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Estimation for the gamma and positive stable frailty models

Wang, Shan-Tair, Ph.D.
The Ohio State University, 1991
ESTIMATION FOR THE GAMMA AND POSITIVE STABLE
FRAILTY MODELS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

by
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1991

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# TABLE OF CONTENTS

ACKNOWLEDGEMENTS ............................................................... ii  
VITA ........................................................................................... iii  
TABLE OF CONTENTS ........................................................... iv  
LIST OF TABLES ......................................................................... vii  
LIST OF FIGURES ......................................................................... ix  

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. LITERATURE REVIEWS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Bivariate Distributions</td>
<td>4</td>
</tr>
<tr>
<td>2.2 Right Censoring</td>
<td>23</td>
</tr>
<tr>
<td>2.3 Analysis of Covariates</td>
<td>30</td>
</tr>
<tr>
<td>2.3.1 Fixed Covariates</td>
<td>32</td>
</tr>
<tr>
<td>2.3.2 Time Dependent Covariates</td>
<td>44</td>
</tr>
<tr>
<td>2.3.3 Random Covariates</td>
<td>45</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. GAMMA FRAILTY MODEL</th>
<th>53</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Semiparametric estimation</td>
<td>56</td>
</tr>
<tr>
<td>3.1.1 Generalized Rank Vectors</td>
<td>58</td>
</tr>
<tr>
<td>3.1.2 Profile likelihood Construction</td>
<td>65</td>
</tr>
<tr>
<td>3.1.3 Counting Process</td>
<td>70</td>
</tr>
</tbody>
</table>

iv
3.1.4 Observed Information Matrices ............................................................. 77
3.2 Weibull Regression Model ........................................................................ 86

IV. POSITIVE STABLE FRAILTY MODEL .............................................. 94

4.1 Semiparametric Estimation ........................................................................ 97
  4.1.1 Profile Likelihood Construction ............................................................ 97
  4.1.2 Counting Process .................................................................................. 103
  4.1.3 Observed Information Matrix ............................................................... 106
4.2 Weibull Regression Model ........................................................................... 110

V. EXAMPLE ................................................................................................. 122

VI. FUTURE WORK ........................................................................................ 171

APPENDICES

A. FORTRAN Program for the EM Algorithm Approach to the
   Estimation of the Dependence Parameter and Regression
   Coefficients in a Gamma Frailty Model ..................................................... 174

B. FORTRAN Program for the EM Algorithm Approach to the
   Estimation of the Dependence Parameter and Regression
   Coefficients in a Positive Stable Frailty Model ....................................... 192

C. FORTRAN Program for the Maximum Likelihood Estimation
   of the Dependence Parameter and Regression Coefficients
   in a Weibull Regression Model with Gamma Frailty ............................... 214
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The Expressions of $J(D_g, \bar{H}_g)$ for $0 \leq D_g \leq 5$</td>
<td>102</td>
</tr>
<tr>
<td>2. Estimates of Parameters for the Two Semiparametric Frailty Models for CHD and CVA Based on Disease-Free Individuals at Age 45</td>
<td>126</td>
</tr>
<tr>
<td>3. Test for Effect of Smoking on Incidences of CHD and CVA under the Two Semiparametric Frailty Models for CHD and CVA</td>
<td>130</td>
</tr>
<tr>
<td>4. Test for Effect of Cholesterol on Incidences of CHD and CVA under the Two Semiparametric Frailty Models for CHD and CVA</td>
<td>131</td>
</tr>
<tr>
<td>5. Test for Effect of Body Mass Index on Incidences of CHD and CVA under the Two Semiparametric Frailty Models for CHD and CVA</td>
<td>132</td>
</tr>
<tr>
<td>6. Estimates of Parameters for the Two Parametric Frailty Models for CHD and CVA Based on Disease-Free Individuals at Age 45</td>
<td>134</td>
</tr>
<tr>
<td>7. Test for Effect of Smoking on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA</td>
<td>138</td>
</tr>
<tr>
<td>8. Test for Effect of Cholesterol on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA</td>
<td>139</td>
</tr>
<tr>
<td>9. Test for Effect of Body Mass Index on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA</td>
<td>140</td>
</tr>
<tr>
<td>10. Summary Information on Sibling Group Size and Number of CHD Events in Groups for Each Size Group for Disease-Free Individuals at Age 45</td>
<td>142</td>
</tr>
<tr>
<td>11. Estimates of Parameters for the Two Semiparametric Frailty Models for Sibling Effects Based on Disease-Free Individuals at Age 45</td>
<td>143</td>
</tr>
</tbody>
</table>
12. Test for Effect of Smoking on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects .................................................. 146

13. Test for Effect of Cholesterol on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects .................................................. 146

14. Test for Effect of Body Mass Index on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects .................................................. 147

15. Estimates of Parameters for the Two Parametric Frailty Models for Sibling Effects Based on Disease-Free Individuals at Age 45 ........................................ 149

16. Test for Effect of Smoking on Incidence of a CHD under the Two Parametric Frailty Models for Sibling Effects .................................................. 152

17. Test for Effect of Cholesterol on Incidence of a CHD under the Two Parametric Frailty Models for Sibling Effects .................................................. 152

18. Test for Effect of Body Mass Index on Incidence of a CHD under the Two Parametric Frailty Models for Sibling Effects .................................................. 153

19. Summary Information on Sibling Group Size and Number of CHD Events in Groups for Each Size Group for Disease-Free Individuals at Entry into the Study .......................................................... 161

20. Estimates of Parameters for the Two Semiparametric Frailty Models for Sibling Effects Based on Disease-Free Individuals at Entry into the Study .................................................. 163

21. Test for Effect of Smoking on Incidence of a CHD for Four Age Groups at Entry under the Two Semiparametric Frailty Models for Sibling Effects .................. 165

22. Test for Effect of Cholesterol on Incidence of a CHD for Four Age Groups at Entry under the Two Semiparametric Frailty Models for Sibling Effects .................................................. 166

23. A Semiparametric Analysis of Example 1 Using the Marginal Likelihood of generalized Rank Vectors to Compute the Observed Information Matrix and a Comparison with a Parametric Analysis .................................................. 168

24. A Semiparametric Analysis of Example 2 Using the Marginal Likelihood of generalized Rank Vectors to Compute the Observed Information Matrix and a Comparison with a Parametric Analysis .................................................. 170
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURES</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Density Functions for the Gamma and Positive Stable When $\tau = 0.2$</td>
<td>95</td>
</tr>
<tr>
<td>2. Density Functions for the Gamma and Positive Stable When $\tau = 0.5$</td>
<td>96</td>
</tr>
<tr>
<td>3. Sizes of the Relative Increase in the Hazard Rates of the Surviving Components When One of the Other Component Fails at Time $t$ Curves are Gamma, Positive Stable</td>
<td>106</td>
</tr>
<tr>
<td>4. Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker, and for a Female Smoker versus a Female Nonsmoker under the Two Semiparametric Frailty Models for CHD and CVA</td>
<td>128</td>
</tr>
<tr>
<td>5. Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker, and for a Female Smoker versus a Female Nonsmoker under the Two Parametric Frailty Models for CHD and CVA</td>
<td>136</td>
</tr>
<tr>
<td>6. Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker, and for a Female Smoker versus a Female Nonsmoker under the Two Semiparametric Frailty Models for Sibling Effects</td>
<td>144</td>
</tr>
<tr>
<td>7. Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker, and for a Female Smoker versus a Female Nonsmoker under the Two Parametric Frailty Models for Sibling Effects</td>
<td>150</td>
</tr>
<tr>
<td>8. A graphical Check on Assuming a Weibull Model for the Baseline Hazard Function Using the EM Algorithm Estimates</td>
<td>154</td>
</tr>
<tr>
<td>9. A graphical Check on Assuming a Weibull Model for the Baseline Hazard Function Using the Kaplan-Meier Estimates</td>
<td>157</td>
</tr>
<tr>
<td>10. A graphical Check on the Proportionality of the Hazards between Male Smokers and Male Nonsmokers, and between Female Smokers and Female Nonsmokers in Predicting CHD under the Independence Model</td>
<td>159</td>
</tr>
</tbody>
</table>
CHAPTER I
INTRODUCTION

The assessment of the effects of covariates or potential risk factors on the times to events in a complex longitudinal study is an important problem in survival analysis. In such studies, individuals often enter at different ages and the particular endpoint of interest may or may not be observed during the study period. Such event times are right censored. Most statistical methods deal with this problem when the individual event times are statistically independent. In many studies, such as Framingham Heart Study (Dawber, 1980), event times between different endpoints on the same individuals (e.g., age at first evidence of hypertension, glucose intolerance, coronary heart disease, cardiovascular disease) may be associated. Also, it is reasonable to presume that individuals in the same household, such as husbands and wives who share common unmeasured environmental hazards (diet, radon levels, etc.), or siblings who share common genetic factors, will have associated times to occurrence of certain diseases or to death. In this report, we model such potential dependencies by the introduction of a "frailty" into the model that represents shared unobservable genetic or environmental random effect.
Chapter 2 of this report reviews the current literature in multivariate survival analysis. Section 2.1 describes some popular bivariate distributions in survival analysis and reliability with an emphasis on the physical and/or biological motivation behind these models. Section 2.2 discusses some important results on competing risks that deal with the identifiability of the marginal distribution of an event time subjected to censoring from the right. Section 2.3 discusses the analysis of the effects of covariates on the event times of interest under a proportional hazards model (Cox, 1972) and the analysis under an accelerated failure time model (Lawless, 1982).

Chapter 3 of this report presents some results on estimation when a frailty modelled by a one parameter gamma distribution is incorporated into a Cox proportional hazards model. Section 3.1 presents three semiparametric estimation procedures for this gamma frailty model when we assume its baseline hazard functions to be some unknown nonnegative functions. The three semiparametric estimation procedures are extensions of an EM algorithm based on a profile likelihood construction proposed by Klein (1991), an approximate EM algorithm based on the marginal likelihood of generalized rank vectors proposed by Clayton and Cuzick (1985), and an EM like algorithm applied to a partial likelihood constructed by a counting process proposed by Self and Prentice (1986). Section 3.2 discusses maximum likelihood estimation when we assume Weibull models for the baseline hazard functions. Section 3.3 records calculations of two observed information matrices for semiparametric estimates.
Chapter 4 of this report presents some results on estimation when the frailty is modelled by a one parameter positive stable distribution (Hougaard, 1986a). Section 4.1 presents two semiparametric estimation procedures for this positive stable frailty model. We adapt the semiparametric approaches proposed by Klein (1991) and Self and Prentice (1986) for the gamma frailty model to the positive stable frailty model. This is the first application of these techniques. Section 4.2 discusses the maximum likelihood estimation in this positive stable case. Section 4.3 records calculations of an observed information matrix for semiparametric estimates.

In Chapter 5 we apply the gamma and positive stable frailty models to three examples from the Framingham Heart Study. In Chapter 6 we outline some future research work.

Appendices A to F contain six FORTRAN programs for the various approaches to the estimation of the frailty parameters and regression coefficients in the gamma and positive stable frailty models.
CHAPTER II
LITERATURE REVIEW

2.1. Bivariate Distributions

Bivariate Exponential Models

Bivariate exponential distributions have been studied extensively both in the context of reliability analysis and in survival analysis. These distributions are reviewed with an emphasis on the biological/physical motivation behind them. To fix ideas, let \((X_1, X_2)\) denote the bivariate event times of interest, and \(S(x_1, x_2)\) denote their joint survival function defined as

\[
S(x_1, x_2) = \Pr (X_1 > x_1, X_2 > x_2).
\]

Gumbel (1960) proposed three bivariate exponential models that are absolutely continuous and have exponential margins.

Gumbel's model A

For this model the joint survival function is

\[
S(x_1, x_2) = \exp (\lambda_1 x_1 - \lambda_2 x_2 - \lambda_{12} x_1 x_2),
\]

\[
x_1, x_2 \geq 0, \lambda_1, \lambda_2 > 0, 0 \leq \lambda_{12} \leq \lambda_1 \lambda_2.
\]
The correlation between $X_1$ and $X_2$ is

$$\rho = \frac{-\lambda_1 \lambda_2}{\lambda_{12}} \exp \left( \frac{\lambda_1 \lambda_2}{\lambda_{12}} \right) E_i \left(\frac{-\lambda_1 \lambda_2}{\lambda_{12}}\right) - 1$$

where $E_i(c) = \int_{-c}^{\infty} \exp \left( \frac{u}{u} \right) \, du$. This correlation varies from $-0.40365$ to $0$ as $\lambda_{12}$ decreases from $\lambda_1 \lambda_2$ to $0$. Here $X_1$ and $X_2$ are independent when $\lambda_{12} = 0$.

**Gumbel's model B**

For this model the joint survival function is

$$S(x_1, x_2) = \exp \left(-\lambda_1 x_1 - \lambda_2 x_2\right) \left[1 + 4\rho \left[1 - \exp (-\lambda_1 x_1) \right] \left[1 - \exp (-\lambda_2 x_2)\right]\right],$$

$$\lambda_1, \lambda_2 > 0, x_1, x_2 \geq 0, -\frac{1}{4} \leq \rho \leq \frac{1}{4}.$$  

The correlation, $\rho$, may be positive or negative. Here $X_1$ and $X_2$ are independent when $\rho = 0$.

**Gumbel's model C**

For this model the joint survival function is

$$S(x_1, x_2) = \exp \left\{ - \left[ (\lambda_1 x_1)^{(1/\theta)} + (\lambda_2 x_2)^{(1/\theta)} \right]^{\theta} \right\},$$

$$\lambda_1, \lambda_2 > 0, 0 < \theta \leq 1, x_1, x_2 \geq 0.$$  \hspace{1cm} (2.1.1)
The correlation is $p = (4 + 2/\theta) \int_{u=0}^{\pi/2} \left[ \frac{(\cos(u + \sin u)^{(1/\theta)}}{(\cos(u^{(1/\theta)}) + \sin (u^{(1/\theta)}))^{2 + 2\theta}} \right] du - 1$

which varies from 0 to 1. Therefore it is always nonnegative. Here $X_1$ and $X_2$ are independent when $\theta = 1$, and as $\theta \to 0$, $S(x_1,x_2) \to \{\exp (-\lambda_1 x_1) \land \exp (-\lambda_2 x_2)\}$, the Fre'chet (1951) upper bound for the margins. Here $A \land B$ denotes the minimum of $A$ and $B$.

There is no biological/physical motivation for Gumbel's first and second models, the forms arising primary due to mathematical convenience. However, for the third model, Hougaard (1986b) provided a biological motivation as follows.

Suppose $X_1$ and $X_2$ are the survival times of two closely related individuals, such as spouses, who experience some common unobservable risk factors. Such an unobservable risk factor is called a frailty (Vaupel et al., 1979). Let $\omega$ be a function of the unobservable risk factors. If we assume the $X_1$ and $X_2$, given $\omega$, are conditionally independent with conditional hazards $(\lambda_1/\theta)(\lambda_1 x_1)^{(1/\theta)} - 1 \omega$ and $(\lambda_2/\theta)(\lambda_2 x_2)^{(1/\theta)} - 1 \omega$, respectively, and $\omega$ follows a standard positive stable distribution (Hougaard, 1986a) with the density function

$$f_\omega(\omega) = \frac{1}{\pi \omega} \sum_{k=1}^{\infty} \frac{\Gamma(k\theta + 1)}{k!} (-\omega^\theta \sin(\theta k \pi)), \omega > 0 \tag{2.1.2}$$

where $\Gamma(c) = \int_{u=0}^{\infty} u^{c-1} \exp(-u) du$ is the gamma function, then the joint survival function of $X_1$ and $X_2$ is of the form (2.1.1).
Downton (1970) suggested modelling the bivariate exponential times by a successive damage model. This model assumes that in a two component system the times between successive shocks on each component have independent exponential distributions and the number of shocks required to cause each component to fail follows a bivariate geometric distribution. The joint survival function of the component lifetimes is

\[ S(x_1, x_2) = \int_{u_1=x_1}^{\infty} \int_{u_2=x_2}^{\infty} \frac{\lambda_1 \lambda_2}{1 - \rho} \exp \left( -\frac{\lambda_1 u_1 + \lambda_2 u_2}{1 - \rho} \right) I_0 \left( \frac{2(\rho \lambda_1 \lambda_2 u_1 u_2)^{1/2}}{1 - \rho} \right) \, du_2 \, du_1 \]

where \( I_0 (\cdot) \) is the modified Bessel function of the first kind of order zero, and \( \lambda_1, \lambda_2 > 0, x_1, x_2 \geq 0, 0 \leq \rho \leq 1 \). For this model \( \rho = 0 \) corresponds to independence. Hawkes (1972) followed Downton's idea, but chose a different bivariate geometric distribution to derive another bivariate exponential distribution. He showed that Downton's model is a submodel of his model.

Marshall and Olkin (1967) derived a bivariate exponential distribution (BVE) using a fatal shock model. This model assumes that the components of a two component system are subject to three independent fatal shocks \( C_1, C_2, \) and \( C_{12} \), where \( C_1 \) is fatal to component 1, \( C_2 \) is fatal to component 2, and \( C_{12} \) is fatal to both components. The occurrence of shocks is governed by Poisson processes \( P_{o1} (x; \lambda_1), P_{o2} (x; \lambda_2), \) and \( P_{o12} (x; \lambda_{12}) \), respectively. With these assumptions, the joint survival function of component lifetimes is given by
\[ S(x_1, x_2) = P_r(P_0 (x_1; \lambda_1) = 0, P_0 (x_2; \lambda_2) = 0, P_{012} (x_1 \vee x_2; \lambda_{12}) = 0) \]
\[ = \exp (-\lambda_1 x_1 - \lambda_2 x_2 - \lambda_{12} (x_1 \vee x_2)), \]
\[ \lambda_1, \lambda_2 > 0, \lambda_{12} \geq 0, x_1, x_2 \geq 0 \]  

(2.1.3)

where \( A \vee B \) denotes the maximum of \( A \) and \( B \). The correlation for this model is
\[ \rho = \frac{\lambda_{12}}{\lambda} \]  
where \( \lambda = \lambda_1 + \lambda_2 + \lambda_{12} \). Here \( X_1 \) and \( X_2 \) are independent when \( \lambda_{12} = 0 \).

An interesting fact about the BVE is that it has a singular component. This component comes from the fact that the event \( X_1 = X_2 \) can occur when the \( C_{12} \) shock arrives before either of the \( C_1, \) or \( C_2 \) shocks. Marshall and Olkin (1967) showed that the joint survival function (2.1.3) can be written as
\[ S(x_1, x_2) = \frac{\lambda_1 + \lambda_2}{\lambda} S_a(x_1, x_2) + \frac{\lambda_{12}}{\lambda} S_s(x_1, x_2), \]  
which a convex combination of a

singular survival function,
\[ S_s(x_1, x_2) = \exp (- \lambda (x_1 \vee x_2)), \]

and an absolutely continuous survival function,
\[ S_a(x_1, x_2) = \frac{\lambda}{\lambda_1 + \lambda_2} \exp (-\lambda_1 x_1 - \lambda_2 x_2 - \lambda_{12} (x_1 \vee x_2)) \]
\[ - \frac{\lambda_{12}}{\lambda_1 + \lambda_2} \exp (-\lambda (x_1 \vee x_2)). \]  

(2.1.4)
Marshall and Olkin (1967) extended the BVE to the Weibull case. They suggested transforming the component lifetimes of the BVE by letting \((X_1)^{\alpha_1}\) and \((X_2)^{\alpha_2}\) follow the BVE where \(X_1\) and \(X_2\) are the transformed component lifetimes and \(\alpha_1, \alpha_2 > 0\). The joint survival function is then given by

\[
S(x_1, x_2) = \exp\left(-\lambda_1 (x_1)^{\alpha_1} - \lambda_2 (x_2)^{\alpha_2} - \lambda_{12} ((x_1)^{\alpha_1} \vee (x_2)^{\alpha_2})\right).
\]

Lee and Thompson (1974) also extended the BVE to the Weibull case. They suggested transforming the interarrival times of the shocks \(C_1, C_2\), and \(C_{12}\) instead of transforming the component lifetimes. Let \(U_1, U_2,\) and \(U_{12}\) be the interarrival times. Assume that \((U_1)^{\alpha_1}\), \((U_2)^{\alpha_2}\), and \((U_{12})^{\alpha_{12}}\), where \(\alpha_1, \alpha_2, \alpha_{12} > 0\), are exponentially distributed with hazards \(\lambda_1, \lambda_2,\) and \(\lambda_{12}\), respectively. The joint survival function of \(X_1\) and \(X_2\) is then given by

\[
S(x_1, x_2) = \Pr (U_1 > x_1, U_2 > x_2, U_{12} > (x_1 \vee x_2)) \\
= \exp\left(-\lambda_1 (x_1)^{\alpha_1} - \lambda_2 (x_2)^{\alpha_2} - \lambda_{12} ((x_1 \vee x_2))^{\alpha_{12}}\right).
\]

Freund (1961) designed a bivariate exponential distribution for the life testing of two-component systems which can function even after one of the components has failed. Suppose \(X_1\) and \(X_2\) are the component lifetimes. Initially \(X_1\) and \(X_2\) are independent exponential random variables with means \((\lambda_1)^{-1}\), and \((\lambda_2)^{-1}\) where \(\lambda_1, \lambda_2 > 0\). If the \(X_1\) component fails first, an additional stress is placed on the \(X_2\) component reducing its mean life from \((\lambda_2)^{-1}\) to \((\lambda_2')^{-1}\) where \(\lambda_2' > \lambda_2\). Similarly, if the \(X_2\) component fails first, an additional stress is placed on the \(X_2\) on the \(X_1\)
component reducing its mean life from $(\lambda_1)^{-1}$ to $(\lambda'_1)^{-1}$ where $\lambda'_1 > \lambda_1$. It can be shown that the joint density function of $X_1$ and $X_2$ is given by

\[ f(x_1, x_2) = \lambda_1 \exp\left(-\left(\lambda_1 + \lambda_2\right) x_1\right) \lambda'_2 \exp\left(\lambda'_2 \left(x_2 - x_1\right)\right), \quad \text{for } 0 < x_1 < x_2, \]
\[ = \lambda_2 \exp\left(-\left(\lambda_1 + \lambda_2\right) x_2\right) \lambda'_1 \exp\left(-\lambda'_1 \left(x_1 - x_2\right)\right), \quad \text{for } 0 < x_2 < x_1. \quad (2.1.5) \]

and the corresponding joint survival function is given by

\[
S(x_1, x_2) = \left\{ \begin{array}{ll}
\frac{\lambda_2}{\lambda_1 + \lambda_2} - \frac{\lambda_1 \lambda'_2}{(\lambda_1 + \lambda_2 - \lambda'_2) (\lambda_1 + \lambda_2)} & \exp(- (\lambda_1 + \lambda_2) x_2) \\
& + \frac{\lambda_1}{\lambda_1 + \lambda_2 - \lambda'_2} \exp\left(-(\lambda_1 + \lambda_2 - \lambda'_2) x_1 - \lambda'_2 x_2\right), \quad \text{for } 0 < x_1 < x_2, \\
\frac{\lambda_1}{\lambda_1 + \lambda_2} - \frac{\lambda_2 \lambda'_1}{(\lambda_1 + \lambda_2 - \lambda'_1) (\lambda_1 + \lambda_2)} & \exp(- (\lambda_1 + \lambda_2) x_1) \\
& + \frac{\lambda_2}{\lambda_1 + \lambda_2 - \lambda'_1} \exp\left(-(\lambda_1 + \lambda_2 - \lambda'_1) x_2 - \lambda'_1 x_1\right), \quad \text{for } 0 < x_2 < x_1. \quad (2.1.6) 
\end{array} \right.
\]

The correlation for this model is

\[
\rho = \frac{\lambda'_1 \lambda'_2 - \lambda_1 \lambda_2}{\left(\lambda'_1 + 2\lambda_1 \lambda_2 + (\lambda_2)^2\right)^{1/2} \left(\lambda'_2 + 2\lambda_1 \lambda_2 + (\lambda_1)^2\right)^{1/2}}. 
\]
Clearly, \( \lambda_1 = \lambda_1' \), and \( \lambda_2 = \lambda_2' \) corresponds to independence.

Block and Basu (1974) considered a three-parameter Freund's model by letting

\[
\lambda_1 = \lambda_1 + \frac{\lambda_{12} \lambda_1}{\lambda_1 + \lambda_2}, \quad \lambda_1' = \lambda_1 + \lambda_{12}, \quad \lambda_2 = \lambda_2 + \frac{\lambda_{12} \lambda_2}{\lambda_1 + \lambda_2}, \quad \text{and} \quad \lambda_2' = \lambda_2 + \lambda_{12}
\]

where \( \lambda_1, \lambda_2, \) and \( \lambda_{12} > 0 \). It follows from (2.1.5) that this three-parameter family has the following density function

\[
f(x_1, x_2) = \frac{\lambda_1 \lambda_2 (\lambda_2 + \lambda_{12})}{\lambda_1 + \lambda_2} \exp \left( -\lambda_1 x_1 - (\lambda_2 + \lambda_{12}) x_2 \right), \quad \text{for} \quad 0 < x_1 < x_2.
\]

It can be shown from (2.1.6) that the corresponding joint survival function is of the form (2.1.4) which is the absolutely continuous component of the BVE.

Spurrier and Weier (1979) derived a bivariate Weibull distribution for the same two-component systems as described by Freund. Their interest was in system reliability rather than component reliability. Therefore the Weibull model was derived in terms of the time until the first failure, \( X_{\text{min}} = X_1 \wedge X_2 \), and the time between the first failure and system failure, \( X_\Delta = (X_1 \vee X_2) - X_{\text{min}} \).

Initially, \( X_1 \) and \( X_2 \) are two independent Weibull random variables with hazards \( \alpha \lambda^\alpha (x_1)^{\alpha - 1} \) and \( \alpha \lambda^\alpha (x_2)^{\alpha - 1} \), respectively. Therefore the hazard function of \( X_{\text{min}} \) is given by \( h_{\text{min}}(x) = 2\alpha \lambda^\alpha (x)^{\alpha - 1} \), for \( 0 < x < \infty \). Upon the
first failure the remaining component switches from a workload proportional to \(\lambda\) to a workload \(c\lambda\) where \(c > 0\). This idea is formalized by assuming that the conditional density function of \(X_\Delta\) given \(X_{\text{min}} = x\) is

\[
f(x_\Delta | X_{\text{min}}=x) = \alpha c \lambda x (c x_\Delta + x)^{\alpha - 1} \exp \left\{ \lambda (c x_\Delta + x) \right\}^{\alpha} + (\lambda x)^\alpha,\]

for \(0 < x_\Delta < \infty\).

The joint density function of \(X_{\text{min}}\) and \(X_\Delta\) is then given by

\[
f(x,x_\Delta) = 2 \alpha^2 c \lambda^2 x^{\alpha - 1} (c x_\Delta + x)^{\alpha - 1} \exp \left\{ \lambda (c x_\Delta + x) \right\}^{\alpha} - (\lambda x)^\alpha.\]

Friday and Patil (1977) generalized Freund's model to allow positive probability on the line \(X_1 = X_2\), and they gave three distinct physical motivations for this generalization. The first leads to what is called a threshold model. The idea is that if the components of a two component system are in close proximity, then an initial shock that is fatal to its corresponding component may also kill the other component provided the intensity of the initial shock exceeds the intensity threshold of that other component. This model assumes that with probability \(1 - p_0\) the initial shock kills both components, and with probability \(p_0\) it kills only its corresponding component. Note that \(X_1 \wedge X_2\) is distributed as the exponential distribution with mean \((\lambda_1 + \lambda_2)^{-1}\). Therefore the joint survival function for this model is

\[
S(x_1,x_2) = p_0 S_a(x_1,x_2) + (1 - p_0) S_S(x_1,x_2) \tag{2.1.7}
\]
where $S_a$ is of the form (2.1.6), and $S_g = \exp(-(\lambda_1 + \lambda_2)(x_1 \vee x_2))$. After some algebraic manipulation, it can be shown that (2.1.7) can be written as

$$S(x_1,x_2) = \phi_1 \exp(- (\lambda_1 + \lambda_2 - \lambda_1^i) x_1 - \lambda_2^i x_2) + (1 - \phi_1) \exp(- (\lambda_1 + \lambda_2) x_2),$$
for $0 < x_1 < x_2$,

$$= \phi_2 \exp(- (\lambda_1 + \lambda_2 - \lambda_1^i) x_2 - \lambda_1^i x_1) + (1 - \phi_2) \exp(- (\lambda_1 + \lambda_2) x_2),$$
for $0 < x_2 < x_1$. \text{(2.1.8)}

where $\phi_1 = p_0 \lambda_1 (\lambda_1 + \lambda_2 - \lambda_1^i)^{-1}$, and $\phi_2 = p_0 \lambda_2 (\lambda_1 + \lambda_2 - \lambda_1^i)^{-1}$. The correlation for this model is

$$\rho = \frac{\lambda_1^i \lambda_2^i - (p_0)^2 \lambda_1 \lambda_2}{((\lambda_1^i)^2 + 2 p_0 \lambda_2 (\lambda_1 + \lambda_2) - (p_0 \lambda_2)^2)^{1/2}} \times \frac{1}{((\lambda_2^i)^2 + 2 p_0 \lambda_1 (\lambda_1 + \lambda_2) - (p_0 \lambda_1)^2)^{1/2}}.$$

The other two motivations, which we are not going to elaborate on, lead to a so called gestation model and warmup model. These two models also have the joint survival function of the form (2.1.8).
Clearly, when \( p_0 = 1 \), (2.1.7) reduces to (2.1.6). We can also see if we let
\[
p_0 = \frac{\lambda_1 + \lambda_2}{\lambda},
\]
and if \( \lambda_1, \lambda_2, \lambda_1', \lambda_2' \) are those defined by Block and Basu (1974),
then (2.1.7) reduces to (2.1.5). Therefore Friday and Patil's (1977) model include
model as special cases.

**Bivariate Frailty Models**

In chronic disease epidemiology we may be concerned with survival times of
individuals who are naturally or artificially paired. For example, in familial studies
of chronic disease incidence we may have data on ages and causes of death of
fathers and sons. Clayton (1978) introduced a model for studying such familial
pairs.

Clayton (1978) derived the model in two different ways. Suppose \( X_1 \) and \( X_2 \)
are the ages at death of a father and son, respectively. Let \( h(x_1 \mid X_2 > x_2) \) be the
age-specific hazard function of a father at age \( x_1 \) whose son survive to at least age
\( x_2 \), and \( h(x_1 \mid X_2 = x_2) \) be that of a father at age \( x_1 \) whose son dies age \( x_2 \). The
first derivation was motivated by the idea that these two hazard functions are
dependent because of the genetic connection between a father and son. It was
assumed that the ratio of \( h(x_1 \mid X_2 = x_2) \) to \( h(x_1 \mid X_2 > x_2) \) is governed by a single
parameter as follows:

\[
\frac{h(x_1 \mid X_2 = x_2)}{h(x_1 \mid X_2 > x_2)} = 1 + \delta, \quad \delta > -1.
\]  

(2.1.9)
Here $\delta = 0$ corresponds to independence, $\delta > 0$ corresponds to positive association, and $\delta < 0$ corresponds to negative association. By definition, 

$$h(x_1 | X_2=x_2) = -\frac{\partial x_1 \partial x_2}{\partial S(x_1,x_2)}, \text{ and } h(x_1 | X_2 > x_2) = -\frac{\partial x_1}{S(x_1,x_2)}.$$ 

Substituting into (2.1.9), and solving for $S(x_1,x_2)$, it can be shown that for $\delta > 0$

$$S(x_1,x_2) = \left[ 1 + \delta \sum_{j=1}^{2} H_{0j}(x_j) \right]^{-1/\delta} \quad (2.1.10)$$

where $H_{01}(x)$ and $H_{02}(x)$ are nondecreasing functions with $H_{01}(0) = 0$, and $H_{02}(0) = 0$. For this model as $\delta \to 0$, $S(x_1,x_2) \to S(x_1,0) S(0,x_2)$ and as $\delta \to \infty$, $S(x_1,x_2) \to \{S(x_1,0) \wedge S(0,x_2)\}$.

The second derivation was motivated by a simple interpretation involving an unobserved frailty shared between a father and son. The idea is that a father-son pair share a common random frailty $\omega$ because of their genetic connection. First, assuming that given the frailty $\omega$, $X_1$ and $X_2$ are conditionally independent with conditional hazards of Cox's (1972) type (conditional survival functions) $\omega h_{01}(x_1) (\exp (- \omega H_{01}(x)))$, and $\omega h_{02}(x_2) (\exp (- \omega H_{02}(x)))$, respectively, where $H_{0j}$'s are the nondecreasing functions in (2.1.10) and $h_{0j}(x) = \frac{dH_{0j}(x)}{dx} \quad (j = 1, 2)$, we can show by a simple conditioning argument that the joint survival function of $X_1$ and $X_2$ is of the form
\[ S(x_1, x_2) = \mathcal{E}^{\omega} \left( \exp \left( -\omega \sum_{j=1}^{2} \mathcal{H}_{0j}(x_j) \right) \right) \]

which is the Laplace transform of the distribution for \( \omega \) evaluated at \( \sum_{j=1}^{2} \mathcal{H}_{0j}(x_j) \).

Second, assuming that \( \omega \) follows a gamma distribution with shape parameter \( \delta^{-1} \), and scale parameter \( \delta^{-1} \) such that its mean is 1 and its variance is \( \delta \), we then obtain from (2.1.11) that the joint distribution of \( X_1 \) and \( X_2 \) is of the form (2.1.10).

Oakes (1982) reparametrizes Clayton's (1978) model by changing the conditional survival functions of \( X_1 \) and \( X_2 \), given \( \omega \), and by assuming a different gamma distribution for \( \omega \). He assumed that the distribution is gamma with shape parameter \( \delta^{-1} \), and scale parameter 1, and the conditional survival functions of \( X_1 \) and \( X_2 \), given \( \omega \), are \( \exp \left( \omega \left( -\frac{1}{S_{x_1}(x_1)} \right)^{\delta} + 1 \right) \), and \( \exp \left( \omega \left( -\frac{1}{S_{x_2}(x_2)} \right)^{\delta} + 1 \right) \), respectively. Here \( S_{x_1}(x_1) \) and \( S_{x_2}(x_2) \) are the marginal survival functions of \( X_1 \) and \( X_2 \), respectively. By a simple conditioning argument, the joint survival function of \( X_1 \) and \( X_2 \) is given by

\[ S(x_1, x_2) = \left[ \left( \frac{1}{S_{x_1}(x_1)} \right)^{\delta} + \left( \frac{1}{S_{x_2}(x_2)} \right)^{\delta} - 1 \right]^{1/\delta}. \]  

(2.1.12)

For this model as \( \delta \to 0 \), \( S(x_1, x_2) \to S_{x_1}(x_1) \cdot S_{x_2}(x_2) \), and as \( \delta \to \infty \), \( S(x_1, x_2) \to \{S_{x_1}(x_1) \wedge S_{x_2}(x_2)\} \).

We can obtain (2.1.12) also by solving (2.1.9) with side conditions \( S(x_1, 0) = S_{x_1}(x_1) \), and \( S(0, x_2) = S_{x_2}(x_2) \).
For the Oakes's (1982) model the conditional distributions of \( X_1 \) and \( X_2 \), given \( \omega \), depend on the frailty parameter \( \delta \), while for the Clayton's (1978) model they are free of \( \delta \). The reverse situations hold for the marginal distributions of \( X_1 \) and \( X_2 \). In essence, Oakes's (1982) model gives us a direct control over the marginal distributions of \( X_1 \) and \( X_2 \), while Clayton's (1978) model gives us a direct control over the conditional distributions of \( X_1 \) and \( X_2 \) given the frailty \( \omega \).

Hougaard (1984, 1986a) considered two more general families of frailty distributions, which both include gamma and inverse Gaussian distributions as subfamilies, for modelling heterogeneity between individuals in population based mortality studies. The first one is a natural exponential family on the positive numbers which has the following density function:

\[
f(\omega) = \frac{\omega^v \exp(-\kappa \omega) C(\omega)}{\eta(\mu, \kappa)},
\]

where \( C(\omega) \) is a function of \( \omega \) only, and the natural parameter space of the exponential family is given by all the \((\mu, \kappa)\)'s that satisfy

\[
\eta(v, \kappa) = \int_{\omega=0}^{\infty} \omega^v \exp(-\kappa \omega) C(\omega) \, d\omega < \infty.
\]

The second one is a three-parameter family on the positive numbers generated from standard stable distributions (Feller, 1971). This family has the density function
for $v > 0$, $\kappa \geq 0$, $\theta \in (0, 1]$, 

where $L_p(s)$ is the Laplace transform of the standard positive stable density (2.1.2) given by $E\{\exp(-s\omega)\} = \exp(-s^\theta)$. Assuming that the hazard rate at age $x$ for a person with frailty $\omega$ is of the Cox's type described by Clayton (1978), Hougaard (1984) compared various properties of the conditional proportional hazards model when $\omega$ follows the inverse Gaussian distributions to those when $\omega$ follows the gamma distributions. Assuming the random frailty $\omega$ follows the standard positive stable density, Hougaard (1986a) showed that the marginal hazards of $X$ has the form of a proportional hazards model.

Hougaard (1986b) also studied a class of multivariate failure time distributions induced by the standard positive stable density. Assuming the conditional independence proportional hazards model (2.1.11) (hereafter called frailty model) holds and the random frailty $\omega$ follows the standard positive stable density, the multivariate distributions in the bivariate case are

$$S(x_1, x_2) = \exp\left(-\sum_{j=1}^{2} H_{0j}(x_j)^\theta\right). \tag{2.1.13}$$

For this model $\theta = 1$ corresponds to independence, and as $\theta \to 0$, $S(x_1, x_2) \to S_{x_1}(x_1) S_{x_2}(x_2)$. 

\[
\text{f}(\omega) = \frac{\text{fp}(\frac{\omega}{(v\theta-1)1/\theta}) \exp(-\kappa \omega)}{(v\theta-1)1/\theta \ L_p(\frac{(v\theta-1)1/\theta}{\kappa})}, \text{ for } v > 0, \kappa \geq 0, \theta \in (0,1],
\]
Lee and Klein (1988) studied some properties of the frailty model (2.1.11) where the distribution of $\omega$ is unspecified. One interesting result is that $\frac{h(x_1 \mid X_2 = x_2)}{h(x_1 \mid X_2 > x_2)} > 1$ for all $x_1, x_2 > 0$. Intuitively, this results implies a positive association between $X_1$ and $X_2$.

Oakes (1989) explored the relationship between the so-called cross-ratio function $\frac{h(x_1 \mid X_2 = x_2)}{h(x_1 \mid X_2 > x_2)}$ and the frailty model (2.1.11) by considering the so-called Archimedean distributions (Genest and Mackay, 1986). The Archimedean distributions take the form

$$S(x_1, x_2) = p[q[S_1(x_1)] + q[S_2(x_2)]] \quad (2.1.14)$$

where $p(s)$ is any nonnegative decreasing function with $p(0) = 1$ and has nonnegative second derivative, and $q(s)$ is its inverse function. When $p(s)$ is the Laplace transform of the distribution for $\omega$, the Archimedean model (2.1.14) reduces to the frailty model (2.1.11). Oakes (1989) proved the following results which unveil the relationship between the cross-ratio function and the Archimedean distributions.

**Lemma 2.1.1:** Suppose that $S(x_1, x_2)$ is Archimedean so that (2.1.14) holds for some twice-differentiable functions $p(s)$ with $p(0) = 1$, $\frac{dp(s)}{ds} > 0$, and $\frac{d^2p(s)}{ds^2} > 0$. Then the cross-ratio function depends on $(x_1, x_2)$ only through some function $\pi(v)$ where $v = S(x_1, x_2)$. 
Lemma 2.1.2: Suppose that (2.1.14) holds for a given bivariate survival function $S(x_1, x_2)$. Then $p(s)$ is uniquely determined up to a scale change in $s$, and its inverse function $q(s)$ is determined in terms of $\pi(v)$ by

$$q(s) = \int_{u=s} \exp \left\{ \int_{v=u}^{1-c} \frac{\pi(v)}{v} \, dv \right\} \, du$$

(2.1.15)

up to a constant multiple specified by $c > 0$.

Theorem 2.1.1: Suppose that $S(x_1, x_2)$ is an absolutely continuous bivariate survival function whose cross-ratio function is expressible as $\pi(S(x_1, x_2))$ for some function $\pi(v)$. Then $S(x_1, x_2)$ satisfies the Archimedean representation (2.1.14) with the function $p(s)$ determined (up to a scale change) (2.1.15).

One implication from the above results is that the bivariate frailty models can be studied by changing the specification of the cross-ratio functions. For example, when $\pi(v)$ is equal to $1 + \delta$, $\delta > 0$, we have the gamma frailty model (Clayton, 1978), and when $\pi(v) = 1 + \frac{1 - \theta}{\theta \ln v}$, $0 < \theta \leq 1$, we have the positive stable frailty model (Hougaard, 1986b).
Point Process Models

Cox (1972) proposed a bivariate model from a point process viewpoint. He described the density function of $X_1$ and $X_2$ in terms of hazard functions $h^*_1(x_1)$, $h^*_2(x_2)$, $h^*_{12}(x_1 \mid x_2)$, and $h^*_{21}(x_2 \mid x_1)$ where

\[
\begin{align*}
 h^*_1(x_1) &= \lim_{\Delta x \to 0} \frac{Pr \left( x_1 \leq X_1 < x_1 + \Delta x \mid X_1 \geq x_1, X_2 \geq x_2 \right)}{\Delta x}, \\
 h^*_2(x_2) &= \lim_{\Delta x \to 0} \frac{Pr \left( x_2 \leq X_2 < x_2 + \Delta x \mid X_1 \geq x_1, X_2 \geq x_2 \right)}{\Delta x}, \\
 h^*_{12}(x_1 \mid x_2) &= \lim_{\Delta x \to 0} \frac{Pr \left( x_1 \leq X_1 < x_1 + \Delta x \mid X_1 \geq x_1, X_2 = x_2 \right)}{\Delta x}, \\
 h^*_{21}(x_2 \mid x_1) &= \lim_{\Delta x \to 0} \frac{Pr \left( x_2 \leq X_2 < x_2 + \Delta x \mid X_1 = x_1, X_2 \geq x_2 \right)}{\Delta x},
\end{align*}
\]

for $x_1 > x_2$, and

for $x_2 > x_1$.

When $x_1 < x_2$ the probability of having no deaths in $[0, x_1)$, and the event $X_1 \in [x_1, x_1 + \Delta x)$ is $\exp \left( \int_{u=0}^{x_1} \left( h^*_1(u) + h^*_2(u) \right) du \right) h^*_1(x_1) \Delta x$. Conditional on this event, the probability of no further deaths in $[x_1, x_2)$ and the event $X_2 \in [x_2, x_2 + \Delta x)$ is $\exp \left( \int_{u=x_1}^{x_2} h^*_{21}(u \mid x_1) du \right) h^*_{21}(x_2 \mid x_1) \Delta x$. Therefore the joint density of $X_1$ and $X_2$ is given by
\[ f(x_1, x_2) = h_1^*(x_1) h_{21}^*(x_2 \mid x_1) \exp \left( - \int_{u=0}^{x_1} (h_1^*(u) + h_2^*(u)) \, du - \int_{u=x_1}^{x_2} h_{21}^*(u \mid x_1) \, du \right) \]

for \( x_1 < x_2 \).

Similarly,

\[ f(x_1, x_2) = h_2^*(x_2) h_{12}^*(x_1 \mid x_2) \exp \left( - \int_{u=0}^{x_2} (h_1^*(u) + h_2^*(u)) \, du - \int_{u=x_2}^{x_1} h_{12}^*(u \mid x_2) \, du \right) \]

for \( x_2 < x_1 \). \hfill (2.1.16)

Note that when \( h_1^*(x_1) = \lambda_1 \), \( h_2^*(x_2) = \lambda_2 \), \( h_{12}^*(x_1 \mid x_2) = \lambda_1' \), and \( h_{21}^*(x_2 \mid x_1) = \lambda_2' \), the point process model (2.1.16) reduces to the Freund's model (2.1.5). Lu and Bhattacharyya (1988) extended Freund's model to the Weibull case by assuming that \( h_1^*(x_1), h_2^*(x_2), h_{12}^*(x_1 \mid x_2) \), and \( h_{21}^*(x_2 \mid x_1) \) are of the form of Weibull hazards. Platz (1984) considered a five-parameter Markov model by adding a singular component in (2.1.16). He showed that both Freund's (1961) model and Marshall and Olkin's (1967) model are submodels of his model.
2.2 Right Censoring

In reliability, medical and biological studies, right censoring may be planned for in order to make inference sooner than is otherwise possible or may occur randomly because some competing causes interrupt the observation of the event of interest. For example, in many reliability studies the lifetimes of experimental unit are observed until some pre-specified time, and in many medical studies patients are withdrawn from the studies because of various complications which result in the interruption of observation before the event of interest occurs. One of the major impacts on the analysis of survival data from the presence of the right censoring is that the distribution of the event time may not be identifiable from such a censored sample. In the sequel some results on nonidentifiability problems under general right censoring are presented.

In the general right censored survival problem, the life process of a subject can be represented by random variables $X$, $T$, and $\xi$. The random variable $X$ is the true survival time under test conditions with survival function $S_X(x)$. In the presence of censoring to the right $X$ can not be observed directly. Instead, we observed the pair $(T, \xi)$, where $T$ is the observed portion of survival time and $\xi$ is the censoring indicator of the observed time $T$ which takes value one if $T = X$, and zero otherwise. An important statistical topic is to estimate $S_X(x)$ from the $T$ and $\xi$ (known as the competing risks problem). Unfortunately, it turns out that $S_X(x)$ is not identifiable from the observable pair $(T, \xi)$ unless some untestable assumptions are made. The following result is due to Basu and Ghosh (1978).
Let the random variable $X_1$ denote the survival time of interest and the random variable $X_2$ denote the censoring time such that

$$T = X_1 \land X_2,$$

and

$$\xi = \begin{cases} 
1 & \text{if } T = X_1 \\
0 & \text{otherwise}
\end{cases}$$

(2.2.1)

Let the joint survival function of $X_1$ and $X_2$ be $S(x_1, x_2)$, and its first partial derivatives be $S_1(x_1, x_2) = \frac{\partial S(x_1, x_2)}{\partial x_1}$, and $S_2(x_1, x_2) = \frac{\partial S(x_1, x_2)}{\partial x_2}$. Suppose that

$$\tilde{G}_1(x_1) = \exp \left( - \int_{u=0}^{x_1} \frac{S_1(u, u)}{S(u, u)} \, du \right),$$

and, similarly,

$$\tilde{G}_2(x_2) = \exp \left( - \int_{u=0}^{x_2} \frac{S_2(u, u)}{S(u, u)} \, du \right).$$

Then under the conditions that $-\ln \tilde{G}_1(\infty) = \infty$, and $-\ln \tilde{G}_2(\infty) = \infty$, it can be shown that $(T, \xi)$ has the same distribution whether $(T, \xi)$ is distributed according to $S(x_1, x_2)$ or $\tilde{G}_1(x_1) \tilde{G}_2(x_2)$. We can see the marginal distribution $S_{x_1}(x_1)$ is different from $\tilde{G}_1(x_1)$. Therefore we can not identify which marginal distribution generates the pair $(T, \xi)$.

A large portion of the survival analysis literature concerning right censored data simply makes the untestable assumption that the censoring is 'noninformative'; i.e., the censoring time $X_2$ is independent of the survival time $X_1$. It was shown by Berman (1963) and Peterson (1975) that $S_{x_1}(x_1)$ is identifiable under this assumption. It is a reasonable assumption for most practical applications. However, in studies like testing the efficacy of some new drugs, patients might be withdrawn from the studies because of serious side effects from taking the new drugs. In this
case, the assumption of 'noninformative' censoring is questionable. So just how far can we relax this assumption so that \( S_{x_1}(x_1) \) is identifiable? In the following we will present some of the results that deal with this issue.

Langberg, Proschan and Quinzi (1978) gave results on the equivalence, in the competing risks framework, of the dependent and independent risks. Let \( X = (X_1, \ldots, X_k) \) be a vector of positive random variables and let \( T = \bigwedge_{m=1}^{k} X_m \) be the observable system lifetime. Let \( I \) denote the collection of nonempty subsets \( \{1,2,\ldots,k\} \). Let \( H \) be the vector of component life lengths in a series system of \((2^k - 1)\) components with system lifetime \( T_H \) where the coordinates of \( H \) are indexed lexicographically by \( I \in I \). Define the failure patterns by

\[
\xi(X) = \begin{cases} 
I & \text{if } T = X_m \text{ for each } m \in I \\
\phi & \text{otherwise}
\end{cases}
\]

and let

\[
\xi^*(H) = \begin{cases} 
I & \text{if } H_I < H_J \text{ for } J \neq I \\
\phi & \text{otherwise}
\end{cases}
\]

We say \( X \) and \( H \) are equivalent in life length and failure pattern (\( X \equiv_{LP} H \)) if \( \Pr(T_H > t, \xi^*(H) = I) = \Pr(T > t, \xi(X) = I) \), \( t \geq 0 \), \( I \in I \). When \( X \equiv_{LP} H \), the two system lifetimes are identically distributed, and corresponding failure patterns have
the same chance of occurring. The following theorem is due to Langberg et al. (1978):

**Theorem 2.2.1:** Let \( T = \bigwedge_{m=1}^{k} X_m \) denote the life length of a \( k \)-component series system where \( X_m \) represents the life length of the \( m \)-th component, \( m = 1, 2, \ldots, k \). Define 
\[ S_I(t) = \Pr(T > t, \xi(X) = 1), \quad F_I(t) = \Pr(T \leq t, \xi(X) = 1), \]
\[ S_T(t) = \Pr(T > t), \quad \nu(S_T) = \sup \{t: S_T(t) > 0\}. \]
Then the following statements hold:

(i) A necessary and sufficient conditions for the existence of a set of independent \( \mathcal{L}_P \) random variables \( (H_l, I_i \in I) \) which satisfy \( X = H \) is that the set of discontinuities of \( F_I(t) \) are pairwise disjoint on the interval \([0, \nu(S_T))\). (ii) The distributions of \( (H_l, I_i \in I) \) in (i) are uniquely determined on the interval \([0, \nu(S_T))\) as follows:

\[
\tilde{G}_I(t) = \Pr(H_I > t) = \exp \left( - \int_{u=0}^{t} \frac{dF^c_I(u)}{S_T(u)} du \right) \prod_{\{j: a(I, j) \leq t\}} \frac{S_T(a(I, j))}{S_T(a^-(I, j))}, \quad 0 \leq t \leq \nu(S_T)
\]

where \( F^c_I \) is the continuous part of \( F_I \), and \( \{j: a(I, j)\} \) is the set of discontinuities of \( F_I(a^-(I, j)) \) denotes the left-hand limit of \( a(I, j) \).

Tsiatis (1975) and Miller (1977) obtained similar results under more restrictive assumptions about the component lifetimes \( X_1, X_2, \ldots, X_k \). Tsiatis assumed that the joint distribution of \( X_1, X_2, \ldots, X_k \) is absolutely continuous. Miller assumed that the probabilities of simultaneous failures are zero.
Based on Theorem 2.2.1, Langberg, et al. (1981) showed the following theorem which characterizes the identifiability dilemma:

**Theorem 2.2.2:** Let $\tilde{M}_i(t) = \Pr (\bigwedge_{m \in I} X_m > t)$, $i \in I$, denote the marginal survival probability corresponding to the failure pattern $I$ operating alone without competition from the other causes. Let $I_1 = \{ J \in I : I \cap I_1 = \emptyset \}$. Then for each $t \in [0, \cup(S_T))$ $\tilde{M}_i(t) = \prod_{J \in I_1} \tilde{G}_J(t)$ if and only if the following two conditions hold:

(i) $\frac{\tilde{M}_i(a^-)}{\tilde{M}_i(a^+)} = \begin{cases} \frac{S_T(a^-)}{S_T(a^+)} & \text{for } a \text{ is a discontinuity point of } F_J \text{ where } J \in I_1 \\ 1 & \text{otherwise.} \end{cases}$

(ii) $\Pr (\bigwedge_{m \in I_1} X_m > t | \bigwedge_{m \in J} X_m = t)$

\[ = \Pr (\bigwedge_{m \in I_1} X_m > t | \bigwedge_{m \in I} X_m > t) \]

where $I_1^c$ is the complement of $I_1$ in $I$ and $\tilde{G}_J(t)$ is given by (2.2.2). We can see from this result that the marginal survival functions $\tilde{M}_i$, $i \in I$, of the dependent system can be recovered from the equivalent in LP independent system when the conditions (i) & (ii) of Theorem 2.2.2 are met.

An important statistical implication of Theorem 2.2.2 is that the Kaplan-Meier estimator (Kaplan and Meier (1958)) under dependent censoring time is no longer consistent. Replace $F_J(t)$ and $S_T(t)$ by their empirical counterparts $\hat{F}_{J,n}(t) = n^{-1} \sum_{i=1}^{n} \chi[T_i \leq t, \xi(X_i) = J]$ and $\hat{S}_{T,n}(t) = n^{-1} \sum_{i=1}^{n} \chi[T_i > t]$, respectively, on the right in (2.2.2) where $\chi[A]$ is an indicator of a set $A$. Let the resulting estimate of $\tilde{G}_J(t)$ be $\hat{G}_{J,n}(t)$. Langberg et al. (1981) showed that
\[ \prod_{J \in I} G_{J,n}(t) \] is strongly consistent for \( \prod_{J \in I} \hat{G}_J(t) \). By some algebraic manipulation, it can be shown that \( \prod_{J \in I} \hat{G}_{J,n}(t) \) is the extended Kaplan-Meier estimator introduced by Peterson (1975) which is defined as

\[ \hat{M}_{I,n}(t) = \prod_i \frac{n - i}{n - i + 1} \] (2.2.3)

where the product is over the ranks \( i \) of those ordered system failure times \( T_{(i)} \), such that \( T_{(i)} \leq t < T_{(n)} \) and \( T_{(i)} \) corresponds to a death from the simultaneous causes \( j \in J, J \in I \). \( \hat{M}_{I,n}(t) \) is zero for \( t > T_{(n)} \) if the \( T_{(n)} \) corresponds to causes in \( J \); otherwise, \( \hat{M}_{I,n}(t) \) is undefined for \( t > T_{(n)} \). Therefore the extended Kaplan-Meier estimator (2.2.3) is consistent for \( \hat{M}_{I,n}(t) \) provided that the conditions (i) & (ii) of Theorem 2.2.2 hold.

Klein and Moeschberger (1984) studied Gumbel's (1960) model and Block and Basu's (1974) model, and Marshall and Olkin's (1967) model under competing risks setting. They showed that the extended Kaplan-Meier estimator is consistent under the BVE of Marshall and Olkin, but not under the other two bivariate exponential distributions.

Williams and Lagokos (1977) examined the conditions (i) & (ii) of Theorem 2.2.2 for the case \( k = 2 \) from another viewpoint. Let \( a(t) = P_\Gamma (\xi = 1 | t \leq X_1 < t + dt) \) and \( dB(t) = P_\Gamma (t \leq T < t + dt | T \geq t) \). They showed that if
\[ a(t) + \int_{u=0}^{t} dB(u) = 1, \quad (2.2.4) \]

then the distribution of \( X_1 \) is identifiable from the observable pair \((T, \xi)\). They called a model satisfying (2.2.4) a constant-sum model. Otherwise, it is called a variable-sum model.

Kalbfleisch and Mackay (1979) gave an equivalent characterization of the constant-sum condition using net and cause specific hazard functions. They showed that a model is constant-sum if and only if
\[
\begin{align*}
\Pr(t \leq X_1 < t + dt \mid T \geq t) &= \Pr(t \leq X_1 < t + dt \mid X_1 \geq t), \quad \text{and} \quad \\
\Pr(t \leq X_2 < t + dt \mid T > t) &= \Pr(t \leq X_2 < t + dt \mid X_2 > t).
\end{align*}
\]

A connection between the constant-sum condition (2.2.4) and the conditions (i) & (ii) of Theorem 2.2.2 was proved by Basu and Klein (1982). They showed that a model is a constant-sum if the set of discontinuities of \( F_i(t) \) are pairwise disjoint for all \( I \in I \), and
\[
\Pr(X_1 \geq t \mid X_2 = t) = \Pr(X_1 \geq t \mid X_2 \geq t).
\]

For further discussions on dependent right censoring, readers can refer to the papers by Basu and Klein (1982), and Lagakos (1979).
2.3 Analysis of Covariates

In medical research the primary objective of many studies concerns the relationship between certain covariates and the event times of interest. For example, a large portion of the research on the Framingham Heart Study (Dawber, 1980) concerns the association between cardiovascular disease and fixed and/or time-dependent covariates such as age, sex, smoking behavior, hypertension, and etc.. Two most widely used regression models in survival analysis are the proportional hazards models introduced by Cox (1972) and the class of log-linear, or accelerated failure time models. Let \( X \) be a continuous event time, and \( z = (z_1, z_2, ..., z_p) \) be a \( p \)-vector of fixed covariates, and \( h (x \mid z) \) denote the hazard function at time \( x \) among individuals with the covariates \( z \). The proportional hazards models assume that the covariates \( z \) affect the hazard function in a multiplicative manner according to

\[
h (x \mid z) = h_0 (x) \exp (\beta z) \tag{2.3.1}
\]

where \( h_0 (x) \) is an unspecified function of \( x \) and \( \beta = (\beta_1, \beta_2, ..., \beta_p) \) is a \( p \)-vector of regression parameters. On the other hand, the accelerated failure time models assume that the covariates \( z \) act multiplicatively on the failure time itself (or linearly on log scale of the failure time) rather than multiplicatively on hazard function. Suppose that \( X_0 = X \exp (\beta z) \), and that \( X_0 \) has a fixed hazard function \( h(x_0 \mid z) \) at time \( x_0 \). Then the hazard function for the failure time \( X \) is given by
\[ h(x \mid z) = h_0(x \exp(\beta \cdot z)) \exp(\beta \cdot z) \] (2.3.2)

In the sequel I will review the existing methods for the estimation of regression parameters under both models.

To fix ideas, let \( t_1, t_2, \ldots, t_n \) be the observed times on study of \( n \) individuals, and \( I_1, I_2, \ldots, I_n \) denote the corresponding censoring indicators where right censoring and failure time processes are independent. Suppose that there are no ties among the death times and \( z_1, z_2, \ldots, z_n \) are the recorded covariates associated with the observed pairs \((t_1, I_1), (t_2, I_2), \ldots, (t_n, I_n)\), respectively, where \( z_i = (z_{i1}, z_{i2}, \ldots, z_{ip}) \), for \( i = 1, 2, \ldots, n \). Williams and Lagakos (1977), and Kalbfleisch and Mackay (1979) showed that the likelihood based on the data \((t_i, I_i)\) is proportional to

\[ L = \prod_{i=1}^{n} f_x(t_i \mid z_i)^{I_i} S_x(t_i \mid z_i)^{1-I_i}, \text{ or equivalently,} \]

\[ L = \prod_{i=1}^{n} h_x(t_i \mid z_i)^{I_i} S_x(t_i \mid z_i). \] (2.3.3)

where \( f_x(x \mid z) \) is the density function of \( X \) conditioning on \( z \), \( S_x(x \mid z) \) is the survival function, and \( h_x(x \mid z) \) is the hazard function. For simplicity, we will suppress the subscript \( x \) in the following.
2.3.1 Fixed Covariates

Parametric Approach

If \( h(x \mid z) \) is specified up to a finite number of parameters \( \theta \) (including the regression coefficients \( \beta \)), ordinary parametric likelihood methods can be applied to (2.3.3). It should be noted, however, that the presence of censoring, except in a few extremely special cases, precludes the possibility of tractable exact distribution theory. So we rely heavily on maximum likelihood large-sample theory for making the inferences about \( \beta \). For example, standard asymptotic likelihood methods would ascribe an asymptotic normal distribution to the maximum likelihood estimator \( \hat{\theta} \) with mean vector the 'true' value of \( \theta \) and variance-covariance matrix \( I^{-1}(\hat{\theta}) \) where \( I(\theta) = -\frac{\partial^2 \ln L}{\partial \theta^2} \) is the observed Fisher information matrix and \( I^{-1} \) denotes its inverse matrix. Readers can refer to the book by Cox and Oakes (1984) or the book by Lawless (1982) for further details on the theory.

One parametric model that has found extensive applications is the two-parameter Weibull regression model given by (2.3.1) with \( h_0(x) = \alpha \lambda^x \alpha^{-1} \) (Pike, 1966; Peto and Lee, 1973; and Nelson, 1972a). It is of some interest to note that this model is in the intersection of the proportional hazards models and accelerated failure time models and further it may be shown that any model with a continuous distribution in this intersection has the hazard function \( h_0(x) \) of the Weibull type. Thus, the Weibull regression model is uniquely characterized as that model in which regression variables act multiplicatively both upon the hazard function and upon the failure time itself. The asymptotic theory mentioned above is
readily applied to the Weibull regression model. Simple algebra shows that the Weibull regression model can be rewritten as \( \ln X = (-\ln \lambda) - \left(\frac{\beta}{\alpha}\right) z + \left(\frac{1}{\alpha}\right) e \) where \( e \) is the 'error' variable with an extreme value density given by \( f(e) = \exp(e - \exp(e)), -\infty < e < \infty \). The minus sign in front of \( \left(\frac{\beta}{\alpha}\right) z \) arises because (2.3.1) is a model for risk and (2.3.2) is a model for failure time and higher risk implies shorter lifetime.

Other parametric special cases of (2.3.2) include log-normal (Glasser, 1965; Nelson and Hann, 1972, 1973; Whittemore and Altschuler, 1976), log-logistic (Bennett, 1983) and the generalized gamma regression models (Farewell and Prentice, 1977) corresponding to error quantities that are normal, logistic and the logarithm of gamma, respectively.

**Semiparametric Approach**

**Cox's Proportional Hazards Models**

If \( h_0(x) \) in (2.3.1) is an arbitrary nonnegative function of \( x \), a modified likelihood function for \( \beta \) is needed for the estimation. Before we review various ideas of constructing such a likelihood, we first introduce some notations and consider an alternative derivation of the likelihood function (2.3.3).

Let \( t(1) < t(2) < ... < t(d) \) denote the \( d = \sum_{i=1}^{n} I_i \) ordered death times in the sample size \( n \). Let \( z(i) \) denote the \( p \)-vector of covariates associated with \( t(i) \) and let \( \mathcal{R}(t(i)) \) be the set of labels of individuals at risk just prior to \( t(i) \). Let \( E_i \) be the label
of the subject who fails at \( t(i) \) and let \( F_i \) be the event that describes the observed process up to time \( t(i) \) including all failure, censoring, and covariate information as well as the information a failure occurs at \( t(i) \). The full likelihood of all the data may then be written as

\[
L_1 = \prod_{i=1}^{d} P_r(E_i | F_i) \prod_{i=1}^{d+1} P_r(E_i | E_{i-1}, F_{i-1})
\]  
\[
\text{(2.3.4)}
\]

where \( E_0, F_0 \) give the history to time 0 and \( F_{d+1} \) the history to time \( \infty \).

It is convenient to treat first the case of no censoring. Note that in this case \((E_1, E_2, ..., E_n)\) and \((t(1), t(2), ..., t(n))\) are jointly equivalent to the original data. Cox (1972) gave a rather informal justification of a so-called 'conditional likelihood' function for \( \beta \). He argued that when \( h_0(x) \) is unspecified, \( t(i) \) can provide little information or no information about \( \beta \), for their distribution will depend heavily on \( h_0(x) \). Attention must, therefore, focus on the \( E_i \)'s. He suggested using \( \prod_{i=1}^{n} P_r(E_i | F_i) \) as a likelihood function for \( \beta \) where \( P_r(E_i | F_i) \) is the conditional probability that the subject \( E_i \) fails at \( t(i) \) given that one individual from the risk set \( \mathcal{R}(t(i)) \) fails at \( t(i) \), which is simply

\[
P_r(E_i | F_i) = \frac{\exp(\beta z(i))}{\sum_{l \in \mathcal{R}(t(i))} \exp(\beta z(l))}.
\]  
\[
\text{(2.3.5)}
\]
By definition $P_r (E_i \mid F_i) = P_r (E_i \mid t(1), t(2),..., t(i), E_1, E_2, ..., E_{i-1})$ and notice from (2.3.5) that $P_r (E_i \mid F_i)$ is functionally independent of $t(1), t(2),..., t(i)$. Therefore we know that $P_r (E_i \mid F_i)$ is equal to $P_r (E_i \mid E_1, E_2, ..., E_{i-1})$ which leads to

$$
\prod_{i=1}^{n} P_r (E_i \mid F_i) = P_r (E_1, E_2, ..., E_n)
$$

where $P_r (E_1, E_2, ..., E_n)$ is just the marginal likelihood of the rank vector $(E_1, E_2, ..., E_n)$. Kalbfleisch and Prentice (1973) argued this rank vector is marginally sufficient for the estimation of $\beta$ by a group invariance argument. Notice that the marginal likelihood of the rank vector can also be obtained by omitting $\prod_{i=1}^{n} P_r (E_i \mid E_{i-1}, F_{i-1})$ from the full likelihood. Cox (1975) called this product a partial likelihood based on $(E_1, E_2, ..., E_n)$. The omitted term contains the information provide by the gaps between successive failures.

From the likelihood function (2.3.3), Johansen (1983) showed that the Cox's partial likelihood for $\beta$ is a partially maximized likelihood for $\beta$ (or a profile likelihood for $\beta$). This is derived as follows:

step 1: Fix $\beta$. To maximize $L$, $h_0(x)$ should at least have nonzero values at failure times $t(i)$. Let $h_0(t(i)) = h_i$, $i = 1, 2, ..., n$.

step 2: To maximize $L$ we should also make

$$
\sum_{i=1}^{n} t(i) \int_{u=0}^{t(i)} h_0(u) \exp (\beta z(t)) \, du
$$

as small as possible. Therefore we should assign zero to $h_0(x)$ at $x \in \{t(1), t(2),..., t(n)\}$. 
step 3: From steps 1 and 2 we solve the equations \( \frac{\partial \ln L}{\partial h_i} = 0, \ i = 1,2,\ldots,n \). It can be shown that the estimate of \( h_i \) is given by

\[
\hat{h}_i = \frac{1}{\sum_{l \in \mathcal{R}(t(i))} \exp (\beta z(i))}
\]

(2.3.6)

step 4: Substitute (2.3.6) for each \( h_i \) in (2.3.3). We can see that the resulting profile likelihood for \( P \) is proportional to the Cox's partial likelihood for \( \beta \).

With right censored data, a partial likelihood for \( \beta \) is given by

\[
L_2(\beta) = \prod_{i=1}^{d} \frac{\exp (\beta z(i))}{\sum_{l \in \mathcal{R}(t(i))} \exp (\beta z(i))}
\]

Kalbfleisch and Prentice (1973) showed that \( L_2(\beta) \) is the marginal probability of possible underlying rank vectors consistent with the observed data (or so-called generalized rank vectors). Suppose, for example, that the subjects 1, 2, 3, 4 are observed to have times on study 40, 10, 20+, 30, respectively, where + indicates a censored observation. Then the possible underlying rank vectors, on the basis of this data, are (2, 3, 4, 1) (i.e., \( X_2 < X_3 < X_4 < X_1 \)), (2, 4, 3, 1), and (2, 4, 1, 3), and the marginal probability of all these rank vectors is given by \( P_r (X_2 < X_4 < X_1, X_3 > X_2) \). \( L_2 (\beta) \) can also be obtained by using the profile
likelihood construction outlined above. With censored data, in order to maximize $L$ we should assign nonzero values to $h_0(x)$ only at uncensored observations.

Cox (1975) argued informally that ordinary maximum likelihood large sample properties still holds for the partial likelihood $L_2(\beta)$ under relatively mild conditions. This was proven to be the case by Anderson and Gill (1982) through formulating the Cox's model in terms of a counting process with a multiplicative intensity structure (Aalen, 1978). Efron (1977) and Oakes (1977) both showed that the maximum likelihood estimator (MLE) of $\beta$ obtained from $L_2(\beta)$ has full asymptotic efficiency under conditions which are likely to be satisfied in many realistic situations.

**Accelerated Failure Time Model**

Accelerated failure time models are akin to ordinary linear regression models. They take the form

$$Y = \mu + \beta z + \sigma e,$$

where $Y = \ln X$, $-\infty < \mu < \infty$, $\sigma > 0$, and the error term $e$ is free of any unknown parameters. If the distribution of the error term $e$ is unspecified, ordinary least squares estimation can be applied to obtain estimates of $\mu$ and $\beta$ provided that the survival time $X$ is free of censoring. Such estimates minimizes $\sum_{i=1}^{n} (y_i - \mu - \beta z_i)^2$. This is equivalent to minimizing $\int_{-\infty}^{\infty} u^2 d\hat{F}_n(u)$ where $\hat{F}_n$ is the empirical
distribution function of \( u_1, u_2, \ldots, u_n \) where \( u_i = y_i - \mu - \beta z_i \). With censoring present, Miller (1976) proposed to replace \( \hat{F}_n \) by the Kaplan-Meier estimator. For simplicity, he considered the case of one covariate (i.e. \( p = 1 \)). Let \( Y_T \) be the logarithm of the time on study (i.e. \( Y_j = \ln T \)), and \( \hat{F}_{KM}(u_T) \) be the Kaplan-Meier estimator based on \( (u_{T_1}, I_1), (u_{T_2}, I_2), \ldots, (u_{T_n}, I_n) \) where \( u_{T_i} = y_{T_i} - \mu - \beta z_i \).

Then in censoring case the least squares estimates minimize \( \sum_{i=1}^{n} \int_{-\infty}^{\infty} u_T^2 \ d\hat{F}_{KM}(u_T) \)

which is equal to

\[
\sum_{i=1}^{n} \hat{w}_i(\beta) (y_{T_i} - \mu - \beta z_i)^2
\]

(2.3.8)

where the weights \( \hat{w}_1, \hat{w}_2, \ldots, \hat{w}_n \) are the jumps of the Kaplan-Meier estimator which depend only on \( \beta \). If the largest observation is censored, change it to be uncensored so that \( \sum_{i=1}^{n} \hat{w}_i(\beta) = 1 \).

To calculate the least squares estimates \( \hat{\mu} \) and \( \hat{\beta} \), we first differentiate (2.3.8) with respect to \( \mu \) and set it equal to zero. We obtain

\[
\hat{\mu} = \sum_{i=1}^{n} \hat{w}_i(\beta) y_{T_i} - \beta \sum_{i=1}^{n} \hat{w}_i(\beta) z_i
\]

We then substitute this expression into (2.3.8). We obtain a function of \( \beta \), say \( H(\beta) \), which can be minimized by a search method. However, it is computationally difficult to do the search in two or more dimensions because \( H(\beta) \) is not continuous. In addition, it is very difficult to study analytically the asymptotic properties of \( \hat{\beta} \).
In light of these difficulties Miller suggested an iterative procedure. Choose the initial estimate of $\beta$ to be the slope of the least-squares line through the uncensored observations. Let $\hat{\beta}(0)$ denote the initial estimate.

Then

$$\hat{\beta}(0) = \frac{\sum_{uc} y_{T_i} (z_i - \bar{z}_{uc})}{\sum_{uc} (z_i - \bar{z}_{uc})^2}$$

where the summation is over uncensored observations only and $\bar{z}_{uc} = \frac{\sum_{uc} z_i}{d}$. With this initial estimate of $\beta$, form

$$u_{T_i}^{(0)} = y_{T_i} - \hat{\beta}(0) z_i, \quad i = 1, 2, \ldots, n. \quad (2.3.9)$$

Let $\hat{F}_{KM}^{(0)}$ be the Kaplan-Meier estimator based on $(u_{T_i}^{(0)}, i_i), \quad i = 1, 2, \ldots, n,$ and let $\hat{w}_i(\hat{\beta}(0)), \quad i = 1, 2, \ldots, n,$ be the jumps of $\hat{F}_{KM}^{(0)}$. Now define the new estimate

$$\hat{\beta}(1) = \frac{\sum_{uc} \hat{w}_i^{*} (\hat{\beta}(0)) y_{T_i} (z_i - \bar{z}_{uc}^{*})}{\sum_{uc} \hat{w}_i^{*} (\hat{\beta}(0)) (z_i - \bar{z}_{uc}^{*})^2} \quad (2.3.10)$$

where $\hat{w}_i^{*} = \frac{\hat{w}_i (\hat{\beta}(0))}{\sum_{uc} \hat{w}_i (\hat{\beta}(0))}$, and $\bar{z}_{uc}^{*} = \sum_{uc} \hat{w}_i (\hat{\beta}(0)) z_i.$

Repeat the computations in (2.3.9) and (2.3.10) until the slope estimates converge. Unfortunately, convergence does not always occur. The sequence of the slope
estimates may become trapped in a loop where they oscillate between two values, in which case we take the average of these two values.

Miller also gave a heuristic argument that shows $\hat{\beta}$ is asymptotically normal with mean $\beta$ and with variance estimated by

$$\text{Var}(\hat{\beta}) = \frac{\sum_{uc} \hat{w}_i^* (\hat{\beta}(0)) (y_{T_i} - \hat{\mu} - \hat{\beta} z_i)^2}{\sum_{uc} \hat{w}_i^* (\hat{\beta}(0)) (z_i - \hat{z}_{uc})^2}.$$ 

Buckley and James (1979) solved the same estimation problem by modifying the least squares normal equations rather than the sum of the squares of residuals proposed by Miller (1976). First, they replaced $y_i$ in normal equations by $y_i^* = y_{T_i} I_i + \hat{E}(Y_i | Y_i > y_{T_i} ) (1 - I_i)$. Then they suggested estimating $\hat{\mu}$ by $\hat{\mu} = \frac{\sum \hat{w}_k u_{T_k}}{1 - \hat{F}_{KM}(u_{T_i})}$. Solving the modified normal equations for $\beta$ we obtain

$$\hat{\beta} = \frac{\sum_{i=1}^{n} \hat{y}_i (z_i - \hat{z})}{\sum_{i=1}^{n} (z_i - \hat{z})^2}$$

(2.3.11)
where \( \hat{y}_i = y_{T_i} I_i + \hat{E} (Y_i | Y_i > y_{T_i}) (1 - I_i) \). We can see an iterative procedure is required to solve (2.3.11). This is an EM algorithm like estimation procedure where in E step the unobservable \( y_i \) is estimated from the data by \( y_i^* \), and then in M step we solve the modified normal equations (2.3.11) for \( \beta \). Like the Miller's (1976) approach, the sequence of estimates of \( \beta \) may eventually oscillate between two values, and again we take the average of these two values.

Buckley and James (1979) also gave an asymptotic normality results for their estimators. The variance estimator is

\[
\text{Var} (\hat{\beta}) = \frac{(\sigma_{uc})^2}{\sum_{uc} (z_i - \tilde{z}_{uc})}
\]

\[
(\sigma_{uc})^2 = \frac{1}{d-2} \sum_{uc} \left( y_{T_i} - \frac{1}{d} \hat{\beta} (z_i - \tilde{z}_{uc}) \right)^2.
\]

Prentice (1978) developed linear rank statistics for testing \( \beta = \beta_0 \) with censored data. Let \( q = y - \beta_0 z \) represent a residual about the hypothesized value. Let \( q(i) < q(2) < ... < q(d) \) denote the ordered uncensored residuals in the sample, \( q(i_1), q(i_2), ..., q(i_m) \) be the right censored residuals in \([q(i), q(i+1))\) for \( i = 0, 1, ..., d \) with \( q(0) = -\infty \) and \( q(d+1) = \infty \), and \( z(i) \) and \( z(i_k) \) represent the covariates associated with \( q(i) \) and \( q(i_k) \), respectively. Let \( R(q) = \{(1), (2), ..., r; ([i_1], (i_2), ..., (i_m))\} \) \( i = 0, 1, 2, ..., d \) where the labels (1), (2), ..., (d) identify uncensored observations from the smallest to the largest and the label \([i_1], (i_2), ..., (i_m)] \) identify censored observations in \([q(i), q(i+1))\) in some arbitrary order. Prentice used the marginal probability of the generalized rank vector \( R(q) \), denoted by \( P_r (R) \), to construct test
statistics for testing $\beta = \beta_0$. $P_r(R)$ can be computed in two steps: first, we calculate the accumulated probability of possible rankings for censored residuals, conditional on the uncensored residuals. It is simply $\prod_{i=1}^{d} \prod_{k=1}^{mi} S_e(\Omega(i) - \gamma z(ik))$

where $\Omega(i) = \frac{Q(i) - \mu}{\sigma}$, $\gamma = \frac{\beta - \beta_0}{\sigma}$, and $S_e$ is the survival function of the error term.

e. Then the marginal probability of $R(q)$, upon unconditioning, is given by

$$Pr(R) = \int_{\Omega(1)<\Omega(2)<...<\Omega(d)} \prod_{i=1}^{d} \prod_{k=1}^{mi} S_e(\Omega(i) - \gamma z(ik)) \, d\Omega(i)$$

(2.3.12)

where $f_e(u) = \frac{dS_e(u)}{du}$. Prentice argued that we can test $\beta = \beta_0$ (or $\gamma = 0$) by using the score statistics $\frac{\partial \ln P_r(R)}{\partial \gamma} |_{\gamma=0}$ based on (2.3.12). Let $\nu_\beta$ denote the score statistics. It can be shown that

$$\nu_\beta = \sum_{i=1}^{d} (z(i) \, sc_i + S(i) \, SC_i)$$

(2.3.13)

where $S(i) = \sum_{k=1}^{mi} z(ik)$, $sc_i$ is a score corresponding to $q(i)$ given by

$$\Omega(1)<\Omega(2)<...<\Omega(d) \left\{ \frac{-d \ln f_e(\Omega(i))}{d\Omega(i)} \right\} \prod_{i=1}^{d} \left\{ n_1 (S_e(\Omega(i)))^{m_1} f_e(\Omega(i)) \, d\Omega(i) \right\}$$

(2.3.14)

and $SC_i$ is a score corresponding to each of the $q(i_1), q(i_2), ..., q(i_m)$ given by
\[ \Omega_i < \Omega_i < \ldots < \Omega_i \text{ for } i = 1, 2, \ldots, d \] 

\[ \prod_{i=1}^d \left\{ n_i \left( S_e(\Omega_i) \right)^{m_1} f_e(\Omega_i) \right\} \]  

where \( n_i = (m_i + 1) + \ldots + (m_d + 1) \) which is the number of individuals with the values of \( q \) known to be equal to or greater than \( q_i \). Let \( b_i = 1 - S_e(\Omega_i) \) for \( i = 1, 2, \ldots, d \) and define for \( 0 < c < 1 \) \( \phi(c) = \frac{-d \ln f_e(u)}{du} \bigg|_{u = S^{-1}(1 - c)} \), and \( \Phi(c) = (1 - c)^{-1} f_e(S^{-1}(1 - c)) \). Then (2.3.14) and (2.3.15) can be written as

\[ s_i = \int_{\Omega_i} \phi(b_i) \prod_{i=1}^d \left\{ n_i (1 - b_i)^{m_1} db_i \right\} \text{, and} \quad S_i = \int_{\Omega_i} \Phi(b_i) \prod_{i=1}^d \left\{ n_i (1 - b_i)^{m_1} db_i \right\} \text{, respectively.} \]  

\[ \text{Special cases of the linear rank statistics (2.3.13) are Peto and Peto's (1972) generalization of the Kruskal-Wallis test statistics and log rank test statistics (Mantel (1966); Cox (1972)) which are obtained by specifying the density function} \]  

\[ f_e \text{ to be a logistic density and an extreme value density, respectively.} \]

In general, (2.3.16) and (2.3.17) are not easy to compute. Prentice suggested the following approximate scores:

\[ s_i = \phi(1 - \hat{s}_{KM}(q_i)), \quad S_i = \Phi(1 - \hat{s}_{KM}(q_i)) \]

where \( \hat{s}_{KM}(q) \) is the Kaplan-Meier estimator based on \( q_i \)’s.
The score statistics $v_\beta$ is asymptotically normal under $\gamma = 0$ and so-called Progressive type II censoring (Crowley, 1974) with mean $0$ and with a variance-covariance matrix that can be consistently estimated by the observed information matrix.

2.3.2 Time Dependent Covariates

Time-dependent covariates can arise in actual survival applications and may be deterministic or random in character. For example, in a simple comparison of two treatments, it may happen that a treatment under study is not applied until some time after the time origin. Then a suitable covariate may be a time-dependent binary covariate that jumps from 0 to 1 at the time of application of the treatment. We can see that this jump is at a fixed time and of a fixed value. In the Framingham Heart Study (Dawber, 1980) blood pressure examinations were performed for the study participants at each examination. These measurements represent the realization of an 'external' process that may affect the chance of having a cardiovascular disease, and their values cannot be determined in advance.

Let $z(u)$ denote a $p$-vector of covariates at time $u$ and $Z(x) = \{z(u); u \leq x\}$ be the whole covariate history up to time $x$. Let the hazard function $h(x \mid Z(x))$ denote the instantaneous risk of failure at time $x$ given that failure has not occurred prior to time $x$ and given that the whole covariate history up to time $x$. If it is assumed that $h(x \mid Z(x))$ depends on $Z(x)$ only through the covariate vector $z(x)$, the proportional hazards model generalizes naturally to
h(x | Z(x)) = h_0(x) \exp (\beta z(x))

with no change in multiplicative interpretation of covariate effects. It h_0(x) is specified to a finite number of parameters we still can use the full likelihood function (2.3.3), where z_i is replaced by z_i(x_i), to make inferences about \beta. If h_0(x) is unspecified, we can use the partial likelihood L_2(\beta), where z(i) is replaced by z(i)(t(i)), to make inferences about \beta. The asymptotic results for partial likelihood estimates by Anderson and Gill (1982), Efron (1977) and Oakes (1977) still hold when time-dependent covariates are present.

Generalizations of the accelerated failure time models (2.3.7) to include time-dependent covariates have received almost no attention at all in statistical literature until very recently (Tsiatis (1991)). In general, the hazard functions (2.3.2) of these models are too complex to be useful when the covariates are time-dependent. In addition, using generalized rank vectors to make inferences about \beta as suggested by Prentice (1978) is no longer possible.

2.3.3 Random Covariates

In Framingham Heart Study (Dawber, 1980) the participants are naturally grouped by family units. As Clayton (1978) pointed out, in epidemiology studies of family tendency in chronic disease the frailty shared between family members should be recognized in the analysis of fixed and/or time-dependent covariates effects on the event times. To this end, he introduced the following frailty model for the bivariate event times (X_1,X_2):
\[ h_j(x \mid z_j, \omega) = h_0j(x) \exp(\beta_j z_j) \omega, \quad j = 1,2, \tag{2.3.18} \]

where \( z_j \) is a \( p \)-vector of fixed covariates associated with the event \( X_j \), \( \beta_j \) is the corresponding regression coefficients, and \( \omega \) is assumed to have the following gamma distribution:

\[
f_G(\omega) = \frac{(1/\delta)(1/\delta) \omega^{(1/\delta - 1)} \exp(-\omega/\delta)}{\Gamma(1/\delta)}, \quad \delta > 0. \tag{2.3.19} \]

He gave a likelihood function based on doubly right censored data from this gamma frailty where \( h_0j(x) \)'s, \( j = 1,2 \), are assumed to be of Weibull hazards.

Clayton and Cuzick (1985) studied the same model where \( h_0j(x) \)'s are unspecified. They developed, following closely the work by Cuzick (1982), likelihood-based estimation procedures using the marginal likelihood of generalized rank vectors. Let \( t_{ij} \), \( i = 1,2,\ldots,n \), \( j = 1,2 \), denote the observed time on study of the \( j^{th} \) individual of the \( i^{th} \) pair, \( I_{ij} \) be the corresponding censoring indicator, and \( z_{ij} \) be the covariates associated with the individual \( (i,j) \). Let \( R_j, j = 1,2 \), denote the generalized rank vector based on the \( j^{th} \) stratum. Applying the transformations \( Q_{ij} = H_0j(t_{ij}) \) where \( H_0j(x) = \int_{u=0}^x h_0j(u) \, du \), they showed that the marginal likelihood of \( (R_1, R_2) \) is given by
$$L_3(\delta, \beta_1, \beta_2)$$

$$= \int \left[ \int \prod_{\omega=0}^{n} \left\{ (\exp(\beta_1 z_{i1}) \omega_{i1})^{l_{i1}} \exp(-\omega_{i1} \exp(\beta_1 z_{i1}) Q_{i1}) dQ_{i1} \right\} \right]$$

$$\times \left[ \int \prod_{(Q_2 \in R_2)}^{n} \left\{ (\exp(\beta_2 z_{i2}) \omega_{i2})^{l_{i2}} \exp(-\omega_{i2} \exp(\beta_2 z_{i2}) Q_{i2}) dQ_{i2} \right\} \right]$$

$$\times \prod_{i=1}^{n} f_G(\omega_i) d\omega_i$$

(2.3.20)

where \( \{Q_j \in R_j\}, j = 1, 2 \), is set of of possible times for the uncensored variables which preserve the order implicit in the generalized rank vector \( R_j \). Using (2.3.20) the score equations for \( (\delta, \beta_1, \beta_2) \) are given by

$$\frac{\partial \ln L_3}{\partial \delta} = \sum_{i=1}^{n} \left( \frac{\partial \ln f_G(\omega_i)}{\partial \delta} \right) \mid R_1, R_2, \text{ and}$$

$$\frac{\partial \ln L_3}{\partial \beta_i} = \sum_{i=1}^{n} E(z_{ij} (I_{ij} - \omega_{ij} Q_{ij} \exp(\beta_j z_{ij}) \mid R_1, R_2)).$$

By some conditioning arguments, it can be shown that

$$\frac{\partial \ln L_3}{\partial \delta} = \frac{1}{\delta^2} \left( \sum_{i=1}^{n} E \left( \frac{1/\delta + D_i}{A_i} \right) \mid R_1, R_2 \right) \mid R_1, R_2$$

$$- n \times (1 - \ln \delta - \Psi(1/\delta))) \tag{2.3.21}$$

$$\frac{\partial \ln L_3}{\partial \beta_j} = \sum_{i=1}^{n} z_{ij} I_{ij} - \sum_{i=1}^{n} z_{ij} \exp(\beta_j z_{ij}) E(Q_{ij} \frac{1/\delta + D_i}{A_i} \mid R_1, R_2) \tag{2.3.22}$$

where \( D_i = \sum_{j=1}^{2} I_{ij}, A_i = 1/\delta + \sum_{j=1}^{2} Q_{ij} \exp(\beta_j z_{ij}) \), and \( \Psi(u) \) is the digamma function $\frac{d \ln \Gamma(u)}{du}$. 

To find the MLE's $\hat{\beta}_j$ and $\hat{\delta}$, Clayton and Cuzick suggested we replace $Q_{ij}$ in (2.3.21), and (2.3.22) by $E(Q_{ij} \mid R_1, R_2)$, denoted by $\bar{Q}_{ij}$, set these equations equal to zeros, and solve iteratively. That is, set $\delta = 0$, compute the estimates of $\beta_j$ from (2.3.22) as in a proportional hazards model, compute $\bar{Q}_{ij}$ using the following iterative approximation with current estimates of $\delta$ and $\beta$:

\[
\bar{Q}_{ij} = \sum \frac{I_{ij}}{Q_{kj}} \leq Q_{ij} \sum \exp (\beta_j z_{1j}) \bar{\omega}_1 \quad \text{and} \\
Q_{kj} \geq Q_{ij} \sum \exp (\beta_j z_{ij}) \bar{\omega}_1 \quad \text{with} \quad Q_{ij} \geq \sum 1/\delta + D_i \\
\bar{\omega}_i = \frac{1}{1/\delta + \sum_{j=1}^{2} \bar{Q}_{ij} \exp (\beta_j z_{ij})}.
\]

Update the estimate of $\delta$ from (2.3.21) with the current estimates of $\beta_j$, and $\bar{Q}_{ij}$ and iterate as necessary.

Once convergence has been obtained, the observed information matrix for the MLE is computed based on the marginal likelihood of the generalized rank vectors $(R_1, R_2)$.

Hougaard (1986b) studied the positive stable frailty model (2.1.13) where covariates are not included. He found estimators of the dependence parameter $\theta$ when the margins are Weibull, as well as by a two stage estimation procedure for the nonparametric model. In the first stage of the two-stage estimation procedure one ignores dependence and estimates the integrated hazards of the marginal...
distributions by the Nelson-Aalen estimator (Nelson 1972b; Aalen, 1978). In the second stage one uses these estimated marginal distributions to find the profile likelihood estimator of the stable dependence parameter. Hougaard (1991) used data on Danish Twins to compare various frailty models based on this two-stage nonparametric procedure.

Motivated by the well-known formulation of Cox regression model in terms of a counting process with multiplicative intensity structure, Self and Prentice (1986) formulated the frailty model as follows.

Let \( N_{ij}(t) \) denote the counting process that counts failures observed in the \( j^{th} \) subject \((1 \leq j \leq n)\) in the \( i^{th} \) group \((1 \leq i \leq G)\) up to time \( t \), and \( Z_{ij}(t) = \{z_{ij}(u); 0 \leq u \leq t\} \) denote a \( p \)-vector of covariate processes available about subject \((i, j)\) up to time \( t \). Let \( F_t \) be the increasing right continuous family of \( \sigma \)-fields generated by failure, censoring and covariate histories of all individuals under study prior to time \( t \), denoted by \( t^- \). It is assumed that the counting process \( N_{ij}(t) \) has a multiplicative intensity structure with respect to \( F_t \circ \sigma(\omega_1, ..., \omega_G) \) given by (assuming \( Z_{ij}(t) \) is a function of \( z_{ij}(t) \) only)

\[
Y_{ij}(t) h_0(t) \exp (\beta z_{ij}(t)) \omega_i
\]

where \( Y_{ij}(t) \) is the predictable process with respect to \( F_t \) that takes value one if subject is under observation at time \( t \) and takes value zero otherwise, and
\( \sigma(\omega_1, \ldots, \omega_Q) \) is the \( \sigma \)-field generated by the \( \omega_i \)'s. It follows from the innovation theorem (Aalen, 1978) that the intensity process with respect to \( F_t \) is given by

\[
Y_{ij}(t) h_0(t) \exp (\beta z_{ij}(t)) E (\omega_i \mid F_t).
\]

Simple algebra shows that

\[
E (\omega_i \mid F_t) = \frac{E (\omega (\tilde{N}_i (t) + 1) \exp (- \tilde{C}_i (t) \omega))}{E (\omega \tilde{N}_i (t) \exp (- \tilde{C}_i (t) \omega))}
\]

where \( \tilde{N}_i (t) = \sum_{j=1}^n N_{ij}(t) \) and \( \tilde{C}_i (t) = \sum_{j=1}^n \int_{u=0}^t y_{ij}(u) \exp (\beta_j z_{ij}(u)) h_0(u) \, du \).

Using the estimation procedure as described in Prentice and Self (1983) for Cox regression models with general relative risk form they suggested the following estimating equations for \( \delta \), and \( \beta \) (and \( H_0(t) \)):

\[
0 = \left\{ \begin{array}{l}
1 \\
0
\end{array} \right\} \sum_{i=1}^G \sum_{j=1}^n \left[ U'_{ij}(t) - \frac{\sum_{r=1}^G \sum_{m=1}^n Y_{rm}(t) \exp \{ \beta z_{rm}(t) + M_r(t) \} U'_{rm}(t) - \sum_{r=1}^G \sum_{m=1}^n Y_{rm}(t) \exp \{ \beta z_{rm}(t) + M_r(t) \} dN_{ij}(t) \right] \text{and}
\]

(2.3.23)
\[
H_0(t) = \int_0^t \frac{\sum_{i=1}^G \sum_{j=1}^n dN_{ij}(s)}{\sum_{r=1}^G \sum_{m=1}^n Y_{rm}(s) \exp\{\beta z_{rm}(s) + M_r(s)\}}, \quad t \in [0, 1] \tag{2.3.24}
\]

where \( M_i(t; \delta, \beta, H_0) = \ln \mathbb{E}[W_i | F_t] \), and \( U'_{ij}(t) = \left[ \frac{\partial M_i(t)}{\partial \delta} z_{ij} + \frac{\partial M_i(t)}{\partial \beta} \right] \).

Calculations of the estimates of \((\delta, \beta)\) can be accomplished by iteration between (2.3.23) and (2.3.24).

Gill (1985) in his brief discussion of Clayton and Cuzick's paper suggested an alternative estimation procedure that uses EM algorithm (Dempster et al., 1977) to extend the partial likelihood techniques described in Cox (1972). In this procedure, one starts with the augmented log likelihood and the E step involves a computation of the expectation of this log likelihood with respect to observable data. Assuming the dependence parameter \( \delta \) were known, the E step yields

\[
2 \sum_{j=1}^2 \left\{ \sum_{i=1}^n I_{ij} (\beta_j z_{ij} + \ln h_{oij}(t_{ij})) - \sum_{i=1}^n H_{oij}(t_{ij}) \exp (\beta_j z_{ij}) \omega_i \right\}
\]

where \( \omega_i = \mathbb{E} (\omega_i | \text{Data, current estimates of } \delta \text{ and } \beta) \). In the M-step a partial likelihood is constructed for estimation of the covariate effects using a profile likelihood technique suggested by Johansen (1983) (see steps 1-4 on p29). The resulting partial likelihood for the covariate effects, in the case of gamma frailties, is similar to the standard Cox partial likelihood and standard estimation programs can
be used. One then iterates between these two steps. Klein (1991) implemented this procedure to the gamma frailty model with no stratification and unequal group sizes. Nielsen et al. (1991) gave a rigorous justification of this EM algorithm approach based on counting processes.

Clayton (1991) recently studied a Bayesian approach to the estimation of the dependence parameter and regression coefficients in the gamma frailty model. He implemented a Gibbs sampling algorithm (Gelfand et. al., 1990) to compute the posterior mode of the dependence parameter and regression coefficients.
A common assumption made in modelling the effects of treatment or of potential risk factors on survival is that the event times of the members of the population are, conditional on the observed covariates, statistically independent. In practice it may be the case that the event times of individuals in some subgroups of the population are associated because members of these groups share a common unobserved trait. In animal studies one may have an association between deaths times among little mates or among cage mates, while in human studies there may be an association in the times to events such as cancer, cardiovascular disease, or death between siblings and/or husbands and wives. If these associations are ignored the estimates of covariate effects are suspect. Clayton and Cuzick (1985) model such associations by incorporating a random effect, $\omega$, into the popular Cox proportional hazards model (Cox, 1972) for the analysis of covariate effects. It is assumed that this random effect, $\omega$, commonly called a frailty (Vaupel et al., 1979), acts multiplicatively on hazard rate.
Estimation of the parameters of such frailty models, when there are no covariates, has been developed by several researchers for the bivariate case. Based on a gamma model for $\omega$, Clayton (1978) finds maximum likelihood estimators based on type I censored samples when, conditional on $\omega$, the marginal survival function of $k$th member of a subgroup, $S_k(\cdot)$, follows an exponential or Weibull model. Oakes (1982) discusses estimation when $S_k(\cdot)$ are exponential and there is no censoring. Lee and Klein (1988) consider maximum likelihood estimators and estimators based on a total time on test statistics for the exponential case. Hougaard (1986b) has found estimators based on modelling $\omega$ by the stable distribution when the margins are Weibull, as well as by a nonparametric procedure.

A recent paper by Klein et al. (1991) discusses maximum likelihood estimation based on modelling $\omega$ both by gamma distributions and by positive stable distributions when, conditional on $\omega$, $S_k(\cdot)$ are Weibull. They set up their model to allow unequal group sizes, but no stratification.

Clayton and Cuzick (1985) have considered estimation of the frailty parameter and covariate effects by using an approximate EM algorithm in the bivariate case. Two strata are included in each subgroup of size 2. The frailty, $\omega$, is assumed to follow a gamma distribution. Their method replaces the actual observations with expected order statistics computed under an assumed parametric model for the generalized rank vectors. In computing the expected order statistics the current estimate of $\omega$ is used. The likelihood is then maximized assuming the
Gill (1985) in his brief discussion of Clayton and Cuzick's paper suggests an alternative estimation procedure that uses EM algorithm (Dempster et al., 1977) to extend the partial likelihood techniques described in Cox (1972). In this procedure, one starts with the full likelihood and the E step involves a computation of the expectation of this likelihood with respect to observable data. In the M-step a partial likelihood is constructed for estimation of the covariate effects using a profile likelihood technique suggested by Johansen (1983). The resulting partial likelihood for the covariate effects, in the case of gamma frailties, is similar to the standard Cox partial likelihood and standard estimation programs can be used. One then iterates between these two steps. Klein (1991) has applied this procedure to the gamma frailty model with no stratification and unequal group sizes. Nielsen et al. (1991) gives a rigorous justification of this EM algorithm approach based on counting processes.

Self and Prentice (1986) have studied some frailty models of special form, which include the gamma frailty model as a special case, with no stratification and equal group sizes. They have approached the estimation problem from a counting process point of view. In their formulation the intensity process of an individual in the ith subgroup is a random multiple of the usual Cox intensity process. Their estimation procedure first replaces this random effect by its expectation given the history generated by the failure and censoring process. A likelihood function is then
constructed using this expected intensity process. This likelihood is a function of
the baseline intensity, which is estimated by a modified Nelson-Aalen (1972b)
estimator. Estimation proceeds by iterating between the solution of the likelihood
equations based on the current estimate of the baseline intensity and estimation of
the intensity using the current estimates of frailty and regression coefficients.

In Section 3.1 we will apply the semiparametric approaches proposed by
Clayton and Cuzick (1985), Klein (1991), and Self and Prentice (1986) to the
gamma frailty model with multiple stratifications and unequal stratified group sizes.
Strata are included to accommodate covariates whose different levels produce
hazard functions that differ markedly from proportionality
(Kalbfleisch and Prentice, 1980, Sections 4.4-4.5). In Section 3.2 we will assume
that, conditional on $\omega$, the margins are Weibull, and discuss maximum likelihood
estimation of the dependence parameter and regression coefficients.

3.1 Semiparametric Estimation

Suppose that we have data on the event times and covariate values of $n$
individuals from some population. Our sample consists of $n_{gj}$ individuals from the
gth group ($1 \leq g \leq G$), and jth stratum ($1 \leq j \leq S$) where $n_{gj} \geq 0$, and $\sum_{j=1}^{S} n_{gj} \geq 1$.
Individuals within the gth subgroup have dependent event times due to some
unobserved covariate information summarized in a frailty, $\omega_g$. If, in a human study,
one groups together siblings, then $\omega_g$ may reflect the combined effect of common
genes and/or the shared early environmental effect on survival of all children of a
given family. If one grouped together married couples, the \( \omega_g \) may represent the shared environmental effect later in life on the survival of husband and wives. Note that in this formulation subgroups of size one are allowed and in such a case that individual is still effected by his own frailty.

For the \( k \)th individual \((1 \leq k \leq n_{gj})\) in the \( g \)th group and the \( j \)th stratum let \( t_{gjk} \) denote their observed time on study, and \( I_{gjk} \) be the observed censoring indicator \((I_{gjk} = 1 \text{ if } t_{gjk} \text{ is a death}; \ I_{gjk} = 0 \text{ otherwise})\). Suppose that the censoring is noninformative. Let \( z_{gjk} = (z_{gjk1}, z_{gjk2}, \ldots, z_{gjkp}) \) denote potential covariates associated with this individual. Some of the \( z_{gjkp} \)'s may be the same for all group members (for example, age of home, age of parents, number of children, years married, diet, etc.) and some of the \( z_{gjkp} \)'s may be specific to the \( g \)th subgroup or \( j \)th stratum member (for example, age, smoking behavior, smoking behavior of partner, etc.). Suppose that, conditional on the frailty, \( \omega_g \), the hazard rate for this individual is of the form \( h_j(x | z_{gjk}, \omega_g) = h_{0j}(x) \exp\{\beta z_{gjk}\} \omega_g \), where \( h_{0j}(x) \) is an arbitrary baseline hazard function associated with the \( j \)th stratum and \( \beta \) is a vector of unknown parameters. Also we assume that \( \omega_g \)'s are independent and identically distributed gamma variates with density given by

\[
f_G(\omega) = \frac{(1/\delta)(1/\delta) \omega^{(1/\delta - 1)} \exp(-\omega/\delta)}{\Gamma(1/\delta)}, \quad \delta > 0. \tag{3.1.1}
\]
For this model the joint survival function for the individuals in the gth group is

\[
P[X_{gjk} > t_{gjk}, j = 1,...,S; k=1,...,n_{gjk} | z_{gjk}, j = 1,...,S; k=1,...,n_{gjk}] = \left\{1 + \delta \sum_{j=1}^{S} \sum_{k=1}^{n_{gjk}} H_{oj}(t_{gjk}) \exp{\{\beta z_{gjk}\}} \right\}^{-1/\delta}
\]  

(3.1.2)

where \(H_{oj}(x) = \int_{0}^{\infty} h_{oj}(u) \, du\). The association between individuals in the gth group, measured by Kendall's \(\tau\), is \(\frac{\delta}{\delta + 2}\) so the strength of association is monotone increasing in \(\delta\), with \(\delta = 0\) corresponding to independence between group members. Note that when \(\delta = 0\) the \(\omega_g\)'s are 1 with probability one.

To estimate the parameters of this model, \(\delta\) and \(\beta\), we proceed with an approximate EM algorithm based on the marginal likelihood of generalized rank vectors (Clayton and Cuzick, 1985), an EM algorithm based on a profile likelihood construction (Gill, 1985; Klein, 1991), and an EM like algorithm applied to a partial likelihood constructed by a counting process (Self and Prentice, 1986).

### 3.1.1 Generalized Rank Vectors

Clayton and Cuzick (1985) proposes an approximate EM algorithm that has the generalized rank vectors (Kalbfleisch and Prentice, 1973) as the incomplete data and the unobservable frailties \(\omega_g\)'s as the missing information. For clarity, we first study the application of this algorithm to the submodel with one stratum, \(S = 1\). Let \((t_{gk}, l_{gk}, z_{gk})\) \((g = 1,...,G, k = 1,...,n_{g})\) denote the observed data, and let's
assume no ties among observed failure times for the moment. Suppose that $d$ items labeled \((1), \ldots, (d)\) give rise to observed failure times $t_(1) < \ldots < t_(d)$ with corresponding covariates $z_(1), \ldots, z_(d)$, and associated unobservable frailties $\omega_(1), \ldots, \omega_(d)$. Suppose further that $m_i$ items with covariates $z_(i1), \ldots, z_(im_i)$, and unobservable frailties $\omega_(i1), \ldots, \omega_(im_i)$, are censored in the $i$th interval $[t_(i), t_(i+1))$, $i = 0, 1, \ldots, d$, where $t_(0) = 0$ and $t_(d+1) = \infty$. The corresponding generalized rank vector $R$ is the set of all rank vectors one could obtain by assigning the unobserved failure times all possible positions consistent with observed failure times. This set of possible rank vectors can be characterized by the following set of inequality:

\[
 t_(1) < \ldots < t_(d) \\
 t_(i) < t_(i1), \ldots, t_(im_i), i = 0, 1, \ldots, d.
\]

where $t_(i1), \ldots, t_(im_i)$ are the unobserved failure times associated with individuals censored in $[t_(i), t_(i+1))$. Kalbfleisch and Prentice (1973) show that given the frailties $\omega_g$'s the probability of the generalized rank vector $R$ is

\[
 \int_0^\infty \int_0^\infty \int_0^\infty \prod_{i=1}^d \left[h_0(t_(i)) \exp(\beta z_(i)) \omega_(i) \exp(- \exp(\beta z_(i)) \omega_(i) H_0(t_(i)))\right] \eta(t_(i)) dt_(d) \ldots dt_(1) (3.1.1.1)
\]

where $\eta(t_(i)) = \exp\left[ - \sum_{j=1}^{m_i} \exp\{\beta z_(ij)\} \omega_(ij) H_0(t_(i))\right]$. Let $Q^i = H_0(t_(i))$. The above integral can be rewritten as
where \( \Lambda^i = \exp(\beta z_{(i)}) \omega(i) + \sum_{j=1}^{m_j} \exp(\beta z_{(j)}) \omega_j^i \). Multiplying (3.1.1.2) by the joint density of \( \omega_g \)'s and integrating over \( \omega_g \)'s gives the marginal probability of \( R \)

\[
\int_0^\infty \int_0^1 \cdots \int_0^1 \left\{ \prod_{i=1}^d \exp \left\{ \beta z_{(i)} \right\} \omega(i) \exp \left\{ - Q^i \Lambda^i \right\} \right\} dQ^d \cdots dQ^1
\]

(3.1.1.3)

Let's denote the logarithm of the marginal probability of \( R \) by \( L_T \). A natural approach to estimation of the frailty parameter and regression coefficients is to find the maximum likelihood estimators, (\( \hat{\delta}, \hat{\beta} \)), based on the marginal rank log likelihood \( L_T \). It can be easily shown that the score function for the \( \delta \) is

\[
\frac{\partial L_T}{\partial \delta} = \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g)}{\partial \delta} | R \]

(3.1.1.4)

Also

\[
\frac{\partial \ln f_G(\omega_g)}{\partial \delta} = (-1/\delta^2) (1 - \ln(\delta)) \cdot \Psi'(1/\delta) + \ln \omega_g - \omega_g.
\]

Recall that \( \Psi(\kappa) \) is the digamma function.
Simple algebra shows that the score function for $\beta$ is

$$\frac{\partial L_r}{\partial \beta} = \sum_{i=1}^{d} E(z(i) - Q^i (\partial \Lambda^i / \partial \beta) \mid R) \quad (3.1.1.5)$$

Slightly abusing notation here, we let $Q_{gk} = Q^i$ if $t(i) \leq t_{gk} < t(i+1)$. The score function (3.1.1.5) for $\beta$ can be rewritten as

$$\sum_{g=1}^{G} \sum_{k=1}^{n_g} z_{gk} E(I_{gk} - \omega_g Q_{gk} \exp{\beta z_{gk}} \mid R) \quad (3.1.1.6)$$

Let $Q = (Q^1, ..., Q^d)$. First, note that it is a simple algebraic fact that given $(Q, R)$ the density of $\omega_g$ is proportional to the joint density of $\omega_g$ and the components of $(Q, R)$ from group $g$ with proportionality constant not dependent on $\omega_g$. From (3.1.1.2) it can be easily seen that given $\omega_g$ the density of the components of $(Q, R)$ from group $g$ is equal to

$$\prod_{k=1}^{n_g} \left[ \exp{\beta z_{gk}} \omega_g \right]^{I_{gk}} \exp[- Q_{gk} \exp{\beta z_{gk}}] \omega_g. \quad (3.1.1.7)$$

Multiplying (3.1.1.7) by the density (3.1.1) of $\omega_g$, and collecting terms that contain $\omega_g$ yields that given $(Q, R)$ the density of $\omega_g$ is proportional to

$$(\omega_g)^{(1/\delta_D + D_g) - 1} \exp[- A_g \omega_g] \quad (3.1.1.8)$$
where $D_g = \sum_{k=1}^{n_g} I_{gk}$, and $A_g = 1/\delta + \sum_{k=1}^{n_g} Q_{gk} \exp(\beta z_{gk})$. The proportionality constant that makes (3.1.1.8) a probability density function is simply $\frac{(A_g)(1/\delta + D_g)}{\Gamma(1/\delta + D_g)}$. So given $(Q, R)$ the density of $\omega_g$ is a gamma density with the shape parameter $1/\delta + D_g$ and the scale parameter $A_g$. Using this fact and the conditional arguments that $E[\omega_g | R] = E\{E[\omega_g | Q, R] | R\}$, and similarly, $E[\ln \omega_g | R] = E\{E[\ln \omega_g | Q, R] | R\}$, we can show that the score functions (3.1.1.4) and (3.1.1.6) are equal to

$$
(-1/\delta^2) \left\{ G \times (1 - \ln \delta - \Psi(1/\delta)) + \sum_{g=1}^{G} E(\Psi(1/\delta + D_g) - \ln A_g - \frac{1/\delta + D_g}{A_g} | R) \right\}, \text{and}
$$

(3.1.1.9)

$$
\sum_{g=1}^{G} \sum_{j=1}^{n_g} z_{gk} E[I_{gk} - \frac{1/\delta + D_g}{A_g} Q_{gk} \exp(\beta z_{gk}) | R], \text{respectively.}
$$

(3.1.1.10)

Following Clayton and Cuzick (1985) we replace each $Q_{gk}$ in (3.1.1.9) and (3.1.1.10) by $\bar{Q}_{gk} = E[Q_{gk} | R]$, which by our definition is equal to $\bar{Q}^i = E[Q^i | R]$ if $t(i) \leq t_{gk} < t(i+1)$. We then set the resulting score functions equal to zeros and solve for the estimates of $\delta$, and $\beta$. The expression for $\bar{Q}^i$ is still intractable. As suggested by Clayton and Cuzick, we use the exponential scores $E[Q^i | \bar{\omega}_g, g = 1, ..., G, R]$ to approximate the $\bar{Q}^i$'s, where $\bar{\omega}_g$ is the expected value of the frailty $\omega_g$, given $\bar{Q}, R$. By this approximation $\bar{Q}^i$'s clearly have to be
solved iteratively when $\delta$ and $\beta$ are known or estimated consistently. We can show by some algebra that the exponential scores are

$$\bar{Q}^i \equiv \sum_{u=1}^{G} \frac{1}{\sum_{g=1}^{G} \sum_{k=1}^{n_g} \exp \{ \beta z_{gk} \} \omega_g}, \quad i = 1, \ldots, d. \tag{3.1.1.11}$$

Obviously,

$$\omega_g = \frac{1/\delta + D_g}{1/\delta + \sum_{k=1}^{n_g} \bar{Q}_{gk} \exp \{ \beta z_{gk} \}}, \quad g = 1, \ldots, G. \tag{3.1.1.12}$$

The estimating algorithm proceeds by making initial guess at the values of the parameters. The estimates of $\beta$ obtained from the standard Cox analysis (i.e., $\delta = 0$) seem to be natural candidates. Compute $\bar{Q}^i$ from (3.1.1.11) with the standard Cox's estimates of $\beta$ (note that the resulting $\bar{Q}^i$ is just the Nelson-Aalen estimate of $H_0(t(u))$), compute the estimate of $\delta$ from (3.1.1.9) with the current estimates of $\beta$ and $\bar{Q}^i$ and iterate as necessary.

Once convergence has been obtained, the observed information matrix, $I_r$, for the estimators ($\hat{\delta}$, $\hat{\beta}$) is computed based on the log marginal likelihood of generalized rank vectors. See Section 3.1.4 for some details of this calculation.
If there exist ties among observed failure times, the probability of the generalized rank vector \( R \) is computed by first breaking up the ties. We propose the following modification of (3.1.1.11) to account for such ties:

\[
\bar{Q}^i = \frac{\sum_{u=1}^{i} \frac{d(u)}{\sum_{g=1}^{G} \sum_{k=1}^{n_g} \exp(\beta z_{gk}) \omega_g}}}{d(\bar{u})}, \quad i=1, \ldots, d
\]  

(3.1.1.13)

where \( d(\bar{u}) \) is the number of observed failure times at \( t(\bar{u}) \).

The methodology we have described can be extended in a straightforward fashion to allow for stratification of the baseline hazard rates. Let \( R_j \) (\( j=1, \ldots, S \)) denote the generalized rank vector associated with the \( j \)-th stratum. Given the frailties \( \omega_g \)'s the probability of the generalized rank vectors \( (R_1, \ldots, R_S) \) is the product of the conditional probabilities of the form (3.1.1.2) over the strata. Note that these conditional probabilities contain only the regression coefficients \( \beta \). It is not hard to show then that the score function for \( \beta \) is the sum of the score functions of the form (3.1.1.10) over the strata, and the score function for \( \delta \) is still the form of (3.1.1.9).

The exponential scores of the form (3.1.1.11) should be computed for each stratum. The "imputed frailties" of the form (3.1.1.12) are computed with the shape parameters \( 1/\delta + D_g \) and scale parameters \( A_g = 1/\delta + \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} Q_{gjk} \exp(\beta z_{gjk}) \).

where \( D_g = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} I_{gjk} \).
To summarize the estimation routine proceeds as follows:

Step 1: Using a modified Cox regression program obtain initial estimates of $\beta$ and the exponential scores for each stratum (i.e., letting $\omega_g = 1$)

Step 2: Update $\delta$ from the score equation for $\delta$ with the current estimate of $\beta$ and the exponential scores for each stratum.

Step 3: Update $\beta$ from the score equation for $\beta$ with the current estimate of $\delta$ and the exponential scores for each stratum.

Step 4: Iterate between the exponential scores for each stratum of the form (3.1.1.11) and the "imputed frailties" of the form (3.1.1.12) adjusted for multiple strata with the current estimates of $\delta$ and $\beta$. Iterate until convergence to obtain updated estimates of the exponential scores for each stratum.

Step 5: Iterate between steps 2 and 5 until convergence.

3.1.2 Profile Likelihood Construction

Klein (1991) fits the semiparametric analysis proposed by Cox (1972) into an EM algorithm that has the observed data as the incomplete data and the unobservable frailties $\omega_g$'s as the missing information. We extend his results to allow for stratification of baseline hazard rates. First, note that if we could observe the $\omega_g$'s the augmented log likelihood is, up to a term free of the parameters values, $L_{AUG}(\delta, \beta, H_{Oj}, j = 1, ..., S | \text{data, } \omega_1, ..., \omega_G) = L_1(\delta) + L_2(\beta, H_{Oj}, j = 1, ..., S)$ where
\[ L_1(\delta) = -G \times (\ln \gamma + \Gamma(1/\delta)) + \sum_{g=1}^{G} \left\{ (1/\delta + D_g - 1) \ln \omega_g - \omega_g /\delta \right\}, \text{ and} \]

\[ L_2(\beta, H_{Oj}, j = 1, \ldots, S) = \sum_{g=1}^{G} \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \left\{ I_{gjk}(\beta z_{gjk} + \ln h_{Oj}(t_{gjk}))-H_{Oj}(t_{gjk}) \exp(\beta z_{gjk}) \omega_g \right\}. \]

The estimating algorithm proceeds by first making an initial guess at the values of the parameters. We use the same initial estimates as those suggested in the generalized rank vectors approach. To apply the E-step of the algorithm we can show by arguments similar to those shown in Section 3.1.1 that, conditional on the observed data, the \( \omega_g \)'s are independent gamma variables with shape parameters \( 1/\delta + D_g \) and inverse scale parameters \( B_g = 1/\delta + \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} H_{Oj}(t_{gjk}) \exp(\beta z_{gjk}) \). The resulting Expectation of \( L_{\text{Aug}} \) given the data and the current values of \( (1/\delta + D_g) \) and \( B_g \) is

\[ L(\delta) = L_1(\delta) + L_2(\beta, H_{Oj}, j = 1, \ldots, S) \]

where

\[ L_1(\delta) = G \times \left[ (\ln \gamma + \Gamma(1/\delta)) \right] + \sum_{g=1}^{G} \left\{ (1/\delta + D_g - 1) \left( \gamma(1/\delta + D_g) - \ln B_g \right) \right\} \left( 1/\delta + D_g \right) (1/\delta), \text{ and} \]

\[ (3.1.2.1) \]

\[ L_2(\beta, H_{Oj}, j = 1, \ldots, S) = \sum_{g=1}^{G} \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \left\{ I_{gjk}(\beta z_{gjk} + \ln h_{Oj}(t_{gjk}))-H_{Oj}(t_{gjk}) \exp(\beta z_{gjk}) \left( 1/\delta + D_g \right) \right\}. \]

\[ (3.1.2.2) \]
The M-step of the EM algorithm require the maximization of (3.2.2.1) and (3.1.2.2) with respect to the unknown parameters \( \delta \) and \( \beta \). The updated estimate of \( \delta \) involves maximizing (3.1.2.1) numerically.

To obtain the updated estimate of \( \beta \) maximization of (3.1.2.2) is needed. This log likelihood contains the nuisance baseline hazard rates, \( H_{0j}, j = 1, \ldots, S \). To obtain an appropriate partial likelihood a profile likelihood construction is used. Fixing \( \beta \), by arguments similar to those in Johansen (1983), one can show that the nonparametric estimate of \( H_{0j} \) is

\[
\hat{H}_{0j}(t) = \frac{\sum_{u=1}^{i} d_{j[u]} n_{gj}}{\sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g}, \quad j = 1, \ldots, S \tag{3.1.2.3}
\]

where \( t_{j[u]} \) is the \( u \)th smallest observed failure time in the \( j \)th stratum; \( d_{j[u]} \) is the number of observed failure times at \( t_{j[u]} \); \( \hat{\omega}_g \) is the expected value of the frailty, given the data, associated with the \( g \)th group. Substituting (3.1.2.3) into (3.1.2.2) yields the profile log likelihood, neglecting a constant term,

\[
L_3(\beta) = \sum_{j=1}^{S} \left[ \sum_{i=1}^{d_j} \beta V_{j[i]} - d_{j[i]} \ln \left( \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g \right) \right] \tag{3.1.2.4}
\]

where \( d_j \) is the number of distinct observed failure times in the \( j \)th stratum; \( V_{j[i]} \) is the sum of the covariates vectors of individuals in \( j \)th stratum who die at time \( t_{j[i]} \).
Note that this log partial likelihood is of the form of a usual partial likelihood for the Cox model with the inclusion of an additional covariate \( \ln [\hat{\omega}_g] \) with known coefficient 1. Hence, a standard Cox regression program can be used to obtain the updated estimate of \( \beta \).

To summarize the estimation routine proceeds as follows:

Step 1: Using a modified Cox regression program obtain initial estimates of \( \beta \) and \( H_{Oj} \)'s from (3.1.2.4) and (3.1.2.3), respectively, with \( \hat{\omega}_g = 1 \).

Step 2: Using the current values of \( \delta, \beta, \) and \( H_{Oj} \) (j = 1,...,S) compute \( (1/\delta + D_g) \) and \( B_g \), and \( \hat{\omega}_g \).

Step 3: Update the estimate of \( \delta \) using (3.1.2.1). Update the estimate \( \beta \) (and \( H_{Oj} \)'s) using (3.1.2.4) (and (3.1.2.3)).

Step 4: Iterate between steps 2 and 3 until convergence.

Once convergence has been obtained, the observed information matrix for the maximum likelihood estimators of \( (\delta, \beta) \) is computed based on the observable log likelihood one obtains using the joint distribution of \( (t_{ijk}, I_{ijk}) \). This calculation is similar to that performed by Klein (1991). We record the details in Section 3.1.4.

There are striking similarities between the EM algorithm based on a profile likelihood construction and the approximate EM algorithm based on the marginal rank likelihood; the estimating equations for \( \delta \) and \( \beta \) in both algorithms are the same. For convenience, we only look at the submodel with one stratum, \( S = 1 \), and assume no ties among observed failure times. From (3.1.2.1) we have
\[ \frac{\partial \ln L_1(\delta)}{\partial \delta} = - \frac{1}{\delta^2} \left\{ G \times (1 - \ln \delta - \Psi(1/\delta)) \right. \\
+ \sum_{k=1}^{n_g} \left( \Psi(1/\delta + D_g) - \ln B_g - \frac{1}{\delta + D_g} \right) \left. \right\}. \tag{3.1.2.5} \]

From (3.1.2.3) we have

\[ \hat{h}_0(t) = \sum_{u=1}^{t} \frac{1}{G \sum_{g=1}^{n_g} \sum_{k=1}^{G} \exp(\beta z_{gk}) \hat{\omega}_g}, \text{ if } t(i) \leq t < t(i+1). \tag{3.1.2.6} \]

Substituting (3.1.2.6) into (3.1.2.5) yields (3.1.1.9) with each \( Q_{gk} \) replaced by \( \bar{Q}_{gk} \). From (3.1.2.4) we have

\[ \begin{aligned} \frac{\partial L_3}{\partial \beta} = \sum_{i=1}^{d} \left\{ \frac{G \sum_{g=1}^{n_g} \sum_{k=1}^{G} z_{gk} \exp(\beta z_{gk}) \hat{\omega}_g}{\sum_{g=1}^{n_g} \sum_{k=1}^{G} \exp(\beta z_{gk}) \hat{\omega}_g} \right\}. \tag{3.1.2.7} \end{aligned} \]
It can be easily shown that (3.1.2.7) is equal to

$$
\sum_{g=1}^{G} \sum_{k=1}^{ng} \{ z_{gk} I_{gk} - z_{gk} \hat{\omega}_g \exp(\beta z_{gk} \hat{\Lambda}_{O}(t_{gk})) \}. \quad (3.1.2.8)
$$

Clearly, (3.1.2.8) is (3.1.1.10) with each $Q_{gk}$ replaced by $\bar{Q}_{gk}$.

This argument extends to the case of multiple strata. It also extends to other frailty distributions such as the inverse Gaussian distributions (Hougaard, 1984).

### 3.1.3 Counting Process

Self and Prentice (1986) approach the estimation of $\delta$ and $\beta$ through the Cox proportional hazards model in terms of a counting process (Aalen, 1978) with multiplicative intensity process. Using counting process notation the observed data for the $k$th subject in the $j$th stratum and the $g$th group may be written as $\{Y_{gjk}(t), N_{gjk}(t), Z_{gjk}; t \in [0, 1]\}$. The censoring process $Y_{gjk}(t)$ takes value one if subject $(g, j, k)$ is under observation at time $t$ and takes value zero otherwise. The counting process $N_{gjk}(t)$ counts failure observed in subject $(g, j, k)$ prior to $t$. Let $\{F_t; t \in [0, 1]\}$ be the increasing right continuous family of sub $\sigma$-fields generated by the failure, censoring and covariate histories of all individuals under study prior to time $t$. The Cox-type frailty model in terms of counting process formulation is equivalent to assuming that the intensity process with respect to $F_1 \circ \sigma(\omega_1, ..., \omega_G)$ for subject $(g, j, k)$ is given by
where \( \sigma(\omega_1, ..., \omega_G) \) is the \( \sigma \)-field generated by the \( \omega_g \)'s. It follows from the innovation theorem (Aalen, 1978) that the intensity process with respect to \( F_t \) is given by

\[
Y_{gjk}(t) \, h_{0j}(t) \exp\{\beta \, z_{gjk}\} \, \omega_g
\]

As proposed by Self and Prentice (1986), if \( H_{0j} \)'s were known, \( \delta \) and \( \beta \) could be estimated using standard partial likelihood techniques. Let

\[
M_g(t; \delta, \beta, H_{0j}, j = 1, ..., S) = \ln E[\omega_g | F_t].
\]

Specifically, these estimators satisfy the following score equations:

\[
0 = \sum_{j=1}^{S} \left\{ \sum_{g=1}^{G} \left[ \frac{1}{n_{gj}} \sum_{k=1}^{n_{gj}} \left( \frac{1}{G} \sum_{r=1}^{G} \sum_{m=1}^{n_{rj}} Y_{rjm}(t) \exp\{\beta \, z_{rjm} + M_r(t)\} \, U'_{gjk}(t) \right) \right] \right\} dN_{gjk}(t)
\]

(3.1.3.1)

where \( U'_{gjk}(t) = \left[ \begin{array}{c} \frac{\partial M_g(t)}{\partial \delta} \\ \frac{\partial M_g(t)}{\partial \beta} \\ z_{gjk} \end{array} \right]. \) These score equations are simply the partial likelihood score equations for Cox-type regression models with general relative risk.
forms as described in Prentice and Self (1983). Since \( H_{Oj} \)'s are not known, the Nelson-Aalen (1972b) estimators of \( H_{Oj} \)'s given by

\[
\tilde{H}_{Oj}(t) = \frac{\sum_{g=1}^{G} \sum_{k=1}^{ngj} dN_{gjk}(s)}{\sum_{r=1}^{G} \sum_{m=1}^{n_{rj}} Y_{rjm}(s) \exp\{\beta z_{rjm} + M_r(s)\}}, \quad j = 1, \ldots, S; \quad t \in [0, 1]
\]

(3.1.3.2)

are proposed to augment (3.1.3.1).

We can show by arguments similar to those shown in Section 3.1.1 that if \( \omega_g \) has the gamma distribution of the form (3.1.1), then

\[
E[\omega_g \mid F_t] = \frac{1 + \delta \tilde{N}_g(t)}{1 + \delta \tilde{C}_g(t)}
\]

(3.1.3.3)

where \( \tilde{N}_g(t) = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} N_{gjk}(t) \), and \( \tilde{C}_g(t) = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \int Y_{gjk}(s) h_{Oj}(s) \exp\{\beta z_{gjk}\} ds. \)

From (3.1.3.3), we have the first and second partial derivatives of \( M_g(t) \) with respect to \( \delta \) and \( \beta \) given by
\[
\frac{\partial M_g(t)}{\partial \delta} = \frac{\bar{N}_g(t)}{1 + \delta \bar{N}_g(t)} - \frac{\bar{C}_g(t)}{1 + \delta \bar{C}_g(t)}
\]

\[
\frac{\partial M_g(t)}{\partial \beta_Y} = \frac{\delta \bar{C}_{gY}(t)}{1 + \delta \bar{C}_g(t)}
\]

\[
\frac{\partial^2 M_g(t)}{\partial \delta^2} = \left[\frac{\bar{N}_g(t)}{1 + \delta \bar{N}_g(t)}\right]^2 + \left[\frac{\bar{C}_g(t)}{1 + \delta \bar{C}_g(t)}\right]^2
\]

\[
\frac{\partial^2 M_g(t)}{\partial \delta \partial \beta_Y} = \frac{\bar{C}_{gY}(t)}{[1 + \delta \bar{C}_g(t)]^2}, \text{ and}
\]

\[
\frac{\partial^2 M_g(t)}{\partial \beta_Y \partial \beta_\varphi} = \frac{\delta \bar{C}_{gY\varphi}(t)}{1 + \delta \bar{C}_g(t)} + \frac{\delta^2 \bar{C}_{gY}(t) \bar{C}_{g\varphi}(t)}{[1 + \delta \bar{C}_g(t)]^2}
\]

where \( \bar{C}_{gY}(t) = S \sum_{j=1}^{n_{gj}} \sum_{k=1}^{t} Y_{gjk}(s) h_{oj}(s) \exp\{\beta z_{gjk}\} z_{gjkY} ds \), and

\( \bar{C}_{gY\varphi}(t) = S \sum_{j=1}^{n_{gj}} \sum_{k=1}^{t} Y_{gjk}(s) h_{oj}(s) \exp\{\beta z_{gjk}\} z_{gjkY} z_{gjk\varphi} ds \). These first and second partial derivatives are needed to solve the partial likelihood score equations (3.1.3.1) numerically.

The estimating algorithm proceeds by first computing the initial estimates of \( \beta \) from standard Cox regression program (i.e., \( \delta = 0 \)). Then compute the estimates of \( H_{oj} \)’s from (3.1.3.2) with the current estimates of \( \beta \) (note that \( M_g(t) = 0, \forall t \)), compute the updated estimates of \( \delta \) and \( \beta \) with current estimates of \( H_{oj} \)’s, and iterate as necessary.
To summarize the estimation routine proceeds as follows:

Step 1: Using a modified Cox regression program obtain initial estimates of $\beta$ and $H_{0j}$'s from (3.1.3.1) and (3.1.3.2), respectively, with $M_g(t) = 0$, $\forall t$.

Step 2: Update $\delta$ and $\beta$ from (3.1.3.1) with current estimates of $H_{0j}$'s.

Step 3: Update $H_{0j}$'s from (3.1.3.2) with current estimates of $\delta$, $\beta$, and $H_{0j}$'s.

Step 4: Iterate between steps 2 and 3 until convergence.

We have shown that the estimating equations for $\delta$ and $\beta$ in the approximate EM algorithm based on marginal rank likelihood are the same as those in the EM algorithm based on a profile likelihood construction. However, the series steps of these two iterative algorithms are different because different informations have been used to estimate the unobservable frailties. We think it is easier to write a program for the EM algorithm based on a profile likelihood construction because it is only a minor modification of a standard Cox regression program. Moreover, it is quite straightforward to extend the EM algorithm to account for time-dependent covariates. On the other hand, it is no longer possible to use generalized rank vectors to make inferences about $\delta$ and $\beta$ when covariates are time-dependent.

The idea of the EM like algorithm applied to a partial likelihood constructed by a counting process is relatively simple. However, note that in this algorithm at each observed death time we have to compute the expected frailty of each group given the history at that time. This computation becomes unmanageably intensive when we try to implement this algorithm to analyze longitudinal data from a large scale study like the Framingham Heart Study. In addition, the asymptotic theory
established by Self and Prentice (1986) for the estimators was based on some false results from the paper by Tsai and Crowley (1985), which were pointed out by Gill (see a correction note by Tsai and Crowley (1990)). Therefore we will not pursue in details this EM like approach in this report.

There are several points to note here. First, the interpretation of the regression coefficients in frailty models should be different from that in proportional hazards models. The regression coefficients in proportional hazards models indicate the effects of various risk factors on survival times, while the regression coefficients in frailty models indicate the effects of the risks on the survival times conditional on the frailties. One way of assessing the effects of risk factors under both models is to examine the risk of experiencing the event of interest for an individual with covariate vector $z_1$ as compared to an individual with covariate vector $z_2$. This quantity is estimated by the ratio of the respective hazard rates. Under proportional hazards models, this ratio of hazard rates is $\exp(\beta (z_1 - z_2))$ which is free of the baseline hazard rate. Under the gamma frailty models, the relative risk is $\exp(\beta (z_1 - z_2)) \frac{1 + \delta H_0(t) \exp (\beta z_2)}{1 + \delta H_0(t) \exp (\beta z_1)}$ which depends on the baseline cumulative hazard rate. That is, the unconditional hazard functions derived from the the gamma frailty models no longer follow proportional hazards models.

Second, in Chapter 5 we will look at examples of left truncated and right censored data from the Framingham Heart Study. In these examples individuals must be free of the diseases of interest at age 45 to be included in our samples.
These individuals are then followed until the diseases of interest occur or other competing events interrupt the observation of the diseases of interest. We use the age measured from birth as the time scale in our analysis. Note that the three semiparametric analyses derived above were based on right censored data. Adjustments of these semiparametric analyses for having left truncation should be made to allow for the fact that individuals are at risk only after they have been included in the samples. However, in these samples individuals had the same age at the time of inclusion. Therefore, after the adjustments we still get the same results as if there were no left truncation.

To see the effects of left truncation on the estimate of dependence parameter suppose we have a pair of individuals with common values of the covariates. Let $S_1$ and $S_2$ denote their respective times to death (or to some disease) measured from birth. At birth a measure of association between the event times of these two individuals is Kendall's $\tau$. Let $\tau(s_1,s_2)$ denote the conditional value of Kendall's $\tau$ given these two individuals are alive (or disease-free) at age $s_1$ and $s_2$, respectively. That is, $\tau(s_1,s_2) = 2 \Pr((S_1 - S_1^*) (S_2 - S_2^*) > 0 \mid S_1 > s_1, S_1^* > s_1, S_2 > s_2, S_2^* > s_2) - 1$ where $(S_1^*, S_2^*)$ is an independent copy of $(S_1, S_2)$. For the gamma frailty models this quantity is $\frac{\delta}{\delta + 2}$ which is independent of $s_1$ and $s_2$. Thus the strength of association is not affected by truncation. A second way to see the effects of delayed entry into the study on the estimate of dependence parameter is to consider the relative change in an individual's hazard rate just after the other individual dies at any given age $s$. This quantity is the cross-ratio function...
(Oakes, 1989), described in Section 2.2, minus one. For the gamma frailty models, it is a constant \( \delta \) for all \( s \), so that the age at which an individual dies has no effect on the relative magnitude of the increased risk for the other individual.

Third, under the gamma frailty models the dependence parameter \( \delta \) is identifiable from the margins. This implies that from a study of the survival times of fathers only we can estimate the dependence between the survival times of fathers and sons. So the dependence parameter \( \delta \) in the gamma frailty models measures something besides dependence. Elbers and Ridder (1982) pointed out this problem is present for any frailty distribution with finite mean.

### 3.1.4 Observed Information Matrices

**Generalized Rank Vectors**

From the marginal rank log likelihood \( L_r \) (3.1.1.3) we have the negative second derivatives of the log marginal rank likelihood, evaluated at \((\delta, \beta)\), given by (for convenience, we leave out \((\delta, \beta)\))

\[
- \frac{\partial^2 L_r}{\partial \delta^2} = -E \left[ \sum_{g=1}^{G} \frac{\partial^2 \ln f_G(\omega_g;\delta)}{\partial \delta^2} + \left( \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g;\delta)}{\partial \delta} \right)^2 \right] R
+ \left( \frac{\partial L_r}{\partial \delta} \right)^2
\]

\[
- \frac{\partial^2 L_r}{\partial \delta \partial \beta_\gamma} = -E \left[ \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g;\delta)}{\partial \delta} \left( \sum_{i=1}^{d} z_{(i)\gamma} - Q_{i} \frac{\partial \Lambda_{i}}{\partial \beta_\gamma} \right) R \right]
+ \left( \frac{\partial L_r}{\partial \delta} \right) \left( \frac{\partial L_r}{\partial \beta_\gamma} \right)
\]
where \( z(.|\gamma) \) is the covariate associated with the regression coefficient \( \beta_\gamma \). Substituting \( \bar{Q}^i \) for \( Q^i \) renders the last term in each of these expressions asymptotically negligible. We can evaluate the conditional expectation in each of these expressions by using the fact that conditional on \( Q \) and \( R \), the \( \omega_g \)'s are independent gamma random variables with the shape parameters \( 1/\delta + D_g \)'s and the scale parameters \( A_g \)'s. The details of this calculation for (3.1.4.1) are shown below.

Straightforward differentiation of \( \partial \ln g(\omega; \delta)/\partial \delta \) yields

\[
\frac{\partial^2 \ln g(\omega_g; \delta)}{\partial \delta^2} = \left( \frac{1}{\delta^3} \right) \left[ \frac{1}{\delta} + \Psi'(1/\delta) - 2 \omega_g - \ln \omega_g + \ln \delta + \Psi(1/\delta) \right]
\]

(3.1.4.4)

where \( \Psi'(\kappa) \) is the trigamma function \( d^2 \ln \Gamma(\kappa)/d\kappa^2 \). Using the facts that \( E[\omega_g | Q, R] = \frac{1/\delta + D_g}{A_g} \) and \( E[\ln \omega_g | Q, R] = \Psi'(1/\delta + D_g) - \ln A_g \), the expectation of (3.1.4.4) given \( R \) can be derived as follows:
$$E \left[ \sum_{g=1}^{G} \frac{\partial^2 \ln f_G(\omega_g; \delta)}{\partial \delta^2} \mid R \right]$$

$$= \sum_{g=1}^{G} E \left[ (1/\delta^3) \left\{ 3 - (1/\delta) \Psi'(1/\delta) - 2[\omega_g - \ln \omega_g + \ln \delta + \Psi(1/\delta)] \right\} \mid R \right]$$

$$= \sum_{g=1}^{G} E \left[ E \left[ (1/\delta^3) \left\{ 3 - (1/\delta) \Psi'(1/\delta) - 2[\omega_g - \ln \omega_g + \ln \delta + \Psi(1/\delta)] \right\} \mid Q, R \right] \mid R \right]$$

$$\approx \sum_{g=1}^{G} E \left[ (1/\delta^3) \left\{ 3 - (1/\delta) \Psi'(1/\delta) \right. \right.$$

$$- 2\left[ \frac{1/\delta + D_g}{A_g} - \Psi(1/\delta + D_g) + \ln A_g + \ln \delta + \Psi(1/\delta) \right] \left. \right\} \mid R \right] \approx \bar{Q}_i.$$

(3.1.4.5)

Expand \( \left( \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g; \delta)}{\partial \delta} \right)^2 \) and write its expectation given \( R \) as follows:

$$E \left[ \left( \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g; \delta)}{\partial \delta} \right)^2 \mid R \right]$$

$$= (1/\delta^4) E \left[ 2 \sum_{g=1}^{G} \sum_{g'<g}^{G} (1 - \ln \delta - \Psi(1/\delta) + \ln \omega_g - \omega_g) \right.$$\n
$$\times (1 - \ln \delta - \Psi(1/\delta) + \ln \omega_g' - \omega_g') + \sum_{g=1}^{G} (1 - \ln \delta - \Psi(1/\delta) + \ln \omega_g - \omega_g)^2 \mid R \right].$$

(3.1.4.6)

Note that for \( g \neq g' \), \( \omega_g \) and \( \omega_{g'} \) are independent. Therefore upon replacement of \( Q_i \)

by \( \bar{Q}_i \) the first term in (3.1.4.6) is equal to

$$2 \sum_{g=1}^{G} \sum_{g'<g}^{G} E \left[ (1 - \ln \delta - \Psi(1/\delta) + \Psi(1/\delta + D_g) - \ln A_g \cdot \frac{1/\delta + D_g}{A_g} \mid R \right] Q_i = \bar{Q}_i$$

$$\times E \left[ (1 - \ln \delta - \Psi(1/\delta) + \Psi(1/\delta + D_{g'} - \ln A_{g'} \cdot \frac{1/\delta + D_{g'}}{A_{g'}} \mid R \right] Q_i = \bar{Q}_i.$$
The calculation of the second term in (3.1.4.6) proceeds by first expanding 
\[ \sum_{g=1}^{G} (1 - \ln \delta - \Psi(1/\delta) + \ln \omega_g - \omega_g)^2 \]
and then using the facts that

\begin{align*}
E[\omega_g \ln \omega_g | Q, R] &= \left(\frac{1/\delta + D_g}{A_g}\right) \{\Psi(1/\delta + D_g + 1) - \ln A_g\} \\
E[(\omega_g)^2 | Q, R] &= \frac{1/\delta + D_g}{(A_g)^2} + \left[\frac{1/\delta + D_g}{A_g}\right]^2, \text{ and} \\
E[(\ln \omega_g)^2 | Q, R] &= \Psi'(1/\delta + D_g) + \{\Psi(1/\delta + D_g) - \ln A_g\}^2.
\end{align*}

We can calculate the conditional expectations in (3.1.4.2) and (3.1.4.3) in a similar way.

**Profile Likelihood Construction**

The joint density of \((t_{gjk}, I_{gjk})\) under the gamma frailty model can be derived as follows (see Section 3.1.1 for similar arguments). For any group \(g\), conditional on \(\omega_g\), the joint density of \((t_{gjk}, I_{gjk})\) is proportional to

\[ (\omega_g)^{D_g} \exp(- \bar{H}_g \omega_g) \times \prod_{j=1}^{S} \prod_{k=1}^{n_{gj}} (h_{oj}(t_{gjk}) \exp(\beta z_{gjk})) I_{gjk}. \]  

(3.1.4.7)

where \(\bar{H}_g = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} h_{oj}(t_{gjk}) \exp(\beta z_{gjk})\). Multiplying (3.1.4.7) by the density (3.1.1) of \(\omega_g\) and integrating out \(\omega_g\) yields the likelihood contribution from any group \(g\).
\[
\frac{\Gamma(D_g + 1/\delta) (1/\delta)^1/\delta}{\Gamma(1/\delta) (H_g + 1/\delta)^D_g + 1/\delta} \times \left( \prod_{j=1}^{S} \prod_{k=1}^{n_{gj}} \{ \log(t_{gjk}) \exp(\beta z_{gjk}) \} I_{gjk} \right). \tag{3.1.4.8}
\]

We can show by a simple algebra that the logarithm of (3.1.4.8) is equal to

\[
\sum_{m=1}^{D_g} \left\{ \ln (D_g + (1/\delta) - m) - D_g \ln (1/\delta) \right\} - (D_g + 1/\delta) \ln (\delta H_g + 1)
\]

\[+ \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} I_{gjk} \{ \ln \log(t_{gjk}) + \beta z_{gjk} \}. \tag{3.1.4.9}\]

Summing (3.1.4.9) over groups yields the log likelihood function

\[
L_G = \sum_{g=1}^{G} \left\{ \sum_{m=1}^{D_g} \left\{ \ln (D_g + (1/\delta) - m) - D_g \ln (1/\delta) \right\} - (D_g + 1/\delta) \ln (\delta H_g + 1)
\]

\[+ \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} I_{gjk} \{ \ln \log(t_{gjk}) + \beta z_{gjk} \} \right\}.
\tag{3.1.4.10}\]

Substituting the Nelson-Aalen (1972b) estimator of Hoj's (3.1.2.3) and its jump sizes at observed failure times into the unaugmented log likelihood \(L_G\) (3.1.4.10) the appropriate negative second derivatives are

\[
- \frac{\partial^2 L_G}{\partial \delta^2} = \sum_{g=1}^{G} \left[ \frac{D_g}{\delta^2} - \frac{1}{(2/\delta^3)} \left\{ \sum_{m=1}^{D_g} \frac{1}{(D_g + 1/\delta - m)} \right\} + \frac{1}{(1/\delta^4)} \left\{ \sum_{m=1}^{D_g} \frac{1}{(D_g + 1/\delta - m)^2} \right\} \right]
\]
\[
\begin{align*}
\mathcal{L}_G &= \sum_{g=1}^{G} \left\{ \frac{2 \ln \left( 1 + \delta \sum_{j=1}^{S} \frac{\sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\delta^3} \right)}{\delta^3} \\
& \quad - \frac{2 \sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\delta^2 \left( 1 + \delta \sum_{j=1}^{S} \frac{\sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\delta^3} \right)} \\
& \quad - \frac{(D_g + 1/\delta) \left[ \sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk}) \right]^2}{\delta^2} \\
& \quad \frac{\sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\left[ 1 + \delta \sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk}) \right]^2} \right\}
\end{align*}
\]

\[
\frac{\partial^2 \mathcal{L}_G}{\partial \beta_g \partial \beta_g} = \sum_{g=1}^{G} \left\{ \frac{\sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\left[ 1 + \delta \sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk}) \right]^2} \right\}
\]

\[
\frac{\partial^2 \mathcal{L}_G}{\partial \beta_g \partial \beta_g} = \sum_{g=1}^{G} \left\{ -\frac{\sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk})}{\left[ 1 + \delta \sum_{j=1}^{S} \sum_{k=1}^{\text{ng}_{ij}} \hat{H}_{gji}(t_{gjk}) \exp(\beta z_{gjk}) \right]^2} \right\}
\]
\[ + \sum_{g=1}^{G} \left\{ \delta (D_g + 1/\delta) \right\} \]
\[
\times \left( \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \left[ \hat{H}_{oj}(t_{gjk}) z_{gjk} z_{gjk \varphi} + z_{gjk} \hat{H}_{oj}(t_{gjk}) + \hat{H}_{oj}(t_{gjk}) z_{gjk} z_{gjk \varphi} + \hat{H}_{oj}(t_{gjk}) \right] \right) \]
\[
\times \exp(\beta z_{gjk}) \times \frac{1}{1 + \delta \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \hat{H}_{oj}(t_{gjk}) \exp(\beta z_{gjk})} \]
\[
- \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} t_{gjk} \left( \hat{h}_{oj}(t_{gjk}) \hat{h}_{oj}(t_{gjk}) - \hat{h}_{oj}(t_{gjk}) \hat{h}_{oj}(t_{gjk}) \right) \left[ \hat{h}_{oj}(t_{gjk}) \right]^2 \]

where

\[ \hat{h}_{oj}(t) = \frac{d_{j(u)}}{G \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g} \text{, if } t = t_{j[u]} \quad (u = 1, \ldots, d_j); \quad 0, \text{ otherwise,} \]
\[ \hat{h}_{oj}(t) = \frac{G \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g z_{gjk \gamma}}{t \geq t_{j[u]}} \]
\[ \hat{h}_{oj}(t) = - \frac{d_{j(u)}}{G \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g} \text{, if } t = t_{j[u]}; \quad 0, \text{ otherwise,} \]
\[ \left[ \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g \right]^2 \]
\[ t \geq t_{j[u]} \]
\[
\hat{h}_{0jy}(t) = -d_{j[u]} \left\{ \left[ \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g z_{gjk} \right] \sum_{t_{gjk} \geq t_{j[u]}} \right. \\
\left. \left[ \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g \right]^2 \right. \\
- \left. \frac{1}{2} \left[ \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} \exp(\beta z_{gjk}) \hat{\omega}_g \right]^3 \right\},
\]

if \( t = t_{j[u]} \); 0, otherwise, and

\[
\hat{h}_{0jy}(t) = \sum_{u=1}^{i} \hat{h}_{0jy}(t_{j[u]}) ; \quad \hat{h}_{0jy}(t) = \sum_{u=1}^{i} \hat{h}_{0jy}(t_{j[u]}). \tag{3.1.4.11}
\]

We can show that using the marginal likelihood of a generalized rank vector to compute the observed information matrix yields the same value for the negative second partial derivative for \( \delta \) as that using the joint distribution of \((t_{gjk}, I_{gjk})\), up to a negligible number. Note that

\[
- \frac{\partial^2 L_G}{\partial \delta^2} = - \frac{\partial^2}{\partial \delta^2} \ln \left[ \prod_{\omega=0}^{\infty} G_g \exp \left( - \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \hat{H}_{0jy}(t_{gjk}) \exp(\beta z_{gjk}) \omega_g \right) \right] \\
\times \left( \prod_{j=1}^{S} \prod_{k=1}^{n_{gj}} \left\{ \hat{h}_{0jy}(t_{gjk}) \exp(\beta z_{gjk}) I_{gjk} \right\} \right) f_G(\omega_g) \, d\omega_g.
\]
Evaluated at the maximum likelihood estimates \((\hat{\delta}, \hat{\beta})\) of the dependence parameter and regression coefficients,

\[ \frac{\partial^2 L_G}{\partial \delta^2} \]

\[ \approx \operatorname{E} \left[ \sum_{g=1}^{G} \frac{\partial^2 \ln f_G(\omega_g; \delta)}{\partial \delta^2} + \left\{ \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g; \delta)}{\partial \delta} \right\}^2 \mid \text{Data} \right] H_{\hat{o}j}(tgjk) = \hat{H}_{\hat{o}j}(tgjk) \]

because the value of \(\frac{\partial L_G}{\partial \delta}\) is negligible. Clearly,

\[ \begin{align*}
- \operatorname{E} \left[ \sum_{g=1}^{G} \frac{\partial^2 \ln f_G(\omega_g; \delta)}{\partial \delta^2} + \left\{ \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g; \delta)}{\partial \delta} \right\}^2 \mid \text{Data} \right] H_{\hat{o}j}(tgjk) &= \hat{H}_{\hat{o}j}(tgjk) \\
= - \operatorname{E} \left[ \sum_{g=1}^{G} \frac{\partial^2 \ln f_G(\omega_g; \delta)}{\partial \delta^2} + \left\{ \sum_{g=1}^{G} \frac{\partial \ln f_G(\omega_g; \delta)}{\partial \delta} \right\}^2 \mid Q, \overline{R} \right] \mid Q_i = \overline{q}_i \\
\end{align*} \]

where the right-hand side is approximately equal to \(-\frac{\partial^2 L_T}{\partial \delta^2}\).

One implication from the above result is that when there are no covariates the variance estimates for \(\hat{\delta}\) computed based on the log likelihoods \(L_G\) and \(L_T\) are approximately equal.
3.2 Weibull Regression Model

As described in Sections 2.1 and 2.2, Weibull models have been widely used to model the component lifetimes of engineering systems and the survival times of human and animal populations. We think there are several reasons why we should consider modelling the baseline hazard functions \( h_{0j}(x) \) in our frailty model by the hazard functions of Weibull distributions. We will assume that

\[
  h_{0j}(x) = \alpha_j x^{\alpha_j - 1} \quad (j = 1, \ldots, S).
\]

First, all the three semiparametric approaches described in the previous section lack of asymptotic theory for the estimators. On the other hand, the asymptotic properties of maximum likelihood estimators are well known. We can compare the estimates of the dependence parameter and regression coefficients and corresponding observed information matrix obtained by maximum likelihood estimation to those obtained by the semiparametric approaches.

Second, in the semiparametric approaches the baseline hazard functions are modelled by nonparametric functions defined on an infinite-dimensional space. Estimating these nonparametric functions generally results in the loss of the efficiency in the estimation of the dependence parameter and regression coefficients. The maximum likelihood estimators of the dependence parameter and regression coefficients are most efficient if the assumed parametric model were correct.
Third, note that the marginal survival functions of the gamma frailty model are of the form of Pareto distributions when we assume \( h_{0j}(x) = \alpha_j x^{\alpha_j - 1} \). This makes the effects of the dependence parameter \( \delta \) and regression coefficients \( \beta \) on margins easier to interpret.

Fourth, the log likelihood function \( L_G \) (3.1.4.10) based on the observed data \((t_{gjk}, I_{gjk})\) from the gamma frailty model has a simple form. So it is relatively simple to find the maximum likelihood estimators of \( \delta \) and \( \beta \) directly from the observable likelihood when we assume \( h_{0j}(x) = \alpha_j x^{\alpha_j - 1} \). In the semiparametric approaches we need to use iterative algorithms to find the likelihood estimates of \( \delta \) and \( \beta \) which are computationally less efficient.

As noted above, in Chapter 5 we will look at examples of right censored and left truncated data from the Framingham Heart Study. The log likelihood function based on such data is obtained by subtracting from (3.1.4.10) the sum of the logarithms of group survival probabilities at truncation times. Let \( t_{gjk}^c \) denote the truncation time, possibly zero, for the \( k \)th individual in the \( g \)th group and the \( j \)th stratum. Using (3.1.2) this log likelihood function is simply

\[
L_G^c = \sum_{g=1}^{G} \left\{ \sum_{m=1}^{D_g} \left\{ \ln \left( D_g + \frac{1}{\delta} \right) - m \right\} - D_g \ln \left( \frac{1}{\delta} \right) \right\} \\
- \left( D_g + \frac{1}{\delta} \right) \ln \left( \delta H_g + 1 \right) + \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} I_{gjk} \left\{ \ln h_{0j}(t_{gjk}) + \beta z_{gjk} \right\} \\
+ \sum_{g=1}^{G} \left( \frac{1}{\delta} \right) \ln \left( \delta \frac{H_g^c}{g} + 1 \right) 
\]

(3.2.1)
where $H_g = \sum_{j=1}^{S} \sum_{k=1}^{ng_i} H_{oij}(\epsilon_{gjk}) \exp(\beta z_{gjk})$.

Maximum likelihood estimates must be found by some appropriate numerical technique. Appropriate first and negative second derivatives of (3.2.1) when $h_{oj}(x) = \alpha_j x^{\alpha_j}^{-1}$ are recorded below:

$$\frac{\partial L_G}{\partial \delta_g} = \sum_{g=1}^{G} \left( \frac{-1/\delta^2}{\delta^2} \left( \sum_{m=1}^{D_p} \frac{1}{1/\delta + D_g - m} - D_g \delta \right) \right)$$

$$+ \sum_{g=1}^{G} \left\{ \ln \left( \frac{1 + \delta H_g}{\delta^2} \right) \left( \frac{1/\delta + D_g}{1 + \delta H_g} \right) \right\}$$

$$- \sum_{g=1}^{G} \left\{ \ln \left( \frac{1 + \delta H_g^{c}}{\delta^2} \right) \left( \frac{1/\delta}{1 + \delta H_g^{c}} \right) \right\}$$

$$\frac{\partial L_G}{\partial \alpha_{\gamma}} = \sum_{g=1}^{G} \left( \frac{\delta (1/\delta + D_g)}{1 + \delta H_g} \right) \times \frac{\partial H_g}{\partial \alpha_{\gamma}} + \sum_{g=1}^{G} \sum_{k=1}^{ng_i} I_{gjk} \left( \frac{1/\alpha_{\gamma} + \ln t_{gjk}}{1 + \delta H_g^{c}} \right)$$

$$+ \sum_{g=1}^{G} \frac{1}{(1 + \delta H_g^{c})} \times \frac{\partial H_g^{c}}{\partial \alpha_{\gamma}}$$
\[
\frac{\partial L_G^c}{\partial \beta \phi} = \sum_{g=1}^{G} \frac{\delta \left(1/\delta + D_g\right)}{1+\delta H_g} \times \frac{\partial H_g^c}{\partial \beta \phi} + \sum_{g=1}^{G} \frac{\delta \left(1/\delta + D_g\right)}{1+\delta H_g} \sum_{j=1}^{S} \sum_{k=1}^{ng} I_{gjk} z_{gjk}\phi
\]

\[
+ \sum_{g=1}^{G} \frac{1}{(1+\delta H_g^c)} \times \frac{\partial H_g^c}{\partial \beta \phi}
\]

\[
\frac{\partial^2 L_G^c}{\partial \beta \phi \partial \alpha \gamma} = \sum_{i=1}^{G} \left\{ -\frac{1}{\delta \left(1+\delta H_g\right)} + \frac{\delta \left(1/\delta + D_g\right)}{1+\delta H_g^c} \right\} \frac{\partial H_g}{\partial \alpha \gamma} - \sum_{i=1}^{G} \left\{ -\frac{1}{\delta \left(1+\delta H_g^c\right)} + \frac{\delta \left(1/\delta + D_g\right)}{1+\delta H_g^c} \right\} \frac{\partial H_g^c}{\partial \alpha \gamma}
\]
\[
- \frac{\partial^2 L_G}{\partial \delta \partial \beta_\phi} = \sum_{i=1}^{G} \left\{ - \frac{1}{\delta (1+\delta H_g)} + \frac{(1/\delta + D_g)}{1+\delta H_g} \delta H_g \right\} \frac{\partial H_g}{\partial \beta_\phi}
\]

\[
- \sum_{i=1}^{G} \left\{ - \frac{1}{\delta (1+\delta H^c_g)} + \frac{(1/\delta)}{1+\delta H^c_g} \right\} \frac{\partial H^c_g}{\partial \beta_\phi}
\]

\[
- \frac{\partial^2 L_G}{\partial \alpha_\gamma^2} = \sum_{i=1}^{G} \left\{ \frac{\delta^2(1/\delta + D_g) (\partial H_g)^2}{(1+\delta H_g)^2} + \frac{\delta (1/\delta + D_g) \frac{\partial^2 H_g}{\partial \alpha_\gamma^2}}{(1+\delta H_g)} \right\}
\]

\[
+ \sum_{g=1}^{G} \sum_{k=1}^{n_{gj}} I_{gjk} (1/\alpha_\gamma)^2 - \sum_{i=1}^{G} \left\{ \frac{\partial H^c_g}{\partial \alpha_\gamma} \right\} \frac{\partial (\frac{\partial H^c_g}{\partial \alpha_\gamma})^2}{(1+\delta H^c_g)^2} + \frac{\partial^2 H^c_g}{\partial \alpha_\gamma^2} \right\} \frac{\partial^2 H^c_g}{\partial \alpha_\gamma^2}
\]

\[
- \frac{\partial^2 L_G}{\partial \alpha_\gamma \partial \alpha_\gamma} = \sum_{g=1}^{G} \left\{ \frac{\delta^2(1/\delta + D_g) (\partial H_g)^2}{(1+\delta H_g)^2} \right\} \frac{\partial H_g}{\partial \alpha_\gamma} \frac{\partial H_g}{\partial \alpha_\gamma} - \sum_{g=1}^{G} \left\{ \frac{\partial H^c_g}{\partial \alpha_\gamma} \right\} \frac{\delta (\frac{\partial H^c_g}{\partial \alpha_\gamma})^2}{(1+\delta H^c_g)^2} + \frac{\partial^2 H^c_g}{\partial \alpha_\gamma^2} \right\} \frac{\partial^2 H^c_g}{\partial \alpha_\gamma^2}
\]
\[
- \frac{\partial^2 L_G}{\partial \alpha_\gamma \partial \beta_\phi} = \sum_{g=1}^G \left\{ \frac{\delta(1/\delta + D_g)}{(1+\delta \bar{H}_g)} \frac{\partial^2 \bar{H}_g}{\partial \alpha_\gamma \partial \beta_\phi} - \frac{\delta^2(1/\delta + D_g)}{(1+\delta \bar{H}_g)^2} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma} \frac{\partial \bar{H}_g}{\partial \beta_\phi} \right\} \\
\]

\[
- \frac{\partial^2 L_G}{\partial \beta_\phi \partial \beta_{\phi'}} = \sum_{g=1}^G \left\{ \frac{\delta(1/\delta + D_g)\partial^2 \bar{H}_g}{\partial \beta_{\phi} \partial \beta_{\phi'}} - \frac{\delta^2(1/\delta + D_g)}{(1+\delta \bar{H}_g)^2} \frac{\partial \bar{H}_g}{\partial \beta_{\phi}} \frac{\partial \bar{H}_g}{\partial \beta_{\phi'}} \right\} \\
\]

where

\[
\frac{\partial \bar{H}_g}{\partial \alpha_\gamma} = \sum_{k=1}^{n_{g\gamma}} \ln(\gamma_{gk}) (t_{g\gamma k})^{\alpha_\gamma} \exp(\beta z_{g\gamma k}) \\
\frac{\partial \bar{H}_g}{\partial \beta_\phi} = \sum_{j=1}^S \sum_{k=1}^{n_{gj}} (t_{gjk})^{\alpha_\kappa} \exp(\beta z_{gjk}) z_{gjk\phi} \\
\frac{\partial^2 \bar{H}_g}{\partial \alpha_\gamma^2} = \sum_{k=1}^{n_{g\gamma}} (\ln(\gamma_{gk}))^2 (t_{g\gamma k})^{\alpha_\gamma} \exp(\beta z_{g\gamma k})
\]
\[ \frac{\partial^2 \mathcal{H}_g}{\partial \alpha \partial \beta} = \sum_{k=1}^{ng} \text{Int}_{g\gamma k} \left( t_{g\gamma k} \right)^{\alpha \gamma} \exp \left( \beta z_{g\gamma k} \right) z_{g\gamma k}, \text{ and} \]

\[ \frac{\partial^2 \mathcal{H}_g}{\partial \beta \partial \beta'} = \sum_{j=1}^{ng} \sum_{k=1}^{ng} \left( t_{gjk} \right)^{\alpha k} \exp \left( \beta z_{gjk} \right) z_{gjk}, \text{ and similarly,} \]

\[ \frac{\partial \mathcal{H}_g}{\partial \alpha} = \sum_{k=1}^{ng} \text{Int}_{g\gamma k} \left( t_{g\gamma k}^{c} \right)^{\alpha \gamma} \exp \left( \beta z_{g\gamma k} \right) \]

\[ \frac{\partial \mathcal{H}_g}{\partial \beta} = \sum_{j=1}^{ng} \sum_{k=1}^{ng} \left( t_{gjk}^{c} \right)^{\alpha k} \exp \left( \beta z_{gjk} \right) z_{gjk} \]

\[ \frac{\partial^2 \mathcal{H}_g}{\partial \alpha \partial \alpha} = \sum_{k=1}^{ng} \left( \text{Int}_{g\gamma k}^{c} \right)^{2} \left( t_{g\gamma k}^{c} \right)^{\alpha \gamma} \exp \left( \beta z_{g\gamma k} \right) \]

\[ \frac{\partial^2 \mathcal{H}_g}{\partial \beta \partial \beta} = \sum_{j=1}^{ng} \sum_{k=1}^{ng} \left( t_{gjk}^{c} \right)^{\alpha k} \exp \left( \beta z_{gjk} \right) z_{gjk}, \text{ and} \]

\[ \frac{\partial^2 \mathcal{H}_g}{\partial \beta \partial \beta'} = \sum_{j=1}^{ng} \sum_{k=1}^{ng} \left( t_{gjk}^{c} \right)^{\alpha k} \exp \left( \beta z_{gjk} \right) z_{gjk}, \text{ and similarly,} \]

(3.2.2)
Note that when $h_{o}j(x) = \lambda_{j}^{x_{j}} \alpha_{j} x^{x_{j} - 1}$, we can write $h_{j}(x_{l} \omega_{g}, z_{gjk})$ as
\[
\alpha_{j} x^{x_{j} - 1} \exp(\beta z_{gjk}) \exp\left(\sum_{j'=1}^{s} \alpha_{j'} \ln \lambda_{j'} \chi_{j'}\right) \omega_{g}
\]
where $\chi_{j'}$ is an indicator for the $j'$th stratum. Therefore the results derived above can be applied to this general case.

In the sequel, Marquart's method (Ralston and Rabinowitz, 1978) was used to obtain the maximum likelihood estimates. Our experience has found that this numerical procedure is highly sensitive to the initial guesses for $\alpha_{j}$, $\beta$, and $\delta$. Using the estimates for $\alpha_{j}$ and $\beta$ obtained by a standard Weibull regression routine based on the data ignoring group effects as initial guesses are in general not acceptable. Following Klein et al. (1991), we find the initial estimates by searching a range of values for the dependence parameters for the maximal profile likelihood estimates of $\alpha_{j}$ and $\beta$ obtained by maximizing (3.2.4) for a given value of $\delta$. The search starts with independence, which gives a baseline profile likelihood and initial guesses for $\alpha_{j}$ and $\beta$ for the least dependent model to be looked at. These new estimates of $\alpha_{j}$ and $\beta$ are used as initial guesses for the next profile likelihood. Once the search has been completed, the values of $\alpha_{j}$, $\beta$ and $\delta$ which corresponds to the maximal profile likelihood seen in the search are used as initial values in Marquart's algorithm to obtain the maximum likelihood estimates. With these initial values the convergence of that algorithm is relatively quick.
CHAPTER IV
POSITIVE STABLE FRAILTY MODEL

Hougaard (1986a, b, 1991) popularized the use of the positive stable distributions with densities

\[ f_p(\omega) = - \frac{1}{\pi \omega} \sum_{k=1}^{\infty} \frac{\Gamma(k\theta + 1)}{k!} (-\omega^{-\theta}) \sin (\theta k \pi), \omega > 0 \]  

(4.1)

for modelling \( \omega \). He cited several reasons why the positive stable distributions are more natural models for the frailty than the gamma distributions. One main reason is that the positive stable variables are infinitely divisible; namely, if \( Y_l, l = 1, \ldots, n \), are independent identically distributed stable variables, then \( \sum_{l=1}^{n} Y_l \) is distributed as \( n^{1/\alpha} Y_1 \). He argued that the infinite divisibility of the positive stable variables allows the splitting of a frailty into cause-specific frailties which may be easier to interpret. He also pointed out that the marginal distributions of the positive stable frailty model do not identify the dependence parameter \( \theta \). The means of the positive stable variables are infinite. As shown in Figures 4.1 and 4.2, the tails of the positive stable densities are thicker than those of the gamma densities (3.1.1).
The Density Function

FIGURE 4.1

Density Function for the Gamma (___),
Positive Stable (___) When $\tau = 0.2$
FIGURE 4.2
Density Function for the Gamma (___),
Positive Stable (___) When \( \tau = 0.5 \)
In Section 4.1 we will adapt the semiparametric approaches proposed by Klein (1991), and Self and Prentice (1986) for the gamma frailty model to the positive stable frailty models with multiple stratifications and unequal stratification group sizes. A modification of Klein's estimation scheme will be made due to the complex form of the positive stable densities. In Section 4.2 we will study the Weibull regression models assuming \( \omega \) follows the positive stable distributions.

4.1 Semiparametric Estimation

4.1.1 Profile Likelihood Construction

Assuming that \( \omega_g \)'s are independent and identically distributed positive stable variables with densities (4.1), it can be easily shown that the joint survival function for the individuals in the \( g \)th group is

\[
P[X_{gjk} > t_{gjk}, j = 1, \ldots, S; k = 1, \ldots, n_{gj} | Z_{gjk}, j = 1, \ldots, S; k = 1, \ldots, n_{gj}] = \exp \left[ - (H_g)^\theta \right].
\]

Recall that \( H_g = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} H_{Oj}(t_{gjk}) \exp\{\beta z_{gjk}\} \). The association between individuals in the \( g \)th group, measured by Kendall's \( \tau \), is \( 1 - \theta \) so the association is monotone decreasing in \( \theta \), with the limiting case \( \theta = 1 \) corresponding to independence.
To estimate the parameters $\theta$ and $\beta$, we fit the semiparametric analysis proposed by Cox (1972) into an EM algorithm that has the observed data as the incomplete data and the unobservable frailties, $\omega_g$'s, as the missing information. We modify Klein's (1991) estimation scheme to take into account the complex form of the positive stable densities. First, note that for fixed $\theta$ if we could observe the $\omega_g$'s, the augmented log likelihood is equal to, up to a term free of the unknown parameters,

$$
\sum_{g=1}^{G} \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} \left( \lambda_{gjk}(\beta z_{gjk} + \ln h_{oj}(t_{gjk}) - H_{oj}(t_{gjk}) \exp{\beta z_{gjk}}) \omega_g \right).
$$

The estimating algorithm proceeds by first making an initial guess at the values of $\beta$ (and $H_{oj}$'s). The initial estimates are obtained by a standard Cox's program. To apply the E-step of the algorithm we use the fact that, conditional on the observed data, the expected values of $\omega_g$'s are

$$
\begin{align*}
E[\omega_g | \text{Data}] &= \\
&= \int_{\omega_g = 0}^\infty (\omega_g)^D g + 1 \exp(-\bar{H}_g \omega_g) \times \left( \prod_{j=1}^{S} \prod_{k=1}^{n_{gj}} (h_{oj}(t_{gjk}) \exp(\beta z_{gjk}))^{I_{gjk}} \right) f_p(\omega_g) \, d\omega_g \\
&\quad + \int_{\omega_g = 0}^\infty (\omega_g)^D g \exp(-\bar{H}_g \omega_g) \times \left( \prod_{j=1}^{S} \prod_{k=1}^{n_{gj}} (h_{oj}(t_{gjk}) \exp(\beta z_{gjk}))^{I_{gjk}} \right) f_p(\omega_g) \, d\omega_g \\
&= \frac{E[\omega_g^D g + 1 \exp(-\bar{H}_g \omega_g)]}{E[\omega_g^D g \exp(-\bar{H}_g \omega_g)]}, \quad g=1, \ldots, G. \quad (4.1.1.2)
\end{align*}
$$
To evaluate \( E[\omega g^{\text{Dg}} + 1 \exp(-\tilde{H}_g \omega_g)] \) we have the following lemma:

**Lemma 4.1:** If \( \omega \) follows a stable law with density function \( f_\theta \) given by (4.1), then

\[
E(\omega^q \exp(-s\omega)) = \int_{\omega=0}^{\omega=\infty} \omega^q \exp\{-s\omega\} g(\omega) \, d\omega = (\theta s^{\theta-1})^q \exp(-s^\theta) J(q, s), \quad q=0, 1, \ldots; \quad s > 0
\]

\[(4.1.1.3)\]

where \( J(q, s) = \sum_{m=0}^{q-1} \Omega_{q,m} s^m \). Here \( \Omega_{q,m} \) is a polynomial of degree \( m \) in \( \phi=1/\theta \) given recursively by

- \( \Omega_{q,0}=1; \)
- \( \Omega_{q,m}=\Omega_{q-1,m} + \Omega_{q-1,m-1} \{(q-1)\phi-(q-m)\}, \quad (m = 1, \ldots, q-2) \)
- \( \Omega_{q,q-1}=(\phi-1)(2\phi-1)\ldots\{(q-1)\phi-1\}=\phi^{q-1} \Gamma(q-\theta) / \Gamma(1-\theta). \)

**Proof:** We know that the Laplace transform of the positive stable distributions is \( \text{LP}_\theta(s) = \exp(-s^\theta) \). We can show by induction that the \( q \)th derivative of \( \exp(-s^\theta) \) with respect to \( s \) is equal to

\[\frac{(-1)^q (\theta s^{\theta-1})^q \exp(-s^\theta) J(q, s)}{\Gamma(q-\theta)} \quad (s > 0). \quad (*)\]
By definition \( LP_\theta (s) = \int_0^\infty \exp \{-s \omega\} f_\theta (\omega) \, d\omega \). Differentiating the integral \( q \) times with respect to \( s \) and using the dominated convergence theorem yields for \( s > 0 \)

\[
\frac{d^q LP_\theta (s)}{ds^q} = (-1)^q \int_0^\infty \omega^q \exp \{-s \omega\} f_\theta (\omega) \, d\omega. 
\]

Equating (*) and (**) yields the equation (4.1.1.3). From (4.1.1.2) and (4.1.1.3) the expectation of the augmented likelihood given the data and the current values of \( \vec{H}_g \) is then given by

\[
L_4(\beta, H_{0j}, j=1,...,S) = \sum_{g=1}^G \sum_{j=1}^S n_{gj} \{ H_{0j} [z_{gjk} \ln h_{0j}(t_{gjk})] \\
- H_{0j}(t_{gjk}) \exp \{\beta z_{gjk}\} \frac{\theta \vec{H}_g^{\theta-1} J(D_g+1, \vec{H}_g)}{J(D_g, \vec{H}_g)} \}. 
\]

The M-step of the EM algorithm requires the maximization of (4.1.1.4) with respect to \( \beta \) (and \( H_{0j} \)'s). Using the profile likelihood construction technique proposed by Johansen (1983), we obtain an estimating equation for \( H_{0j} \)'s given by (3.1.2.3) and a profile likelihood for \( \beta \) given by (3.1.2.4).
One iterates between the E and M steps until convergence. The resulting $\beta$ as a function of $\theta$ is used to construct a point on a likelihood profile for $\theta$ using the unaugmented likelihood. A search technique on this profile likelihood, such as golden search technique (cf. Press et al., 1986) is used to find the estimate of $\theta$. The unaugmented likelihood in this case is given by

$$L_P = \sum_{g=1}^{G} \left\{ D_g [\ln \theta + (\theta-1) \ln \bar{H}_g] - (\bar{H}_g)^\theta + \ln J(D_g, \bar{H}_g) \right\}$$

$$+ \sum_{j=1}^{S} \sum_{l=1}^{n_{gj}} I_{gjk} [\ln [h_{o(j\tau_{gjk})}] + \beta z_{gjk}] \right\}. \tag{4.1.1.5}$$

The observed information matrix is obtained directly from (4.1.1.5) in a similar way for the gamma frailty model. Note that as $D_g$ increases the form of $J(D_g, \bar{H}_g)$ will be getting more complex and so is the calculation of the observed information matrix. The examples we are going to look at in the next chapter have at most four events in any group. For our examples' need, we derive the expressions of $J(D_g, \bar{H}_g)$ for $0 < D_g < 5$ and list them in Table 1. The calculation of the observed information matrix is recorded in Section 4.1.3.
TABLE 4.1

The Expressions of $J(D_g, \tilde{H}_g)$ for $0 \leq D_g \leq 5$

<table>
<thead>
<tr>
<th>$D_g$</th>
<th>$J(D_g, \tilde{H}_g)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1</td>
<td>1 + $(1/\theta) (1 - \theta) \tilde{H}_g^{-\theta}$</td>
</tr>
<tr>
<td>2</td>
<td>$1 + (3/\theta) (1 - \theta) \tilde{H}_g^{-\theta} + (1/\theta^2) (2 - \theta) (1 - \theta) \tilde{H}_g^{-2\theta}$</td>
</tr>
<tr>
<td>3</td>
<td>$1 + (6/\theta) (1 - \theta) \tilde{H}_g^{-\theta} + (1/\theta^2) (1 - \theta) (11 - 7\theta) \tilde{H}_g^{-2\theta}$ + $(1/\theta^3) (3 - \theta) (2 - \theta) (1 - \theta) \tilde{H}_g^{-3\theta}$</td>
</tr>
<tr>
<td>4</td>
<td>$1 + (10/\theta) (1 - \theta) \tilde{H}_g^{-\theta} + (1/\theta^2) (1 - \theta) (35 - 25\theta) \tilde{H}_g^{-2\theta}$ + $(1/\theta^3) (1 - \theta) (2 - \theta) (25 - 15\theta) \tilde{H}_g^{-3\theta}$ + $(1/\theta^4) (1 - \theta) (2 - \theta) (3 - \theta) (4 - \theta) \tilde{H}_g^{-4\theta}$</td>
</tr>
</tbody>
</table>

To summarize the estimation routine proceeds as follows:

Step 1: Using a modified Cox regression program obtain initial estimates of $\beta$
(and $\hat{H}_{Oj}$'s) from (3.1.2.4) and (3.1.2.3), respectively, with $\hat{\omega}_g = 1$.

Step 2: Fix $\theta$. Using the current values $\beta$, (and $\hat{H}_{Oj}$'s) compute $\tilde{H}_g$, and $\hat{\omega}_g$.

Step 3: Update the estimate $\beta$ (and $\hat{H}_{Oj}$'s) using (3.1.2.4) and (3.1.2.3)).

Step 4: Iterate between steps 2 and 3 until convergence, and substitute the resulting $\beta$ (and $\hat{H}_{Oj}$'s) into (4.1.1.5).

Step 5: Repeat steps 2 to 4 to construct a profile likelihood on $\theta$ and search for the $\theta$ that maximizes the profile likelihood using the Golden Section Search.
4.1.2 Counting Process

The EM like algorithm discussed in Section 3.1.3 can be easily applied to the estimation of the dependence parameter \( \theta \) and regression coefficients in the positive stable frailty models. The series steps of this EM like algorithm have been summarized in Section 3.1.3. Using the fact that

\[
E[\omega g | F_t] = \frac{E[\omega g \tilde{N}_g(t) + \exp(-\tilde{C}_g(t) \omega g)]}{E[\omega g \tilde{N}_g(t) \exp(-\tilde{C}_g(t) \omega g)]}
\]

and applying Lemma 4.1, the expected frailty given the filtration \( F_t \) in this case is given by

\[
E[\omega g | F_t] = \theta \left( \tilde{C}_g(t) \right)^{\theta-1} \frac{J(\tilde{N}_g(t) + 1, \tilde{C}_g(t))}{J(\tilde{N}_g(t), \tilde{C}_g(t))}
\]

(4.1.2.1)

Recall that \( \tilde{C}_g(t) = \sum \sum \int_0^t Y_{gjk}(s) h_{0j}(s) \exp(\beta z_{gjk}) \, ds \). From (4.1.2.1), we can calculate the first and second partial derivatives of \( M_g(t) \) with respect to \( \delta \) and \( \beta \) in this case. We will not record the details here. Similar differentiations can be found in Section 4.2.

The estimates of the dependence parameter \( \theta \) and the regression coefficients can be found by iterating between the partial likelihood score equations (3.1.3.1) for Cox-type regression models with general relative risk forms and the modified
Nelson-Aalen (1972b) estimators (3.1.3.2) of the baseline cumulative hazard functions.

There are difficulties in applying the semiparametric approach based on generalized rank vectors proposed by Clayton and Cuzick (1985) to the positive stable frailty models. First, it is unclear whether the score function for the dependence parameter of the form (3.1.1.4) is obtainable from differentiating the marginal rank log likelihood $L_T$ (3.1.1.3) with respect to dependence parameter when the form of the density function of $\omega$ is an infinite series such as the positive stable densities (4.1). Second, even if it were obtainable, it is mathematically intractable to approximate the score function.

There are two points to note here. First, under the positive stable frailty models the relative risk for an individual with covariate vector $z_1$ with respect to an individual with covariate vector $z_2$ is $\exp (\theta (z_1 - z_2))$ which is free of the baseline hazard rates. That is, the unconditional hazard functions derived from the positive stable frailty models still follow the proportional hazards models. Compared to the relative risk $\exp (\beta (z_1 - z_2))$ under the proportional hazards models we can see the dependence parameter $\theta$ is a scaling factor in the exponent that reduces the absolute magnitude of $\beta (z_1 - z_2)$. 
Second, the effect of delayed entry on the dependence parameter under the positive stable frailty models is no longer a constant over time. The conditional value of Kendall's $\tau$ given a pair of individuals both are alive at age $t$ in this case is (Klein et al., 1991)

$$\tau(t, t) = (1 - \theta) \left(1 - 2^{1/\theta} (-\ln S(t, t))^\theta \exp (2 (- \ln S(t, t))) \int_{2(-\ln S(t, t))}^{\infty} u^{-1/\theta} e^{-u} \, du.\right.$$ 

where $S(t, t)$ is the probability that these two individuals both are alive at time $t$. This quantity is a decreasing function of $t$. The magnitude of the relative increase in the hazard rates of the surviving components when one of the other components fails at time $t$ is $\frac{1 - \theta}{- \theta \ln S(t, t)}$. As shown in Figure 4.3, this quantity is also a decreasing function of $t$. Note that positive stable frailty models reflect a strong association that washes out over time as the more frail pairs die.
4.1.3 Observed Information Matrix

Following Klein's (1991) suggestion, we use the joint distribution of \((t_{gjk}, I_{gjk})\) given by (4.1.1.5) for the positive stable frailty models to calculate the observed information matrix in the EM algorithm approach. Let

\[
\hat{H}_{g\gamma} = \sum_{j=1}^{S} \sum_{k=1}^{n_{gj}} [\hat{H}_{oij}(t_{gjk}) z_{gjk\gamma} + \hat{H}_{oij}(t_{gjk})] \exp(\beta z_{gjk})
\]
\[ \hat{H}_{g\gamma} = \sum_{j=1}^{S} \sum_{k=1}^{n_i} \left[ \hat{H}_{o_j} (t_{gjk}) z_{gjk\gamma} z_{gjk\gamma} + z_{gjk\gamma} \hat{H}_{o_j} (t_{gjk}) + \hat{H}_{o_j} (t_{gjk}) z_{gjk\gamma} + \hat{H}_{o_jy} (t_{gjk}) \right] \times \exp(\beta z_{gjk}), \]

\[ \hat{h}_{g\gamma} = \sum_{j=1}^{S} \sum_{k=1}^{n_i} \frac{\hat{h}_{o_j} (t_{gjk}) \hat{h}_{o_jy} (t_{gjk}) - \hat{h}_{o_jy} (t_{gjk}) \hat{h}_{o_j} (t_{gjk})}{[\hat{h}_{o_j} (t_{gjk})]^2} \]

The \( \hat{H}_{o_j}, \hat{h}_{o_j}, \hat{H}_{o_jy}, \hat{h}_{o_jy}, \) and \( \hat{H}_{o_jy} \) are given in (3.1.4.11). The appropriate negative second derivatives, when at most three events are observed in any group, are recorded below:

\[ -\frac{\partial^2 L_P}{\partial \theta^2} = \sum_{g=1}^{G} D_g / \theta^2 + \sum_{g=1}^{G} \hat{h}_{o_j} \theta \left[ \ln \hat{H}_{g} \right]^2 \]

\[ -\chi[D_g = 2] \left\{ \sum_{g=1}^{G} \left[ \frac{1/\theta^2 + (1/\theta - 1) \ln \hat{H}_{g}^2 \hat{H}_{g}^{-2\theta}}{J(2,\hat{H}_{g})^2} \right] \hat{H}_{g}^{-\theta} \right\} \]

\[ + \sum_{g=1}^{G} \left[ \frac{2/\theta^3 + 2 \ln \hat{H}_{g} / \theta^2 + (1/\delta - 1) \left[ \ln \hat{H}_{g} \right]^2 \hat{H}_{g}^{-\theta}}{J(2,\hat{H}_{g})} \right] \]

\[ -\chi[D_g = 3] \left\{ \sum_{g=1}^{G} \left[ \frac{3/\theta^2 + 3(1/\delta - 1) \ln \hat{H}_{g}^2 \hat{H}_{g}^{-2\theta}}{J(3,\hat{H}_{g})^2} \right] \hat{H}_{g}^{-\theta} \right\} \]

\[ + \sum_{g=1}^{G} \left[ \frac{3/\theta^3 + 2 \ln \hat{H}_{g} / \theta^2 + (1/\delta - 1) \left[ \ln \hat{H}_{g} \right]^2 \hat{H}_{g}^{-\theta}}{J(3,\hat{H}_{g})} \right] \]

\[ - \sum_{g=1}^{G} \left[ \frac{1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \hat{H}_{g}^2 \hat{H}_{g}^{-4\theta}}{J(3,\hat{H}_{g})^2} \right] \]
\[
+ \sum_{g=1}^{G} \left[ (12/\theta^4 - 6/\theta^3) + (16/\theta^3 - 12/\theta^2) \ln \hat{H}_g \right] + 4 (2/\theta - 1) (1/\theta - 1) \left[ \ln \hat{H}_g \right]^2 \hat{H}_g^{-20} \frac{1}{J(3, \hat{H}_g)}
\]

\[
- 2 \sum_{g=1}^{G} \left[ \frac{3/\theta^2 + 3(1/\theta - 1) \ln \hat{H}_g}{J(3, \hat{H}_g)} \hat{H}_g^{-6} \right] \times \left[ \frac{[1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \hat{H}_g] \hat{H}_g^{-20}}{J(3, \hat{H}_g)} \right]
\]

\[
- \frac{\partial^2 L_P}{\partial \theta \partial \beta_\gamma} = \sum_{g=1}^{G} D_g \frac{\hat{H}_{g\gamma}}{\hat{H}_g} + \sum_{g=1}^{G} \hat{H}_g \theta^{-1} [1 + \theta \ln \hat{H}_g] \frac{\hat{H}_g^{-1}}{J(2, \hat{H}_g)} \left[ \frac{(1 - \theta) \left[ - 1/\theta^2 - (1/\theta - 1) \ln \hat{H}_g \right] \hat{H}_g^{-20} \hat{H}_{g\gamma}}{\hat{H}_g \gamma} \right]
\]

\[
- \chi[D_g=2] \left\{ \frac{G}{\sum_{g=1}^{G} \left[ 1 + (1 - \theta) \ln \hat{H}_g \right] \hat{H}_g^{-1} \hat{H}_{g\gamma}}{J(2, \hat{H}_g)} \right\}
\]

\[
+ \sum_{g=1}^{G} \left[ \frac{1 - \theta}{J(2, \hat{H}_g)} \right]^2 \left[ \frac{3}{\sum_{g=1}^{G} \left[ 1 + (1 - \theta) \ln \hat{H}_g \right] \hat{H}_g^{-1} \hat{H}_{g\gamma}}{J(3, \hat{H}_g)} \right]
\]

\[
- \chi[D_g=3] \left\{ \frac{9}{\sum_{g=1}^{G} \left[ 1/\theta^2 + (1/\theta - 1) \ln \hat{H}_g \right] \hat{H}_g^{-20} \hat{H}_{g\gamma}}{J(3, \hat{H}_g)} \right\}
\]

\[
- \sum_{g=1}^{G} \left[ \frac{1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \hat{H}_g]}{J(3, \hat{H}_g)} \right] \hat{H}_g^{-30} \hat{H}_{g\gamma} \left[ \frac{3 (1 - \theta)}{J(3, \hat{H}_g)^2} \right]
\]
\[+ \sum_{g=1}^{G} \left[ (4/\theta^2 - 2) + 4\theta (2/\theta - 1) (1/\theta - 1) \ln \hat{H}_g \right] \hat{H}_g^{-2\theta - 1} \hat{H}_g \gamma \]

\[- \sum_{g=1}^{G} \left[ 1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \hat{H}_g \right] \times \left[ 2\theta (2/\theta - 1)(1/\theta - 1) \right] \hat{H}_g^{-4\theta - 1} \hat{H}_g \gamma \]

\[- \sum_{g=1}^{G} \left\{ \left[ 1/\theta^2 + (1/\theta - 1) \ln \hat{H}_g \right] \left[ 2\theta (2/\theta - 1)(1/\theta - 1) \right] \hat{H}_g^{-3\theta - 1} \hat{H}_g \gamma \right\} \left[ J(3, \hat{H}_g) \right]^2 \]

\[- \frac{\partial^2 L_P}{\partial \beta \gamma \partial \beta \phi} = - \sum_{g=1}^{G} D_g (\theta - 1) \left\{ \hat{H}_g \gamma \phi - \hat{H}_g \gamma \phi \right\} \]

\[+ \sum_{g=1}^{G} \left\{ (\theta - 1) \hat{H}_g -2 \hat{H}_g \gamma \hat{H}_g \phi + \theta \hat{H}_g -1 \hat{H}_g \gamma \phi \right\} \]

\[- \chi[D_g = 2] \left\{ - \sum_{g=1}^{G} (1 - \theta) \left[ \frac{\hat{H}_g -1 \hat{H}_g \gamma \phi}{J(2, \hat{H}_g)} \right] \right\} \]

\[+ \left( \frac{1 - \theta}{J(2, \hat{H}_g)} \right) \left( \frac{(1 + \theta) \hat{H}_g -2}{J(2, \hat{H}_g)} \right) \hat{H}_g \gamma \hat{H}_g \phi \]

\[- \chi[D_g = 3] \left\{ - 3 \sum_{g=1}^{G} (1 - \theta) \left[ \frac{\hat{H}_g -1 \hat{H}_g \gamma \phi}{J(3, \hat{H}_g)} \right] \right\} \]

\[+ \left( \frac{3 (1 - \theta) \hat{H}_g -2}{J(3, \hat{H}_g)} \right) \left( \frac{(1 + \theta) \hat{H}_g -2}{J(3, \hat{H}_g)} \right) \hat{H}_g \gamma \hat{H}_g \phi \]

\[- \sum_{g=1}^{G} 2\theta (2/\theta - 1)(1/\theta - 1) \left[ \frac{\hat{H}_g -2 \hat{H}_g \gamma \phi}{J(3, \hat{H}_g)} \right] \]
\[
+ \left[ \frac{2\theta (2/\theta - 1) (1/\theta - 1)}{J(3, \hat{\Pi}_g)^2} \right] \hat{\Pi}_{g\gamma} \] 
\[
\frac{(1 + 2\theta) \hat{\Pi}_g^{-2\theta - 2} \hat{\Pi}_{g\varphi}}{J(3, \hat{\Pi}_g)} \] 
\[
- 2 \sum_{g=1}^{G} \left\{ \frac{3 (1 - \theta)}{J(3, \hat{\Pi}_g)^2} \right\} \left[ \frac{2\theta (2/\theta - 1)(1/\theta - 1)}{J(3, \hat{\Pi}_g)^2} \right] \hat{\Pi}_{g\gamma} \hat{\Pi}_{g\varphi} \right\}
\[
- \hat{\Pi}_{g\gamma\varphi}
\]

where \( \chi[A] \) is an indicator of a set \( A \).

When there are four events in a group, we simply add appropriate negative second derivatives of \( J(4, \hat{\Pi}_g) \) with respect to \( \theta \) and \( \beta \) to the above equations. The expressions of these derivatives are quite complicated. So we will not record them here. Readers can refer to Appendix B for details.

4.2 Weibull Regression Model

As mentioned in Chapter 3, we will look at examples of right censored and left truncated data from the Framingham Heart Study. As noted above, assuming \( \omega \) follows the positive stable distributions, the observable log likelihood based on a right censored sample \( (t_{gjk}, I_{gjk}) \) is of the form (4.1.1.5). Using (4.1.1.1) the observable log likelihood based on a right censored and left truncated sample \( (t_{gjk}, I_{gjk}, t^c_{gjk}) \) in this case is given by

\[
L^c_P = \sum_{g=1}^{G} \left\{ D_g \left[ \ln \theta + (\theta - 1) \ln \hat{\Pi}_g \right] - (\hat{\Pi}_g)^\theta + \ln [J(D_g, \hat{\Pi}_g)] \right\}
\]
Recall that $\bar{H}_g^c = \sum_{j=1}^{S} \sum_{k=1}^{ngj} H_{oj}(t_{gjk}) \exp\{\beta z_{gjk}\}$.

Maximum likelihood estimates must be found by some appropriate numerical technique. Appropriate first and negative second derivatives of (4.2.1) when $h_{oj}(x) = \alpha_j x^{a_j}$ ($j = 1, ..., S$), and at most three events are observed in any group are recorded below:

\[
\frac{\partial \mathcal{L}_P^c}{\partial \theta} = \sum_{g=1}^{G} D_g \left[ 1/\theta + \ln \bar{H}_g \right] - \sum_{g=1}^{G} \bar{H}_g^\theta \ln \bar{H}_g
\]

\[
+ \chi[D_g = 2] \sum_{g=1}^{G} \left[ \frac{1}{\theta^2} + (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-\theta} \quad J(2, \bar{H}_g)
\]

\[
+ \chi[D_g = 3] \sum_{g=1}^{G} \left[ - 3 \left[ 1/\theta^2 + (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-\theta} - \right. \]

\[
\left. \left[ 1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-2\theta} \right] \times \frac{1}{J(3, \bar{H}_g)}
\]

\[
+ \sum_{g=1}^{G} \bar{H}_g^{c\theta} \ln \bar{H}_g^c
\]
\[
\begin{align*}
\frac{\phi_{dH}}{\delta_{He}} \frac{3^H}{(1 - \theta/1)(1 - \theta/2)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X + \\
\frac{\phi_{dH}}{\delta_{He}} \frac{3^H}{(\theta - 1)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X - \\
\frac{\phi_{dH}}{\delta_{He}} \frac{3^H}{(1 - \theta)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X + \\
\frac{\lambda_{Pe}}{\delta_{He}} \frac{3^H}{(1 - \theta/1)(1 - \theta/2)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X + \\
\frac{\lambda_{Pe}}{\delta_{He}} \frac{3^H}{(\theta - 1)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X - \\
\frac{\lambda_{Pe}}{\delta_{He}} \frac{3^H}{(1 - \theta)} & \times \frac{I = 3}{\delta} \left[ \varepsilon = \delta \right] X + \\
\end{align*}
\]
\[ + \sum_{g=1}^{G} \sum_{j=1}^{N_g} I_{gjk} z_{gjk}\phi + \sum_{g=1}^{G} \theta H_g^{\Theta-1} \frac{\partial H_g^c}{\partial \beta_\phi} \]

\[ \frac{\partial^2 L_P^c}{\partial \Theta^2} = \sum_{g=1}^{G} \frac{D_g}{\Theta^2} + \sum_{g=1}^{G} \frac{H_g^\Theta [\ln H_g]^2}{J(2, H_g)} \]

\[ - \chi[D_g = 2] \left[ \sum_{g=1}^{G} - \frac{\left\{ 1/\Theta^2 + (1/\Theta - 1) \ln H_g \right\}^2 H_g^{-2\Theta}}{J(2, H_g)} \right] \]

\[ + \sum_{g=1}^{G} \left\{ 2/\Theta^3 + 2 \ln H_g / \Theta^2 + (1/\Theta - 1) [\ln H_g]^2 \right\} H_g^{-\Theta} \frac{J(2, H_g)}{J(3, H_g)} \]

\[ - \chi[D_g = 3] \left[ \sum_{g=1}^{G} - \frac{3 \left\{ 1/\Theta^2 + (1/\Theta - 1) \ln H_g \right\}^2 H_g^{-2\Theta}}{J(3, H_g)} \right] \]

\[ + \sum_{g=1}^{G} \frac{3 \left\{ 2/\Theta^3 + 2 \ln H_g / \Theta^2 + (1/\Theta - 1) [\ln H_g]^2 \right\} H_g^{-\Theta}}{J(3, H_g)} \]

\[ - \sum_{g=1}^{G} \frac{1/\Theta^2 (4/\Theta - 3) + 2 (2/\Theta - 1) (1/\Theta - 1) \ln H_g \right\}^2 H_g^{-4\Theta}}{J(3, H_g)} \]

\[ + \sum_{g=1}^{G} \left\{ (12/\Theta^4 - 6/\Theta^3) + (16/\Theta^3 - 12/\Theta^2) \ln H_g + 4 (2/\Theta - 1) (1/\Theta - 1) [\ln H_g]^2 \right\} H_g^{-2\Theta} \]

\[ \times \frac{1}{J(3, H_g)} - 2 \sum_{g=1}^{G} \left\{ \frac{3/\Theta^2 + 3 (1/\Theta - 1) \ln H_g \right\} H_g^{-\Theta} \]

\[ J(3, H_g) \]

\[ \times \frac{1/\Theta^2 (4/\Theta - 3) + 2 (2/\Theta - 1) (1/\Theta - 1) \ln H_g \right\} H_g^{-2\Theta}}{J(3, H_g)} \]
\[
- \frac{\partial^2 L^c_P}{\partial \theta \partial \alpha_\gamma} = - \sum_{g=1}^{G} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma} \sum_{g=1}^{G} \bar{H}_g^{\theta-1} [1 + \theta \ln \bar{H}_g] \frac{\partial \bar{H}_g}{\partial \alpha_\gamma} \\
- \chi[D_g=2] \left[ \sum_{g=1}^{G} \frac{[1 + (1 - \theta) \ln \bar{H}_g] \bar{H}_g^{\theta-1} \theta \frac{\partial \bar{H}_g}{\partial \alpha_\gamma}}{J(2, \bar{H}_g)} \right] \\
+ \sum_{g=1}^{G} \frac{(1 - \theta) [-1/\theta^2 - (1/\theta - 1) \ln \bar{H}_g] \bar{H}_g^{-2\theta - 1} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma}}{(J(2, \bar{H}_g))^2} \\
- \chi[D_g=3] \left[ \sum_{g=1}^{G} \frac{[1 + (1 - \theta) \ln \bar{H}_g] \bar{H}_g^{\theta-1} \theta \frac{\partial \bar{H}_g}{\partial \alpha_\gamma}}{J(3, \bar{H}_g)} \right] \\
- 9 \sum_{g=1}^{G} \frac{(1 - \theta) [1/\theta^2 + (1/\theta - 1) \ln \bar{H}_g] \bar{H}_g^{-2\theta - 1} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma}}{(J(3, \bar{H}_g))^2} \\
- \sum_{g=1}^{G} \left[ 1/\theta^2 (4/\theta - 3) + 2 (2/\theta - 1) (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-2\theta} \left[ (1 - \theta) \bar{H}_g^{-\theta - 1} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma} \right] \\
\times \frac{1}{(J(3, \bar{H}_g))^2} \\
+ \sum_{g=1}^{G} \frac{[(4/\theta^2 - 2) + 4 \theta (2/\theta - 1) (1/\theta - 1) \ln \bar{H}_g] \bar{H}_g^{-2\theta - 1} \frac{\partial \bar{H}_g}{\partial \alpha_\gamma}}{J(3, \bar{H}_g)}
\]
\[- \sum_{g=1}^{G} \left[ 1/\theta^2 \left( 4/\theta - 3 \right) + 2 \left( 2/\theta - 1 \right) \left( 1/\theta - 1 \right) \ln \bar{H}_g \right] \]

\[= \sum_{g=1}^{G} \frac{H_g^{-2\theta} \left[ 2\theta \left( 2/\theta - 1 \right) \left( 1/\theta - 1 \right) \bar{H}_g^{2\theta-1} \frac{\partial \bar{H}_g}{\partial \alpha_{\gamma}} \right]}{\{J(3, B_g)\}^2} \]

\[- \sum_{g=1}^{G} 3 \left[ 1/\theta^2 + (1/\theta-1) \ln \bar{H}_g \right] \bar{H}_g^\theta \]

\[= \sum_{g=1}^{G} \frac{\bar{H}_g^{\theta-1} \left[ 1 + \theta \ln \bar{H}_g^\theta \right]}{\partial \alpha_{\gamma}} \]

\[- \frac{\partial^2 L_c}{\partial \theta \partial \beta_{\phi}} = - \sum_{g=1}^{G} D_g \frac{\partial \bar{H}_g}{\partial \phi} + \sum_{g=1}^{G} \bar{H}_g^{\theta-1} \left[ 1 + \theta \ln \bar{H}_g \right] \frac{\partial \bar{H}_g}{\partial \beta_{\phi}} \]

\[- \chi[D_g = 2] \left[ \sum_{g=1}^{G} \frac{\left[ 1 + \left( 1 - \theta \right) \ln \bar{H}_g \right] \bar{H}_g^{\theta-1} \cdot \theta \frac{\partial \bar{H}_g}{\partial \beta_{\phi}} }{J(2, \bar{H}_g)} \right] \]

\[+ \sum_{g=1}^{G} \frac{(1 - \theta) \left[ - 1/\theta^2 - (1/\theta-1) \ln \bar{H}_g \right] \bar{H}_g^{2\theta-1} \frac{\partial \bar{H}_g}{\partial \beta_{\phi}} \right]}{\{J(2, \bar{H}_g)\}^2} \]

\[- \chi[D_g = 3] \left[ 3 \sum_{g=1}^{G} \frac{\left[ 1 + \left( 1 - \theta \right) \ln \bar{H}_g \right] \bar{H}_g^{\theta-1} \cdot \theta \frac{\partial \bar{H}_g}{\partial \beta_{\phi}} }{J(3, \bar{H}_g)} \right] \]
\[ - 9 \sum_{g=1}^{G} \frac{(1 - \theta) \left[ \frac{1}{\theta^2} + (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-2\theta -1} \frac{\partial \bar{H}_g}{\partial \beta_\phi}}{\left\{ J(3,\bar{H}_g) \right\}^2} \]

\[ - \sum_{g=1}^{G} \left[ \frac{1}{\theta^2} \left( \frac{4}{\theta} - 3 \right) + 2 \left( \frac{2}{\theta} - 1 \right) \left( 1/\theta - 1 \right) \ln \bar{H}_g \right] \bar{H}_g^{-2\theta} \left[ 3 \left( 1 - \theta \right) \bar{H}_g^{-\theta -1} \frac{\partial \bar{H}_g}{\partial \beta_\phi} \right] \]

\[ \times \frac{1}{\left\{ J(3,\bar{H}_g) \right\}^2} \]

\[ + \sum_{g=1}^{G} \frac{\left[ (4/\theta^2 - 2) + 4 \theta \left( 2/\theta - 1 \right) \left( 1/\theta - 1 \right) \ln \bar{H}_g \right] \bar{H}_g^{-2\theta -1} \frac{\partial \bar{H}_g}{\partial \beta_\phi}}{J(3,\bar{H}_g)} \]

\[ \sum_{g=1}^{G} \left[ \frac{1}{\theta^2} \left( \frac{4}{\theta} - 3 \right) + 2 \left( \frac{2}{\theta} - 1 \right) \left( 1/\theta - 1 \right) \ln \bar{H}_g \right] \]

\[ \bar{H}_g^{-2\theta} \left[ 2\theta \left( \frac{2}{\theta} - 1 \right) \left( 1/\theta - 1 \right) \bar{H}_g^{-2\theta -1} \frac{\partial \bar{H}_g}{\partial \beta_\phi} \right] \]

\[ \times \frac{1}{\left\{ J(3,\bar{H}_g) \right\}^2} \]

\[ - \sum_{g=1}^{G} \left[ \frac{1}{\theta^2} + (1/\theta - 1) \ln \bar{H}_g \right] \bar{H}_g^{-\theta} \]

\[ \left[ 2\theta \left( \frac{2}{\theta} - 1 \right) \left( 1/\theta - 1 \right) \bar{H}_g^{-2\theta -1} \frac{\partial \bar{H}_g}{\partial \beta_\phi} \right] \]

\[ \left\{ J(3,\bar{H}_g) \right\}^2 \]

\[ \frac{\partial \bar{H}_g^c}{\partial \beta_\phi} \]

\[ - \sum_{g=1}^{G} \bar{H}_g^c \left[ 1 + \theta \ln \bar{H}_g^c \right] \frac{\partial \bar{H}_g^c}{\partial \beta_\phi} \]
\[
\frac{\partial^2 L_p}{\partial \alpha_\gamma^2} = - \sum_{g=1}^G D_g (\theta - 1) \left\{ \frac{\partial^2 H_g}{\partial \alpha_\gamma^2} - \frac{\partial (H_g^{-1})}{\partial \alpha_\gamma} \right\} \\
+ \sum_{g=1}^G \left\{ \theta (\theta - 1) H_g \frac{\partial H_g}{\partial \alpha_\gamma} + \theta H_g \frac{\partial^2 H_g}{\partial \alpha_\gamma^2} \right\} \\
+ \chi[D_g = 2] \left[ \sum_{g=1}^G (1 - \theta) \frac{H_g^{-1}}{J(2,H_g)} \frac{\partial^2 H_g}{\partial \alpha_\gamma^2} + \frac{\partial H_g^{-2\theta-2}}{J(2,H_g)^2} - \frac{\partial H_g^{-2\theta-2}}{J(2,H_g)} \right] \\
+ \chi[D_g = 3] \left[ -3 \sum_{g=1}^G (1 - \theta) \frac{H_g^{-1}}{J(3,H_g)} \frac{\partial^2 H_g}{\partial \alpha_\gamma^2} + \frac{3 (1 - \theta) H_g^{-2\theta-2}}{J(3,H_g)^2} - \frac{3 (1 + \theta) H_g^{-2\theta-2}}{J(3,H_g)} \frac{\partial H_g^{-2\theta-2}}{\partial \alpha_\gamma^2} \right] \\
- \sum_{g=1}^G 2\theta (2/\theta - 1) (1/\theta - 1) \frac{H_g^{-1}}{J(3,H_g)} \frac{\partial^2 H_g}{\partial \alpha_\gamma^2} \\
+ \frac{2\theta (2/\theta - 1) (1/\theta - 1) H_g^{-4\theta-2}}{J(3,H_g)^2} - \frac{2\theta (2/\theta - 1) (1/\theta - 1) H_g^{-4\theta-2}}{J(3,H_g)} \frac{\partial H_g^{-2\theta-2}}{\partial \alpha_\gamma^2} \right\]
\]
\[
- \sum_{g=1}^{G} \theta (\theta - 1) \frac{\partial^2 H_g^c}{\partial \alpha' \partial \alpha} - \frac{\partial H_g^c}{\partial \alpha' \partial \alpha' \partial \alpha''} \\
\frac{\partial^2 L_P^c}{\partial \beta \partial \beta'} = - \sum_{g=1}^{G} D_g (\theta - 1) \left\{ \begin{array}{ll}
\frac{\partial^2 H_g}{\partial \beta \partial \beta'} & \frac{\partial H_g}{\partial \beta' \partial \beta'} \\
H_g & H_g^2 
\end{array} \right\} \\
+ \sum_{g=1}^{G} \left\{ \theta (\theta - 1) \frac{\partial^2 H_g}{\partial \beta \partial \beta'} + \theta \frac{\partial^2 H_g^c}{\partial \beta \partial \beta' \partial \alpha'} \right\} \\
+ \chi[D_g = 2] \left[ \sum_{g=1}^{G} (1 - \theta) \left\{ \begin{array}{ll}
\frac{\partial^2 H_g}{\partial \beta \partial \beta'} & \\
J(2,H_g) & 
\end{array} \right\} \\
+ \left[ (1 - \theta) \frac{\partial \beta \partial \beta'}{J(2,H_g)^2} - (1 + \theta) \frac{\partial \beta \partial \beta'}{J(2,H_g)} \right] \right\} \\
- \chi[D_g = 3] \left[ - 3 \sum_{g=1}^{G} (1 - \theta) \left\{ \begin{array}{ll}
\frac{\partial^2 H_g}{\partial \beta \partial \beta'} & \\
J(3,H_g) & 
\end{array} \right\} \\
+ \left[ \frac{3 (1 - \theta) \partial \beta \partial \beta'}{J(3,H_g)^2} - (1 + \theta) \frac{\partial \beta \partial \beta'}{J(3,H_g)} \right] \right\} \\
- \sum_{g=1}^{G} 2 \theta (2/\theta - 1) (1/\theta - 1) \left\{ \begin{array}{ll}
\frac{\partial^2 H_g}{\partial \beta \partial \beta'} & \\
J(3,H_g) & 
\end{array} \right\} \\
+ \left[ \frac{2 \theta (2/\theta - 1) (1/\theta - 1) \partial \beta \partial \beta'}{J(3,H_g)^2} - (1 + 2 \theta) \frac{\partial \beta \partial \beta'}{J(3,H_g)} \right] \right\} 
\]
The first and second derivatives of \( \bar{H}_g \) and \( \bar{H}_g^C \) with respect to \((\alpha_j, \theta, \beta)\) are given in (3.2.1). When there are four events in a group, we simply add the appropriate first and second derivatives of \( J(4, \bar{H}_g) \) to the above equations. The expressions of these derivatives are quite complicated. So we will not record them here. Readers can refer to Appendix D for details. As in the gamma case, there are numerical problems with finding the maximum likelihood estimates of \((\alpha_j, \theta, \beta)\).

In the sequel, Marquart’s method (Ralston and Rabinowitz, 1978) was used to obtain the maximum likelihood estimates. Our experience has found that this numerical procedure is highly sensitive to the initial guesses for \(\alpha_j\), \(\beta\), and \(\theta\). Using the estimates for \(\alpha_j\), and \(\beta\) obtained by a standard Weibull regression routine based on the data ignoring group effects as initial guesses are in general not acceptable. Following Klein et al. (1991), we find the initial estimates by searching a range of values for the dependence parameters for the maximal profile likelihood estimates of \(\alpha_j\) and \(\beta\) obtained by maximizing (4.2.1) for a given value of \(\theta\). The search starts with independence, which gives a baseline profile likelihood and initial
guesses for $\alpha_j$ and $\beta$ for the least dependent model to be looked at. These new estimates of $\alpha_j$ and $\beta$ are used as initial guesses for the next profile likelihood. Once the search has been completed, the values of $\alpha_j$, $\beta$ and $\theta$ which corresponds to the maximal profile likelihood seen in the search are used as initial values in Marquart’s algorithm to obtain the maximum likelihood estimates. With these initial values the convergence of that algorithm is relatively quick.
CHAPTER V
EXAMPLE

In the sequel, we present three examples from the well known Framingham Heart Study (Dawber, 1980) to illustrate the EM algorithm approach, described in Sections 3.1 and 4.1, to the estimation of the dependence parameters and regression coefficients in the gamma and positive stable frailty models. There are several points we would like to demonstrate by these examples. First, we will show that one would underestimate the relative risks between individuals with different coverts if the association induced by a frailty were ignored. Second, we will show that the positive stable model is not a reasonable model to use for truncated data. Third, we will show that the estimates of the dependence parameters and regression coefficients using the EM algorithm approach are generally close to the maximum likelihood estimates using the parametric approach described in Sections 3.2 and 4.2. Fourth, we will show that using the joint density function of observable data \((t_{gjk}, I_{gjk})\) to compute the observed information matrix is very encouraging, although asymptotic theory for the estimators is still elusive.
EXAMPLE 1: We shall consider two endpoints, the time to the first evidence of coronary heart disease and the time to the first evidence of cerebrovascular accident, within an individual. It is believed that some biological processes may induce an association between the two event times within the same individual. The data set used in this example consists of all individuals in the Framingham Heart Study who survived to age 45 disease-free. Individuals were considered disease-free if they had no prior history of hypertension, glucose intolerance, coronary heart disease (CHD) or cerebrovascular accident (CVA) prior to their 45th birthday. Since examinations were conducted every two years, we included in our example individuals who had an exam at age 44 or 45 and were disease-free at that exam. A consequence of this approach is that individuals will be in different cohorts, i.e., some will be in the study several years prior to inclusion into the data set. To control this cohort effect, we have included a covariate, waiting time (WAIT) in the study until the individual reaches 45 years of age, along with the traditional risk factors of interest, namely; gender (SEX), systolic blood pressure (SBP), body mass index (BMI), defined as the individual's weight divided by the square of their height, cholesterol level (CHOL), smoking (SMK), and interactions of these covariates with gender. All covariate values were taken from the biannual exam at which an individual was entered into the data set and individuals were excluded from the sample if their covariate values on inclusion were missing. Of the 1,571 individuals who were disease-free at age 45, 41.4% were male and 62.8% were smokers. The average waiting time in the study, until an individual reached age 45 disease-free, was 7.37 years. The average systolic blood pressure was 122.03 mm.Hg, the average cholesterol reading was 230.86 mg/dL and the average body
mass index was 24.38 (kg/m^2). The time scale used in our analysis was the age measured from birth.

**EXAMPLE 2:** We shall consider a single endpoint, the time to the first evidence of coronary heart disease, and use frailty models for sibling effects. It is believed that siblings should have event times more associated than nonsiblings because they share a common genetic code and are exposed to the same environment during their early lives. The same set of data used in Example 1 is used here. The time scale used in our analysis was the age measured from birth.

**EXAMPLE 3:** We shall consider a single endpoint, the time to the first evidence of coronary heart disease, and use frailty models for sibling effects. The data set used in this example consists of 4178 non-diabetics who were followed for a maximum of 30 years. Individuals were included in the sample if they had cholesterol measured at the second Framingham examination cycle (1951-1956). Patients were excluded from the sample if they developed either cardiovascular disease or cancer prior to their second examination cycle. Following Anderson et al. (1987) potential covariates considered were sex, age (4 categories ≤ 39, 40-47, 48-54, ≥ 55), age by sex interactions, cholesterol by sex interaction, smoking by sex interaction, age by cholesterol interactions, age by smoking interactions, systolic blood pressure, body mass index, smoking behavior (yes or no), and cholesterol level. Also included were three age by sex by cholesterol covariates and three age by sex by smoking covariates, for a total of 26 potential covariates. The individuals were stratified by the above four age groups. Of the 4,178 individuals who were
disease-free at entry into the study 44.4% were male and 57.9% were smokers. The average systolic blood pressure was 133.89 mm.Hg, the average cholesterol reading was 227.08 mg/dL and the average body mass index was 0.0361 (kg/cm^2 \times 10). There were 1590 individuals under age 40, 1178 individuals between ages 40 and 47, 854 individuals between ages 48 and 54, and 556 individuals above age 54. The time scale used in our analysis was the time measured from entry.

Example 1

The two endpoints of interest for this example are the first evidence of coronary heart disease and the first evidence of cerebrovascular accident within the same individual. Table 5.1 presents the results for the Cox model under independence and the two frailty models discussed in Section 3.1 and Section 4.1 using the EM algorithm approach. The continuous covariates cholesterol, systolic blood pressure, body mass index, and waiting time before inclusion were centered at their mean. The average waiting time in the study, until an individual reached age 45 disease-free, was 7.37 years. The average systolic blood pressure was 122.03 mm.Hg, the average cholesterol reading was 230.86 mg/dL and the average body mass index was 24.38 (kg/m^2). We coded gender to have the value of one when it is female; zero otherwise. We dichotomized the covariate smoking behavior so that it takes the value of one if an individual smokes; zero otherwise. The time scale used in our analysis is the age measured from birth. Cholesterol, smoking, and systolic blood pressure were consistently significant in predicting CHD. Systolic blood pressure was marginally significant in predicting CVA. The dependence parameters are significant in the two frailty models. Kendall's \( \tau \) for the gamma is
considerably larger than that for the positive stable models, although the likelihoods for the two frailty models do not show much difference.

TABLE 5.1

Estimates of Parameters for the Two Semiparametric Frailty Models for CHD and CVA Based on Disease-Free Individuals at Age 45

First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>SEX</td>
<td>-0.367</td>
<td>0.253</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.566</td>
<td>0.196</td>
</tr>
<tr>
<td>BMI</td>
<td>0.409</td>
<td>0.265</td>
</tr>
<tr>
<td>SMK</td>
<td>0.501</td>
<td>0.221</td>
</tr>
<tr>
<td>SBP</td>
<td>1.559</td>
<td>0.520</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.367</td>
<td>0.309</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.143</td>
<td>0.363</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.336</td>
<td>0.301</td>
</tr>
</tbody>
</table>
The analysis shows that the estimates of the regression coefficients for time to first evidence of coronary heart disease were quite similar under the various frailty models. To better interpret these coefficients we present in Figures 5.1 the relative risk of coronary heart disease for a smoker as compared to a nonsmoker for males and females. In these calculations all covariates other than smoking were set
at their mean values. We note from these figures that had one ignored any possible association and simply fit an independence model that the relative risk of smoking's effect on time to CHD would be underestimated until advanced age.

**FIGURE 5.1**

Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker under the Two Semiparametric Frailty Models for CHD and CVA Independence Model (lower horizontal line), Positive Stable Model (upper horizontal line), Gamma Model (curve)
FIGURE 5.1 (CONTINUED)

a Female Smoker versus a Female Nonsmoker

Independence Model (lower horizontal line), Positive Stable Model
(upper horizontal line), Gamma Model (curve)
Tables 5.2, 5.3 and 5.4 present the results on the effects of smoking, cholesterol, and body mass index on incidence of a CHD or CVA for males and females, respectively.

**TABLE 5.2**

Test for Effect of Smoking on Incidences of CHD and CVA under the Two Semiparametric Frailty Models for CHD and CVA

**Males**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>CHD</td>
<td>0.501</td>
<td>0.221</td>
</tr>
<tr>
<td>CVA</td>
<td>1.048</td>
<td>0.618</td>
</tr>
</tbody>
</table>

**Females**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>CHD</td>
<td>0.165</td>
<td>0.203</td>
</tr>
<tr>
<td>CVA</td>
<td>0.429</td>
<td>0.422</td>
</tr>
</tbody>
</table>
TABLE 5.3

Test for Effect of Cholesterol on Incidences of CHD and CVA under the Two Semiparametric Frailty Models for CHD and CVA

Males

<table>
<thead>
<tr>
<th>EVENT</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.566</td>
<td>0.196</td>
<td>0.004</td>
<td>0.668</td>
<td>0.238</td>
<td>0.005</td>
<td>0.607</td>
<td>0.211</td>
<td>0.004</td>
</tr>
<tr>
<td>CVA</td>
<td>0.468</td>
<td>0.464</td>
<td>0.313</td>
<td>0.521</td>
<td>0.480</td>
<td>0.278</td>
<td>0.523</td>
<td>0.485</td>
<td>0.282</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>EVENT</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
<th>( \gamma )</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.199</td>
<td>0.243</td>
<td>0.412</td>
<td>0.223</td>
<td>0.265</td>
<td>0.401</td>
<td>0.242</td>
<td>0.258</td>
<td>0.349</td>
</tr>
<tr>
<td>CVA</td>
<td>-0.090</td>
<td>0.502</td>
<td>0.858</td>
<td>-0.090</td>
<td>0.509</td>
<td>0.860</td>
<td>-0.012</td>
<td>0.516</td>
<td>0.981</td>
</tr>
</tbody>
</table>
TABLE 5.4
Test for Effect of Body Mass Index on Incidences of CHD and CVA
under the Two Semiparametric Frailty Models for CHD and CVA

Males

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>CHD</td>
<td>$0.409$</td>
<td>$0.265$</td>
</tr>
<tr>
<td>CVA</td>
<td>$0.939$</td>
<td>$0.622$</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>CHD</td>
<td>$0.266$</td>
<td>$0.251$</td>
</tr>
<tr>
<td>CVA</td>
<td>$0.334$</td>
<td>$0.501$</td>
</tr>
</tbody>
</table>

We can see the effects of smoking were consistently significant in predicting CHD, but were not significant in predicting CVA for males. The effects of smoking were not significant in predicting both CHD and CVA for females. The effects of cholesterol were consistently significant in predicting CHD, but were not significant in predicting CVA for males. The effects of cholesterol were not significant in
predicting both CHD and CVA for females. The effects of body mass index were not significant in predicting both CHD and CVA for males and females.

Table 5.5 presents results for the Weibull regression model under independence and the two frailty models discussed in Section 3.2 and Section 4.2 using the maximum likelihood estimation. We assumed two-parameter Weibull models for the baseline hazard functions. So we included in our analysis a stratum indicator (INT) for each of the two endpoints CHD and CVA, as described in Section 3.2. All continuous covariates were centered at their mean. The ages of individuals at the time of inclusion, 44 or 45, were used as truncation times in our analysis. Here cholesterol, systolic blood pressure, and smoking were consistently significant in predicting CHD. Systolic blood pressure was marginally significant in predicting CVA. The dependence parameters are significant in the two frailty models. Kendall's $\tau$ for the gamma is considerably larger than that for the positive stable models, although the likelihoods for the two frailty models do not show much difference.
### TABLE 5.5

Estimates of Parameters for the Two Parametric Frailty Models for CHD and CVA Based on Disease-Free Individuals at Age 45

First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>INT</td>
<td>-32.04</td>
<td>2.563</td>
</tr>
<tr>
<td>α</td>
<td>7.211</td>
<td>0.605</td>
</tr>
<tr>
<td>SEX</td>
<td>-0.370</td>
<td>0.254</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.572</td>
<td>0.196</td>
</tr>
<tr>
<td>BMI</td>
<td>0.418</td>
<td>0.266</td>
</tr>
<tr>
<td>SMK</td>
<td>0.500</td>
<td>0.221</td>
</tr>
<tr>
<td>SBP</td>
<td>1.600</td>
<td>0.520</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.013</td>
<td>0.018</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.368</td>
<td>0.310</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.155</td>
<td>0.364</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.335</td>
<td>0.301</td>
</tr>
</tbody>
</table>
TABLE 5.5
(CONTINUED)

First Evidence of Cerebrovascular Accident

<table>
<thead>
<tr>
<th>Effect</th>
<th>INDEPENDENCE</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>INT</td>
<td>-31.36</td>
<td>5.628</td>
<td>&lt;.001</td>
<td>-32.76</td>
<td>5.683</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>α</td>
<td>6.496</td>
<td>1.321</td>
<td>&lt;.001</td>
<td>6.829</td>
<td>1.336</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SEX</td>
<td>0.338</td>
<td>0.684</td>
<td>0.620</td>
<td>0.353</td>
<td>0.701</td>
<td>0.615</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.462</td>
<td>0.463</td>
<td>0.317</td>
<td>0.543</td>
<td>0.487</td>
<td>0.265</td>
</tr>
<tr>
<td>BMI</td>
<td>0.933</td>
<td>0.621</td>
<td>0.133</td>
<td>1.031</td>
<td>0.670</td>
<td>0.123</td>
</tr>
<tr>
<td>SMK</td>
<td>1.039</td>
<td>0.617</td>
<td>0.092</td>
<td>1.137</td>
<td>0.634</td>
<td>0.073</td>
</tr>
<tr>
<td>SBP</td>
<td>2.079</td>
<td>1.131</td>
<td>0.066</td>
<td>2.320</td>
<td>1.170</td>
<td>0.047</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.026</td>
<td>0.040</td>
<td>0.511</td>
<td>0.026</td>
<td>0.041</td>
<td>0.525</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.547</td>
<td>0.678</td>
<td>0.420</td>
<td>-0.625</td>
<td>0.701</td>
<td>0.373</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.607</td>
<td>0.792</td>
<td>0.444</td>
<td>-0.659</td>
<td>0.852</td>
<td>0.440</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.601</td>
<td>0.749</td>
<td>0.422</td>
<td>-0.667</td>
<td>0.769</td>
<td>0.386</td>
</tr>
<tr>
<td>DEPENDENCE PARAMETER</td>
<td>1.327</td>
<td>0.507</td>
<td>.0044</td>
<td>0.889</td>
<td>0.047</td>
<td>0.009</td>
</tr>
<tr>
<td>Kendall τ</td>
<td>0</td>
<td>0.399</td>
<td>0.111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLIKE</td>
<td>-1716.16</td>
<td>-1710.44</td>
<td>-1711.81</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The analysis shows that the estimates of the regression coefficients for time to first evidence of coronary heart disease were quite similar under the various frailty models. To better interpret these coefficients we present in Figures 5.2 the relative risk of coronary heart disease for a smoker as compared to a nonsmoker for males and females. In these calculations all covariates other than smoking were set at their mean values. We note from these figures that had one ignored any possible association and simply fit an independence model that the relative risk of smoking's effect on time to CHD would be underestimated until advanced age.

![Relative Risk](image)

**FIGURE 5.2**
Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker under the Two Parametric Frailty Models for CHD and CVA
Curves are Gamma Model (_____), Positive Stable Model (_ . _ ._), and Independence Model (_ _ _ _)
FIGURE 5.2 (CONTINUED)

RELATIVE RISK

1.3

1.25

1.2

1.15

A G E

50. 55. 60. 65. 70.

a Female Smoker versus a Female Nonsmoker

Curves are Gamma Model (_____), Positive Stable Model (._._._),
and Independence Model (_ _ _)
Tables 5.6, 5.7 and 5.8 present the results on the effects of smoking, cholesterol and body mass index on incidence of a CHD or CVA for males and females, respectively.

**TABLE 5.6**

Test for Effect of Smoking on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA

**Males**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>CHD</td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>0.500</td>
<td>0.221</td>
<td>0.024</td>
</tr>
<tr>
<td>CVA</td>
<td>1.039</td>
<td>0.617</td>
</tr>
</tbody>
</table>

**Females**

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td>CHD</td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>0.165</td>
<td>0.203</td>
<td>0.417</td>
</tr>
<tr>
<td>CVA</td>
<td>0.438</td>
<td>0.423</td>
</tr>
</tbody>
</table>
TABLE 5.7

Test for Effect of Cholesterol on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA

Males

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA POSITIVE STABLE</th>
<th>INDEPENDENCE FRAILTY</th>
<th>FRAILTY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>CHD</td>
<td>0.572</td>
<td>0.196</td>
<td>0.004</td>
</tr>
<tr>
<td>CVA</td>
<td>0.462</td>
<td>0.463</td>
<td>0.317</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>EVENT</th>
<th>GAMMA POSITIVE STABLE</th>
<th>INDEPENDENCE FRAILTY</th>
<th>FRAILTY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>CHD</td>
<td>0.204</td>
<td>0.243</td>
<td>0.401</td>
</tr>
<tr>
<td>CVA</td>
<td>-0.085</td>
<td>0.503</td>
<td>0.866</td>
</tr>
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</table>
TABLE 5.8
Test for Effect of Body Mass Index on Incidences of CHD and CVA under the Two Parametric Frailty Models for CHD and CVA

Males

<table>
<thead>
<tr>
<th>EVENT</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.418</td>
<td>0.266</td>
<td>0.117</td>
<td>0.519</td>
<td>0.335</td>
<td>0.121</td>
<td>0.430</td>
<td>0.300</td>
<td>0.152</td>
</tr>
<tr>
<td>CVA</td>
<td>0.933</td>
<td>0.621</td>
<td>0.133</td>
<td>1.031</td>
<td>0.670</td>
<td>0.123</td>
<td>0.940</td>
<td>0.661</td>
<td>0.155</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>EVENT</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.263</td>
<td>0.252</td>
<td>0.297</td>
<td>0.264</td>
<td>0.293</td>
<td>0.367</td>
<td>0.300</td>
<td>0.279</td>
<td>0.283</td>
</tr>
<tr>
<td>CVA</td>
<td>0.326</td>
<td>0.502</td>
<td>0.517</td>
<td>0.372</td>
<td>0.535</td>
<td>0.487</td>
<td>0.442</td>
<td>0.529</td>
<td>0.404</td>
</tr>
</tbody>
</table>

We can see the effects of smoking were consistently significant in predicting CHD, but were not significant in predicting CVA for males. The effects of smoking were not significant in predicting both CHD and CVA for females. The effects of cholesterol were consistently significant in predicting CHD, but were not significant in predicting CVA for males. The effects of cholesterol were not significant in
predicting both CHD and CVA for females. The effects of body mass index were not significant in predicting both CHD and CVA for males and females.

Note that using either the EM algorithm approach or the parametric approach gives us the same conclusions. The curves of the relative risk of coronary heart disease for a smoker as compared to a nonsmoker for males and females in Figures 5.2 are almost identical to the corresponding ones in Figures 5.1. It appears that using the joint density function of \((t_{gjk}, I_{gjk})\) to compute the observed information matrix in the EM algorithm approach is very encouraging. A simulation study will be performed in the future to examine the behavior of the EM algorithm estimates for moderate and large sample sizes and the appropriateness of using the joint density function of \((t_{gjk}, I_{gjk})\) to compute the observed information matrix.
Example 2

The endpoint of interest in this example is the time to the first evidence of coronary heart disease. We use frailty models to group siblings who were disease-free at age 45. The sizes of the various sibling groups and the number of groups experiencing Dg events for each family size are reported in Table 5.9.

**TABLE 5.9**

Summary Information on Sibling Group Size and Number of CHD Events in Groups for Each Size Group for Disease-Free Individuals at Age 45

<table>
<thead>
<tr>
<th>SIZE OF SIBLING GROUP</th>
<th>NUMBER WITH NO DEATHS</th>
<th>NUMBER WITH 1 DEATH</th>
<th>NUMBER WITH 2 DEATHS</th>
<th>NUMBER WITH 3 DEATHS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1060</td>
<td>201</td>
<td>0</td>
<td>0</td>
<td>1261</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>29</td>
<td>2</td>
<td>0</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1159</td>
<td>235</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.10 presents the results for the Cox model under independence and the two frailty models. The continuous covariates cholesterol, systolic blood pressure, body mass index, and waiting time before inclusion were centered at their mean. The average waiting time in the study, until an individual reached age 45 disease-free, was 7.37 years. The average systolic blood pressure was 122.03 mmHg, the average cholesterol reading was 230.86 mg/dL and the average body mass index was 24.38(kg/m²). The time scale used in our analysis is the age measured from birth. Here cholesterol, smoking, and systolic blood pressure were
consistently significant, as before. The dependence parameter for the positive stable frailty is indistinguishable from independence. For the gamma, the dependence parameter is significant, and Kendall's $\tau$ is .392.

**TABLE 5.10**

Estimates of Parameters for the Two Semiparametric Frailty Models for Sibling Effects Based on Disease-Free Individuals at Age 45 First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>$\beta$</th>
<th>SE</th>
<th>P</th>
<th>$\beta$</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX</td>
<td>-0.367</td>
<td>0.253</td>
<td>0.148</td>
<td>-0.440</td>
<td>0.281</td>
<td>0.118</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.566</td>
<td>0.196</td>
<td>0.004</td>
<td>0.630</td>
<td>0.236</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI</td>
<td>0.409</td>
<td>0.265</td>
<td>0.124</td>
<td>0.458</td>
<td>0.318</td>
<td>0.150</td>
</tr>
<tr>
<td>SMK</td>
<td>0.501</td>
<td>0.221</td>
<td>0.024</td>
<td>0.594</td>
<td>0.252</td>
<td>0.018</td>
</tr>
<tr>
<td>SBP</td>
<td>1.559</td>
<td>0.520</td>
<td>0.003</td>
<td>1.858</td>
<td>0.595</td>
<td>0.002</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.001</td>
<td>0.019</td>
<td>0.955</td>
<td>-0.001</td>
<td>0.021</td>
<td>0.958</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.367</td>
<td>0.309</td>
<td>0.236</td>
<td>-0.415</td>
<td>0.350</td>
<td>0.234</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.143</td>
<td>0.363</td>
<td>0.694</td>
<td>-0.211</td>
<td>0.419</td>
<td>0.615</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.336</td>
<td>0.301</td>
<td>0.264</td>
<td>-0.398</td>
<td>0.333</td>
<td>0.232</td>
</tr>
<tr>
<td>DEPENDENCE PARAMETER</td>
<td>1.086</td>
<td>0.396</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KENDALL $\tau$</td>
<td>0</td>
<td>0.392</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLIKE</td>
<td>-1935.77</td>
<td></td>
<td></td>
<td>-1933.63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The analysis shows that the estimates of the regression coefficients were quite similar under the various models, as before. We present in Figures 5.3 the relative risk of coronary heart disease for a smoker as compared to a non-smoker for males and females. Once again had one ignored any possible association and simply fit a Cox model that the relative risk of smoking's effect on time to CHD would be underestimated until advanced age.

**FIGURE 5.3**

Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker under the Two Semiparametric Frailty Models for Sibling Effects

- Independence and Positive Stable Models (horizontal line),
- Gamma Model (curve)
FIGURE 5.3 (CONTINUED)

a Female Smoker versus a Female Nonsmoker

Independence and Positive Stable Models (horizontal line),

Gamma Model (curve)
Tables 5.11, 5.12 and 5.13 present the results on the effects of smoking, cholesterol and body mass index on incidence of a CHD for males and females, respectively.

**TABLE 5.11**

Test For Effect of Smoking on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects

Males and Females

<table>
<thead>
<tr>
<th>SEX</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.501</td>
<td>0.221</td>
<td>0.024</td>
<td>0.594</td>
<td>0.252</td>
<td>0.018</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.165</td>
<td>0.203</td>
<td>0.416</td>
<td>0.196</td>
<td>0.219</td>
<td>0.371</td>
</tr>
</tbody>
</table>

**TABLE 5.12**

Test For Effect of Cholesterol on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects

Males and Females

<table>
<thead>
<tr>
<th>SEX</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.566</td>
<td>0.196</td>
<td>0.004</td>
<td>0.630</td>
<td>0.236</td>
<td>0.008</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.199</td>
<td>0.243</td>
<td>0.412</td>
<td>0.215</td>
<td>0.261</td>
<td>0.411</td>
</tr>
</tbody>
</table>
TABLE 5.13
Test For Effect of Body Mass Index on Incidence of a CHD under the Two Semiparametric Frailty Models for Sibling Effects Males and Females

POSITIVE STABLE FRAILTY AND INDEPENDENCE GAMMA FRAILTY

<table>
<thead>
<tr>
<th>SEX</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.409</td>
<td>0.265</td>
<td>0.124</td>
<td>0.458</td>
<td>0.318</td>
<td>0.150</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.266</td>
<td>0.251</td>
<td>0.290</td>
<td>0.247</td>
<td>0.278</td>
<td>0.374</td>
</tr>
</tbody>
</table>

We can see the effects of smoking were consistently significant in predicting CHD for males, but not for females, as before. The effects of cholesterol were consistently significant in predicting CHD for males, but not for females, as before. The effects of body mass index were not significant in predicting CHD for both males and females, as before.

As noted above, in this example, the dependence parameter for the positive stable model is indistinguishable from independence. One reason is that, for the positive stable model, the older an individual is when they first shows evidence of coronary heart disease the smaller the relative change in their sibling's risk of showing evidence of disease (see Figure 4.3). Therefore, when the sample is truncated much of the possible association between an individual's event times has been washed out by the time of truncation. One can argue, due to the relative poor
fit of the positive stable model that it is not a reasonable model to use for truncated data.

Table 5.14 presents the results for the Weibull regression models under independence and the two frailty models. All continuous covariates were centered at their mean. The ages of individuals at the time of inclusion, 44 or 45, were used as truncation times in our analysis. Here cholesterol, systolic pressure, and smoking were consistently significant in predicting CHD, as before. We present in Figures 5.4 the relative risk of coronary heart disease for a smoker as compared to a nonsmoker for males and females. Note that the lines for the positive stable model and the independence model are almost indistinguishable. Once again had we ignored any possible association and simply fit a Cox model that the relative risk of smoking's effect on time to CHD would be underestimated until advanced age.
TABLE 5.14
Estimates of Parameters for the Two Parametric Frailty Models
for Sibling Effects Based on Disease-Free individuals at Age 45
First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT</td>
<td>-32.04</td>
<td>2.563</td>
<td>&lt;.001</td>
<td>-37.15</td>
<td>3.660</td>
<td>&lt;.001</td>
<td>-32.59</td>
<td>3.962</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>α</td>
<td>7.211</td>
<td>0.605</td>
<td>&lt;.001</td>
<td>8.458</td>
<td>0.880</td>
<td>&lt;.001</td>
<td>7.334</td>
<td>0.911</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SEX</td>
<td>-0.370</td>
<td>0.254</td>
<td>0.145</td>
<td>-0.472</td>
<td>0.298</td>
<td>0.113</td>
<td>-0.381</td>
<td>0.264</td>
<td>0.149</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.572</td>
<td>0.196</td>
<td>0.004</td>
<td>0.663</td>
<td>0.257</td>
<td>0.010</td>
<td>0.579</td>
<td>0.204</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI</td>
<td>0.418</td>
<td>0.266</td>
<td>0.117</td>
<td>0.507</td>
<td>0.348</td>
<td>0.145</td>
<td>0.426</td>
<td>0.275</td>
<td>0.121</td>
</tr>
<tr>
<td>SMK</td>
<td>0.500</td>
<td>0.221</td>
<td>0.024</td>
<td>0.636</td>
<td>0.273</td>
<td>0.020</td>
<td>0.509</td>
<td>0.230</td>
<td>0.027</td>
</tr>
<tr>
<td>SBP</td>
<td>1.600</td>
<td>0.520</td>
<td>0.003</td>
<td>1.986</td>
<td>0.653</td>
<td>0.002</td>
<td>1.577</td>
<td>0.539</td>
<td>0.003</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.013</td>
<td>0.018</td>
<td>0.465</td>
<td>0.008</td>
<td>0.021</td>
<td>0.720</td>
<td>0.014</td>
<td>0.019</td>
<td>0.471</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.368</td>
<td>0.310</td>
<td>0.235</td>
<td>-0.436</td>
<td>0.369</td>
<td>0.238</td>
<td>-0.374</td>
<td>0.317</td>
<td>0.239</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.155</td>
<td>0.364</td>
<td>0.671</td>
<td>-0.263</td>
<td>0.449</td>
<td>0.558</td>
<td>-0.159</td>
<td>0.372</td>
<td>0.670</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.335</td>
<td>0.301</td>
<td>0.265</td>
<td>-0.428</td>
<td>0.352</td>
<td>0.223</td>
<td>-0.342</td>
<td>0.308</td>
<td>0.268</td>
</tr>
</tbody>
</table>

| DEPENDENCE PARAMETER | 1.478 | 0.778 | 0.029 | 0.980 | 0.096 | 0.417 |
| KENDALL τ            | 0     | 0.428 | 0.020 |
| LLIKE                 | -1354.91 | -1351.67 | -1354.88 |
FIGURE 5.4
Relative Risk of CHD for a Male Smoker versus a Male Nonsmoker
under the Two Parametric Frailty Models for Sibling Effects

Curves are Gamma (___),
Positive Stable and Independence (_. _._)
FIGURE 5.4  (CONTINUED)

a Female Smoker versus a Female Nonsmoker

Curves are Gamma (_____),
Positive Stable and Independence (____)
Tables 5.15, 5.16 and 5.17 present the results on the effects of smoking, cholesterol and body mass index on incidence of a CHD for males and females, respectively.

**TABLE 5.15**

Test for Effect of Smoking on Incidence of a CHD under the Two Parametric Frailty Models for Sibling Effects

Females and Males

<table>
<thead>
<tr>
<th>SEX</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.500</td>
<td>0.221</td>
<td>0.024</td>
<td>0.636</td>
<td>0.273</td>
<td>0.020</td>
<td>0.509</td>
<td>0.230</td>
<td>0.027</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.165</td>
<td>0.203</td>
<td>0.417</td>
<td>0.208</td>
<td>0.228</td>
<td>0.361</td>
<td>0.167</td>
<td>0.207</td>
<td>0.420</td>
</tr>
</tbody>
</table>

**TABLE 5.16**

Test for Effect of Cholesterol on Incidence of a CHD under the Two Parametric Frailty Models for Sibling Effects

Females and Males

<table>
<thead>
<tr>
<th>SEX</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
<th>( \beta )</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALE</td>
<td>0.572</td>
<td>0.196</td>
<td>0.004</td>
<td>0.663</td>
<td>0.257</td>
<td>0.010</td>
<td>0.579</td>
<td>0.204</td>
<td>0.004</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.204</td>
<td>0.243</td>
<td>0.401</td>
<td>0.227</td>
<td>0.269</td>
<td>0.400</td>
<td>0.205</td>
<td>0.247</td>
<td>0.406</td>
</tr>
</tbody>
</table>
TABLE 5.17
Test for Effect of Body Mass Index on Incidence of a CHD
under the Two Parametric Frailty Models for Sibling Effects
Females and Males

<table>
<thead>
<tr>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
</tr>
<tr>
<td></td>
<td>FRAILTY</td>
</tr>
<tr>
<td>SEX</td>
<td>β</td>
</tr>
<tr>
<td>MALE</td>
<td>0.418</td>
</tr>
<tr>
<td>FEMALE</td>
<td>0.263</td>
</tr>
</tbody>
</table>

We can see the effects of smoking were consistently significant in predicting CHD for males, but not for females, as before. The effects of cholesterol were consistently significant in predicting CHD for males, but not for females, as before. The effects of body mass index were not significant in predicting CHD for both males and females, as before.

To check whether assuming a Weibull model for the baseline hazard function in the various frailty models is appropriate for the data, we present in Figure 5.5 and Figure 5.6 two graphical methods. The first method is based on the EM algorithm estimates of the baseline cumulative hazard function given by (3.1.2.3). If assuming a Weibull model for the baseline hazard function were appropriate, then the plot of the EM algorithm estimates versus the observed times on study on a log-log paper should be approximately a straight line. Figure 5.5 presents the results of this graphical checking for the various frailty models. It
appears that assuming a Weibull model for the baseline hazard function in the
various models is appropriate.

FIGURE 5.5
A Graphical Check on Assuming a Weibull Model for the Baseline
Hazard Function Using the EM Algorithm Estimates
Independence and Positive Stable Models
FIGURE 5.5 (CONTINUED)

-LOG CUMULATIVE HAZARD

LOG OBSERVED TIME ON STUDY

Gamma Model
The second graphical method is based on the Nelson-Aalen (1972b) estimates of marginal cumulative hazard functions or the Kaplan-Meier (1958) estimates of marginal survival functions assuming no group effect. Under the independence and positive stable models if assuming a Weibull model for the baseline hazard function were appropriate, then the marginal hazard functions of these two models would be of the form of Weibull hazards too. So the plot of the Nelson-Aalen estimates of their marginal cumulative hazard function versus the observed times on study on a log-log paper should be approximately a straight line if assuming a Weibull model for the baseline hazard function were correct. Under the gamma model the marginal survival function of an individual is of the form (3.1.2) with G=1. If assuming a Weibull model for the baseline hazard function were correct, then the plot of (Kaplan-Meier estimates)⁻²⁻¹ versus the observed times on study should be approximately a straight line. Figure 5.6 presents the result of this graphical checking for the gamma model. The result of this graphical checking for the independence and positive stable models is the same as that using the first method. It appears that assuming a Weibull model for the baseline hazard function in the various models is appropriate.
FIGURE 5.6

A Graphical Check on Assuming a Weibull Model for the Baseline Hazard Function Using the Kaplan-Meier Estimates

Gamma Model
It is important to remember that the validity of the interpretations of covariate effects using the relative risk function depends on whether the proportionality assumption for the conditional hazard function $h_j(x \mid z, \omega_g)$ is met. We can do a check on proportionality of hazards in the independence case (i.e., $\omega_g = 1$ almost surely) by partitioning the data according to joint values of two or more covariates, and fitting separate proportional hazards model to each group (Lawless, 1982). If the proportionality assumption is met, the curves obtained by plotting the minus log cumulative baseline hazard functions for different groups against the log observed time on study should be approximately parallel. Figure 5.7 gives the resulting plots for smokers versus nonsmokers by male and female in predicting CHD. The curves in Figure 5.7 are seen to have approximately constant differences over time. In the dependent case, checking the proportionality assumption becomes somewhat complicated because of the presence of the random frailty $\omega_g$. We currently are investigating this problem.
FIGURE 5.7
A Graphical Check on the Proportionality of Hazards between Male Smokers and Male Nonsmokers in Predicting CHD under the Independence Model
FIGURE 5.7 (CONTINUED)

-LOG CUMULATIVE HAZARD

Female Smokers and Female Nonsmokers
Example 3

The event of interest in this example is the first evidence of coronary heart disease. Here time is measured from entry into the study. We consider grouping siblings who were disease-free at the times of entry. The sizes of the various sibling groups and the number of groups experiencing D_g events for each family size are reported in Table 5.18. To account for the effect of ages at entry on the onset of coronary heart disease, we stratified the individuals into four groups (4 categories ≤ 39, 40-47, 48-54, ≥ 55) by their ages at entry into the study.

### TABLE 5.18

Summary Information on Sibling Group Size and Number of CHD Events in Groups for Each Size Group for Disease-Free Individuals at Entry into the Study

<table>
<thead>
<tr>
<th>SIZE OF SIBLING GROUP</th>
<th>NUMBER WITH 0 DEATHS</th>
<th>NUMBER WITH 1 DEATH</th>
<th>NUMBER WITH 2 DEATHS</th>
<th>NUMBER WITH 3 DEATHS</th>
<th>NUMBER WITH 4 DEATHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2315</td>
<td>824</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>206</td>
<td>106</td>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>48</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6 b</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2563</td>
<td>988</td>
<td>30</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 5.19 presents results for the Cox model under independence and the two frailty models. The continuous covariates cholesterol, systolic blood pressure, and body mass index were centered at their mean. The average systolic blood pressure was 133.89 mm.Hg, the average cholesterol reading was 227.02 mg/dL and the average body mass index was 0.0361(\text{kg/cm}^2 \times 10). Gender, systolic pressure, and body mass index were consistently significant in predicting CHD. The values of the Kendall's $\tau$ for the two frailty models are small. The dependence parameter in the positive stable model was not significant, but the dependence parameter in gamma frailty model was significant.
TABLE 5.19
Estimates of Parameters for the Two Semiparametric Frailty Models for Sibling Effects Based on Disease-Free Individuals at Entry into the Study

First Evidence of Cardiovascular Event

<table>
<thead>
<tr>
<th>Effect</th>
<th>GAMMA INDEPENDENCE</th>
<th>GAMMA FRAILTY</th>
<th>POSITIVE STABLE FRAILTY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>SEX</td>
<td>-.781</td>
<td>0.193</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SBP</td>
<td>1.358</td>
<td>0.155</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI</td>
<td>24.41</td>
<td>5.658</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.356</td>
<td>0.200</td>
<td>0.076</td>
</tr>
<tr>
<td>SMK</td>
<td>0.032</td>
<td>0.177</td>
<td>0.857</td>
</tr>
<tr>
<td>SEX*AGE≤39</td>
<td>0.627</td>
<td>0.324</td>
<td>0.053</td>
</tr>
<tr>
<td>SEX*AGE 40-47</td>
<td>0.302</td>
<td>0.278</td>
<td>0.277</td>
</tr>
<tr>
<td>SEX*AGE≥55</td>
<td>0.393</td>
<td>0.311</td>
<td>0.207</td>
</tr>
<tr>
<td>CHOLAGE≤39</td>
<td>0.443</td>
<td>0.247</td>
<td>0.073</td>
</tr>
<tr>
<td>CHOLAGE 40-47</td>
<td>0.389</td>
<td>0.246</td>
<td>0.114</td>
</tr>
<tr>
<td>CHOLAGE≥55</td>
<td>0.040</td>
<td>0.345</td>
<td>0.908</td>
</tr>
<tr>
<td>CHOLSEX</td>
<td>-.191</td>
<td>0.280</td>
<td>0.496</td>
</tr>
<tr>
<td>CHOLSEXAGE≤39</td>
<td>0.027</td>
<td>0.395</td>
<td>0.946</td>
</tr>
<tr>
<td>CHOLSEXAGE 40-47</td>
<td>0.357</td>
<td>0.373</td>
<td>0.338</td>
</tr>
<tr>
<td>CHOLSEXAGE≥55</td>
<td>0.007</td>
<td>0.454</td>
<td>0.988</td>
</tr>
<tr>
<td>SMKAGE≤39</td>
<td>0.539</td>
<td>0.286</td>
<td>0.059</td>
</tr>
</tbody>
</table>
Table 5.19 presents the results on the effects of smoking on incidence of a CHD for males and females in four age groups. We can see the effects of smoking were consistently significant in predicting CHD for males under age 40 at entry into the study, but the effects for males in other age groups and the females of all age groups were not significant.
TABLE 5.20
Test for Effect of Smoking on Incidence of a CHD for Four Age Groups at Entry under the Two Semiparametric Models for Sibling Effects

Males

<table>
<thead>
<tr>
<th>AGE</th>
<th>INDEPENDENCE</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
<th>FRAILTY</th>
<th>FRAILTY</th>
<th>FRAILTY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>≤ 39</td>
<td>0.571</td>
<td>0.224</td>
<td>0.011</td>
<td>0.626</td>
<td>0.235</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.570</td>
<td>0.229</td>
<td>0.013</td>
</tr>
<tr>
<td>40-47</td>
<td>0.272</td>
<td>0.184</td>
<td>0.140</td>
<td>0.329</td>
<td>0.202</td>
<td>0.104</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.272</td>
<td>0.188</td>
<td>0.148</td>
</tr>
<tr>
<td>48-54</td>
<td>0.032</td>
<td>0.177</td>
<td>0.857</td>
<td>0.055</td>
<td>0.198</td>
<td>0.729</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.035</td>
<td>0.181</td>
<td>0.847</td>
</tr>
<tr>
<td>≥ 55</td>
<td>0.304</td>
<td>0.241</td>
<td>0.208</td>
<td>0.397</td>
<td>0.266</td>
<td>0.136</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.311</td>
<td>0.246</td>
<td>0.207</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>AGE</th>
<th>INDEPENDENCE</th>
<th>GAMMA</th>
<th>POSITIVE STABLE</th>
<th>FRAILTY</th>
<th>FRAILTY</th>
<th>FRAILTY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>≤ 39</td>
<td>0.065</td>
<td>0.205</td>
<td>0.751</td>
<td>0.082</td>
<td>0.211</td>
<td>0.697</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.072</td>
<td>0.209</td>
<td>0.730</td>
</tr>
<tr>
<td>40-47</td>
<td>-.097</td>
<td>0.185</td>
<td>0.601</td>
<td>-.108</td>
<td>0.196</td>
<td>0.581</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-.102</td>
<td>0.191</td>
<td>0.593</td>
</tr>
<tr>
<td>48-54</td>
<td>0.327</td>
<td>0.191</td>
<td>0.087</td>
<td>0.350</td>
<td>0.206</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.326</td>
<td>0.196</td>
<td>0.096</td>
</tr>
<tr>
<td>≥ 55</td>
<td>0.322</td>
<td>0.236</td>
<td>0.172</td>
<td>0.376</td>
<td>0.262</td>
<td>0.151</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.331</td>
<td>0.242</td>
<td>0.171</td>
</tr>
</tbody>
</table>
Table 5.21 presents the results on the effects of cholesterol on incidence of a CHD for males and females in four age groups. We can see the effects of cholesterol were consistently significant in predicting CHD for both males and females under age 48 at entry into the study, but the effects were not significant for males and females over age 48.

**TABLE 5.21**

Test for Effect of Cholesterol on Incidence of a CHD for Four Age Groups at Entry under the Two Semiparametric Models

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Males</th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GAMMA</td>
<td>POSITIVE STABLE</td>
<td></td>
<td>GAMMA</td>
<td>POSITIVE STABLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
<td>FRAILTY</td>
<td>INDEPENDENCE</td>
<td>FRAILTY</td>
<td>FRAILTY</td>
<td></td>
</tr>
<tr>
<td>≤ 39</td>
<td>0.799</td>
<td>0.144</td>
<td>&lt;.001</td>
<td>0.928</td>
<td>0.169</td>
<td>&lt;.001</td>
<td>0.836</td>
</tr>
<tr>
<td>40-47</td>
<td>0.745</td>
<td>0.143</td>
<td>&lt;.001</td>
<td>0.830</td>
<td>0.172</td>
<td>&lt;.001</td>
<td>0.759</td>
</tr>
<tr>
<td>48-54</td>
<td>0.356</td>
<td>0.200</td>
<td>0.076</td>
<td>0.431</td>
<td>0.229</td>
<td>0.059</td>
<td>0.369</td>
</tr>
<tr>
<td>≥ 55</td>
<td>0.396</td>
<td>0.280</td>
<td>0.157</td>
<td>0.484</td>
<td>0.312</td>
<td>0.121</td>
<td>0.406</td>
</tr>
</tbody>
</table>
Finally, recall that using the approximate EM algorithm based on the marginal likelihood of generalized rank vectors give the same estimates of the dependence parameter and regression coefficients in the semiparametric gamma frailty models as those obtained by the EM algorithm approach. However, using the marginal likelihood of generalized rank vectors to compute the observed information matrix has several disadvantages. First, it requires a series of approximations, as described in Section 3.1.4, to be computationally feasible. Second, the approximations seems to be inadequate. We have observed that the conclusions about the effects of some discrete covariates on survival under the semiparametric models were inconsistent with those obtained under the Weibull regression models, if we use the approximations. Table 5.22 and Table 5.23 present the results on using the approximate EM algorithm to reanalyze Example 1 and Example 2, respectively. We can see in Table 5.22 that the p-value for SEX in
predicting CHD changes from 0.155 under the Weibull regression models to 0.011 under the semiparametric models, and in Table 5.23 that the p-value changes from 0.113 to 0.006.

TABLE 5.22
A Semiparametric Analysis of Example 1 Using the Marginal Likelihood of Generalized Rank Vectors to Compute the Observed Information Matrix and a Comparison with a Parametric Analysis
First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>SEMIPARAMETRIC</th>
<th>WEIBULL REGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
</tr>
<tr>
<td>SEX</td>
<td>-0.406</td>
<td>0.160</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.668</td>
<td>0.238</td>
</tr>
<tr>
<td>BMI</td>
<td>0.476</td>
<td>0.310</td>
</tr>
<tr>
<td>SMK</td>
<td>0.599</td>
<td>0.127</td>
</tr>
<tr>
<td>SBP</td>
<td>1.900</td>
<td>0.598</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.0004</td>
<td>0.020</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.465</td>
<td>0.354</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.212</td>
<td>0.416</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.394</td>
<td>0.253</td>
</tr>
</tbody>
</table>
### Table 5.22 (Continued)

First Evidence of Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>SEMIPARAMETRIC</th>
<th></th>
<th></th>
<th>WEIBULL REGRESSION</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>SE</td>
<td>P</td>
<td>β</td>
<td>SE</td>
<td>P</td>
</tr>
<tr>
<td>SEX</td>
<td>0.367</td>
<td>0.333</td>
<td>0.270</td>
<td>0.353</td>
<td>0.701</td>
<td>0.615</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.521</td>
<td>0.480</td>
<td>0.278</td>
<td>0.543</td>
<td>0.487</td>
<td>0.265</td>
</tr>
<tr>
<td>BMI</td>
<td>1.011</td>
<td>0.635</td>
<td>0.111</td>
<td>1.031</td>
<td>0.670</td>
<td>0.123</td>
</tr>
<tr>
<td>SMK</td>
<td>1.118</td>
<td>0.243</td>
<td>&lt;.001</td>
<td>1.137</td>
<td>0.634</td>
<td>0.073</td>
</tr>
<tr>
<td>SBP</td>
<td>2.262</td>
<td>1.148</td>
<td>0.049</td>
<td>2.320</td>
<td>1.170</td>
<td>0.047</td>
</tr>
<tr>
<td>WAIT</td>
<td>0.025</td>
<td>0.039</td>
<td>0.522</td>
<td>0.026</td>
<td>0.041</td>
<td>0.525</td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.611</td>
<td>0.694</td>
<td>0.379</td>
<td>-0.625</td>
<td>0.701</td>
<td>0.373</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.640</td>
<td>0.819</td>
<td>0.435</td>
<td>-0.659</td>
<td>0.852</td>
<td>0.440</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.667</td>
<td>0.498</td>
<td>0.180</td>
<td>-0.667</td>
<td>0.769</td>
<td>0.386</td>
</tr>
<tr>
<td>δ</td>
<td>1.120</td>
<td>0.407</td>
<td>0.003</td>
<td>1.327</td>
<td>0.507</td>
<td>0.0044</td>
</tr>
</tbody>
</table>
TABLE 5.23
A Semiparametric Analysis of Example 2 Using the Marginal Likelihood of Generalized Rank Vectors to Compute the Observed Information Matrix and a Comparison with a Parametric Analysis First Evidence of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Effect</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEX</td>
<td>-0.440</td>
<td>0.159</td>
<td>0.006</td>
<td>-0.472</td>
<td>0.298</td>
<td>0.113</td>
</tr>
<tr>
<td>CHOL</td>
<td>0.630</td>
<td>0.236</td>
<td>0.008</td>
<td>0.663</td>
<td>0.257</td>
<td>0.010</td>
</tr>
<tr>
<td>BMI</td>
<td>0.458</td>
<td>0.311</td>
<td>0.141</td>
<td>0.507</td>
<td>0.348</td>
<td>0.145</td>
</tr>
<tr>
<td>SMK</td>
<td>0.594</td>
<td>0.138</td>
<td>&lt;.001</td>
<td>0.636</td>
<td>0.273</td>
<td>0.020</td>
</tr>
<tr>
<td>SBP</td>
<td>1.858</td>
<td>0.597</td>
<td>0.002</td>
<td>1.986</td>
<td>0.653</td>
<td>0.002</td>
</tr>
<tr>
<td>WAIT</td>
<td>-0.001</td>
<td>0.020</td>
<td>0.960</td>
<td>0.021</td>
<td>0.720</td>
<td></td>
</tr>
<tr>
<td>SEX*CHOL</td>
<td>-0.415</td>
<td>0.349</td>
<td>0.234</td>
<td>-0.436</td>
<td>0.369</td>
<td>0.238</td>
</tr>
<tr>
<td>SEX*BMI</td>
<td>-0.211</td>
<td>0.414</td>
<td>0.610</td>
<td>-0.263</td>
<td>0.449</td>
<td>0.558</td>
</tr>
<tr>
<td>SEX*SMK</td>
<td>-0.398</td>
<td>0.257</td>
<td>0.121</td>
<td>-0.428</td>
<td>0.352</td>
<td>0.223</td>
</tr>
<tr>
<td>δ</td>
<td>1.086</td>
<td>0.506</td>
<td>0.016</td>
<td>1.478</td>
<td>0.778</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Third, it is unlikely that we can compare the gamma frailty models with other frailty models using the marginal likelihood of generalized rank vectors to compute the observed information matrix because it is mathematically intractable to do similar approximations for other frailty models such as the inverse Gaussian and positive stable frailty models.
CHAPTER VI
FUTURE WORK

The EM algorithm based on a profile likelihood construction is a powerful tool for finding the maximum likelihood estimates of the dependence parameter and regression coefficients in semiparametric frailty models. However, the algorithm is generally slow. The slow convergence of EM algorithms is well known for finding maximum likelihood estimates for parameters describing incomplete data parametric models. To this end, Louis (1982) and Meilijson (1989) proposed two different acceleration methods to improve the speed of convergence. There is a need to develop acceleration methods for semiparametric frailty models.

We have seen in Chapters 3 and 4 that the magnitude of the relative increase in the hazard rates of the surviving components when one of the other components fails is a constant over time for the gamma frailty model, while for the positive stable model this magnitude decreases with time. These two frailty models are appropriate for modelling the survival times of the individuals who share a common frailty induced by factors that might dissipate over time. For example, it is not an unreasonable assumption that the association between the survival times of siblings, induced by their exposure to the same environment at early times, should decrease as they leave their families. However, there are situations where the association
between the survival times of group individuals increases with time and these two frailty models may not be appropriate. For example, it is reasonable to believe that the association between the survival times of a married couple should increase as they live together longer.

In our modelling of associated event times we incorporate a random frailty into a Cox proportional hazards model that acts multiplicatively on the hazard rate (Cox, 1972). This is partly because the Cox proportional hazards models are well studied in statistical literature. It is relatively simple to modify existing techniques to account for such a frailty. One important, and yet unanswered question is how to check this crucial model assumption. Oakes (1989) has suggested some graphical techniques when there are no covariates. Further work needs to be done to extend these techniques to include covariates. An alternative way is to incorporate the random frailty into an accelerated failure time model. However, semiparametric estimation is quite difficult in this model.

A drawback of frailty models is that the association that is modeled must always be nonnegative. One can postulate situations in modeling the onset times of two chronic diseases where the onset times may be negatively associated. This problem is because frailty models, as described above, assume that the unobservable covariates act on each disease in the same way. This may not be reasonable in many situations. A recent work by Shih (1991) studied four families of bivariate distributions belonging to the Archimedean models, described in Section 2.1. One of the bivariate models, called Frank's model, will allow negative
association. She had a two-stage nonparametric estimation procedure for the models when there are no covariates. This nonparametric procedure is very similar to that proposed by Hougaard (1986b) for the positive stable frailty model. However, it is still unclear how to extend her nonparametric estimation procedure to include covariates and how to interpret the Frank's model in the context of survival analysis.

Finally, there are situations where we want to incorporate more than one frailty into a model. Hougaard (1986b) briefly discussed this and had a simple example. In general, there are considerable technical difficulties associated with implementing this idea.
APPENDIX A

FORTRAN PROGRAM FOR THE EM ALGORITHM APPROACH TO THE ESTIMATION OF THE DEPENDENCE PARAMETER AND REGRESSION COEFFICIENTS IN A GAMMA FRAILTY MODEL

```fortran
C*********************************************************************************
C******************************** MAIN PROGRAM ****************************************
C*********************************************************************************
EXTERNAL PSIP
EXTERNAL DFCN

C*********************************************************************************
C INPUT:
C N: NO. OF COVARIATES
C NOBS: NO OF OBSERVATIONS
C NS: NO OF STRATA
C NG: NO OF GROUPS
C*********************************************************************************
PARAMETER(N=22,NOBS=4178,NS=4,NG=3587)
PARAMETER(LIM=1000)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION THETA(N), ITHETA(N)
DIMENSION C1(NG),C2(NG), W(NG), WL(NG)
DIMENSION IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NOBS)
DIMENSION A(NG), B(NG)
DIMENSION EHF(NS,NOBS),ECHF(NS,NOBS)
DIMENSION ID(N)
DIMENSION ALIKE(NG), BLIKE(NG), CLIKE(NG), DALIKE(NG)
DIMENSION FISHER (N+1,N+1), FISHERI(N+1,N+1)
DIMENSION DEHF(N),DDEHF(N,N)
DIMENSION DEHFA(N), DDEHFA(N,N)
DIMENSION S1(N), S2(N,N)
DIMENSION SUM1(N),SUM2(N,N)
DIMENSION H2(N,N,NG), B1(N,NG), B2(N,N,NG)
DIMENSION Z1(N,NG), Z2(N,NG), Z3(N,N,NG)
DIMENSION IORDER(NOBS)
INTEGER A
REAL LLIKE
```
REAL ITHETA
REAL MTHETA, MAXDIF
EXTERNAL SFCN, SJAC, LIKELI, MULT, LRNG
DATA UPP/0.0001/

C******************************************************************************
C INPUT:
C DELTAR: AN INITIAL GUESS AT THE DEPENDENCE PARAMETER
C******************************************************************************

C DATA DELTAR/0.4/
DELTOL=0.0001
DFTOL=.001
NLIM=50
UTOL = 0.01
TTOL = 0.001
ITMAX = 100

C******************************************************************************
C INPUT:
C IJ(I) = 1, COVARIATE I IS INCLUDED
C = 0, COVARIATE I IS USED IN COMPUTATION,
C = -1, COVARIATE I IS OUT
C******************************************************************************

DO 56565 1=1,N
IJ(I)=1
56565 CONTINUE

DO 8014 I=1,N
IF (IJ(I) .EQ. 1) THEN
ITHETA(I)=0.0
ENDIF
8014 CONTINUE

C******************************************************************************
C INPUT:
C T: OBSERVED TIME ON STUDY
C IND: CENSORING INDICATOR
C MEL: GROUP NO.
C NEL: STRATUM NO.
C Z: COVARIATES
C******************************************************************************

DO 70000 J=1,NOBS
READ(1,*) T(J),IND(J),MEL(J),NEL(J),(Z(K,J),K=1,N)
70000 CONTINUE

CALL ORDER (T,IND, NOBS, IORDER)
NOBSN=N*NOBS
CALL ARRANG(IORDER,NOBS,N,NOBSN,Z)
CALL ARRANG(IORDER,NOBS,1,NOBS,T)
CALL ARRANG(IORDER,NOBS,1,NOBS,IND)
CALL ARRANG(IORDER,NOBS,1,NOBS,NEL)
CALL ARRANG(IORDER,NOBS,1,NOBS,MEL)
JRANK=1
IRANK(1)=JRANK
DO 60000 I=2,NOBS
   IF(IND(I) .EQ. 0) GO TO 50000
   IF(T(I) .NE. T(I-1)) JRANK=JRANK+1
50000 IRANK(I)=JRANK
60000 CONTINUE
MAX=IRANK(NOBS)
J=1
DO 1225 I=1,NOBS
   IF (IRANK(I) .NE. J) GO TO 1225
   I1=IRANK(I)
   NP(I1)=1
   J=J+1
1225 CONTINUE
J1=1
DO 1226 I=1,N
   IF (IJ(I) .NE. 1 ) GO TO 1226
   ID(J1)=I
   THETA(J1)=ITHETA(I)
   J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
   IF (IJ(I) .NE. 0) GO TO 1227
   ID(J1)=I
   THETA(J1)=ITHETA(I)
   J1=J1+1
1227 CONTINUE
MD=J1-1
DO 90000 J=1,NG
   A(J)=0
90000 CONTINUE
DO 95555 I=1,NOBS
   IF (IND(I) .EQ. 0) GO TO 95555
   J=MEL(I)
   A(J)=A(J)+1
95555 CONTINUE
DO 60333 J=1,MD
   ITHETA(I)=THETA(I)
60333 CONTINUE
DO 63333 J=1,NG
   W(J)=1.0
63333 CONTINUE
C ***********************************************
C STARTING THE EM ALGORITHM
C ***********************************************
C
DO 85555 NITER=1,LIM
   IF (NITER .EQ. 1) GO TO 86666
   PDIF = 1.0
   IERR = 0
20000 DELTA1=DELTA1/PDIF
   DELTA2=DELTA2*PDIF
   DF1=DFCN(NG,CONST,DELTA1)
   DF2=DFCN(NG,CONST,DELTA2)
   IF (DF1*DF2 .LT. 0.0) GO TO 30000
   PDIF = PDIF*2.0
   IERR = IERR +1
   IF (IERR .LT. 9) GO TO 20000
   WRITE (6,11111)
11111 FORMAT(//,IX,'THE PROGRAM TERMINATES BECAUSE
             & INADEQUATE PICKS OF IDELTA1 AND IDELTA2')
   STOP
C ***********************************************
C BISEC:
C USING THE BISECTION METHOD TO FIND THE MLE OF
C THE DEPENDENCE PARAMETER
C ***********************************************
C
30000 CALL BISEC (NG,CONST,DELTA1,DELTA2,DF1,DF2,DELTOL
            & ,DFTOL,NLIM,DELTAR,DFCN,KK)
C
C ***********************************************
C SMAQ:
C USING THE LEVENBERG-MARQUARDT ITERATION METHOD TO
C FIND THE MLE'S OF REGRESSION COEFFICIENTS BASED ON
C A MODIFIED COX'S PARTIAL LIKELIHOOD
C ***********************************************
C
86666 CALL SMAQ(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK
            & ,MAX,W, NITER,ITMAX,UTOL,TTOL,THETA,ID,XX,MC,MD,
            & EHF,ECHF,
            & NP,JJ,SFCN, SJAC, LIKELI,MULT,LINRG)
   IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
   DO 97777 J=1,NG
      CLIKE(J)=0.0
   B(J)=0.0
97777 CONTINUE
   DO 98888 I=1,NOBS
      J=MEL(I)
      K=IRANK(I)
      L=NEL(I)
      IF (IND(I) .EQ. 0) GO TO 97878
      CLIKE(J)=CLIKE(J)+IND(I)*(ALOG(EHF(L,K))
             & +ALOG(XX(I)/W(J)))
   98888 CONTINUE
B(J) = B(J) + ECHF(L,K) * XX(I) / W(J)

98888 CONTINUE
   IF (NITER .EQ. 1) GO TO 87777
   LLIKE = 0.0
   DO 117 I = 1, NG
   ALIKE(I) = 0.0
   IF (A(I) .LE. 1) GO TO 97
   SUM = 0.0
   DO 107 J = 1, A(I)
   SUM = SUM + ALOG(A(I) + 1/DELTAR - J)
   107 CONTINUE
   ALIKE(I) = SUM - A(I) * ALOG(1/DELTAR)
   BLIKE(I) = (A(I) + 1/DELTAR) * ALOG(DELTAR * B(I) + 1)
   LLIKE = LLIKE + ALIKE(I) - BLIKE(I) + CLIKE(I)
   117 CONTINUE
   IF (LLIKE .LT. TEMP) GO TO 47
   DL = LLIKE - TEMP
   IF (DL .LE. 0.00001) GO TO 68
   TEMP = LLIKE
   MTHETA = -1.0
   DO 75555 I = 1, MC
   DIFF1 = THETA(I) - ITHETA(I)
   IF (ABS(DIFF1) .GE. MTHETA) MTHETA = ABS(DIFF1)
   75555 CONTINUE
   DIFF2 = DELTAR - FRAIL
   IF (ABS(DIFF2) .GE. MTHETA) GO TO 76666
   MAXDIF = MTHETA
   GO TO 78888
   76666 MAXDIF = ABS(DIFF2)
   78888 IF (MAXDIF .LE. UPP) GO TO 48
   FRAIL = DELTAR
   DELTA1 = DELTAR / 4.0
   DELTA2 = DELTAR * 4.0
   DO 79999 I = 1, MC
   ITHETA(I) = THETA(I)
   79999 CONTINUE
   GO TO 79998
   87777 FRAIL = DELTAR
   DELTA1 = DELTAR / 4.0
   DELTA2 = DELTAR * 4.0
   DO 89999 I = 1, MC
   ITHETA(I) = THETA(I)
   89999 CONTINUE
   LLIKE = 0.0
   DO 167 I = 1, NG
   LLIKE = LLIKE + CLIKE(I) - B(I)
   167 CONTINUE
   TEMP = LLIKE
   WRITE (6,*) 'LOGLIKELIHOOD UNDER INDP.=', LLIKE
   79998 DO 56666 J = 1, NG
   C1(J) = FLOAT(A(J)) + 1/DELTAR
   C2(J) = B(J) + 1/DELTAR
W(J) = C1(J) / C2(J)
WL(J) = PSI(C1(J)) - ALOG(C2(J))

CONTINUE
CONST = 0.0
DO 11 I = 1, NG
CONST = CONST + WL(I) - W(I)
11 CONTINUE

CONTINUE
WRITE (6, 63)
63 FORMAT (///, 1X, 'THE NUMBER OF ITERATIONS EXCEEDS NITER')
WRITE (6, *) ' THE MAX. OF DIFF. = ', MAXDIF
GO TO 49
47 WRITE (6, 61)
61 FORMAT (///, 1X, 'THE LOGLIKELIHOOD DECREASES', ///)
LLIKE = TEMP
WRITE (6, *) 'LOGLIKELIHOOD= ', LLIKE
WRITE (6, *) NITER, MAXDIF
DELTAR = FRAIL
DO 777 I = 1, MC
THETA(I) = ITHETA(I)
777 CONTINUE
GO TO 49
48 WRITE (6, 62)
62 FORMAT (///, 1X, 'THE TOLERANCE FOR UPP IS MET', ///)
WRITE (6, *) 'LOGLIKELIHOOD= ', LLIKE
WRITE (6, *) NITER, MAXDIF
GO TO 49
68 WRITE (6, 67)
67 FORMAT (///, 1X, 'THE TOLERANCE FOR LLIKE IS MET', ///)
WRITE (6, *) 'LOGLIKELIHOOD= ', LLIKE
WRITE (6, *) NITER

C
C ****************************************************************************
C COMPUTING THE OBSERVED INFORMATION MATRIX IN AN
C EM ALGORITHM BASED ON A PROFILE LIKELIHOOD CONSTRUCTION
C ****************************************************************************
C
C
49 DO 66 I = 1, NG
 B(I) = 0.0
 DO 66 J = 1, MC
 B1(J, I) = 0.0
 DO 66 K = 1, MC
 B2(J, K, I) = 0.0
 H2(J, K, I) = 0.0
66 CONTINUE
DO 9225 I = 1, NOBS
 XX(I) = 0.0
 DO 9226 J = 1, MD
 K = ID(J)
9226 XX(I) = XX(I) + THETA(J) * Z(K, I)
 MM = MEL(I)
9225 XX(I) = EXP(XX(I)) * W(MM)
 DO 71 I = 1, NOBS
J=MEL(I)
K=IRANK(I)
L=NEL(I)
M2=K
SUM=0.0
CHF=0.0
EHFA=0.0
DO 713 L1=1,MC
    DEHFA(L1)=0.0
    SI(L1)=0.0
    SUM1(L1)=0.0
    DO 713 L2=1,MC
        SUM2(L1,L2)=0.0
        DDEHFA(L1,L2)=0.0
        S2(L1,L2)=0.0
    713 CONTINUE
308 CONTINUE
HF=0.0
DO 513 L1=1,MC
    DEHF(L1)=0.0
    DO 513 L2=L1,MC
        DDEHF(L1,L2)=0.0
    513 CONTINUE
MI=0
IP=NP(M2)
DO 3108 N1=IP,NOBS
    IF (M2 .EQ. K) GO TO 2318
    IF (IRANK(N1) .NE. M2) GO TO 3208
2318 IF (NEL(N1) .NE. L) GO TO 3108
    SUM=SUM+XX(N1)
    DO 73 12=1,MC
        SUM1(12)=SUM1(12)+XX(N1)*Z(ID(12),N1)
        DO 73 13=12,MC
            SUM2(12,13)=SUM2(12,13)+XX(N1)*Z(ID(12),N1)*Z(ID(13),N1)
        73 CONTINUE
    IF (M2 .EQ. K) GO TO 3048
    IF (IND(N1) .EQ. 0) GO TO 3108
    GO TO 4804
3048 IF (IRANK(N1) .NE. M2 .OR. IND(N1) .EQ. 0) GO TO 3108
4804 MI=MI+1
3108 CONTINUE
3208 CONTINUE
    IF (MI .EQ. 0) GO TO 4208
    HF=FLOAT(MI)/SUM
    DO 813 L1=1,MC
        DEHF(L1)=-MI*SUM1(L1)/SUM**2
        DO 813 L2=L1,MC
            DDEHF(L1,L2)=-MI*(SUM2(L1,L2)/SUM**2-
                             & 2*SUM1(L1)*SUM1(L2)/SUM**3)
        813 CONTINUE
    IF (M2 .LE. K-1 .OR. IND(I) .EQ. 0) GO TO 4208
    EHFA=HF
    DO 913 L1=1,MC
DEHF(L1) = DEHF(L1)
DO 913 L2 = L1, MC
DEHF(L1, L2) = DEHF(L1, L2)

913 CONTINUE

DO 4208 CONTINUE
CHF = CHF + HF
DO 613 L1 = 1, MC
S1(L1) = S1(L1) + DEHF(L1)
DO 613 L2 = L1, MC
S2(L1, L2) = S2(L1, L2) + DEHF(L1, L2)

613 CONTINUE
M2 = M2 - 1
IF (M2 .GE. 1) GO TO 308
B(J) = B(J) + CHF*XX(I)/W(J)
DO 673 I2 = 1, MC
B1(I2, J) = B1(I2, J) + (CHF*Z(ID(I2), I) + S1(I2))
& *XX(I)/W(J)
DO 673 I3 = I2, MC
& + S1(I2)*Z(ID(I3), I) + S1(I3)*Z(ID(I2), I)
& + S2(I2, I3)*XX(I)/W(J)
IF (IND(I) .EQ. 0) GO TO 673
H2(I2, I3, J) = H2(I2, I3, J) + IND(I) * (EHFA*DDEHF(I2, I3) -
& DEHF(I2)*DEHF(I3))/EHFA**2

673 CONTINUE

DO 1015 I = 1, N+1
DO 1015 J = 1, N+1
FISHER(I, J) = 0.0
1015 CONTINUE

DO 42 I = 1, NG
DALIKE(I) = 0.0
IF (A(I) .LE. 1) GO TO 42
DSUM = 0.0
DDSUM = 0.0
DO 43 J = 1, A(I)
DSUM = DSUM + 1/(A(I) + 1/DELTAR - J)
DDSUM = DDSUM + 1/(A(I) + 1/DELTAR - J)**2
43 CONTINUE
DALIKE(I) = 2/DELTAR**3*DSUM + A(I)/DELTA**2
& + 1/DELTA**4*DDSUM

42 CONTINUE

DO 46 I = 1, NG
FISHER(I, 1) = FISHER(I, 1) + DALIKE(I)
& + 2*ALOG(1 + DELTAR*B(I))/DELTA**3
& - 2*B(I)/(DELTA**2*(1 + DELTAR*B(I)))
& - (A(I) + 1/DELTA)*B(I)**2/(1 + DELTAR*B(I))**2

46 CONTINUE

DO 81 I = 1, MC
DO 881 J = 1, NG
FISHER(I, I+1) = FISHER(I, I+1) + (A(J)/(1 + DELTAR*B(J)) -
& (DELTA*A(J) + 1)*B(J)/(1 + DELTAR*B(J))**2)*B1(I, J)
81 CONTINUE
881 CONTINUE
CONTINUE
FISHER(I+1,1)=FISHER(I+1,I+1)

CONTINUE
DO 83 I=1,MC
DO 83 J=1,MC
DO 883 K=1,NG
FISHER(I+1,J+1)=FISHER(I+1,J+1)-
& DELTAR**2*(A(K)+1/DELTAR)/(1+
& DELTAR*B(K))**2*B1(I,K)*B1(J,K)
& +DELTAR*(A(K)+1/DELTAR)/(1+DELTAR*B(K))*B2(I,J,K)-H2(I,J,K)

CONTINUE
FISHER(J+1,I+1)=FISHER(I+1,J+1)

CONTINUE
CALL LINRG (MC+1,FISHER,N+1,FISHERI,N+1)
WRITE(6,678)
678 FORMAT(IX,//)
DO 1073 I=1,MC+1
DO 1073 J=I,MC+1
WRITE(6,*) 'COV(',I ',',J ',',')=',FISHERI(I,J)

CONTINUE
WRITE(6,778)
778 FORMAT(IX,//)
SE=SQRT(FISHERI(1,1))
TEST=DELTAR/SE
PVAL=1.-ANORDF(ABS(TEST))
WRITE(6,771) DELTAR,SE,PVAL
771 FORMAT(' EST OF ASSOC.=',F12.7,2X,'SE=',F16.8,2X,'PVAL=',F7.4)
DO 9876 J=1,MC
SE=SQRT(FISHERI(J+1,J+1))
PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE(6,8761) J,THETA(J),SE,PVAL
8761 FORMAT(' BETA(',I2,') = ',F13.8,
& SE=',F13.8,2X,'PVALUE=',F7.5)

CONTINUE

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DIA = PSI(1/DeltaR)
TRI = PSI(1/DeltaR)
DO 446 I = 1, NG
DO 4446 J = I + 1, NG
FISHER(1, 1) = FISHER(1, 1)
& - 2*(1/DeltaR)**4)*(1-ALOG(DeltaR) - DIA
& + W(I) - W(J) *(1-ALOG(DeltaR) - DIA + W(J) - W(J))
4446 CONTINUE
FISHER(1, 1) = FISHER(1, 1) - (1/DeltaR)**4)*(C1(I)/C2(I)**2
& + W(I)**2 + PSI(C1(I)) + W(I)**2 - 2*W(I)*(PSI(C1(I) + 1)
& + (1-ALOG(DeltaR) - DIA)**2)
FISHER(1, 1) = FISHER(1, 1) - (1/DeltaR**3)
& * (3 - (1/DeltaR) * TRI - 2*(W(I) - W(L)) + ALOG(DeltaR)
& + DIA)
446 CONTINUE
DO 471 I = 1, NOBS
J = MEL(I)
K = IRANK(I)
L = NEL(I)
DO 473 I2 = 1, MC
21(I2, J) = 21(I2, J) + IND(I) * Z(ID(I2), I)
22(I2, J) = 22(I2, J) + ECHF(L, K) * XX(I) / W(J) * Z(ID(I2), I)
DO 473 I3 = I2, MC
23(I2, I3, J) = 23(I2, I3, J) + ECHF(L, K) * XX(I) / W(J) * Z(ID(I2), I)
& * Z(ID(I3), I)
473 CONTINUE
471 CONTINUE
DO 481 I = 1, MC
DO 481 J = 1, NG
DO 581 K = J + 1, NG
FISHER(1, I+J) = FISHER(1, I+J) - (1/DeltaR)**2)*(W(J) - W(K))
& - 1 + ALOG(DeltaR) + DIA) *(Z1(I, K) - Z2(I, K) * W(K))
FISHER(1, I+J) = FISHER(1, I+J) - (1/DeltaR)**2)*(W(K) - W(J))
& - 1 + ALOG(DeltaR) + DIA) *(Z1(I, J) - Z2(I, J) * W(J))
581 CONTINUE
FISHER(1, I+J) = FISHER(1, I+J) - (1/DeltaR)**2)*(W(J) - W(K))
& - 1 + ALOG(DeltaR) + DIA) * Z1(I, J)
FISHER(1, I+J) = FISHER(1, I+J) + (1/DeltaR)**2)*Z2(I, J)
& * (C1(J)/C2(J)**2 + W(J)**2 - 2*W(J) *(PSI(C1(J) + 1) - ALOG(C2(J)))
& + W(J) * (-1 + ALOG(DeltaR) + DIA))
FISHER(I+1, 1+I) = FISHER(1, I+J)
481 CONTINUE
DO 483 I = 1, MC
DO 483 J = 1, MC
DO 583 K = 1, NG
DO 683 L = K + 1, NG
FISHER(1+I, 1+J) = FISHER(1+I, 1+J) - (Z1(I, K) - Z2(I, K) * W(K))
& * (Z1(J, L) - Z2(J, L) * W(L))
FISHER(1+I, 1+J) = FISHER(1+I, 1+J) - (Z1(I, L) - Z2(I, L) * W(L))
& * (Z1(J, K) - Z2(J, K) * W(K))
683 CONTINUE
FISHER(1+I, 1+J) = FISHER(1+I, 1+J) - (Z1(I, K) * Z1(J, K)
& \quad -Z1(I,K) * Z2(J,K) * W(K) - Z2(I,K) * Z1(J,K) * W(K)
& \quad + Z2(I,K) * Z2(J,K) * (C1(K) / C2(K)**2 + W(K)**2))
FISHER(1+I,1+J) = FISHER(1+I,1+J) + W(K) * Z3(I,J,K)

583 CONTINUE
FISHER(1+J,1+I) = FISHER(1+I,1+J)

483 CONTINUE
CALL LINRG (MC+1, FISHER, N+1, FISHERI, N+1)
WRITE(6, 878)

878 FORMAT(IX, //)
DO 1076 I = 1, MC+1
DO 1076 J = I, MC+1
WRITE(6, *) 'COVC, I=', FISHERI(I, J)
1076 CONTINUE
WRITE(6, 978)

978 FORMAT(IX, //)
SE = SQRT(FISHERI(1,1))
TEST = DELTAR / SE
PVAL = 1. - ANORDF(ABS(TEST))
WRITE(6, 773) DELTAR, SE, PVAL

773 FORMAT(' EST OF ASSOC.=', F12.7, 2X, 'SE=', F16.8, 2X, 'PVAL=', F7.4)
DO 9873 J = 1, MC
SE = SQRT(FISHERI(J+1, J+1))
PVAL = 2. * (1. - ANORDF(ABS(THETA(J) / SE)))
WRITE(6, 8763) J, THETA(J), SE, PVAL
9873 CONTINUE
STOP
END
FUNCTION PSIP(Z)
    PSIP = 0
    Q = Z
    377  IF (Q.GT.5.0) GO TO 388
    PSIP = PSIP + 1.0 / Q**2
    Q = Q + 1.0
    GO TO 377
    388  W = 1. / Q
    PSIP = PSIP + W**11 / 66 - 691 * W**13 / 2730
    RETURN
END

SUBROUTINE BISEC(NG, CONST, DELTA1, DELTA2, DF1, DF2, DELTOL, DFTOL, NLIM, DELTAR, DFCN, KK)
    DO 30 J = 1, NLIM
         DELTAR = (DELTA1 + DELTA2) / 2.0
         DFR = DFCN(NG, CONST, DELTAR)
         XERR = ABS(DELTA1 - DELTA2) / 2.0
         IF (XERR .LE. DELTOL) GO TO 40
         IF (ABS(DFR) .LE. DFTOL) GO TO 50
         IF (DFR * DF1 .LT. 0) GO TO 60
         DELTA1 = DELTAR
         DF1 = DFR
         GO TO 30
    60  DELTA2 = DELTAR
         DF2 = DFR
    30  CONTINUE
    WRITE (6, 44444)
44444 FORMAT (//, 1X, 'THE NUMBER OF ITERATIONS EXCEEDS NLIM')
    KK = 3
    RETURN
    40  KK = 1
    RETURN
    50  KK = 2
    RETURN
END

FUNCTION DFCN(NG, CONST, DELTA)
    DFCN = FLOAT(NG) * (1 - ALLOG(DELTA) - PSI(1 / DELTA)) + CONST
    RETURN
END

SUBROUTINE SMAQ(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK, MAX, W, NITER, ITMAX, UTOL, TTOL, THETA, ID, XX, MC, MD, EHF, ECHF, NP, JJ, SFCN, SJAC, LIKELI, MULT, LINRG)
PARAMETER(NN=22,NNOBS=4178,NNS=4,NNG=3587)
PARAMETER(IITMAX=100)
DIMENSION THETA(N),THETAJ(NN,NN),FISHI(NN,NN)
DIMENSION U(NN)
DIMENSION Z(N,NNOBS),T(NNOBS),IND(NNOBS),NEL(NNOBS),
& MEL(NNOBS)
DIMENSION W(NNG)
DIMENSION IRANK(NNOBS),NP(NNOBS)
DIMENSION IJ(N)
DIMENSION XX(NNOBS)
DIMENSION EHF(NS,NNOBS),ECHF(NS,NNOBS)
DIMENSION ID(N)
DIMENSION SS(NN),SI1(NN),SI2(NN,NN)
DIMENSION SAVE(NN,NN),SSAVE(NN)
DIMENSION SHS(NN,NN),SHSINV(NN,NN)
& FINV(NN,NN)
DIMENSION COR(NN)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SJAC,SFCN,LIKELI,MULT,LINRG
REAL LIKE,LOGLIK
REAL MAXCOR,MAXU
REAL LAMDA
MAXCOR=5.0
LAMDA = 2.0
DO 20 M=1,IITMAX
393 DO 2225 I=1,NNOBS
XX(I)=0.0
DO 2226 J=1,MD
K=ID(J)
XX(I)=XX(I)+THETA(J)*Z(K,I)
MM=MEL(I)
2225 XX(I)=EXP(XX(I))*W(MM)
LIKE =0.0
DO 2227 I=1,N
U(I) = 0.0
DO 2227 J=1,N
THETAJ(I,J)=0.0
2227 CONTINUE
DO 2224 I=1,NS
DO 2224 J=1,MAX
EHF(I,J)=0.0
2224 CONTINUE
LI=1
2228 II=MAX
SI=0.0
DO 2335 I=1,N
   SI1(I)=0.0
DO 2335 J=1,N
   SI2(I,J)=0.0
2335 CONTINUE
2336 CONTINUE
MI=0
DO 2337 I=1,N
2337 SS(I)=0.0
   IP=NP(II)
   DO 2445 I=IP,NOBS
      IF(IRANK(I) .NE. II) GO TO 2446
      IF(NEL(I) .NE. LL) GO TO 2445
      XI =XX(I)
      SI=SI+XI
   DO 2449 K=1,MC
      Sll(K)=Sll(K)+XI*Z(ID(K),I)
   DO 2449 J=K,MC
      SI2(K,J)=SI2(K,J)+XI*Z(ID(K),I)*Z(ID(J),I)
2449 CONTINUE
   IF (IND(I) .EQ. 0) GO TO 2445
   MI=MI+1
   DO 2448 J=1,MD
      SS(J)=SS(J)+Z(ID(J),I)
2448 CONTINUE
2445 CONTINUE
2446 CONTINUE
   IF (MI .EQ. 0) GO TO 2556
   EHF(LL,II)=MI/SI
   CALL LIKELI(N,THETA,MD,MI,SS,SI,LIKE)
   CALL SFCN(N,MC,MI,SS,SI,Sll,SI2,THETAJ)
2556 CONTINUE
II =II-1
IF (II .GE. 1) GO TO 2336
LL =LL+1
IF(LL .LE. NS) GO TO 2228
IF (M .EQ. 1) GO TO 2557
IF (LIKE .GE. LOGLIK(M-1)) GO TO 2558
DO 800 1=1,MC
800 THETA(I) = THETA(I)-COR(I)
DO 810 1=1,N
   U(I)=SSAVE(I)
   DO 810 J=1,N
810 THETAJ(I,J)=SAVE(I,J)
NERRS=NERRS+1
LAMDA=LAMDA*2
IF(NERRS .LE. 20) GO TO 2559
WRITE(6,55555) M
55555 FORMAT(//,1X,'ERRORS IN MARQUARDT ',I4, ' ITERATIONS')
RETURN
2558 LOGLIK(M) = LIKE
LAMDA=LAMDA/1.5
GO TO 2775

2557 LOGLIK(1)=LIKE

2775 NERRS = 0
IF (MAXCOR .LE. TTOL) GO TO 1300
SUM = 0.
MAXU=-1.0
DO 100 J=1,MC
SUM = SUM + U(J)**2
IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))

100 CONTINUE
UNORM = SQRT(SUM)
IF (MAXU .LE. UTOL) GO TO 1100

2559 CALL MULT(N,THETAJ,THETAJ, SHS)
DO 400 I = 1,MC
SHS(I,I) = SHS(I,I) + LAMDA

400 CONTINUE
DO 993 I=1,N
DO 993 J=1,N
SHSINV(I,J)=0.0

993 CONTINUE
CALL LINRG(MC, SHS,N,SHSINV,N)
DO 994 I=1,N
DO 994 J=1,N
FINV(I,J)=0.0

994 CONTINUE
CALL MULT (N,SHSINV,THETAJ,FINV)
DO 500 I =1,MC
COR(I) = 0.0

500 CONTINUE
DO 600 I=1,MC
DO 600 J=1,MC
COR(I) = COR(I) - FINV(I,J)*U(J)

600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,MC
IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
THETA(I)=THETA(I)+COR(I)

700 CONTINUE
DO 710 I=1,N
SSAVE(I)= U(I)
DO 710 J=1,N
SAVE(I,J)=THETAJ(I, J)

710 CONTINUE
IF (NERRS .GE. 1) GO TO 393

20 CONTINUE
WRITE (6,66666)
66666 FORMAT(//'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
JJ = 3
RETURN

1100 DO 2324 I=1,NS
DO 2324 J=1,MAX
ECHF(I,J)=0.0

2324 CONTINUE
DO 2223 LL=1,NS
DO 2223 I=1,MAX
DO 2223 J=1,I
ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2223 CONTINUE
JJ=1
IF (NITER .EQ. 1) GO TO 1003
GO TO 1000
1300 DO 2325 I=1,NS
DO 2325 J=1,MAX
ECHF(I,J)=0.0
2325 CONTINUE
DO 2233 LL=1,NS
DO 2233 I=1,MAX
DO 2233 J=1,I
ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2233 CONTINUE
JJ=2
IF (NITER .EQ. 1) GO TO 1003
GO TO 1000
1003 DO 1008 I=1,MC
DO 1008 J=1,MC
THETAJ(I,J)=-THETAJ(I,J)
1008 CONTINUE
CALL LINRG (MC,THETAJ,N,FISHI,N)
DO 9076 I=1,MC
DO 9076 J=I,MC
WRITE(6,*) 'COV(',I,',',J,')=',FISHI(I,J)
9076 CONTINUE
WRITE (6,976)
976 FORMAT(IX,//)
DO 9874 J=1,MC
SE=SQR(FISHI(J))
PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE(6,8764) J,THETA(J),SE,PVAL
8764 FORMAT('  BETA(',I2,')=',F13.8,
& ' SE=',F13.8,2X,'PVALUE=',F7.5)
9874 CONTINUE
WRITE (6,956)
956 FORMAT(IX,//)
1000 RETURN
END
SUBROUTINE SFCN(N,MC,MI,SS,SI,S1, U)
DIMENSION SS(N),S1(N),U(N)
XXMI=MI
DO 22 K=1,MC
U(K)=U(K)+SS(K)-XXMI*SI1(K)/SI
22 CONTINUE
RETURN
END
SUBROUTINE SJAC(N,MC,MI,SS,SI,S12,THETAJ)
DIMENSION SS(N),S1(N),S12(N,N), THETAJ(N,N)
XXMI=MI
DO 27 K=1,MC
DO 27 L=K,MC
T1=SI2(K,L)/SI
T2=SI1(K)*SI1(L)/SI**2
THETAJ(K, L)=THETAJ(K,L)-XXXMI*(T1-T2)
THETAJ(L,K)=THETAJ(K,L)
27 CONTINUE
RETURN
END

SUBROUTINE LIKELI (N,THETA,MD,MI,SS,SI,LIKE)
DIMENSION THETA(N), SS(N)
REAL LIKE
S=0.0
DO 32 J=1,MD
S=S+SS(J)*THETA( J)
32 CONTINUE
XMI=MI
LIKE=LIKE+S-XMI*ALOG(SI)
RETURN
END

SUBROUTINE MULT(N, AO, BO, CO)
DIMENSION AO(N,N), BO(N,N), CO(N,N)
DO 1 I=1,N
DO 1 J=1,N
CO(I,J) = 0.0
DO 1 K=1,N
CO(I,J) = CO(I,J) + AO(I,K)*BO(K,J)
1 CONTINUE
RETURN
END

SUBROUTINE ORDER (T, IND, NOBS, PTRS)
DIMENSION T(NOBS), IND(NOBS), PTRS(NOBS)
INTEGER PTRS
INTEGER P ,PJ,PJ1,HTOP,HEND
DO 5020 1=1,NOBS
PTRS(I) = I
5020 CONTINUE
HTOP = NOBS/2 + 1
HEND=NOBS
2000 IF (HTOP .LE. 1) GO TO 2500
HTOP=HTOP-1
P=PTRS(HTOP)
GO TO 3000
2500 P = PTRS(HEND)
HEND =HEND -1
IF (HEND.EQ.1) GO TO 9000
3000 J=HTOP
4000 I=J
J=J+J
IF (J .GT. HEND) GO TO 8000
PJ=PTRS(J)
IF (J.EQ.HEND) GO TO 6000
PJ1 =PTRS(J+1)
IF(T(PJ) = T(PJ1)) 5050, 5010, 6000
5010 IF (IND(PJ) .LE. IND(PJ1)) GO TO 6000
5050 J = J + 1
6000 IF(T(P) = T(PJ)) 7000, 6010, 8000
6010 IF (IND(P) .LE. IND(PJ)) GO TO 8000
7000 PTRS(I) = PTRS(J)
      GO TO 4000
8000 PTRS(I) = P
      GO TO 2000
9000 PTRS(1) = P
RETURN
END

SUBROUTINE ARRANG(IORDER, NOBS, N, NOBSN, COVAR)
DIMENSION IORDER(NOBS), COVAR(NOBSN)
DIMENSION KEEP(20)
REAL KEEP
DO 7007 I = 1, NOBS
      IF((IORDER(I) .LE. 0) .OR. (IORDER(I) .EQ. I)) GO TO 7010
      L1 = N * (I - 1)
      DO 7001 L = 1, N
            KEEP(L) = COVAR(L1 + L)
      7001 CONTINUE
      J = I
5002 K = IORDER(J)
      IORDER(J) = -K
      LJ = N * (J - 1)
      LK = N * (K - 1)
      DO 7003 L = 1, N
            COVAR(LJ + L) = COVAR(LK + L)
5003 CONTINUE
      J = K
      IF(IORDER(J) .NE. I) GO TO 5002
      IORDER(J) = -I
5004 L1 = N * (J - 1)
      DO 7004 L = 1, N
            COVAR(L1 + L) = KEEP(L)
5004 CONTINUE
7010 IORDER(I) = IABS(IORDER(I))
7007 CONTINUE
RETURN
END
APPENDIX B

FORTRAN PROGRAM FOR THE EM ALGORITHM APPROACH TO THE ESTIMATION OF THE DEPENDENCE PARAMETER AND REGRESSION COEFFICIENTS IN A POSITIVE STABLE FRAILTY MODEL

PARAMETER(N=22, NOBS=4178, NS=4, NG=3587)
PARAMETER (GR=0.61803399, GC=1.-GR)
PARAMETER (LIM=1000)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION THETA(N), ITHETA(N), BTHETA(N)
DIMENSION W(NG)
DIMENSION IRANK(NOBS), NP(NOBS), IORDER(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NOBS)
DIMENSION A(NG), B(NG), BB(NG)
DIMENSION ID(N)
DIMENSION CLIKE(NG)
DIMENSION EHF(NS,NOBS), ECHF(NS,NOBS)
DIMENSION FISHER (N+1,N+1), FISHERI(N+1,N+1)
DIMENSION DEHF(N), DDEHF(N,N)
DIMENSION DEHFA(N), DDEHFA(N,N)
DIMENSION S1(N), S2(N,N)
DIMENSION SUM1(N), SUM2(N,N)
DIMENSION H2(N,N,NG), B1(N,NG), B2(N,N,NG)
INTEGER A
REAL ITHETA
REAL LLIKE
EXTERNAL SJAC, SFCN, LIKELI, MULT, LINRG
EXTERNAL SMAQ
EXTERNAL F2,F3,F4,F5
DATA UPP/0.0001/
C
C ***********************************************
C INPUT:
C IJ(I) = 1, COVARIATE I IS INCLUDED
C = 0, COVARIATE I IS USED IN COMPUTATION,
C BUT NOT IN MAXIMIZATION
C = -1, COVARIATE I IS OUT
C ***********************************************
C
DO 56565 I=1,N
   IJ(I)=1
56565 CONTINUE
C
UTOL = 0.01
TTOL = 0.001
ITMAX = 100
TOLER=0.0001
C
C ***********************************************
C INPUT:
C T: OBSERVED TIME ON STUDY
C IND: CENSORING INDICATOR
C MEL: GROUP NO
C NEL: STRATUM NO
C Z: COVARIATES
C ***********************************************
C
DO 70000 J=1,NOBS
   READ(1,*) T(J), IND(J), MEL(J), NEL(J), (Z(K,J), K=1,N)
70000 CONTINUE
C
C ***********************************************
C ARRANGING DATA BY THE ORDER OF OBSERVED TIMES ON STUDY
C ***********************************************
C
CALL ORDER (T,IND, NOBS, IORDER)
NOBSN=N*NOBS
CALL ARRANG(IORDER,NOBS,N,NOBSN,Z)
CALL ARRANG(IORDER,NOBS,1,NOBS,T)
CALL ARRANG (IORDER,NOBS,1,NOBS,IND)
CALL ARRANG (IORDER,NOBS,1,NOBS,MEL)
CALL ARRANG(IORDER,NOBS,1,NOBS,MEL)
JRANK=1
IRANK(I)=JRANK
DO 60000 I=2,NOBS
   IF(IND(I) .EQ. 0) GO TO 50000
   IF(T(I) .NE. T(I-1)) JRANK=JRANK+1
50000 IRANK(I)=JRANK
60000 CONTINUE
MAX=IRANK(NOBS)
J=1
DO 1225 I=1,NOBS
   }
IF (IRANK(I) .NE. J) GO TO 1225
I1=IRANK(I)
NP(I1)=I
J=J+1
1225 CONTINUE
DO 8014 I=1,N
IF (IJ(I) .EQ. 1) THEN
ITHETA(I)=0.0
ENDIF
8014 CONTINUE
J1=1
DO 1226 I=1,N
IF (IJ(I) .NE. 1 )  GO TO 1226
ID(J1)=I
THETA(J1)=ITHETA(ID(J1))
J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
IF(IJ(I) .NE. 0) GO TO 1227
ID(J1)=I
THETA(J1)=ITHETA(ID(J1))
J1=J1+1
1227 CONTINUE
MD=J1-1
DO 90000 J=1,NG
A(J)=0
90000 CONTINUE
DO 95555 I=1,NOBS
IF (IND(I) .EQ. 0) GO TO 95555
J=MEL(I)
A(J)=A(J)+1
95555 CONTINUE
DO 63333 J=1,NG
W(J)=1.0
63333 CONTINUE
IA=0

C *********************************************************
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO
C FIND THE MLE'S OF REGRESSION COEFFICIENTS BASED ON
C A MODIFIED COX'S PARTIAL LIKELIHOOD
C *********************************************************
C
CALL SMAQ(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,
& IA,ITMAX,UTOL,TTOL,THETA,ID,XX,MC,MD,EHF,ECHF,
& NP,JJ,SFCN, SJAC, LIKELI,MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
DO 90777 J=1,NG
CLIKE(J)=0.0
B(J)=0.0
90777 CONTINUE
DO 90888 I=1,NOBS
   J=MEL(I)
   K=IRANK(I)
   L=NEL(I)
   IF (IND(I) .EQ. 0) GO TO 90878
   CLIKE(J)=CLIKE(J)+IND(I)* (ALOG(EHF(L,K))
   & +ALOG(XX(I)) )
90878  B(J)=B(J)+ECHF(L,K)*XX(I)
90888 CONTINUE

LLIKE=0.0
DO 167 1=1,NG
   LLIKE=LLIKE+CLIKE(I)-B(I)
167 CONTINUE
WRITE(6,*) 'LOGLIKELIHOOD=', LLIKE
WRITE (6,778)
778 FORMAT(IX,//)

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
STARTING THE GOLDEN SECTION SEARCH
***********************************
***********************************
*

INPUT:
AX, BX, CX: THREE STARTING POINTS FROM THE SMALLEST
TO THE LARGEST FOR THE SEARCH OF THE
MLE OF THE DEPENDENCE PARAMETER
*

IA=1
CX=0.99
DELTAR=CX

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
EM:
FINDING THE MLE'S OF REGRESSION COEFFICIENTS
WHEN THE DEPENDENCE PARAMETER IS FIXED
* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

CALL EM(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,A,B,
& IA,UPP,LIM,ITMAX,UTOL,TTOL,DELTAR,ITHETA,THETA,FL,ID,XX
& ,MC,MD,NP,F2,F3,F4,F5,SJAC,SFCN,LIKELI,MULT,LINRG,SMAQ)
FCX=FL
WRITE(6,*) DELTAR
WRITE (6,'(F10.4)') FCX
BX=0.98
DELTAR=BX
CALL EM(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,A,B,
& IA,UPP,LIM,ITMAX,UTOL,TTOL,DELTAR,ITHETA,THETA,FL,ID,XX
& ,MC,MD,NP,F2,F3,F4,F5,SJAC,SFCN,LIKELI,MULT,LINRG,SMAQ)
FBX=FL
WRITE(6,*) DELTAR
WRITE (6,'(F10.4)') FBX
DO 9077 1=1,MD
BTHETA(I) = THETA(I)

9077 CONTINUE
DO 9066 J = 1, NG
BB(J) = B(J)
9066 CONTINUE

AX = 0.95
DELTAR = AX
CALL EM(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK, MAX, W, A, B,
& IA, UPP, LIM, ITMAX, UTOL, TTOL, DELTAR, ITHETA, THETA, FL, ID, XX
& , MC, MD, NP, F2, F3, F4, F5, SJAC, SFCN, LIKELI, MULT, LINRG, SMAQ)
FAX = FL
WRITE(6, *) DELTAR
WRITE(6, *) FAX
IF (FAX .GT. FBX .AND. FCX .GT. FBX) GO TO 3088
WRITE (6, 478)
478 FORMAT(1X, //, 'WRONG PICKS OF DELTARS')
STOP

3088 X0 = AX
X3 = CX
IF (ABS(CX - BX) .GT. ABS(BX - AX)) THEN
X1 = BX
X2 = BX + GC*(CX - BX)
ELSE
X2 = BX
X1 = BX - GC*(BX - AX)
ENDIF
DO 9087 I = 1, MD
THETA(I) = BTHETA(I)
9087 CONTINUE
DO 9044 J = 1, NG
B(J) = BB(J)
9044 CONTINUE

DELTAR = X1
CALL EM(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK, MAX, W, A, B,
& IA, UPP, LIM, ITMAX, UTOL, TTOL, DELTAR, ITHETA, THETA, FL, ID, XX
& , MC, MD, NP, F2, F3, F4, F5, SJAC, SFCN, LIKELI, MULT, LINRG, SMAQ)
FLIKE1 = FL
DELTAR = X2
CALL EM(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK, MAX, W, A, B,
& IA, UPP, LIM, ITMAX, UTOL, TTOL, DELTAR, ITHETA, THETA, FL, ID, XX
& , MC, MD, NP, F2, F3, F4, F5, SJAC, SFCN, LIKELI, MULT, LINRG, SMAQ)
FLIKE2 = FL

1111 IF (ABS(X3 - X0) .GT. TOLER*(ABS(X1) + ABS(X2))) THEN
IF (FLIKE2 .LT. FLIKE1) THEN
X0 = X1
X1 = X2
X2 = GR*X1 + GC*X3
FLIKE0 = FLIKE1
FLIKE1 = FLIKE2
DELTAR = X2
CALL EM(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK, MAX, W, A, B,
& IA, UPP, LIM, ITMAX, UTOL, TTOL, DELTAR, ITHETA, THETA, FL, ID, XX
& , MC, MD, NP, F2, F3, F4, F5, SJAC, SFCN, LIKELI, MULT, LINRG, SMAQ)
FLIKE2=FL
ELSE
  X3=X2
  X2=X1
  X1=GR*X2+GC*X0
  FLIKE3=FLIKE2
  FLIKE2=FLIKE1
  DELTAR=X1
CALL EM(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,A,B,&IA,UPP,LIM,ITMAX,UTOL,TTOL,DELTAR,ITHETA,THERA,FL,ID,XX&MC,MD,FP,F3,F4,F5,SA,FCN,LIKEI,MULT,LINEG,SAQ)
FLIKE1=FL
ENDIF
GO TO 1111
ENDIF
IF (FLIKE1 .LT. FLIKE2) THEN
DELTAR=X1
CALL EM(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,A,B,&IA,UPP,LIM,ITMAX,UTOL,TTOL,DELTAR,ITHETA,THERA,FL,ID,XX&MC,MD,FP,F3,F4,F5,SA,FCN,LIKEI,MULT,LINEG,SAQ)
FL=-FL
WRITE(6,578)
578 FORMAT(IX,//)
WRITE(6,*,'(LOGLIKELIHOOD= ',FL
ELSE
DELTAR=X2
CALL EM(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,A,B,&IA,UPP,LIM,ITMAX,UTOL,TTOL,DELTAR,ITHETA,THERA,FL,ID,XX&MC,MD,FP,F3,F4,F5,SA,FCN,LIKEI,MULT,LINEG,SAQ)
FL=-FL
WRITE(6,678)
678 FORMAT(IX,//)
WRITE(6,*,'(LOGLIKELIHOOD= ',FL
ENDIF
C
**********************************************************************************
C COMPUTING THE OBSERVED INFORMATION MATRIX
C IN THE EM ALGORITHM BASED ON A PROFILE LIKELIHOOD CONSTRUCTION
**********************************************************************************
C
DO 66 1=1,NG
  B(I)=0.0
  DO 66 J=1,MC
    B(J,I)=0.0
  DO 66 K=1,MC
    B2(J,K,I)=0.0
    H2(J,K,I)=0.0
66 CONTINUE
DO 9225 I=1,NOBS
  XX(I)=0.0
  DO 9226 J=1,MD
    K=ID(J)
 9226 XX(I)=XX(I)+THETA(J)*Z(K,I)
MM=MEL(I)

9225 XX(I)=EXP(XX(I))*W(MM)

DO 71 I=1,NOBS
    J=MEL(I)
    K=IRANK(I)
    L=NEL(I)
    M2=K
    SUM=0.0
    CHF=0.0
    EHFA=0.0
    DO 713 L1=1,MC
        DEHFA(L1)=0.0
        SI(L1)=0.0
        SUM1(L1)=0.0
        SUM2(L1,L2)=0.0
        DDEHFA(L1,L2)=0.0
        S2(L1,L2)=0.0
    713 CONTINUE

308 CONTINUE
    HF=0.0
    DO 513 L1=1,MC
        DEHF(L1)=0.0
        DO 513 L2=L1,MC
            DDEHF(L1,L2)=0.0
    513 CONTINUE

MI=0
    IP=NP(M2)
    DO 3108 N1=IP,NOBS
        IF (M2.EQ.K) GO TO 2318
        IF (IRANK(N1).NE.M2) GO TO 3208
    2318 IF (NEL(N1).NE.L) GO TO 3108
        SUM=SUM+XX(N1)
        DO 73 12=1,MC
            SUM1(12)=SUM1(12)+XX(N1)*Z(ID(12),N1)
            DO 73 13=12,MC
                SUM2(12,13)=SUM2(12,13)+XX(N1)*Z(ID(12),N1)*Z(ID(13),N1)
        73 CONTINUE
        IF (M2.EQ.K) GO TO 3048
        IF (IND(N1).EQ.0) GO TO 3108
    3048 IF (IRANK(N1).NE.M2.OR.IND(N1).EQ.0) GO TO 3108
    4804 MI=MI+1
    3108 CONTINUE

3208 CONTINUE
    IF (MI.EQ.0) GO TO 4208
    HF=FLOAT(MI)/SUM
    DO 813 L1=1,MC
        DEHF(L1)=-MI*SUM1(L1)/SUM**2
        DO 813 L2=L1,MC
            DDEHF(L1,L2)=-MI*(SUM2(L1,L2)/SUM**2-
                               & 2*SUM1(L1)*SUM1(L2)/SUM**3)
    813 CONTINUE
199

IF (M2 .LE. K-1 .OR. IND(I) .EQ. 0) GO TO 4208
EHFA=HF
DO 913 L1=1,MC
DEHFA(L1)=DEHF(L1)
DO 913 L2=L1,MC
DDEHFA(L1,L2)=DDEHF(L1,L2)
913 CONTINUE
4208 CONTINUE
CHF=CHF+HF
DO 613 L1=1,MC
S1(L1)=S1(L1)+DEHF(L1)
DO 613 L2=L1,MC
S2(L1,L2)=S2(L1,L2)+DDEHF(L1,L2)
613 CONTINUE
M2=M2-1
IF (M2 .GE. 1) GO TO 308
B(J)=B(J)+CHF*XX(I)/W(J)
DO 673 I2=1,MC
B1(I2,J)=B1(I2,J)+(CHF*Z(ID(I2),I)+S1(I2))
& *XX(I)/W(J)
DO 673 I3=I2,MC
& *XX(I)/W(J)
DO 673 I3=I2,MC
& *XX(I)/W(J)
IF (IND(I) .EQ. 0) GO TO 673
H2(I2,I3,J)=H2(I2,I3,J)+IND(I)*(EHFA*DDEHFA(I2,I3)-
& DEHFA(I2)*DEHFA(I3))/EHFA**2
673 CONTINUE
71 CONTINUE
DO 1050 I=1,N+1
DO 1050 J=1,N+1
FISHER(I,J)=0.0
1050 CONTINUE
DO 11 I=1,NG
IF (B(I) .EQ. 0.0) GO TO 11
IF (A(I) .LE. 1) GO TO 701
CONST=DELTAR*B(I)**DELTAR
IF (A(I) .EQ. 2) GO TO 771
IF (A(I) .EQ. 3) GO TO 871
IF (A(I) .EQ. 4) GO TO 971
971 CJ=F4(DELTAR,CONST)
XT=0.0
XT=XT-(1/CJ)*(1)
& 3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)/(DELTAR*
& CONST**3)+(1-DELTAR)*(2-DELTAR)/CONST**3
& +1*(1-DELTAR)*(3-DELTAR)/CONST**3
& +2*(1-DELTAR)*(3-DELTAR)/CONST**3)
XT=XT-(1/CJ)*(1)
& 2*(11-7*DELTAR)*(1-DELTAR)/(DELTAR*CONST**2)
& +(11-7*DELTAR)/CONST**2+7*(1-DELTAR)/CONST**2
& +6*(1-DELTAR)/(DELTAR*CONST)+6/CONST)
XT=XT-(1/CJ)*(1)
200

& 3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*ALOG(B(I))/
& CONST**3 + 2*(11-7*DELTAR)*(1-DELTAR)*ALOG(B(I))/
& CONST**2+6*(1-DELTAR)*ALOG(B(I))/CONST
FISHER(1,1)=FISHER(1,1)-XT**2
FISHER(1,1)=FISHER(1,1)+(1/CJ)*( 
& 12*(1-DELTAR)**2)*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)/CONST**3
& + 6*(1/DELTAR)*(1-DELTAR)*(2-DELTAR)/CONST**3+
& 6*(1/DELTAR)*(1-DELTAR)*(3-DELTAR)/CONST**3+
& 6*(1/DELTAR)*(2-DELTAR)*(3-DELTAR)/CONST**3+
& 2*(1-DELTAR)/CONST**3+2*(2-DELTAR)/CONST**3+
& 2*(3-DELTAR)/CONST**3)
FISHER(1,1)=FISHER(1,1)+(1/CJ)* ( 
& 6*(11-7*DELTAR)*(1-DELTAR)*(1/DELTAR**2)/CONST**2+
& 4*(11-7*DELTAR)*(1/DELTAR)/CONST**2+28*(1-DELTAR)* 
& (1/DELTAR)/CONST**2+4*(11-7*DELTAR)/CONST**2+
& 12*(1-DELTAR)*(1/DELTAR**2)/CONST+12*(1/DELTAR)*/
& (1/CJ)* (2-DELTAR)**2+12*(1-DELTAR)*ALOG(B(I)) /
& (DELTAR*CONST**3)+ 6*(1-DELTAR)*ALOG(B(I))/CONST**3+
& 6*(1-DELTAR)*ALOG(B(I))/CONST**3+
& 6*(2-DELTAR)*ALOG(B(I))/CONST**3+
& 8*(11-7*DELTAR)*(1-DELTAR)*ALOG(B(I)) / (DELTAR*CONST**2) 
& +4*(11-7*DELTAR)*ALOG(B(I))/CONST**2+28*(1-DELTAR)* 
& ALOG(B(I))/CONST**2+12*(1-DELTAR)*ALOG(B(I))
& / (DELTAR**2+12*(1-DELTAR)*ALOG(B(I))/CONST)
FISHER(1,1)=FISHER(1,1)+(1/CJ)* ( 
& 9*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*ALOG(B(I))**2/
& (DELTAR**2*B(I)**DELTAR)*DELTAR**2)+3*(1+(DELTAR-DELTAR**2) * 
& ALOG(B(I)))/(DELTAR**2*B(I)**DELTAR*CONST))**2
FISHER(1,1)=FISHER(1,1)-(3*(1+(DELTAR-DELTAR**2)* 
& ALOG(B(I)))/(DELTAR**2*B(I)**DELTAR*CONST))**2
FISHER(1,1)=FISHER(1,1)+(4/DELTAR 
& -3)+2*(2-DELTAR)*(1-DELTAR)*ALOG(B(I)))/(B(I)**(2* 
& DELTAR)**2*CONST)) 
& +3*((2*DELTA**2+DELTA**2-DLTAR**3)* 
& ALOG(B(I))**2)/ (DELTAR**3*CONST*B(I)**DELTA)) 
& -((4/DELTAR-3)+2*(2-DELTAR)*(1-DELTAR)*ALOG(B(I)))/ 
& (B(I)**(2*DELTAR)*DELTA**2*CONST)**2)
FISHER(1,1)=FISHER(1,1)+(4/DELTAR 
& -3)+2*(2-DELTAR)*(1-DELTAR)*ALOG(B(I)))/(B(I)**(2* 
& DELTAR)**2*CONST)) 
& *3*(1+(DELTAR-DELTA**2)* 
& ALOG(B(I)))/(DELTAR**2*B(I)**DELTA*CONST))
FISHER(1,1)=FISHER(1,1)+(16*DELTA-12*DELTA**2)*ALOG(B(I)) +4*(2* 
& DELTA-DELTA**2)*(DELTA-DELTA**2)*ALOG(B(I)) 
& **2)/(DELTAR**4*B(I)**(2*DELTA)**2*CONST)
GO TO 701
\begin{verbatim}
771  CONST=F2(DELTAR, CONST)
  FISHER(1,1)=FISHER(1,1) - ((1+(DELTAR-DELTAR**2) * 
    ALOG(B(I))) / (DELTAR**2*B(I)**DELTAR*CONST) )**2 
  + (2+2*DELTAR*ALOG(B(I)) ) / (DELTAR**2-DELTAR**3) 
  * ALOG(B(I))**2 / (DELTAR**3*CONST)*B(I)**DELTAR
701  FISHER(1,1)=FISHER(1,1)-A(I)/DELTAR**2-B(I)**DELTAR
      + (2+2*DELTAR*ALOG(B(I)) + (DELTAR**2-DELTAR**3) 
    * ALOG(B(I))**2 ) / (DELTAR**3*CONST*B(I))
986  CJ=F4(DELTAR,CONST)
      XT=0.0
      YT=0.0
      XT=XT-(1/CJ)*(
        6*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)/(DELTAR*
          CONST**3)+6*(1-DELTAR)*(2-DELTAR)/(DELTAR*
          CONST**3)+6*(1-DELTAR)*(3-DELTAR)/(DELTAR*
          CONST**3)+6*(2-DELTAR)*(3-DELTAR)/(DELTAR*
          CONST**3)
      )
      XT=XT-(1/CJ)*(
        3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*B1(I,J)/(B(I)*
          CONST**3)+3*(1-DELTAR)*(3-DELTAR)*B1(I,J)/(B(I)*
          CONST**3)+3*(2-DELTAR)*(3-DELTAR)*B1(I,J)/(B(I)*
          CONST**3)
      )
      YT=YT-(1/CJ)*(
        3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*ALOG(B(I))*B1(I,J)/(B(I)*
          CONST**3)+3*(1-DELTAR)*(3-DELTAR)*ALOG(B(I))*B1(I,J)/(B(I)*
          CONST**3)+3*(2-DELTAR)*(3-DELTAR)*ALOG(B(I))*B1(I,J)/(B(I)*
          CONST**3)
      )
11  CONTINUE
    DO 81  I=1,MC
    DO 881 J=1,NG
      IF (B(J) .EQ. 0.0) GO TO 881
      IF (A(J) .LE. 1) GO TO 86
      CONST=DELTAR*B(J)**DELTAR
      IF(A(J) .EQ. 2) GO TO 786
      IF(A(J) .EQ. 3) GO TO 886
      IF (A(J) .EQ. 4) GO TO 986
986  CJ=F4(DELTAR,CONST)
      XT=0.0
      YT=0.0
      XT=XT-(1/CJ)*(
        3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)/ (DELTAR*
          CONST**3)+ (1-DELTAR)*(2-DELTAR)/CONST**3
        + (1-DELTAR)*(3-DELTAR)/CONST**3
      )
      XT=XT-(1/CJ)*(
        2*(11-7*DELTAR)*(1-DELTAR)/ (DELTAR*CONST**2)
        + (11-7*DELTAR)/CONST**2+7*(1-DELTAR)/CONST**2
      )
      XT=XT-(1/CJ)*(
        3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*ALOG(B(J))/
          CONST**3 + 2*(11-7*DELTAR)*(1-DELTAR)*ALOG(B(J))/
          CONST**2+6*(1-DELTAR)*ALOG(B(J))/CONST)
      YT=YT-(1/CJ)*(
        3*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)+2*(11-7*DELTAR)*(1-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)+6*DELTAR*(1-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)
      )
      FISHER(1,1+1)=FISHER(1,1+1) - XT*YT
      FISHER(1,1+1)=FISHER(1,1+1) + (1/CJ)*(
        6*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*B1(I,J)/(B(J)*
          CONST**3)+3*DELTAR*(1-DELTAR)*(2-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)+3*DELTAR*(1-DELTAR)*(3-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)+3*DELTAR*(2-DELTAR)*(3-DELTAR)*B1(I,J)/
          (B(J)*CONST**3)
      )
      FISHER(1,1+1)=FISHER(1,1+1)+(1/CJ)*(
        2*(11-7*DELTAR)*(1-DELTAR)*B1(I,J)/(B(J)*CONST**2)
        + 2*DELTAR*(11-7*DELTAR)*B1(I,J)/(B(J)*CONST**2)
        + 14*DELTAR*(1-DELTAR)*B1(I,J)/(B(J)*CONST**2)
        + 6*DELTAR*B1(I,J)/(B(J)*CONST)
      )
      FISHER(1,1+1)=FISHER(1,1+1)+(1/CJ)*(
        9*DELTAR*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*ALOG(B(J))
        + B1(I,J)/(B(J)*CONST**3)+4*DELTAR*(11-7*DELTAR)
        + (1-DELTAR)*ALOG(B(J))*B1(I,J)/(B(J)*CONST**2)
    
\end{verbatim}
& +6*DELTAR*(1-DELTAR)*ALOG(B(J))*B1(I,J)/(B(J)*CONST))
GO TO 86

886  CONST=F3(DELTAR,CONST)
FISHER(1,1+I)=FISHER(1,1+I)+3*(1+(1-DELTAR)*
& ALOG(B(J)))*B1(I,J)/(B(J)**(1+DELTAR)*CONST)
FISHER(1,1+I)=FISHER(1,1+I)-9*(1-DELTAR)
& *(1+(DELTAR-DELTAR**2)*ALOG(B(J)))*B1(I,J)
& /((DELTAR**2*B(J)**(1+2*DELTAR)*CONST)**2)
& -(3*(1+(DELTAR-DELTAR**2)*
& ALOG(B(J)))/(DELTAR**2*B(J)**(1+2*DELTAR)*CONST))
& *(2*DELTAR*(2-DELTAR)*(1-DELTAR)/(B(J)
& *(2*DELTAR+1)*CONST*DELTAR**2)*B1(I,J))
& *((4
& -2*DELTAR**2)+4*DELTAR*(2-DELTAR)*(1-DELTAR)*ALOG(B(J)))*B1(I,J)/(B(J)
& *(1+2*DELTAR)*CONST)
& -((3+DELTAR)*B1(I,J)/(B(J)**(1+2*DELTAR)*CONST)
& *(1+(DELTAR-DELTAR**2)*ALOG(B(J)))/(B(J)**(1+2*DELTAR)*CONST)
& *(2*DELTAR*(2-DELTAR)*(1-DELTAR)*B1(I,J))
& *+4/DELTAR
& -3)*+2*(2-DELTAR)*(1-DELTAR)*ALOG(B(J)))/(B(J)**(2*DELTAR)*CONST)
& *(3*(1-DELTAR)/(B(J)*CONST*DELTAR)*B1(I,J))
GO TO 86

786  CONST=F2(DELTAR,CONST)
FISHER(1,1+I)=FISHER(1,1+I)+(1+(1-DELTAR)*
& ALOG(B(J)))*B1(I,J)/(B(J)**(1+DELTAR)*CONST)-(1-DELTAR)
& *(1+(DELTAR-DELTAR**2)*ALOG(B(J)))*B1(I,J)
& /((DELTAR**2*B(J)**(1+2*DELTAR)*CONST)**2)
& -B(J)**(1+1)*A(I,J)+B(J)**(1+1)*A(I,J)
& -B(J)**(1+1)*A(I,J)
86  CONTINUE
FISHER(I+1+1)=FISHER(I+1+1)
81  CONTINUE
DO 83 I=1,MC
DO 83 J=I,MC
DO 883 K=1,NG
IF (B(K) .EQ. 0.0) GO TO 883
IF (A(K) .LE. 1) GO TO 136
CONST=DELTAR*B(K)**DELTAR
IF (A(K) .EQ. 2) GO TO 7136
IF (A(K) .EQ. 3) GO TO 8136
IF (A(K) .EQ. 4) GO TO 9136
9136  CJ=F4(DELTAR,CONST)
FISHER(1+I,1+J)=FISHER(1+I,1+J)-((1/CJ)*
& 3*DELTAR*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*B1(I,K)/
& (B(K)*CONST**3)+2*DELTAR*(11-7*DELTAR)*(1-DELTAR)
& *B1(I,K)/(B(K)*CONST**2)+6*DELTAR*(1-DELTAR)*B1(I,K)/
& (B(K)*CONST)) *((1/CJ)*
& 3*DELTAR*(1-DELTAR)*(2-DELTAR)*(3-DELTAR)*B1(J,K)/
& (B(K)*CONST**3)+2*DELTAR*(11-7*DELTAR)*(1-DELTAR)
& *B1(J,K)/(B(K)*CONST**2)+6*DELTAR*(1-DELTAR)*B1(J,K)/
& $(B(K) \ast \text{CONST})$

FISHER(1+I,1+J) = FISHER(1+I,1+J) + (1/CJ) \ast \\
& 3 \ast \text{DELTAR} \ast (1-3 \ast \text{DELTAR}) \ast (1-\text{DELTAR}) \ast (2-\text{DELTAR}) \ast (3-\text{DELTAR}) \ast \\
& (B1(I,K) \ast B1(J,K)) / (B(K) \ast \text{CONST})^2 + 2 \ast \text{DELTAR} \ast (1+2 \ast \text{DELTAR}) \ast \\
& (11-7 \ast \text{DELTAR}) \ast (B1(I,K) \ast B1(J,K)) \\
& / (B(K) \ast \text{CONST})^2 \ast 6 \ast \text{DELTAR} \ast (1+\text{DELTAR}) \ast (1-\text{DELTAR}) \\
& \ast (B1(I,K) \ast B1(J,K)) / (B(K) \ast \text{CONST})^2 \\
& \text{FISHER}(1+I,1+J) = \text{FISHER}(1+I,1+J) - (1/CJ) \ast \\
& 3 \ast \text{DELTAR} \ast (1-\text{DELTAR}) \ast (2-\text{DELTAR}) \ast (3-\text{DELTAR}) \ast B2(I,J,K) / \\
& (B(K) \ast \text{CONST})^3 + 2 \ast \text{DELTAR} \ast (11-7 \ast \text{DELTAR}) \ast (1-\text{DELTAR}) \\
& \ast B2(I,J,K) / (B(K) \ast \text{CONST})^2 + 6 \ast \text{DELTAR} \ast (1-\text{DELTAR}) \ast B2(I,J,K) / \\
& (B(K) \ast \text{CONST})$

GO TO 136

8136 CONST = F3(\text{DELTAR}, \text{CONST})

FISHER(1+I,1+J) = FISHER(1+I,1+J) - \\
& 3 \ast (1-\text{DELTAR}) \ast \\
& (B2(I,J,K)) / (B(K) \ast \text{CONST})^2 \\
& - (1+\text{DELTAR}) / \\
& (B(K) \ast \text{CONST})^2 \\
& \text{FISHER}(1+I,1+J) = \text{FISHER}(1+I,1+J) - 9 \ast (1-\text{DELTAR})^2 \\
& / (B(K) \ast \text{CONST})^2 \\
& \ast (B1(I,K) \ast B1(J,K)) \\
& - (3 \ast (1-\text{DELTAR}) \ast (B(K) \ast \text{CONST})^2 + 2 \ast \text{DELTAR} \ast (1+2 \ast \text{DELTAR}) \ast (1-\text{DELTAR}) \\
& \ast (B2(I,J,K)) / (B(K) \ast \text{CONST}) \\
& \text{GO TO 136}$
CALL LINRG (MC+1,FISHER,N+1,FISHERI,N+1)
WRITE(6,718)

718 FORMAT (1X, //)
DO 1073 I=1,MC+1
DO 1073 J=I,MC+1
WRITE(6,*) 'COV(',I,',',J,')=',FISHERI(I,J)
1073 CONTINUE
WRITE(6,878)

878 FORMAT (1X, //)
SE=SQRT(FISHERI(1,1))
TEST=(DELTAR-1.0)/SE
PVAL=1.-ANORDF(ABS(TEST))
WRITE (6,7171) DELTAR,SE,PVAL

7171 FORMAT (' EST OF
& ASSOC.=',F12.7,2X,'SE=',F16.8,2X,'PVAL=',F7.4)
DO 9876 J=1,MC
SE=SQRT(FISHERI(J+1, J+1))
PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE (6,8761) J,THETA(J),SE,PVAL
9876 CONTINUE
STOP
END
****SUBROUTINES**

**C**

SUBROUTINE EM(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK,
  & MAX, W, A, B, IA, UPP, LIM, ITMAX, UTOL, TTOL, DELTAR
  & , ITHETA, THETA, FL, ID, XX, MC, MD, NP, F2, F3, F4, F5
  & , SJAC, SFCN, LIKELI, MULT, LINRG, SMAQ)

**C**

**INPUT:**

C NNN: NO OF COVARIATES
C NNNOBS: NO OF OBSERVATIONS
C NNNS: NO OF STRATA
C NNNG: NO OF GROUPS

**PARAMETER** (NNN=22, NNNOBS=4178, NNNS=4, NNNG=3587)

DIMENSION Z(N, NOBS), T(NOBS), IND(NOBS), NEL(NOBS),
  & MEL(NOBS)

DIMENSION THETA(N), ITHETA(N)

DIMENSION W(NG)

DIMENSION IRANK(NOBS), NP(NOBS)

DIMENSION IJ(N)

DIMENSION XX(NOBS)

DIMENSION A(NG), B(NG)

DIMENSION EHF(NNNS, NNNOBS), ECHF(NNNS, NNNOBS)

DIMENSION ID(N)

DIMENSION ALIKE(NNNG), BLIKE(NNNG), CLIKE(NNNG)

INTEGER A

REAL LLIKE

REAL ITHETA

REAL MTHETA

EXTERNAL SFCN, SJAC, LIKELI, MULT, LINRG

EXTERNAL SMAQ

EXTERNAL F2, F3, F4,F5

DO 7087 I=1, MD

ITHETA(I)=THETA(I)

7087 CONTINUE

DO 50666 J=1, NG

IF (B(J) .EQ. 0.0) THEN

W(J)=1.0

ELSE

C1=DELTAR*B(J)**(DELTAR-1)

C2=DELTAR*B(J)**DELTAR

IF (A(J) .EQ. 0) W(J)=C1

IF (A(J) .EQ. 1) W(J)=F2(DELTAR, C2) *C1

IF (A(J) .EQ. 2) W(J)=F3(DELTAR, C2) /F2(DELTAR, C2) *C1

IF (A(J) .EQ. 3) W(J)=F4(DELTAR, C2) /F3(DELTAR, C2) *C1

IF (A(J) .EQ. 4) W(J)=F5(DELTAR, C2) /F4(DELTAR, C2) *C1

ENDIF

50666 CONTINUE
C STARTING THE EM ALGORITHM
C
DO 85555 NITER=1,LIM
CALL SMAQ(N,NOBS,NS,NG,Z,T,IND,NEL,MEL,IJ,IRANK,MAX,W,
& IA,ITMAX,UTOL,TTL,TOL,THETA,ID,XX,MC,MD,EHF,ECHF,
& NP,JJ,SFCN, SJAC, LIKELI,MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
DO 97777 J=1,NG
CLIKE(J)=0.0
B(J)=0.0
97777 CONTINUE
DO 98888 I=1,NOBS
J=MEL(I)
K=IRANK(I)
L=NEL(I)
IF (IND(I) .EQ. 0) GO TO 97878
CLIKE(J)=CLIKE(J)+IND(I)*(ALOG(EHF(L,K))
& +ALOG(XX(I)/W(J)))
97878 B(J)=B(J)+ECHF(L,K)*XX(I)/W(J)
98888 CONTINUE
LLIKE=0.0
DO 117 I=1,NG
ALIKE(I)=0.0
IF (A(I) .LE. 1) GO TO 97
CONST=DELTAR*B(I)**DELTAR
IF (A(I) .EQ. 2) ALIKE(I)=ALOG(F2(DELTAR,CONST))
IF (A(I) .EQ. 3) ALIKE(I)=ALOG(F3(DELTAR,CONST))
IF (A(I) .EQ. 4) ALIKE(I)=ALOG(F4(DELTAR,CONST))
97 IF (B(I) .EQ. 0.0) THEN
BLIKE(I)=0.0
ELSE
BLIKE(I)=A(I)*(ALOG(DELTAR)+(DELTAR-1)*ALOG(B(I)))
& -B(I)**DELTAR
ENDIF
LLIKE=LLIKE+ALIKE(I)+BLIKE(I)+CLIKE(I)
117 CONTINUE
IF (NITER .EQ. 1) GO TO 147
IF (LLIKE .LT. TEMP) GO TO 47
DL=LLIKE-TEMP
IF (DL .LE. 0.00001) GO TO 49
147 TEMP=LLIKE
MTHETA=-1.0
DO 75555 I=1,MC
DIFF1=THETA(I)-ITHETA(I)
IF (ABS(DIFF1) .GE. MTHETA) MTHETA=ABS(DIFF1)
75555 CONTINUE
IF (MTHETA .LE. UPP) GO TO 49
DO 79999 I=1,MC
ITHETA(I)=THETA(I)
79999 CONTINUE
DO 56666 J=1,NG
IF (B(J) .EQ. 0) THEN
W(J)=1.0
ELSE
C1=DELTAR*B(J)**(DELTAR-1)
C2=DELTAR*B(J)**DELTAR
IF (A(J) .EQ. 0) W(J)=C1
IF (A(J) .EQ. 1) W(J)=F2(DELTAR,C2)*C1
IF (A(J) .EQ. 2) W(J)=F3(DELTAR,C2)/F2(DELTAR,C2)*C1
IF (A(J) .EQ. 3) W(J)=F4(DELTAR,C2)/F3(DELTAR,C2)*C1
IF (A(J) .EQ. 4) W(J)=F5(DELTAR,C2)/F4(DELTAR,C2)*C1
ENDIF
56666 CONTINUE
85555 CONTINUE
WRITE(6,63)
63 FORMAT(///,1X,'THE NUMBER OF ITERATIONS EXCEEDS NITER')
WRITE (6,*) ' THE MAX OF DIFF. = ',MTETA
GO TO 49
47 LLIKE=TEMP
DO 777 I=1,MC
THETA(I)=ITHETA(I)
777 CONTINUE
49 FL=-LLIKE
RETURN
END
FUNCTION F2(DELTAR,C2)
F2=1+(1-DELTAR)/C2
RETURN
END
FUNCTION F3(DELTAR,C2)
F3=1+3*(1-DELTAR)/C2+(2-DELTAR)*(1-DELTAR)/C2**2
RETURN
END
FUNCTION F4(DELTAR,C2)
F4=1+6*(1-DELTAR)/C2+(1-DELTAR)*(11-7*DELTAR)/C2**2
& +(3-DELTAR)*(2-DELTAR)*(1-DELTAR)/C2**3
RETURN
END
FUNCTION F5(DELTAR,C2)
F5=1+10*(1-DELTAR)/C2+(1-DELTAR)*(35-25*DELTAR)/C2**2
& +(1-DELTAR)*(2-DELTAR)*(25-15*DELTAR)/C2**3
& +(4-DELTAR)*(3-DELTAR)*(2-DELTAR)*(1-DELTAR)/C2**4
RETURN
END
SUBROUTINE SM208
& SMAQ(N, NOBS, NS, NG, Z, T, IND, NEL, MEL, IJ, IRANK
& , MAX, W, IA, ITMAX, UTOL, TTOL, THETA, ID, XX, MC, MD
& , EHF, ECHF, NP, JJ, SFCN, SJAC, LIKELI, MULT, LINRG)
C
C ****************************************************************
C INPUT:
C NN: NO OF COVARIATES
C NNOBS: NO OF OBSERVATIONS
C NNS: NO OF STRATA
C NNG: NO OF GROUPS
C ****************************************************************
C
PARAMETER (NN=22, NNOBS=4178, NNS=4, NNG=358)
PARAMETER (ITMAX=100)
DIMENSION THETA(N), THETAJ(NN, NN), FISHI(NN, NN)
DIMENSION U(NN)
DIMENSION Z(N, NOBS), T(NOBS), IND(NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION W(NG)
DIMENSION IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NOBS)
DIMENSION EHF(NS, NOBS), ECHF(NS, NOBS)
DIMENSION ID(N)
DIMENSION SS(NN), SI1(NN), SI2(NN, NN)
DIMENSION SAVE(NN, NN), SSAVE(NN)
DIMENSION SHS(NN, NN), SHSINV(NN, NN)
&
DIMENSION COR(NN)
DIMENSION LOGLIK(ITMAX)
REAL ITHETA, LIKE, LOGLIK
REAL MAXCOR, MAXU
EXTERNAL SFCN, SJAC, LIKELI, MULT, LINRG
MAXCOR=5.0
LAMDA = 2.0
DO 20 M=1, ITMAX
339 DO 2225 1=1, NOBS
    XX(I)=0.0
2225 CONTINUE
K=ID(J)
XX(I)=XX(I)+THETA(J)*Z(K, I)
MM=MEL(I)
XX(I)=EXP(XX(I))*W(MM)
LIKE = 0.0
DO 2227 I=1, N
    U(I) = 0.0
2227 CONTINUE
ELSE IF(J=1, N)
    THETAJ(I, J)=0.0
2227 CONTINUE
DO 2224 I=1, NS
DO 2224 J=1, MAX
    EHF(I, J)=0.0
2224 CONTINUE
LL = 1
2228 II = MAX
   SI = 0.0
   DO 2335 I = 1, N
   SI1(I) = 0.0
   DO 2335 J = 1, N
   SI2(I, J) = 0.0
2335 CONTINUE
2336 CONTINUE
   MI = 0
   DO 2337 I = 1, N
2337 SS(I) = 0.0
   IP = NP(II)
   DO 2445 I = IP, NOBS
      IF (IRANK(I) .NE. II) GO TO 2446
      IF (NEL(I) .NE. LL) GO TO 2445
      XI = XX(I)
      SI = SI + XI
      DO 2449 K = 1, MC
         SI1(K) = SI1(K) + XI * Z(ID(K), I)
      DO 2449 J = K, MC
         SI2(K, J) = SI2(K, J) + XI * Z(ID(K), I) * Z(ID(J), I)
2449 CONTINUE
   IF (IND(I) .EQ. 0) GO TO 2445
   MI = MI + 1
   DO 2448 J = 1, MD
      SS(J) = SS(J) + Z(ID(J), I)
2448 CONTINUE
2445 CONTINUE
2446 CONTINUE
   IF (MI .EQ. 0) GO TO 2556
   EHF(LL, II) = MI / SI
   CALL LIKELI(N, THETA, MD, MI, SS, SI, LIKE)
   CALL SFCN(N, MC, MI, SS, SI, SI1, U)
   CALL SJAC(N, MC, MI, SS, SI, SI1, SI2, THETAJ)
2556 CONTINUE
   II = II - 1
   IF (II .GE. 1) GO TO 2336
   LL = LL + 1
   IF (LL .LE. NS) GO TO 2228
   IF (M .EQ. 1) GO TO 2557
   IF (LIKE .GE. LOGLIK(M - 1)) GO TO 2558
   DO 800 I = 1, MC
800   THETA(I) = THETA(I) - COR(I)
   DO 810 I = 1, N
      U(I) = SSAVE(I)
   DO 810 J = 1, N
810   THETAJ(I, J) = SAVE(I, J)
   NERRS = NERRS + 1
   LAMDA = LAMDA * 2
   IF (NERRS .LE. 20) GO TO 2559
   WRITE(6, 55555) M
55555 FORMAT(//, 1X, 'ERRORS IN MARQUARDT ', I4, ' ITERATIONS')
JL = 4
RETURN

2558 LOGLIK(M) = LIKE
      LAMDA = LAMDA / 1.5
      GO TO 2775

2557 LOGLIK(1) = LIKE

2775 NERRS = 0
      IF (MAXCOR .LE. TTOL) GO TO 1300
      SUM = 0.
      MAXU = -1.0
      DO 100 J = 1, MC
      SUM = SUM + U(J)**2
      IF (ABS(U(J)) .GE. MAXU) MAXU = ABS(U(J))

100 CONTINUE
      UNORM = SQRT(SUM)
      IF (MAXU .LE. UTOL) GO TO 1100

2559 CALL MULT(N, THETAJ, THETAJ, SHS)
      DO 400 I = 1, MC
      SHS(I, I) = SHS(I, I) + LAMDA

400 CONTINUE
      DO 933 I = 1, N
      DO 933 J = 1, N
      SHSINV(I, J) = 0.0

933 CONTINUE
      CALL LINRG(MC, SHS, N, SHSINV, N)
      DO 944 I = 1, N
      DO 944 J = 1, N
      FINV(I, J) = 0.0

944 CONTINUE
      CALL MULT(N, SHSINV, THETAJ, FINV)
      DO 500 I = 1, MC
      COR(I) = 0.0

500 CONTINUE
      DO 600 I = 1, MC
      DO 600 J = 1, MC
      COR(I) = COR(I) - FINV(I, J) * U(J)

600 CONTINUE
      MAXCOR = -1.0
      DO 700 I = 1, MC
      IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR = ABS(COR(I))
      THETA(I) = THETA(I) + COR(I)

700 CONTINUE
      DO 710 I = 1, N
      SSAVE(I) = U(I)
      DO 710 J = 1, N
      SAVE(I, J) = THETAJ(I, J)
      IF (NERRS .GE. 1) GO TO 339

20 CONTINUE
      WRITE (6, 66666)
56666 FORMAT(//, 1X, 'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
      JJ = 3
      RETURN

1100 DO 2324 I = 1, NS
DO 2324 J=1,MAX
ECHF(I,J)=0.0
2324 CONTINUE
DO 2223 LL=1,NS
DO 2223 I=1,MAX
DO 2223 J=1,I
ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2223 CONTINUE
JJ=1
IF (IA .EQ. 0) GO TO 1003
GO TO 1000
1300 DO 2325 I=1,NS
DO 2325 J=1,MAX
ECHF(I,J)=0.0
2325 CONTINUE
DO 2233 LL=1,NS
DO 2233 I=1,MAX
DO 2233 J=1,I
ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2233 CONTINUE
JJ=2
IF (IA .NE. 0) GO TO 1000
1003 DO 1008 I=1,MC
DO 1008 J=1,MC
THETAJ(I,J)=-THETAJ(I,J)
1008 CONTINUE
CALL LINRG (MC,THETAJ,N,FISHI,N)
DO 1093 I=1,MC
DO 1093 J=I,MC
WRITE(6,*) 'COV(',I,',1,J ,')=',FISHI(I,J)
1093 CONTINUE
DO 9874 J=1,MC
SE=SQRT(FISHI(J,J))
PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE(6,8764) J,THETA(J),SE,PVAL
8764 FORMAT( 'B E T A (',12,F 13.8,2X,'PVALUE=',F 7.5)
9874 CONTINUE
WRITE(6,828)
828 FORMAT(IX,//)
1000 RETURN
END
SUBROUTINE SFCN(N,MC,MI,SS,SI,SI1, U)
DIMENSION SS(N),SI1(N),U(N)
XXMI=MI
DO 22 K=1,MC
U(K)=U(K)+SS(K)—XXMI*SI1(K)/SI
22 CONTINUE
RETURN
END
SUBROUTINE SJAC(N,MC,MI,SS,SI,SI1,SI2,THETAJ)
DIMENSION SS(N),SI1(N),SI2(N,N), THETAJ(N,N)
XXMI=MI
DO 27 K=1,MC
DO 27 L=K,MC
T1=SI2(K,L)/SI
T2=SI1(K)*SI1(L)/SI**2
THETAJ(K,L)=THETAJ(K,L)-XXXMI*(T1-T2)
THETAJ(L,K)=THETAJ(K,L)
27 CONTINUE
RETURN
END

SUBROUTINE LIKELI (N,THETA,MD,MI,SS,SI,LIKE)
DIMENSION THETA(N), SS(N)
REAL LIKE
S=0.0
DO 32 J=1,MD
S=S+SS(J)*THETA(J)
32 CONTINUE
XMI=MI
LIKE=LIKE+S-XMI*ALOG(SI)
RETURN
END

SUBROUTINE MULT(N,AO,BO,CO)
DIMENSION AO(N,N), BO(N,N), CO(N,N)
DO 1 I=1,N
DO 1 J=1,N
CO(I,J) = 0.0
DO 1 K=1,N
CO(I,J) = CO(I,J) + AO(I,K)*BO(K,J)
1 CONTINUE
RETURN
END

SUBROUTINE ORDER (T,IND,NOBS,PTRS)
DIMENSION T(NOBS), IND(NOBS), PTRS(NOBS)
INTEGER P,PJ,PJ1,HTOP,HEND
DO 5020 1=1,NOBS
P=PTRS(I)
5020 CONTINUE
HTOP = NOBS/2 + 1
HEND=NOBS
2000 IF (HTOP .LE. 1) GO TO 2500
HTOP=HTOP-1
P=PTRS(HTOP)
GO TO 3000
2500 P = PTRS(HEND)
PTRS(HEND) = PTRS(1)
HEND = HEND -1
IF (HEND.EQ.1) GO TO 9000
3000 J=HTOP
4000 I=J
J=J+J
IF (J .GT. HEND) GO TO 8000
PJ=PTRS(J)
IF (J.EQ.HEND) GO TO 6000
SUBROUTINE ARRANG (IORDER, NOBS, N, NOBSN, COVAR)

DIMENSION IORDER(NOBS), COVAR(NOBSN)
DIMENSION KEEP(20)
REAL KEEP

DO 7007 I=1, NOBS
IF((IORDER(I) .LE. 0) .OR. (IORDER(I) .EQ. I)) GO TO 7010
L1=N*(I-1)
DO 7001 L=1, N
KEEP(L) = COVAR(L1+L)
CONTINUE
J=I
7002 K=IORDER(J)
IORDER(J) = -K
LJ=N*(J-1)
LK=N*(K-1)
DO 7003 L=1, N
COVAR(LJ+L) = COVAR(LK+L)
CONTINUE
J=K
IF(IORDER(J) .NE. I) GO TO 7002
IORDER(J) = -I
L1=N*(J-1)
DO 7004 L=1, N
COVAR(L1+L) = KEEP(L)
CONTINUE
7010 IORDER(I) =IABS(IORDER(I))
7007 CONTINUE
RETURN
END
APPENDIX C

FORTRAN PROGRAM FOR THE MAXIMUM LIKELIHOOD
ESTIMATION OF THE DEPENDENCE PARAMETER AND
REGRESSION COEFFICIENTS
IN A WEIBULL REGRESSION MODEL WITH GAMMA FRAILTY

* * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

************* MAIN PROGRAM *************

INPUT:
NU: NO. OF UNKNOWN PARAMETERS (=N+NS+1)
N: NO OF COVARIATES PLUS THE INTERCEPTS
NOBS: NO OF OBSERVATIONS
NS: NO OF STRATA
NG: NO OF GROUPS

PARAMETER (NU=23, N=20, NOBS=3142, NS=2, NG=1571)
DIMENSION THETA (NU), JACOB (NU, NU)
DIMENSION BETA (N)
DIMENSION ALPHA (NS)
DIMENSION T (NOBS), IND (NOBS), Z (N, NOBS), NEL (NOBS),
& MEL (NOBS)
DIMENSION TS (NOBS)
DIMENSION IJ (N)
DIMENSION A (NG), B (NG)
DIMENSION DEL (7), TA (NS), TB (N)
REAL JACOB
EXTERNAL SFCN, SJAC, LIKELI
EXTERNAL SFCNI, SJACI, LIKELII, MULT, LINRG

INPUT:
IJ(I) = 1, COVARIATE I IS INCLUDED
IJ(I) = 0, COVARIATE I IS USED IN COMPUTATION,
BUT NOT IN MAXIMIZATION
IJ(I) = -1, COVARIATE I IS OUT

DO 8010 I=1,N
IJ(I)=1
CONTINUE
DO 8014 I=1,N
   IF (IJ(I) .EQ. 1) THEN
      BETA(I)=0.0
   ENDIF
8014 CONTINUE
DO 2013 I=1,NS
   ALPHA(I)=1.0
2013 CONTINUE
DEL(1)=0.1
DEL(2)=0.2
DEL(3)=0.4
DEL(4)=0.6
DEL(5)=0.7
DEL(6)=0.85
DEL(7)=1.0
UTOL = 0.01
TTOL = 0.001
ITMAX = 100
C
C ******************************************************************************************
C INPUT:
C T: OBSERVED TIME ON STUDY
C TS: TRUNCATION TIME, POSSIBLY ZERO
C IND: CENSORING INDICATOR
C MEL: GROUP NO
C NEL: STRATUM NO
C Z: COVARIATES
C ******************************************************************************************
C
DO 70000 I=1,NOBS
   READ (1,*) T(I), TS(I), IND(I), MEL(I), NEL(I) &
      ,(Z(K,I), K=NS+1,N)
70000 CONTINUE
DO 8321 I=1,NOBS
   DO 8421 J=1,NS
      IF (NEL(I) .EQ. J) THEN
         Z(J,I)=1.0
      ELSE
         Z(J,I)=0.0
      ENDIF
8421 CONTINUE
8321 CONTINUE
DO 90000 I=1,NG
   A(I)=0
90000 CONTINUE
DO 95555 I=1,NOBS
   IF(IND(I) .EQ. 0) GO TO 95555
      J=MEL(I)
      A(J)=A(J)+1
95555 CONTINUE
DO 10000 I=1,NU
   THETA(I)=0.0
216

10000 CONTINUE
C
C ***********************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO FIND
C THE MLE'S OF THE REGRESSION COEFFICIENTS UNDER INDEPENDENCE
C ***********************************************
C
CALL SMAQI (NU,N,NOBS,NS,NG,T,IND,Z,NEL,MEL,TS,IJ,A,B,
& MC,MD,ITMAX,UTOL,TTOL,BETA,ALPHA,JACOB,THETA,XL,JJ,
& SFCTN, SJACI,LIKELII, MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
TD=0.0
DO 7013 I=1,NS
 TA(I)=ALPHA(I)
7013 CONTINUE
DO 8013 I=1,MD
 TB(I)=BETA(I)
8013 CONTINUE
C
C ***********************************************
C STARTING A PROFILE LIKELIHOOD SEARCH
C FOR THE DEPENDENCE PARAMETER
C ***********************************************
C
DO 4013 I=1,7
 DELTA=DEL(I)
 IA=0
 DO 10010 J=1,NU
  THETA(J)=0.0
10010 CONTINUE
C
C ***********************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO
C FIND THE MLE'S OF THE REGRESSION COEFFICIENTS AND DEPENDENCE
C PARAMETER (WHEN IT IS NOT FIXED) UNDER ADJUSTMENT FOR FRAILTY
C ***********************************************
C
CALL SMAQ (IA,NU,N,NOBS,NS,NG,T,IND,Z,NEL,MEL,TS,IJ,A,B,
 & MC,MD,ITMAX,UTOL,TTOL,BETA,ALPHA,DELTA,JACOB,THETA
 & ,YL,JJ,SFCN, SJAC,LIKELI, MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
IF (YL .GT. XL) THEN
XL=YL
 TD=DELTA
 DO 3014 L=1,NS
  TA(L)=ALPHA(L)
3014 CONTINUE
DO 4014 LJ=1,MD
 TB(LJ)=BETA(LJ)
4014 CONTINUE
ENDIF
4013 CONTINUE
   IF (TD .EQ. 0.0) THEN
      WRITE (6,*) ' PROBABLY NO ASSOCIATION ' STOP
   ELSE
      GO TO 8621
   ENDIF
8621 IA=1
   DELTA=TD
   DO 5014 I=1,NS
      ALPHA(I)=TA(I)
   5014 CONTINUE
   DO 6014 I=1,MD
      BETA(I)=TB(I)
   6014 CONTINUE
   CALL SMAQ(IA,NU,N,NOBS,NS,NG,T,IND,Z,NEL,MEL,TS,IJ,A,B,
       & MC,MD,ITMAX,UTOL,TTOL,BETA,ALPHA,DELTA,JACOB,THETA
       & ,YL,JJ,SFCN, SJAC,LIKELI, MULT,LINRG)
   IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
   STOP
END
SUBROUTINE SMAQI(NU,N,NOBS,NS,NG,T,IND,Z,NEL,T,S, IJ
& A, B, MC, MD, ITMAX, UTOL, TTOL, BETA, ALPHA, JACOB,
& THETA, LIKE, JJ,
& SFCNI, SJACI, LIKELII, MULT, LINRG)

INPUT:
NNU: NO. OF UNKNOWN PARAMETERS
NN: NO OF COVARIATES, INCLUDING THE INTERCEPTS
NNOBS: NO OF OBSERVATIONS
NNS: NO OF STRATA
NNG: NO OF GROUPS

PARAMETER (NNU=23, NN=20, NNS=2, NNG=1571, NNOBS=3142)
PARAMETER (IITMAX=100)
DIMENSION THETA(NU), U(NNU), JACOB (NU, NU)
& JACOBI(NNU, NNU)
DIMENSION ALPHA(NS)
DIMENSION BETA(N)
DIMENSION T(NOBS), IND(NOBS), Z(N, NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION TS(NOBS)
DIMENSION XX(NNOBS)
DIMENSION A(NG), B(NG)
DIMENSION BS(NNG)
DIMENSION ID(NN), IJ(N)
DIMENSION CLIKE(NNG)
DIMENSION DBA (NNS, NNG), AZ (NNS, NNG), DBB (NN, NNG),
& BZ (NN, NNG)
DIMENSION DBAA (NNS, NNG), AZZ (NNS, NNG),
& DBBB (NN, NN, NNG)
DIMENSION DBBB (NN, NN, NNG)
DIMENSION DSDBA (NN, NNS, NNG), SDBB (NN, NNG), SDBAA (NNS, NNG)
DIMENSION DSDBAB (NN, NNS, NNG), SDBBB (NN, NN, NNG)
DIMENSION SHS (NN, NNU), SHSINV (NN, NNU)
& FINV (NNU, NNU)
DIMENSION COR(NNU)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SFCNI, SJACI, LIKELII, MULT, LINRG
REAL JACOB, JACOBI
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
DO 23 I=1, NS
THETA(I)=ALPHA(I)
23 CONTINUE
JL=1
DO 1226 I=1, N
IF (IJ(I) .NE. 1) GO TO 1226
ID(J1)=I
THETA(J1+NS)=BETA(I)
J1=J1+1

1226 CONTINUE
MC=J1-1
DO 1227 I=1, N
IF (IJ(I) .NE. 0) GO TO 1227
ID(J1)=I
THETA(J1+NS)=BETA(I)
J1=J1+1

1227 CONTINUE
MD=J1-1
DO 3013 I=1, MD
BETA(I)=THETA(I+NS)

3013 CONTINUE
ND=MD+NS
NC=MC+NS
MAXCOR=5.0
LAMDA=2.0
DO 20 M=1, ITMAX

399 DO 2225 I=1, NOBS
XX(I)=0.0
DO 2226 J=1, MD
K=ID(J)
XX(I)=XX(I)+BETA(J)*Z(K,I)

2225 XX(I)=EXP(XX(I))
DO 126 J=1, NG
CLIKE(J)=0.0
B(J)=0.0
BS(J)=0.0
DO 127 I=1, NS
DBA(I,J)=0.0
SDBA(I,J)=0.0
AZ(I,J)=0.0
DBAA(I,J)=0.0
SDBAA(I,J)=0.0
AZZ(I,J)=0.0
DO 127 K=1, N
DBAB(K,I,J)=0.0
SDBAB(K,I,J)=0.0

127 CONTINUE
DO 126 I=1, N
DBB(I,J)=0.0
SDBBB(I,J)=0.0
BZ(I,J)=0.0
DO 126 K=1, N
DBBB(I,K,J)=0.0
SDBBB(I,K,J)=0.0

126 CONTINUE
DO 226 I=1, NOBS
J=MEL(I)
L=NEL(I)
\[
\begin{align*}
\text{CLIKE}(J) &= \text{CLIKE}(J) + \text{IND}(I) \times (\text{ALOG}(\alpha(L) \times T(I)) \times (\alpha(L) - 1)) + \text{ALOG}(XX(I)) \\
B(J) &= B(J) + T(I) \times \alpha(L) \times XX(I) \\
BS(J) &= BS(J) + TS(I) \times \alpha(L) \times XX(I) \\
DBA(L,J) &= DBA(L,J) + T(I) \times \alpha(L) \times XX(I) \\
AZ(L,J) &= AZ(L,J) + \text{IND}(I) \times (1/\alpha(L) + \text{ALOG}(T(I))) \\
AZZ(L,J) &= AZZ(L,J) + \text{IND}(I)/\alpha(L)^2 \\
\text{IF} (T(I) \text{ EQ} 0) \text{ GO TO 3016} \\
SDBA(L,J) &= SDBA(L,J) + \text{ALOG}(TS(I)) \times TS(I) \times \alpha(L) \times XX(I) \\
SDBAA(L,J) &= SDBAA(L,J) + \text{ALOG}(TS(I)) \times TS(I) \times \alpha(L) \times XX(I) \\
& \times \text{Z(ID(KKK)), I} \\
\text{IF} (TS(I) \text{ EQ} 0) \text{ GO TO 4016} \\
SDBAB(KKK,L,J) &= SDBAB(KKK,L,J) + \text{ALOG}(T(I)) \times T(I) \times \alpha(L) \times XX(I) \\
& \times \text{Z(ID(KKK), I)} \\
& \times \text{Z(ID(JJJ), I)} \\
& \times \text{Z(ID(KKK), I)} \\
& \times \text{Z(ID(JJJ), I)} \\
& \times \text{Z(ID(KKK), I)} \\
& \times \text{Z(ID(JJJ), I)} \\
& \times \text{Z(ID(KKK), I)} \\
& \times \text{Z(ID(JJJ), I)} \\
& \times \text{Z(ID(KKK), I)} \\
& \times \text{Z(ID(JJJ), I)} \\
226 \text{ CONTINUE} \\
\text{LIKE} &= 0.0 \\
\text{CALL LIKELI2(NG,B,CLIKE,BS,LIKE)} \\
\text{IF} (M \text{ EQ} 1) \text{ GO TO 2557} \\
\text{IF} (\text{LIKE} \text{ GE} \text{ LOGLIK(M-1)}) \text{ GO TO 2558} \\
397 \text{ DO 800 } I=1,\text{NC} \\
800 \text{ THETA}(I) = \text{THETA}(I) - \text{COR}(I) \\
\text{NERRS} = \text{NERRS} + 1 \\
\text{LAMDA} = \text{LAMDA} \times 3.0 \\
\text{IF} (\text{NERRS} \text{ LE} 20) \text{ GO TO 2559} \\
\text{WRITE}(6,55555) M \\
55555 \text{ FORMAT}(1X,'ERRORS IN MARQUARDT ',14, 'ITERATIONS') \\
JJ = 4 \\
\text{RETURN} \\
2558 \text{ LOGLIK(M) = LIKE} \\
\text{LAMDA} = \text{LAMDA}/3.0 \\
\text{GO TO 2775} \\
2557 \text{ LOGLIK(1) = LIKE} \\
2775 \text{ NERRS} = 0 \\
\text{DO 2227 } I=1,\text{NU} \\
\text{U(I)} = 0.0 \\
\text{DO 2227 } J=1,\text{NU} \\
\text{JACOB}(I,J) = 0.0 \\
2227 \text{ CONTINUE} \\
\text{ CALL SFICNI(NU,N,NG,MC,DBA,AZ,DBB,BZ,SDBA,SDBB,U) } \\
\text{ CALL SJACN(NU,N,NG,MC,DBA,DBB,DA,DAAB,DAAB,DAAB,DAAB,DAAB,DAAB,DAAB,DAAB,JACOB) } \\
\text{IF} (\text{MAXCOR} \text{ LE} \text{ TTOL}) \text{ GO TO 1300}
SUM = 0.
MAXU=-1.0
DO 100 J=1,NC
SUM = SUM + U(J)**2
IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))
100 CONTINUE
UNORM = SQRT(SUM)
IF (MAXU .LE. UTOL) GO TO 1100
2559 CALL MULT(NU,JACOB,JACOB, SHS)
DO 400 I = 1,NC
SHS(I,I) = SHS(I,I) + LAMDA
400 CONTINUE
DO 993 I=1,NU
DO 993 J=1,NU
SHSINV(I,J)=0.0
993 CONTINUE
CALL LINRG(NC,SHS,NU,SHSINV,NU)
DO 500 I =1,NC
COR(I) = 0.0
500 CONTINUE
DO 600 I=1,NC
DO 600 J=1,NC
COR(I) = COR(I) - FINV(I,J)*U(J)
600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,NC
IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
THETA(I)=THETA(I)+COR(I)
700 CONTINUE
DO 133 I=1,NS
ALPHA(I)=THETA(I)
IF (ALPHA(I) .LE. 0.0) GO TO 397
133 CONTINUE
DO 233 I=1,MC
BETA(I)=THETA(I+NS)
233 CONTINUE
IF (NERRS .GE. 1) GO TO 399
20 CONTINUE
WRITE (6,66666)
66666 FORMAT(1X,'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
WRITE (6,33335) UNORM
33335 FORMAT(/,6X,'THE NORM OF SCORE VECTOR = ',E15.8)
JJ = 3
RETURN
1100 WRITE (6,77777) M
77777 FORMAT(1X,'THE TOLERANCE FOR SCORE VECTOR IS MET IN', &
I4,' ITERATIONS')
JJ=1
GO TO 1000

1300 SUM = 0.
DO 901 J=1,NC
  SUM = SUM + U(J)**2
901 CONTINUE

UNORM = SQRT(SUM)
WRITE (6,99999) M

99999 FORMAT(1X,'THE TOLERANCE FOR BETA IS MET IN',&
  I4,' ITERATIONS')
JJ=2

1000 WRITE(6,11115) UNORM

11115 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
WRITE (6,22225) LIKE

22225 FORMAT(/,6X,'LOGLIKELIHOOD UNDER INDP. = ',E15.8)
DO 366 I=1,NC
  DO 366 J=1,NC
    JACOB(I,J)=-JACOB(I,J)
366 CONTINUE
CALL LINRG (NC,JACOB,NU,JACOBI,NU)
WRITE(6,778)

778 FORMAT(IX,//)
DO 1073 I=1,NC
  DO 1073 J=I,NC
    WRITE(6,*) 'COV(',I,',',J,')=',JACOBI(I,J)
1073 CONTINUE
WRITE (6,678)

678 FORMAT(IX,//)
DO 9876 J=1,NS
  SE=SQRT(JACOBI(J,J))
  PVAL=1.-ANORDF(ABS(THETA(J)/SE))
  WRITE(6,8761) J,THETA(J),SE,PVAL
9876 CONTINUE

8761 FORMAT( 'ALPHA(',I2,')=',F13.8,' SE=',F13.8,2X,
  'PVALUE=',F7.5)

9876 CONTINUE
DO 9976 J=NS+1,NC
  SE=SQRT(JACOBI(J,J))
  PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
  JL=J-NS
  WRITE(6,8861) JL,THETA(J),SE,PVAL
9976 CONTINUE

8861 FORMAT( 'BETA(',I2,')=',F13.8,
  ' SE=',F13.8,2X,'PVALUE=',F7.5)

9976 CONTINUE
WRITE(6,878)

878 FORMAT(IX,//)
RETURN
END

SUBROUTINE SFCNI(NU,N,NG,NS,MC,DBA,AZ,DBB,BZ,SDBA,&SDBB,U)
DIMENSION U(NU)
DIMENSION DBA(NS,NG), AZ(NS,NG), DBB(N,NG), BZ(N,NG)
DIMENSION SDBA(NS,NG), SDBB(N,NG)
DO 7 I=1,NS
  DO 7 J=1,NG
    ..
U(I) = U(I) - DBA(I,J) + AZ(I,J) + SDBA(I,J)
7 CONTINUE
DO 8 I = 1, MC
DO 8 J = 1, NG
U(NS+I) = U(NS+I) - DBB(I,J) + BZ(I,J) + SDBB(I,J)
8 CONTINUE
RETURN
END

SUBROUTINE SJACI(NU, N, NS, NG, MC, DBA, DBB, DBAA, DBAB, DBBB, A, B, AZZ, BS, SDBA, SDBB, SDBAA, SDBAB, SDBBB, JACOB)
DIMENSION JACOB(NU,NU)
DIMENSION DBA(NS,NG), DBB(N,NG)
DIMENSION SDBA(NS,NG), SDBB(N,NG)
DIMENSION DBAA(NS,NG), AZZ(NS,NG), DBAB(N,NS,NG)
DIMENSION DBBB(N,N,NG)
DIMENSION SDBAA(NS,NG), SDBAB(N,NS,NG), SDBBB(N,N,NG)
DIMENSION A(NG), B(NG)
DIMENSION BS(NG)
REAL JACOB
DO 18 I = 1, NS
DO 19 J = 1, NG
JACOB(I,I) = JACOB(I,I) - DBAA(I,J) - AZZ(I,J) + SDBAA(I,J)
19 CONTINUE
DO 31 J = I + 1, NS
JACOB(I,J) = 0.0
JACOB(J,I) = JACOB(I,J)
31 CONTINUE
DO 34 L = 1, MC
DO 36 LJ = 1, NG
JACOB(I,NS+L) = JACOB(I,NS+L) - DBAB(L,I,LJ) + SDBAB(L,I,LJ)
36 CONTINUE
JACOB(NS+L,I) = JACOB(I,NS+L)
34 CONTINUE
18 CONTINUE
DO 44 I = 1, MC
DO 44 J = I, MC
DO 47 K = 1, NG
JACOB(NS+I,NS+J) = JACOB(NS+I,NS+J) - DBBB(I,J,K) + SDBBB(I,J,K)
47 CONTINUE
JACOB(NS+J,NS+I) = JACOB(NS+I,NS+J)
44 CONTINUE
RETURN
END

SUBROUTINE LIKELII(NG,B, CLIKE, BS, LIKE)
DIMENSION B(NG), CLIKE(NG)
DIMENSION BS(NG)
REAL LIKE
DO 4 I = 1, NG
LIKE = LIKE - B(I) + CLIKE(I) + BS(I)
4 CONTINUE
RETURN
END
SUBROUTINE SMAQ (IA, NU, N, NOBS, NS, NG, T, IND, Z, NEL, MEL, TS, IJ & A, B, MC, MD, ITMAX, UTOL, TTOL, BETA, ALPHA & DELTA, JACOB, THETA, LIKE, JJ, & SFCN, SJAC, LIKELI, MULT, LINRG)

C ****************************************************************
C INPUT:
C NNU: NO. OF UNKNOWN PARAMETERS
C NN: NO. OF COVARIATES , INCLUDING THE INTERCEPTS
C NNOBS: NO OF OBSERVATIONS
C NNS: NO OF STRATA
C NNG: NO OF GROUPS
C ****************************************************************
C
PARAMETER (NNU=23, NN=20, NNS=2, NNG=1571, NNOBS=3142)
PARAMETER (IITMAX=100)
DIMENSION THETA(NU), U(NNU), JACOB(NU,NU)
& JACOBI(NNU,NU)
DIMENSION ALPHA(NS)
DIMENSION BETA(N)
DIMENSION T(NOBS), IND(NOBS), Z(N,NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION TS(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NNOBS)
DIMENSION A(NG), B(NG)
DIMENSION BS(NNG)
DIMENSION ID(NN)
DIMENSION ALIKE(NNG), BLIKE(NNG), CLIKE(NNG), DLIKE(NNG)
DIMENSION ELIKE(NNG), FLIKE(NNG), GLIKE(NNG)
DIMENSION SBLIKE(NNG), SELIKE(NNG), SGLIKE(NNG)
DIMENSION DBA(NNS,NNN), AZ(NNS,NNN), DBB(NN,NNN),
& BZ(NN,NNN)
DIMENSION DBAA(NNS,NNN), A2Z(NNS,NNN),
& DBAB(NN,NNN,NNN)
DIMENSION DBBB(NN,NNN,NNN)
DIMENSION SDBA(NNS,NNN,NNN), SDBB(NN,NNN,NNN)
DIMENSION SDBB(NN,NNN,NNN)
DIMENSION SHS(NNU,NNU), SHSINV(NNU,NNU)
& FINV(NNU,NNU)
DIMENSION COR(NNU)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SFCN, SJAC, LIKELI, MULT, LINRG
REAL JACOB, JACOBI
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
J1=1
IF (IA .EQ. 0) GO TO 5555
THETA(1)=DELTA
5555 DO 23 I=1, NS
THETA(IA+I)=ALPHA(I)
23 CONTINUE
DO 1226 I=1,N
IF (IJ(I) .NE. 1) GO TO 1226
ID(J1)=I
THETA(J1+NS+IA)=BETA(I)
J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
IF(IJ(I) .NE. 0) GO TO 1227
ID(J1)=I
THETA(J1+NS+IA)=BETA(I)
J1=J1+1
1227 CONTINUE
MD=J1-1
DO 1031 I=1,MD
BETA(I)=THETA(I+IA+NS)
1031 CONTINUE
ND=MD+NS+IA
NC=MC+NS+IA
MAXCOR=5.0
LAMDA=2.0
DO 20 M=1,ITMAX
739 DO 2225 I=1,NOBS
XX(I)=0.0
DO 2226 J=1,MD
K=ID(J)
2225 XX(I)=XX(I)+BETA(J)*Z(K,I)
2226 XX(I)=EXP(XX(I))
DO 126 J=1,NG
CLIKE(J)=0.0
B(J)=0.0
BS(J)=0.0
DO 127 I=1,NS
DBA(I,J)=0.0
SDBA(I,J)=0.0
AZ(I,J)=0.0
DBAA(I,J)=0.0
SDBAA(I,J)=0.0
AZZ(I,J)=0.0
DO 127 K=1,N
DBAB(K,I,J)=0.0
SDBAB(K,I,J)=0.0
127 CONTINUE
DO 126 I=1,N
DBB(I,J)=0.0
SDBB(I,J)=0.0
BZ(I,J)=0.0
DO 126 K=1,N
DBBB(I,K,J)=0.0
SDBBB(I,K,J)=0.0
126 CONTINUE
DO 226 I=1,NOBS
J=MEL(I)
L = NEL(I)

CLIKE(J) = CLIKE(J) + IND(I) * (ALOG(ALPHA(L) * T(I)) ** (ALPHA(L) - 1))

B(J) = B(J) + T(I) ** ALPHA(L) * XX(I)

BS(J) = BS(J) + TS(I) ** ALPHA(L) * XX(I)

DBA(L, J) = DBA(L, J) + ALOG(T(I)) * T(I) ** ALPHA(L) * XX(I)

AZ(L, J) = AZ(L, J) + IND(I) * (1/ALPHA(L) + ALOG(T(I)))

DBAA(L, J) = DBAA(L, J) + ALOG(T(I)) ** 2 * T(I) ** ALPHA(L) * XX(I)

AZZ(L,J) = AZZ(L,J) + IND(I)/ALPHA(L)**2

IF (TS(I) .EQ. 0) GO TO 6016

SDBA(L, J) = SDBA(L, J) + ALOG(TS(I)) * TS(I) ** ALPHA(L) * XX(I)

SDBB(A, L, J) = SDBB(A, L, J) + ALOG(TS(I)) * TS(I) ** ALPHA(L) * XX(I)

6016 DO 226 KKK = 1, MC

DBB(KKK, J) = DBB(KKK, J) + T(I) ** ALPHA(L) * XX(I) * Z(ID(KKK), I)

SDBB(KKK, J) = SDBB(KKK, J) + TS(I) ** ALPHA(L) * XX(I) * Z(ID(KKK), I)

BS(KKK, J) = BS(KKK, J) + IND(I) * Z(ID(KKK), I)

DBAB(KKK, L, J) = DBAB(KKK, L, J) + ALOG(T(I)) * T(I) ** ALPHA(L) * XX(I)

& * Z(ID(KKK), I)

IF (TS(I) .EQ. 0) GO TO 7016

SDBAB(KKK, L, J) = SDBAB(KKK, L, J) + ALOG(TS(I)) * TS(I) ** ALPHA(L) * XX(I)

& * XX(I) * Z(ID(KKK), I)

7016 DO 226 JJJ = KKK, MC

DBBB(KKK, JJJ, J) = DBBB(KKK, JJJ, J) + T(I) ** ALPHA(L) * XX(I)

& * Z(ID(KKK), I) * Z(ID(JJJ), I)

SDBBB(KKK, JJJ, J) = SDBBB(KKK, JJJ, J) + TS(I) ** ALPHA(L) * XX(I)

& * Z(ID(KKK), I) * Z(ID(JJJ), I)

226 CONTINUE

DO 336 I = 1, NG

ALIKE(I) = 0.0

DLIKE(I) = 0.0

FLIKE(I) = 0.0

IF (A(I) .LE. 1) GO TO 339

SUM = 0.0

SUM1 = 0.0

SUM2 = 0.0

DO 337 J = 1, A(I)

SUM = SUM + 1/(A(I) + 1/DELTA - J)

SUM1 = SUM1 + ALOG(A(I) + 1/DELTA - J)

SUM2 = SUM2 + 1/(A(I) + 1/DELTA - J) ** 2

337 CONTINUE

ALIKE(I) = SUM1 - A(I) * ALOG(1/DELTA)

DLIKE(I) = -1/DELTA**2 * (SUM - A(I) * DELTA)

FLIKE(I) = 2/DELTA**3 * SUM - A(I) / DELTA**2 - 1/DELTA**4 * SUM2

339 CONTINUE

BLIKE(I) = -(A(I) + 1/DELTA) * ALOG(B(I) * DELTA + 1)

SBLIKE(I) = (1/DELTA) * ALOG(BS(I) + DELTA) + 1

ELIKE(I) = ALOG(1 + DELTA*B(I)) / DELTA**2 - (A(I) + 1/DELTA) * B(I) / (1 + DELTA*B(I))

& (1 + DELTA*B(I))

SELIKE(I) = -ALOG(1 + DELTA*BS(I)) / DELTA**2 + (1/DELTA) * BS(I) / (1 + DELTA*BS(I))

& (1 + DELTA*BS(I))

GLIKE(I) = -2 * ALOG(1 + DELTA*B(I)) / DELTA**3 + 3*2*B(I)/(DELTA**2 & * (1 + DELTA*B(I))) + A(I) + 1/DELTA) * B(I) / (1 + DELTA*B(I)) ** 2

SGLIKE(I) = 2 * ALOG(1 + DELTA*BS(I)) / DELTA**2 - 3*2*BS(I)/(DELTA**2 & * (1 + DELTA*BS(I))) -(1/DELTA) * (BS(I) / (1 + DELTA*BS(I))) ** 2
CONTINUE
LIKE=0.0
CALL LIKELI(NG, ALIKE, BLIKE, CLIKE, SBLIKE, LIKE)
IF (M .EQ. 1) GO TO 2557
IF (LIKE .GE. LOGLIK(M-1)) GO TO 2558
349 DO 800 I=1, NC
800 THETA(I) = THETA(I) - COR(I)
NERRS=NERRS+1
LAMDA=LAMDA*3.0
IF (NERRS .LE. 20) GO TO 2559
WRITE(6,55555) M
55555 FORMAT(1X, 'ERRORS IN MARQUARDT ', I4, ' ITERATIONS')
JJ = 4
RETURN
2558 LOGLIK(M) = LIKE
LAMDA=LAMDA/3.0
GO TO 2775
2557 LOGLIK(1)=LIKE
2775 NERRS = 0
DO 2227 I=1, NU
U(I)=0.0
DO 2227 J=1, NU
JACOB(I,J)=0.0
2227 CONTINUE
CALL SFCN(IA, NU, N, NG, NS, MC, DELTA, A, B, DLIKE, ELIKE, DBA, AZ
& DBB, BS, SELIKE, SDBA, SDBB, U)
CALL SJAC(IA, NU, N, NG, NS, MC, DBA, DBB, DBAA, DBAB, DDBB, AZZ,
& FLIKE, GLIKE, DELTA, A, B,
& BS, SGLIKE, SDBA, SDBB, SDBAA, SDBAB, SDBBB, JACOB)
IF (MAXCOR .LE. TTOL) GO TO 1300
SUM = 0.
MAXU=-1.0
DO 100 J=1, NC
SUM = SUM + U(J)**2
IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))
100 CONTINUE
UNORM = SQRT(SUM)
IF (MAXU .LE. UTOL) GO TO 1100
2559 CALL MULT(NU, JACOB, JACOB, SHS)
DO 400 I = 1, NC
SHS(I,I) = SHS(I,I) + LAMDA
400 CONTINUE
DO 993 I=1, NU
DO 993 J=1, NU
SHSINV(I,J)=0.0
993 CONTINUE
CALL LINRG(NC, SHS, NU, SHSINV, NU)
DO 994 I=1, NU
DO 994 J=1, NU
FINV(I,J)=0.0
994 CONTINUE
CALL MULT(NU, SHSINV, JACOB, FINV)
DO 500 I = 1, NC
COR(I) = 0.0
500 CONTINUE
DO 600 I=1,NC
   DO 600 J=1,NC
      COR(I) = COR(I) - FINV(I,J)*U(J)
600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,NC
   IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
   COR(I) = COR(I) + COR(I)
700 CONTINUE
IF (IA .EQ. 0) GO TO 6666
DELTA=THETA(1)
IF (DELTA .LE. 0.0) GO TO 349
DO 133 I=1,NS
   ALPHAI = THETA(IA+I)
   IF (ALPHAI .LE. 0.0) GO TO 349
133 CONTINUE
DO 233 I=1,MC
   BETA(I) = THETA(I+NS+IA)
233 CONTINUE
IF (NERRS .GE. 1) GO TO 739
20 CONTINUE
WRITE (6,66666)
66666 FORMAT(1X,'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
WRITE (6,33335) UNORM
33335 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
JJ=3
RETURN
1100 WRITE (6,77777) M
77777 FORMAT(1X,'THE TOLERANCE FOR SCORE VECTOR IS MET IN', &
   I4,' ITERATIONS')
JJ=1
GO TO 1000
1300 SUM = 0.
   DO 901 J=1,NC
      SUM = SUM + U(J)**2
901 CONTINUE
UNORM = SQRT(SUM)
WRITE (6,99999) M
99999 FORMAT(/,6X,'THE TOLERANCE FOR BETA IS MET IN', &
   I4,' ITERATIONS')
JJ=2
1000 IF (IA .EQ. 0) GO TO 1003
   WRITE (6,575)
575 FORMAT(1X,'THE FINAL SOLUTIONS ',/)
1003 WRITE(6,11115) UNORM
11115 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
WRITE (6,22225) LIKE
22225 FORMAT(/,6X,'LOGLIKELIHOOD = ',E15.8,/)
   IF (IA .EQ. 0) GO TO 7777
   DO 366 I=1,NC
      DO 366 J=1,NC
JACOB(I,J) = -JACOB(I,J)

366 CONTINUE
CALL LINRG( NC, JACOB, NU, JACOBI, NU)
WRITE(6, 788)

788 FORMAT(1X, //)
DO 1073 I=1, NC
DO 1073 J=I, NC
WRITE(6, *) ' COV(', I-1, ', ', J-1, ') = ', JACOBI(I,J)
1073 CONTINUE
WRITE(6, 888)

888 FORMAT(1X, //)
SE = SQRT(JACOBI(1,1))
TEST = THETA(1)/SE
PVAL = 1. - ANORDF(ABS(TEST))
WRITE(6, 7171) THETA(1), SE, PVAL

7171 FORMAT(' EST OF ASSOC. = ', F12.7, 2X, 'SE = ', F16.8, 2X, 'PVAL = ', F7.4)
DO 9876 J=2, NS+1
SE = SQRT(JACOBI(J,J))
PVAL = 1. - ANORDF(ABS(THETA(J)/SE))
JL = J-1
WRITE(6, 8761) JL, THETA(J), SE, PVAL
8761 FORMAT( ' ALPHA(', I2, ') = ', F13.8,
& ' SE = ', F13.8, 2X, 'PVALUE = ', F7.5)
9876 CONTINUE

DO 9976 J=NS+2, NC
SE = SQRT(JACOBI(J,J))
PVAL = 2.* (1. - ANORDF(ABS(THETA(J)/SE)))
JL = J-NS-1
WRITE(6, 8861) JL, THETA(J), SE, PVAL
8861 FORMAT(' BETA(', I2, ') = ', F13.8,
& ' SE = ', F13.8, 2X, 'PVALUE = ', F7.5)
9976 CONTINUE

7777 RETURN
END

SUBROUTINE SFCN(IA, NU, N, NG, NS, MC, DELTA, A, B, DLIKE, ELIKE, DBA
& , AZ, DBB, BZ, BS, SELIKE, SDBA, SDBB, U)
DIMENSION U(NU)
DIMENSION DLIKE(NG), ELIKE(NG)
DIMENSION SELIKE(NG)
DIMENSION A(NG), B(NG)
DIMENSION BS(NG)
DIMENSION DBA(NS,NG), AZ(NS,NG), DBB(N,NG), BZ(N,NG)
DIMENSION SDBA(NS,NG), SDBB(N,NG)
IF (IA .EQ. 0) GO TO 8888
DO 6 I=1, NC
U(I) = U(I) + DLIKE(I) + ELIKE(I) + SELIKE(I)
6 CONTINUE

8888 DO 7 I=1, NS
DO 7 J=1, NC
U(IA+I) = U(IA+I) - (DELTA*A(J)+1) / (1+DELTA*B(J)) * DBA(I,J)
&   + AZ(I,J) + 1 / (1+DELTA*BS(J)) * SDBA(I,J)
7 CONTINUE
DO 8 I=1,MC
DO 8 J=1,NG
U(IA+NS+I)=(U(IA+NS+I)-(DELTA*A(J)+1)/(1+DELTA*B(J))*DBB(I,J)
& +BZ(I,J) + 1/(1+DELTA*BS(J))*SDBB(I,J)
8 CONTINUE
RETURN
END

SUBROUTINE SJAC(IA,NU,N,NS,NG,MC,DBA,DBB,DBAA,DBAB,DBBB
& ,AZZ, FLIKE,GLIKE, DELTA,A,B,
& BS,SGLIKE,SDBA,SDBB,SDBAA,SDBAB,SDBBB,JACOB)
DIMENSION JACOB(NU,NU)
DIMENSION DBA(NS,NG),  DBB(N,NG)
DIMENSION DBAA(NS,NG),  AZZ(NS,NG), DBAB(N,NS,NG)
DIMENSION DBBB(N,N,NG)
DIMENSION SDAA(NS,NG),SDBB(N,NG)
DIMENSION SDDBB(N,N,NG)
DIMENSION A(NG),  B(NG)
DIMENSION BS(NG)
DIMENSION FLIKE(NG), GLIKE(NG)
DIMENSION SGLIKE(NG)
REAL JACOB
IF (IA .EQ. 0 )  GO TO 8898
DO 11 1=1,NG
JACOB(1,1)=JACOB(1,1)+FLIKE(I)+GLIKE(I)+SGLIKE(I)
11 CONTINUE
DO 12 1=1,NS
DO 16 J=1,NG
JACOB(1,1+1)=JACOB(1,1+1)+DBA(I,J)* (-A(J)/(1+DELTA*B(J))
& + (DELTA*A(J)+1)
& *(B(J)/(1+DELTA*B(J))**2)
& - SDBA(I,J)*BS(J)/(1+DELTA*BS(J))**2
16 CONTINUE
JACOB(1+1,1)=JACOB(1,1+1)
12 CONTINUE
DO 14 1=1,MC
DO 17 J=1,NG
JACOB(1,1+NS+I)=JACOB(1,1+NS+I)+DBB(I,J)*(-A(J)
& / (1+DELTA*B(J)) + (DELTA*A(J)+1)
& +1)*B(J)/(1+DELTA*B(J))**2)
& - SDBB(I,J)*BS(J)/(1+DELTA*BS(J))**2
17 CONTINUE
JACOB(1+NS+I,1)=JACOB(1,1+NS+I)
14 CONTINUE
8898 DO 18 I=1,NS
DO 19 J=1,NG
JACOB(IA+1,IA+1)=JACOB(IA+1,IA+1)+DELTA*(DELTA*A(J)+1)
& / (1+DELTA*B(J))**2*DBA(I,J)**2-(DELTA*A(J)+1)
& / (1+DELTA*B(J))**2*DBAA(I,J)-AZZ(I,J)
& -DELTA**2*SDBA(I,J)**2+1/(1+DELTA*BS(J))
& *SDBAA(I,J)
19 CONTINUE
DO 31 J=I+1,NS
DO 33 L = 1, NG
   JACOB (IA + I, IA + J) = JACOB (IA + I, IA + J) + DELTA * (DELTA * A (L) + 1) / (1 + DELTA * B (L)) ** 2 * DBA (I, L) * DBA (J, L) - DELTA / (1 + DELTA * BS (L)) ** 2 * SDBA (I, L) * SDBA (J, L)
33 CONTINUE
JACOB (IA + J, IA + I) = JACOB (IA + I, IA + J)
31 CONTINUE
DO 34 L = 1, MC
   DO 36 LJ = 1, NG
      JACOB (IA + I, IA + NS + L) = JACOB (IA + I, IA + NS + L) - (DELTA * A (LJ) + 1) / (1 + DELTA * B (LJ)) * DBAB (L, I, LJ) + DELTA * (DELTA * A (LJ) + 1) / (1 + DELTA * B (LJ)) ** 2 * DBA (I, LJ) * DBB (L, LJ) + 1 / (1 + DELTA * BS (LJ)) * SDBAB (L, I, LJ) - DELTA / (1 + DELTA * BS (LJ)) ** 2 * SDBA (I, LJ) * SDBB (L, LJ)
36 CONTINUE
JACOB (IA + NS + L, IA + I) = JACOB (IA + I, IA + NS + L)
34 CONTINUE
18 CONTINUE
   DO 44 I = 1, MC
      DO 44 J = I, MC
         DO 47 K = 1, NG
            JACOB (IA + NS + I, IA + NS + J) = JACOB (IA + NS + I, IA + NS + J) - (DELTA * A (K) + 1) / (1 + DELTA * B (K)) * DBBB (I, J, K) + DELTA * (DELTA * A (K) + 1) / (1 + DELTA * B (K)) ** 2 * DBB (I, K) * DBB (J, K) + 1 / (1 + DELTA * BS (K)) * SDBBB (I, J, K) - DELTA / (1 + DELTA * BS (K)) ** 2 * SDBB (I, K) * SDBB (J, K)
47 CONTINUE
JACOB (IA + NS + J, IA + NS + I) = JACOB (IA + NS + I, IA + NS + J)
44 CONTINUE
RETURN
END
SUBROUTINE LIKELI (NG, ALIKE, BLIKE, CLIKE, SBLIKE, LIKE)
DIMENSION ALIKE (NG), BLIKE (NG), CLIKE (NG)
DIMENSION SBLIKE (NG)
REAL LIKE
   DO 4 I = 1, NG
      LIKE = LIKE + ALIKE (I) + BLIKE (I) + CLIKE (I) + SBLIKE (I)
4 CONTINUE
RETURN
END
SUBROUTINE MULT (NU, AO, BO, CO)
DIMENSION AO (NU, NU), BO (NU, NU), CO (NU, NU)
   DO 1 I = 1, NU
      DO 1 J = 1, NU
         CO (I, J) = 0.0
1 CONTINUE
RETURN
END
APPENDIX D

FORTRAN PROGRAM FOR THE MAXIMUM LIKELIHOOD ESTIMATION OF THE DEPENDENCE PARAMETER AND REGRESSION COEFFICIENTS IN A WEIBULL REGRESSION MODEL WITH POSITIVE STABLE FRAILTY

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INPUT:
NU: NO OF UNKNOWN PARAMETERS (=N+NS+1)
N: NO OF COVARIATES PLUS THE INTERCEPTS
NOBS: NO OF OBSERVATIONS
NS: NO OF STRATA
NG : NO OF GROUPS
C******************************************************************************
C******************************************************************************
PARAMETER(NU=23,N=20,NOBS=3142,NS=2,NG=1571)
DIMENSION THETA(NU),  JACOB(NU,NU)
DIMENSION BETA(N)
DIMENSION ALPHA(NS)
DIMENSION T(NOBS),  IND(NOBS),  Z(N,NOBS),  NEL(NOBS),
&    MEL(NOBS)
DIMENSION TS(NOBS)
DIMENSION IJ(N)
DIMENSION A(NG),  B(NG)
DIMENSION DEL(7),  TA(NS),  TB(N)
REAL JACOB
EXTERNAL SFCNI,SJACI,LIKELII,MULT,LINRG
EXTERNAL SFCN,SJAC,LIKELI

INPUT:
IJ(I) = 1, COVARIATE I IS INCLUDED
IJ(I) = 0, COVARIATE I IS USED IN COMPUTATION,
      BUT NOT IN MAXIMIZATION
IJ(I) = -1, COVARIATE I IS OUT
DO 8016 I=1,N
IJ(I)=1
CONTINUE
    DO 8014 I=1,N
    IF (IJ(I) .EQ. 1) THEN
        BETA(I)=0.0
    ENDIF
8014 CONTINUE
    DO 2013 I=1,NS
        ALPHA(I)=1.0
2013 CONTINUE
    DEL(1)=0.98
    DEL(2)=0.96
    DEL(3)=0.94
    DEL(4)=0.92
    DEL(5)=0.90
    DEL(6)=0.88
    DEL(7)=0.86
    UTOL = 0.01
    TTOL = 0.001
    ITMAX = 100

C

***
C INPUT:
C T: OBSERVED TIME ON STUDY
C TS: TRUNCATION TIME, POSSIBLY ZERO
C IND: CENSORING INDICATOR
C MEL: GROUP NO
C NEL: STRATUM NO
C Z: COVARIATES
C
70000 CONTINUE
    DO 70000 I=1,NOBS
        READ (1,*) T(I), TS(I),IND(I), MEL(I), NEL(I),
            & (Z(K,I),K=NS+1,N)
    70000 CONTINUE
    DO 8321 J=1,NS
        IF (NEL(I) .EQ. J) THEN
            Z(J,I)=1.0
        ELSE
            Z(J,I)=0.0
        ENDIF
8321 CONTINUE
    DO 90000 I=1,NG
        A(I)=0
    90000 CONTINUE
    DO 95555 I=1,NOBS
        IF (IND(I) .EQ. 0) GO TO 95555
        J=MEL(I)
        A(J)=A(J)+1
    95555 CONTINUE
    DO 10000 I=1,NU
        THETA(I)=0.0
10000 CONTINUE
10000 CONTINUE  
C  
C ***************************************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO FIND
C THE MLE'S OF THE REGRESSION COEFFICIENTS UNDER INDEPENDENCE
C ***************************************************************
C
CALL SMAQI (NU, N, NOBS, NS, NG, T, IND, Z, NEL, MEL, TS, IJ, A, B, 
& MC, MD, ITMAX, UTOL, TTOL, BETA, ALPHA, JACOB, THETA, XL, JJ, 
& SFCNI, SJACI, LIKELI, MULT, LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
TD=1.0
DO 7013 I=1,NS
TA(I)=ALPHA(I)
7013 CONTINUE
DO 8013 I=1,MD
TB(I)=BETA(I)
8013 CONTINUE
C  
C ***************************************************************
C STARTING A PROFILE LIKELIHOOD SEARCH
C FOR THE DEPENDENCE PARAMETER
C ***************************************************************
C
DO 4013 I=1,7
DELTA=DEL(I)
IA=0
DO 10010 J=1,NU
THETA(J)=0.0
10010 CONTINUE
C  
C ***************************************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO
C FIND THE MLE'S OF THE REGRESSION COEFFICIENTS AND DEPENDENCE
C PARAMETER (WHEN IT IS NOT FIXED) UNDER ADJUSTMENT FOR FRAILTY
C ***************************************************************
C
CALL SMAQ (IA, NU, N, NOBS, NS, NG, T, TS, IND, Z, NEL, MEL, IJ, A, B, 
& MC, MD, ITMAX, UTOL, TTOL, BETA, ALPHA, DELTA, JACOB, THETA, 
& YL, JJ, SFCN, SJAC, LIKELI, MULT, LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
IF (YL .GT. XL) THEN
XL=YL
TD=DELTA
DO 3014 L=1,NS
TA(L)=ALPHA(L)
3014 CONTINUE
DO 4014 LJ=1,MD
TB(LJ)=BETA(LJ)
4014 CONTINUE
ENDIF
CONTINUE
IF (TD .EQ. 1.0) THEN
WRITE(6,*) ' PROBABLY NO ASSOCIATION ' STOP ELSE GO TO 8621 ENDIF
8621 IA=1
DELTA=TD DO 5014 I=1,NS ALPHA(I)=TA(I)
5014 CONTINUE DO 6014 I=1,MD BETA(I)=TB(I)
6014 CONTINUE CALL SMAQ(IA,NU,N,NOBS,NS,NG,T,TS,IND,Z,NEL,MEL,IJ,A,B,
& MC,MD,ITMAX,UTOL,TTOL,BETA,ALPHA,DELTA,JACOB,THETA,
& YL,JJ,SFCN,SJAC,LIKELI,MULT,LINRG) IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP STOP END
SUBROUTINE SMAQI (NU, N, NOBS, NS, NG, T, IND, Z, NEL, MEL, TS, IJ, A, B,
& MC, MD, ITMAX, UTOL, TTOL, BETA, ALPHA, JACOB,
& THETA, LIKE, JJ,
& SFCNI, SJACI, LIKELII, MULT, LINRG)

**INPUT:**
NNU: NO. OF UNKNOWN PARAMETERS
NN: NO OF COVARIATES, INCLUDING THE INTERCEPTS
NNOBS: NO OF OBSERVATIONS
NNS: NO OF STRATA
NNG: NO OF GROUPS

PARAMETER (NNU=23, NN=20, NNS=2, NNG=1571, NNOBS=3142)
PARAMETER (IITMAX=100)
DIMENSION THETA(NU), U(NNU), JACOB(NU,NU), JACOBI(NNU,NU)
DIMENSION ALPHA(NS)
DIMENSION BETA(N)
DIMENSION T(NOBS), IND(NOBS), Z(N,NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION TS(NOBS)
DIMENSION XX(NNOBS)
DIMENSION A(NG), B(NG)
DIMENSION BS(NNG)
DIMENSION ID(NN), IJ(N)
DIMENSION CLIKE(NNG)
DIMENSION DBA(NNS,NNG), AZ(NNS,NNG), DBB(NN,NNG), BZ(NN,NNG)
DIMENSION DBAA(NNS,NNG), AZZ(NNS,NNG), DBAB(NN,NNS,NNG)
DIMENSION DBBB(NN,NN,NNG)
DIMENSION SDBA(NNS,NNG), SDBB(NN,NNG), SDBAA(NNS,NNG)
DIMENSION SDBAB(NN,NNS,NNG), SDBBB(NN,NN,NNG)
DIMENSION SHS(NNU,NNU), SHSINV(NNU,NNU)
& , FINV(NNU,NNU)
DIMENSION COR(NNU)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SFCNI, SJACI, LIKELII, MULT, LINRG
REAL JACOB, JACOBI
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
DO 23 I=1, NS
THETA(I)=ALPHA(I)
23 CONTINUE
J1=1
DO 1226 I=1,N
IF (IJ(I) .NE. 1) GO TO 1226
ID(J1)=I
THETA(J1+NS)=BETA(I)
J1=J1+1

1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
  IF(IJ(I) .NE. 0) GO TO 1227
  ID(I)=I
  THETA(I+NS)=BETA(I)
J1=J1+1

1227 CONTINUE
MD=J1-1
DO 3013 I=1,MD
  BETA(I)=THETA(I+NS)
3013 CONTINUE

ND=MD+NS
NC=MC+NS
MAXCOR=5.0
LAMDA = 2.0
DO 20 M=1,ITMAX

399 DO 2225 I=1,NOBS
  XX(I)=0.0
X X (I)=EXP(XX(I))
DO 126 J=1,MD
  K=ID(J)
XX(I)=XX(I)+BETA(J)*2*(K, I)
2225 XX(I)=EXP(XX(I))

DO 127 1=1,NS
  DBA(I,J)=0.0
  SDBA(I,J)=0.0
  AZ(I,J)=0.0
  DBAA(I,J)=0.0
  SDBAA(I,J)=0.0
  AZZ(I,J)=0.0
  DBAB(K,I,J)=0.0
  SDBAB(K,I,J)=0.0
  DBB(I,J)=0.0
  SDBB(I,J)=0.0
  BZ(I,J)=0.0
  DBBB(I,K,J)=0.0
  SDBBB(I,K,J)=0.0
127 CONTINUE

DO 126 I=1,NOBS
  J=MEL(I)
  L=NEL(I)
  CLIKE(J)=CLIKE(J)+IND(I)*((ALOG(ALPHA(L)*T(I))**((ALPHA(L)-1))
& +ALOG(XX(I)))
  B(J)=B(J)+T(I)**(ALPHA(L)*XX(I))
BS(J) = BS(J) + TS(I) ** ALPHA(L) * XX(I)
DBA(L,J) = DBA(L,J) + ALOG(T(I)) * T(I) ** ALPHA(L) * XX(I)
AZ(L,J) = AZ(L,J) + IND(I) / ALPHA(L) ** 2
IF(TS(I) .EQ. 0) GO TO 3016
SDBA(L,J) = SDBA(L,J) + ALOG(TS(I)) * TS(I) ** ALPHA(L) * XX(I)
SDBAA(L,J) = SDBAA(L,J) + ALOG(TS(I)) ** 2 * TS(I) ** ALPHA(L) * XX(I)
3016 DO 226 KKK = 1, MC
    DBB(KKK,J) = DBB(KKK,J) + T(I) ** ALPHA(L) * XX(I) * Z(ID(KKK),I)
    SDBB(KKK,J) = SDBB(KKK,J) + TS(I) ** ALPHA(L) * XX(I) * Z(ID(KKK),I)
    BZ(KKK,J) = BZ(KKK,J) + IND(I) * Z(ID(KKK),I)
    DBAB(KKK,L,J) = DBAB(KKK,L,J) + ALOG(T(I)) * T(I) ** ALPHA(L) * XX(I)
    IF (TS(I) .EQ. 0) GO TO 4016
    SDBAB(KKK,L,J) = SDBAB(KKK,L,J) + ALOG(TS(I)) * TS(I) ** ALPHA(L) * XX(I)
4016 DO 226 JJJ = KKK, MC
    DBBB(KKK,JJJ,J) = DBBB(KKK,JJJ,J) + T(I) ** ALPHA(L) * XX(I) * Z(ID(KKK),I) * Z(ID(JJJ),I)
    SDBBB(KKK,JJJ,J) = SDBBB(KKK,JJJ,J) + TS(I) ** ALPHA(L) * XX(I) * Z(ID(KKK),I) * Z(ID(JJJ),I)
226 CONTINUE
LIKE = 0.0
CALL LIKELII(NG,B,CLIKE,BS,LIKE)
IF (M .EQ. 1) GO TO 2557
IF (LIKE .GE. LOGLIK(M-1)) GO TO 2558
349 DO 800 I = 1, NC
    THETA(I) = THETA(I) - COR(I)
    NERRS = NERRS + 1
    LAMDA = LAMDA * 3.0
    IF (NERRS .LE. 20) GO TO 2559
    WRITE(6,55555) M
    55555 FORMAT(IX,'ERRORS IN MARQUARDT ',14, 'ITERATIONS')
    JJ = 4
    RETURN
2558 LOGLIK(M) = LIKE
    LAMDA = LAMDA / 3.0
    GO TO 2775
2557 LOGLIK(1) = LIKE
2775 NERRS = 0
    DO 2227 I = 1, NU
        U(I) = 0.0
    DO 2227 J = 1, NU
        JACOB(I,J) = 0.0
2227 CONTINUE
CALL SFCNI(NU,N,NG,MC,DBA,AZ,DBB,BZ,SDBA,SDBB,U)
CALL SJACI(NU,N,NS,NG,MC,DBA,DBB,DBAA,DBAB,DBBB,AZZ,
      & A,B,BS,SDBA,SDBB,SDBAB,SDBBB,JACOB)
    IF (MAXCOR .LE. TTOL) GO TO 1300
    SUM = 0.
    MAXU = -1.0
    DO 100 J = 1, NC


`SUM = SUM + U(J)**2`

`IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))`

100 CONTINUE

`UNORM = SQRT(SUM)`

`IF (MAXU .LE. UTOL) GO TO 1000`

2559 CALL MULT(NU,JACOB,JACOB, SHS)

DO 400 I = 1,NC
  `SHS(I,I) = SHS(I,I) + LAMDA`

400 CONTINUE

DO 934 I=1,NU
  DO 934 J=1,NU
    `SHSINV(I,J)=0.0`

934 CONTINUE

CALL LINRNG(NC,SHS,NU,SHSINV,NU)

DO 944 I=1,NU
  DO 944 J=1,NU
    `FINV(I,J)=0.0`

944 CONTINUE

CALL MULT(NU,SHSINV,JACOB,FINV)

DO 500 I =1,NC
  `COR(I) = 0.0`

500 CONTINUE

DO 600 I=1,NC
  DO 600 J=1,NC
    `COR(I) = COR(I) - FINV(I,J)*U(J)`

600 CONTINUE

`MAXCOR = -1.0`

`DO 700 I = 1,NC`

`IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))`

`THETA(I) = THETA(I) + COR(I)`

700 CONTINUE

DO 133 I=1,NS
  `ALPHA(I) = THETA(I)`

`IF (ALPHA(I) .LE. 0.0) GO TO 349`

133 CONTINUE

DO 233 I=1,MC
  `BETA(I) = THETA(I+NS)`

233 CONTINUE

`IF (NERRS .GE. 1) GO TO 399`

20 CONTINUE

WRITE (6,66666)

66666 FORMAT(IX,'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')

WRITE (6,33335) UNORM

33335 FORMAT(/,6X,'THE NORM OF SCORE VECTOR = ',E15.8)

`JJ = 3`

RETURN

1100 WRITE (6,77777) M

77777 FORMAT(IX,'THE TOLERANCE FOR SCORE VECTOR IS MET IN', & & 14,' ITERATIONS')

`JJ=1`

GO TO 1000

1300 SUM = 0.

DO 901 J=1,NC
SUM = SUM + U(J)**2
901 CONTINUE
UNORM = SQRT(SUM)
WRITE (6,99999) M
99999 FORMAT(1X,'THE TOLERANCE FOR BETA IS MET IN',
& ' ITERATIONS')
JJ=2
1000 WRITE(6,11115) UNORM
11115 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
WRITE (6,22225) LIKE
22225 FORMAT(/,6X,' LOGLIKELIHOOD UNDER INDP.= ',E15.8)
DO 366 1=1,NC
DO 366 J=l,NC
JACOB(I,J)=-JACOB(I,J)
366 CONTINUE
CALL LINRG (NC,JACOB,NU,JACOBI,NU)
WRITE(6,778)
778 FORMAT(IX,//)
DO 1073 1=1,NC
DO 1073 J=I,NC
WRITE(6,*) 'COV(',I, ' ,  ',J , ' )  = ',JACOBI(I, J)
1073 CONTINUE
WRITE(6,678)
678 FORMAT(IX,//)
DO 9876 J=1,NS
SE=SQRT(JACOBI(J,J))
PVAL=(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE(6,8761) J,THETA(J),SE,PVAL
8761 FORMAT('  ALPHA(',12,')=',F 1 3 .8,
& '  SE=',F13.8,2X,'PVALUE=',F 7 .5)
9876 CONTINUE
DO 9976 J=NS+1,NC
SE=SQRT(JACOBI(J,J))
PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
JL=J-NS
WRITE(6,8861) JL,THETA(J),SE,PVAL
8861 FORMAT('  B E T A (',12,')=',F 1 3 .8,
& '  SE=',F13.8,2X,'PVALUE=',F 7 .5)
9976 CONTINUE
WRITE(6,878)
878 FORMAT(1X,/) RETURN
END
SUBROUTINE SFCNI(NU,N,NG,NS,MC,DBA,AZ,DBB,BZ,SDBA,SDBB,U)
DIMENSION U(NU)
DIMENSION DBA(NS,NG),  AZ(NS,NG), DBB(N,NG),  BZ(N,NG)
DIMENSION SDBA(NS,NG),  SDBB(N,NG)
DO 7 I=1,NS
DO 7 J=1,NG
U(I)=U(I)-DBA(I,J)+AZ(I,J)+SDBA(I, J)
7 CONTINUE
DO 8 I=1,MC
DO 8 J=1,NG
SUBROUTINE SJACI(NU,N,NS,NG,MC,DBA,DBB,DBAA,DBAB,DBBB,AZZ,
& A,B,BS,SDBA,SDBB,SDBAA,SDBAB,SDBBB,JACOB)

DIMENSION JACOB(NU,NU)
DIMENSION DBA(NS,NG), DBB(N,NG)
DIMENSION SDBA(NS,NG), SDBB(N,NG)
DIMENSION DBAA(NS,NG), AZZ(NS,NG), DBAB(N,NS,NG)
DIMENSION DBBB(N,N,NG)
DIMENSION SDBAA(NS,NG), SDBAB(N,NS,NG), SDBBB(N,N,NG)
DIMENSION A(NG), B(NG)
DIMENSION BS(NG)
REAL JACOB

DO 18 I=1,NS
DO 19 J=1,NG
JACOB(I,I)=JACOB(I,I)-DBAA(I,J)-AZZ(I,J)+SDBAA(I,J)
19 CONTINUE
DO 31 J=I+1,NS
JACOB(I,J)=0.0
JACOB(J,I)=JACOB(I,J)
31 CONTINUE
DO 34 L=1,MC
DO 36 LJ=1,NG
JACOB(I,NS+L)=JACOB(I,NS+L)-DBAB(L,I,LJ)+SDBAB(L,I,LJ)
36 CONTINUE
JACOB(NS+L,I)=JACOB(I,NS+L)
34 CONTINUE
18 CONTINUE
DO 44 I=1,MC
DO 44 J=I,MC
DO 47 K=1,NG
JACOB(NS+I,NS+J)=JACOB(NS+I,NS+J)-DBBB(I,J,K)+SDBBB(I,J,K)
47 CONTINUE
JACOB(NS+J,NS+I)=JACOB(NS+I,NS+J)
44 CONTINUE
RETURN
END

SUBROUTINE LIKELII (NG,B,CLIKE,BS,LIKE)
DIMENSION B(NG), CLIKE(NG)
DIMENSION BS(NG)
REAL LIKE
DO 4 I=1,NG
LIKE=LIKE-B(I)+CLIKE(I)+BS(I)
4 CONTINUE
RETURN
END

SUBROUTINE SMAQ(IA,NU,N,NOBS,NS,NG,T,TS,IND,Z,NEL,MEL,IJ,A,
& B,MC,MD, ITMAX,UTOL,TTOL,BETA,ALPHA,DELTA,JACOB,
& THETA,LIKE,JJ,
& SFCN,SJAC,LIKELI,MULT,LINRG)
PARAMETER (NU=23, NN=20, NNS=2, NNG=1571, NNOBS=3142)
PARAMETER (IITMAX=100)
DIMENSION THETA(NU), U(NNU), JACOB(NU, NU), JACOBI(NNU, NNU)
DIMENSION ALPHA(NS)
DIMENSION BETA(N)
DIMENSION T(NOBS), IND(NOBS), Z(N, NOBS), NEL(NOBS),
& MEL(NOBS)
DIMENSION TS(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NNOBS)
DIMENSION A(NG), B(NG)
DIMENSION BS(NNG)
DIMENSION ID(NN)
DIMENSION CLIKE(NNG), R(NNG)
DIMENSION DBA(NNS, NNG), AZ(NNS, NNG), DBB(NN, NNG), BZ(NN, NNG)
DIMENSION SDBA(NNS, NNG), SDBB(NN, NNG)
DIMENSION DBAA(NNS, NNG), AZZ(NNS, NNG), DBAB(NN, NNS, NNG)
DIMENSION SDBAA(NNS, NNG), SDBAB(NN, NNS, NNG)
DIMENSION DBBB(NN, NN, NNG)
DIMENSION SDBBB(NN, NN, NNG)
DIMENSION SHS(NNU, NNU), SHSINV(NNU, NNU),
& FINV(NNU, NNU)
DIMENSION COR(NNU)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SJAC, SFCN, LIKELI, MULT, LINRG
REAL JACOB, JACOBI
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
J1=1
IF (IA .EQ. 0) GO TO 5555
THETA(1)=DELTA
5555 DO 23 I=1, NS
THETA(IA+I)=ALPHA(I)
23 CONTINUE
DO 1226 I=1, N
IF (IJ(I) .NE. 1) GO TO 1226
ID(J1)=I
THETA(J1+NS+IA)=BETA(I)
J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1, N
IF (IJ(I) .NE. 0) GO TO 1227
ID(J1) = I
THETA(J1+NS+IA) = BETA(I)
J1 = J1 + 1

1227 CONTINUE
MD = J1 - 1
DO 8073 I = 1, MD
BETA(I) = THETA(I+IA+NS)
8073 CONTINUE
ND = MD + NS + IA
NC = MC + NS + IA
MAXCOR = 5.0
LAMDA = 2.0
DO 20 M = 1, ITMAX
399 DO 2225 I = 1, NOBS
XX(I) = 0.0
DO 2226 J = 1, MD
K = ID(J)
2226 XX(I) = XX(I) + BETA(J) * Z(K, I)
2225 XX(I) = EXP(XX(I))

DO 126 J = 1, NG
CLIKE(J) = 0.0
B(J) = 0.0
BS(J) = 0.0
R(J) = 1.0
DO 127 I = 1, NS
DBA(I, J) = 0.0
SDBA(I, J) = 0.0
AZ(I, J) = 0.0
DBAA(I, J) = 0.0
SDBAA(I, J) = 0.0
AZZ(I, J) = 0.0
DO 127 K = 1, N
DBAB(K, I, J) = 0.0
SDBAB(K, I, J) = 0.0
127 CONTINUE
DO 126 I = 1, N
DBB(I, J) = 0.0
SDBB(I, J) = 0.0
BZ(I, J) = 0.0
DO 126 K = 1, N
DBBB(I, K, J) = 0.0
SDBBB(I, K, J) = 0.0
126 CONTINUE

DO 226 I = 1, NOBS
J = MEL(I)
I = NEL(I)
CLIKE(J) = CLIKE(J) + IND(I) * (ALOG(ALPHA(L) * T(I) ** (ALPHA(L) - 1))
& + ALOG(XX(I)))
B(J) = B(J) + T(I) ** ALPHA(L) ** XX(I)
BS(J) = BS(J) + TS(I) ** ALPHA(L) ** XX(I)
DBA(L, J) = DBA(L, J) + T(I) ** ALPHA(L) ** XX(I)
AZ(L, J) = AZ(L, J) + IND(I) * (1/ALPHA(L) + ALOG(T(I)))
DBAA(L, J) = DBAA(L, J) + ALOG(T(I)) ** 2 * T(I) ** ALPHA(L) * XX(I)
AZZ(L,J) = AZZ(L,J) + IND(I) / ALPHA(L)**2
IF (TS(I) .EQ. 0) GO TO 2366
SDBA(L,J) = SDBA(L,J) + ALOG(TS(I))*TS(I)**ALPHA(L)*XX(I)
SDBAA(L,J) = SDBAA(L,J) + ALOG(TS(I))**2*TS(I)**ALPHA(L)*XX(I)
2366 DO 226 KKK = 1, MC
DBB(KKK,J) = DBB(KKK,J) + T(I)**ALPHA(L)*XX(I)*Z(ID(KKK),1)
SDBB(KKK,J) = SDBB(KKK,J) + TS(I)**ALPHA(L)*XX(I)*Z(ID(KKK),1)
BZ(KKK,J) = BZ(KKK,J) + IND(I)*Z(ID(KKK),1)
DBAB(KKK,L,J) = DBAB(KKK,L,J) + ALOG(T(I))*T(I)**ALPHA(L)*XX(I)
& *Z(ID(KKK),1)
IF (TS(I) .EQ. 0) GO TO 2377
SDBAB(KKK,L,J) = SDBAB(KKK,L,J) + ALOG(TS(I))*TS(I)**ALPHA(L)*XX(I)
& *Z(ID(KKK),1)
2377 DO 226 JJJ = KKK, MC
DBBB(KKK,JJJ,J) = DBBB(KKK,JJJ,J) + T(I)**ALPHA(L)*XX(I)*Z(ID(KKK),1)*Z(ID(JJJ),1)
SDBBB(KKK,JJJ,J) = SDBBB(KKK,JJJ,J) + TS(I)**ALPHA(L)*XX(I)*Z(ID(KKK),1)*Z(ID(JJJ),1)
226 CONTINUE
DO 338 I=1, NG
IF (A(I) .LE. 1) GO TO 338
IF (A(I) .EQ. 2) R(I) = 1 + (1-DELTA)/(DELTA*B(I)**DELTA)
IF (A(I) .EQ. 3) R(I) = 1 + 3*(1-DELTA)/(DELTA*B(I)**DELTA)
& + (2-DELTA)*(1-DELTA)/(DELTA*B(I)**DELTA)**2
IF (A(I) .EQ. 4) R(I) = 1 + 6*(1-DELTA)/(DELTA*B(I)**DELTA)
& + (1-DELTA)*(11-7*DELTA)/(DELTA*B(I)**DELTA)**2
& + (3-DELTA)*(2-DELTA)*(1-DELTA)/(DELTA*B(I)**DELTA)**3
338 CONTINUE
LIKE = 0.0
CALL LIKELI(NG, DELTA, CLIKE, R, A, B, BS, LIKE)
IF (M .EQ. 1) GO TO 2557
IF (LIKE .GE. LOGLIK(M-1)) GO TO 2558
349 DO 800 I=1, NC
800 THETA(I) = THETA(I) - COR(I)
NERRS = NERRS + 1
LAMDA = LAMDA * 3.0
IF (NERRS .LE. 20) GO TO 2559
WRITE (6,55555) M
55555 FORMAT (IX,'ERRORS IN MARQUARDT ',I4, 'ITERATIONS')
JJ = 4
RETURN
2558 LOGLIK(M) = LIKE
LAMDA = LAMDA / 3.0
GO TO 2775
2557 LOGLIK(1) = LIKE
2775 NERRS = 0
DO 2227 I=1, NU
U(I) = 0.0
DO 2227 J=1, NU
JACOB(I,J) = 0.0
2227 CONTINUE
CALL SFCN(IA, NU, N, NG, NS, MC, DELTA, A, B, R, DBA, AZ, DBB, BZ, 
& BS, SDBA, SDBB, U)
CALL SJAC(IA,NU,N,NS,NG,MC,R,DBA,DBB,DBAA,DBAB,DBBB,AZZ, & DELTA,A,B,BS,SDBA,SDBB,SDBAA,SDBAB,SDBBB,JACOB)
IF (MAXCOR .LE. TTOL) GO TO 1300
SUM = 0.
MAXU=-1.0
DO 100 J=1,NC
   SUM = SUM + U(J)**2
   IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))
100 CONTINUE
UNORM = SQRT(SUM)
IF (MAXU .LE. UTOL) GO TO 1100
2559 CALL MULT(NU,JACOB,JACOB, SHS)
DO 400 I = 1,NC
   SHS(I,I) = SHS(I,I) + LAMDA
400 CONTINUE
DO 934 1=1,NU
   DO 934 J=1,NU
      SHSINV(I,J)=0.0
934 CONTINUE
CALL LINRG(NC,SHS,NU,SHSINV,NU)
DO 944 1=1,NU
   DO 944 J=1,NU
      FINV(I,J)=0.0
944 CONTINUE
CALL MULT (NU,SHSINV,JACOB,FINV)
DO 500 I =1,NC
   COR(I) =0.0
500 CONTINUE
DO 600 1=1,NC
   DO 600 J=1,NC
      COR(I) = COR(I) - FINV(I,J)*U( J)
600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,NC
   IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
   THETA(I)=THETA(I)+COR(I)
700 CONTINUE
IF (IA .EQ. 0) GO TO 6666
DELTA=THETA(1)
IF (DELTA .GT. 1.0) GO TO 349
6666 DO 133 I=1,NS
   ALPHA(I)=THETA(IA+I)
   IF (ALPHA(I) .LE. 0.0) GO TO 349
133 CONTINUE
DO 233 I=1,MC
   BETA(I)=THETA(I+NS+IA)
233 CONTINUE
IF (NERRS .GE. 1) GO TO 399
20 CONTINUE
WRITE (6,66666)
66666 FORMAT(IX,'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
WRITE (6,33335) UNORM
33335 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
JJ = 3
RETURN
1100 WRITE (6,77777) M
77777 FORMAT(1X,'THE TOLERANCE FOR SCORE VECTOR IS MET IN', &
    I4,' ITERATIONS')
JJ=1
GO TO 1000
1300 SUM = 0.
   DO 901 J=1,NC
   SUM = SUM + U(J)**2
901 CONTINUE
UNORM = SQRT(SUM)
WRITE (6,99999) M
99999 FORMAT(1X,'THE TOLERANCE FOR BETA IS MET IN', &
   I4,' ITERATIONS')
JJ=2
   1000 IF (IA .EQ. 0) GO TO 1003
   WRITE (6,575)
575 FORMAT (1X,//,' THE FINAL SOLUTIONS ',//)
1003 WRITE(6,11115) UNORM
11115 FORMAT(/,6X,'THE NORM OF THE SCORE VECTOR = ',E15.8)
WRITE (6,22225) LIKE
22225 FORMAT(/,6X,' LOG LIKELIHOOD = ',E15.8,/)
PVAL=2.*((1.-ANORDF ABS (THETA (J)/SE)))
JL=J-NS-1
WRITE(6,8861) JL, THETA (J), SE, PVAL
8861 FORMAT ('BETA (',I2,')=',F13.8,
& 'SE=',F13.8,2X,'PVALUE=',F7.5)
9976 CONTINUE
7777 RETURN
END
SUBROUTINE SFCN (IA,NU,N,NG,NS,MC,DELTA,A,B,R,DBA,AZ,
& DBB,BZ,BS,SDBA,SDBB,U)
DIMENSION U(NU)
DIMENSION R(NG)
DIMENSION A(NG), B(NG)
DIMENSION BS(NG)
DIMENSION DBA(NS,NG), AZ(NS,NG), DBB(N,NG), BZ(N,NG)
DIMENSION SDBA(NS,NG), SDBB(N,NG)
IF (IA .EQ. 0) GO TO 8888
DO 6 I=1,NG
IF (A(I) .LE. 1) GO TO 61
IF (A(I) .EQ. 2) U(1)=U(1) -(1+(DELTA-DELTA**2)*
& ALOG (B(I)))/(DELTA**2*B(I)**DELTA*R(I))
IF (A(I) .EQ. 3) U(1)=U(1)-3*(1+(DELTA-DELTA**2)*
& ALOG(B(I)))/(DELTA**2*B(I)**DELTA*R(I))-((4/DELTA
& -3)+2*(2-DELTA)**(1-DELTA)*ALOG(B(I)))/(B(I)**(2*
& DELTA)*DELTA**2*R(I))
CONST=DELTA*B(I)**DELTA
IF (A (I)  .EQ. 4) U(1)=U(1)-(1/R(I) )  *
& 3*(1-DELTA)**(2-DELTA)**(3-DELTA)/(DELTA*
& CONST**3)+ (1-DELTA)**(2-DELTA)/CONST**3
& +(2-DELTA)**(3-DELTA)/CONST**3)
IF (A(I) .LE. 3) GO TO 61
U(1)=U(1)-(1/R(I)) *
& 2* (11-7*DELTA)**(1-DELTA)/(DELTA*CONST**2)
& + (11-7*DELTA)/CONST**2+7*(1-DELTA)/CONST**2
& +6*(1-DELTA)/(DELTA*CONST)+6/CONST)
IF (A(I) .LE. 3) GO TO 61
U(1)=U(1)-(1/R(I)) *
& 3*(1-DELTA)**(2-DELTA)**(3-DELTA)*ALOG(B(I))/
& CONST**3 + 2*(11-7*DELTA)**(1-DELTA)*ALOG(B(I))/
& CONST**2+6*(1-DELTA)*ALOG(B(I))/CONST)
61 IF (BS(I) .EQ. 0) THEN
U(1)=U(1)+A(I)*(1/DELTA+ALOG(B(I)))-B(I)**DELTA*ALOG(B(I))
ELSE
U(1)=U(1)+A(I)*(1/DELTA+ALOG(B(I)))-B(I)**DELTA*ALOG(B(I))
& + BS(I)**DELTA*ALOG(BS(I))
ENDIF
6 CONTINUE
8888 DO 7 I=1,NS
DO 7 J=1,NG
IF (A(J) .LE. 1) GO TO 62
IF (A(J) .EQ. 2) U(IA+I)=U(IA+I)-(1-DELTA)/(B(J)**(DELTA
& +1)*R(J))*DBA(I,J)
IF (A(J) .EQ. 3) U(IA+I)=U(IA+I) - 3*(1-DELTA)/(B(J)**(DELTA+1))*R(J)*DBA(I,J) - 2*(2*DELTA+1)*R(J)*DELTA**2)*DBA(I,J)
CONST=DELTA*B(J)**DELTA
IF (A(J) .EQ. 4) U(IA+I)=U(IA+I) - (1/R(J))*DBB(I,J)
& E*DELTA**(DELTA-1)*DBB(I,J) + DELTA*BS(J)**(DELTA-1)*SDBA(I,J)
ELSE
U(IA+I)=U(IA+I) + A(J)*(DELTA-1)/B(J)*DBA(I,J) + A(J)*DELTA*B(J)**(DELTA-1)*DBA(I,J)
& E*DELTA*B(J)**(DELTA-1)*SDBA(I,J) + DELTA*BS(J)**(DELTA-1)*SDBA(I,J)
ENDIF
7 CONTINUE
DO 8 1=1,MC
DO 8 J=1,NG
IF (A(J) .LE. 1) GO TO 63
IF (A(J) .EQ. 2) U(IA+NS+I)=U(IA+NS+I) - (1-DELTA)/(B(J)**(DELTA+1))*R(J)*DBB(I,J)
& E*DELTA**(DELTA-1)*DBB(I,J) + DELTA*BS(J)**(DELTA-1)*SDBB(I,J)
ELSE
U(IA+NS+I)=U(IA+NS+I) + A(J)*(DELTA-1)/B(J)*DBB(I,J) + A(J)*DELTA*B(J)**(DELTA-1)*SDBB(I,J)
& E*DELTA*B(J)**(DELTA-1)*SDBB(I,J) + DELTA*BS(J)**(DELTA-1)*SDBB(I,J)
ENDIF
8 CONTINUE
RETURN
END
SUBROUTINE SJAC(IA,NU,N,NS,NG,MC,R,DBA,DBB,DBAA,DBAB,DBBB, AzZ,DELTA,A,B,BS,SDA,SDBB,SDBA,SDBAB,SDDBB,JACOB)
DIMENSION JACOB(NU,NU)
DIMENSION DBA(NS,NG), DBB(N,NG)
DIMENSION SDAA(NS,NG), SDDB(NS,NG)
DIMENSION DBAA(NS,NG), AZZ(NS,NG), DBAB(N,NS,NG)
DIMENSION SDAA(NS,NG), SDDB(N,NS,NG)
DIMENSION DBBB(N,N,NG)
DIMENSION SDDBB(N,N,NG)
DIMENSION A(NG), B(NG)
249

DIMENSION BS(NG)
DIMENSION R(NG)
REAL JACOB

IF (IA .EQ. 0) GO TO 8898
DO 11 I=1,NG
IF (A(I) .LE. 1) GO TO 71
IF (A(I) .EQ. 2) GO TO 771
IF (A(I) .EQ. 3) GO TO 871
IF (A(I) .EQ. 4) GO TO 971
971 CONST=DELTA*B(I)**DELTA
XT=0.0
XT=XT—(1/R(I))*(
& 3*(1-DELTA)*(2-DELTA)*(3-DELTA)/(DELTA*
& CONST**3) + (1-DELTA)*(2-DELTA)/CONST**3
& + (2-DELTA)*(3-DELTA)/CONST**3)
XT=XT—(1/R(I))*(
& 2*(11-7*DELTA)*(1-DELTA)/(DELTA*CONST**2)
& + (11-7*DELTA)/CONST**2+7*(1-DELTA)/CONST**2
& + 6*(1-DELTA)/(DELTA*CONST)+6/CONST)
XT=XT—(1/R(I))*(
& 3*(1-DELTA)*(2-DELTA)*(3-DELTA)*ALOG(B(I))/
& CONST**3 + 2*(11-7*DELTA)*(1-DELTA)*ALOG(B(I))/
& CONST**2+6*(1-DELTA)*ALOG(B(I))/CONST)
JACOB(1,1)=JACOB(1,1)—XT**2

871 JACOB(1,1)=JACOB(1,1)—(3*(1+(DELTA-DELTA**2)*ALOG(B(I))**2/CONST**3)}
GO TO 71

JACOB(1,1)=JACOB(1,1)+ (1/R(I)) *(
& 12*(1/DELTA)**2)*(1-DELTA)*(2-DELTA)*(3-DELTA)/CONST**3+
& 6*(1/DELTA)*(1-DELTA)*(2-DELTA)/CONST**3+
& 6*(1/DELTA)*(2-DELTA)*(3-DELTA)/CONST**3+
& 2*(1-DELTA)/CONST**3+2*(2-DELTA)/CONST**3+
& 2*(3-DELTA)/CONST**3)
JACOB(1,1)=JACOB(1,1)+ (1/R(I)) *(
& 5*(11-7*DELTA)*(1-DELTA)*(1/DELTA)**2)/CONST**2
& + 4*(11-7*DELTA)*(1/DELTA)/CONST**2+28*(1-DELTA)*
& (1/DELTA)/CONST**2+12*(1-DELTA)*2*(1/DELTA)**2+12*(1/DELTA)
& /CONST+12*(1/DELTA)/CONST)

JACOB(1,1)=JACOB(1,1)+ (1/R(I)) *(
& 18*(1-DELTA)*(2-DELTA)*(3-DELTA)*ALOG(B(I))/DELTA*
& CONST**3)+6*(1-DELTA)*(2-DELTA)*ALOG(B(I))/CONST**3+
& 6*(1-DELTA)*(3-DELTA)*ALOG(B(I))/CONST**3+
& 6*(2-DELTA)*(3-DELTA)*ALOG(B(I))/CONST**3+
& 8*(11-7*DELTA)*(1-DELTA)*ALOG(B(I))/(DELTA*CONST**2)
& + 4*(11-7*DELTA)*ALOG(B(I))/CONST**2+28*(1-DELTA)*
& ALOG(B(I))/CONST**2+12*(1-DELTA)*ALOG(B(I))/(DELTA*CONST)
& + 12*ALOG(B(I))/CONST)
JACOB(1,1)=JACOB(1,1)+ (1/R(I)) *(
& 9*(1-DELTA)*(2-DELTA)*(3-DELTA)*ALOG(B(I))*2/
& CONST**3 + 4*(11-7*DELTA)*(1-DELTA)*ALOG(B(I))*2/
& CONST**2+6*(1-DELTA)*ALOG(B(I))*2/CONST)
GO TO 71

871 JACOB(1,1)=JACOB(1,1)
& - (3*(1+(DELTA-DELTA**2)*
& \text{JACOB}(1,1) = \text{JACOB}(1,1) - \left(3 + \frac{1 + (\Delta - \Delta^2) \cdot \text{ALOG}(B(I))}{\Delta^2} \right) \cdot \left(2 + 2 \cdot \Delta \cdot \text{ALOG}(B(I)) + \frac{3}{\Delta^2} \right) \cdot \left(2 \cdot \Delta \cdot \text{ALOG}(B(I)) + \frac{2}{\Delta^2} \right) \cdot \left(1 + (\Delta - \Delta^2) \cdot \text{ALOG}(B(I)) \right) / \left(\Delta^2 \cdot B(I) \cdot \text{ALOG}(B(I))^2 \right)

\text{GO TO 71}

771 \quad \text{JACOB}(1,1) = \text{JACOB}(1,1) - \left(3 \cdot \frac{1 + (\Delta - \Delta^2) \cdot \text{ALOG}(B(I))}{\Delta^2} \right) \cdot \left(2 + 2 \cdot \Delta \cdot \text{ALOG}(B(I)) + \frac{3}{\Delta^2} \right) \cdot \left(2 \cdot \Delta \cdot \text{ALOG}(B(I)) + \frac{2}{\Delta^2} \right) \cdot \left(1 + (\Delta - \Delta^2) \cdot \text{ALOG}(B(I)) \right) / \left(\Delta^2 \cdot B(I) \cdot \text{ALOG}(B(I))^2 \right)

71 \quad \text{IF (B(S(I)) = 0) THEN}

\quad \text{JACOB}(1,1) = \text{JACOB}(1,1) - \frac{A(I)}{\Delta^2} - \frac{B(I) \cdot \text{ALOG}(B(I))^2}{\Delta^2}

\quad \text{ELSE}

\quad \text{JACOB}(1,1) = \text{JACOB}(1,1) - \frac{A(I)}{\Delta^2} - \frac{B(I) \cdot \text{ALOG}(B(I))^2}{\Delta^2} + \frac{B(S(I)) \cdot \text{ALOG}(B(S(I))^2}{\Delta^2}

\quad \text{ENDIF}

11 \quad \text{CONTINUE}

\quad \text{DO 12 I = 1, NS}

\quad \text{DO 16 J = 1, NG}

\quad \text{IF (A(J) \leq 1) GO TO 76}

\quad \text{IF (A(J) = 2) GO TO 776}

\quad \text{IF (A(J) = 3) GO TO 876}

\quad \text{IF (A(J) = 4) GO TO 976}

\quad 976 \quad \text{CONST} = \Delta \cdot B(J) \cdot \text{ALOG}(B(J))^2

\quad \text{XT} = 0.0

\quad \text{YT} = 0.0

\quad \text{XT} = \text{XT} - (1 / R(J)) \cdot (\ldots)

\quad \text{3} \cdot (1 - \Delta) \cdot (2 - \Delta) \cdot (3 - \Delta) / (\Delta^3) \cdot \text{CONST}^2 + (1 - \Delta) \cdot (2 - \Delta) / (\Delta^3) \cdot \text{CONST} \cdot \text{CONST}^2 + (1 - \Delta) \cdot (3 - \Delta) / (\Delta^3) \cdot \text{CONST}^2

\quad \text{XT} = \text{XT} - (1 / R(J)) \cdot (\ldots)

\quad 2 \cdot (11 - 7 \cdot \Delta) \cdot (1 - \Delta) / (\Delta^2 \cdot \text{CONST}^2) \cdot (11 - 7 \cdot \Delta) / (\Delta^2 \cdot \text{CONST}^2) + 6 \cdot (1 - \Delta) / (\Delta^2 \cdot \text{CONST}^2) + 6 / \appro{\text{CONST}}

\quad \text{XT} = \text{XT} - (1 / R(J)) \cdot (\ldots)

\quad 3 \cdot (1 - \Delta) \cdot (2 - \Delta) \cdot (3 - \Delta) \cdot \text{ALOG}(B(J)) / (\Delta^3) \cdot \text{CONST}^3 + 2 \cdot (11 - 7 \cdot \Delta) \cdot (1 - \Delta) \cdot \text{ALOG}(B(J)) / (\Delta^3) \cdot \text{CONST}^3
& CONST*2 + 6*(1-DELTA)*ALOG(B(J))/CONST
YT = YT - (1/R(J))*(
& 3*DELTA*(1-DELTA)*(2-DELTA)*(3-DELTA)*DBA(I, J)/(B(J)*
& (B(J)*CONST**3)+2*DELTA*(11-7*DELTA)*(1-DELTA)
& *DBA(I, J)/(B(J)*CONST**2)+6*DELTA*(1-DELTA)*DBA(I, J)/
& (B(J)*CONST))
JACOB(1, 1+I) = JACOB(1, 1+I) - XT*YT
JACOB(1, 1+I) = JACOB(1, 1+I) + 1/(R(J))*(
& 6*(1-DELTA)*(2-DELTA)*(3-DELTA)*DBA(I, J)/(B(J)*
& (B(J)*CONST**3)+3*DELTA*(1-DELTA)*(2-DELTA)*DBA(I, J)/
& (B(J)*CONST**3)+3*DELTA*(3-DELTA)*DBA(I, J)/(B(J)*CONST**2)
& + 6*DELTA*DBA(I, J)/(B(J)*CONST))
JACOB(1, 1+I) = JACOB(1, 1+I) + (1/R(J))*(
& 9*DELTA*(1-DELTA)*(2-DELTA)*(3-DELTA)*ALOG(B(J))
& *DBA(I, J)/(B(J)*CONST**3)+4*DELTA*(11-7*DELTA)
& *(1-DELTA)*ALOG(B(J))*DBA(I, J)/(B(J)*CONST**2)
& + 6*DELTA*(1-DELTA)*ALOG(B(J))*DBA(I, J)/(B(J)*CONST))
GO TO 76
876 JACOB(1, 1+I) = JACOB(1, 1+I) + 3*(1+(1-DELTA)*
& ALOG(B(J)))*DBA(I, J)/(B(J)*R(J))
JACOB(1, 1+I) = JACOB(1, 1+I) - 9*(1-DELTA)
& *(1+DELTA-DELTA**2)*ALOG(B(J)))*DBA(I, J)
& /(DELTA**2*B(J)**R(J))
& - ((3*(1+DELTA-DELTA**2)*
& ALOG(B(J)))/(DELTA**2*B(J)**R(J))
& * ((2*DELTA**2*B(J)**R(J))
& * ((2*DELTA**2*B(J)**R(J))
& (-((4-2*DELTA**2)+4*DELTA*(1-DELTA)*ALOG(B(J))
& *DBA(I, J)/(B(J)**R(J))
& - ((4/DELTA
& -3)+2*(1-DELTA)*ALOG(B(J))
& *2*DELTA**2*B(J)**R(J))
& **(4*DELTA+1)**R(J)**2*DELTA**4)
JACOB(1, 1+I) = JACOB(1, 1+I) - ((4/DELTA
& -3)+2*(1-DELTA)*ALOG(B(J)))/(B(J)**R(J))
& *(3*(1-DELTA)/R(J))*DBA(I, J)
& +1)*R(J))*DBA(I, J)
GO TO 76
776 JACOB(1, 1+I) = JACOB(1, 1+I) + (1+(1-DELTA)*
& ALOG(B(J)))*DBA(I, J)/(B(J)**R(J)) - (1-DELTA)
& *(1+(DELTA-DELTA**2)*ALOG(B(J)))*DBA(I, J)
& /(DELTA**2*B(J)**R(J))
76 IF (BS(J) .EQ. 0) THEN
JACOB(1, 1+I) = JACOB(1, 1+I) + A(J)*DBA(I, J)/B(J)
& - B(J)**(DELTA-1)*(1+DELTA*ALOG(B(J)))*DBA(I, J)
ELSE
JACOB(1, 1+1) = JACOB(1, 1+1) + A(J)*DBA(I, J)/B(J)
& - B(J)**(DELTA-1) * (1 + DELTA*ALOG(B(J))) * DBA(I, J)
& + BS(J)**(DELTA-1) * (1 + DELTA*ALOG(BS(J))) * SDBA(I, J)
ENDIF
16 CONTINUE
JACOB(1+1, 1) = JACOB(1, 1+1)
12 CONTINUE
DO 14 I=1, MC
DO 17 J=1, NG
IF (A(J) .LE. 1) GO TO 86
IF (A(J) .EQ. 2) GO TO 786
IF (A(J) .EQ. 3) GO TO 886
IF (A(J) .EQ. 4) GO TO 986
986 CONST = DELTA*B(J)**DELTA
XT = 0.0
YT = 0.0
XT = XT - (1/R(J))*(3*(1-DELTA)*DBB(I, J)/B(J)**3 + 2*DELTA*(11-7*DELTA)*DBB(I, J)/B(J)**2 + 6*DELTA*DBB(I, J)/B(J))
YT = YT - (1/R(J))*(3*DELTA*(1-DELTA)*DBB(I, J)/B(J)**3 + 2*DELTA*(11-7*DELTA)*DBB(I, J)/B(J)**2 + 6*DELTA*DBB(I, J)/B(J))
JACOB(1, 1+NS+I) = JACOB(1, 1+NS+I) + XT*YT
JACOB(1, 1+NS+I) = JACOB(1, 1+NS+I) + (1/R(J))*(2*(11-7*DELTA)*DBB(I, J)/B(J)**2 + 2*DELTA*(11-7*DELTA)*DBB(I, J)/B(J)**2 + 14*DELTA*DBB(I, J)/B(J))
GO TO 86
886 JACOB(1, 1+NS+I) = JACOB(1, 1+NS+I) + 3*(1 + DELTA)*
& ALOG(B(J)) * DBB(I, J) / (B(J) ** (1 + DELTA) * R(J))
JACOB(1, I+NS+1) = JACOB(1, I+NS+1) - 9 * (1 - DELTA)
& *(1 + (DELTA - DELTA**2) * ALOG(B(J))) * DBB(I, J)
& / (DELTA**2 * B(J) ** (1 + 2 * DELTA) * R(J) ** 2)
& - (3 * (1 + (DELTA - DELTA**2) *
& ALOG(B(J))) / (DELTA**2 * B(J) ** DELTA * R(J)))
& * (2 * DELTA**2 * B(J) ** DELTA * R(J))
& ** (2 * DELTA**2 * R(J))
& + (4)
& -2 * DELTA**2 + 4 * DELTA**2 * (2 - DELTA) * (1 - DELTA) * ALOG(B(J))
& * DBB(I, J) / (DELTA**2 * B(J) ** (1 + 2 * DELTA) * R(J))
& - ((4/DELTA - 3) + 2 * (2 - DELTA) * (1 - DELTA) * ALOG(B(J)))
& ** (4 * DELTA**2 * R(J))
JACOB(1, I+NS+1) = JACOB(1, I+NS+1) - ((4/DELTA - 3) + 2 * (2 - DELTA) * (1 - DELTA) * ALOG(B(J)) / (B(J)**2 * DELTA**2 * R(J)))
& * (3 * (1 - DELTA) / (B(J) ** DELTA)
& + 1) * R(J) / (DBB(I, J))
GO TO 86
786 JACOB(1, I+NS+1) = JACOB(1, I+NS+1) + (1 + (1 - DELTA) *
& ALOG(B(J)) * DBB(I, J) / (B(J) ** (1 + DELTA) * R(J)) - (1 - DELTA)
& * 2 * DELTA**2 * (2 - DELTA) * (1 - DELTA) * DBB(I, J) / (B(J))
& ** (4 * DELTA**2 * R(J))
JACOB(1, I+NS+1) = JACOB(1, I+NS+1) - ((4/DELTA - 3) + 2 * (2 - DELTA) * (1 - DELTA) * ALOG(B(J)) / (B(J) ** (1 + DELTA) * R(J)))
& ** (2 * DELTA**2 * R(J))
86 IF (BS(J) .EQ. 0) THEN
JACOB(1, I+NS+1) = JACOB(1, I+NS+1) + A(J) * DBB(I, J) / B(J)
& - B(J) ** (DELTA - 1) * (1 + DELTA) * ALOG(B(J)) / B(J)
ELSE
JACOB(1, I+NS+1) = JACOB(1, I+NS+1) + A(J) * DBB(I, J) / B(J)
& - B(J) ** (DELTA - 1) * (1 + DELTA) * ALOG(B(J)) / B(J)
& + BS(J) ** (DELTA - 1) * (1 + DELTA) * ALOG(BS(J)) * SDBB(I, J)
ENDIF
17 CONTINUE
JACOB(1+NS+I, 1) = JACOB(1, 1+NS+I)
14 CONTINUE
8898 DO 18 I = 1, NS
DO 19 J = 1, NG
IF (A(J) .LE. 1) GO TO 96
IF (A(J) .EQ. 2) GO TO 796
IF (A(J) .EQ. 3) GO TO 896
IF (A(J) .EQ. 4) GO TO 996
996 CONST = DELTA**2 * B(J) ** DELTA
JACOB(IA+I, IA+I) = JACOB(IA+I, IA+I) - ((1/R(J)) * (3 * DELTA**2 * (3 - DELTA) * DBA(I, J) / (B(J)*CONST**3) + 2 * DELTA**2 * (11 - 7 * DELTA) / (B(J)*CONST) ** 6)
& * DBA(I, J) / (B(J)*CONST**2) + 6 * DELTA**2 * (1 - DELTA) * DBA(I, J) / (B(J)*CONST**2)
& *(B(J)*CONST**2)
JACOB(IA+I, IA+I) = JACOB(IA+I, IA+I) + (1/R(J)) *
& 3 * DELTA**2 * (1 - DELTA) * (2 - DELTA) * (3 - DELTA) * DBA(I, J) / (B(J)*CONST**3) + 2 * DELTA**2 * (11 - 7 * DELTA) / (B(J)*CONST**2)
& * DBA(I, J) / (B(J)*CONST**2)
& + 6 * DELTA**2 * (1 - DELTA) / (B(J)*CONST))
JACOB(IA+I,IA+I)=JACOB(IA+I,IA+I)-(1/R(J))*(
3*DELTA*(1-DELTA)*(2-DELTA)*(3-DELTA)*DBAA(I,J)/
(B(J)*CONST**3)+2*DELTA*(11-7*DELTA)*(1-DELTA)
*DBAA(I,J)/(B(J)*CONST**2)+6*DELTA*(1-DELTA)*DBAA(I,J)/
(B(J)*CONST))
GO TO 96

JACOB(IA+I,IA+I)=JACOB(IA+I,IA+I) - 3*(1-DELTA)*
(DBAA(I,J)/(B(J)**(1+DELTA)*R(J))
+(2+DELTA)*R(J)*DBA(I,J)**2)
GO TO 96

IF (BS(J) .EQ. 0) THEN
JACOB(IA+I,IA+I)=JACOB(IA+I,IA+I)+A(J)*(DELTA-1)*
(DBAA(I,J)/B(J)**(1+DELTA)*R(J))+((1-DELTA)
*DBAA(I,J)/B(J)**2)-AZZ(I,J)
ELSE
JACOB(IA+I,IA+I)=JACOB(IA+I,IA+I)+A(J)*(DELTA-1)*
(DBAA(I,J)/B(J)-DBA(I,J)**2/B(J)**2)-(DELTA*(DELTA-1)*
*DBA(I,J)**2/B(J)**(2*(1-DELTA))+DELTA*DBAA(I,J)/B(J)
*(1-DELTA)-AZZ(I,J)
ENDIF

CONTINUE
DO 31 J=I+1,NS
DO 33 L=1,NG
IF (A(L) .LE. 1) GO TO 106
IF (A(L) .EQ. 2) GO TO 7106
IF (A(L) .EQ. 3) GO TO 8106
IF (A(L) .EQ. 4) GO TO 9106
9106 CONST=DELTA*B(L)**DELTA
JACOB(IA+I,IA+J)=JACOB(IA+I,IA+J)-(1/R(L))*(
3*DELTA*(1-DELTA)*(2-DELTA)*(3-DELTA)*DBA(I,L)/
& \((B(L) \cdot \text{CONST}^2) + 2 \cdot \text{DELTA} \cdot (11 - 7 \cdot \text{DELTA}) \cdot (1 - \text{DELTA})\)
& * \text{DBA}(I,L) / (B(L) \cdot \text{CONST}^2) + 6 \cdot \text{DELTA} \cdot (1 - \text{DELTA}) \cdot \text{DBA}(I,L) / (B(L) \cdot \text{CONST})\)
& \((1/R(L)) \cdot (\text{JACOB}(I+I, I+J) - \text{JACOB}(I+I, I+J)) + 3 \cdot (1 - \text{DELTA})\)
& \((1 + \text{DELTA}) / (B(L)**(2 + \text{DELTA}) \cdot R(L)) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L) - 9 \cdot (1 - \text{DELTA})^2 / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)^2) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (3 \cdot (1 - \text{DELTA})\)
& \((1/R(L)) \cdot (\text{JACOB}(I+I, I+J)) - (3 \cdot (1 - \text{DELTA})\)
& \((1 - \text{DELTA}) / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)^2) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{GO TO 106}\)

8106 \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) + 3 \cdot (1 - \text{DELTA})\)
& \((1 + \text{DELTA}) / (B(L)**(2 + \text{DELTA}) \cdot R(L)) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \(-9 \cdot (1 - \text{DELTA})^2 / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)^2) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (3 \cdot (1 - \text{DELTA})\)
& \((1/R(L)) \cdot (\text{JACOB}(I+I, I+J)) - (3 \cdot (1 - \text{DELTA})\)
& \((1 - \text{DELTA}) / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)^2) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{GO TO 106}\)

7106 \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (1 - \text{DELTA})\)
& \((1 - \text{DELTA}) / (B(L)**(2 + \text{DELTA}) \cdot R(L)^2) - (1 + \text{DELTA})\)
& \((2 + \text{DELTA}) / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (1 - \text{DELTA})\)
& \((1 - \text{DELTA}) / (B(L)**(2*(1+\text{DELTA}) \cdot R(L)^2) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{GO TO 106}\)

106 \text{IF (BS(L) .EQ. 0) THEN}\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (\text{DELTA}-1)\)
& \((\text{DELTA}-1) / (B(L)**(2*(1-\text{DELTA}) \cdot R(L)^2) - (1-\text{DELTA})\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (\text{DELTA}-1)\)
& \((\text{DELTA}-1) / (B(L)**(2*(1-\text{DELTA}) \cdot R(L)) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{ELSE}\)
& \text{JACOB}(I+I, I+J) = \text{JACOB}(I+I, I+J) - (\text{DELTA}-1)\)
& \((\text{DELTA}-1) / (B(L)**(2*(1-\text{DELTA}) \cdot R(L)) \cdot \text{DBA}(I,L) \cdot \text{DBA}(J,L)\)
& \text{ENDIF}\)

33 \text{CONTINUE}\)
& \text{JACOB}(I+J, I+I) = \text{JACOB}(I+I, I+J)\)

31 \text{CONTINUE}\)
& \text{DO 34 L=1,MC}\)
& \text{DO 36 LJ=1,NG}\)
& \text{IF (A(LJ) .LE. 1) GO TO 126}\)
IF (A(LJ) .EQ. 2) GO TO 7126
IF (A(LJ) .EQ. 3) GO TO 8126
IF (A(LJ) .EQ. 4) GO TO 9126

9126   CONST=DELTA*B(LJ)**DELTA
       JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) - \((1/R(LJ))\) *( 
& 3*DELTA* (1-Delta) *(2-Delta) *(3-Delta) *DBA(I,LJ) / 
& (B(LJ) *CONST**3) + 2*DELTA*(11-7*DELTA) * (1-Delta) 
& *(DBA(I,LJ) / (B(LJ) *CONST**2) + 6*DELTA*(1-Delta) *DBA(I,LJ) / 
& (B(LJ) *CONST)) ) *( (1/R(LJ)) *) 
& 3*DELTA*(1-Delta) *(2-Delta) *(3-Delta) *DBB(L,LJ) / 
& (B(LJ) *CONST**3) + 2*DELTA*(11-7*DELTA) * (1-Delta) 
& *(DBB(L,LJ) / (B(LJ) *CONST**2) + 6*DELTA*(1-Delta) *DBB(L,LJ) / 
& (B(LJ) *CONST)) )
       JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) - 9* (1-DELTA)**2 
& (B(LJ)*R(LJ)**2) * DBA(I,LJ)*DBB(L,LJ) 
& *(3*(1-DELTA)/ (B(LJ)**2) *DBA(I,LJ)) 
& *(2*DELTA*(2-Delta) *(1-Delta) / (B(LJ)) 
& *(2*DELTA+1) *R(LJ) *DELTA**2) *DBB(L,LJ)) 
& - (2*DELTA* (2-Delta) *(1-Delta) /DELTA**2) * (DBAB(L,I,LJ) / 
& (B(LJ) **(2*DELTA+1) *R(LJ) ) 
& - (2*DELTA+1) / 
& (B(LJ) **(2*DELTA+2) *R(LJ) ) *DBA(I,LJ)*DBB(L,LJ)) 
& - (2*DELTA*(2-Delta) *(1-Delta) /DELTA**2) *DBB(L,LJ) 
& *DBA(I,LJ) *DBB(L,LJ) 
& - (2*DELTA*(2-Delta) *(1-Delta) / (B(LJ)) 
& **(2*DELTA+1) *R(LJ) *DELTA**2) *DBA(I,LJ)) 
& * (3*(1-DELTA) / (B(LJ) **(2*DELTA+1) *R(LJ) ) 
& + 1) *R(LJ) ) *DBB(L,LJ)) 
GO TO 126

8126   JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) + (1/R(LJ)) *( 
& -3* (1-Delta) *(DBAB(L,I,LJ) / (B(LJ) **(1+DELTA) *R(LJ)) 
& -(1+DELTA) / 
& (B(LJ) **(2+DELTA) *R(LJ) ) *DBA(I,LJ)*DBB(L,LJ)) 
JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) - 9* (1-DELTA)**2 
& (B(LJ)*R(LJ)**2) * DBA(I,LJ)*DBB(L,LJ) 
& -(3*(1-DELTA)/ (B(LJ)**2) *DBA(I,LJ)) 
& *(2*DELTA*(2-Delta) *(1-Delta) / (B(LJ)) 
& *(2*DELTA+1) *R(LJ) *DELTA**2) *DBB(L,LJ)) 
& - (2*DELTA* (2-Delta) *(1-Delta) /DELTA**2) * (DBAB(L,I,LJ) / 
& (B(LJ) **(2*DELTA+1) *R(LJ) ) 
& - (2*DELTA+1) / 
& (B(LJ) **(2*DELTA+2) *R(LJ) ) *DBA(I,LJ)*DBB(L,LJ)) 
& - (2*DELTA*(2-Delta) *(1-Delta) / (B(LJ)) 
& **(2*DELTA+1) *R(LJ) *DELTA**2) *DBA(I,LJ)) 
& * (3*(1-DELTA) / (B(LJ) **(2*DELTA+1) *R(LJ) ) 
& + 1) *R(LJ) ) *DBB(L,LJ)) 
GO TO 126

7126   JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) 
& -(1-Delta) *(DBAB(L,I,LJ) / (B(LJ) **(1+DELTA) *R(LJ)) 
& +(1-Delta) / (B(LJ) **(2* (1+DELTA) ) *R(LJ) )**2 - (1+DELTA) / 
& (B(LJ) **(2*DELTA) *R(LJ)))) *DBA(I,LJ)*DBB(L,LJ)) 
126 IF (BS(LJ) .EQ. 0) THEN
JACOB(IA+I,IA+NS+L) = JACOB(IA+I,IA+NS+L) + A(LJ) *(DELTA-1) *
\( \frac{(DBAB(L,I,LJ)/B(LJ) - DBA(I,LJ) \cdot DBB(L,LJ)/B(LJ)^2)}{(1+\Delta) \cdot (1-\Delta)} \)

\( +\Delta \cdot DBAB(L,I,LJ)/B(LJ) \cdot (1-\Delta) \)

ELSE

\( JACOB(IA+I, IA+NS+L) = JACOB(IA+I, IA+NS+L) + A(LJ) \cdot \Delta \cdot (1-\Delta) \)

\( DBAB(L,I,LJ)/B(LJ) - DBA(I,LJ) \cdot DBB(L,LJ)/B(LJ)^2 \)

\( +\Delta \cdot DBAB(L,I,LJ)/B(LJ) \cdot (1-\Delta) \)

\( +\Delta \cdot SDBA(I,LJ) \cdot SDBB(L,LJ)/BS(LJ) \cdot (1-\Delta) \)

ENDIF

36 CONTINUE

\( JACOB(IA+NS+L, IA+I) = JACOB(IA+I, IA+NS+L) \)

34 CONTINUE

18 CONTINUE

DO 44 I=1,MC

DO 44 J=I,MC

DO 47 K=1,NG

IF (A(K) .LE. 1) GO TO 136

IF (A(K) .EQ. 2) GO TO 7136

IF (A(K) .EQ. 3) GO TO 8136

IF (A(K) .EQ. 4) GO TO 9136

9136 CONST=\Delta.B(K)^{\Delta}

\( JACOB(IA+NS+I, IA+NS+J) = JACOB(IA+NS+I, IA+NS+J) - ((1/R(K)) \cdot (3 \cdot \Delta \cdot (1-\Delta) \cdot (2-\Delta) \cdot (3-\Delta) \cdot DBB(I,K)/B(K) \cdot CONST^3) + 2 \cdot \Delta \cdot (11-7 \cdot \Delta) \cdot (1-\Delta) \cdot DBB(I,K)/B(K) \cdot CONST^2) + 6 \cdot \Delta \cdot (1-\Delta) \cdot DBB(I,K)/B(K) \cdot CONST) \)

\( JACOB(IA+NS+I, IA+NS+J) = JACOB(IA+NS+I, IA+NS+J) + (1/R(K)) \cdot (3 \cdot \Delta \cdot (1+3 \cdot \Delta) \cdot (1-\Delta) \cdot (2-\Delta) \cdot (3-\Delta) \cdot (DBB(I,K) \cdot DBB(J,K)) /B(K)^2 \cdot CONST^3) + 2 \cdot \Delta \cdot (1+2 \cdot \Delta) \cdot (11-7 \cdot \Delta) \cdot (1-\Delta) \cdot (DBB(I,K) \cdot DBB(J,K)) /B(K)^2 \cdot CONST^2) + 6 \cdot \Delta \cdot (1+\Delta) \cdot (1-\Delta) \cdot (DBB(I,K) \cdot DBB(J,K)) /B(K)^2 \cdot CONST) \)

\( JACOB(IA+NS+I, IA+NS+J) = JACOB(IA+NS+I, IA+NS+J) - 3 \cdot (1-\Delta)^2/(B(K)^2 \cdot (1+\Delta) \cdot R(K)) \cdot DBB(I,K) \)

GO TO 136

8136 JACOB(IA+NS+I, IA+NS+J) = JACOB(IA+NS+I, IA+NS+J) - 3 \cdot (1-\Delta) \)

\( - \cdot (DBB(I,K) /B(K) \cdot (1+\Delta) \cdot R(K)) \)

\( - \cdot (1+\Delta) \)

\( - \cdot (B(K) \cdot (2+\Delta) \cdot R(K) \cdot DBB(I,K) \cdot DBB(J,K)) \)

\( JACOB(IA+NS+I, IA+NS+J) = JACOB(IA+NS+I, IA+NS+J) - 9 \cdot (1-\Delta)^2/(B(K)^2 \cdot (1+\Delta) \cdot R(K)) \cdot DBB(I,K) \)

\( - \cdot (DBB(I,K) \cdot DBB(J,K) - 3 \cdot (1-\Delta) \)

\( + \cdot (1+\Delta) \)

\( DBB(I,K) \)
258

& * (2 * DELTA * (2 - DELTA) * (1 - DELTA) / (B(K)
& ** (2 * DELTA + 1) * R(K) * DELTA ** 2) * DBB(J, K))
& - (2 * DELTA * (1 - DELTA) / DELTA ** 2) * DBB(I, K)
& - (B(K) ** (2 * DELTA + 1) * R(K))
& - (2 * DELTA + 1) / (B(K) * (2 * DELTA + 2) * R(K))
& / (B(K) ** (2 * DELTA + 1) * R(K) ** 2)
& * DBB(I, K) * DBB(J, K)
& - (2 * DELTA * (1 - DELTA) / B(K)
& * (2 * (2 - DELTA) * (1 - DELTA) / DELTA ** 2) ** 2
& * DBB(I, K) * DBB(J, K))
& - (3 * (1 - DELTA) / B(K) ** (DELTA
& + 1) ** (B(K) ** (1 + DELTA) * R(K))
& + ((1 - DELTA) / (B(K) ** (2 * (1 + DELTA)) / R(K))
& + ((1 - DELTA) / (B(K) ** (2 * (2 + DELTA)) * R(K))
& * DBB(I, K) * DBB(J, K))
& + (DELTA * (DELTA - 1) * SDBB(I, K) * SDBB(J, K) / BS(K) ** (2 - DELTA)
& + DELTA ** (2 - DELTA) * DBB(I, K) * DBB(J, K))

GO TO 136

7136 JACOB(IA + NS + I, IA + NS + J) = JACOB(IA + NS + I, IA + NS + J)
& - (1 - DELTA) * (DBBB(I, J, K) / (B(K) ** (1 + DELTA) * R(K))
& + ((1 - DELTA) / (B(K) ** (2 * (1 + DELTA)) / R(K)) ** 2) - (1 + DELTA) / (B(K) ** (2 * DELTA) * R(K))
& - (2 * DELTA + 1) / (B(K) ** (2 * DELTA + 2) * R(K))
& * DBB(I, K) * DBB(J, K))
& - (3 * (1 - DELTA) / B(K) ** (DELTA
& + 1) ** (B(K) ** (1 + DELTA) * R(K))
& + ((1 - DELTA) / (B(K) ** (2 * (1 + DELTA)) / R(K))
& + ((1 - DELTA) / (B(K) ** (2 * (2 + DELTA)) * R(K))
& * DBB(I, K) * DBB(J, K))
& + (DELTA * (DELTA - 1) * SDBB(I, K) * SDBB(J, K) / BS(K) ** (2 - DELTA)
& + DELTA ** (2 - DELTA) * DBB(I, K) * DBB(J, K))

136 IF (BS(K) .EQ. 0) THEN
JACOB(IA + NS + I, IA + NS + J) = JACOB(IA + NS + I, IA + NS + J)
& + A(K) * (DELTA - 1) * (DBBB(I, J, K) / B(K) - DBB(I, K)
& * DBB(J, K) / B(K) ** 2) - (DELTA * (DELTA - 1) * DBB(I, K) * DBB(J, K)
& / B(K) ** (2 - DELTA) + DELTA ** DBB(I, J, K) / B(K) ** (1 - DELTA))
& ELSE
JACOB(IA + NS + I, IA + NS + J) = JACOB(IA + NS + I, IA + NS + J)
& + A(K) * (DELTA - 1) * (DBBB(I, J, K) / B(K) - DBB(I, K)
& * DBB(J, K) / B(K) ** 2) - (DELTA * (DELTA - 1) * DBB(I, K) * DBB(J, K)
& / B(K) ** (2 - DELTA) + DELTA ** DBB(I, J, K) / B(K) ** (1 - DELTA))
& + DELTA * SDBBB(I, J, K) / BS(K) ** (2 - DELTA)
& + DELTA ** SDBBB(I, J, K) / BS(K) ** (1 - DELTA))
ENDIF

47 CONTINUE
JACOB(IA + NS + J, IA + NS + I) = JACOB(IA + NS + I, IA + NS + J)

44 CONTINUE
RETURN
END
SUBROUTINE LIKELI (NG, DELTA, CLIKE, R, A, B, BS, LIKE)
DIMENSION CLIKE(NG), R(NG)
DIMENSION A(NG), B(NG)
DIMENSION BS(NG)
REAL LIKE
DO 4 I = 1, NG
LIKE = LIKE + A(I) * (ALOG(DELTA) + (DELTA - 1) * ALOG(B(I)))
& + B(I) ** DELTA + ALOG(R(I)) + CLIKE(I) + BS(I) ** DELTA
4 CONTINUE
RETURN
END
SUBROUTINE MULT (NU, AO, BO, CO)
DIMENSION AO(NU, NU), BO(NU, NU), CO(NU, NU)
DO 1 I = 1, NU
DO 1 J = 1, NU
CO(I, J) = 0.0
DO 1 K = 1, NU
CO(I,J) = CO(I,J) + AO(I,K) * BO(K,J)
1 CONTINUE
RETURN
END
APPENDIX E

FORTRAN PROGRAM FOR THE COUNTING PROCESS APPROACH TO THE ESTIMATION OF THE DEPENDENCE PARAMETER AND REGRESSION COEFFICIENTS IN A GAMMA FRAILTY MODEL

C******************************************************************************
C******************************************************************************
C******************************************************************************
C******************************************************************************
C********** MAIN PROGRAM **********
C******************************************************************************
C******************************************************************************
C************************************************************************************
C INPUT:
C N: NO OF COVARIATES
C NOBS: NO FO OBSERVATIONS
C NG: NO OF GROUPS
C NS: NO OF STRATA
C************************************************************************************
C PARAMETER(N=1,NOBS=150,NG=50,NS=1)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), MEL(NOBS),
 & NEL(NOBS)
DIMENSION THETA(N+1), BETA(N)
DIMENSION IORDER(NOBS),IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION ECHF(NS,NOBS)
EXTERNAL SFCN, SJAC, LIKELI,MULT, LINRG
DATA UPP/0.0001/
C
C******************************************************************************
C INPUT:
C IJ(I) = 1, COVARIATE I IS INCLUDED
C = 0, COVARIATE I IS USED IN COMPUTATION, BUT NOT IN MAXIMIZATION
C = -1, COVARIATE I IS OUT
C******************************************************************************
C DO 3103 I=1,N
IJ(I)=1
3103 CONTINUE

260
**INPUT:**

DELTA: AN INITIAL GUESS AT THE DEPENDENCE PARAMETER

```
DELTA=1.0
DO 8014 I=1,N
   IF (IJ(I) .EQ. 1) THEN
      BETA(I)=0.0
   ENDIF
8014 CONTINUE
```

UTOL = 0.01
TTOL = 0.001
ITMAX = 100

**INPUT:**

T: OBSERVED TIME ON STUDY
IND: CENSORING INDICATOR
MEL: GROUP NO
NEL: STRATUM NO
Z: COVARIATES

```
DO 70000 I=1,NOBS
   READ(1,*) T(I), IND(I),MEL(I), NEL(I),(Z(K,I),K=1,N)
70000 CONTINUE
```

**ARRANGING DATA BY THE ORDER OF OBSERVED TIME ON STUDY**

```
CALL ORDER (T,IND, NOBS, IORDER)
NOBSN=N*NOBS
CALL ARRANG(IORDER,NOBS,N,NOBSN,Z)
CALL ARRANG(IORDER,NOBS,1,NOBS,T)
CALL ARRANG (IORDER,NOBS,1,NOBS,IND)
CALL ARRANG (IORDER,NOBS,1,NOBS,NEL)
CALL ARRANG (IORDER,NOBS,1,NOBS,MEL)
JRANK=1
IRANK(I)=JRANK
DO 60000 I=2,NOBS
   IF(IND(I) .EQ. 0) GO TO 50000
   IF(T(I) .NE. T(I-1)) JRANK=JRANK+1
50000 IRANK(I)=JRANK
60000 CONTINUE
J=1
DO 1225 I=1,NOBS
   IF (IRANK(I) .NE. J) GO TO 1225
   I1=IRANK(I)
   NP(I1)=I
   J=J+1
1225 CONTINUE
```
C ******************************************************************************
C STARTING THE EM LIKE ALGORITHM
C ******************************************************************************
C
IA=0
DO 8566 NITER=1,50
IF (NITER .NE. 1) IA=1
DO 10000 I=1,N+1
THETA(I)=0.0
10000 CONTINUE
C
C ******************************************************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO
C FIND THE MLE'S OF THE DEPENDENCE PARAMETER AND REGRESSION
C COEFFICIENTS BASED ON A MODIFIED COX'S PARTIAL LIKELIHOOD
C ******************************************************************************
C
CALL SMAQ(IA,N,NOBS,NG,NS,Z,T,IND,MEL,NEL,IJ,IRANK,NP,MC,
  & ITMAX,UTOL,TTOL,DELTA,BETA,THETA,JJ,
  & ECHF,SFCN, SJAC, LIKELI,MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
IF (IA .EQ. 0) GO TO 8588
DTHETA=-1.0
DO 8362 1=1,MC
  DIFF1=THETA(1+1)-BETA(I)
  IF (ABS(DIFF1) .GE. DTHETA) DTHETA=ABS(DIFF1)
8362 CONTINUE
  DIFF2=THETA(1)-DELTA
  IF (ABS(DIFF2) .GE. DTHETA) GO TO 8363
  DIF=DTHETA
  GO TO 8364
8363 DIF=ABS(DIFF2)
8364 IF (DIF .LE. UPP) GO TO 5051
  DELTA=THETA(1)
  DO 8577 I=1,MC
    BETA(I)=THETA(I+1)
8577 CONTINUE
  GO TO 8566
8588 DO 8599 I=1,MC
    BETA(I)=THETA(I)
8599 CONTINUE
8566 CONTINUE
WRITE(6,3051)
3051 FORMAT(5X,'NO CONVERGENCE',//)
  WRITE(6,*) 'THE MAX. OF DIFF. =',DIF
  GO TO 4051
5051 WRITE(6,278)
278 FORMAT(1X,//)
  WRITE(6,8766) THETA(1)
8766 FORMAT(1X,'EST OF ASSOC. = ',F13.8,/)
8765  FORMAT('  BETA(',12,')=',F13.8)
6051  CONTINUE
4051  STOP
END
C
C***********************************************************************
C***********************************************************************
C***********************************************************************
SUBROUTINE ORDER (T,IND,NOBS,PTRS)
DIMENSION T(NOBS), IND(NOBS), PTRS(NOBS)
INTEGER PTRS
INTEGER P,PJ,PJ1,HTOP,HEND
DO 5020 I=1,NOBS
PTRS(I) = I
5020  CONTINUE
HTOP = NOBS/2 + 1
HEND=NOBS
2000 IF (HTOP .LE. 1) GO TO 2500
HTOP=HTOP-1
P=PTRS(HTOP)
GO TO 3000
2500  P = PTRS(HEND)
PTRS(HEND) = PTRS(1)
HEND =HEND -1
IF (HEND.EQ.1) GO TO 9000
3000  J=HTOP
4000  I=J
J=J+J
IF (J .GT. HEND) GO TO 8000
PJ=PTRS(J)
IF (J.EQ.HEND) GO TO 6000
PJ1 =PTRS(J+1)
IF(T(PJ)-T(PJ1))  5050, 5010, 6000
5010 IF (IND(PJ) .LE. IND(PJ1)) GO TO 6000
5050  J=J+1
PJ=PJ1
6000 IF(T(P)-T(PJ)) 7000, 6010, 8000
6010 IF (IND(P) .LE. IND(PJ)) GO TO 8000
7000  PTRS(I) =PTRS(J)
GO TO 4000
8000  PTRS(I)=P
GO TO 2000
9000  PTRS(1) =P
RETURN
END
SUBROUTINE ARRANG (IORDER,NOBS,N,NOBSN,COVAR)
DIMENSION IORDER(NOBS), COVAR(NOBSN)
DIMENSION KEEP(20)
REAL KEEP
DO 7007 I=1,NOBS
IF((IORDER(I) .LE. 0) .OR. (IORDER(I) .EQ. I)) GO TO 7010
L1=N*(I-1)
7007  CONTINUE
DO 7001 L=1,N
   KEEP(L) = COVAR(L1+L)
7001 CONTINUE
J=I
7002 K=IORDER(J)
IORDER(J) = -K
LJ =N*(J-1)
LK =N*(K-1)
DO 7003 L=1,N
   COVAR(LJ+L) = COVAR(LK+L)
7003 CONTINUE
J=K
IF(IORDER(J) .NE. I) GO TO 7002
IORDER(J) = -I
L1 =N*(J-1)
DO 7004 L=1,N
   COVAR(L1+L) = KEEP(L)
7004 CONTINUE
7010 IORDER(I)  =IABS(IORDER(I))
7007 CONTINUE
RETURN
END

SUBROUTINE SMAQ( IA,N,NOBS,NG,NS,Z,T,IND,MEL,NEL,IJ,IRANK,
& NP,MC,ITMAX,UTOL,TTL,DELTA,BETA,THETA,JJ,
& ECHF,SFCN,SJAC,LIKELI,MULT,LINRG)

C ************************************************************
C INPUT:
C NN: NO OF COVARIATES
C NNOBS: NO OF OBSERVATIONS
C NNG: NO OF GROUPS
C NNS : NO OF STRATA
C ************************************************************

PARAMETER(NN=1,NNOBS=150,NNG=50,NNS=1)
PARAMETER(IITMAX=100)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), MEL(NOBS),NEL(NOBS)
DIMENSION BETA(N),THETA(N+1)
DIMENSION U(NN+1), THETAJ(NN+1,NN+1),FISHI(NN+1,NN+1)
DIMENSION IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NNOBS)
DIMENSION EHF(NNS,NNOBS), ECHF(NS,NOBS)
DIMENSION ID(NN)
DIMENSION SS(NN+1), SI1(NN+1), SI2(NN+1,NN+1)
DIMENSION S2(NN)
DIMENSION H1(NN), H2(NN,NN)
DIMENSION AZ(NN+1)
DIMENSION DWG(NN+1),DDWG(NN+1,NN+1), SDDWG(NN+1,NN+1)
DIMENSION SAVE(NN+1,NN+1), SSAVE(NN+1)
DIMENSION SHS(NN+1,NN+1), SHSINV(NN+1,NN+1)
& FINV(NN+1,NN+1)
DIMENSION COR(NN+1)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SJAC,SFCN,LIKELI,MULT,LINRG
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
MAX=IRANK(NOBS)
IF (IA .EQ. 0) GO TO 1221
THETA(1)=DELTA
1221 J1=1
DO 1226 I=1,N
IF (IJ(I) .NE. 1 ) GO TO 1226
ID(J1)=I
THETA(J1+IA)=BETA(I)
J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
IF(IJ(I) .NE. 0) GO TO 1227
ID(J1)=1
THETA(J1+IA)=BETA(I)
J1=J1+1
1227 CONTINUE
MD=J1-1
DO 4013 I=1,MD
BETA(I)=THETA(IA+I)
4013 CONTINUE
MAXCOR=5.0
LAMDA =2.0
DO 20 M=1,IITMAX
393 LIKE =0.0
DO 2227 I=1,N+IA
U(I) = 0.0
DO 2226 J=1,MD
L1=ID(J)
XX(I)=XX(I)+THETA(J+IA)*Z(L1,I)
2226 CONTINUE
XX(I)=EXP(XX(I))
2227 CONTINUE
DO 2225 I=1,NOBS
XX(I)=0.0
DO 2226 J=1,MD
L1=ID(J)
XX(I)=XX(I)+THETA(J+IA)*Z(L1,I)
2226 CONTINUE
XX(I)=EXP(XX(I))
2225 CONTINUE
DO 2588 I=1,NS
DO 2588 J=1,MAX
EHF(I,J)=0.0
2588 CONTINUE
LL=1
2228 II=MAX
2336 CONTINUE
DO 2335 I=1,N+IA
SII(I)=0.0
DO 2335 J=1,N+IA
SI2(I,J)=0.0
2335 CONTINUE
MI=0
SI=0.0
WG=1.0
SWG=0.0
DO 2367 I=1,N
SZ(I)=0.0
2367 CONTINUE
DO 2337 I=1,N+IA
SS(I)=0.0
DWG(I)=0.0
DO 2337 J=1,N+IA
DDWG(I,J)=0.0
SDDWG(I,J)=0.0
2337 CONTINUE
IP=NP(II)
DO 2445 I=IP,NOBS
IF(NEL(I) .NE. LL) GO TO 2445
K=MEL(I)
IF (IA .EQ. 0) GO TO 2349
NT=0
DO 2689 J1=1,IP-1
IF (MEL(J1) .NE. K .OR. IND(J1) .EQ. 0 )  GO TO 2689
NT=NT+1
2689 CONTINUE
H = 0.0
DO 2789 11=1,MC
HI(II)=0.0
DO 2789 12=11,MC
H2(II,12)=0.0
2789 CONTINUE
DO 7689 J1=1,NOBS
IF (MEL(J1) .NE. K) GO TO 7689
LJ=NEL( J1)
IF (  J1 .GE. IP) GO TO 2989
H=H+ECHF(LJ,IRANK(J1))*XX(J1)
DO 9333 11=1,MC
HI(II)=HI(II)+ECHF(LJ,IRANK(J1))*XX(J1)*Z[ID(II),J1]
DO 9333 12=11,MC
H2(II,12)=H2(II,12)+ECHF(LJ,IRANK(J1))*XX(J1)*Z[ID(II),J1]*
& Z[ID(12),J1]
9333 CONTINUE
GO TO 7689
2989 H=H+ECHF(LJ,II)*XX(J1)
DO 9332 II=1,MC
H1(II)=H1(II)+ECHF(LJ,II)*XX(J1)*Z[ID(II),J1]
DO 9332 II=1,MC
H2(II,II)=H2(II,II)+ECHF(LJ,II)*XX(J1)*Z[ID(II),J1]*
& Z[ID(II),J1]
9332 CONTINUE
7689 CONTINUE
WG=(1+THETA(1)*FLOAT(NT))/(1+THETA(1)*H)
D W G (1) = \frac{\text{FLOAT}(NT)}{(1+\text{THETA}(1) \times \text{FLOAT}(NT))} \& -\frac{\text{H}}{(1+\text{THETA}(1) \times \text{H})}

D D W G (1, 1) = -\left(\frac{\text{FLOAT}(NT)}{(1+\text{THETA}(1) \times \text{FLOAT}(NT))}\right)^2 + \left(\frac{\text{H}}{(1+\text{THETA}(1) \times \text{H})}\right)^2

\text{DO 9338 I1=1, MC}

D W G (I1+1) = -\frac{\text{THETA}(1)}{(1+\text{THETA}(1) \times \text{H})} \times \text{H1(I1)}

D D W G (1, I1+1) = -\frac{1}{(1+\text{THETA}(1) \times \text{H})^2} \times \text{H1(I1)}

\text{DO 9338 I2=I1, MC}

D D W G (I1+1, I2+1) = -\frac{\text{THETA}(1)}{(1+\text{THETA}(1) \times \text{H})} \times \text{H2(I1, I2)}

\& \left(\frac{1}{(1+\text{THETA}(1) \times \text{H})^2} \times \text{H1(I1)} \times \text{H1(I2)}\right)

9338 \text{ CONTINUE}

A Z (1) = D W G (1)

2349 \text{ DO 2351 JI=1, MC}

A Z (JI+IA) = Z(ID(JI), I) + D W G (JI+IA)

2351 \text{ CONTINUE}

S I = S I + W G \times X X (I)

\text{DO 2449 K=1, MC+IA}

S I 1 (K) = S I 1 (K) + W G \times X X (I) \times A Z (K)

\text{DO 2449 J=K, MC+IA}

S I 2 (K, J) = S I 2 (K, J) + W G \times X X (I) \times (A Z (K) \times A Z (J) + D D W G (K, J))

2449 \text{ CONTINUE}

I F (I R A N K (I) .NE. II .AND. M I .EQ. 0) G O T O 2446

I F (I R A N K (I) .NE. II .OR. I N D (I) .EQ. 0) G O T O 2445

M I = M I + 1

D O 2448 J=1, M D + I A

S S (J) = S S (J) + A Z (J)

2448 \text{ CONTINUE}

S W G = S W G + A L O G (W G)

\text{DO 2569 J=1, M D}

S Z (J) = S Z (J) + Z(ID(J), I)

2569 \text{ CONTINUE}

\text{DO 2568 J=1, MC+IA}

\text{DO 2568 J K=J, MC+IA}

S D D W G (J, JK) = S D D W G (J, JK) + D D W G (J, JK)

2568 \text{ CONTINUE}

2445 \text{ CONTINUE}

2446 \text{ CONTINUE}

I F (M I .EQ. 0) G O T O 2556

E H F (L L, I I ) = M I / S I


C A L L S F C N (N, M C, M I, I A, S S, S I, S I 1, U)


2556 \text{ CONTINUE}

I I = I I - 1

I F (I I .GE. 1) G O T O 2336

L L = L L + 1

I F (L L .LE. N S) G O T O 2228

I F (M .EQ. 1) G O T O 2557

I F (L I K E .GE. L O G L I K (M-1)) G O T O 2558

793 \text{ D O 800 I=1, MC+IA}

800 \text{ T H E T A (I) = T H E T A (I) - C O R (I)}

D O 810 I=1, N+I A
U(I)=SSAVE(I)
DO 810 J=1,N+IA
810 THETAJ(I,J)=SAVE(I,J)
NERRS=NERRS+1
LAMDA=LAMDA*2
IF(NERRS .LE. 20) GO TO 2559
WRITE(6,55555) M
55555 FORMAT(1X,'ERRORS IN MARQUARDT ','I4, 'ITERATIONS')
JJ =4
RETURN
2558 LOGLIK(M) = LIKE
LAMDA=LAMDA/1.5
GO TO 2775
2557 LOGLIK(1)=LIKE
2775 NERRS = 0
IF (MAXCOR .LE. TTOL) GO TO 1300
MAXU=-1.0
DO 100 J=1,MC+IA
IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))
100 CONTINUE
IF (MAXU .LE. UTOL) GO TO 1100
2559 CALL MULT(N+1,THETAJ,THETAJ, SHS)
DO 400 I = 1,MC+IA
SHS(I,I) = SHS(I,I) + LAMDA
400 CONTINUE
DO 494 1=1,N+1
DO 494 J=1,N+1
SHSINV(I,J)=0.0
494 CONTINUE
CALL LINRG(MC+IA,SHS,N+1,SHSINV,N+1)
DO 594 I =1,N+1
DO 594 J=1,N+1
FINV(I,J)=0.0
594 CONTINUE
CALL MULT (N+1,SHSINV,THETAJ,FINV)
DO 500 I =1,MC+IA
COR(I) = 0.0
500 CONTINUE
DO 600 I=1,MC+IA
DO 600 J=1,MC+IA
COR(I) = COR(I) - FINV(I,J)*U(J)
600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,MC+IA
IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
THETA(I)=THETA(I)+COR(I)
700 CONTINUE
IF (IA .EQ. 0) GO TO 693
IF (THETA(I) .LT. 0.0) GO TO 793
693 DO 710 I=1,N+IA
SSAVE (I)=U(I)
DO 710 J=1,N+IA
710 SAVE(I,J)=THETAJ(I,J)
IF (NERRS .GE. 1) GO TO 393
20 CONTINUE
WRITE (6,66666)
66666 FORMAT('THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
JJ = 3
RETURN
1100 DO 6015 I=1,NS
   DO 6015 J=1,MAX
      ECHF(I,J)=0.0
6015 CONTINUE
DO 2343 LL=1,NS
   DO 2343 I=1,MAX
      DO 2343 J=1,I
         ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
   2343 CONTINUE
JJ=1
IF (IA .EQ. 0) GO TO 1003
GO TO 1000
1300 DO 5015 I=1,NS
   DO 5015 J=1,MAX
      ECHF(I,J)=0.0
5015 CONTINUE
DO 2333 LL=1,NS
   DO 2333 I=1,MAX
      DO 2333 J=1,I
         ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
   2333 CONTINUE
JJ=2
IF (IA .EQ. 0) GO TO 1003
GO TO 1000
1003 DO 1008 I=1,MC
   DO 1008 J=1,MC
      ThetaJ(I,J)=-ThetaJ(I,J)
1008 CONTINUE
CALL LINRG (MC,ThetaJ,N+1,FISHI,N+1)
DO 9874 J=1,MC
   SE=SQRT(FISHI(J,J))
   PVAL=2.*(1.-ANORDF(ABS(Theta(J)/SE)))
9874 CONTINUE
8764 FORMAT(' BETA('','I2,'')='',F13.8,
   &    ',' SE='',F13.8,2X,' PVALUE='',F7.5)
9874 CONTINUE
1000 RETURN
END
SUBROUTINE SFCN(N,MC,MI,IA,SS,SI,SI1, U)
DIMENSION SS(N+1),SI1(N+1),U(N+1)
XXMI=MI
DO 22 K=1,MC+IA
   U(K)=U(K)+SS(K)-XXMI*SI1(K)/SI
22 CONTINUE
RETURN
END
SUBROUTINE SJAC(N,MC,MI,IA,SI,SI1,SI2,SDDWG,ThetaJ)
DIMENSION SI1(N+1), SI2(N+1,N+1), THETAJ(N+1,N+1)
DIMENSION SDDWG(N+1,N+1)
XXXMI=MI
DO 27 K=1,MC+IA
   DO 27 L=K,MC+IA
      T1=SI2(K,L)/SI
      T2=SI1(K)*SI1(L)/SI**2
      THETAJ(K,L)=THETAJ(K,L)+SDDWG(K,L)-XXXMI*(T1-T2)
      THETAJ(L,K)=THETAJ(K,L)
27 CONTINUE
RETURN
END

SUBROUTINE LIKELI (N, THETA, MD, MI, IA, SZ, SWG, SI, LIKE)
DIMENSION THETA(N+1), SZ(N)
REAL LIKE
S=0.0
DO 32 J=1,MD
   S=S+SZ(J)*THETA(J+IA)
32 CONTINUE
S=S+SWG
XMI=MI
LIKE=LIKE+S-XMI*ALOG(SI)
RETURN
END

SUBROUTINE MULT(N, A, B, C)
DIMENSION A(N,N), B(N,N), C(N,N)
DO 1 I=1,N
   DO 1 J=1,N
      C(I,J) = 0.0
1   CONTINUE
RETURN
END
APPENDIX F

FORTRAN PROGRAM FOR THE COUNTING PROCESS APPROACH TO THE ESTIMATION OF THE DEPENDENCE PARAMETER AND REGRESSION COEFFICIENTS IN A POSITIVE STABLE FRAILTY MODEL

C**************************************************************************************************************************
C**************************************************************************************************************************
C**************************************************************************************************************************
C**************************************************************************************************************************
C INPUT:
C N: NO OF COVARIATES
C NOBS: NOF OF OBSERVATIONS
C NG: NO OF GROUPS
C NS: NO OF STRATA
C**************************************************************************************************************************

PARAMETER(N=1,NOBS=150,NG=50,NS=1)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), MEL(NOBS),
& NEL(NOBS)
DIMENSION THETA(N+1), BETA(N)
DIMENSION IORDER(NOBS),IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION ECHF(NS,NOBS)
EXTERNAL SFCN, SJAC, LIKELI,MULT, LINRG
EXTERNAL F2, F3, F4
DATA UPP/0.0001/

C**************************************************************************************************************************
C INPUT:
C IJ(I) = 1, COVARIATE I IS INCLUDED
C = 0, COVARIATE I IS USED IN COMPUTATION,
C BUT NOT IN MAXIMIZATION
C = -1, COVARIATE I IS OUT
C**************************************************************************************************************************

DO 3103 I=1,N
   IJ(I)=1
3103 CONTINUE
C INPUT:
C DELTA: AN INITIAL GUESS AT THE DEPENDENCE PARAMETER
C
DELTA=0.8
DO 8014 I=1,N
   IF (IJ(I) .EQ. 1) THEN
      BETA(I)=0.0
   ENDIF
8014 CONTINUE
UTOL = 0.01
TTOL = 0.001
ITMAX = 100

C INPUT:
C T: OBSERVED TIME ON STUDY
C IND: CENSORING INDICATOR
C MEL: GROUP NO
C NEL: STRATUM NO
C Z : COVARIATES
C
DO 70000 I=1,NOBS
   READ(1,*) T(I), IND(I) ,MEL(I), NEL(I),(Z(K,I), K=1,N)
70000 CONTINUE

C ARRANGING DATA BY THE ORDER OF OBSERVED TIMES ON STUDY
C
CALL ORDER (T,IND, NOBS, IORDER)
NOBSN=N*NOBS
CALL ARRANG(IORDER,NOBS,N,NOBSN,Z)
CALL ARRANG(IORDER,NOBS,1,NOBS,T)
CALL ARRANG (IORDER,NOBS,1,NOBS,IND)
CALL ARRANG (IORDER,NOBS,1,NOBS,NEL)
CALL ARRANG (IORDER,NOBS,1,NOBS,MEL)
JRANK=1
IRANK(I)=JRANK
DO 60000 I=2,NOBS
   IF(IND(I) .EQ. 0) GO TO 50000
   IF(T(I) .NE. T(I-1)) JRANK=JRANK+1
50000 IRANK(I)=JRANK
60000 CONTINUE
J=1
DO 1225 I=1,NOBS
   IF (IRANK(I) .NE. J) GO TO 1225
      II=IRANK(I)
      NP (II)=I
   J=J+1
1225 CONTINUE
C ***************************************************************
C STARTING THE EM LIKE ALGORITHM
C ***************************************************************
C
IA=0
DO 8566 NITER=1,50
IF (NITER .NE. 1) IA=1
DO 10000 I=1,N+1
THETA(I)=0.0
10000 CONTINUE
C
C ***************************************************************
C SMAQ:
C USING THE LEVENBERG-MARQUADT ITERATION METHOD TO
C FIND THE MLE'S OF THE DEPENDENCE PARAMETER AND REGRESSION
C COEFFICIENTS BASED ON A MODIFIED COX'S PARTIAL LIKELIHOOD
C ***************************************************************
C
CALL SMAQ(IA,N,NOBS,NG,NS,Z,T,IND,MEL,NEL,IJ,IRANK,NP,MC,
& ITMAX,UTOL,TTOL,DELTA,BETA,THETA,JJ,
& ECHF,F2,F3,F4,SFCN,SJAC,LIKELI,MULT,LINRG)
IF (JJ .EQ. 3 .OR. JJ .EQ. 4) STOP
IF (IA .EQ. 0) GO TO 8588
DTHETA=-1.0
DO 8362 I=1,MC
DIFF1=THETA(1+1)-BETA(I)
IF (ABS(DIFF1) .GE. DTHETA) DTHETA=ABS(DIFF1)
8362 CONTINUE
DIFF2=THETA(1)-DELTA
IF (ABS(DIFF2) .GE. DTHETA) GO TO 8363
DIF=DTHETA
GO TO 8364
8363 DIF=ABS(DIFF2)
8364 IF (DIF .LE. UPP) GO TO 5051
DELTA=THETA(1)
DO 8577 I=1,MC
BETA(I)=THETA(I+1)
8577 CONTINUE
GO TO 8566
8588 DO 8599 I=1,MC
BETA(I)=THETA(I)
8599 CONTINUE
8566 CONTINUE
WRITE(6,3051)
3051 FORMAT(5X,'NO CONVERGENCE',//)
WRITE(6,*) 'THE MAX. OF DIFF. =',DIF
GO TO 4051
5051 WRITE(6,278)
278 FORMAT(1X, //)
WRITE(6,8766) THETA(1)
8766 FORMAT(1X,'DELTA= ',F13.8, //)
DO 6051 J=1,MC
WRITE(6,8765) J,THETA(J+1)
SUBROUTINE ORDER (T, IND, NOBS, PTRS)
DIMENSION T(NOBS), IND(NOBS), PTRS(NOBS)
INTEGER PTRS
INTEGER P,PJ,PJ1,HTOP, HEND
DO 5020 I=1,NOBS
  PTRS(I) = I
5020 CONTINUE
HTOP = NOBS/2 + 1
HEND = NOBS
2000 IF (HTOP .LE. 1) GO TO 2500
HTOP = HTOP - 1
P = PTRS(HTOP)
GO TO 3000
2500 P = PTRS(HEND)
PTRS(HEND) = PTRS(1)
HEND = HEND - 1
IF (HEND .EQ. 1) GO TO 9000
3000 J = HTOP
4000 I = J
  J = J + J
  IF (J .GT. HEND) GO TO 8000
  PJ = PTRS(J)
  IF (J .EQ. HEND) GO TO 6000
  PJ1 = PTRS(J+1)
  IF (T(PJ) - T(PJ1)) 5050, 5010, 6000
5010 IF (IND(PJ) .LE. IND(PJ1)) GO TO 8000
5050 J = J + 1
  PJ = PJ1
6000 IF (T(PJ) - T(PJ1)) 7000, 6010, 8000
6010 IF (IND(P) .LE. IND(PJ1)) GO TO 8000
7000 PTRS(I) = PTRS(J)
GO TO 4000
8000 PTRS(I) = P
GO TO 2000
9000 PTRS(I) = P
RETURN
END

SUBROUTINE ARRANG (IORDER, NOBS, N, NOBSN, COVAR)
DIMENSION IORDER(NOBS), COVAR(NOBSN)
DIMENSION KEEP(20)
REAL KEEP
DO 7007 I=1,NOBS
  IF (IORDER(I) .LE. 0) .OR. (IORDER(I) .EQ. I) GO TO 7010
  L1 = N * (I-1)
7007 CONTINUE
4010 STOP
END
DO 7001 L=1,N
   KEEP(L) = COVAR(L1+L)
7001 CONTINUE
J=I
7002 K=IORDER(J)
   IORDER(J) = -K
   LJ =N*(J-1)
   LK =N*(K-1)
   DO 7003 L=1,N
      COVAR(LJ+L) = COVAR(LK+L)
7003 CONTINUE
J=K
   IF(IORDER(J) .NE. I) GO TO 7002
   IORDER(J) = -I
   LI =N*(J-1)
   DO 7004 L=1,N
      COVAR(L1+L) = KEEP(L)
7004 CONTINUE
7010 IORDER(I) =IABS(IORDER(I))
7007 CONTINUE
RETURN
END

SUBROUTINE SMAQ(IA,N,NOBS,NG,NS,Z,T,IND,MEL,NEL,IJ,IRANK,
& NP,MC,ITMAX,UTOL,TTOL,DELTA,BETA,THETA,JJ,
& ECHF,F2,F3,F4,SFCN,SJAC,LIKELI,MULT,LINRG)
C
C * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
C INPUT:
C NN: NO OF COVARIATES
C NNOBS: NO OF OBSERVATIONS
C NNG: NO OF GROUPS
C NNS: NO OF STRATA
C ******************************************************************************************************************
C
C PARAMETER(NN=1,NNOBS=150,NNG=50,NNS=1)
PARAMETER(IITMAX=100)
DIMENSION Z(N,NOBS), T(NOBS), IND(NOBS), MEL(NOBS),NEL(NOBS)
DIMENSION BETA(N),THETA(N+1)
DIMENSION U(NN+1), THETAJ(NN+1,NN+1),FISHI(NN+1,NN+1)
DIMENSION IRANK(NOBS), NP(NOBS)
DIMENSION IJ(N)
DIMENSION XX(NNOBS)
DIMENSION EHF(NNS,NNOBS), ECHF(NS,NOBS)
DIMENSION ID(NN)
DIMENSION SS(NN+1), SI1(NN+1), SI2(NN+1,NN+1)
DIMENSION S2(NN)
DIMENSION H1(NN), H2(NN,NN)
DIMENSION AZ(NN+1)
DIMENSION DWG(NN+1), DDWG(NN+1,NN+1), SDDWG(NN+1,NN+1)
DIMENSION SAVE(NN+1,NN+1), SSAVE(NN+1)
DIMENSION SHS(NN+1,NN+1), SHSINV(NN+1,NN+1)
& , FINV(NN+1,NN+1)
DIMENSION COR(NN+1)
DIMENSION LOGLIK(IITMAX)
EXTERNAL SJAC, SFCN, LIKELI, MULT, LINRG
EXTERNAL F2, F3, F4
REAL LIKE, LOGLIK
REAL MAXCOR, MAXU
REAL LAMDA
MAX=IRANK(NOBS)
IF (IA .EQ. 0) GO TO 1221
1221 J1=1
DO 1226 I=1,N
IF (IJ(I) .NE. 1 ) GO TO 1226
ID(J1)=I
THETA(J1+IA)=BETA(I)
J1=J1+1
1226 CONTINUE
MC=J1-1
DO 1227 I=1,N
IF (IJ(I) .NE. 0) GO TO 1227
ID(J1)=I
THETA(J1+IA)=BETA(I)
J1=J1+1
1227 CONTINUE
MD=J1-1
DO 4013 I=1,MD
BETA(I)=THETA(IA+I)
4013 CONTINUE
MAXCOR=5.0
LAMDA = 2.0
DO 20 M=1,IITMAX
393 LIKE = 0.0
DO 2227 I=1,N+IA
U(I) = 0.0
DO 2227 J=1,N+IA
THETAJ(I,J)=0.0
2227 CONTINUE
DO 2225 I=1,NOBS
XX(I)=0.0
DO 2226 J=1,MD
L1=ID(J)
XX(I)=XX(I)+THETA(J+IA)*Z(L1, I)
2226 CONTINUE
XX(I)=EXP(XX(I))
2225 CONTINUE
DO 2588 I=1,NS
XX(I)=0.0
DO 2588 J=1,MAX
EHF(I, J)=0.0
2588 CONTINUE
LL=1
II=MAX
2336 CONTINUE
DO 2335 I=1,N+IA
SI1(I)=0.0
DO 2335 J=1,N+IA
SI2(I,J)=0.0

CONTINUE
MI=0
SI=0.0
WG=1.0
SWG=0.0
DO 2367 I=1,N
SZ(I)=0.0

CONTINUE
DO 2337 I=1,N+IA
SS(I)=0.0
DWG(I)=0.0
DO 2337 J=1,N+IA
DDWG(I,J)=0.0
SDDWG(I,J)=0.0

CONTINUE
IP=NFP(I)
DO 2445 I=IP,NOBS
IF(NEL(I) .NE. LL) GO TO 2445
K=MEL(I)
IF (IA .EQ. 0) GO TO 2349
NT=0
DO 2689 J1=1,IP-1
IF (MEL(J1) .NE. K .OR. IND(J1) .EQ. 0 )  GO TO 2689
NT=NT+1

CONTINUE
H=0.0
DO 2789 I1=1,MC
H1(I1)=0.0
DO 2789 I2=I1,MC
H2(I1,I2)=0.0

CONTINUE
DO 2789 J1=1,NOBS
IF (MEL(J1) .NE. K) GO TO 7689
LJ=NEL(J1)
IF ( J1 .GE. IP) GO TO 2989
H=H+ECHF(LJ,IRANK(J1))*XX(J1)
DO 9333 I1=1,MC
H1(I1)=H1(I1)+ECHF(LJ,IRANK(J1))*XX(J1)*Z(ID(I1),J1)
DO 9333 I2=I1,MC
H2(I1,I2)=H2(I1,I2)+ECHF(LJ,IRANK(J1))*XX(J1)*Z(ID(I1),J1)*Z(ID(I2),J1)

CONTINUE
GO TO 7689

CONTINUE
DO 2989 I1=1,MC
H=H+ECHF(LJ,I1)*XX(J1)

CONTINUE
GO TO 2989

CONTINUE
IF (H .EQ. 0.0) THEN
278

WG=1.0
DO 555 MK=1,N+1
   DWG(MK)=0.0
DO 555 ML=1,N+1
   DDWG(MK,ML)=0.0
555 CONTINUE
GO TO 31005
ENDIF
DEL=THETA(1)
C1=DEL*H**DEL
C2=DEL*H**6DEL
IF (NT .EQ. 0) GO TO 31000
IF (NT .EQ. 1) GO TO 31001
IF (NT .EQ. 2) GO TO 31002
IF (NT .EQ. 3) GO TO 31003
31000 WG=C1
   DWG(1)=1/DEL+ALOG(H)
   DDWG(1,1)=-1/DEL**2
DO 32000 II=1,MC
   DWG(II+1)=(DEL-1)*H1(II)/H
   DDWG(1,II+1)=H1(II)/H
DO 32000 II=1,MC
   DDWG(II+1,II+1)=(DEL-1)*(H2(II,II)/H - H1(II)*H1(II)/H**2)
32000 CONTINUE
GO TO 31005
31001 R2=F2(DEL,C2)
   WG=R2*C1
   DWG(1)=1/DEL+ALOG(H)
   RN=0.0
   RN = RN-(1+(DEL-DEL**2)*ALOG(H)) / (DEL**2*H**DEL*R2)
   DWG(1)=DWG(1)+RN
   DDWG(1,1)=-1/DEL**2
   RN=0.0
   RN=RN-(1-DEL)/ (H**(DEL+1)*R2)*H1(II)
   DWG(II+1)=DWG(II+1)+RN
DO 32001 II=1,MC
   DWG(II+1)=(DEL-1)*H1(II)/H
   RN=0.0
   RN=RN-(1-DEL)/ (H**(DEL +1)*R2)*H1(II)
   DWG(II+1)=DWG(II+1)+RN
   DDWG(1,II+1)=H1(II)/H
   RN=0.0
   RN=RN+(1+(1-DEL)*ALOG(H))*H1(II)/ (H**(1+DEL)*R)**2
   & *(1+(DEL-DEL**2)*ALOG(H)) / (DEL**2*R2*H**DEL)
   DDWG(1,II+1)=DDWG(1,II+1)+RN
DO 32001 I2=I1,MC
DDWG(I1+1,I2+1)=(DEL-1)*(H2(I1,I2)/H
&-H1(I1)*H1(I2)/H**2)
RN=0.0
RN = RN
&- (1-DEL)* (H2(I1,I2)/(H***(1+DEL)*R2)+((1-DEL)
&/(H***(2*(1+DEL))*R2**2)-(1+DEL)/
& (H***(2+DEL)*R2))*H1(I1)*H1(I2))
DDWG(I1+1,I2+1)=DDWG(I1+1,I2+1)+RN
32001 CONTINUE
GO TO 31005
31002 R2=F2(DEL,C2)
R3=F3(DEL,C2)
WG=R3/R2*C1
DWG(1)=1/DEL+ALOG(H)
RN=0.0
RN=RN-3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3)-((4/DEL
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H***(2*
& DEL)*DEL**2*R3)
DWG(1)=DWG(1)+RN
RD=0.0
RD = RD-(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R2)
DWG(1)=DWG(1)-RD
DDWG(1,1)=-1/DEL**2
RN=0.0
RN=RN
&- (3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3))**2
RN=RN-3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3)
&* ((4/DEL
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H***(2*
& DEL)*DEL**2*R3)
&+3*((2+2*DEL*ALOG(H)+(DEL**2-DEL**3)
& *ALOG(H)**2)/((4-DEL)**3*R3*H**DEL)
&-((4-DEL)**3*(1-DEL)*ALOG(H))
& /((2+2*DEL*ALOG(H)+(DEL**2-DEL**3)
& *ALOG(H)**2)**2
&- ((4/DEL
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H***(2*
& DEL)*DEL**2*R3)
&* (3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3))
RN=RN+(12-6*DEL+
& (16*DEL-12*DEL**2)*ALOG(H)+4*(2*
& DEL-DEL**2)*(DEL-DEL**2)*ALOG(H)
& **2)/(DEL**4*H***(2*DEL)*R3)
DDWG(1,1)=DDWG(1,1)+RN
RD=0.0
RD=RD-(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R2))**2
&+(2+2*DEL*ALOG(H)+(DEL**2-DEL**3)
& *ALOG(H)**2)/(DEL**3*R2*H**DEL)
DDWG(1,1)=DDWG(1,1)-RD
DO 32002 I1=1,MC
DWG(I1+1)=(DEL-1)*H1(I1)/H
RN=0.0
RN=RN-3*(1-DEL)/(H**DEL)
& +1)*R3)*H1(I1)-2*(2/DEL-1)*(1-DEL)/(H
& **(2*DEL+1)*R3)*H1(I1)
DDWG(I1+1)=DDWG(I1+1)+RN
RD=0.0
RD=RD-(1-DEL)/(H**DEL)
& +1)*R2)*H1(I1)
DDWG(I1+1)=DDWG(I1+1)-RD
DDWG(1,I1+1)=H1(I1)/H
RN=0.0
RN=RN+3*(1+(1-DEL)*ALOG(H))*H1(I1)/(H**(1+DEL)*R3)
RN=RN-9*(1-DEL)*
& *(1+(DEL-DEL**2)*ALOG(H))/DEL**2**H**R3**2)
& - (3*(1+(DEL-DEL**2)*ALOG(H)))/(H**DEL**R3)
& *(2*DEL*R3)*H1(I1)/(H
& **(2*DEL+1)*R3)*H1(I1))
& +((4
& -2*DEL**2)+4*DEL*(2-DEL)*(1-DEL)*ALOG(H))
& *H1(I1)/(DEL**2*H**DEL**2)*R3)
& - ((4/DEL
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))
& *2*DEL*(2-DEL)*(1-DEL)/H
& **(4*DEL+1)*R3)*H1(I1))
& *(3*(1-DEL)/(H**DEL
& +1)*R3)*H1(I1))
DDWG(1,1+1)=DDWG(1,1+1)+RN
RD=0.0
RD=RD+(1+(1-DEL)*
& ALOG(H))/*H1(I1)/(H**DEL**2*R3)-1-DEL)
& *(1+(DEL-DEL**2)*ALOG(H))/DEL**2**H**R3**2)
DDWG(1,I1+1)=DDWG(1,I1+1)-RD
DO 32002 I2=1,MC
DDWG(I1+1,I2+1)=(DEL-1)*(H2(I1,I2)/H
& *(1+DEL)**2)/(H**DEL**R3)
& -(1+DEL)/
& *(H**2+DEL)**R3)*H1(I1)**H1(I2))
RN=RN- 9*(1-DEL)**2
\[(H^* (2*(1+DEL) \cdot R3^2) \cdot H1(I1) \cdot H1(I2) - (3*(1-DEL)/(H^* (1+DEL) \cdot R2) + (3-DEL)/(H^* (1+DEL) \cdot R2^2)))/(H^*(2*(1+DEL) \cdot R2) \cdot H1(I1) \cdot H1(I2))\]

\[DDWG(1+1,12+1)=DDWG(11+1,12+1)+RN\]

\[RD=0.0\]

\[RD=RD-(1-DEL) \cdot (H2(I1,I2)/(H^*(1+DEL) \cdot R2)+(1-DEL)/(H^*(1+DEL) \cdot R2))\]

\[DDWG(11+1,12+1)=DDWG(11+1,12+1)-RD\]

32002 CONTINUE

GO TO 31005

31003 R3=F3(DEL,C2)
R4=F4(DEL,C2)
WG=R4/R3*C1
DWG(1)=1/DEL+ALOG(H)
RN=0.0
RN=RN-(1/R4)*{
& 3*(1-DEL)*(2-DEL)*(3-DEL)/(DEL*
& C2**3)+ (1-DEL)/(DEL*C2**2)
& + (2-DEL)/(DEL*C2**3)
\}[1/DEL]

DDWG(1)=DWG(1)+RN

RN=RN-(1/R4)*{
& 2*(11-7*DEL)*(1-DEL)/(DEL*C2**2)
& + (11-7*DEL)/(DEL*C2**2)+7*(1-DEL)/(DEL*C2**2)
& +6*(1-DEL)/(DEL*C2+6/C2)
\}[1/DEL]

DDWG(1)=DWG(1)+RN

RD=0.0
RD=RD-3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3)-((4/DEL
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H***(2*
& DEL)*DEL**2*R3)

DDWG(1)=DWG(1)-RD

DDWG(1,1)=-1/DEL**2

RN=0.0

XT=0.0
\begin{align*}
XT &= XT - \frac{1}{R4} \times (3 \times (1 - \text{DEL}) \times (2 - \text{DEL}) \times (3 - \text{DEL}) / (\text{DEL}^2) \\
&\quad + C2^3 + (1 - \text{DEL}) \times (2 - \text{DEL}) / C2^3 \\
&\quad + (1 - \text{DEL}) \times (3 - \text{DEL}) / C2^3 \\
&\quad + (2 - \text{DEL}) \times (3 - \text{DEL}) / C2^3) \\
RN &= RN - XT^2 \\
RN &= RN + \frac{1}{R4} \times (12 \times (1 - \text{DEL}) \times (2 - \text{DEL}) \times (3 - \text{DEL}) / C2^3 \\
&\quad + 6 \times (1 - \text{DEL}) \times (2 - \text{DEL}) / C2^3 \\
&\quad + 6 \times (1 - \text{DEL}) \times (3 - \text{DEL}) / C2^3 \\
&\quad + 6 \times (2 - \text{DEL}) \times (3 - \text{DEL}) / C2^3 \\
&\quad + 2 \times (1 - \text{DEL}) \times (2 - \text{DEL}) / C2^3 \\
DDWG(1,1) &= DDWG(1,1) + RN \\
RD &= 0.0 \\
RD &= RD - \left( 3 \times (1 + (\text{DEL} - \text{DEL}^2) \times \text{DEL}^2) \right) \\
&\quad \times (4/\text{DEL} \\
&\quad - 3) \times 2 \times (2 - \text{DEL}) \times (1 - \text{DEL}) \times \text{ALOG}(H) / (\text{DEL}^2) \\
&\quad \times (H^2 \times (2 - \text{DEL}) \times \text{DEL}^2 \times R3) \\
&\quad + 3 \times (2 \times 2 \times \text{DEL} \times \text{ALOG}(H) + (\text{DEL}^2 - \text{DEL}^3) \\
&\quad \times \text{ALOG}(H) \times (\text{DEL} \times (3 \times R3 \times H \times \text{DEL}^2)) \\
&\quad + (H^2 \times (2 \times \text{DEL} \times \text{DEL}^2 \times R3)) \times 2)
\end{align*}


```plaintext
& \ - (\((4/DEL
& \ -3)+2*(2-DEL)*(1-DEL)*ALOG(H)/(H**2*DEL**2*R3))
& *(3*(1+(DEL-DEL**2)*
& ALOG(H))/(DEL**2*H**DEL*R3))
& RD=RD+(12-6*DEL+
& (16*DEL-12*DEL**2)*ALOG(H)+4*(2*
& DEL-DEL**2)*(DEL-DEL**2)*ALOG(H)
& **2)/(DEL**4*H**2*(2*DEL)*R3)
DDWG(1,1)=DDWG(1,1)-RD
DO 32003 I1=1,MC
DDWG(I1+1)=(DEL-1)*H1(I1)/H
RN=0.0
RN=RN-(1/R4)*(
& 3*DEL*(1-DEL)*(2-DEL)*(3-DEL)*H1(I1)/
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL)
& *H1(I1)/(H*C2**2)+6*DEL*(1-DEL)*H1(I1)/
& (H*C2))
DDWG(I1+1)=DDWG(I1+1)+RN
RD=0.0
RD=RD-3*(1-DEL)/(H*(DEL
& +1)*R3)*H1(I1)-2*(2/DEL-1)*(1-DEL)/(H
& **2/(DEL+1)*R3)*H1(I1)
DDWG(I1+1)=DDWG(I1+1)-RD
DDWG(1,11+1)=H1(I1)/H
RN=0.0
XT=0.0
YT=0.0
XT=XT-(1/R4)*(
& 3*(1-DEL)*(2-DEL)*(3-DEL)/(DEL*
& C2**3)+(1-DEL)*(2-DEL)/C2**3
& +(1-DEL)*(3-DEL)/C2**3
& +(2-DEL)*(3-DEL)/C2**3)
XT=XT-(1/R4)*(
& 2*(11-7*DEL)*(1-DEL)/(DEL*C2**2)
& +*(11-7*DEL)/C2**2+7*(1-DEL)/C2**2
& +6*(1-DEL)/(DEL*C2)+6/C2
XT=XT-(1/R4)*(
& 3*(1-DEL)*(2-DEL)*(3-DEL)*ALOG(H)/
& C2**3 + 2*(11-7*DEL)*(1-DEL)*ALOG(H)/
& C2**2+6*(1-DEL)*ALOG(H)/C2)
YT=YT-(1/R4)*(
& 3*DEL*(1-DEL)*(2-DEL)*(3-DEL)*H1(I1)/
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL)
& *H1(I1)/(H*C2**2)+6*DEL*(1-DEL)*H1(I1)/
& (H*C2))
RN=RN-XT*YT
RN=RN+(1/R4)*(
& 6*(1-DEL)*(2-DEL)*(3-DEL)*H1(I1)/(H*
& C2**3)+3*DEL*(1-DEL)*(2-DEL)*H1(I1)/
& (H*C2**3)+3*DEL*(1-DEL)*(3-DEL)*H1(I1)/
& (H*C2**3))
```

283
RN = RN + (1/R4) * ( \\
& 2*(11-7*DEL)*(1-DEL)*H1(I1)/(H*C2**2) \\
& + 2*DEL*(11-7*DEL)*H1(I1)/(H*C2**2) \\
& +14*DEL*(1-DEL)*H1(I1)/(H*C2**2) \\
& +6*DEL*H1(I1)/(H*C2) ) \\
RN = RN + (1/R4) * ( \\
& 9*DEL*(1-DEL)*(2-DEL)*(3-DEL)*ALOG(H) \\
& *H1(I1)/(H*C2**3)+4*DEL*(11-7*DEL) \\
& *(1-DEL)*ALOG(H)*H1(I1)/(H*C2**2) \\
& +6*DEL*(1-DEL)*ALOG(H)*H1(I1)/(H*C2) ) \\
DDWG(1,I1+1)=DDWG(1,I1+1)+RN \\
RD = 0.0 \\
RD = RD + 3*(1+(1-DEL) * \\
& ALOG(H))*H1(I1)/(H**2*(1+DEL)*R3) \\
RD = RD - 9*(1-DEL) \\
& *(1+(DEL-DEL**2) *ALOG(H))*H1(I1)/(DEL**2*H**2) \\
& (1+2*DEL)*R3**2) \\
& - (3*(1+(DEL-DEL**2) * \\
& ALOG(H)))/(DEL**2*H**2*DEL*R3) \\
& * (2*DEL*(2-DEL)*(1-DEL)/(H \\
& **2*DEL+1)*R3**2*DEL**2)*H1(I1) \\
& +((4 \\
& -2*DEL**2)+4*DEL*(1-DEL)*)ALOG(H) \\
& *H1(I1)/(DEL**2*H**2*(1+2*DEL)*R3) \\
& - ((4/DEL \\
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H)) \\
& *2*DEL*(2-DEL)*(1-DEL)*H1(I1)/(H \\
& **2*DEL+1)*R3**2*DEL**4) \\
RD = RD - ((4/DEL \\
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H**2*(DEL \\
& +1)*R3)*H1(I1) \\
DDWG(1,1+1)=DDWG(1,1+1)-RD \\
DO 32003 I2=11,MC \\
DDWG(I1+1,I2+1)=(DEL-1)*(H2(I1,I2)/H \\
& -H1(I1)*H1(I2)/(H**2)) \\
RN = 0.0 \\
RN = RN - ((1/R4) * ( \\
& 3*DEL*(1-DEL)*(2-DEL)*(3-DEL)*H1(I1)/ \\
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL) \\
& *H1(I1)/(H*C2**2)+6*DEL*H1(I1)/(H*C2) ) \\
& (1/R4) * ( \\
& 3*DEL*(1-DEL)*(2-DEL)*(3-DEL)*H1(I2)/ \\
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL) \\
& *H1(I2)/(H*C2**2)+6*DEL*H1(I2)/(H*C2) ) \\
RN = RN - ((1/R4) * ( \\
& 3*DEL*(1+3*DEL)*(1-DEL)*H1(I2)/ \\
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL) \\
& *H1(I1)/(H*C2**2)+6*DEL*H1(I1)/(H*C2) ) \\
& (H**2*C2)) \\
RD = RD + 3*(1+(1-DEL) * \\
& ALOG(H))*H1(I1)/(H**2*(1+DEL)*R3) \\
RD = RD - 9*(1-DEL) \\
& *(1+(DEL-DEL**2) *ALOG(H)) \\
& / (DEL**2*H**2*DEL*R3) \\
& * (2*DEL*(2-DEL)*(1-DEL)/(H \\
& **2*DEL+1)*R3**2*DEL**2)*H1(I1) \\
& +((4 \\
& -2*DEL**2)+4*DEL*(1-DEL)*)ALOG(H) \\
& *H1(I1)/(DEL**2*H**2*(1+2*DEL)*R3) \\
& - ((4/DEL \\
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H)) \\
& *2*DEL*(2-DEL)*(1-DEL)*H1(I1)/(H \\
& **2*DEL+1)*R3**2*DEL**4) \\
RD = RD - ((4/DEL \\
& -3)+2*(2-DEL)*(1-DEL)*ALOG(H))/(H**2*(DEL \\
& +1)*R3)*H1(I1) \\
DDWG(1,1+1)=DDWG(1,1+1)-RD \\
DO 32003 I2=11,MC \\
DDWG(I1+1,I2+1)=(DEL-1)*(H2(I1,I2)/H \\
& -H1(I1)*H1(I2)/(H**2))
RN=RN-(1/R4)*(
& 3*DEL*(1-DEL)*(2-DEL)*(3-DEL)*H2(I1,I2)/
& (H*C2**3)+2*DEL*(11-7*DEL)*(1-DEL)
& *H2(I1,I2)/(H*C2**2)+6*DEL*(1-DEL)*H2(I1,I2)/
& (H*C2))
DDWG(I1+1,I2+1)=DDWG(I1+1,I2+1)+RN
RD=0.0
RD = RD
& - 3*(1-DEL)*
& (H2(I1,I2)/(H**(1+DEL)*R3)
& -(1+DEL)/
& (H**(2+DEL)*R3)*H1(I1)*H1(I2))
RD=RD- 9*(1-DEL)**2
&/(H**(2*(1+DEL))*R3**2)*H1(I1)*H1(I2)
& - (3*(1-DEL)/(H**(DEL
& +1)*R3)*H1(I1)
& *(2+DEL)*(2-DEL)*(1-DEL)/(H
& **(2+DEL+1))*R3**2)*H1(I1))
& -(2+DEL+1)/
& (H**(2+DEL)*R3)*H1(I1)*H1(I2))
& -(2+DEL)*(2-DEL)*(1-DEL)/(H
& **(2+DEL+1))*R3**2)*H1(I1)
& *(3*(1-DEL)/(H**(DEL
& +1)*R3)*H1(I1)
& *(2+DEL+1)*R3)*H1(I2)
& - (2+DEL+1)*(1-DEL)/(H
& **(2+DEL+1))*R3**2)*H1(I1)
& *(3*(1-DEL)/(H**(DEL
& +1)*R3)*H1(I2)
& *(2+DEL+1)**2/(H**(2*(2+DEL+1))*R3**2)*H1(I2)
& *(2+DEL+1)*(1-DEL)/(H
& **(2+DEL+1))*R3**2)*H1(I1)
& *(3*(1-DEL)/(H**(DEL
& +1)*R3)*H1(I2)
& *(2+DEL+1)**2)/(H**(2*(2+DEL+1))*R3**2)*H1(I2)
32003 CONTINUE
31005 CONTINUE
AZ(1)=DWG(1)
2349 DO 2351 JI=1,MC
AZ(JI+IA)=Z(ID(JI),I)+DWG(JI+IA)
2351 CONTINUE
SI=SI+WG*XX(I)
DO 2449 K=1,MC+IA
SI1(K)=SI1(K)+WG*XX(I)*AZ(K)
DO 2449 J=K,MC+IA
SI2(K,J)=SI2(K,J)+WG*XX(I)*(AZ(K)*AZ(J)+DDWG(K,J))
2449 CONTINUE
IF(IRANK(I) .NE. II .AND. MI .EQ. 0) GO TO 2446
IF (IRANK(I) .NE. II .OR. IND(I) .EQ. 0) GO TO 2445
MI=MI+1
DO 2448 J=1,MD+IA
SS(J)=SS(J)+AZ(J)
2448 CONTINUE
SWG=SWG+ALOG(WG)
DO 2569 J=1,MD
SZ(J)=SZ(J)+Z(ID(J),I)
2569 CONTINUE
DO 2568 JK=J,MC+IA
   SDDWG(J,JK)=SDDWG(J,JK)+DDWG(J,JK)
2568 CONTINUE
2445 CONTINUE
2446 CONTINUE
   IF (MI .EQ. 0) GO TO 2556
   EHF(LL,II)=MI/SI
   CALL LIKELI(N,THETA,MD,MI,IA,SZ,SWG,SI,LIKE)
   CALL SFCN(N,MC,MI,IA,SS,SI,SI1,U)
   CALL SJAC(N,MC,MI,IA,SI,SI1,SI2,SDDWG,THETAJ)
2556 CONTINUE
   II=II-1
   IF (II .GE. 1) GO TO 2336
   LL=LL+1
   IF (LL .LE. NS) GO TO 2228
   IF (M .EQ. 1) GO TO 2557
   IF (LIKE .GE. LOGLIK(M-1)) GO TO 2558
795 DO 800 1=1,MC+IA
800 THETA(I)=THETA(I)-COR(I)
   DO 810 1=1,N+IA
     U(I)=SAVE(I)
   810 THETAJ(I,J)=SAVE(I,J)
   NERRS=NERRS+1
   LAMDA=LAMDA/2
   IF (NERRS .LE. 20) GO TO 2559
5555 FORMAT(IX,'ERRORS IN MARQUARDT ',14, 'ITERATIONS'
   JJ=4
   RETURN
2558 LOGLIK(M)=LIKE
   LAMDA=LAMDA/1.5
   GO TO 2775
2557 LOGLIK(1)=LIKE
2775 NERRS=0
   IF (MAXCOR .LE. TTOL) GO TO 1300
   MAXU=-1.0
   DO 100 J=1,MC+IA
     IF (ABS(U(J)) .GE. MAXU) MAXU=ABS(U(J))
   100 CONTINUE
   IF (MAXU .LE. UTOL) GO TO 1100
2559 CALL MULT(N+1,THETAJ,THETAJ,SHS)
   DO 400 I=1,MC+IA
     SHS(I,I)=SHS(I,I)+LAMDA
   400 CONTINUE
   DO 494 I=1,N+1
     DO 494 J=1,N+1
       SHSINV(I,J)=0.0
   494 CONTINUE
   CALL LINRG(MC+IA,SHS,N+1,SHSINV,N+1)
   DO 594 I=1,N+1
     DO 594 J=1,N+1
       FINV(I,J)=0.0
CALL MULT (N+1,SHSINV,THETAJ,FINV)
DO 500 I =1,MC+IA
   COR(I) = 0.0
500 CONTINUE
DO 600 I=1,MC+IA
   DO 600 J=1,MC+IA
   COR(I) = COR(I) - FINV(I,J)*U(J)
600 CONTINUE
MAXCOR = -1.0
DO 700 I = 1,MC+IA
   IF (ABS(COR(I)) .GE. MAXCOR) MAXCOR=ABS(COR(I))
   THETA(I)=THETA(I)+COR(I)
700 CONTINUE
IF (IA .EQ. 0) GO TO 695
IF (THETA(1) .GT. 1.0) GO TO 795
695 DO 710 I=1,N+IA
   SSAVE (I)=U(I)
   DO 710 J=1,N+IA
    SAVE(I,J)=THETAJ(I,J)
710 CONTINUE
IF (NERRS .GE. 1) GO TO 393
20 CONTINUE
WRITE (6,66666)
66666 FORMAT(IX,'THE NUMBER OF ITERATIONS EXCEEDS ITMAX')
J= 3
RETURN
1100 DO 6015 I=1,NS
   DO 6015 J=1,MAX
       ECHF(I,J)=0.0
6015 CONTINUE
DO 2343 LL=1,NS
   DO 2343 I=1,MAX
      DO 2343 J=1,I
         ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2343 CONTINUE
JJ=1
IF (IA .EQ. 0) GO TO 1003
GO TO 1000
1300 DO 5015 I=1,NS
   DO 5015 J=1,MAX
       ECHF(I,J)=0.0
5015 CONTINUE
DO 2333 LL=1,NS
   DO 2333 I=1,MAX
      DO 2333 J=1,I
         ECHF(LL,I)=ECHF(LL,I)+EHF(LL,J)
2333 CONTINUE
JJ=2
IF (IA .EQ. 0) GO TO 1003
GO TO 1000
1003 DO 1008 I=1,MC
   DO 1008 J=1,MC
       THETAJ(I,J)=-THETAJ(I,J)
CONTINUE
CALL LINRG (MC,THETAJ,N+1,FISHI,N+1)
DO 9874 J=1,MC
  SE=SQRT(FISHI(J,J))
  PVAL=2.*(1.-ANORDF(ABS(THETA(J)/SE)))
WRITE(6,8764) J,THETA(J),SE,PVAL
8764 FORMAT(' BETA(',I2,')=',F13.8,  
  SE=',F13.8,2X,'PVALUE=',F7.5)
9874 CONTINUE
1000 RETURN
END
SUBROUTINE SFCN(N,MC,MI,IA,SS,SI,SIL, U)
DIMENSION SS(N+1),SIL(N+1),U(N+1)
XXMI=MI
DO 22 K=1,MC+IA
  U(K)=U(K)+SS(K)-XXMI*SIL(K)/SI
22 CONTINUE
RETURN
END
SUBROUTINE SJAC(N,MC,MI,IA,SI,SIL,SI2,SDDWG,THETAJ)
DIMENSION SIL(N+1),SI2(N+1,N+1),THETAJ(N+1,N+1)
DIMENSION SDDWG(N+1,N+1)
XXXMI=MI
DO 27 K=1,MC+IA
  DO 27 L=K,MC+IA
    T1=SI2(K,L)/SI
    T2=SIL(K)*SIL(L)/SI**2
    THETAJ(K,L)=THETAJ(K,L)+SDDWG(K,L)-XXXMI*(T1-T2)
    THETAJ(L,K)=THETAJ(K,L)
27 CONTINUE
RETURN
END
SUBROUTINE LIKELI (N,THETA,MD,MI,IA,SZ,SWG,SI,LIKE)
DIMENSION THETA(N+1), SZ(N)
REAL LIKE
S=0.0
DO 32 J=1,MD
  S=S+SZ(J)*THETA(J+IA)
32 CONTINUE
S=S+SWG
XMI=MI
LIKE=LIKE+S-XMI*ALOG(SI)
RETURN
END
FUNCTION F2(DELTAR,C2)
  F2=l+(1-DELTAR)/C2
RETURN
END
FUNCTION F3(DELTAR,C2)
  F3=l+3*(1-DELTAR)/C2+(2-DELTAR)*(1-DELTAR)/C2**2
RETURN
END
FUNCTION F4(DELTAR,C2)
F4 = \frac{1+6(1-\Delta R)/C2+(1-\Delta R)(11-7\Delta R)/C2^2}{(3-\Delta R)(2-\Delta R)(1-\Delta R)/C2^3}

RETURN

SUBROUTINE MULT(N,A,B,C)
  DIMENSION A(N,N), B(N,N), C(N,N)
  DO 1 I=1,N
  DO 1 J=1,N
    C(I,J) = 0.0
  DO 1 K=1,N
    C(I,J) = C(I,J) + A(I,K)*B(K,J)
  1 CONTINUE
RETURN
END
REFERENCES


