Joint modelling of longitudinal measurements and survival times via a copula approach

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ABSTRACT
Joint modelling of longitudinal and time-to-event data is usually described by a random effect joint model which uses shared or correlated latent effects to capture associations between the two processes. Under this framework, the joint distribution of the two processes can be derived straightforwardly by assuming conditional independence given the latent effects. Alternative approaches to induce interdependency into sub-models have also been considered in the literature and one such approach is using copulas, to introduce non-linear correlation between the marginal distributions of the longitudinal and time-to-event processes. A Gaussian copula joint model has been proposed in the literature to fit joint data by applying a Monte Carlo expectation-maximisation algorithm. Enlightening as it is, its original estimation procedure comes with some limitations. In the original approach, the log-likelihood function can not be derived analytically thus requires a Monte Carlo integration, which not only comes with intensive computation but also introduces extra variation/noise into the estimation. The combination with the EM algorithm slows down the computation further and convergence to the maximum likelihood estimators can not be always guaranteed. In addition, the assumption that the length of planned measurements is uniform and balanced across all subjects is not suitable when subjects have varying number of observations. In this paper, we relax this restriction and propose an exact likelihood estimation approach to replace the more computationally expensive Monte Carlo expectation-maximisation algorithm. We also provide a straightforward way to compute dynamic predictions of survival probabilities, showing that our proposed model is comparable in prediction performance to the shared random effects joint model.

KEYWORDS
Longitudinal data; Time-to-event data; Joint modelling; Copula; Dynamic prediction; Likelihood approach

1. Introduction

In clinical studies, longitudinal measurement data with repeated measurements of response variables at a sequence of time points (informative or uninformative) and the time (censored or uncensored) until an event of particular interest occurs (time-to-event data) are often collected jointly for each sample unit. Both of these types of data have been thoroughly studied in their own field and methods have been developed to analyse them separately (Verbeke and Molenberghs, 2000[30] and Kalbfleisch and Prentice, 2002[13]). However, separate modelling is inadequate when biomarkers are associated with patients’ healthy status, thus correlated with event time. Wulfsohn and Tsiatis...
and Guo and Carlin (2004) point out a separate or two stage modelling (Ye et al, 2008 and Dafni and Tsiatis, 1998) for longitudinal and time to event data are likely to produce biased estimation and a joint modelling approach is proposed to alleviate this issue. Exhaustive overviews on joint modelling can be found on Tsiatis and Davidian (2004), Ibrahim et al. (2010) and Papageorgiou et al. (2019). Much of the literature work focuses on linking the two sub-models by either latent classes, shared or correlated random effects (normally a latent Gaussian process). Given latent variables and covariates of the two processes, conditional independence is assumed between the sub-models as well as within the longitudinal sub-model. There have been a variety of extensions on modelling these unobservable latent variables. Song, Davidian and Tsiatis (2002) relaxed the normality assumption of the random effects by allowing them to have a smooth density. Baghfalaki et al. (2017) modelled the random effects in the joint model with a finite mixture of multidimensional normal distributions to propose a heterogeneity joint model (see Verbeke and Molenberghs, 2000 for homogeneity mixed model). Henderson et al. (2000), Wang et al. (2001) and Xu et al. (2001) have discussed applying two correlated elaborate mean-zero stochastic process random effects to characterise correlation between the two sub-models and within the longitudinal measurements. A latent class model for joint analysis of longitudinal biomarker and event process data was proposed by Lin et al. (2002). Liu et al. (2015) proposed a latent class model with shared random effects, which is essentially a distinct shared random effects joint model of longitudinal and survival data within each latent class.

The most common and simple shared random effects approach naturally implies the association between the two processes is linear, an assumption which might not always hold. Copula (Hofert et al, 2018) is a very useful tool to introduce non-linear correlation between marginals, in our case, the longitudinal and survival processes. The dependency structure is adjustable while keeping the marginal distributions the same. Although the use of copulas to link multivariate or bivariate outcomes either for longitudinal or survival data has been studied extensively, e.g. see references therein, not much work has been done on the use of copulas to connect longitudinal and time-to-event data. Rizopoulos et al. (2008a and 2008b) consider applying copulas to specify the joint distribution of the random effects in the two processes instead of assuming common frailty terms. This increases the flexibility in considering different dependence structures between the two sub-models by using various copula functions. Malehi et al. (2015) adopt the same idea to model random effects but using them to join the longitudinal measurements and gap time between recurrent events. Alternatively, copulas can link the two marginals directly. Suresh et al. (2019) apply a bivariate Gaussian copula directly on event time and biomarker measured at a single time point and maximise a pseudo-likelihood to perform a dynamic prediction on event time. Diggle et al. (2008) fit the joint distribution of longitudinal measurements and the log-transformed event time using a multivariate normal distribution (a special case of applying a Gaussian copula to longitudinal and survival data, where the marginals are normal and log-normal distributions, respectively). This approach is very attractive in terms of computational ease but may lack some flexibility regarding the distribution assumption on event time. Joint modelling of all longitudinal measurements and event time formulated by a multivariate Gaussian copula, wherein all subjects are assumed to have balanced measurements at the same time points, is proposed by Ganjali and Baghfalaki (2015). The authors use a Monte Carlo expectation-maximisation algorithm for the estimation. However, uniformity in time points is not always realistic in practice. We extend the simulations of Diggle et al. (2008) and Ganjali and Baghfalaki (2015) by allowing the model to have a random visiting pattern for the longitudinal process. Our approach has more flexibility on event time distribution compared to Diggle et al. (2008) while improving the estimation process by replacing the Monte Carlo expectation-maximisation algorithm in Ganjali and Baghfalaki (2015) with an exact likelihood estimation approach. A dynamic method for predicting survival probabilities is also proposed based on the fitted copula joint model.
The remainder of the paper is organised as follows. In Section 2, notations and model specifications are briefly introduced. In Section 3, two simulation studies with the same parameterisation as in Ganjali and Baghfalaki (2015)[7] are conducted then compared. A third simulation which allows a more general correlation between the two sub-models with a random visiting and intermittent missing pattern for the longitudinal process is also conducted. A real data application is performed based on aids. The outputs of our approach are compared with that of standard R functions if available. Dynamic predictions of survival probabilities are computed and compared with the predictions by the shared random effects joint model approach. In Section 4, some limitations of this copula joint model are discussed and possible future work is proposed.

2. Copula joint model

Suppose there are \( n \) subjects \((i = 1, ..., n)\) followed over time. Let \( y_i = (y_{i1}, ..., y_{im_i}) \) be the biomarkers measured over time for the \( i \)th subject. An observed event time \( T_i = \min(C_i, T_i^*) \) is also recorded for this subject, where \( C_i \) and \( T_i^* \) denote the right censoring time and true event time, respectively. Let \( \delta_i = I(T_i^* < C_i) \) be the associated censoring indicator, which takes value 1 if the event is observed and 0 otherwise.

Consider a longitudinal process specified by the following model:

\[
y_i = x_{i1} \beta_1 + \varepsilon_i, \quad i = 1, ..., n,
\]

where \( x_{i1} \) is a \( m_i \times p \) matrix of explanatory variables with corresponding regression coefficient vector \( \beta_1 \) and \( \varepsilon_i = (\varepsilon_{i1}, ..., \varepsilon_{im_i}) \) is a \( m_i \)-dimensional vector of random errors with \( \varepsilon_i \sim N_{m_i}(0, \Sigma(\sigma, \rho_y(y_i))) \). Thus, the within subject correlation for longitudinal measurements \( y_i \) is introduced by \( \sigma \) and \( \rho_y \).

Following Ganjali and Baghfalaki (2015)[7], a relative risk model with a Weibull baseline function is considered for time-to-event data, given by:

\[
h_i(t) = rt^{r-1} \exp(x_{i2}' \beta_2)
\]

where \( x_{i2} \) denotes a \( q \)-dimensional vector of explanatory variables with corresponding regression coefficient \( \beta_2 \). In other words, the time-to-event data follow a Weibull distribution with shape parameter \( r \) and scale parameter \( \exp\left(-\frac{x_{i2}' \beta_2}{r}\right) \). A more general but computationally intensive non-parametric baseline hazard function can also be specified. For comparison, this Weibull baseline hazard function is used in the simulation study in the next section.

Instead of considering shared or correlated random effects to link the two processes, a multivariate Gaussian copula is proposed to join the marginal cdfs of the longitudinal process \( F_{y_i} \) and the event time process \( F_{T_i} \). A \( t \) copula can also be used, however it does not result in a closed form joint pdf as in (1) and (2) when normality is assumed for the longitudinal process, which can increase computational complexity. There are also some limitations for using other types of copulas due to the high dimensionality of the joint distribution of the longitudinal and time to event data. For example, Archimedean copulas with three dimensions or higher are only allowed to have positive correlation between marginals (Yuan, 2007).

Let \( \theta = \{\beta_1, \beta_2, \sigma, \rho = (\rho_y, \rho_y), r\} \) denote the vector of parameters for the joint model and \( Z_i(\beta_1, \beta_2, r) = (Z_{i1}(\beta_2, r), Z_{yi}(\beta_1))' \), where \( Z_{i1}(\beta_2, r) = \Phi^{-1}(F_{T_i}(t_i; x_{i2}' \beta_2, r)) \) is a scalar and \( Z_{yi}(\beta_1) = y_i - x_{i1}' \beta_1 \) is a vector. The variance-covariance matrix of \( Z_i(\beta_1, \beta_2, r) \) can be divided
correspondingly, i.e.,

\[
\Sigma((\sigma, \rho)(t, y)) = \begin{pmatrix}
1 & \Sigma(\sigma, \rho)(t, y)) \\
\Sigma(\sigma, \rho)(y, t)) & \Sigma(\sigma, \rho)(y, t))
\end{pmatrix} = \begin{pmatrix}
1 & 0 \\
0 & \sigma \rho
\end{pmatrix} R((\sigma, \rho)(y, t)) \begin{pmatrix}
1 & 0 \\
0 & \sigma \rho
\end{pmatrix}
\]

Let \( \phi_j(\cdot; \mu, \Sigma) \) and \( \Phi_j(\cdot; \mu, \Sigma) \) denote the pdf and cdf of a \( j \)-dimensional normal random variable with mean \( \mu \) and \( \Sigma \). When the mean is \( 0 \) they are further simplified as \( \phi_j(\cdot; \Sigma) \) and \( \Phi_j(\cdot; \Sigma) \).

Assuming the time points for the longitudinal measurements and censoring process are uninformative, a subject \( i \) with measurements of length \( m_i \) and \( \delta_i = 1 \) has a joint cdf of \( (T_i, y_i) \) given by:

\[
F_{T_i, y_i}(t_i, y_i) = \Phi_{m+i} \left( \Phi^{-1} \left( F_T(t_i; x_i^2 \beta_2, r) \right), \Phi^{-1} \left( \frac{y_{i1} - x_i^{11} \beta_1}{\sigma} \right), \ldots \right)
\]

\[
= \Phi_{m+i} \left( \Phi^{-1} \left( F_T(t_i; x_i^2 \beta_2, r) \right), \frac{y_{i1} - x_i^{11} \beta_1}{\sigma}, \frac{y_{im_i} - x_i^{im_i} \beta_1}{\sigma}; R(\rho(t, y)) \right)
\]

\[
= \Phi_{m+i} \left( Z_i(\beta_1, \beta_2, r); \Sigma(\sigma, \rho)(t, y) \right)
\]

The corresponding joint pdf is given by:

\[
f_{T_i, y_i}(t_i, y_i) = \phi_{m+i} \left( Z_i(\beta_1, \beta_2, r); \Sigma(\sigma, \rho)(t, y) \right) \frac{f_{T_i}(t_i; x_i^2 \beta_2, r)}{\phi(Z_i(\beta_2, r))}.
\] (1)

If this individual is censored at \( T_i = t_i \), the joint pdf is given by:

\[
f_{T_i, y_i}(T_i^* > t_i, y_i) = \int_{t_i}^{\infty} \phi_{m+i} \left( Z_i(\beta_1, \beta_2, r); \Sigma(\sigma, \rho)(t, y) \right) \frac{f_{T_i}(u; x_i^2 \beta_2, r)}{\phi(Z_i(\beta_2, r))} du
\]

\[
= \phi_{m_i} \left( Z_i(\beta_1); \Sigma(\sigma, \rho)(y) \right) \int_{t_i}^{\infty} \phi \left( Z_i(\beta_2, r); \mu_i t_i | y_i, \sigma_i t_i | y_i \right) du
\]

\[
= \phi_{m_i} \left( Z_i(\beta_1); \Sigma(\sigma, \rho)(y) \right) \int_{Z_i(\beta_2, r)}^{\infty} \phi \left( z; \mu_i t_i | y_i, \sigma_i t_i | y_i \right) dz
\]

\[
= \phi_{m_i} \left( Z_i(\beta_1); \Sigma(\sigma, \rho)(y) \right) \Phi \left( \frac{Z_i(\beta_2, r) - \mu_i t_i | y_i}{\sigma_i t_i | y_i} \right).
\] (2)
where

\[ \mu_{ti|y_i} = \Sigma(\sigma, \rho_{ty}(t_i))(y_i) \Sigma(\sigma, \rho_{ty}(y_i)) Z_{y_i}(\beta_1), \]

\[ \left( \sigma_{ti|y_i}^2 \right) = 1 - \Sigma(\sigma, \rho_{ty}(t_i))(y_i) \Sigma(\sigma, \rho_{ty}(y_i))^{-1} \Sigma(\sigma, \rho_{ty}(y_i))(t_i). \]

The log-likelihood function can be written analytically as:

\[ l(\theta) = \sum_{i} \delta_i \log f_{T_i, y_i}(t_i, y_i) + \sum_{i} (1 - \delta_i) \log f_{T_i, y_i}(T_i > t_i, y_i), \quad (3) \]

which applies to all subjects, unlike the approach in Ganjali and Baghfalaki (2015)[7], which requires four different categories of log-likelihood functions. Also, there is no requirement for subjects' biomarkers to be recorded at the same time points. The relaxation in recording time points makes this unified log-likelihood equation (3) more general in practice and no longer requires the data to be divided into different groups in order to derive the log-likelihood function. Compared to the approach in Ganjali and Baghfalaki (2015)[7], the direct maximisation of (3) is expected to be faster in convergence since it does not use the EM algorithm for the optimisation process and it is expected to be more accurate since there is no Monte Carlo integration to introduce extra noise into the estimation. In addition, standard errors for the estimators are more straightforward to obtain, compared to when using the EM algorithm, as they are the by-products of maximising (3). The score function of (3) can be solved numerically and we apply a Newton-type algorithm (Dennis, et al, 1983[3]) and the approach of Nelder and Mead (1965)[19] for maximising (3), which are implemented by the nlm and optim functions in R. Analytical solutions for some of the parameters are only available when the true event times of all subjects are observed. Details are provided in the Appendix. Three simulation studies and a real data application on the aids data (Goldman et al., 1996[8]) are carried out in Section 3. The aids data is included in R packages such as JM (Rizopoulos, 2010[23]) or joiner (Philipson, et al, 2017[21]).

3. Simulation and application

Three simulation studies are conducted. For comparison, we perform the first two simulation studies based on the same set up as Ganjali and Baghfalaki (2015)[7]. The third simulation study relaxes the restrictions on the longitudinal measurement process to allow it to not only be unbalanced but also deviated from the scheduled time point. A more general correlation structure between the two sub-models is also proposed. There are \( N = 500 \) Monte Carlo samples with sample size \( n = 200 \) and 500 for each scenario in the first two simulation studies, respectively, and \( N = 500 \) Monte Carlo samples with sample size \( n = 200 \) for the last simulation study. Finally, our estimating algorithm is applied to fit a joint model to the aids data. The proposed approach provides better estimating accuracy under the same model specification compared with Ganjali and Baghfalaki (2015)[7].
3.1. Simulation study 1

A longitudinal process with two measurements at $t_1 = 2$ and $t_2 = 6$ is simulated from the following model:

$$y_{ij} = \beta_{01} + \beta_{11} t_j + \beta_{21} t_j x_{i1} + \beta_{31} x_{i2} + \varepsilon_{ij}, \quad i = 1, \ldots, n, \ j = 1, 2,$$

where $x_{i1}$ follows a Bernoulli distribution with probability 0.2 taking 1 and $x_{i2}$ follows a $N(1, 2^2)$ distribution. An associated proportional hazard model with Weibull baseline function is specified for the event time process as:

$$h_i(t) = rt^{r-1}\exp(\beta_{02} + \beta_{12} t_j x_{i1} + \beta_{22} x_{i2}),$$

The correlation matrix in the Gaussian copula linking the marginals is a 3-dimensional symmetric positive definite matrix with diagonal 1s. Two vectors of regression parameters for the survival process with 19.3% and 55% dropout rate are considered (The original paper indicates the dropout rate associated with these two vectors are 25% and 50%, respectively, which is incorrect).

The estimates of parameters based on the 500 Monte Carlo samples are listed in Tables 1 and 2, where we define relative bias(θ) = $\frac{1}{N} \sum_{k=1}^{N} \left( \frac{\hat{\theta}_k}{\theta} - 1 \right)$ and roots of mean square errors RMSE(θ) = $\sqrt{\frac{1}{N} \sum_{k=1}^{N} \left( \frac{\hat{\theta}_k - \theta}{\theta} \right)^2}$ with $\hat{\theta}_k$ being the parameter estimates for the $k$th sample. Empirical standard errors based on these 500 sets of parameter estimations are summarised in brackets (denoted as SD) along with standard errors obtained from the inverse Hessian matrix (denoted as SE). Parameter estimations tend to have higher accuracies based on larger sample size $n$ with smaller SE, relative bias and RMSE.

**Table 1.** Parameter estimates based on $N = 500$ samples with sample size $n = 200$ and 500 for 19.3% dropout rate.

|       | Real value | Est.  | SE (SD)       | Rel. Bias | RMSE  | Est.  | SE (SD)       | Rel. Bias | RMSE  |
|-------|------------|-------|---------------|-----------|-------|-------|---------------|-----------|-------|
| $\beta_{01}$ | 5.000     | 5.006 | 0.261 (0.278) | 0.001     | 0.246 | 4.994 | 0.165 (0.166) | -0.001    | 0.152 |
| $\beta_{11}$ | 1.000     | 1.002 | 0.034 (0.034) | 0.002     | 0.033 | 1.000 | 0.021 (0.022) | -0.001    | 0.021 |
| $\beta_{21}$ | 2.000     | 2.002 | 0.058 (0.058) | 0.001     | 0.054 | 2.002 | 0.037 (0.038) | 0.001     | 0.034 |
| $\beta_{31}$ | 1.000     | 1.015 | 0.110 (0.110) | 0.015     | 0.105 | 0.990 | 0.069 (0.068) | -0.010    | 0.059 |
| $\beta_{02}$ | -5.000    | -5.010 | 0.540 (0.523) | 0.002     | 0.441 | -5.043 | 0.328 (0.345) | 0.009     | 0.262 |
| $\beta_{12}$ | -1.000    | -1.007 | 0.437 (0.428) | 0.007     | 0.505 | -1.022 | 0.265 (0.264) | 0.022     | 0.234 |
| $\beta_{22}$ | -1.000    | -1.004 | 0.115 (0.126) | 0.004     | 0.102 | -1.012 | 0.069 (0.070) | 0.012     | 0.061 |
| $\rho_{12}$ | 0.700     | 0.707 | 0.069 (0.073) | 0.023     | 0.067 | 0.712 | 0.043 (0.048) | 0.018     | 0.039 |
| $\rho_{13}$ | 0.700     | 0.696 | 0.112 (0.120) | 0.018     | 0.114 | 0.703 | 0.069 (0.071) | 0.005     | 0.064 |
| $\rho_{23}$ | 0.900     | 0.900 | 0.015 (0.015) | 0.000     | 0.014 | 0.900 | 0.009 (0.010) | -0.001    | 0.009 |
| $r$     | 2.000     | 2.012 | 0.276 (0.264) | 0.006     | 0.229 | 2.018 | 0.169 (0.172) | 0.009     | 0.131 |
| $\sigma_1$ | 3.000     | 3.010 | 0.156 (0.155) | 0.003     | 0.135 | 2.999 | 0.099 (0.100) | -0.000    | 0.082 |
| $\sigma_2$ | 3.000     | 3.008 | 0.166 (0.171) | 0.003     | 0.148 | 3.002 | 0.106 (0.110) | 0.001     | 0.089 |
Table 2. Parameter estimates based on \( N = 500 \) samples with sample size \( n = 200 \) and 500 for 55% dropout rate

| Parameter | Real value | Est. | SE (SD) | Rel. Bias | RMSE | Est. | SE (SD) | Rel. Bias | RMSE |
|-----------|------------|------|---------|-----------|------|------|---------|-----------|------|
| \( \beta_{01} \) | 5.000 | 4.997 | 0.277 (0.281) | 0.005 | 0.255 | 5.003 | 0.175 (0.168) | 0.001 | 0.141 |
| \( \beta_{11} \) | 1.000 | 0.998 | 0.050 (0.051) | -0.002 | 0.051 | 0.998 | 0.031 (0.031) | -0.002 | 0.027 |
| \( \beta_{21} \) | 2.000 | 2.000 | 0.092 (0.097) | 0.000 | 0.088 | 2.000 | 0.057 (0.060) | 0.000 | 0.054 |
| \( \beta_{31} \) | 1.000 | 0.991 | 0.134 (0.137) | -0.010 | 0.128 | 1.007 | 0.085 (0.083) | 0.007 | 0.077 |
| \( \beta_{02} \) | -5.000 | -5.027 | 0.362 (0.358) | 0.005 | 0.302 | -4.998 | 0.225 (0.222) | 0.000 | 0.161 |
| \( \beta_{12} \) | 1.000 | 1.036 | 0.196 (0.205) | 0.036 | 0.183 | 1.023 | 0.122 (0.130) | 0.023 | 0.103 |
| \( \beta_{22} \) | 1.000 | 1.005 | 0.078 (0.079) | 0.005 | 0.064 | 0.997 | 0.049 (0.049) | -0.003 | 0.038 |
| \( \rho_{12} \) | 0.700 | 0.705 | 0.056 (0.059) | 0.022 | 0.053 | 0.707 | 0.035 (0.037) | 0.011 | 0.035 |
| \( \rho_{13} \) | 0.700 | 0.705 | 0.099 (0.107) | 0.028 | 0.087 | 0.711 | 0.061 (0.062) | 0.016 | 0.049 |
| \( \rho_{23} \) | 0.900 | 0.900 | 0.019 (0.020) | 0.000 | 0.019 | 0.901 | 0.012 (0.012) | 0.001 | 0.011 |
| \( r \) | 2.000 | 2.012 | 0.152 (0.151) | 0.006 | 0.131 | 1.998 | 0.095 (0.094) | -0.001 | 0.078 |
| \( \sigma_1 \) | 3.000 | 6.137 | 0.179 (0.182) | 0.006 | 0.176 | 3.009 | 0.114 (0.118) | 0.003 | 0.106 |
| \( \sigma_2 \) | 3.000 | 3.022 | 0.208 (0.209) | 0.007 | 0.188 | 3.007 | 0.133 (0.133) | 0.002 | 0.114 |

3.2. Simulation study 2

A longitudinal process with five measurements at \( t_1 = 0 \), \( t_2 = 2 \), \( t_3 = 6 \), \( t_4 = 12 \) and \( t_5 = 18 \) is generated from the following model:

\[
y_{ij} = \beta_{01} + \beta_{11}t_j + \beta_{21}t_jx_{i1} + \beta_{31}x_{i2} + \beta_{41}x_{i3} + \beta_{51}x_{i4} + \epsilon_{ij}, \quad i = 1, \ldots, n, \quad j = 1, \ldots, 5, \tag{4}
\]

where \( x_{i1}, x_{i2}, x_{i3} \) and \( x_{i4} \) follow Bernoulli distributions with probabilities (0.84, 0.85, 0.18, 0.19) taking value 1, resulting in roughly a 50% dropout rate. An associated event time process with a Weibull proportional hazard model is specified as:

\[
h_i(t) = r t^{r-1} \exp \left( \beta_{02} + \beta_{12}x_{i1} + \beta_{22}x_{i2} + \beta_{32}x_{i3} + \beta_{42}x_{i4} \right) \tag{5}
\]

A continuous AR1 structure with correlation decaying as time distance \( |\Delta t| \) increases (\( \rho_{y_{\Delta t}} \)) and an exchangeable structure with constant correlation \( \rho_y \) are considered to model the correlation among the longitudinal measurements. For both scenarios, the correlation between the longitudinal and transformed survival processes is assumed to be constant \( \rho_{ty} \), which is probably not that realistic as an assumption (Diggle et al, 2008[5]) but we assume this to match the simulation setup in Ganjali and Baghfalaki (2015)[7]. The biomarkers measured are assumed to have common variance \( \sigma \) at all five time points.

The estimations of parameters based on the 500 Monte Carlo samples are listed in Tables 3 and 4. Comparing Tables 1 to 4 with Tables 1 to 4 in Ganjali and Baghfalaki (2015)[7], our approach has better accuracy as it produces generally smaller relative biases and RMSE, although these two quantities are already quite small in the original paper. More importantly, there are some discrepancies in estimations of standard errors between our approach and that in the original paper, e.g. in Table 1, we notice a 5-fold decrease in the standard error of \( \beta_{31} \) under our approach when \( n = 200 \). Discrepancy in standard errors to this scale leads to different significance levels for parameters, which further makes an impact on the interpretation of the model. By comparing standard errors calculated from the inverse Hessian matrix and the empirical ones summarised from the 500 Monte Carlo samples, we can conclude that our model based standard errors are sufficiently accurate.

Intuitively, our approach also has an advantage in terms of computation time, due to the fact that the log-likelihood expression is much simpler and analytically tractable. On the other hand,
the computation time in the original paper varies with the size of Monte Carlo integration, and a longer computation time would have been required for higher accuracy.

Table 3. Parameter estimates based on $N = 500$ samples each with sample size $n = 200$ and 500 for autoregressive model.

| Parameter | Real value | Est. | SE (SD) | Rel. Bias | RMSE |
|-----------|------------|------|---------|-----------|------|
| $\beta_{01}$ | 5.000 | 5.011 | 0.419 (0.412) | 0.000 | 0.367 |
| $\beta_{11}$ | 1.000 | 0.998 | 0.046 (0.050) | -0.002 | 0.042 |
| $\beta_{21}$ | 2.000 | 2.000 | 0.045 (0.051) | -0.000 | 0.041 |
| $\beta_{31}$ | 1.000 | 1.018 | 0.419 (0.422) | 0.018 | 0.388 |
| $\beta_{41}$ | -2.000 | -1.986 | 0.426 (0.458) | -0.007 | 0.377 |
| $\beta_{51}$ | -1.000 | -0.974 | 0.379 (0.403) | -0.026 | 0.349 |
| $\beta_{02}$ | -5.000 | -4.954 | 0.527 (0.545) | -0.009 | 0.465 |
| $\beta_{12}$ | -1.000 | -1.023 | 0.232 (0.251) | 0.023 | 0.208 |
| $\beta_{22}$ | -1.000 | -1.012 | 0.251 (0.262) | 0.012 | 0.212 |
| $\beta_{32}$ | 2.000 | 2.039 | 0.235 (0.233) | 0.019 | 0.213 |
| $\beta_{42}$ | 1.000 | 1.029 | 0.235 (0.237) | 0.029 | 0.213 |
| $\rho_{ty}$ | 0.400 | 0.407 | 0.048 (0.048) | 0.017 | 0.044 |
| $\rho_{y}$ | 0.500 | 0.500 | 0.018 (0.021) | -0.001 | 0.028 |
| $r$ | 2.000 | 1.987 | 0.175 (0.181) | -0.007 | 0.152 |
| $\sigma$ | 3.000 | 2.997 | 0.090 (0.094) | -0.001 | 0.078 |

Table 4. Parameter estimates based on $N = 500$ samples each with sample size $n = 200$ and 500 for exchangeable model.

| Parameter | Real value | Est. | SE (SD) | Rel. Bias | RMSE |
|-----------|------------|------|---------|-----------|------|
| $\beta_{01}$ | 5.000 | 5.022 | 0.429 (0.440) | 0.005 | 0.335 |
| $\beta_{11}$ | 1.000 | 1.000 | 0.032 (0.034) | 0.000 | 0.030 |
| $\beta_{21}$ | 2.000 | 1.999 | 0.035 (0.035) | -0.001 | 0.031 |
| $\beta_{31}$ | 1.000 | 0.993 | 0.436 (0.450) | -0.007 | 0.350 |
| $\beta_{41}$ | -2.000 | -2.034 | 0.419 (0.454) | 0.017 | 0.363 |
| $\beta_{51}$ | -1.000 | -1.008 | 0.398 (0.412) | 0.008 | 0.364 |
| $\beta_{02}$ | -5.000 | -4.989 | 0.432 (0.425) | -0.002 | 0.295 |
| $\beta_{12}$ | -1.000 | -1.004 | 0.126 (0.131) | 0.004 | 0.109 |
| $\beta_{22}$ | -1.000 | -0.994 | 0.213 (0.228) | -0.006 | 0.176 |
| $\beta_{32}$ | 2.000 | 2.023 | 0.206 (0.220) | 0.011 | 0.176 |
| $\beta_{42}$ | 1.000 | 1.020 | 0.199 (0.201) | 0.020 | 0.175 |
| $\rho_{ty}$ | 0.400 | 0.404 | 0.048 (0.048) | 0.017 | 0.044 |
| $\rho_{y}$ | 0.500 | 0.500 | 0.018 (0.021) | 0.000 | 0.028 |
| $r$ | 2.000 | 1.990 | 0.175 (0.181) | -0.007 | 0.152 |
| $\sigma$ | 3.000 | 2.997 | 0.090 (0.094) | -0.001 | 0.078 |

3.3. Simulation study 3

The first two simulation studies are implemented with biomarkers measured at fixed points, which are assumed to be the same across all individuals. In this simulation, subject $i$ is assumed to have longitudinal measurements at $t_{i1} = 0$, $t_{i2} = 2 + \epsilon_{i2}$, $t_{i3} = 6 + \epsilon_{i3}$, $t_{i4} = 12 + \epsilon_{i4}$, and $t_{i5} = 18 + \epsilon_{i5}$, where $\epsilon_{ij} \sim N(0, 0.1^2)$ are i.i.d. random variables. $t_{i5}$ are truncated to be less than or equal to 18. Measurements after $t_{i1}$ are further assumed to be missing with probability 0.3. The specification of longitudinal and survival sub-models is the same as in (4) and (5), respectively.
Table 5. Parameter estimates based on $N = 500$ samples each with sample size $n = 200$ for ARMA(1,1) model with random visiting and intermittent missing pattern.

| Real value | Est. | SE (SD) | Rel. Bias | RMSE |
|------------|------|---------|-----------|------|
| $\beta_{01}$ | 5.000 | 4.997 | 0.368 (0.367) | -0.001 | 0.366 |
| $\beta_{11}$ | 1.000 | 0.994 | 0.048 (0.048) | -0.006 | 0.049 |
| $\beta_{21}$ | 2.000 | 2.006 | 0.046 (0.046) | 0.003 | 0.047 |
| $\beta_{31}$ | 1.000 | 1.015 | 0.378 (0.376) | 0.015 | 0.376 |
| $\beta_{41}$ | -2.000 | -2.000 | 0.373 (0.372) | -0.000 | 0.381 |
| $\beta_{51}$ | -1.000 | -1.000 | 0.329 (0.344) | -0.009 | 0.344 |
| $\rho_{ty}$ | 1.000 | 1.000 | 0.000 | 0.000 |
| $\rho_y$ | 0.500 | 0.475 | 0.081 (0.109) | -0.050 | 0.112 |
| $\gamma$ | 0.400 | 0.410 | 0.374 (0.366) | -0.007 | 0.366 |
| $\sigma$ | 3.000 | 2.986 | 0.088 (0.088) | -0.007 | 0.087 |

Compared with the first two simulation studies, a more flexible ARMA(1,1) correlation structure is proposed between transformed observed event time and biomarker measured at $t_{ij}$ as $\gamma \rho_{ty} |18-t_{ij}|$, while the same AR(1) correlation structure is assumed for the longitudinal process as in simulation study 2. Let $\rho_{ty} = 1$, $\gamma = 0.4$, $\rho_{ty} = 0.8$, $\gamma = 0.8$ and $\rho_{ty} = 0.9$, $\gamma = 0.6$, where the first two scenarios are the special cases of ARMA(1,1) correlation corresponding to exchangeable and continuous AR1 correlation structure between the two sub-models. The estimations of parameters based on $N = 500$ Monte Carlo samples each with sample size $n = 200$ are summarised in Table 5. The estimations of parameters are accurate and SE and SD are relatively close to each other, which shows this estimating approach is capable of dealing with more complicated correlation structures and a random visiting pattern with intermittent missing, as opposed to the simulations in Ganjali and Baghfalaki (2015)[7] and Diggle et al (2008)[5].

3.4. Application to the aids data

The aids data (Goldman et al., 1996[8]) has already been built in many R packages such as JM (Rizopoulos, 2010[23]) or joineR (Philipson, et al, 2017[21]). The dataset comprises of the square
root of CD4 cell counts per cubic millimeter \((mm^3)\) in blood for 467 subjects with advanced human immunodeficiency virus infection at study entry and later on at 2, 6, 12, and 18 months. The CD4 cell count is an important indicator for the progression from HIV infection to acquired immune deficiency syndrome (AIDS). A higher CD4 level indicates a stronger immune system, thus less likely to lead to AIDS diagnosis or death. Some other covariates such as gender, randomly assigned treatment by didanosine (ddI) or zalcitabine (ddC) are also recorded at baseline. The main purpose of this study is to compare the efficacy and safety of ddI and ddC. By the end of the study 188 patients had died, resulting in about 59.7% censoring, and out of the 2335 planned measurements, 1405 were actually recorded, leading to 39.8% missing responses.

We fit the same copula joint model as in Ganjali and Baghfalaki (2015)\(^7\) for comparison.

The longitudinal process is specified as:

\[
y_{ij} = \beta_0 + \beta_1 t_j + \beta_2 drug_i + \beta_3 gender_i + \beta_4 prevOI_i + \beta_5 AZT_i + \varepsilon_{ij}, \quad i = 1, \ldots, 467, \quad 1 \leq j \leq 5,
\]

where \(\varepsilon_{ij} \sim N(0, \sigma^2)\) and \(y_{ij}\) is the squared root of the \(j\)th CD4 count for the \(i\)th subject. The time to event process is specified as:

\[
h_i(t) = r t^{-1} \exp(\beta_0 + \beta_1 drug_i + \beta_2 gender_i + \beta_3 prevOI_i + \beta_4 AZT_i),
\]

where \(drug_i = 1\) for ddI, \(gender_i = 1\) for male, \(prevOI = 1\) (previous opportunistic infection) for AIDS diagnosis and \(AZT_i = 1\) for failure.

The correlation matrix within the longitudinal process is assumed to be either a continuous AR1 or an exchangeable structure, which is the same setup as in simulation study 2. The correlations \(\rho_{iy}\) between longitudinal and time-to-event processes are also assumed to be constant. When \(\rho_{iy} = 0\) (Separate Model), our joint modelling approach is expected to yield the same estimation as when separately fitting the two marginals (Separate Fitting). Three information criteria are applied to gauge the goodness of fit of the proposed models.

\[
\text{AIC} = -2l(\hat{\theta}) + 2k, \\
\text{BIC} = -2l(\hat{\theta}) + k \log n, \\
\text{HQ} = -2l(\hat{\theta}) + 2\log(\log n),
\]

where \(\hat{\theta}\) are the parameter estimates of the joint model, \(k\) is the number of parameters being estimated and \(n\) is the sample size.

Table 6 summarises the estimation results under our copula joint model approach and standard approaches, such as \texttt{glm} and \texttt{survreg} in \texttt{R}, for separately analysing the longitudinal and survival processes in the aids data. Detectable but not significant differences can be found between the estimates of the regression parameters for the joint and separate models. In both joint models, \(\rho_{iy}\) are highly significant, indicating the necessity for applying a joint model on this dataset, which is consistent with the conclusion according to all the information criteria (in favor of joint models). The results from separately fitting by standard approaches (along with log-likelihood values) match our outputs for the separate models, hence validating that our approach is correct.
Table 6. Parameter estimates from proposed model and standard R functions based on the aids data.

|                | Autoregressive Model | Separate Fitting (by standard functions in R) | Exchangeable Model |
|----------------|----------------------|-----------------------------------------------|-------------------|
|                | Joint Model ($\rho_{ty} \neq 0$) | Separate Model ($\rho_{ty} = 0$) (Autoregressive) | Joint Model ($\rho_{ty} = 0$) |
|                | Longitudinal Survival | Longitudinal Survival (Exchangeable) | Separate Model Joint Model |
|                | (Est. SE) (Est. SE) | (Est. SE) (Est. SE) (Est. SE) (Est. SE) | (Est. SE) (Est. SE) |
| $\beta_{01}$  | 10.575 0.646 10.366 0.642 | 10.366 0.644 10.603 0.659 | 10.603 0.658 10.755 0.656 |
| $\beta_{11}$  | -0.176 0.027 -0.148 0.027 | -0.148 0.027 -0.159 0.017 | -0.159 0.017 -0.168 0.017 |
| $\beta_{21}$  | 0.040 0.036 0.048 0.036 | 0.047 0.036 -0.017 0.024 | 0.017 0.024 0.016 0.024 |
| $\beta_{31}$  | -0.348 0.633 -0.266 0.631 | -0.206 0.633 -0.305 0.651 | -0.305 0.649 -0.464 0.646 |
| $\beta_{41}$  | -4.599 0.461 -4.522 0.458 | -4.522 0.459 4.623 0.477 | 4.723 0.463 -4.663 0.476 |
| $\beta_{51}$  | -0.288 0.458 -0.225 0.456 | -0.225 0.457 -0.266 0.471 | -0.266 0.470 -0.322 0.468 |
| $\beta_{02}$  | -5.356 0.387 -5.362 0.387 | -5.362 0.387 -5.320 0.387 | -5.362 0.387 -5.320 0.386 |
| $\beta_{12}$  | 0.214 0.137 0.213 0.146 | 0.213 0.146 0.236 0.135 | 0.213 0.146 0.236 0.135 |
| $\beta_{22}$  | -0.300 0.246 -0.357 0.245 | -0.357 0.245 -0.287 0.247 | -0.357 0.245 -0.287 0.247 |
| $\beta_{32}$  | 1.355 0.228 1.300 0.227 | 1.300 0.227 1.328 0.226 | 1.300 0.227 1.328 0.226 |
| $\beta_{42}$  | 0.150 0.162 0.158 0.163 | 0.158 0.163 0.148 0.162 | 0.158 0.163 0.148 0.162 |
| $\beta_{52}$  | 0.408 0.051 | 0.436 0.051 | 0.436 0.051 |
| $\beta_{0y}$  | 0.944 0.004 0.943 0.004 | 0.943 0.004 0.798 0.014 | 0.798 0.014 0.799 0.014 |
| $\beta_{1y}$  | 1.368 0.094 1.418 0.094 | 1.418 0.094 1.355 0.094 | 1.355 0.094 1.355 0.094 |
| $\beta_{2y}$  | 4.408 0.119 4.367 0.117 | 4.367 0.119 4.353 0.125 | 4.353 0.125 4.372 0.126 |
| $\beta_{3y}$  | 4.367 | 4.367 | 4.367 |
| $\beta_{4y}$  | -4314.968 -4340.638 | -3546.463 -3516.425 | -3410.601 -4282.462 |
| $\beta_{5y}$  | -4314.968 -4340.638 | -3546.463 -3516.425 | -3410.601 -4282.462 |
| Loglik        | 8659.937 8709.276 | 7108.925 1600.4 | 8649.201 8594.923 |
| AIC           | 8722.132 8767.325 | 1625.278 7090.833 | 8707.25 8657.118 |
| BIC           | 8633.569 8684.908 | 1625.278 7090.833 | 8624.833 8568.555 |
| HQ            | 8633.569 8684.908 | 1592.032 7036.812 | 8624.833 8568.555 |
Comparing the results of Table 6 to those in Table 5 in Ganjali and Baghfalaki (2015)[7], we notice some differences in the parameter estimates for both the joint and separate models. The parameter estimates for survival sub-models in Ganjali and Baghfalaki (2015)[7] are not consistent in the two separate models with different correlation structures, which conflicts the theoretical results. This, as well as some discrepancies we found in the information criteria between the joint and separate models, raises some questions about the validity of their approach. We also note that while their approach prefers the model with autoregressive correlation structure, we find that the simpler exchangeable correlation is better. Based on the results in Table 6, a more general exchangeable joint model with ARMA(1,1) correlation structure between the two sub-models is also fitted. The fitting is slightly improved giving a larger log-likelihood value of -4280.186 and a smaller AIC value of 8592.372 compared with the exchangeable joint model with a constant correlation in Table 6, but there is no improvement in terms of BIC. In practice, it might be reasonable to start with a saturated model for correlation structure in a study with a small number of longitudinal measurements, then fit a parsimonious one if a clear pattern can be observed from the fitted saturated correlation structure.

The prediction of the survival probability for subjects with some baseline covariates and longitudinal measurements is also of interest after a joint model is fitted. Even though there are no subject specific random effects to distinguish the individual trajectory from the population trend, this copula approach for joint modelling is capable of predicting survival probabilities at individual level.

Suppose a 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 a set of longitudinal measurements \( Y_i(t) = \{y_i(s); 0 \leq s < t\} \) up to \( t \) and a vector of baseline covariates \( x_{i2} \) are given by:

\[
\pi_i(u|t) = P(T_i > u|T_i > t, Y_i(t), x_{i2}, D_n; \theta) = P(T_i > u|T_i > t, Y_i(t), x_{i2}; \theta)
= \frac{P(T_i > u|Y_i(t), x_{i2}, b_i; \theta)}{P(T_i > t|Y_i(t), x_{i2}, b_i; \theta)}
= \frac{1}{
\Phi\left( \frac{\Phi^{-1}\left(S_{T_i}(u; x_{i2}^{T} \beta_{2}, r) + \mu_i^{u|y_i}\right)}{\sigma_i^{u|y_i}} \right) \bigg/ \Phi\left( \frac{\Phi^{-1}\left(S_{T_i}(t; x_{i2}^{T} \beta_{2}, r) + \mu_i^{t|y_i}\right)}{\sigma_i^{t|y_i}} \right) \bigg), \tag{6}
\]

which reduces to

\[
\frac{S_{T_i}(u; x_{i2}^{T} \beta_{2}, r)}{S_{T_i}(t; x_{i2}^{T} \beta_{2}, r)} = \exp\left\{- \int_{t}^{u} h_i(s) ds \right\}
\text{ given } R(\rho_{ty})(t;y_i) = 0 \text{ and } R(\rho_{ty})(u;y_i) = 0.
\]

Subjects 13 and 130, are both male treated by ddC with no AIDS diagnosis and AZT intolerance, therefore have the same baseline covariates. While the CD4 levels in subject 13 (event time at \( t = 12.23 \)) are lower than 5 for all the measurements at 0, 2 and 6, the CD4 levels in subject 130 (censored at \( t = 19.2 \)) are generally greater than 10. Dynamic predictions of survival probabilities, which can be updated as new longitudinal information becomes available, for these two subjects are calculated based on the fitted separate and copula joint models under the exchangeable model in Table 6. The results are presented in Figure 1.

For comparison, a shared random effects joint model is also fitted and presented by the green line in Figure 1. It is specified as:

\[
y_{ij} = \beta_{01} + \beta_{11} t_{ij} + \beta_{21} t_{ij} \text{drug}_i + \beta_{31} \text{gender}_i + \beta_{41} \text{prevOI}_i + \beta_{51} \text{AZT}_i + b_{i0} + b_{i1} t + \varepsilon_{ij} \tag{7}
\]
and

$$h_i(t) = h_0(t)\exp\{\beta_{12}\text{drug}_i + \beta_{22}\text{gender}_i + \beta_{32}\text{prevOI}_i + \beta_{42}\text{AZT}_i + \alpha(b_{i0} + b_{i1}t)\},$$

(8)

where $\varepsilon_{ij} \sim N(0, \sigma^2)$ and $h_0(t)$ is a piecewise-constant baseline function with eight knots equally spaced. The fitted outputs are briefly summarised in Table 7.

Figure 1. Dynamic prediction of survival probabilities and fitted longitudinal trajectories for a subject 13 and 130 for Aids data. The black, red and green lines represent exchangeable copula joint model, separate model and shared random effects joint model, respectively.
Although there are significant differences in the CD4 levels between the two subjects, the fitted longitudinal trajectories are identical due to the fact that the marginal models only capture the population trend. While the fitted longitudinal trajectories between the separate (red lines) and copula joint models (black line) almost overlap, we notice a huge difference in the prediction of survival probabilities between the two models. The separate model does not take the effects of longitudinal measurements into account, which results in the same prediction of survival probabilities for the two individuals. On the other hand, the copula joint model calculates the predictions on survival probabilities via the conditional distribution of the event time given the longitudinal process. For example, subject 13 has a CD4 trajectory lower than the population trend, resulting in lower predicted survival probabilities than the ones under the separate model. Subject 130 displays an opposite trend regardless of sharing the same baseline information as subject 13. This may be due to the fact that the few covariates included in the separate model are not sufficient to capture all the variations in the longitudinal response. The additional information contained in the error is reflected in the significance of $\rho_{xy}$, which has an impact on the predictions of survival probabilities. The difference in regression parameters may not be significant between the joint and separate approaches, but the joint model approach is vital for obtaining more accurate predictions in terms of survival probabilities. Besides, the copula joint model provides predictions of survival probabilities which are comparable to the shared random effects joint model and would be a good alternative for that model when interest is on population inference for the longitudinal process while getting accurate individual predictions of survival probabilities, by still taking into account any longitudinal effects but without introducing random effects in the models (thus require less computation). The differences in prediction are evident across most subjects, particularly when the observed CD4 responses lie further from the mean fitted longitudinal trajectory.

### Table 7

Parameter estimates based on the shared random effects joint model specified by (7) and (8) for aids data.

| $\beta_0$ | $\beta_{11}$ | $\beta_{21}$ | $\beta_{31}$ | $\beta_{41}$ | $\beta_{51}$ | $\beta_{12}$ | $\beta_{22}$ | $\beta_{32}$ | $\beta_{42}$ | $\alpha$ | $\sigma$ |
|---------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|--------|
| Est.    | 10.611      | -0.186      | 0.017       | -0.249      | -4.695      | -0.284      | 0.301       | -0.308      | 1.744       | 0.171   | -0.246  | 1.738  |
| SE      | 0.799       | 0.021       | 0.030       | 0.755       | 0.493       | 0.474       | 0.167       | 0.452       | 0.395       | 0.201   | 0.046  | 0.048  |

Loglik: -4255.669  AIC: 8555.338  BIC: 8646.557  HQ: 8514.97

### 4. Discussion

In this paper, we propose an improved exact likelihood approach for estimation in the copula joint model, first introduced in Ganjali and Baghfalaki (2015)[7], with subjects allowed to have different number of longitudinal measurements at distinct time points. Computational cost is expected to be reduced while the accuracies of parameter estimations are improved. The model is flexible in the sense that the marginals are allowed to be whatever parametric or non-parametric distribution fits the marginals best before connecting them by a Gaussian copula, though this might make estimation more computationally intensive. The model requires very little computation cost when normality is assumed for the marginals under a Gaussian copula, it is capable of providing predictions on survival probabilities at individual level (comparable to a latent random effects joint model) and can be very useful when interest is on the survival event, while also taking into account any effects of longitudinal biomarkers. However, the drawbacks of marginal models are not neglectable, especially when compared with random effects models (Diggle et al. 2002). Unlike shared or correlated random effects models, it is difficult to place a scientific interpretation on the association parameters (Diggle et al, 2008[5]). Proposing a reasonable structure for the correlation matrix between the two sub-models is also problematic, especially when there is a large number of longitudinal measurements.
Suresh et al (2019) overcome the issue of finding an appropriate correlation structure between the two sub-models since their approach only requires the specification of two dimensional copulas. However, their approach still falls under the marginal model regime and therefore may be improved by the addition of random effects. A marginal model is only capable to capture the characteristics of a population trend, thus subjects with the same covariates are going to exhibit exactly the same tendency for biomarkers, except differences in measurement errors. A standard deviation of 4.372 for the random errors under the exchangeable joint model in Table 6 is quite large compared to the magnitude of the longitudinal measurements, indicating there is still a certain amount of individual information contained in the random error. The shared random effects joint model can effectively reduce the standard deviation for random errors to 1.738 (Table 7), as subject deviation from the population is accounted for by random effects. This is consistent with the fitted curves in the longitudinal process in Figure 1, where the green lines capture the observed individual measurements much better than the red and black ones. We can also observe the shared random effects joint model still has an overall better fitting than the marginal models in terms of AIC, BIC and HQ as shown in Tables 6 and 7.

Although Rizopoulos et al. (2008a\[25\] and 2008b\[26\]) and Malehi et al. (2015)\[18\] extent the flexibility of dependency between event time and longitudinal processes by using copula, their models are still under the framework of conditional independence assumption, which can be tricky to verify for real data. We would like to explore the possibility of combining the advantages of a copula joint model (introducing non linear correlation or even checking the assumption of conditional independence between the two processes) and the shared or correlated random effects joint model (straightforward for subject-specific study). To achieve this, we are currently extending the estimation approach proposed in this paper to fit a copula joint model with latent random effects and initial results seem very promising. The key step of this new model is to use copula to link the marginal distributions of the longitudinal and survival processes conditional on random effects.

Other further extensions could include exploring various families of copulas (e.g. $t$-copula, where a closed form expression of the likelihood may not exist), which can cope with different types of non-linear association and also considering different specifications for the baseline hazard function.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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Appendix

Suppose the true event times are observed for all the subjects in a group with sample size \( n \). Taking \( Z = Z(\cdot) \) for simplicity, the log-likelihood is given by:

\[
l(\theta) = \text{Const} - \frac{1}{2} \sum_{i=1}^{n} \log |\Sigma(\sigma, \rho)_{(t_i, y_i)}| - \frac{1}{2} \sum_{i=1}^{n} Z_i' \Sigma(\sigma, \rho)^{-1}_{(t_i, y_i)} Z_i \\
+ \sum_{i=1}^{n} \log f_T(t_i; x_i' \beta_2, r) - \sum_{i=1}^{n} \log \phi(Z_{t_i}),
\]

Let

\[
\Sigma(\sigma, \rho)^{-1}_{(t_i, y_i)} = \begin{pmatrix} A_i & B_i' \\ B_i & D_i \end{pmatrix}
\]

where (take \( R = R(\cdot) \) for simplicity)

\[
A_i = \left( 1 - R_{(t_i, y_i)} R^{-1}_{(y_i)} R_{(y_i)(t_i)} \right)^{-1},
\]

\[
B_i = \frac{-1}{\sigma} \left( 1 - R_{(t_i, y_i)} R^{-1}_{(y_i)} R_{(y_i)(t_i)} \right)^{-1} R^{-1}_{(y_i)} R_{(y_i)(t_i)}
\]

and

\[
D_i = \frac{1}{\sigma^2} R^{-1}_{(y_i)} + \frac{1}{\sigma^2} R^{-1}_{(y_i)} R_{(y_i)(t_i)} \left( 1 - R_{(t_i, y_i)} R^{-1}_{(y_i)} R_{(y_i)(t_i)} \right)^{-1} R_{(t_i, y_i)} R^{-1}_{(y_i)}.
\]
Thus we can rewrite the log-likelihood as:

\[
l(\theta) = \text{Const} - \sum_{i=1}^{n} m_i \log \sigma - \frac{1}{2} \sum_{i=1}^{n} \log |R_{(t_i, y_i)}| - \frac{1}{2} \sum_{i=1}^{n} \left( Z_{t_i} \mathbf{Z}_{y_i} \right) \left( \begin{array}{cc} A_i & B_i \\ B_i & D_i \end{array} \right) \left( \begin{array}{c} Z_{t_i} \\ \mathbf{Z}_{y_i} \end{array} \right) \\
+ \sum_{i=1}^{n} \log f_{T_i}(t_i; x_i; \beta_2, r) - \sum_{i=1}^{n} \log \phi (Z_{t_i})
\]

\[
= \text{Const} - \sum_{i=1}^{n} m_i \log \sigma - \frac{1}{2} \sum_{i=1}^{n} \log |R_{(t_i, y_i)}| - \frac{1}{2} \sum_{i=1}^{n} \left( A_i Z_{t_i}^2 + Z_{y_i}^2 B_i Z_{t_i} + Z_{t_i} B_i^2 Z_{y_i} + Z_{y_i}^2 D_i \right)
+ \sum_{i=1}^{n} \log f_{T_i}(t_i; x_i; \beta_2, r) - \sum_{i=1}^{n} \log \phi (Z_{t_i})
\]  

(9)

The score equation of \( \beta_1 \) is given as follow:

\[
\frac{\partial l(\theta)}{\partial \beta_1} = \partial \left\{ - \frac{1}{2} \sum_{i=1}^{n} \left( Z_{y_i} B_i Z_{t_i} + Z_{t_i} B_i^2 Z_{y_i} + Z_{y_i} D_i \right) \right\} / \partial \beta_1
\]

\[
= - \frac{1}{2} \sum_{i=1}^{n} \left( -2 X_{i}^t B_i Z_{t_i} - 2 X_{i}^t D_i \right)
\]

\[
= X_1^t B Z_t + X_1^t D (Y - X_1^t \beta_1)
\]

\[
= 0
\]

Solving the equation gives

\[
\hat{\beta}_1(\beta_2, \alpha, r) = \left( X_1^t D X_1 \right)^{-1} X_1^t (B Z_t + D Y)
\]

\[
= \sigma^2 \left( X_1^t F X_1 \right)^{-1} X_1^t \left( \frac{1}{\sigma^2} E Z_t + \frac{1}{\sigma^2} F Y \right)
\]

\[
= \left( X_1^t F X_1 \right)^{-1} X_1^t (\sigma E Z_t + F Y), 
\]

(10)

where \( X_1 = (X_{11}, ..., X_{n1})^t \), \( Y = (y_1, ..., y_n)^t \), \( Z_t = (Z_{t1}, ..., Z_{tn})^t \), \( E = \sigma B \), \( F = \sigma^2 D \), \( B = \left( \begin{array}{cccc} B_1 & \cdots & B_n \end{array} \right)^t \), \( D = \left( \begin{array}{cccc} D_1 & \cdots & D_n \end{array} \right) \), \( E = \left( \begin{array}{cccc} E_1 & \cdots & E_n \end{array} \right) \)

and \( F = \left( \begin{array}{cccc} F_1 & \cdots & F_n \end{array} \right) \).

Substituting (10) back in the log-likelihood function (9) then differentiating with respect to \( \sigma \) leads to
\[
\frac{\partial l(\theta)}{\partial \sigma} = \partial \left\{ -\sum_{i=1}^{n} m_i \log \sigma - \frac{1}{2} \sum_{i=1}^{n} \left( 2Z_i B_i^2 \left( y_i - X_i \hat{\beta}_1 \right) + \left( y_i - X_i \hat{\beta}_1 \right)' D_i \left( y_i - X_i \hat{\beta}_1 \right) \right) \right\} / \partial \sigma
\]

\[
= \partial \left\{ -\sum_{i=1}^{n} m_i \log \sigma - \frac{1}{2} \sum_{i=1}^{n} \left( 2Z_i E_i^2 \left( y_i - X_i \hat{\beta}_1 \right) + \frac{1}{\sigma^2} \left( y_i - X_i \hat{\beta}_1 \right)' E_i \left( y_i - X_i \hat{\beta}_1 \right) \right) \right\} / \partial \sigma
\]

\[
= \partial \left\{ -\sum_{i=1}^{n} m_i \log \sigma - \frac{1}{\sigma} Z_i E_i \left( Y - X_i \hat{\beta}_1 \right) - \frac{1}{2\sigma^2} \left( Y - X_i \hat{\beta}_1 \right)' F \left( Y - X_i \hat{\beta}_1 \right) \right\} / \partial \sigma
\]

\[
= 0
\]

part of the numerator of equation (11) can be simplified as:

\[
-\frac{1}{\sigma} Z_i E_i \left( Y - X_i \hat{\beta}_1 \right) - \frac{1}{2\sigma^2} \left( Y - X_i \hat{\beta}_1 \right)' F \left( Y - X_i \hat{\beta}_1 \right)
\]

\[
= -\frac{1}{\sigma} Z_i E_i \left( Y - X_1 \left( X_1' E X_1 \right)^{-1} X_1' (\sigma E Z_i + FY) \right)
\]

\[
- \frac{1}{2\sigma^2} \left( Y - X_1 \left( X_1' E X_1 \right)^{-1} X_1' (\sigma E Z_i + FY) \right) \left( Y - X_1 \left( X_1' E X_1 \right)^{-1} X_1' (\sigma E Z_i + FY) \right)
\]

\[
= -\frac{1}{2\sigma^2} Y \left( F - F X_1 \left( X_1' E X_1 \right)^{-1} X_1' F \right) Y - \frac{1}{\sigma} Z_i \left( F' - F X_1 \left( X_1' E X_1 \right)^{-1} X_1' F \right) Y
\]

\[
+ \frac{1}{2} Z_i E X_1 \left( X_1' E X_1 \right)^{-1} X_1' E Z_i
\]

\[
= \frac{1}{\sigma^2} G + \frac{1}{\sigma} H + Const
\]

(12)

where \( G = -\frac{1}{2} Y \left( F - F X_1 \left( X_1' E X_1 \right)^{-1} X_1' F \right) Y \), \( H = -Z_i \left( F' - F X_1 \left( X_1' E X_1 \right)^{-1} X_1' F \right) Y \).

(Note: \( G \) is nonpositive since \( G = -\frac{1}{2} (Y - X_1 \tilde{\beta})' F (Y - X_1 \tilde{\beta}) \), where \( \tilde{\beta} = \left( X_1' E X_1 \right)^{-1} X_1' FY \).)

Substituting (12) back to (11) gives:

\[
\left( \sum_{i=1}^{n} m_i \right) \sigma^2 + H \sigma + 2G = 0
\]

(13)

The MLE of \( \sigma \) is the positive root of equation (13), i.e.,

\[
\hat{\sigma}(\beta_2, \rho, r) = -H + \sqrt{H^2 - 8\left( \sum_{i=1}^{n} m_i \right) G} / 2\left( \sum_{i=1}^{n} m_i \right)
\]

(14)

Assuming the survival data follows a Weibull distribution, \( \frac{\partial l(\theta)}{\partial \beta_2} = 0, \frac{\partial l(\theta)}{\partial r} = 0 \) and \( \frac{\partial l(\theta)}{\partial \rho} = 0 \) do not have explicitly solutions, thus numerical optimisation technique is required.