Meta-Analysis of Diagnostic Studies by Means of (S)ROC-Modelling – a Profile-likelihood Approach based upon the Lehmann-family

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Often studies are done in medicine or psychology to determine:

discriminatory ability of a diagnostic test to separate people

- **with** a specific disease (or condition)
- from those **without**

Measures of Diagnostic Accuracy

- **Specificity**: $P(T-|D-) = 1-u$
  Probability of a negative test result for a healthy person
- **Sensitivity**: $P(T+|D+) = p$
  Probability of a positive test result for a diseased person

Estimating Diagnostic Accuracy

- **Specificity**: $P(\widehat{T-|D}-) = 1 - \hat{u} = \frac{n-x}{n}$
  where x are the number of false-positives out of n healthy individuals, $n - x$ are the true-negatives

- **Sensitivity**: $P(\widehat{T+|D}+) = \hat{p} = \frac{y}{m}$
  where y are the number of true-positives out of m healthy individuals, $y - m$ are the false-negatives

Frequently available:

- a variety of diagnostic studies
- providing diagnostic measures

$$x_i, n_i \text{ (specificity)}$$

$$y_i, m_i \text{ (sensitivity)}$$

- for $i = 1, \ldots, k$
- leading to the field of **meta-analysis**

An Example: Meta-Analysis of Diagnostic Accuracy of Natriuretic Peptides for Heart Failure

- diagnosis of heart failure is difficult
- overdiagnosis and underdiagnosis is occurring
- natriuretic peptides have been proposed as a diagnostic test
- meta-analysis provided by Doust *et al.* (2004) for brain natriuretic peptide (BNP)
- restriction on studies that use left ventricular ejection fraction of 40% or less as gold standard

Data of Meta-Analysis on Diagnostic Accuracy of BNP for Heart Failure

	diseased		healthy		
study	y(TP)	$m-y$(FN)	$n-x$(TN)	x(FP)	$n+m$
Bettenc. 2000	29	7	46	19	101
Choy 1994	34	6	22	13	75
Valli 2001	49	9	78	17	153
Vasan 2002a	4	6	1612	85	1707
Vasan 2002b	20	40	1339	71	1470
Hutcheon 2002	29	2	102	166	299
Landray 2000	26	14	75	11	126
Smith 2000	11	1	93	50	155

The Cut-off Value Problem

- Why not proceed with the **available armada of meta-analysis methods**?
- continuous or ordered categorical test uses **cut-off value**
- sensitivities and specificities from different studies **not comparable**
- different values for sensitivity and specificity might be due to different **diagnostic accuracy** or **different cut-off value**
- cut-off problem introduces **bias of unknown direction and size**

Illustration of the cut-off value problem for a **single study**:

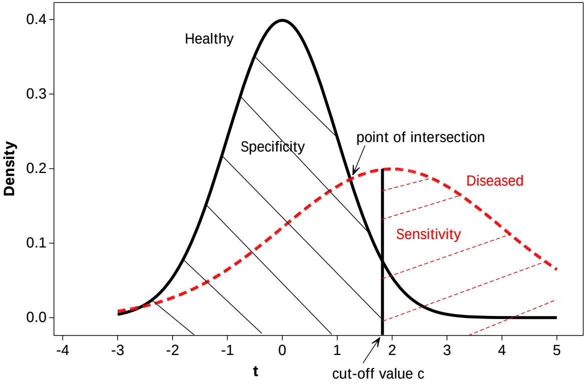

Healthy
Specificity
point of intersection
Diseased
Sensitivity
Density
t
cut-off value c
0.4
0.3
0.2
0.1
0.0
-4
-3
-2
-1
0
1
2
3
4
5

Illustration for a single study on Depression

- Lotrakul *et al.* (2008) seek to determine the diagnostic accuracy for the Thai version of the **Patient Health Questionnaire (PHQ-9)**
- a screening tool for major depression in primary care patients
- sensitivity and specificity were estimated in a diagnostic study involving 279 patients for different cut-off values
- Mini International Neuropsychiatric Interview and the Hamilton Rating Scale for Depressions were used as **gold standards**
- Lotrakul *et al.* (2008) consider different cut-off values and determine associated sensitivities and specificities

Illustration for a single study

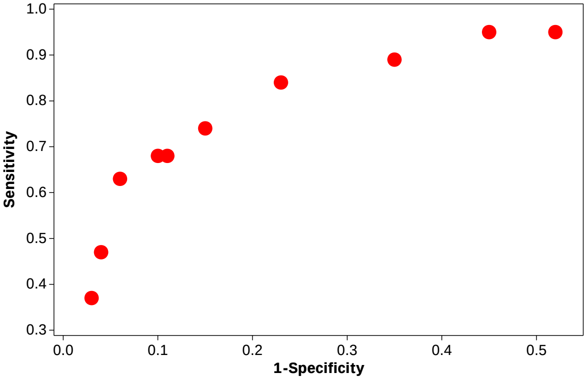
Table: *Performance of various PHQ-9 cut-off scores in detecting major depression (following Lotrakul* et al. *2008)*

Cut-off	Sensitivity	Specificity
6	0.95	0.48
7	0.95	0.55
8	0.89	0.65
9	0.84	0.77
10	0.74	0.85
11	0.68	0.89
12	0.68	0.90
13	0.63	0.94
14	0.47	0.96
15	0.37	0.97

Coping with the cut-off value problem for a single study: The ROC-curve

- let $\hat{p}_i$ and $\hat{u}_i$ be the different values of sensitivity and 1-specificity according to different cut-off values c_i, $i = 1, ..., k$
- construct a diagram with pairs $(\hat{p}_i, \hat{u}_i)$
- called the **Receiver Operating Characteristic (ROC)**
- benefit: **incorporates** the different values of the cut-off

Illustration of the cut-off value problem for a **single study**:


Sensitivity
1-Specificity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
0.1
0.2
0.3
0.4
0.5

The SROC-diagram for meta-analytic situations

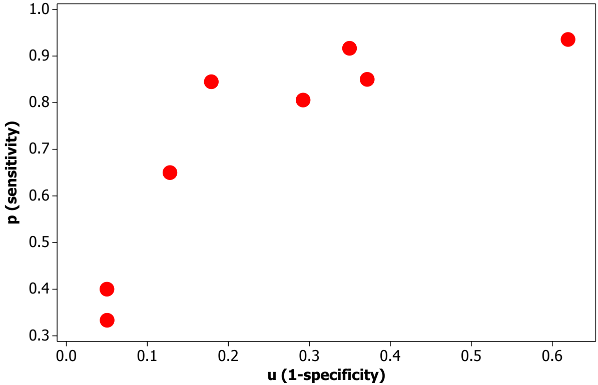
- Consider the pairs (sensitivity, 1-specificity) estimated by

$$(\hat{p}_i, \hat{u}_i) = (y_i/m_i, x_i/n_i)$$

  for $i = 1, ..., k$

- include them in a ROC diagram
- it is called **summary** ROC because the points relate to **different studies** instead of **different cut-off values**

SROC-diagram for MA of BNP and Heart Failure



Modelling of the SROC-diagram

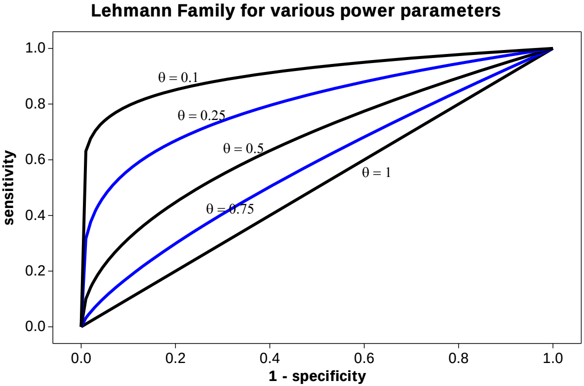
- Consider the **Lehmann family** for $\theta > 0$ and $i = 1, ..., k$ (Le 2006):

$$p_i = u_i^\theta$$

- or as a simple slope-only model

$$\log p_i = \theta \log u_i$$

- note model has **one parameter of interest** θ and k **nuisance parameters** $u_1, ..., u_k$
- note that θ represents the **diagnostic power** whereas the nuisance parameter captures heterogeneity in the specificities


Lehmann Family for various power parameters
θ = 0.1
θ = 0.25
θ = 0.5
θ = 0.75
θ = 1
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0

Inference

- consider the product-binomial likelihood as the joint distribution of Y_i and X_i for the $i-$th study (index is suppressed for notational convenience)

$$\binom{m}{y} p^y (1-p)^{m-y} \times \binom{n}{x} u^x (1-u)^{n-x}$$

- which we replace by the normal approximation for $\log Y_i$ and $\log X_i$

$$\frac{1}{\sqrt{2\pi s^2}} \exp\{-\frac{1}{2}\frac{(\log y - \log(mp))^2}{s^2}$$

$$\times \frac{1}{\sqrt{2\pi t^2}} \exp\{-\frac{1}{2}\frac{(\log x - \log(nu))^2}{t^2}$$

Inference

- the normal approximation for $\log Y_i$ and $\log X_i$

$$\frac{1}{2\pi st}\exp\{-\frac{1}{2}\frac{(\log y-\log(mp))^2}{s^2}\}\times\exp\{-\frac{1}{2}\frac{(\log x-\log(nu))^2}{t^2}\}$$

- with the Taylor-series variance estimates
  $s^2=\frac{1}{y}-\frac{1}{m}$ and $t^2=\frac{1}{x}-\frac{1}{n}$
- the normal approximation is justified if **the sizes per study are not small** and matches well with the Lehmann family
- consider now the log-likelihood for study i

$$-\frac{1}{2}\frac{(\log y-\log(mp))^2}{s^2}-\frac{1}{2}\frac{(\log x-\log(nu))^2}{t^2}$$

Inference

- and further with setting brackets differently

$$-\frac{1}{2s^2}(\log y - \log m - \log p)^2 - \frac{1}{2t^2}(\log x - \log n - \log u)^2$$

$$= -\frac{1}{2s^2}(\underbrace{\log y - \log m}_{z} - \log p)^2 - \frac{1}{2t^2}(\underbrace{\log x - \log n}_{w} - \log u)^2$$

$$= -\frac{1}{2s^2}(z - \overbrace{\theta \log u}^{\log p})^2 - \frac{1}{2t^2}(w - \log u)^2$$

Inference

- leading to the log-likelihood

$$\ell(\theta, u') = -\frac{1}{2s^2}(z - \theta u')^2 - \frac{1}{2t^2}(w - u')^2$$

- maximizing $\ell(\theta, u')$ in u' for **fixed** θ leads to

$$\hat{u}'_\theta = \frac{\theta t^2 z + s^2 w}{t^2\theta^2 + s^2}$$

- plugging $\hat{u}'_\theta$ in provides the **profile log-likelihood**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2s^2}(z - \theta\hat{u}'_\theta)^2 - \frac{1}{2t^2}(w - \hat{u}'_\theta)^2$$

Inference

- plugging $\hat{u}'_\theta$ in provides the **profile log-likelihood**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2s^2}(z - \theta\hat{u}'_\theta)^2 - \frac{1}{2t^2}(w - \hat{u}'_\theta)^2$$

  with $\hat{u}'_\theta = \frac{\theta t^2 z + s^2 w}{t^2\theta^2 + s^2}$

- ... **after some work** ... simplifies to

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2}\frac{(z - w\theta)^2}{t^2\theta^2 + s^2}$$

  a profile log-likelihood of **remarkable simplicity**

Why profile likelihood?

- eliminates nuisance parameter
- **two forms** of the model:

$$\log p = \theta \log u \ \textbf{or} \ \log u = \frac{1}{\theta} \log p$$

- it is invariant if u or p chosen to be the nuisance parameter

$$\ell(\theta, \hat{u}'_\theta) = \ell(\theta, \hat{p}'_\theta)$$

- suitable for **symmetric** regression problems

Profile or Adjusted Profile Likelihood?

- $\ell(\theta)$ is **almost Gaussian**

$$\ell(\theta) = \ell(\theta, \hat{u}'_\theta) = -\frac{1}{2} \frac{(z - w\theta)^2}{\underbrace{t^2\theta^2 + s^2}_{\sigma^2(\theta)}}$$

- it differs **only** from

$$L(\theta) = -\frac{1}{2} \log \sigma^2(\theta) - \frac{1}{2} \frac{(z - w\theta)^2}{\sigma^2(\theta)}$$

by $\log \sigma^2(\theta)$

Profile or Adjusted Profile Likelihood?

- disadvantage of profile likelihood: it is **not** a likelihood
- hence, first and second order properties not necessarily valid
- in particular, it is thought that the curvature of the profile likelihood is **not** correct to give a valid variance estimate
- since the profile likelihood takes the estimated nuisance parameter as a true parameter value it is thought of **underestimating the variance** of the parameter of interest

Profile or Adjusted Profile Likelihood?

- but **adjustment factor** $\hat{I}(\hat{u}_\theta)^{-1/2}$ available (Cox and Reed 1987; Lee, Nelder Pawitan 2006; Murphy and van der Vaart 2000)

$$\hat{I}(\hat{u}_\theta) = -\frac{\partial^2}{\partial u'^2}\ell(\theta, u') = \frac{\partial^2}{\partial u'^2}\left(\frac{1}{2s^2}(z-\theta\hat{u}')^2 + \frac{1}{2t^2}(w-\hat{u}')^2\right)$$

- where, for fixed θ, $\hat{I}(\hat{u}_\theta)$ is the **observed Fisher information** $\hat{I}(u)$ evaluated at $\hat{u}_\theta$

Profile or Adjusted Profile Likelihood?

- as can be seen directly from above

$$\hat{I}(\hat{u}_\theta) = \frac{\partial^2}{\partial u'^2}\left(\frac{1}{2s^2}(z-\theta\hat{u}')^2 + \frac{1}{2t^2}(w-\hat{u}')^2\right) = \frac{t^2\theta^2+s^2}{s^2t^2}$$

- so that

$$-\frac{1}{2}\log[\hat{I}(\theta)] + \ell(\theta) = L(\theta)$$

- providing an **excellent** justification of the adjusted profile likelihood

Full Sample Profile Likelihoods

for a sample of k studies

- we have the **full-sample profile** log-likelihood

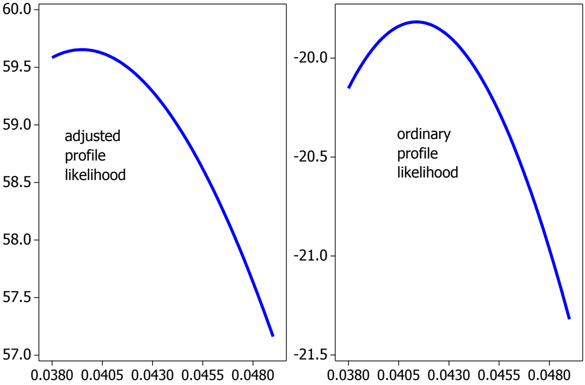
$$\ell(\theta) = -\sum_i \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

- and the **full-sample adjusted profile** log-likelihood

$$L(\theta) = -\sum_i \frac{1}{2} \log \sigma_i^2(\theta) - \sum_i \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

where $\sigma_i^2(\theta) = t_i^2\theta^2 + s_i^2$.

Ordinary and Adjusted Profile Likelihoods



Estimation: Maximum Profile Likelihood

- score for the ordinary profile likelihood

$$\frac{d}{d\theta}\ell(\theta) = -\frac{d}{d\theta}\sum_i \frac{1}{2}\frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

$$= \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} + \frac{1}{2}\frac{(z_i - w_i\theta)^2\sigma_i^2(\theta)'}{\sigma_i^4(\theta)}$$

- and the score for the adjusted profile likelihood

$$\frac{d}{d\theta}L(\theta) = \frac{d}{d\theta}\ell(\theta) - \frac{d}{d\theta}\sum_i \frac{1}{2}\log\sigma_i^2(\theta)$$

$$= \frac{d}{d\theta}\ell(\theta) - \frac{1}{2}\frac{\sigma_i^2(\theta)'}{\sigma_i^2(\theta)}$$

Estimating Equation Approach

- suggestion: fix θ in $\sigma_i^2(\theta)$ and maximize the Gaussian loss in θ:

$$-\sum_i \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

- or solve the estimating equation

$$\sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} = 0$$

- leading to the **iterative reweighted least-squares** approach:

$$\theta = \frac{\sum_i z_i w_i / \sigma_i^2(\theta)}{\sum_i w_i^2 / \sigma_i^2(\theta)}$$

Estimating Equation Approach

- neither ordinary nor adjusted profile likelihood is equivalent to IWLS
- but ... the latter is close because:
- look at the score for the **adjusted profile likelihood**

$$= \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} + \frac{1}{2}\frac{\overbrace{(z_i - w_i\theta)^2}^{\sigma_i^2(\theta)}\sigma_i^2(\theta)'}{\sigma_i^4(\theta)} - \frac{1}{2}\frac{\sigma_i^2(\theta)'}{\sigma_i^2(\theta)}$$

$$\approx \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)}$$

- equals **estimating equation** approach

Simulation Study

- previous analysis suggests: profile and adjusted profile likelihood inference differs
- but how much? Look at **Bias and variance**!
- ... and
- how **valid** are the second derivate approximations of the true variances for both likelihoods

Fisher Information

- we developed before:

$$L(\theta) = \sum_i L_i(\theta) = -\sum_i \frac{1}{2} \log \sigma_i^2(\theta) - \sum_i \frac{1}{2} \frac{(z_i - w_i\theta)^2}{\sigma_i^2(\theta)}$$

-

$$\frac{d}{d\theta} L(\theta) = \sum_i \frac{d}{d\theta} L_i(\theta)$$

$$= \sum_i \frac{(z_i - w_i\theta)w_i}{\sigma_i^2(\theta)} + \frac{1}{2} \frac{(z_i - w_i\theta)^2 \sigma_i^2(\theta)'}{\sigma_i^4(\theta)} - \frac{1}{2} \frac{\sigma_i^2(\theta)'}{\sigma_i^2(\theta)}$$

- so that

$$\widehat{var(\hat{\theta})} = 1 / \sum_i \left(\frac{d}{d\theta} L_i(\hat{\theta}) \right)^2$$

Fisher Information

- Recall, if

$$U(\theta) = \frac{d}{d\theta} L(\theta) = \sum_i \frac{d}{d\theta} L_i(\theta) = \sum_i U_i(\theta)$$

- Fisher information

$$I(\theta) = E[U(\theta)^2] = \sum_i E[U_i(\theta)^2]$$

- which leads to the **plug-in estimate**

$$\hat{I}(\hat{\theta}) = \sum_i U_i(\hat{\theta})^2$$

Simulation Study: Design

for $i = 1, ..., k = 10$:

1. $u_i \sim U[0.05, .5]$
2. use model: $p_i = u_i^\theta$ for $\theta = 0.1, 0, 2, 0.3$
3. $n_i, m_i \sim Po(100)$ or $n_i, m_i \sim Po(10)$ (sparsity case)
4. $Y_i \sim Bin(p_i, m_i)$ and $X_i \sim Bin(u_i, n_i)$
5. determine various estimators of θ
6. replicate this process 1,000 times

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.1$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 100$			
IWLS	0.0961	0.0104	-
PMLE	0.0977	0.0104	0.0119
APMLE	0.0960	0.0101	0.0117
$E(n_i) = E(m_i) = 10$			
IWLS	0.0899	0.0291	-
PMLE	0.0981	0.0313	0.0561
APMLE	0.0812	0.0260	0.0468

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.2$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE}(\hat{\theta})$
$E(n_i) = E(m_i) = 100$			
IWLS	0.1959	0.0153	-
PMLE	0.1988	0.0153	0.0194
APMLE	0.1955	0.0151	0.0191
$E(n_i) = E(m_i) = 10$			
IWLS	0.1722	0.0499	-
PMLE	0.1917	0.0536	0.0838
APMLE	0.1597	0.0442	0.0654

Simulation Study: Results

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator*

estimator for $\theta = 0.3$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE}(\hat{\theta})$
$E(n_i) = E(m_i) = 100$			
IWLS	0.2953	0.0210	-
PMLE	0.3004	0.0211	0.0262
APMLE	0.2953	0.0208	0.0255
$E(n_i) = E(m_i) = 10$			
IWLS	0.2693	0.0694	-
PMLE	0.3011	0.0742	0.1137
APMLE	0.2517	0.0622	0.0869

Simulation Study: Results for small n but large k

Table: *Mean and Variance for Profile (PMLE), Adjust Profile (APMLE) and Iterative Weighted Least Squares (IWLS) Estimator* k*=100*

estimator for $\theta = 0.3$	$E(\hat{\theta})$	$SE(\hat{\theta})$	$\widehat{SE(\hat{\theta})}$
$E(n_i) = E(m_i) = 20$			
IWLS	0.2753	0.0153	-
PMLE	0.2970	0.0156	0.0189
APMLE	0.2718	0.0143	0.0164

Simulation Study: Conclusions

large n_i, m_i

- all three estimators behave similar
- minimal gain in efficiency with APMLE
- Fisher information estimate a bit conservative for variance estimation

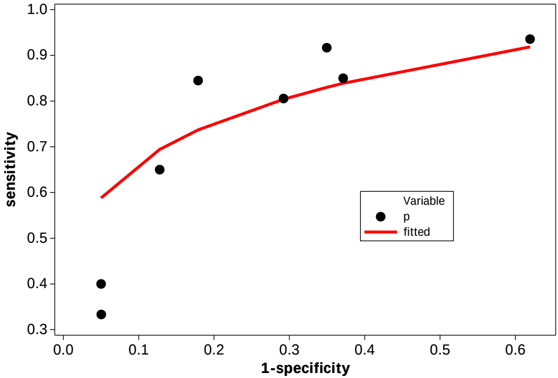
small n_i, m_i

- ordinary PMLE less biased
- APMLE more efficient
- Fisher information estimate overestimates variance of PMLE and APMLE

Application to BNP Meta-Analysis

- APMLE for $L(\theta)$ provides $\hat{\theta} = 0.1774$
- PMLE for $\ell(\theta)$ provides $\hat{\theta} = 0.1802$
- and IWLS gives $\hat{\theta} = 0.1755$

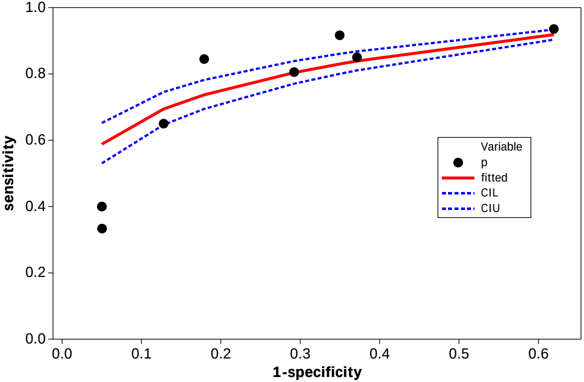
Observed and Fitted Lehmann Model



Fisher Information

- finally
$$\widehat{var(\hat{\theta})} = 1 / \sum_i \left(\frac{d}{d\theta} L_i(\hat{\theta}) \right)^2$$
- hence, 95% CI: $\hat{\theta} \pm 1.96 \sqrt{var(\hat{\theta})}$

Incorporating SE of Estimate



Goodness-of-Fit

- since $E(Z_i) = \theta \log u_i$ and $E(W_i) = \log u_i$
- it follows
$$E(Z_i - \theta W_i) = 0$$
- also $Var(Z_i) = s_i^2$ and $Var(\theta W_i) = \theta^2 t_i^2$
- hence
$$Var(Z_i - \theta W_i) = s_i^2 + \theta^2 t_i^2$$
- so that
$$\frac{Z_i - \theta W_i}{\sqrt{s_i^2 + \theta^2 t_i^2}} \sim N(0,1)$$

Goodness-of-Fit

χ^2- statistic

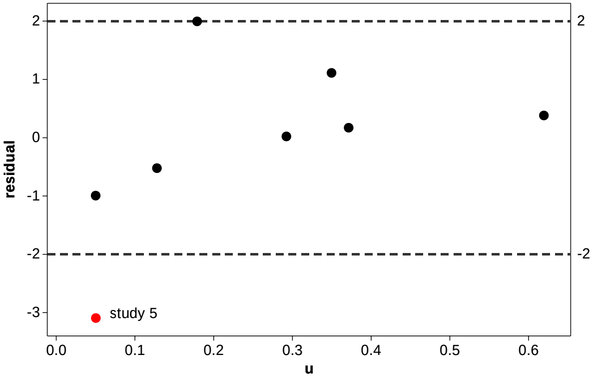
$$\chi^2_{k-1} = \sum_{i=1}^{k} \frac{(Z_i - \hat{\theta} W_i)^2}{s_i^2 + \hat{\theta}^2 t_i^2}$$

BNP meta-analysis

based upon **all** 8 studies: $\chi^2_7 = 16.23$ and $P = 0.0231$
based upon 7 Studies (without **study 5**): $\chi^2_6 = 6.66$ and $P = 0.4655$ since plot of residuals:

$$\frac{Z_i - \hat{\theta} W_i}{\sqrt{s_i^2 + \hat{\theta}^2 t_i^2}}$$

provides evidence that study 5 is source of heterogeneity


2
1
0
-1
-2
-3
residual
2
-2
study 5
0.0
0.1
0.2
0.3
0.4
0.5
0.6
u

Signposts on the Road Map

- mixed model approach to include residual heterogeneity as a further variance component
- nonparametric mixture approach to model unobserved heterogeneity
- classification of studies into different components of homogeneous diagnostic accuracy