Testing the Differences of Mean Life Spans under Dependent Competing Risks

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1. Introduction

In the analysis of experimental data for competing risks, we often encounter the cases where their competing risks are correlated. We consider theoretical life spans Y_1 and Y_2 of an individual failing from competing risks C_1 and C_2 following with a Marshall-Olkin type bivariate Weibull distribution with parameter θ. Under some assumptions, we derive the asymptotic distributions of a maximum likelihood estimator (MLE) of θ (see Moeschberger) and test statistics. Based on them, we construct a test procedure for the differences of mean life spans between a treatment group and a control group, together with testing the dependence between the life spans. Testing procedures obtained here are applied to an analysis of survival data concerning specific types of tumors of female mice caused by X-ray irradiation (treatment group) and not by that (control group). Further we compare this result with that of Sato et al. (1990) yielded under the assumption that competing risks are independent.

2. Setting the model and the assumptions for the asymptotic theory

Assume that Y_i's follow the bivariate Weibull distribution of which survival function with a parameter vector $\theta = (\lambda_1, c_1, \lambda_2, c_2, \lambda_{12})$ is
$\bar{F}_{Y_1,Y_2}(y_1, y_2) = \exp\{-\lambda_1 y_1^{c_1} - \lambda_2 y_2^{c_2} - \lambda_{12}\max(y_1^{c_1}, y_2^{c_2})\}$, m_i individuals die from C_i with $m = m_1 + m_2$ and r individuals survive with $r = n - m$. Let R be a random variable taking value r and $p_j = P(Y_1 > \beta_j, Y_2 > \beta_j)$, where β_j denotes a censoring time of the j th individual. We here set the following assumptions:

For each number α and for $i = 1, 2; \lambda \neq i; c_i > c_\lambda;\ j = 1, 2, \ldots, n$, there exist constants to which

$$\frac{1}{n}E(R|c_i > c_\lambda),\quad \frac{1}{n}\sum_j \beta_j^{\alpha},\quad \frac{1}{n}\sum_j (\log \beta_j)\beta_j^{\alpha},\quad \frac{1}{n}\sum_j p_j \beta_j^{\alpha},\quad \sum_j p_j (\log \beta_j)\beta_j^{\alpha}$$ converge as n

tends to infinity, respectively. By these assumptions we have the following asymptotic theory for the test statistics.

3. Testing the hypotheses by the statistics obtained with asymptotic optimal properties

We set a hypothesis for the differences of mean life spans between a treatment group and a control group for i and k such that $c_i > c_\lambda$,

$$H_0 : \underline{\mu}_0^{(i)} - \underline{\mu}_1^{(i)} = \underline{0} \quad \text{against} \quad H_1 : \underline{\mu}_0^{(i)} - \underline{\mu}_1^{(i)} \neq \underline{0} \quad .$$

To test this hypotheses, we obtain a Wald type statistic having a limit distribution such that

$$W^{(i)} = (\hat{\underline{\mu}}_0^{(i)} - \hat{\underline{\mu}}_1^{(i)})^t [Q(\hat{\underline{\theta}}_0^{(i)}, \hat{\underline{\theta}}_1^{(i)})]^{-1} (\hat{\underline{\mu}}_0^{(i)} - \hat{\underline{\mu}}_1^{(i)})$$

$$\sim \chi_2^2((\underline{\mu}_0 - \underline{\mu}_1)^t [Q(\underline{\theta}_0, \underline{\theta})]^{-1} (\underline{\mu}_0 - \underline{\mu}_1)) \quad (n_0 \to \infty, n \to \infty),$$

where $\hat{\underline{\mu}} = (\hat{\mu}_1, \hat{\mu}_2)^t$, $\hat{\underline{\theta}} = (\hat{\lambda}_1, \hat{c}_1, \hat{\lambda}_2, \hat{c}_2, \hat{\lambda}_{12})$, $I(\hat{\underline{\theta}}) = \frac{1}{n}E\left[\nabla_{\underline{\theta}} \log L_n(\underline{\theta})\{\nabla_{\underline{\theta}} \log L_n(\underline{\theta})\}^t\right]_{\underline{\theta}=\hat{\underline{\theta}}}$,

$$\underset{5\times 2}{D}(\hat{\underline{\theta}}) = \left(\frac{\partial \underline{\mu}}{\partial \underline{\theta}}\right)_{\underline{\theta}=\hat{\underline{\theta}}},\ Q(\hat{\underline{\theta}}_0, \hat{\underline{\theta}}) = \frac{1}{n_0} D(\hat{\underline{\theta}}_0)^t I(\hat{\underline{\theta}}_0)^{-1} D(\hat{\underline{\theta}}_0) + \frac{1}{n} D(\hat{\underline{\theta}})^t I(\hat{\underline{\theta}})^{-1} D(\hat{\underline{\theta}}),$$ and $\log L_n(\underline{\theta})$

is given by Moeschberger(1974). This property leads to a critical region of H_0 against H_1.

Further we consider a problem of testing the dependence between the life spans:

$$H_0 : \lambda_{12} = 0 \quad \text{against} \quad H_1 : \lambda_{12} > 0.$$

Under H_0 with $c_i > c_\lambda$, both a likelihood ratio statistic $\lambda_n^{(i)} = -2\log \dfrac{\sup L_n(\underline{\theta}|H_0)}{\sup L_n(\underline{\theta})}$ and a Wald

type test statistic $W_n^{(i)} = n\,\hat{\lambda}_{12}^{(i)}\left[(0,0,0,0,1)\{I(\hat{\underline{\theta}}^{(i)})\}^{-1}(0,0,0,0,1)\right]^{-1} \hat{\lambda}_{12}^{(i)} \xrightarrow{d} \chi_1^2(0) \quad (n \to \infty)$.

REFERENCES

Moeschberger, M. L. (1974). Life Tests under Dependent Competing Causes of Failure, Technometrics, 16, 1, 39-47.

Sato, F. et al. (1990). An analysis of experimental radiation carcinogenesis with model setting for competing risks, J. of Radiat. Res., 31, 147-155.

RÉSUMÉ

En cas d'il y a une corrélation entre des causes de la mort dans un problème d'analyse survivante, nous considérons des propriétés asymptotiques d'EMV des paramètres de la distribution Weibull bivariée, ensuite établissons un test pour la différance des longévités moyennes entre le groupe du traitement et celui de contrôle, un test d' hypothèse nulle sur la dépendence entre des causes. Les procédures obtenues ici sont appliquées à une analyse des données expérimentales concernant des souris irradiées par les rayons X.