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Small-Sample Inference for Incomplete Longitudinal Data with Truncation and Censoring in Tumor Xenograft Models

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SUMMARY. In cancer drug development, demonstrating activity in xenograft models, where mice are grafted with human cancer cells, is an important step in bringing a promising compound to humans. A key outcome variable is the tumor volume measured in a given period of time for groups of mice given different doses of a single or combination anticancer regimen. However, a mouse may die before the end of a study or may be sacrificed when its tumor volume quadruples, and its tumor may be suppressed for some time and then grow back. Thus, incomplete repeated measurements arise. The incompleteness or missingness is also caused by drastic tumor shrinkage (<0.01 cm^3) or random truncation. Because of the small sample sizes in these models, asymptotic inferences are usually not appropriate. We propose two parametric test procedures based on the EM algorithm and the Bayesian method to compare treatment effects among different groups while accounting for informative censoring. A real xenograft study on a new antitumor agent, temozolomide, combined with irinotecan is analyzed using the proposed methods.

KEY WORDS: Bayesian analysis; EM algorithm; Informative censoring; Longitudinal data; Truncation; t-Test; Tumor xenograft models.

1. Introduction

Animal models play an important role in translational research that bridges basic biological discoveries and patient care. For example, in cancer-drug development, demonstrating anticancer activity in xenograft models, where mice are grafted with human cancer cells, is an important translational step in bringing a promising compound to humans. The analysis of data arising from tumor xenograft models presents several statistical challenges. First, not only are the xenograft experiments costly, the grafts themselves may fail to grow the tumor under study due to body rejection or some xeno antigens in the xenograft process. Thus, it is not easy to obtain samples (subjects) that possess the tumor under study. This limits final available samples. Usually a relatively small group (7–14) of tumor-bearing mice are treated with different doses of the experimental anticancer agent and then followed for a limited period of time (say, 12 weeks). The aim of the experiment is to compare antitumor activities between two (or more) different groups of subjects. A key outcome variable for the activity is the tumor volume measured each week over a given period of time. However, if a tumor is drastically shrunken and its volume is less than 0.01 cm^3, the volume of the tumor cannot be measured. A mouse may die of toxicity or may be sacrificed when its tumor volume is quadrupled, resulting in incomplete repeated measurements. Another complication is that tumors may be suppressed for some time and then grow back. Thus, it is important to measure the sustained tumor suppression effect, such as the area under the tumor growth curve, of the anticancer agent. The analysis of these data is complicated by incompleteness due to either drastic tumor shrinkage or mice sacrificed. Such missing data are either informatively censored or missing at random (Diggle, Liang, and Zeger, 1994; Little, 1995).

The analysis of longitudinal data with informative censoring itself has attracted a great deal of attention in recent years. Various parametric, semiparametric, and nonparametric methods have been proposed. For example, Yao, Wei, and Hogan (1998) considered the two-sample problem and proposed a location-shift model using estimating equation methods. Some nonparametric Wilcoxon-type statistics for test problems of two-sample and multisample are proposed by Davis and Wei (1988), Dawson and Lagakos (1993), and Sun and Song (2001). Sun and Song (2001) also considered the semiparametric regression analysis. Some parametric methods for repeated measurement data in the presence of informative censoring can be found in Diggle and Kenward (1994), Fitzmaurice, Molenberghs, and Lipsitz (1995), Hogan and Laird (1997), Little (1995), Schluchter (1992), Wu and Bailey (1989), and Wu, Hunsberger, and Zucker (1994). Unfortunately, most of the current methods are based on asymptotic properties of large samples and ignore the pattern of informativeness. Shih and Quan (1997) give an analysis of the mul-

tiple testings of a composite hypotheses with finite samples, however, only for noninformative missing data.

The purpose of this article is therefore to develop small-sample inferential methods for incomplete longitudinal data with small sample sizes where both truncation and censoring may arise. Our research is motivated by the need for methods to analyze the tumor xenograft models. We first formulate a unified inferential framework, which, in the xenograft models, would include both tumor volume and area under the tumor growth curve. We then develop inferential procedures to compare different groups while accounting for the incompleteness and informative censoring, thus using the available data most efficiently. The first test is derived heuristically from the t-test of two samples with complete observations. With incomplete repeated measurement data of small sample size, we utilize the maximum likelihood estimate of the mean and variance–covariance parameters using the EM algorithm (Dempster, Laird, and Rubin, 1977) in the t-test to obtain a quasi–t-test, avoiding the large-sample variance–covariance estimates. However, a real small-sample test can be developed from a Bayesian approach. To avoid uncertainties associated with assessing the convergence in the Markov chain Monte Carlo (MCMC) methods, we have adopted the noniterative inverse Bayes formula (IBF) methods proposed by Tan, Tian, and Ng (2001) and Tan, Tian, and Xiong (2001) for computation.

The rest of the article is organized as follows. In Section 2, we formulate the model and introduce a method for testing multivariate normality. Section 3 develops a t-test via the EM algorithm and a Bayesian test via IBF methods. Section 4 applies the proposed methods to analyzing real xenograft models on a new anticancer agent. We conclude with a discussion in Section 5 and leave the mathematical and computational details to the Appendix.

2. Model Formulation

Consider a longitudinal study with m prespecified follow-up times, $t_1 < t_2 < \cdots < t_m$, for n subjects. The goal of the study is to compare two treatment groups. Let $\boldsymbol{Y}_i^{(k)} = (Y_{i1}^{(k)}, \ldots, Y_{im}^{(k)})^{\mathrm{T}}$ be an $m \times 1$ vector of outcomes from the ith subject in the kth group, $i = 1, 2, \ldots, n_k$, $k = 1, 2$, and $n = n_1 + n_2$. Because cancer chemotherapy usually consists of a protracted treatment schedule (e.g., the same amount of drug is administered to subjects daily for 10 days), a major goal in the xenograft model is to assess the effectiveness of such schedules, e.g., the mean tumor sizes at different time points. This is different from the goals in growth-curve model analysis. The nonlinearity of tumor responses over the follow-up period and the limited amount of data in xenograft models also preclude a growth-curve analysis. In addition, historic data of xenograft models (for a series of drugs in a host of cell lines) are usually available within a developmental therapeutics program and should be utilized to assist model checking and the selection of a transformation to approximate normality. In our case, our historic xenograft data suggest that a multivariate normality of the tumor volume (in log scale) $\boldsymbol{Y}_i^{(k)}$ is a reasonable assumption. Thus, in this article, we shall focus on the model where $\boldsymbol{Y}_i^{(k)}$ has a multivariate normal distribution with mean vector and covariance matrix of the toeplitz form

$$\begin{aligned} \mathrm{E}\left(\boldsymbol{Y}_i^{(k)}\right) &= \boldsymbol{\mu}^{(k)} \doteq \left(\mu_1^{(k)}, \ldots, \mu_m^{(k)}\right)^{\mathrm{T}}, \\ \mathrm{cov}\left(\boldsymbol{Y}_i^{(k)}\right) &= \boldsymbol{\Sigma}_m = \sigma^2 \boldsymbol{R}_m \doteq \sigma^2 \left(\rho_{ij}\right), \end{aligned} \tag{2.1}$$

$k = 1, 2$, where the (i, j)th element of $\boldsymbol{R}_m$ is $\rho_{ij} = \rho^{|i-j|}$ for $\rho \in (-1, 1)$. ρ is the correlation between successive measurements on the same subject and the correlation structure suggests that tumor volumes at two close time points have higher correlation than those at two distant time points.

Our goal is to test hypotheses

$$\mathrm{H}_0\colon \boldsymbol{d}^{\mathrm{T}}\boldsymbol{\mu}^{(1)} = \boldsymbol{d}^{\mathrm{T}}\boldsymbol{\mu}^{(2)}$$

versus

$$\mathrm{H}_1\colon \boldsymbol{d}^{\mathrm{T}}\boldsymbol{\mu}^{(1)} < \boldsymbol{d}^{\mathrm{T}}\boldsymbol{\mu}^{(2)},$$

where $\boldsymbol{d} = (d_1, \ldots, d_m)^{\mathrm{T}}$ is a known contrast vector chosen based on the goal of the scientific study. For example, if we want to find out if a different dosing schedule can decrease the total tumor volumes (or area under the tumor growth curve) further than does another schedule in the xenograft models, the contrast vector $\boldsymbol{d}$ would be the m-dimensional vector with unit component. If our goal is to compare tumor response after the first course of treatment (consisting of multiple doses of a drug), the components of the contrast vector $\boldsymbol{d}$ should be weighted more after the first course.

To make full use of the available data, we distinguish missing at random and informative censoring, both of which are present in our data. Some missing observations depend only on the observed outcomes. For example, a mouse died because of toxicity or is sacrificed when its tumor volume quadrupled in xenograft models. This type of missing observations is missing at random, and once a missing observation occurs at a prespecified observation time, all observations thereafter are missing. However, other missing observations are missing because they are too low or too high. In xenograft models, if the tumor volume is less than 0.01 cm^3, it cannot be measured; thus, the data are truncated and this missingness may occur between observable data points. This type of missingness is informative. Hence, the outcome $\boldsymbol{Y}_i^{(k)}$ can be divided into three parts: the observed part $\boldsymbol{Y}_{i,\mathrm{obs}}^{(k)}$, the informative missing part $\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)}$ and the missing at random part $\boldsymbol{Y}_{i,\mathrm{mis}}^{(k)}$, $i = 1, \ldots, n_k$ and $k = 1, 2$.

Although it was alluded to earlier that, in practice, we should use historic data to assess informally the appropriateness of normality, it is of interest to test statistically if multivariate normality holds in this setting of incomplete longitudinal data with small sample size. We propose applying the projection test for complete data proposed by Liang et al. (2000) to our case with incomplete data. This method is based on the properties of left-spherical matrix distributions and affine invariant statistics and is especially suited for cases with a small sample size n but a large dimension m ($m \geq n$) by choosing a projection dimension $q < \min(m, n-1)$. For incomplete data, because the EM algorithm to be described in Section 3.1 gives maximum likelihood estimates $\hat{\theta}$ of all the parameters in the model, the projection tests for multinormality are obtained by replacing missing data with their conditional expectations for given observed data and $\hat{\theta}$.

3. Statistical Tests

3.1 *Test Based on the EM Algorithm*

In this section, we consider testing the hypothesis H_0 using results from the EM algorithm. If we had the complete-data $\boldsymbol{Y}_{\text{com}} = \{\boldsymbol{Y}_i^{(k)} : i = 1, \ldots, n_k,\ k = 1, 2\}$, where $\boldsymbol{Y}_i^{(k)} \sim \text{N}_m(\boldsymbol{\mu}^{(k)}, \sigma^2 \boldsymbol{R}_m)$, we could simply use the t-statistic (cf., Rao, 1973) to test H_0,

$$t = \frac{\boldsymbol{d}^{\text{T}}\bar{\boldsymbol{Y}}^{(1)} - \boldsymbol{d}^{\text{T}}\bar{\boldsymbol{Y}}^{(2)}}{\sqrt{\boldsymbol{d}^{\text{T}}(S^{(1)} + S^{(2)})\boldsymbol{d}}} \sqrt{\frac{n_1 n_2 (n_1 + n_2 - 2)}{n_1 + n_2}}, \tag{3.1}$$

where

$$\bar{\boldsymbol{Y}}^{(k)} = \frac{1}{n_k} \sum_{i=1}^{n_k} \boldsymbol{Y}_i^{(k)},$$

$$S^{(k)} = \sum_{i=1}^{n_k} \boldsymbol{Y}_i^{(k)} \boldsymbol{Y}_i^{(k)\text{T}} - n_k \bar{\boldsymbol{Y}}^{(k)} \bar{\boldsymbol{Y}}^{(k)\text{T}}$$

$$= \left(1 - \frac{1}{n_k}\right) \sum_{i=1}^{n_k} \boldsymbol{Y}_i^{(k)} \boldsymbol{Y}_i^{(k)\text{T}} - \frac{1}{n_k} \sum_{i \neq j} \boldsymbol{Y}_i^{(k)} \boldsymbol{Y}_j^{(k)\text{T}}$$

for $k = 1, 2$. If H_0 holds, then the t-statistic in (3.1) has t-distribution with degree of freedom $n_1 + n_2 - 2$.

Denote the unknown parameter vector by $\theta = (\boldsymbol{\mu}^{(1)}, \boldsymbol{\mu}^{(2)}, \sigma^2, \rho)^{\text{T}}$. For the complete-data $\boldsymbol{Y}_{\text{com}}$, the log-likelihood function of θ is

$$\ell(\theta \mid \boldsymbol{Y}_{\text{com}}) = -\frac{mn}{2} \log \sigma^2 - \frac{n}{2} \log |\boldsymbol{R}_m| - \frac{1}{2\sigma^2} \text{tr}\left\{\boldsymbol{R}_m^{-1}\left(S^{(1)} + S^{(2)}\right)\right\}$$

$$- \frac{1}{2\sigma^2} \sum_{k=1}^{2} n_k \left(\bar{\boldsymbol{Y}}^{(k)} - \boldsymbol{\mu}^{(k)}\right)^{\text{T}} \times \boldsymbol{R}_m^{-1} \left(\bar{\boldsymbol{Y}}^{(k)} - \boldsymbol{\mu}^{(k)}\right).$$

Because $|\boldsymbol{R}_m| = (1 - \rho^2)^{m-1}$ and

$$\boldsymbol{R}_m^{-1} = \frac{1}{1 - \rho^2} \left\{\boldsymbol{I}_m + \rho^2 \boldsymbol{K}_m - \rho\left(\boldsymbol{H}_m + \boldsymbol{H}_m^{\text{T}}\right)\right\},$$

the maximum likelihood estimates (MLEs) of θ are determined by

$$\boldsymbol{\mu}^{(k)} = \bar{\boldsymbol{Y}}^{(k)},$$

$$\sigma^2 = \frac{\text{tr}\left\{\boldsymbol{R}_m^{-1}\left(S^{(1)} + S^{(2)}\right)\right\}}{mn},$$

and

$$\rho^3 (m-1) \text{tr}\left\{\boldsymbol{K}_m \left(S^{(1)} + S^{(2)}\right)\right\} - \rho\, \text{tr}\left\{\left(\boldsymbol{I}_m + m\boldsymbol{K}_m\right)\left(S^{(1)} + S^{(2)}\right)\right\} + \left\{\frac{m}{2} + \rho^2\left(1 - \frac{m}{2}\right)\right\} \text{tr}\left\{\left(\boldsymbol{H}_m + \boldsymbol{H}_m^{\text{T}}\right)\left(S^{(1)} + S^{(2)}\right)\right\} = 0, \tag{3.2}$$

where $\boldsymbol{K}_m = \text{diag}(0, \boldsymbol{1}_{m-2}^{\text{T}}, 0)$ and

$$\boldsymbol{H}_m = \begin{pmatrix} 0 & 0 \\ \boldsymbol{I}_{m-1} & 0 \end{pmatrix}.$$

When there are missing data, we use the EM algorithm to obtain maximum likelihood estimates of the parameters of interest. Recall the complete data $\boldsymbol{Y}_i^{(k)}$ is divided into three parts: the observed part $\boldsymbol{Y}_{i,\text{obs}}^{(k)}$ with length $p_i^{(k)}$, the informative missing part $\boldsymbol{Y}_{i,\text{inf}}^{(k)}$ with length $q_i^{(k)}$ (i.e., the value of each component in $\boldsymbol{Y}_{i,\text{inf}}^{(k)}$ is less than a known constant a), and the missing-at-random part $\boldsymbol{Y}_{i,\text{mis}}^{(k)}$ with length $r_i^{(k)}$, where $p_i^{(k)} + q_i^{(k)} + r_i^{(k)} = m$. Denote the observed part by $\boldsymbol{Y}_{\text{obs}} = \{\boldsymbol{Y}_{i,\text{obs}}^{(k)} : i = 1, \ldots, n_k,\ k = 1, 2\}$, the informative missing part by $\boldsymbol{Y}_{\text{inf}} = \{\boldsymbol{Y}_{i,\text{inf}}^{(k)} : i = 1, \ldots, n_k,\ k = 1, 2\}$, the missing-at-random part by $\boldsymbol{Y}_{\text{mis}} = \{\boldsymbol{Y}_{i,\text{mis}}^{(k)} : i = 1, \ldots, n_k,\ k = 1, 2\}$. We further denote the observed data by $\boldsymbol{Y}_{\text{obs}}^* = \{\boldsymbol{Y}_{\text{obs}}, \boldsymbol{Y}_{\text{inf}} < a\}$, where $\boldsymbol{Y}_{\text{inf}} < a$ means that each component of $\boldsymbol{Y}_{i,\text{inf}}^{(k)}$ is less than a. Given an initial value of θ, the E-step finds the conditional expectation of the log-likelihood function of θ based on the complete data $\boldsymbol{Y}_{\text{com}}$ conditionally on $\boldsymbol{Y}_{\text{obs}}^*$ and $\theta^{(t)}$ from the previous iteration of the algorithm, $Q(\theta \mid \theta^{(t)}) = \text{E}\{\ell(\theta \mid \boldsymbol{Y}_{\text{com}}) \mid \boldsymbol{Y}_{\text{obs}}^*, \theta^{(t)}\}$, i.e. the conditional expectation of the complete-data sufficient statistics,

$$\text{E}\left(\boldsymbol{Y}_i^{(k)} \mid \boldsymbol{Y}_{\text{obs}}^*, \theta^{(t)}\right) \quad \text{and} \quad \text{E}\left(\boldsymbol{Y}_i^{(k)} \boldsymbol{Y}_i^{(k)\text{T}} \mid \boldsymbol{Y}_{\text{obs}}^*, \theta^{(t)}\right), \quad i = 1, \ldots, n_k;\ k = 1, 2. \tag{3.3}$$

The M-step calculates $\theta^{(t+1)}$ using (3.2) with $\boldsymbol{Y}_i^{(k)}$ and $\boldsymbol{Y}_i^{(k)} \times \boldsymbol{Y}_i^{(k)\text{T}}$ being replaced by the corresponding conditional expectations in (3.3), respectively. The algorithm is iterated until $|\theta^{(t+1)} - \theta^{(t)}|$ is sufficiently small and the MLE $\hat{\theta}$ is obtained, then the t-test given in (3.1) is performed, as shown in detail in the Appendix.

3.2 *Bayesian Test*

The Bayesian hypothesis testing requires calculating the observed posterior probability of the one-sided alternative hypothesis H_1: $\boldsymbol{d}^{\text{T}}\boldsymbol{\mu}^{(1)} < \boldsymbol{d}^{\text{T}}\boldsymbol{\mu}^{(2)}$, namely,

$$\Pr\{H_1 \mid \boldsymbol{Y}_{\text{obs}}^*\} = \Pr\left\{\boldsymbol{d}^{\text{T}}\left(\boldsymbol{\mu}^{(1)} - \boldsymbol{\mu}^{(2)}\right) < 0 \mid \boldsymbol{Y}_{\text{obs}}^*\right\} \doteq \frac{1}{N} \sum_{\ell=1}^{N} I\left(\boldsymbol{d}^{\text{T}}\left(\boldsymbol{\mu}^{(1,\ell)} - \boldsymbol{\mu}^{(2,\ell)}\right) < 0\right), \tag{3.4}$$

where $\{(\boldsymbol{\mu}^{(1,\ell)}, \boldsymbol{\mu}^{(2,\ell)}) : \ell = 1, \ldots, N\}$ is an i.i.d. sample from the observed posterior density $f(\boldsymbol{\mu}^{(1)}, \boldsymbol{\mu}^{(2)} \mid \boldsymbol{Y}_{\text{obs}}^*)$ and $I(\cdot)$ denotes the indicator function. If the posterior probability of H_1 is greater than or equal to a certain level (e.g., 95%), we reject the null hypothesis. We chose the posterior probability (over the Bayes factor) for its ease of interpretation to biologists. The likelihood function of θ for the complete data $\boldsymbol{Y}_{\text{com}} = \{\boldsymbol{Y}_i^{(k)} : i = 1, \ldots, n_k,\ k = 1, 2\}$ is

$$L(\theta \mid \boldsymbol{Y}_{\text{com}}) = |\boldsymbol{\Sigma}_m|^{-n/2} \exp\left\{-\frac{1}{2} \text{tr} \boldsymbol{\Sigma}_m^{-1}\left(B^{(1)} + B^{(2)}\right)\right\} = \left(\sigma^2\right)^{-nm/2} \left(1 - \rho^2\right)^{-n(m-1)/2} \times \exp\left\{-\frac{1}{2\sigma^2} \text{tr} \boldsymbol{R}_m^{-1}\left(B^{(1)} + B^{(2)}\right)\right\},$$

where $B^{(k)} = \Sigma_{i=1}^{n_k} (\boldsymbol{Y}_i^{(k)} - \boldsymbol{\mu}^{(k)})(\boldsymbol{Y}_i^{(k)} - \boldsymbol{\mu}^{(k)})^{\text{T}}$ for $k = 1, 2$.

We shall use diffuse priors on $\boldsymbol{\mu}^{(k)}$: $\boldsymbol{\mu}^{(k)} \sim \mathrm{N}_m(\boldsymbol{a}_0, \boldsymbol{A}_0^{-1})$ with $\boldsymbol{a}_0 = 0$ and $\boldsymbol{A}_0 \to 0$, an inverse gamma prior on σ^2: $\sigma^2 \sim \mathrm{IG}(q_0/2, \lambda_0/2)$ with density

$$\mathrm{IG}(u \mid q_0/2, \lambda_0/2) = \frac{(\lambda_0/2)^{q_0/2}}{\Gamma(q_0/2)} u^{-1-q_0/2} \exp\left\{-\frac{\lambda_0}{2u}\right\},$$

where q_0 and λ_0 are known constants, and a uniform prior on ρ in the interval $(-1, 1)$: $\rho \sim \mathrm{U}(-1, 1)$. We further assume that these priors are independent.

The complete-data posterior distribution for $\theta = (\boldsymbol{\mu}^{(1)}, \boldsymbol{\mu}^{(2)}, \sigma^2, \rho)^{\mathrm{T}}$ is given by

$$\begin{aligned} f(\theta \mid \boldsymbol{Y}_{\mathrm{com}}) &= \left\{\prod_{k=1}^{2} f\left(\boldsymbol{\mu}^{(k)} \mid \boldsymbol{Y}_{\mathrm{com}}, \sigma^2, \rho\right)\right\} \\ &\quad \times f\left(\sigma^2 \mid \boldsymbol{Y}_{\mathrm{com}}, \rho\right) \times f(\rho \mid \boldsymbol{Y}_{\mathrm{com}}) \\ &= \left\{\prod_{k=1}^{2} \mathrm{N}_m\left(\boldsymbol{\mu}^{(k)} \mid \bar{\boldsymbol{Y}}^{(k)}, \frac{\boldsymbol{\Sigma}_m}{n_k}\right)\right\} \\ &\quad \times \mathrm{IG}\left(\sigma^2 \mid \frac{q^*}{2}, \frac{\lambda^*}{2}\right) \times f(\rho \mid \boldsymbol{Y}_{\mathrm{com}}), \end{aligned} \tag{3.5}$$

where $q^* = q_0 + (n-2)m$, $\lambda^* = \lambda_0 + \mathrm{tr}\, \boldsymbol{R}_m^{-1}(S^{(1)} + S^{(2)})$,

$$f(\rho \mid \boldsymbol{Y}_{\mathrm{com}}) \propto |\boldsymbol{R}_m|^{1-\frac{n}{2}} / (\lambda^*)^{\frac{q^*}{2}}, \qquad -1 < \rho < 1, \tag{3.6}$$

$|\boldsymbol{R}_m| = (1-\rho^2)^{m-1}$, and

$$\boldsymbol{R}_m^{-1} = \frac{1}{1-\rho^2}\left\{\boldsymbol{I}_m + \rho^2 \boldsymbol{K}_m - \rho\left(\boldsymbol{H}_m + \boldsymbol{H}_m^{\mathrm{T}}\right)\right\}.$$

Because the range of ρ is finite, we can use the grid method (Gelman et al., 1995, p. 302) to sample from (3.6).

We know that $\boldsymbol{Y}_i^{(k)} \overset{\text{ind.}}{\sim} \mathrm{N}_m(\boldsymbol{\mu}^{(k)}, \boldsymbol{\Sigma}_m)$ and $\boldsymbol{\Sigma}_m = \sigma^2 \boldsymbol{R}_m$. Partition $\boldsymbol{Y}_i^{(k)}$, $\boldsymbol{\mu}^{(k)}$, and $\boldsymbol{\Sigma}_m$ as follows:

$$\boldsymbol{Y}_i^{(k)} = \begin{pmatrix} \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)} \\ \boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} \\ \boldsymbol{Y}_{i,\mathrm{mis}}^{(k)} \end{pmatrix} \begin{matrix} p_i^{(k)} \\ q_i^{(k)} \\ r_i^{(k)} \end{matrix},$$

$$\boldsymbol{\mu}^{(k)} = \begin{pmatrix} \boldsymbol{\mu}_{\mathrm{obs}}^{(k)} \\ \boldsymbol{\mu}_{\mathrm{inf}}^{(k)} \\ \boldsymbol{\mu}_{\mathrm{mis}}^{(k)} \end{pmatrix} \begin{matrix} p_i^{(k)} \\ q_i^{(k)} \\ r_i^{(k)} \end{matrix},$$

$$\begin{aligned} \boldsymbol{\Sigma}_m &= \begin{pmatrix} \boldsymbol{\Sigma}_{\mathrm{obs,obs}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{obs,inf}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{obs,mis}}^{(i,k)} \\ \boldsymbol{\Sigma}_{\mathrm{inf,obs}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{inf,inf}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{inf,mis}}^{(i,k)} \\ \boldsymbol{\Sigma}_{\mathrm{mis,obs}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{mis,inf}}^{(i,k)} & \boldsymbol{\Sigma}_{\mathrm{mis,mis}}^{(i,k)} \end{pmatrix} \\ &= \begin{pmatrix} \boldsymbol{\Sigma}_{11}^{(i,k)} & \boldsymbol{\Sigma}_{12}^{(i,k)} & \boldsymbol{\Sigma}_{13}^{(i,k)} \\ \boldsymbol{\Sigma}_{21}^{(i,k)} & \boldsymbol{\Sigma}_{22}^{(i,k)} & \boldsymbol{\Sigma}_{23}^{(i,k)} \\ \boldsymbol{\Sigma}_{31}^{(i,k)} & \boldsymbol{\Sigma}_{32}^{(i,k)} & \boldsymbol{\Sigma}_{33}^{(i,k)} \end{pmatrix} \begin{matrix} p_i^{(k)} \\ q_i^{(k)} \\ r_i^{(k)} \end{matrix}, \end{aligned}$$

where $p_i^{(k)} + q_i^{(k)} + r_i^{(k)} = m$ and $\boldsymbol{\Sigma}_{\ell\ell'}^{(i,k)}(\ell, \ell' = 1, 2, 3)$ depends on the mouse label i and group label k only via $p_i^{(k)}$, $q_i^{(k)}$, and $r_i^{(k)}$. The definitions of $\boldsymbol{Y}_{\mathrm{obs}}$, $\boldsymbol{Y}_{\mathrm{inf}}$, $\boldsymbol{Y}_{\mathrm{mis}}$, and $\boldsymbol{Y}_{\mathrm{obs}}^*$ are given as before. The conditional predictive density is

$$\begin{aligned} &f(\boldsymbol{Y}_{\mathrm{inf}}, \boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}^*, \theta) \\ &\quad = \prod_{k=1}^{2}\prod_{i=1}^{n_k} f\left(\boldsymbol{Y}_{i,\mathrm{mis}}^{(k)} \mid \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)}, \theta\right) * f\left(\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} \mid \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)*}, \boldsymbol{Y}_{i,\mathrm{mis}}^{(k)}, \theta\right), \end{aligned} \tag{3.7}$$

where

$$\begin{aligned} &f\left(\boldsymbol{Y}_{i,\mathrm{mis}}^{(k)} \mid \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)}, \theta\right) \\ &\quad = N_{r_i^{(k)}}\left(\boldsymbol{Y}_{i,\mathrm{mis}}^{(k)} \mid \boldsymbol{\mu}_{\mathrm{mis}}^{(k)} + \boldsymbol{\Sigma}_{31}^{(i,k)}\boldsymbol{\Sigma}_{11}^{(i,k)-1}\left(\boldsymbol{Y}_{i,\mathrm{obs}}^{(k)} - \boldsymbol{\mu}_{\mathrm{obs}}^{(k)}\right), \right. \\ &\qquad \left. \boldsymbol{\Sigma}_{33}^{(i,k)} - \boldsymbol{\Sigma}_{31}^{(i,k)}\boldsymbol{\Sigma}_{11}^{(i,k)-1}\boldsymbol{\Sigma}_{13}^{(i,k)}\right) \end{aligned}$$

and $\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} \mid (\boldsymbol{Y}_{i,\mathrm{obs}}^{(k)*}, \boldsymbol{Y}_{i,\mathrm{mis}}^{(k)}, \theta)$ is distributed as a $q_i^{(k)}$-dimensional normal with mean vector

$$\begin{aligned} \boldsymbol{\delta}_i^{(k)} &= \boldsymbol{\mu}_{\mathrm{inf}}^{(k)} + \left(\boldsymbol{\Sigma}_{21}^{(i,k)}, \boldsymbol{\Sigma}_{23}^{(i,k)}\right)\begin{pmatrix} \boldsymbol{\Sigma}_{11}^{(i,k)} & \boldsymbol{\Sigma}_{13}^{(i,k)} \\ \boldsymbol{\Sigma}_{31}^{(i,k)} & \boldsymbol{\Sigma}_{33}^{(i,k)} \end{pmatrix}^{-1} \\ &\quad \times \begin{pmatrix} \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)} - \boldsymbol{\mu}_{\mathrm{obs}}^{(k)} \\ \boldsymbol{Y}_{i,\mathrm{mis}}^{(k)} - \boldsymbol{\mu}_{\mathrm{mis}}^{(k)} \end{pmatrix} \end{aligned}$$

and covariance matrix

$$\begin{aligned} \boldsymbol{V}_i^{(k)} &= \boldsymbol{\Sigma}_{22}^{(i,k)} - (\boldsymbol{\Sigma}_{21}^{(i,k)}, \boldsymbol{\Sigma}_{23}^{(i,k)})\begin{pmatrix} \boldsymbol{\Sigma}_{11}^{(i,k)} & \boldsymbol{\Sigma}_{13}^{(i,k)} \\ \boldsymbol{\Sigma}_{31}^{(i,k)} & \boldsymbol{\Sigma}_{33}^{(i,k)} \end{pmatrix}^{-1} \\ &\quad \times \begin{pmatrix} \boldsymbol{\Sigma}_{12}^{(i,k)} \\ \boldsymbol{\Sigma}_{32}^{(i,k)} \end{pmatrix} \end{aligned}$$

but truncated to the region $\{(Z_1, \ldots, Z_{q_i^{(k)}})^{\mathrm{T}} : Z_j < a, j = 1, \ldots, q_i^{(k)}\}$, namely,

$$\begin{aligned} &f\left(\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} \mid \boldsymbol{Y}_{i,\mathrm{obs}}^{(k)*}, \boldsymbol{Y}_{i,\mathrm{mis}}^{(k)}, \theta\right) \\ &\quad = \frac{\exp\left\{-\left(\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} - \boldsymbol{\delta}_i^{(k)}\right)^{\mathrm{T}}\left(\boldsymbol{V}_i^{(k)}\right)^{-1}\left(\boldsymbol{Y}_{i,\mathrm{inf}}^{(k)} - \boldsymbol{\delta}_i^{(k)}\right)/2\right\}}{(\sqrt{2\pi})^{q_i^{(k)}} |\boldsymbol{V}_i^{(k)}|^{1/2} \Phi_{q_i^{(k)}}\left(a, \ldots, a; \boldsymbol{\delta}_i^{(k)}, \boldsymbol{V}_i^{(k)}\right)}, \end{aligned}$$

where $\Phi_{q_i^{(k)}}(\cdot, \ldots, \cdot; \boldsymbol{\delta}_i^{(k)}, \boldsymbol{V}_i^{(k)})$ denotes the c.d.f. of $\mathrm{N}_{q_i^{(k)}}(\boldsymbol{\delta}_i^{(k)}, \boldsymbol{V}_i^{(k)})$.

The difficulty is then simply how to calculate the posterior probability. The block MCMC approach (e.g., the two-block Gibbs sampler based on (3.5) and (3.7)) is cumbersome because each cycle of the Markov chain requires another MCMC cycle to generate truncated multivariate normal samples, whereas a Gibbs sampler with parameters $\{\boldsymbol{\mu}^{(1)}, \boldsymbol{\mu}^{(2)}, \sigma^2, \rho\}$ and a total of $\Sigma_{k=1}^{2}\Sigma_{i=1}^{n_k}(r_i^{(k)} + q_i^{(k)})$ missing data variables would take a long time to complete one cycle. More important, both involve the problematic issues of assessing convergence to the stationary distribution of the Markov chain. Therefore, we adopt a noniterative sampling procedure, i.e., the inverse Bayes formulae (IBF) method (Tan et al., 2001), to obtain independent samples from the observed posterior distribution, eliminating the convergence issue. To briefly introduce the IBF method, let Y denote the observed data, Z the missing data, and θ the parameter vector of interest. The complete-data posterior distribution $f_{(\theta|Y,Z)}(\theta \mid Y, z)$ and the conditional predictive distribution

$f_{(Z|Y,\theta)}(z \mid Y,\theta)$ are assumed to be available. The observed posterior $f_{\theta|Y}(\theta \mid Y)$ can be obtained by the samplingwise IBF

$$f_{\theta|Y}(\theta \mid Y) \propto \frac{f_{(\theta|Y,Z)}(\theta \mid Y, z_0)}{f_{(Z|Y,\theta)}(z_0 \mid Y,\theta)} \tag{3.8}$$

for some arbitrary $z_0 \in \mathcal{S}_{(Z|Y)}$ and all $\theta \in \mathcal{S}_{(\theta|Y)}$, where $\mathcal{S}_{(Z|Y)}$ and $\mathcal{S}_{(\theta|Y)}$ denote the supports of $Z \mid Y$ and $\theta \mid Y$. Therefore, the IBF sampler via the sampling/importance resampling method (Rubin, 1988) is as follows: (i) Draw a large sample of size J of θ from $f_{(\theta|Y,Z)}(\theta \mid Y, z_0)$, denoted by $\theta^{(1)},\ldots,\theta^{(J)}$; (ii) calculate the weights $\omega_j = f^{-1}_{(Z|Y,\theta)}(z_0 \mid Y,\theta^{(j)})/\Sigma_{\ell=1}^{J} f^{-1}_{(Z|Y,\theta)}(z_0 \mid Y,\theta^{(\ell)})$ for $j = 1,\ldots,J$; (iii) resample without replacement from the discrete distribution on $\theta^{(1)},\ldots,\theta^{(J)}$ with probabilities $\omega_1,\ldots,\omega_J$ to obtain an i.i.d. sample of size $N < J$ from $f_{\theta|Y}(\theta \mid Y)$. Tan et al. (2001) suggested taking $z_0 = \mathrm{E}(Z \mid Y,\tilde{\theta})$, where $\tilde{\theta}$ denotes the posterior mode of $f_{\theta|Y}(\theta \mid Y)$. In Section 4 below, let $Y = \boldsymbol{Y}^*_{\mathrm{obs}}$, $Z = \{\boldsymbol{Y}_{\mathrm{inf}}, \boldsymbol{Y}_{\mathrm{mis}}\}$, and replace $\tilde{\theta}$ with the MLE $\hat{\theta}$ obtained via the EM algorithm and then take $z_0 = \mathrm{E}(\boldsymbol{Y}_{\mathrm{inf}}, \boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \hat{\theta})$ because $\hat{\theta}$ is quite close to $\tilde{\theta}$ when the priors are noninformative and/or flat.

4. Analysis of Tumor Xenograft Models

We now consider the analysis of a real study on xenograft models for 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 other tumors. CPT-11 has demonstrated broad activity against both murine and human tumor xenograft models and clinically significant activity against many types of cancer. The primary objective was to determine whether the responses obtained with different combinations of TMZ and CPT-11 were significantly different in antitumor activities. There were six or nine different treatment regimens for each of eight independent xenograft models (four neuroblastomas, three rhabdomyosarcomas, and one glioblastoma) (Houghton et al., 2000). Mice from the same strain were used and they are virtually genetically identical. Table 1 shows the responses of three different treatment regimens for rhabdomyosarcoma in xenograft models (Rh18).

At each time of administration, each mouse received TMZ 42 mg/kg and CPT-11 0.61 mg/kg in group I, TMZ 28 mg/kg and CPT-11 0.61 mg/kg in group II, and CPT-11 0.61 mg/kg in group III. TMZ was administered daily for 5 consecutive days (days 1–5) of each cycle and 1 hour prior to administration of CPT-11. The treatment was repeated twice at 21-day intervals. CPT-11 for group III was administered intravenously (i.v.) daily for two 5-day courses (1–5, 8–12) per 21-day cycle. However, no drug was given in the last 3 weeks of the 12-week follow-up period. The tumor volumes were measured at the initial time and once every week for 12 weeks. Missing data arose because a mouse died of toxicity or was sacrificed when its tumor volume quadrupled. If a tumor volume was less than 0.01 cm^3, it could not be measured.

Let $\boldsymbol{Y}_i^{(k)} = (Y_{i0}^{(k)},\ldots,Y_{i,12}^{(k)})^{\mathrm{T}}$ be the logarithmic transformation of the observation of the ith subject in the kth group, $i = 1,\ldots,6$, or 7 and $k = 1,2,3$. Then $Y_{ij}^{(k)}$ is truncated if $Y_{ij}^{(k)} < \log 0.01$. If $Y_{ij}^{(k)} \geq Y_{i0}^{(k)} + \log 4$ or the mouse died before the $(j+1)$th week, $Y_{ih}^{(k)}$, $h = j+1,\ldots,12$, are missing at random. Because the sample sizes are very small (≤ 7), we use the projection tests proposed in Section 2 for testing multinormality with the projection dimension

Table 1
Volumes (cm^3) of Rh18 tumor measured in 12 weeks for different treatments[a]

		Week												
Group	No.	0	1	2	3	4	5	6	7	8	9	10	11	12
I	1	0.03	0.26	0.24	0.17	0.01	*	*	*	*	*	*	*	*
	2	0.52	0.15	0.14	0.01	*	*	*	*	*	*	*	*	*
	3	1.57	0.34	0.18	0.15	0.01	*	*	*	*	*	*	*	*
	4	0.89	0.38	0.24	0.36	0.12	0.14	0.10	0.14	0.14	0.30	1.42	2.91	4.57
	5	1.28	0.48	0.22	0.25	0.01	*	*	*	0.01	0.20	1.31	2.62	5.73
	6	0.53	0.34	0.16	0.20	0.01	*	*	*	0.01	0.18	1.06	1.94	3.13
	7	1.49	0.12	0.10	0.01	*	–	–	–	–	–	–	–	–
II	1	0.70	0.32	0.14	0.19	0.01	*	*	*	0.01	0.17	0.65	1.08	2.74
	2	0.37	0.09	0.09	0.01	*	*	*	*	*	*	*	*	*
	3	0.30	0.08	0.01	*	*	*	*	*	*	*	*	*	*
	4	0.26	0.15	0.01	*	*	0.01	0.28	0.26	0.25	0.39	0.58	0.67	0.83
	5	0.22	0.11	0.08	0.06	0.01	*	*	*	*	–	–	–	–
	6	1.08	0.23	0.09	0.15	0.01	0.01	0.24	0.24	0.27	0.92	2.39	4.12	6.75
	7	0.87	0.31	0.15	0.22	–	–	–	–	–	–	–	–	–
III	1	1.75	0.95	0.54	0.64	0.24	0.69	1.16	1.80	1.22	3.17	5.96	6.06	8.17
	2	0.16	0.09	0.09	0.14	0.10	0.13	0.21	0.22	0.28	0.42	0.93	–	–
	3	0.83	0.39	0.29	0.43	0.36	0.34	0.61	0.74	0.57	1.46	1.99	2.59	3.33
	4	1.54	0.94	0.30	0.42	0.30	0.41	0.87	1.32	0.96	2.10	4.27	5.76	6.63
	5	0.91	0.24	0.10	0.01	*	*	*	*	*	*	*	*	*
	6	0.78	0.22	0.07	0.01	*	*	*	*	*	*	*	*	*

[a] "–" means that the mouse died or the tumor grew to four times its initial volume. "*" means that the tumor volume was <0.01 cm^3.

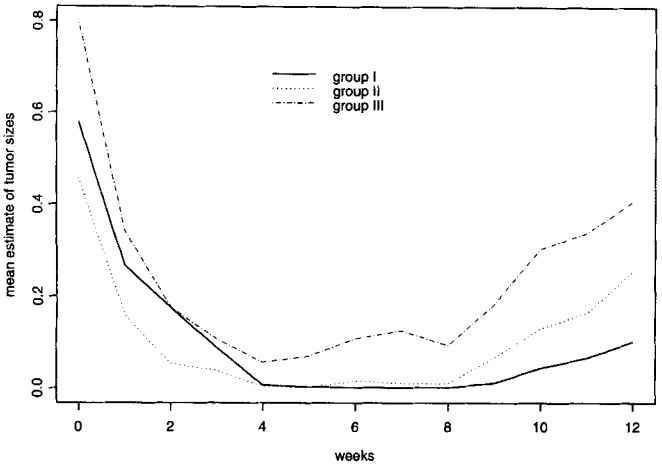

Figure 1. Mean estimates of tumor sizes.

$q = 1$. For the skewness statistic (2.17) and the kurtosis statistic (2.18) in Liang et al. (2000), the p-values are 0.70712 and 0.52604 for group I, 0.51682 and 0.77406 for group II, and 0.67822 and 0.91024 for group III, respectively. Thus, both tests failed to reject the assumption of multinormality in each of the three groups.

Based on the data of groups I and II, the MLEs of $\boldsymbol{\mu}^{(1)}$, $\boldsymbol{\mu}^{(2)}$, σ^2, and ρ via the EM algorithm, which converged at 50 iterations, are $\hat{\boldsymbol{\mu}}^{(1)} = (-0.55, -1.32, -1.74, -2.41, -4.99, -5.82, -6.55, -6.50, -6.34, -4.48, -3.10, -2.70, -2.27)^{\mathrm{T}}$, $\hat{\boldsymbol{\mu}}^{(2)} = (-0.784, -1.83, -2.92, -3.26, -5.44, -6.20, -4.15, -4.55, -4.59, -2.69, -2.03, -1.80, -1.37)^{\mathrm{T}}$, $\hat{\sigma}^2 = 5.276$, and $\hat{\rho} = 0.953$. Similar results based on the data of groups II and III and groups I and III have also been obtained. The corresponding MLEs of average tumor sizes at every week are plotted in Figure 1. Note the mean estimates for each group (say, I) based on comparisons of two groups (I vs. II and I vs. III) are almost the same, and they coincide in the figure.

Table 2 gives results of the quasi–t-test with contrast vectors $\boldsymbol{d}_1 = \mathbf{1}_{13}$ and $\boldsymbol{d}_2 = (0, 0, 0, 0, 1, 1, 1, 1, 1, 1, 1, 0, 0)^{\mathrm{T}}$. The contrast vector $\boldsymbol{d}_2$ is used to measure the treatment effect after the first cycle of therapy (3 weeks) up to the third cycle of therapy with one additional week of follow-up (the 10th week). These results show that there is no significant difference among the three groups (choosing $\boldsymbol{d}_1$) but the antitumor activity in group I is significantly greater than that in group III (choosing $\boldsymbol{d}_2$, p-value = 0.0275).

In Bayesian analysis, because the complete-data posterior density (3.5) of θ is proper, we can directly use $\boldsymbol{a}_0 = 0$ and $\boldsymbol{A}_0 = 0$ in the diffuse prior, namely, a flat prior for $\boldsymbol{\mu}^{(k)}$, to yield (3.5). The noninformative prior on σ^2 is obtained by taking $q_0 = \lambda_0 = 0$ in inverse gamma distribution, and the prior on ρ is uniform in the interval $(-1, 1)$. To perform the Bayesian computation using the IBF sampler, we first need to choose one z_0 in (3.8). Using the MLE $\hat{\theta} = (\hat{\boldsymbol{\mu}}^{(1)}, \hat{\boldsymbol{\mu}}^{(2)}, \hat{\sigma}^2, \hat{\rho})^{\mathrm{T}}$ obtained above, we have $z_0 = \mathrm{E}(Z \mid Y, \hat{\theta}) = \mathrm{E}(\boldsymbol{Y}_{\mathrm{inf}}, \boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \hat{\theta})$. With $J = 1250$ and $N = 1000$, the IBF sampler gives an i.i.d. sample of size $N = 1000$ from the observed posterior distribution $f(\boldsymbol{\mu}^{(1)}, \boldsymbol{\mu}^{(2)}, \sigma^2, \rho \mid \boldsymbol{Y}^*_{\mathrm{obs}})$. From (3.4), the observed posterior probability $\Pr\{\mathrm{H}_1 \mid \boldsymbol{Y}^*_{\mathrm{obs}}\}$ was calculated for various contrast vectors $\boldsymbol{d}$. We list $1 - \Pr\{\mathrm{H}_1 \mid \boldsymbol{Y}^*_{\mathrm{obs}}\}$ in the last column of Table 2. The conclusion drawn from the Bayesian analysis is similar to that obtained with the EM algorithm.

5. Discussion

We proposed two small-sample parametric inference procedures for incomplete longitudinal data with truncation and informative censoring that arise in translational studies in cancer therapy development. One is a heuristic test and the other is developed from a Bayesian approach. We found the methods especially useful in designed xenograft experiments in our own experience in a developmental therapeutics program. The main advantage of the proposed procedures is that they utilize all the data (censored or truncated) and are based on small samples. As shown in Fang and Zhang (1990), the t-statistic is invariant in the class of elliptical distributions; because the proposed procedure is essentially a t-test, it applies to elliptically distributed outcomes as well. Furthermore, as shown in Pearson and Please (1975), the t-test for normal means is remarkably robust against skewness of the underlying distribution but can be sensitive to outliers. Therefore, the trade-off for the small-sample inference proposed here is that the response (or a transformation of it) needs to be approximately normal or elliptical and can be affected by outliers. Both our historical data and the normality test suggest the multivariate normal assumption in our example is reasonable. Some experience with data from similar experiments (e.g., previous compounds against the same cancer) would be useful to identify an appropriate transformation of the data to satisfy normality. Because most xenograft experiments use virtually genetically identical mice and designed (controlled) experiments, outliers are less likely to occur. A practical recommendation is that it is important to use designed experiments in translational studies as well. Although we have focused on the toeplitz correlation structure, the simpler compound symmetry may be justified for within-cluster

Table 2
Results of statistical analysis

Weight	Groups	t-Statistic	d.f.	p-Value	$1 - \Pr\{\mathrm{H}_1 \mid \boldsymbol{Y}^*_{\mathrm{obs}}\}$
$\boldsymbol{d}_1$	I vs. II	−0.5516	12	0.2956	0.299
	II vs. III	−1.2185	11	0.1243	0.146
	I vs. III	−1.6495	11	0.0636	0.075
$\boldsymbol{d}_2$	I vs. II	−0.9533	12	0.1796	0.167
	II vs. III	−1.4053	11	0.0938	0.071
	I vs. III	−2.1458	11	0.0275	0.014

correlation. On the other hand, when the sample sizes are moderate, more complicated covariance structures may be incorporated in model (2.1). A useful extension is to include quantal response models or more generally the generalized linear models, which we shall report in the future.

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Résumé

Au cours du développement de médicaments anti-tumoraux, la démonstration d'activité dans des modèles de xénogreffe, où des cellules cancéreuses humaines sont greffées à des souris, est une étape importante pour introduire chez l'homme un composé prometteur. Une variable-clé est le volume de la tumeur mesuré pendant une période fixée, alors que des groupes de souris reçoivent différentes doses d'un régime anti-tumoral simple ou combiné. Cependant, une souris peut mourir avant la fin de l'étude, ou être sacrifiée quand le volume de sa tumeur quadruple, et sa tumeur peut être supprimée pendant un certain temps, puis réapparaî tre à nouveau. Ainsi des mesures répétées incomplètes apparaissent. L'incomplétude ou les valeurs manquantes peuvent également être produites par la réduction drastique de la tumeur (<0.01 cm^3) ou la troncature aléatoire. Du fait de la petite taille des échantillons dans ces modèles, les inférences asymptotiques ne sont généralement pas adaptées. Nous proposons deux procédures de test paramétriques basées sur l'algorithme EM et la méthode bayésienne pour comparer les effets des traitements dans les différents groupes, en prenant en compte la censure informative. Une étude réelle de xénogreffe sur le nouvel agent anti-tumoral temozolomide en combinaison avec irinocetan est analysée en utilisant les méthodes proposées.

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APPENDIX

The following gives the derivation of the conditional expectations in (3.3) used in the EM algorithm. Let $\boldsymbol{Y} = (Y_1, \ldots, Y_m)^{\mathrm{T}} \sim \mathrm{N}_m(\boldsymbol{\mu}, \boldsymbol{\Sigma}_m)$, where $\boldsymbol{\Sigma}_m$ is defined by (2.1). Without loss of generality, we denote the observed part by $\boldsymbol{Y}_{\mathrm{obs}} = (Y_1, \ldots, Y_p)^{\mathrm{T}}$, the informative censoring part by $\boldsymbol{Y}_{\mathrm{inf}} = (Y_{p+1}, \ldots, Y_{p+q})^{\mathrm{T}}$, where $Y_j < a$ for some constant a, $j = p+1, \ldots, p+q$, and the random missing part by $\boldsymbol{Y}_{\mathrm{mis}} = (Y_{p+q+1}, \ldots, Y_{p+q+r})^{\mathrm{T}}$ with $p+q+r = m$. We further denote the observed data by $\boldsymbol{Y}^*_{\mathrm{obs}} = \{\boldsymbol{Y}_{\mathrm{obs}}, \boldsymbol{Y}_{\mathrm{inf}} < a\}$. Partition the mean vector $\boldsymbol{\mu}$ and the covariance matrix $\boldsymbol{\Sigma}_m$ in the same fashion as $\boldsymbol{Y}$,

$$\boldsymbol{\mu} = \begin{pmatrix} \boldsymbol{\mu}_{\mathrm{obs}} \\ \boldsymbol{\mu}_{\mathrm{inf}} \\ \boldsymbol{\mu}_{\mathrm{mis}} \end{pmatrix}, \qquad \boldsymbol{\Sigma}_m = \begin{pmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} & \boldsymbol{\Sigma}_{13} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} & \boldsymbol{\Sigma}_{23} \\ \boldsymbol{\Sigma}_{31} & \boldsymbol{\Sigma}_{32} & \boldsymbol{\Sigma}_{33} \end{pmatrix}.$$

The conditional expectations in (3.3) can be induced in the following forms:

$$\mathrm{E}(\boldsymbol{Y} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta) = \begin{pmatrix} \boldsymbol{Y}_{\mathrm{obs}} \\ \mathrm{E}(\boldsymbol{Y}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta) \\ \mathrm{E}(\boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta) \end{pmatrix}$$

and

$$\mathrm{E}\left(\boldsymbol{Y}\boldsymbol{Y}^{\mathrm{T}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) = \begin{pmatrix} \boldsymbol{Y}_{\mathrm{obs}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{obs}} & \boldsymbol{Y}_{\mathrm{obs}}\mathrm{E}\left(\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) & \boldsymbol{Y}_{\mathrm{obs}}\mathrm{E}\left(\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right) \\ * & \mathrm{E}\left(\boldsymbol{Y}_{\mathrm{inf}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) & \mathrm{E}\left(\boldsymbol{Y}_{\mathrm{inf}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) \\ * & * & \mathrm{E}\left(\boldsymbol{Y}_{\mathrm{mis}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right) \end{pmatrix}.$$

Based on the properties of multivariate normal distributions, we have

$$\mathrm{E}\left(\boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right) = \boldsymbol{\mu}_{\mathrm{mis}} + \boldsymbol{\Sigma}_{31}\boldsymbol{\Sigma}_{11}^{-1}(\boldsymbol{Y}_{\mathrm{obs}} - \boldsymbol{\mu}_{\mathrm{obs}}), \tag{A.1}$$

$$\mathrm{E}\left(\boldsymbol{Y}_{\mathrm{mis}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right) = \left(\boldsymbol{\Sigma}_{33} - \boldsymbol{\Sigma}_{31}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}^{\mathrm{T}}_{31}\right) + \mathrm{E}\left(\boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right)\mathrm{E}\left(\boldsymbol{Y}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \theta\right)^{\mathrm{T}}. \tag{A.2}$$

Consider the conditional moments of the informative missing part $\boldsymbol{Y}_{\mathrm{inf}}$ given $\boldsymbol{Y}^*_{\mathrm{obs}}$ and θ. If $q = 1$, then $\boldsymbol{Y}_{\mathrm{inf}} = Y_{p+1} \sim \mathrm{N}(\mu_{p+1}, \sigma^2_{p+1})$. The conditional distribution of Y_{p+1} given $\boldsymbol{Y}^*_{\mathrm{obs}}$ is a truncated normal distribution, and its density function is given by

$$f(z \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta) = \frac{\exp\left\{-(z-\tilde{\mu})^2/\left(2\tilde{\sigma}^2\right)\right\}}{\sqrt{2\pi}\tilde{\sigma} \cdot \Phi((a-\tilde{\mu})/\tilde{\sigma})} \cdot I(z < a),$$

where $\Phi(\cdot)$ denotes the c.d.f. of $\mathrm{N}(0,1)$, $\tilde{\mu} = \mu_{p+1} + \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}(\boldsymbol{Y}_{\mathrm{obs}} - \boldsymbol{\mu}_{\mathrm{obs}})$, and $\tilde{\sigma}^2 = \sigma^2_{p+1} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}^{\mathrm{T}}_{21}$. Therefore, we obtain

$$\begin{aligned} \mathrm{E}(Y_{p+1} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta) &= \tilde{\mu} - \tilde{\sigma}H\left(\frac{a-\tilde{\mu}}{\tilde{\sigma}}\right), \\ \mathrm{E}\left(Y^2_{p+1} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) &= \tilde{\mu}^2 + \tilde{\sigma}^2 - \tilde{\sigma}\,(a+\tilde{\mu})\,H\left(\frac{a-\tilde{\mu}}{\tilde{\sigma}}\right), \end{aligned} \tag{A.3}$$

where $H(x) = \phi(x)/\Phi(x)$ and $\phi(x)$ is the p.d.f. of $\mathrm{N}(0,1)$.

When $q > 1$, the conditional distribution of $\boldsymbol{Y}_{\mathrm{inf}}$ given $\boldsymbol{Y}^*_{\mathrm{obs}}$ and θ is a multivariate truncated normal distribution, denoted by $\boldsymbol{Y}_{\mathrm{inf}} \mid (\boldsymbol{Y}^*_{\mathrm{obs}}, \theta) \sim T\mathrm{N}_q(\tilde{\boldsymbol{\mu}}, \tilde{\boldsymbol{\Sigma}}; a)$. Its p.d.f. is

$$f(\boldsymbol{z} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta) = c^{-1}\exp\left\{-\frac{1}{2}(\boldsymbol{z}-\tilde{\boldsymbol{\mu}})^{\mathrm{T}}\tilde{\boldsymbol{\Sigma}}^{-1}(\boldsymbol{z}-\tilde{\boldsymbol{\mu}})\right\} I(\boldsymbol{z} < a), \tag{A.4}$$

where c is the normalizing constant, $\tilde{\boldsymbol{\mu}} = \boldsymbol{\mu}_{\mathrm{inf}} + \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}(\boldsymbol{Y}_{\mathrm{obs}} - \boldsymbol{\mu}_{\mathrm{obs}})$, and $\tilde{\boldsymbol{\Sigma}} = \boldsymbol{\Sigma}_{22} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}^{\mathrm{T}}_{21}$. Note that the marginals of a multivariate truncated normal distribution are usually no longer truncated normal distributions. However, the full conditional distribution $f(z_i \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta, z_1, \ldots, z_{i-1}, z_{i+1}, \ldots, z_q)$ for $i = 1, \ldots, q$ is a univariate truncated normal distribution. Using Gibbs sampling (Robert, 1995), we can obtain dependent samples from (A.4), which then give estimates of the conditional moments $\mathrm{E}(\boldsymbol{Y}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta)$ and $\mathrm{E}(\boldsymbol{Y}_{\mathrm{inf}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta)$.

Finally, the conditional mixture moment of $\boldsymbol{Y}_{\mathrm{inf}}$ and $\boldsymbol{Y}_{\mathrm{mis}}$ given $\boldsymbol{Y}^*_{\mathrm{obs}}$ and θ is given by

$$\mathrm{E}\left(\boldsymbol{Y}_{\mathrm{inf}}\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right) = \mathrm{E}\left\{\boldsymbol{Y}_{\mathrm{inf}}\mathrm{E}\left[\boldsymbol{Y}^{\mathrm{T}}_{\mathrm{mis}} \mid \boldsymbol{Y}_{\mathrm{obs}}, \boldsymbol{Y}_{\mathrm{inf}}\right] \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta\right\}$$

$$= \left(\mathrm{E}\left\{ \boldsymbol{Y}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta \right\} (\boldsymbol{Y}_{\mathrm{obs}} - \boldsymbol{\mu}_{\mathrm{obs}})^{\mathrm{T}}, \mathrm{E}\left\{ \boldsymbol{Y}_{\mathrm{inf}} \boldsymbol{Y}^{\mathrm{T}}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta \right\} - \mathrm{E}\left\{ \boldsymbol{Y}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta \right\} \boldsymbol{\mu}^{\mathrm{T}}_{\mathrm{inf}} \right) \boldsymbol{V}_{11}^{-1} \boldsymbol{V}_{12}$$
$$+ \mathrm{E}\left\{ \boldsymbol{Y}_{\mathrm{inf}} \mid \boldsymbol{Y}^*_{\mathrm{obs}}, \theta \right\} \boldsymbol{\mu}^{\mathrm{T}}_{\mathrm{mis}}, \tag{A.5}$$

where

$$\boldsymbol{V}_{11} = \begin{pmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} \end{pmatrix}, \quad \text{and} \quad \boldsymbol{V}_{12} = \begin{pmatrix} \boldsymbol{\Sigma}_{13} \\ \boldsymbol{\Sigma}_{23} \end{pmatrix}.$$