CHAPTER 1

INTRODUCTION

1.1 Survival Analysis

The survivor function $S(t)$ is the probability that an individual survives for a time greater than or equal to t. The estimation of the survivor function is very often complicated by the censoring done to the data. The survival time of an individual is said to be censored when the individual's end-point of interest has not been observed.

There are various types of censoring. Consider the situation when an individual enters a study at time t_0 and dies at time t ($t > t_0$). If the individual has been lost to follow-up at time t_c ($t_c < t$), or the analysis of the study is done at time t_c, then t is unknown and the time t_c is called a censored survival time. This censoring is known as right censoring because t is to the right of t_c.

Other forms of censoring may be illustrated by the following example. Suppose t_0 is the time of surgical removal of the primary tumour, t_i the time of the i-th examination to determine if the cancer has recurred, i =1, 2 ($t_1 < t_2$), and the end-point of interest is the time t of recurrence of the cancer. If the cancer is found to have recovered at time t_1 then the actual recurrence time is less than t_1 (t is to the left of t_1) and left censoring is said to have occurred. If the recurrence is not observed at t_1, but is detected at t_2, then t satisfies $t_1 < t < t_2$ and interval censoring is said to have occurred.

Censoring is also classified into Type I and Type II censoring. In Type I censoring, there is a cut-off date t in the study. The observed death times before t are the uncensored observations and the individuals who are still alive by time t constitute censored observations. In Type II censoring only the first r (r is fixed before the survival data are seen) death times are observed.

Using the method of maximum likelihood, Kaplan and Meier (1958) derived an estimate called the product-limit estimate for the survivor function. The standard error of the Kaplan-Meier estimate was given by Greenwood (1926). Based on the standard error, a confidence interval for the survivor function at a particular given time can be found.

The construction of confidence bands for the complete survivor function was given by Hall and Wellner (1980) and Efron (1981). The construction of confidence intervals for the median survival time was described by Brookmeyer and Crowley (1982), Emerson (1982), Nair (1984), Simon and Lee (1982) and Slud et al. (1984).

The comparison of two survivor functions may be performed via the log-rank test which results from the work of Mantel and Haenszel (1959) and Mantel (1966).

The hazard function $h(t)$ is a function such that $h(t)dt$ represents the probability that an individual dies in $(t, t + dt)$ conditional on he or she having survived to that time. Its relation with the survivor function $S(t)$ can be shown to be given by

$$h(t) = -\frac{d}{dt} \log S(t) \quad . \tag{1.1}$$

To explore how the survival experience of a group of patients depends on the values of one or more explanatory valuables, whose values have been recorded for each patient at the time origin, we may model the hazard function as a function of the explanatory variables.

The proportional hazards model for survival data was proposed by Cox (1972) and considered in greater detail by Cox (1975). In the proportional hazards model the hazard function of the i-th individual is written as

$$h_i(t) = \psi(\mathbf{x}_i) h_0(t), \tag{1.2}$$

where $\psi(\mathbf{x}_i)$ is a function of the values of the vector $\mathbf{x}_i$ of explanatory variables for the i-th individual and $h_0(t)$ is the baseline hazard function for an individual for whom the values of all the explanatory variables are zero. The estimates of the baseline survivor function were introduced by Kalbfleisch and Prentice (1973) and Breslow (1972, 1974).

If the hazard function can be specified by a specific functional form, then statistical inferences will be more precise. A probability distribution which plays an important role in the analysis of survival data is the Weibull distribution introduced by W. Weibull in 1951. Estimation of the shape and the scale parameters of the Weibull distribution has been extensively discussed in the literature (see for example, Mann (1968), Mann and Fertig (1973), McCool (1970), Thoman et al. (1969), Lawless (1982) and Mann et al. (1974)). Gibbons and Vance (1981) compared seven estimators of the Weibull parameters for complete and Type II censored samples. Confidence intervals based on pivotal quantities for the Weibull parameters were derived by Lawless (1973, 1978). Comparison of confidence intervals based on pivotal quantities for the Weibull parameters was carried by Chao and Hwang (1986). The confidence intervals compared include those which are obtained by using the conditional procedure and unconditional procedure based on the best linear invariant estimator and on the maximum likelihood estimator.

A confidence interval for the Weibull quantile may be obtained by using the asymptotic variance of the estimator for the quantile. Alternatively, a confidence interval for the Weibull quantile may also be obtained by using the bootstrap procedure (see for example Heo et al. (2001) and Yong et al. (2008)).

The present thesis deals mainly with interval estimation in survival models. The parameters of interest include the survivor function $S(t)$ when t is fixed, the Weibull scale and shape parameters and the Weibull quantiles.

1.2 Summary of the Dissertation

In Chapter 2, we propose a confidence interval based on the first four moments of the Kaplan-Meier estimate for the survivor function at a particular given time. It is found that the proposed confidence interval tends to be better than the confidence interval based on Greenwood's formula in terms of both coverage probability and expected length.

In Chapter 3, we first obtain a more satisfactory approximation for the distribution of the log-rank test statistic U_L given by the sum of differences between the observed and expected Group I individuals. Based on the resulting approximate distribution for U_L, we construct a test for determining whether there are differences in the survival experiences of the individuals in two groups (Groups I and II). It is found that compared to the log-rank test, the resulting test has a rejection probability which tends to be closer to the target value when the initial size of Group I is larger than that of Group II.

In Chapter 4 we show that the estimate $\hat{\gamma}$ for the Weibull shape parameter γ can be expressed in terms of five random variables. We also find an approximate multivariate nonnormal distribution for the five random variables. This multivariate nonnormal distribution with fairly low dimensions will form the basis for the derivation of the distribution of $\hat{\gamma}$ by means of numerical integration.

The construction of confidence intervals for the Weibull scale and shape parameters and Weibull quantiles is given in Chapter 5. The method used for constructing confidence intervals is one which is based on hypothesis testing. It is found that the resulting confidence intervals tend to have expected lengths which are shorter than those of the bootstrap confidence intervals while still possessing satisfactory coverage probability.

We end the dissertation by some concluding remarks in Chapter 6.