A Partial Score Test for Di®erence among Heteroscedastic Populations

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Summary

Comparison between distributions are made by logrank test in the literature of event time data analysis. When the data appear to have hazards cross phenomenon, nonparametric weighted logrank statistics have usually been suggested to accommodate di®erent stage of cross to increase power. In this paper, however, we propose a score-type statistic based on a semiparametric-, heteroscedastic-hazards regression model. Under this model, hazards cross is modeled explicitly via a power element of the baseline cumulative hazard, in view of the ordinary Cox's model. Our score test is obtained from the partial likelihood based on the model considered. Simulation results show the superiority of the proposed score test over a class of weighted log-rank tests. Application of this test is demonstrated by analyses of actual data in clinical trials.

Key Words: heteroscedasticity; crossing hazards; proportional hazards; weighted logrank test.

1 Introduction

When one is dealing with event time data in comparative trials, the proportional hazards (PH) model (Cox, 1972) is usually used to estimate the relative e®ect of a new treatment, adjusted for prognostic factors. It often happens, however, that nonproportionality is present and using PH model leads to a biased e®ect-measure estimate. In this situation, the log-rank test for equality between distributions may have very poor power against the crossing hazards alternatives (Andersen et al., 1993, page 390). For the latter point, weighted log-rank test can be used to implement the power (Prentice and Marek ,1979; Gill ,1980; Moreau et al., 1992). In particular, a class of weighted log-rank statistics, termed as the $G^{½;°}$-class, was presented in Fleming and Harrington (1991, Chapter 7), where early, middle, or late di®erence among groups can be stressed by imposing di®erent ½-° con¯gurations. Under the nonproportional hazards situation, nevertheless, the nonparametric weighted log-rank test sometimes still fails to detect di®erence between treatments. Therefore, seeking a model to explicitly account for the nonproportional hazards (or crossing hazards) phenomenon is the forthcoming e®ort. Heuristically if a model, parametric or semiparametric, do explain the data well enough, statistical tests constructed from a likelihood derived on the basis of that model will generally outperform the nonparametric ones. Well known competing choice other than the PH analysis includes the accelerated failure time model (Wei and Gail,...), the additive hazards model (Aalen, 1977; Lin and Ying, 1994), and the accelerated hazards model (Chen and Wang, 2000), among others. In this paper, a heteroscedastic hazards model considered by Quantin et al. (1996) and Hsieh (2000) is adopted to model the nonproportionality. If this model does ¯t well to the data observed, statistical power will be improved substantially based on the model setting.

In the next section, we give some description about the HH model. Parametric and semiparametric set-up satisfying the model formulation, including considerations on covariates, is discussed. In addition, estimation procedure borrowed from 'partial likelihood' is also introduced. Section 3 gives our score test. Simulation studies of the performance of the proposed test are reported in section 4. Finally, actual data collected in some clinical trials will also be analyzed, demonstrating the applicability of the HH model, its fitness, and the realization of the partial score test.

2 Estimation of The Model

2.1 Model formulation

In view of the fact that the PH model can be derived as a special case of transformation model with homoscedastic error distributions (Dabrowska, 1988; Cheng, 1995), a contrasting, heteroscedastic version was considered in Hsieh (1995, 1996) for a two-sample case:

$$\Lambda_1(t) = \{\Lambda_0(t)\}^{\sigma}\mu; \tag{1}$$

where $\Lambda(\cdot)$ stands for a cumulative hazard. Extending (1) to regression set-up can be found in Quantin et al. (1996), which constructed a score-type statistic for checking the proportional hazards assumption; and in Hsieh (2000), which offered concrete estimation procedures. This generalisation,

$$\Lambda(t; Z; X) = \{\Lambda_0(t)\}^{\exp(\gamma' X)} \exp\{\beta' Z\}; \tag{2}$$

referred to as a heteroscedastic hazards (HH) regression model in the sequal, considers natural extension of model (1) with $\mu = \exp(\beta' Z)$ and $\sigma = \exp(\gamma' X)$, where covariates Z and X are two set of time-dependent vectors and they can share common component. Heuristics of applying the HH model to give a more powerful test for comparing treatments rely on model adequacy. In this stage, we only suggest the data analyzer to put trust in visual fitness, which will be illustrated by an example of actual data in Section 5.

Parametric set-up

Since the Weibull class with the fixed shape parameter, Weibull$(t; \alpha_j; \eta)$, satisfies the proportional hazards formulation, a question arises when the shape is different individually. That is, one can consider the class Weibull$(t; \alpha_j; \eta_j)$. In two-sample case, $j = 0; 1$, Hsieh (1996) demonstrated that formula (1) is satisfied with

$$\sigma = \eta_1 / \eta_0; \nu = \{\alpha_1 / \alpha_0\}^{\eta_1}:$$

To extend to regression set-up, one can model the parameters as $\alpha_j = \exp(\beta' z_j)$ and $\eta_j = \exp(\phi' x_j)$. Semiparametric set-up

Recently, the linear transformation model have attracted much attention, since it attempts to give a very general framework on survival data analysis (Cheng et al. (1995); Wei and Cheng (1999?)). Consider the following model:

$$h(T) = -\beta' z + \epsilon: \quad (3)$$

Different specification of function $h(\cdot)$ and the distribution of ϵ, F_ϵ, makes (3) to be the proportional hazards model or the proportional odds model (Cheng et al. (1995); Wei and Cheng (1999?)). Contrastingly, if the error is subject to heteroscedasticity, (3) can be written as

$$h(T) = -\beta' z + \sigma \epsilon: \quad (4)$$

Specifically, (4) can further be expressed as

$$g\{S_z(T)\} = -\beta' z + \sigma g^* \{S_0(T)\};$$

according to different choice of link functions g and g^*. If g^* is totally unspecified, it reduces to (3). If g^* and g are both specified as logit or complementary log-log link when $\sigma = 1$, it corresponds to the proportional hazards model or proportional odds model, respectively. On the other hand, when σ is not specified as 1, the above specification on the link functions g and g^* gives the heteroscedastic hazards model (Quantin et al., 1996; Hsieh, 2000) and the generalized odds model (Hsieh, 1995).

2.2 On the covariates and heteroscedasticity

In model (2), there are two components expressed as linear combinations of two set of risk factors and/or covariates. The first part, Z, appears at the same place as the ordinary Cox's model, $\exp\{\beta' z\}$; the second part, $\exp\{\gamma' x\}$, appears as the power of the baseline cumulative hazard. Generally, vector X determines the 'shapes' of cumulative hazards, referred to as the heteroscedasticity component in this paper. In the experience of analyses of actual data, it is recognized that if the heteroscedasticity is not accounted for, the estimates of effect measures associated with z are biased. This is similar to the arguments given in Gail et al. (1984) which dealt with the case of omitting an important explanatory variable in nonlinear regression. Analytical computation mimicing those of Gail et al. can be easily accomplished via Tsiatis's (1981) work. The vector X, however, may share common components with Z, and those common part is the mechanism which results in location shift as well as shape difference among groups. A simple and extreme example is that when $Z = X = 1; 0$, corrresponding to two heteroscedastic populations such that the two groups have crossing hazards, the heteroscedasticity resulted from the treatment (coded as $Z = X = 1$) itself.

2.3 The partial score equations and computational algorithm

With the usual counting process notations and terminology, let $N_i(t)$ be the counting process of individual i associated with intensity $\lambda_i = \lambda_0(t)\exp\{\beta Z_i\}\sigma_i\{\Lambda_0(t)\}^{\sigma_i - 1}$. Further denotes

$$S_K(t) = (1/n)\sum Y_i(t)J_i(t)\exp\{\beta Z_i\}\sigma_i\{\Lambda_0(t)\}^{\sigma_i - 1};$$

for any predictable process $J(t)$, and $\sigma_i = \exp\{\phi X_i\}$. According to (2), the full likelihood, L_F is

$$L_F(\theta; \Lambda_0) = \prod \int_0^\tau \lambda_i(u) dN_i(u) \exp\{-\int_0^\tau \lambda_i(u) du\}.$$

With Johansen's (1983) decomposition of the full likelihood, we have the following $\sqrt{n}$-scaled partial log-likelihood:

$$l_p = (1/\sqrt{n}) \sum \log\{\int_0^\tau \frac{\lambda_i(u) dN_i(u)}{S_1(u)}\}.$$

Taking partial derivatives of l_p with respect to β and ϕ gives the following estimating functions:

$$E_\beta = (1/\sqrt{n}) \sum \int_0^t \{Z_i - \frac{S_Z(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\} dN_i(u); \tag{5}$$

$$E_\phi = (1/\sqrt{n}) \sum \int_0^t \{V_i - \frac{S_V(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\} dN_i(u); \tag{6}$$

where $V_i(t) = X_i(t)[1 + \exp(\phi' X_i) \log\{\Lambda_0(t)\}]$. In addition, there is the baseline Λ_0 needs to be estimated. The Breslow-type estimator of Λ_0 solving the following equation can be considered:

$$\Lambda_0(t) = \sum \int_0^t [\sum Y_i(u) \exp\{\beta Z_i\} \sigma_i \{\Lambda_0(u)\}^{\sigma_i - 1}]^{-1} dN_i(u). \tag{7}$$

Instead of solving (7) directly, however, we consider a finite-dimensional approximation of $\Lambda_0(t)$:

$$\Lambda_{0m}(t) = \int_0^t \sum_1^m \alpha_i 1\{\tau_{i-1} < u \le \tau_i\} du; \tag{8}$$

where τ_j's are appropriate points and m, a smoothing factor, is the dimension of Λ_{0m} chosen to approximate the function Λ_0. An algorithm used to compute the parameters β, ϕ and $\{\alpha_i\}$ is as follows:

$$\Lambda_{0m}^{(j)}(t) = \sum \int_0^t [\sum Y_i(u) \exp\{\beta^{(j-1)} Z_i\} \sigma_i^{(j-1)} \{\Lambda_{0m}^{(j-1)}(u)\}^{\sigma_i^{(j-1)} - 1}]^{-1} dN_i(u); \tag{9}$$

where $\Lambda_{0m}^{(j)}(t)$, $\beta^{(j)}$, and $\sigma^{(j)} = \exp\{\phi^{(j)} X\}$, are the estimated values solved from the j-th iteration, $j = 0, 1, 2, 3, \ldots$. Initial guess of β and Λ_0 (i.e. $\beta^{(0)}$ and $\Lambda_{0m}^{(0)}$) can be obtained from the estimates of ordinary Cox's model. Furthermore, $\gamma^{(0)} = 0$.

3 Proposed Test

Model (2) is a nonproportional hazards model, under which the hazards according to heteroscedastic populations cross at some point(s). In this paper, goodfitness of this model in suggested to be checked only via visual diagnostics. If the visual fitness is thought to be good enough, we expect that for detection of difference among heteroscedastic populations, a test constructed on the basis of this model can be a more powerful one compared with those without model assumption. The remaining issue is the fitness of the model used.

Here, we treat E_β and E_ϕ as the true score functions. With regards to the present heteroscedastic model (2), a score-type test statistic can be written as

$$\omega = \{E_\beta; E_\phi\} I^{-1} \{E_\beta; E_\phi\}';$$

evaluated at $(\beta; \phi) = (0; 0)$. The information matrix, I, is defined as:

$$I = \begin{pmatrix} I_{\beta\beta} & I_{\beta\phi} \\ I_{\phi\beta} & I_{\phi\phi} \end{pmatrix};$$

where

$$I_{\beta\beta} = (1/n) \sum \int_0^t \{Z_i - \frac{S_Z(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\}^{\otimes 2} dN_i(u);$$

$$I_{\phi\phi} = (1/n) \sum \int_0^t \{V_i - \frac{S_V(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\}^{\otimes 2} dN_i(u);$$

and

$$I_{\beta\phi} = I_{\phi\beta} = (1/n) \sum \int_0^t \{Z_i - \frac{S_Z(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\}\{V_i - \frac{S_V(u; \Lambda_0; \theta)}{S_1(u; \Lambda_0; \theta)}\} dN_i(u):$$

The symbol $A^{\otimes 2}$ means the product of column vector A and its transpose A^T. Asymptotically, ω is distributed as χ^2_{p+q}, where p and q are the dimensions of Z and X, respectively. In the special case of two-sample problem, $Z = X = 0$ or 1, ω is distributed as χ^2_2 under null hypothesis. We are interested in comparing the performance of ω to the class of weighted log-rank test (Fleming and Harrington, 1991, Chapter 7):

$$\int K(s) \frac{Y_1(s) Y_2(s)}{Y_1(s) + Y_2(s)} \frac{d(\sum N_i(u))}{\sum Y_{1i}(s) + \sum Y_{2i}(s)};$$

equipped with an appropriate predictable weight process $K(t)$. Especially, we consider the weight function to be a member of the Fleming-Harrington's $G^{\rho,\gamma}$-class, which put variant emphases on the difference of early-, middle-, and late-stage between the two groups according to $(\rho,\gamma) = (1,0), (1,1)$, and $(0,1)$. The corresponding statistic is termed as the $G^{\rho,\gamma}$-statistic. When $(\rho,\gamma) = (0,0)$, the $G^{0,0}$-statistic corresponds to the ordinary log-rank statistic. Note also that, under null, the $G^{\rho,\gamma}$-statistics are distributed as χ^2_1. Power comparisons are made via simulation studies reported in the next section.

4 Simulations

Let T_z be the failure time random variable distributed as F=Weibull(a,b) with $a = \exp(\beta' z)$ and $b = \exp(\phi' z)$. To make comparison between the ω-statistic and the weighted log-rank $G^{\rho,\gamma}$-statistic in two-sample setting, we choose there to be half of the sample according to $z = 0, 1$, respectively. In any condition, the baseline group ($z = 0$) is chosen to be distributed as Weibull(1,1) (or exponential(1)), and the other group is distributed as Weibull$(\exp(\beta), \exp(\phi))$. Consider the situations when the cumulative hazards, and thus the survival functions, of these two groups cross at some point t_c such that $\mathrm{Prob}(T_0 \geq t_c) = \mathrm{Prob}(T_1 \geq t_c) = r, 0 < r < 1$. When r takes value close to 1 or 0, this means the cumulative hazards cross at early- or late-stage of observations, respectively. In our simulations, the parameter configurations of β and ϕ are: β = 0, log2, $-$log2 versus ϕ = 0, log2, $-$log2. Sample size is 100 for each study with 1000 replications. Censoring mechanism C_z is chosen to make 25% failures (right) censored in the following way: Let C_z be distributed as G=Weibull(a^*, b); that is, the shape parameter b is chosen to be the same for both T_z and C_z to simplified the situation. It is easily computed from $\int G(u)dF(u) = 0.25$ that $a^* = a/3$. Nonetheless, the results may depend on the distribution of C_z.

To check the behaviour of ω and the weighted log-rank statistics under H_0, Table 1 gives the empirical rejection probabilities ($\hat{p}$) according to the true $p = 0.01, 0.05, 0.1, 0.9, 0.95, 0.99$. Table 1 shows that, under H_0, the empirical distributions of ω and the $G^{\rho,\gamma}$ weighted log-rank statistics have satisfactory tail behaviour in both the 0%- and 25%- censored cases. Under H_a, rejection proportions in 1000 replications are tabulated in Table 2.

[Put Table 1 and Table 2 about here.]

From Table 2, it is as expected that the ordinary log-rank test has the best performance in power when $\phi = 0$. However, even in this case, the partial score test ω still is comparable with others. For early crossing, the preformance of $G^{1,0}$-test, which put much weight on early stage observations, has lower power than other tests; similarly, for late crossing, the performance of $G^{0,1}$-test is very poor. The performance of $G^{1,1}$ cannot be summarized in a few words, depends on the data and the stochastic distributions of T and C. Generally, the power of ω is superior to most of the weighted log-rank class considered, revealing benefit of considering the present semiparametric modeling.

5 Actual Data Analysis

In this section, the data quoted in Piantadosi (1997, Chapter 12) concerning the survival times of lung cancer patients and those analyzed in Stablin (1981) and Hsieh (2000) concerning a set of gastric carcinoma patients, are used to illustrate the application of model (2) and the corresponding ω-statistic, compared with the performance of the weighted log-rank $G^{\rho,\gamma}$-class. For both data sets, the event time is defined to be the 'survival' time of cancer patients. Refers to Piantadosi (1997), chapter 12, and Stablin (1981) and Hsieh (2000) for more information.

It is crucial that model (2) is appropriate in order that ω-statistic can be applied to test for difference. In the case of proportional hazards, checking model adequacy can be accomplished by omnibus tests, includes those of Schoenfeld (1980), Wei(1984), Gill and Schumacher (1987), and Lin (1991). Regarding the HH model (2), a chi-square goodness-of-fit test is suggested in Hsieh (2000) for a similar purpose, based on an over-identified estimating equation (OEE) approach. As mentioned in the previous context, however, we suggest the data practitioners to diagnose the fitness of model (2) by simply plotting the fitted survivor curves of different groups ($\hat{S}_{HH}$) according to distinct covariate values, and to compare them with the associated Kaplan-Meier estimates ($\hat{S}_{KM}$). (See Fig. 1 for the lung cancer data and refer to Hsieh (2000) for the gastric cancer data.) The rationale lies in that when the model is adequate and consistent estimators $\hat{\beta}$, $\hat{\gamma}$, and $\hat{\Lambda}_0$ had been solved from Sec. 2, the plotted survivals based on the semiparametric model,

$$\hat{S}_{HH}(t; x; z) = \exp\{-[\hat{\Lambda}_0(t)]^{\exp(\hat{\gamma}' x)} \exp(\hat{\beta}' z)\}; \qquad (10)$$

must be close to the nonparametric Kaplan-Meier (KM) estimates for all $x - z$ configurations. On the other hand, estimated survivals based on the ordinary Cox's PH model are also plotted and compared with the KM estimates (Fig. 2). We observe that $\hat{S}_{HH}$ fits better than $\hat{S}_{PH}$ does. Furthermore, in most of the place, the fitness of $\hat{S}_{HH}$ is fine, except for the early stage (before 8 months) of group A. In this situation, ω-statistic is applicable.

Table 3 gives the results of analyzing lung cancer data (Piantadosi, 1997) and gastric carcinoma data (????) for illustration of ω- and $G^{\rho;\gamma}$- statistics. For lung cancer data, we see from the analysis that the Kaplan-Meier estimate of survivor functions according to the two different treatments cross around 33 months, near the terminal of this study. So it is expected that $G^{0;1}$ is unable to detect the difference (p-value=0.994). In addition, $G^{1;1}$ still is poor for the goal (p-value=0.555). For the gastric carcinoma data, the situation is a little different. Kaplan-Meier estimates cross between the second and third month (????; Hsieh, 2000), which is around the late-middle stage. The p-values of $G^{0;1}$ and $G^{0;1}$ are 0.150 and 0.902, respectively. For both data, $G^{1;0}$ performs well for detecting the difference (p-value=0.074, 0.047), whereas they are still a little more poor than the !-statistic does (p-value=0.050, 0.019). These results show the superiority of modeling the nonproportionality to choosing di®erent weights in a nonparametric class.

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Table 1:

		$G^{0;0}$	$G^{1;0}$	$G^{1;1}$	$G^{0;1}$	!
0% censored	p					
	0.005	0.003	0.002	0.007	0.001	0.006
	0.025	0.020	0.021	0.026	0.016	0.022
	0.050	0.042	0.047	0.058	0.041	0.052
	0.950	0.937	0.942	0.934	0.923	0.939
	0.975	0.963	0.975	0.966	0.956	0.969
	0.995	0.995	0.997	0.993	0.991	0.993
25% censored	p					
	0.005	0.009	0.006	0.004	0.004	0.004
	0.025	0.024	0.027	0.018	0.022	0.022
	0.050	0.044	0.044	0.037	0.045	0.042
	0.950	0.941	0.950	0.943	0.945	0.946
	0.975	0.970	0.970	0.973	0.969	0.974
	0.995	0.995	0.993	0.996	0.992	0.996

Table 2:

¯	0			log(2)			¡ log(2)		
°	0	log(2)	¡ log(2)	0	log(2)	¡ log(2)	0	log(2)	¡ log(2)
s	£	0.368	0.368	£	0.607	0.018	£	0.135	0.779
0% censored									
G½;°									
(0,0)	0.063	0.139	0.122	0.935	0.803	0.915	0.918	0.207	0.994
(1,0)	0.058	0.134	0.142	0.845	0.215	0.998	0.848	0.776	0.799
(1,1)	0.066	0.334	0.308	0.878	0.931	0.783	0.855	0.117	0.998
(0,1)	0.077	0.781	0.787	0.854	0.998	0.276	0.837	0.175	1.000
!	0.061	0.975	0.969	0.873	0.999	1.000	0.870	0.969	1.000
25% censored									
(0,0)	0.043	0.051	0.034	0.829	0.416	0.964	0.824	0.393	0.895
(1,0)	0.043	0.212	0.190	0.750	0.096	0.998	0.764	0.823	0.548
(1,1)	0.059	0.175	0.173	0.769	0.759	0.802	0.759	0.147	0.982
(0,1)	0.064	0.422	0.456	0.716	0.905	0.424	0.704	0.066	0.992
!	0.047	0.886	0.887	0.756	0.947	0.999	0.736	0.950	0.992

Table 3:

Statistic:	$G^{0;0}$	$G^{1;0}$	$G^{1;1}$	$G^{0;1}$	!
Lung Cancer Data					
Estimate	1.2745	3.1774	0.3489	0.0001	5.9977
(P-value)	(0.2589)	(0.0747)	(0.5547)	(0.9940)	(0.0498)
Gastric Carcinoma Data					
Estimate	0.2218	3.9630	0.0153	2.0711	7.9408
(P-value)	(0.6376)	(0.0465)	(0.9017)	(0.1501)	(0.0189)