

Diagnostic meta-analysis

Paolo Eusebi

16/09/2021

Recap

- Important points from previous sessions

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

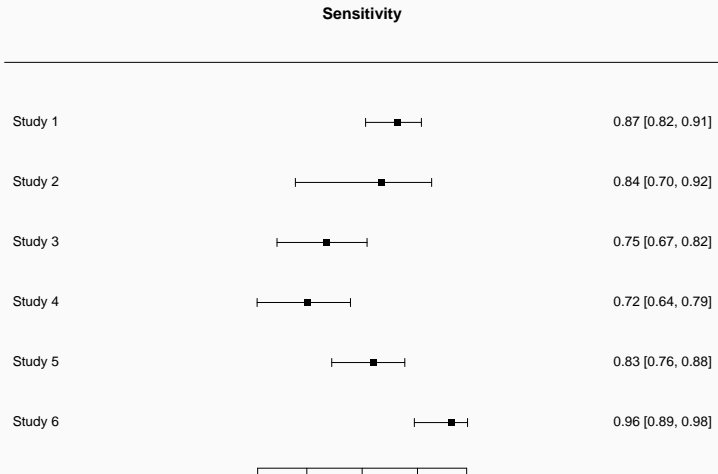
- Serological tests for covid-19 from 5 studies (but 6 observations) on evaluation of ELISA assay for covid-19 (Bastos et al 2020).

Study	TP	FN	TN	FP
Liu W	186	28	100	0
Adams	34	6	50	0
Whitman [commercial]	98	32	140	20
Whitman [in-house]	94	36	152	8
Liu L	127	26	116	4
Freeman	95	4	515	4

DTA-MA: perfect reference test

- Forest plot of sensitivity

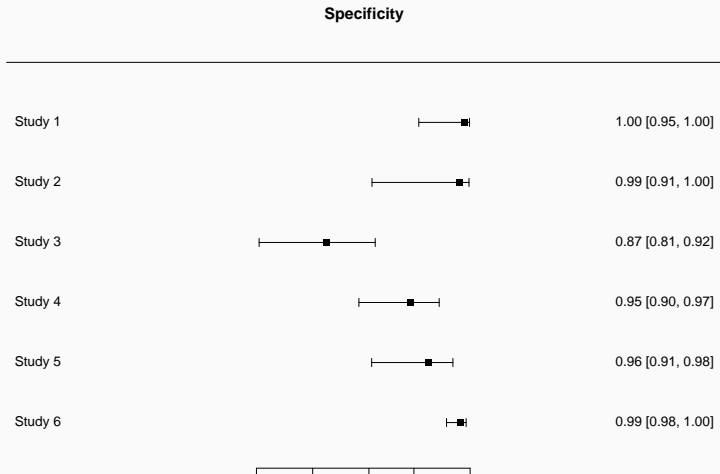
`## Warning: Unknown or uninitialised column: 'names'.`



DTA-MA: perfect reference test

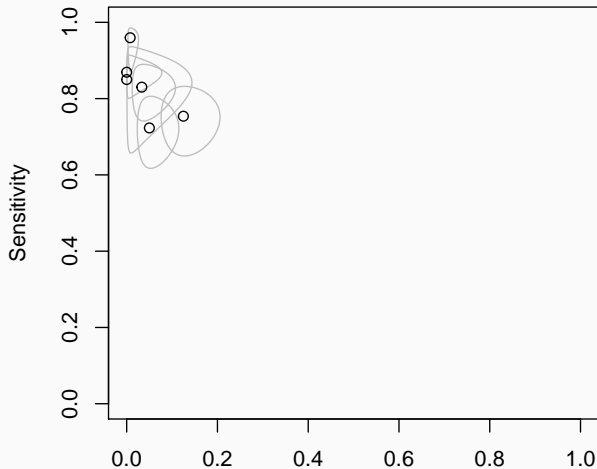
- Forest plot of specificity

Warning: Unknown or uninitialised column: 'names'.



DTA-MA: perfect reference test

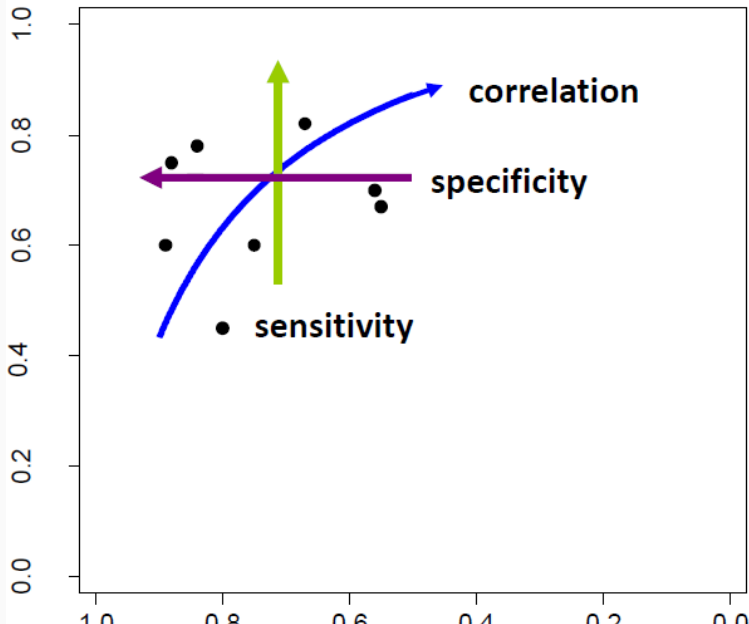
- Data points with confidence ellipses on a ROC space



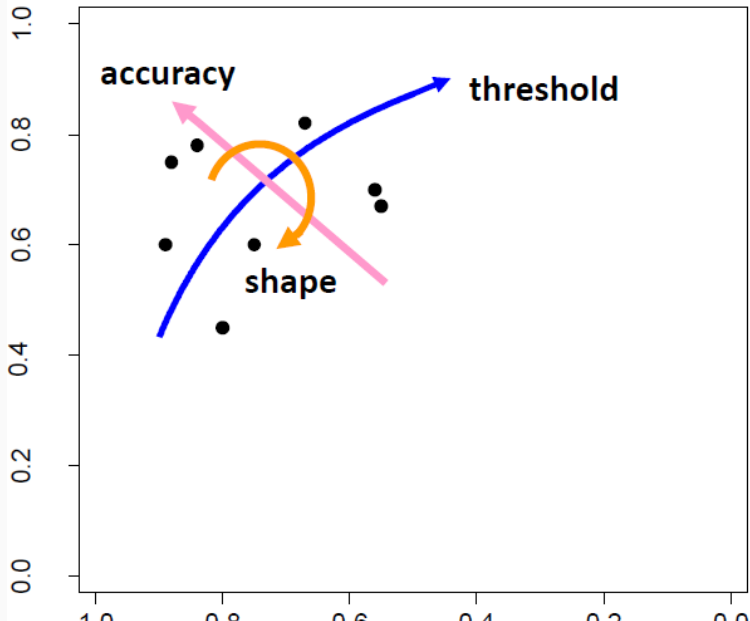
Two main frameworks:

- 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



DTA-MA: hierarchical summary ROC (HSROC)



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)

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

- 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

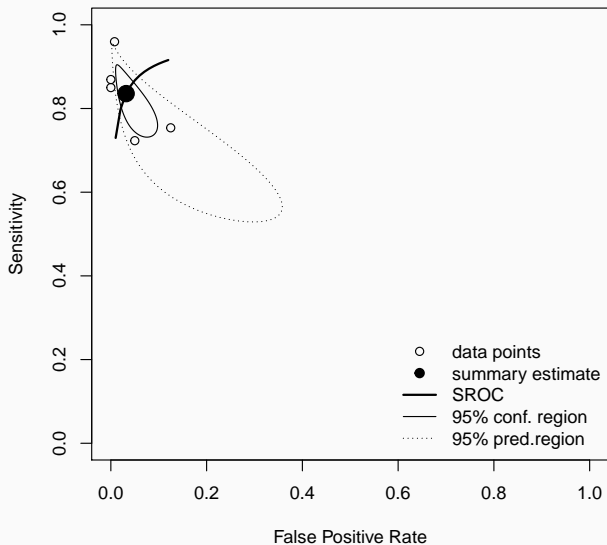
Let's run the model with reitsma function (mada R package)

```
fit.reitsma <- reitsma(d)
```

DTA-MA: bivariate analysis of sensitivity and specificity

##	Estimate	95%ci.lb	95%ci.ub
## tsens.(Intercept)	1.63	1.13	2.13
## tfpr.(Intercept)	-3.41	-4.37	-2.46
## sensitivity	0.84	0.76	0.89
## false pos. rate	0.03	0.01	0.08

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

```
## $coef_hsroc
## $coef_hsroc$Theta
## [1] -0.14
##
## $coef_hsroc$Lambda
## [1] 4.7
##
## $coef_hsroc$beta
## [1] 0.62
##
## $coef_hsroc$sigma2theta
## [1] 0.02
##
## $coef_hsroc$sigma2alpha
```

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 threshold 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)
```

Imperfect Reference Test

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 reference (T_2)

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

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

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

- 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`