

Hybrid copula mixed models for combining case-control and cohort studies in meta-analysis of diagnostic tests

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Abstract

Copula mixed models for trivariate (or bivariate) meta-analysis of diagnostic test accuracy studies accounting (or not) for disease prevalence have been proposed in the biostatistics literature to synthesize information. However, many systematic reviews often include case-control and cohort studies, so one can either focus on the bivariate meta-analysis of the case control studies or the trivariate meta-analysis of the cohort studies, as only the latter contains information on disease prevalence. In order to remedy this situation of wasting data we propose a hybrid copula mixed model via a combination of the bivariate and trivariate copula mixed model for the data from the case-control studies and cohort studies, respectively. Hence, this hybrid model can account for study design and also due its generality can deal with dependence in the joint tails. We apply the proposed hybrid copula mixed model to a review of the performance of contemporary diagnostic imaging modalities for detecting metastases in patients with melanoma.

Keywords: Generalized linear mixed model; composite likelihood, maximum likelihood, sensitivity/specificity/prevalence.

1 Motivating study and background

Melanoma is the least common but most deadly type of skin cancer and occurs in melanocytes, which are cells that produce the skin pigment melanin (Jerant et al., 2000). A systematic review of published

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studies by Xing et al. (2011) has examined the accuracy of contemporary diagnostic imaging modalities for detecting metastases in patients with melanoma and identified 60 cohort and 43 case-control studies.

Xing et al. (2011) applied the generalized linear mixed model (GLMM), proposed by Chu and Cole (2006), to account for the association between the sensitivity and specificity across studies. However, it is reported in the literature that the assumption of independence between the sensitivity/specificity with disease prevalence in the bivariate GLMM is likely to be violated (Brenner and Gefeller, 1997; Leeflang et al., 2009, 2013). By fitting the bivariate GLMM the information on prevalence of melanoma, which is available only in cohort studies, has been totally neglected, and, thus an important amount of data has been wasted.

Chu et al. (2009) extended the bivariate GLMM to a trivariate GLMM by also accounting for disease prevalence. Nevertheless, this model can only meta-analyse data from the cohort studies, since the disease prevalence is not available in case-control studies. Very recently, Chen et al. (2015) developed a hybrid model that exploits the use of both the bivariate and trivariate GLMM for combining case-control and cohort studies (hereafter hybrid GLMM) and applied the model to fully analyse the systematic review of published studies in Xing et al. (2011). Due to the fact that they noticed computational problems such as non-convergence and singularities, they developed a composite likelihood (CL) method to overcome the computational difficulties on the estimation of the hybrid GLMM. The CL method is well established in the statistical literature as a surrogate alternative of maximum likelihood when the joint likelihood is too difficult to compute (Varin, 2008; Varin et al., 2011). The advantage of the CL approach in this application domain is that the likelihood can be derived conveniently under the assumption of independence between the random effects, i.e., the latent vector of transformed sensitivity, specificity, and disease prevalence.

Nikoloulopoulos (2015b,c) proposed copula mixed models for bivariate and trivariate meta-analysis of diagnostic test accuracy studies and made the argument for moving to the general class of copula random effects models. The copula mixed models include the bivariate and trivariate GLMMs (Chu and Cole, 2006; Chu et al., 2009) as special cases and can also operate on the original scale of sensitivity, specificity, and disease prevalence.

In this paper, we propose a hybrid copula mixed model to combine case-control and cohort studies. We call on both the bivariate and trivariate copula mixed model and perform maximum likelihood estimation. The hybrid copula mixed has as special case the hybrid GLMM and features several other advantages: (a) the random effects distributions are expressed via copulas which allow for flexible dependence modelling, different from assuming simple linear correlation structures, normality and tail independence (b) can also operate on the original scale of sensitivity, specificity, and prevalence, and (c) estimation can be approached by the ‘gold standard’ maximum likelihood method.

The remainder of the paper proceeds as follows. Section 2 introduces the hybrid copula mixed model for diagnostic test accuracy (case-control and cohort) studies. A maximum likelihood estimation technique and computational details are provided in Section 3. Section 4 contains small-sample efficiency calculations to investigate the effect of misspecifying the random effects distributions and compare the proposed methodology to the CL approach proposed by Chen et al. (2015). In Section 5 we analyse the systematic review of the accuracy of contemporary diagnostic imaging modalities for detecting metastases in patients with melanoma and show efficiency gains with respect to the CL approach. We conclude with some discussion in Section 6.

2 The hybrid copula mixed model

In this section we introduce the hybrid copula mixed model. Before that we provide some background about important tools to form the hybrid copula mixed model. These are a brief introduction to copulas in Subsection 2.1, the bivariate copula mixed model in Subsection 2.2, and the vine copula mixed model in Subsection 2.3.

2.1 Overview and relevant background for copulas

A copula is a multivariate cdf with uniform $U(0, 1)$ margins (Joe, 1997, 2014; Nelsen, 2006). If F is a d -variate cdf with univariate margins F_1, \dots, F_d , then Sklar’s (1959) theorem implies that there is a copula C such that

$$F(x_1, \dots, x_d) = C\left(F_1(x_1), \dots, F_d(x_d)\right).$$

The copula is unique if F_1, \dots, F_d are continuous. If F is continuous and $(Y_1, \dots, Y_d) \sim F$, then the unique copula is the distribution of $(U_1, \dots, U_d) = (F_1(Y_1), \dots, F_d(Y_d))$ leading to

$$C(u_1, \dots, u_d) = F\left(F_1^{-1}(u_1), \dots, F_d^{-1}(u_d)\right), \quad 0 \leq u_j \leq 1, j = 1, \dots, d,$$

where F_j^{-1} are inverse cdfs (Nikoloulopoulos and Joe, 2015). For example, if $\Phi_d(\cdot; \mathbf{R})$ is the MVN cdf with correlation matrix

$$\mathbf{R} = (\rho_{jk} : 1 \leq j < k \leq d)$$

and $N(0,1)$ margins, and Φ is the univariate standard normal cdf, then the MVN copula is

$$C(u_1, \dots, u_d) = \Phi_d\left(\Phi^{-1}(u_1), \dots, \Phi^{-1}(u_d); \mathbf{R}\right). \quad (1)$$

Table 1: Parametric families of bivariate copulas and their Kendall's τ as a strictly increasing function of the copula parameter θ .

Copula	$C^{-1}(v u; \theta)$	τ
BVN	$\Phi\left(\sqrt{1 - \theta^2}\Phi^{-1}(v) + \theta\Phi^{-1}(u)\right)$	$\frac{2}{\pi} \arcsin(\theta) \quad , \quad -1 \leq \theta \leq 1$
Frank	$-\frac{1}{\theta} \log \left[1 - \frac{1 - e^{-\theta}}{(v^{-1} - 1)e^{-\theta u} + 1}\right]$	$1 - 4\theta^{-1} - 4\theta^{-2} \int_{\theta}^0 \frac{t}{e^t - 1} dt \quad , \quad \theta < 0$ $1 - 4\theta^{-1} + 4\theta^{-2} \int_0^{\theta} \frac{t}{e^t - 1} dt \quad , \quad \theta > 0$
Clayton	$\left\{(v^{-\theta/(1+\theta)} - 1)u^{-\theta} + 1\right\}^{-1/\theta}$	$\theta/(\theta + 2) \quad , \quad \theta > 0$
Clayton by 90	$\left\{(v^{-\theta/(1+\theta)} - 1)(1 - u)^{-\theta} + 1\right\}^{-1/\theta}$	$-\theta/(\theta + 2) \quad , \quad \theta > 0$
Clayton by 180	$1 - \left[\left\{(1 - v)^{-\theta/(1+\theta)} - 1\right\}(1 - u)^{-\theta} + 1\right]^{-1/\theta}$	$\theta/(\theta + 2) \quad , \quad \theta > 0$
Claytonby 270	$1 - \left[\left\{(1 - v)^{-\theta/(1+\theta)} - 1\right\}u^{-\theta} + 1\right]^{-1/\theta}$	$-\theta/(\theta + 2) \quad , \quad \theta > 0$

In the bivariate case there are many parametric families of copulas; see Table 1 for a sufficient list for meta-analysis of diagnostic test accuracy studies. However, their multivariate extensions have limited dependence structures. An approach to successfully subside this restriction is the vine pair-copula construction (Kurowicka and Joe, 2011; Joe, 2014) which is based on $d(d - 1)/2$ bivariate copulas, of which some are used to summarize conditional dependence. Vine copulas include the MVN as special case, but can also cover reflection asymmetry and have upper/lower tail dependence parameters being different for each bivariate margin (Joe et al., 2010). Vines require a decision on the indexing of variables. For example, for a 3-dimensional vine copula there are 3 distinct permutations:

$$\{12, 13, 23|1\}, \quad \{12, 23, 13|2\}, \quad \text{and} \quad \{13, 23, 12|3\}.$$

For each of them, the 3-dimensional vine is decomposed on 3 bivariate copulas, of which the one is used to summarize conditional dependence; see Nikoloulopoulos (2015c) for more details.

2.2 Bivariate copula mixed model

For each study i , the within-study model assumes that the number of true positives Y_{i1} and true negatives Y_{i2} are conditionally independent and binomially distributed given $\mathbf{X} = \mathbf{x}$, where $\mathbf{X} = (X_1, X_2)$ denotes the bivariate latent (random) pair of (transformed) sensitivity and specificity. That is

$$\begin{aligned} Y_{i1}|X_1 = x_1 &\sim \text{Binomial}\left(n_{i1}, l^{-1}(x_1)\right); \\ Y_{i2}|X_2 = x_2 &\sim \text{Binomial}\left(n_{i2}, l^{-1}(x_2)\right), \end{aligned} \quad (2)$$

where $l(\cdot)$ is a link function.

The stochastic representation of the between studies model takes the form

$$\left(F(X_1; l(\pi_1), \delta_1), F(X_2; l(\pi_2), \delta_2)\right) \sim C(\cdot; \theta), \quad (3)$$

where $C(\cdot; \theta)$ is a parametric family of copulas with dependence parameter θ and $F(\cdot; l(\pi), \delta)$ is the cdf of the univariate distribution of the random effect. The copula parameter θ is a parameter of the random effects model and it is separated from the univariate parameters, the univariate parameters π_1 and π_2 are the meta-analytic parameters for the sensitivity and specificity, and δ_1 and δ_2 express the variability between studies. For N studies with data (y_{ij}, n_{ij}) , $i = 1, \dots, N$, $j = 1, 2$, the models in (5) and (3) together specify a copula mixed model with joint likelihood

$$L(\pi_1, \pi_2, \delta_1, \delta_2, \theta) = \prod_{i=1}^N \int_0^1 \int_0^1 \prod_{j=1}^2 g\left(y_{ij}; n_{ij}, l^{-1}\left(F^{-1}(u_j; l(\pi_j), \delta_j)\right)\right) c(u_1, u_2; \theta) du_1 du_2, \quad (4)$$

where $c(u_1, u_2; \theta) = \partial^2 C(u_1, u_2; \theta) / \partial u_1 \partial u_2$ is the copula density and $g(y; n, \pi) = \binom{n}{y} \pi^y (1 - \pi)^{n-y}$, $y = 0, 1, \dots, n$, $0 < \pi < 1$, is the binomial probability mass function (pmf). The choices of the $F(\cdot; l(\pi), \delta)$ and l are given in Table 2.

Table 2: The choices of the $F(\cdot; l(\pi), \delta)$ and l in the copula mixed model.

$F(\cdot; l(\pi), \delta)$	l	π	δ
$N(\mu, \sigma)$	logit, probit, cloglog	$l^{-1}(\mu)$	σ
$\text{Beta}(\pi, \gamma)$	identity	π	γ

2.3 Trivariate copula mixed model

For each study i , the within-study model assumes that the number of true positives Y_{i1} , true negatives Y_{i2} , and diseased persons Y_{i3} are conditionally independent and binomially distributed given $\mathbf{X} = \mathbf{x}$, where $\mathbf{X} = (X_1, X_2, X_3)$ denotes the trivariate latent (random) vector of (transformed) sensitivity, specificity, and disease prevalence. That is

$$\begin{aligned}
 Y_{i1}|X_1 = x_1 &\sim \text{Binomial}\left(n_{i1}, l^{-1}(x_1)\right); \\
 Y_{i2}|X_2 = x_2 &\sim \text{Binomial}\left(n_{i2}, l^{-1}(x_2)\right); \\
 Y_{i3}|X_3 = x_3 &\sim \text{Binomial}\left(n_{i3}, l^{-1}(x_3)\right),
 \end{aligned} \tag{5}$$

where $l(\cdot)$ is a link function.

The stochastic representation of the between studies model takes the form

$$\left(F(X_1; l(\pi_1), \delta_1), F(X_2; l(\pi_2), \delta_2), F(X_3; l(\pi_3), \delta_3)\right) \sim C(\cdot; \boldsymbol{\theta}), \tag{6}$$

where $C(\cdot; \boldsymbol{\theta})$ is a vine copula with dependence parameter vector $\boldsymbol{\theta} = (\theta_{12}, \theta_{13}, \theta_{23|1})$ and $F(\cdot; l(\pi), \delta)$ is the cdf of the univariate distribution of the random effect. To be concrete, we use the permutation $\{12, 13, 23|1\}$. The theory though also apply to the other two permutations. The joint density $f_{123}(x_1, x_2, x_3)$ of the transformed latent proportions is:

$$\begin{aligned}
 f_{123}(x_1, x_2, x_3; \pi_1, \pi_2, \pi_3, \delta_1, \delta_2, \delta_3, \theta, \theta_{12}, \theta_{13}) = \\
 c_{12}\left(F(x_1; l(\pi_1), \delta_1), F(x_2; l(\pi_2), \delta_2); \theta_{12}\right) \times \\
 c_{13}\left(F(x_1; l(\pi_1), \delta_1), F(x_3; l(\pi_3), \delta_3); \theta_{13}\right) \prod_{j=1}^3 f(x_j; l(\pi_j), \delta_j), \tag{7}
 \end{aligned}$$

where $f(\cdot; l(\pi), \delta)$ is the density of F .

In (7) we assume conditional independence between X_1 and X_3 given X_2 , i.e., the density of the (independence) copula $C_{13|2}(u, v) = uv$ is $c_{13|2}(u, v) = 1$. Joe et al. (2010) show that in order

for a vine copula to have (tail) dependence for all bivariate margins, it is only necessary the non-conditional bivariate copulas to have (tail) dependence and it is not necessary for the conditional bivariate copulas to have tail dependence. That provides the theoretical justification for the idea of conditional independence. For more details see Nikoloulopoulos (2015c).

For N studies with data (y_{ij}, n_{ij}) , $i = 1, \dots, N$, $j = 1, 2, 3$, the models in (5) and (6) together specify a vine copula mixed model with joint likelihood

$$L(\pi_1, \pi_2, \pi_3, \delta_1, \delta_2, \delta_3, \theta_{12}, \theta_{13}) = \prod_{i=1}^N \int_0^1 \int_0^1 \int_0^1 \prod_{j=1}^3 g\left(y_{ij}; n_{ij}, l^{-1}\left(F^{-1}(u_j; l(\pi_j), \delta_j)\right)\right) c_{12}(u_1, u_2; \theta_{12}) c_{13}(u_1, u_3; \theta_{13}) du_j. \quad (8)$$

The choices of the $F(\cdot; l(\pi), \delta)$ and l are the same as in the bivariate case; see Table 2.

2.4 Hybrid copula mixed model

To form the hybrid copula mixed model we combine the aforementioned models. For ease of exposition, let the first N_1 studies be the case-control studies and the remaining N_2 studies be the cohort studies. A combination of the bivariate likelihood for the data from N_1 case-control studies and the trivariate likelihood for the data from N_2 cohort studies leads to

$$L(\pi_1, \pi_2, \pi_3, \delta_1, \delta_2, \delta_3, \theta, \theta_{12}, \theta_{13}) = \prod_{i=1}^{N_1} \int_0^1 \int_0^1 \prod_{j=1}^2 g\left(y_{ij}; n_{ij}, F^{-1}(u_j; l(\pi_j), \delta_j)\right) c(u_1, u_2; \theta) du_j \times \prod_{i=N_1+1}^{N_1+N_2} \int_0^1 \int_0^1 \int_0^1 \prod_{j=1}^3 g\left(y_{ij}; n_{ij}, F^{-1}(u_j; l(\pi_j), \delta_j)\right) c_{12}(u_1, u_2; \theta_{12}) c_{13}(u_1, u_3; \theta_{13}) du_j. \quad (9)$$

Our general statistical model allows for selection of $c(\cdot; \theta)$, $c_{12}(\cdot; \theta_{12})$ and $c_{13}(\cdot; \theta_{13})$ independently among a variety of parametric copula families, i.e., there are no constraints in the choices of parametric copulas.

3 Maximum likelihood estimation and computational details

Estimation of the model parameters $(\pi_1, \pi_2, \pi_3, \delta_1, \delta_2, \delta_3, \theta, \theta_{12}, \theta_{13})$ can be approached by the standard maximum likelihood (ML) method, by maximizing the logarithm of the joint likelihood in (9).

The estimated parameters can be obtained by using a quasi-Newton Nash (1990) method applied to the logarithm of the joint likelihood. This numerical method requires only the objective function, i.e., the logarithm of the joint likelihood, while the gradients are computed numerically and the Hessian matrix of the second order derivatives is updated in each iteration. The standard errors (SE) of the ML estimates can be also obtained via the gradients and the Hessian computed numerically during the maximization process.

Numerical evaluation of the mixed joint pmf is easily done with a combination of the algorithms in Nikoloulopoulos (2015b,c):

1. Calculate Gauss-Legendre quadrature points $\{u_q : q = 1, \dots, n_q\}$ and weights $\{w_q : q = 1, \dots, n_q\}$ in terms of standard uniform; see e.g., Stroud and Secrest (1966).
2. (a) Convert from independent uniform random variables $\{u_{q_1} : q_1 = 1, \dots, n_q\}$ and $\{u_{q_2} : q_2 = 1, \dots, n_q\}$ to dependent uniform random variables $\{u_{q_1} : q_1 = 1, \dots, n_q\}$ and $\{C^{-1}(u_{q_2}|u_{q_1}; \theta) : q_1 = q_2 = 1, \dots, n_q\}$ that have distribution $C(\cdot; \theta)$. The inverse of the conditional distribution $C(v|u; \theta) = \partial C(u, v; \theta) / \partial u$ corresponding to the copula $C(\cdot; \theta)$ is used to achieve this.
- (b) Convert from independent uniform random variables $\{u_{q_1} : q_1 = 1, \dots, n_q\}$, $\{u_{q_2} : q_2 = 1, \dots, n_q\}$, and $\{u_{q_3} : q_3 = 1, \dots, n_q\}$ to dependent uniform random variables $\{v_{q_1} = u_{q_1} : q_1 = 1, \dots, n_q\}$, $\{v_{q_2|q_1} = C_{12}^{-1}(u_{q_2}|u_{q_1}; \theta_{12}) : q_1 = q_2 = 1, \dots, n_q\}$, and $\{v_{q_2q_3|q_1} = C_{13}^{-1}(C_{23|1}^{-1}(u_{q_3}|u_{q_2}; \theta_{23|1} \rightarrow 0)|u_{q_1}; \theta_{13}) : q_1 = q_2 = q_3 = 1, \dots, n_q\}$ that have vine distribution $C(\cdot; \theta_{12}, \theta_{13})$. The simulation algorithm of a C-vine copula in Joe (2011) is used to achieve this.
3. (a) Numerically evaluate the bivariate pmf

$$\int_0^1 \int_0^1 \prod_{j=1}^2 g(y_j; n_j, F^{-1}(u_j; l(\pi_j), \delta_j)) c(u_1, u_2; \theta) du_1 du_2$$

in a double sum:

$$\sum_{q_1=1}^{n_q} \sum_{q_2=1}^{n_q} w_{q_1} w_{q_2} g(y_1; n_1, F^{-1}(u_{q_1}; l(\pi_1), \delta_1)) g(y_2; n_2, F^{-1}(C^{-1}(u_{q_2}|u_{q_1}; \theta); l(\pi_2), \delta_2)).$$

(b) Numerically evaluate the trivariate pmf

$$\int_0^1 \int_0^1 \int_0^1 \prod_{j=1}^3 g\left(y_{ij}; n_{ij}, F^{-1}(u_j; l(\pi_j), \delta_j)\right) c_{12}(u_1, u_2; \theta_{12}) c_{13}(u_1, u_3; \theta_{13}) du_1 du_2 du_3$$

in a triple sum

$$\sum_{q_1=1}^{n_q} \sum_{q_2=1}^{n_q} \sum_{q_3=1}^{n_q} w_{q_1} w_{q_2} w_{q_3} g\left(y_1; n_1, F^{-1}(v_{q_1}; l(\pi_1), \delta_1)\right) g\left(y_2; n_2, F^{-1}(v_{q_2|q_1}; l(\pi_2), \delta_2)\right) \times \\ g\left(y_3; n_3, F^{-1}(v_{q_2q_3|q_1}; l(\pi_3), \delta_3)\right)$$

.

The inverse conditional copula cdfs $C^{-1}(v|u; \theta)$ are given in Table 1.

With Gauss-Legendre quadrature, the same nodes and weights are used for different functions; this helps in yielding smooth numerical derivatives for numerical optimization via quasi-Newton Nash (1990). Our comparisons show that $n_q = 21$ is adequate with good precision to at least at four decimal places.

4 Small-sample efficiency–Misspecification

An extensive simulation study is conducted (a) to gauge the small-sample efficiency of the ML method, and (b) to investigate in detail the misspecification of the parametric margin or family of copulas of the random effects distributions.

To generate the data we have combined the simulation algorithms in Nikoloulopoulos (2015b,c):

1. For $i = 1, \dots, N_1$:
 - (a) Simulate the study size n from a shifted gamma distribution, i.e., $n \sim \text{sGamma}(\alpha = 1.2, \beta = 0.01, \text{lag} = 30)$ and round off to the nearest integer.
 - (b) Simulate (u_1, u_2) from a parametric family of copulas $C(; \tau)$; τ is converted to the copula parameter θ via the relations in Table 1.
 - (c) Convert to beta or normal realizations via $x_j = l^{-1}\left(F_j^{-1}(u_j, l(\pi_j), \delta_j)\right)$ for $j = 1, 2$.

- (d) Draw the number of diseased n_1 from a $B(n, 0.43)$ distribution.
- (e) Set $n_2 = n - n_1$, $y_j = n_j x_j$ and then round y_j for $j = 1, 2$.
2. For $i = N_1 + 1, \dots, N_1 + N_2$
- (a) Simulate the study size n from a shifted gamma distribution, i.e., $n \sim \text{sGamma}(\alpha = 1.2, \beta = 0.01, \text{lag} = 30)$ and round off to the nearest integer.
- (b) Simulate (u_1, u_2, u_3) from a C-vine $C(; \tau_{12}, \tau_{13}, \tau_{23|1} = 0)$ via the algorithm in Joe (2011); τ 's are converted to θ 's via the relations in Table 1.
- (c) Convert to beta or normal realizations via $x_j = l^{-1}\left(F_j^{-1}(u_j, l(\pi_j), \delta_j)\right)$ for $j = 1, 2$.
- (d) Set number of diseased and non-diseased as $n_1 = nx_3$ and $n_2 = n - n_1$, respectively.
- (e) Set $y_j = n_j x_j$ and then round y_j for $j = 1, 2$.

Tables 3 and 4 contain the resultant biases, root mean square errors (RMSE), and standard deviations (SD) for the MLEs under different copula and marginal choices from 1000 randomly generated samples of size $N_1 = N_2 = 25$ from the hybrid copula mixed model with normal and beta margins, respectively. We also report these summaries for the CL estimates in Chen et al. (2015) to allow for a comprehensive comparison. The true (simulated) copula distributions are the Clayton and Clayton rotated by 90 degrees for the $C_{12}(\cdot; \tau_{12})$ and $\{C(\cdot; \tau), C_{13}(\cdot; \tau_{13})\}$ copulas, respectively. We also include comparisons with the hybrid GLMM in Chen et al. (2015); that is, a hybrid copula mixed model composed of a BVN copulas and normal margins. In Chen et al. (2015) it has been assumed that the association τ_{12} between sensitivity and specificity for cohort studies is the same as the association τ between sensitivity and specificity for case-control studies, i.e., $\tau = \tau_{12}$. This is a strong assumption given the fact that the sensitivity/specificity depends on disease prevalence in cohort studies, thus the association between sensitivity and specificity is likely to be affected. In our simulations we emphasize that by allowing heterogeneity in association in cohort and case control studies.

Conclusions from the values in the tables are the following:

- ML with the true hybrid copula mixed model is highly efficient according to the simulated biases and standard deviations.

Table 3: Biases, root mean square errors (RMSE) and standard deviations (SD) for the ML estimates under different copula choices and margins and CL estimates under normal margins from small sample of sizes $N_1 = N_2 = 25$ simulations (10^3 replications) from the hybrid copula mixed model with normal margins. The true (simulated) copula distributions are the Clayton and Clayton rotated by 90 degrees for the $C_{12}(\cdot; \tau_{12})$ and $\{C(\cdot; \tau), C_{13}(\cdot; \tau_{13})\}$ copulas, respectively.

			$\pi_1 =$	$\pi_2 =$	$\pi_3 =$	$\sigma_1 =$	$\sigma_2 =$	$\sigma_3 =$	$\tau_{12} =$	$\tau_{13} =$	$\tau =$
Copula		Margin	0.7	0.9	0.7	1.5	1	1.5	0.5	-0.5	-0.5
50 Bias	Clayton by 0/90	Normal	0.04	-0.39	-0.29	-1.38	-4.12	0.01	0.83	0.92	-6.62
		Beta	-2.74	-1.96	-1.69	-	-	-	1.24	1.23	-5.74
	BVN	Normal	-0.06	-0.39	-0.26	-2.72	-5.46	-3.19	4.38	-2.22	-6.47
		Beta	-2.74	-1.90	-1.63	-	-	-	4.76	-2.03	-5.04
	Clayton by 180/270	Normal	-0.20	-0.32	-0.08	-2.20	-6.17	-3.13	7.06	-2.16	-4.97
		Beta	-2.96	-1.75	-1.22	-	-	-	7.38	-2.02	-2.84
Independence (CL)	Normal	-0.64	-0.15	-0.21	-6.08	-7.15	-5.01	-	-	-	
50 SD	Clayton by 0/90	Normal	1.79	0.50	3.05	8.98	6.52	11.51	12.68	7.49	6.45
		Beta	1.52	0.69	2.15	2.16	1.29	2.62	13.85	7.14	6.32
	BVN	Normal	1.72	0.50	2.83	8.39	6.07	9.83	8.70	6.01	7.02
		Beta	1.44	0.69	2.06	2.09	1.15	2.21	9.16	5.92	6.46
	Clayton by 180/270	Normal	1.75	0.51	2.86	8.67	6.39	9.62	7.10	5.20	11.47
		Beta	1.47	0.69	2.13	2.16	1.16	2.16	6.73	5.35	10.49
Independence (CL)	Normal	2.22	0.63	3.41	7.77	5.96	9.67	-	-	-	
50 RMSE	Clayton by 0/90	Normal	1.79	0.64	3.07	9.08	7.71	11.51	12.71	7.55	9.24
		Beta	3.13	2.08	2.74	-	-	-	13.90	7.25	8.54
	BVN	Normal	1.72	0.64	2.84	8.82	8.16	10.34	9.74	6.40	9.54
		Beta	3.10	2.02	2.63	-	-	-	10.32	6.25	8.19
	Clayton by 180/270	Normal	1.76	0.60	2.86	8.95	8.88	10.12	10.02	5.63	12.50
		Beta	3.31	1.88	2.45	-	-	-	9.99	5.72	10.87
Independence (CL)	Normal	2.31	0.65	3.42	9.87	9.31	10.89	-	-	-	

- The CL method yields estimates that are almost as good as the ML estimates for the meta-analytic parameters under the assumption of normal margins.
- The CL method slightly underestimates the between-studies variability parameters.
- The ML estimates of the meta-analytic parameters are slightly underestimated under copula misspecification.
- The SDs are rather robust to the copula misspecification.
- The meta-analytic ML and CL estimates are not robust to the margin misspecification, while the ML estimate of τ is.

The meta-analytic parameters are a univariate inference, and hence it is the univariate marginal

Table 4: Biases, root mean square errors (RMSE) and standard deviations (SD) for the ML estimates under different copula choices and margins and CL estimates under beta margins from small sample of sizes $N_1 = N_2 = 25$ simulations (10^3 replications) from the hybrid copula mixed model with normal margins. The true (simulated) copula distributions are the Clayton and Clayton rotated by 90 degrees for the $C_{12}(\cdot; \tau_{12})$ and $\{C(\cdot; \tau), C_{13}(\cdot; \tau_{13})\}$ copulas, respectively.

			$\pi_1 =$	$\pi_2 =$	$\pi_3 =$	$\gamma_1 =$	$\gamma_2 =$	$\gamma_3 =$	$\tau_{12} =$	$\tau_{13} =$	$\tau =$	
Copula			0.7	0.9	0.7	0.15	0.1	0.15	0.5	-0.5	-0.5	
50 Bias	Clayton by 0/90	Normal	1.64	1.43	0.66	-	-	-	2.17	0.45	-7.40	
		Beta	0.00	-0.16	-0.19	-0.39	-0.58	-0.09	2.38	0.90	-7.43	
	BVN	Normal	1.57	1.46	0.76	-	-	-	4.95	-2.49	-7.04	
		Beta	0.02	-0.09	-0.09	-0.75	-0.85	-0.72	4.98	-2.53	-6.49	
	Clayton by 180/270	Normal	1.45	1.47	0.82	-	-	-	7.12	-3.54	-6.36	
		Beta	-0.08	-0.05	0.09	-0.62	-0.89	-0.69	7.36	-3.61	-4.93	
	Independence (CL)	Normal	1.38	1.59	0.80	-	-	-	-	-	-	
	50 SD	Clayton by 0/90	Normal	1.08	0.46	1.90	7.05	8.17	8.23	11.66	9.29	6.71
			Beta	1.04	0.57	1.64	1.56	1.19	2.01	12.89	9.21	6.62
		BVN	Normal	1.03	0.45	1.76	6.13	7.49	6.94	8.03	6.61	7.67
Beta			0.99	0.54	1.53	1.35	1.05	1.58	8.38	6.51	7.38	
Clayton by 180/270		Normal	1.09	0.46	1.76	6.02	7.88	7.00	7.49	5.76	12.37	
		Beta	1.05	0.54	1.56	1.42	1.10	1.55	7.12	5.87	12.10	
Independence (CL)		Normal	1.41	0.57	2.13	5.64	7.33	6.70	-	-	-	
50 RMSE		Clayton by 0/90	Normal	1.96	1.50	2.01	-	-	-	11.86	9.30	9.99
			Beta	1.04	0.59	1.65	1.61	1.33	2.01	13.11	9.26	9.95
		BVN	Normal	1.88	1.53	1.92	-	-	-	9.43	7.06	10.41
	Beta		0.99	0.55	1.53	1.55	1.35	1.74	9.75	6.98	9.83	
	Clayton by 180/270	Normal	1.81	1.54	1.94	-	-	-	10.33	6.76	13.91	
		Beta	1.06	0.55	1.56	1.55	1.41	1.70	10.24	6.89	13.06	
	Independence (CL)	Normal	1.97	1.69	2.28	-	-	-	-	-	-	

distribution that matters and not the type of the copula; see also Nikoloulopoulos (2015b,c). Chen et al. (2015) constraint themselves to normal margins; this it is too restrictive and as shown in Table 4 leads to overestimation of the meta-analytic parameters when the true univariate distribution of the latent sensitivity, specificity, and disease prevalence is beta.

5 Systematic review of modern diagnostic imaging modalities for surveillance of melanoma patients

To assess the diagnostic imaging modalities for the surveillance of melanoma patients we apply hybrid copula mixed models. The diagnostic modalities under investigation are ultrasonography (US) for regional lymph node metastasis ($N_1 = 6, N_2 = 15$) and a combination of computed tomography and, positron emission tomography (PET-CT) for both distant ($N_1 = 15, N_2 = 15$) and regional

($N_1 = 5, N_2 = 17$) lymph node metastasis. We fit the hybrid copula mixed model for all different permutations, choices of parametric families of copulas and margins. To make it easier to compare strengths of dependence, we convert from θ 's to τ 's via the relations in Table 1. Since the number of parameters is the same between the models, we use the log-likelihood at estimates as a rough diagnostic measure for goodness of fit between the models. We also estimate the model parameters with the CL method in Chen et al. (2015).

In Table 5 we report the resulting maximized log-likelihoods, estimates, and standard errors of the hybrid copula mixed models with different choices of parametric families of copulas and margins for the US modality to diagnose regional lymph node metastasis. All models roughly agree on the estimated sensitivity $\hat{\pi}_1$ and specificity $\hat{\pi}_2$, but the estimate of disease prevalence is higher when beta margins are assumed. In fact, the log-likelihoods show that a hybrid copula mixed with copula distributions the Clayton rotated by 180 and 270 degrees for the $C_{13}(\cdot; \tau_{13})$ and $\{C(\cdot; \tau), C_{13}(\cdot; \tau_{13})\}$ copulas, respectively, and beta margins provides the best fit. The CL method in Chen et al. (2015) underestimates the disease prevalence of metastases.

In Table 6 we report the resulting maximized log-likelihoods, estimates, and standard errors of the hybrid copula mixed models with different choices of parametric families of copulas and margins for the for the PET-CT modality to diagnose regional lymph node metastasis. All models roughly agree on the estimated sensitivity $\hat{\pi}_1$, specificity $\hat{\pi}_2$ and disease prevalence $\hat{\pi}_3$ for the surveillance of regional lymph node metastasis. The log-likelihoods show that a hybrid copula mixed model with Frank copulas and normal margins provides the best fit. In this dataset it revealed that there is heterogeneity in association between cohort and case control studies, i.e. $\hat{\tau}$ is positive, while $\hat{\tau}_{12}$ is negative.

Finally, in Table 7 we report the resulting maximized log-likelihoods, estimates, and standard errors of the hybrid copula mixed models with different choices of parametric families of copulas and margins for the PET-CT modality to diagnose distant lymph node metastasis. All models roughly agree on the estimated sensitivity $\hat{\pi}_1$, and disease prevalence $\hat{\pi}_3$, but the estimate $\hat{\pi}_2$ of specificity is smaller when beta margins are assumed. The log-likelihoods show that a hybrid copula mixed model with Frank copulas and normal margins provides the best fit.

Table 5: Maximized log-likelihoods, estimates, and standard errors of the hybrid copula mixed models with different choices of parametric families of copulas and margins for the US modality to diagnose regional lymph node metastasis.

Normal margins														
	BVN		Frank		Clayton by 180/270		Clayton by 90/180		Clayton by 0/270		Clayton by 0/90		CL	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
π_1	0.68	0.11	0.69	0.10	0.71	0.10	0.68	0.11	0.74	0.09	0.64	0.13	0.68	0.11
π_2	0.98	0.01	0.98	0.01	0.98	0.01	0.98	0.01	0.98	0.01	0.98	0.01	0.98	0.01
π_3	0.19	0.06	0.15	0.06	0.15	0.05	0.15	0.05	0.13	0.05	0.18	0.09	0.15	0.08
σ_1	1.94	0.37	1.91	0.37	1.97	0.42	2.01	0.43	1.92	0.41	2.03	0.43	1.97	0.14
σ_2	1.54	0.37	1.54	0.36	1.53	0.35	1.56	0.41	1.53	0.35	1.53	0.38	1.42	0.06
σ_3	2.53	0.57	2.59	0.57	2.56	0.55	2.56	0.55	2.57	0.56	2.54	0.57	2.58	0.15
τ_{12}	-0.26	0.16	-0.31	0.17	-0.28	0.17	-0.21	0.19	-0.28	0.16	-0.21	0.16	0.00	-
τ_{13}	0.01	0.16	-0.05	0.20	-0.15	0.17	-0.13	0.24	-0.25	0.11	0.09	0.16	0.00	-
τ	-0.40	0.34	-0.37	0.35	-0.47	0.30	-0.22	0.46	-0.46	0.31	-0.23	0.43	0.00	-
$\log L$	-194.38		193.94		-193.59		-194.96		-193.05		-195.22			

Beta margins														
	BVN		Frank		Clayton by 180/270		Clayton by 90/180		Clayton by 0/270		Clayton by 0/90			
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
π_1	0.61	0.07	0.61	0.07	0.63	0.07	0.61	0.07	0.63	0.07	0.60	0.08		
π_2	0.95	0.02	0.96	0.01	0.95	0.01	0.95	0.02	0.95	0.01	0.95	0.02		
π_3	0.28	0.05	0.27	0.06	0.26	0.07	0.26	0.05	0.29	0.06	0.27	0.06		
γ_1	0.36	0.07	0.36	0.07	0.38	0.08	0.38	0.08	0.36	0.07	0.37	0.08		
γ_2	0.10	0.04	0.09	0.04	0.09	0.04	0.10	0.05	0.09	0.04	0.10	0.05		
γ_3	0.35	0.09	0.36	0.08	0.35	0.08	0.35	0.08	0.35	0.08	0.36	0.09		
τ_{12}	-0.27	0.16	-0.32	0.16	-0.30	0.16	-0.19	0.16	-0.30	0.16	-0.19	0.17		
τ_{13}	-0.04	0.18	-0.01	0.14	-0.19	0.12	-0.16	0.14	-0.08	0.15	0.00	0.16		
τ	-0.42	0.33	-0.38	0.34	-0.49	0.29	-0.25	0.43	-0.48	0.29	-0.23	0.44		
$\log L$	-191.98		-191.68		-190.98		-192.68		-191.24		-192.95			

Table 6: resulting maximized log-likelihoods, estimates, and standard errors of the hybrid copula mixed models with different choices of parametric families of copulas and margins for the PET-CT modality to diagnose regional lymph node metastasis.

Normal margins														
	BVN		Frank		Clayton by 180/270		Clayton by 90/180		Clayton by 0/270		Clayton by 0/90		CL	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
π_1	0.82	0.02	0.82	0.02	0.83	0.03	0.82	0.02	0.82	0.03	0.82	0.02	0.85	0.02
π_2	0.87	0.02	0.87	0.02	0.87	0.03	0.87	0.02	0.87	0.03	0.87	0.02	0.88	0.02
π_3	0.57	0.06	0.56	0.06	0.57	0.06	0.55	0.06	0.59	0.07	0.59	0.06	0.59	0.07
σ_1	0.65	0.16	0.65	0.16	0.65	0.17	0.64	0.15	0.68	0.17	0.65	0.15	0.64	0.09
σ_2	0.94	0.21	0.91	0.20	0.94	0.23	1.01	0.22	0.93	0.23	0.99	0.21	0.89	0.10
σ_3	0.87	0.20	0.93	0.21	0.94	0.21	0.92	0.21	0.89	0.22	0.84	0.19	0.97	0.18
τ_{12}	-0.31	0.25	-0.45	0.27	-0.19	0.40	-0.28	0.25	-0.27	0.38	-0.30	0.27	0.00	-
τ_{13}	0.52	0.20	0.51	0.21	0.51	0.21	0.46	0.21	0.53	0.22	0.49	0.22	0.00	-
τ	0.60	0.41	0.57	0.36	0.63	0.61	0.73	0.32	0.63	0.59	0.72	0.32	0.00	-
$\log L$	-174.50		-174.46		-175.98		-175.03		-174.93		-173.93			
Beta margins														
	BVN		Frank		Clayton by 180/270		Clayton by 90/180		Clayton by 0/270		Clayton by 0/90			
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE		
π_1	0.80	0.03	0.80	0.03	0.81	0.03	0.80	0.02	0.80	0.03	0.80	0.02		
π_2	0.84	0.03	0.83	0.03	0.84	0.03	0.84	0.03	0.83	0.03	0.84	0.03		
π_3	0.56	0.05	0.55	0.05	0.55	0.05	0.54	0.05	0.57	0.06	0.58	0.05		
γ_1	0.06	0.03	0.06	0.03	0.06	0.03	0.05	0.02	0.06	0.03	0.06	0.03		
γ_2	0.10	0.04	0.09	0.04	0.10	0.04	0.11	0.04	0.10	0.04	0.10	0.04		
γ_3	0.14	0.05	0.15	0.05	0.16	0.05	0.15	0.05	0.15	0.06	0.13	0.05		
τ_{12}	-0.31	0.24	-0.46	0.27	-0.23	0.49	-0.26	0.25	-0.29	0.38	-0.27	0.25		
τ_{13}	0.53	0.20	0.53	0.21	0.51	0.21	0.47	0.21	0.55	0.22	0.50	0.22		
τ	0.65	0.38	0.60	0.35	0.66	0.58	0.76	0.30	0.67	0.56	0.76	0.30		
$\log L$	-175.76		-175.69		-177.17		-176.37		-176.14		-175.33			

Table 7: Maximised ML and CL log-likelihoods, estimates and standard errors (SE) for the PET-CT modality to diagnose distant lymph node metastasis.

Normal margins										
	BVN		Frank		Clayton		Clayton by 180		CL	
	Est.	SE	Est.	SE	Est.	SE	Est.	SE	Est.	SE
π_1	0.50	0.14	0.52	0.14	0.50	0.13	0.56	0.14	0.47	0.13
π_2	0.96	0.02	0.96	0.02	0.96	0.02	0.95	0.02	0.97	0.02
π_3	0.37	0.04	0.37	0.04	0.36	0.04	0.37	0.04	0.35	0.05
σ_1	2.33	0.55	2.22	0.53	2.32	0.50	2.44	0.53	2.27	0.13
σ_2	1.67	0.54	1.69	0.58	1.72	0.52	1.51	0.45	1.75	0.29
σ_3	0.65	0.16	0.64	0.15	0.68	0.16	0.64	0.16	0.71	0.04
τ_{12}	0.02	0.18	-0.01	0.20	0.00	0.12	-0.05	0.19	0.00	-
τ_{13}	0.54	0.17	0.54	0.16	0.60	0.17	0.55	0.20	0.00	-
τ	0.50	0.45	0.35	0.79	0.38	0.43	0.63	0.36	0.00	-
$\log L$	-154.45		-154.12		-154.80		-154.33			
Beta margins										
	BVN		Frank		Clayton		Clayton by 180			
	Est.	SE	Est.	SE	Est.	SE	Est.	SE		
π_1	0.50	0.07	0.51	0.07	0.49	0.07	0.49	0.07		
π_2	0.89	0.03	0.89	0.04	0.89	0.03	0.90	0.03		
π_3	0.38	0.04	0.38	0.04	0.38	0.04	0.37	0.04		
γ_1	0.44	0.09	0.42	0.08	0.44	0.08	0.43	0.07		
γ_2	0.22	0.07	0.22	0.07	0.22	0.07	0.24	0.08		
γ_3	0.08	0.04	0.08	0.03	0.09	0.04	0.07	0.03		
τ_{12}	0.02	0.18	-0.02	0.20	0.00	0.10	0.04	0.20		
τ_{13}	0.55	0.17	0.54	0.16	0.60	0.17	0.52	0.19		
τ	0.44	0.44	0.26	0.77	0.36	0.39	-0.32	0.14		
$\log L$	-157.36		-157.03		-157.69		-156.74			

In all the meta-analyses, improvement over the hybrid copula mixed model composed of BVN copulas and normal margins, that is the same with the hybrid GLMM in Chen et al. (2015), has been revealed in terms of the likelihood principle. Chen et al. (2015), instead of relying to separate meta-analyses for each type of imaging modality and type of metastasis, analyzed all the data by assuming normal margins for the random effects with equal between-studies variances in transformed sensitivity, specificity, and disease prevalence for different imaging modalities or stages of metastasis. These assumptions are quite strong and we have shown, with the subgroup analysis in Tables 5-7, that are substantially violated. In fact, between study variances are distinct in each type of imaging modality or stage of metastasis and for the US imaging modality even the assumption of normal

margins is not valid.

6 Discussion

We have proposed a hybrid copula mixed model for meta-analysis of diagnostic test accuracy studies. It jointly models the disease prevalence along with diagnostic test sensitivity and specificity in cohort studies, and sensitivity and specificity in case-control studies. Our general model includes the hybrid GLMM in Chen et al. (2015) as a special case and can provide an improvement over the latter based on log-likelihood. Hence, a better statistical inference for the meta-analytic parameters and their between-study variances is achieved. This improvement relies on the fact that the random effects distribution is expressed via copulas which can model asymmetries and dependence in the joint tails.

It has been reported in the literature that in the trivariate GLMM (Chu et al., 2009) and hybrid GLMM (Chen et al., 2015) estimation problems relating to the correlation parameters exist, such as non-convergence. Here instead of a trivariate normal distribution we use a vine copula distribution, and in particular a truncated at level-1 vine copula (conditional independence), which allows both parsimony and flexible (tail) dependence. In fact, we propose a numerically stable maximum likelihood estimation technique based on Gauss-Legendre quadrature; the crucial step is to convert from independent to dependent quadrature points.

Software

R functions to implement the hybrid vine copula mixed model for meta-analysis of diagnostic test accuracy case-control and cohort studies will be part of the next major release of the R package `CopulaREMADA` (Nikoloulopoulos, 2015a).

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