Bimodality of the likelihood function of the random-effects model in meta-analysis

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Random-Effects Model

- let y_i be an estimate of some underlying parameter θ_i with (approximately) known sampling variance v_i
- assume $y_i|\theta_i \sim \mathrm{N}(\theta_i, v_i)$ (at least approximately)
- have $i, \ldots, k$ studies, each providing such an estimate
- assume $\theta_i \sim \mathrm{N}(\mu, \tau^2)$
- want to estimate μ and τ^2

Random-Effects Model

- random-effects model:

$$y_i = \mu + u_i + e_i$$

where $u_i \sim \mathrm{N}(0, \tau^2)$ and $e_i \sim \mathrm{N}(0, v_i)$

- assume $\mathrm{Cov}[u_i, u_{i'}] = \mathrm{Cov}[e_i, e_{i'}] = \mathrm{Cov}[u_i, e_i] = 0$

$$y_i \sim \mathrm{N}(\mu, \tau^2 + v_i)$$

Example: BCG Vaccine

- meta-analysis by Colditz et al. (1994) on the effectiveness of the Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis
- each included study provides the proportion of TB positive cases in the vaccinated and non-vaccinated group

Results from One Trial

	Positive	Negative	Total
Vaccinated	4	119	123
Not Vaccinated	11	128	139

$$p_T = 4/123 = .0325$$

$$p_C = 11/139 = .0791$$

$$RR = \frac{4/123}{11/139} = .41$$

$$y = \ln\left[\frac{4/123}{11/139}\right] = -.89$$

$$v = \frac{1}{4} - \frac{1}{123} + \frac{1}{11} - \frac{1}{139} = .326$$

Results from 13 Trials

trial	author	year	tpos	tneg	cpos	cneg	yi	vi
1	Aronson	1948	4	119	11	128	-0.89	0.326
2	Ferguson & Simes	1949	6	300	29	274	-1.59	0.195
3	Rosenthal et al	1960	3	228	11	209	-1.35	0.415
4	Hart & Sutherland	1977	62	13536	248	12619	-1.44	0.020
5	Frimodt-Moller et al	1973	33	5036	47	5761	-0.22	0.051
6	Stein & Aronson	1953	180	1361	372	1079	-0.79	0.007
7	Vandiviere et al	1973	8	2537	10	619	-1.62	0.223
8	TPT Madras	1980	505	87886	499	87892	0.01	0.004
9	Coetzee & Berjak	1968	29	7470	45	7232	-0.47	0.056
10	Rosenthal et al	1961	17	1699	65	1600	-1.37	0.073
11	Comstock et al	1974	186	50448	141	27197	-0.34	0.012
12	Comstock & Webster	1969	5	2493	3	2338	0.45	0.533
13	Comstock et al	1976	27	16886	29	17825	-0.02	0.071

Maximum Likelihood Estimation

- log likelihood function (Hardy & Thompson, 1996):

$$ll(\mu, \tau^2) = -\frac{1}{2}\sum_{i=1}^{k} \ln(\tau^2 + v_i) - \frac{1}{2}\sum_{i=1}^{k} \frac{(y_i - \mu)^2}{\tau^2 + v_i}$$

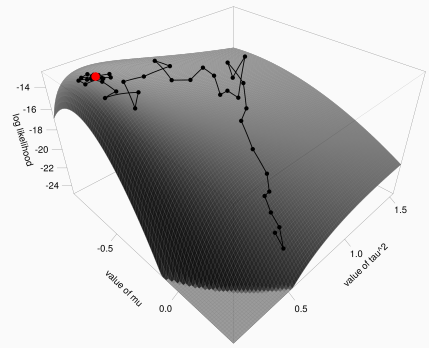
- MLEs of μ and τ^2:

$$\hat{\mu} = \frac{\sum_{i=1}^{k} w_i y_i}{\sum_{i=1}^{k} w_i}$$

$$\hat{\tau}^2 = \frac{\sum_{i=1}^{k} w_i^2 \left((y_i - \mu)^2 - v_i\right)}{\sum_{i=1}^{k} w_i^2}$$

  where $w_i = 1/(\tau^2 + v_i)$
- can use standard optimization techniques to obtain the MLEs (e.g., quasi-Newton methods, Nelder-Mead, ...)

Log Likelihood Surface with Optimization Trace



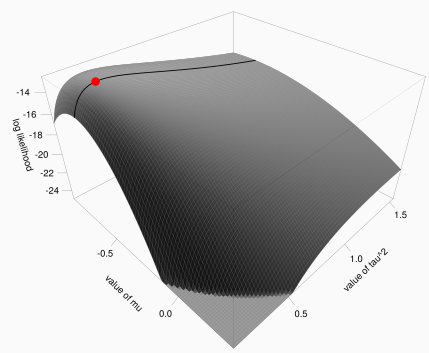
Profiled Log Likelihood

- given τ^2, the MLE of μ is $\hat{\mu}$ as defined above
- can reduce this to a one-dimension optimization problem
- profiled log likelihood function:

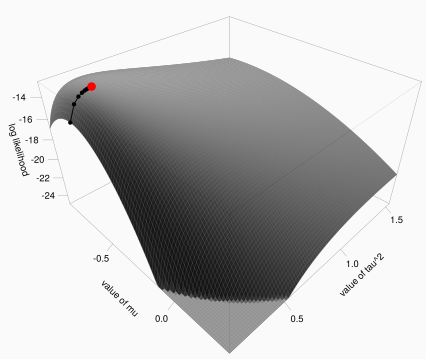
$$ll_P(\tau^2) = -\frac{1}{2}\sum_{i=1}^{k} \ln(\tau^2 + v_i) - \frac{1}{2}\sum_{i=1}^{k} \frac{(y_i - \hat{\mu})^2}{\tau^2 + v_i}$$

- now only need to optimize over τ^2

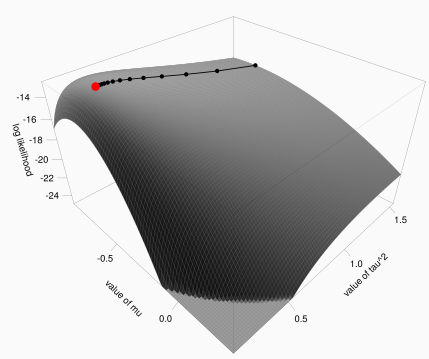
Profiled Log Likelihood



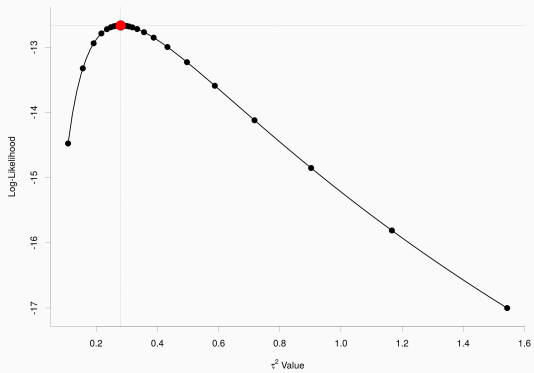
Profiled Log Likelihood with Optimization Trace



Profiled Log Likelihood with Optimization Trace



Profile of the Log Likelihood Function



Restricted Maximum Likelihood Estimation

- restricted log likelihood function (Viechtbauer, 2005):

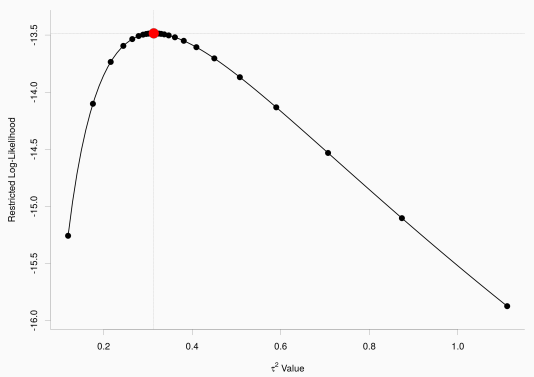
$$ll_R(\tau^2) = -\frac{1}{2}\sum_{i=1}^{k}\ln(\tau^2 + v_i) - \frac{1}{2}\ln\sum_{i=1}^{k}\frac{1}{\tau^2 + v_i} - \frac{1}{2}\sum_{i=1}^{k}\frac{(y_i - \hat{\mu})^2}{\tau^2 + v_i}$$

- REML estimator of τ^2:

$$\hat{\tau}^2 = \frac{\sum_{i=1}^{k} w_i^2\left((y_i - \hat{\mu})^2 - v_i\right)}{\sum_{i=1}^{k} w_i^2} + \frac{1}{\sum_{i=1}^{k} w_i}$$

  where $w_i = 1/(\tau^2 + v_i)$ and $\hat{\mu}$ as defined previously
- one-dimensional optimization problem

Profile of the Restricted Log Likelihood Function



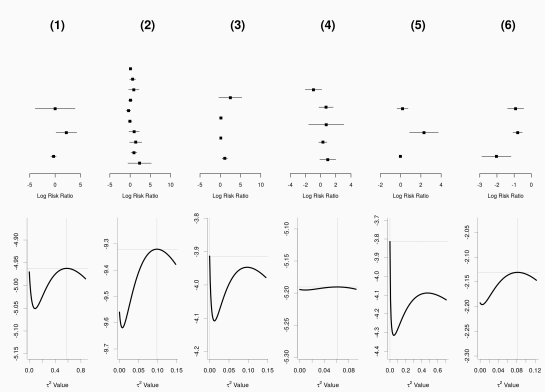
Can There Be Local Optima?

- checked for non-unimodality by profiling the (restricted) log likelihood function and searching for multiple peaks in 1991 meta-analyses from Cochrane Database of Systematic Reviews
- analyses conducted using odds/risk ratios and risk differences
- restricted to meta-analyses with at least three studies
- will focus here on results when using risk ratios as the outcome measure and when using ML estimation

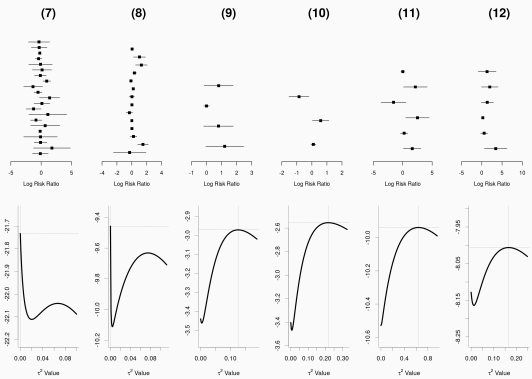
Results

- found 12 cases where the log likelihood function was bimodal
- one peak at $\hat{\tau}^2 = 0$ and another at $\hat{\tau}^2 > 0$
- either one of the two peaks could be the ML estimate of τ^2

Results



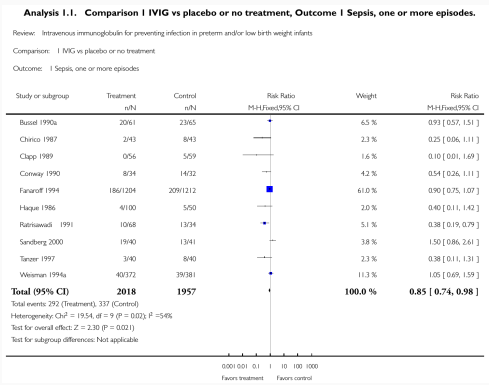
Results



Illustrative Case

- review on intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants (Ohlsson & Lacy, 2013)
- ten studies provided data on the occurrence of sepsis
- authors used the Mantel-Haenszel method for the meta-analysis

Illustrative Case: Cochrane Review Results



Analysis 1.1. Comparison 1 IVIG vs placebo or no treatment, Outcome 1 Sepsis, one or more episodes.

Review: Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants

Comparison: 1 IVIG vs placebo or no treatment

Outcome: 1 Sepsis, one or more episodes

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bussel 1990a	20/61	23/65		6.5 %	0.93 [0.57, 1.51]
Chirico 1987	2/43	8/43		2.3 %	0.25 [0.06, 1.11]
Clapp 1989	0/56	5/59		1.6 %	0.10 [0.01, 1.69]
Conway 1990	8/34	14/32		4.2 %	0.54 [0.26, 1.11]
Fanaroff 1994	186/1204	209/1212		61.0 %	0.90 [0.75, 1.07]
Haque 1986	4/100	5/50		2.0 %	0.40 [0.11, 1.42]
Ratrisawadi 1991	10/68	13/34		5.1 %	0.38 [0.19, 0.79]
Sandberg 2000	19/40	13/41		3.8 %	1.50 [0.86, 2.61]
Tanzer 1997	3/40	8/40		2.3 %	0.38 [0.11, 1.31]
Weisman 1994a	40/372	39/381		11.3 %	1.05 [0.69, 1.59]
Total (95% CI)	**2018**	**1957**		**100.0 %**	**0.85 [0.74, 0.98]**

Total events: 292 (Treatment), 337 (Control)
Heterogeneity: $Chi^2 = 19.54$, df = 9 (P = 0.02); $I^2 = 54\%$
Test for overall effect: Z = 2.30 (P = 0.021)
Test for subgroup differences: Not applicable

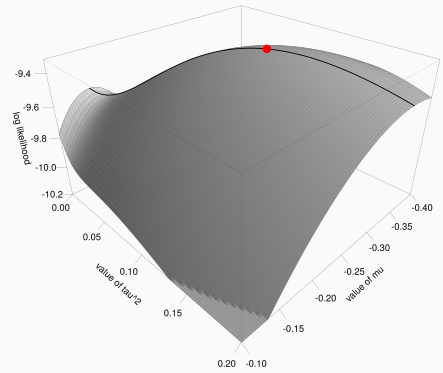
Illustrative Case: Mantel-Haenszel Method

```
Fixed-Effects Model (k = 10)

I^2 (total heterogeneity / total variability):  53.95%
H^2 (total variability / sampling variability): 2.17

Test for Heterogeneity:
Q(df = 9) = 19.54, p-val = 0.02

Model Results (log scale):

estimate    se   zval  pval  ci.lb  ci.ub
   -0.17  0.07  -2.30  0.02  -0.31  -0.02

Model Results (RR scale):

estimate  ci.lb  ci.ub
    0.85   0.74   0.98
```

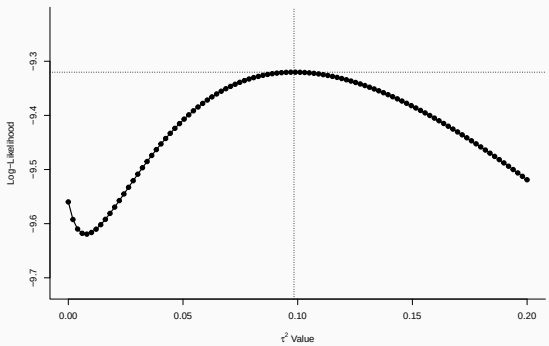

Illustrative Case: Random-Effects Model ($\hat{\tau}^2 = 0$)

```
Random-Effects Model (k = 10; tau^2 estimator: ML)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.01)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 9) = 19.47, p-val = 0.02

Model Results:

estimate    se   zval  pval  ci.lb  ci.ub
   -0.15  0.07  -2.02  0.04  -0.29  -0.00


 pred ci.lb ci.ub cr.lb cr.ub
 0.86  0.75  1.00  0.75  1.00
```


Illustrative Case: Log Likelihood Surface



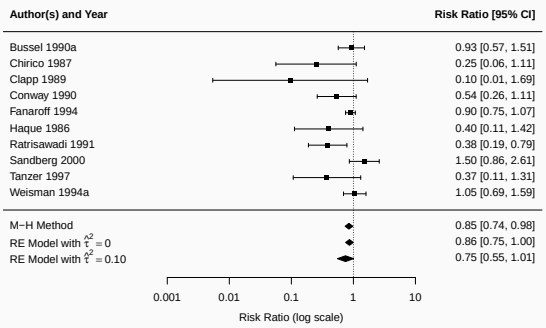
Illustrative Case: Profiled Log Likelihood



Illustrative Case: Random-Effects Model ($\hat{\tau}^2 = 0.10$)

```
Random-Effects Model (k = 10; tau^2 estimator: ML)

tau^2 (estimated amount of total heterogeneity): 0.10 (SE = 0.09)
tau (square root of estimated tau^2 value):      0.31
I^2 (total heterogeneity / total variability):   55.08%
H^2 (total variability / sampling variability):  2.23

Test for Heterogeneity:
Q(df = 9) = 19.47, p-val = 0.02

Model Results:

estimate    se   zval  pval  ci.lb  ci.ub
   -0.29  0.15  -1.91  0.06  -0.59   0.01


 pred ci.lb ci.ub cr.lb cr.ub
 0.75  0.55  1.01  0.38  1.48
```


Illustrative Case: Forest Plot



Conclusions

- local maxima in likelihood function can occur for various types of models (e.g., Henn & Hodges, 2014; Hoeschele, 1989)
- this can also happen in the meta-analytic random-effects model (for both ML and REML estimation)
- estimates obtained using iterative algorithms may then not reflect the true ML/REML estimates, which can lead to over- or underestimation of the amount of heterogeneity
- is it time to **panic**? probably not ...
- still good to check for this (construct a profile likelihood plot!)
- or fit the model with a low and a high starting value for $\hat{\tau}^2$
- can this also happen in other meta-analytic models? **yes!**

Acknowledgments

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