

APPLICATIONS OF A FRAILTY MODEL TO SEQUENTIAL SURVIVAL ANALYSIS

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In honor of Professor Herbert Robbins on his 80th birthday

Abstract: The purpose of this paper is to indicate that the time-dependent frailty model for multivariate counting processes of Chang and Hsiung (1996) can be applied to sequential analysis of paired survival data with staggered entry. It is shown that the efficient estimating function in calendar time is a martingale and, with a data-dependent change of time, it is asymptotically a Brownian motion process, which paves the way for sequential analysis. This approach is illustrated by re-examining the Freireich et al. (1963) data of remission lengths in leukemia. A simulation study is also included to indicate its performance numerically.

Key words and phrases: Multivariate counting processes, paired survival data, sequential analysis, time-dependent frailty.

1. Introduction

The purpose of this paper is to indicate that the time-dependent frailty model for multivariate counting processes introduced in Chang and Hsiung (1996) (henceforth CH(96)) can be applied to sequential analysis of paired survival data with staggered entry.

A typical example of survival data with paired design where calendar time monitoring is desired is provided by Freireich et al. (1963). They conducted a remission maintenance therapy to compare 6-MP with placebo for prolonging the duration of remission in leukemia. After having been judged to be in a state of partial or complete remission for the primary treatment with prednisone, a patient was paired with a second patient in the same state. One randomly chosen patient in each pair received the maintenance treatment 6-MP and the other a placebo. Success (failure) was defined to occur in the i th pair if the time from remission to relapse or censoring for the patient on 6-MP (placebo) exceeded the time to relapse for the patient on placebo (6-MP). The trial was stopped once the number of successes or failures had reached significance.

Based on the theory of sequential analysis of survival data with staggered entry developed in Sellke and Siegmund (1983), Siegmund (1985), Chapter V re-examined the data of Freireich et al. (1963) and indicated that earlier termination of the trial might be possible. We note that both Sellke and Siegmund (1983) and Siegmund (1985) meant to provide a general theory for survival data in proportional hazards models with staggered entry and did not consider the case of paired design.

In the following sections, we indicate that, by making use of the proportional hazards model with time-dependent frailties discussed in CH(96), where the asymptotic efficiency of a Cox type estimator is established, sequential analysis of paired survival data with staggered entry is theoretically easier to handle and has a neater solution. In fact, we show that the efficient estimating function of CH(96) remains a martingale relative to the calendar time filtration, unlike the situation without paired design treated by Sellke and Siegmund (1983) and Gu and Lai (1991). Our situation is also different from the parametric sequential analysis studied by Chang and Hsiung (1988), where the score function itself is a calendar time martingale.

Our plan to present the sequential analysis of paired data is as follows. Section 2 introduces a model for paired survival data with staggered entry and shows that it is a time-dependent frailty model of counting processes, which implies that the efficient estimating function is a calendar time martingale studied in CH(96). This is done by establishing a relation between the calendar time filtration and the survival time filtration, which implies that martingales for survival time transform naturally into martingales for calendar time.

We would like to point out that time-dependent frailty appears naturally in our problem when entry time is considered, even if the baseline hazard of the survival time is a deterministic function (cf. Theorem 2.2). Because of this, we introduce a frailty variable into the model from the beginning in order to have a more general theory in a neater presentation.

Following the idea of rescaling time by Fisher information developed in Sellke and Siegmund (1983), Section 3 introduces a data-dependent change of time into the efficient martingale estimating function so that it behaves asymptotically like a Brownian motion process, which paves the way for sequential analysis.

Section 4 illustrates the theory developed in Sections 2 and 3 by re-examining the data of Freireich et al. (1963) and compare our method with that of Freireich et al. (1963). It suggests that our method is a very good alternative.

The simulation study in Section 5 supports the theory by indicating that in case there is no association within pairs, it is better to use the standard Cox partial likelihood score as developed in Sellke and Siegmund (1983) for repeated significance testing; otherwise, it is better to use the method of the present work.

2. The Model and the Basic Martingales

Let Y_j denote the entry time of the j th pair in a clinical trial with paired design. Let X_{ji}, C_{ji} and Z_{ji} denote respectively the survival time, censoring time and the covariate of the i th member of the j th pair. Here $i = 1, 2$ and $j = 1, 2, \dots$. We note that the entry time Y_j of the j th pair is the calendar time when they were paired for the clinical trial, and the survival time X_{ji} is the interval from time of pairing to time of occurrence of the event in consideration.

Let $H = \{\lambda \mid \lambda : [0, \infty) \rightarrow [a, b] \text{ is a measurable function}\}$ with $0 \leq a < b < \infty$, \mathcal{H} be the σ -field on H generated by the sup-norm, and Λ_j be an H -valued random element.

We assume that $Y_j, X_{j1}, X_{j2}, C_{j1}$ and C_{j2} are random variables such that conditional on $Y_j, \Lambda_j(\cdot) = \lambda(\cdot)$ and $Z_{ji} = z, X_{ji}$ has intensity $\lambda(t)e^{\theta z}$ and $(X_{j1}, X_{j2}), (C_{j1}, C_{j2})$ are independent. Here Λ_j is considered as an unobservable frailty variable, varying from pair to pair, and θ is an unknown parameter of interest representing the treatment effect.

The statistical problem we are interested in is to make inference on θ based on the data $\{Y_j \wedge t, Z_{ji}, (Y_j + X_{ji} \wedge C_{ji}) \wedge t, 1_{[(Y_j + X_{ji}) \wedge t \leq (Y_j + C_{ji}) \wedge t]} \mid i = 1, 2, j = 1, \dots, J, t \leq T\}$, where T is a stopping time.

To make the previous statement more precise, we study the following filtrations closely. Let

$$\bar{\mathcal{F}}_{j,t} = \sigma\{[Y_j \leq s], [Y_j + X_{ji} \leq s], C_{ji}, Z_{ji} \mid 0 \leq s \leq t, i = 1, 2\},$$

which is the filtration with respect to calendar time t .

We will see that this calendar time filtration $\bar{\mathcal{F}}_{j,t}$ is convenient in studying the martingale structures in our statistical problem, although it is a little bigger than the ordinary filtration. The concepts of filtration, stopping time and stochastic integrals used freely in this paper can be found in, for example, Elliott (1982). The following proposition characterizes the corresponding filtration for survival time.

Proposition 2.1. $\bar{\mathcal{F}}_{j,Y_j+t} = \sigma\{Y_j, [X_{ji} \leq s], C_{ji}, Z_{ji} \mid 0 \leq s \leq t, i = 1, 2\}$.

Proof. (i) Since both $Y_j \leq Y_j + t$ are $\bar{\mathcal{F}}_{j,a}$ -stopping times, we know Y_j is $\bar{\mathcal{F}}_{j,Y_j+t}$ -measurable. We now show that $[X_{ji} \leq s]$ belongs to $\bar{\mathcal{F}}_{j,Y_j+t}$. Observe that, for $s \leq t \leq a$

$$[X_{ji} \leq s][Y_j \leq a - t] \subset [Y_j \leq a - t][Y_j + X_{ji} \leq a]. \quad (2.1)$$

Using (2.1) and the fact that every Borel subset of $[Y_j \leq a - t][Y_j + X_{ji} \leq a]$ is in $\bar{\mathcal{F}}_{j,a}$, we know that $[X_{ji} \leq s][Y_j + t \leq a] \in \bar{\mathcal{F}}_{j,a}$. This shows that $[X_{ji} \leq s] \in \bar{\mathcal{F}}_{j,Y_j+t}$. Hence $\bar{\mathcal{F}}_{j,Y_j+t} \supset \sigma\{Y_j, [X_{ji} \leq s], C_{ji}, Z_{ji} \mid 0 \leq s \leq t, i = 1, 2\}$.

(ii) Let $A \in \bar{\mathcal{F}}_{j, Y_j+t}$. We will conclude $A \in \sigma\{Y_j, [X_{ji} \leq s], C_{ji}, Z_{ji} \mid 0 \leq s \leq t, i = 1, 2\}$ by showing that if $X_{ji}(\omega_0) > t$ for some $\omega_0 \in A$, then $\{\omega \mid X_{ji}(\omega) > t, Y_j(\omega) = Y_j(\omega_0)\} \subset A$.

Let $a = Y_j(\omega_0) + t$. Then $\omega_0 \in A[Y_j + t \leq a] \in \bar{\mathcal{F}}_{j, a}$. Note that every Borel subset B in $\bar{\mathcal{F}}_{j, a}$ has the property that the ‘‘half line’’ $[X_{ji} > s, Y_j = a - s]$ is either contained in B or disjoint with B . Because $X_{ji}(\omega_0) > t, Y_j(\omega_0) = a - t$, we know that $[X_{ji} > t, Y_j = Y_j(\omega_0)] \subset A[Y_j + t \leq a] \subset A$. This shows that $\bar{\mathcal{F}}_{j, Y_j+t} \subset \sigma\{Y_j, [X_{ji} \leq s], C_{ji}, Z_{ji} \mid 0 \leq s \leq t, i = 1, 2\}$.

With (i) and (ii), the proof is complete.

It follows from Proposition 2.1 in CH(96), and the above Proposition 2.1 that $\tilde{N}_{ji}(t) \equiv 1_{[X_{ji}, \infty)}(t \wedge C_{ji})$ has intensity

$$\Lambda_j(t) e^{\theta Z_{ji}} 1_{(0, X_{ji} \wedge C_{ji})}(t) \quad (2.2)$$

relative to the filtration $\mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$. To be able to handle (2.2) more effectively, we need to introduce $\mathcal{F}_{j, t} \equiv \mathcal{H} \otimes \bar{\mathcal{F}}_{j, t}$, and establish the following relation.

Proposition 2.2. $\mathcal{F}_{j, Y_j+t} = \mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$.

Proof. We need only show $\mathcal{F}_{j, Y_j+t} \subset \mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$, because the other direction is trivial. The proof for $\mathcal{F}_{j, Y_j+t} \subset \mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$ is also standard. First we argue that if $A = A_1 \times A_2$ with $A_1 \in \mathcal{H}$, $A_2 \in \bar{\mathcal{F}}_{j, \infty}$ and $A \in \mathcal{F}_{j, Y_j+t}$, then $A_2 \in \bar{\mathcal{F}}_{j, Y_j+t}$ and hence $A \in \mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$. This together with the fact that $\mathcal{F}_{j, Y_j+t} \cap \mathcal{H} \otimes \bar{\mathcal{F}}_{j, Y_j+t}$ is a σ -field completes the proof.

It follows from (2.2) and Proposition 2.2 that we have the following basic martingale relative to survival time filtration.

Theorem 2.1. For $i = 1, 2$,

$$\tilde{M}_{ji}(t) \equiv \tilde{N}_{ji}(t) - \int_0^t \Lambda_j(s) e^{\theta Z_{ji}} 1_{(0, X_{ji} \wedge C_{ji})}(s) ds \quad (2.3)$$

is a martingale relative to \mathcal{F}_{j, Y_j+t} .

Let $N_{ji}(t) = \tilde{N}_{ji}((t - Y_j)^+)$, $M_{ji}(t) = \tilde{M}_{ji}((t - Y_j)^+)$. Observe that

$$\begin{aligned} & M_{ji}(t) \\ &= \tilde{N}_{ji}((t - Y_j)^+) - \int_0^{(t - Y_j)^+} \Lambda_j(s) e^{\theta Z_{ji}} 1_{(0, X_{ji} \wedge C_{ji})}(s) ds \\ &= 1_{[X_{ji}, \infty)}((t - Y_j)^+ \wedge C_{ji}) - \int_{Y_j \wedge t}^t \Lambda_j((s - Y_j)^+) e^{\theta Z_{ji}} 1_{(0, X_{ji} \wedge C_{ji})}((s - Y_j)^+) ds \\ &= 1_{[Y_j + X_{ji}, \infty)}(t \wedge (Y_j + C_{ji})) - \int_0^t \Lambda_j(s - Y_j) e^{\theta Z_{ji}} 1_{(Y_j, Y_j + (X_{ji} \wedge C_{ji}))}(s) 1_{(Y_j, \infty)}(s) ds \\ &= 1_{[Y_j + X_{ji}, \infty)}(t \wedge (Y_j + C_{ji})) - \int_0^t \Lambda_j(s - Y_j) e^{\theta Z_{ji}} 1_{(Y_j, Y_j + (X_{ji} \wedge C_{ji}))}(s) ds, \quad (2.4) \end{aligned}$$

where we adopt the convention that $\Lambda_j(s) = 0$ if $s < 0$. With (2.4), we show in the following Theorem 2.2 that even if Λ_j degenerates into a deterministic function, $(N_{j1}(t), N_{j2}(t))$ is a proportional hazards model with time-dependent frailty $\Lambda_j(t - Y_j)$, which depends on the entry time Y_j .

Theorem 2.2 is proved by the standard random time-change technique, appearing in Chang and Hsiung (1994).

Theorem 2.2. $M_{ji}(t)$ is a $\mathcal{F}_{j,t}$ -martingale, for $i = 1, 2$.

Proof. That $M_{ji}(t)$ is adapted to $\mathcal{F}_{j, Y_j + (t - Y_j)^+} \subset \mathcal{F}_{j,t}$ is obvious. Furthermore, for any $\mathcal{F}_{j,t}$ -stopping time T , by Theorem 2.1, $EM_{ji}(T) = E\tilde{M}_{ji}((T - Y_j)^+) = 0$, since $(T - Y_j)^+$ is a $\mathcal{F}_{j, Y_j + t}$ -stopping time. This completes the proof.

Assume that we have i.i.d. random vectors $(\Lambda_j, Y_j, X_{j1}, X_{j2}, C_{j1}, C_{j2}, Z_{j1}, Z_{j2})$ for $j = 1, \dots, J$. Then Theorem 2.2 holds more generally as follows.

Theorem 2.3. $M_{ji}(t)$ is an $\mathcal{F}_t^{(J)}$ -martingale, where $\mathcal{F}_t^{(J)} = \bigotimes_{j=1}^J \mathcal{F}_{j,t}$ is the σ -field generated by $\mathcal{F}_{j,t}$, for $j = 1, \dots, J$.

Theorem 2.3 concludes that the counting process $\{N_{ji}(t) \mid j = 1, \dots, J; i = 1, 2\}$ forms a time-dependent frailty model studied in CH(96).

3. Asymptotics for the Cox Type Estimating Function

Following CH(96), we now introduce the Cox type estimating function

$$G_J(\theta, t) = \sum_{j=1}^J \sum_{i=1}^2 \int_0^t \left(Z_{ji} - \frac{S_j^{(1)}(\theta, s)}{S_j^{(0)}(\theta, s)} \right) dN_{ji}(s), \quad (3.1)$$

where

$$S_j^{(q)}(\theta, s) = \sum_{i=1}^2 \mathbf{1}_{(Y_j, Y_j + (X_{ji} \wedge C_{ji})]}(s) e^{\theta Z_{ji}} Z_{ji}^q,$$

with $q = 0, 1, 2$.

We note that (3.1) produces a martingale structure, which is not present in the usual time-sequential setup. This trick here is that each pair is assumed to have the same entry time and that the comparison is done within each pair.

Let $P^{J(\alpha)}$ denote the probability measure corresponding to the parameter $\theta = \theta_0 + \alpha/\sqrt{J}$. Assuming the boundedness of Z_{ji} , we have the following asymptotics of $G_J(\theta_0, t)/\sqrt{J}$ for J large.

Theorem 3.1. Under $P^{J(\alpha)}$, $G_J(\theta_0, t)/\sqrt{J}$ converges weakly to a Gaussian process $G(t)$ with the property that $G(t) - \alpha g(t)$ is a mean zero martingale with variance $g(t)$, where

$$g(t) = E \left\{ \int_0^t \left(\frac{S_1^{(2)}(\theta_0, s)}{S_1^{(0)}(\theta_0, s)} - \frac{(S_1^{(1)}(\theta_0, s))^2}{(S_1^{(0)}(\theta_0, s))^2} \right) \Lambda_1(s - Y_1) S_1^{(0)}(\theta_0, s) ds \right\}. \quad (3.2)$$

Theorem 3.1 can be proved by using the martingale central limit theorem and mean value theorem or LeCam's third lemma. Because the proof is quite standard now, we will only sketch it with important formulas for later use.

We note that, under $P^{J(\alpha)}$, Theorem 2.3 implies that $G_J(\theta_0 + \alpha/\sqrt{J}, t)/\sqrt{J}$ is a martingale and that $g(t)$ is the weak limit of the predictable variation of the martingale $G_J(\theta_0 + \alpha/\sqrt{J}, t)/\sqrt{J}$. In fact, we have

$$\begin{aligned} & \langle G_J(\theta_0 + \alpha/\sqrt{J}, \cdot) \rangle_t \\ &= \sum_{j=1}^J \sum_{i=1}^2 \int_0^t \left(Z_{ji} - \frac{S_j^{(1)}(\theta_0 + \alpha/\sqrt{J}, s)}{S_j^{(0)}(\theta_0 + \alpha/\sqrt{J}, s)} \right)^2 \Lambda_j(s - Y_j) 1_{(Y_j, Y_j + (X_{ji} \wedge C_{ji})]}(s) \cdot \\ & \quad e^{(\theta_0 + \alpha/\sqrt{J})Z_{ji}} ds \\ &= \sum_{j=1}^J \int_0^t \left(S_j^{(2)}(\theta_0 + \alpha/\sqrt{J}, s) - \frac{(S_j^{(1)}(\theta_0 + \alpha/\sqrt{J}, s))^2}{S_j^{(0)}(\theta_0 + \alpha/\sqrt{J}, s)} \right) \Lambda_j(s - Y_j) ds. \end{aligned} \quad (3.3)$$

Applying the mean-value theorem, we get

$$G_J(\theta_0, t)/\sqrt{J} = G_J(\theta_0 + \alpha/\sqrt{J}, t)/\sqrt{J} + \frac{\partial G_J(\theta_*(t), t)}{\partial \theta} \alpha/J, \quad (3.4)$$

where $\theta_*(t)$ is on the line segment joining θ_0 and $\theta_0 + \alpha/\sqrt{J}$.

Applying the martingale central limit theorem to $G_J(\theta_0 + \alpha/\sqrt{J}, t)/\sqrt{J}$ and using (3.4), we can get the weak convergence of $G_J(\theta_0, t)/\sqrt{J}$ as desired.

Let

$$I_J(\theta_0, t) = - \left. \frac{\partial}{\partial \theta} G_J(\theta, t) \right|_{\theta=\theta_0}. \quad (3.5)$$

Since $I_J(\theta_0, t)/J$ converges to $g(t)$ as J goes to infinity, the following stopping time is well-defined.

Let $\nu_0 < \sup\{g(t) \mid t \in R^+\}$. Define, for $\nu \in [0, \nu_0]$, $\tau_J(\nu) = \inf\{t > 0 \mid I_J(\theta_0, t)/J > \nu\}$. A straight-forward calculation shows that $\tau_J(\nu)$ converges weakly to $g^{-1}(\nu)$ as J goes to infinity. This together with Theorem 3.1 gives the following asymptotics for the random time change version of the estimating function. (cf. Billingsley (1968), p.145.)

Theorem 3.2. *Under $P^{J(\alpha)}$, $G_J(\theta_0, \tau_J(\nu))/\sqrt{J}$ converges weakly to a Gaussian process $W_\alpha(\nu)$ with the property that $W_\alpha(\nu) - \alpha\nu$ is a standard Brownian motion for $\nu \in [0, \nu_0]$.*

4. A Worked Example

In this section, we indicate that the theory developed in Sections 2 and 3 provides a way to propose repeated significance tests for paired survival data

with staggered entry. The significance level and power of the tests can then be calculated by using the theory for tests with curved stopping boundaries as presented in Siegmund (1985). We will illustrate it by examining the data of Freireich et al. (1963) as explained in the introduction.

With the same model assumption and notation introduced in Section 2, we denote by X_{j1} the remission length of the patient in the j th pair receiving 6-MP and X_{j2} that receiving placebo, and set $Z_{j1} = 1, Z_{j2} = 0$.

We are interested in proposing a repeated significance test of the hypothesis $H_0 : \theta = \theta_0 = 0$ versus $H_1 : \theta \neq \theta_0 = 0$, based on the Cox type partial score $G_J(\theta_0, t)$, given in (3.1).

We first rewrite G_J and I_J as follows. It follows from (3.1) and (3.5) respectively that

$$\begin{aligned} G_J(t) &\equiv G_J(\theta_0, t) \\ &= \frac{1}{2} \sum_{j=1}^J \left(1_{\{X_{j1} \leq (t-Y_j) \wedge X_{j2} \wedge C_{j1} \wedge C_{j2}\}} - 1_{\{X_{j2} \leq (t-Y_j) \wedge X_{j1} \wedge C_{j1} \wedge C_{j2}\}} \right) \end{aligned} \quad (4.1)$$

and

$$\begin{aligned} I_J(t) &\equiv I_J(\theta_0, t) \\ &= \frac{1}{4} \sum_{j=1}^J \left(1_{\{X_{j1} \leq (t-Y_j) \wedge X_{j2} \wedge C_{j1} \wedge C_{j2}\}} + 1_{\{X_{j2} \leq (t-Y_j) \wedge X_{j1} \wedge C_{j1} \wedge C_{j2}\}} \right). \end{aligned} \quad (4.2)$$

Let J_0 be a positive integer,

$$t_0 = \inf\{t > 0 \mid I_J(t) \geq J_0/4\} \quad (4.3)$$

and

$$T_J = \inf \left\{ t \geq t_0 \mid |G_J(t)| \geq b\sqrt{I_J(t)} \right\} \quad (4.4)$$

for some $b > 0$.

The repeated significance test that we propose is to stop sampling at $T_J \wedge t_1$ and reject H_0 if and only if $T_J < t_1$. Here

$$t_1 = \inf\{t > 0 \mid I_J(t) \geq J_1/4\}, \quad (4.5)$$

and $J_0 < J_1 \leq J$ are positive integers.

In the following we calculate the significance level and power of the test so as to compare it with the approach of Freireich et al. (1963).

Let

$$T'_J = \inf \left\{ \nu \geq J_0/(4J) \mid |G_J(\tau_J(\nu))/\sqrt{J}| \geq b\sqrt{\nu} \right\} \quad (4.6)$$

and

$$T' = \inf \{ \nu \geq J_0/(4J) \mid |W_\alpha(\nu)| \geq b\sqrt{\nu} \}, \quad (4.7)$$

where W_α is a Brownian motion with drift α .

It follows from (4.4) and Theorem 3.2 that

$$P^{J(\alpha)}[T_J < t_1] = P^{J(\alpha)}[T'_J < J_1/(4J)] \quad (4.8)$$

is approximately

$$P_\alpha[T' < J_1/(4J)], \quad (4.9)$$

where P_α is the probability when T' is defined by W_α in (4.7).

Using Corollary 4.19 and Theorem 4.21 of Siegmund (1985), we get

$$P_0[T' < J_1/(4J)] = (b - b^{-1})\phi(b) \log(J_1/J_0) + 4b^{-1}\phi(b) + o(b^{-1}\phi(b)), \quad (4.10)$$

and

$$\begin{aligned} & P_\alpha[T' < J_1/(4J)] \\ &= 1 - \Phi \left[(J_1/(4J))^{1/2} (b/\sqrt{J_1/(4J)} - \alpha) \right] \\ & \quad + \left\{ \phi \left[(J_1/(4J))^{1/2} (b/\sqrt{J_1/(4J)} - \alpha) \right] / \alpha \sqrt{J_1/(4J)} \right\} (1 + o(1)), \end{aligned} \quad (4.11)$$

where ϕ and Φ are respectively the density and distribution function of a standard normal random variable.

In order to make more meaningful comparison with the test of Freireich et al. (1963), we choose $J = J_1 = 66$, $J_0 = 9$. Now it follows from (4.10) that we choose b to be 2.791 so that the significance level is about 0.05. Using (4.11), we know that the power of the test at $\alpha = 8.936$ is about 0.975. We note that the corresponding $\theta = \alpha/\sqrt{J}$ is about 1.1, which is chosen to compare with the results reported in Freireich et al. (1963).

Since both $G_J(t)$ and $I_J(t)$ are step functions and they change their values only at $Y_j + X_{j1} \wedge X_{j2}$, the time T_J to stop sampling can be expressed in terms of the difference between the number of pairs that have given preferences to 6-MP and the number for placebo. In particular, we do not need the entry times Y_j to perform the test.

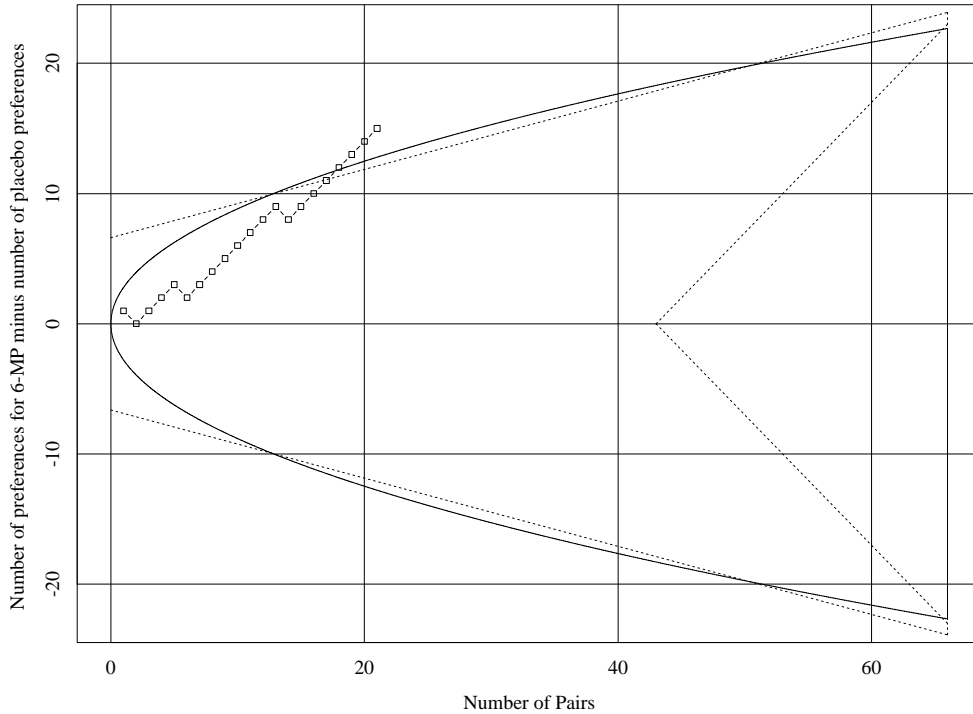


Figure 1.

Figure 1 plots the number of preferences for 6-MP minus the number of placebo preferences against the number of pairs in the order of $Y_j + X_{j1} \wedge X_{j2}$. The corresponding stopping boundary for (4.4) is given by the parabola, $y = \pm 2.791 \cdot \sqrt{x}$.

The sequential test of Freireich et al. (1963) was to stop the experiment when the difference between the number of 6-MP and placebo preferences cross the boundary consisting of the dotted line segments in Figure 1. The corresponding upper and lower line segments are given by the equations $y = \pm(6.62 + 0.2679 \cdot x)$. (cf. Armitage (1957), Table 5.) Let $p = P[X_{j1} > X_{j2}]$ denote the probability of a success for 6-MP. Their test has the property that the significance level is 0.05 for the null hypothesis $p = 1/2$ and power 0.95 at $p = 0.75$.

We note that when the survival times are exponential, then $p = 0.75$ corresponds to $\theta = \log 3$ (cf. Siegmund (1985), p.135), which is about 1.1.

Remarks 1. Comparing the power of our test and the power of the test used by Freireich et al. (1963), we know our method is quite a good alternative. We

note that both tests would stop the experiment when there are 18 preferences available.

2. According to Andersen, Borgan, Gill and Keiding (1993), p.672 and CH(96), p.23, there seems very little association within pairs in the study of Freireich et al. (1963). With this understanding, it would be desirable to ignore the paired design and use the proportional hazards model of Sellke and Siegmund (1983) to propose a repeated significance test. Unfortunately, the published data do not contain times of entry into the study, so we do not compare their method with ours in this example. However, if there is association within pairs, it would be better to use our method in view of the simulation study in Section 5.

3. It is obvious that our method can be generalized to the case when there are more than two treatments.

5. A Simulation Study

The simulation study intends to indicate that in case there is association within pairs, our estimating function G_J performs more satisfactorily than the standard Cox partial score used in Sellke and Siegmund (1983); and in case there is no association, the standard Cox partial score performs better.

The distributions of $\Lambda_j, Y_j, X_{ji}, C_{ji}$ and Z_{ji} for this simulation study are described as follows. $P[\Lambda_j = \lambda_a] = P[\Lambda_j = \lambda_b] = 1/2$, Y_j is uniformly distributed in the interval $[y_a, y_b]$, $C_{ji} = \infty$, $Z_{j1} = 1$, and $Z_{j2} = 0$. Conditional on $\Lambda_j = \lambda$, X_{j1} has intensity λe^θ , X_{j2} has intensity λ . We generate data with different values of $\lambda_a, \lambda_b, y_a, y_b, \exp(\theta)$. The simulation results presented in the following are based on 1000 replicates of the data.

Let

$$G_J^{(c)}(\theta_0, t) = \sum_{j=1}^J \sum_{i=1}^2 \int_0^t \left(Z_{ji} - \frac{\sum_{j=1}^J \sum_{i=1}^2 1_{(Y_j, Y_j + X_{ji} \wedge C_{ji})}(s) e^{\theta_0 Z_{ji}} Z_{ji}}{\sum_{j=1}^J \sum_{i=1}^2 1_{(Y_j, Y_j + X_{ji} \wedge C_{ji})}(s) e^{\theta_0 Z_{ji}}} \right) dN_{ji}(s)$$

and

$$I_J^{(c)}(\theta_0, t) = - \left. \frac{\partial}{\partial \theta} G_J^{(c)}(\theta, t) \right|_{\theta=\theta_0}$$

be respectively the standard Cox partial score and information.

For positive numbers m_0 and d , we can define a repeated significance test of $H_0 : \theta = \theta_0 = 0$ against $H_1 : \theta \neq \theta_0$ by means of the stopping rule based on $G_J^{(c)}$,

$$T^{(c)} \equiv \inf \left\{ t \mid I_J^{(c)}(\theta_0, t) \geq m_0, |G_J^{(c)}(\theta_0, t)| \geq d \sqrt{I_J^{(c)}(\theta_0, t)} \right\},$$

truncated as soon as $I_J^{(c)}(\theta_0, t) \geq m$ for some $m > m_0$. The test rejects H_0 if $T^{(c)} < t_1^{(c)}$, where $t_1^{(c)} = \inf\{t | I_J^{(c)}(0, t) \geq m\}$ is the truncation time. Similarly,

Table 1. Comparison of \tilde{F}_θ and \tilde{C}_θ under null hypothesis $\exp(\theta) = 1$ and under alternative $\exp(\theta) = 2$ for different values of $y_a, y_b, \lambda_a, \lambda_b$ and m_0 .

y_a	y_b	λ_a	λ_b	m_0	d	$\exp(\theta) = 1$			$\exp(\theta) = 2$		
						α	\tilde{C}_θ	\tilde{F}_θ	β	\tilde{C}_θ	\tilde{F}_θ
0	0	1	1	3	2.843	0.05	0.044	0.041	0.896	0.881	0.865
0	0	1	1	10	2.631	0.05	0.049	0.045	0.931	0.912	0.908
0	0	1	5	3	2.843	0.05	0.025	0.043	0.896	0.791	0.882
0	0	1	5	10	2.631	0.05	0.032	0.052	0.931	0.856	0.907
0	0	1	7	3	2.843	0.05	0.022	0.040	0.896	0.750	0.870
0	0	1	7	10	2.631	0.05	0.025	0.044	0.931	0.817	0.914
0	3/4	1	1	3	2.843	0.05	0.044	0.038	0.896	0.889	0.867
0	3/4	1	1	10	2.631	0.05	0.051	0.039	0.931	0.925	0.899
0	3/4	1	5	3	2.843	0.05	0.014	0.041	0.896	0.693	0.875
0	3/4	1	5	10	2.631	0.05	0.019	0.051	0.931	0.774	0.922
0	3/4	1	7	3	2.843	0.05	0.009	0.036	0.896	0.565	0.867
0	3/4	1	7	10	2.631	0.05	0.004	0.038	0.931	0.648	0.913

another repeated significance test based on G_J can be defined by letting

$$T \equiv \inf \left\{ t \mid I_J(\theta_0, t) \geq m_0, |G_J(\theta_0, t)| \geq d\sqrt{I_J(\theta_0, t)} \right\},$$

truncated as soon as $I_J(\theta_0, t) \geq m$, and the test rejects H_0 if $T < t_1$, where $t_1 = \inf\{t | I_J(0, t) \geq m\}$.

Let $F_\theta = P^{(\theta)}[T < t_1]$ and $C_\theta = P^{(\theta)}[T^{(c)} < t_1^{(c)}]$ be respectively the power functions of T and $T^{(c)}$, where $P^{(\theta)}$ is the probability corresponding to the parameter θ .

We present approximated values of F_θ , denoted by \tilde{F}_θ , by calculating the percentage of the 1000 replicates for which $T < t_1$. A similar calculation is also done for C_θ , and denoted by \tilde{C}_θ . We take the sample size $J = 120$, and $m = 30$. In Table 1, \tilde{C}_θ and \tilde{F}_θ are presented for different values of $y_a, y_b, \lambda_a, \lambda_b$ and m_0 under both null hypothesis $\exp(\theta) = 1$ and alternative $\exp(\theta) = 2$.

Let $T' = \inf\{t | t \geq m_0, |W_\mu(t)| \geq d\sqrt{t}\}$, where W_μ is a Brownian motion with drift μ . Then from Corollary 4.19 and Theorem 4.21 of Siegmund (1985),

$$P_0[T' < m] = (d - d^{-1})\phi(d) \log(m/m_0) + 4d^{-1}\phi(d) + o(d^{-1}\phi(d)), \quad (5.1)$$

$$P_\mu[T' < m] = 1 - \Phi[m^{1/2}(dm^{-1/2} - \mu)] + \{\phi[m^{1/2}(dm^{-1/2} - \mu)] / (\mu m^{1/2})\}(1 + o(1)), \quad (5.2)$$

where P_μ is the probability corresponding to W_μ . The nominal significance level α in Table 1 is set to be 0.05 and for different values of m_0 , d is obtained

accordingly by using (5.1). For each d , the corresponding “approximate” power β at the alternative $\mu = \theta\sqrt{120}$ with $\exp(\theta) = 2$ is obtained by using (5.2).

The simulation results indicate that when $\lambda_a = \lambda_b$, which is the case when there is no frailty, $G_J^{(c)}$ performs a little better because of bigger power; and when there is frailty effect, i.e., $\lambda_a \neq \lambda_b$, the significance levels \tilde{C}_θ of the test based on $G_J^{(c)}$ are not as close to 0.05 as those \tilde{F}_θ for the test based on G_J , and the powers \tilde{C}_θ of $G_J^{(c)}$ are farther from β than those \tilde{F}_θ of G_J .

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