- **Copulas** are a more general approach for modeling inter-study heterogeneity and dependences between sensitivity and specificity in meta-analysis of DTA studies than using Gaussian random effects
- Resulting models for meta-analysis of full ROC curves are more **flexible** than available alternatives but numerically **unstable**
- Models use stacked marginals to model bivariate interval-censored time-to-event data
- Applied to meta-analysis to screen for type 2 diabetes, copula models yield **plausible** results

Increasing flexibility for the meta-analysis of full ROC curves – a copula approach

Ferdinand V. Stoye*[1] • Oliver Kuss[2] • Annika Hoyer[1]

1 Introduction

- Diagnostic test accuracy (DTA) studies typically report sensitivity and specificity for multiple diagnostic thresholds, aggregated in receiver operating characteristic (ROC) curves
- Meta-analysis of DTA studies deals with pairs of sensitivity and specificity, re-interpreted by us as interval-censored bivariate time-to-event data
- Copulas can increase modeling flexibility of the random effects compared to existing methods

2 Methods

For bivariate data, a copula C expresses the bivariate cdf $F(x_1, x_2)$ as

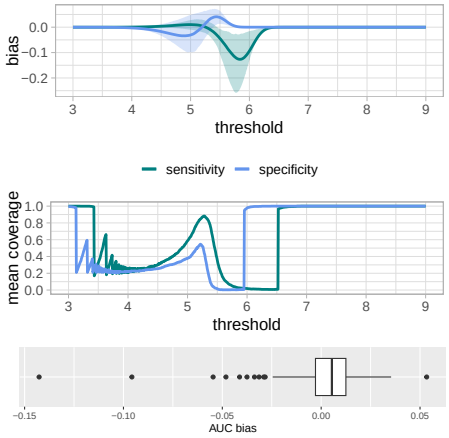
$$F(x_1, x_2) = C(F_1(x_1), F_2(x_2)).$$

Our model defines the number of events in the non-diseased (X_h) and diseased population (X_d) to be distributed as

$$X_h \sim \text{Bin}\big(H, F_h(y_h)\big),$$
$$X_d \sim \text{Bin}\big(D, F_d(y_d)\big).$$

- H are number of non-diseased, D are number of diseased individuals in the studies
- F_h and F_d are cdfs of suitable parametric distributions for the diagnostic test values, e.g., Weibull distributions
- y_h and y_d are the individual test values
- Binomial distributions can be approximated by normal distributions
- log-likelihood is composed according to interval censoring and maximized numerically

3 Simulation



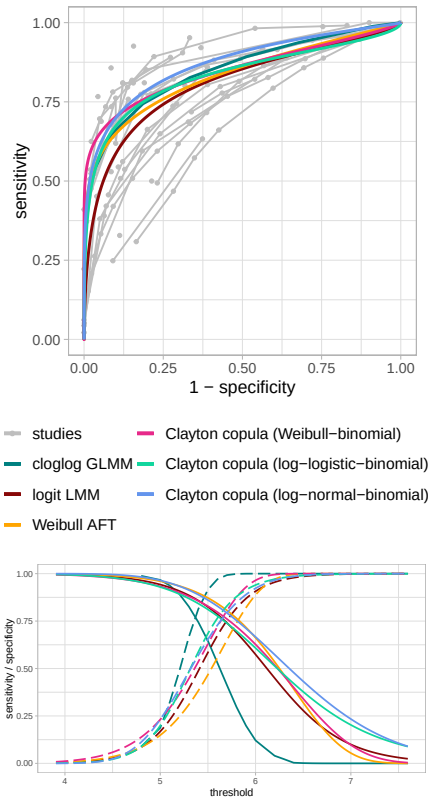
- Comparable bias to alternative models
- Low coverage due to hard-to-estimate standard errors and high variation in point estimates
- Convergence probability close to 100%

4 Conclusion

Our copula models. . .

- . . . are very flexible and modular, structure of the random effect can be hand-picked
  → Potential for fine-tuning to specific applications
- . . . have similar properties to comparable models regarding bias but vary more in point estimates
  → Need for robust optimization structure

Application – type 2 diabetes



- HbA_{1c} for screening of type 2 diabetes (gold standard: OGTT)
- Similar point estimates for all models assuming parametric distributions of test values (cloglog GLMM is a discrete model)
- Wider 95%-bootstrap CIs for copula models than for alternative models
- Copula models predict an AUC between 0.791 and 0.889, depending on choice of copula and marginals

[1] Biostatistics and Medical Biometry, Medical School OWL, Bielefeld University * ferdinand.stoye@uni-bielefeld.de
[2] Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Institute for Diabetes Research at Heinrich Heine University Düsseldorf

← Gitlab repository

UNIVERSITÄT BIELEFELD