always reflect latest beliefs
- **People naturally think as Bayesians:** they have degrees of belief about the effects of treatment, which change when they see new data
- **Probability statements about true effects of treatment easier to understand than confidence intervals and $p$-values**
Why use Bayesian statistics for MTM?

- Bayesian approach is easier to account for correlations induced by multi-arm trials
- Estimation of predictive intervals is straightforward
- Estimation of ranking probabilities is straightforward

- MTM with two-arm trials only
  Easy in frequentist meta-regression
Network of experimental comparisons

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

Lancet 2009  Cipriani, Fukurawa, Salanti et al
Network of experimental comparisons

Indirect estimation

\[ LOR_{SC} = LOR_{SF} + LOR_{FC} \]

\[ \text{Var}(LOR_{SC}) = v_5 = v_1 + v_2 \]

Combine the direct estimate with the indirect estimate using IV methods

Get a combined \( LOR! \)

\( v_4 < v_3 \)
Expand the idea in the entire network!
All other contrasts are functional!
Distributions of the observations

\[ y_{i}^{AC} \sim \mathcal{N}(\theta_{i}^{AC}, \sigma_{e_i}^2) \]

Distributions of the random effects

\[ \theta_{i}^{AC} \sim \mathcal{N}(\mu^{AC}, \tau^2) \]
Distributions of the observations

\begin{align*}
y_{i}^{AC} & \sim N(\theta_{i}^{AC}, \text{se}_{i}^{2}) \\
y_{i}^{BC} & \sim N(\theta_{i}^{BC}, \text{se}_{i}^{2}) \\
y_{i}^{AB} & \sim N(\theta_{i}^{AB}, \text{se}_{i}^{2})
\end{align*}

Distributions of the random effects

\begin{align*}
\theta_{i}^{AC} & \sim N(\mu^{AC}, \tau^{2}) \\
\theta_{i}^{BC} & \sim N(\mu^{BC}, \tau^{2}) \\
\theta_{i}^{AB} & \sim N(\mu^{AB}, \tau^{2})
\end{align*}

\[\mu^{AB} = \mu^{AC} - \mu^{BC}\]
What’s the problem with multi-arm trials?

- We need to take into account the correlations between the estimates that come from the same study

\[
\begin{array}{ccc}
A & B & C \\
\_\_\_\_\_\_ & y_i^{BC} \\
\_\_\_\_\_\_\_\_\_ & y_i^{AC}
\end{array}
\]

- The random effects \((\theta_i^{BC}, \theta_i^{AC})\) that refer to the same trial are correlated as well

- You have to build in *the correlation matrix for the observed effects, and the correlation matrix for the random effects*
Distributions of the observations

\[ y_i^{AC} \sim N(\theta_i^{AC}, se_i^2) \]
\[ y_i^{BC} \sim N(\theta_i^{BC}, se_i^2) \]
\[ y_i^{AB} \sim N(\theta_i^{AB}, se_i^2) \]

\[(y_i^{AC}, y_i^{BC}) \sim \text{MVN}((\theta_i^{AC}, \theta_i^{BC}), S)\]

S is the variance-covariance matrix estimated from the data

Distributions of the random effects

\[ \theta_i^{AC} \sim N(\mu^{AC}, \tau^2) \]
\[ \theta_i^{BC} \sim N(\mu^{BC}, \tau^2) \]
\[ \theta_i^{AB} \sim N(\mu^{AB}, \tau^2) \]

\[(\theta_i^{AC}, \theta_i^{BC}) \sim \text{MVN}((\mu^{AC}, \mu^{BC}), \Sigma)\]

\[ \Sigma \text{ is the variance-covariance matrix of the random effects (involves } \tau^2/2 \text{)} \]

which is unknown

\[ \mu^{AB} = \mu^{AC} - \mu^{BC} \]
Correlated observations

\((y_i^{AC}, y_i^{BC}) \sim \text{MVN}(\mu, \Sigma)\)

\(\Sigma\) is the variance-covariance matrix estimated from the data

\[
S = \begin{pmatrix}
\text{var}_1 & c \\
c & \text{var}_2 \\
\end{pmatrix}
\]

c depends on the measure \(y_i\)

e.g. When we observe mean difference \(\text{Cov}(y_i^{AC}, y_i^{BC}) = \text{var}_c\)
Correlated random effects

\((\theta_i^{AC}, \theta_i^{BC}) \sim \text{MVN}(\mu^{AC}, \mu^{BC}, \Sigma)\)

\(\Sigma\) is the variance-covariance matrix of the random effects (involves \(\tau^2/2\))

which is unknown

\[
\Sigma = \begin{pmatrix}
\tau_{AC}^2 & c \\
c & \tau_{BC}^2
\end{pmatrix}
\]

c depends on \(\tau^2\)

e.g. Assuming equal heterogeneities

\(\text{Cov}(\theta_i^{AC}, \theta_i^{BC}) = \tau^2/2\)

For each study arm $j, k$ in study $i$
According to a baseline treatment $l$
### Treatments for first bleeding in cirrhosis

<table>
<thead>
<tr>
<th>No. studies</th>
<th>Control</th>
<th>Sclerotherapy</th>
<th>Beta-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>(x^C/n^C)</td>
<td>(x^S/n^S)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(x^C/n^C)</td>
<td></td>
<td>(x^B/n^B)</td>
</tr>
<tr>
<td>2</td>
<td>(x^C/n^C)</td>
<td>(x^S/n^S)</td>
<td>(x^B/n^B)</td>
</tr>
</tbody>
</table>

\[
x_i^C \sim B(\pi_i^C, n_i^C)
\]

\[
x_i^S \sim B(\pi_i^S, n_i^S)
\]

\[
x_i^B \sim B(\pi_i^B, n_i^B)
\]

\[
\text{Logit}(\pi_i^C) = u_i
\]

\[
\text{Logit}(\pi_i^S) = u_i + \theta_i^{CS}
\]

\[
\text{Logit}(\pi_i^B) = u_i + \theta_i^{CB}
\]

\[
\theta_i^{CS} \sim N(\mu^{CS}, \tau^2)
\]

\[
\theta_i^{CB} \sim N(\mu^{CB}, \tau^2)
\]

In the two 3-arms trials we only substitute

\[
(\theta_i^{CS}, \theta_i^{CB}) \sim \text{MVN}((\mu^{CS}, \mu^{CB}), \Sigma)
\]

\[
\mu^{SB} = \mu^{CB} - \mu^{CS}
\]

---

l,j,k random treatments
y_i the outcome of experiment i
θ_i the random effect

\[
\begin{pmatrix}
y_{1,l_1,j_1} \\
y_{2,l_2,j_2} \\
\vdots \\
y_{N,l_N,j_N}
\end{pmatrix}
\sim N
\begin{pmatrix}
\theta_{1,l_1,j_1} \\
\theta_{2,l_2,j_2} \\
\vdots \\
\theta_{N,l_N,j_N}
\end{pmatrix}, S
\]

\[
\begin{pmatrix}
\mu_{1,l_1,j_1} \\
\mu_{2,l_2,j_2} \\
\vdots \\
\mu_{N,l_N,j_N}
\end{pmatrix}
\sim N
\begin{pmatrix}
\tau_1^2 \\
\tau_2^2 \\
\vdots \\
\tau_N^2
\end{pmatrix}, \begin{pmatrix}
c & c & c \\
c & \tau_2^2 & c & c \\
\vdots & \vdots & \ddots & \vdots \\
c & c & c & \tau_N^2
\end{pmatrix}
\]

\[
\mu_{lj} = \mu_{lk} + \mu_{kj}
\]

Winbugs Code

\[
\text{model}{
\text{for(i in 1:NHtH)}{\text{delta[i]~dnorm(mean[i],precision )}}
\text{delta[(NHtH+1):N]~dmnorm(mean[(NHtH+1):N],K[,] )}
\text{for(i in 1:(N-NHtH))}{\text{for(j in 1:(N-NHtH))}{\text{K[i,j]<-precision*H[i,j]}}}
\text{for(i in 1:N)}{\text{mean[i] <- d[t[i]] - d[b[i]] }}
\text{for (k in 1:NT) } \{ \text{d[k] ~ dnorm(0,.0001) } \}
\text{for (c in 1:(NT-1)) }\{ \text{for (k in (c+1):NT) } \{ \text{mean[c,k] <- d[k] - d[c]}
\text{OR[c,k] <- exp(mean[c,k] )} \}\}
\}
\text{precision<-1/pow(sd,2) }\text{sd~dnorm(0,1)I(0,)}
\]

Likelihood
Random effects
Coherence equations
Priors
How to do it?

Models within a Bayesian Framework

Advantages of the methods

Presentation of results

Assumption of consistency

Maths Warning!
Advantages

– Ranking of many treatments for the same condition (see later)
– Comprehensive use of all available data (indirect evidence)
– Comparison of interventions which haven’t been directly compared in any experiment
OR(B vs M) = 0.79 (0.72, 1)

Lancet 2009 Cipriani, Fukurawa, Salanti et al
Advantages

– Ranking of many treatments for the same condition (see later)
– Comprehensive use of all available data (indirect evidence)
– Comparison of interventions which haven’t been directly compared in any experiment
– Improved precision for each comparison
Network of experimental comparisons

Fluoxetine vs Milnacipran (response to treatment)
Meta-analysis: 1.15 (0.72, 1.85)
MTM: 0.97 (0.69, 1.32)
Only 2 studies: LOR \(_{BS} = -0.77\) \((-7.74, 6.23)\)

All studies: LOR \(_{BS} = -0.18\) \((-1.22, 0.82)\)

We gained precision
How to do it?

Models within a Bayesian Framework
Advantages of the methods
Presentation of results
Assumption of consistency
Ranking measures from MTM

• With many treatments judgments based on pairwise effect sizes are difficult to make

• Example: Antidepressants
OR > 1 means the treatment in top-left is better
Ranking measures from MTM

• With many treatments judgments based on pairwise effect sizes are difficult to make
• Example: Antidepressants
• Example: Antiplatelet regimens for serious vascular events
Odds ratios for severe vascular events compared to placebo.

**Means**

- Aspirin + Dipyridamole
- Thienopiridines + Aspirin
- Thienopiridines
- Aspirin

**Predictions**

Odds-ratios for serious vascular events with antiplatelet treatments compared to placebo.
Serious vascular events with antiplatelet regimens

<table>
<thead>
<tr>
<th>P-value</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.32</td>
<td>Aspirin+Dipyridamole vs Aspirin+Thienopyridines</td>
</tr>
<tr>
<td>0.03</td>
<td>Aspirin+Dipyridamole vs Thienopyridines</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>Aspirin+Dipyridamole vs Aspirin</td>
</tr>
<tr>
<td>0</td>
<td>Aspirin+Dipyridamole vs Placebo</td>
</tr>
<tr>
<td>0.23</td>
<td>Aspirin+Thienopyridines vs Thienopyridines</td>
</tr>
<tr>
<td>0.05</td>
<td>Aspirin+Thienopyridines vs Aspirin</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>Aspirin+Thienopyridines vs Placebo</td>
</tr>
<tr>
<td>0.19</td>
<td>Thienopyridines vs Aspirin</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>Thienopyridines vs Placebo</td>
</tr>
<tr>
<td>&lt;0.01</td>
<td>Aspirin vs Placebo</td>
</tr>
</tbody>
</table>

Odds Ratio for serious vascular event

J Clin Epidemiol. 2010 Salanti, Ades, Ioannidis
Probabilities

• Estimate for each treatment *the probability to be the best*

• This is straightforward within a Bayesian framework
  – In each MCMC cycle rank the treatments
  – Run 1,000 000 cycles
  – \((#J=1)/ 1,000 000\) is the probability that J is the best treatment

• But this does not convey the entire picture…
### 12 new generation antidepressants

19 **meta-analyses** published in the last two years

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Probability to be the best</th>
</tr>
</thead>
<tbody>
<tr>
<td>paroxetine ——— reboxetine</td>
<td>paroxetine 0%</td>
</tr>
<tr>
<td>duloxetine ——— mirtazapine</td>
<td>sertraline 7%</td>
</tr>
<tr>
<td>escitalopram ——— fluvoxamine</td>
<td>citalopram 0%</td>
</tr>
<tr>
<td>milnacipran ——— citalopram</td>
<td>escitalopram 26%</td>
</tr>
<tr>
<td>sertraline ——— venlafaxine</td>
<td>fluoxetine 0%</td>
</tr>
<tr>
<td>bupropion ——— fluoxetine</td>
<td>fluvoxamine 0%</td>
</tr>
<tr>
<td>milnacipran ——— paroxetine</td>
<td>milnacipran 1%</td>
</tr>
<tr>
<td>sertraline ——— duloxetine</td>
<td>venlafaxine 11%</td>
</tr>
<tr>
<td>bupropion ——— escitalopram</td>
<td>reboxetine 0%</td>
</tr>
<tr>
<td>fluvoxamine ——— milnacipran</td>
<td>bupropion 0%</td>
</tr>
<tr>
<td></td>
<td>duloxetine 0%</td>
</tr>
</tbody>
</table>
The areas under the cumulative curves for the four treatments of the example above are:
A = 0.5
B = 0.75
C = 0.67
D = 0.08
Ranking for efficacy (solid line) and acceptability (dotted line). Ranking: probability to be the best treatment, to be the second best, the third best and so on, among the 12 comparisons.)
Use posterior probabilities for each treatment to be among the $n$-best options

\[
\text{Cumulative ranking curve } j = \frac{\sum_{l=1}^{T-1} p_{j,l}}{T-1}
\]

Treatments $j, l$

Total number of treatments $T$
Surface under the cumulative ranking curve

Rank of paroxetine: 35%

Rank of sertraline: 77%

Rank of reboxetine: 1%

Rank of mirtazapine: 92%
Warning: measures based on probabilities are attractive, but can be unstable and should be presented along with the effect sizes!

Salanti, Ades, Ioannidis
Aspirin+ Dipyridamole
Thienopyridines+Aspirin
aspirin
placebo
thienopyridines

1
2
3
4
5

% probability to rank at each place

J Clin Epidemiol. 2010 Salanti, Ades, Ioannidis
How to do it?

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Maths Warning!
Inconsistency

$LOR (SE)$ for MI

Calculate a difference between direct and indirect estimates

Direct $t$-PA vs Angioplasty = $-0.41 (0.36)$

Indirect $t$-PA vs Angioplasty = $-0.46 (0.18)$

Inconsistency Factor $IF = 0.05$
Inconsistency

Calculate IF for all ‘triangles’ and an associated 95% CI
Inconsistency - Heterogeneity

- **Heterogeneity**: ‘excessive’ discrepancy among study-specific effects
- **Inconsistency**: it is the excessive discrepancy among source-specific effects (direct and indirect)

Multiple meta-analyses of RCTs
- With consistency

Meta-analysis of RCTs
- With homogeneity

RCTs

2 interventions

best intervention
Inconsistency

Empirical Evidence

• In 3 cases out of 44 there was an important discrepancy between direct/indirect effect.
• Direction of the discrepancy is inconsistent

Glenny et al HTA 2005
What can cause inconsistency?

*Inappropriate common comparator*

Compare Fluoride treatments in preventing dental caries

I cannot learn about Toothpaste versus Gel through Placebo!

Direct SMD(T – G) = –0.12 (0.06)

Indirect SMD(T – G) = –0.01 (0.06)

IF = 0.11 (0.08)

*J Clin Epidemiol. 2009 Salanti, Marinho, Higgins*
What can cause inconsistency?

Confounding by trial characteristics

Different characteristics across comparisons may cause inconsistency
Assumptions of MTM

• There is not confounding by trial characteristics that are related to both the comparison being made and the magnitude of treatment difference

• The trials in two different comparisons are exchangeable (other than interventions being compared)

• Equivalent to the assumption ‘the unobserved treatment is missing at random’
  – Is this plausible?
  – Selection of the comparator is not often random!
Inconsistency

Detecting

• Consistency is an assumption for MTM
  – Untestable?

• Check the distribution of important characteristics per treatment comparison
  – Usually unobserved….
  – Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM
## Compare the characteristics!

<table>
<thead>
<tr>
<th>No. studies</th>
<th>T (yes/no)</th>
<th>G (yes/no)</th>
<th>R (yes/no)</th>
<th>V (yes/no)</th>
<th>P (yes/no)</th>
<th>Fup</th>
<th>Baseline</th>
<th>Year</th>
<th>Water F (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td></td>
<td></td>
<td></td>
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<td>1968</td>
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<td>2.8</td>
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<td></td>
<td></td>
<td>2.5</td>
<td>7.6</td>
<td>1981</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*J Clin Epidemiol. 2009 Salanti, Marinho, Higgins*
Inconsistency

Detecting

- Consistency is an assumption for MTM
  - Untestable?

- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM

- Get a taste by looking for inconsistency in closed loops
Evaluation of consistency within closed loops

*IF estimates with 95% confidence intervals*

Closed loops

- A, S, t-PA
- Ac t-PA, Ang, S
- Ac t-P, R, S
- Ang, S, t-PA

*Warning!*
this is not a formal test!

An R code can be found in [http://www.dhe.med.uoi.gr/R%20routine.htm](http://www.dhe.med.uoi.gr/R%20routine.htm)
An example can be found in *[J Clin Epidemiol.]* 2009 Salanti, Marinho, Higgins
Inconsistency

Detecting

- Consistency is an assumption for MTM
  - Untestable?
- Check the distribution of important characteristics per treatment comparison
  - Usually unobserved….
  - Time (of randomization, of recruitment) might be associated with changes to the background risk that may violate the assumptions of MTM
- Get a taste by looking for inconsistency in closed loops
- Fit a model that relaxes consistency
Inconsistency models

• Separate basic and functional parameters
• Add an inconsistency term at each consistency equation
• Estimate the extend of inconsistency
Survival with chemotherapy regimens (Colorectal Cancer)

Lancet Oncol 2007 Golfinopoulos V, Salanti G et al
Survival with chemotherapy regimens (Colorectal Cancer)

Survival with chemotherapy regimens (Colorectal Cancer)

Fluorouracil + oxaliplatin

Fluorouracil + irinotecan + bevacizumab

Fluorouracil + oxaliplatin + bevacizumab

Irinotecan

Irinotecan + oxaliplatin

Oxaliplatin

Bevacizumab

Fluorouracil

Fluorouracil + irinotecan

Fluorouracil + bevacizumab

Fluorouracil + irinotecan + oxaliplatin

Lancet Oncol 2007 Golfinopoulos V, Salanti G et al
Survival with chemotherapy regimens (Colorectal Cancer)

Fluorouracil + oxaliplatin

Fluorouracil + irinotecan + oxaliplatin

Fluorouracil + irinotecan + bevacizumab

Fluorouracil + oxaliplatin + bevacizumab

Irinotecan

Irinotecan + oxaliplatin

Oxaliplatin

Bevacizumab

Survival with chemotherapy regimens (Colorectal Cancer)

Lancet Oncol 2007 Golfinopoulos V, Salanti G et al
Inconsistency models

- $w_i \sim N(0, \sigma^2)$
- Look at the individual $w$ values to locate any inconsistencies
- Compare $\sigma^2$ to $\tau^2$ (*heterogeneity*)
  - $P(\sigma^2 > \tau^2)$
Results

- $w_1 = -0.08$, $w_2 = -0.07$, $w_3 = -0.06$, $w_4 = -0.03$
  - No loop is remarkably inconsistent
- $\sigma^2 = 0.11(0.04)$, $\tau^2 = 0.19(0.18)$
  - $P(\sigma^2 > \tau^2) = 0.41$
- No important changes in posterior HRs or fit
More assumptions of MTM!

- **Appropriate modelling of data** (sampling distributions)
- **Normality** of true effects in a random-effects analysis
- **Comparability of studies**
  - exchangeability in all aspects other than particular treatment comparison being made
- **Equal heterogeneity variance in each comparison**
  - not strictly necessary
Model diagnostics

- D, pD, DIC
- Leverage plots
Estimate the fit of a model: Continuous data

\[ \theta_i, \tilde{\theta}_i \]  
The fitted values \((y_i \sim N(\theta_i, \text{var}_i))\) and their posterior mean

\[ \tilde{D}_i = \frac{(y_i - \theta_i)^2}{\text{var}_i} \]  
residual deviance  
(estimated within WinBUGS at each iteration)

\[ \overline{D}_i \]  
Posterior mean of residual deviance for each data point (mean taken from M iterations)

\[ D(\tilde{\theta}_i) = \frac{(y_i - \tilde{\theta}_i)^2}{\text{var}_i} \]  
Deviance at the posterior mean of the fitted values

\[ pD = \sum pD_i = \sum \left[ \overline{D}_i - D(\tilde{\theta}_i) \right] \]  
Effective number of parameters

Posterior mean of residual deviance minus deviance at posterior mean
Estimate the fit of a model: Binary Data

\[ p_{i,k}, \tilde{p}_{i,k} \] The fitted probability values and their posterior mean

\[ \tilde{D}_{i,k} = r \log \left( \frac{pn}{r} \right) + (n - r) \log \left( \frac{(1 - p)n}{n - r} \right) \] residual deviance

Posterior mean of residual deviance for each data point (mean taken from M iterations)

\[ \overline{D}_{i,k} \quad \text{Summarised by posterior mean in WinBUGS} \]

\[ D(\tilde{p}_{i,k}) = r \log \left( \frac{\tilde{pn}}{r} \right) + (n - r) \log \left( \frac{(1 - \tilde{p})n}{n - r} \right) \] Deviance at the posterior mean of the fitted values

\[ pD = \sum pD_i = \sum \left[ \overline{D}_i - D(\tilde{\theta}_i) \right] \] Effective number of parameters

Posterior mean of residual deviance minus deviance at posterior mean
Estimate the fit of a model: Measures

For fit of the model to the data

$$\overline{D} = \sum \overline{D}_i$$ Should approximate the number of data points

Bad fitted observations

Plot $$\sqrt{\tilde{D}_i}$$ vs $$pD_i$$

Studies outside $$x^2 + y = 3$$ show poor fit

Compare models

$$DIC = \overline{D} + pD$$ Can be used to compare different models

*JRSS (B) 2002* Spiegelhalter et al
Network of treatments for advanced breast cancer. AcLD = Low-dose anthracycline (combination regimen); AcSD = Standard-dose anthracycline (combination regimen); AsLD = Low-dose anthracycline (single agent); AsSD = Standard-dose anthracycline (single agent); A+tzmbSD = Standard-dose anthracycline + trastuzumab; AN SD = Standard-dose anthracycline + novel non-taxane agents; ANT SD = Standard-dose anthracycline + novel non-taxane agents + taxanes; AT SD = Standard-dose anthracycline + taxanes; McLD = Lowdose mitoxantrone (combination regimen); McSD = Standard-dose mitoxantrone (combination regimen); MsSD = Standard-dose mitoxantrone (single agent); Nc = Novel non-taxane agents (combination regimen); Ns = Novel non-taxane agents (single agent); N+Bmab = Novel non-taxane agents + bevacizumab (single agent); N+lpnb = Novel non-taxane agents + lapatinib; NT = Novel non-taxane agents + taxanes; Oc = Old agents (combination regimen); Os = Old agents (single agent); Tc = Taxanes (combination regimen); Ts = Taxanes (single agent); T+tzmb = Taxanes + trastuzumab; Ts+lpnb = Taxanes + lapatinib

Example: Breast Cancer
Example: Breast Cancer

Arm of study 130
Example: Breast Cancer

<table>
<thead>
<tr>
<th>Model</th>
<th>$\bar{D}$</th>
<th>$p_D$</th>
<th>DIC</th>
<th>Data Points</th>
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<tbody>
<tr>
<td>Original Data</td>
<td>168.3</td>
<td>77.5</td>
<td>245</td>
<td>148</td>
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<tr>
<td>Without 130</td>
<td>166.4</td>
<td>68.6</td>
<td>235</td>
<td>147</td>
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</tbody>
</table>
Multiple-Treatments Meta-regression

Adjust for and quantify the effect of a covariate in each network

**HOW:** Multidimensional extensions of meta-regression

$y_{i}^{AB}$ the outcome of experiment A vs B

**Likelihood:** $y_{i}^{AB} \sim N(\theta_{i}^{AB}, (\text{var}_{i}^{AB})^2)$

**Bias adjusted** estimate $\theta_{i}^{AB} = \mu_{i}^{AB} + \beta_{i}I_{AB}$

Coefficient

Index, (0 or 1) depending on whether A is favored by bias compared to B

*Random effects in the effect of the covariate*

$\beta_{i} \sim N(B, \tau_{r}^2)$

**Adjusted for sponsoring bias**

Stat Med 2010 Salanti et al
JRSS 2010 Dias et al
Multiple-Treatments Meta-regression

- **Compared the models** (adjusted and unadjusted) and examine
  - Improvement in fit as measured by DIC
  - Changes in heterogeneity $\tau^2$, $\tau_r^2$
  - The distribution of the effect of the covariate ($\beta$)

- It is expected that MTMr has the same problems (low power, prone to bias) as regular meta-regression
List of publications on methodological issues


List of applied publications (from Cochrane-related authors...)


Tudur SC, Marson AG, Chadwick DW, Williamson PR. 2007. Multiple treatment comparisons in epilepsy monotherapy trials. Trials 8:34.