Hands-on training session 6

Meta-analyses with imperfect reference test

Paolo Eusebi

2020-02-21

Introduction

Overview

Date/time:

- 20th February 2020
- 16.00 - 17.00

Teachers:

- Paolo Eusebi (presenter)
- Giles Innocent

Recap

- Important points from previous sessions

Session 6a: Meta-Analysis of Diagnostic Test Accuracy Studies: Perfect Reference Test

DTA-MA: perfect reference test

- There is an increasing interest in meta-analyzing data from diagnostic accuracy studies
- The data from the primary studies are summarized in a 2-by-2 cross-tabulation of the dichotomized test result against the true disease status (assuming we have a perfect reference test)

	D+	D-
T+	TP	FP
T-	FN	TN

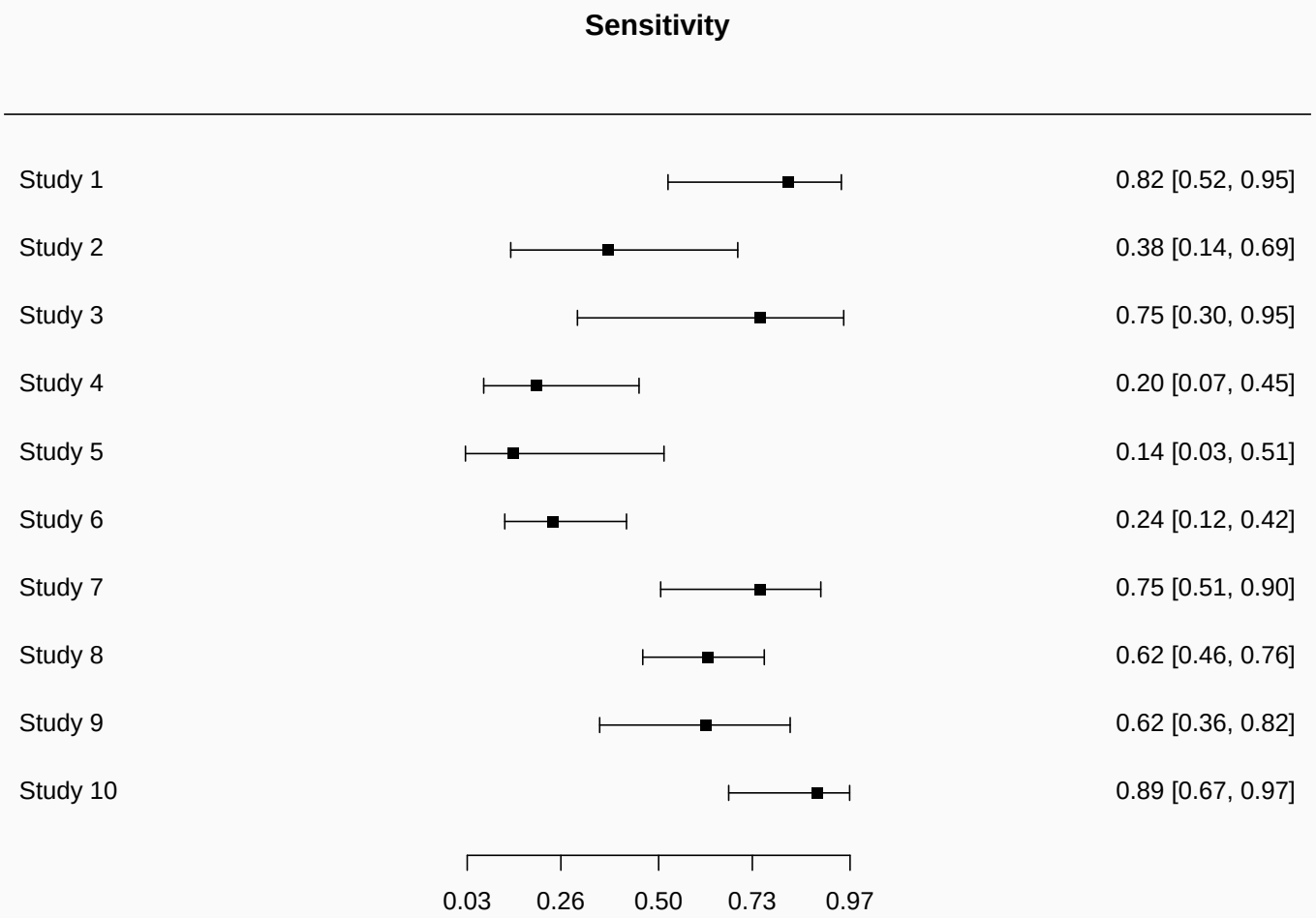
DTA-MA: perfect reference test

- Data on magnetic resonance (MR) imaging from 10 studies on evaluation of lymph node metastases in patients with cervical cancer (Scheidler et al 1997).

StudyID	TP	FP	FN	TN
Study 1	9	2	2	44
Study 2	3	6	5	32
Study 3	3	2	1	16
Study 4	3	1	12	44
Study 5	1	1	6	16
Study 6	7	2	22	167
Study 7	12	4	4	29
Study 8	23	5	14	230
Study 9	8	5	5	53
Study 10	16	2	2	22

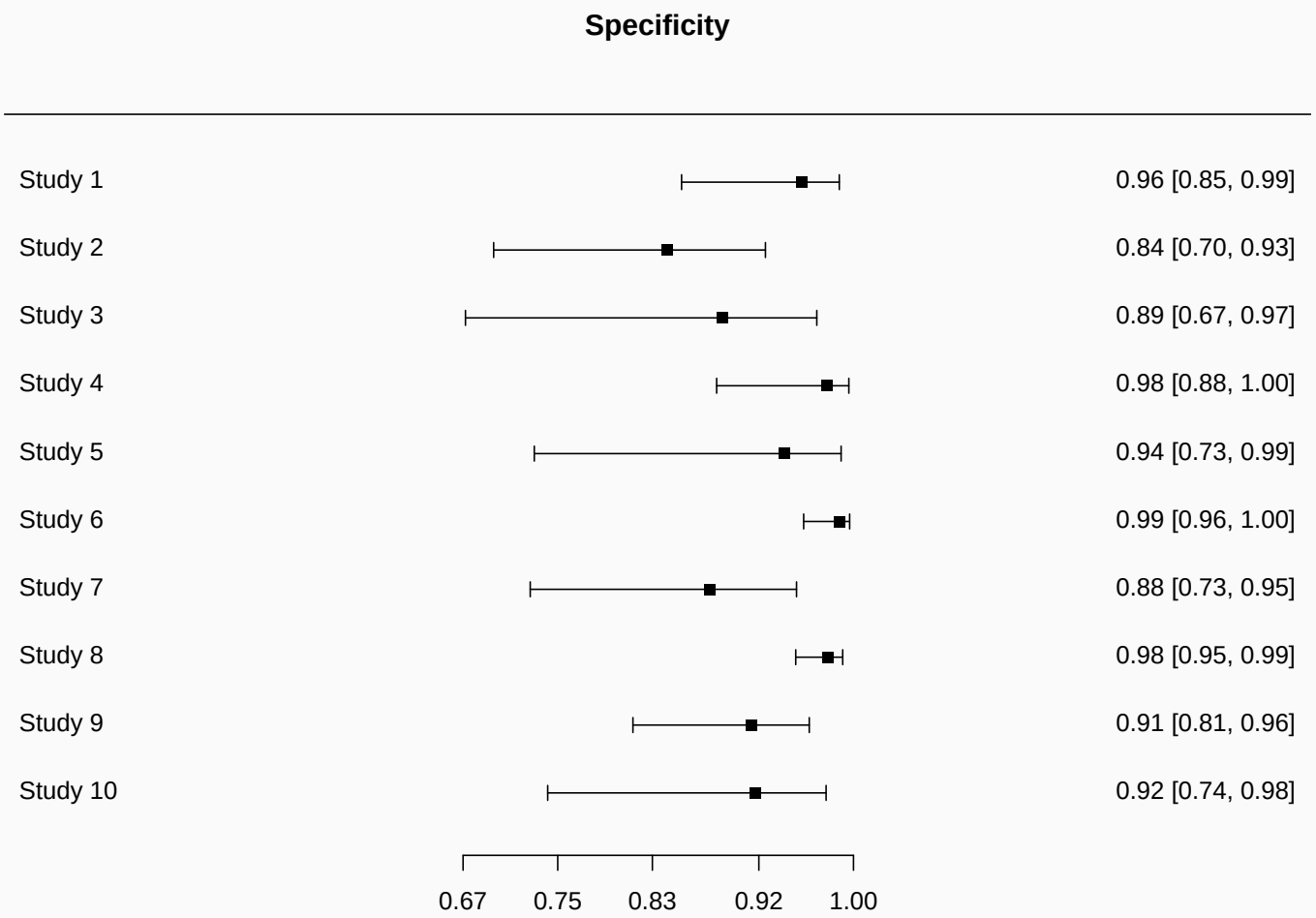
DTA-MA: perfect reference test

- Forest plot of sensitivity



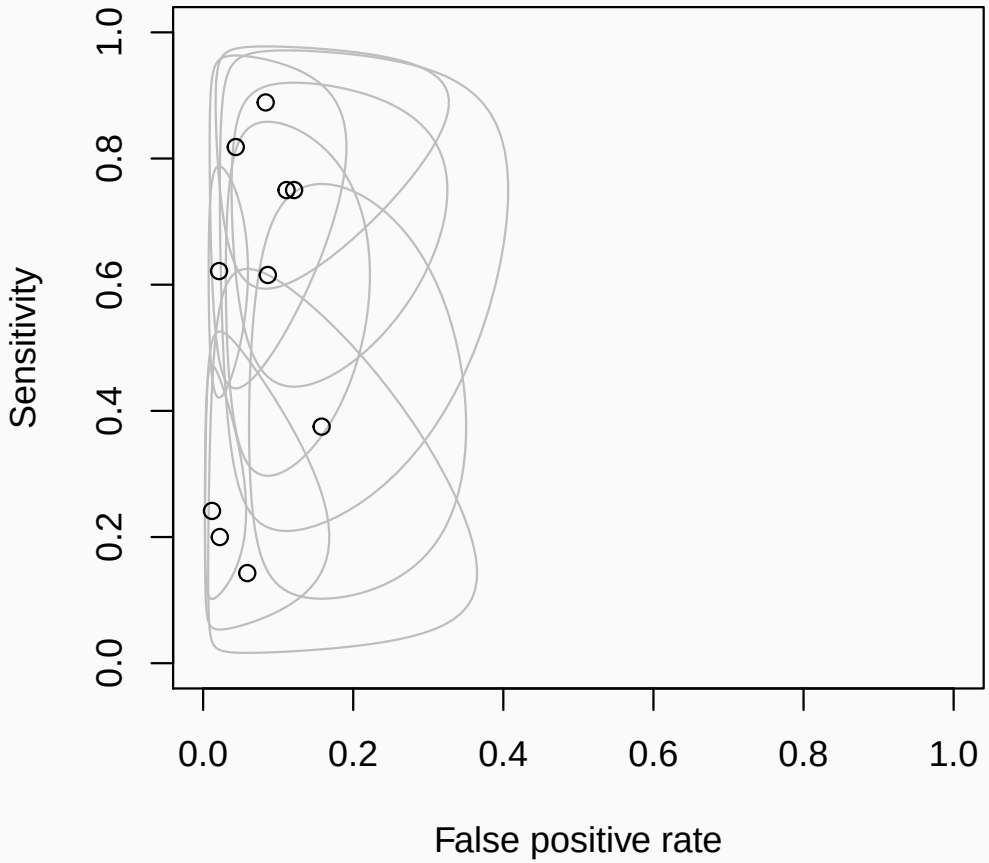
DTA-MA: perfect reference test

- Forest plot of specificity



DTA-MA: perfect reference test

- Data points with confidence ellipses on a ROC space



DTA-MA: perfect reference test

Two main frameworks:

- Hierarchical Summary ROC (Rutter and Gatsonis 2001)
- Bivariate analysis of sensitivity and specificity (Reitsma et al. 2005)

DTA-MA: bivariate analysis of sensitivity and specificity

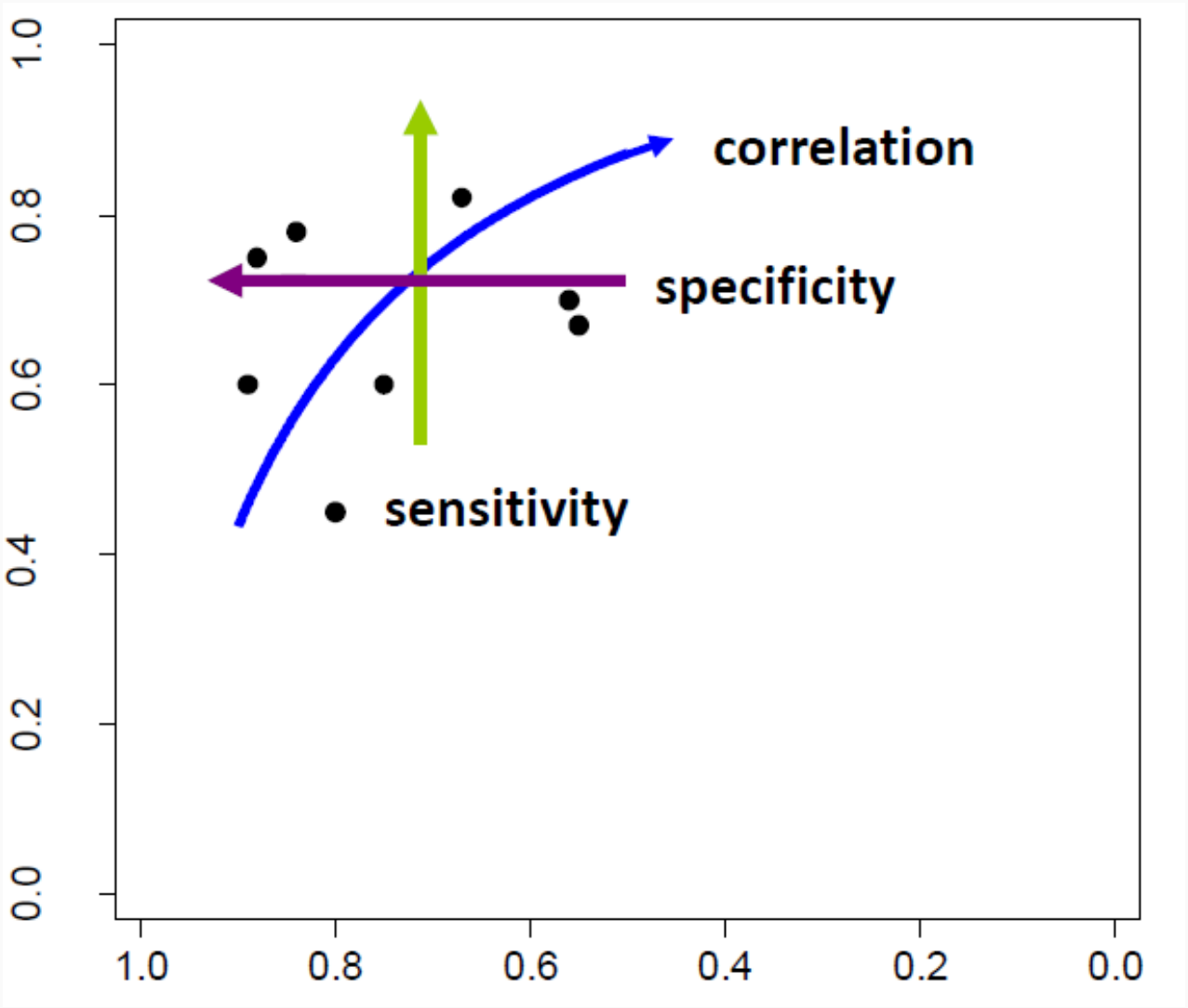


Figure 1: Alt text

DTA-MA: hierarchical summary ROC (HSROC)

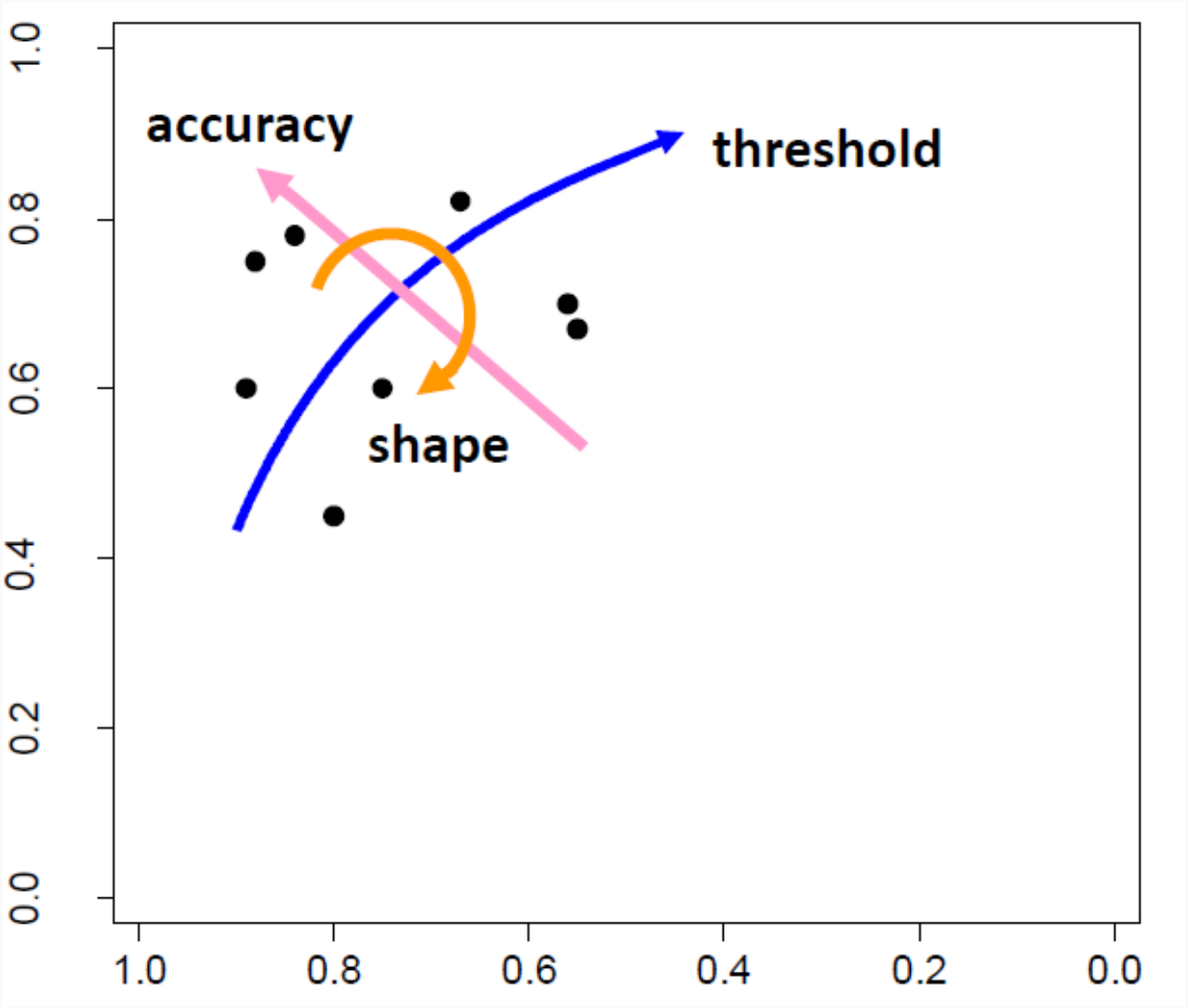


Figure 2: Alt text

DTA-MA: bivariate analysis of sensitivity and specificity

Some notation/definitions (no covariates)

$$(\mu_{A_i}\mu_{B_i}) \sim N((\mu_A\mu_B), \Sigma_{AB})$$

with

$$\Sigma_{AB} = \begin{pmatrix} \sigma_A^2 & \sigma_{AB}^2 \\ \sigma_{AB}^2 & \sigma_B^2 \end{pmatrix}$$

μ_{A_i} is the logit-transformed sensitivity in study i μ_{B_i} is the logit-transformed specificity in study i

DTA-MA: hierarchical summary ROC (HSROC)

Some notation/definitions (no covariates)

- level I (within study)

$$logit(\pi_{ij}) = (\theta_i + \alpha_i D_{ij}) \cdot exp(-\beta \cdot D_{ij})$$

- level II (between studies)

$$\theta_i \sim N(\Theta, \sigma_\theta^2)$$

$$\alpha_i \sim N(\Lambda, \sigma_\alpha^2)$$

θ_i are cutpoint parameters (or positivity criteria)

α_i are accuracy parameters

β is a shape parameter, allowing true-positive and false-positive fractions to increase at different rates as θ_i increases

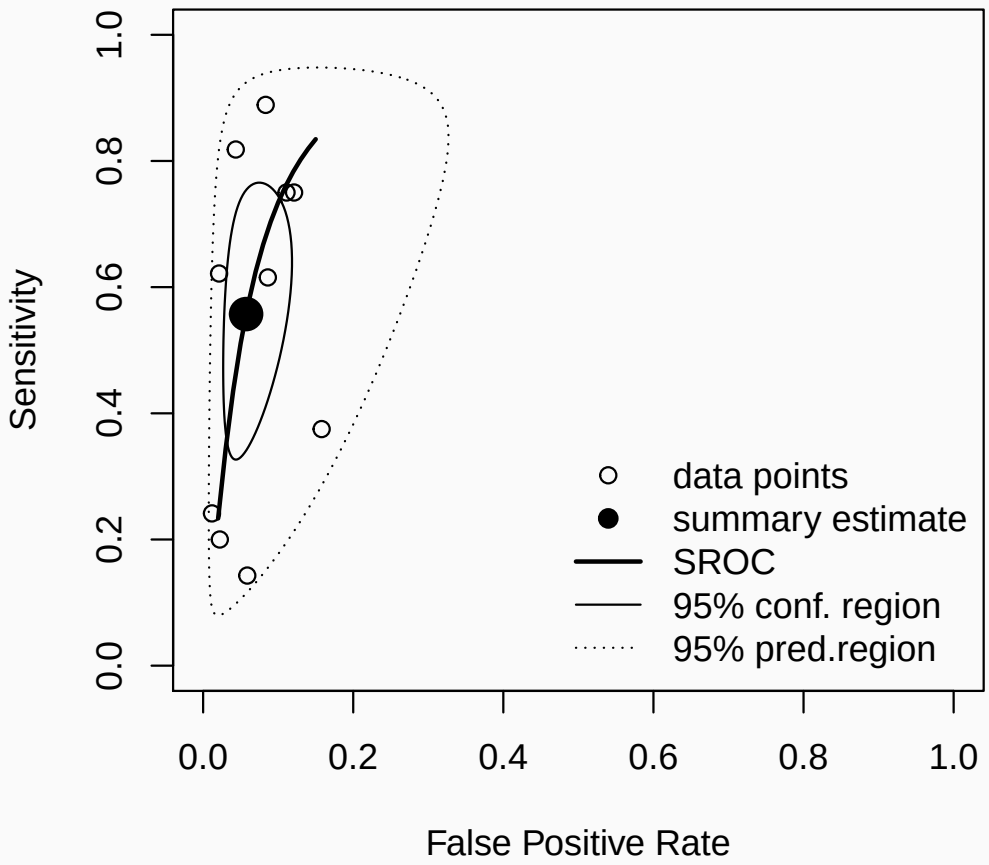
DTA-MA: bivariate analysis of sensitivity and specificity

Let's run the model with reitsma function (mada R package)

```r
fit.reitsma <- reitsma(MRI2)
print(summary(fit.reitsma), digits = 2)
```

```
## Call:  reitsma.default(data = MRI2)
##
## Bivariate diagnostic random-effects meta-analysis
## Estimation method: REML
##
## Fixed-effects coefficients
##                     Estimate Std. Error     z Pr(>|z|)
## tsens.(Intercept)       0.23       0.39  0.59     0.55
## tfpr.(Intercept)       -2.80       0.32 -8.64     0.00
## sensitivity             0.56          -     -        -
## false pos. rate         0.06          -     -        -
##                     95%ci.lb 95%ci.ub
## tsens.(Intercept)      -0.53     0.99
## tfpr.(Intercept)       -3.44    -2.17 ***
## sensitivity             0.37     0.73
```

DTA-MA: bivariate analysis of sensitivity and specificity



DTA-MA: bivariate analysis of sensitivity and specificity

- Where is the summary measure of heterogeneity?
- There is I^2 for DTA-MA?

DTA-MA: bivariate analysis of sensitivity and specificity

The function returns also HSROC parameters

```
print(summary(fit.reitsma)[20], digits = 2)
```

```
## $coef_hsroc
## $coef_hsroc$Theta
## [1] -1.5
##
## $coef_hsroc$Lambda
## [1] 3.4
##
## $coef_hsroc$beta
## [1] -0.26
##
## $coef_hsroc$sigma2theta
## [1] 0.62
##
## $coef_hsroc$sigma2alpha
## [1] 0.72
```

DTA-MA: bivariate analysis of sensitivity and specificity

This is because Bivariate and HSROC approaches are equivalent when covariates are not included (Harbord et al. 2007)

- Parameter estimates from either model can be used to produce a summary operating point, an SROC curve, confidence regions, or prediction regions.
- The choice between these parameterizations depends partly on the degrees of and reasons for between-study heterogeneity and the treshold effect.

DTA-MA: hierarchical summary ROC (HSROC)

Use of HSROC package

```
HSROC(data = MRI,
      iter.num = 5000,
      init = init)

HSROCSummary(data = MRI,
             burn_in = 1000,
             print_plot = T)
```

DTA-MA: hierarchical summary ROC (HSROC)

- The HSROC package allows to run multiple chains
- A single call to the function HSROCSummary will summarize all chains (3 in our example)

```
HSROC(data = MRI,
      iter.num = 5000,
      init = init,
      chain = dir.chain1)

HSROCSummary(data = MRI,
             burn_in = 1000,
             print_plot = T,
             chain = list(dir.chain1, dir.chain2, dir.chain3))
```

DTA-MA: imperfect reference test(s)

Why?

- Ignoring the imperfect nature of the reference may result in biased estimates of pooled sensitivity and specificity of the test under evaluation

DTA-MA: imperfect reference test(s)

How?

- Multivariate generalized linear mixed model (MGLMM)
- Hierarchical summary receiver operating characteristic (HSROC)
- Exact relations between the parameters of these models can be provided.
- But some submodels of the MGLMM do not have corresponding equivalent submodels of the HSROC model, and vice versa.

DTA-MA: HSROC for imperfect reference test(s)

Dendukuri et al. Biometrics. 2012

- The data from the primary studies are summarized in a 2-by-2 cross-tabulation of the index test (T_1) result against the imperfect refernce (T_2)

	T2+	T2-
T1+	TP	FP
T1-	FN	TN

The sensitivity and the specificity of the reference test are defined as:

- $S_2 = P(T_2 = +|D+)$
- $C_2 = P(T_2 = -|D-)$

DTA-MA: discussion

- Comments?
- Questions?
- Ideas?

DTA-MA: hierarchical summary ROC (HSROC)

Let's do it with rjags

Exercise

Use Timsit paper data (Prev Vet Med 2016)

StudyID	TP	FP	FN	TN
Gardner	49	53	38	64
Buhman	37	1	90	18
Thompson	265	196	606	969
Schneider	121	42	910	592
Leach	195	60	1395	373
Tennant	157	29	1344	806
Rezac	127	157	4591	8316

1. Fit a bivariate model assuming perfect reference with reitsma() in mada
2. Fit a HSROC model assuming imperfect reference with HSROC() in HSROC
3. Fit a HSROC model assuming imperfect reference with model definitions in rjags