A time-varying bivariate copula joint model for longitudinal and time-to-event data

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ABSTRACT
A time-varying bivariate copula joint model, which models the repeatedly measured longitudinal outcome at each time point and the survival data jointly by both the random effects and time-varying bivariate copulas, is proposed in this paper. A regular joint model normally supposes there exist subject-specific latent random effects or classes shared by the longitudinal and time-to-event processes and the two processes are conditionally independent given these latent variables. Under this assumption, the joint likelihood of the two processes is straightforward to derive and their association, as well as heterogeneity among the population, are naturally introduced by the unobservable latent variables. However, because of the unobservable nature of these latent variables, the conditional independence assumption is difficult to verify. Therefore, besides the random effects, a time-varying bivariate copula is introduced to account for the extra time-dependent association between the two processes. The proposed model includes a regular joint model as a special case under some copulas. Simulation studies indicates the parameter estimators in the proposed model are robust against copula misspecification and it has superior performance in predicting survival probabilities compared to the regular joint model. A real data application on the Primary biliary cirrhosis (PBC) data is performed.

KEYWORDS
Bivariate copula; Dynamic prediction; Joint modelling; Longitudinal data; Time-to-event data.

1. Introduction

Joint modelling of longitudinal measurements and time-to-event data has become increasingly popular in recent decades, as previous studies indicate separately modelling (Tsiatis, DeGruttola and Wulfsohn, 1995[40] and Guo and Carlin, 2004[15]) or a two-stage modelling (Wulfsohn and Tsiatis, 1997[45]) of the two processes can result in biased estimations due to not fully considering the association between the two sub-models. The classical joint model in Faucett and Thomas, (1996)[11] and Wulfsohn and Tsiatis (1997)[45] assumes a linear mixed effects model and a proportional hazard model for the longitudinal and survival sub-models, respectively. Thereafter, joint models with non-linear mixed longitudinal process modelled by cubic B-splines or functional principal components have been proposed by Brown et al. (2005)[4], Yao (2007)[46] and Li et al. (2021)[22]. Li and Luo (2017)[23] and (2019)[24] incorporate functional covariates, which is a continuous curve over some domain, into the joint model. A latent class joint model is discussed by Lin et al. (2002)[26], (2004)[25] and Proust-Lima et al. (2009)[31]. Excellent overviews on joint modelling can be found in Tsiatis and Davidian (2004)[39], Ibrahim et al. (2010)[19], Papageorgiou et al. (2019)[30] and Alsefri et al. (2020)[1]. Despite the diverse extension of the joint modelling framework in recent years, conditional independence of the two sub-models given the latent variables is an assumption which has always remained stable. This assumption is tricky to verify as the latent variables are...
not observable. Roy (2003)[37], Guo et al. (2006)[14] and Jacqmin-Gadda et al. (2010)[21] proposed some tests to assess conditional independence given latent classes via a score test or testing the dependency within each class after randomly allocating the subjects into classes using the estimated posterior class-membership probabilities, but these tests apply only to the latent class joint model.

Emura et al. (2017)[10] pointed out joint analysis of two survival outcomes, such as death and relapse of cancer, by a joint frailty model (Rondeau et al., 2015[36]), which assumes conditional independence between the two survival outcomes given a shared study-specific frailty term, may not be sufficient to account for all the dependency between outcomes in a subject level, especially when the covariates information are insufficiently collected. For this reason, they introduced a joint frailty-copula model, which associates the two survival outcomes by both shared frailty terms and copula. It is reasonable to have the same doubts about conditional independence in the joint modelling of longitudinal and time-to-event data when there are only a few covariates or the latent variable structure is too simple. To alleviate this issue, Henderson et al. (2000)[16] replaced the simple shared random effects in the two sub-models by a combination of correlated random effects and a mean-zero bivariate Gaussian stochastic process, representing a long-term trend and local variation at subject-level. However, the infinite dimension of the stochastic process comes with intensive computation and the baseline hazard function is only allowed to be modelled nonparametrically by taking mass at each failure time due to integrability issues. In addition, Hsieh et al. (2006)[18] pointed out the unspecified baseline hazard leads to underestimation of the standard errors for parameters in the EM algorithm. Similar to Henderson et al. (2000)[16], Wang et al. (2001)[41] applied a random intercept and an integrated Ornstein-Uhlenbeck stochastic process for the latent variables. As a compromise, the stochastic process was treated as a piecewise constant function for estimation. In more recent work, Dutta et al. (2021)[9] modelled the joint distribution of log-transformed survival time and the longitudinal measurement, conditional on the shared random effects, by a multivariate normal distribution. This model introduced dependency between the two processes by both the random effects and covariance matrix of the multivariate normal distribution, but the assumption of log normal distribution on the event time may be too restrictive.

Associating the longitudinal and survival sub-models by copula (Hofert et al., 2018)[17] has also been considered. Rizopoulos et al. (2008a)[32], 2008b[33]) and Malehi et al. (2015)[27] applied copulas to model the joint distribution of the latent random effects, which offered greater flexibility of association compared with the traditional shared random effects joint model, by allowing different copulas and marginal distributions for random effect components. However, conditional independence is still assumed in these models. Applying multivariate copulas directly on marginals of all the longitudinal measurements and event time data for each subject was considered by Ganjali and Baghfalaki (2015)[12], Zhang et al.(2023a)[48] and Cho et al.(2024)[5]. The non-linear correlation introduced by the copula between the two sub-models is different to the linear one arising from latent random effects, but the lack of random effects in the joint models compromises their capability to capture the longitudinal trajectories at the subject level. For this reason, Zhang et al.(2023b)[49] further proposed modelling the joint distribution of all the longitudinal and survival outcomes in each subject, given the random effects, by a multivariate Gaussian copula. This model has two layers of correlation between the two sub-models and a regular joint model of conditional independence becomes a specially case when the correlation matrix in the multivariate Gaussian copula is an identity matrix. However, in these multivariate copula approaches of joint modelling, the difficulty of modelling the correlation matrix in the copula increases with the number of repeated longitudinal measurements. The approach of Suresh et al.(2021)[38] can solve this issue by applying a bivariate Gaussian copula on the conditional joint distribution of survival time and a longitudinal measurement at a single time point given the subject being alive by that time point, since the correlation matrix of a two-dimensional copula is easier to model. But their model still falls under the marginal models as Zhang et al.(2023a)[48] for not including the latent effects.
In this paper, we propose a time-varying bivariate copula joint model by modelling the joint
distribution of survival time and a single longitudinal measurement, conditional on the random
effects and that the subject survives beyond the time point of this longitudinal observation, through
a time-varying bivariate copula. The time-invariant random effects introduce the dominant or long-
term association between the two sub-models, while the time-varying bivariate copula captures
the residual correlation from the local biological variation. A cubic B-spline function is applied to
characteristic the possible dynamic nature of the correlation structure in the bivariate copula.

The remainder of the paper is organised as followed. Section 2 describes the notations and spec-
ification of the proposed model. In Section 3, simulations are conducted to assess the performance
of the proposed model in terms of parameter estimation and dynamic prediction of survival prob-
abilities and its performance under copula misspecification is investigated. A real data application
is carried out in Section 4. The limitations of the proposed model are discussed and some future
work is suggested in Section 5.

2. Time-varying bivariate copula joint model framework

Suppose there are \( n \) subjects being followed over a period of time. For the \( i \)th, \( i = 1, \ldots, n \), subject,
its longitudinal observations \( Y_i = \{Y_{i1} = Y_i(s_{i1}), \ldots, Y_{in} = Y_i(s_{in})\} \) are measured intermittently
at time points \( s_i = (s_{i1}, \ldots, s_{in}) \) and are terminated by the observed event time \( T_i = \min(C_i, T^*_i) \)
with \( C_i \) and \( T^*_i \) being the right censoring time and true event time, respectively. Thus, observing
a longitudinal measurement \( Y_{ij} \) at \( s_{ij} \), \( 1 \leq j \leq n_i \), implicitly implies \( Y_{ij}|T^*_i > s_{ij}. \) We also denote \( \delta_i = I(T^*_i < C_i) \) as the corresponding event indicator, which takes value 1 if the true event time is
observed and 0 otherwise, for subject \( i \). The observation time points \( s_i \) and the censoring process
\( C_i \) are assumed to be uninformative conditional on the baseline covariates.

Suppose the longitudinal process for subject \( i \) is specified by the following model:

\[
Y_{ij} = x_{ij}' \beta_1 + z_{ij}' b_i + \varepsilon_{ij}, \quad i = 1, \ldots, n, \; j = 1, \ldots, n_i, \tag{1}
\]

where \( x_{ij} = x_i(s_{ij}) \) is a \( p \times 1 \) covariate vector with fixed effects \( \beta_1 \), \( z_{ij} = z_i(s_{ij}) \) is a \( r \times 1 \) covariate
vector for random effects \( b_i \sim N_r(0, D) \), and the unexplained variation \( \varepsilon_{ij} = \varepsilon_i(s_{ij}) \sim N(0, \sigma^2) \).

The corresponding survival process for this subject is given by a proportional hazard model (Cox,
1972[6]) with frailty terms as:

\[
h_i(t) = h_0(t) \exp \left\{ w_i' \beta_2 + \gamma z_i(t)' b_i \right\}, \tag{2}
\]

where \( w_i \) is a \( q \times 1 \) vector of baseline explanatory variables for the survival process with associated
regression parameter vector \( \beta_2 \), the parameter \( \gamma \) characterises the dependency between the two sub-
models. Common covariates are allowed for \( x_i \) and \( w_i \). The baseline hazard function is common for
all subjects and assumed to be a piecewise-constant function having \( K - 1 \) equally spaced internal
knots (Rizopoulos, 2010[34]) as:

\[
h_0(t) = \sum_{k=1}^{K} \lambda_k I(v_{k-1} < t \leq v_k),
\]

where \( 0 = v_0 < v_1 < \cdots < v_K = t_{\text{max}} = \max \{t_i, \; i = 1, \ldots, n\} \), such that \([0, t_{\text{max}}]\) is split into \( K \)
intervals, each with a constant baseline hazard \( \lambda_k \).
According to the recording time point $s_i$ of the longitudinal process, the information contributed by subject $i$ can be described in a progressive way as follows:

i. At the origin of the two processes, i.e. at $t = 0$, some baseline covariates are taken. Does the event occur before the first scheduled longitudinal measurement planned at $t = s_{i1}$? If not, the two processes continue;

ii. At $t = s_{ij}$, $j = 1, \ldots, n_i - 1$, a longitudinal measurement is observed and we monitor if the event is censored or observed before the next scheduled longitudinal measurement planned at $t = s_{i(j+1)}$. If not, the two processes continue;

iii. At $t = s_{in_i}$, a longitudinal measurement is observed, then the event is censored or observed at $T_i = t$ before the next longitudinal measurement can be recorded. The two processes are terminated at $T_i = t_i$ with an associated event indicator $\delta_i$.

The above steps decompose the observed likelihood of subject $i$ as:

$$L_i = f_{T_i}Y_i(t_i, y_i) = \int f_{T_i, Y_i}(t_i, y_i | b_i) f_{b_i}(b_i) \, db_i$$

$$= \int_{b_i} P_{T_i}(T_i > s_{1i}) \times f_{T_i, Y_i}(T_i > s_{1i}, y_{1i} | T_i > s_{1i}) \times f_{T_i, Y_i}(T_i > s_{3}, y_{12} | T_i > s_{3}, y_{12}) \times \cdots \times f_{T_i, Y_i(n_{i-1})}(T_i > s_{1i}, y_{i(n_{i-1})} | T_i > s_{1i}, y_{i(n_{i-1})})^{1-\delta_i} \times f_{T_i, Y_i}(T_i > s_{1i}, y_{i1}, \ldots, y_{i(n_{i-1})}) \, db_i.$$

Each term can be interpreted as the information updated between interval $[s_{ij}, s_{i(j+1)}]$ conditional on the previous information. Suppose the dependency between the intervals are introduced by the time-invariant subject-specific random effects $b_i$, then (3) can be rewritten as:

$$L_i = f_{T_i}Y_i(t_i, y_i) = \int f_{T_i, Y_i}(t_i, y_i | b_i) f_{b_i}(b_i) \, db_i$$

$$= \int_{b_i} P_{T_i}(T_i > s_{1i}) \times f_{T_i, Y_i}(T_i > s_{1i}, y_{1i} | T_i > s_{1i}, b_i) \times f_{T_i, Y_i}(T_i > s_{3}, y_{12} | T_i > s_{3}, y_{12}) \times \cdots \times f_{T_i, Y_i(n_{i-1})}(T_i > s_{1i}, y_{i(n_{i-1})} | T_i > s_{1i}, y_{i(n_{i-1})})^{1-\delta_i} \times f_{T_i, Y_i}(T_i > s_{1i}, y_{i1}, \ldots, y_{i(n_{i-1})}) \, db_i.$$

Model (4) implies $\varepsilon_{ij}$ includes both the measurement error and local biological variation. While the local biological variations could be regraded as independent if the gaps of the two adjacent visit times are large (Tsiatis and Davidian, 2004[39]), it may still have impact on the survival process. Unlike the permanent effect imposed by the random effects, the local biological variation only has local influence on the survival process, thus conditional independence between intervals is assumed.

According to the two sub-models in (1) and (2), the distribution of the two processes, conditional on the random effects $b_i$ and subject $i$ being alive up to $t = s_{ij}$, are given by:

$$F_{T_i}(t | b_i, T_i > s_{ij}) = 1 - \exp \left\{ - \int_{s_{ij}}^t h_i(u) du \right\},$$

and

$$F_{Y_i}(y_{ij} | b_i, T_i > s_{ij}) = \Phi \left( \frac{y_{ij} - x_{ij}' \beta_i - z_{ij} b_i}{\sigma} \right).$$
In the remaining paper, we denote \( U_t|b_i, s_{ij} = F_{T_i} (t|b_i, T_i^* > s_{ij}) \) and \( U_{y_{ij}|b_i, s_{ij}} = F_{Y_{ij}} (y_{ij}|b_i, T_i^* > s_{ij}) \) for convenience. The joint distribution of \( U_{T_i}|b_i, s_{ij} \) and \( U_{Y_{ij}|b_i, s_{ij}} \) at each \( s_{ij} \) is modelled by the bivariate copulas with a Kendall’s correlation \( \tau_{ij} \) capturing their residual dependency arising from local biological variation. The bivariate Gaussian and \( t_\nu \) copulas are considered here since they are comprehensive copulas which have an unrestricted Kendall’s \( \tau \) between -1 and 1. Although the bivariate Clayton and Frank copulas also claim to be comprehensive, their formulas are actually defined separately on the copula parameters to take full range and numerical problems could occur when performing estimation (Yuan, 2007[47]). Nevertheless, their joint likelihood under these two copulas are also provided in Appendix A for completeness.

Let \( \phi(\cdot) \) and \( \psi(\cdot; \nu) \), \( \Psi(\cdot; \nu) \) be the pdfs and cdfs of the standard normal distribution and Student’s \( t \) distribution with \( \nu \) degrees of freedom, respectively.

### 2.1. Bivariate Gaussian copula joint model

Suppose the bivariate Gaussian copula is applied to characterise the joint distribution of \( U_{T_i}|b_i, s_{ij} \) and \( U_{Y_{ij}|b_i, s_{ij}} \). Let \( Z_{t|b_i, s_{ij}} = \Phi^{-1}(U_{t|b_i, s_{ij}}) \) and \( Z_{y_{ij}|b_i, s_{ij}} = \Phi^{-1}(U_{y_{ij}|b_i, s_{ij}}) = (y_{ij} - x_{ij} \beta_1 - z_{ij} \beta_2)/\sigma \). Let \( \Phi_2(\cdot; \alpha) \) and \( \phi_2(\cdot; \alpha) \) denote the joint CDF and pdf of a bivariate standardised normal random vector with mean 0 and the Pearson’s correlation \( \alpha \). The joint PDF of \( T_i^*, Y_{ij}|T_i^* > s_{ij}, b_i, j = 1, ..., n_i \) is given by:

\[
F_{T_i^*, Y_{ij}} (t, y_{ij}|b_i, T_i^* > s_{ij}) = \Phi_2 \left( Z_{t|b_i, s_{ij}}, Z_{y_{ij}|b_i, s_{ij}}; \alpha_{ij} \right),
\]

Therefore its likelihood, depending on censored or not, can be derived as:

\[
f_{T_i^*, Y_{ij}} (t, y_{ij}|b_i, T_i^* > s_{ij}) = \sigma^{-1} \phi_2 \left( Z_{t|b_i, s_{ij}}, Z_{y_{ij}|b_i, s_{ij}}; \alpha_{ij} \right) \frac{dU_{t|b_i, s_{ij}}/dt}{\phi(Z_{t|b_i, s_{ij}})}, \tag{5}
\]

or

\[
f_{T_i^*, Y_{ij}} (T_i^* > t, y_{ij}|b_i, T_i^* > s_{ij}) = \Phi \left( \frac{Z_{t|b_i, s_{ij}} - \alpha_{ij} Z_{y_{ij}|b_i, s_{ij}}}{\sqrt{1 - \alpha^2_{ij}}} \right) \frac{dU_{y_{ij}|b_i, s_{ij}}}{dy_{ij}}, \tag{6}
\]

where \(-1 < \alpha_{ij} < 1\) controls the strength of dependency and it is a function of Kendall’s correlation as \( \alpha_{ij} = \sin(\pi \tau_{ij}/2) \). The complete likelihood under the bivariate Gaussian copula joint model can be obtained by substituting (6) and (5) back into (4).

### 2.2. Bivariate \( t_\nu \) copula joint model

Suppose the bivariate \( t_\nu \) copula is used to characterise the joint distribution of \( U_{T_i}|b_i, s_{ij} \) and \( U_{Y_{ij}|b_i, s_{ij}} \). Let \( W_{t|b_i, s_{ij}} = \Psi^{-1}(U_{t|b_i, s_{ij}}; \nu) \) and \( W_{y_{ij}|b_i, s_{ij}} = \Psi^{-1}(U_{y_{ij}|b_i, s_{ij}}; \nu) \). Let \( \Psi_2(\cdot; \alpha, \nu) \) and \( \psi_2(\cdot; \alpha, \nu) \) denote the joint CDF and pdf of a bivariate \( t_\nu \) random vector with mean 0 and Pearson’s correlation \( \alpha \). The joint PDF of \( T_i^*, Y_{ij}|T_i^* > s_{ij}, b_i, j = 1, ..., n_i \) is given by:

\[
F_{T_i^*, Y_{ij}} (t, y_{ij}|b_i, T_i^* > s_{ij}) = \Psi_2 \left( W_{t|b_i, s_{ij}}, W_{y_{ij}|b_i, s_{ij}}; \alpha_{ij}, \nu \right)
\]
The modelling of \( \tau \) functions, the direct estimation of which is achieved by using fewer nodes in (9) compared to the original parameterisation in (4). Around subject-specific random effects. Thus higher accuracy of numerical approximation can be concentrated around \( 0 \) while the main mass of the integrand in (4) is more likely to locate around \( \nu \). The expressions for the \( \nu \) coefficient vector such that \( \psi \) is the pdf of multivariate normal distribution with mean vector \( \mathbf{0} \) and covariance matrix \( \mathbf{V}_y \), which normally concentrates around \( \mathbf{0} \). The expressions for \( f_{T_1|T_2}(t_1|y_1, b_1) \) under the four bivariate copula joint models are provided in Appendix B.

The quadrature points of the weighting kernel \( f_b(b_1|y_1) \) in (9) are subject adaptive by including the information from the longitudinal process and expected to be closer to the subject-specific random effects as well as the main mass of the integrand \( f_{T_1}(t_1|y_1, b_1) \), which normally concentrates around subject-specific random effects. Thus higher accuracy of numerical approximation can be achieved by using fewer nodes in (9) compared to the original parameterisation in (4).

Although the Kendall’s correlation function can be modelled continuously by cubic B-spline basis functions, the direct estimation of \( \tau(t) \) is restricted by its range of \([-1,1]\). Therefore we consider \( r(t) = \log \{|1 + \tau(t)| / |1 - \tau(t)|\} \) in the estimating process, then transform \( r(t) \) back to \( \tau(t) \). The modelling of \( r(t) \) is performed by a linear combination of \( l \) cubic B-spline basis functions, \( B_l(t) = [B_1(t), ..., B_l(t)]' \), with \( l \times 1 \) coefficient vector \( \eta \), such that \( r(t) = B_l(t) \eta \). Once the
estimations of the coefficient vector \( \eta \) are obtained, the estimation of the \( r(t) \) can be constructed as \( \hat{r}(t) = B_i(t) \hat{\eta} \).

The maximisation of (9) can be carried out numerically through a Newton-type algorithm (Dennis, et al., 1983[8]) or the approach in Nelder and Mead (1965)[29], which are implemented by the \texttt{nlm} and \texttt{optim} functions, respectively, in \texttt{R}, and the standard errors can be estimated from the inverse Hessian matrix as a by-product from the two functions. The initial values for the longitudinal and survival sub-models can be obtained by fitting a regular joint model through \texttt{jointModel} or \texttt{joint} functions from \texttt{JM} or \texttt{joinerR} packages, respectively, while the correlation parameters in the bivariate copula functions can be initialised as \( \tilde{\theta} \).

\subsection{Copula misspecification}

Since our model assume a parametric bivariate copula, we would like to investigate the impacts of misspecifying copulas on parameter estimation. Assume the two sub-models and random effects distribution are correctly specified. Denote \( \theta = (\theta_y', \theta_t', \theta_b') \) as the parameters of interest, where \( \theta_y = (\beta_1', \sigma') \), \( \theta_t = (\beta_2', \gamma, \lambda_1, \ldots, \lambda_K) \), \( \theta_b = \text{vec}(D) \) and \( \theta_\alpha \) is the parameters in the bivariate copulas. According to the likelihood function in (9), its log-likelihood is:

\[
\log \left\{ f_{T_i} (t_i | y_i, b_i) \right\} = \log \left\{ \phi_{n_i} \left( y_i - x_i\beta_1, \ldots, x_i\beta_1; V_{y_i} \right) \right\} + \log \left\{ \int_{b_i} f_{T_i} (t_i | y_i, b_i) f_b (b_i | y_i) \, db_i \right\}
\]

Denote \( \tilde{\phi} \) as the maximum likelihood estimators under the correct and misspecified log-likelihoods. The difference between \( f_{T_i} (t_i | y_i, b_i) \) and \( \tilde{f}_{T_i} (t_i | y_i, b_i) \) would result in biases in \( \hat{\theta} \).

We then investigate the performance of \( \tilde{\theta} \) as \( n_i \rightarrow \infty \). Note that \( \log \{ f_b (b_i | y_i) \} = \text{Constant} + \log \{ f_y (y_i | b_i) \} + \log \{ f_b (b_i) \} \). Since \( \log \{ f_y (y_i | b_i) \} = \sum_{j=1}^{n_i} \log \{ f_{y_j} (y_{ij} | b_i) \} \) is \( O(n_i) \), while \( \log \{ f_b (b_i) \} \) is \( O(1) \) and smooth functions with regard to \( b_i \). The asymptotic Bayesian theory (Cox and Hinkley, 1974[7]) states that \( \tilde{f}_b (b_i | y_i) \) converges to a multivariate normal density, with mean vector \( \tilde{b}_i = \arg \max_b \log \{ f_{Y_i} (y_i | b_i) \} \) and variance-covariance matrix \( \tilde{D}_i = \left[ -\partial^2 \log \{ f_{Y_i} (y_i | b_i) \} / \partial b_i \partial b_i^\top | b_i = b_i \right]^{-1} \) as \( n_i \) increases. Moreover, this distribution is going to degenerate to its mean \( \tilde{b}_i \) as \( n_i \rightarrow \infty \).

Denote \( \hat{\theta} \) and \( \tilde{\theta} \) as the maximum likelihood estimators under the correct and misspecified log-likelihoods. The difference between \( f_{T_i} (t_i | y_i, b_i) \) and \( \tilde{f}_{T_i} (t_i | y_i, b_i) \) would result in biases in \( \hat{\theta} \).

Note that \( \log \left\{ \phi_{n_i} \left( y_i - x_i\beta_1, \ldots, x_i\beta_1; V_{y_i} \right) \right\} \) is \( O_p(n_i) \), while the second terms of (10) and (11) converge to \( \log \{ f_{T_i} (t_i | y_i, \tilde{b}_i) \} \) and \( \log \{ f_{T_i} (t_i | y_i, \tilde{b}_i) \} \), respectively, and they are both \( O_p(1) \). For fixed sample size \( n \), let \( m = \min \{ n_i, i = 1, \ldots, n \} \rightarrow \infty \), the correct and misspecified log-likelihood, after normalising by \( m \), are:

\[
\frac{1}{m} I = \frac{1}{m} \sum_{i=1}^{n} \log \left\{ \phi_{n_i} \left( y_i - x_i\beta_1, \ldots, x_i\beta_1; V_{y_i} \right) \right\} + \frac{1}{m} \sum_{i=1}^{n} \log \left\{ f_{T_i} (t_i | y_i, \tilde{b}_i) \right\}
\]
\[ \frac{1}{m} \hat{l} = \frac{1}{m} \sum_{i=1}^{n} \log \left\{ \phi_n \left( y_{i1} - x_{i1}^{'} \beta_1, \ldots, y_{in_i} - x_{in_i}^{'} \beta_1; V_{y_i} \right) \right\} + \frac{1}{m} \sum_{i=1}^{n} \log \left\{ \hat{f}_T(t_i|y_i, \hat{b}_i) \right\}. \]

The second terms of \( l/m \) and \( \hat{l}/m \) are both \( o_p(1) \), while their first term are the same and \( O_p(1) \). Therefore, \( l/m \xrightarrow{p} \hat{l}/m \) and the maximum likelihood estimators of \( \theta_y \) and \( \theta_b \) under \( l \) and \( \hat{l} \) both converge in probability to the maximiser of \( 1/m \sum_{i=1}^{n} \log \left\{ \phi_n \left( y_{i1} - x_{i1}^{'} \beta_1, \ldots, y_{in_i} - x_{in_i}^{'} \beta_1; V_{y_i} \right) \right\} \), which means \( \hat{\theta}_y \xrightarrow{p} \theta_y \) and \( \hat{\theta}_b \xrightarrow{p} \theta_b \) as \( m \to \infty \).

3. Simulation studies

Simulation studies are conducted to investigate the finite sample performance of the proposed model. The following sub-models for the two processes are applied throughout the simulation studies. The longitudinal process is specified as:

\[ Y_{ij} = \beta_{10} + \beta_{11}s_{ij} + \beta_{12}x_{i1} + \beta_{13}x_{i2} + \beta_{14}I(\text{cat}_i = x_3) + \beta_{15}I(\text{cat}_i = x_4) + b_{0i} + b_{1i}s_{ij} + \varepsilon_{ij}, \quad (12) \]

and the survival process is taken to be:

\[ h_i(t) = h_0(t) \exp \left\{ \beta_{21}x_{i1} + \beta_{22}x_{i2} + \beta_{23}I(\text{cat}_i = x_3) + \beta_{24}I(\text{cat}_i = x_4) + \gamma(b_{0i} + b_{1i}t) \right\}, \quad (13) \]

where \( x_{i1} \) and \( x_{i2} \) have probability 0.5 taking value 1 or 0, while \( \text{cat}_i \) is a factor following a categorical distribution with probability 0.3, 0.5 and 0.2 being one of the categories of \( x_3, x_4 \) and \( x_5 \), emulating a covariate having three levels with \( x_5 \) as the reference level. The measurement error \( \varepsilon_{ij} \sim N(0, \sigma^2) \) is independent of the random effects \( (b_{0i}, b_{1i}) \sim N_2(0, D) \) with \( \text{vech}(D) = (D_{11}, D_{12}, D_{22}) \). A constant baseline hazard function, \( h_0(t) = 1 \), is selected for simplicity.

The four bivariate copulas discussed in Section 2 are used to link the two sub-models and three cases of Kendall’s tau correlations are considered, namely case 1: constant positive correlation with \( \tau(t) = 0.5 \), case 2: time-varying correlation with \( \tau(t) = [\exp \{ r(t) \} - 1] / [\exp \{ r(t) \} - 1] \), where \( r(t) \) are consist of 6 cubic B-spline basis functions with equally spaced knots over \([0, 10.2] \) and coefficient vector \( \eta = (0.1, -1, 2, -4, 4, -0.1) \), and case 3: constant negative correlation with \( \tau(t) = -0.5 \).

The above setup are used for simulating data in the two scenarios of \( n_i \) with scenario 1: the measurement times are scheduled at \( t = 0, 1, \ldots, 9, 10 \) with up to max\( (n_i) = 11 \) measurements per subject and scenario 2: the measurements are planned at \( t = 0, 2, \ldots, 8, 10 \) with up to max\( (n_i) = 6 \) measurements per subject. Except the origin \( t = 0 \), the time points are subjected to a uniform distribution error between \([-0.2, 0.2] \). An independent censoring process following an exponential distribution of rate 0.011 is considered with the event process finally terminated at \( t = 11 \), resulting in around 50% censoring rate for the event times.

In each scenario, \( N = 500 \) Monte Carlo samples each with sample size \( n = 200 \) subjects are generated under all the combinations of copulas and Kendall’s tau functions. The following candidate models are used to fit the simulated datasets.

- **Bivariate Gaussian copula joint model (GJM-k)**: the marginals are correctly specified as (12) and (13), while the correlation between the two sub-models after conditioning on the random effects is introduced by the bivariate Gaussian copula function with \( r(t) \) modelled by \( k \) cubic B-spline basis functions with equally spaced knots over \([0, 10.2] \).
- **Bivariate \( t_4 \) copula joint model (T4JM-k)**: the marginals are correctly specified as (12)
and (13), while the correlation between the two sub-models after conditioning on the random effects is introduced by the bivariate $t_4$ copula function with $r(t)$ modelled by $k$ cubic B-spline basis functions with equally spaced knots over $[0,10.2]$.

- **Regular joint model (RJM):** the marginals are correctly specified as (12) and (13) and assumed to be conditionally independent given the random effects.

### 3.1. Fitted results

In each scenario, twelve types of datasets are generated under different combinations of copulas and Kendall’s tau functions while four types of datasets under the four types of bivariate copulas are simulated in each case. Denote them as Gaussian, $t_4$, Frank and Clayton datasets for simplicity. Each type of dataset are fitted by the three candidate models. We present and discuss some of the results from scenario 1. In Tables 1 and 2, SE denotes the model based standard calculated from the observed Fisher information matrix, SD is the standard deviation calculated from the estimates based on the 500 Monte Carlo samples and CP are coverage probability for the 95% confidence intervals based on SE. The remaining outputs for the full simulation studies are available in the supplementary materials.

**Case 1: positive constant Kendall’s tau correlation:** $\tau(t) = 0.5$

Table 1 displays the results fitted by GJM-4, T4JM-4 and RJM for the four types of data in case 1 of scenario 1. In this case, except the random effects, there is a strong positive constant correlation introduced by the bivariate copula functions between the two processes in the simulated data. The RJM completely ignore the correlation in the copulas, thus obvious biases is observed in some of the parameter estimations. Specifically, the association parameter $\gamma$ is severely overestimated to compensate for the extra dependency from the bivariate copula functions. Moderate biases can be observed in the regression parameters $\beta_2$ of the survival sub-model and $\beta_{11}$ of the longitudinal sub-model, although the biases in the remaining parameters of $\beta_1$ is small. If comparing the fitted outputs by RJM across the four types of dataset, the most significant biases can be found for the dataset from the bivariate Clayton copula joint model, while the least biases are observed when fitting the Frank datasets. The biases of fitting RJM to the Gaussian and $t_4$ datasets are roughly the same and between that of the previous two datasets.

On the other hand, even the max($n_i$) is just 11, the parameters estimated by GJM-4 and T4JM-4 are almost unbiased across the four types datasets no matter the bivariate copula functions are misspecified or not. Denote $f_{T_i, Y_i}(t_i, y_i)$ as the likelihood of the data under the exact joint model (EJM), which is the correct model with the true parameter values substituted in. White (1982)\textsuperscript{[44]} states that the maximum likelihood estimator $\hat{\theta}$ will converge in probability to the value that minimise the Kullback-Leibler divergence $D_{KL}(f^*\|\hat{f}) = \int f_{T_i, Y_i}(t_i, y_i)\log\{f_{T_i, Y_i}(t_i, y_i)/\hat{f}_{T_i, Y_i}(t_i, y_i)\}dy_idt_i$. According to the log likelihood in (10) and (11), the minimisation can be achieved by setting $\hat{\theta}_y$ and $\hat{\theta}_t$ around their true values then select the values of $\hat{\theta}_y$ and $\hat{\theta}_t$ to minimise $\|\log\{f_{T_i}(t_i|b_i, y_i)\} - \log\{f_{T_i}^*(t_i|b_i, y_i)\}\|$. In fact, for GJM-4 and T4JM-4, the simulation results further suggest that their $\hat{\theta}_t$ are also close to its true value and their $\|\log\{f_{T_i}(t_i|b_i, y_i)\} - \log\{f_{T_i}^*(t_i|b_i, y_i)\}\|$ can be effectively reduce by adjusting the copula parameters $\theta_{ta}$, while the RJM lacks this flexibility and results in biased $\hat{\theta}_t$.

We calculate values of $\log\{f_{T_i}(t_i|b_i, y_i)\}$ under different models for a Monte Carlo sample of sample size 200 under the Clayton and Frank datasets. Figure 1 presents the boxplot of $\log\{f_{T_i}(t_i|b_i, y_i)\}$ under the EJM, and the $\log\{f_{T_i}^*(t_i|b_i, y_i)\}$ under the GJM-4, T4JM-4 and RJM with the true values of $\theta_y$, $\theta_t$, $\theta_b$ and the estimated $\hat{\tau}(t)$ in Figure 2 substituted in. This posterior density under the
GJM-4 and T4JM-4 are very close to that of EJM, while the density under the RJM are quite different from that of them and their differences are more prominent under the Clayton dataset, which validates our aforementioned arguments.

![Figure 1](image1.png)

**Figure 1.** The logarithm of $f_{T_i}(t_i | b, y_i)$ by the EJM, GJM-4, T4JM-4 and RJM with the true value of $\theta_y, \theta_z, \theta_b$ and the estimated $\hat{\tau}(t)$ in Figure 2 substituted in under the Clayton and Frank datasets from case 1 of scenario 1.

![Figure 2](image2.png)

**Figure 2.** The fitted Kendall’s correlation functions $\hat{\tau}(t)$ (solid lines) with their corresponding 95% confidence interval functions (dashed lines) by the GJM-4 and T4JM-4 for the Clayton and Frank datasets. Under the same strength of Kendall’s tau correlation, the bivariate Clayton joint model introduce stronger dependency between the sub-models than the bivariate Gaussian and $t_4$ copula joint models, while the dependency among the bivariate Frank one is the weakest among the four models. These conclusions are consistent with the discussions regarding biases of parameter estimations fitted by RJM under the four datasets in Table 1.

Therefore, only the copula parameters $\theta_\alpha$ are biasedly estimated in GJM-4 and T4JM-4. Figure 2 presents the $\hat{\tau}(t)$ estimated by GJM-4 and T4JM-4 for the Clayton and Frank datasets. Under the same strength of Kendall’s tau correlation, the bivariate Clayton joint model introduce stronger dependency between the sub-models than the bivariate Gaussian and $t_4$ copula joint models, while the dependency among the bivariate Frank one is the weakest among the four models. These conclusions are consistent with the discussions regarding biases of parameter estimations fitted by RJM under the four datasets in Table 1.

Although, there is also moderate biases in $\hat{\theta}_b$ by fitting the RJM to the simulated datasets, these biases has been decreasing as $n_i$ increase by comparing to the fitted results in scenario 2 with max($n_i$) = 6. This tendency agrees with the discussion in Section 2.4.
Overall, apart from misusing the independence copula, i.e. RJM, the estimations for $\theta_y$, $\theta_t$ and $\theta_b$ are very robust against to the copula misspecification under the proposed joint models even with a moderate number of repeated measurements in each subject.

In the case of $\tau(t) = -0.5$, the conclusions are very similar to that of $\tau(t) = 0.5$, except the biases of parameter estimations are in the opposite direction, thus it is not discussed here. The results are provided in the supplementary materials.

**Case 2: Time Varying Kendall’s Tau Correlation**

In this case, the Kendall’s tau correlation function is time-varying and designed in the way that the duration and magnitude of positive and negative parts are roughly equivalent. Table 2 lists the fitted outputs by the GJM-6, T4JM-6 and RJM for the four types datasets in scenario 1. As discussed in case 1, the estimators for $\theta_y$, $\theta_t$ and $\theta_b$ are robust against copula misspecification, thus the results are almost unbiased by fitting GJM-6 and T4JM-6.

In contrast to case 1, the same level of robustness is also observed for the parameter estimations by RJM here. Note that the estimators of $\theta_y$, $\theta_t$ and $\theta_b$ fitted by RJM are biased in opposite direction for datasets between cases 1 and 3, thus it is possible to shrink the biases by selecting some correlation functions with almost equal impact from the negative and positive sides.

**Table 1.** Average AIC and BIC for the candidate models fitted on the Gaussian datasets from case 2 in scenario 1.

|               | GJM-4     | GJM-5     | GJM-6     | GJM-7     | GJM-8     |
|---------------|-----------|-----------|-----------|-----------|-----------|
| AIC           | 12802.43  | 12806.35  | 12770.16  | 12772.97  | 12771.02  |
| BIC           | 12868.39  | 12875.61  | 12842.73  | 12848.83  | 12850.18  |

Unlike case 1, there is also a risk of misspecifying correlation function in case 2. Following Yao (2007)[46] and Wang et al. (2024a[42] and 2024b[43]), we select the optimal numbers and locations of knots by AIC and BIC criteria. Taking the Gaussian datasets for example, given the two sub-models, random effects distribution and copula function are correctly specified. As shown in Table 1, the two criteria are able to select the true model among the candidate models with 4, 5, 6, 7 and 8 cubic B-spline basis functions with equally space knots over $[0, 10.2]$. Figure 3 presents the fitted correlation functions with 4, 6 and 8 B-spline basis functions. The correlation function is best-fitted by 6 cubic B-spline basis functions, as this is the correct model, but the fitted curved by 8 basis functions is quite close. On the other hand, 4 cubic B-spline basis functions are no enough to provide adequate fit for the correlation function. However, if the interest is only on estimating $\theta_y$, $\theta_t$ and $\theta_b$, then the specification for the correlation function does not matter for the datasets from case 2, since all the candidates can provide accurate estimations on these parameters for the reasons discussed above.

**Figure 3.** The fitted Kendall’s correlation functions $\hat{\tau}(t)$ (solid lines) with their corresponding 95% confidence interval functions (dashed lines) by the GJM-4, GJM-6 and GJM-8 when the true datasets are the Gaussian datasets from case 2 of scenario 1.
| True | $\beta_{10}$ | $\beta_{11}$ | $\beta_{12}$ | $\beta_{13}$ | $\beta_{14}$ | $\beta_{15}$ | $\beta_{21}$ | $\beta_{22}$ | $\beta_{23}$ | $\beta_{24}$ | $D_{11}$ | $D_{22}$ | $D_{12}$ | $\sigma$ | $\gamma$ |
|------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| GJM-4 | 9.890 -0.562 | 1.066 0.534 | 0.526 0.101 | -0.265 -1.013 | -1.130 -3.063 | -2.104 -2.062 | 0.014 0.006 | -0.213 0.234 | -0.562 0.101 | -0.265 0.341 | 1.066 0.534 | 0.526 0.101 | -0.265 -1.013 | -1.130 -3.063 | -2.104 -2.062 |
| SE | 0.350 0.032 | 0.237 0.206 | 0.355 0.327 | 0.262 0.346 | 0.236 0.314 | 0.298 0.305 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 | 0.030 0.030 |
| CP | 0.956 0.963 | 0.936 0.948 | 0.948 0.954 | 0.954 0.952 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 | 0.946 0.946 |
| Data generated by the bivariate Frank copula joint model (Frank dataset) |

Table 2. Estimation of the parameters by GJM-4, T4JM-4 and RJM for simulated data from case 1 of scenario 1.
Table 3. Estimation of the parameters by GJM-6, T4JM-6 and RJM for simulated data from case 2 of scenario 1.

| True value | β₁₀ | β₁₁ | β₁₂ | β₁₃ | β₁₄ | β₁₅ | β₂₁ | β₂₂ | β₂₃ | β₂₄ | D₁₁ | D₁₂ | D₁₃ | σ | γ |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|---|
| GJM-6      |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   |
| Est.       | 0.95 | 0.93 | 0.94 | 0.95 | 0.95 | 0.90 | 0.89 | 0.91 | 0.92 | 0.93 | 0.87 | 0.92 | 0.93 | 0.93 | 0.93 |
| SE         | 0.03 | 0.03 | 0.04 | 0.03 | 0.04 | 0.03 | 0.04 | 0.03 | 0.04 | 0.03 | 0.04 | 0.03 | 0.04 | 0.03 | 0.03 |
| SD         | 0.05 | 0.07 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| CP         | 0.94 | 0.94 | 0.95 | 0.96 | 0.94 | 0.92 | 0.94 | 0.93 | 0.94 | 0.94 | 0.92 | 0.94 | 0.93 | 0.94 | 0.93 |
| T4JM-6     |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   |
| Est.       | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 |
| SE         | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| SD         | 0.04 | 0.05 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 | 0.04 |
| CP         | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 |
| RJM        |     |     |     |     |     |     |     |     |     |     |     |     |     |   |   |
| Est.       | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 | 0.95 |
| SE         | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| SD         | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| CP         | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 | 0.94 |

Data generated by the bivariate Gaussian copula joint model (Gaussian dataset)
3.2. Dynamic prediction

After a joint model is fitted, we also focus on predictions of the subject-specific survival probabilities based on some baseline covariates and updated longitudinal information. The quality of the predictions is of interest as well and can be assessed by some metrics like the area under the receiver operating characteristic curve (AUC) and calibration by PE.

3.2.1. Formula for prediction

Suppose a time-varying bivariate copula joint model is fitted based on a random sample of n subjects \( D_n = \{ T_i, \delta_i, y_i; i = 1, \ldots, n \} \). Predictions of survival probabilities at time \( u > t \) for a new subject \( i \), which has \( j, 1 \leq j \leq n_i \), longitudinal measurements \( Y_i(t) = \{ y_i(s); 0 \leq s < t \} \) up to \( t \) and a vector of baseline covariates \( w_i \), can be derived as:

\[
\hat{\pi}_i(u|t) = P(T_i^* > u|T_i^* > t, Y_i(t), w_i, D_n; \theta) = P(T_i^* > u|T_i^* > t, Y_i(t), w_i; \theta)
= \int_{b_i} P(T_i^* > u|T_i^* > t, Y_i(t), w_i, \hat{b}_i; \theta) f_{b_i}(b_i|T_i^* > t, Y_i(t), w_i; \theta) db_i
= \int_{b_i} P_T(T_i^* > u|T_i^* > s_{ij}, Y_i(t), w_i, \hat{b}_i; \theta) f_{b_i}(b_i|T_i^* > t, Y_i(t), w_i; \theta) db_i. \tag{14}
\]

The integral in (14) can be approximated by its first-order estimate (Rizopoulos, 2011[35]) using the empirical Bayes estimate for \( b_i \):

\[
\hat{\pi}_i(u|t) \approx \frac{P_T(T_i^* > u|T_i^* > s_{ij}, Y_i(t), w_i, \hat{b}_i; \theta)}{P_T(T_i^* > t|T_i^* > s_{ij}, Y_i(t), w_i, \hat{b}_i; \theta)}, \tag{15}
\]

where \( \hat{b}_i \) denotes the mode of the conditional distribution \( f_{b_i}(b_i|T_i^* > t, Y_i(t), w_i; \hat{\theta}) \).

According to (6), the bivariate Gaussian copula joint model has the following expression for (15):

\[
\hat{\pi}_i(u|t) \approx \Phi \left( -\frac{Z_u|b_i, s_{ij} - \hat{\alpha}(s_{ij})Z_{y_i|b_i, s_{ij}}}{\sqrt{1 - \hat{\alpha}(s_{ij})^2}} \right) \div \Phi \left( -\frac{Z_u|b_i, s_{ij} - \hat{\alpha}(s_{ij})Z_{y_i|b_i, s_{ij}}}{\sqrt{1 - \hat{\alpha}(s_{ij})^2}} \right), \tag{16}
\]

which reduces to \( P_T(T_i^* > u|w_i, \hat{b}_i; \hat{\theta})/P_T(T_i^* > t|w_i, \hat{b}_i; \hat{\theta}) = \exp\{ -\int_t^u h_i(s|w_i, \hat{b}_i; \hat{\theta}) ds \} \) for the regular joint model given \( \alpha(t) \) is a constant function of 0.

According to (8), the bivariate \( t_u \) copula joint model has the following expression for (15):

\[
\hat{\pi}_i(u|t) \approx \Psi \left( -\frac{W_u|b_i, s_{ij} - \hat{\alpha}(s_{ij})W_{y_i|b_i, s_{ij}}}{\hat{\sigma}(s_{ij})^2} \right) \div \Psi \left( -\frac{W_u|b_i, s_{ij} - \hat{\alpha}(s_{ij})W_{y_i|b_i, s_{ij}}}{\hat{\sigma}(s_{ij})^2} \right) \cdot \tag{17}
\]

3.2.2. Assessments of prediction performance

The overall performance of the model in predicting survival probabilities are evaluated in terms of discrimination by AUC and calibration by PE. Consider a pair of randomly selected subjects at risk by \( t \), denoted as \( i_1 \) and \( i_2 \), from the population. Suppose subject \( i_1 \) experiences the event
in the interval \((t, u]\) whereas subject \(i_2\) does not. A good predictive model is supposed to assign higher predicted survival probabilities to subject \(i_2\) than subject \(i_1\) (Garre et al., 2008[13]). The AUC defined as:

\[
AUC(u|t) = P \{ \pi_{i_2}(u|t) > \pi_{i_1}(u|t)|T_{i_2}^* > u, t < T_{i_1}^* \leq u \}
\]

is a popular tool to assess the discriminative performance of the model. An AUC value closer to 1 implies a better discriminative capability of the model. On the other hand, if a subject \(i\) is event free up to time \(u\), an accurate predicting model is expected to provide \(\pi_i(u|t)\) close to 1 and close to 0 otherwise. The PE, or the Brier score, defined as:

\[
PE(u|t) = E \left[ \{ I(T_i^* > u) - \pi_i(u|t) \}^2 | T_i^* > t \right]
\]

is a common approach to calibrate the predictive accuracy of the model. A model with a smaller PE value (closer to 0) is preferable. To account for censoring in the population, the weighted AUC and PE estimators from Andrinopoulou et al. (2018)[3] are adopted.

3.2.3. Predicted results

We simulate \(N = 100\) new Monte Carlo datasets each with sample size \(n = 200\) under the same parameter settings as cases 1 and 2 in simulation studies with longitudinal measurements scheduled at time points \(t = 0, 1, \ldots, 9, 10\).

Case 1: prediction under copula misspecification

In case 1 of the simulation study, the fitted results suggest the misspecification on copula function has minimal impact on the estimators for \(\theta_y, \theta_t, \) and \(\theta_b\) at the price of distorting the estimators of \(\theta_\alpha\) in the bivariate copula functions. We investigate its impact on the predictions of survival probabilities. Parameter estimations from Table 1 and \(\hat{\tau}(t)\) from Figure 2 are substitute into (16) and (17) to make predictions under GJM-4, T4JM-4 and RJM. In addition, the results predicted by the EJM is also provided for comparison.

![Figure 4](image-url). The AUC and PE by the EJM, GJM-4, T4JM-4 and RJM from 100 Monte Carlo samples with sample size 200 from case 1 in scenario 1.

Figure 4 presents the boxplots of AUC and PE calculated from the 100 Monte Carlo samples
under the four models at $t = 1$ with $\Delta t = u - t = 1$. The Kendall’s tau correlation of 0.5 is introduced between the two-submodels by the bivariate copula functions for the simulated datasets, but the RJM fails to capture all the copula association and its performance on survival prediction is inferior to the other models. The performance of GJM-4 and T4JM-4 are almost identical and they are both as good as EJM, which suggests that copula misspecification has minimal impact on predicting survival probability provided that the sub-models and structure of the copula correlation function are correctly specified.

Note that $\hat{\pi}(u|t)$ can also be calculated by $P_{T^*}(t_i > u|\hat{b}_i, Y_i(t)) / P_{T^*}(t_i > t|\hat{b}_i, Y_i(t))$. As explained in Section 3.1, $|\hat{f}_{T^*}(t_i|b_i, y_i) - \tilde{f}_{T^*}(t_i|b_i, y_i)|$ is significantly decreased by fitting GJM-4 and T4JM-4, while it cannot be effectively reduced in RJM. Thus except misspecifying as the independence copula, the predicted survival probability is robust under copula misspecification.

**Case 2: prediction under correlation function misspecification**

In this case, we investigate the impact of misspecifying the correlation function in the bivariate copula given the copula is correctly chosen. Taking the Gaussian datasets from case 2 as an example, Figure 3 indicates the lack of fit of the correlation functions by GJM-4, while GJM-8 provides similar fitting to the correct model GJM-6. In fact, underfitting is more of an issue than overfitting here, as there is no measurement error in the correlation function. Nevertheless, the most appropriate number and locations of knots could be selected by AIC and BIC.

Figure 5 shows the dynamic AUC and PE for the EJM, GJM-8, GJM-6, GJM-4 and RJM at $t = 2$ and 6 with $\Delta t = u - t = 1$. At $t = 2$, the five models provide almost equivalent prediction, and this is expected, as the correlation introduced by copula is about 0 at this time point and the five models have similar estimates of parameters. However, the prediction by EJM, GJM-6 and GJM-8 are superior than that of GJM-4 and RJM at $t = 6$. This is because the simpler correlation structures in the latter two models fail to capture the strong negative local correlation and are unable to use all the information from the longitudinal process for predicting at this time point.

Since the estimations on parameters and predictions on survival probabilities are insensitive to copula misspecification, the bivariate Gaussian copula is recommended in practice due to its computational simplicity. But the structure of the correlation function in the copula should be treated with caution, especially avoiding lack of fit.

**Figure 5.** The AUC and PE by the EJM, GJM-8, GJM-6, GJM-4 and RJM from 100 Monte Carlo samples with sample size 200 for Gaussian datasets from case 2 in scenario 1.

### 4. Application to the PBC data

The PBC data (Murtaugh, et al, 1994[28]) records the information of 312 patients with primary biliary cirrhosis from 1974 to 1984. The main task of this study is to evaluate the treatment effect of D-penicillamine (158 randomised patients) compared with placebo (154 randomised patients). Baseline covariates such as age at the entry of study, gender and treatment are recorded. In the
Meanwhile, several biomarkers, such as serum bilirubin level (mg/dl), the presence of spiders and hepatomegaly (indicator variables), are monitored as follow-up. Among them, the serum bilirubin level is considered as a stronger indicator for the progression of the disease. After the baseline measurement, each patient was scheduled for visits at six months, one year and yearly afterwards, but not all patients attended the appointments at the scheduled time points and some even missed appointments, leading to an unbalanced dataset. Also due to death and censoring, only 1945 measurements of serum bilirubin levels are recorded, with the maximum measurement time up to 14.106 years and the number of measurements for each patient vary from 1 to 16. By the end of study, 149 patients died, 29 had a transplantation and 143 were still alive.

Due to the relatively long gap between successive measurements and the high variability presented in the longitudinal trajectories of this dataset, we would like to investigate if there is local residual correlation between the two processes due to the unexplained local biological variation.

The proposed time-varying bivariate copula joint model is used to model the PBC data, with the longitudinal process specified as follows:

\[
y_{ij} = \mu(s_{ij}) + \beta_{11}drug_i + \beta_{12}sex_i + \beta_{13}age_i + b_{i0} + b_{i1}s_{ij} + \varepsilon_{ij},
\]

where \( \varepsilon_{ij} \sim N(0, \sigma^2) \), \((b_{i0}, b_{i1}) \sim N(0, D)\) and \(y_{ij}\) is the logarithm of serum bilirubin level for the \(i\)th subject at time \(s_{ij}\). Unlike in the simulation study, we model the population mean function \(\mu(t)\) non-linearly by B-spline basis functions to allow more flexibility. Death or transplantation is defined as the composite event. The time to event process is specified as:

\[
h_i(t) = h_0(t)\exp\{\beta_{21}drug_i + \beta_{22}sex_i + \beta_{23}age_i + \gamma (b_{i0} + b_{i1}t)\},
\]

where \(drug_i = 1\) for D-penicillamine, \(gender_i = 1\) for female and \(h_0(t)\) is a piecewise-constant function with equally spaced knots between 0 and the maximum observed event time at 14.306.

Three candidate models are applied for fitting the PBC dataset:

- **The bivariate Gaussian copula joint model (PGJM)**: the two sub-models are specified as (18) and (19), while the correlation between them is introduced by the bivariate Gaussian copula with \(\mu(t)\) and \(\tau(t)\) modelled by \(k\) and \(l\) cubic B-spline basis functions with knots located at the quantiles of the longitudinal measurement time points.

- **The bivariate t\(\nu\) copula joint model (PT\(\nu\)JM)**: the two sub-models are specified as (18) and (19), while the correlation between them is introduced by the bivariate t\(\nu\) copula function with \(\mu(t)\) and \(\tau(t)\) modelled by \(k\) and \(l\) cubic B-spline basis functions with knots located at the quantiles of the longitudinal measurement time points.

- **The regular joint model (PRJM)**: the two sub-models are specified as (18) and (19) and assumed to be conditionally independent given the random effects, which is equivalent to \(\tau(t) = 0\) in the bivariate Gaussian copula joint model.

We select the optimal number of piecewise-constant baseline hazard function and knots of cubic B-spline basis functions by AIC and BIC. Unlike the simulation study, the knots of the basis functions are located at the sample quantiles of the longitudinal measurements time points. The optimal combination is 6 cubic B-spline basis functions for \(\mu(t)\), 7 cubic B-spline basis functions for \(\tau(t)\) and a piecewise-constant baseline hazard function with 7 pieces. We also notice that the fitted trajectories of \(\hat{\mu}(t)\) and \(\hat{\tau}(t)\) remain approximately the same when increasing the numbers of basis function beyond the optimal selection, while there are some significant changes in the trajectories by decreasing the numbers. Although we are aware that the fitted results is not sensitive to the choice of copula function, we still try to find the optimal \(\nu\) for the PT\(\nu\)JM. Under the same sub-models as
in PGJM, its log-likelihood value is increasing before \( \nu = 18 \) and gradually decreasing later on, thus the optimal value of \( \nu \) is 18. The fitted results of the three candidate models are summarised in Table 4. The two bivariate copula joint models provide similar fits in terms of parameter estimation and they result in a similar fitted population mean function \( \hat{\mu}(t) \) and Kendall’s tau correlation function \( \hat{\tau}(t) \), according to Figures 6 and 7. These results are consistent with the discussions in Section 2.4. In addition, the two bivariate copula joint models both provide significantly better fitting than the PRJM in terms of AIC and BIC. The correlation between the two sub-models is close to 0 during \( 0 \leq t \leq 7 \), while it is stronger during \( 7 \leq t \leq 10 \) and the confidence intervals are much wider, especially for PT18JM, after \( t = 11 \), as there are fewer data beyond this point. This correlation structure indicates a larger negative (positive) local longitudinal variations during 7 to 10 years after entry could implies a better (worse) condition for the subject at this period, while there is no such implication in the earlier stage.

Despite the big differences in AIC and BIC, we notice that the parameter estimates and fitted mean function \( \hat{\mu}(t) \) of the PRJM are generally similar to that of the bivariate copula joint models. This is because the correlation functions stay around 0 for half of the time. In fact, the fitted mean function of PRJM is only slightly higher than that of the bivariate copula joint models at the later stage and this may be due to the stronger correlation after \( t \geq 7 \). Therefore, the proposed model does not tell us much new information compared to the PRJM in terms of the interpretations of the regression parameters. This is similar to the case 2 of the simulation study. However, we shall see the main improvements of the proposed model is in predicting survival probability.

**Table 4.** Parameter estimates for the PBC data by the three candidate models.

| Parameter | PRJM | PGJM | P18TJM |
|-----------|------|------|--------|
| \( \beta_{11} \) | -0.126 | -0.135 | -0.136 |
| \( \beta_{12} \) | -0.166 | -0.207 | -0.212 |
| \( \beta_{13} \) | -0.001 | -0.0005 | -0.0004 |
| \( \beta_{21} \) | -0.190 | -0.167 | -0.167 |
| \( \beta_{22} \) | -0.173 | -0.199 | -0.185 |
| \( \beta_{23} \) | 0.041 | 0.044 | 0.045 |
| \( D_{11} \) | 0.959 | 0.966 | 0.965 |
| \( D_{22} \) | 0.038 | 0.033 | 0.032 |
| \( D_{12} \) | 0.083 | 0.070 | 0.070 |
| \( \sigma \) | 0.342 | 0.342 | 0.342 |
| \( \gamma \) | 1.318 | 1.243 | 1.243 |
| Loglik | -1928.047 | -1889.185 | -1887.934 |
| AIC | 3904.094 | 3840.37 | 3837.868 |
| BIC | 3993.926 | 3956.403 | 3953.901 |

**Figure 6.** The fitted mean functions \( \hat{\mu}(t) \) for PBC dataset by the PGJM, PT18JM and PRJM with the corresponding 95% confidence band (dashed lines).
As the visit is scheduled yearly after the first year, the AUC and PE are calculated for the follow-up times \( t = 1, \ldots, 10 \) with \( \Delta t = 1 \) by leave-one-out cross-validation. The results are summarised in Table 5. When the correlation is weak between the two sub-models, such as when \( 3 \leq t \leq 7 \), the discriminative performance of the three candidate models are similar, with PRJM sometimes even having slightly better performance, e.g. at \( t = 4 \) and 5. When the correlation between the two sub-models is strong, for example at \( t = 8, 9 \) and 10, the two bivariate copula joint models have significantly better performance than the PRJM. The calculation of AUC and PE values are terminated for \( t \geq 11 \) as there are only three events beyond this time point. Generally, the bivariate copula joint model provides a better prediction by utilising the residual information in the local biological variation and the choice of copula function is of less importance. The bivariate Gaussian copula joint model is recommended in practice as it requires less computation.

![Figure 7](image)

**Figure 7.** The fitted Kendall’s tau correlation functions \( \hat{\tau}(t) \) for PBC dataset by the PGJM model and PT18JM with the corresponding 95% confidence band (dashed lines) and reference lines (horizontal dashed lines) at zero.

**Table 5.** AUC and PE for three candidate models at different timepoints with \( \Delta t = 1 \) for the PBC dataset.

|       | \( t = 1 \) | \( t = 2 \) | \( t = 3 \) | \( t = 4 \) | \( t = 5 \) | \( t = 6 \) | \( t = 7 \) | \( t = 8 \) | \( t = 9 \) | \( t = 10 \) |
|-------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| **AUC** |            |            |            |            |            |            |            |            |            |            |
| PGJM  | 0.772      | 0.932      | 0.853      | 0.843      | 0.757      | 0.869      | 0.799      | 0.782      | 0.883      | 0.929      |
| PT18JM| 0.774      | 0.931      | 0.848      | 0.843      | 0.760      | 0.875      | 0.799      | 0.778      | 0.878      | 0.928      |
| PRJM  | 0.739      | 0.928      | 0.847      | 0.852      | 0.770      | 0.879      | 0.793      | 0.746      | 0.796      | 0.864      |
| **PE** |            |            |            |            |            |            |            |            |            |            |
| PGJM  | 0.044      | 0.066      | 0.060      | 0.061      | 0.064      | 0.079      | 0.052      | 0.090      | 0.070      |            |
| PT18JM| 0.043      | 0.067      | 0.060      | 0.061      | 0.064      | 0.079      | 0.052      | 0.091      | 0.071      |            |
| PRJM  | 0.043      | 0.068      | 0.059      | 0.062      | 0.064      | 0.077      | 0.054      | 0.109      | 0.107      | 0.097      |

The first panel of Figure 8 displays the predicted survival probabilities of subject 21 from the PBC dataset at \( t = 8.017 \), 9.008 and 9.618 by the PGJM, PT18JM and PRJM. It is noticeable that all the three models provide almost indistinguishable fitting for the longitudinal sub-model, while the predicted survival probabilities present obvious differences. To be more specific, all three models produce similar predictions in survival probabilities at \( t = 8.017 \), where the longitudinal observations scatter relatively evenly around the fitted curves. At \( t = 9.008 \), the new longitudinal observation is obviously lower than the fitted trajectories and the Kendall’s tau correlation is quite strong at this time according to Figure 7, thus results in more optimistic predictions in survival probabilities by the two time-varying bivariate copula joint models than the PRJM. On the contrary, at \( t = 9.618 \), where the Kendall’s correlation remains strong, an updated longitudinal measurement...
higher than the fitted curves makes the two time-varying bivariate copula joint models produce lower predicted survival probabilities than the PRJM. Given the subject is still alive at $t = 9.618$, the PGJM and PT18JM provide more accurate expected event times at 10.798 and 10.820 than that of PRJM at 12.627, since the death time of this subject is at 10.013.

The second panel of Figure 8 presents another example of subject 32, whose event time is censored at $t = 14.215$. Unlike subject 21, the longitudinal process of this subject experiences a downward trend. The fitted longitudinal trajectories of the three models are almost overlapped and their predicted survival probabilities are generally very similar over time, with an exception at $t = 8.107$, where a relatively lower longitudinal observation make the PGJM and PT18JM raise their predicted survival probability more than that of PRJM.

In fact, the predictions by the PRJM remain relatively stable across the time while the two time-varying bivariate copula joint models have more flexibility by accounting extra information from the large local variation if the correlation between the two sub-models is also strong at this moment.

5. Discussion

In the paper, the regular joint model is generalised to have two layer of correlation, allowing us to relax the usually assumed but rarely checked assumption of conditional independence given the random effects in an old joint model. But the interpretations of the two dependencies are different. The predominant trend in longitudinal process acts on the event process directly by the commonly shared baseline covariates and time-invariant random effects, whose impacts are permanent and directly related to the marginal distribution of the survival sub-model. On the other hand, the

Figure 8. Dynamic prediction of survival probabilities and fitted longitudinal trajectories for subjects 21 and 32 from the PBC dataset. The solid (black), dotted (red) and dash-dotted (green) lines represent PGJM, PT18JM and PRJM, respectively, in Table 4.
unexplained variations have a dynamic but local influence on the event process via a time-varying bivariate copula and it does not affect the marginal distribution of the survival process.

In simulation studies, all the sub-models are correctly specified but fitted under different copulas. The estimators from the regular joint model may or may not present biases depending on the correlation structures in the bivariate copula for generating the data, while the estimators from the bivariate $t_\nu$ and Gaussian copula joint models are generally robust. The proposed models also have superior performance in predicting survival probability compared to the regular joint model for having stronger discrimination capability and lower prediction error, and this is especially obvious when the correlation in the bivariate copulas, described by Kendall’s tau function $\tau(t)$, is high.

The simulations also suggest both the parameter estimation and survival prediction are insensitive to the selection of the bivariate copula. Due to computational simplicity, selecting the bivariate Gaussian copula joint model seems to be a reasonable choice in practice. More attention should be paid on how to select a correlation function that are complicated enough to capture the real one and AIC and BIC criteria are applied to determine the optimal knot locations. Although even more computational expensive, the approaches of using larger number of knots by adding a roughness penalty term on the log-likelihood could also be explored in the future.

The real data application on the PBC dataset indicates our model provides significantly better fitting than the regular joint model. Despite that there are no obvious differences in the regression parameters between the proposed models and the regular joint model, the fitted correlation $\hat{\tau}(t)$ indicates there is strong extra correlation between the two processes arising from the local biological variation. The dynamic prediction of survival probabilities also shows the proposed models provide significant better predictions between $t = 7$ and 11, where the correlation is strongest.

Although assuming conditional independence within the longitudinal process, conditional on the random effects, may not be unreasonable given the relatively large gap between the two successive measurement times, what happens under the violation of this assumption is still not clear and it might be interesting to investigate this issue. A more flexible non-parametric mean function is used to capture any non-linear trends in the longitudinal trajectories, but the fixed effect regression parameters and random effects are modelled as fixed in terms of $t$. In future work, we could also consider modelling these components functionally as in Brown et al. (2005)[4] and Yao (2007)[46]. It could also be interesting to develop a similar score test for testing the conditional independence on the random effects like in Jacqmin-Gadda et al. (2010)[21].

Software

R code is available at https://github.com/zhangzili0916/bivfun-copula-jointmodel-randomeffect on Github.
Appendix A

Bivariate Clayton copula joint model

Suppose the bivariate Clayton copula is used to characterise the joint distribution of $U_{T_i^{*}|b_i,s_{ij}}$ and $U_{Y_{ij}|b_i,s_{ij}}$. Then the joint CDF of $T_i^{*}, Y_{ij}|T_i^{*} > s_{ij}, b_i, j = 1, ..., n_i$ is given by:

$$F_{T_i^{*}|Y_{ij}}(t, y_{ij}|b_i, T_i^{*} > s_{ij}) = \left\{ (U_{t|b_i,s_{ij}})^{-\alpha_{ij}} + (U_{y_{ij}|b_i,s_{ij}})^{-\alpha_{ij}} - 1 \right\}^{-\frac{1}{\alpha_{ij}}}.$$

Therefore its likelihood, depending on censored or not, can be derived as:

$$f_{T_i^{*}|Y_{ij}}(t, y_{ij}|b_i, T_i^{*} > s_{ij}) = \frac{(1 + \alpha_{ij}) \left( U_{t|b_i,s_{ij}} \times U_{y_{ij}|b_i,s_{ij}} \right)^{-\alpha_{ij}-1} \frac{dU_{t|b_i,s_{ij}}}{dt} \frac{dU_{y_{ij}|b_i,s_{ij}}}{dy_{ij}}}{\left\{ (U_{t|b_i,s_{ij}})^{-\alpha_{ij}} + (U_{y_{ij}|b_i,s_{ij}})^{-\alpha_{ij}} - 1 \right\}^{\frac{1}{\alpha_{ij}}+2}} \quad (20)$$

or

$$f_{T_i^{*}|Y_{ij}}(T_i^{*} > t, y_{ij}|b_i, T_i^{*} > s_{ij}) = \left[ 1 - (U_{y_{ij}|b_i,s_{ij}})^{-\alpha_{ij}-1} \left\{ (U_{t|b_i,s_{ij}})^{-\alpha_{ij}} + (U_{y_{ij}|b_i,s_{ij}})^{-\alpha_{ij}} - 1 \right\}^{-\frac{1}{\alpha_{ij}}} \right] \times \frac{dU_{y_{ij}|b_i,s_{ij}}}{dy_{ij}} \quad (21)$$

where $\alpha_{ij} > 0$ controls the strength of dependency and it is a function of Kendall’s correlation as $\alpha_{ij} = \frac{2\tau_{ij}}{1 - \tau_{ij}}$. The complete likelihood under the bivariate Clayton copula joint model can be obtained by substituting (20) and (21) back into (4). Note that the Clayton copula can be extended to allow $\alpha_{ij} \geq -1$ but the formulas for $-1 \leq \alpha_{ij} < 0$ are defined separately. Nevertheless, it can be extended to be a comprehensive copula in this way.

Bivariate Frank copula joint model

Suppose the bivariate Frank copula is used to characterise the joint distribution of $U_{T_i^{*}|b_i,s_{ij}}$ and $U_{Y_{ij}|b_i,s_{ij}}$. Then the joint CDF of $T_i^{*}, Y_{ij}|T_i^{*} > s_{ij}, b_i, j = 1, ..., n_i$ is given by:

$$F_{T_i^{*}|Y_{ij}}(t, y_{ij}|b_i, T_i^{*} > s_{ij}) = -\frac{1}{\alpha_{ij}} \log \left[ 1 + \frac{\exp(-\alpha_{ij}U_{t|b_i,s_{ij}}) - 1}{\exp(-\alpha_{ij}) - 1} \right] \frac{\exp(-\alpha_{ij}U_{y_{ij}|b_i,s_{ij}}) - 1}{\exp(-\alpha_{ij}) - 1}.$$

Therefore its likelihood, depending on censored or not, can be derived as:

$$f_{T_i^{*}|Y_{ij}}(t, y_{ij}|b_i, T_i^{*} > s_{ij}) = \frac{\alpha_{ij} \exp(-\alpha_{ij}) - 1}{\left[ \exp(-\alpha_{ij}) - 1 + \exp(-\alpha_{ij}U_{t|b_i,s_{ij}} + U_{y_{ij}|b_i,s_{ij}}) \right]^2} \times \frac{dU_{t|b_i,s_{ij}}}{dt} \frac{dU_{y_{ij}|b_i,s_{ij}}}{dy_{ij}} \quad (22)$$
Firstly, under the assumption in (4), we have
\[
\text{copula.}
\]
where \( \alpha_{ij} \in (\infty, \infty) \setminus \{0\} \) controls the strength of dependency and it is a function of Kendall’s correlation via the Debye function. The complete likelihood under the bivariate Frank copula joint model can be obtained by substituting (22) and (23) back into (4). Note that the Frank copula can be extended to be comprehensive by allowing \( \alpha_{ij} = 0 \), which then includes the independence copula.

\section*{Appendix B}

Firstly, under the assumption in (4), we have \( f_{Y_i}(y_i|b_i) = \prod_{j=1}^{n_i} f_{Y_{ij}}(y_{ij}|b_i) = \prod_{j=1}^{n_i} dU_{y_{ij}|b_i,s_{ij}}/dy_{ij} \). As \( f_{T^*_i}(t_i|y_i,b_i) \) are available in Sections 2.1, 2.2 and Appendix A, we are able to derive \( f_{T^*_i}(t_i|y_i,b_i) = f_{T^*_i,y_{ij}}(t_i,y_{ij}|b_i)/f_{Y_i}(y_i|b_i). \)

The posterior distribution of \( T^*_i \) under the bivariate Gaussian copula joint model is given by
\[
f_{T^*_i}(t_i|y_i,b_i) = P_{T^*_i}(T^*_i > s_{i1}|b_i) \frac{n_i-1}{\exp(-\alpha_{ij} U_{y_{ij}|b_i,s_{ij}})} \exp(-\alpha_{ij} U_{y_{ij}|b_i,s_{ij}}) \left\{ \prod_{j=1}^{n_i} \Phi \left( \frac{Z_{s_{i(j+1)}|b_i,s_{ij} - \alpha_{ij} Z_{y_{ij}|b_i,s_{ij}}}}{\sqrt{1-\alpha_{ij}^2}} \right) \right\} I(n_i \geq 2) \times \left\{ \frac{1}{\sqrt{1-\alpha_{ij}^2}} \phi \left( \frac{Z_{t_i|b_i,s_{in}} - \alpha_{in} Z_{y_{in}|b_i,s_{in}}}{\sqrt{1-\alpha_{in}^2}} \right) \frac{dU_{t_i|b_i,s_{in}}/dt_i}{\phi(Z_{t_i|b_i,s_{in}})} \right\} \delta_i \times \Phi \left( \frac{Z_{t_i|b_i,s_{in}} - \alpha_{in} Z_{y_{in}|b_i,s_{in}}}{\sqrt{1-\alpha_{in}^2}} \right)^{(1-\delta_i)}
\]

The posterior distribution of \( T^*_\nu \) under the bivariate \( t_\nu \) copula joint model is given by
\[
f_{T^*_\nu}(t_i|y_i,b_i) = P_{T^*_\nu}(T^*_\nu > s_{i1}|b_i) \left\{ \prod_{j=1}^{n_i} \psi \left( \frac{-W^\nu_{s_{i(j+1)}|b_i,t_{ij}} - \alpha_{ij} W^\nu_{y_{ij}|b_i,t_{ij}}}{\sigma(s_{ij}|b_i,y_{ij})} \right) \right\} I(n_i \geq 2) \times \left\{ \frac{1}{\sigma(s_{in}|b_i,y_{in})} \psi \left( \frac{W^\nu_{t_i|b_i,s_{in}} - \alpha_{in} W^\nu_{y_{in}|b_i,s_{in}}}{\sigma(s_{in}|b_i,y_{in})} \right) \frac{dU_{t_i|b_i,s_{in}}/dt_i}{\psi(W^\nu_{t_i|b_i,s_{in}}; \nu)} \right\} \delta_i \times \psi \left( \frac{W^\nu_{t_i|b_i,s_{in}} - \alpha_{in} W^\nu_{y_{in}|b_i,s_{in}}}{\sigma(s_{in}|b_i,y_{in})} \right)^{(1-\delta_i)}
\]

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The posterior distribution of $T_i^*$ under the bivariate Clayton copula joint model is given by

$$f_{T^*_i}(t_i | y_i, b_i) = P_{T^*_i}(T^*_i > s_{i1} | b_i)$$

$$= \left( \prod_{j=1}^{n_i-1} \left[ 1 - \left( U_{y_{i,j}} | b_i, s_{i,j} \right)^{-\alpha_{i,j} - 1} \left\{ \left( U_{s_{i,j+1}} | b_i, s_{i,j} \right)^{-\alpha_{i,j}} + \left( U_{y_{i,j}} | b_i, s_{i,j} \right)^{-\alpha_{i,j} - 1} \right\}^{-\frac{1}{\alpha_{i,j} - 1}} \right)^{I(n_i \geq 2)} \right)$$

$$\times \left( 1 + \alpha_{i,n_i} \right) \frac{dU_{Y_{i,n_i}} | b_i, s_{i,n_i}}{\alpha_{i,n_i} - 1} \left( 1 - U_{Y_{i,n_i}} | b_i, s_{i,n_i} \right)^{-\alpha_{i,n_i} - 1}$$

The posterior distribution of $T_i^*$ under the bivariate Frank copula joint model is given by

$$f_{T^*_i}(t_i | y_i, b_i) = P_{T^*_i}(T^*_i > s_{i1} | b_i)$$

$$= \left( \prod_{j=1}^{n_i-1} \left[ 1 - \exp \left( -\alpha_{i,j} U_{s_{i,j+1}} | b_i, s_{i,j} \right) - 1 \right] \frac{\exp \left( -\alpha_{i,j} U_{y_{i,j}} | b_i, s_{i,j} \right) - 1}{\exp \left( -\alpha_{i,j} U_{y_{i,j}} | b_i, s_{i,j} \right) - 1} \right)^{I(n_i \geq 2)}$$

$$\times \left( \frac{\alpha_{i,n_i} \left\{ \exp \left( -\alpha_{i,n_i} - 1 \right) \exp \left( -\alpha_{i,n_i} U_{Y_{i,n_i}} | b_i, s_{i,n_i} \right) \right\} - 1 \right) \frac{dU_{Y_{i,n_i}} | b_i, s_{i,n_i}}{\alpha_{i,n_i} - 1} \left( 1 - U_{Y_{i,n_i}} | b_i, s_{i,n_i} \right)^{-\alpha_{i,n_i} - 1}$$

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