META ANALYSIS OF DTA STUDIES USING BAYESIAN LATENT CLASS MODELS

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OUTLINE

- What is a meta-analysis of diagnostic accuracy studies
- Current methods-OVERVIEW
- Bayesian LATENT: BIVARIATE and HSROC
- Model definition of HSROC
- Example-Campylobacter

-problem definition

-Model

-Results/discussion

- Conclusions-recommendations

WHAT IS A META-ANALYSIS OF DTA STUDIES

- Studies that evaluate the accuracy of a diagnostic test
- Results of a diagnostic test study as a 2X2 table
- Sensitivity SE
- Specificity SP

	Disease +	Disease -
Test +	TP (SE=$\mathbb{P}(T = 1 \mid D = 1)$)	FP (1-SP)
Test -	FN (1-SE)	TN (SP=$\mathbb{P}(T=0 \mid D = 0)$

- statistical pooling of the results of primary studies to derive summary estimates of sensitivity and specificity from several separately performed test studies.
- summary points->summary SE, SP, DOR, or summary ROC curve
- SE and SP are often negatively correlated, so problematic pooling separate estimates

METHODS-OVERVIEW

- Bivariate analysis of sensitivity and specificity (Reitsma et al.2005)

pairs of sensitivity and specificity are jointly analysed

correlation btw Se and Sp -> random effects

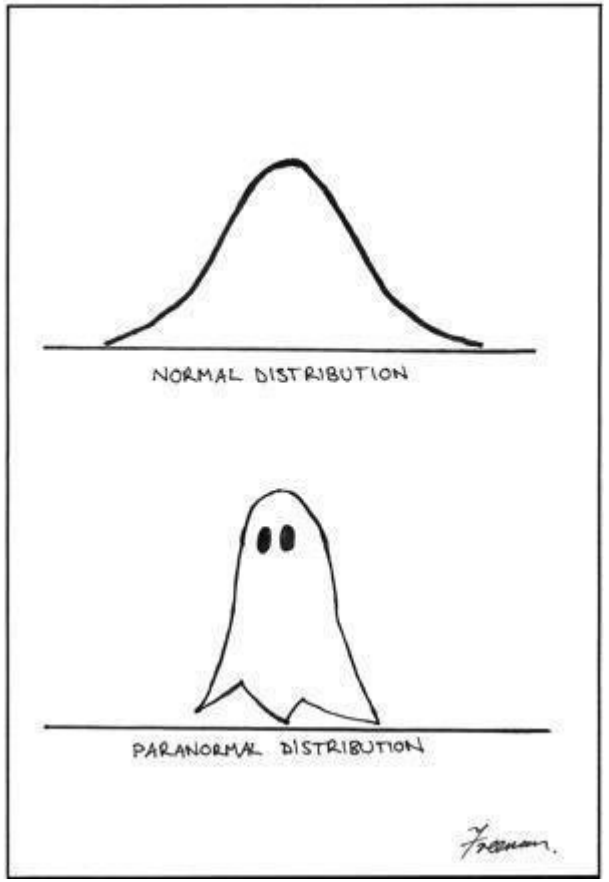
Upgrades of the bivariate: binomial exact (Chu and Cole 2006), beta-binomial (Chen et al. 2011 and Kuss et al. 2014)

- Split component synthesis(SCS)(Doi et al. 2015, Furuya-Kanamori et al. 2020)

Distribution free model

Estimation of the DOR and then split into its components

Threshold resistant



BAYESIAN LATENT CLASS

- Bivariate hierarchical latent class with or without a reference standard:

Correlation matrix

Shiny app

- Hierarchical summary ROC (HSROC) latent class with or without a reference standard:

Hierarchical Summary ROC (Rutter and Gatsonis 2001)

Dendukuri N. et al 2012

Accounts for threshold differences

HSROC-MODEL DEFINITION

- level I (within study)

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

- level II (between studies)

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

$$TP = \text{logit}^{-1}[(\Theta + \Lambda/2)e^{-\beta/2}]$$
$$FP = \text{logit}^{-1}[(\Theta - \Lambda/2)e^{\beta/2}]$$

- Level III (prior specifications)
- 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 θi increases

MODEL DEFINITION

	T_2 +	T_2 -
T_1 +	TP	FP
T_1 -	FN	TN

- Let D denote the latent disease status. The multinomial probabilities can be expressed as

$$p_{ij} = P(T_1, T_2) = P(T_1, T_2 \mid \mathrm{D}+)\ \mathrm{P}(\mathrm{D}+) + P(T_1, T_2 | D-)P(D-)$$

$$\boldsymbol{P(T_1 = 1, T_2 = 1)} = P(T_1 = 1, T_2 = 1|\mathrm{D}+)\ \mathrm{P}(\mathrm{D}+) + \mathrm{P}(T_1 = 1, T_2 = 1|\mathrm{D}-)\ \mathrm{P}(\mathrm{D}-)$$

$$= P(T_1 = 1|\mathrm{D}+)P(T_2 = 1|\mathrm{D}+)\mathrm{P}(\mathrm{D}+) + P(T_1 = 1|\mathrm{D}-)P(T_2 = 1|\mathrm{D}-)\mathrm{P}(\mathrm{D}-)$$

$$= \boldsymbol{S_1 S_2 \pi + (1 - C_1)(1 - C_2)(1 - \pi)}$$

LATENT CLASS MODEL- WITHOUT A REFERENCE STANDARD

```
for(i in 1:l) {
cell[i,1:4] ~ dmulti(cell_prob[i,1:4],n[i])
# Positive_Index - Positive_reference
cell_prob[i,1] <- pi[i]*(  pp[i]    *  s2  ) + (1-pi[i])*(  pn[i]    * (1-c2))
# Positive_Index - Negative_reference
cell_prob[i,2] <- pi[i]*(  pp[i]    * (1-s2) ) + (1-pi[i])*(  pn[i]    *  c2)
 # Negative - Positive_reference
cell_prob[i,3] <- pi[i]*( (1-pp[i]) *  s2  ) + (1-pi[i])*( (1-pn[i]) * (1-c2))
# Negative_Index - Negative_reference
cell_prob[i,4] <- pi[i]*( (1-pp[i]) * (1-s2) ) + (1-pi[i])*( (1-pn[i]) *  c2)

se[i] <- pp[i]
sp[i] <- 1-pn[i]
```

LATENT CLASS MODEL- WITHOUT A REFERENCE STANDARD

HSROC

- Level I:

logit(pp[i]) <- (theta[i] + 0.5*alpha[i])/exp(beta/2)

logit(pn[i]) <- (theta[i] - 0.5*alpha[i])*exp(beta/2)

pp = True positive rate

pn = False positive rate= 1-SP

- Study level SE and Sp of index test:

se[i] <- pp[i]

sp[i] <- 1-pn[i]

- Level II-Hierarchical prior distributions

theta[i] ~ dnorm(THETA,tau[1])

alpha[i] ~ dnorm(LAMBDA,tau[2])

Pooled sensitivity and specificity

Pooled_S<-1/(1+exp((-THETA-0.5*LAMBDA)/exp(beta/2)))

Pooled_C<-1/(1+exp((THETA-0.5*LAMBDA)*exp(beta/2)))

Bivariate

- Level I:

logit(se[i]) <- I1[i,1]

logit(sp[i]) <- I1[i,2]

I1[i,1:2] ~ dmnorm(mu[,], T[,])

- Level II- Hierarchical prior distributions

mu[1] ~ dnorm(0,0.25)

mu[2] ~ dnorm(0,0.25)

- BETWEEN-STUDY VARIANCE-COVARIANCE MATRIX

TAU[1,1] <- tau[1]*tau[1]

TAU[2,2] <- tau[2]*tau[2]

TAU[1,2] <- rho*tau[1]*tau[2]

TAU[2,1] <- rho*tau[1]*tau[2]

Pooled sensitivity and specificity

Pooled_S<-1/(1+exp(-mu[1]))

Pooled_C<-1/(1+exp(mu[2]))

CAMPYLOBACTER-META ANALYSIS

Review

Diagnostic accuracy of multiplex nucleic acid amplification tests for *Campylobacter* infection: a systematic review and meta-analysis

Xanthoula Rousou, Luis Furuya-Kanamori, Polychronis Kostoulas & Suhail A.R. Doi

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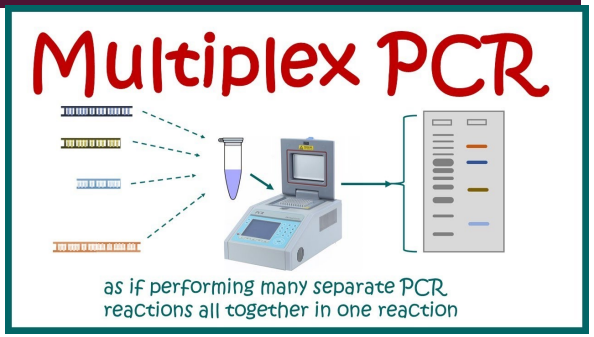
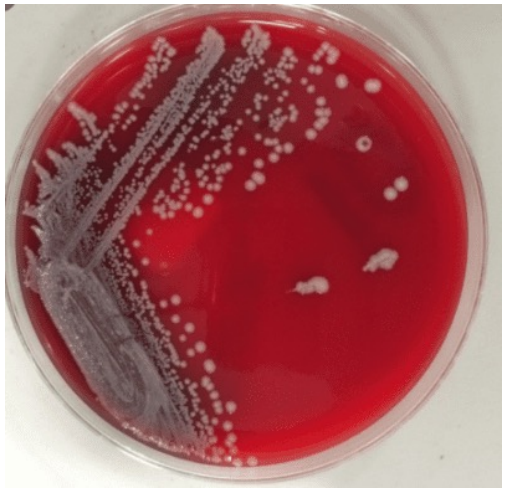


- 34 studies
- Diagnostic test->multiplex PCR
- Reference test-> culture
- SCS method
- The overall Se and Sp of multiplex PCR were 95.3% (92.3; 97.1) and 97.1% (95.1; 98.3) respectively

Multiplex NAT/PCR test	Se (95%CI)	Sp (95%CI)	Studies
BD Max EBP	0.981 (0.961,0.99)	0.985 (0.97,0.993)	(13, 38, 39)
EntericBio	0.977 (0.906,0.995)	0.986 (0.941, 0.997)	(40, 41)
FilmArray	0.97 (0.924,0.989)	0.983 (0.954,0.994)	(8, 14, 19, 43)
Luminex	0.938 (0.892,0.966)	0.982 (0.965, 0.99)	(11, 16, 18, 20, 22, 24, 48–52)
Seeplex	0.852 (0.631, 0.951)	0.957 (0.84, 0.99)	(21, 23, 55)



PROBLEM DEFINITION

- Problem:

->excess positives->FALSE or TRUE?

LOW SP of multiplex PCR or LOW SE of culture?

->Composite reference standard->singleplex or other multiplex PCR (results favoring index) or/and Antigen-based tests (low sensitivity)

->Many manufacturers->different cut-off values, different *Camp.spp*

Bayesian approach latent class model without a reference standard

HSROC or Bivariate?

LATENT CLASS MODEL - LEVEL III - PRIORS

HYPER PRIOR DISTRIBUTIONS FOR INDEX TEST

- HSROC

THETA ~ dunif(-10,10)

LAMBDA ~ dunif(-6,6)

beta ~ dunif(-2,2)

for(j in 1:2) {

tau[j] <- pow(sigma[j],-2)

sigma[j] ~ dgamma(4,2)

- Bivariate

mu[1] ~ dnorm(0,0.25)

mu[2] ~ dnorm(0,0.25)

rho ~ dunif(-1,1)

prec[1] ~ dgamma(2,0.5)

prec[2] ~ dgamma(2,0.5)

tau[1]<-pow(prec[1],-0.5)

tau[2]<-pow(prec[2],-0.5)

PRIORS FOR REFERENCE STANDARD

- Non-informative priors

#s2 ~ dbeta(1,1)

#c2 ~ dbeta(1,1)

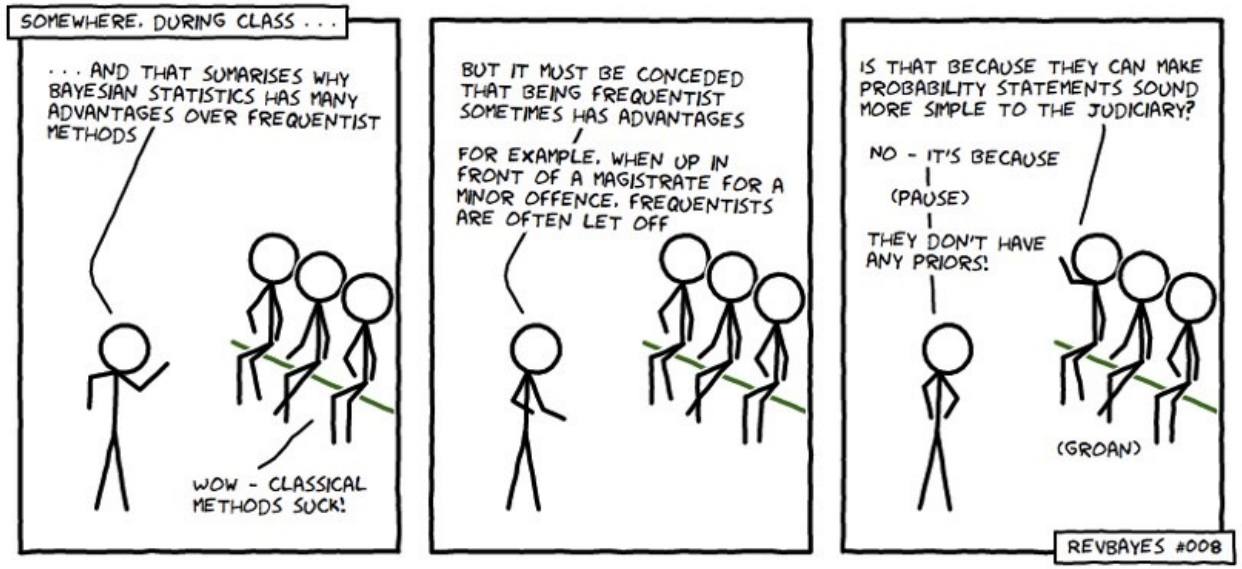
- Restrictive priors

#s2 ~ dbeta(1,1)I(0.3,)

#c2 ~ dbeta(1,1)I(0.7,)

- Informative priors

Parameter	Mean	Range (min-max)	Be (a, b)
Se	0.8	0.66-0.9	beta (126.13, 31.53)
Se	0.75	0.62-0.86	beta (142.57, 47.52)
Sp	0.95	0.8-0.999	beta (63.2, 3.33)



RESULTS

- Updated additional 5 studies -> total 39 studies
- Similar SE and SP btw the different methods
- Higher SP and SE for culture

Model	Index test		Culture test	
	Sensitivity % (95%CI)	Specificity % (95%CI)	Sensitivity % (95%CI)	Specificity % (95%CI)
SCS method	95.5 (9.,2,97.1)	96.9 (95.2,98)		
Bayesian HSROC without gold standard	94.1 (92.32,95.83)	95.78 (94.35,97.09)	97.09 (95.19,98.92)	99.98 (99.99,1)
Bayesian HSROC	94.54 (92.98,96.09)	95.47 (94.09,96.77)		
Bivariate method (mada package)	94.8 (93,96.2)	97.2 (96.3,97.9)		

BIVARIATE LATENT CLASS ANALYSIS-SHINNY APP

- https://bayesdta.shinyapps.io/meta-analysis/
- https://crsu.shinyapps.io/MetaBayesDTA/

CONCLUSIONS-RECOMMENDATIONS

- Bayesian approach to be preferred if the accuracy of the reference test is questioned
- When high heterogeneity is expected -> Bayesian or SCS method
- Threshold differences->Bayesian HSROC or SCS method
- Meta-regression-> Bayesian or bivariate meta-analysis model
- It is easier nowadays to implement Bayesian due to shinny apps and R packages
- Decision-making trees and cost-benefit analyses
- Prediction models

THANK YOU, ANY QUESTIONS?