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Statistical methods for multivariate interval-censored recurrent events

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SUMMARY

Multi-type recurrent event data arise when two or more different kinds of events may occur repeatedly over a period of observation. The scientific objectives in such settings are often to describe features of the marginal processes and to study the association between the different types of events. Interval-censored multi-type recurrent event data arise when the precise event times are unobserved, but intervals are available during which the events are known to have occurred. This type of data is common in studies of patients with advanced cancer, for example, where the events may represent the development of different types of metastatic lesions which are only detectable by conducting bone scans of the entire skeleton. In this setting it is of interest to characterize the incidence of the various types of bone lesions, to estimate the impact of treatment and other covariate effects on the development of new lesions, and to understand the relationship between the processes generating the bone lesions. We develop joint models for multi-type interval-censored recurrent events which accommodate dependencies between different types of events and enable one to examine the covariate effects via regression. However, since the marginal likelihood resulting from the multivariate random effect model is intractable, we describe a Gibbs sampling algorithm to facilitate model fitting and inference. We use generalized estimating equations for estimation and inference based on marginal models. The finite sample properties of the marginal approach are studied via simulation. The estimates of both the regression coefficients and the variance–covariance parameters are shown to have negligible bias and 95 per cent confidence intervals based on the asymptotic variance formula are shown to have excellent empirical coverage probabilities in all of the settings considered. The application of these methods to data from a trial of women with advanced breast cancer provides insight into the clinical course of bone metastases in this population.

KEY WORDS: generalized estimating equation; interval-censoring; multi-type recurrent events; random effects

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1. INTRODUCTION

Multi-type recurrent event data arise when two or more different types of events may occur repeatedly over a period of observation. The scientific objectives in such settings are often to characterize features of the marginal processes generating the particular types of events and to study the association between the different types of events. Counting process models provide a very powerful framework for the analysis of such event history data when subjects are under continuous observation [1]. Random effect models [2] and marginal models [3] are also convenient to adopt in this setting.

Interval-censored multi-type recurrent event data arise when the event times are not known, but when one can specify intervals during which the events occurred. This type of data is common in studies of patients with advanced cancer, for example, where the events may represent the development of different types of metastatic lesions only detectable upon completion of bone scans of the entire body. In this setting it is of interest to characterize the incidence of the various types of bone lesions, to estimate the impact of treatment and other covariate effects on the development of new lesions, and to understand the association between the different types of bone lesions. Numerous examples exist in other settings when the events of interest are only detected by periodic intensive examination. For example, in gastroenterology studies it is of interest to detect different types of polyps via periodic endoscopy, in urology different types of recurrent superficial bladder cancer tumours may be detected via periodic examination, and in studies of osteoporosis different types of skeletal changes may be of interest and detectable only by periodic radiographic examination.

Several non-parametric and semiparametric methods have been developed for estimating and comparing rate functions for univariate point processes subject to interval-censoring. Thall and Lachin [4] consider this problem and develop non-parametric tests for comparing mean functions between groups. Sun and Kalbfleisch [5, 6] consider the most extreme form of interval-censoring and develop nonparametric estimates of cumulative mean functions for point processes under current status and panel observation schemes. Staniswalis *et al.* [7] describe methods for fitting semiparametric regression models for interval-censored recurrent event data using splines. More recently, Lawless and Zhan [8] develop convenient methods for fitting regression models for univariate interval-censored recurrent event data via maximum likelihood based on a gamma-Poisson random effect model, and via estimating functions based on assumptions regarding the first and second moments. Both frameworks discussed in Lawless and Zhan [8] exploit the tractability and robustness resulting from specification of piecewise constant baseline rate functions. However, not much work has been done in the context of interval-censored multi-type recurrent events.

The purpose of this paper is to develop methods for the analysis of multi-type interval-censored point process data. We considered approaches based on mixed Poisson models and marginal methods. With the former approach, each individual is thought to have a latent vector valued subject-specific effect, where the kth component of this vector helps characterize their rate for the kth event type. These latent random effects may be thought of as representing unobserved covariates which, if available, could be used to characterize the variation in the Poisson rates between event types and among subjects in the population. By making these latent subject effects stochastic, a correlation is induced between counts over disjoint intervals for each subject and event type, and by making these random effects correlated, a correlation is induced between counts from each subject for *different* types of events. Marginal methods are

typically formulated based on generalized estimating functions which are constructed from means and variances of the unconditional distribution obtained by marginalizing over the random effects. Since these estimating functions do not rely on full specification of the model and robust variance estimates are available for estimating functions, this approach is often viewed as providing more robust inferences than full models.

We describe methods based on a mixed Poisson model with piecewise constant baseline intensities and multivariate log-normal random effects. The multivariate log-normal random effect distribution is chosen because it is a so-called *genuine multivariate* distribution [9] which enables one to separately characterize the marginal variance functions and the associations between the different types of event processes. Then the marginal likelihood is obtained by averaging over the random effect. Since the marginal likelihood is intractable for this model, a Bayesian formulation and Gibbs sampling algorithm [10] are described which can be conveniently implemented using the software package BUGS [11]. Since the covariate effects can be interpreted more directly in the marginal model approach, generalizations of the univariate marginal methods for interval-censored recurrent events developed by Lawless and Zhan [8] are also provided to deal with multi-type recurrent event data.

The remainder of the paper is organized as follows. In Section 2, we introduce notation and define piecewise constant functions for baseline rates. In Section 3, we set up the random effect model for multivariate recurrent event processes, and describe a Gibbs sampling algorithm. Generalized estimating equations are given in Section 4 for estimation and inference in the context of marginal models for multi-type interval-censored recurrent event data. Both the random effect and marginal methods of analysis are applied to data on the occurrence of three types of bone lesions from a trial of patients with advanced breast cancer [12]. The results are reported in Section 5. The finite sample frequency properties of the marginal methods are assessed via simulation studies and the results are reported in Section 6. General remarks are made in Section 7.

2. SPECIFICATION OF THE RATE FUNCTIONS

Consider a sample of m subjects in which each subject is at risk of J different types of recurrent events. Let i index subjects and j index the event types so $i=1,\ldots,m$ and $j=1,\ldots,J$. Let $N_{ij}(s)$ be the number of type j events occurring over the interval $(0,s]$ for subject i, where $\{N_{ij}(t), t>0\}$ arises from a point process with rate function $\lambda_{ij}(t)=E\{\mathrm{d}N_{ij}(t)\}/\mathrm{d}t$ and cumulative mean function

$$\Lambda_{ij}(t)=E\{N_{ij}(t)\}, \quad i=1,\ldots,m \quad \text{and} \quad j=1,\ldots,J \tag{1}$$

Here $\Lambda_{ij}(t)$ can be written as an integral of the rate function,

$$\Lambda_{ij}(t)=\int_0^t \lambda_{ij}(s)\,\mathrm{d}s$$

Let $0=b_{ij0}<b_{ij1}<\cdots<b_{ijk_{ij}}=\tau_{ij}$ denote the times at which process j of subject i is observed. As a result, the numbers of events in the interval $R_{ijk}=(b_{ij,k-1},b_{ijk}]$, $k=1,\ldots,k_{ij}$ are known and denoted by $n_{ijk}=N_{ij}(b_{ijk})-N_{ij}(b_{ij,k-1})$, $k=1,\ldots,k_{ij}$ respectively, but the exact event times are unobserved. The observation times $\{b_{ijk}\}$'s may be fixed or random, but when they

are random they are assumed to be predictable, which means that each observation point is conditionally independent of the corresponding count given the history of the observed processes and recurrent event [8].

Suppose that associated with subject i and process j is a $p \times 1$ covariate vector $\mathbf{x}_{ij} = (x_{ij1}, \ldots, x_{ijp})'$. The effects of covariates can be modelled a number of ways, but it is common to adopt a multiplicative rate model of the form

$$\lambda_{ij}(t|\mathbf{x}_{ij}) = \lambda_{0j}(t)\exp(\mathbf{x}_{ij}'\boldsymbol{\beta}_j) \quad \text{for } i = 1, \ldots, m, \quad \text{and} \quad j = 1, \ldots, J$$

where $\boldsymbol{\beta}_j$ is a $p \times 1$ vector of regression coefficients and $\lambda_{0j}(t)$ is the baseline rate function for the type j events. In general, the baseline rate $\lambda_{0j}(t)$ can be modelled parametrically, weakly parametrically by piecewise constant intensities, or nonparametrically. We consider piecewise constant rate functions which are convenient to work with and provide robustness.

Let $\mathbf{a}_j = (a_{j0}, a_{j1}, \ldots, a_{j,r_j})'$ be vectors of cut-points satisfying $0 = a_{j0} < a_{j1} < \cdots < a_{j,r_j} = +\infty$, for $j = 1, \ldots, J$. For piecewise constant rate functions we set $\lambda_{0j}(t) = \rho_{jh}$ for $t \in A_{jh} = (a_{j,h-1}, a_{jh}]$, $h = 1, \ldots, r_j$, $j = 1, \ldots, J$ and let $\boldsymbol{\rho} = \{\rho_{jh}, j = 1, \ldots, J;\ h = 1, \ldots, r_j\}$. The cumulative mean function can then be written as

$$\begin{aligned}\Lambda_{ij}(t) &= \int_0^t \lambda_{0j}(s)\,\mathrm{d}s \exp(\mathbf{x}_{ij}'\boldsymbol{\beta}_j) \\ &= \Lambda_{0j}(t)\exp(\mathbf{x}_{ij}'\boldsymbol{\beta}_j)\end{aligned}$$

where $\Lambda_{0j}(t) = \sum_{h=1}^{r_j} \rho_{jh} a_{jh}(t)$ and $a_{jh}(t) = \max\{0, \min(a_{jh}, t) - a_{j,h-1}\}$ equals the length of the intersection of interval $(0, t]$ with interval A_{jh}. The integral of the baseline intensity function over the interval R_{ijk} is

$$\Lambda_{0ijk}(\rho) = \int_{R_{ijk}} \lambda_{0j}(s)\,\mathrm{d}s = \sum_{h=1}^{r_j} \rho_{jh} a_{jh}(i,k) \tag{2}$$

where $a_{jh}(i,k)$ is the length of the intersection of the interval R_{ijk} and A_{jh}. This is calculated as $a_{jh}(i,k) = \max\{0, \min(a_{jh}, b_{ijk}) - \max(a_{j,h-1}, b_{ij,k-1})\}$. In most situations it is satisfactory to use piecewise constant baseline intensities with 4–10 pieces [8].

3. THE RANDOM EFFECT APPROACH

To model the associations between different types of event processes here we introduce distributional assumptions for the event process. Specifically, we assume that conditional on the random effect u_{ij} and covariate vector $\mathbf{x}_{ij}$, $N_{ij}(t)$ has an intensity function

$$\lambda_{ij}(t|u_{ij}, \mathbf{x}_{ij}) = u_{ij}\lambda_{0j}(t)\exp(\mathbf{x}_{ij}'\boldsymbol{\beta}_j) \tag{3}$$

where $i = 1, \ldots, m$, and $j = 1, \ldots, J$. The multivariate random effects $\mathbf{u}_i = (u_{i1}, \ldots, u_{iJ})'$ are assumed to be independent and identically distributed with a cumulative joint distribution function $G(\mathbf{u}; \boldsymbol{\phi})$. This conditional intensity function corresponds to a mixed Poisson regression model since the intensity function is the same as the rate function for Poisson processes. The

baseline rate functions $\lambda_{0j}(t)$, $j=1,\ldots,J$, are taken to be piecewise constant functions as described in Section 2.

For convenience of notation, we define

$$\Lambda_{ijk}(\boldsymbol{\beta},\boldsymbol{\rho})=\Lambda_{0ijk}(\boldsymbol{\rho})\exp(\mathbf{x}_{ij}'\boldsymbol{\beta}_j) \quad \text{and} \quad \Lambda_{ij+}(\boldsymbol{\beta},\boldsymbol{\rho})=\sum_{k=1}^{K_j}\Lambda_{ijk}(\boldsymbol{\beta},\boldsymbol{\rho})$$

Since the observation points are assumed to be noninformative, under the mixed Poisson process assumption we specify the conditional likelihood for subject i as

$$L_i(\boldsymbol{\beta},\boldsymbol{\rho}|u_{ij},\mathbf{x}_{ij})=\prod_{j=1}^{J}\left[u_{ij}^{n_{ij+}}\exp\{-u_{ij}\Lambda_{ij+}(\boldsymbol{\beta},\boldsymbol{\rho})\}\prod_{k=1}^{K_j}\Lambda_{ijk}^{n_{ijk}}(\boldsymbol{\beta},\boldsymbol{\rho})\right],$$

where $n_{ij+}=\sum_{k=1}^{K_j}n_{ijk}$. If $\boldsymbol{\theta}=(\boldsymbol{\beta}',\boldsymbol{\rho}',\boldsymbol{\phi}')'$ and $A_i(\boldsymbol{\beta},\boldsymbol{\rho})=\prod_{j=1}^{J}\prod_{k=1}^{K_j}\Lambda_{ijk}^{n_{ijk}}(\boldsymbol{\beta},\boldsymbol{\rho})$, the marginal likelihood for subject i is given by

$$L_i(\boldsymbol{\theta})=A_i(\boldsymbol{\beta},\boldsymbol{\rho})\int_0^{\infty}\cdots\int_0^{\infty}\prod_{j=1}^{J}u_{ij}^{n_{ij+}}\exp\left\{-\sum_{j=1}^{J}u_{ij}\Lambda_{ij+}(\boldsymbol{\beta},\boldsymbol{\rho})\right\}\mathrm{d}G(\mathbf{u}_i;\boldsymbol{\phi}) \tag{4}$$

There are several classes of multivariate random effect distributions one could consider including shared frailties ($u_{i1}=u_{i2}=\cdots=u_{iJ}$), generalized shared frailties ($u_{ij}=e^{a_jw_i}$ for any $a_j\in R$ and random variable w_i), additive frailties ($u_{ij}=v_{i0}+v_{ij}$, with $v_{i0},v_{i1},\ldots,v_{iJ}$ independent), or log normal frailties ($\mathbf{u}_i$ follows a multivariate log normal distribution). Here we use multivariate log normal frailties since it accommodates both positive and negative correlations between frailties and does not impose a direct relationship between the variances and the correlations. In this case, the required integrals in (4) can be approximated by *Gauss–Hermite* quadrature [13].

Let $\ell(\boldsymbol{\theta})=\sum_{i=1}^{m}\ell_i(\boldsymbol{\theta})$ denote the log likelihood for all subjects. A Newton–Raphson algorithm can be applied to obtain the maximum likelihood estimate $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$. If $\boldsymbol{\theta}^{(0)}$ denotes an initial value of $\boldsymbol{\theta}$, we have,

$$\boldsymbol{\theta}^{(k+1)}=\boldsymbol{\theta}^{(k)}+\left\{-\left.\frac{\partial^2\ell(\boldsymbol{\theta})}{\partial\boldsymbol{\theta}\partial\boldsymbol{\theta}'}\right|_{\boldsymbol{\theta}^{(k)}}\right\}^{-1}\left\{\left.\frac{\partial\ell(\boldsymbol{\theta})}{\partial\boldsymbol{\theta}}\right|_{\boldsymbol{\theta}^{(k)}}\right\}$$

By iterating the above equation until the difference between $\boldsymbol{\theta}^{(k+1)}$ and $\boldsymbol{\theta}^{(k)}$ is below some specified tolerance, we obtain the maximum likelihood estimate. The maximum likelihood estimator $\hat{\boldsymbol{\theta}}$ is consistent and asymptotically normally distributed with the variance–covariance matrix estimated by

$$\widehat{\mathrm{asvar}}(\hat{\boldsymbol{\theta}})=-\left\{\left.\frac{\partial^2\ell(\boldsymbol{\theta})}{\partial\boldsymbol{\theta}\partial\boldsymbol{\theta}'}\right|_{\hat{\boldsymbol{\theta}}}\right\}^{-1}$$

Therefore the observed information matrix can be used to carry out Wald tests for effects of covariates and to assess the association among different types of events.

One may alternatively consider the use of a Gibbs sampler [10] to facilitate Bayesian inference in the context of fully specified models such as this. To help in the specification of the conditional dependencies between the parameters, random effects, and responses

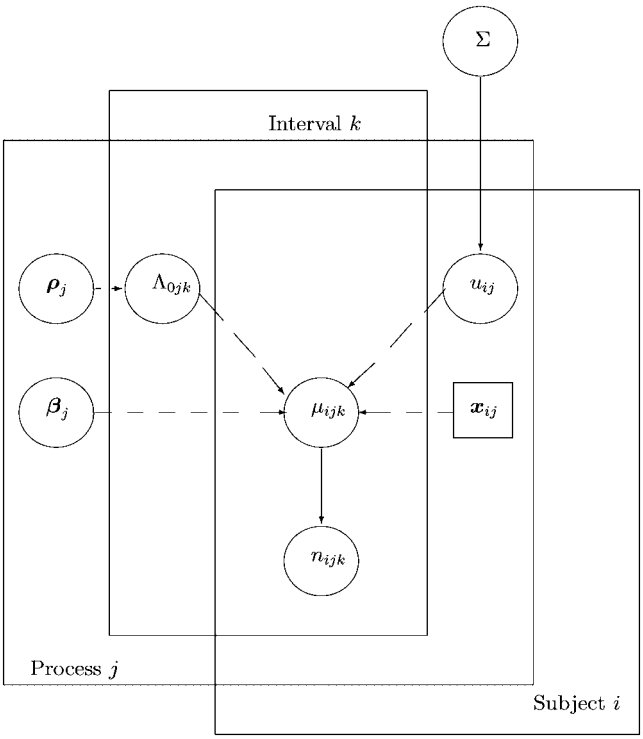

Figure 1. Directed graphical model for the interval-censored multivariate recurrent events process.

in the full model, a *directed graphical model* [11] can be constructed. In directed graphs, quantities are represented as nodes and arrows which run into nodes to indicate how some quantities (parents) influence other quantities (children). For the currently specified model, we make the assumption that, given its parent node, each node is independent of all other nodes in the graph except for its descendants. The directed graph for the model specified for interval-censored multivariate recurrent events is given in Figure 1. Here the node ($\mathbf{x}_{ij}$) is a constant node (denoted by a rectangle) which is fixed by the design of the study. All the other nodes are stochastic nodes (denoted as circles in the graph). The stochastic nodes can be observed data (such as n_{ijk} in Figure 1) or unobserved parameters (such as $\Sigma, \boldsymbol{\rho}_j, \boldsymbol{\beta}_j, u_{ij}, \Lambda_{0jk}, \mu_{ijk}$). There are two types of links in Figure 1. A dashed arrow indicates a logical function (e.g. $\mu_{ijk} = u_{ij}\Lambda_{0jk}(\boldsymbol{\rho}_j)\exp(\mathbf{x}_{ij}\boldsymbol{\beta}_j)$), whereas a solid arrow indicates a stochastic dependency (e.g. $n_{ijk} \sim \text{Poisson}(\mu_{ijk})$).

Bayesian Inference using Gibbs sampling (`BUGS`) [11] is a package of routines which have been written specifically to facilitate implementation of the Gibbs sampler for a wide range of problems such as the one at hand. One of the appealing features of the BUGS package is that the full set of conditional distributions required for Gibbs sampling are derived by specifying a rather limited set of conditional distributions. Appendix 1 gives the distributions specified as well as the BUGS code for fitting the model of interest. For computational convenience, instead of parameterizing the variance–covariance matrix Σ, we parameterize the unknown

variance–covariance parameters of the vector of random effects $\mathbf{v}_i = \log(\mathbf{u}_i)$ directly in the linear predictor as follows:

$$\begin{aligned} v_{i1} &= \omega_{11} z_{i1} \\ v_{i2} &= \omega_{12} z_{i1} + \omega_{22} z_{i2} \\ &\cdots \\ v_{iJ} &= \omega_{1J} z_{i1} + \omega_{2J} z_{i2} + \cdots + \omega_{JJ} z_{iJ} \end{aligned} \tag{5}$$

where the latent random effect $\mathbf{z}_i$, has a completely specified standard multivariate normal distribution. The variance–covariance matrix of $\{v_{i1}, \ldots, v_{iJ}\}'$ is obtained by computing $\Sigma = [\sigma_{jk}]_{J \times J}$, with

$$\sigma_{jk} = \sum_{\ell=1}^{j \wedge k} \omega_{\ell j} \omega_{\ell k}, \quad 1 \leqslant j, k \leqslant J \tag{6}$$

where $j \wedge k = \min(j, k)$. We fit this model to the data from Hortobagyi *et al.* [12] in Section 5. With Bayesian 'non-informative' priors, one can use the median of the posterior distribution as a point estimate and symmetric 100 $(1-\alpha)$ per cent credibility intervals for interval estimation. Two-sided probability values, somewhat analogous to *p*-values in a frequentist setting, can be computed by doubling the tail area beyond the null value [30]. In what follows, 'CI' and '*p*-value' under Bayesian analyses should be taken to mean credibility interval and probability value respectively, with Bayesian significance testing based on the latter.

The simulated values from successive iterations of `BUGS` may be analysed using the convergence diagnosis and output analysis software (`CODA`) of Best *et al.* [14] to diagnose the convergence of the algorithm. For example, both the Geweke z score tests [15] and the Heidelberger stationary tests [16] were used as convergence diagnostics for the output of Gibbs samplers.

4. MARGINAL METHODS FOR INTERVAL-CENSORED DATA

Here we consider a natural generalization of the estimating function approach described for univariate interval-censored recurrent event processes by Lawless and Zhan [8]. The robustness arises from that fact that the estimating functions are derived based only on assumptions about the first two moments of the processes.

Using the same notation for n_{ijk} and R_{ijk} as in Section 2, we let $\mathbf{n}_{ij} = (n_{ij1}, \ldots, n_{ij,k_{ij}})'$ for $j = 1, \ldots, J$, and $\mathbf{n}_i = (\mathbf{n}_{i1}', \ldots, \mathbf{n}_{iJ}')'$, $i = 1, \ldots, m$. Under the random effects formulation of Section 3, for each of these J counting processes, the marginal moments for n_{ijk} can be specified as:

$$\begin{aligned} E(n_{ijk}) &= \Lambda_{ijk} = \Lambda_{0ijk}(\boldsymbol{\rho}) \exp(\mathbf{x}_{ij}' \boldsymbol{\beta}_j) \\ \operatorname{var}(n_{ijk}) &= \Lambda_{ijk} + \phi_j^2 \Lambda_{ijk}^2 \\ \operatorname{cov}(n_{ijk}, n_{ij\ell}) &= \phi_j^2 \Lambda_{ijk} \Lambda_{ij\ell} \quad \text{for all } k \neq \ell \end{aligned}$$

where $\Lambda_{0ijk}(\boldsymbol{\rho})$ is given by (2) and $\operatorname{var}(n_{ij}) = \phi_j^2$. Note that the mean and covariance functions are motivated by a mixed Poisson formulation but no such distributional assumptions

are required for estimation and inference of regression coefficients. Again we use piecewise constant functions to approximate the baseline rates but we use generalized estimating equation (GEE) methodology to take the association between the different processes into account. The random effect formulation above gives a working inter-type correlation structure of the form

$$\operatorname{cov}(n_{ij_1k}, n_{ij_2\ell}) = \psi_{j_1j_2}\Lambda_{ij_1k}\Lambda_{ij_2\ell} \quad \text{for } 1 \leqslant j_1 < j_2 \leqslant J$$

where $\operatorname{cov}(n_{ij_1}, n_{ij_2}) = \psi_{j_1j_2}$. Let $\boldsymbol{\phi} = (\phi_1, \ldots, \phi_J,\ \{\psi_{j_1j_2}, j_1 < j_2\})'$ be the parameter vector for the covariance matrix. We denote the marginal means for the jth process by $\boldsymbol{\Lambda}_{ij} = (\Lambda_{ij1}, \ldots, \Lambda_{ij,k_{ij}})'$. Letting $k_i = k_{i1} + \cdots + k_{iJ}$, we denote the $k_i \times 1$ column vector for the marginal means $\boldsymbol{\Lambda}_i = \mathrm{E}(\mathbf{n}'_{i1}, \ldots, \mathbf{n}'_{iJ})' = (\boldsymbol{\Lambda}'_{i1}, \ldots, \boldsymbol{\Lambda}'_{iJ})'$, and a $k_i \times k_i$ working correlation matrix, $\Sigma_i = [\Sigma_{i,j_1j_2}]_{k_i \times k_i}$, where $\Sigma_{i,jj} = \operatorname{var}(\mathbf{n}_{ij}) = \operatorname{diag}(\boldsymbol{\Lambda}_{ij}) + \phi_j^2 \boldsymbol{\Lambda}_{ij}\boldsymbol{\Lambda}'_{ij}$ for $j = 1, \ldots, J$, and $\Sigma'_{i,j_2j_1} = \Sigma_{i,j_1j_2} = \operatorname{cov}(\mathbf{n}_{ij_1}, \mathbf{n}_{ij_2}) = \psi_{j_1j_2}\Lambda_{ij_1}\Lambda'_{ij_2}$ for $1 \leqslant j_1 < j_2 \leqslant J$. From the theory of generalized estimating equations [18], the generalized estimating equations for $\boldsymbol{\beta}$ and $\boldsymbol{\rho}$ are then given by

$$\mathbf{U}_1(\boldsymbol{\beta}, \boldsymbol{\rho}) = \sum_{i=1}^{m} D'_i \Sigma_i^{-1}(\mathbf{n}_i - \boldsymbol{\Lambda}_i) = \mathbf{0} \tag{7}$$

where $D_i = \partial\boldsymbol{\Lambda}_i / \partial(\boldsymbol{\beta}', \boldsymbol{\rho}')$ is a $k_i \times p$ derivative matrix of Λ_i with respect to $(\boldsymbol{\beta}', \boldsymbol{\rho}')'$.

If the value of $\boldsymbol{\phi}$ is known, (7) is a set of equations for $\boldsymbol{\beta}$ and $\boldsymbol{\rho}$. By solving equation (7) using Newton's method, for example, one can obtain the estimates $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\rho}}$. Under mild conditions on the event processes and the observational scheme [19], both $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\rho}}$ are consistent and asymptotically normally distributed as $m \to \infty$. To estimate the unknown parameter $\boldsymbol{\phi}$, the following moment equations are useful,

$$\begin{aligned} U_{2,j}(\phi_j) &= \sum_{i=1}^{m} w_{ij} \sum_{k} \{(n_{ijk} - \Lambda_{ijk})^2 - (\Lambda_{ijk} + \phi_j^2 \Lambda_{ijk}^2)\}, \quad j = 1, \ldots, J \\ U_{2,j_1j_2}(\boldsymbol{\psi}) &= \sum_{i=1}^{m} w_{i,j_1j_2} \sum_{k,\ell} \left\{ \frac{(n_{ij_1k} - \Lambda_{ij_1k})(n_{ij_2\ell} - \Lambda_{ij_2\ell})}{\psi_{j_1j_2}\Lambda_{ij_1k}\Lambda_{ij_2k\ell}} - 1 \right\}, \quad j_1 < j_2 \end{aligned} \tag{8}$$

where w_{ij} and w_{i,j_1j_2} are weight functions. It is perhaps most common to let $w_{ij} = 1$ but alternative weight functions are possible [8]. To estimate $\boldsymbol{\theta} = (\boldsymbol{\beta}, \boldsymbol{\rho}, \boldsymbol{\phi})'$, given an initial value $\boldsymbol{\phi}^{(0)}$, one can solve (7) to get $\boldsymbol{\beta}^{(1)}, \boldsymbol{\rho}^{(1)}$. Then, upon inserting $\boldsymbol{\beta}^{(1)}$ and $\boldsymbol{\rho}^{(1)}$ in (8) for $\boldsymbol{\beta}$ and $\boldsymbol{\rho}$ respectively, this in turn can be solved to give $\boldsymbol{\phi}^{(1)}$. By iterating between (7) and (8), the estimates are obtained when $(\boldsymbol{\beta}^{(k)}, \boldsymbol{\rho}^{(k)}, \boldsymbol{\phi}^{(k)})$, $(k = 1, 2, \ldots,)$ converges to a stable value, $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\rho}}, \hat{\boldsymbol{\phi}})'$, and hence the difference between solutions in successive iterations becomes negligible.

Under regularity conditions [19], even if the form of the Σ_i is incorrectly specified, the estimate $(\widehat{\boldsymbol{\beta}}', \widehat{\boldsymbol{\rho}}')'$ is consistent and asymptotically normally distributed as $m \to \infty$. The robust estimate of the asymptotic variance–covariance matrix of $\sqrt{m}\{(\widehat{\boldsymbol{\beta}}' - \boldsymbol{\beta}'), (\widehat{\boldsymbol{\rho}}' - \boldsymbol{\rho}')\}$ is given by

$$\widehat{M}_0^{-1}\widehat{M}_1(\widehat{M}'_0)^{-1} \tag{9}$$

with $\widehat{M}_0 = m^{-1}\sum_{i=1}^{m}\hat{D}_i'\hat{\Sigma}_i^{-1}\hat{D}_i$ and $\widehat{M}_1 = m^{-1}\sum_{i=1}^{m}\hat{D}_i'\hat{\Sigma}_i^{-1}(\mathbf{n}_i - \hat{\boldsymbol{\Lambda}}_i)(\mathbf{n}_i - \hat{\boldsymbol{\Lambda}}_i)'\hat{\Sigma}_i^{-1}\hat{D}_i$ [17]. Here estimates of Λ_i, D_i and Σ_i are obtained by evaluating the corresponding functions at $\hat{\boldsymbol{\theta}}$.

To conduct inference on the parameter $\boldsymbol{\phi}$, the asymptotic distribution of

$$\sqrt{m}\{(\widehat{\boldsymbol{\beta}}' - \boldsymbol{\beta}'), (\widehat{\boldsymbol{\rho}}' - \boldsymbol{\rho}'), (\widehat{\boldsymbol{\phi}}' - \boldsymbol{\phi}')\}'$$

is required. For this to be valid, the structure of the working covariance matrix needs to be correctly specified. If the random effect follows a multivariate log-normal distribution and conditionally on this random effect, the processes are governed by rate functions $\lambda_{ij}(t)$, the first two marginal moments of the counting processes are correctly specified [3]. Thus, the estimates $(\widehat{\boldsymbol{\beta}}', \widehat{\boldsymbol{\rho}}', \widehat{\boldsymbol{\phi}}')'$ are consistent and asymptotically normally distributed with asymptotic variance–covariance matrix consistently estimated by

$$\widehat{\Phi} = \widehat{P}^{-1}\widehat{Q}(\widehat{P}^{-1})' \tag{10}$$

where $\widehat{Q}$ is the variance–covariance matrix of the estimating function evaluated at $\widehat{\boldsymbol{\theta}}$ and $\widehat{P}$ is the expected value of the minus first order partial derivative of the estimating function, also evaluated at $\widehat{\boldsymbol{\theta}}$.

The above results give the asymptotic joint distribution of the baseline rate, regression coefficients, and variance–covariance parameters. A primary interest in many trials is in testing for treatment effects. The treatment covariate, denoted by x_{j1} say, will be used in marginal models for each of the processes. The asymptotic joint distribution of the associated regression coefficients will facilitate construction of global tests of significance of no treatment effect. Weights for these tests will be taken to maximize power to detect treatment effects in the spirit of Wei *et al.* [20] for multivariate survival data.

Here we describe how to carry out a global test of treatment effects based on the estimator $\hat{\boldsymbol{\beta}}$. Let β_{j1} denote the coefficient of the treatment covariate x_{j1} on the jth process. We now write $\boldsymbol{\theta} = (\boldsymbol{\theta}_1', \boldsymbol{\theta}_2')'$ where $\boldsymbol{\theta}_1 = (\beta_{11}, \beta_{21}, \ldots, \beta_{J1})'$ and θ_2 is the vector containing all other parameters. The asymptotic variance–covariance matrix of $\sqrt{m}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta})$ can be estimated by $\hat{\Phi}$, as given by (10). We partition $\hat{\Phi}$ into four blocks:

$$\hat{\Phi} = \begin{pmatrix} \hat{\Phi}_{11} & \hat{\Phi}_{12} \\ \hat{\Phi}_{21} & \hat{\Phi}_{22} \end{pmatrix}$$

conformably with the partition of $\boldsymbol{\theta} = (\boldsymbol{\theta}_1', \boldsymbol{\theta}_2')'$. Our objective is to test the null hypothesis of no treatment effect on all of the processes, i.e.,

$$H_0: \ \beta_{11} = \beta_{21} = \cdots = \beta_{J1} = 0$$

Under H_0, we know that the marginal distribution of $\sqrt{m}(\hat{\beta}_{11}, \hat{\beta}_{21}, \ldots, \hat{\beta}_{J1})'$ is asymptotically normally distributed with the mean vector $\mathbf{0} = (0, 0, \ldots, 0)'$ and variance–covariance matrix estimated by $\hat{\Phi}_{11}$. Thus, the test statistic

$$T = (\hat{\beta}_{11}, \hat{\beta}_{21}, \ldots, \hat{\beta}_{J1})\hat{\Phi}_{11}^{-1}(\hat{\beta}_{11}, \hat{\beta}_{21}, \ldots, \hat{\beta}_{J1})' \tag{11}$$

follows an asymptotic χ^2 distribution with J degrees of freedom under H_0. Furthermore, suppose that there is a common treatment effect for all processes such that $\beta_{11} = \beta_{21} = \cdots = \beta_{J1} = \beta_0$. Wei and Johnson [21] show that β_0 can be estimated efficiently by a linear combination of $\hat{\beta}_{11}, \ldots, \hat{\beta}_{J1}$,

$$\hat{\beta}_0 = \sum_{j=1}^{J} w_j \hat{\beta}_{j1} \tag{12}$$

where $(w_1, w_2, \ldots, w_J)' = (\mathbf{e}'\hat{\Phi}_{11}^{-1}\mathbf{e})^{-1}\hat{\Phi}_{11}^{-1}\mathbf{e}$ and $\mathbf{e} = (1, 1, \ldots, 1)'$. Then $\hat{\beta}_0$ has the smallest asymptotic variance among all the linear estimators. Hence $\sqrt{m}(\hat{\beta}_0 - \beta_0)$ asymptotically follows a normal distribution with mean 0 and variance estimated by $(\mathbf{e}'\hat{\Phi}_{11}^{-1}\mathbf{e})^{-1}$. One may also consider tests based on (11) in which the estimated variance–covariance matrix is computed under H_0.

5. A TRIAL OF CANCER PATIENTS WITH BONE METASTASES

In this section, we used the proposed joint model for interval-censored multivariate recurrent processes to study the treatment effect on the occurrence of bone lesions for patients with breast cancer metastatic to bone [12]. The three types of bone lesions of interest are (i) lytic, (ii) blastic, and (iii) mixed, where mixed bone lesions have features of both lytic and blastic lesions. Let $N_{i1}(t)$, $N_{i2}(t)$, and $N_{i3}(t)$ denote the counting processes for each of these respective processes. Here we concentrate on comparing the cumulative incidence rates over the 12 month period following randomization. For this purpose, we considered data on 216 patients who were observed over this period, 109 and 107 of whom were in the treated and control groups respectively.

Figure 2 displays a sample of profiles from 6 subjects, here labelled A–F, in the control group. The vertical bars indicate the times of the radiographic examinations, and the numbers in parentheses indicate the number of lytic, blastic and mixed lesions developing between consecutive examinations. Note that some patients were not observed to develop any new bone lesions (e.g. subjects A and D), some were only observed to develop new lesions of a particular type (e.g. subject E), and some were observed to develop lesions of multiple types (e.g. subjects B, C and F). Table I contains a summary of the incidence of the three types of bone lesions for all patients by treatment group.

Both the random effect and marginal models were fit to these data, with a single covariate x_i equal 1 if subject i was in the treatment group and 0 otherwise. For both types of models, piecewise constant baseline rate functions were adopted with the cut-points for each process at the 4 months, 8 months, and 12 months from entry into the study. Other sets of cut-points were considered and all gave broadly similar point estimates and standard errors. The covariate of interest for each process was the treatment indicator of the new drug, pamidronate. For the random effect model fit via the Gibbs sampling algorithm, we used the model specified in (3) with $J = 3$. The unknown variance–covariance matrix of the random effect $\mathbf{u}_i$ was parameterized in terms of the linear predictor as in equation (5), while the random effect $\mathbf{v}_i$ was assumed to have a completely specified standard multivariate normal distribution. For the marginal approach, estimating equations (7) and (8) were solved using an initial value

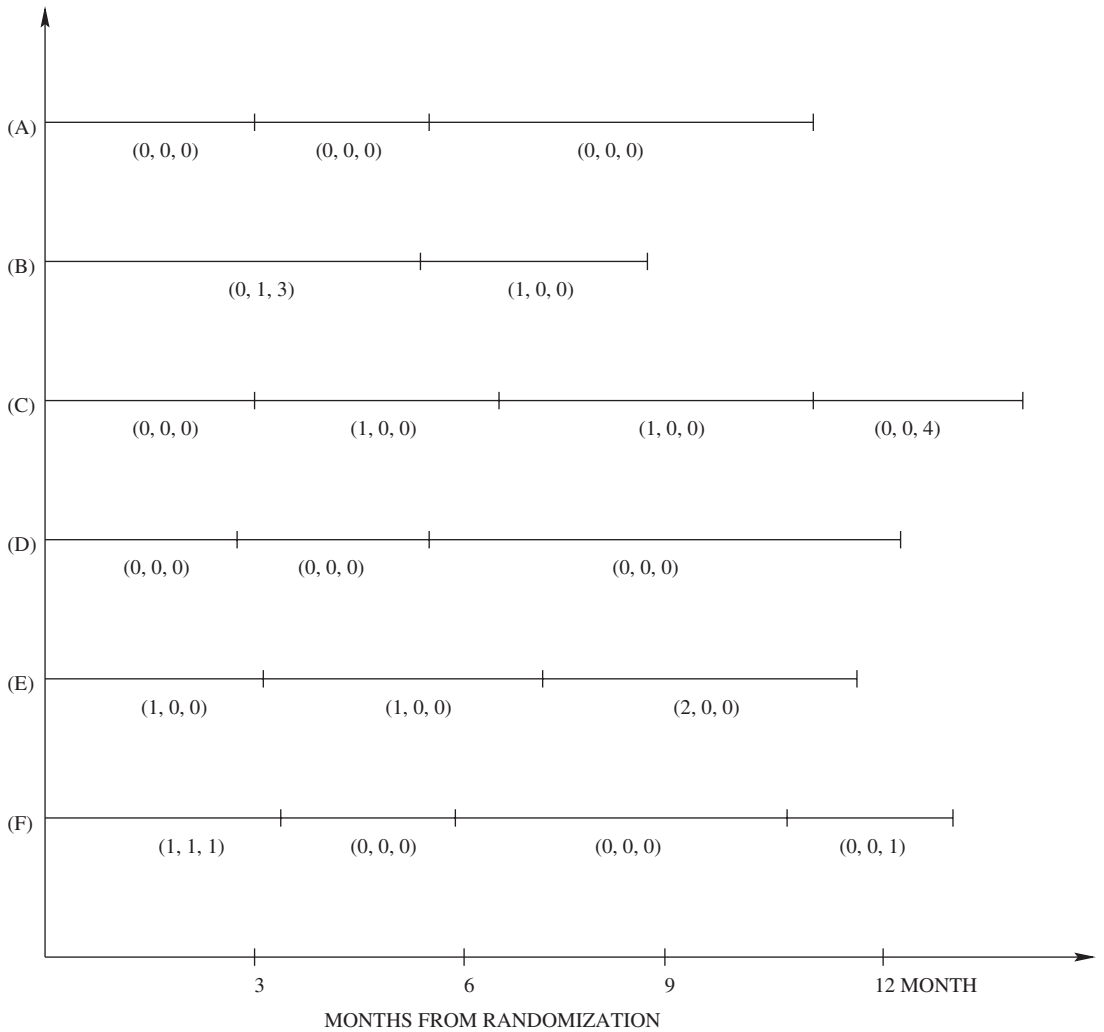

Figure 2. Sample profile features for various bone lesions.

$\boldsymbol{\theta}_0 = (\boldsymbol{\rho}_0', \boldsymbol{\beta}_0', \boldsymbol{\phi}_0')'$. After roughly 15 iterations between equations (7) and (8), $\boldsymbol{\theta}_k$ converged to $\hat{\boldsymbol{\theta}}$ with the convergence criteria

$$\frac{||\boldsymbol{\theta}_{k+1} - \boldsymbol{\theta}_k||}{||\boldsymbol{\theta}_{k+1}||} \leqslant 1.0 \times 10^{-6} \quad \text{and} \quad ||\mathbf{U}(\boldsymbol{\theta}_{k+1})|| \leqslant 1.0 \times 10^{-6}$$

Different initial values of $\boldsymbol{\theta}_0$ were considered and were all shown to converge to the same estimate.

Three different models were fit to the data using each modelling strategy, the results of which are reported in Table II. In Model 1, three separate Poisson process models were fit for the three types of bone lesions. In Model 2, the data were fit according to three independent

Table I. Total numbers of new lytic, blastic, and mixed bone lesions by treatment group.

	Number of patients	Total No. of new lytic lesions	Total No. of new blastic lesions	Total No. of new mixed lesions
Control	107	83	36	68
Treatment	109	50	54	47

mixed Poisson models (i.e. without considering the associations between the lytic, blastic and mixed bone lesion processes). The third type of model, Model 3, addresses both heterogeneity and association between the three types of processes.

The results from fitting Model 2 via the random effect formulation gave coefficients ω_{11}, ω_{22}, and ω_{33} which were all significantly different from zero. This indicates the existence of strong heterogeneity (extra-Poisson variation) for each process. Wald tests based on the marginal formulation also suggested all three dispersion parameters are significantly greater than zero. Moreover, both the random effect and the marginal analyses suggest a significant treatment effect on the incidence of lytic bone lesions and a trend towards a reduction in the development of mixed bone lesions.

The random effect and marginal estimates for Model 3 reveal a strong positive association between the three different types of bone lesion processes suggesting that this is the preferred model for this data. Using equation (6), one can show that the correlation coefficient matrix of $\log(\mathbf{u}_i)$ is estimated as

$$\begin{bmatrix} 1.000 & 0.964 & 0.946 \\ 0.964 & 1.000 & 0.958 \\ 0.946 & 0.958 & 1.000 \end{bmatrix}$$

based on the random effect formulation. The corresponding estimate based on the marginal model is

$$\begin{bmatrix} 1.000 & 0.938 & 0.955 \\ 0.938 & 1.000 & 0.958 \\ 0.955 & 0.958 & 1.000 \end{bmatrix}$$

The null hypotheses $H_0 : \psi_{12} = 0$, $\psi_{13} = 0$, and $\psi_{23} = 0$ are all rejected with $p < 0.00001$, indicating strong evidence against the null hypothesis that the lytic, blastic and mixed bone lesion processes are independent. The estimated effect of treatment on the development of new lytic bone lesions remains significant for the random effect (RR = 0.447, 95 per cent CI = [0.249, 0.795], p-value = 0.0053) and marginal (RR = 0.528, 95 per cent CI = [0.306,0.911], p-value = 0.022) models, even when the inter-type association is taken into account. A global test of the null hypothesis of no treatment effect on the incidence of all three types of bone lesions based on (12) (for the marginal model 3) gives $\hat{\beta}_0 = 0.498$ with standard error 0.252, where the weights for the lytic, blastic and mixed lesions were 0.48, 0.08 and 0.44, respectively. The data therefore provide significant evidence ($p = 0.0481$) against the null hypothesis that pamidronate has no effect on the incidence of new bone metastases.

Figure 3 gives the plots of expected cumulative mean functions for the number of new bone lesions (lytic, blastic, and mixed) over time (from 0 to 12 months). In each plot, the marginal cumulative mean functions obtained from the random effect model are very close to the estimated cumulative mean functions obtained from the marginal model estimated using the generalized estimating equation approach.

6. SIMULATION STUDIES

Consider the setting in which $m=200$ subjects are randomized to treatment or control groups in a balanced fashion. Let x_i be the treatment indicator taking on the value 1 for treated subjects and 0 for control subjects respectively. Suppose there are two types of events ($J=2$) that may occur over a maximum duration of $\tau=1$ year of observation. For the jth recurrent event process, we take the baseline rate function as 'Weibull' with $\lambda_{0j}(t)=\rho_j t^{\rho_j-1}$ where ρ_j was chosen so that the expected number of events over the one year period was two for both types of events. Four cut-points were adopted for the piecewise constant baseline function for each process and these were located at 0.25, 0.50, 0.75, and 1.00. The data were generated by following four steps:

Step 1: Randomize subject i to the treatment or control group in a balanced fashion.

Step 2: Generate independent and identically distributed bivariate normal random variables $v_i=(v_{i1},v_{i2})'$, with mean zero and variance–covariance matrix

$$\Sigma=\begin{pmatrix}\sigma_{11} & \sigma_{12}\\ \sigma_{12} & \sigma_{22}\end{pmatrix}$$

and let $u_{ij}=\exp(v_{ij}-\sigma_{jj}/2)$, $j=1,2$. This gives $\mathrm{E}(u_{ij})=1$, $\mathrm{var}(u_{ij})=\phi_j^2=\exp(\sigma_{jj})-1$, $j=1,2$ and a correlation coefficient between u_{i1} and u_{i2} of

$$\mathrm{corr}(u_{i1},u_{i2})=\frac{\exp(\sigma_{12})-1}{\{\exp(\sigma_{11})-1\}^{1/2}\{\exp(\sigma_{22})-1\}^{1/2}}$$

which we denoted by ψ.

Step 3: Generate event times from a nonhomogeneous Poisson process with rate function $u_{ij}\lambda_{0j}(s)\exp(x_i\beta_j)$, for $i=1,\ldots,200$, $j=1$ and 2.

Step 4: Generate $k_{ij}=5$ random observation points $b_{ij\ell}$'s in $(0,\tau_i]$ for process $N_{ij}(t)$ and evaluate the total number of events $n_{ij\ell}$ in interval $(b_{ij,\ell-1},b_{ij\ell}]$, $\ell=1,\ldots,k_{ij}$, $j=1,2$.

To examine the finite sample performance of the estimators of $\boldsymbol{\beta}$ and $\boldsymbol{\phi}$, the marginal model was fit for each of 500 data sets. The biases of parameter estimators, the empirical type I errors rates and power for certain hypotheses, and the empirical coverage probabilities of 95 per cent confidence intervals were assessed.

The above work was closely related to simulations conducted by Lawless and Zhan [8] for univariate interval-censored recurrent events. Here we therefore emphasized performance related to the multivariate aspects of the processes, such as the estimation of the correlation

Table II. Parameter estimates and the corresponding standard errors for the multivariate log normal random effect models (JOINT) using BUGS and multivariate marginal methods based on generalized estimating equation (MARGINAL) for the bone metastases data.

	Model 1				Model 2				Model 3			
	Joint		Marginal		Joint		Marginal		Joint		Marginal	
Parameters	EST	SE	EST	SE	EST	SE	EST	SE	EST	SE	EST	SE
β_1	−0.632	0.181	−0.607	0.276	−0.783	0.298	−0.632	0.277	−0.805	0.296	−0.637	0.279
β_2	0.277	0.219	0.319	0.327	0.266	0.362	0.289	0.325	0.082	0.369	0.298	0.326
β_3	−0.457	0.186	−0.462	0.280	−0.497	0.310	−0.462	0.279	−0.617	0.308	−0.486	0.278
σ_{11}					1.708	0.625	2.720	0.911	2.176	0.548	2.814	0.935
σ_{22}					3.182	1.257	4.390	1.580	3.377	0.876	4.389	1.576
σ_{33}					1.863	0.704	3.332	0.938	2.375	0.617	3.274	0.920
σ_{12}									2.615	0.569	3.809	0.803
σ_{13}									2.152	0.459	2.788	0.590
σ_{23}									2.741	0.617	3.475	0.734

Note: β_1 is the treatment effect on lytic lesions, β_2 is the treatment effect on the blastic lesions, and β_3 is the treatment effect on the mixed lesions, where negative values are consistent with efficacy of pamidronate over placebo treatment. The estimates (EST) and standard errors (SE) under the joint analyses represent the median and standard deviation of the respective posterior distributions.

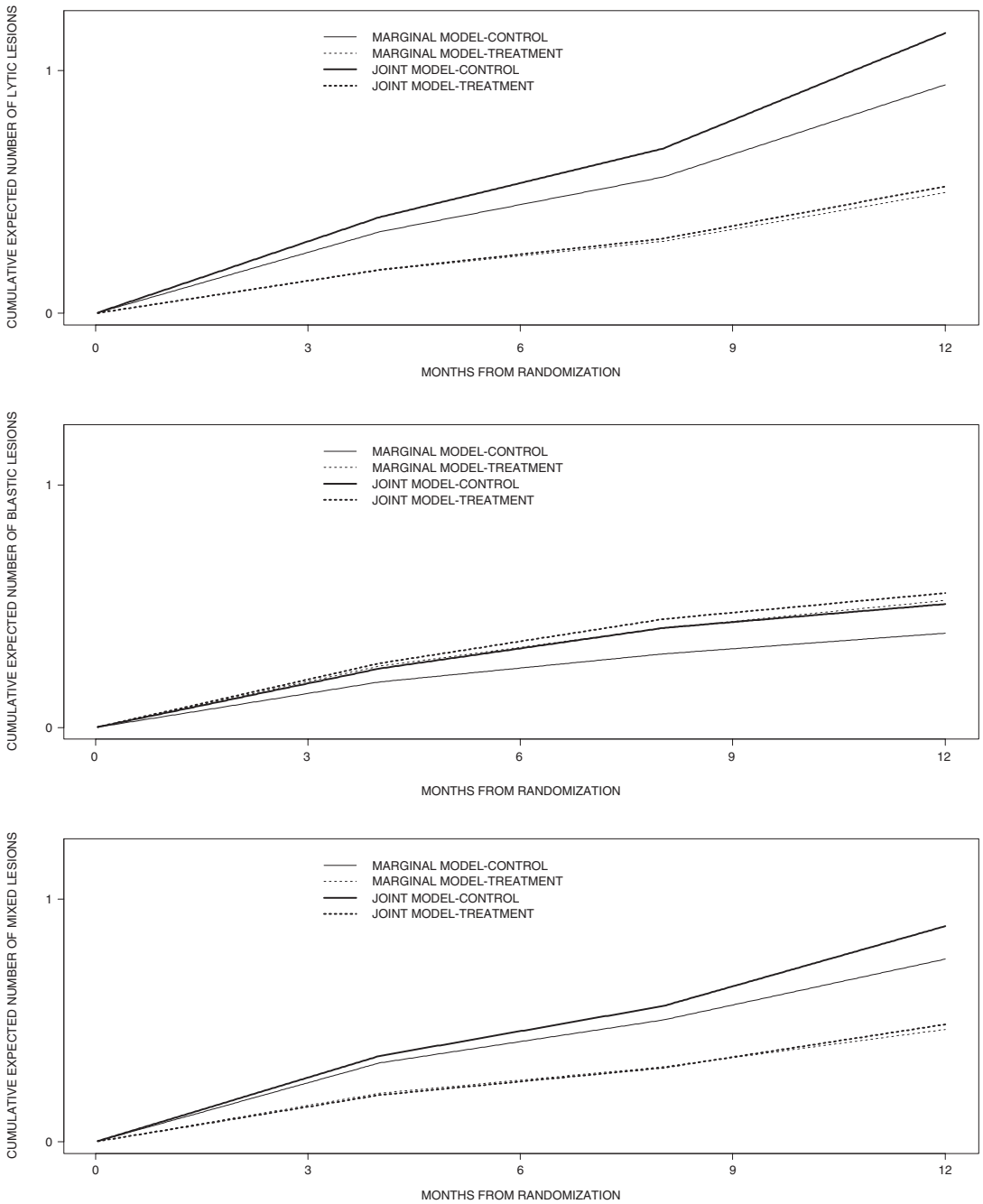

Figure 3. Plot of cumulative mean functions for the number of new bone lesions.

Table III. Finite sample properties of regression estimators for the marginal method as a function of treatment effects (β_1 and β_2), variances of random effects (ϕ_1 and ϕ_2), and correlation of random effects (ψ); 500 simulations with sample size $m = 200$.

					$\hat{\beta}_1$			$\hat{\beta}_2$			
e^{β_1}	e^{β_2}	ψ	ϕ_1	ϕ_2	BIAS*	CP†	%REJ‡	BIAS	CP	%REJ	GLOBAL§
1.0	1.0	0.0	0.25	0.25	0.0035	95.6	4.4	0.0060	95.0	5.0	4.8
1.0	1.0	0.0	0.50	0.25	0.0064	96.0	4.0	0.0043	94.8	5.2	5.4
1.0	1.0	0.0	0.50	0.50	−0.0034	94.2	5.8	0.0064	94.8	5.2	5.8
1.0	1.0	0.2	0.25	0.25	0.0053	94.4	5.6	−0.0038	94.4	5.6	4.4
1.0	1.0	0.2	0.50	0.25	0.0033	93.4	6.6	−0.0052	95.0	5.0	6.6
1.0	1.0	0.2	0.50	0.50	0.0093	95.8	4.2	0.0004	94.8	5.2	5.4
1.5	1.0	0.0	0.25	0.25	0.0024	96.2	95.4	0.0007	94.6	5.4	74.0
1.5	1.0	0.0	0.50	0.25	0.0011	95.4	86.8	−0.0047	95.6	4.4	52.2
1.5	1.0	0.0	0.50	0.50	0.0013	96.2	87.0	−0.0061	95.8	4.2	57.4
1.5	1.0	0.2	0.25	0.25	0.0035	93.4	92.6	−0.0009	95.2	4.8	64.4
1.5	1.0	0.2	0.50	0.25	0.0064	94.6	87.6	−0.0019	94.4	5.4	42.8
1.5	1.0	0.2	0.50	0.50	−0.0067	95.4	83.8	0.0048	93.8	6.2	52.6
1.5	1.5	0.0	0.25	0.25	−0.0011	96.2	95.6	−0.0001	95.2	95.4	99.8
1.5	1.5	0.0	0.50	0.25	−0.0026	95.8	85.8	−0.0084	94.4	92.2	99.8
1.5	1.5	0.0	0.50	0.50	0.0008	95.0	85.8	0.0098	96.8	88.8	99.4
1.5	1.5	0.2	0.25	0.25	0.0005	96.4	96.0	−0.0023	95.4	95.8	99.2
1.5	1.5	0.2	0.50	0.25	−0.0028	95.8	84.6	−0.0080	93.4	93.4	98.8
1.5	1.5	0.2	0.50	0.50	−0.0058	94.4	84.0	0.0051	94.0	84.4	97.2

*Empirical bias computed as mean estimate minus true value.
†Empirical coverage probability.
‡Marginal empirical rejection rate given as the percentage of simulations for which the corresponding null hypothesis was rejected.
§Global empirical rejection rate given as the percentage of simulations for which the null hypothesis $H_0 : \beta_1 = \beta_2 = 0$ was rejected based on the global test statistic.

coefficients and the global tests. The following four separate null hypotheses: $H_{10} : \beta_1 = 0$, $H_{20} : \beta_2 = 0$, $H_{30} : \beta_1 = \beta_2 = 0$ and $H_{40} : \psi = 0$, were considered in the simulation study.

First, we studied the finite sample properties of the estimates $\hat{\beta}_1$, $\hat{\beta}_2$, and the global test statistic $\hat{Q}$, which is the standardized statistic based on $\hat{\beta}_0$ given by (12). Data were generated for different configurations of $\exp(\beta_1) = 1.0$ or 1.5, $\exp(\beta_2) = 1.0$ or 1.5, $\psi = 0.0$ or 0.2, $\phi_1^2 = 0.25$ or 0.50, and $\phi_2^2 = 0.25$ or 0.50. A summary of the simulation results based on 500 samples are reported in Table III. In the column headed BIAS, we reported the empirical biases of estimators for the corresponding parameters β_1 and β_2. Table III reveals that the empirical biases for both β_1 and β_2 are extremely small, suggesting that point estimates for regression coefficients perform well for the settings considered. The column headed per cent REJ displays the percent of simulations leading to rejection of the simple null hypothesis that the corresponding parameter equals zero based on a Wald test statistic assessed at the nominal 5 per cent significance level. For settings in which the treatment parameter is set to zero, this empirical rejection rate is the empirical type I error rate. The empirical type I error rates for the global test statistic under the null hypothesis H_{30} are reported under the column headed

Table IV. Finite sample properties of variance and correlation estimators for the marginal method as a function of treatment effects (β_1 and β_2), variances of random effects (ϕ_1 and ϕ_2), and correlation of random effects (ψ); 500 simulations with sample size $m = 200$.

					$\hat{\phi}_1$		$\hat{\phi}_2$		$\hat{\psi}$		
e^{β_1}	e^{β_2}	ψ	ϕ_1	ϕ_2	BIAS*	CP†	BIAS	CP	BIAS	CP	%REJ‡
1.0	1.0	0.0	0.25	0.25	−0.0221	95.6	−0.0217	96.0	−0.0028	94.0	6.0
1.0	1.0	0.0	0.50	0.25	−0.0199	93.2	−0.0182	95.4	0.0007	95.4	4.6
1.0	1.0	0.0	0.50	0.50	−0.0180	94.4	−0.0207	95.0	−0.0033	94.4	5.6
1.0	1.0	0.2	0.25	0.25	−0.0195	96.8	−0.0208	95.0	0.0227	94.2	96.6
1.0	1.0	0.2	0.50	0.25	−0.0235	93.6	−0.0227	95.2	0.0133	95.5	90.2
1.0	1.0	0.2	0.50	0.50	−0.0112	93.8	−0.0187	94.2	0.0221	93.6	76.6
1.5	1.0	0.0	0.25	0.25	−0.0132	95.4	−0.0161	94.8	−0.0010	95.4	4.6
1.5	1.0	0.0	0.50	0.25	−0.0205	92.8	−0.0177	95.4	0.0023	93.2	6.8
1.5	1.0	0.0	0.50	0.50	−0.0176	93.8	−0.0117	93.2	−0.0031	94.2	5.8
1.5	1.0	0.2	0.25	0.25	−0.0172	96.0	−0.0221	96.0	0.0175	93.8	98.2
1.5	1.0	0.2	0.50	0.25	−0.0178	94.4	−0.0183	96.6	0.0216	93.4	94.2
1.5	1.0	0.2	0.50	0.50	−0.0237	95.0	−0.0231	95.2	0.0197	95.4	84.6
1.5	1.5	0.0	0.25	0.25	−0.0160	94.8	−0.0170	92.8	0.0044	95.2	4.8
1.5	1.5	0.0	0.50	0.25	−0.0174	93.8	−0.0162	95.2	0.0036	95.6	4.4
1.5	1.5	0.0	0.50	0.50	−0.0172	95.2	−0.0174	96.2	−0.0003	94.2	5.8
1.5	1.5	0.2	0.25	0.25	−0.0162	96.0	−0.0196	94.6	0.0134	95.2	98.2
1.5	1.5	0.2	0.50	0.25	−0.0202	94.4	−0.0162	95.2	0.0196	92.8	94.0
1.5	1.5	0.2	0.50	0.50	−0.0164	95.2	−0.0184	94.8	0.0219	93.4	84.0

*Empirical bias computed as mean estimate minus true value.
†Empirical coverage probability.
‡Empirical rejection rate for the test of $H_0 : \psi = 0$.

GLOBAL in the first six rows of Table III. It is clear that all test statistics have type I errors close to the nominal level of 5 per cent.

For data generated under the alternative hypotheses, the column headed per cent REJ displays the empirical power of the corresponding Wald tests. Note that as one would expect, as the variances of the random effects increase, the empirical power for detecting departures from the null hypotheses decreases. Moreover, the power for the global test statistic is somewhat smaller when $\psi = 0.2$ than when $\psi = 0.0$. This is a natural consequence of the higher variation in the numerator of the global statistic resulting from the correlation of the random effects.

Table IV reports the finite sample properties of the estimators for the variance parameters ϕ_1 and ϕ_2 as well as the covariance parameter ψ. The columns headed BIAS suggest standard deviations are slightly underestimated, however, all of the empirical biases are less than 0.03. The biases for ψ also tend to be small and their absolute values are also all less than 0.025. The empirical coverage probabilities for the 95 per cent confidence intervals for parameters $\beta_1, \beta_2, \phi_1, \phi_2$, and ψ are reported in the column headed *CP* in both Table III and IV. The empirical coverage is in close agreement with the nominal level in the settings we have examined.

7. DISCUSSION

When more than one type of event may recur in a patient, it is often of interest to investigate the association between different types of processes. This objective becomes more challenging to meet when the recurrent event processes are interval-censored. In this paper, we developed joint models for multi-type interval-censored recurrent event data. We first extended the piecewise constant baseline rate models for univariate interval-censored recurrent events described by Lawless and Zhan [8] to deal with multivariate processes. Correlated random effects were used from genuine multivariate distributions to model the heterogeneity and associations between different processes. A Bayesian approach using BUGS was adopted to deal with the high dimensional integrals required to obtain the marginal likelihood. Natural adaptations were made to the estimating equation approach of Lawless and Zhan [8] for inference based on marginal models.

Both types of models were fit to data from Hortobagyi *et al.* [12] on breast cancer patients with bone metastases. In this context, interest was in the treatment effect on the development of lytic, blastic, and mixed bone lesions. Both models suggested that patients in the treatment group have lower rates of developing new lytic bone lesions, and there was an insignificant trend towards a benefit in terms of mixed bone lesions. There was strong evidence of associations between the three event processes, reflecting the fact that many breast cancer patients develop lesions of all three types over time. This represents an interesting clinical finding since there have been attempts to classify patients as being primarily at risk of a particular type of bone lesion based on the types of lesions present at the time of diagnosis of metastatic bone disease. The strong association between processes suggests that attempts at such classification are not particularly well-founded. It is of interest to examine whether data from patients with other primary tumour types (e.g. prostate cancer) are consistent with these findings.

Dean and Balshaw [22] compare the efficiency of the analysis of recurrent event data based simply on counts of events over a particular period of observation with analyses which use the event times. They point out that analyses based on counts can lead to little loss of efficiency compared to analyses based on actual event times when interest lies in estimates of treatment effect, but the baseline rates are far less efficiently estimated. This finding suggests that for settings like the breast cancer trial discussed here, where counts are available from periodic assessment, the estimates of treatment effects should be highly efficient and the estimates of the baseline rate parameters somewhat better than one would have based simply on total counts. The relationships between the number of assessments and the efficiency of the regression coefficients, baseline rate parameters, and association parameters warrant further research.

A considerable amount of attention has been given in recent years to problems involving the characterization of cumulative processes terminated by death [23]. This work has been carried out in the context of quality of life studies [24, 25], health economics [26], and recurrent events [27, 28]. Each of these settings involved continuous observation of the process up until the time of censoring and so are not amenable to applications involving interval-censored data. We are currently investigating methods based on weighted estimating functions which may be used in settings with interval-censored data, as well as adaptations to deal with multiple types of recurrent event processes.

APPENDIX A

What follows is background information on the formulation of the random effect model necessary for the construction of BUGS program used in the analyses, as well as the BUGS code itself. As in all BUGS programs, constants are specified in the `const` line, the `var` line lists vector variables used in the program, and initial values are given in `inits` line. In what follows the initial values of $\boldsymbol{\beta}, \boldsymbol{\omega}$, and $\boldsymbol{\rho}$ are set to zero. Data to be analyzed are specified via variables in the `data` line. Random effects z_{i1}, z_{i2}, and z_{i3} are generated follow standard normal distribution. Given the random effect u_{ij}, the number of type j events for subject i in the kth interval R_{ijk} is n_{ijk}, which is assumed to follow a Poisson distribution. Therefore, we have the following model specification,

$$
\begin{aligned}
n_{ijk}|u_{ijk} &\sim \text{Poisson}(\mu_{ijk}) \\
\log \mu_{ijk} &= \log \Lambda_{0jk}(\boldsymbol{\rho}) + \mathbf{x}'_{ij}\boldsymbol{\beta}_j + u_{ij} \\
v_{i1} &= \omega_1 \times z_{i1} \\
v_{i2} &= \omega_2 \times z_{i1} + \omega_3 \times z_{i2} \\
v_{i3} &= \omega_4 \times z_{i1} + \omega_5 \times z_{i2} + \omega_6 \times z_{i3} \\
z_{ij} &\sim \text{Normal}(0.0, 1.0), \;\; j = 1,\; 2,\; 3
\end{aligned}
$$

There are no restrictions on the parameters $\boldsymbol{\beta}$, and $\boldsymbol{\omega}$, and we use independent normal distributions with means zero and variances 1000 as priors for all of these parameters. One may consider using a standard noninformative prior for $\boldsymbol{\rho}$, however, this specification leads to a non log-concave sampling distribution [29]. Gilks and Wild [29] suggest handling this problem by discretizing the prior distribution to create a categorical variable, but monitoring and summarizing $\boldsymbol{\rho}$ as if it were continuous. These prior distributions are specified at the end of the program. In this application, we run the sampling procedure with 10 000 iterations after a 5000 iteration burn-in.

```
model bls;
const
  B = 80,  # number of discrete points for baseline parameters
  m = 216, # number of patients
 K1 = 4,   # number of pieces for lytic bone lesions
 K2 = 4,   # number of pieces for blastic bone lesions
 K3 = 4;   # number of pieces for mixed bone lesions
var
  trt[m], beta[3], p[B], w[6], Sigma[3,3],indx[m], bmat[m, 28],
  n1[m,6],v1[m],z1[m],tau1[m,7,4],rho1[K1],r1[K1],Lambda1[m,7],
  n2[m,6],v2[m],z2[m],tau2[m,7,4],rho2[K2],r2[K2],Lambda2[m,7],
  n3[m,6],v3[m],z3[m],tau3[m,7,4],rho3[K3],r3[K3],Lambda3[m,7];
data
  trt  in "trt.dat", indx in "bls.indx",
  bmat in "bls.bmat",  n1 in "bls.n1mat",
  n2   in "bls.n2mat", n3 in "bls.n3mat";
inits in "bls.in";
{
  for(i in 1:m) {
```



```
    z1[i]~dnorm(0.0, 1.0); z2[i]~dnorm(0.0, 1.0); z3[i]~dnorm(0.0, 1.0);
    v1[i] <- w[1] * z1[i];
    v2[i] <- w[2] * z1[i] + w[3] * z2[i];
    v3[i] <- w[4] * z1[i] + w[5] * z2[i] + w[6] * z3[i];
    # process ONE
    for(j in 1:(indx[i])) {
      for(k in 1:K1) {tau1[i, j, k] <- exp(rho1[k])*bmat[i,K1*(j-1)+k];}
      log(Lambda1[i, j])<-log(sum(tau1[i, j, ])) + beta[1]*trt[i] + v1[i];
      n1[i, j] ~ dpois(Lambda1[i, j]);
    }
    # process TWO
    for(j in 1:(indx[i])) {
      for(k in 1:K2) {tau2[i, j, k] <- exp(rho2[k])*bmat[i,K2*(j-1)+k];}
      log(Lambda2[i, j])<-log(sum(tau2[i, j, ])) + beta[2]*trt[i] + v2[i];
      n2[i, j] ~ dpois(Lambda2[i, j]);
    }
    # process THREE
    for(j in 1:(indx[i])) {
      for(k in 1:K3) {tau3[i, j, k] <- exp(rho3[k])*bmat[i,K3*(j-1)+k];}
      log(Lambda3[i, j])<-log(sum(tau3[i, j, ])) + beta[3]*trt[i] + v3[i];
      n3[i, j] ~ dpois(Lambda3[i, j]);
    }
  }
  Sigma[1,1] <- w[1] * w[1];
  Sigma[1,2] <- w[1] * w[2];
  Sigma[1,3] <- w[1] * w[4];
  Sigma[2,2] <- w[2] * w[2] + w[3] * w[3];
  Sigma[2,3] <- w[2] * w[4] + w[3] * w[5];
  Sigma[3,3] <- w[4] * w[4] + w[5] * w[5] + w[6] * w[6];
  for(k in 1:6)  {   w[k] ~ dnorm(0.0, 1.0E-4); }
  for(k in 1:3)  {beta[k] ~ dnorm(0.0, 1.0E-4); }
  for(k in 1:B)  {   p[k] <-1.0/B; }
  for(k in 1:K1) { r1[k] ~ dcat(p[]); rho1[k] <- r1[k]/10.0 - 8.0; }
  for(k in 1:K2) { r2[k] ~ dcat(p[]); rho2[k] <- r2[k]/10.0 - 8.0; }
  for(k in 1:K3) { r3[k] ~ dcat(p[]); rho3[k] <- r3[k]/10.0 - 8.0; }
}
```

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