A Discrete Time Sequential Process for Analyzing Censored Exponentially Distributed Survival Data

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Abstract A sequential testing procedure for comparing exponentially distributed binary responses is considered. The data are monitored according to a discrete time process of reviewing the situation using the likelihood ratio as a test statistic. Monte Carlo simulation is used to model and estimate the power of the process, that is the probability of finding a significant difference if it exists between the hazard rates characterizing the survival distributions to be compared. The power is expressed as a function of the sample size, the level of type I error risk and the hazard rates, provided that a maximum duration of the study has been stated. The better understanding of the relative incidence of the previous parameters on the power of the process may be helpful in designing a proper experimental design for a wide range of risk assessment studies (e.g. environmental health studies, clinical trials). Particular attention is paid to the gain of efficiency resulting from the sequential approach.

1. INTRODUCTION

The statistical methods which are used in a great variety of biomedical or environmental health investigations are often dealing with survival data analysis since the principle interest during follow-up concerns the occurrence or non-occurrence of a particular event (e.g. death, local recurrence or any other clinical observation). Several non-parametric and parametric approaches are available to plan, and ultimately analyze the results of comparative studies or trials aiming at comparing several survival distributions with respect to longevity [Bernstein and Lagakos,1978; Gehan, 1961; Freedman, 1982; George and Desu, 1974; Peto et al., 1976, 1977].
In most cases currently encountered in practice the duration of the study is predetermined and the total number of individuals required is calculated so as to ensure a sufficient number of events to be observed. This is done in order to provide adequate power to the comparative test at the scheduled termination of the trial. Most of the studies therefore emphasize the sample size, though the duration of the study should also be considered an aspect of major importance when designing a comparative test. On the one hand, inferences about the parameters of interest or the power of the tests of comparison obviously tend to improve as the available information which is accumulated over time increases. On the other hand, considering the possible implications for public health intervention, prevention policy or ethical aspects, it is desirable that the outcome of the study be stated within the shortest possible period of time. A compromise between the two previous antagonistic time constraints can be reached by reviewing the situation in a sequential way at successive chronological terms.
The purpose of the present paper is to outline a sequential procedure to perform comparative analysis of survival distributions. The method is based on a discrete time expression of the hazard while examining the different study subjects individually and by themselves. It should be pointed out that sequential analysis of survival data with prolonged observation of each individual has been proposed by Whitehead [1992], among others. However, the method suggested here introduces a new dimension of flexibility into the analysis of survival data within the framework of a stepwise assessment by taking explicit account of the discrete nature of the data. It is therefore appropriate to deal with data sets which may contain an important number of censored values or tied failure times as a result of the sequential process when carrying out a follow-up study.
Survival times are assumed exponentially distributed. The stopping rule and decision criteria of the sequential procedure are based on the

The characteristics of the DTBLRS method are compared with the approach based on i) the exponential model, assuming an approximate normal distribution of the ln maximum-likelihood estimate of the hazard rates [Bernstein and Lagakos, 1978; Schoenfeld and Richter, 1982] and ii) the non parametric method using the logrank test [Freedman, 1982] under the assumption that the hazard function is expressed as the well known semi-parametric proportional hazards model [Cox, 1972]. To facilitate comparison between the different methods, all the patients are assumed to have been entered at the same time in the study, i.e. $t = 0$. Moreover, statistical analysis of the results is assumed to occur after a follow-up time which is fixed at $t = 24$ months when the first two methods are considered. The benefit of the sequential approach over the other two methods can be assessed by comparing the relative power and/or the total expected number of events needed before a decision is planned to be made (methods i) and ii)) or can be made (DTBLRS method). However, when doing such a comparison between the different methods (see Table 1) one should be aware that the proportional hazards model is used in the approach developed by Freedman [1982] whereas the simple but also more restrictive exponential model is used in the other two methods.

Note that the mean number of events, $\overline{n - k_1 - k_2}$, observed by the end of the sequential procedure ($t \leq c_{max}$) provides an over-estimate of the mean number of events corresponding to the power level which is actually mentioned in Table 1. The results presented in the Table show that a continuous monitoring of the data within the framework of the sequential procedure suggested in this paper allows a decision to be made (i.e. deciding whether a treatment is promising relative to another one) at a time, and subsequently a number of events, which are both considerably smaller than those given by the other two approaches which, in turn, are comparable.

5. CONCLUDING REMARKS

The DTBLRS method provides a particularly convenient way for designing appropriate tests for comparing survival distributions in a wide class of biomedical (e.g. clinical trials) or environmental health (e.g. risk analysis) investigations. Both the duration and the number of events are substantially smaller than one could expect had one used a current method based on the analysis of the data observed at a predetermined value of the time. Conversely, both the number of individuals required and the duration of the trial can be assessed on the basis of i) the combination of power and level of significance to be attained, and ii) the prior knowledge of the hazard rates in each group or, seen another way, the smallest difference in the relative hazard rates one wishes the trial to be able to detect reliably. Finally, the great generality of the statistical model considered accommodates the possibility of handling data sets comprising high rates of single censored values or tied failure times. It should be pointed out that the discrete time expression of the hazard while examining the different study subjects individually and by themselves allows to carry out the sequential procedure in case the individuals may be entered for the study at any different times.

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