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Medical Biometry

Meta-Analysis of Diagnostic Test Accuracy Studies: Statistical Perspectives and Practical Implications

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Joined work with: Oliver Kuss[2] and Ferdinand V. Stoye[1]

Symposium Recent Advances in Meta-Analysis

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Overview

Motivation

Meta-analysis of diagnostic studies

Meta-analysis of ROC curves

Applications

Outlook and Implications

Motivation

Example Type 2 Diabetes

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- Prevalence of diagnosed type 2 diabetes in Germany: 8%

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→ Increased mortality compared to people without diabetes, late complications

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- Prevalence of undiagnosed type 2 diabetes in Germany

→ Increased mortality compared to people without diabetes, late complications

→ BUT: Due to missing diagnosis no chance for treatment

Diagnostic tests

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→ Provide the basis for efficient treatment

Diagnostic tests

Diagnostic tests

1. Determination of a suitable diagnostic test

Diagnostic tests

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2. Determination of optimal thresholds

Diagnostic test accuracy studies

	Reference standard	
Index Test	diseased	non-diseased
	D^+	D^-
positive T^+	TP	FP
negative T^-	FN	TN

Diagnostic test accuracy studies

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positive T^+	TP	FP
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- Sensitivity: $Se = P(T^+ \mid D^+) = \frac{TP}{TP+FN}$

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- Sensitivity: $Se = P(T^+ \mid D^+) = \frac{TP}{TP+FN}$
- Specificity: $Sp = P(T^- \mid D^-) = \frac{TN}{FP+TN}$

Diagnostic test accuracy studies

HbA1c	**OGTT** Type 2 diabetes D^+	 No type 2 diabetes D^-
positive T^+	65	82
negative T^-	50	1602

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Diagnostic test accuracy studies

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- Sensitivity: $Se = \frac{65}{65+50} \approx 56\%$
- Specificity: $Sp = \frac{1602}{1602+82} \approx 95\%$

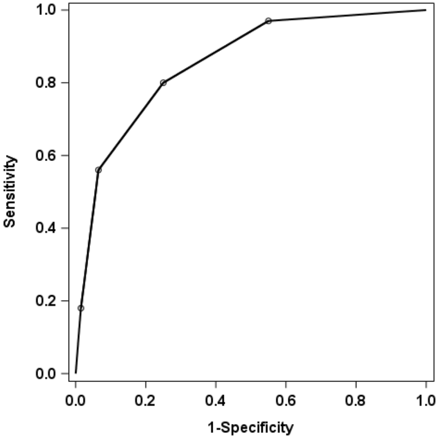
Common situation in clinical practice

Class	HbA1c (in %)	Type 2 diabetes	No type 2 diabetes
1	<5.5	150	900
2	5.5 to <6.0	850	600
3	6.0 to <6.5	1200	370
4	6.5 to <7.0	1900	100
5	≥ 7.0	900	30
	Sum	5000	2000

Common situation in clinical practice

Threshold	Sensitivity	Specificity
5.5	97%	45%
6.0	80%	75%
6.5	56%	94%
7.0	18%	99%

Receiver Operating Characteristic Curve



What is the best threshold?

Threshold	Sensitivity	Specificity	Youden-index
5.5	97%	45%	42
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→ weighted Youden-index

Meta-analysis of diagnostic studies

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Study	Sensitivity	Specificity
1	65/115	1602/1684
2	181/252	3877/5865
...	...	...

Meta-analysis of diagnostic studies

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Se_{MA}=... Sp_{MA}=...

negatively correlated

Statistical models

TP_i, TN_i binomially distributed with Se_i, Sp_i

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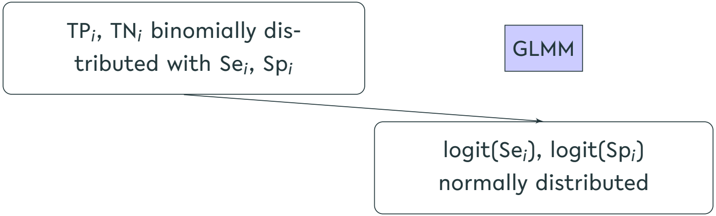
GLMM

Statistical models



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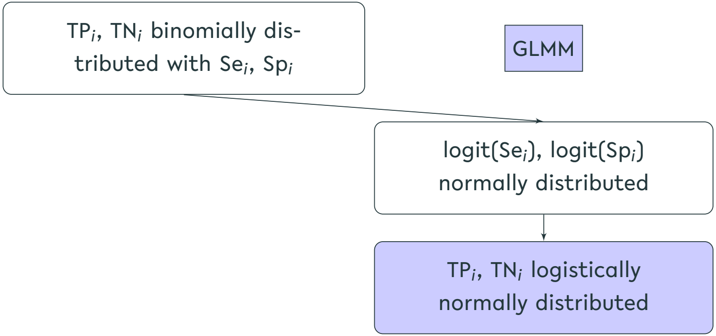
logit(Se_i), logit(Sp_i) normally distributed

Statistical models



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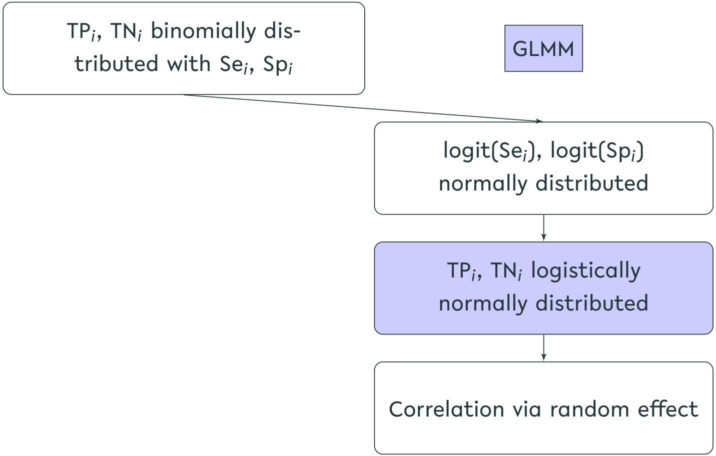

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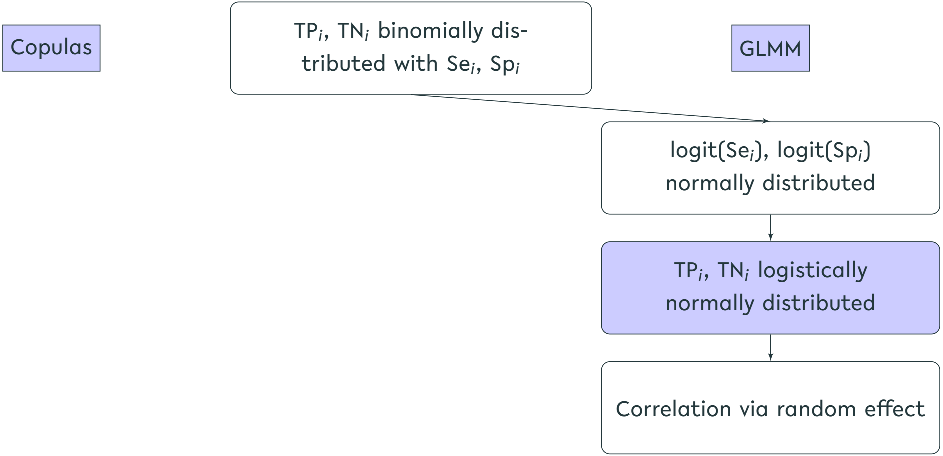
Correlation via random effect

Statistical models



Copulas

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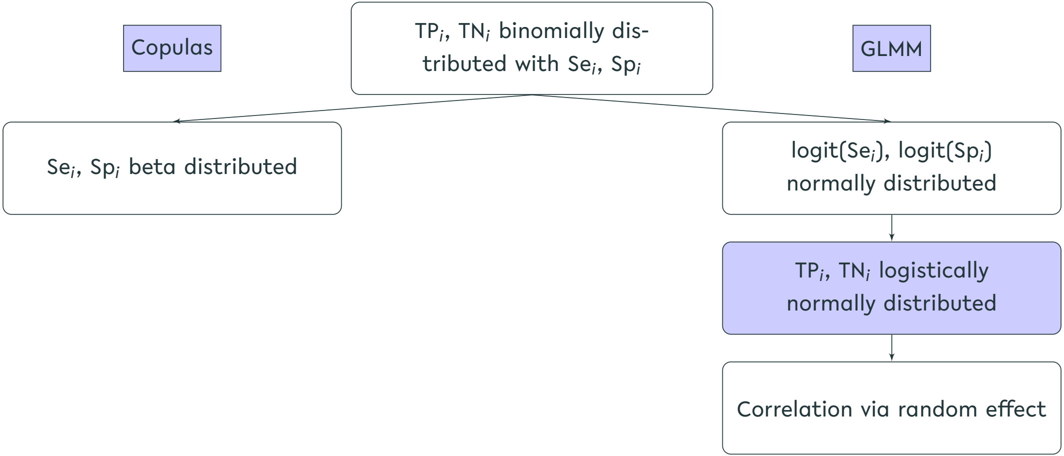

Copulas

TP$_i$, TN$_i$ binomially distributed with Se$_i$, Sp$_i$

GLMM

Se$_i$, Sp$_i$ beta distributed

logit(Se$_i$), logit(Sp$_i$) normally distributed

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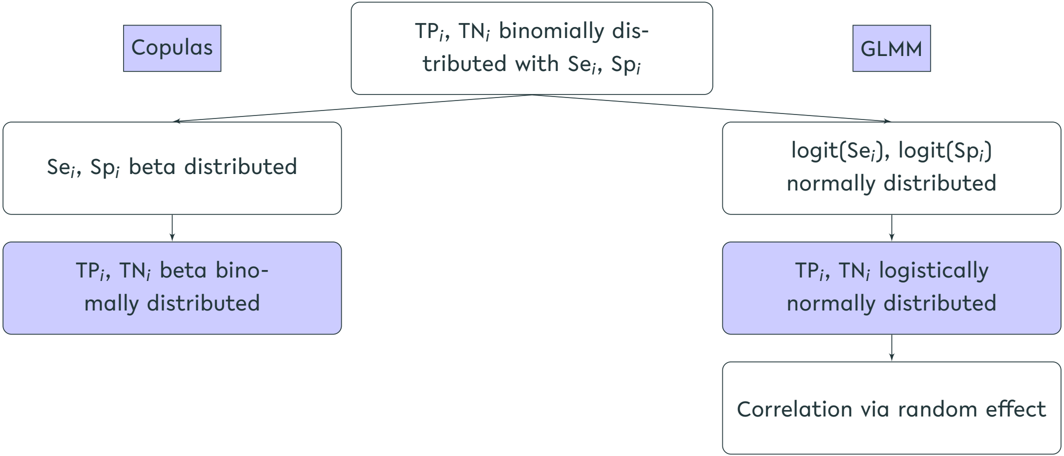

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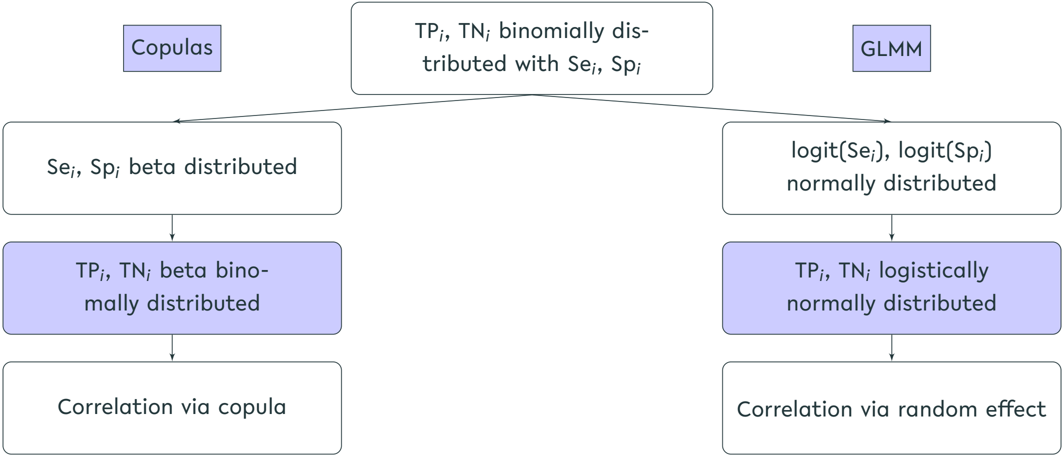

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Copula model: An overview

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- Distribution assumption:

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- Modelling of dependencies using copulas

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- Sklar's Theorem: $F(x_1, x_2) = C(F_{Se}(x_1), F_{Sp}(x_2))$
- Likelihood: Product of likelihoods of the copula and the marginal distributions

Example

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GLMM	76,7% [68,8%; 83,1%]	90,4% [71,5%; 97,2%]

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Gaussian-Copula	79,4% [74,8%; 83,4%]	81,9% [65,7%; 91,4%]
Plackett-Copula	77,6% [72,2%; 82,2%]	86,5% [70,0%; 94,6%]

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→ quadrivariate Model (doi: 10.1002/sim.7556, doi: 10.1177/0962280216661587)

Meta-analysis of ROC curves

Common situation

Study	Threshold	Sensitivity	Specificity
1	5.3	89/115	1382/1684
1	5.5	72/115	1558/1684
1	5.6	65/115	1602/1684
2	5.8	207/252	2704/5865
2	5.9	196/252	3308/5865
...	...	...	...

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- Challenge: ROC curves from single studies with different pairs of sensitivities and specificities at multiple thresholds

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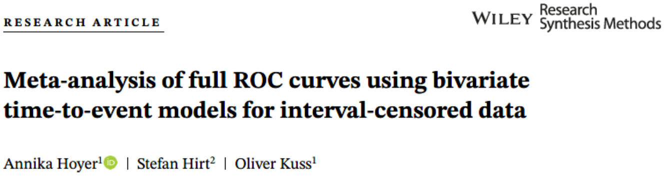
- Additional challenge: Values and number of thresholds may vary between studies

Meta-analysis of ROC curves

- New approach motivated from survival analysis:

Meta-analysis of ROC curves

- New approach motivated from survival analysis:



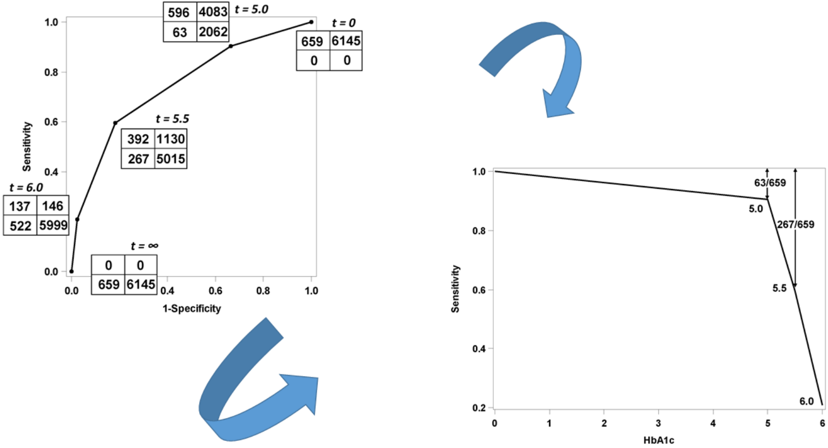
RESEARCH ARTICLE

WILEY Research Synthesis Methods

Meta-analysis of full ROC curves using bivariate time-to-event models for interval-censored data

Annika Hoyer[1] | Stefan Hirt[2] | Oliver Kuss[1]

Bivariate time-to-event model in a nutshell



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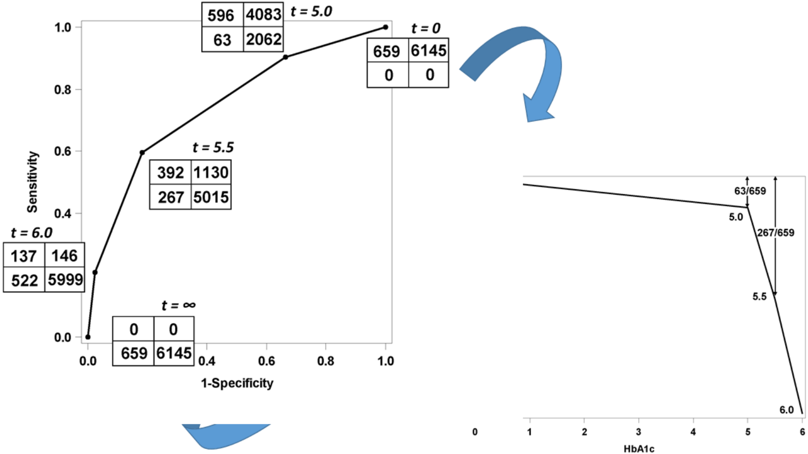

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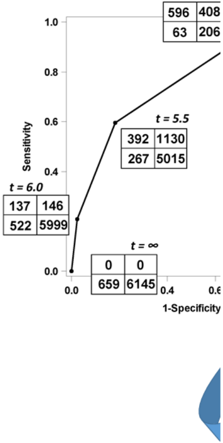

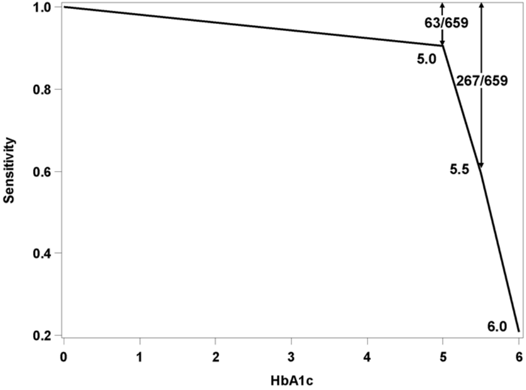

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$$\log(y_{0i}) = b_0 + \epsilon_0 + u_{0i},\ \log(y_{1i}) = b_1 + \epsilon_1 + u_{1i}, \tag{1}$$

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$$\begin{pmatrix} u_{0i} \\ u_{1i} \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_0^2 & \rho\sigma_0\sigma_1 \\ \rho\sigma_0\sigma_1 & \sigma_1^2 \end{pmatrix}\right] \tag{2}$$

Parameter estimation

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- Not directly interested in model parameters, but in S(ummary) ROC curve

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- Predict sensitivity and specificity at various thresholds based on BLUP-principle (best linear unbiased prediction)

Example

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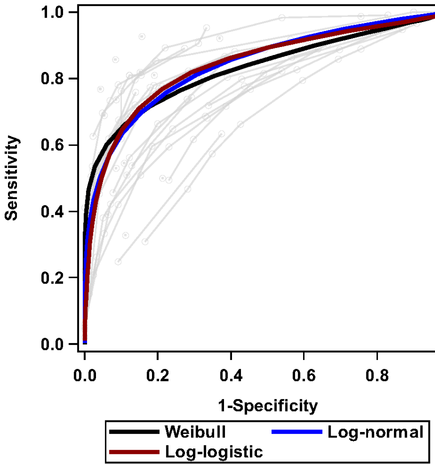
→ Analysis with only 38 pairs would discard about 70% of the available observations

Example



1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1-Specificity
Weibull
Log-normal
Log-logistic

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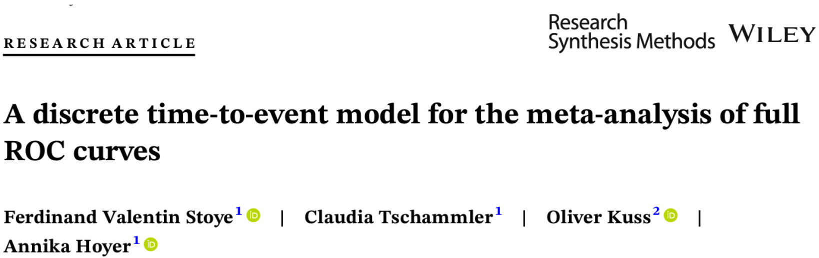
→ funded by the German Research Foundation

Discrete time-to-event model



RESEARCH ARTICLE

Research Synthesis Methods WILEY

A discrete time-to-event model for the meta-analysis of full ROC curves

Ferdinand Valentin Stoye[1] | **Claudia Tschammler**[1] | **Oliver Kuss**[2] | **Annika Hoyer**[1]

Discrete time-to-event model

1. Transfer data from diagnostic studies into the desired format

Discrete time-to-event model

1. Transfer data from diagnostic studies into the desired format
2. Select distribution assumption and link function

Discrete time-to-event model

1. Transfer data from diagnostic studies into the desired format
2. Select distribution assumption and link function
3. Model estimation

$$y_k \sim Bern(\lambda_{c_k}), \quad \textit{(Bernoulli distribution)}$$

$$\lambda_{c_k} = h\left(\alpha_{0k} + \boldsymbol{x}_1^\top \cdot \boldsymbol{\beta}_1 + \boldsymbol{x}_1^\top \cdot \boldsymbol{\beta}_2 \cdot x_2 + \gamma_1 \cdot x_2 + \gamma_2 \cdot (1 - x_2)\right),$$

$$h(x) = 1 - \exp(-\exp(x)) \quad \textit{(inverse cloglog-link)}$$

$$\begin{pmatrix} \gamma_1 \\ \gamma_2 \end{pmatrix} \sim \mathcal{N}\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_h^2 & \rho\sigma_h\sigma_d \\ \rho\sigma_h\sigma_d & \sigma_d^2 \end{pmatrix}\right) \quad \textit{(Bivariate Normal distribution)}$$

Copula model

1. Transfer data from diagnostic studies into the desired format

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Copula model

1. Transfer data from diagnostic studies into the desired format
2. Select copula
3. Select marginal distributions
   - Mixture distributions

   → Distribution of test values, e.g. Weibull: $F_W(y, b, \lambda) = 1 - \exp\left(-(y \exp(-b))^{\frac{1}{\lambda}}\right)$

   → Distribution of events, e.g. Binomial
4. Formulate log-likelihood and estimate model parameters

Both models – Parameter → Sensitivity & Specificity → SROC

Final step: Calculate sensitivity and specificity from the estimated parameters

discrete GLMM:

$$\widehat{\text{sens}}(c_k) = \prod_{t=1}^{k} \exp(-\exp(\widehat{\beta_{1t}}))$$

$$\widehat{\text{spec}}(c_k) = 1 - \prod_{t=1}^{k} \exp(-\exp(\widehat{\beta_{1t}} + \widehat{\beta_{2t}}))$$

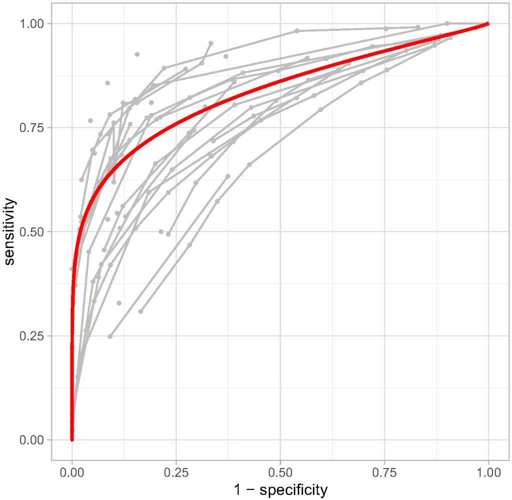
Copula model:

$$\widehat{\text{sens}}(y) = 1 - F_d(y \mid \hat{b}_d, \hat{\lambda}_d)$$

$$\widehat{\text{spec}}(y) = F_h(y \mid \hat{b}_h, \hat{\lambda}_h)$$

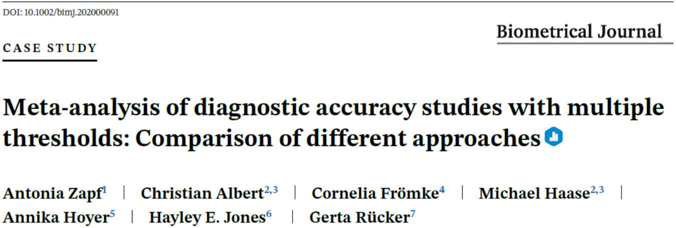
Code: `https://gitlab.ub.uni-bielefeld.de/stoyef/metaROC`

Both models – Parameter → Sensitivity & Specificity → SROC



Applications

Fair comparison of different approaches - Benchmark study



DOI: 10.1002/bimj.202000091

Biometrical Journal

CASE STUDY

Meta-analysis of diagnostic accuracy studies with multiple thresholds: Comparison of different approaches

Antonia Zapf[1] | Christian Albert[2,3] | Cornelia Frömke[4] | Michael Haase[2,3] |
Annika Hoyer[5] | Hayley E. Jones[6] | Gerta Rücker[7]

Fair comparison of different approaches

- Data set from nephrology

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    2. the estimated specificity is at least 95%
    3. the estimated sum of sensitivity and specificity is maximized (optimal Youden index)

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4. Nonparametric model by Frömke et al. (2020)

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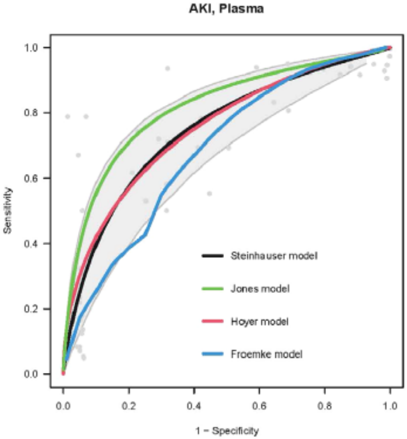
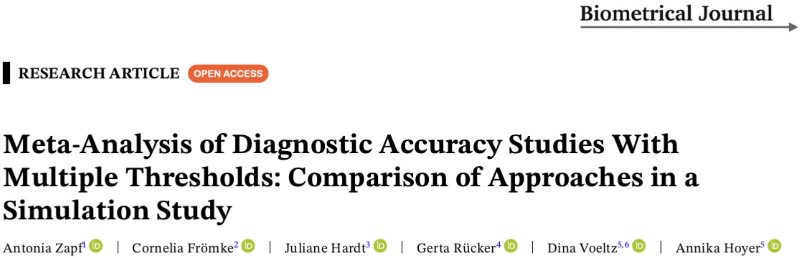


Fair comparison of different approaches - Simulation study



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Meta-Analysis of Diagnostic Accuracy Studies With Multiple Thresholds: Comparison of Approaches in a Simulation Study

Antonia Zapf[1] | Cornelia Frömke[2] | Juliane Hardt[3] | Gerta Rücker[4] | Dina Voeltz[5,6] | Annika Hoyer[5]

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Three methods are compared:

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- Systematic simulation study, motivated by an example from medical research

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→ All three approaches worked partially well

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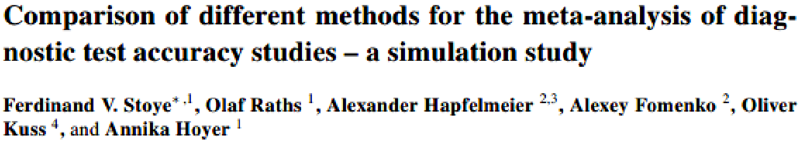
- The approach by Hoyer and colleagues was slightly superior in most scenarios and is recommended in practice

Fair comparison of different approaches - Work in progress



Comparison of different methods for the meta-analysis of diagnostic test accuracy studies – a simulation study

Ferdinand V. Stoye[*,1], **Olaf Raths**[1], **Alexander Hapfelmeier**[2,3], **Alexey Fomenko**[2], **Oliver Kuss**[4], and **Annika Hoyer**[1]

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- Comparison of 5 single threshold methods and 6 multiple threshold methods (MTM)

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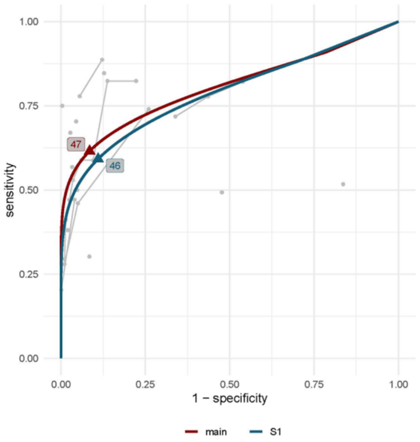
→ Main advantage of MTM: Threshold-dependent estimates of sensitivity and specificity

Application: Reassessment of HbA1c

Reassessment of the diagnostic accuracy of HbA_{1c} and glucose for type 2 diabetes: a systematic review and meta-analysis of observational studies

Christina Baechle[1,2] Ferdinand V. Stoye[3], Nafiseh Shokri-Mashhadi[1,2], Anna-Therese Klötzsch[1,2], Brenda Bongaerts[4], Annika Hoyer[3], Oliver Kuss[1,2], Rüdiger Landgraf[5], Wolfgang Rathmann[1], Sabrina Schlesinger[1,2]

Application: Reassessment of HbA1c



Outlook and Implications

Networks of diagnostic tests

- Extension of network meta-analysis of clinical trials

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- Comparison of at least two diagnostic tests with a common gold standard

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- Comparison of at least two diagnostic tests with a common gold standard
- Example type 2 diabetes: HbA1c in comparison to fasting plasma glucose

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- One could ask:
  1. whether making the diagnostic test is beneficial at all (“Test-HDA“)
  2. whether personalised thresholds in testing should be applied (“Threshold-HDA”)
  3. whether there are different diagnostic procedures from which a tested person would benefit differently (“Device-HDA”)

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- Meta-analysis of ROC curves: statistical challenge

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→ **BUT:** Standard approaches neglect the majority of observations

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- New models motivated from survival analysis show plausible and reliable results in practical applications