A SURVEY OF COMPETING RISK ANALYSIS: A MEDICAL APPLICATION

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ABSTRACT

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The theory of competing risks deals with a situation where an organism or a system is exposed to two or more causes of failure or death but its eventual failure is obtained from only one of these causes of failure. In physical sciences the competing risks data can be obtained in life testing or reliability analysis when there is more than one possible cause or mode of failure. Competing causes of failure must be taken into account in the study of how risk factors affect a specific cause of failure. In the analysis of failure times with competing causes of failure problems include the estimation of treatment effects on specific failure types, the study of interrelations among failure modes and the estimation of failure rates for some causes when certain other failure types are removed. Since this is the first study about competing risks in Turkey, it includes most of the methods used in statistics to analyze competing risks data. Cause-specific hazard functions are shown to be used as basic estimable quantities for analyzing such data. Some computer programs are developed to apply the methods and important factors are specified for acute leukemia in the presence of competing risks.

Keywords: Competing risks, cause-specific hazard function, the crude, net and partial crude probabilities, survival probability, incidence function,Cox regression model.

ÖZ

YARIŞAN RİSK ANALİZİNE GENEL BAKIŞ: BİR TIBBİ UYGULAMA

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Yarışan riskler teorisi, bir sistemin ya da bir organizmanın iki ve daha fazla sebepten başarısızlığa veya ölüme maruz kaldığı fakat başarısızlığın bu sebeplerden sadece biri tarafından meydana geldiği durumlarla ilgilenir. Fiziki bilimlerde, birden fazla başarısızlık nedeni varsa yarışan riskler verisi yaşam testlerinden ya da güvenilirlik analizlerinden elde edilir. Eğer risk faktörlerinin belirli bir başarısızlık nedenini nasıl etkilediği araştırılıyorsa yarışan riskler göz önüne alınmalıdır.Yarışan başarısızlık sebepleri ile başarısızlık zamanı analizindeki problemler, üzerinde çalışılan grupların belirli bir başarısızlık tipine etkisinin tahminini, başarısızlık modları arasındaki ilişkinin tespitini ve belirli bir başarısızlık tipinin yok edilmesi durumunda diğer nedenlerin başarısızlık oranlarının belirlenmesini içerir. Bu çalışma Türkiye'de yarışan riskler konusundaki ilk çalışma olduğu için, yarışan riskler verisinin analizindeki bir çok istatistiki yöntem ele alınmıştır. Bu tip veri için elde edilmesi gereken temel birimlerin sebebe bağlı başarısızlık fonksiyonları olduğu gösterilmiştir. Kullanılan metodların analizi için bazı bilgisayar programları geliştirilmiş ve yarışan riskler mevcutken akut lösemideki önemli faktörler belirlenmiştir.

Anahtar Sözcükler: Yarışan riskler, sebebe bağlı başarısızlık fonksiyonu, ham, net ve kısmi ham olasılıklar, yaşam olasılıkları ve olay ihtimalleri, Cox regresyon modeli.

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CHAPTER 1

INTRODUCTION

The theory of competing risks is concerned with the assessment of a specific risk in the presence of other risks acting on the population to fail a system or an organism. In clinical trials, the principle endpoint for each study subject may be a complex phenomenon involving type of outcome and time to its occurrence. For instance, in a cancer treatment study the endpoint might be cause of death and survival time, or an indicator for disease remission or progression plus time to failure. Many units, systems, subsystems, or components have more than one cause of failure. For example, a capacitor can fail open or as a short, any of many solder joints in a circuit board can fail, A semiconductor device can fail at a junction or at a lead, and a device can fail because a manufacturing defect or because of mechanical wearout. Competing risk models are used to describe and analyze such data.

The problem presents itself in different terms since the aim is not to measure overall mortality but to establish the impact of a specific cause of death. Suppose that, for individuals in a particular population, there are k, ($k > 1$) possible causes of failure. Then, each member of the population is regarded as subject to k risks competing for his life. Which one of these risks wins is the cause of death for that patient.

Competing risks literature deals with observable and non-observable probabilities. The formers are quantities expressed as a function of the cause-specific hazard rate; corresponding the original observations with all causes of

risks acting. Non-observable probabilities are needed when an epidemiologist, for example, is interested in predicting what would happen if one or more causes of death were removed. Computations of non-observable probabilities are strictly dependent on the distributional models of failure times. The concept of latent failure time for each cause has been found mathematically convenient for the theoretical modelling of competing risks.

Available data on each study subject include $t \geq 0$, time to failure; $C \in \{1,..,k\}$, the type of failure and a regression vector, Z may record the treatment assignment as well as other disease, personal or demographic characteristics of the patient. T may describe time from entry into the study to death. Two approaches have been followed for analyzing cause-specific survival data. First one simply involves fitting models separately for each cause in turn, treating other failure types as censored data. Second involves fitting more complex models in corporating the different failure types. A difficulty with this alternative is that the standard software is not available.

Three distinct problems arise in the analysis of failure times with competing risks. These are 1) inference on the effects of treatment, exposure or other regression variables on specific type of failure, 2) the study of the interrelations among failure types under specific study conditions, and 3) the estimation of failure rates for some causes given the removal of some or all other causes. Due to heterogeneity of patient population, a major concern in the analysis of competing risks data is the relationship of covariates such as sex, age and disease-severity with the type of outcome and its timing.

Since the theory of competing risks is concerned for the first time in Turkey, it is decided that this thesis must contain lots of statistical methods used to analyze the competing risk data. The aim of this thesis is to outline the existing theory and to do an application of competing risk data set obtained in Turkey. It

can be applied in various areas. That is why demographers, vital statisticians and actuaries have long been concerned with the theory.

In this study, the acute leukemia data are used to analyze competing risks models. From 1st.August.1987 to 5th.March.1999 randomly selected 84 patients are taken from the Marmara Medical School Hospital in Istanbul. There are two competing risks as relapse/progression type risk and refractor/wrong medical treament related risk of deaths for acute leukemia patients. Data set also contains six prognostic factors for the acute leukemia patients. These are type of leukemia, age, existence of other illnesses besides acute leukemia, the amount of normal white blood cells, platelets and red blood cells in the patient's blood. Parametric, non-parametric and semi-parametric models are used in the data analysis. Parametric models contain determination of the appropriate theoretical distribution for each cause, estimation of the parameters of the underlying distribution and calculation of the crude, net and partial crude probabilities. For parameter estimation, Newton-Raphson iteration method is used. Kaplan-Meier survival probabilities and crude cumulative incidence probabilities are discussed in the non-parametric analysis. To determine the effects of covariates into survival probabilities in the presence of competing risks, semi-parametric Cox regression model is proposed. For all these analysis, the two competing risks factors are assumed to be independent.

Previous studies about competing risks analysis are examined in Chapter 2. Chapter 3 contains parametric methods with independent and dependent competing risks, estimation of cause-specific hazard functions, follow-up studies in the presence of competing risks, methods for construction of life tables, non-parametric tests and models used in competing risks analysis. Chapter 4 is devoted to the application of competing risks theory. Because of the nature and structure of the data and other restrictions, in the application part of this thesis only certain methods are considered. And finally the conclusion, discussion and suggestions for some possible future studies are given.

CHAPTER 2

LITERATURE SURVEY

The theory of competing risks was first introduced by Daniel Bernoulli in 1760. His basic question of interest at time is " if in a given population the smallpox could be eradicated, what would be the effect on the population mortality structure at different ages? ". This Bernoulli's question is still with us today if for smallpox, some form of cancer, heart disease, etc. are substituted. A natural extension is to ask for the effect of changing the importance of one or more causes of death. D'Alembert (1761) derived a method to determine the change in population composition that would take place if smallpox were eliminated as a cause of death.

Makeham (1874) introduced the first formulation of a theory of decremental forces and usage in practical application. An interesting account of the development is found by Todhunter (1949). Greville (1948) discussed deterministically multiple decrement tables. Fix and Neyman (1951) studied the problem of competing risks for cancer patients and Chiang (1961) approached the problem from stochastic viewpoint. Chiang, in his paper he gave the follow-up studies in competing risks.

Samford (1952) who discusses an accidental death model in connection with the estimation of response time distributions and Berkson and Elveback (1960) dealing with the problem of competing exponential risks give two special cases of the general method. Boardman and Kendell (1970) consider the case of underlying exponentially distributed lifetimes.

The basic reference regarding the development of competing risks theory is given by Chiang (1968) who defines the particular probabilities of interest like crude, net and partial crude probabilities and obtains such probabilities from the basic parameters of k underlying life distributions. In theory, this approach is general and applicable to any set of lifetimes arising from continuous distributions, provided the causes of failure act independently. Chiang obtains the relation between the crude, net and partial crude probabilities and from this relation he uses the estimates of the crude probability to estimate net and partial crude probabilities. Although this method is free from any underlying distribution, the assumption of constant relative forces of mortality holds only for certain classes of continuous distributions of interest. David (1970) has shown that the assumption will be satisfied whenever the underlying distributions of life have one of the three possible forms of the extreme-value distribution of the minimum, and hence in particular for exponential or Weibull distributions with equal shape parameters. A simple general method, based on the grouped observations, has been put forward by Kimball (1957). Moeschberger and David (1971) pointed out that Chiang's and Kimball's crude and net probabilities depend on how the time intervals are chosen. However, they showed that the parametric method tends to smooth out these probabilities over the life span of the individual. Kanie and Nonaka (1985) give the estimation technique of Weibull shape parameters for two independent competing risks. They use the relations among cumulative hazard functions of the system at virtual observation limit for estimation.

Hoel (1972) considers the mortality data in competing risks framework. He represents cohort mortality data by a probabilistic combination of competing risks and describes each risk by an age-at-death distribution and net probability of occurrence. This representation is illustrated by a set of pathology data from a well-controlled laboratory animal experiment. These data are used in many applications in competing risk analysis.

Gail (1975) has treated the actuarial model of competing risks in detail, comparing it with other models and giving useful variance formula both for the case when times of death are available and for the case when they are not.

Seal (1977) reviewed the history of actuarial and the concepts in the relevant literature. She considers the problem started with Bernoulli's smallpox mathematics and gives all proper techniques developed during the nineteenth century.

David and Moeschberger (1978) prepared a monograph for the theory of competing risks. They considered the concept in large prospect. They gave the parametric approach under both independent and dependent risks. Moreover, they gave graphical methods and use of concomitant information in competing risks analysis.

Sinha (1986) explains competing risks model with the exponentially distributed components and exponential failure time distribution. He develops a maximum likelihood estimators of parameters.

Thompson (1988) takes the competing risk model as a Markov chain model. In competing risks theory, individual is alive initially, denoted by state 0 and at death, the individual makes a transition to being dead because of some cause R_δ, $\delta=1,\ldots,k$. Also, he represents the reactor safety studies under competing risks framework and points out the delayed fatalies.

In 1978, Prentice, Kalbfleisch, Peterson, Flourney, Farewell and Breslow analyzed the failure times in the presence of competing risks. They showed that cause-specific hazard functions were the basic estimable quantities in competing risk analysis. A method, involving the estimation of parameters that relate time-dependent risk indicators for some causes to cause-specific hazard functions for other causes was proposed for the study of interrelations among failure types. In

addition, it was argued that the problem of estimation of failure rates under the removal of certain causes was not well posed until a mechanism for cause removal was specified clearly. They used a well-known clinical trial in competing risk analysis in bone marrow transplantation for leukemia.

Kay (1986) analyzes data from a randomized clinical trial comparing treatment for patients with prostate cancer in the presence of competing risks. Like Kalbfleish and Prentice (1980), fit models separately for each type of failure in turn, treating other failure types as censored data. Lunn and McNeil (1995) apply Cox regression to competing risks with proportional hazard regression model with censored data. They give two methods for the joint estimation of parameters in models for competing risks in survival analysis. In both cases Cox's proportional hazard regression model is fitted using the data duplication method.

The hazard function representation of failure time is generalized in competing risks theory by Kalbfleisch and Prentice (1980). They propose methods to study the relationship between covariates and certain cause-specific hazard functions. The use of time dependent covariates gives a promising approach to other competing risks problem.

Larson (1984) proposed a log-linear model for analysing competing risks data with discrete covariates. He approximates the cause-specific hazard rates by step functions. His work shows how to summarize competing risks data in contingency table and how to analyze these data by log-linear techniques.

Another alternative approach for analysing cause-specific survival data in competing risks theory is used by Larson and Dinse (1985) and Kuk (1992). They fit more complex models incorporating the different failure types. Larson and Dinse (1985) use a mixture model for the regression analysis of competing risks data. They use an EM algorithm to obtain maximum likelihood analysis and Kuk (1992) needed to use Monte Carlo simulation to accommodate two failure types in

a survival analysis model. A difficulty of these models is that standard software is not available.

Distribution free test for the equality of failure rates due to two competing risks is considered by Bagai (1986) and Bagai, Deshpande and Kochar (1989). They found distribution free tests which are proposed for testing the equality of the two failure distributions against location, scale and general stochastic ordering alternatives. After deriving locally most powerful rank test, they propose a generalization of the Wilcoxon test under independent competing risks assumption. In 1992, Yip and Lam derived a class of non-parametric tests by martingale theory to test equality of failure rates in a competing risks model, when data are the cause of failure and the observed time to failure. Aly, Kochar and McKeague (1984) propose some tests whether two risks are equal or whether one is more serious than the other. They compare the cumulative incidence functions and cause-specific hazard rates without making any assumption on the nature of dependence between two risks. Sun and Tiwari (1995) consider the same case with censored data. They develop on asymptotic normal distributions of the test statistic by expressing the statistic in terms of counting process and using martingale central theory. They use a set of mortality data given by Hoel (1972). Kochar (1995) gives a review of some distribution free tests for the equality of cause specific hazard rates. Recently, Sun and Tiwari (1997) determine a simple non-parametric test for comparing the cumulative incidence functions of a competing risks model when two causes of failure are possibly statistically dependent. The test statistic is the weighted sum of the differences of two cumulative incidence functions at system failure times. The test is based on an asymptotic normal distribution. The latest work on the equality of cause-specific hazard rates in a competing risk model is introduced by Lam (1998). He proposes a class of asymptotically distribution free tests for the equality of the k risks and tests are derived by martingale theory or by a marginal likelihood approach.

Estimation of occurrence/exposure rate in competing risk models is introduced by Babu, Rao and Rao (1992). Under mixed censoring procedure they develop a non-parametric estimator of specific occurrence/exposure rate. Huang and Wang (1995) show that there is a one-to-one correspondence between the crude hazard functions and occurrence probabilities. To estimate occurrence rate they use different sampling procedures. The maximum likelihood property and asymptotic behaviour of estimation procedure are studied.

In competing risks framework, the observed data are time to failure, T=min(X, Y) where X is the time to failure of the cause of death and Y is the time point of the occurrence of other competing event, and type of failure $\delta = I (X \leq Y)$. Basu and Klein (1982) pointed out that the pair (T, I) provides insufficient information to determine the joint distribution of X and Y. There may be both an independent and one or more dependent models for X and Y producing the same joint distribution for (T, I). However, these joint distributions may have different marginal distributions. This problem is known as the identifiability problem. In the light of this untestable independence assumption some bounds on the marginal survival are found by Peterson (1976). In 1983, Slud and Rubinstein developed much tighter bounds than those of Peterson. Slud and Byar (1988) show by using the results of Slud and Rubinstein (1983), that competing latent failure times t and C and a two level covariate V, that is, V = 0 or 1, assuming T and C are independent for each V level, can lead the wrong conclusion about the ordering of $Pr (T \geq t \mid V = 1)$ and $Pr (T \geq t \mid V = 0)$ for every t. To estimate the marginal survival function of X in using the product-limit estimator, Klein and Moeschberger (1988) propose bounds on this function based on the observable random variables (T, I) and some assumptions on the joint behaviour of X and Y.

David and Moeschberger (1978) propose the parametric models when the competing events are dependent. In 1984 and 1987, Moeschberger and Klein investigated the consequences of departures from independence when the component lifetimes in a series system are exponentially distributed. They

considered first in theoretical modelling of series system when the distribution of the component lifetimes is assumed. Second, they discussed errors in parametric and non-parametric estimation of component reliability and component mean life when the independence assumption is made erroneously.

To test the independency between failure times in a competing risks framework Carling (1996) examines the performance of the conventional likelihood ratio test. He points out that the dependence between failure times arises stochastically related unobserved components that are estimated non-parametrically. He uses a dependent competing risks model of the mixed proportional hazard type.

Lanberg, Proshan and Quinzi (1978) show that under certain conditions it is possible to establish a particular equivalence between system of dependent components and a system of independent components. In 1981, they developed methods that could be used to unify and simplify the non-parametric approach toward estimation of dependent life lengths in competing risks model using their 1978 work. Also, they obtained an elementary proof of the strong consistency of the Kaplan-Meier estimator.

CHAPTER 3

THE THEORY OF COMPETING RISKS

3.1. Basic Definitions

The theory of competing risks is concerned with the assessment of a specific risk in the complicating presence of other risks.

A useful analogy can be drawn between an individual subject to a number of components. System break dawn due to failure of a particular component then corresponds to death due to a particular risk.

Assessment of a new treatment for a particular form of cancer where inferences must often be made on the basis of a limited number of cases. The experiment consists of an operation of other treatment followed by a period of observation. This form of life testing has come to be known as survival analysis when human subjects are involved. If the patient dies during the course of the study, the cause of death and time to death are noted. For the survivors at the end of the experiment the length of time in the experiment is recorded; these values are said to be censored since observation was stopped prior to death. Such censoring, of frequent occurrence in practice, may be regarded as effectively as a competing risks, since censoring at a certain time x prevents an individual from dying from a particular cause during the experiment just as surely as does death at

time x from some other cause. Thus, competing risks are in the ordinary sense, but only a single risk with censoring.

Death is not a repetitive event and it is usually attributed to a single cause; however, various risks competing for the life of an individual must be considered in the cause-specific studies. In such kind of studies it is considered that there are k components arranged in series, failure of one or more components leading to failure of the system of individual. To be more familiar with the methodology understanding the following three types of probability of death from a specific cause is required.

1. The crude probability: The probability of death from a specific cause in the presence of all other risks acting in a population, or

$Q_{i\delta}$ = Pr {an individual alive at time x_i will die in the interval (x_i, x_{i+1}) from cause R_δ in the presence of all other risks in the population}.

2. The net probability: The probability of death if a specific risk is the only risk in effect in the population or, conversely, the probability of death if a specific risk is eliminated from the population.

$q_{i\delta}$ = Pr {an individual alive at x_i will die in the interval (x_i,x_{i+1}) if R_δ is the only risk acting on the population.};

$q_{i.\delta}$ = Pr {an individual alive at x_i will die in the interval (x_i,x_{i+1}) if R_δ is eliminated as a risk of death.}

3. The partial crude probability: The probability of death from a specific cause when another risk (or risks) is eliminated from the population.

$Q_{i\delta.1}$ = Pr {an individual alive at x_i will die in the interval (x_i,x_{i+1}) from R_δ if R_1 is eliminated as a risk of death};

$Q_{i\delta.12}$ = Pr {an individual alive at x_i will die in the interval (x_i,x_{i+1}) from R_δ if R_1 and R_2 are eliminated as a risk of death};

When the cause of death is not specified, then the probabilities are

p_i = Pr {an individual alive at x_i will survive in the interval (x_i,x_{i+1}) }

and

q_i = Pr {an individual alive at x_i will die in the interval (x_i,x_{i+1})}

with $p_i + q_i = 1$.

The use of the term risk and cause needs clarification. Both terms may refer to same condition, but are distinguished by their position in time relative to the occurrence of death. Prior to death the condition referred to is a risk; after death the same condition is the cause.

The distinctive feature of data admitting a competing risk analysis is that, for each individual, both causes of death and time to death (exactly or in interval) must be available.

3.2. Basic Formulation

Let R_p (p=1,…,k) denote the k competing risks that are causes of failure and the theoretical random variable Y_i (i=1,…,k) represent an individual's length of life if the particular risk R_i are the only risk present in the population. Then the cumulative distribution function (d.f.) of Y_i is $P_i(x)$ = Pr $\{Y_i \leq x\}$ and the corresponding probability density function is, usually assumed to exist, denoted by

$p_i(x)$. Apart from the cause of failure only the minimum Z of the k theoretical lifetimes is obtained. So, Z can be shown as

$$Z = \min (Y_1, Y_2,\ldots,Y_k) = \min_p Y_p$$

Now, if Z exceeds x, each Y_i must also exceed x and it is obtained that

$$\Pr \{Z > x \} = \Pr \{Y_1 > x ,\ldots,Y_k > x\} \tag{3.1}$$

Pr {Z > x } can be written as $\bar{F}_Z(x) = 1 - F_Z(x)$, F (rather than P) being used for the d.f. of z to emphasize that Z is observable, unlike the Y_i. The bar denotes complementation and $\bar{F}_Z(x)$ is called the survival (or survivor) function of Z. Further, let

$$\lambda_Z (x) = f_z (x) / \bar{F}_Z(x) \tag{3.2}$$

be the conditional failure rate function for Z. Reflecting its areas of application in actuarial work, demography, vital statistics, renewal theory, and reliability, $\lambda_Z (x)$ is variously known as the force of decrement, force of mortality, age-specific death (failure) rate, intensity function, and hazard function.

Let $g_i(x)dx$ (i=1,…,k) denote the probability of failure from R_i in (x,x+dx), in the presence of all k risks, of an individual alive at time x. It is assumed that the probability of more than on failure in (x, x+dx) is negligible (of order $(dx)^2$). Then since $\lambda_Z (x)dx$ is the probability of failure in (x, x+dx) from any cause, given survival to time x, it is obtained that

$$\lambda_Z (x) = \sum_{i=1}^{k} g_i(x), \tag{3.3}$$

showing that the (total) force of mortality is the sum of the component forces.

It is to be noted that it is not required so far the risks R_i to act independently. If this assumption is made, it can be more formally expressed as the mutual independence of the Y_i, (3.1) becomes

$$\Pr\{Z > x\} = \Pr\{Y_1 > x\} \ldots \Pr\{Y_k > x\}$$

or

$$\bar{F}_Z(x) = \prod_{i=1}^{k} \bar{P}_i(x). \tag{3.4}$$

In this case it is also obtained that

$$g_i(x) = p_i(x) \prod_{\substack{j=1 \\ j \neq i}}^{k} \bar{P}_j(x) / \bar{F}_Z(x) = p_i(x) / \bar{P}_i(x)$$

The last ratio, which is the failure rate function for Y_i, may be denoted by $\lambda_i(x)$ and termed a cause-specific failure rate or marginal intensity function. Hence for independent risks it can be shown that

$$g_i(x) = \lambda_i(x), \quad i=1,..,k \tag{3.5}$$

which says that the probability of failure from R_i in (x, x+dx), given survival to time x, is the same whether R_i is one of k risks or the only risk present. From (3.3) and (3.5) it is seen that

$$\lambda_Z(x) = \sum_{i=1}^{k} \lambda_i(x), \tag{3.6}$$

a result which follows also directly from (3.4) in conjunction with

$$\lambda_Z(x) = -\frac{d}{dx}\ln \overline{F}_Z(x), \qquad \lambda_i(x) = -\frac{d}{dx}\ln \overline{P}_i(x). \tag{3.7}$$

The net, crude, and partial crude probabilities mentioned in Section 3.1 may be expressed in terms of the $\lambda_i(x)$, $\lambda_Z(x)$, and $g_i(x)$ functions. For a time interval (a, b), it is obtained that

$$\int_a^b \lambda_i(x)\,dx = -\ln\left[\overline{P}_i(b)/\overline{P}_i(a)\right],$$

or

$$\exp\left[-\int_a^b \lambda_i(x)\,dx\right] = \overline{P}_i(b)/\overline{P}_i(a)$$

= Probability of surviving R_i in (a, b) after surviving R_i to a

$= 1\text{-}q_i(a, b)$,

where $q_i(a, b)$ is the net probability of death from R_i in (a, b). Thus

$$q_i(a,b) = 1 - \exp\left[-\int_a^b \lambda_i(x)\,dx\right]. \tag{3.8}$$

Also since

$$\exp\left[-\int_a^x \lambda_Z(t)\,dt\right] = \text{Probability of surviving all risks in (a, x),}$$

having survived to a,

it is seen that the crude probability, $Q_i(a, b)$, of death from R_i in (a, b) is obtained by multiplying this expression by $g_i(x)$ and then integrating out over this interval. Thus

$$Q_i(a,b) = \int_a^b g_i(x)\, \exp\left[-\int_a^x \lambda_Z(t)dt\right]dx. \qquad (3.9)$$

The corresponding partial crude probability with R_j eliminated is formally given by

$$Q_{i,j}(a,b) = \int_a^b g_i^{(-j)}(x)\exp\left[-\int_a^x \lambda_Z^{(-j)}(t)dt\right]dx \qquad (3.10)$$

where $g_i^{(-j)}(x)dx$ and $\lambda_Z^{(-j)}(t)$ are respectively the probability of failure on (x,x+dx) from R_i, and the hazard rate after elimination of R_j. Note that the probabilities q_i, Q_i, and $Q_{i,j}$ are all conditional on survival to time a. In fact, (3.9) can also be written as

$$Q_i(a,b) = \frac{1}{\bar{F}_Z(a)}\int_a^b g_i(x)\bar{F}_Z(x)dx \qquad (3.9a)$$

When the risks are independent, $g_i^{(-j)}(x) = g_i(x) = \lambda_i(x)$ and $\lambda_Z^{(-j)}(t)=\lambda_Z(t)=\lambda_j(t)$. So that (3.10) reduces to

$$Q_{i,j}(a,b) = \int_a^b \lambda_i(x)\exp\left\{-\int_a^x \left[\lambda_Z(t)-\lambda_j(t)\right]dt\right\}dx \qquad (3.10a)$$

3.3. Parametric Approach, Independent Risks

3.3.1. Introduction:

The distinguishing feature of parametric approaches to competing risks theory is assuming the functional form of underlying life (failure time) distributions to be known apart from unknown parameter estimated by maximum likelihood methods and hence, the maximum likelihood estimates of the crude, net and partial crude probabilities may be obtained. In this section it is assumed that the risks to which each individual is exposed act independently.

The particular functional form of the theoretical life distributions used to make inferences depends upon one's understanding of the failure mechanism. Several specific families of life distributions have been advocated, namely, exponential, Weibull, normal (or lognormal), gamma, and Makeham-Gompertz. Perhaps the most important characterization of such life distributions, which have been used as a criterion for selection, is the conditional failure rate (hazard rate). Before considering specific life distributions, it is more convenient to introduce general likelihood functions appropriate to various frequently arising experimental situations.

3.3.2. All Lifetimes and Associated Causes of Failure are Known Case:

Let the nonnegative random variable Y_i denote the theoretical lifetime of an individual when R_i is the only cause of failure ($i = 1,\ldots,k$). In the simultaneous presence of all k causes R_p ($p = 1,\ldots,k$) only the smallest of the Y_p, namely $Z=\min_p Y_p$, is in fact observable, together with the actual cause of failure, say R_i.

There are several choices of notational devices. First, one might write the observed lifetime, conditional on knowing the cause of failure to be R_i, as X_i, where

$$X_i = Y_i \mid Y_i = \min_p Y_p . \tag{3.11}$$

A second notational device would be to write the observed lifetime and cause of failure as a random vector, namely (δ, Z), where δ=i denotes failure due to R_i. In this section the first notation is employed.

Let the probability of failure due to cause R_i be

$$\pi_i = \Pr\{ Y_i = \min_p Y_p \}, \ \pi_i > 0, \ \sum_{i=1}^{k} \pi_i = 1, \tag{3.12}$$

where without essential loss of generality one can omit causes of failure associated with zero probability. Then, from (3.11) and the independence of the Y_i, the p.d.f. $f_i(x)$ of X_i is given, ignoring terms of lower order, by

$$f_i(x) = \frac{1}{\pi_i} \Pr\{x - dx < Y_i \le x\} \prod_{\substack{j=1 \\ j \neq i}}^{k} \Pr\{Y_j > x\}$$

that is, by

$$f_i(x) = \frac{1}{\pi_i} p_i(x) \prod_{\substack{jl=1 \\ j \neq i}}^{k} \bar{P}_j(x). \tag{3.13}$$

This basic result may equivalently be expressed as

$$f_i(x) = \frac{1}{\pi_i}\lambda_i(x)\prod_{j=1}^{k}\bar{P}_j(x) \tag{3.13a}$$

$$= \frac{1}{\pi_i}\lambda_i(x)\bar{F}_Z(x). \tag{3.13b}$$

In this section the form in (3.13) is used.

If N_i individuals fail from cause R_i, and X_{ij} denotes the lifetime of the j-th individual failing from cause R_i ($j=1,\ldots,n_i$; $i=1,\ldots,k$), then the joint p.d.f. of the X_{ij} may be written as

$$f\left(x_{11},\ldots,x_{1n_1},\ldots\ldots,x_{k1},\ldots,x_{kn_k}\right) = \prod_{i=1}^{k}\frac{1}{\pi_i^{n_i}}\prod_{j=1}^{n_i}p_i\left(x_{ij}\right)\prod_{\substack{p=1\\p\neq i}}^{k}\bar{P}_p\left(x_{ij}\right) \tag{3.14}$$

It must be noted that this pdf is conditional on $N_i = n_i$ ($i=1,\ldots,k$). The N_i's are random variables with the multinomial probability function;

$$f\left(n_1,\ldots,n_k\right) = \frac{n!}{\prod_{i=1}^{k}n_i!}\prod_{i=1}^{k}\pi_i^{n_i} \quad \text{where } n = \sum_{i=1}^{k}n_i. \tag{3.15}$$

Hence, the likelihood function of interest is

$$L = \frac{n!}{\prod_{i=1}^{k}n_i!}\prod_{i=1}^{k}\prod_{j=1}^{n_i}p_i\left(x_{ij}\right)\prod_{\substack{p=1\\p\neq i}}^{k}\bar{P}_p\left(x_{ij}\right) \tag{3.16}$$

Note that the terms of L may be rearranged so that

$$L = \frac{n!}{\prod_{i=1}^{k} n_i!} \prod_{i=1}^{k} L_i , \tag{3.17}$$

where

$$L_i = \left[\prod_{j=1}^{n_i} p_i(x_{ij}) \right] \left[\prod_{\substack{p=1 \\ p \neq i}}^{k} \prod_{j=1}^{n_i} \bar{P}_p(x_{ij}) \right]. \tag{3.18}$$

If each theoretical life distributions have a different set of parameters then the estimation can be performed individually for each cause by maximizing L_i with respect to the parameters associated with the p.d.f. $p_i(y)$. An important consequence is that the numerical estimates of the parameters associated with $p_i(y)$ may be obtained individually even though the functional form of the densities may be different (Weibull, normal). It should be noted, however, that although the point estimates of the parameters of $p_i(y)$ may be obtained without any further knowledge of $p_p(y)$, $p \neq i$, the distribution of such estimators will depend upon the distributional form of the $p_p(y)$, $p \neq i$.

Alternatively, one might estimate the parameters associated with cause R_i by regarding each of the lifetimes whose failure was due to some cause other than R_i as being censored. In other words, lifetimes whose failure was due to R_p ($p \neq i$) may be regarded as censored, in the sense that those individuals had not yet reached their theoretical time to failure from R_i. Thus, this procedure essentially treats a competing risk problem as one in which there is only a single mode of failure with censoring. In the context of competing risk theory, this method leads to k different analyses on the same set of data.

3.3.3. The Case of Censored Lifetimes:

Consider the situation in which an individual's failure is observed only if it occurs within some specified time period. The length of such periods may vary from individual to individual.

This form of censoring, commonly termed (generalized) Type I censoring, is applicable to medical follow-up studies in which patient usually enter the study (that is; receive some treatment or have an operation performed) at different times but the terminal point of the study is frequently the same for all patients; this may be either because he has a time schedule to meet. Also, if contact with some patients is lost this type of censoring again becomes applicable. In such medical follow-up studies it is convenient, but not necessary, to assume that the period for which as under observation begins at time zero.

Suppose that, for n (fixed) individuals, each individual is under observation until censoring time γ_t (t=1,…,n); that is, the lifetime V_t of the t-th individual (t=1,…,n) will be known iff $V_t \leq \gamma_t$. If $V_t > \gamma_t$, then the t-th individual, will be considered as survivor. Let M and S denote the total number of failures and survivors, respectively, so that n = S+M. Suppose M_i individuals have failed from cause R_i, i.e.,$M = \sum_{i=1}^{k} M_i$, and let X_{ij} denote the time to failure of the j-th individual whose failure was due to cause R_i (i=1,…,; j=1,…,m_i).

Then the likelihood function for Type I censoring is given by

$$L \propto \prod_{i=1}^{k} \prod_{j=1}^{m_i} p_i(x_{ij}) \prod_{\substack{p=1 \\ p\neq i}}^{k} \bar{P}_p(x_{ij}) \times \prod_{u=1}^{s} \prod_{i=1}^{k} \bar{P}_i(\gamma_{(u)}) \,, \; x_{ij} < \gamma_{ij} \qquad (3.19)$$

where γ_{ij} denotes the censoring time of the j-th individual failing from cause R_i, and $\gamma_{(u)}$ denotes the censoring times of the s survivors (u=1,…,s). Note that if all $x_{ij} > \gamma_{ij}$ for some i, then $m_i=0$ and $\prod_{j=1}^{m_i}$ in (3.19) may be defined as 1. It is possible to write

$$L_I \propto \prod_{i=1}^{k} L_{Ii}\,, \tag{3.20}$$

where

$$L_{Ii} \propto \left[\prod_{j=1}^{m_i} p_i(x_{ij})\right] \cdot \left[\prod_{\substack{p=1 \\ p\neq i}}^{k} \prod_{j=1}^{m_l} \bar{P}_i(x_{pj})\right] \cdot \left\{\prod_{u=1}^{s} \bar{P}_i(\gamma_{(u)})\right\}, \quad x_{ij} < \gamma_{ij}\,. \tag{3.21}$$

A separate maximization of L_{Ii} may be accomplished provided each $p_i(y)$ has a different set of parameters.

When the lifetimes of s individuals are known only to be confined in the s intervals (a_u, b_u), u=1,..,s, then the counterpart of (3.21) is

$$L_{Ii} = \left[\prod_{j=1}^{m_i} p_i(x_{ij})\right] \cdot \left[\prod_{\substack{l=1 \\ l\neq i}}^{k} \prod_{j=1}^{m_l} \bar{P}_i(x_{lj})\right] \cdot \left[\prod_{u=1}^{s} \left[P_i(b_u) - P_i(a_u)\right]\right], \quad x_{ij} < \gamma_{ij} \tag{3.22}$$

Sometimes individuals may enter a study in some manner, that is, the censoring times will be random. It may be noted that (3.21) and (3.22) are conditional on the censoring times being fixed. However, it is clear that if the distribution of censoring times contains no common parameters with $p_i(y)$, the numerical value of the maximum likelihood estimators of the parameters in $p_i(y)$

may still be obtained from (3.21) and (3.22). Yet, the distribution of such estimators may be influenced by the distribution of the random censoring times.

Alternatively, it may be desirable to observe only the failure of the first m individuals, where m is some predetermined integer (m<n). This kind of censoring is known as Type II censoring. Here it is assumed that all individuals are under observation for the same length of time. Suppose that M_i and s denote the same quantities as in Type I censoring. Then, $M_1,\ldots,M_k$ are random variables, but $m = \sum_{i=1}^{k} M_i$ and s are known.

Let $X_{i(j)}$ denote the time of the individual with the j-th longest lifetime among those individuals whose failure is attributed to cause R_i. It will be useful to let $V_{(t)}$ be the time to failure of the individual with the t-th longest lifetime, irrespective of the cause of failure. Thus, the sample consists of the observations $X_{i(j)}$ (i=1,....k; j=1,...,m_i) or, alternatively, $V_{(t)}$ (t=1,...,m).

Note that $V_{(m)} = \max_i X_{i(m_i)}$ denotes the m-th individual to fail and, hence, $V_{(m)}$ will be common censoring time for all individuals.

The likelihood function for Type II censoring is given by

$$L_{II} \propto \prod_{i=1}^{k} L_{IIi}\,, \tag{3.23}$$

where

$$L_{IIi} = \left[\prod_{j=1}^{m_i} p_i(x_{ij})\right]\left[\prod_{\substack{p=1\\p\neq i}}^{k}\prod_{j=1}^{m_l}\bar{P}_i(x_{p(j)})\right]\cdot\left[\bar{P}_i(v_{(m)})\right]^s,\ x_{i(1)} < \ldots < x_{i(m_i)} \tag{3.24}$$

From (3.21) with $\gamma_{(u)} = \gamma$ for all u and (3.24) it is noted that the maximization of the two likelihood functions L_I and L_{II} yields the same estimators if one takes $\gamma = \nu_{(m)}$.

3.3.4. The Case of Grouped Lifetimes

Suppose that the range of variation (g_0, g_{h+1}) of the lifetimes is partitioned into h+1 intervals $I_\alpha = (g_\alpha, g_{\alpha+1})$ such that $0 \le g_0 < g_1 < \ldots < g_{h+1} \le \infty$. Let $N_{i\alpha}$ $(\alpha=0,1,\ldots,h)$ denote the number of individuals failing from cause R_i in I_α. Then $N_{i.} = \sum_{\alpha=0}^{h} N_{i\alpha}$ individuals have failed from cause R_i and $N_{.\alpha} = \sum_{i=1}^{k} N_{i\alpha}$ individuals have failed in I_α. The total sample size is $n = \sum_{i=1}^{k} \sum_{\alpha=0}^{h} N_{i\alpha}$.

The distinguishing feature of such grouped data is that the $N_{i\alpha}$ and g_α contain all the information in the sample. Clearly, the observed number of deaths classified in a two-way table according to cause of death and time interval of death follow a multinomial distribution, i.e., the likelihood function of the $N_{i\alpha}$ is

$$L_G = \frac{n!}{\prod_{i=1}^{k} \prod_{\alpha=0}^{h} n_{i\alpha}!} \prod_{i=1}^{k} \prod_{\alpha=0}^{h} \pi_{i\alpha}^{n_{i\alpha}} , \qquad (3.25)$$

where $\pi_{i\alpha}$ = Pr {individual fails from R_i in I_α}. But

$$\pi_{i\alpha} = \pi_i \left[F_i (g_{\alpha+1}) - F_i(g_\alpha) \right] , \qquad (3.26)$$

where π_i = Pr {failure due to R_i } and F_i is the d.f. of X_i whose p.d.f. is given in (3.13).

3.3.5. The Case of Possible Immunity for Some Individuals

If the net probability of failure from cause R_i over the entire life span, denoted by q_i, is some fraction less than unity then the previous formulae in Sections 3.3.2-3.3.4 need to be altered by replacing $p_i(y)$ and $P_i(y)$ by $q_i p_i(y)$ and $q_i P_i(y)$, respectively.

Note that one q_i, say q_k, may always be taken to be unity by letting R_k represent failure due to all causes other than $R_1,\ldots,R_{k-1}$.

From (3.13) it is seen that the probability of fair due to R_i in the presence of all other risks is

$$\pi_i = \int_0^\infty q_i p_i(x) \prod_{\substack{p=1 \\ p\neq i}}^{k} \left[1 - q_p P_p(x)\right] dx. \tag{3.27}$$

Thus, (3.27) implies that $q_i \geq \pi_i$, which merely states the intuitively obvious fact that as one introduces risks, other than R_i, into the life pattern of an individual the probability of failing from R_i decreases (i.e., is nonincreasing).

The d.f. of X_i and the mean time to failure from cause R_i, from (3.13), is

$$F_i(x) = \frac{1}{\pi_i} \int_0^x q_i p_i(t) \prod_{\substack{p=1 \\ p\neq i}}^{k} \left[1 - q_p P_p(t)\right] dt \tag{3.28}$$

and

$$\mu_{x_i} = E(X_i) = \frac{1}{\pi_i} \int_0^\infty t q_i p_i(t) \prod_{\substack{p=1 \\ p\neq i}}^{k} \left[1 - q_p P_p(t)\right] dt \tag{3.29}$$

3.3.6. Combination of Cases Already Considered:

Suppose M individual lifetimes are observed exactly within some specified time interval (δ_1, δ_2) with M_i individuals failing from cause R_i. Further assume that $N_{i\alpha}$ individuals have failed from R_i in the α-th interval, $(g_\alpha, g_{\alpha+1})$ (the intervals being such that there is no overlap with (δ_1, δ_2) and such that they may be adjacent to one another but need not be) and that

$$S=n-\sum_{i=1}^{k} M_i - \sum_{i=1}^{k}\sum_{\alpha=0}^{h} N_{i\alpha}$$

individuals are known only to be confined in the S intervals (a_u, b_u), u=1,...,s, where (a_u, b_u) do not intersect (δ_1, δ_2) or $(g_\alpha, g_{\alpha+1})$.

Then the general likelihood function is

$$L \propto \prod_{i=1}^{k}\prod_{j=1}^{m_i}\lambda_i(x_{ij}) \prod_{\substack{p=1 \\ p\neq i}}^{k}\bar{P}_i(x_{pj}) \prod_{i=1}^{k}\prod_{\alpha=0}^{h}\pi_{i\alpha}^{n_{i\alpha}} \prod_{u=1}^{s}\prod_{i=1}^{k}[P_i(b_u)-P_i(a_u)] \tag{3.30}$$

where x_{ij} is the lifetime of the j-th individual from R_i in the specified time period (δ_1, δ_2) and $\pi_{i\alpha}$ is as in (3.16). If q_i, the net probability of death due to cause R_i over the entire life span, is not unity for all i, then $p_i(x_{ij})$ and $P_i(x_{ij})$ need to be replaced by $q_i p_i(x_{ij})$ and $q_i P_i(x_{ij})$, respectively.

If there are no observations failing into the categories of being exactly known, grouped, and/or confined, then the first, second, and/or third terms respectively of (3.30) are each taken to be unity, thus, when the causes of failure act independently, most special cases of interest may be deduced from (3.30).

3.4. Relations between Crude, Net, and Partial Crude Probabilities

In the human population the net and partial crude probabilities cannot be estimated directly, but only through their relations with the crude probabilities.

Suppose that k risks of death are acting simultaneously on each individual in the population, and let these risks be denoted by $R_1,\ldots,R_k$. For each risk, R_δ, there is a corresponding hazard rate (or intensity function) $\lambda(t;\delta)$ such that

$\lambda(t;\delta)\Delta + o(\Delta) = Pr$ {an individual alive at time t will die in the interval

$$(t,t+\Delta) \text{ from cause } R_\delta\}, \ \delta=1,\ldots,k \qquad (3.31)$$

and the sum

$$\lambda(t;1)+\ldots+\lambda(t;k)=\lambda(t) \qquad (3.32)$$

is the total intensity. Even though for each risk R_δ the intensity $\lambda(t;\delta)$ is a function of time t, it is assumed that within the time interval (x_i, x_{i+1}) the ratio

$$\frac{\lambda(t;\delta)}{\lambda(t)} = c_{i\delta} \qquad (3.33)$$

is independent of time t, but is a function of the interval (x_i, x_{i+1}) and risk R_δ. The above assumption permits the risk specific intensity $\lambda(t;\delta)$ to vary in absolute magnitude, but requires that it remain a constant proportion of the total intensity in an interval.

If the cause of death is unspecified, the probability that an individual alive at x_i will survive the interval (x_i, x_{i+1}) is

$$p_i = \exp\left\{ - \int_{x_i}^{x_{i+1}} \lambda(t)\, dt \right\}, \quad i = 0,1,.... \tag{3.34}$$

and the probability of dying in this interval for this person is $q_i = 1 - p_i$.

Consider a point t within the interval (x_i, x_{i+1}). The probability that an individual alive at x_i will die from R_δ in interval (t, t+dt) is

$$\exp\left\{ - \int_{x_i}^{t} \lambda(\tau)\, d\tau \right\} \lambda(t;\delta)\, dt \tag{3.35}$$

The first part of this probability gives the probability of surviving from x_i to t when all risks are acting on the population and the second part is the instantaneous death probability from cause R_δ in the time interval (t, t+dt). The crude probability is obtained by summing (3.35) over all possible values of t for $x_i < t \leq x_{i+1}$.

$$Q_{i\delta} = \int_{x_i}^{x_{i+1}} \exp\left\{ - \int_{x_i}^{t} \lambda(\tau)\, d\tau \right\} \lambda(t;\delta)\, dt \tag{3.36}$$

By using the assumption (3.33) of a constant intensity (3.36) may be rewritten as

$$Q_{i\delta} = \frac{\lambda(t;\delta)}{\lambda(t)} \int_{x_i}^{x_{i+1}} \exp\left\{ - \int_{x_i}^{t} \lambda(\tau)\, d\tau \right\} \lambda(t)\, dt \tag{3.37}$$

Integration gives

$$Q_{i\delta} = \frac{\lambda(t;\delta)}{\lambda(t)} \left[1 - \exp\left\{ \int_{x_i}^{x_{i+1}} \lambda(t)\, dt \right\} \right] = \frac{\lambda(t;\delta)}{\lambda(t)} q_i \tag{3.38}$$

so

$$\frac{\lambda(t;\delta)}{\lambda(t)} = \frac{Q_{i\delta}}{q_i} \quad , x_i < t < x_{i+1} \; ; \delta = 1,...,k \tag{3.39}$$

This equality is valid if the ratio of the risk-specific intensity to the total intensity is constant in the interval, and this constant also equal to the ratio of the corresponding probabilities of dying over the entire interval. A trivial equality is obtained, by using (3.32) and (3.39), as

$$Q_{1\delta} + ... + Q_{ik} = q_i \; , \quad i = 0,1,... \tag{3.40}$$

3.4.1. Relations between Crude and Net Probabilities

The net probability of death in the interval $(x_i \; , \; x_{i+1})$ when R_δ is the only operating risk is

$$q_{i\delta} = 1 - \exp\left\{ - \int_{x_i}^{x_{i+1}} \lambda(t;\delta)\, dt \right\} \tag{3.41}$$

Again considering (3.33), (3.41) can be rewritten as

$$q_{i\delta} = 1 - \exp\left\{ - \frac{\lambda(t;\delta)}{\lambda(t)} \int_{x_i}^{x_{i+1}} \lambda(t)\, dt \right\} = 1 - p_i^{\lambda(t;\delta)/\lambda(t)} \tag{3.42}$$

With equation (3.39), (3.42) gives the relation between the net and the crude probabilities,

$$q_{i\delta} = 1 - p_i^{Q_{i\delta}/q_i} \quad , \qquad \delta = 1, ..., k \tag{3.43}$$

The net probability of death when risk R_δ is eliminated can be expressed as

$$q_{i.\delta} = 1 - \exp\left\{ - \int_{x_i}^{x_{i+1}} [\lambda(t) - \lambda(t;\delta)]\,dt \right\}$$
$$= 1 - p_i^{(q_i - Q_{i\delta})/q_i} \qquad (3.44)$$

The net probability is always greater than the corresponding crude probability due to the absence of other competing risks.

$$q_{i\delta} > Q_{i\delta} \qquad (3.45)$$

Moreover, if two risks R_δ and R_ε are such that

$$Q_{i\delta} > Q_{i\varepsilon}$$

then

$$q_{i\delta} > q_{i\varepsilon} \quad \text{and} \quad q_{i.\delta} < q_{i.\varepsilon} \qquad (3.46)$$

3.4.2. Relations between Crude and Partial Crude Probabilities

If the risk R_1 is eliminated from the population, in the presence of all other risks, $Q_{i\delta.1}$ is the partial crude probability that an individual alive at time x_i will die in the interval (x_i, x_{i+1}) from cause R_δ, $\delta = 2,3,\ldots,k$. $Q_{i\delta.1}$ can be expressed in terms of the probabilities p_i and q_i and the crude probabilities Q_{i1} and $Q_{i\delta}$. Using the multiplication and addition theorems as in (3.36), it is obtained that

$$Q_{i\delta.1} = \int_{x_i}^{x_{i+1}} \exp\left\{ - \int_{x_i}^{t} [\lambda(\tau)\,d\tau] \right\} \lambda(t;\delta)\,dt \qquad (3.47)$$

To be able to obtain a simple form of (3.47), it is used from (3.39) that the ratio $\lambda(t;\delta) / [\lambda(t) - \lambda(t;1)]$ is equal to $Q_{i\delta} / (q_i - Q_{i1})$ and is independent of time t. Then the partial crude probability can be rewritten as

$$Q_{i\delta.1} = \frac{\lambda(t;\delta)}{\lambda(t)-\lambda(t;1)} \int_{x_i}^{x_{i+1}} \exp\left\{ -\int_{x_i}^{t} [\lambda(\tau)-\lambda(\tau;1)] \right\} [\lambda(t)-\lambda(t;1)]\,dt$$

$$= \frac{Q_{i\delta}}{q_i - Q_{i1}} \left[1 - \exp\left\{ -\int_{x_i}^{x_{i+1}} [\lambda(t)-\lambda(t;1)] \right\} \right]$$

$$= \frac{Q_{i\delta}}{q_i - Q_{i1}} q_{i.1}\,, \qquad (3.48)$$

Substituting (3.44) for $\delta = 1$ in (3.48) gives the final form

$$Q_{i\delta.1} = \frac{Q_{i\delta}}{q_i - Q_{i1}} \left[1 - p_i^{(q_i - Q_{i1})/q_i} \right], \quad \delta = 2,....,k\,. \qquad (3.49)$$

The sum of $Q_{i\delta.1}$ for $\delta = 2,\ldots,k$ is equal to the net probability of death when risk R_1 is eliminated from the population, and it is obtained that

$$\sum_{i=2}^{k} Q_{i\delta.1} = \sum_{i=2}^{k} \frac{Q_{i\delta}}{q_i - Q_{i1}} \left[1 - p_i^{(q_i - Q_{i1})/q_i} \right] = 1 - p_i^{(q_i - Q_{i1})/q_i} = q_{i.1}, \qquad (3.50)$$

For these three types of probability, p_i and q_i must be between 0 and 1 (with no equality). If q_i is zero ($p_i = 1$), then the crude probability of risk R_δ, $Q_{i\delta}$ is also zero for $\delta = 1,\ldots,k$. Thus, all the formulas related with this becomes meaningless. In other words, if an individual's survival is certain in an interval, it is meaningless to speak of his chance of dying from a specific risk. On the other hand, if p_i is zero ($q_i = 1$), the integral $\int_{x_i}^{x_{i+1}} \lambda(t)\,dt$ in formula (3.34) approaches infinity which is very unrealistic.

3.4.3. Joint Probability Distribution of the Numbers of Death and the Numbers of Survivors

In a given population, deaths are classified according to cause and the number of deaths from each specific cause is the basic random variable for estimating the corresponding probability for the competing risk studies. It is assumed that l_0 denotes the initial population size at age x_0 and l_i represents the number of survivors at the beginning of the interval (x_i, x_{i+1}). The number of deaths, d_i in each time interval is composed with the deaths from risks, $d_{i\delta}$'s , $\delta=1,\ldots,k$ so that

$$d_i = d_{i1}+\ldots+d_{ik} \tag{3.51}$$

and

$$l_i = d_{i1}+\ldots+d_{ik}+l_{i+1},\ i = 0,1,\ldots,k \tag{3.52}$$

Given an individual alive at x_i, the probability $Q_{i\delta}$ of his dying in (x_i, x_{i+1}) from R_δ, $\delta= 1,\ldots,k$, and his probability of surviving, p_i in the interval satisfy the condition

$$1 = Q_{i1}+\ldots+Q_{ik}+p_i \tag{3.53}$$

Hence, given l_i individuals alive at x_i, the conditional distribution of $d_{i\delta}$ and l_{i+1} is multinomial with probability distribution

$$\frac{l_i!}{\prod_{\delta=1}^{k} d_{i\delta}!\, l_{i+1}!} \prod_{\delta=1}^{k} Q_{i\delta}^{d_{i\delta}}\, p_i^{l_{i+1}}, \tag{3.54}$$

and the corresponding probability generating function, p.g.f., is

$$g_{d_{i\delta}, l_{i+1}|\, l_i}(s_{i\delta}, s_{i+1}) = E\left(\prod_{\delta=1}^{k} s_{i\delta}^{d_{i\delta}}\, s_{i+1}^{l_{i+1}} \,|\, l_i\right) = \left(\sum_{\delta=1}^{k} Q_{i\delta}\, s_{i\delta} + p_i\, s_{i+1}\right)^{l_i}, \qquad (3.55)$$

where $|s_{i\delta}| \le 1$ and $|s_i| \le 1$.

From (3.54) and (3.55), for any positive integer u the joint probability distribution of all the random variables $d_{i1}, \ldots, d_{ik}, l_{i+1}$ for i=0,1,…,u is

$$\prod_{i=0}^{u} \frac{l_i!}{\prod_{\delta=1}^{k} d_{i\delta}!\, l_{i+1}!} Q_{i1}^{d_{i1}} \ldots Q_{ik}^{d_{ik}}\, p_i^{l_{i+1}} \qquad (3.56)$$

with $d_{i\delta}$ and l_{i+1} satisfying (3.52). Then, the corresponding p.g.f. is defined as

$$G_{d_{i\delta}, l_{i+1}|\, l_0}(s_{i\delta}, s_{i+1}) = E\left(\prod_{i=0}^{u} s_{i1}^{d_{i1}} \ldots s_{ik}^{d_{ik}} s_{i+1}^{l_{i+1}} \,|\, l_0\right) \qquad (3.57)$$

Direct computation gives

$$G_{d_{i\delta}, l_{i+1}|\, l_0}(s_{i\delta}, s_{i+1}) = \left[\sum_{\delta=1}^{k} Q_{0\delta}\, s_{0\delta} + \sum_{j=1}^{u}\left(\prod_{i=0}^{j-1} p_i\, s_{i+1}\right)\left(\sum_{\delta=1}^{k} Q_{j\delta}\, s_{j\delta}\right) + \prod_{i=0}^{u} p_i\, s_{i+1}\right]^{l_0} \qquad (3.58)$$

(3.58) holds true for u=0. In this case (3.58) becomes

$$\left(\sum_{\delta=1}^{k} Q_{0\delta}\, s_{0\delta} + p_0\, s_1\right)^{l_0} \qquad (3.59)$$

which is identical to (3.55) for i=0. Suppose that (3.58) is true for u=1; then it will be proved that (3.58) is true also for u. By this inductive assumption, it is obtained that

$$E\left(\prod_{i=0}^{u-1}\prod_{\delta=1}^{k} s_{i\delta}^{d_{i\delta}}\, s_{i+1}^{l_{i+1}} \mid l_0\right)=\left[\sum_{\delta=1}^{k} Q_{0\delta}\, s_{0\delta}+\sum_{j=1}^{u-1}\left(\prod_{i=0}^{j-1} p_i\, s_{i+1}\right)\left(\sum_{\delta=1}^{k} Q_{j\delta}\, s_{j\delta}\right)+\prod_{i=0}^{u-1} p_i\, s_{i+1}\right]^{l_0} \tag{3.60}$$

Then the p.g.f. (3.57) can be rewritten as

$$G_{d_{i\delta},\, l_{i+1}\mid l_0}(s_{i\delta}, s_{i+1})=E\left[\left\{\prod_{i=0}^{u-1}\left(\prod_{\delta=1}^{k} s_{i\delta}^{d_{i\delta}}\, s_{i+1}^{l_{i+1}}\right)\right\} E\left\{\prod_{\delta=1}^{k} s_{u\delta}^{d_{u\delta}}\, s_{u+1}^{l_{u+1}}\right\} \mid l_0\right] \tag{3.61}$$

Since the distribution of $d_{u1},\ldots,d_{uk}$ and l_{u+1} is dependent only on the number of survivors (l_u) at the beginning of the interval (x_u , x_{u+1}). Then, the above conditional expectation is the p.g.f. of the conditional probability distribution of $d_{u1},\ldots,d_{uk}$ and l_{u+1}. Thus, (3.55) can be substituted in (3.61) to give

$$\begin{aligned} G_{d_{i\delta},\, l_{i+1}\mid l_0}(s_{i\delta}, s_{i+1}) &= E\left[\left\{\prod_{i=0}^{u-1}\left(\prod_{\delta=1}^{k} s_{i\delta}^{d_{i\delta}}\, s_{i+1}^{l_{i+1}}\right)\right\} E\left\{\prod_{\delta=1}^{k} Q_{u\delta}\, s_{u\delta}+p_u\, s_{u+1}\right\} \mid l_0\right] \\ &= E\left[\left\{\prod_{i=0}^{u-2}\left(\prod_{\delta=1}^{k} s_{i\delta}^{d_{i\delta}}\, s_{i+1}^{l_{i+1}}\right)\right\}\left\{\prod_{\delta=1}^{k} s_{u-1,\delta}^{d_{u-1}}\, z_u^{l_u}\right\} \mid l_0\right] \end{aligned} \tag{3.62}$$

where

$$z_u = s_u\left\{\sum_{\delta=1}^{k} Q_{u\delta}\, s_{u\delta}+p_u\, s_{u+1}\right\} \tag{3.63}$$

is less than unity in absolute value. Due to (3.60), the formula (3.62) becomes

$$G_{d_{i\delta},\, l_{i+1}|\, l_0}(s_{i\delta}, s_{i+1}) = \left[\sum_{\delta=1}^{k} Q_{0\delta}\, s_{0\delta} + \sum_{j=1}^{u-1} \left(\prod_{i=0}^{j-1} p_i\, s_{i+1} \right) \left(\sum_{\delta=1}^{k} Q_{j\delta}\, s_{j\delta} \right) + \left(\prod_{i=0}^{u-2} p_i\, s_{i+1} \right) p_{u-1} z_u \right]^{l_0} \tag{3.64}$$

Using (3.63), the last term inside the brackets can be rewritten as

$$\begin{aligned} \left(\prod_{i=0}^{u-2} p_i\, s_{i+1} \right) p_{u-1}\, z_u &= \left(\prod_{i=0}^{u-2} p_i\, s_{i+1} \right) p_{u-1}\, s_u \left(\sum_{\delta=1}^{k} Q_{u\delta}\, s_{u\delta} + p_u\, s_{u+1} \right) \\ &= \left(\prod_{i=0}^{u-1} p_i\, s_{i+1} \right) \left(\sum_{\delta=1}^{k} Q_{u\delta}\, s_{u\delta} \right) + \prod_{i=0}^{u} p_i\, s_{i+1} \end{aligned} \tag{3.65}$$

When (3.65) is substituted in (3.64), the resulting expression becomes identical to (3.58) and the proof is complete.

The generating function (3.58) assumes a value of unity at the point $(s_{i1},\ldots,s_{ik},s_{i+1}) = (1,\ldots,1,1)$ for $i = 0,1,\ldots,u$,

$$\begin{aligned} G_{d_{i\delta},\, l_{i+1}|\, l_0}(1,1) &= \left[\sum_{\delta=1}^{k} Q_{0\delta} + \sum_{j=1}^{u} \left(\prod_{i=0}^{j-1} p_i \right) \left(\sum_{\delta=1}^{k} Q_{j\delta} \right) + \prod_{i=0}^{u} p_i \right]^{l_0} \\ &= \left(q_0 + p_0 q_1 + \ldots + p_0 p_1 \ldots p_{u-1} q_u + p_0 p_1 \ldots p_u \right)^{l_0} = 1 \end{aligned} \tag{3.66}$$

Hence, the sum of the probabilities in (3.66) over all possible values of the random variables is one.

By using the p.g.f. in (3.58), the moments of the random variables $d_{i\delta}$ and l_i can be calculated easily. Then, the expectations are

$$E\left(d_{i\delta} \,|\, l_0 \right) = l_0\, p_{0i}\, Q_{i\delta} \;,\; \delta = 1,\ldots,k, \tag{3.67}$$

and

$$E\left(l_i \,|\, l_0 \right) = l_0\, p_{0i} \;,\; i = 0,1,\ldots, \tag{3.68}$$

where $p_{0i} = p_0\, p_1 \ldots p_{i-1}$ is the probability that an individual alive at age x_0 will survive to x_i, and $p_{0i}\, Q_{i\delta}$ is the probability that an individual will die in the interval (x_i, x_{i+1}) from cause R_δ.

Moreover, the variances and the covariances are

$$\sigma^2_{d_{i\delta}|l_0} = l_0 p_{0i} Q_{i\delta} (1 - p_{0i} Q_{i\delta}), \tag{3.69}$$

and

$$\sigma_{d_{i\delta}, d_{j\delta}|l_0} = -l_0 p_{0i} Q_{i\delta} p_{0j} Q_{i\varepsilon}, \quad \delta \neq \varepsilon; \quad \delta, \varepsilon = 1,\ldots,k; \; i, j = 0,1,\ldots \tag{3.70}$$

The covariance between the number dying and the number surviving can be obtained in a similar way as

$$\sigma^2_{d_{i\delta}, l_j|l_0} = -l_0 p_{0i} Q_{i\delta}\, p_{0j}, \tag{3.71}$$

and

$$\sigma_{l_i, d_{j\delta}|l_0} = l_0 (1 - p_{0i}) p_{0j} Q_{j\delta}, \quad \delta = 1,..,k; \; i < j; \; i, j = 0,1,\ldots, \tag{3.72}$$

The positive covariance in (3.72) indicates that the larger the number of survivors at age x_i, the greater the probability that a larger number of deaths from R_δ will occur in a subsequent interval (x_j, x_{j+1}). The covariance between l_i and l_j for $i \leq j$

$$\sigma_{l_i, l_j|l_0} = l_0 (1 - p_{0i}) p_{0j} \tag{3.73}$$

As a conclusion of all the above work it can be said that, for each u, the random variables $d_{i\delta}$ and l_{i+1} for i = 0,1,…,u; δ = 1,…,k form a chain of multinomial distributions with the probability distribution and the p.g.f. in (3.56) and (3.58), respectively.

3.4.4. Estimation of the Crude, Net and Partial Crude Probabilities

By using the relations among crude, net and partial crude probabilities and the joint probability distribution of $d_{i\delta}$ and l_i, first the crude probabilities and then net and partial crude probabilities are estimated.

The estimators of the crude probabilities $Q_{i\delta}$ and p_i can be found from the joint probability function

$$\prod_{i=0}^{u} \frac{l_i!}{d_{i1}!\dots d_{ik}!\,l_{i+1}!} Q_{i1}^{d_{i1}} \dots Q_{ik}^{d_{ik}} p_i^{l_{i+1}} \tag{3.74}$$

by using the maximum likelihood principle. In addition, the Neyman's reduced χ^2 method [Neyman, (1949)] can be used to estimate crude probabilities.

According to Neyman's theory, the best estimators of $Q_{i\delta}$ minimize the reduced form of the χ^2:

$$\chi_0^2 = \sum_{i=0}^{u} \left[\sum_{\delta=1}^{k} \frac{(d_{i\delta} - l_0 p_{0i} Q_{i\delta})^2}{d_{i\delta}} + \frac{\left\{ l_{i+1} - l_0 p_{0i} \left(1 - \sum_{\delta=1}^{k} Q_{i\delta} \right) \right\}^2}{l_{i+1}} \right]. \tag{3.75}$$

The substitution of

$$p_i = 1 - \sum_{\delta=1}^{k} Q_{i\delta} \tag{3.76}$$

in (3.75) makes it necessary to derive only the minimizing value $\hat{Q}_{i\delta}$. The complement of the sum of $\hat{Q}_{i\delta}$ is the estimator $\hat{p}_i$. Taking derivatives of χ_0^2 with respect to $Q_{i\delta}$ and setting the derivatives equal to zero gives the equations

$$\frac{\hat{Q}_{i\delta}}{d_{i\delta}} = \frac{\hat{p}_i}{l_{i+1}}, \delta = 1,\ldots,k \tag{3.77}$$

For each i, sum of (3.77) is taken over δ and obtains

$$\frac{\hat{p}_i}{l_{i+1}} = \frac{\sum_{\delta=1}^{k} \hat{Q}_{i\delta} + \hat{p}_i}{\sum_{\delta=1}^{k} d_{i\delta} + l_{i+1}} \frac{1}{l_i}. \tag{3.78}$$

Substituting (3.78) in (3.77) gives the estimate of p_i and $Q_{i\delta}$ as

$$\hat{p}_i = \frac{l_{i+1}}{l_i} \tag{3.79}$$

and

$$\hat{Q}_{i\delta} = \frac{d_{i\delta}}{l_i}. \tag{3.80}$$

It is understand from reduced χ^2 in (3.75) that if for some age x_w all the l_w individuals alive at x_w die during the interval (x_w, x_{w+1}), the $d_{i\delta} = 0$ and $l_i = 0$ for all $i > w$, so that there is no contribution to the reduced χ^2 beyond the w-th term.

The estimators in (3.79) and (3.80) are recognized as maximizing values of the joint probability (3.56). Hence, Neyman's reduced χ^2 methods yields the same estimators found by the maximum likelihood principle. These estimators are unique, unbiased and efficient estimators of the corresponding probabilities.

Variances and covariances of the estimators in (3.79) and (3.80) can be obtained by direct computation.

$$\mathrm{Var}\left(\hat{Q}_{i\delta}\middle| l_0\right)=E\left(\frac{1}{l_i}\right)Q_{i\delta}\left(1-Q_{i\delta}\right), \tag{3.81}$$

$$\sigma^2_{\hat{p}_i|\,l_0}=\sigma^2_{\hat{q}_i|\,l_0}=E\left(\frac{1}{l_i}\right)p_i\,q_i\,, \tag{3.82}$$

$$\mathrm{Cov}\left(\hat{Q}_{i\delta},\hat{Q}_{j\varepsilon}\middle| l_0\right)=\begin{cases}-E\left(\frac{1}{l_i}\right)Q_{i\delta}\,Q_{i\varepsilon}, & j=i\\ 0\,, & j\neq i\end{cases} \tag{3.83}$$

$$\mathrm{Cov}\left(\hat{p}_i,\hat{p}_j\middle| l_0\right)=\mathrm{Cov}\left(\hat{q}_i,\hat{q}_j\middle| l_0\right)=0, \quad j\neq i \tag{3.84}$$

and

$$\mathrm{Cov}\left(\hat{p}_i,\hat{Q}_{i\delta}\middle| l_0\right)=\begin{cases}-E\left(\frac{1}{l_i}\right)p_i\,Q_{i\delta}\,, & j=i\\ 0, & j\neq i\end{cases} \tag{3.85}$$

When the original cohort l_0 is large, the expectation of the reciprocal of l_i may be approximated by the reciprocal of the expectation $E(l_i)$.

Using the relation with the crude probabilities can derive formulas for the estimators of the net and partial crude probabilities. Substituting (3.79) and (3.80) in the formulas (3.43), (3.44) and (3.49) gives the following estimators;

$$\hat{q}_{i\delta} = 1 - \left(\frac{l_{i+1}}{l_i} \right)^{d_{i\delta}/d_i}, \quad \delta = 1,\ldots,k ; \tag{3.86}$$

$$\hat{q}_{i.\delta} = 1 - \left(\frac{l_{i+1}}{l_i} \right)^{(d_i - d_{i\delta})/d_i}, \quad \delta = 1,\ldots,k ; \tag{3.87}$$

$$\hat{Q}_{i\delta.1} = \frac{d_{i\delta}}{d_i - d_{i1}} \left[1 - \left(\frac{l_{i+1}}{l_i} \right)^{(d_i - d_{i1})/d_i} \right], \quad \delta = 2,\ldots,k ; \tag{3.88}$$

$$\hat{Q}_{i\delta.12} = \frac{d_{i\delta}}{d_i - d_{i1} - d_{i2}} \left[1 - \left(\frac{l_{i+1}}{l_i} \right)^{(d_i - d_{i1} - d_{i2})/d_i} \right], \quad \delta = 3, \ldots, k ; \; i = 0, 1,\ldots,u \tag{3.89}$$

For each i, the sum of the estimators $\hat{Q}_{i\delta.1}$ over δ is equal to $\hat{q}_{i.1}$:

$$\sum_{\delta=1}^{k} \hat{Q}_{i\delta.1} = \sum_{\delta=1}^{k} \frac{d_{i\delta}}{d_i - d_{i1}} \left[1 - \left(\frac{l_{i+1}}{l_i} \right)^{(d_i - d_{i1})/d_i} \right]$$

$$= 1 - \left(\frac{l_{i+1}}{l_i} \right)^{(d_i - d_{i1})/d_i} = \hat{q}_{i.1}. \tag{3.90}$$

The variances and covariances of the net and the partial crude probabilities were found by Chiang, 1968.

3.5. Identifiability

Let X be an observable random variable with distribution function F_θ and let $F_\theta \varepsilon \Im = \{F_\theta : \theta \varepsilon \Omega\}$, a family of distributions indexed by a parameter θ, where θ could be a scalar or vector valued. θ is said to be nonidentifiable by X if there is at

least one pair (θ,θ'), $\theta\neq\theta'$, where θ and θ' are both in Ω, such that $F_\theta(x)=F_{\theta'}(x)$ for all x. In the contrary case, θ is said to be identifiable.

In many cases, where θ is not identifiable, there exists a nonconstant function $\gamma(\theta)$ which is identifiable. That is, for any $\theta,\theta' \varepsilon \Omega$, $F_\theta(x)=F_{\theta'}(x)$ for all x implies $\gamma(\theta)=\gamma(\theta')$. In this case θ is said to be partially identifiable.

In case θ is not identifiable by X, it may be possible to introduce an additional random variable Δ so that θ is identifiable by the augmented random variable (X,Δ). In this case the original identifiability problem is called rectifiable.

Suppose the nonnegative random variable Y_i represents the theoretical lifetime of an individual when R_i is the only cause of failure (i=1,...,k). In the presence of all k causes R_p (p=1,...,k), only the smallest of the Y_p can be observed with the actual cause of failure, say R_i. Hence, observed values can be expressed as $X_i=\min_p Y_p$ conditional on knowing the cause of failure to be R_i. Then, the probability of failure due to cause R_i is $\pi_i=\Pr(Y_i=\min_p Y_p)$. If the Y_p have an absolutely continuous joint distribution with pdf $p(y_1,...,y_k)$, then the pdf of the observed lifetime X_i (i=1,...,k) of an individual dying from R_i can be written as

$$f_i(x)=\frac{1}{\Pi_i}\int_x^\infty\cdots\int_x^\infty p(y_1,\ldots,y_{i-1},x,y_{i+1},\ldots,y_k)\prod_{\substack{p=1\\p\neq i}}^{k}dy_p$$

$$=\frac{1}{\Pi_i}p_i(x)\int_x^\infty\cdots\int_x^\infty p(y_1,\ldots,y_{i-1},y_{i+1},\ldots,y_k|Y_i=x)\prod_{\substack{p=1\\p\neq i}}^{k}dy_p \qquad (3.91)$$

It is seen that the distribution of X_i (i=1,...,k) is determined by the joint distribution of Y_p (p=1,...,k). The reverse is not true. This means that, the distributions of X_i's do not identify the joint distribution of Y_i's.

The question of identifiability has arisen when there is a departure from the assumption of independence among competing risks.

It can be shown that the pdf of $f_i(x)$ in (3.91) can always be represented in the form

$$f_i(x)) = \frac{1}{\pi_i} p_i(x) \prod_{\substack{p=1 \\ p \neq i}}^{k} \bar{P}\ (x) \tag{3.92}$$

where $p_i(x)$ is the pdf of Y_i and $\bar{P}_p(x) = Pr(Y_p > x)$, by suitable choice of independent varieties Y_i^* having pdf $p_i^*(y)$ (i=1,…,k). Hence, the dependent risk model with pdf $p(y_1,\ldots,y_k)$ is distinguishable from the independent risk model with pdf $\prod_{i=1}^{k} p_i^*(y_i)$.

A result of independent interest linking the densities of Z=min Y_p and of the X_i is stated as $f_Z(x) = \sum_{i=1}^{k} \pi_i f_i(x)$. This follows that Z equals X_i with probability π_i (i=1,..,k). Applied to Y_i^* in $f_i(x) = \frac{1}{\pi_i} \lambda_i(x) \bar{F}_Z(x)$ where $\lambda_i(x)$ is the hazard function and $\bar{F}_Z(x)$ is the survival function of Z, it is seen that

$$\pi_i\ f_i(x) = \lambda_i^*(x)\, \bar{F}_Z^*(x) \tag{3.93}$$

Then, $f_Z(x)=\lambda_Z^*(x)\ \bar{F}_Z^*(x) = f_Z^*(x)$. Correspondingly $\bar{F}_Z(x) = \bar{F}_Z^*(x)$, so that

$$\lambda_i^*(x) = \frac{\pi_i f_i(x)}{\bar{F}_Z(x)} \tag{3.94}$$

This leads to

$$P_i^*(x) = \exp\left[-\int_0^x \frac{\pi_i f_i(t)}{\bar{F}_Z(t)}\,dt\right] \tag{3.95}$$

by specifying the independent risk model. If the risks are in fact independent, then

$$\lambda_i^*(x) = \frac{p_i(x)\prod_{\substack{p=1\\p\neq i}}^{k}\bar{P}_p(x)}{\prod_{i=1}^{k}\bar{P}_i(x)} = \lambda_i(x) \tag{3.96}$$

If the joint pdf of $Y_1,\ldots,Y_k$ is specified as the known distribution functions, then there will be no difficulty in identifying the model fully. Since the unknown parameters can be estimated from the likelihood function. With respect to such a model the independence assumption can be tested.

3.6. Specific Distributions - Independent Risks

3.6.1. Exponential Life Distributions

The exponential distribution has an important position in describing the time to failure of items in reliability studies, in describing human and animal lifetimes. The fundamental reasons for the exponential distribution's popularity are due to its ability to provide a reasonable fit to some life data, its simple mathematical form so that inferential statements can be made with more tractability, and its association with the theory of Poisson processes. It holds the unique position of being the only continuous distribution with a constant hazard rate and lack of memory property. Because an understanding of the exponential distribution is helpful in studying the more general distributions, it will be introduced first.

3.6.1.1. All Lifetimes and Associated Causes of Failure Known

The exponential p.d.f. of a random variable with mean θ_i is

$$p_i(y) = (1/\theta_i) \exp(-y/\theta_i) \ , \ \theta_i>0 \ , \ y>0, \ i = 1,\ldots,k \qquad (3.97)$$

It will often be convenient to use the hazard rate $\lambda_i = 1/\theta_i$. From (3.18), the likelihood estimates (MLE's) are

$$\hat{\theta}_i = t/n_i, \ i = 1,..,k, \qquad (3.98)$$

where $t = \sum_{i=1}^{k}\sum_{j=1}^{n_i} x_{ij}$.

It follows from the likelihood function $L = \prod_{i=1}^{k} L_i$, that $(T, N_1, \ldots, N_{k-1})$ is a sufficient statistics for $(\theta_1,\ldots,\theta_k)$ and so $\left(\hat{\theta}_1,...,\hat{\theta}_k\right)$ is sufficient for $(\theta_1,\ldots,\theta_k)$; completeness may also be established. It seen from (3.13) and the readily obtained result

$$\pi_i = \lambda_i / \lambda \qquad (3.99)$$

and

$$f_i(x) = \lambda \exp(-\lambda x), \quad x>0 \qquad (3.100)$$

where $\lambda = \sum_{i=1}^{k}\lambda_i = \sum_{i=1}^{k}\left(1/\theta_i\right)$.

Hence, the observed lifetimes are identically distributed irrespective of the cause of failure. Also the density of $Z = \min_{p} Y_p$ is identically equal to those of the X_i in (3.100). This property holds for a much larger class of distributions.

Since the X_{ij}'s are independent and identical exponential variates, the density of T is

$$f(t) = \left[\lambda^n / \Gamma(n)\right] t^{n-1} \exp(-\lambda t) \ , \ t>0. \tag{3.101}$$

This density is conditional on $N_i = n_i$ (i = 1,...,k) but it is clearly identical to the unconditional density. Hence T is independent of N_i. The asymptotic variance to order 1/n is

$$\mathrm{Var}\left(\hat{\theta}_i\right) = \lambda\theta_i^3 / n \ , \ i = 1,\ldots,k \tag{3.102}$$

which may be determined from the information matrix or directly from (3.98) employing the independence of T and N_i.

For finite samples, it is tempted to use

$$E(\hat{\theta}_i^r) = E(T^r)\, E(1/N_i^r) \tag{3.103}$$

but $E(1/N_i^r)$, where r is a positive integer, is infinite since a finite probability is associated with the event $N_i = 0$. Thus a slight modification of the estimator is needed if one is to examine finite sample properties. Consider the estimator $\hat{\theta}_i^*$, where $\hat{\theta}_i^*$ is $\hat{\theta}_i$ conditional on $N_i>0$. The p.d.f. of this conditional estimator $\hat{\theta}_i^* = T/N_i^*$, where N_i^* is a binomial (n, π_i) variate truncated at 0, is obtained to be

$$f\left(\hat{\theta}_i^*\right) = \frac{\lambda^n \hat{\theta}_i^{*\,n-1}}{\Gamma(n)\left[1-(1-\pi_i)^n\right]} \sum_{n_i=1}^{n} \left[\binom{n}{n_i} \pi_i^{n_i} (1-\pi_i)^{n-n_i} n_i^n \exp\left[-\lambda n \hat{\theta}_i^*\right]\right], \hat{\theta}_i^*>0. \tag{3.104}$$

The moments of $\hat{\theta}_i^*$ can be evaluated directly from (3.104) or taken advantage of the independence of T and N_i^*. It is found that

$$E(\hat{\theta}_i^*) = [\, n \; E(\, 1/N_i^*)] \,/\, \lambda \tag{3.105}$$

and

$$\text{Var}\,(\hat{\theta}_i^*) = n \,\{\, (n+1)\, E(\, 1/N_i^{*\,2}) - n \,[\, E(\, 1/N_i^*)]^2 \;\} \,/\, \lambda^2. \tag{3.106}$$

Also, from (3.104), by making the transformation $\frac{1}{2}x = \lambda n_i \hat{\theta}_i^*$ it is obtained that

$$\Pr\left\{\hat{\theta}_i^* \geq \theta_0\right\} = \frac{(1-\pi_i)^n}{1-(1-\pi_i)^n} \sum_{n_i=1}^{n} \binom{n}{n_i} \cdot \left(\frac{\pi_i}{1-\pi_i}\right)^{n_i} \int_{2\lambda n_i \theta_0}^{\infty} \frac{1}{\Gamma(n) 2^n} x^{n-1} e^{-x/2} dx \tag{3.107}$$

which is just a weighted sum of chi-squared integrals.

It is of interest to note that, for discrete time models with a single cause of failure, estimators of conception rate (a type of hazard rate) are of the same form as $\hat{\lambda}_i = 1/\hat{\theta}_i$, which from (3.98) and the invariance property of MLE's is

$$\hat{\lambda}_i = n_i / t, \quad i = 1,\ldots,k \tag{3.108}$$

namely, the number of conceptions divided by the number of months of exposure. These estimators are sufficient, as below (3.98).

Since from (3.101) it is observed that

$$E(1/T) = \lambda / (n-1), \qquad E(1/T^2) = \lambda^2 / (n-1)(n-2),$$

it follows that

$$\hat{\lambda}_i' = \left(\frac{n-1}{n}\right) \cdot \left(\frac{N_i}{T}\right) \tag{3.109}$$

it is the best unbiased estimate of λ_i and that for $n>2$

$$\text{var}(\hat{\lambda}_i') = [(n-1)\lambda\lambda_i + \lambda_i^2] / n(n-2) \tag{3.110}$$

$$\text{cov}(\hat{\lambda}_i^2, \hat{\lambda}_j') = \lambda_i \lambda_j / n(n-2), \; i \neq j. \tag{3.111}$$

Therefore unbiased, consistent estimators of the hazard rate, λ_i, whose variances and covariances are relatively simple quantities are obtained.

3.6.1.2. Censored Observations

Employing the notation for Type I censoring of Section 3.3.3., the MLE of θ_i from (3.21) can be obtained as

$$\hat{\theta}_i = \left(t + \sum_{u=1}^{s} \gamma_{(u)}\right) / m_i \tag{3.112}$$

The asymptotic variances to order 1/n are given by (3.102).

For Type II censoring, the MLE of θ_i, similar to (3.112), can be written as

$$\hat{\theta}_i = \left(t + s\nu_{(m)}\right) / m_i . \tag{3.113}$$

Like (3.112), this has the familiar interpretation total time on test/number of failed items. Asymptotic variances may be obtained from the information matrix, using lower moments of order statistics from an exponential variate, as

$$\text{var}(\hat{\theta}_i) = \lambda\ \theta_i^3/m. \tag{3.114}$$

3.6.1.3. Grouped Observations

To avoid duplication of methods, the details for exponential will be given as a special case of the Weibull distribution with c=1 in section 3.6.2.3.

3.6.1.4. Crude, Net, and Partial Crude Probabilities

Invoking the invariance property of MLE's, the MLE of crude, net, and partial crude probabilities of failure from R_i (as defined in Section 3.2) within the interval (a,b) can be written as

$$\hat{Q}_i(a,b) = \hat{\lambda}_i\left\{1-\exp\left[-\hat{\lambda}(b-a)\right]\right\}/\hat{\lambda}, \tag{3.115}$$

$$\hat{q}_i = 1-\exp\left[-\hat{\lambda}_i(b-a)\right], \tag{3.116}$$

and

$$\hat{Q}_{i.j}(a,b) = \hat{\lambda}_i\left\{1-\exp\left[-(\hat{\lambda}-\hat{\lambda}_j)\cdot(b-a)\right]\right\}/(\hat{\lambda}-\hat{\lambda}_j), \quad i \neq j, \tag{3.117}$$

where $\hat{\lambda} = \sum_{i=1}^{k}\hat{\lambda}_i$ and $\hat{\lambda}_i = 1/\hat{\theta}_i$. Berkson and Elveback (1960) arrive (3.115) and (3.116) in their discussion of competing exponential risks in the reference to smoking and lung cancer.

All the formulas used in the above section are referenced to David and Moeschberger (1978).

3.6.2. Weibull Lifetime Distribution

As early as 1939, Weibull proposed a distribution, to which his name has later become affixed, to describe the life length of materials. Although the Weibull distribution whose p.d.f. may be written as

$$p_i(y) = \left[c_i (y - w_i)^{c_i - 1} / \theta_i\right] \exp\left[-(y - w_i)^{c_i} / \theta_i\right], \; y > w_i, \; \theta_i > 0, \; c_i > 0 \qquad (3.118)$$

has been discussed in the literature under various topics, for example; extreme value theory and reliability theory, it has only recently been advanced as also a very desirable family of distributions for describing human or animal survival. The Weibull distribution has a finite starting point and is thus logical choice within the framework of survival studies. Furthermore, within the class of distributions possessing proportional failure rates the Weibull appears to be the most appropriate choice in describing lifetimes.

Efforts to determine the Weibull distribution's ability to describe survival data adequately include studies involving time to occurrence of skin tumors or cancer in experimental mice that were painted with various carcinogenic agents and many types of human cancers. Each of above studies concluded that Weibull model did quite well in fitting the data.

Moreover, the Weibull distribution possesses the interesting property of allowing its hazard rate to be increasing ($c_i > 1$), constant ($c_i = 1$), or decreasing ($c_i < 1$). This degree of flexibility would appear to be desirable.

In the remainder of this discussion the lower limit of the lifetimes will be taken as zero, that is, $w_i=0$ in (3.118), so that the working p.d.f. will be

$$p_i(y) = \left[c_i (y)^{c_i-1} / \theta_i\right] \left[\exp\left[-(y)^{c_i} / \theta_i\right]\right], \quad y>0, \theta_i>0, c_i>0 \tag{3.119}$$

3.6.2.1. Type I Censoring with Equal Shape Constants

If there exists different censoring times for each individual, the forms in (3.19) and (3.119) becomes

$$\ln L_I = \text{const.} + m \ln c - \sum_{i=1}^{k} m_i \ln \theta_i + (c-1) \sum_{i=1}^{k} \sum_{j=1}^{m_i} \ln x_{ij} - \lambda \left(\sum_{i=1}^{k} \sum_{j=1}^{m_i} x_{ij}^{c} + \sum_{u=1}^{s} \gamma_{(u)}^{c} \right), \tag{3.120}$$

where $\lambda = \sum_{i=1}^{k} (1/\theta_i)$.

Thus the likelihood equations are

$$\hat{\theta}_i = \left(\hat{t}_c + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}} \right) / m_i, \; i = 1,\ldots,k \tag{3.121}$$

and

$$\left(\frac{m}{\hat{c}} + \sum_{i=1}^{k} \sum_{j=1}^{m_i} \ln x_{ij} \right) \left(\hat{t}_c + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}} \right) / m = \sum_{i=1}^{k} \sum_{j=1}^{m_i} \left(x_{ij}^{\hat{c}} \ln x_{ij} \right) + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}} \ln_{(u)} \tag{3.122}$$

where $\hat{t}_c = \sum_i \sum_j x_{ij}^{\hat{c}}$. Clearly, once $\hat{c}$ is obtained by iterative techniques from (3.122), the $\hat{\theta}_i$ will be trivially determined.

From (3.120), the second derivatives are found to be

$$\frac{\partial^2 \ln L_I}{\partial \theta^2} = \frac{m_i}{\theta_i^2} - \frac{2}{\theta_i^3}\left[t_c + \sum_{u=1}^{s} \gamma_{(u)}^c\right], \; i = 1,\ldots,k \qquad (3.123)$$

$$\frac{\partial^2 \ln L_I}{\partial \theta_i \partial c} = \frac{\partial^2 \ln L_I}{\partial c \partial \theta_i} = \left[\sum_{i=1}^{k}\sum_{j=1}^{m_i}\left(x_{ij}^c \ln x_{ij}\right) + \sum_{u=1}^{s} \gamma_{(u)}^c \ln \gamma_{(u)}\right] / \theta_i^2, \qquad (3.124)$$

and

$$\frac{\partial^2 \ln L_I}{\partial c^2} = -\frac{m}{c^2} - \lambda\left[\sum_{i=1}^{k}\sum_{j=1}^{m_i} x_{ij}^c \left(\ln x_{ij}\right)^2 + \sum_{u=1}^{s} \gamma_{(u)}^c \left(\ln \gamma_{(u)}\right)^2\right]. \qquad (3.125)$$

as in the exponential case, it will often be notationally convenient to set $\lambda_i = 1/\theta_i$ (David and Moeschberger, 1978).

If there are no censored observations, then the density of observed time to failure from cause R_i is found from (3.13), upon noting that $\pi_i = \lambda_i / \lambda$ as in (3.99), to be

$$f_i(x) = c\lambda x^{c-1} \exp\left(-\lambda x^c\right), \; x>0. \qquad (3.126)$$

Thus the observed lifetimes are again identically distributed irrespective of the cause of failure. Also, as for the exponential case, the density of $Z = \min_p Y_p$ is identically equal to those of the X_i in (3.126).

In the light of (3.126) it will be useful to return to the notation introduced in Section 3.3.3. Let $V_1,\ldots,V_n$ be the lifetimes of the n sampled individuals, irrespective of cause of death, with corresponding censoring times $\gamma_1,\ldots,\gamma_n$. Now, (3.126) gives the common density of the V_t (t=1,…,n) and hence, for the censoring situation of primary interest in this section, one has

$$f(v_t | V_t < \gamma_t) = c\lambda v_t^{c-1} \exp(-\lambda v_t^c) / [1 - \exp(-\lambda \gamma_t^c)], \tag{3.127}$$

where $\Pr\{V_t < \gamma_t\} = 1 - \exp(-\lambda \gamma_t^c)$.

It may be shown that

$$E(-\partial^2 \ln L_I / \partial \theta_i^2) = \left\{ \sum_{t=1}^{n} [1 - \exp(-\lambda \gamma_t^c)] \right\} / \lambda \theta_i^3 \tag{3.128}$$

$$E\left(\frac{\partial^2 \ln L_I}{\partial \theta_i \partial c} \right) = -\sum_{t=1}^{n} \{ [1 - \exp(-\lambda \gamma_t^c)] E(V_t^c \ln V_t | V_t < \gamma_t) + \gamma_t^c \ln \gamma_t \exp(-\lambda \gamma_t^c) \} / \theta_i^2 \tag{3.129}$$

$$\begin{aligned} E\left(-\frac{\partial^2 \ln L_I}{\partial c^2} \right) = {} & \frac{1}{c^2} \sum_{t=1}^{n} [1 - \exp(-\lambda \gamma_t^c)] + \\ & + \lambda \sum_{t=1}^{n} \{ [1 - \exp(-\lambda \gamma_t^c)] E[V_t^c (\ln V_t)^2 | V_t < \gamma_t] + \\ & + \gamma_t^c (\ln \gamma_t)^2 \exp(-\lambda \gamma_t^c) \}. \end{aligned} \tag{3.130}$$

The expression $E[V_t^c (\ln V_t)^i | V_t < \gamma_t]$, i=1,2, are cumbersome but may be evaluated by a numerical integration if all the censoring times γ_t (t=1,…,n) are known. If all the censoring times are not known, then expressions (3.128), (3.129), and (3.130) may be approximated by the negatives of (3.123), (3.124) and (3.125), respectively. The inverse of the information matrix can be formed in the usual way.

If all the censoring times are equal, the estimators and the quantities leading to the information matrix may be obtained by setting $\gamma_t = \gamma_0$ (t=1,…,n) in (3.121), (3.122) and (3.128), (3.129), (3.130), respectively.

Furthermore, if $\gamma_0 = \infty$, that is, no observations are censored, then the MLE's are

$$\hat{\theta}_i = \hat{t}_c / n_i,$$

and

$$\left(\frac{1}{\hat{c}} + \frac{1}{n}\sum_{i=1}^{k}\sum_{j=1}^{n_i} \ln x_{ij}\right)\hat{t}_c = \sum_{i=1}^{k}\sum_{j=1}^{n_i}\left(x_{ij}^{\hat{c}} \ln x_{ij}\right), \tag{3.131}$$

where $\hat{t}_c = \sum_{i=1}^{k}\sum_{j=1}^{n_i} x_{ij}^{\hat{c}}$. The inverse of the information matrix is

$$V_{k+1,k+1} = n^{-1}\begin{vmatrix} \lambda_1^3/\lambda & \dots & 0 & \dots & \lambda_1^2 A \\ \vdots & & & & \vdots \\ 0 & \dots & \lambda_k^3/\lambda & \dots & \lambda_k^2 A \\ \vdots & & & & \vdots \\ \lambda_1^2 A & \dots & \lambda_k^2 A & \dots & D \end{vmatrix}^{-1} \tag{3.132}$$

where

$$A = -\int_0^{\infty} c\,\lambda\, x^{2c-1} \ln x \, \exp\left(-\lambda x^c\right) dx$$

and

$$D = \frac{1}{c^2} + \int_o^{\infty} c\,\lambda^2 \, x^{2c-1} (\ln x)^2 \exp\left(-\lambda x^c\right) dx.$$

Employing the first two moments of the extreme-value distribution and following a matrix inversion given in Rao (1973, p.33), (3.132) becomes

$$V_{k+1,k+1} = n^{-1}\begin{vmatrix} G_{k,k} & F_{k,1} \\ F'_{1,k} & H \end{vmatrix} \tag{3.133}$$

where

$$G_{k,k} = \lambda \begin{vmatrix} \theta_1^3 & & 0 \\ & \ddots & \\ 0 & & \theta_k^3 \end{vmatrix} + \frac{6(1-\gamma-\ln\lambda)^2}{\pi^2}\theta\theta', \tag{3.134}$$

$$F_{k,1} = [\, 6\,c\,(1-\gamma-\ln\lambda) - \pi^2\,]\,\theta,$$

$$H = 6\,c^2/\pi^2,\ \theta' = (\theta_1,\ldots,\theta_k),$$

and

$$\gamma = 0.5772157\ldots \text{ (Euler's constant).}$$

3.6.2.2. Type II Censoring with Equal Shape Constants

Invoking the notation for Type II censoring from Section 3.3.3, one have from (3.121) and (3.122) upon replacing x_{ij} ($i = 1,\ldots,k$; $j = 1,\ldots,m_i$) and $\gamma_{(u)}$ ($u=1,..,s$) by $\nu_{(t)}$ ($t = 1,\ldots,m$) and $\nu_{(m)}$, respectively, the following MLE's

$$\hat{\theta}_i = \left(\hat{t}_c + s\nu_{(m)}^{\hat{c}}\right)/m_i,\ i = 1,\ldots,k \tag{3.135}$$

and

$$\left(\frac{m}{\hat{c}} + \sum_{t=1}^{n}\ln\nu_{(t)}\right)\left(\hat{t}_c + s\nu_{(m)}^{\hat{c}}\right) = m\left[\sum_{t=1}^{n}\left(\nu_{(t)}^{\hat{c}}\ln\nu(t)\right) + s\nu_{(m)}^{\hat{c}}\ln\nu(m)\right], \tag{3.136}$$

where $\hat{t}_c = \sum_{t=1}^{n} v_{(t)}^{\hat{c}}$.

From (3.120), the second derivatives of ln L used for Type II censoring may be determined as

$$\partial^2 \ln L_{II} / \partial \theta_i^2 = m_i / \theta_i^2 - 2\left(t_c + s v_{(m)}^c\right) / \theta_i^3 , \qquad (3.137)$$

$$\partial^2 \ln L_{II} / \partial \theta_i \partial c = \left(\sum_{t=1}^{n} v_{(t)}^c \ln v(t) + s v_{(m)}^c \ln v_{(m)} \right) / \theta_i^2 , \qquad (3.138)$$

and

$$\partial^2 \ln L_{II} / \partial c^2 = -m/c^2 - \lambda \left[\sum_{t=1}^{n} v_{(t)}^c \left(\ln v_{(t)}\right)^2 + s v_{(m)}^c \left(\ln v(m)\right)^2 \right]. \qquad (3.139)$$

Now,

$$E(M_i) = \frac{m}{\theta_i \lambda}, \qquad E\left(V_{(t)}^c\right) = \left(\sum_{j=1}^{t} \frac{1}{n-j+1} \right) / \lambda \qquad (3.140)$$

since if a statistic X has a p.d.f. given by (3.126), which is how the unordered V_t (t=1,…,n) are distributed, then X^c is distributed as an exponential variate, and the lower moments of order statistics from an underlying exponential population are well known.

Using (3.140) it can be found that the expected values of terms in (3.137), (3.138), and (3.139). Hence

$$E\left(-\partial^2 \ln L_{II} / \partial \theta_i^2\right) = m / \theta_i^3 \lambda , \qquad (3.141)$$

$$E(-\partial^2 \ln L_{II} / \partial\theta_i \partial c) = -\left\{ \sum_{t=1}^{m-1} E\left[V_{(t)}^c \ln V_{(t)}\right] + (s+1)\, E\left[V_{(m)}^c \ln V_{(m)}\right] \right\} / \theta_i^2 \tag{3.142}$$

and

$$E\left(-\partial^2 \ln L_{II} / \partial c^2\right) = m/c^2 + \lambda \left\{ \sum_{t=1}^{m-1} E\left[V_{(t)}^c \left(\ln V_{(t)}\right)^2\right] + (s+1)\, E\left[V_{(m)}^c \left(\ln V_{(m)}^c\right)^2 \right] \right\} \tag{3.143}$$

where

$$f(v_{(t)}) = \frac{n!}{(t-1)!(n-t)!} (c\lambda) v_{(t)}^{c-1} \left[1 - \exp\left(-\lambda v_{(t)}^c\right)\right]^{t-1} \exp\left[-\lambda (n-t+1) v_{(t)}^c\right], \; 0 < v_{(t)} < \infty \tag{3.144}$$

3.6.2.3. Grouped Observations for Equal Shape Constants

Employing the notation of Section 3.3.4 it is obtained from (3.25) that

$$\pi_{i\alpha} = \lambda_i \left[\exp\left(-\lambda\, g_\alpha^c\right) - \exp\left(-\lambda\, g_{\alpha+1}^c\right) \right] / \lambda \,, \; i = 1,\ldots,k; \; \alpha = 0,1,\ldots,h \tag{3.145}$$

For notational convenience let $a_\alpha = \exp(-\lambda\ g_\alpha^c)$. Then, from (3.25),

$$L_G \propto \left[\prod_{i1}^{k} \lambda_i^{n_{i.}} \right] \left[\prod_{\alpha=0}^{h} (a_\alpha - a_{\alpha+1})^{n.\alpha} \right] / \lambda^n \,, \tag{3.146}$$

where $\lambda_i = 1/\theta_i$ and $\lambda = \sum_{i=1}^{k} \lambda_i$.

Therefore, the MLE's of θ_i are

$$\hat{\theta}_i = \left[\frac{n}{\hat{\lambda}} + \sum_{\alpha=0}^{h} n_{.\alpha} \left(\frac{g_\alpha^{\hat{c}}\, \hat{a}_\alpha - g_{\alpha+1}^{\hat{c}}\, \hat{a}_{\alpha+1}}{\hat{a}_\alpha - \hat{a}_{\alpha+1}} \right) \right] / n_{i.}, \; i = 1,\ldots,k \qquad (3.147)$$

and

$$\sum_{\alpha=0}^{h} n_{.\alpha} \left[\frac{\hat{a}_{\alpha+1}\, g_{\alpha+1}^{\hat{c}} \ln g_{\alpha+1} - \hat{a}_\alpha\, g_\alpha^{\hat{c}} \ln g_\alpha}{\hat{a}_\alpha - \hat{a}_{\alpha+1}} \right] = 0, \qquad (3.147)$$

where $\hat{a}_\alpha = \exp\left(-\lambda\, g_\alpha^c\right)$ and $\hat{\lambda} = \sum_{i=1}^{k} \left(1/\hat{\theta}_i\right)$.

The obvious simplifications $g_0 = 0$, $g_{h+1} = \infty$, $a_0 = 1$, $a_{h+1} = 0$ can be made at one's convenience. From the k equations in (3.146) the following relationship can be obtained.

$$\sum_{\alpha=0}^{h} n_{.\alpha} \left[\frac{\hat{a}_\alpha\, g_\alpha^{\hat{c}} - \hat{a}_{\alpha+1}\, g_{\alpha+1}^{\hat{c}}}{\hat{a}_\alpha - \hat{a}_{\alpha+1}} \right] = 0. \qquad (3.148)$$

Also (3.147) and (3.148) can be rewritten as

$$\sum_{\alpha=0}^{h-1} \frac{n_{.\alpha} \left(g_{\alpha+1}^{\hat{c}} \ln g_{\alpha+1} - g_\alpha^{\hat{c}} \ln g_\alpha \right)}{\exp\left[\hat{\lambda} \left(g_{\alpha+1}^{\hat{c}} - g_\alpha^{c} \right)\right] - 1} - \sum_{\alpha=1}^{h} n_{.\alpha}\, g_\alpha^{\hat{c}} \ln g_\alpha = 0 \qquad (3.149)$$

and

$$\sum_{\alpha=0}^{h-1} \frac{n_{.\alpha} \left(g_{\alpha+1}^{\hat{c}} - g_\alpha^{\hat{c}} \right)}{\exp\left[-\hat{\lambda} \left(g_{\alpha-1}^{\hat{c}} - g_\alpha^{\hat{c}} \right)\right] - 1} - \sum_{\alpha=1}^{h} n_{.\alpha} g_\alpha^{\hat{c}} = 0. \qquad (3.150)$$

Solving (3.147) and (3.148) or, alternatively, (3.149) and (3.150) by some iterative technique will give $\hat{\lambda}$ and $\hat{c}$. Then, substituting (3.148) into (3.149) yields

$$\hat{\theta}_i = n/\hat{\lambda}\, n_{i.}, \; i = 1,\ldots,k \tag{3.151}$$

Thus the $\hat{\theta}_i$ are trivially determined after $\hat{\lambda}$ and $\hat{c}$ have been obtained.

The information matrix may be found directly using the facts that $E(N_{i.})=n/\theta_i\lambda$ and $E(N_{.\alpha})=n(a_\alpha - a_{\alpha+1})$.

For the exponential case, c = 1, the likelihood equations are given by (3.150), where $\hat{c}$ is replaced by 1, and by (3.151).

Moreover, for the important case of equidistant group limits $g_0 = 0$, $g_\alpha=\alpha g_1$, for $\alpha = 0,1,\ldots,h$, (h is finite) the likelihood equations are

$$\hat{\theta}_i = \frac{n\, g_1}{n_{i.} \ln\left[1+(n-n_{.h})/\sum_{\alpha=1}^{h}\alpha n_{.\alpha}\right]}, \tag{3.152}$$

Furthermore, the asymptotic covariance matrix of $\hat{\theta}$, the vector of the $\hat{\theta}_i$, is

$$V(\hat{\theta}) = \frac{1}{n}\begin{bmatrix} \lambda\theta_1^3+\gamma'\theta_1^2 & \gamma'\theta_1\theta_2 & \cdot & \cdot & \cdot & \gamma'\theta_1\theta_k \\ \gamma'\theta_1\theta_2 & \cdot & & & & \cdot \\ \cdot & & \cdot & & & \cdot \\ \cdot & & & \cdot & & \cdot \\ \cdot & & & & \cdot & \gamma'\theta_{k-1}\theta_k \\ \gamma'\theta_1\theta_k & \cdot & \cdot & \cdot & \gamma'\theta_{k-1}\theta_k & \lambda\theta_k^3+\gamma'\theta_k^2 \end{bmatrix} \tag{3.153}$$

where

$$\gamma' = \frac{[\exp(\lambda g_1)-1]^2}{\lambda^2 g_1^2 \exp(\lambda g_1)\,[1-\exp(-\lambda h g_1)]} - 1.$$

3.6.2.4. Type I Censoring with Unequal Shape Constants

Since Type I censoring is the case of the most practical interest, only this part is considered for Weibull distributions with unequal shape constants.

Assuming underlying Weibull populations as in (3.119) it is obtained from (3.21) that the likelihood equations are

$$\hat{\theta}_i = \frac{1}{m_i}\left(\sum_{p=1}^{k} \sum_{j=1}^{m_p} x_{pj}^{\hat{c}_i} + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}_i} \right) \tag{3.154}$$

and

$$\frac{1}{m_i}\left(\frac{m_i}{\hat{c}_i} + \sum_{j=1}^{m_i} \ln x_{ij} \right) \left(\sum_{p=1}^{k} \sum_{j=1}^{m_p} x_{pj}^{\hat{c}_i} + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}_i} \right)$$

$$= \sum_{p=1}^{k} \sum_{j=1}^{m_p} x_{pj}^{\hat{c}_i} \ln x_{pj} + \sum_{u=1}^{s} \gamma_{(u)}^{\hat{c}_i} \ln \gamma_{(u)}, \quad i=1,\ldots,k. \tag{3.155}$$

From (3.13) the density of an observed failure from cause R_i, assuming no censoring, is

$$f_i(x) = \frac{x^{c_i - 1} \exp\left(- \sum_{p=1}^{k} x^{cp} / \theta_p \right)}{\int_0^{\infty} z^{c_i - 1} \exp\left(- \sum_{p=1}^{k} z^{cp} / \theta_p \right) dz}, \tag{3.156}$$

that is, the observed lifetimes are no longer identically distributed.

The following relationships can be obtained

$$E\left(\sum_p\sum_j X_{pj}^{c_i}\right)=\sum_{t=1}^{n}\sum_{p=1}^{k}\left(\frac{c_p}{\theta_p}\right)\int_0^{\gamma_t} z^{c_i+c_p-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz, \qquad (3.157)$$

$$E\left(\sum_{u=1}^{r}\gamma_{(u)}^{c_i}\right)=\sum_{t=1}^{n}\gamma_t^{c_i}\exp\left(-\sum_{p=1}^{k}\gamma_t^{c_p}/\theta_p\right), \qquad (3.158)$$

and

$$E(M_i)=\left(\frac{c_i}{\theta_i}\right)\sum_{t=1}^{n}\int_0^{\gamma_t} z^{c_i-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz, \qquad (3.159)$$

which in turn may be used to find

$$E\left(-\frac{\partial^2 \ln L_I}{\partial\theta_i^2}\right)=\left(\frac{2}{\theta_i^3}\right)\left[\sum_{t=1}^{n}\sum_{pl=1}^{k}\left(\frac{c_p}{\theta_p}\right)\int_0^{\gamma_t} z^{c_i+c_p-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz+\right.$$
$$+\sum_{t=1}^{n}\gamma_t^{c_i}\exp\left(-\sum_{p=1}^{k}\gamma_t^{c_p}/\theta_p\right)-$$
$$\left.-\left(\frac{c_i}{\theta_i^3}\right)\sum_{t=1}^{n}\int_0^{\gamma_t} z^{c_i-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz\right], \qquad (3.160)$$

$$E\left(-\frac{\partial^2 \ln L_I}{\partial\theta_i\partial c_i}\right)=-\left(\frac{c_i}{\theta_i^2}\right)\left[\sum_{t=1}^{n}\sum_{p=1}^{k}\left(\frac{c_p}{\theta_p}\right)\int_0^{\gamma_t} z^{c_i+c_p-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz+\right.$$
$$\left.+\sum_{t=1}^{n}\gamma_t^{c_i}(\ln\gamma_t)\exp\left(-\sum_{p=1}^{k}\gamma_t^{c_p}/\theta_p\right)\right], \qquad (3.161)$$

and

$$E\left(-\frac{\partial^2 \ln L_I}{\partial c_i^2}\right)=\frac{1}{\theta_i c_i}\sum_{t=1}^{n}\int_0^{\gamma_t} z^{c_i-1}\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz+$$

$$+\frac{1}{\theta_i}\left[\sum_{t=1}^{n}\sum_{p=1}^{k}\left(\frac{c_p}{\theta_p}\right)\int_0^{\gamma_t} z^{c_i+c_p-1}(\ln z)^2\exp\left(-\sum_{p=1}^{k} z^{c_p}/\theta_p\right)dz+\right.$$

$$\left.+\sum_{t=1}^{n}\gamma_t^{c_i}[\ln\gamma_t]^2\exp\left(-\sum_{p=1}^{k}\gamma_t^{c_p}/\theta_p\right)\right]. \qquad (3.162)$$

For underlying Weibull populations with unequal shape constants, the crude, net, and partial crude probabilities are

$$Q_i(a,b)=c_i\lambda_i\int_a^b t^{c_i-1}\exp\left\{-\sum_{p=1}^{k}\left[\lambda_p\left(t^{c_p}-a^{c_p}\right)\right]\right\}dt, \qquad (3.163)$$

$$q_i(a,b)=1-\exp\left[-\lambda_i\left(b^{c_i}-a^{c_i}\right)\right], \qquad (3.164)$$

and

$$Q_{i,j}(a,b)=c_i\lambda_i\int_a^b t^{c_i-1}\exp\left\{-\sum_{\substack{p=1\\p\neq j}}^{k}\left[\lambda_p\left(t^{c_p}-a^{c_p}\right)\right]\right\}dt,\ i\neq j. \qquad (3.165)$$

When $c_i = c$, (3.163) and (3.165) reduce to

$$Q_i(a,b)=\lambda_i\left\{1-\exp\left[-\lambda\left(b^c-a^c\right)\right]\right\}/\lambda \qquad (3.166)$$

$$Q_{i,j}(a,b)=\lambda_i\{\,1-\exp\left[-(-\lambda_j)(b^c-a^c)\right]\,\}/(\lambda-\lambda_j),\ i\neq j \qquad (3.167)$$

3.6.3. Normal Life Distributions

Generally, the normal distribution has not found great deal of acceptance in describing the distribution of observed times to failure in biological life testing problems. However, since the logarithm of observed data is often considered to be approximately normal, this case continues to draw attention.

3.6.3.1. Case of Unequal Means and Unequal Variances

Suppose $Y_i \sim N(\mu_i, \sigma_i^2)$, $i = 1,\ldots,k$. Let ϕ, Φ, and $\overline{\Phi}$ be the p.d.f., c.d.f., and survival function of N (0, 1) random variables, respectively. Here uncensored case is considered but censoring may be readily handled in the usual manner. Employing the notation of Section 3.2, it is obtained from (3.18) that

$$\ln L_i = \text{const.} - n_i \ln \sigma_i - \frac{1}{2} \sum_{j=1}^{n_i} u_{ij}^2 + \sum_{\substack{p=1 \\ p \neq i}}^{k} \sum_{j=1}^{n_p} \ln \overline{\Phi}(u_{pj,i}), \tag{3.168}$$

where $u_{ij} = (x_{ij} - \mu_i) / \sigma_i$ and $u_{pj,i} = (x_{pj} - \mu_i) / \sigma_i$.

Then the likelihood equations, which are k sets of two equations in two unknowns, can be written as

$$\sum_{j=1}^{n_i} \hat{u}_{ij} + \sum_{\substack{p=1 \\ p \neq i}}^{k} \sum_{j=1}^{n_p} \hat{A}_{pj,i} = 0 \tag{3.169}$$

and

$$n_i = \sum_{j=1}^{n_i} u_{ij}^2 + \sum_{\substack{p=1 \\ p\neq i}}^{k} \sum_{j=1}^{n_p} \hat{u}_{pj,i}\hat{A}_{pj,i},\ i=1,...,k, \qquad (3.170)$$

where $A_{lj,i} = \phi(u_{pj,i}) / \bar{\Phi}(u_{pj,i})$ and $\hat{u}_{ij}, \hat{u}_{pj,i}$ and $\hat{A}_{pj,i}$ are the functions corresponding to u_{ij}, $u_{pj,i}$ and $A_{lj,i}$ when $\hat{\mu}_i$ and $\hat{\sigma}_i$ replace μ_i and σ_i, respectively.

For the case of k=2, it is obtained from (3.13) that the p.d.f. of observed lifetimes where failure is due to R_1 and R_2, respectively, is

$$f_1(x_{1j}) = \frac{\phi(u_{1j})\,\bar{\Phi}(u_{1j,2})}{\sigma_1\,\bar{\Phi}(\xi)}$$
$$f_2(x_{2j}) = \frac{\phi(u_{2j})\,\bar{\Phi}(u_{2j,1})}{\sigma_2\,\bar{\Phi}(\xi)} \qquad (3.171)$$

where $\xi = (\mu_1 - \mu_2)/\sqrt{\sigma_1^2 + \sigma_2^2}$. Moreover, is easily verified that

$$\pi_1 = 1 - \Phi(\xi) \quad \text{and} \quad \pi_2 = \Phi(\xi) \qquad (3.172)$$

Upon transforming the variables in (3.171), it is obtained that the p.d.f. of U_{ij} and $U_{pj,i}$ ($i \neq p$). These densities can be used to evaluate the expected values of the negative second derivatives of the log likelihood function (3.168). Then the following quantities are obtained by David nad Moeschberger (1978) as

$$E\left(-\frac{\partial^2 \ln L_1}{\partial \mu_1^2}\right) = \frac{n}{\sigma_1^2}\left\{\bar{\Phi}(\xi) + \frac{\exp\left(-\frac{1}{2}\xi^2\right)}{\sqrt{2\pi}}\left[\frac{\sigma_1^2\xi}{\sigma_1^2+\sigma_2^2} + \frac{\sigma_1 D_1}{\sigma_2\sqrt{2\pi}}\right]\right\} \qquad (3.173)$$

where

$$D_1 = \int_{-\infty}^{\infty} r(z) \exp\left\{ -\frac{\left(\sigma_1^2 + \sigma_2^2\right)}{2\sigma_2^2} \left[z + \frac{\xi \sigma_1}{\left(\sigma_1^2 + \sigma_2^2\right)^{1/2}} \right]^2 \right\} dz,$$

$$E\left(-\frac{\partial^2 \ln L_I}{\partial \mu_1 \, \partial \sigma_1} \right) = \frac{n \exp\left(-1/2\, \xi^2\right)}{\sigma_1 \sqrt{2\pi}} \left[\frac{D_2}{\sigma_2 \sqrt{2\pi}} - \frac{1}{\left(\sigma_1^2 + \sigma_2^2\right)^{1/2}} - \frac{\left(\sigma_2^2 + \sigma_1^2 \xi^2\right)}{\left(\sigma_1^2 + \sigma_2^2\right)^{3/2}} \right] \tag{3.174}$$

where

$$D_2 = \int_{-\infty}^{\infty} r(z)\, z \exp\left\{ -\frac{\left(\sigma_1^2 + \sigma_2^2\right)}{2\sigma_2^2} \left[z + \frac{\xi \sigma_1}{\left(\sigma_1^2 + \sigma_2^2\right)^{1/2}} \right]^2 \right\} dz,$$

and

$$E\left(-\frac{\partial^2 \ln L_I}{\partial \sigma_1^2} \right) = \frac{n}{\sigma_1^2} \left\{ 2\overline{\Phi}(\xi) + \frac{\exp\left(-1/2 \xi^2\right)}{\sqrt{2\pi}} \left[\frac{\sigma_1^2 \xi}{\sigma_1^2 + \sigma_2^2} + \frac{\left(\sigma_1^2 \xi^2 + 3\sigma_2^2\right) \xi \sigma_1^2}{\left(\sigma_1^2 + \sigma_2^2\right)^2} + \right. \right.$$
$$\left. \left. + \frac{\sigma_1 D_3}{\sigma_2 \sqrt{2\pi}} \right] \right\} \tag{3.175}$$

where

$$D_3 = \int_{-\infty}^{\infty} r(z)\, z^2 \exp\left\{ -\frac{\left(\sigma_1^2 + \sigma_2^2\right)}{2\sigma_2^2} \left[z + \frac{\xi \sigma_1}{\left(\sigma_1^2 + \sigma_2^2\right)^{1/2}} \right]^2 \right\} dz,$$

where $r(z) = \phi / \overline{\Phi}(z)$.

$E\left(-\frac{\partial^2 \ln L_2}{\partial \mu_2^2}\right)$, $E\left(-\frac{\partial^2 \ln L_2}{\partial \mu \, \partial \sigma_2}\right)$, and $E\left(-\frac{\partial^2 \ln L_2}{\partial \sigma_2^2}\right)$ may be obtained from (3.173), (3.174) and (3.175), respectively, by symmetry, on replacing μ_1 by μ_2 and σ_1 by σ_2.

3.6.3.2. Case of Unequal Means and Equal Variances

When the theoretical life distributions have one or more parameters, the maximization of the likelihood function is usually complicated. It is assumed that $Y_i \sim N(\mu_i, \sigma^2)$. In this section there are k+1 unknowns that are desired to solve in k+1 equations. When k = 2 the likelihood equations are

$$\hat{\mu}_1 = \bar{x}_1 + \frac{\hat{\sigma}}{n_1}\sum_{j=1}^{n_2} \hat{B}_j, \quad \hat{\mu}_2 = \bar{x}_2 + \frac{\hat{\sigma}}{n_2}\sum_{j=1}^{n_1} \hat{A}_j, \tag{3.176}$$

$$n = \left(\frac{1}{\hat{\sigma}^2}\right)\left[\sum_{j=1}^{n_1}(x_{1j}-\hat{\mu}_1)^2 + \sum_{j=1}^{n_2}(x_{2j}-\hat{\mu}_2)^2\right] + \sum_{j=1}^{n_1}\hat{u}'_j\hat{A}_j + \sum_{j=1}^{n_2}\hat{v}'_j\hat{B}_j,$$

where

$$\bar{x}_i = \sum_{j=1}^{n_i} x_{ij}/n_i, \; i=1,2,$$

$$A_j = \phi(u'_j)/\bar{\Phi}(u'_j), \; B_j = \phi(v'_j)/\bar{\Phi}(v'_j),$$
$$u'_j = (x_{1j}-\mu_2)/\sigma, \; v'_j = (x_{2j}-\mu_2)/\sigma,$$

and $\hat{u}'_j$, $\hat{v}'_j$, $\hat{A}_j$, $\hat{B}_j$ are the functions corresponding to u'_j, v'_j, A_j, B_j with $\hat{\mu}_i$ and $\hat{\sigma}$ replacing μ_i and σ, respectively (i = 1,2).

The p.d.f. of X_i has the same basic structure as (3.171). The p.d.f. of observed lifetimes where failures are from cause 1 and 2 for the case of unequal means and equal variances is

$$f_1(x_{1j}) = \frac{\phi(u_j)\,\overline{\Phi}(u'_j)}{\sigma\,\overline{\Phi}(\xi)}, \quad f_2(x_{2j}) = \frac{\phi(v_j)\,\overline{\Phi}(v'_j)}{\sigma\,\Phi(\xi)} \tag{3.177}$$

where

$$u_j = u'_j - \sqrt{2}\xi = (x_{1j} - \mu_1)/\sigma, \quad v_j = v'_j + \sqrt{2}\xi = (x_{2j} - \mu_2)/\sigma,$$

and

$$\xi = (\mu_1 - \mu_2)/\sqrt{2}\sigma.$$

Note that π_i are also as in (3.172) with ξ defined above.

To be able to find the variance-covariance matrix, the elements of the information matrix are found as

$$E\left(-\frac{\partial^2 \ln L}{\partial \mu_1^2}\right) = \frac{n}{\sigma^2}\left\{\overline{\Phi}(\xi) + \frac{\exp(-1/2\,\xi^2)}{\sqrt{2\pi}}\left[\frac{\xi}{2} + \frac{D_1(\xi)}{\sqrt{2\pi}}\right]\right\} \tag{3.178}$$

$$E\left(-\frac{\partial^2 \ln L}{\partial \mu_2^2}\right) = \frac{n}{\sigma^2}\left\{\overline{\Phi}(\xi) + \frac{\exp(-1/2\,\xi^2)}{\sqrt{2\pi}}\left[-\frac{\xi}{2} + \frac{D_1(-\xi)}{\sqrt{2\pi}}\right]\right\} \tag{3.179}$$

where

$$D_1(\xi) = \int_{-\infty}^{\infty} r(z) \exp\left[-\left(z + \frac{\xi}{\sqrt{2}}\right)^2\right] dz,$$

$$E\left(-\frac{\partial^2 \ln L}{\partial \sigma\, \partial \mu_1}\right) = \frac{n \exp(-1/2\,\xi^2)}{\sigma^2\, 2\sqrt{\pi}}\left[\frac{D_2(\xi)}{\sqrt{\pi}} - \frac{(3+\xi^2)}{2}\right], \tag{3.180}$$

$$E\left(-\frac{\partial^2 \ln L}{\partial\sigma\,\partial\mu_2}\right)=\frac{n\exp(-1/2\,\xi^2)}{\sigma^2\,2\sqrt{\pi}}\left[\frac{D_2(-\xi)}{\sqrt{\pi}}-\frac{(3+\xi^2)}{2}\right], \tag{3.181}$$

where

$$D_2(\xi)=\int_{-\infty}^{\infty} r(z)\,z\exp\left[-\left(z+\frac{\xi}{2}\right)^2\right]dz,$$

$$E\left(-\frac{\partial^2 \ln L}{\partial\sigma^2}\right)=\frac{n}{2\sigma^2}\left\{4+\frac{\exp(-1/2\,\xi^2)}{\pi}\left[D_3(\xi)+D_3(-\xi)\right]\right\}, \tag{3.182}$$

where

$$D_3(\xi)=\int_{-\infty}^{\infty} r(z)\,z^2\exp\left[-\left(z+\frac{\xi}{2}\right)^2\right]dz.$$

3.7. Estimation of the Cause-Specific Hazard Function

Competing risks data includes an underlying failure time T of each study subject, a covariate vector Z where $Z = \{ z(u) ; u \geq 0 \}$ and $J \in \{ 1,\ldots,k \}$, failure type. Suppose that failure time is continuous and the covariate $Z = \{ z(u) ; u \geq 0 \}$ is fixed. The overall failure rate or hazard rate with covariate is defined as

$$\lambda(t;Z)=\lim_{\Delta t\to 0}\frac{\Pr\left\{t\leq T<t+\Delta t \,\middle|\, T\geq t, Z\right\}}{\Delta t}. \tag{3.183}$$

The cause-specific hazard function is found similarly as

$$\lambda_j(t;Z)=\lim_{\Delta t\to 0}\frac{\Pr\left\{t\leq T<t+\Delta t,\ J=j \,\middle|\, T\geq t, Z\right\}}{\Delta t} \tag{3.184}$$

for j = 1,...,k. λ_j (t; Z) is the instantaneous rate for failure type j at time t given Z in the presence of all other failure types acting on the population. Assuming that failure type j must be a unique element of { 1,...,k } gives

$$\lambda(t;Z)=\sum_{j=1}^{k}\lambda_j(t;Z). \tag{3.185}$$

By using cause-specific hazard function the survivor function given Z is written as

$$S(t;\ Z)=\exp\left[-\int_0^t \lambda(u;\ Z)\,du\right]. \tag{3.186}$$

The failure time density function for failure type j, given Z is

$$f_j(t;\ Z)=\lim_{\Delta t\to 0}\frac{\Pr\left\{t\le T<t+\Delta t;\ J=j\,|\,Z\right\}}{\Delta t}=\lambda_j(t;\ Z)\ \ S(t;\ Z),\ j=1,..,k \tag{3.187}$$

The overall hazard function and the failure time density function of cause j, given Z are identifiable, that is, they can be estimated from data of type (t, j; Z) without any further assumption.

If there are n subjects in the study, the data contains (t_i, δ_i, j_i ; Z_i), i=1,...,n where t_i is the observed survival time, δ_i is the censoring indicator, j_i is the cause of death and Z_i is the covariates of the i-th individual. Under an independent non-informative censoring mechanism the likelihood function is proportional to

$$\prod_{i=1}^{n}\left\{\left(\lambda_{ji}(t_{ji};Z_i)\right)^{\delta_i}\ S(t_{ji};Z_i)\right\}=\prod_{i=1}^{n}\left\{\left(\lambda_{ji}(t_{ji};Z_i)\right)^{\delta_i}\prod_{j=1}^{m}\exp\left[-\int_0^{t_i}\lambda_j(u;Z_i)\,du\right]\right\} \tag{3.188}$$

This likelihood function is obtained by regarding all failure types other than j-th cause of failure as censored at the individual's failure time.

It is convenient to denote

$$S_j(t;Z) = \exp\left[-\int_0^t \lambda_j(u;Z)\,du \right], j = 1,\ldots,k \qquad (3.189)$$

which has no survival function interpretation, for $k > 1$.

Consider first no covariates competing risks data. Two useful graphical estimators of the distribution of (T, J) are the cumulative incidence plots and the cumulative hazard plots. Cumulative hazard plots provide estimators of $-\log S_j(t)$ with S_j as defined in (3.189). Cumulative incidence function is defined as

$$I_j(t) = \Pr\{T < t, J = j\} = \int_0^t f_j(u)\,du, j = 1,\ldots,k \qquad (3.190)$$

The non-parametric estimation technique of Kaplan-Meier is generalized in competing-risks data as follows. Let $t_{j1} < t_{j2} < \ldots < t_{jk_j}$ denote the k_j failure times for failures of type j, j = 1,…,k. Suppose that failure type j occurs at d_{ji} times at t_{ji}. The likelihood function can be expressed as

$$L = \prod_{j=1}^{k}\left[\prod_{i=1}^{k_j}\left\{ \left[S_j(t_{ji}) - S(t_{ji}+0)\right] \prod_{\substack{p=1 \\ p\neq i}}^{k} S_p(t_{ji}) \right\}^{d_{ji}} \prod_{q=1}^{C_{ji}} S_j(t_{jiq+0}) \right] \qquad (3.191)$$

where $t_{ji1},\ldots,t_{jiC_{ji}}$ denote the C_{ji} censored times from t_{ji} to the next failure time. The likelihood (3.189) factors into a component for each failure type. It follows that the non-parametric maximum likelihood estimator of S_j is

$$\hat{S}_j(t) = \prod_{\{i|t_{ji}<t\}} \left(\frac{n_{ji} - d_{ji}}{n_{ji}} \right) \tag{3.192}$$

where n_{ji} is the number of individuals at risk prior to time t_{ji}. Since there are no ties with different cause of failures, the overall Kaplan-Meier survival function is estimated by

$$\hat{S}(t) = \prod_{j=1}^{k} \hat{S}_j(t) \tag{3.193}$$

The corresponding estimators of the cause-specific hazard function $\lambda_j(t)$ has value d_{ji} / n_{ji} at t_{ji}, $i = 1,\ldots,k_j$ and value 0 elsewhere. By using these estimators, the cumulative incidence function in (3.190) is estimated non-parametrically by

$$\hat{I}_j(t) = \sum_{\{i|t_{ji}<t\}} d_{ji}\, n_{ji}^{-1}\, \hat{S}(t_{ji}) \;, j = 1,\ldots,k \tag{3.194}$$

When there is a single mode of failure, (3.194) reduces to $1-\hat{S}(t)$. A plot of $\hat{I}_j(t)$ versus t gives estimates of the probability that failure type j will occur before time t within the range of observations. The plot of cumulative hazard, $-\log \hat{S}(t)$ versus t, provides a visual impression by means of its slope over specific time intervals of the rate of occurrence of failures of type j.

To find the relation between cause-specific hazard functions and regression vector Z, the Cox regression model is used. Assuming proportional hazard model,

the cause-specific hazard function at time t depends on Z in terms of observed z(t) values is written as

$$\lambda_j(t) = \lambda_{0j}(t) \exp\left[z(t) \beta_j \right], j = 1,\ldots,k \qquad (3.195)$$

Here, both the shape function λ_{0j} and the regression coefficients β_j have been permitted to vary arbitrarily over the k failure types.

The k_j failure types, j = 1,...,k are shown as $t_{j1} < \ldots < t_{jk_j}$ and β_{ji} is the regression function for the individuals failing at t_{ji}. To estimate the covariates the maximum likelihood estimators from the partial likelihood is found. The method of partial likelihood gives

$$L(\beta_1,\ldots,\beta_k) = \prod_{j=1}^{k} \prod_{i=1}^{k_j} \left(\frac{\exp(z_{ji}(t_{ji})\ \beta_j)}{\sum_{l \in R(t_{ji})} \exp(z_l(t_{ji})\ \beta_j)} \right) \qquad (3.196)$$

where $R(t_{ji})$ is the number of individuals under risk of failure from cause j at time t_{ji}. The β_j's are estimated separately for each cause with deaths from remaining causes treated as censored observations. The maximum likelihood estimators of β_j's are found from (3.196) and standard errors of parameter estimates are obtained through estimated second derivatives of the log partial likelihood and significance tests are based on comparing parameter estimates with standard errors. Also, Wald statistic can be used to test the β_j values with null hypothesis H_0: $\beta_{jg} = 0$ for each cause of failure. It is based on the maximum likelihood estimator $\hat{\beta}_{jg}$. The test statistic is

$$Q_W = (\hat{\beta}_{jg} - \beta_{jg0})' \left[I^{-1}_{jg \times jg}(\hat{\beta}_{jg}, \hat{\beta}_{jr}) \right]^{-1} (\hat{\beta}_{jg} - \beta_{jg0}) \qquad (3.197)$$

The test imposes jg restrictions on the parameters to be estimated for cause j. The notation β_{jr} indicates the set of the remaining jr = k_j+1-jg parameters which are left unspecified by the hypothesis tested. Under H_0, Q_W is asymptotically distributed as χ^2 with jg degrees freedom. If H_0 imposes one restriction only, jg=1, on the parameter β_{jk}, H_0: $\beta_{jk}=\beta_{jk0}$ then (3.197) reduces to the square of the Gaussian standardized deviate

$$Q_W = \frac{\left(\hat{\beta}_{jk} - \beta_{jk0}\right)^2}{\mathrm{Var}(\hat{\beta}_{jk})} \tag{3.198}$$

The cause-specific hazard function for cause j is estimated as

$$\hat{\lambda}_j(t;Z) = \hat{\lambda}_{0j}(t)\ \exp(z(t)\hat{\beta}_j) = \hat{\lambda}_{oj}(t)\exp(z_1(t)\hat{\beta}_{j1} + \ldots + z_p(t)\hat{\beta}_{jp}) \tag{3.199}$$

where there are p prognostic factors for covariate β_j. The estimated underlying hazard for cause j, $\hat{\lambda}_{oj}(t)$, is obtained parametrically as

$$\hat{\lambda}_{0j}(t) = \begin{cases} 1 & \text{, for the exponential} \\ \hat{c}_j\, t^{\hat{c}_j - 1} & \text{, for the Weibull and } c_j > 0 \\ \hat{c}_j\, e^{\hat{c}_j t} & \text{, for the extreme value and } c_j > 0 \end{cases}$$

where c_j is the shape parameter from causej.

This value is estimated non-parametrically by assuming it to be zero except at times at which a death from cause j occurs, in which case

$$\hat{\lambda}_{0j}(t) = m_j \left(\sum_{l \in R(t)} e^{z_l \hat{\beta}_j} \right)^{-1} \tag{3.200}$$

where R(t) is the collection of individuals alive and in the study just prior to time t and m_j is the number of cause j deaths at t. This value is the generalization of the single cause procedure given in Kalbfleish and Prentice (1980, pp. 85-86) for estimating $\lambda_0(t)$. Then, the overall hazard function for survival is

$$\hat{\lambda}(t; Z) = \sum_{j=1}^{k} \hat{\lambda}_j(t; Z) \tag{3.201}$$

with survival function

$$\hat{S}(t; Z) = Pr_{est}(T \geq t; Z) = \exp\left[- \int_0^t \hat{\lambda}(u; Z)\, du \right] \tag{3.202}$$

The corresponding estimators of the cumulative incidence is estimated by

$$\hat{I}_j(t; Z) = Pr_{est}(T < t, J = j; Z) = \int_0^t \hat{\lambda}_j(u; Z)\, \hat{S}(u; Z)\, du, j = 1, ..., k. \tag{3.203}$$

3.8. Graphical Methods in Competing Risks

By graphical analysis, a preliminary information about the data can be obtained. This may be helpful in fitting the particular family distributions to a set of data visually. Also, settled upon the family distributions, graphical methods may be useful in finding the starting points for parameters to be estimated by some iterative procedures.

3.8.1. Distribution Function Technique

If there is a single cause of failure or the failure type is unspecified, there are lots of methods of probability plotting. One approach is plotting the ordered observations against the corresponding suitably standardized quantiles of the assumed underlying distribution. That is, $x_{(i)}$, i=1,...,n against $P^{*-1}(p_i)$ where $p_i=(i-1/2)/n$ and P^* is the assumed standardized distribution function. Plotting on the suitable probability paper corresponding to P^*, an approximate straight line indicates the correct distributional assumption.

In the competing risk analysis, the ordered failure times for a particular cause of failure, say C_i, against the appropriate quantiles of the corresponding distribution function is plotted. The plotting positions are $p_i=(n-r_{ij})/(n-r_{ij}+1)$,i=1,...,r and j=1,...,$n_i$, where p_i is the surviving probability of cause C_i. Here, the time scaling is divided into n+1 intervals as $[0,x_{i(1)}),[x_{i(1)},x_{i(2)}),\ldots,[x_{i(ni)},\infty)$ and the ranks of $x_{i(1)},x_{i(2)},\ldots,x_{i(n_i)}$ among all n ordered lifetimes are $r_{i1},r_{i2},\ldots,r_{in_i}$, respectively. An approximate straight line in this plot indicates the appropriate family distribution associated with cause C_i and this plotting must be done for each cause of failure.

3.8.2. Cumulative Hazard Function Technique

Hazard plotting is similar to probability plotting but ordered lifetimes are plotted against the estimated cumulative hazard functions. In competing risks analysis, hazard plotting is easier than probability plotting.

The cumulative hazard function associated with cause C_i is

$$R_i(y) = \int_{-\infty}^{y} \lambda_i(t)\,dt = -\ln\left[\bar{P}_i(y)\right] \qquad (3.204)$$

where $\lambda_i(t)=p_i(t)/\overline{P}_i t)$.

Hazard plotting papers for five theoretical distributions can be obtained by the work of Nelson (1970, 1972).

In the case of Weibull distribution:

Let the cause C_i have the pdf

$$p_i(y) = \left(c_i y^{c_i-1}/\theta_i\right)e^{-y^{c_i}/\theta}, y > 0, \theta_i > 0, c_i > 0 \qquad (3.205)$$

Then, corresponding cumulative hazard function can be obtained as

$$R_i(y) = y^{c_i/\theta_i} \qquad (3.206)$$

which can be rewritten as

$$\log y = \frac{1}{c_i}\log R_i(y) + \frac{1}{c_i}\log \theta_i \qquad (3.207)$$

The Weibull hazard paper is ordinary log-log graph paper with the slope $1/c_i$ and the time point y_0, corresponding to $R_i(y_0)=1$. Then, $\theta_i = y_0^{c_i}$.

When there are k competing risks ($k\geq 2$), the theoretical lifetimes, y will not be known. Instead, the ordered failure times, $x_{i(1)},\ldots,x_{i(n_i)}$ are available for each cause C_i, i=1,..,k. Also, the ranks $r_{i1},\ldots,r_{in_i}$ corresponding observed ordered failure times can be available.

Weibull hazard plotting in competing risks analysis suggests plotting log $x_{i(j)}$, $j=1,\ldots,n_i$ against the logarithm of an estimated $R_i(y)$ which takes the ranks $r_{i1},\ldots,r_{in_i}$.

3.8.3. General Method:

Let $s_j=n-r_{ij}+1$ be the number of survivors prior to time $x_{i(j)}$. Then, the cumulative hazard function may be estimated by summing the hazard functions as in the following table.

These hazard values are the number of failures at $\nu_{(t)}$ from cause C_i divided by the number of survivors prior to time $\nu_{(t)}$. The estimated cumulative hazard function at time x is

$$\hat{R}_i(x)=\begin{cases}0 & , x < x_{i(1)} \\ \sum_{l=1}^{j} 1/s_l, & x_{i(j)} \le x \le x_{i(j+1)}\end{cases} \tag{3.208}$$

In present notation,

$$-\ln \hat{\bar{P}}_i(x)=\begin{cases}0 & , x < x_{i(1)} \\ -\sum_{l=1}^{j}\ln\left(1-1/s_l\right), & x_{i(j)} \le x < x_{i(j+1)}\end{cases} \tag{3.209}$$

which will be close to $\hat{R}_i(x)$.

The estimation of cumulative hazard function of ordered lifetimes is given in Table 3.1.

Table 3.1. **Estimation of the Cumulative Hazard Function (c.h.f.) Ordered Lifetimes**

Ordered lifetimes and censoring times	Hazard Values	Estimated chf
$\nu_{(1)}$	0	0
.	.	.
.	.	.
.	.	.
$\nu_{(n-s_1)}$	0	0
$\nu_{(n-s_1+1)}=x_{i(1)}$	$1/s_1$	$1/s_1$
$\nu_{(n-s_1+2)}$	0	$1/s_1$
.	.	.
.	.	.
.	.	.
$\nu_{(n-s_2)}$	0	$1/s_1$
$\nu_{(n-s_2+1)}=x_{i(2)}$	$1/s_2$	$1/s_1+1/s_2$
$\nu_{(n-s_2+2)}$	0	$1/s_1+1/s_2$
.	.	.
.	.	.
.	.	.
$\nu_{(n-s_j)}$	0	$\sum_{l=1}^{j-1} 1/s_l$
$\nu_{(n-s_j+1)}=x_{i(j)}$	$1/s_j$	$\sum_{l=1}^{j} 1/s_l$
$\nu_{(n-s_j+2)}$	0	$\sum_{l=1}^{j} 1/s_l$
.	.	.
.	.	.
.	.	.
$\nu_{(n-s_{n_i})}$	0	$\sum_{l=1}^{n_i-1} 1/s_l$
$\nu_{(n-s_{n_i}+1)} = x_{i(n_i)}$	$1/s_{n_i}$	$\sum_{l=1}^{n_i} 1/s_l$

If more than one failure is obtained at the same time point, the hazard value and estimated cumulative hazard function must be changed accordingly. For instance, if c failures due to cause C_i occur after (j-1)-th failure, then the hazard value at point $x_{i(j)}$ would be c/s_j.

In the Weibull case, the hazard plot corresponding to cause C_i requires plotting log $x_{i(j)}$ against log $\hat{R}_i(x_{i(j)})$ or plotting $x_{i(j)}$ against $\hat{R}_i(x_{i(j)})$ on log-log paper. For all causes of failures, separate plots must be made.

3.9. Nonparametric Test for Comparing Failure Rates of Competing Risks

In competing risks model, there is a system, which is exposed to more than one cause of failure, but its actual failure is from one of these causes of failure. Each cause of death has its own latent or conceptual failure time , X_j, j = 1,..,k. In the presence of all causes of failures, only the smallest of X_j is observable with the actual cause of failure. Hence, the basic available information in the competing risks model is the time to failure of the system, T = min X_j and the corresponding cause of failure, δ.

The marginal distributions or the joint distribution of the latent failure times are generally not independent but they are assumed to be independent (Kalbfleish and Prentice, 1980). Otherwise, to estimate the joint distribution a parametric model is used (Moeschberger, 1974). On the contrary, in many practical situations, the causes of failure are dependent, that is, the latent failure time of an individual failing from one cause of failure might be correlated with the latent failure time of an individual failing from different cause of failure. Moreover, the selection of the parametric family can be difficult and misleading. It is easier to model the hazard function or the cumulative incidence function for the failure from cause j.

Consider that there are two risks acting in the population and their lifetimes are X and Y, respectively. The actual observations are T = min (X, Y), the time that the system is failed and δ = I (X > Y), the failure type. It is assumed that X and Y are independent and absolutely continuous random variables with

distribution functions F and G such that F(0) = G(0) = 0. Since there is nonidentifiability problems in the bases of the competing risk set up the assumption of independence can not be tested. Let $\overline{F}$ and $\overline{G}$ be the survival functions, f and g be the p.d.f.s and $\lambda_F = f/\overline{F}$ and $\lambda_G = g/\overline{G}$, the failure rates of the two risks X and Y, respectively. Let $X_1,\ldots X_n$ and $Y_1,\ldots,Y_n$ be two independent random samples from F and G denoting the hypothetical times to failure of the n individuals in the sample under the two risks. On the basis of the observed information $T_i = \min(X_i, Y_i)$ and $\delta_i = I(X_i > Y_i)$, of two hazard functions is tested by the null hypothesis

$H_0 : \lambda_F = \lambda_G$, for every x, that is,

$F(x) = G(x)$, for every x

Against the alternative

$H_A : \lambda_F \leq \lambda_G$, for every x, and with a inequality over a set of nonzero probabilities.

The equality of the two competing risks is tested in industrial reliability when it is important to determine which of the two components in series is more reliable than the other. Reliable component has the smaller failure rate. If the dominance of the one survival function is interested, the graphical methods based on the sample survival functions obtained from the competing risks data are used. These are the product-limit estimators or the Kaplan-Meier estimators obtained from the two samples assuming one type of the risk factor is censored. Since the graphical methods are not associate with any error rates and may be misleading, the nonparametric tests are appropriate for the problem of testing the equality of the two competing risks.

Under the alternative H_A the failure rate due to the first risk is required to be uniformly smaller than the failure rate due to the second risk. So, it is expected that the failure due to second risk is at earlier stage than the first one. Hence, if (X_1, Y_1) and (X_2, Y_2) are the hypothetical lifetimes of the two individuals due to two risks, respectively, then arrangements of the type Y's preceding X's (YYXX) and Y's being centred between X's (XYYX) tend to favour the alternative H_A, whereas arrangements of the type (XXYY) and (YXXY) would tend to favour a smaller failure rate due to second risk (Kochar, 1979). For testing H_0 against H_A, the following function is described;

$$\Delta(F, G) = P(YYXX) + P(XYYX) - P(XXYY) - P(YXXY) \qquad (3.209)$$

where

$$P(YYXX)=P\{(Y_1<Y_2<X_1<X_2)\cup(Y_2<Y_1<X_1<X_2)\cup(Y_1<Y_2<X_2<X_1)\cup(Y_2<Y_1<X_1<X_2)\}.$$

X_1, X_2, Y_1 and Y_2 are independent observations with the first two from F and following two from G. Under H_0, $\Delta(F, G) = 0$ and under H_A, $\Delta(F, G) > 0$. A test is based on U-statistic estimator of $\Delta(F, G)$ with the complete samples.

Let (X_i, Y_i) and (X_j, Y_j) be two independent pairs from which the available information is (T_i, δ_i) and (T_j, δ_j). All mutually exclusive and exhaustive arrangements of the pairs (T_i, δ_i) and (T_j, δ_j) are described in the Table (3.2).

Using these arrangements the following Kernel is considered by Kochar (1979)

$$\varphi^*\left\{(T_i,\delta_i),(T_j,\delta_j)\right\}=\begin{cases}1, \text{if } \delta_i = 1 \text{ and } T_i > T_j \\ \quad \text{or } \delta_j = 1 \text{ and } T_i < T_j \\ -1, \text{otherwise}\end{cases} \qquad (3.210)$$

Table 3.2. Information Regarding (X_i, Y_i) and (X_j, Y_j) Available in (T_i, δ_i) and (T_j, δ_j).

	$\delta_i = 1, \delta_j = 1$	$\delta_i = 1, \delta_j = 0$	$\delta_i = 0, \delta_j = 1$	$\delta_i = 0, \delta_j = 0$
$T_i > T_j$	$Y_j < Y_i < X_i$ $Y_j < X_j$	$X_j < Y_i < X_i$ $X_j < Y_i$	$Y_j < X_i < Y_i$ $Y_j < X_j$	$X_j < X_i < Y_i$ $X_j < Y_j$
$T_i < T_j$	$Y_i < Yj < X_j$ $Y_i < X_i$	$Y_i < X_i < Y_j$ $Y_i < X_i$	$X_i < Y_i < X_j$ $X_i < Y_i$	$X_i < X_j < Y_i$ $X_i < Y_i$

Let U^* be the corresponding U-statistic defined by

$$U^* = \left[\binom{n}{2}\right]^{-1} \sum_{1 \le i < j \le n} \varphi^* \left\{(T_i, \delta_i), (T_j, \delta_j)\right\} \tag{3.211}$$

Kochar (1979) proposed this U-statistic for testing H_0 against H_A.

On the other hand, Bagai, Deshpande and Kochar (1989) derived an equivalent statistic

$$U = \left[\binom{n}{2}\right]^{-1} \sum_{1 \le i < j \le n} \varphi \left\{(T_i, \delta_i), (T_j, \delta_j)\right\} \tag{3.212}$$

where

$$\varphi\left\{(T_i, \delta_i), (T_j, \delta_j)\right\} = \begin{cases} 1, \text{if } \delta_i = 1 \text{ and } T_i > T_j \\ \quad \text{or } \delta_j = 1 \text{ and } T_i < T_j \\ 0, \text{otherwise} \end{cases} \tag{3.213}$$

Large values of U are significant for testing H_0 against the one sided alternative H_A. If $R_1, \ldots, R_n$ are the ranks of $T_1, \ldots, T_n$, then U can also be defined as

$$\binom{n}{2} U = \sum_{i=1}^{n} (R_i - 1)\delta_i = \sum_{i=1}^{n} R_i \delta_i - \sum_{i=1}^{n} \delta_i \qquad (3.214)$$

where $\sum_{i=1}^{n} \delta_i$ is the sign statistic and $\sum_{i=1}^{n} R_i \delta_i$ is the Wilcoxon signed rank statistic.

The asymptotic distribution of $n^{1/2}$ (U – E (U)) as $n \to \infty$ is normal with mean zero and variance $4\varphi_1$ where

$$\varphi_1 = E [\psi^2(X_1, Y_1)] - E^2 (U) \qquad (3.215)$$

$$\psi (x_1, y_1) = E [\Phi (x, y, X_2, Y_2)]. \qquad (3.216)$$

For the proof one can see Puri and Sen (1971). Under H_0, E (U) = 1 / 2 and $\lim_{n\to\infty} n \sigma_U^2 = 1/3$ .The test based on rejecting H_0 for large values of U is consistent and unbiased for testing against H_A (Bagai, 1986).

3.10. Construction of the Life Table in the Presence of Competing Risks Data

In mortality studies with competing risks data, the estimators of the probabilities are different from the estimators, which are found before. For the time interval (x_i, x_{i+1}), the length of the interval is $n_i = x_{i+1} - x_i$. P_i is the midyear population and D_i is the number of deaths occurring during the calender year. The average fraction of the interval lived by each of the D_i individuals is a_i and N_i is the number of people alive at x_i among whom D_i deaths occur.

The age-specific death rate is

$$M_i = \frac{D_i}{P_i} \qquad (3.217)$$

This rate is generally a poor measure of mortality since it does not take age structure into account. In many developing countries this rate is lower than those of in highly developed countries because the former have a much younger age structure.

One important use of the age-specific death rate is to calculate crude rate of the natural increase, the difference between the age-specific birth rate and the age-specific death rate, in the population. It measures the current rate of population growth.

The probability of dying in the interval (x_i, x_{i+1}) is estimated from

$$\hat{q}_i = \frac{D_i}{N_i}. \tag{3.218}$$

When N_i is expressed in terms of P_i and D_i, that is,

$$N_i = [\, P_i + (1 - a_i)\, n_i\, D_i \,] / n_i, \tag{3.219}$$

Then, equation (3.218) becomes

$$\hat{q}_i = \frac{n_i\, M_i}{1 + (1 - a_i)\, n_i\, M_i}, \tag{3.220}$$

and its complement, the probability of surviving in the interval (x_i, x_{i+1}) is given by

$$\hat{p}_i = \frac{1 - a_i\, n_i\, M_i}{1 + (1 - a_i)\, n_i\, M_i}. \tag{3.221}$$

The D_i deaths contains k different death types. So, D_i is defined as

$$D_i = D_{i1} + \ldots + D_{ik} \tag{3.222}$$

So that

$$M_{i\delta} = \frac{D_{i\delta}}{P_i}\ ,\ \delta = 1,\ldots,k\ , \tag{3.223}$$

are the age-cause-specific death rates.

The crude probability of dying from cause R_δ in the presence of all causes acting on the population is estimated by

$$\hat{Q}_{i\delta} = \frac{D_{i\delta}}{N_i} \tag{3.224}$$

Substituting (3.219) in (3.224) gives

$$\hat{Q}_{i\delta} = \frac{n_i M_{i\delta}}{1 + (1 - a_i)\, n_i M_i}\ ,\ \delta = 1,\ldots,k;\ i = 0,1,\ldots \tag{3.225}$$

By using the relation between the crude and net, and the relation between crude and partial crude probabilities these probabilities are obtained as

$$\hat{q}_{i\delta} = 1 - \hat{p}_i^{D_{i\delta}/D_i}\ , \tag{3.226}$$

$$\hat{q}_{i.\delta} = 1 - \hat{p}_i^{(D_i - D_{i\delta})/D_i}\ ,\ \delta = 1,..,k \tag{3.227}$$

$$\hat{Q}_{i\delta.1} = \frac{D_{i\delta}}{D_i - D_{i1}}\left[1 - \hat{p}_i^{(D_i - D_{i1})/D_i}\right],\ \delta = 2,\ldots,k \tag{3.228}$$

$$\hat{Q}_{i\delta.21} = \frac{D_{i\delta}}{D_i - D_{i1} - D_{i2}} \left[1 - \hat{p}_i^{(D_i - D_{i1} - D_{i2})/D_i} \right], \delta = 3,\ldots,k, i = 0,1,\ldots \qquad (3.229)$$

The ratio $D_{i\delta} / D_i$ represents the proportionate mortality.

By substitution of $l_0 p_{0i} = N_i$, the approximate formulas for the sample variances and covariances can be found where l_0 is the initial population size at age x_0;

$$\frac{1}{l_0 p_{0i}} = \frac{n_i}{P_i + (1 - a_i) n_i D_i} \qquad (3.230)$$

The sample variance of the net probability of dying in interval (x_i, x_{i+1}) when R_δ is eliminated as a risk of death, $\hat{q}_{i.\delta}$ is

$$s^2_{\hat{q}i.\delta} = \frac{n_i (1 - \hat{q}_{i.\delta})^2}{(P_i + (1 - a_i) n_i D_i} \left[\hat{p}_i \log(1 - \hat{q}_{i\delta}) \log(1 - \hat{q}_{i.\delta}) + \left(\hat{q}_i - \hat{Q}_{i\delta} \right)^2 \right], \delta = 1,\ldots,k;$$

$$i = 0,1,\ldots \qquad (3.231)$$

To construct a current life tables for a population with respect to a particular cause of death, for example, the case where risk R_δ is eliminated from the population is assumed. The basic quantity is the estimator $\hat{q}_{i.\delta}$ of the net probability of dying in (x_i, x_{i+1}) when R_δ is eliminated. The proportion of individuals alive at age x_α who will survive to age x_i is calculated as

$$\hat{p}_{\alpha\, j.\delta} = \prod_{i=\alpha}^{j-1} (1 - \hat{q}_{i.\delta}) \qquad (3.232)$$

with the sample variance

$$s^2_{\hat{p}_{\alpha\, j.\delta}} = \hat{p}^2_{\alpha\, j.\delta} \sum_{i=\alpha}^{j-1} (1-\hat{q}_{i.\delta})^{-2} s^2_{\hat{q}_{i\delta}} \quad \alpha < j\ ;\ \alpha, j = 0,1,\ldots \tag{3.233}$$

When $\alpha = 0$ the quantity in formula (3.232) is equivalent to l_j / l_0.

The difference $\hat{q}_i - \hat{q}_{i.\delta}$ is the reduction in the probability of dying in age interval (x_i, x_{i+1}) if cause δ were eliminated as a risk of death or, alternatively, the excess probability of dying due to the presence of cause δ.

When risk R_δ is eliminated, the observed expectation of life at age x_α is

$$\hat{e}_{\alpha.\delta} = a_\alpha\, n_\alpha + \sum_{j \geq \alpha} c_j\, \hat{p}_{\alpha\, j.\delta}\ , \tag{3.234}$$

where $c_j = (\,1 - a_{j-1}\,)\, n_{j-1} + a_j\, n_j$ and the sample variance is

$$s^2_{\hat{e}_{\alpha..\delta}} = \sum_{j \geq \alpha} \hat{p}^2_{\alpha\, j.\delta} \left[\hat{e}_{j+1.\delta} + (1-a_j)\, n_j\right]^2 s^2_{\hat{q}_{j.\delta}},\ \alpha = 0,\ 1,\ldots. \tag{3.235}$$

Since $\hat{q}_{i.\delta}$ is less than $\hat{q}_i$, the probability of surviving at age x_α who will alive at age x_i when the risk R_δ is eliminated, $\hat{p}_{\alpha\, j.\delta}$ in (3.232) is greater than the corresponding proportion $\hat{p}_{\alpha\, j}$ of survivors when R_δ is operating in the population; and $\hat{e}_{\alpha.\delta}$ in (3.234) is greater than the corresponding observed expectation of life $\hat{e}_\alpha$ when all risks are acting, or

$$\hat{e}_{\alpha.\delta} - \hat{e}_\alpha > 0\,. \tag{3.236}$$

The difference between $\hat{e}_{\alpha.\delta}$ and $\hat{e}_\alpha$ in (3.236) is the additional years of life at an individual of age x_α could expect to live if risk R_δ were eliminated, or the years of life lost to an individual of age x_α due to the presence of risk R_δ.

3.11. Medical Follow-Up Studies in Competing Risks

In the medical follow-up and life testing the main objective of statistical studies is the estimation of life expectancy and survival rates for a defined population at risk. These studies must usually be applied before all survival information is complete and hence the study is said to be truncated.

In a typical follow-up study, a group of individuals with some common morbidity experience is followed from a well defined zero point, such as date of hospital admission. The purpose of the study might be to evaluate a certain therapeutic measure by comparing the expectation of life and survival rates of treated patients with those of untreated patients, or by comparing the expectation of life of treated and presumably cured patients with that of the general population. When the period of observation ends, there will usually remain a number of individuals for whom the mortality data is incomplete. Of first importance among these are the patients still alive at the end of the study. Second, some patients will have died from causes other than that under study, so that the chance of dying from the specific cause can not be determined directly. Finally, some patients will be lost to the study because of follow-up failure. These three sources of incomplete information have lots of statistical problem in the estimation of the expectation of life and survival rates.

Most follow-up studies are conducted to determine the survival rates of patients affected with a specific disease. These patients are also exposed to other risks of death from which some of them may eventually die. In such cases, the theory of competing risks is indispensable, and the crude, net and partial crude probabilities play important roles.

It is assumed that k risks, denoted by R_1, R_2,...,R_k, are acting simultaneously on each patient in the study. For risk R_i there is a corresponding intensity function $\lambda(\tau,i)$, i=1,2,...,k, and the sum

$$\lambda(\tau,1)+...+\lambda(\tau,k)=\lambda(\tau) \qquad (3.237)$$

is the total intensity function. Within the time interval (x, x+1) it is assumed that a constant force of mortality for each risk, $\lambda(\tau,i) = \lambda(x,i)$, which depends only on the interval (x, x+1) and the risk R_i; for all risks, $\lambda(\tau) = \lambda(x)$ for $x < \tau \leq x+1$.

If a subinterval (x, x+1) is considered and $Q_{x_i}(t)$ is the crude probability that an individual alive at time x will die prior to x+t, $0< t \leq 1$, from R_i in the presence of all other risks in the population, then the crude probability can be written as

$$Q_{x_i}(t) = \int_x^{x+1} \exp\{-(\tau - x)\,\lambda(x)\}\lambda(x;i)\,d\tau \qquad (3.238)$$

Integrating (3.238) gives

$$Q_{x_i}(t) = \frac{\lambda(x;i)}{\lambda(x)}\left[1-e^{-t\lambda(x)}\right] = \frac{\lambda(x;i)}{\lambda(x)}\left[1-p_x(t)\right] \qquad (3.239)$$

where $0<t\leq 1$, $i = 1,\ldots,k$ and $p_x(t)$ denotes the probability that a patient alive at time x will survive the interval (x, x+t).

It can be easily seen that, the sum of the crude probabilities in (3.239) is equal to the complement of $p_x(t)$ as

$$Q_{x_1}(t)+...+Q_{x_k}+p_x(t)=1, 0<t\leq 1 \qquad (3.240)$$

This implies that

$$Q_{x_1}(1+p_x^{1/2})^{-1}+...+Q_{x_k}(1+p_x^{1/2})^{-1}+p_x^{1/2}=1, \text{ where } x=0,1,...,y-1. \qquad (3.241)$$

when t=2.

The assumption of a constant relative risk required for the relations between the crude, net and partial crude probabilities derived respectively as

$$q_{x_i} = 1 - p_x^{Q_{x_i}/q_x}, x = 0,1,...,y-1$$

$$q_{x.i} = 1 - p_x^{(q_x - Q_{x_i})/q_x}, i = 1,...,k$$

$$Q_{x_{i.1}} = \frac{Q_{x_i}}{q_x - Q_{x_1}}\left[1 - p_x^{(q_x - Q_{x_1})/q_x}\right], i = 2,...,k \qquad (3.242)$$

and

$$Q_{x_{i.12}} = \frac{Q_{x_i}}{q_x - Q_{x_1} - Q_{x_2}}\left[1 - p_x^{(q_x - Q_{x_1} - Q_{x_2})/q_x}\right] \text{ where } i = 3,...,k$$

The main problem here is to estimate Q_{x_i}, p_x and q_x.

3.11.1. Basic Random Variables and Likelihood Function

For each interval (x, x+1) let N_x denote the number of patients alive at the beginning of the interval. That is, N_x represents the number of survivors of the patients entered in the study at least x years before the end of the study or date of last reporting for patients. The number N_x decreases as x increases due to termination of the study.

The N_x survivors beginning the interval (x,x+1) can be divided into two mutually exclusive groups according to their date of entrance into the study at time x. A group of m_x patients who entered the study more than x+1 years before the closing date will be observed for the entire interval. A second group of n_x patients who entered the study less than x+1 years before its termination is due to withdraw in the interval. Out of m_x patients, d_x will die in the interval and s_x will survive to begin the next interval of the n_x patients d_x' will die before the closing

date and w_x will survive to the closing date of the study. The sum $d_x+d_x'=D_x$ is the total number of deaths in the interval. The m_x patients to be observed for the entire interval (x,x+1) will be divided into k+1 mutually exclusive groups with s_x surviving the interval and d_{x_i} dying from cause R_i in the interval, i=1,…,k. Hence s_x, d_x, w_x and d_x', the basic random variables, will be used to estimate the probability p_x that a patient alive at x will survive the interval (x, x+1) and its complement q_x. In Table 3.3. the distribution of N_x patients according to withdrawal status, survival status and cause of death in the interval (x,x+1) is given.

Since the sum corresponding probabilities equal to unity, the random variables s_x, $d_{x_1},\ldots,d_{x_k}$ have the joint probability distribution

$$f_{x_1}(s_x,d_{x_i};p_x,Q_{x_i})=\binom{m_x}{d_{x_1},\ldots,d_{x_k}}p_x^{s_x}Q_{x_1}^{d_{x_1}}\ldots Q_{x_k}^{d_{x_k}} \qquad (3.243)$$

where $m_x=s_x+d_{x_1}+\ldots+d_{x_k}$. Then their expectations are

$$E[s_x|m_x]=m_xp_x \text{ and } E\left[d_{x_i}|m_x\right]=m_xQ_{x_i} \qquad (3.244)$$

respectively.

In the group of n_x patients due to withdraw in interval (x, x+1), w_x will be alive at the closing date of the study and d_{x_i}' will die from R_i before the closing date. The distribution of the random variables in the group of n_x patients depends on the time of withdrawal. It is assumed that the withdrawals take place at random during the interval (x, x+1). Under this assumption the probability that a patient will survive to the closing date is

Table 3.3. **The Distribution of N_x Patients According to Withdrawal Status, Survival Status and Cause of Death in the Interval (x,x+1).**

	Withdrawal Status in the Interval		
	Total number of patients	Number to be observed for the entire interval	Number due to withdraw during the interval
Total	N_x	m_x	n_x
Survivors	s_x+w_x	s_x	w_x
Deaths(all causes)	D_x	d_x	$d_{x'}$
Deaths due to cause			
R_1	D_{x_1}	d_{x_1}	d'_{x_1}
.	.	.	.
.	.	.	.
.	.	.	.
R_k	D_{x_k}	d_{x_k}	d'_{x_k}

$$\int_x^{x+1} \exp[-(\tau - x)\lambda(x)]d\tau = -\frac{1-p_x}{\log p_x} \qquad (3.245)$$

which is approximately equal to $p_x^{1/2}$ (Chiang, 1961) or

$$-\frac{1-p_x}{\log p_x} = p_x^{1/2}.$$

Since the probability p_x of surviving the interval is almost always large. So, each of the n_x individuals has the survival probability $p_x^{1/2}$ and the probability of dying from risk R_i before the closing date

$$Q_{x_i}\left(\frac{1}{2}\right) = Q_{x_i}\left(1+p_x^{1/2}\right)^{-1}, i = 1,...,k \tag{3.246}$$

Since $p_x^{1/2}$ and $Q_{x_1}\left(\frac{1}{2}\right),...,Q_{x_k}\left(\frac{1}{2}\right)$ add to unity, the random variables w_x, $d'_{x_1},...,d'_{x_k}$ have the joint probability distribution

$$f_{x_2}\left(s_x, d'_{x_i}; p_x, Q_{x_i}\right) = \binom{n_x}{d'_{x_1},...,d'_{x_r}} p_x^{(1/2)w_x} \prod_{i=1}^{r}\left[Q_{x_i}\left(1+p_x^{1/2}\right)^{-1}\right]^{d'_{x_i}} \tag{3.247}$$

where $w_x + d'_{x_1} + ... + d'_{x_k} = n_x$. The expectations are

$$E[w_x|n_x] = n_x\, p_x^{1/2} \text{ and } E[d'_{x_i}|n_x] = n_x\, Q_{x_i}\,(1+p_x^{1/2})^{-1} \tag{3.248}$$

respectively. Because of independence of the two patient groups, observed and withdraw, the likelihood function of all the random variables can be written as

$$\begin{aligned} L_x &= f_{x_1}\left(s_x, d_{x_i}; p_x, Q_{x_i}\right) f_{x_2}\left(w_x, d'_{x_i}; p_x, Q_{x_i}\right) \\ &= c\, p_x^{s_x+(1/2)w_x} \prod_{i=1}^{k} Q_{x_i}^{d_{x_i}}\left[Q_{x_i}\left(1+p_x^{1/2}\right)^{-1}\right]^{d'_{x_i}} \end{aligned} \tag{3.249}$$

where $c = \binom{m_x}{d_{x_1},...,d_{x_k}} \cdot \binom{n_x}{d'_{x_1},...,d'_{x_k}}$.

This likelihood function can be simplified as

$$L_x = c\, p_x^{s_x+(1/2)w_x}\,(1+p_x^{1/2})^{-d'_x} \prod_{i=1}^{k} Q_{x_i} \tag{3.250}$$

3.11.2. Estimation of Crude , Net and Partial Crude Probabilities

To obtain the estimators of probabilities p_x, $Q_{x_1},...,Q_{x_k}$, the maximum likelihood principle is used. The logarithm of the likelihood function (3.250) is

$$\log L_x = \log c + \left(s_x + \frac{1}{2}w_x\right)\log p_x - d_x' \log\left(1 + p_x^{1/2}\right) + \sum_{i=1}^{k} D_{x_i} \log Q_{x_i} \quad (3.251)$$

which is to be maximized subject to the condition

$$p_x + Q_{x_1} + ... + Q_{x_k} = 1.$$

Using the LaGrange method it is maximized that

$$\begin{aligned}\Phi_x = {} & \log c + \left(s_x + \frac{1}{2}w_x\right)\log p_x - d_x' \log\left(1 + p_x^{1/2}\right) \\ & + \sum_{i=1}^{k} D_{x_i} \log Q_{x_i} - \lambda\left(p_x + \sum_{i=1}^{k} Q_{x_i} - 1\right)\end{aligned} \quad (3.252)$$

Differentiating Φ_x with respect to p_x, $Q_{x_1},...,Q_{x_k}$ and setting derivatives equal to zero yield equations

$$\frac{\partial}{\partial p_x}\Phi_x = \frac{s_x + \frac{1}{2}w_x}{\hat{p}_x} - \frac{\frac{1}{2}d_x'}{\left(1 + \hat{p}_x^{1/2}\right)\hat{p}_x^{1/2}} - \lambda = 0 \quad (3.253)$$

and

$$\frac{\partial}{\partial Q_{x_i}} = \frac{D_{x_i}}{\hat{Q}_{x_i}} - \lambda = 0, i = 1,...,k \tag{3.254}$$

Since (3.254) holds true for each i, it is obtained that

$$\hat{\lambda} = \frac{\sum_{i=1}^{k} D_{x_i}}{\sum_{i=1}^{k} \hat{Q}_{x_i}} \text{ or } \hat{\lambda} = \frac{D_x}{\hat{q}_x} \text{ with } \hat{q}_x = 1 - \hat{p}_x \tag{3.255}$$

and hence

$$\frac{D_{x_i}}{\hat{Q}_{x_i}} = \frac{D_x}{\hat{q}_x} \tag{3.256}$$

Using the second equation in (3.255), the quadratic equation can be found from (3.256)

$$\left(N_x - \frac{1}{2}n_x\right)\hat{p}_x + \frac{1}{2}d_x'\hat{p}_x^{1/2} - \left(s_x + \frac{1}{2}w_x\right) = 0 \tag{3.257}$$

Hence, the estimators

$$\hat{p}_x = \left[\frac{-\frac{1}{2}d'_x + \sqrt{\frac{1}{4}\left(d'_x\right)^2 + 4\left(N_x - \frac{1}{2}n_x\right)\left(s_x + \frac{1}{2}w_x\right)}}{2\left(N_x - \frac{1}{2}n_x\right)} \right]^2, \text{where } x = 0,1,\ldots,y-1$$

(3.258)

with the complement $\hat{q}_x = 1 - \hat{p}_x, x = 0,1,\ldots,y\text{-}1$. Substituting (3.258) in (3.256) yields the estimators of the crude probabilities,

$$\hat{Q}_{x_i} = \frac{D_{x_i}}{D_x}\,\hat{q}_x, i = 1,\ldots,k, \quad x = 0,1,\ldots,y\text{-}1. \tag{3.259}$$

Thus, the net and partial crude probabilities can be estimated as

$$\hat{q}_{x_i} = 1 - \hat{p}_x^{D_{x_i}/D_x}, x = 0,1,\ldots,y\text{-}1$$
$$\hat{q}_{x.i} = 1 - \hat{p}_x^{(D_x - D_{x_i})/D_x}, i = 1,\ldots,k$$
$$\hat{Q}_{x_{i.1}} = \frac{D_{x_i}}{D_x - D_{x_1}}\left[1 - \hat{p}_x^{(D_x - D_{x_1})/D_x}\right], i = 2,\ldots,k \tag{3.260}$$

and

$$\hat{Q}_{x_{i.12}} = \frac{D_{x_i}}{D_x - D_{x_1} - D_{x_2}}\left[1 - \hat{p}_x^{(D_x - D_{x_1} - D_{x_2})/D_x}\right], i = 3,\ldots,k$$

3.12. Dependent Competing Risks

In biological and medical studies, estimation of the marginal survival function of the time T, from some specified starting point, until some event of interest occurs, such as the occurrence of a particular disease, remission, relapse, death due to some specific disease or simply death, is a common problem.

Sometimes it is impossible to measure T due to the occurrence of some other competing event at time C (<T). This competing event may be the withdrawal of the subject from the study, death from some cause other than the death from the main event of interest or any event precluding the occurrence of the main event of interest. In such cases, the actual time until the main event of interest occurs can be regarded as censored. With such a competing risks framework, right-censored survival data are analyzed as though the latent random time T is independent of the latent time C. However, many biomedical experiments put forward to the inplausibleness of the assumption of the independence of T and C.

In the competing risks framework, data consists of the failure time of death or censoring, X=minimum(T, C) and $\Delta = I(T < C)$ where I(.) denotes the indicator function.

Since the papers of Tsiatis (1975) and Peterson (1976), it has been well understood that the survival function $S_T(t) = Pr(T_i \geq t)$ cannot be identified from data of the form $\{X_i, \Delta_i\}$, i=1,2,...,n. Because there exists both an independent and one or more dependent models for (X, Y) that produce the same joint distribution for (X, Δ). However, these equivalent independent and dependent joint distributions may have quite different marginal distributions. In order to analyze such data one must make an unverifiable assumption. Under the assumption of independent T_i and C_i, methods of analysis based on Kaplan and Meier (1958) consistent estimator $\hat{S}_T(t)$ of $S_T(t)$ are available. If the joint density of T_i and C_i is assumed to have a known parametric form f(t, c; θ), then the estimators for θ based on the likelihood function of $\{(X_i, \Delta_i)\}$ allow consistent estimation of $S_T(t)$.

In the light of the consequences of the untestable independence assumption in using the product-limit estimator to estimate the marginal survival function of T, it is important to have bounds on this function based on the

observable random variables (X, Δ) and some assumptions on the joint behaviour of T and C.

In the case of dependent competing risks Peterson (1976) has obtained bounds on the unobservable marginal survival probabilities $S_i(.)$, in terms of observable crude survival probabilities $S_i^*(.)$, in the case of k = 2. He also obtains a bound on the joint survival function $S(x_1,x_2) = P(T > x_1, C > x_2)$ in the following theorem:

Theorem 1: (Peterson (1976))

Let $S_1(x) = P(T > x)$ and $S_2(x) = P(C > x)$, $S_1^*(x)=P(T>x, \min (T, C))$, $S_2^*(x)=P(C>x, \min (T, C))$, $p_1=P(T<C)$ and $p_2=P(T>C)$ then

$$\begin{aligned} S(t,c)&=S_1^*(t)+S_2^*(c)-P(t<T<C<c) \quad \text{if } t<c \\ &=S_1^*(t)+S_2^*(c)-P(c<C<T<t) \quad \text{if } t>c \end{aligned} \tag{3.261}$$

Also

$$S_1^*[\max(t,c)]+S_2^*[\max(t,c)] \le S(t,c) \le S_1^*(t)+S_2^*(c) \tag{3.262}$$

and

$$S_1^*(t)+S_2^*(t) \le S_1(t) \le S_1^*(t)+p_2 \tag{3.263}$$

$$S_1^*(c)+S_2^*(c) \le S_2(c) \le S_2^*(c)+p_2 . \tag{3.264}$$

These bounds allow for any possible dependence structure and can be very wide.

Alternatively, Slud and Rubinstein (1983) give a simple and completely general, although strictly hypothetical, quantification of the degree of dependence between latent failure time random variables T and C by defining the ratio ρ(t)

(the rho-function) of the conditional hazard function for T at t given C<t to the conditional hazard function for T at t given C≥t.

Formally, the rho-function is given by

$$\rho(t)=\frac{h_T(t\,|\,C<t)}{h_T(t\,|\,C\geq t)}=\lim_{\varepsilon\to 0}\frac{\Pr\{t\leq T\leq t+\varepsilon\,|\,T\geq t, C<t\}}{\Pr\{t\leq T\leq t+\varepsilon\,|\,T\geq t, C\geq t\}} \qquad (3.265)$$

which measures the relative risk that would be felt at time t on test for the failure time T among previously censored individuals as compared with individuals not yet censored.

Assuming ρ(t) is known, they produce a consistent estimator $\hat{S}_\rho(t)$ of $S_T(t)$ analogous to Kaplan-Meier estimator, and note that if reasonable bounds $\rho_1(.)$ and $\rho_2(.)$ can be postulated from the unknown ρ(.), then the marginal survival function $S_T(.)$ is correctly estimated to line between $\hat{S}_{\rho 1}(t)$ and $\hat{S}_{\rho 2}(t)$ for all t as the following:

When ρ(.) is assumed known, there is a simple consistent estimator of the marginal survival curve S(.) which immediately generalizes the Kaplan-Meier (1958) estimator. Suppose that in the sample $\{X_i,\Delta_i: 1\leq i\leq N\}$, the ordered times of X_i for $\Delta_i=1$ are $X_{(1)}\leq\ldots\leq X_{(d)}$ and the number of X_i with $\Delta_i=0$ between $X_{(j)}$ and $X_{(j+1)}$ is c_j, with c_0 censored before $X_{(1)}$. Let n_j be the number of i with $X_i \geq X_j$. Then the empirical odds of an uncensored surviving individual's dying at $X_{(j)}$ is 1: (n_j-1), and the empirical odds of a previously censored surviving individual's dying at $X_{(j)}$ is $\rho(X_{(j)})$: (n_j-1). The product-limit estimator of the probability of being censored before $X_{(j)}$ is therefore

$$N^{-1}\sum_{k=0}^{j-1}c_k\prod_{i=k+1}^{j}\left[1-\rho\left(X_{(i)}\right)/\left\{n_i-1+\rho\left(X_{(i)}\right)\right\}\right] \qquad (3.266)$$

while the probability of not being censored before $X_{(j)}$ is empirically estimated by $(n_j-1)/N$. Altogether this product-limit estimator for S(.) based on $\{(X_i, \Delta_i)\}$ is

$$\hat{S}_\rho(t) = N^{-1}\left\{ n(t) + \sum_{k=0}^{d(t)-1} c_k \prod_{i=k+1}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1} \right\} \qquad (3.1267)$$

where

$$n(t) = \Sigma\, I(X_t > t),\ \ d(t) = \Sigma\, I(\Delta_t=1, X_t \le t),\ \ \rho_t = \rho(X_{(t)})$$

After some algebra with the identities $c_k=n_k+n_{k+1}-1$, where $n_0=N+1$, it can be found that

$$\hat{S}_\rho(t) = \prod_{i=1}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1} + N^{-1} \sum_{k=1}^{d(t)} (\rho_k - 1) \prod_{i=k}^{d(t)} \frac{n_i - 1}{n_i + \rho_i - 1} \qquad (3.268)$$

It is clear from (3.267) that $\hat{S}_\rho(t)$ is a decreasing function of ρ for fixed t. If ρ(t) is defined as (3.265), then in sufficiently large sample

$$\hat{S}_{\rho 2}(t) \le \hat{S}_\rho(t) \le \hat{S}_{\rho 1}(t) \qquad (3.269)$$

if $\rho_1(.) \le \rho(.) \le \rho_2(.)$. When $\rho_1(.)=0$ and $\rho_2(.)=\infty$, one can obtain the Peterson's (1976) general bound.

It can be seen easily that, when T and C are independent, ρ(t) = 1 for all t and the Kaplan-Meier estimator for $S_T(t)$ is consistent. Values of ρ(t)>1 for all t may be interpreted to mean that among those who are censored before t, individuals with smaller T_i will be overrepresented as compared with the whole population under study, and thus if independence of T and C is assumed, the survival curve will be overestimated. On the other hand, if ρ(t)<1 for all t,

individuals with large T_i will be overrepresented, and the independence assumption will lead to underestimation of the survival curve.

Alternative bounds on the marginal survival function utilizing different additional information are produced by Klein and Moeschberger (1988). They assume that the joint distribution of the time until death and censoring, (T, C), belongs to a family of distributions indexed by a dependence measure θ with arbitrary marginal. For this family, knowledge of θ, along with the observable information, (X, Δ), is sufficient to determine uniquely the marginal distributions of T and C. The resulting estimator $\hat{S}_\theta(x)$ is a decreasing function of θ so that bounds on S(x) for the family of the joint distributions is obtained by specifying a range of possible values for $\theta=(1+\tau)/(1-\tau)$ where τ is the coefficient of concordance.

Hence the bounds on marginal survival functions are obtained as follows:

Let $S(t)=P(T \geq t)$ be the univariate survival function of death and $R(c)=P(C \geq c)$ be the probability of not being censored before time c. Also suppose that T and C have the bivariate joint distribution defined as

$$F(t,c)=P(T>t, C>c)=\left\{\left[\frac{1}{S(t)}\right]^{\theta-1}+\left[\frac{1}{R(c)}\right]^{\theta-1}-1\right\}^{-1/(\theta-1)} \qquad (3.270)$$

where $\theta \geq 1$ and $X=\min(T, C)$; then the survival function of X is

$$F(x)=\left\{\left[\frac{1}{S(x)}\right]^{\theta-1}+\left[\frac{1}{R(x)}\right]^{\theta-1}-1\right\}^{-1/(\theta-1)} \qquad (3.271)$$

and the crude density function associated with T,

$$q_1(x)=\frac{d}{dt}P(X<x,T<C)=\frac{s(x)}{S^{\theta}(x)}\left[F(x)\right]^{\theta}. \qquad (3.272)$$

where $s(x)=-dS(x)/d(x)$.

Considering the differential equation

$$s(x)/S^{\theta}(x)=q_1(x)/[F(t)]^{\theta} \qquad (3.273)$$

and suppose θ is known, it can be obtained by

$$S_{\theta}(x)=\begin{cases}\left[1+(\theta-1)\int_0^x \frac{q_1(u)}{[F(u)]^{\theta}}du\right]^{-1/(\theta-1)} & \text{if } \theta>1\\ \exp\left[-\int_0^x \frac{q_1(u)}{F(u)}du\right] & \text{if } \theta=1\end{cases} \qquad (3.274)$$

The functions $F(.)$ and $q_1(.)$ are directly estimable from the data as

$$\hat{F}(x)=\sum_{i=1}^{n}\frac{I(X_i\geq x)}{n} \text{ and } \hat{Q}_1(x)=\sum_{i=1}^{n}\frac{I(X_i\leq x,\Delta_i=1)}{n} \qquad (3.275)$$

Then if θ is known, an estimator of $S_{\theta}(x)$ is

$$\hat{S}_{\theta}(x)=\begin{cases}\left\{1+(\theta-1)\int_0^x \frac{d\hat{Q}_1(u)}{[\hat{F}(u)]^{\theta}}\right\}^{-1/(\theta-1)} & \text{if } \theta>1\\ \exp\left[-\int_0^x \frac{d\hat{Q}_1(u)}{\hat{F}(u)}\right] & \text{if } \theta=1\end{cases} \qquad (3.276)$$

For the computation purposes

$$\hat{S}_\theta(x)=\begin{cases}\left[1+(\theta-1)n^{\theta-1}\sum\limits_{\substack{x_{(i)}\le x\\ \Delta_{(i)}=1}}\dfrac{1}{(n-i+1)}\theta\right]^{-1/(\theta-1)} & \text{if } \theta>1\\ \exp\left[-\sum\limits_{\substack{x_{(i)}\le x\\ \Delta_{(i)}=1}}\dfrac{1}{(n-i+1)}\right] & \text{if } \theta=1\end{cases} \qquad (3.277)$$

For θ known and if the true underlying joint distribution of (T,C) is of the form (3.270), then $\hat{S}_\theta(x)$ is a consistent estimator of S(x).

To obtain bounds on the net survival function based on data from a competing risks experiment, first note that $S_\theta(x)$ is a decreasing function of θ for fixed x. Also, as $\theta\to 1^+$, it is obtained that

$$S_\theta(x)\uparrow \exp\left[-\int_0^x F^{-1}(u)\,dQ_1(u)\right] \qquad (3.278)$$

which provides an upper bound on S(x). This upper bound corresponds to an assumption of independence. As $\theta\to\infty$, it can be shown that $S_\theta(x)\downarrow F(x)$, which corresponds to Peterson's(1976) lower bound.

Tighter bounds, in the spirit of Slud and Rubinstein (1983) may be obtained if an investigator can specify a range of possible values for θ, (θ_1, θ_2). If the sample size is sufficiently large and $\theta_1\le\theta\le\theta_2$, then $\hat{S}_{\theta_1}(x)\ge S(x)\ge\hat{S}_{\theta_2}(x)$. Two approaches to specifying θ_1 and θ_2 appropriate. Note that $\theta=h_T(t\,|\,C=c)/h_T(t\,|\,C>c)$ for all t, c so that θ_1 and θ_2 are reflections of the investigator's belief in how the hazard rate of T would be affected by knowledge of the occurrence of censoring at time c. Second, specifying θ_1,θ_2 is equivalent to

specifying a range of values for the coefficient of concordance, τ, between failure time T and censoring time C, since $\theta=(1+\tau)/(1-\tau)$.

Dependence between two causes of death can arise whenever a shared risk factor is ignored or unknown. The dependence will be positive when the ignored risk factor increases risk for both causes, and negative when its effects on the two causes are opposite. For example, smoking is a risk factor for both coronary heart disease and some forms of cancer, but other evidence suggests that alcohol may increase risk for some cancers but decrease risk for coronary heart disease. Different ignored risk factors could be important for patients with high or low levels of the risk factor under study.

3.12.1. Dependent Competing Risks with Bivariate Normal Distribution

Let the non-negative random variable Y_i represent the theoretical lifetime of an individual when R_i is the only cause of failure (i=1,...,k). In the presence of all k causes R_p (p=1,...,k) only the smallest of the Y_l, is observable, together within the actual cause of failure , say R_i. Then the observed lifetime can be written, conditional on knowing the cause of failure to be R_i, as X_i, where $X_i= Y_i \mid Y_i=\min Y_p$. Also, let the probability of failure due to cause R_i be

$$\Pi_i = \Pr\left\{ Y_i = \min_p Y_p \right\},\ \Pi_i > 0,\ \sum_{i=1}^{k} \Pi_i = 1 \qquad (3.279)$$

If the Y_p (p=1,...,k) have an absolutely continuous joint distribution with probability density function (pdf) $p(y_1,y_2,...,y_k)$, then the pdf of the observed lifetime X_i (i=1,...,k) of an individual dying from cause R_i is

$$f_i(x)=\frac{1}{\Pi_i}\int_x^\infty\cdots\int_x^\infty p(y_1,\ldots,y_{i-1},x,y_{i+1},\ldots,y_k)\prod_{\substack{p=1\\p\neq i}}^{k}dy_p \tag{3.280}$$

$$=\frac{1}{\Pi_i}p_i(x)\int_x^\infty\cdots\int_x^\infty p(y_1,\ldots,y_{i-1},y_{i+1},\ldots,y_k|Y_i=x)\times$$

$$\times\prod_{\substack{p=1\\p\neq i}}^{k}dy_p \tag{3.280a}$$

With the help of the result of (3.280), it is easy to write down the likelihood function. In the case of Type I censoring, likelihood function can be written as

$$L_I=\prod_{i=1}^{k}\prod_{j=1}^{m_i}\pi_i f_i(x_{ij})\times\prod_{u=1}^{s}\int_{\gamma(u)}^\infty\cdots\int_{\gamma(u)}^\infty p(y_1,\ldots,y_k)\prod_{i=1}^{k}dy_i,\ x_{ij}<\gamma_{ij} \tag{3.281}$$

where γ_t is the censoring time, m_i is the individuals have failed from cause R_i, s is the number of survivors and $\gamma_{(u)}$ denotes the censoring times of the s survivors (u=1,…,s).

Suppose that k=2. Then (3.280a) can be written as

$$f_1(x)=\frac{1}{\Pi_1}p_1(x)\int_x^\infty p(y_2|Y_1=x)dy_2 \tag{3.282}$$

with the corresponding expression for $f_2(x)$. When Y_1 and Y_2 are bivariate normal, $BVN(\mu_1,\mu_2,\sigma_1^2,\sigma_2^2,\rho)$, the probability of failure due to cause R_1 becomes

$$\pi_1=Pr\{Y_2Y_1>0\}=1\Phi(\xi)=\overline{\Phi}(\xi) \tag{3.283}$$

where

$$\xi = \frac{\mu_1 - \mu_2}{(\sigma_1^2 - 2\rho\sigma_1\sigma_2 + \sigma_2^2)^{1/2}}.$$

Since $Y_2 \mid Y_1 = x \sim N(\mu_2 + \rho\sigma_2(x-\mu_1)/\sigma_1,\ \sigma_2^2(1-\rho^2))$, it is found that

$$f_1(x) = \begin{cases} \frac{1}{\pi_1\sigma_1}\phi\left(\frac{x-\mu_1}{\sigma_1}\right)\overline{\Phi}\left(\frac{x-\mu'}{\sigma_1'}\right) & \text{if } \rho\sigma_2 \neq \sigma_1 \\ \frac{1}{\sigma_1}\phi\left(\frac{x-\mu_1}{\sigma_1}\right) & \text{if } \rho\sigma_2 = \sigma_1 \end{cases} \tag{3.284}$$

where $\mu' = \alpha_1\mu_2 + (1-\alpha_1)\mu_1, \sigma_1' = \alpha_1\sigma_2(1-\rho^2)^{1/2}, \alpha_1 = |1 - \rho\sigma_2/\sigma_1|^{-1}$ with $f_2(x)$ similarly expressed, the likelihood function is readily written down.

From (3.281), $E(X_1)$ can be obtained and compared with $E(Y_1)$. Such a comparison is of particular interest when one wishes to estimate the expected lifetime under some prime cause of failure which suffers interference from nuisance cause R_2. When Y_1 and Y_2 are bivariate normal from (3.283), on setting $u=(x-\mu_1)/\sigma_1$

$$E(X_1) = \frac{1}{\pi_1}\int_{-\infty}^{\infty}(\sigma_1 u + \mu_1)\phi(u)\int_{(\sigma_1 u+\mu_1-\mu_1')/\sigma_1'}^{\infty}\phi(y)dydu$$

This, on reversing the order of integration, reduces to

$$\begin{aligned} E(X_1) &= \mu_1 - \frac{\sigma_1}{\sqrt{2\pi}} \times \frac{\sigma_1}{\left(\sigma_1^2 + \sigma_1'^2\right)^{1/2}} \times \frac{e^{-\frac{1}{2}\frac{(\mu_1'-\mu_1)^2}{\sigma_1^2+\sigma_1'^2}}}{\overline{\Phi}(\xi)} \\ &= \mu_1 - \sigma_1 \times \frac{|\sigma_1 - \rho\sigma_2|}{\left(\sigma_1^2 - 2\rho\sigma_1\sigma_2 + \sigma_2^2\right)^{1/2}} \times \frac{\phi(\xi)}{\overline{\Phi}(\xi)} \end{aligned} \tag{3.285}$$

3.12.2. The Dependent Competing Risks with Bivariate Exponential Distribution

3.12.2.1. Marshall and Olkin's Bivariate Exponential Model

In this model, a bivariate exponential distribution has two exponential marginal distributions and the lack of memory property. The model can be written as

$$\overline{P}(y_1, y_2) = \Pr(Y_1 > y, Y_2 > y) = \exp\{-\lambda_1 y_1 - \lambda_2 y_2 - \lambda_{12} \max[y_1, y_2]\} \quad (3.286)$$

where $y_1>0$ and $y_2>0$.

This model assumes that three independent Poisson processes $Z_1(t;\lambda_1)$, $Z_2(t;\lambda_2)$ and $Z_{12}(t;\lambda_{12})$ describe the occurrence of failures. Here, $Z(t;\lambda)$ denotes the number of fatal shocks in time t for a Poisson process with parameter λ, Z_1 refers to shocks fatal to component 1, Z_2 refers to shocks fatal to component 2 and Z_{12} to both components simultaneously.

The probability that component 1 and 2 are still functioning at time y_1 and y_2, respectively, is given by

$$\overline{P}(y_1, y_2) = \Pr\{Z_1(y_1;\lambda_1) = 0, Z_2(y_2;\lambda_2) = 0, Z_{12}(\max(y_1, y_2);\lambda_{12}) = 0\} \quad (3.287)$$

Let U_1, U_2 and U_{12} be exponentially distributed times to first occurrence of events in the corresponding Poisson processes, then $Y_1=\min(U_1,U_{12})$ and $Y_2=\min(U_2,U_{12})$. By using this representation, it can be obtained that

$$\Pr(Y_1 = Y_2) = \Pr\{U_{12} = \min(U_1, U_2, U_{12})\} = \frac{\lambda_{12}}{\lambda_1 + \lambda_2 + \lambda_{12}} \quad (3.288)$$

In the competing risk theory, Marshall-Olkin model can be used, if the two components were arranged in series. So that failure of any component fails the whole system. When the system fails, the identified minimum of U_1,U_2 and U_{12} is obtained. The U's correspond to an individual's time to death from cause 1, cause 2 or from both causes, respectively.

3.12.2.2. Gumbel Bivariate Exponential Model

Consider a two component series system with component life lengths X_1, X_2. Suppose that X_i has an exponential survival function

$$\bar{F}_i(t) = \Pr(X_i > t) = \exp(-\lambda_i t),\ t>0,\ \lambda_i>0,\ i=1,2. \qquad (3.289)$$

It is assumed that the value of λ_i is known. If X_1, X_2 are independent , the time to system failure has an exponential distribution with failure rate $\lambda_1+\lambda_2$, and the system reliability is

$$\bar{F}_1(t) = \Pr[\min(X_1, X_2) > t] = e^{-\lambda t} \qquad (3.290)$$

Suppose that the actual joint distribution of (X_1,X_2), has the form proposed by Gumbel (1960)

$$P(X_1>x,X_2>x)=[\exp(-\lambda_1 x_1-\lambda_2 x_2)][1+\alpha(1-\exp(-\lambda_1 x_1))(1-\exp(-\lambda_2 x_2)] \qquad (3.291)$$

where $x_1,x_2,\lambda_1,\lambda_2>0$, $-1\le \alpha \le 1$ and the joint density function of (X_1,X_2) is

$$f(x_1,x_2)=\lambda_1\lambda_2[\exp(-\lambda_1 x_1-\lambda_2 x_2)][1-\alpha(2\exp(-\lambda_1 x_1)-1)(2\exp(-\lambda_2 x_2)-1) \qquad (3.292)$$

where $x_1,x_2,\lambda_1,\lambda_2>0$, $-1\le \alpha \le 1$. This distribution has marginal survival functions equivalent to those for the independent model.

The correlation between X_1, X_2 is $\rho=\alpha/4$ and $\alpha=0$ represents the independence between X_1, X_2 for $\rho>0$ (<0) the components are positively (negatively) quadrant-dependent. Moreover, the conditional expectation of X_1 given $X_2=x_2$ is

$$E[X_1|X_2 = x_2] = \frac{1}{\lambda_1}[1 + 2\rho - 4\rho\exp(-\lambda_2 x_2)] \tag{3.293}$$

If (X_1,X_2) have the joint distribution $f(x_1,x_2)$, then the true system reliability is

$$\bar{F}_D(t) = P[\min(X_1, X_2) > t] = \exp(-\lambda t)[1 + 4\rho(1 - \exp(-\lambda_1 t)(1 - \exp(-\lambda_2 t)].$$
(3.294)

Then, the error in modelling system reliability dependent or independent is

$$\Delta(t) = \bar{F}_D(t) - \bar{F}_I(t) = 4\rho[1 - e^{-\lambda_1 t}][1 - e^{-\lambda_2 t}][e^{-(\lambda_1+\lambda_2)t}] \tag{3.295}$$

For fixed λ_1, λ_2 and t, $|\Delta(t)|$ increases as $|\rho|$ increases. When $\lambda_1=\lambda_2=\varnothing$, $\Delta(t)$ is maximized at $t=[\ln 2]/\varnothing$ (fixing ρ and $\varnothing$). The value of $|\Delta(t)|$ at this point is $|\rho|/4$ which is at most 1/16.

The mean time to failure assuming independence is

$$\mu_I=1/(\lambda_1+\lambda_2) \tag{3.296}$$

and assuming dependence

$$\mu_D = \frac{1}{\lambda_1 + \lambda_2} + 4\rho\left[\frac{3}{2(\lambda_1 + \lambda_2)} - \frac{1}{(2\lambda_1 + \lambda_2)} - \frac{1}{(\lambda_1 + 2\lambda_2)}\right] \tag{3.297}$$

Then the error in modelling system mean lifetime is

$$\mu_D - \mu_I = \frac{6\rho\lambda_1\lambda_2}{(\lambda_1+\lambda_2)(2\lambda_1+\lambda_2)(\lambda_1+2\lambda_2)} = \frac{6\rho\lambda_1\lambda_2\mu_I}{(2\lambda_1+\lambda_2)(\lambda_1+2\lambda_2)} \qquad (3.298)$$

where its absolute value increases as $|\rho|$ increases. If $\lambda_1=\lambda_2$, this error reduces to $2\rho\mu_I/3$ which has a maximum absolute value of $\mu_I/6$.

3.12.2.3. Oakes Bivariate Exponential Model

For this model, the joint survival probability is given by

$$P(X_1>x_1, X_2>x_2)=[\exp(\lambda_1(\theta-1)x_1)+\exp(\lambda_2(\theta-1)x_2)-1]^{-1/(\theta-1)} \qquad (3.299)$$

where $\lambda_1,\lambda_2>0$; $\theta \geq 1$; $x_1,x_2\geq 0$ and $\theta=\frac{1+\tau}{1-\tau}$ where τ is the Kendall's coefficient of concordance, $0\leq\tau\leq 1$. When $\theta=1$, X_1, X_2 are independent.

This model has the following interpretation: If $r(x_1|X_2=x_2)$ and $r(x_1|X_2>x_2)$ are the conditional failure rates of X_1 given $X_2=x_2$ and $X_2>x_2$, respectively,

$$r(x_1|X_2=x_2)=\theta\, r(x_1|X_2>x_2). \qquad (3.300)$$

CHAPTER 4

APPLICATION OF COMPETING RISKS DATA

Leukemia is a cancer of the blood-forming cells. It occurs when immature or mature cells multiply in an uncontrolled manner in the bone marrow. It is classified as lymphocytic or myeloid, according to the type of cell multiplying abnormally, and either acute, signifying rapidly progressing disease with a predominance of highly immature (blastic) cells, or chronic, which denotes slowly progressing disease with greater numbers of more mature cells.

In this study, randomly selected 84 patients suffering from acute leukemia between 1st August 1987 and 5th March 1999 are obtained from the Marmara Medical School Hospital. The time from diagnosis until death is considered as the survival time of the patient. Two of the types of acute leukemia are Acute Lymphocytic Leukemia (ALL) and Acute Myeloid Leukemia (AML). These are, in general, classified into certain categories referred to as French-American-British classification. According to this classification, Acute Lymphocytic Leukemia is sub-classified as:

L1 The lymphoblasts tend to be small, with little cytoplasm and regularly shaped nuclei; they are maturer in appearance than other subtypes.

L2 The lymphoblasts appear more immature, varying in size and nuclear shape.

L3 The lymphoblasts tend to be large, with abundant cytoplasm and similarly shaped nuclei.

Acute Myeloid Leukemia is sub-classified as:

M0 Undifferentiated leukemia

M1 Acute myeloblastic leukemia with immature cells

M2 Acute myeloblastic leukemia with some mature cells

M3 Acute promyelocytic leukemia

M4 Acute myelomonocytic leukemia

M5 Acute monocytic leukemia

M6 Erythroleukemia (immature red and white blood cells)

Types of leukemia are classified as AML, AML-M3 and ALL in this work, since, usually risk of death from AML-M3 is the lowest among the other types. In contrast, ALL type may have higher survival probability in early phases of the illness.

When leukemia develops, the body produces large numbers of abnormal blood cells. In most types of leukemia, the abnormal cells are white blood cells and all the normal blood forming elements are affected. So the white cells, infection fighters, platelets, clot forming cells, and red blood cells, oxygen carrying cells, are all eventually depleted. The lower number of normal white blood cells makes leukemic patients more vulnerable to infection. The depletion of normal platelets interferes with the patients clotting ability and makes the patient more susceptible to abnormal bleeding and bruising. Anemia is caused by the decreased production of normal red blood cells. By using all these information the amount of white blood cells (WBL), platelets (thrombocytes) (PLT) and red blood cells (haemoglobin) (HB) are taken as the prognostic factors. Another important prognostic factor is the existence of haematological or systemic illness besides acute leukemia. The six covariates of interest considered are:

I. Type of leukemia 1 - AML

2 – AML-M3

3 – ALL

II.	Age (in years)	1 - >55 years of age 2 - 35 – 55 years of age 3- 35> years of age
III.	Existence of another illnesses beside acute leukemia	0 – no illness 1 – haematological illness 2 – systemic illness
IV.	WBL	1 - < 1000 2 – 1000 – 4000 3 – 4000 – 10000 4 – 10000 – 30000 5 – 30000 – 100000 6 – 100000 <
V.	PLT	1 - < 10000 2 – 10000 – 30000 3 – 30000 – 50000 4 – 50000 – 100000 5 – 100000 <
VI.	HB	1 - < 8 2 – 8 – 12 3 – 12 <

Of 84 acute leukemia patients 35 deaths are from relapse or progression, 27 are from refractor or wrong medical treatment related and 22 are alive. The data set is shown in Table 4.1. In this table, survival times are recorded in days.

Table 4.1. **Survival Times and Covariates of Acute Leukemia Patients**

0*	I	II	III	IV	V	VI	Diagnosis Date	Closing Date	Survival
2	3	1	2	5	2	1	03.01.95	03.02.95	1
2	1	1	1	2	2	2	10.28.93	11.02.93	5
1	1	2	1	6	5	2	10.06.94	10.14.94	8
1	1	1	1	5	5	2	09.22.92	09.30.92	8
2	1	1	0	2	1	2	09.23.94	10.03.94	10
2	1	2	0	5	3	1	06.12.95	06.23.95	11
2	1	2	0	4	2	1	11.01.95	11.15.95	14
2	1	1	0	6	5	2	06.15.96	06.30.96	15
2	1	3	2	4	2	1	07.24.93	08.11.93	18
2	3	2	0	4	2	1	05.02.93	05.21.93	19
2	1	2	1	5	1	1	11.28.94	12.19.94	21
2	1	3	0	3	3	1	03.18.92	04.13.92	26
2	1	1	2	6	2	1	04.09.93	05.08.93	29
2	1	3	0	2	2	2	10.01.91	11.02.91	32
2	1	2	2	4	1	1	08.11.95	09.14.95	34
1	3	3	2	4	1	1	09.02.94	10.12.94	40
1	1	1	1	5	4	1	05.29.90	07.11.90	43
2	1	2	1	5	3	1	06.01.96	07.19.96	48
2	1	3	0	2	2	1	01.09.97	03.01.97	51
2	1	3	2	3	3	3	06.01.98	08.22.98	82
2	3	2	0	3	2	1	04.26.94	07.18.94	83
1	1	2	1	5	5	1	11.05.97	02.01.98	88
1	3	3	0	2	2	1	02.01.95	05.01.95	89
2	1	3	0	2	4	1	09.01.95	12.01.95	91
2	1	3	0	2	2	2	09.08.95	12.10.95	93
1	3	3	0	1	3	1	02.05.97	05.11.97	95
2	3	3	1	4	3	3	09.01.95	12.21.95	111
1	1	2	0	5	3	2	01.01.96	05.25.96	145
1	1	1	0	2	2	1	03.01.90	08.01.90	153
1	3	3	0	1	2	1	06.14.93	11.26.93	165
2	1	3	0	2	3	1	08.24.93	02.21.94	181
1	1	1	1	2	4	1	06.01.91	12.01.91	183
1	1	1	2	2	4	1	03.01.98	10.01.98	214
1	1	2	0	6	3	1	11.05.90	06.12.91	219
1	1	3	0	1	2	2	06.25.92	02.01.93	221
2	3	3	0	5	1	1	06.20.97	02.05.98	230
2	1	3	1	2	5	2	04.01.97	11.20.97	233
1	3	3	0	2	1	1	05.16.97	01.05.98	234
1	3	3	0	5	2	3	12.25.94	09.01.95	250

Table 4.1. **(Continued)**

0*	I	II	III	IV	V	VI	Diagnosis Date	Closing Date	Survival
1	1	3	0	5	2	2	09.01.93	06.01.94	273
2	3	3	2	1	2	1	05.01.90	02.04.91	279
2	2	3	0	1	2	1	01.01.93	11.01.93	304
1	1	2	2	2	2	2	09.01.91	07.07.92	310
2	1	3	0	1	2	1	08.20.91	06.26.92	311
1	1	3	2	2	2	2	07.01.91	05.21.92	325
1	1	3	0	4	1	1	02.17.95	01.27.96	344
1	1	3	2	5	1	1	07.07.94	09.01.95	421
1	3	3	0	2	2	1	11.24.96	02.03.98	436
1	1	1	0	2	3	2	10.01.97	01.01.99	457
1	3	3	0	3	5	3	02.01.97	06.15.98	499
1	1	3	0	2	4	2	06.14.90	11.07.91	511
1	1	3	0	4	3	1	05.20.96	02.04.98	625
1	3	3	0	1	1	1	05.31.93	04.01.95	670
1	1	1	0	2	1	1	05.01.92	03.28.94	696
2	2	3	0	1	1	1	04.15.91	05.26.93	772
1	3	3	0	5	4	2	02.28.92	05.03.94	795
1	3	3	0	5	2	1	02.01.93	05.02.95	820
1	2	1	1	2	3	2	08.01.87	11.01.89	823
3	3	3	0	4	4	2	07.26.96	03.05.99	952
3	1	3	0	2	2	1	06.24.96	03.05.99	984
1	1	3	0	2	1	1	08.01.93	07.01.96	1065
3	1	3	0	2	3	1	03.28.96	03.05.99	1072
1	3	3	0	2	2	1	08.01.90	10.11.93	1167
3	3	3	0	5	4	2	06.25.95	03.05.99	1349
3	2	3	0	3	5	2	06.09.95	03.05.99	1365
3	1	3	0	5	2	1	06.01.95	03.05.99	1373
3	1	3	0	4	4	2	03.16.95	03.05.99	1450
3	2	3	0	1	1	1	02.26.94	03.05.99	1833
3	1	3	0	3	4	1	12.07.93	03.05.99	1914
3	2	3	0	3	4	2	08.17.93	03.05.99	2026
1	3	3	0	5	4	2	06.25.92	03.01.98	2075
3	3	3	0	5	2	1	03.12.93	03.05.99	2184
3	2	3	0	3	4	2	10.27.92	03.05.99	2320
1	3	3	0	2	4	1	08.01.90	02.01.97	2376
3	3	3	0	3	3	2	05.08.92	03.05.99	2492
3	1	3	0	3	2	2	08.03.91	03.05.99	2771
3	1	3	0	3	4	2	07.15.91	03.05.99	2790

Table 4.1. **(Continued)**

0*	I	II	III	IV	V	VI	Diagnosis Date	Closing Date	Survival
3	1	3	0	5	1	1	07.01.91	03.05.99	2804
3	3	3	0	3	2	1	06.17.91	03.05.99	2818
3	1	3	0	5	2	2	02.10.91	03.05.99	2945
3	1	3	0	4	4	1	01.30.91	03.05.99	2956
3	1	3	0	3	3	2	08.01.90	03.05.99	3138
3	3	3	0	5	3	1	05.19.90	03.05.99	3212
3	1	3	0	4	4	2	12.20.89	03.05.99	3362

* Failure types: 1-Death from relapse or progression, 2-Death from refractor or wrong medical treatment and 3- Alive.

The treatment of leukemia continues to progress. Clear understanding of the basic disease process as well as better drugs and supportive care are leading to more cures and remissions. The treatment is divided into three categories;

1. Supportive care
2. Chemotherapy treatment with chemical drugs
3. Radiation therapy and/or bone marrow transplantation (BMT)

Supportive care refers to treatment which helps the patient to feel the pain less, but does not attempt to fight the leukemia. This includes blood transfusion, to relieve the anemia, platelets transfusion, to help prevent bleeding, and antibiotics, to control various infections.

4.1. Data Analysis

In the data analysis, only the parametric modelling of the survival data, construction of the Kaplan-Meier survival curves and crude cumulative incidence curves, and proportional Cox regression model were applied. Other methods given in the Chapter 3 are not appropriate to apply.

4.1.1. Parametric Approach:

By using cumulative hazard plotting technique, as seen in Figures 4.1 and 4.2, Weibull distribution fits each failure distribution slightly better than the other possible distributions such as exponential, extreme value, normal and lognormal distributions. In these figures the slopes are nearly equal to each other and the graphical estimates of the shape parameters (c_i, i=1,2) are $\hat{c}_1$ = 1.02 and $\hat{c}_2$=0.93. These graphical estimates are used as the starting points of the Newton-Raphson iteration procedure.

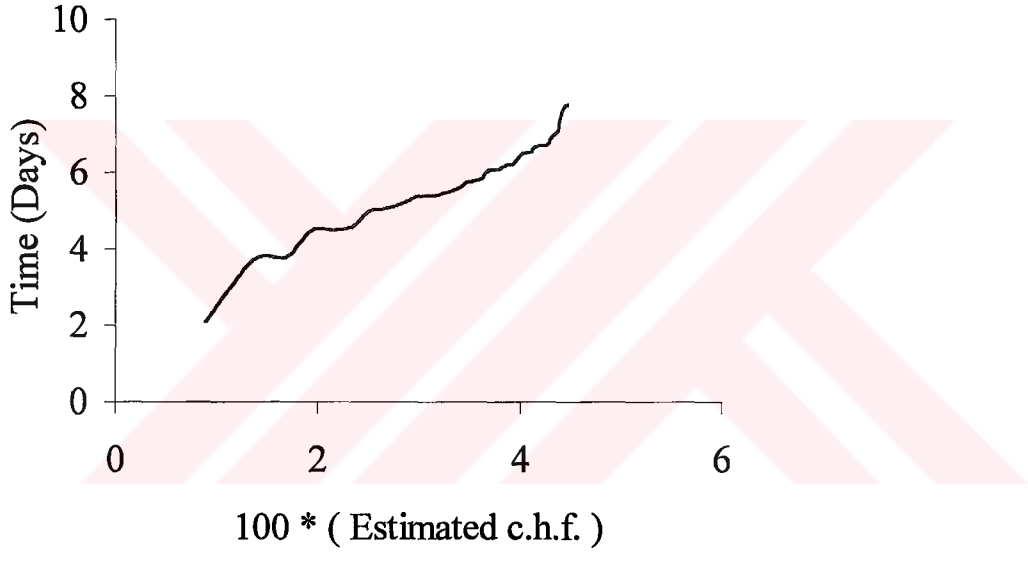

Figure 4.1. Weibull Hazard Plot for Relapse or Progression Type Deaths.

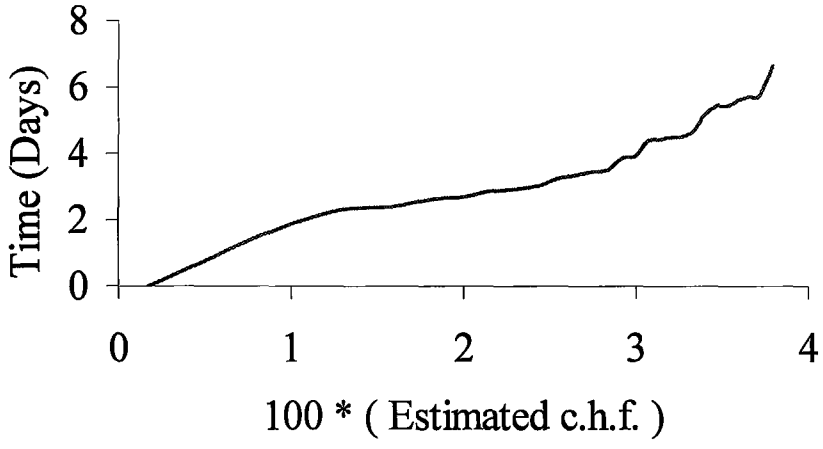

Figure 4.2. Weibull Hazard Plot for Refractor or Wrong medical treatment Related Deaths.

The data are analyzed under the more general assumption that the two types of failure do not depend on each other. The failure distributions associated with those patients, who died from relapse or progression and those who died from refractor or wrong medical treatment, respectively, follow Weibull distributions with unequal shape parameters. Moreover, since the individual's failure is observed within some specified time period, then Type I censoring is applied. The estimates of the scale parameter, θ_i obtained from Figures 4.1 and 4.2 will only be approximate values. To obtain the maximum likelihood estimators (MLE) of shape and scale parameters from (3.154) and (3.155) the FORTRAN program, given in Appendix A, has been written and Newton-Raphson iteration method is applied. The MLE's are found as

$$\hat{c}_1 = 0.674226 \; ; \; \hat{\theta}_1 = 184.35$$
$$\hat{c}_2 = 0.369492 ; \; \hat{\theta}_2 = 29.7435$$

In order to estimate the asymptotic variances of the maximum likelihood estimators, using equations (3.160), (3.161) and (3.162), as elements of the information matrix, it is required to know the different censoring times for each

individual. Such detailed information is not available in this study; the negatives of the second partial derivatives of the log likelihood function are used to approximate the elements of the information matrix. Such an approximation yields the following estimated standard deviations;

$$s.d.(\hat{c}_1) = 0.01541844\,;\ s.d.(\hat{\theta}_1) = 20.754270$$
$$s.d.(\hat{c}_2) = 0.01209473\,;\ s.d.(\hat{\theta}_2) = 2.608132$$

Then, the crude, net and partial crude probabilities are obtained from the following formulas:

Crude Probability:

$$Q_i(a,b) = c_i\,\lambda_i \int_a^b t^{c_i-1} \exp\left\{ -\sum_{l=1}^{k} (\lambda_l (t^{c_l} - a^{c_l}) \right\} dt \qquad (4.1)$$

Net Probability:

$$q_i = 1 - \exp\left\{ -\lambda_i\,(b^{c_i} - a^{c_i}) \right\} \qquad (4.2)$$

Partial Crude Probability:

$$Q_{i,j}(a,b) = c_i\,\lambda_i \int_a^b t^{c_i-1} \exp\left\{ -\sum_{\substack{l=1 \\ l\neq j}}^{k} (\lambda_l (t^{c_l} - a^{c_l}) \right\} dt \qquad (4.3)$$

where $\lambda_i = 1/\theta_i$, θ_i, $i=1,2$ is the scale parameter and c_i is the shape parameter of the Weibull distribution.

The calculated values of the crude, net and partial crude probabilities for certain time intervals for the two causes of death are given in Table 4.2. According to this table, the probability of death from relapse or progression between first and second month after diagnosis is slightly less than the probability

of death from refractor or wrong medical treatment. On the other hand, as time passes the estimated crude probability of death from relapse or progression is greater than that of death from refractor or wrong medical treatment. The same thing can also be shown in estimated values of net and partial crude probabilities. This means that refractor or wrong medical treatment related deaths for acute leukemia patients appear in shorter time periods after diagnosis. Consideration of other risk factors reduces the probability of death. When crude and net probabilities are compared, this fact can be seen easily. The partial crude probabilities are same as the net probabilities, because there are only two causes. Elimination of one cause means the existence of only one cause acting on the population.

Table 4.2. **The Crude, Net and Partial Crude Probabilities for the Two Competing Risks**

	Crude Probabilities		Net Probabilities*	
Time Intervals	$\hat{Q}_1$	$\hat{Q}_2$	$\hat{q}_1$	$\hat{q}_2$
(30, 60)	0.0306	0.0332	0.0315	0.0339
(60, 90)	0.0263	0.0239	0.0266	0.0244
(30,90)	0.0555	0.0355	0.0573	0.0574
(90, 120)	0.0236	0.0193	0.0238	0.0197
(100, 500)	0.2271	0.1254	0.2111	0.1391
(1000, 1500)	0.1589	0.0619	0.1645	0.0674
(1,1000)	0.3420	0.2838	0.4324	0.3340

* Net probabilities = Partial crude probabilities

In Figures 4.3 and 4.4, the crude survival probabilities and crude cumulative incidence curves, respectively based on the underlying distribution can

be seen. In terms of the clinical decision on optimal treatment, crossing survival curves require some subjective judgement to choose an appropriate treatment regime for that patient. However, since this study is not made with the cooperation of any hospital and not a part of any planning project, there is not any treatment factor.

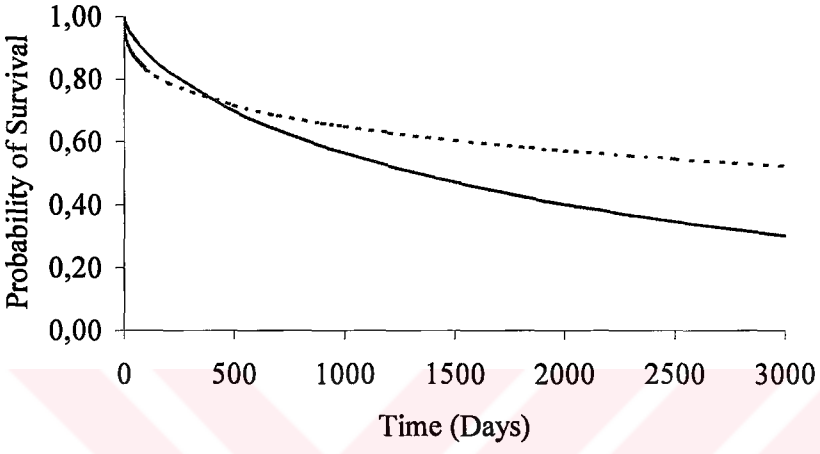

Figure 4.3: The crude survival probabilities of relapse or progression type deaths (____) and refractor or wrong medical treatment related deaths (-----) using the underlying distribution.

Up to 400 days probability of survival for relapse or progression type failure is higher than that for refractor or wrong medical treatment related failure. However, after 400 days from diagnosis, probability of dying from relapse or progression type deaths is higher than that for the other cause of death for acute leukemia.

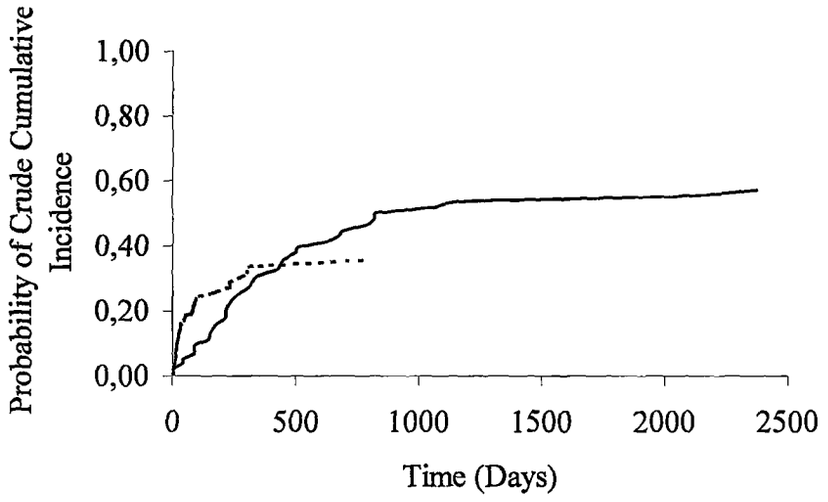

Figure 4.4. The crude cumulative incidence curves of relapse or progression type deaths (_____) and refractor or wrong medical treatment related deaths (-----) using the underlying distribution.

4.1.2. Nonparametric Approach:

The Kaplan-Meier survival and crude cumulative incidence curves are constructed for each cause as in Tables 4.3 and 4.4. These curves can be seen in Figures 4.5 and 4.6. The cause-specific curves do not have a true survivorship interpretation, but represent $\exp(-H_t)$, where H_t is the cumulative cause-specific hazard function to time t, for each failure type.

In trying to describe the pattern of occurrence of event 1, one can think of regarding event 2 as censored at the subject's failure time and for the pattern of event 2, event 1 is considered as censored. Again, it is assumed that the two failure types are independent of each other.

Table 4.3. **Computation of Kaplan-Meier Survival Probabilities and Crude Cumulative Incidence of Relapse or Progression Type Deaths for Acute Leukemia Patients**

Diagnosis Date	Failure Date	Survival	d(1,t)*	n(t)**	(n(t)-d(1,t))/n(t)	S(t)	d(t)/n(t)*S(t)	I(t)
10.06.94	10.14.94	8	0	84	1,0000	1,0000	0,0000	0,0000
09.22.92	09.30.92	8	2	82	0,9756	0,9756	0,0238	0,0238
09.02.94	10.12.94	40	1	69	0,9855	0,9615	0,0139	0,0377
05.29.90	07.11.90	43	1	68	0,9853	0,9473	0,0139	0,0517
11.05.97	02.01.98	88	1	63	0,9841	0,9323	0,0148	0,0665
02.01.95	05.01.95	89	1	62	0,9839	0,9173	0,0148	0,0813
02.05.97	05.11.97	95	1	59	0,9831	0,9017	0,0153	0,0965
01.01.96	05.25.96	145	1	57	0,9825	0,8859	0,0155	0,1121
03.01.90	08.01.90	153	1	56	0,9821	0,8701	0,0155	0,1276
06.14.93	11.26.93	165	1	55	0,9818	0,8543	0,0155	0,1431
06.01.91	12.01.91	183	1	53	0,9811	0,8381	0,0158	0,1590
03.01.98	10.01.98	214	1	52	0,9808	0,8220	0,0158	0,1748
11.05.90	06.12.91	219	1	51	0,9804	0,8059	0,0158	0,1906
06.25.92	02.01.93	221	1	50	0,9800	0,7898	0,0158	0,2064
05.16.97	01.05.98	234	1	47	0,9787	0,7730	0,0164	0,2228
12.25.94	09.01.95	250	1	46	0,9783	0,7562	0,0164	0,2393
09.01.93	06.01.94	273	1	45	0,9778	0,7394	0,0164	0,2557
09.01.91	07.07.92	310	1	44	0,9773	0,7226	0,0164	0,2721
07.01.91	05.21.92	325	1	40	0,9750	0,7045	0,0176	0,2897
02.17.95	01.27.96	344	1	39	0,9744	0,6864	0,0176	0,3073

Table 4.3. **(Continued)**

Diagnosis Date	Failure Date	Survival	d(1,t)*	n(t)**	(n(t)-d(1,t))/n(t)	S(t)	d(t)/n(t)*S(t)	I(t)
07.07.94	09.01.95	421	1	38	0,9737	0,6684	0,0176	0,3249
11.24.96	02.03.98	436	1	37	0,9730	0,6503	0,0176	0,3425
10.01.97	01.01.99	457	1	36	0,9722	0,6322	0,0176	0,3600
02.01.97	06.15.98	499	1	35	0,9714	0,6142	0,0175	0,3776
06.14.90	11.07.91	511	1	34	0,9706	0,5961	0,0175	0,3951
05.20.96	02.04.98	625	1	33	0,9697	0,5781	0,0175	0,4126
05.31.93	04.01.95	670	1	32	0,9688	0,5600	0,0175	0,4301
05.01.92	03.28.94	696	1	31	0,9677	0,5419	0,0175	0,4476
02.28.92	05.03.94	795	1	29	0,9655	0,5232	0,0180	0,4657
02.01.93	05.02.95	820	1	28	0,9643	0,5045	0,0180	0,4837
08.01.87	11.01.89	823	1	27	0,9630	0,4859	0,0180	0,5017
08.01.93	07.01.96	1065	1	26	0,9615	0,4672	0,0180	0,5196
08.01.90	10.11.93	1167	1	25	0,9600	0,4485	0,0179	0,5376
06.25.92	03.01.98	2075	1	24	0,9583	0,4298	0,0179	0,5555
08.01.90	02.01.97	2376	1	23	0,9565	0,4111	0,0179	0,5734

*d(1,t): Number of deaths from cause 1 at time t.
**n(t): Number of survivals at time t.

Table 4.4. **Computation of Kaplan-Meier Survival Probabilities and Crude Cumulative Incidence of Refractor or Wrong Medical Treatment Related Deaths for Acute Leukemia Patients**

Diagnosis Date	Failure Date	Survival	d(2,t)*	n(t)**	(n(t)-d(2,t))/n(t)	S(t)	D(t)/n(t)*S(t)	I(t)
0	0	0	0	84	1,0000	1,0000	0,0000	0,0000
03.01.95	03.02.95	1	1	84	0,9881	0,9881	0,0118	0,0118
10.28.93	11.02.93	5	1	83	0,9880	0,9762	0,0118	0,0235
09.23.94	10.03.94	10	1	80	0,9875	0,9640	0,0120	0,0356
06.12.95	06.23.95	11	1	79	0,9873	0,9518	0,0120	0,0476
11.01.95	11.15.95	14	1	78	0,9872	0,9396	0,0120	0,0597
06.15.96	06.30.96	15	1	77	0,9870	0,9274	0,0120	0,0717
07.24.93	08.11.93	18	1	76	0,9868	0,9152	0,0120	0,0838
05.02.93	05.21.93	19	1	75	0,9867	0,9030	0,0120	0,0958
11.28.94	12.19.94	21	1	74	0,9865	0,8908	0,0120	0,1078
03.18.92	04.13.92	26	1	73	0,9863	0,8786	0,0120	0,1199
04.09.93	05.08.93	29	1	72	0,9861	0,8664	0,0120	0,1319
10.01.91	11.02.91	32	1	71	0,9859	0,8542	0,0120	0,1439
08.11.95	09.14.95	34	1	70	0,9857	0,8420	0,0120	0,1560
06.01.96	07.19.96	48	1	67	0,9851	0,8294	0,0124	0,1683
01.09.97	03.01.97	51	1	66	0,9848	0,8168	0,0124	0,1807
06.01.98	08.22.98	82	1	65	0,9846	0,8043	0,0124	0,1931
04.26.94	07.18.94	83	1	64	0,9844	0,7917	0,0124	0,2055
09.01.95	12.01.95	91	1	61	0,9836	0,7787	0,0128	0,2182
09.08.95	12.10.95	93	1	60	0,9833	0,7657	0,0128	0,2310

Table 4.4. **(Continued)**

Diagnosis Date	Failure Date	Survival	d(2,t)*	n(t)**	(n(t)-d(2,t))/n(t)	S(t)	d(t)/n(t)*S(t)	I(t)
09.01.95	12.21.95	111	1	58	0,9828	0,7525	0,0130	0,2440
08.24.93	02.21.94	181	1	54	0,9815	0,7386	0,0137	0,2576
06.20.97	02.05.98	230	1	49	0,9796	0,7235	0,0148	0,2724
04.01.97	11.20.97	233	1	48	0,9792	0,7085	0,0148	0,2872
05.01.90	02.04.91	279	1	44	0,9773	0,6924	0,0157	0,3029
01.01.93	11.01.93	304	1	43	0,9767	0,6763	0,0157	0,3186
08.20.91	06.26.92	311	1	41	0,9756	0,6598	0,0161	0,3347
04.15.91	05.26.93	772	1	30	0,9667	0,6378	0,0213	0,3560

*d(2,t): Number of deaths from cause 2 at time t.
**n(t): Number of survivals at time t.

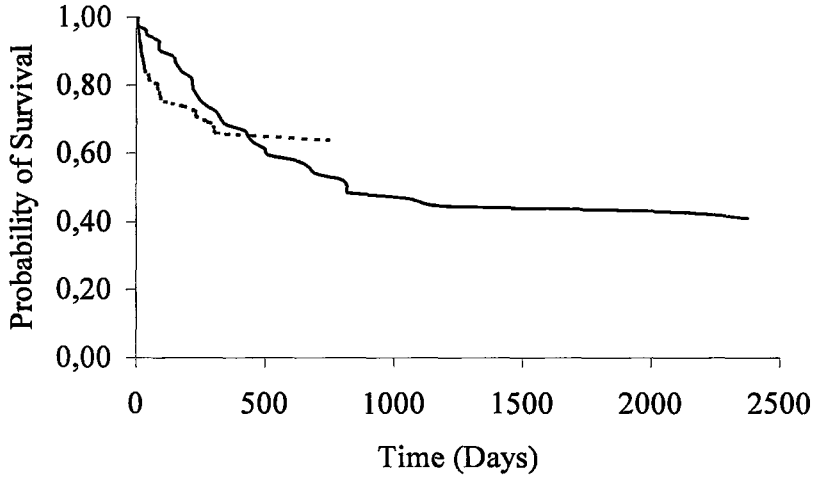

Figure 4.5. The Kaplan-Meier Survival Curves for relapse or progression type deaths (_____) and refractor or wrong medical treatment related deaths (----).

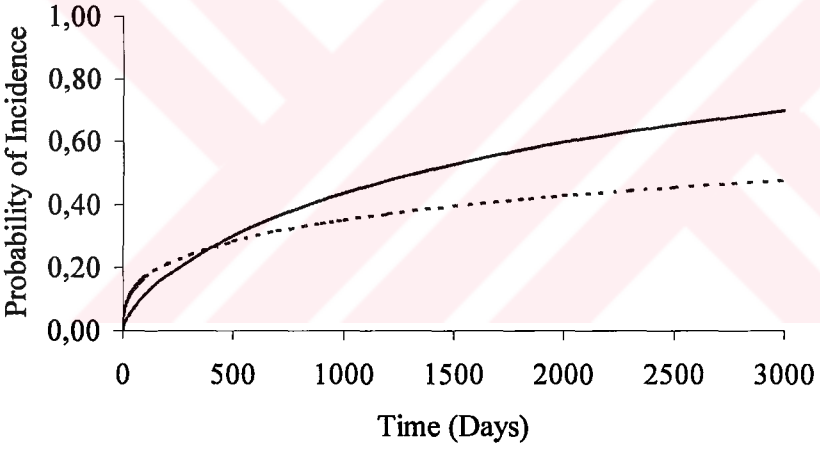

Figure 4.6. Crude Cumulative Incidence Curves for relapse or progression type deaths (_____) and refractor or wrong medical treatment related deaths (.....).

These curves give the same pattern with the curves for underlying distribution (Figures 4.3 and 4.4). It clearly appears that the two curves are notably divergent. It is seen that the crude survival and crude cumulative incidence curves are crossing. Crossing survival curves requires more attention in deciding the proper treatment. In the long run, probability of survival for refractor

or wrong medical treatment related failures is higher. To summarize, refractor or wrong medical treatment related deaths appear in early phase of the acute leukemia after diagnosis.

4.1.3. Semi-parametric Approach:

In this part, failure types by covariate interaction in a Weibull regression model for survival times, which is proposed by Cox (1972), is identified. Proportional hazard model is assumed. The model for cause i, i = 1,2 is described as

$$\lambda_i(t;x) = \lambda_{0i}(t)\ \exp(x_i\beta_i) \tag{4.4}$$

where $x = (x_1,\ldots,x_6)$ is explanatory variables vector. For Weibull regression model underlying hazard is $\lambda_{0i}(t) = c_i\ t^{c_i-1}$, $c_i > 0$, where c_i is the shape parameter of the Weibull distribution which is estimated in section 4.1. The quantity $\lambda_i(t; x)$ is the instantaneous risk of death from cause i at time t. Here, underlying hazard and the coefficients of the explanatory variables are specific to cause. As it is given in section 3.7

$$\lambda(t; x) = \lambda_1(t; x) + \lambda_2(t; x) \tag{4.5}$$

For parameter estimation, FORTRAN program, given in Appendix B, was prepared. This gives the maximum likelihood estimators of covariates by using Newton-Raphson iteration for simultaneously solved non-linear equations. Then the estimated cause-specific hazard function is written as

$$\hat{\lambda}_i(t;x) = (\hat{c}_i\ t^{\hat{c}_i-1}) \exp(x_i\hat{\beta}_i) \tag{4.6}$$

Table 4.5. **Acute Leukemia Patients: Results of the Regression Analysis Carried Out by Modelling Cause-Specific Hazard Rates by Cox Model.**

	Deaths from progression or relapse				**Deaths from refractor or wrong medical treatment**			
	Parameter estimates $\hat{\beta}_{i1}$	Standard error	Q_W	Risk ratio $e^{\hat{\beta}_{i1}}$	Parameter estimates $\hat{\beta}_{i2}$	Standard error	Q_W	Risk ratio $e^{\hat{\beta}_{i2}}$
Type of leukemia	0.21906	0.1817	1.4529	1.2449	-0.14661	0.2129	0.4741	0.8636
Age	-0.89973	0.1853	23.5783	0.4067	-0.5343	0.2108	6.4267	0.5861
Leukemia with other illness	0.71313	0.2062	11.9648	2.0404	0.43713	0.2096	4.3487	1.5483
WBC	0.15056	0.1440	1.0932	1.1625	0.06749	0.1577	0.1634	1.0698
PLT	-0.03725	0.1660	0.0540	0.9634	-0.28451	0.1817	2.4505	0.7524
HB	-0.23369	0.2343	0.9952	0.79166	-0.07209	0.2634	0.0749	0.9305

Standard errors are obtained through estimated second derivatives of the log partial likelihood and significance tests are based on Wald statistic. As each of the Wald statistics has one degree of freedom, the critical value at $\alpha = 0.05$ is 3.84. In Table 4.5, the results of the Cox regression analysis can be seen. By using 95% significance, only the age and the existence of other illness besides acute leukemia are significant prognostic factors for each of the two causes of failure. If risk ratios are considered, for age and the amount of normal red blood cells in the patient's blood have lower significance in relapse or progression type deaths. Type of leukemia and existence of other illness do better with regard to refractor or wrong medical treatment related deaths, yet worse as regards relapse or progression type deaths. Risk ratios are used only to show the comparison between the risk ratios of competing risk factors. The major point here is the determination of which covariates are important with regard to death from the various causes. The competing risks analysis give more direct answers to this aspect.

Negative signs of the regression coefficients suggest decreased risk of developing for that cause of death. For example, as age increases from 1 to 3, that is, age greater than 55 to age less than 35, risk of death from progression or relapse reduces. The same thing can be seen in the other type of death. Moreover, if the type of leukemia is increased from 1 to 3, that is, AML to ALL, risk of death from refractor or wrong medical treatment decreased. However, in progression or relapse type death this can not be seen.

Then, the survival function is estimated as

$$\hat{S}(t;x) = \exp\left\{ -\int_0^t \hat{\lambda}(u;x)\, du \right\}. \qquad (4.7)$$

If only the type of leukemia is considered, taking other covariates as constant, ALL patients has more chance to survive up to 500 days after diagnosis.

However, after this time survival chance of AML-M3 patients are greater than others are. The worse group is the AML patients according to our data. In real life, it is expected that the ALL patients have lower probability of surviving in long time.

As it is expected, younger patients have more chance to survive (Figures 4.7, 4.8 and 4.9). Patients greater than 55 years of age have the worst survival probability among the other age groups.

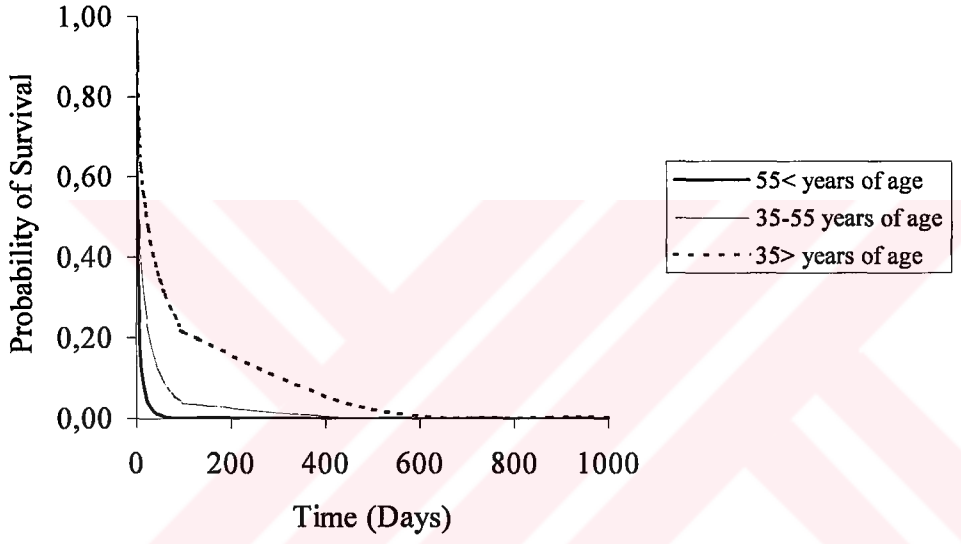

Figure 4.7. Estimated Survival Curves for a Patient with 1,4,5,6=1; 3=0 and 2=1,2,3.

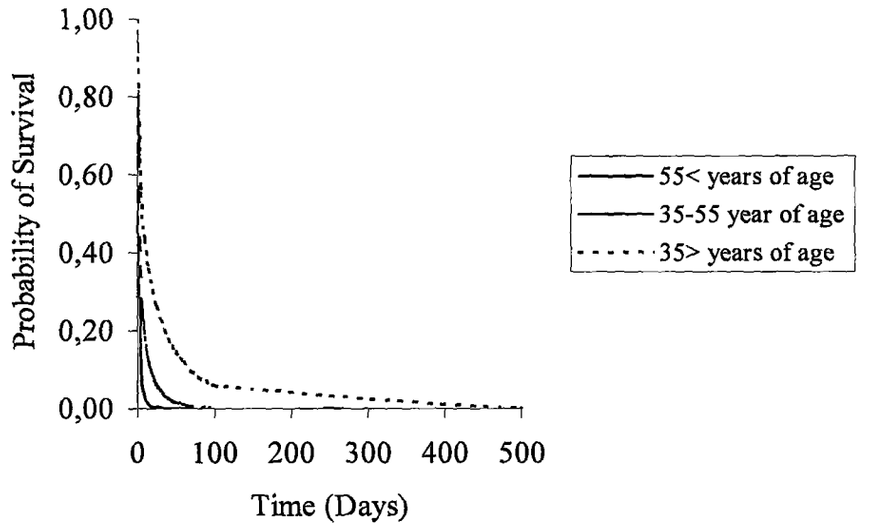

Figure 4.8. Estimated Survival Curves for a Patient with 1,4,5,6=1; 3=1 and 2=1,2,3.

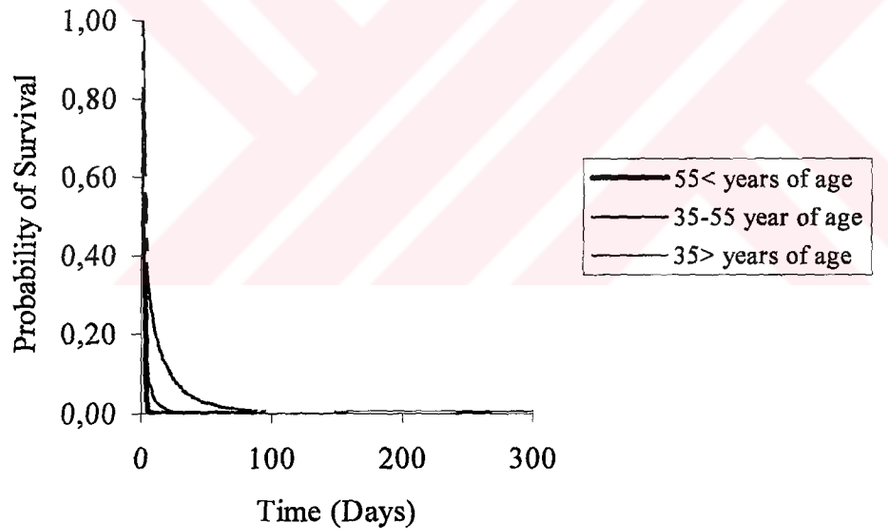

Figure 4.9. Estimated Survival Curves for a Patient with 1,4,5,6=1; 3=2 and 2=1,2,3.

When the Figures 4.7, 4.8 and 4.9 are compared, it is seen that survival probabilities decreases from existence of no other illness to existence of systemic illness besides acute leukemia when age groups are changed.

If the existence of other illness besides acute leukemia is our interest, from Figure 4.10 it can be seen that the probability of death with systemic illness, not related with blood, is lower than that of haematological illness. If a patient has no other illness besides acute leukemia, he has better chance to survive.

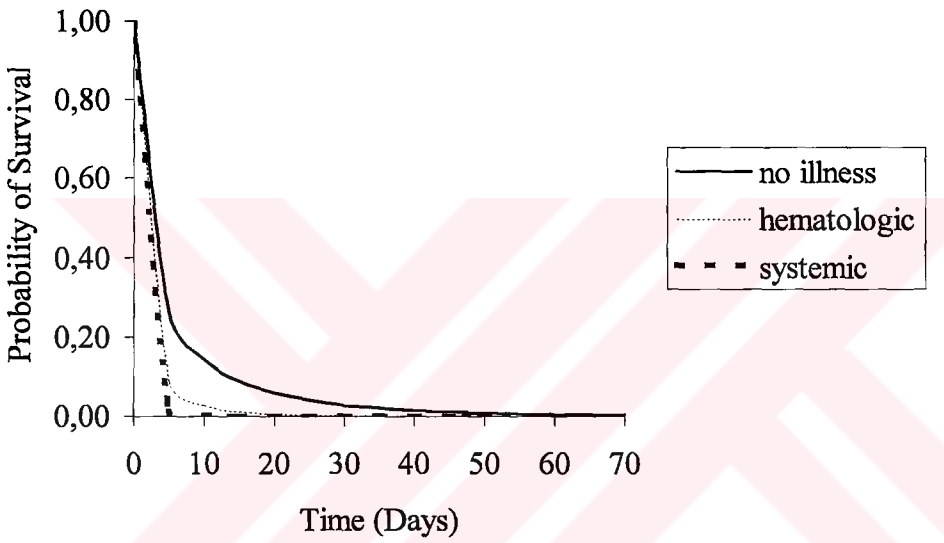

Figure 4.10. Estimated Survival Curves for a Patient with 1,2,4,5,6=1 and 3=0,1,2.

Comparing figures 4.10, 4.11 and 4.12 gives the basic phenomenon that existence of no other illness besides acute leukemia with age less than 35 has the best chance of survival if the amount of normal white and red blood cells and platelets have the minimum values.

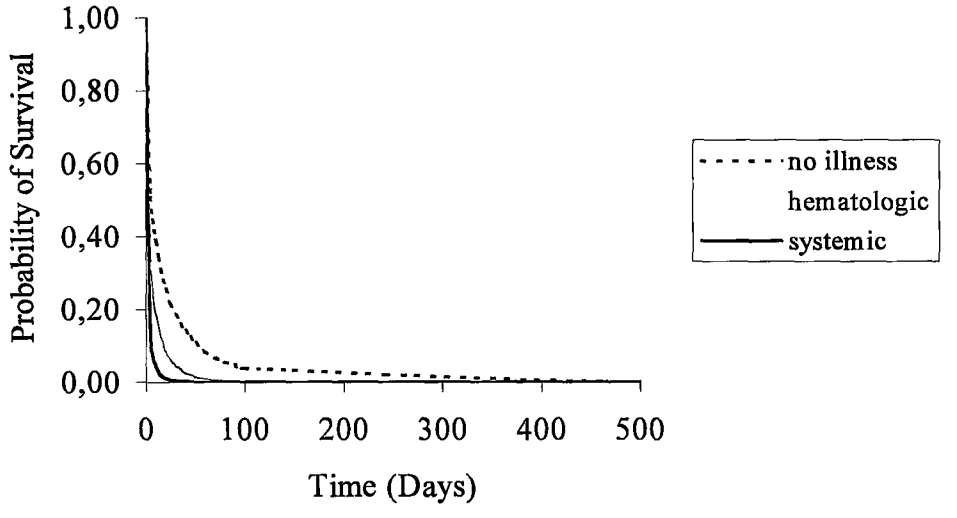

Figure 4.11. Estimated Survival Curves for a Patient with 1,4,5,6=1 ; 2=2 and 3=0,1,2.

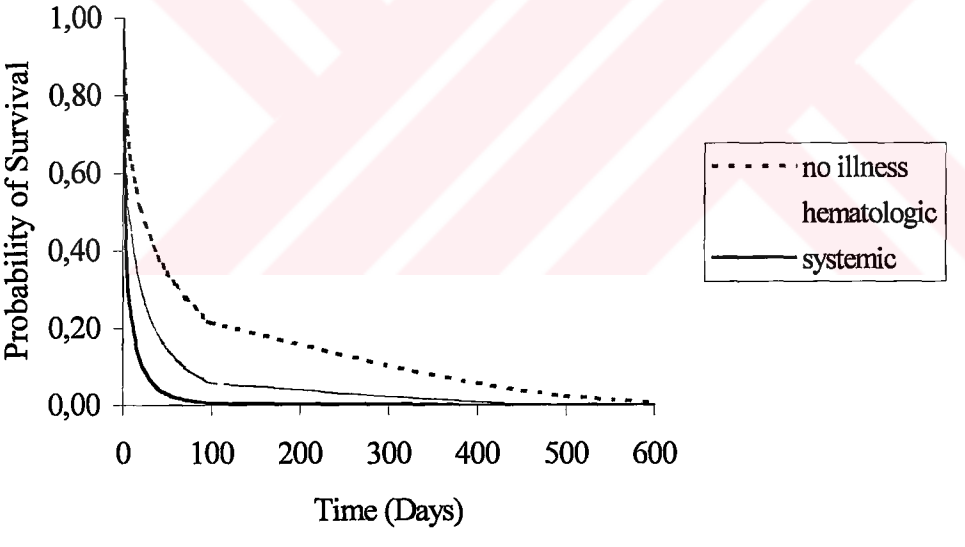

Figure 4.12. Estimated Survival Curves for a Patient with 1,4,5,6=1; 2=3 and 3=0,1,2.

As it is seen from figure 4.13, the maximum probability of survival is obtained when the combination of ALL type leukemia, age less than 35, no other

illness besides acute leukemia and the amount of normal white, red blood cells and platelets at the highest level in the blood.

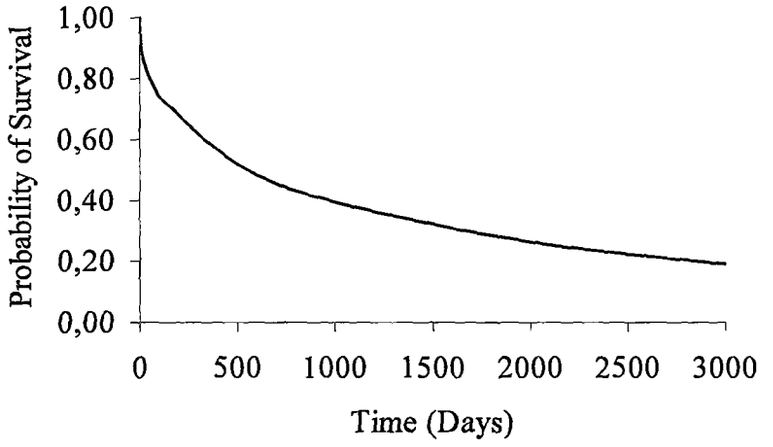

Figure 4.13. Estimated Survival Curve for a Patient with 1=3 ; 2=3 ; 3=0 ; 4=6 ; 5=5 and 6=3.

CHAPTER 5

CONCLUSION AND REMARKS

In this study, an attempt has been made to show how important the notion of competing risks is in investigations of the reliability of individuals and systems. In contrast to the usual reliability analysis, competing risk theory requires and takes advantage of data containing not only the time to failure of the system but also the cause of failure. In practice, there may be various complications due to censoring of the observation. Regarding censoring as a form of competing risk these complications may not be faced.

Competing risk analysis has been considered under the independence of component lifetimes and of the competing causes of failure assumptions. Under parametric, non-parametric and semi-parametric conditions some possible determinations of the properties of the system are examined. The parametric methods may be numerically difficult depending on the complexity of the assumed model. Necessities of some additional measurements have been shown to determine the effects of the prognostic factors on the types of failures and treatments. Graphical methods, particularly hazard plotting, provide simple means of checking on the distributional assumptions in the case of independent risks. In the last part of the study, some dependent models are discussed. However, more work is needed for dependent risk models.

The acute leukemia data have been used to show how competing risk analyses are performed. By using the types of failure and time to failures, the

Weibull distribution under Type I censoring has been proposed by the cumulative hazard plotting. The shape and scale parameters have been determined by Newton-Raphson iteration. The estimated shape parameters for both causes are less than one. By using the estimated parameters, the crude, net and partial crude probabilities have been found. It has been shown that in the early phases of the illness, the probability of dying from relapse or progression type risk of deaths are higher than that from refractor of wrong medical treatment related risk of deaths. In the presence of competing risks the survival probabilities are greater. Since there are two causes, the partial crude probabilities give the same values with the net probabilities. Because, removal of one cause means the existence of only one risk acting on the population. Up to 400 days after diagnosis, refractor or wrong medical treatment related deaths appear frequently. This means that treatment regimes must be made very seriously in the early phases for acute leukemia patients. Parametric and non-parametric analysis gave approximately the same results.

To determine the effect of the covariates on the failure types, Cox's proportional hazard model has been proposed under Weibull underlying hazard. To estimate parameters of covariates Newton-Raphson iteration for simultaneously solved non-linear equations is used. For two competing risks, age and the existence of other illnesses besides acute leukemia are the significant factors. Older patients with systemic illness besides acute leukemia and minimum amount of normal white blood cells, platelets and red blood cells have the lowest chance of survival. Also, risks of age group and amount of haemoglobin in the blood of patient are greater in refractor or wrong medical treatment related risk of deaths. If a patient with Acute Lymphocytic Leukemia, age less than 35, no other illness besides acute leukemia and amount of normal white, red blood cells and platelets at maximum levels is observed, this patient has the highest chance of survival. For future studies, it is proposed to compare the methods used in the application part for competing risks and the methods used for the single cause models. By using this, dominance of competing risk analysis will be pointed out.

Further studies must be dealt with the dependency structure of the competing risks. If, in a specific application, the assumption of independent risks has to be abandoned, how does one go about constructing a suitable model of dependency? How does one test the assumption of the independence when he is in doubt? The answers of these questions must be determined. Problems of identifiability are in general avoided if a parametric alternative to independence is assumed. Under such a model independence can be tested from the ratio of the likelihood functions under independence and under dependence. The practicability and effectiveness of such a test need to be examined. In this study, only the series system is considered. Many important systems are more complex. Simple examples such as two component parallel system of eyes, ears, kidneys or lungs have been studied by Freund (1961) and Gross (1973). For more general systems it is likely that fault tree analysis can be usefully combined with competing risk considerations. Incorporation of different failure types in more complex models like mixture models will be considered. Since, in this study a certain failure type is considered separately, treating others as censored, more complex models may give more efficient results by considering all causes together. Moreover, robustness analysis must be taken into consideration in future studies. For the application of competing risk analysis, accurate studies must be developed with hospitals or medicine companies to show, for instance, the effect of new drug on patients under different competing risks or the effect of new treatment when there are competing causes of failure. Investigators must become aware of the importance of this concept in Turkey and use it in their applications to get better and more explanatory results.

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APPENDIX A

FORTRAN Program for Finding the Maximum Likelihood Estimators of Weibull Distribution with Type I Censoring Unequal Shape Parameters in the Consideration of Competing Risks.

```
INTEGER N,S,I,ITER
      REAL
A,B,D,M,Y,Z,W,Q,C,TC,YC,F,FC,CNEW,E,G,MO,MOR,DC,DT,DCT,VARC,V
ART,COVCT
      REAL X(100,100),U(100),V(200),SVARC,SVART,DET
      OPEN (5,FILE='C:\MSDEV\PROJECTS\BETA.DAT',STATUS='OLD')
      WRITE(*,*) "WRITE THE TOTAL NUMBER OF
FAILURE,DEATHS FROM THIS CAUSE AND CENSORING"
      READ(*,*) N,M,S
      WRITE(*,*) "WRITE THE CAUSE OF DEATH"
      READ(*,*) J
      DO 2 I=1,N+S
        READ(5,*) V(I)
    2 CONTINUE
      DO 5 I=1,N
            X(I,J)=V(I)
  5 CONTINUE
      DO 7 J=1,S
         K=N+J
         U(J)=V(K)
    7 CONTINUE
      WRITE(*,*) "WRITE THE STARTING POINT FOR C"
      READ(*,*) C
      A=0.0
      B=0.0
      E=0.0
      G=0.0
      MO=0.0
      MOR=0.0
      ITER=1
    1 T=0.0
      Y=0.0
      Z=0.0
      W=0.0
      Q=0.0
      TC=0.0
      YC=0.0
```

Appendix A (Continued)

```
      DO 10 I=1,M
            J=1
            T=T+LOG(X(I,J))
     10 CONTINUE
     DO 20 I=1,N
            Y=Y+X(I,J)**C
20 CONTINUE
      DO 30 K=1,S
            Z=Z+U(K)**C
30 CONTINUE
      DO 40 I=1,N
            W=W+(X(I,J)**C)*(LOG(X(I,J)))
40 CONTINUE
      DO 50 K=1,S
            Q=Q+(U(K)**C)*LOG(U(K))
50 CONTINUE
      F=(1/M)*(M/C+T)*(Y+Z)-W-Q
      DO 60 I=1,N
            TC=TC+(X(I,J)**C)*((LOG(X(I,J)))**2)
     60 CONTINUE
      DO 70 K=1,S
            YC=YC+(U(K)**C)*((LOG(U(K)))**2)
     70 CONTINUE
      FC=((1/M)*(-M/C**2)*(Y+Z))+((1/M)*((M/C)+T)*(W+Q))-TC-YC
      CNEW=C-F/FC
      IF (ABS(C-CNEW).LT.(1.0E-6)) GOTO 80
      IF (ITER .GT.15) GOTO 90
      C=CNEW
      ITER=ITER+1
      GOTO 1
80  WRITE(*,85) CNEW
85  FORMAT (1X,2E15.6)
      WRITE(*,*) "ITERATION=",ITER
102  DO 110 I=1,N
            A=A+X(I,J)**CNEW
110  CONTINUE
   DO 120 K=1,S
            B=B+U(K)**CNEW
120  CONTINUE
   D=1/M*(A+B)
      WRITE(*,130) D
130  FORMAT (1X, 2E15.6)
      DO 140 I=1,N
                  E=E+X(I,J)**CNEW*LOG(X(I,J))**2
```

Appendix A (Continued)

```
140   CONTINUE
          DO 150 K=1,S
                    G=G+U(K)**CNEW*LOG(U(K))**2
 150   CONTINUE
      DO 160 I=1,N
                    MO=MO+X(I,J)**CNEW*LOG(X(I,J))
 160   CONTINUE
          DO 170 K=1,S
                    MOR=MOR+U(K)**CNEW*LOG(U(K))
 170   CONTINUE
      WRITE(*,*) D
      DC=-1*(-M/(CNEW**2)-(1/D)*(E+G))
          DT=-1*(M/(D**2)-(2/D**3)*(A+B))
          DCT=-1*(1/D**2)*(MO+MOR)
          DET= DT*DC-DCT**2
          VARC=(1/M)*(DT/DET)
          SVARC=SQRT(VARC)
          VART=(1/M)*(DC/DET)
          SVART=SQRT(VART)
          COVCT=(-1/M)*(DCT/DET)
          WRITE(*,*) "SVARC=",SVARC,"SVART=",SVART
          GOTO 101
  90   WRITE(*,100)
 100   FORMAT (1X,'THE PROCESS DID NOT CONVERGE IN 15
ITERATIONS')
 101   CLOSE(5)
STOP
END
```

APPENDIX B

FORTRAN Program to Find the Maximum Likelihood Estimators of Six Covariates and Their Standard Deviations.

```
DIMENSION X(100,100), XL(100,100), A(10,10), ADJ(10,10), AT(100)
REAL TOTX(10), D(100), TC(100), T(100), FB(10), BNEW(10), DER(100),
     D1(100), B(10), CEY(1000)
REAL PAY(10), PAYDA(10), PP(10), E, G, C, F, N, M, DETF, ITER, GT,
     INFO(10), V, D2(100)
INTEGER R, Z, U
PARAMETER (U=4)
OPEN (U, FILE='C:\MSDEV\PROJECTS\BETA1.DAT',STATUS='OLD')
WRITE(*,*) "ENTER THE CODE OF THE CAUSE OF FAILURE"
READ *, R
WRITE(*,*) "WRITE THE NUMBER OF OBSERVETIONS IN THE STUDY"
READ *, N
WRITE(*,*) "WRITE THE NUMBER OF DEATHS FROM CAUSE",R
READ *, M
WRITE(*,*) "WRITE THE NUMBER OF COVARIATES"
READ *, Z
DO 4 I=1,833
      READ(U,*) CEY(I)
4 CONTINUE
DO 10 I=1,M
      TC(I)=CEY(I)
10 CONTINUE
DO 20 J=1,N
      T(J)=CEY(M+J)
20 CONTINUE
DO 30 I=1,M
      DO 40 L=1,Z
            K=N+M+(Z*(I-1))+L
         XL(I,L)=CEY(K)
40 CONTINUE
30 CONTINUE
DO 60 I=1,N
      DO 70 J=1,Z
            K=(N+M+Z*M)+Z*(I-1)+J
                  X(I,J)=CEY(K)
70 CONTINUE
60 CONTINUE
DO 90 I=1,Z
      B(I)=0.0
```

Appendix B (Continued)

```
90 CONTINUE
ITER=0.0
1 DO 110 J=1,Z
        TOTX(J)=0.0
110 CONTINUE
DO 120 J=1,Z
        DO 130 K=1,Z
        GT=0.0
        DO 140 I=1,M
        D(I)=0.0
                DO 150 II=1,62
                        IF (TC(I).GE.T(II)) D(I)=D(I)+1
                150 CONTINUE
        G=0.0
        C=0.0
        E=0.0
        F=0.0
                DO 160 L=D(I)+1,N
        E=E+EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+X(L,4)*B(4)+X(L,5)
*B(5)+X(L,6)*B(6))
        G=G+X(L,J)*X(L,K)*EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+X(L
,4)*B(4)+X(L,5)*B(5)+X(L,6)*B(6))
        C=C+X(L,J)*EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+X(L,4)*B(4)
+X(L,5)*B(5)+X(L,6)*B(6))
        F=F+X(L,K)*EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+X(L,4)*B(4)
+X(L,5)*B(5)+X(L,6)*B(6))
160 CONTINUE
                        GT=GT+((G*E-C*F)/(E**2))
140 CONTINUE
        A(J,K)=-GT
130 CONTINUE
120 CONTINUE
DO 170 J=1,Z
        DO 180 I=1,M
                TOTX(J)=TOTX(J)+XL(I,J)
180 CONTINUE
170 CONTINUE
DO 190 J=1,Z
        PP(J)=0.0
DO 200 I=1,M
D1(I)=0.0
        DO 210 K=1,62
                IF (TC(I).GE.T(K)) D1(I)=D1(I)+1
        210 CONTINUE
```

Appendix B (Continued)

```
        PAY(J)=0.0
        PAYDA(J)=0.0
        DO 220 L=D1(I)+1,N
        PAY(J)=PAY(J)+X(L,J)*EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+
X(L,4)*B(4)+X(L,5)*B(5)+X(L,6)*B(6))
        PAYDA(J)=PAYDA(J)+EXP(X(L,1)*B(1)+X(L,2)*B(2)+X(L,3)*B(3)+X
(L,4)*B(4)+X(L,5)*B(5)+X(L,6)*B(6))
220 CONTINUE
        PP(J)=PP(J)+PAY(J)/PAYDA(J)
200 CONTINUE
190 CONTINUE
DO 230 I=1,Z
        FB(I)=TOTX(I)-PP(I)
230 CONTINUE
ADJ(1,1)=A(2,2) * A(3,3) * A(4,4) * A(5,5) * A(6,6) - A(2,6) * A(3,5) * A(4,4) *
A(5,3) * A(6,2)
ADJ(1,2)= - (A(2,1) * A(3,3) * A(4,4) * A(5,5) * A(6,6) - A(2,6) * A(3,5) *
A(4,4) * A(5,3) * A(6,1))
ADJ(1,3)=A(2,1) * A(3,2) * A(4,4) * A(5,5) * A(6,6) -A(2,6) * A(3,5) * A(4,4) *
A(5,2) * A(6,1)
ADJ(1,4)= - (A(2,1) * A(3,2) * A(4,3) * A(5,5) * A(6,6) - A(2,6) * A(3,5) *
A(4,3) * A(5,2) * A(6,1))
ADJ(1,5)=A(2,1) * A(3,2) * A(4,3) * A(5,4) * A(6,6) - A(2,6) * A(3,4) * A(4,3) *
A(5,2) * A(6,1)
ADJ(1,6)= - (A(2,1) * A(3,2) * A(4,3) * A(5,4) * A(6,5) - A(2,5) * A(3,4) *
A(4,3) * A(5,2) * A(6,1))
ADJ(2,1)= - (A(1,2) * A(3,3) * A(4,4) * A(5,5) * A(6,6) - A(1,6) * A(3,5) *
A(4,4) * A(5,3) * A(6,2))
ADJ(2,2)=A(1,1) * A(3,3) * A(4,4) * A(5,5) * A(6,6) - A(1,6) * A(3,5) * A(4,4) *
A(5,3) * A(6,1)
ADJ(2,3)= - (A(1,1) * A(3,2) * A(4,4) * A(5,5) * A(6,6) -A(1,6) * A(3,5) *
A(4,4) * A(5,2) * A(6,1))
ADJ(2,4)=A(1,1) * A(3,2) * A(4,3) * A(5,5) * A(6,6) -A(1,6) * A(3,5) * A(4,3) *
A(5,2) * A(6,1)
ADJ(2,5)= - (A(1,1) * A(3,2) * A(4,3) * A(5,4) * A(6,6) - A(1,6) * A(3,4) *
A(4,3) * A(5,2) * A(6,1))
ADJ(2,6)=A(1,1) * A(3,2) * A(4,3) * A(5,4) * A(6,5) - A(1,5) * A(3,4) * A(4,3) *
A(5,2) * A(6,1)
ADJ(3,1)=A(1,2) * A(2,3) * A(4,4) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(4,4) *
A(5,3) * A(6,2)
ADJ(3,2)= - (A(1,1) * A(2,3) * A(4,4) * A(5,5) * A(6,6) -A(1,6) * A(2,5) *
A(4,4) * A(5,3) * A(6,1))
ADJ(3,3)=A(1,1) * A(2,2) * A(4,4) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(4,4) *
A(5,2) * A(6,1)
```

Appendix B (Continued)

ADJ(3,4)= - (A(1,1) * A(2,2) * A(4,3) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(4,3) * A(5,2) * A(6,1))
ADJ(3,5)=A(1,1) * A(2,2) * A(4,3) * A(5,4) * A(6,6) - A(1,6) * A(2,4) * A(4,3) * A(5,2) * A(6,1)
ADJ(3,6)= - (A(1,1) * A(2,2) * A(4,3) * A(5,4) * A(6,5) - A(1,5) * A(2,4) * A(4,3) * A(5,2) * A(6,1))
ADJ(4,1)= - (A(1,2) * A(2,3) * A(3,4) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(3,4) * A(5,3) * A(6,2))
ADJ(4,2)=A(1,1) * A(2,3) * A(3,4) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(3,4) * A(5,3) * A(6,1)
ADJ(4,3)= - (A(1,1) * A(2,2) * A(3,4) * A(5,5) * A(6,6) – A(1,6) * A(2,5) * A(3,4) * A(5,2) * A(6,1))
ADJ(4,4)=A(1,1) * A(2,2) * A(3,3) * A(5,5) * A(6,6) - A(1,6) * A(2,5) * A(3,3) * A(5,2) * A(6,1)
ADJ(4,5)= - (A(1,1) * A(2,2) * A(3,3) * A(5,4) * A(6,6) - A(1,6) * A(2,4) * A(3,3) * A(5,2) * A(6,1))
ADJ(4,6)=A(1,1) * A(2,2) * A(3,3) * A(5,4) * A(6,5) -A(1,5) * A(2,4) * A(3,3) * A(5,2) * A(6,1)
ADJ(5,1)=A(1,2) * A(2,3) * A(3,4) * A(4,5) * A(6,6) –A(1,6) * A(2,5) * A(3,4) * A(4,3) * A(6,2)
ADJ(5,2)= - (A(1,1) * A(2,3) * A(3,4) * A(4,5) * A(6,6) - A(1,6) * A(2,5) * A(3,4) * A(4,3) * A(6,1))
ADJ(5,3)=A(1,1) * A(2,2) * A(3,4) * A(4,5) * A(6,6) - A(1,6) *A (2,5) * A(3,4) * A(4,2) * A(6,1)
ADJ(5,4)= - (A(1,1) * A(2,2) * A(3,3) * A(4,5) * A(6,6) - A(1,6) * A(2,5) * A(3,3) * A(4,2) * A(6,1))
ADJ(5,5)=A(1,1) * A(2,2) * A(3,3) * A(4,4) * A(6,6) - A(1,6) * A(2,4) * A(3,3) * A(4,2) * A(6,1)
ADJ(5,6)= - (A(1,1) * A(2,2) * A(3,3) * A(4,4) * A(6,5) - A(1,5) * A(2,4) * A(3,3) * A(4,2) * A(6,1))
ADJ(6,1)= - (A(1,2) * A(2,3) * A(3,4) * A(4,5) * A(5,6) - A(1,6) * A(2,5) * A(3,4) * A(4,3) * A(5,2))
ADJ(6,2)=A(1,1) * A(2,3) * A(3,4) * A(4,5) * A(5,6) - A(1,6) * A(2,5) * A(3,4) * A(4,3) * A(5,1)
ADJ(6,3)= - (A(1,1) * A(2,2) * A(3,4) * A(4,5) * A(5,6) - A(1,6) * A(2,5) * A(3,4) * A(4,2) *A(5,1))
ADJ(6,4)=A(1,1) * A(2,2) * A(3,3) * A(4,5) * A(5,6) - A(1,6) * A(2,5) * A(3,3) * A(4,2) * A(5,1)
ADJ(6,5)= - (A(1,1) * A(2,2) * A(3,3) * A(4,4) * A(5,6) -A(1,6) * A(2,4) * A(3,3) * A(4,2) * A(5,1))
ADJ(6,6)=A(1,1) * A(2,2) * A(3,3) * A(4,4) * A(5,5) - A(1,5) * A(2,4) * A(3,3) * A(4,2) * A(5,1)

Appendix B (Continued)

```
DETF=A(1,1) * (A(2,2) * A(3,3) * A(4,4) * A(5,5) * A(6,6) - A(2,6) * A(3,5) *
A(4,4) * A(5,3) * A(6,2) ) + A(1,2) * (A(2,3) * A(3,4) * A(4,5) * A(5,6) * A(6,1)
- A(2,1) * A(3,6) * A(4,5) * A(5,4) * A(6,3) ) + A(1,3) * (A(2,4) * A(3,5) *
A(4,6) * A(5,1) * A(6,2) - A(2,2) * A(3,1) * A(4,6) * A(5,5) * A(6,4) ) + A(1,4) *
( A(2,5) * A(3,6) * A(4,1) * A(5,2) * A(6,3) - A(2,3) * A(3,2) * A(4,1) * A(5,6) *
A(6,5) ) + A(1,5) * (A(2,6) * A(3,1) * A(4,2) * A(5,3) * A(6,4) - A(2,4) * A(3,3)
* (4,2) * A(5,1) * A(6,6) ) + A(1,6) * (A(2,1) * A(3,2) * A(4,3) * A(5,4) * A(6,5)
- A(2,5) * A(3,4) * A(4,3) * A(5,2) * A(6,1) )
DER(1)=(1/DETF)*(ADJ(1,1)*FB(1)+ADJ(1,2)*FB(2)+ADJ(1,3)*FB(3)+ADJ(1,
4)*FB(4)+ADJ(1,5)*FB(5)+ADJ(1,6)*FB(6))
DER(2)=(1/DETF)*(ADJ(2,1)*FB(1)+ADJ(2,2)*FB(2)+ADJ(2,3)*FB(3)+ADJ(2,
4)*FB(4)+ADJ(2,5)*FB(5)+ADJ(2,6)*FB(6))
DER(3)=(1/DETF)*(ADJ(3,1)*FB(1)+ADJ(3,2)*FB(2)+ADJ(3,3)*FB(3)+ADJ(3,
4)*FB(4)+ADJ(3,5)*FB(5)+ADJ(3,6)*FB(6))
DER(4)=(1/DETF)*(ADJ(4,1)*FB(1)+ADJ(4,2)*FB(2)+ADJ(4,3)*FB(3)+ADJ(4,
4)*FB(4)+ADJ(4,5)*FB(5)+ADJ(4,6)*FB(6))
DER(5)=(1/DETF)*(ADJ(5,1)*FB(1)+ADJ(5,2)*FB(2)+ADJ(5,3)*FB(3)+ADJ(5,
4)*FB(4)+ADJ(5,5)*FB(5)+ADJ(5,6)*FB(6))
DER(6)=(1/DETF)*(ADJ(6,1)*FB(1)+ADJ(6,2)*FB(2)+ADJ(6,3)*FB(3)+ADJ(6,
4)*FB(4)+ADJ(6,5)*FB(5)+ADJ(6,6)*FB(6))
DO 240 I=1,Z
        BNEW(I)=B(I)-DER(I)
240 CONTINUE
IF ((ABS(BNEW(1)-B(1)).LE.1.0E-6).AND.(ABS(BNEW(2)-B(2)).LE.1.0E-
6).AND.(ABS(BNEW(3)-B(3)).LE.1.0E-6).AND.(ABS(BNEW(4)-
B(4)).LE.1.0E-6).AND.(ABS(BNEW(5)-B(5)).LE.1.0E-
6).AND.(ABS(BNEW(6)-B(6)).LE.1.0E-6))  GOTO 1000
ITER=ITER+1
IF (ITER.GT.20) GOTO 270
DO 250 I=1,Z
        B(I)=BNEW(I)
250 CONTINUE
GOTO 1
1000 DO 260 I=1,Z
                WRITE(*,*) "The MLE of Covariate", I,"is:",BNEW(I)
260 CONTINUE
DO 265 I=1,Z
INFO(I)=SQRT((-ADJ(I,I)/DETF)/M)
265 CONTINUE
DO 266 I=1,Z
WRITE(*,*) INFO(I)
266 CONTINUE
WRITE(*,*) "ITERATION=",ITER
GOTO 290
```

Appendix B (Continued)

```
270 WRITE(*,280)
280 FORMAT(1X,"PROCESS DID NOT CONVERGE IN 20 ITERATIONS")
290 CLOSE (U)
STOP
END
```