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Joint longitudinal and survival-cure models with constrained parameters in tumour xenograft experiments

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SUMMARY. In tumour xenograft experiments, treatment regimens are administered and the tumour volume of each individual is measured repeatedly over time. Survival data are recorded due to the death of some individuals during the observation time period. Also, cure data are observed due to a portion of individuals who are completely cured in the experiments. When modelling these data, certain constraints have to be imposed on the parameters in the models to account for the intrinsic growth of the tumour in the absence of treatment. Also, the likely inherent association of longitudinal and survival-cure data has to be taken into account in order to obtain unbiased estimators of parameters. In this paper, we propose such models for the joint modelling of longitudinal and survival-cure data arising in xenograft

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experiments. Estimators of parameters in the joint models are obtained using a Markov chain Monte Carlo approach. Real data analysis of a xenograft experiment is carried out and simulation studies are also conducted, showing that the proposed joint modelling approach outperforms the separate modelling methods in the sense of mean squared errors.

KEY WORDS: Constrained parameters; joint longitudinal and survival-cure model; Markov chain Monte Carlo; xenograft experiment.

1. Introduction

In cancer drug development, demonstrating anti-tumor activity in an *in vivo* experiment is an important and necessary step to make a promising experimental treatment available to humans. The xenograft model is a commonly used *in vivo* model in cancer research, for which severe combined immunodeficient (scid) mice are grafted with human cancer cells after which they receive a treatment and are then followed up. Tan *et. al.* (2005a) presented a typical xenograft experiment, where several treatment regimens are administered and an outcome variable, tumour volume, is measured at the start of the treatment and then at regular follow-up times. In the literature, methodology has been developed to analyze repeated measurements and survival times collected from xenograft experiments. For example, Tan *et. al.* (2002) developed a t-test via the EM algorithm and also a Bayesian approach for testing for differences in effects between two treatment regimens. If no treatment were given to the tumour-bearing mice, the tumours would keep growing until the mice died or are sacrificed. Therefore, certain constraints have to be imposed on the parameters in the model to account for the intrinsic growth of a tumour in the absence of treatment. Tan *et. al.* (2005a) considered a class of regression models for longitudinal outcomes with constrained parameters. Fang *et. al.* (2004) proposed a Bayesian hierarchical model to account for the parameter constraints. However, these authors ignored the very likely inherent association between longitudinal responses and survival outcomes for data coming from the same subject. As a result, such statistical inferences may be biased.

Joint models for both longitudinal and survival data have been developed

in recent years and are extensively reviewed by Tsiatis and Davidian (2004). It is well known nowadays that analyzing combined longitudinal data and survival data can lead to a significant improvement in the efficiency of statistical modelling compared to the separate analyses - see, for example, Tsiatis *et. al.* (1995), Wulfsohn and Tsiatis (1997), Henderson *et. al.* (2000) and Xu and Zeger (2001). Moreover, a separate analysis of longitudinal data using traditional linear mixed models may be biased when the data contain non-ignorable missing values arising from informative drop outs (Elashoff *et. al.* 2007). When there are cured individuals in the survival studies, either due to immunes or long-term survivors, joint models for survival and cured data have been considered by Sy and Taylor (2000). Longitudinal and survival-cure models have been further developed by Yu *et. al.* (2004) and Yu *et. al.* (2008) in a study of prostate cancer data, where longitudinal data not only have an inherent relationship with survival outcomes but are also related to the probability of cure of an individual. However, these models are not suitable for analyzing the tumour data arising in xenograft experiments for the following reasons. a) These models assume the cure probability only depends on the baseline covariates, rather than the true values of longitudinal measurements. This assumption may not be true in xenograft experiments because the cure probability of a mouse will clearly depend on the tumor volume which varies over time. b) These models place no constraints on parameters in the longitudinal models and take no account of the intrinsic growth of a tumour in the absence of treatment.

In this paper, motivated by a dataset from an xenograft experiment for mice, we propose new joint models for longitudinal and survival-cure data by

taking into account not only the likely inherent association of the different types of data but also the intrinsic growth of a tumour in the absence of any treatment. The random effects in linear mixed models for longitudinal data, after being properly scaled, are incorporated into the Cox hazard model for survival data and the logistic model for cure data, so that the inherent association between the different types of data can be accounted for. The fixed effects in the longitudinal linear mixed models, on the other hand, are imposed constraints similar to those of Tan *et. al.* (2005b) in order to account for the intrinsic growth of a tumour in the absence of treatment. Posterior inferences for the parameters in the models are obtained by using a Markov chain Monte Carlo (MCMC) method involving a Gibbs sampling technique implemented with adaptive rejection sampling.

The rest of the paper is organized as follows. In Section 2, we define the joint longitudinal and survival-cure models for the xenograft experimental data and provide the log-likelihood function for the complete data. In Section 3, we specify prior distributions for the parameters and provide model selection criteria for finding the best model. In Section 4, we use a MCMC method to generate random samples from the posterior distributions of the parameters and apply to the real xenograft data analysis involving two new anticancer agents against rhabdomyosarcomas. In Section 5 we carry out simulation studies to access the performance of the proposed approach. Numerical results show that the proposed joint modelling strategy outperforms the separate modelling methods. Further comments and discussions are given in Section 6. Technical details on deriving the posterior distributions and further data information are provided in the Supplementary Web Materials.

2. Data and Models

2.1 *Data set*

The xenograft experimental data in Tan *et. al.* (2005a) and Houghton *et. al.* (2000) are about two new anticancer agents: temozolomide (TMZ) and irinotecan (CPT-11). TMZ is a methylating agent that has been approved for treatment of astrocytoma and is entering various phases of clinical evaluation against tumours. CPT-11 has demonstrated a broad activity against both murine and human tumour xenograft models and clinically significant activity against many types of cancer. A DNA analysis has formed the biochemical rationale for combining TMZ and CPT-11. Our primary objective is to analyze the activity of TMZ combined with CPT-11 against one rhabdomyosarcoma (Rh18) xenograft. Mice from the same strain were used and they are virtually genetically identical. In total, we have 51 subjects (mice) observed, which are divided into eight groups for different treatment regimens. Tumor-bearing mice were treated with TMZ by oral gavage for 5 days (days 1-5) or two 5 day courses (1-5 and 8-12) per 21-day cycle. Alternatively, mice received three 5-day courses per 28-day cycle. In subsequent combination studies, TMZ was administered daily for two consecutive days (days 1-5) of each cycle, because this was found optimal in initial studies. TMZ was administered 1 hour prior to administration of CPT-11. Cycles of therapy were repeated twice at 21-day intervals. CPT-11, at doses listed for individual experiments, was administered daily for two consecutive days for two consecutive weeks. Table 1 in the Supplementary Web Materials provides weekly total doses of TMZ and CPT-11 assigned to different groups. The tumour volume was measured at the initial time and once a week within

the follow-up period of 12 weeks. Figure 1 shows the change of tumor volume (cm^3) with time for mice in each of the eight treatment groups.

[Figure 1 about here.]

From Figure 1, it is clear that in the control group (i.e., no treatment) the tumor volume increases with time, while in other treatment groups the tumor volume may decrease in the beginning and then increase at later times. Figure 1 displays the longitudinal measurements observed until mice died or were sacrificed due to the tumour volume quadrupled. Among these 51 mice, in total 25 mice either died of toxicity or were sacrificed and the remaining 26 mice survived longer than the 12-week observation period. For these survived ones, their lifetimes cannot be observed but were censored at the end of 12 weeks. On the other hand, 15 mice quickly shrank their tumour volumes smaller than $0.01cm^3$, which became too small to be observable by a reading machine, and had no recurrent growth of tumour in the rest period of the experiment. For this portion of mice, it is believed that they are very likely cured already, see Tan *et. al.* (2005a) for more details. We also note that a few of the mice had the tumour disappear ($< 0.01cm^3$) first but grow back in later weeks up to the end of the experiment. These mice cannot be considered as cured ones but the intermittent missing values are truncated as $0.01cm^3$. We are therefore motivated by this dataset to build longitudinal models for repeated measurements of the tumour volume, survival models for time-to-death or sacrifice of the mice, and cure models for the cured mice, simultaneously. The longitudinal models have to account for the intrinsic growth of a tumour in the absence of any treatment in order to have unbiased statistical inferences.

2.2 *Longitudinal data sub-model*

Consider in general the anti-tumour activity of S agents. Suppose that there are $n+1$ pre-specified follow-up times $t_0 < t_1 < \cdots < t_n$ for each of the m subjects/mice. Let Y_{i0} and $Y_i = (Y_{i1}, ..., Y_{in_i})'$ $(n_i \leq n)$ be the initial tumour volume and the n_i-dimensional vector of tumour volumes of the ith mouse measured at the times $t_1, t_2, \cdots, t_{n_i}$, respectively. To make the data normally distributed, we assume that a log scale has been introduced to Y_{i0} and Y_{ij} $(j = 1, ..., n_i)$. Let $x_{ij}^{(s)}$ be the cumulative dose of the sth agent administered to the ith mouse until the time t_j for $s = 1, ..., S$, and their interaction terms for $s = S+1, ..., p_1$, where p_1 is the total number of the S agents and the associated interactions, $j = 1, ..., n_i$ and $i = 1, ..., m$. Denote $x_i^{(s)} = (x_{i1}^{(s)}, \cdots, x_{in_i}^{(s)})'$ as the anti-tumour activity of the sth agent received by the ith mouse. The responses Y_i $(i = 1, ..., m)$ may be modelled by a linear mixed model

$$Y_i = \Psi_i + X_i\beta + \mathbf{1}_{n_i}U_i + \varepsilon_i, \tag{1}$$

where $\Psi_i = (\psi_1, ..., \psi_{n_i})'$ and $\beta = (\beta_0, ..., \beta_{p_1})'$ are unknown parameter vectors, $X_i = (Y_{i0}\mathbf{1}_{n_i}, x_i^{(1)}, ..., x_i^{(p_1)})$ is the $n_i \times (p_1+1)$ known design matrix, $\mathbf{1}_{n_i}$ is the n_i-dimensional vector with components 1, U_i is the univariate independent random effects from the Normal distribution $N(0, \sigma_u^2)$ and the error term ε_i is assumed to follow the n_i-dimensional normal distribution with mean 0 and covariance matrix $\sigma_\varepsilon^2 I_{n_i}$.

In the model (1), the first column of X_i is the initial tumour volume Y_{i0}, i.e., it is treated as a covariate. The corresponding regression coefficient β_0 reflects the effect of the initial tumour volume. The other columns of X_i

consist of the cumulative doses of agents received by the ith mouse at each observation time and the associated interactions among the S agents. Therefore, the design matrices X_i $(i = 1, \cdots, m)$ may vary from mouse to mouse though all mice in the same treatment group may have the same schedule of administration. For simplicity, in the model (1) we only consider univariate random effects U_i, which are incorporated to account for the within-subject correlation. It is possible to extend U_i to multivariate random effects but the linkage to the survival-cure models discussed later may become complicated. In this paper, we focus on the simple case of univariate random effects. On the other hand, it is common in the literature that the components of the intercept vector Ψ_i are treated to be identical. As pointed out by Tan *et. al.* (2005a), however, in the xenograft experiments the tumour born by a immunosuppressants mouse in the control group keeps growing over the follow-up period. Ignoring this fact can lead to misleading inferences, for example, resulting in underestimates of treatment effects. In order to reflect this fact in the model, the components of Ψ_i are assumed to be in an increasing order over the follow-up periods. In other words,

$$\psi_1 \leq \psi_2 \leq \cdots \leq \psi_{n_i} \tag{2}$$

for $i = 1, ..., m$. To estimate the constrained parameters in (2), following Tan *et. al.* (2005b) we make a transformation $\Psi_i = Q_i r$, where the $(n_i \times n)$ matrix Q_i is obtained by removing the last $n - n_i$ rows of the $(n \times n)$ matrix Q that is a lower-triangular matrix with $1's$ as the diagonal and below diagonal entries, and $r = (r_1, \cdots, r_n)' \in \mathrm{R} \times \mathrm{R}_+^{n-1}$ with

$$\mathrm{R} \times \mathrm{R}_+^{n-1} = \Big\{ r : -\infty < r_1 < \infty,\ r_j \geq 0,\ j = 2, \cdots, n \Big\}. \tag{3}$$

2.3 *Proportional hazard and cure sub-models*

A mouse is said to be cured if its tumour volume is smaller than 0.01cm^3 and no recurrent growth of the tumour occurs in the rest period of the experiment. Let $\xi_i = 0$ denote the ith mouse cured by agents and $\xi_i = 1$ be not cured. Assume $p_i = Pr(\xi_i = 1)$, that is, p_i is the probability of incidence that the event, death caused by the tumour problem or toxicity of agents, eventually occurs. Obviously, a cured mouse does not experience the death or sacrifice in the experiment period. Conversely, a mouse who died or was sacrificed during the experiment period must have the incidence $\xi_i = 1$. Let T_i be the time to death for the ith individual, defined only for those with $\xi_i = 1$, with the hazard function $h(t|\xi_i = 1)$ and the survival function $S(t|\xi_i = 1)$. If a mouse survives longer than the experiment period, the survival time of the mouse is censored as the mouse is either cured or has no enough follow-up times. In other words, we actually observe $\tilde{T}_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$ where C_i is the censoring time and δ_i is the relative failure indicator. Clearly, when the censoring occurs the incidence indicator ξ_i becomes not observable. We actually observe $\xi_i = 1$ if the failure indicator $\delta_i = 1$.

The marginal survival function of T_i therefore is given by

$$\begin{aligned} S_i(t) &= Pr(T_i \geq t) \\ &= Pr(T_i \geq t|\xi_i = 0)Pr(\xi_i = 0) + Pr(T_i \geq t|\xi_i = 1)Pr(\xi_i = 1) \\ &= 1 - p_i + p_i S(t|\xi_i = 1) \end{aligned} \tag{4}$$

for $t < \infty$. Note that $S_i(t) \to (1 - p_i)$ as $t \to \infty$, implying that the marginal survival function $S_i(t)$ tends to the cure probability $(1 - p_i)$ for large t. As

long as the incidence probability p_i and the conditional survival function $S(t|\xi_i = 1)$, or the conditional hazard function $h(t|\xi_i = 1)$, are obtained, the marginal survival function $S_i(t)$ can be formed using (4). In what follows we discuss how to model $h(t|\xi_i = 1)$ and p_i in terms of covariates of interest. For simplicity, we assume the censoring mechanism is noninformative and is independent of the longitudinal response Y.

Farewell (1982) proposed to use the following logistic regression model

$$p(z_i) = Pr(\xi_i = 1|z_i) = \frac{\exp(z_i'\lambda)}{1 + \exp(z_i'\lambda)}$$

to model the incidence probability p_i, where z_i and λ are $(p_3 \times 1)$ vectors of covariates and parameters, respectively. He also suggested a parametric survival model for $S(t|\xi = 1)$. Sy and Taylor (2000) generalized the work of Farewell (1982) to the following Cox proportional hazard model

$$h_i(t|\xi_i = 1, w_i) = h_0(t|\xi_i = 1)\exp(w_i'\alpha),$$

where w_i and α are $(p_2 \times 1)$ vectors of covariates and parameters, respectively, and $h_0(t|\xi_i = 1)$ is the conditional baseline hazard function.

The models above, however, take no account of the likely dependence of the incidence probability and the conditional hazard function on the tumour volume Y. As a result, the separate use of those models may lead to biased statistical inferences. Instead, we propose to use the random effects U_i in the longitudinal model (1), multiplied by a constant, to link the longitudinal and survival-cure models. In other words, we use the following logistic regression model

$$Pr(\xi_i = 1|z_i, U_i) = \frac{\exp(z_i'\lambda + \pi_2 U_i)}{1 + \exp(z_i'\lambda + \pi_2 U_i)} \tag{5}$$

to model the incidence probability, and use the following proportional hazard frailty model

$$h_i(t|\xi_i = 1, U_i) = h_0(t|\xi_i = 1)\exp(w_i'\alpha + \pi_1 U_i) \tag{6}$$

to model the conditional hazard function, where π_1 in (5) and π_2 in (6) are unknown link parameters. If the estimators of π_1 and π_2 are statistically significant, we conclude that the joint modelling of the longitudinal and survival-cure data is really necessary. Otherwise, the separate modelling strategy may be preferred.

2.4 *Complete log-likelihood function*

Given the random effect U_i, we assume the longitudinal data and survival-cure data are independent. It is noted that the incidence ξ_i may be observable or unobservable, depending whether or not the censoring occurs. Define $\xi = \{\xi^o, \xi^m\}$ as the set of all the incidences ξ_i's, where ξ^o and ξ^m are the collections of the observable and unobservable incidences, respectively. The observed data are $\mathcal{D} = \{(Y_i, T_i, \delta_i, X_i, w_i, z_i) : i = 1, ..., m\}$ and ξ^o. Then the complete log-likelihood function of the parameters $\Theta = (r, \beta, \alpha, \lambda, \sigma_\varepsilon^2, \sigma_u^2, \pi_1, \pi_2, h_0)$ and the unobservable data (U, ξ^m), apart from a constant, can be written as

$$\begin{aligned}
& \ell(\Theta, U, \xi^m|\mathcal{D}, \xi^o) \\
= \; & -\frac{N}{2}\log\sigma_\varepsilon^2 - \frac{1}{2\sigma_\varepsilon^2}\sum_{i=1}^{m}(Y_i - Q_i r - X_i\beta - \mathbf{1}_{n_i}U_i)'(Y_i - Q_i r - X_i\beta - \mathbf{1}_{n_i}U_i) \\
& + \sum_{i=1}^{m}\Big\{\delta_i\xi_i\Big(\log h_0(\tilde{T}_i|\xi_i = 1) + w_i'\alpha + \pi_1 U_i\Big) \\
& - \xi_i\int_0^{\tilde{T}_i} h_0(t|\xi_i = 1)\exp(w_i'\alpha + \pi_1 U_i)dt\Big\} - \frac{m}{2}\log\sigma_u^2 \\
& + \sum_{i=1}^{m}\Big\{\xi_i(z_i'\lambda + \pi_2 U_i) - \log(1 + \exp(z_i'\lambda + \pi_2 U_i))\Big\} - \frac{1}{\sigma_u^2}\sum_{i=1}^{m}U_i^2. \qquad (7)
\end{aligned}$$

Note that in the complete log-likelihood function (7), the conditional cumulative hazard function

$$H(t|\xi_i = 1) = \int_0^t h_0(t|\xi_i = 1) \exp(w_i'\alpha + \pi_1 U_i) dt$$

involves an integral which is usually analytically intractable when the time-varying covariates $w_i = w_i(t)$ are not linear in t. For the xenograft experiments we study, the covariates w_i are piecewise constants within the $(n+1)$ pre-specified follow-up time intervals, although they are really time-varying. In other words, $w_i(t) = w_{ik}$ if $t_{k-1} \le t < t_k$ where w_{ik} are known constants $(k = 1, \cdots, n)$. For the baseline hazard function $h_0(t|\xi_i = 1)$, we assume it is a piecewise constant function as well, that is,

$$h_0(t|\xi_i = 1) = h_{0k}, \quad \text{for } t_{k-1} \le t < t_k \quad (k = 1, \cdots, n), \tag{8}$$

where $h_0 = (h_{01}, \cdots, h_{0n})'$ are unknown parameters. In this case, the complete log-likelihood function (7) has the analytical form

$$\begin{aligned}
& \ell(\Theta, U, \xi^m | \mathcal{D}, \xi^o) \\
= \; & -\frac{N}{2}\log\sigma_\varepsilon^2 - \frac{1}{2\sigma_\varepsilon^2}\sum_{i=1}^{m}(Y_i - Q_i r - X_i\beta - \mathbf{1}_{n_i}U_i)'(Y_i - Q_i r - X_i\beta - \mathbf{1}_{n_i}U_i) \\
& + \sum_{i=1}^{m}\sum_{k=1}^{n} I(t_{k-1} \le \tilde{T}_i < t_k)\Big\{\delta_i\xi_i\left(\log h_{0k} + w_{ik}'\alpha + \pi_1 U_i\right) \\
& - \xi_i\sum_{j=1}^{k} h_{0j}\exp(w_{ij}'\alpha + \pi_1 U_i)(t_j - t_{j-1})\Big\} - \frac{m}{2}\log\sigma_u^2 \\
& + \sum_{i=1}^{m}\Big\{\xi_i(z_i'\lambda + \pi_2 U_i) - \log\left(1 + \exp(z_i'\lambda + \pi_2 U_i)\right)\Big\} - \frac{1}{\sigma_u^2}\sum_{i=1}^{m} U_i^2,
\end{aligned} \tag{9}$$

so that the calculation of the parameter estimators is straightforward.

3. Bayesian Inference

We propose to use a Bayesian approach to make statistical inferences for the joint models (1), (5) and (6) to avoid the analytical intractable integral problem involved in the marginalized log-likelihood function. Markov chain Monte Carlo (MCMC) is applied in our implementation. Rather than integrating out the random effects U_i and the missing values ξ^m from (9), we sample U and ξ^m, as well as other parameters, from their corresponding conditional posterior distributions.

3.1 *Priors and Gibbs sampler with adaptive rejection sampling method*

We specify independent normal priors for the parameters β, α, λ and r, of which all are assumed to have very large variances. We also specify inverse Gamma priors for the random errors variance σ_ε^2 and random effects variance σ_u^2. We choose a Gamma prior for each h_{0j} $(j = 1, 2, ..., n)$, so that a conjugate posterior distribution for h_{0j} is easy to obtain.

We assume a mixture normal distribution, $\kappa N(\tau_1, \varsigma_1) + (1 - \kappa)N(\tau_2, \varsigma_2)$, as the prior for each of the link parameters π_1 and π_2, where $0 < \kappa < 1$, $-\infty < \tau_k < \infty$ and $\varsigma_k > 0$ $(k = 1, 2)$. Mixture normal priors may come up if investigators are not sure on the choice of a prior, or they would like to mix a small proportion of a diffuse prior with a relatively sharp one. Mixture normal priors also have relatively desirable properties for sensitivity assessments. For example, we may change the mixture weight κ to assess the sensitivity of statistical inferences to the priors. We may also specify $\tau_1 = 0$ (but $\tau_2 \neq 0$) and vary κ, ς_1 and ς_2 to see how the parameter estimators are sensitive to the priors of π_1 and π_2 focusing on the origin, and to study if the joint models for longitudinal and survival-cure data are really necessary.

Since the joint log-likelihood $\ell(\Theta, U, \xi^m|\mathcal{D}, \xi^o)$ in (9) is complicated, the full posterior distributions of the parameters, except β, σ_ε^2, σ_u^2, h_0 and ξ^m, are not analytically tractable. In order to sample from the posterior distributions of these parameters, we propose to use the Gibbs sampler with adaptive rejection sampling method (Gilks and Wild, 1992). The technical details on the sampling distributions are provided in the Supplementary Web Materials.

3.2 *Model selection*

We propose to use the DIC value to select the most appropriate model. The DIC value consists of two terms, one for goodness-of-fit measured by the deviance evaluated at the posterior mean of parameters, and the other accounting for a penalty defined by twice of the effective number of parameters. The latter is defined by the mean deviance minus the deviance evaluated at the posterior mean. Under the model assumption with missing data, the DIC is defined by

$$DIC = -4E_{\Theta,U,\xi^m}[\ell(\Theta, U, \xi^m|\mathcal{D}, \xi^o)|\mathcal{D}, \xi^o)] + 2E_{U,\xi^m}[\ell(\tilde{\Theta}, U, \xi^m|\mathcal{D}, \xi^o)|\mathcal{D}, \xi^o)]$$

where $\tilde{\Theta} = E[\Theta|\mathcal{D}, U, \xi^m, \xi^o]$. See Spiegelhalter *et. al.* (2002) and Celeux *et. al.* (2006) for more details.

4. Real data analysis

Denote n_i as the number of repeated measurements for the ith mouse ($n_i \leq 12$). Let Y_{i0} and $Y_i = (Y_{i1}, \cdots, Y_{in_i})'$ be the logarithmic transformations of the initial tumour volume and the n_i-dimensional vector of tumour volumes in the follow-up weeks for the ith mouse, respectively. If $Y_{ij} < \log 0.01$ for some j satisfying $1 < j < n_i$, then Y_{ij} is truncated to be $\log 0.01$. Let $x_{ij}^{(1)}$ be the cumulative weekly total doses/100 of TMZ and $x_{ij}^{(2)}$ be the cumulative

weekly total doses of CPT-11, which are received by the ith mouse at jth week ($j = 1, ..., n_i,\ i = 1, ..., 51$). To account for the synergism of the two drugs, following Tan *et. al.* (2005a) we take $x_{ij}^{(3)} = \sqrt{x_{ij}^{(1)} x_{ij}^{(2)}}$ as the interaction term. Let $x_i^{(s)} = (x_{i1}^{(s)}, \cdots, x_{in_i}^{(s)})'$ $(s = 1, 2, 3)$ and $X_i = (Y_{i0}\mathbf{1}_{n_i}, x_i^{(1)}, x_i^{(2)}, x_i^{(3)})$. The longitudinal sub-model

$$Y_i = \Psi_i + Y_{i0}\mathbf{1}_{n_i}\beta_0 + x_i^{(1)}\beta_1 + x_i^{(2)}\beta_2 + x_i^{(3)}\beta_3 + \mathbf{1}_{n_i}U_i + \varepsilon_i \tag{10}$$

is then used to model the activity of the TMZ combined with CPT-11 against Rh18 tumour growth for the ith mouse in the xenograft experiments ($i = 1, ..., 51$). In the literature, Tan *et. al.* (2005a) used the linear model with the same covariates as (10) to model the tumour volume of Rh18 tumour, but completely ignored the within-subject correlation and survival-cure outcomes.

Among the 51 mice, in total 25 mice died of toxicity or were sacrificed as the tumour volumes were quadrupled. On the other hand, 15 mice quickly shrank their tumour volumes smaller than 0.01cm^3 and had no recurrent growth of the tumour in the rest period of experiment, so that they were considered to be cured. The remaining 11 mice were not cured but survived longer than 12 week so that their true lifetimes are not observable and censored at 12 weeks. We then use the survival model (6) to model the conditional hazard function $h_i(t|\xi_i = 1, U_i)$, where $w_i(t) = (Y_{i0}, x_{ij}^{(1)}, x_{ij}^{(2)}, x_{ij}^{(3)})'$ for $t_{j-1} \leq t < t_j$ $(j = 1, ..., n)$ and $x_{ij}^{(s)}$ $(s = 1, 2, 3)$ are the same as these in (10). We also use the model (5) to model the incidence probability $Pr(\xi_i = 1|z_i, U_i)$, where $z_i = (Y_{i0}, x_{\tilde{T}_i}^{(1)}, x_{\tilde{T}_i}^{(2)}, x_{\tilde{T}_i}^{(3)}, 1)'$, $x_{\tilde{T}_i}^{(1)}$ and $x_{\tilde{T}_i}^{(2)}$ are the cumulative total doses of TMZ and CPT-11 up to the time $\tilde{T}_i$, respectively, and $x_{\tilde{T}_i}^{(3)}$ is the associated interaction term. The model involves time-dependent

covatiates $x^{(1)}_{\tilde{T}_i}$ and $x^{(2)}_{\tilde{T}_i}$ because the incidence probability of a mouse may depend on the total doses taken by the mouse. The parameters of interest in the survival-cure models are the fixed effects parameters $\alpha' = (\alpha_0, \alpha_1, \alpha_2, \alpha_3)$, $\lambda' = (\lambda_0, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and the link parameters π_1 and π_2, where the intercept λ_4 is introduced to the incidence model to take account of the fact that the incidence probability $p_i = Pr(\xi_i = 1|z_i, U_i)$ can be very close to 1 if no treatment is given. This is because there is an intrinsic growth of a tumour in the absence of treatment, which eventually leads to the death or sacrifice of the mouse.

Following Tan *et. al.* (2005b), the prior for r is chosen to be a truncated n-dimensional normal distribution $r \sim TN_n(\mathbf{0}, \sigma_r^2 I_n)$ with $\sigma_r^2 = 100$. The prior for each element of β and λ is chosen to be $N(0, 10000)$. The priors for σ_ϵ^{-2}, σ_u^{-2} and each element of h_0 are all chosen to be Gamma$(0.001, 0.001)$. For the link parameters π_1 and π_2, a non-informative normal prior $N(0, 100)$ is considered first, and then sensitivity assessment is made by using a variety of mixture normal priors.

To see if the model links are really necessary, we consider the following four possible link scenarios.

Case 1: longitudinal and survival-cure models are linked by π_1 and π_2.

Case 2: longitudinal and survival models are linked by π_1 (i.e. $\pi_2 = 0$).

Case 3: longitudinal and cure models are linked by π_2 (i.e. $\pi_1 = 0$).

Case 4: neither of these models are linked (i.e. $\pi_1 = \pi_2 = 0$).

By assuming the normal prior $N(0, 100)$ for π_1 and π_2, in Table 1 we summarize the posterior means and 95% credit intervals of the parameters in the models for each case above. We also provide the relative DIC values for all

the four possible scenarios. In each case, we uses 10,000 iterations of MCMC sampling chains following a 5,000-iteration 'burn-in' period.

[Table 1 about here.]

From Table 1, it turns out that the smallest DIC value is achieved by the model that links all the three sub-models, implying that the joint modelling may be necessary. The baseline tumour size has a significant positive influence on the tumour growth, while the TMZ and CPT-11 treatments both have significant negative effects on the tumour growth, implying the treatments work in reducing the tumour growth. However, there is no evidence on the interaction of the two treatments in reducing the tumour size. In contrast, Tan *et. al.* (2005a) concluded that the baseline tumour size and the CPT-11, but not the TMZ, are significant factors that influence the Rh18 tumour growth. In the cure model, the estimate of λ_4 in Case 1 is about 4.14, leading to the incidence probability being 98% in the absence of treatments. In other words, without treatments the tumour-beard mice have only 2% chances to be cured. This incidence probability for the control group may be underestimated if the inherent association between longitudinal and survival-cure models is ignored. Within the joint longitudinal and survival modelling framework (Case 1 and Case 2), the CPT-11 has a significant positive effect on both the incidence probability and the survival time, but the TMZ-11 and the interaction of two treatments are not significant. When the longitudinal model and the survival model are not connected (Case 3 and 4), both the TMZ and CPT-11 are two significant factors of increasing the cure probability. Temozolomide is, however, considered to be toxic and suggested

to be combined with CPT-11 to reduce the toxicity, see Tan *et. al.* (2005a). Hence it is more likely that only the CPT-11 is significant in reducing the hazard rate and increasing the cure probability, see Case 1 and Case 2 above. The proposed joint models for longitudinal and survival-cure data seem to be more reasonable than the separate models on this nature. The link parameter π_1, on the other hand, is statistically significant, showing that there is an evidence of inherent association between the longitudinal and survival data. The link parameter π_2, however, is not significant, implying that the incidence probability of the mice may not be directly related to the tumour volumes for this dataset. But the estimated link parameters π_1 and π_2 are both positive, showing that the bigger the Rh18 tumour volume the higher the hazard rate of death, and so does the incidence rate.

In Table 2 and Figure 1 in the Supplementary Web Materials we also provide the estimators of the constrained parameters r and $\Psi = Qr$. The latter is the estimated average growth curve of the Rh18 tumour volume of mice in the control group. We observe that there is a sharp increasing of the tumour volume after the 6th week if no treatment is provided.

[Table 2 about here.]

Finally, we change the priors of π_1 and π_2 to mixture normal distributions in order to carry out sensitivity analysis. We consider the following four mixture normal distributions by varying the mixture weights and the variances: (1) $0.1N(0, 100) + 0.9N(4, 0.1)$, (2) $0.9N(0, 0.1) + 0.1N(4, 100)$, (3) $0.5N(0, 0.1) + 0.5N(4, 100)$, and (4) $0.5N(0, 100) + 0.5N(4, 0.1)$. These mixture normal priors consider different weights at the origin. For example,

the prior in (2) above places a great weight (90%) at the origin and a very small weight (10%) on $N(4, 100)$, implying the majority of the random samples from the priors of π_1 and π_2 are around zero. For the joint modelling of longitudinal and survival-cure data, numerical results in Table 2 show that parameter estimators are quite similar under the above four different priors. Comparing Table 2 to Table 1, it is clear that the estimation results under the mixture normal priors are also similar to those under the non-informative normal prior. We therefore conclude that the parameter estimators in the joint models are robust against the priors of π_1 and π_2.

5. Simulation studies

We mimic the real data in Section 4 in the following simulation studies. Assume we have four covariates: baseline tumour size, two treatments TMZ and CPT-11, and their interaction. These covariates are included in both the longitudinal and survival models. For simplicity, we only choose the TMZ 42 mg/kg and the CPT-11 0.61 mg/kg as the treatment regimens and then consider four groups of treatments: control, TMZ 42 mg/kg, CPT-11 0.61 mg/kg, and TMZ 42 mg/kg + CPT-11 0.61 mg/kg. We increase the sample size to $m = 400$ and allocate 100 samples to each of the four groups. Let $x_{ij}^{(1)}$, $x_{ij}^{(2)}$ be the cumulative weekly doses of the TMZ 42 mg/kg and CPT-11 0.61 mg/kg groups, respectively, and $x_{ij}^{(3)}$ be the interaction of $x_{ij}^{(1)}$ and $x_{ij}^{(2)}$. For each group, we have the model (1) where X_i is the design matrix with the jth row $x_{ij} = (Y_{i0}, x_{ij}^{(1)}, x_{ij}^{(2)}, x_{ij}^{(3)})$ $(j = 1, ..., n_i; i = 1, ..., m)$. Y_{i0} is the logarithm of the baseline tumour volume, which can be generated from the Normal distribution $N(\mu_{Y_0}, \sigma_{Y_0}^2)$, where $\mu_{Y_0} = -0.5$ and $\sigma_{Y_0} = 0.83$ are the sample mean and sample standard deviation from the real data. The independent

random effects U_i are assumed to follow Normal distribution $N(0, \sigma_u^2)$, the random errors ε_i follow Normal distribution $N(0, \sigma_\varepsilon^2 I_{n_i})$, and U_i and ε_i are mutually independent.

Given the random effects U_i, the incidence probability satisfying

$$\text{logit}(p_i) = Y_{i0}\lambda_0 + z_i\lambda_1 + \pi_2 U_i$$

is used to generate the uncure random indicator ξ_i from the Bernoulli distribution with probability p_i, where z_i is a group indicator with $z_i = 1$ if the ith subject is from control group and $z_i = 0$ otherwise. We only consider the covariate z_i as a group indicator here, rather than the cumulative weekly dose as given in the real data in Section 4, in order to avoid a logical dilemma arising in simulation studies. The reason is that the incidence indicator ξ and the cumulative dose of a treatment may have causal effects to each other. For example, the cumulative dose received by a mouse may depend on its death status and time-to-death. Thus it is not sensible to fix the cumulative dose of a treatment first and then generate the incidence indicator ξ.

For these subjects with incidence indicator $\xi_i = 1$, on the other hand, the survival model (6) is used to generate the survival outcomes T_i, where $w_i(t) = (Y_{i0}, x_{ij}^{(1)}, x_{ij}^{(2)}, x_{ij}^{(3)})'$ for $t_{j-1} \leq t < t_j$. The baseline hazard rate $h_0(t|\xi_i = 1)$ is assumed to be a piecewise constant function

$$h_0(t|\xi_i = 1) = h_{0j} = \exp(-3 + 0.45 * j)$$

for $t_{j-1} \leq t < t_j$ $(j = 1, ..., n)$. It is assumed that the baseline hazard has an increasing jump because the hazard rate increases in the absence of treatments. In the simulation studies, we choose the parameter estimators obtained in the real data analysis as the true values of the parameters.

To measure the effects of the association of the longitudinal and survival-cure models, we consider two scenarios, that is, with the association ($\pi_1 \neq 0$ and $\pi_2 \neq 0$) and without the association ($\pi_1 = \pi_2 = 0$). For each scenario, we simulate 100 data sets and calculate the sample mean and the sample standard deviation for each parameter estimator. For each data set, we draw 1,000 random samples from the posterior distributions following a 4,000-iteration 'burn-in' period in order to estimate the parameters. Table 3 and Table 4 provide the parameter estimators, standard deviations and mean squared errors(MSE) defined by $\text{MSE}(\theta) = \sum_{k=1}^{100}(\theta - \hat{\theta}_k)^2/100$, where $\hat{\theta}_k$ is the estimator of parameter θ in the kth run of simulations.

When the latent association of longitudinal and survival-cure data does exist, i.e., $\pi_1 \neq 0$ and $\pi_2 \neq 0$, the proposed joint modelling approach performs very well. For example, the link parameter estimators of π_1 and π_2 are statistically significant, which correctly identifies that the joint models are really necessary. On the contrary, the separated modelling approach that ignores the existing inherent association gives considerably biased estimators of the parameters in the survival and cure models. By introducing the link parameters π_1 and π_2, the longitudinal and survival-cure models are linked inherently and the resulting parameter estimators are unbiased. When the association exists but is ignored, the survival and cure model based inferences are affected considerably, although little effect on the parameter estimators in the longitudinal model is found.

[Table 3 about here.]

When there is no latent association of the longitudinal and survival-cure models, it is concluded that the separate modelling approach produces better

results in terms of smaller values of the MSE for most of the parameters, see Table 4. This is what we expect. The joint modelling approach, on the other hand, performs very well too, in the sense of not only giving unbiased estimators but also having relatively small values of the MSE. The link parameter estimators of π_1 and π_2 in this case are actually not significant, implying that the proposed joint modelling method correctly identifies that the link is not necessary. So, the separate modelling approach fits the data best in this case.

[Table 4 about here.]

In summary, the proposed joint modelling approach is very reliable even if longitudinal and survival-cure data do not have an inherent association. It gives much better results than the separated modelling approach when the inherent association exists.

6. Discussion

In this paper we propose a joint modelling approach to account for the likely inherent association for longitudinal data and survival-cure outcomes. We propose to use common random effects, after being properly scaled, to connect the different models. The approach is then used to analyze a real dataset arising from tumour xenograft experiments. Bayesian inferences are obtained using a MCMC approach, showing the parameter estimators from the posteriors are robust against the priors of the link parameters. Our conclusion on the data analysis is mostly consistent with Houghton *et. al.* (2000) but the inherent association of different types of data is taken into account so that more information is discovered. Simulation studies show that the proposed

joint modelling approach produces very satisfactory parameter estimators.

Some further research needs to be studied when each mouse has multiple tumours. Tan *et. al.* (2005b) described an example of preclinical studies evaluating the anti-tumour effects of exemestane and tamoxifen for postmenopausal breast cancer, in which each mouse received subcutaneous injections at two sites and developed four tumours in the process. It is anticipated that multivariate longitudinal responses and multi-dimensional random effects will be involved and additional correlation between tumours for the same mice should be accounted for. We will report this in a follow-up paper.

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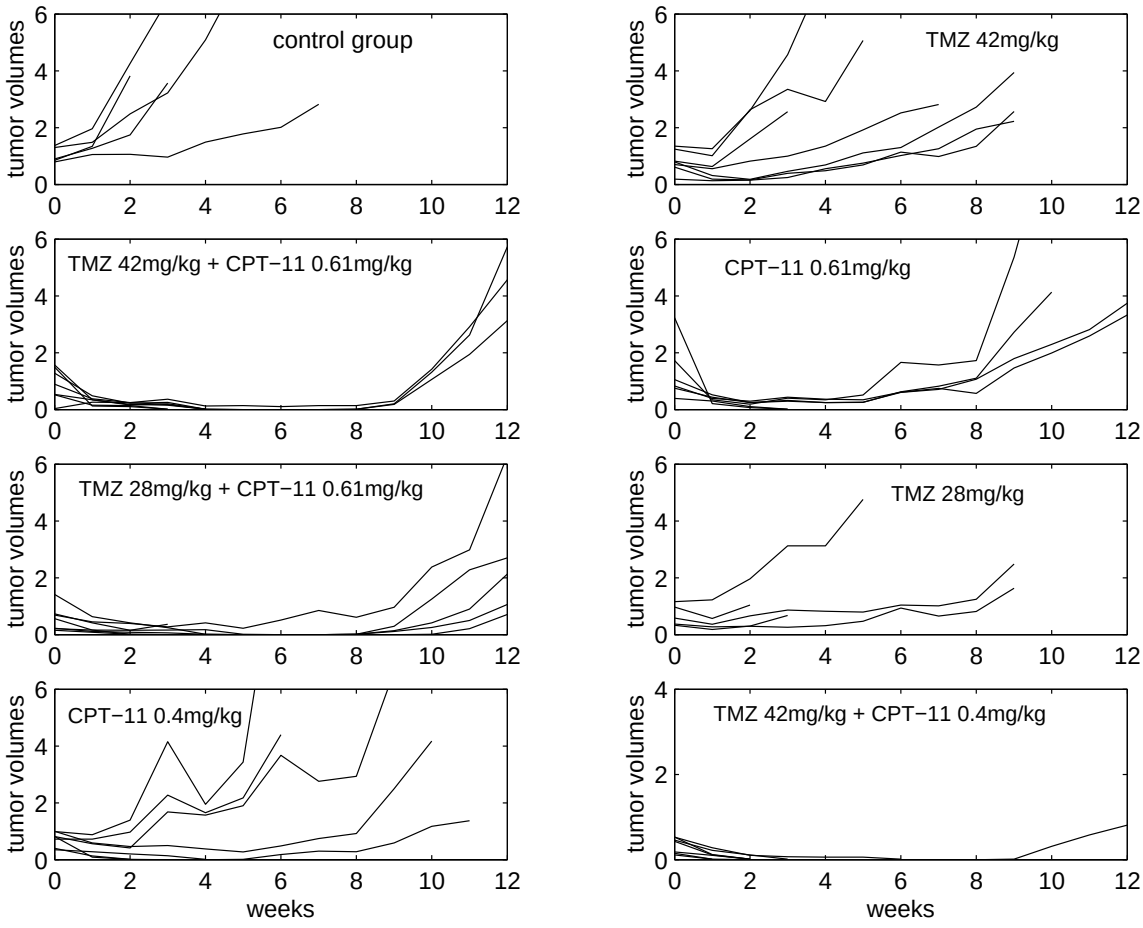

Figure 1. Observed tumor sizes for the eight treatment groups.

Table 1

Posterior mean (95% credit interval) of the parameters and the DIC values.

Par.	Case 1	Case 2	Case 3	Case 4
DIC	614.5	674.6	681.9	688.3
β_0	0.8616	0.8295	0.8324	0.8527
	(0.4091 1.3835)	(0.3412 1.2422)	(0.4676 1.2388)	(0.5484 1.2704)
β_1	-0.5567	-0.5628	-0.5525	-0.5510
	(-0.6832 -0.4096)	(-0.7014 -0.4230)	(-0.7025 -0.4260)	(-0.7102 -0.4285)
β_2	-0.4103	-0.4009	-0.3948	-0.4014
	(-0.4745 -0.3478)	(-0.4516 -0.3361)	(-0.4490 -0.3411)	(-0.4568 -0.3555)
β_3	0.0789	0.1524	-0.0340	-0.1970
	(-3.4472 4.0170)	(-4.4393 3.9468)	(-4.2190 3.9682)	(-3.2439 3.7544)
α_0	0.3634	0.3569	0.7421	0.6643
	(-0.7022 1.2606)	(-0.7193 1.3840)	(-0.1494 1.5168)	(-0.3595 1.3594)
α_1	-0.2445	-0.2064	-0.1284	-0.0651
	(-0.5345 0.0967)	(-0.5035 0.0654)	(-0.3704 0.1489)	(-0.3426 0.2878)
α_2	-0.2730	-0.2472	-0.2097	-0.1645
	(-0.4020 -0.0842)	(-0.4267 -0.0819)	(-0.3579 -0.0205)	(-0.3453 0.0153)
α_3	-0.0513	0.0393	-0.1507	0.0003
	(-3.5973 3.7937)	(-3.6933 4.2151)	(-4.8075 4.0492)	(-3.7621 3.6113)
λ_0	0.1672	-0.0398	0.2529	-0.0355
	(-1.3126 1.6016)	(-1.3370 1.5346)	(-0.8815 1.4278)	(-1.4610 1.3311)
λ_1	-0.3169	-0.3162	-0.3040	-0.3275
	(-0.6948 0.0037)	(-0.7040 0.0098)	(-0.5576 -0.0156)	(-0.7052 -0.0233)
λ_2	-0.2551	-0.2619	-0.2292	-0.2627
	(-0.4357 -0.1304)	(-0.4249 -0.1095)	(-0.3738 -0.1020)	(-0.4447 -0.1200)
λ_3	0.0781	0.2724	0.2718	-0.1434
	(-3.6592 4.1942)	(-3.1518 4.0833)	(-2.7524 3.3410)	(-4.3685 3.8604)
λ_4	4.1369	3.8725	4.0205	3.9354
	(2.5493 6.2047)	(2.2288 5.6393)	(2.4436 5.7740)	(2.2531 6.3405)
σ_ε^2	1.4443	1.3791	1.3551	1.3897
	(0.8235 2.4107)	(0.9292 2.1738)	(0.8262 2.1431)	(0.8290 2.3188)
σ_u^2	1.4616	1.4420	1.4547	1.4570
	(1.2264 1.7022)	(1.1895 1.7257)	(1.2048 1.7872)	(1.2128 1.7340)
π_1	0.7142	0.7410	0	0
	(0.0728 1.3774)	(0.0524 1.5126)	(0 0)	(0 0)
π_2	0.5496	0	0.6139	0
	(-0.4693 1.5104)	(0 0)	(-0.6380 1.7556)	(0 0)

Table 2

Posterior mean (95% credit interval) of the parameters and the DIC values with priors: (1) 0.1N(0,100)+0.9N(4,0.1); (2) 0.9N(0,0.1)+0.1N(4,100); (3) 0.5N(0,0.1)+0.5N(4,100); (4) 0.5N(0,100)+0.5N(4,0.1).

Par.	(1)	(2)	(3)	(4)
DIC	673.6	636.9	690.6	648.2
β_0	0.791	0.780	0.803	0.842
	(0.369 1.208)	(0.301 1.274)	(0.349 1.272)	(0.415 1.245)
β_1	-0.560	-0.545	-0.551	-0.554
	(-0.727 -0.403)	(-0.735 -0.379)	(-0.691 -0.390)	(-0.709 -0.390)
β_2	-0.407	-0.404	-0.405	-0.403
	(-0.459 -0.344)	(-0.459 -0.351)	(-0.459 -0.350)	(-0.455 -0.346)
β_3	0.006	-0.032	-0.059	-0.013
	(-3.881 3.868)	(-3.616 3.9055)	(-4.095 3.872)	(-3.912 3.865)
α_0	0.209	0.229	0.274	0.249
	(-0.832 1.299)	(-0.899 1.307)	(-0.800 1.471)	(-0.763 1.247)
α_1	-0.281	-0.221	-0.208	-0.265
	(-0.639 0.063)	(-0.606 0.182)	(-0.557 0.183)	(-0.627 0.121)
α_2	-0.279	-0.246	-0.238	-0.269
	(-0.466 -0.100)	(-0.433 -0.054)	(-0.404 -0.045)	(-0.445 -0.094)
α_3	-0.041	-0.041	-0.033	0.051
	(-3.755 3.889)	(-3.857 3.797)	(-4.157 3.776)	(-3.846 3.769)
λ_0	0.094	-0.014	-0.032	0.127
	(-1.507 1.458)	(-1.405 1.451)	(-1.384 1.402)	(-1.306 1.613)
λ_1	-0.325	-0.343	-0.327	-0.312
	(-0.752 0.040)	(-0.756 0.001)	(-0.714 0.017)	(-0.721 0.026)
λ_2	-0.263	-0.272	-0.279	-0.257
	(-0.448 -0.111)	(-0.463 -0.111)	(-0.455 -0.119)	(-0.440 -0.096)
λ_3	-0.035	-0.017	-0.031	-0.056
	(-4.015 4.065)	(-4.083 3.874)	(-3.985 3.992)	(-4.050 3.939)
λ_4	4.222	4.204	4.139	4.104
	(2.327 6.426)	(2.300 6.795)	(2.262 6.226)	(2.196 6.381)
σ_ε^2	1.391	1.418	1.370	1.383
	(0.818 2.289)	(0.834 2.284)	(0.792 2.192)	(0.807 2.208)
σ_u^2	1.449	1.446	1.452	1.455
	(1.218 1.735)	(1.221 1.731)	(1.219 1.734)	(1.229 1.742)
π_1	0.814	0.694	0.765	0.786
	(0.133 1.586)	(0.010 1.576)	(0.035 1.613)	(0.131 1.636)
π_2	0.506	0.382	0.315	0.496
	(-0.630 1.758)	(-0.433 1.839)	(-0.449 1.658)	(-0.670 1.834)

Table 3

Simulation results for the case that there is a latent association, i.e., $\pi_1 \neq 0$ and $\pi_2 \neq 0$. The sample size m=400.

Par.	True	Separate modelling			Joint modelling		
		Estimates	St.D.	MSE	Estimates	St.D.	MSE
β_0	0.86	0.8506	0.0795	0.0063	0.8649	0.0643	0.0041
β_1	-0.56	-0.5622	0.0365	0.0013	-0.5733	0.0373	0.0016
β_2	-0.41	-0.4078	0.0109	0.0001	-0.4167	0.0120	0.0002
β_3	0.08	0.0818	0.0256	0.0007	0.0866	0.0295	0.0009
b_0	0.36	0.2554	0.0972	0.0227	0.3300	0.0933	0.0095
b_1	-0.24	-0.1171	0.0364	0.0164	-0.2077	0.0406	0.0027
b_2	-0.27	-0.2857	0.0322	0.0048	-0.2718	0.0380	0.0014
b_3	-0.05	-0.1311	0.3348	0.1176	-0.0216	0.1387	0.0199
a_0	0.17	0.1014	0.1184	0.0140	0.1933	0.1199	0.0148
a_1	4.14	3.9065	0.5227	0.3250	4.0588	0.5359	0.2909
σ_ε^2	1.44	1.4418	0.0421	0.0018	1.4419	0.0387	0.0015
σ_u^2	1.46	1.4348	0.1247	0.0160	1.4687	0.1134	0.0128
π_1	0.71	-	-	-	0.6380	0.0951	0.0141
π_2	0.55	-	-	-	0.5743	0.1279	0.0168

Table 4

Simulation results for the case that there is no latent association, i.e., $\pi_1 = \pi_2 = 0$. *The sample size m=400.*

Par.	True	Separate modelling			Joint modelling		
		Estimates	St.D.	MSE	Estimates	St.D.	MSE
β_0	0.86	0.8636	0.0782	0.0061	0.8610	0.1034	0.0106
β_1	-0.56	-0.5710	0.0345	0.0013	-0.5780	0.0712	0.0053
β_2	-0.41	-0.4167	0.0102	0.0001	-0.4150	0.0444	0.0020
β_3	0.08	0.0867	0.0867	0.0005	0.0894	0.0266	0.0008
b_0	0.36	0.3301	0.0988	0.0106	0.3364	0.0842	0.0076
b_1	-0.24	-0.1984	0.0376	0.0031	-0.1950	0.0424	0.0038
b_2	-0.27	-0.2933	0.0847	0.0076	-0.2871	0.0780	0.0063
b_3	-0.05	0.0008	0.2295	0.0547	0.0020	0.1846	0.0364
a_0	0.17	0.1809	0.1299	0.0168	0.2014	0.1386	0.0200
a_1	4.14	3.9943	0.5002	0.2690	3.8913	0.6740	0.5116
σ_ε^2	1.44	1.4472	0.0364	0.0014	1.4233	0.1450	0.0211
σ_u^2	1.46	1.4797	0.1274	0.0165	1.4464	0.1729	0.0298
π_1	0.0	-	-	-	0.0117	0.0725	0.0053
π_2	0.0	-	-	-	0.0130	0.1182	0.0140