CURE RATE AND DESTRUCTIVE CURE RATE MODELS UNDER PROPORTIONAL ODDS LIFETIME DISTRIBUTIONS
CURE RATE AND DESTRUCTIVE CURE RATE MODELS UNDER PROPORTIONAL ODDS LIFETIME DISTRIBUTIONS

BY
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TITLE: CURE RATE AND DESTRUCTIVE CURE RATE MODELS UNDER PROPORTIONAL ODDS LIFETIME DISTRIBUTIONS

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To my husband Dr. Hon-yiu So

To my parents Mr. Shenghu Feng, Ms. Jingping Yuan

To my grandmother Ms. Xiumei Tian
Abstract

Cure rate models, introduced by Boag (1949), are very commonly used while modelling lifetime data involving long time survivors. Applications of cure rate models can be seen in biomedical science, industrial reliability, finance, manufacturing, demography and criminology. In this thesis, cure rate models are discussed under a competing cause scenario, with the assumption of proportional odds (PO) lifetime distributions for the susceptibles, and statistical inferential methods are then developed based on right-censored data.

In Chapter 2, a flexible cure rate model is discussed by assuming the number of competing causes for the event of interest following the Conway-Maxwell (COM) Poisson distribution, and their corresponding lifetimes of non-cured or susceptible individuals can be described by PO model. This provides a natural extension of the work of Gu et al. (2011) who had considered a geometric number of competing causes. Under right censoring, maximum likelihood estimators (MLEs) are obtained by the use of expectation-maximization (EM) algorithm. An extensive Monte Carlo simulation study is carried out for various scenarios, and model discrimination between some well-known cure models like geometric, Poisson and Bernoulli is also examined. The goodness-of-fit and model diagnostics of the model are also discussed. A cutaneous melanoma dataset example is used to illustrate the models as well as the inferential methods.

Next, in Chapter 3, the destructive cure rate models, introduced by Rodrigues et al.
(2011), are discussed under the PO assumption. Here, the initial number of competing causes is modelled by a weighted Poisson distribution with special focus on exponentially weighted Poisson, length-biased Poisson and negative binomial distributions. Then, a damage distribution is introduced for the number of initial causes which do not get destroyed. An EM-type algorithm for computing the MLEs is developed. An extensive simulation study is carried out for various scenarios, and model discrimination between the three weighted Poisson distributions is also examined. All the models and methods of estimation are evaluated through a simulation study. A cutaneous melanoma dataset example is used to illustrate the models as well as the inferential methods.

In Chapter 4, frailty cure rate models are discussed under a gamma frailty wherein the initial number of competing causes is described by a Conway-Maxwell (COM) Poisson distribution in which the lifetimes of non-cured individuals can be described by PO model. The detailed steps of the EM algorithm are then developed for this model and an extensive simulation study is carried out to evaluate the performance of the proposed model and the estimation method. A cutaneous melanoma dataset as well as a simulated data are used for illustrative purposes.

Finally, Chapter 5 outlines the work carried out in the thesis and also suggests some problems of further research interest.

KEY WORDS: Cure rate models; Mixture model; Long-term survivors; COM-Poisson distribution; Weighted Poisson distribution; EM algorithm; Right censoring; Non-informative censoring; Profile likelihood; Asymptotic variances and covariances; Maximum likelihood estimation; Likelihood-ratio test; Exponential distribution; Proportional odds model; Weibull distribution; Log-logistic distribution; Gamma distribution; Mixture of chi-square;
Akaike Information Criterion (AIC); Bayesian Information Criterion (BIC); Model discrimination; Monte Carlo simulations; Goodness-of-fit test; Cutaneous melanoma.
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Notation and abbreviations

- AIC... Akaike Information Criterion
- BIC... Bayesian Information Criterion
- cdf...cumulative distribution function
- COM-Poisson...Conway-Maxwell Poisson
- CP...coverage probability
- i.i.d. ...independent and identically distributed
- MCMC...Markov chain Monte Carlo
- pdf...probability density function
- PO...proportional odds
- RMSE...root mean square error
- SE...standard error
- sf...survival function
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Chapter 1

Introduction

1.1 Cure rate model

Due to the significant progress in technology and medical science in the past several decades, it is highly likely that many patients can be cured and do not experience the disease again over a long period of time following a good prognosis and efficient treatment. So, the cured proportion of the overall population should not be ignored and becomes an important indicator for the effect of the treatment. Recently, the methodology that accounts for cure has received considerable wide attention in the survival analysis literature. The patients who are cured are called long-time survivors or immune individuals, while the others, who still experience the disease or relapse or recurrence of the disease, are called susceptibles. Statistical models accommodating such a surviving fraction are generally referred to as cure rate models.

The basic cure rate model can be seen as a two-component mixture model. Suppose we have an indicator variable $I$ such that $I = 0$ if the subject is immune/cured (belongs to set $I_0$) with probability $p_0$ and $I = 1$ if the subject is susceptible (belongs to set $I_1$) with
probability \(1 - p_0\), where \(p_0\) is the cure rate. The cumulative distribution function of the overall population can be viewed as a mixture of the two populations as follows:

\[
F_p(y) = P[Y \leq y|I = 0]P(I = 0) + P[Y \leq y|I = 1]P(I = 1)
= F_s(y)(1 - p_0);
\] (1.1)

thus, the survival function of the overall population is then evidently

\[
S_p(y) = p_0 + (1 - p_0)S_s(y),
\] (1.2)

where \(p_0\) is the probability of cure, \(S_s(y)\) is the survival function of the non-cured or susceptible individuals in the population, and \(F_s(y)\) is the corresponding distribution function of the susceptibles. It is to be noted that \(S_p(y)\) is an improper survival function since it approaches \(p_0\) as \(y\) goes to \(\infty\). The improper density function can be easily obtained as \(f_p(y) = -\frac{dS_p(y)}{dy}\). Moreover, a proper survival function of the susceptible population can be found from the overall population and the cure rate as

\[
S_s(y) = \frac{S_p(y) - p_0}{1 - p_0}, \quad y > 0.
\] (1.3)

More generally, a cure model can be approached through a competing risks set-up as follows. Suppose \(M\) is an unobservable random variable denoting the number of competing causes related to the occurrence of an event of interest. Let \(W_j, j = 1, \ldots, m\), be the random variable denoting the time-to-event for the \(j\)th competing cause. Given \(M = m\), \(W_1, \ldots, W_m\) are assumed to be independent and identically distributed (i.i.d.) with a common cumulative distribution function (c.d.f.) \(F(w) = 1 - S(w)\). Then, the population
time-to-event or lifetime is given by

\[ Y = \min\{W_0, W_1, \ldots, W_m\}, \]  

(1.4)

where \( W_0 \) is corresponding to the individual who are not susceptible to the event occurrence (namely, with infinite lifetime); that is, \( P(\omega_0 = \infty) = 1 \). This leads to a proportion of the cured group, known as cure rate. The survival function for the entire population is then given by [Rodrigues et al. (2009)]

\[ S_p(y) = \sum_{m=0}^{\infty} P(M = m)[S(y)]^m = A_M(S(y)), \]  

(1.5)

where \( A_M(\cdot) \) is the probability generating function (p.g.f.) of \( M \).

1.2 A brief literature review

The cure rate model was first introduced by Boag (1949) followed by Berkson and Gage (1952), and have been subsequently studied by many authors. Primarily, cure data have been analyzed in the literature by the structure of the underlying survival model of the non-cured individuals \( S_s(t) \) as proportional hazards (PH) mixture cure model [Peng and Dear (2000), Liu et al. (2012), and Sy and Taylor (2000)], accelerated failure time (AFT) mixture cure rate model [Zhang and Peng (2007), Lu (2010), and Li and Taylor (2002)], accelerated hazards (AH) mixture cure rate model [Zhang and Peng (2009)], and proportional odds (PO) mixture cure rate model [Gu et al. (2011), and Mao and Wang (2010)]. Later, Chen et al. (1999) pointed out that the mixture cure rate model has several drawbacks from both frequentist and Bayesian perspective, and so introduced a promotion time cure model from
Bayesian point of view.

Rodrigues et al. (2009) proposed the Conway-Maxwell-Poisson cure rate model by extending the model in Chen et al. (1999) and also including the models of Boag (1949) and Berkson and Gage (1952). Subsequently, these authors developed a destructive cure rate model which assumes the initial number of competing causes to undergo a destructive process due to a treatment, such as chemotherapy or radiation. This model has a more realistic interpretation of the underlying biological mechanism than the usual proportion time cure model.

Vaupel et al. (1979) introduced a frailty model which provides a convenient way to accommodate unobserved covariates and/or heterogeneity in survival data in the form of a frailty term. The frailty model was then studied by Clayton (1978) for bivariate data and Greenwood and Yule (1920) for recurrent data. Common choices for the frailty distribution is the gamma distribution and positive stable distribution [Hougaard (1986)] as they all have simple Laplace transforms and are therefore convenient to use. Balakrishnan and Peng (2006) introduced a generalized gamma frailty model, which includes gamma, Weibull and log-normal frailty models all as special cases.

Applications of cure rate models are not limited to biomedical studies, and can also be seen in many other fields such as industrial reliability, finance, manufacturing, demography, and criminology. For a detailed research in these applications, interested readers may refer to Klebanov et al. (1993), Ibrahim et al. (2005), and Hoggart and Griffin (2001).

1.3 COM-Poisson cure rate model

The Conway-Maxwell (COM) Poisson distribution, introduced by Conway and Maxwell (1962), is a generalization of the Poisson distribution allowing for under- and over-dispersion,
depending on the value of the dispersion parameter. It thus provides a continuous bridge between under- and over-dispersion.

Suppose the number of the competing causes $M$ follows a COM-Poisson distribution. The probability mass function (p.m.f.) of $M$ is given by

$$P(M = m; \eta, \phi) = \frac{1}{Z(\eta, \phi)} \frac{\eta^m}{(m!)^\phi}, \ m = 0, 1, 2, \ldots, \tag{1.6}$$

where the normalization constant is given by,

$$Z(\eta, \phi) = \sum_{j=0}^{\infty} \frac{\eta^j}{(j!)^\phi}, \tag{1.7}$$

with $\phi \geq 0$ and $\eta > 0$. Here, the proportion of cured individuals from the whole population is the probability of no competing risk, that is,

$$p_0 = P(M = 0; \eta, \phi) = (Z(\eta, \phi))^{-1}. \tag{1.8}$$

As a weighted Poisson random variable (r.v.), $M$ leads to a Poisson r.v. with mean equal to $\eta$ when $\phi = 1$, and $M$ leads to a under- or over-dispersion if $\phi > 1$ or $\phi < 1$ [see Shmueli et al. (2005), Kadane et al. (2006), and Kokonendji et al. (2008, 2009)]. For example, $M$ approaches the Bernoulli r.v. with parameter $\frac{1}{1+\eta}$ when $\phi \to \infty$ and $Z(\eta, \phi) \to 1 + \eta$, and $M$ reduces to a Geometric r.v. with parameter $1 - \eta$ if $\phi = 0$, $\eta < 1$ and $Z(\eta, \phi) = \frac{1}{1-\eta}$. Note that $M$ is undefined for $\eta \geq 1$ and $\phi = 0$. The population survival function and
density function of the time-to-event $Y$ is then

$$S_p(y) = \frac{Z(\eta S(y), \phi)}{Z(\eta, \phi)},$$  \hspace{1cm} (1.9)

$$f_p(y) = \frac{1}{Z(\eta, \phi)} \frac{f(y)}{S(y)} \sum_{j=1}^{\infty} \frac{j(\eta S(y))^j}{(j!)^\phi},$$  \hspace{1cm} (1.10)

Note that as $y \to \infty$, $S_p(y) \to p_0 > 0$. Hence, $S_p(y)$ is not a proper survival function.


### 1.4 Destructive weighted Poisson cure rate models

Suppose $M$ is an unobservable random variable representing the initial number of competing causes. Given $M = m$, let $X_j, j = 1, \ldots, m$, be independent Bernoulli variables with success probability $p \in (0, 1)$, independently of $M$. Define the following “damage” random variable $D$ for the number of initial competing causes which are still not destroyed:

$$D = \begin{cases} 
X_1 + X_2 + \cdots + X_M, & M > 0 \\
0, & M = 0.
\end{cases}$$  \hspace{1cm} (1.11)

The distribution of $D$, conditional on $M = m$, is known as the “damaged” distribution. It is distributed binomially with parameters $m$ and $p$; see Rodrigues et al. (2011) for details. Note that $D \leq M$. Also, $p = 1$ means no damage or destruction occurs. Given the undamaged number of initial competing causes $D = d$, let $W_j$ (latent) be the time-to-event associated with the $j$-th competing cause. In the competing causes scenario, the number of competing causes $D$ and the lifetimes $W$ associated with these causes are not observable.
latent variables). Given \( M = m, W_1, \ldots, W_D \) are assumed to be independent and identically distributed with common cumulative distribution function \( F(w) \) and survival function \( S(w) \). The observed lifetime is then given by

\[
Y = \min\{W_0, W_1, \ldots, W_D\},
\]

(1.12)

where \( P(w_0 = \infty) = 1 \) as before.

A random variable \( X \) follows a weighted Poisson distribution if its p.m.f. is given by

\[
p(x; \phi, \lambda) = \frac{\omega(x; \tau)p(x; \lambda)}{E_\lambda(\omega(X; \tau))},
\]

(1.13)

where \( \omega(X; \tau) \) is a non-negative weight function with parameter vector \( \tau \), \( p(x; \lambda) \) is the p.m.f. of a standard Poisson distribution with parameter \( \lambda > 0 \), and \( E_\lambda \) denotes the expectation with respect to \( p(x; \lambda) \), i.e.,

\[
E_\lambda(\omega(X; \tau)) = \sum_{x=0}^{\infty} \omega(x; \tau)p(x; \lambda).
\]

(1.14)

From the above weighted Poisson model, we focus here in this thesis on three special cases.

### 1.4.1 Destructive negative binomial cure rate model

Suppose \( M \) follows a weighted Poisson distribution with parameter \( \frac{\eta\phi}{1 + \eta\phi} \) and weighted function \( \Gamma(m + \frac{1}{\phi}) \) with \( \eta > 0 \) and \( \phi > 0 \), and with p.m.f. as,

\[
P[M = m; \eta, \phi] = \frac{\Gamma(m + \frac{1}{\phi})}{\Gamma(\frac{1}{\phi})m!} \left( \frac{\eta\phi}{1 + \eta\phi} \right)^m \left( \frac{1}{1 + \eta\phi} \right)^{\frac{1}{\phi}}, m = 0, 1, 2, 3, \ldots
\]

(1.15)
It can be seen that (1.15) is a negative binomial distribution with parameters $\eta > 0$ and $\phi > 0$. If we set $\phi = 1$, (1.15) becomes

$$P[M = m; \eta, \phi] = \left(\frac{\eta}{1 + \eta}\right)^m \frac{1}{1 + \eta}, \quad m = 0, 1, 2, 3, \ldots, \quad (1.16)$$

a geometric distribution with probability of success $\frac{1}{1+\eta}$. The mass function of the damage distribution $D$ in (1.11) in this case is

$$P[D = d; \eta, \phi, p] = \sum_{m=d}^{\infty} P(M = m; \eta, \phi)P(D = d|M = m) = \frac{\Gamma(d + \frac{1}{\phi})}{\Gamma(d + \frac{1}{\phi}d!)} \left(\frac{\eta\phi p}{1 + \eta\phi p}\right)^d \left(\frac{1}{1 + \eta\phi p}\right)^{\frac{d}{\phi}},$$

$$d = 0, 1, 2, 3, \ldots, m = 0, 1, 2, 3, \ldots, d \leq m, \quad (1.17)$$

which is also a negative binomial distribution. The cure rate then is,

$$P(D = 0; \eta, \phi, p) = \left(\frac{1}{1 + \eta\phi p}\right)^{\frac{1}{\phi}}. \quad (1.18)$$

The overall population survival function of the time-to-event $Y$ is given by

$$S_{p}(y) = P[Y > y] = \sum_{d=0}^{\infty} P(D = d)[S(y)]^d = (1 + \eta\phi pF(y))^{-\frac{1}{\phi}}.$$

It is to be noticed that the population function $S_{p}(y)$ defined above is not a proper survival function. The improper density function can be easily obtained as

$$f_{p}(y) = -\frac{\delta S_{p}(y)}{\delta y} = \frac{\eta pf(y)S_{p}(y)}{1 + \eta\phi pF(y)}. \quad (1.19)$$
1.4.2 Destructive exponentially weighted Poisson cure rate model

Suppose $M$ follows a weighted Poisson distribution with parameter $\eta > 0$ and exponential weight function $e^{\phi m}$, where $\phi \in \mathbb{R}$, i.e.,

$$P[M = m; \eta, \phi] = e^{-\eta \phi} \frac{(\eta e^{\phi})^m}{m!}, \quad m = 0, 1, 2, 3, \ldots$$

(1.20)

It can be seen that (1.20) is a Poisson distribution with parameter $\eta e^{\phi}$. If $\phi = 0$, (1.20) becomes

$$P[M = m; \eta, \phi] = e^{-\eta m} \frac{\eta^m}{m!}, \quad m = 0, 1, 2, 3, \ldots$$

(1.21)

a Poisson distribution parameter $\eta$. The p.m.f. of $D$ is,

$$P[D = d; \eta, \phi, p] = e^{-\eta p e^{\phi}} \frac{(\eta p e^{\phi})^d}{d!}, \quad d = 0, 1, 2, 3, \ldots, m = 0, 1, 2, 3, \ldots, d \leq m.$$  

(1.22)

The cure rate in this case is,

$$P(D = 0; \eta, \phi, p) = e^{-\eta p e^{\phi}}.$$  

(1.23)

The overall population survival function of the time-to-event $Y$ is given by

$$S_p(y) = P[Y > y] = \sum_{d=0}^{\infty} P(D = d) [S(y)]^d = \sum_{d=0}^{\infty} e^{-\eta p e^{\phi}} \frac{(\eta p e^{\phi} S(y))^d}{d!} = e^{-\eta p e^{\phi} F(y)}.$$  

9
The corresponding density function is given by

\[ f_p(y) = S_p(y)f(y)\eta p e^\phi \]  

(1.24)

### 1.4.3 Destructive length-biased Poisson cure rate model

Suppose \( M \) follows a weighted Poisson distribution with parameter \( \eta > 0 \) and weight function \( m \), i.e.,

\[ P[M = m; \eta, \phi] = \frac{m e^{-\eta m}}{m!} = e^{-\eta} \frac{\eta^{m-1}}{(m-1)!}, m = 0, 1, 2, 3, \ldots \]  

(1.25)

It is to be noted that \( D \) is a weighted Poisson random variable with parameter \( \eta p \) and a weighted function \( d + \eta(1 - p) \). The p.m.f. of \( D \) is as follows,

\[ P[D = d; \eta, p] = \frac{e^{-\eta p}(\eta p)^d}{d!} \left(1 - p + \frac{d}{\eta}\right), \]

\[ d = 0, 1, 2, 3, \ldots, m = 0, 1, 2, 3, \ldots, d \leq m, \]  

(1.26)

The cure rate in this case is,

\[ p_0 = P(D = 0; \eta, p) = (1 - p) e^{-\eta p}. \]  

(1.27)

The overall population survival function of the time-to-event \( Y \) is given by

\[ S_p(y) = P[Y > y] = \sum_{d=0}^{\infty} P(D = d)[S(y)]^d = e^{-\eta p F(y)}(1 - p F(y)), \]
and the corresponding p.d.f. is,

\[ f_p(y) = p\left\{ \eta + \frac{1}{1 - pF(y)} \right\} S_p(y)f(y) \]  \hspace{1cm} (1.28)

For a detailed discussion on the three special cases of the weighted Poisson model, interested readers may refer to Balakrishnan and Pal (2013, 2016), and Pal and Balakrishnan (2016, 2017, 2018).

### 1.5 Proportional odds model for lifetime data

In this thesis, we assume a proportional odds model for the distribution of \( W_j \) with a parametric assumption on the baseline odds function. To be more specific, the odds function of \( W_j \) is taken as

\[ O(w) = \theta O_0(w), \]  \hspace{1cm} (1.29)

where \( O(w) = S(w)/F(w) \) is the odds of survival up to \( w \), the proportionality term \( \theta \) is linked to covariates as \( e^{x_c'\gamma_2} \) with \( x_c = (x_1, \ldots, x_p)' \) being a vector of \( p \) covariates, \( \gamma_2 = (\gamma_{21}, \ldots, \gamma_{2p})' \) is the proportional odds regression coefficients, and \( O_0(w) \) is the baseline odds function. We can further obtain the survival function of \( W_j \) as

\[ S(w) = \left[ 1 + e^{-x_c'\gamma_2}(S_0(w)^{-1} - 1) \right]^{-1}, \]  \hspace{1cm} (1.30)

with the corresponding probability density function (p.d.f.)

\[ f(w) = f_0(w)e^{-x_c'\gamma_2}\left[ (1 - S_0(w))e^{-x_c'\gamma_2} + S_0(w) \right]^{-2}. \]  \hspace{1cm} (1.31)
where $S_0$ and $f_0$ are the baseline survival function and baseline p.d.f., respectively.

In this thesis, two different baseline distributions for the proportional odds survival model corresponding to the time-to-event random variable are considered, namely, Weibull and log-logistic distributions. It should also be noted that the log-logistic distribution in fact processes the proportional odds property, while the Weibull distribution does not.

### 1.5.1 Proportional odds model with Weibull baseline

The survival function of $W$ under a proportional odds model with Weibull baseline is

$$S(w; \gamma) = \left[1 + e^{-\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1}\right]^{-1}, w > 0,$$

and the corresponding p.d.f. is

$$f(w; \gamma) = \left(\gamma_1 w\right)^{1/\gamma_0} e^{\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1 - 1} \left[e^{\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1} + 1\right]^{-2}/(\gamma_0 w), w > 0,$$

where $\gamma_0 > 0$ and $\gamma_1 > 0$ are the shape and scale parameters, respectively.

### 1.5.2 Proportional odds model with log-logistic baseline

Suppose the baseline distribution is a log-logistic distribution with $\gamma_0 > 0$ and $\gamma_1 > 0$ as the scale and shape parameters, respectively. Then, the corresponding odds function of $W_i$ is given by

$$O(w; x_i^\gamma, \gamma) = \frac{\gamma_0 \gamma_1 w^{\gamma_1} e^{\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1}}{w^{\gamma_1} e^{\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1}} = O_0(w; \gamma_0, \gamma_1) e^{\gamma_0 \gamma_1 w (e^{\gamma_1 w})^{1/\gamma_0} - 1}.$$

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We observe that $W_i$ still follows a two-parameter log-logistic distribution $(\gamma_0, \gamma_1 > 0)$ with shape parameter $\gamma_1$ and scale parameter $\gamma_0 e^{-x^\prime \gamma_2 / \gamma_1}$, and with corresponding survival function

$$S(w, \gamma) = \frac{\gamma_0^{\gamma_1} e^{x^\prime \gamma_2}}{\gamma_0^{\gamma_1} e^{x^\prime \gamma_2} + w^{\gamma_1}}, w > 0.$$ (1.35)

Note that the mean does not exist if $\gamma_1 < 1$ and the variance does not exist if $\gamma_1 < 2$.  

### 1.6 Gamma frailty proportional odds model

Frailty models provide a convenient way to accommodate unobserved covariates and/or heterogeneity in survival data in the form of a frailty term. Assume a proportional odds model with frailty term for the distribution of $W_j$ ($j = 1, 2, \ldots$), with a parametric assumption on the baseline odds function. To be more specific, the odds function of $W_j$ is taken as

$$O(w|\theta) = r \theta O_0(w)$$ (1.36)

where $O(w) = S(w)/F(w)$ is the odds of survival up to time $w$, the probability term $\theta$ is linked to covariates as $e^{\alpha x_e}$ with $x_e = (x_1, \ldots, x_p)'$ is a vector of $p$ covariates, $\alpha = (\alpha_1, \ldots, \alpha_p)'$ is the proportional odds regression coefficients, $O_0(w)$ is the baseline odds function, and $r$ is the frailty parameter following a gamma distribution with shape $k > 0$ and scale $\xi > 0$. The mean and variance of $r$ is $k/\xi$ and $k/\xi^2$, respectively. Here, we set mean equal to 1 to avoid non-identifiability in the model so that $k = \xi$. Therefore, the p.d.f.
of \( r \) can be written as

\[
f(r) = \frac{r^{\xi-1}e^{-r\xi}}{\Gamma(\xi)}, \quad r \geq 0, \quad \xi > 0.
\] (1.37)

We can further obtain the survival function of \( W_j \), through unconditioning, as

\[
S(t_i) = \int_0^\infty \frac{r_i S_0(t_i)e^{\alpha x_i}}{r_i S_0(t_i)e^{\alpha x_i} + F_0(t_i)} f_r(r_i) dr_i, \quad t_i > 0,
\] (1.38)

with the corresponding probability density function (p.d.f.) as

\[
f(t_i) = \int_0^\infty \frac{r_i f_0(t_i)e^{\alpha x_i}}{(r_i S_0(t_i)e^{\alpha x_i} + F_0(t_i))^2} f_r(r_i) dr_i, \quad t_i > 0.
\] (1.39)

### 1.6.1 Gamma frailty proportional odds model with Weibull baseline

The survival function of \( W \) under a gamma frailty proportional odds model with Weibull baseline is given by

\[
S(w, \gamma) = \int_0^\infty [1 + e^{-\alpha x_i}/r_i(e^{(\gamma_1 w)^{1/\gamma_0}} - 1)]^{-1} f_r(r_i) dr_i, \quad w > 0,
\] (1.40)

and the corresponding p.d.f. is

\[
f(w, \gamma) = \int_0^\infty (\gamma_1 w)^{1/\gamma_0} r_i e^{\alpha x_i} e^{-(\gamma_1 w)^{1/\gamma_0} [e^{(\gamma_1 w)^{1/\gamma_0} (r_i e^{\alpha x_i} - 1) + 1} - 1]} f_r(r_i) dr_i, \quad w > 0,
\] (1.41)

where \( \gamma_0 > 0 \) and \( \gamma_1 > 0 \) are the shape and scale parameters, respectively.
1.6.2 Gamma frailty proportional odds model with log-logistic baseline

Suppose the baseline distribution is a log-logistic distribution with \( \gamma_0 > 0 \) and \( \gamma_1 > 0 \) as the scale and shape parameters, respectively. Then, the corresponding odds function of \( W_i \) is given by

\[
O(w_i; x, \gamma) = \frac{\gamma_1 w_i^{\gamma_1}}{\gamma_0^{\gamma_1}} e^{\alpha' x} = r_i O_0(w_i; \gamma_0, \gamma_1) e^{\alpha' x}. \tag{1.42}
\]

We observe that \( W_i \) still follows a two-parameter log-logistic distribution \((\gamma_0, \gamma_1 > 0)\) with shape parameter \( \gamma_1 \) and scale parameter \( \gamma_0 e^{-\alpha' x / \gamma_1} \), and with corresponding survival function

\[
S(w_i, \gamma) = \int_{0}^{\infty} \frac{\gamma_1 w_i^{\gamma_1}}{\gamma_0^{\gamma_1} e^{\alpha' x} + w_i^{\gamma_1}} f_r(r_i) dr_i, \ w_i > 0. \tag{1.43}
\]

Note that the mean does not exist if \( \gamma_1 < 1 \) and the variance does not exist if \( \gamma_1 < 2 \).

1.7 Data and the likelihood

Suppose the time-to-event is not completely observed and is subject to non-informative right censoring, which means that the data above a certain value is not observed. Therefore, the observation time \( T_i \), for the \( i \)th subject, would be the minimum of the censoring time \( C_i \) and the actual lifetime \( Y_i \), i.e.,

\[
T_i = \min\{Y_i, C_i\}, i = 1, \ldots, n. \tag{1.44}
\]
We define an indicator function \( \delta_i = I(Y_i \leq C_i) \) for the \( i \)-th subject such that \( \delta_i = 1 \) if the lifetime is observed while \( \delta_i = 0 \) if the lifetime is right censored. \( \Delta_0 \) and \( \Delta_1 \) are sets with all the \( i \)'s equal to 0 and 1, respectively, and set \( \Delta^* \) contains all the \( i \)'s. It is to be noted that the cure rate \( p_0 = Z(\eta, \phi)^{-1} \) is purely a function of \( \eta \) for a fixed value of \( \phi \). The range of \( 1/p_0 \) is from 1 to infinity and it is monotone in \( \eta \). Therefore, it is natural to use a logistic regression model \( H_\phi(\eta) = 1 + e^{x_i^T \beta} \) to link the covariate \( x_i \) to the cured proportion \( p_0 \), i.e.,

\[
 p_{0i} = p_0(\beta, x_i) = Z(\eta, \phi)^{-1} = H_\phi(\eta)^{-1} = (1 + e^{x_i^T \beta})^{-1},
\]

where \( p_{0i} \) is the cured proportion for the \( i \)th category, \( x_i = (1, x_{ic}, x_i')' = (1, x_{i1}, \ldots, x_{ip})' \) is a vector of \( p + 1 \) covariates, and \( \beta \) is the vector of regression coefficients. Under this link function, \( \eta \) would equal \( H^{-1}(1 + e^{x_i^T \beta}) \), i.e., \( \eta \) can be calculated from the inverse function of \( H_\phi(.) \) analytically for the Geometric, Poisson and Bernoulli distributions, and by using numerical method for the general COM-Poisson distribution.

For \( n \) pairs of observations \( \{(t_1, \delta_1), \ldots, (t_n, \delta_n)\} \), the observed data likelihood function under the non-informative censoring is then given by

\[
 L(\theta; t, \delta) \propto \prod_{i=1}^{n} \{f_p(t_i; \theta)\}^{\delta_i} \{S_p(t_i; \theta)\}^{1-\delta_i},
\]

where \( \theta \) is the set of parameters \( (\phi, \beta', \gamma') \), which is equivalent to

\[
 L(\theta; t, \delta) \propto \prod_{i=1, \{\delta_i=1\}} f_p(t_i; \theta) \prod_{i=1, \{\delta_i=0\}} S_p(t_i; \theta)
 = \prod_{i \in \Delta_1} f_p(t_i; \theta) \prod_{i \in \Delta_0} \{p_0 + (1 - p_0)S_s(t_i; \theta)\}.
\]
1.8 Likelihood inference

1.8.1 EM algorithm

We develop here an Expectation-Maximization (EM) algorithm for obtaining the MLE of $\theta$, and a profile likelihood approach for the estimation of the dispersion parameter $\phi$. It is well-known that EM is an effective technique for finding the MLEs of unknown parameters of a model involving unobserved variables (for further discussion, refer to McLachlan and Krishnan (2007)). In our model, the random variable $I_i$’s are observed for $i$ in the set $\Delta_1$ and unobserved for $i$ in the set $\Delta_0$, where $I_i = 1$ if the individual is susceptible and $I_i = 0$ if the individual is cured. Let us denote the set of complete data by $(t, \delta, x, I) = \{(t_1, \delta_1, x_1, I_1), \ldots, (t_n, \delta_n, x_n, I_n)\}$. The complete data likelihood function is then

$$L_c(\theta; t, x, \delta, I) \propto \prod_{i \in \Delta_1} f_p(t_i, x_i, \theta) \prod_{i \in \Delta_0} p_0(\beta, x_i)^{1-I_i} [(1 - p_0(\beta, x_i))S(t_i, x_{ic}; \theta)]^{I_i}, \quad (1.48)$$

where $I = (I_1, \ldots, I_n)'$, $x_{ic} = (x_{i1}, \ldots, x_{ip})'$ and $x_i = (1, x_{ic}')'$. The corresponding complete log-likelihood function

$$l_c(\theta; t, x, \delta, I) = \text{constant} + \sum_{i \in \Delta_1} \log f_p(t_i, x_i, \theta) + \sum_{i \in \Delta_0} (1 - I_i) \log p_0(\beta, x_i)$$

$$+ \sum_{i \in \Delta_0} I_i \log [1 - p_0(\beta, x_i)] + \sum_{i \in \Delta_0} I_i \log S(t_i, x_{ic}; \theta). \quad (1.49)$$
1.8.2 E-step

The expectation step is achieved by calculating the expected value of the complete data log-likelihood function with respect to the conditional distribution of the unobserved \( I_i \)'s \((i \in \Delta_0)\), given the observed data \( O = \{(t_i, \delta_i, x_i), i \in \Delta_1\} \) and the current estimates of the parameters \( \theta^{(k)} = (\beta', \gamma')' \) for a fixed value of \( \phi \). Let us denote this function as

\[
Q(\theta, \pi^{(k)}) = E(l_c(\theta; t, x, \delta, I)|O, \theta^{(k)}),
\]

(1.50)

at the \( k \)-th iteration step. In our model, \( I_i \)'s are Bernoulli random variables and we can easily find the conditional expectation if the \( i \)th individual is susceptible as

\[
\pi^{(k)}_i = E(I_i|O, \theta^{(k)})
\]

\[
= P(I_i = 1|T > t)
\]

\[
= \frac{(1 - p_0(\beta^{(k)}, x_i))S_s(t_i, x_{ic}; \theta^{(k)})}{S_p(t_i, x_i; \theta^{(k)})}\bigg|_{\theta=\theta^{(k)}}.
\]

(1.51)

Now, for a fixed value of \( \phi \), the \( Q \) function is given by

\[
Q(\theta, \pi^{(k)}) = \sum_{I \in \Delta_1} \log f_p(t_i, x_i, \theta) + \sum_{i \in \Delta_0} (1 - \pi^{(k)}_i) \log p_0(\beta, x_i)
\]

\[
+ \sum_{i \in \Delta_0} \pi^{(k)}_i \log(1 - p_0(\beta, x_i)) + \sum_{i \in \Delta_0} \pi^{(k)}_i \log S_s(t_i, x_{ic}; \theta).
\]

(1.52)
1.8.3 M-step

The M-step is done by maximizing the $Q(\theta, \pi^{(k)})$ function in (1.52) in order to obtain the improved estimate of $\theta$, i.e.,

$$\theta^{*(k+1)} = \arg \max_{\theta} Q(\theta, \pi^{(k)}).$$  \hspace{1cm} (1.53)

The MLEs of $\beta$ and $\gamma$ do not have explicit expressions. Here, the numerical maximization is carried out by Newton-Raphson method.

For a fixed value of $\phi$, the E-step and M-step are alternated until the parameter estimate converges to a desired level of accuracy. The parameter $\phi$ is determined by using the profile likelihood technique. For this purpose, we consider a range of $\phi$ with small increment, and then for each value of $\phi$, the MLEs of other parameters are found, and the estimate with the largest likelihood is chosen as the final estimate. The explicit forms of the first- and second-order derivatives of the Q function as well as the update function for the case of COM-Poisson distribution and the special cases are presented in the Appendix.

1.8.4 Estimation of standard errors

We may approximate the asymptotic variance-covariance matrix of the MLEs $(\hat{\beta}', \hat{\gamma}')'$ by inverting the observed Fisher information matrix of $\beta$ and $\gamma$, for a fixed value of $\phi$. The components of the observed Fisher information matrix can then be calculated from the negative of the second-order derivatives of the complete data likelihood function with respect to $\beta$ and $\gamma$ (for detailed information, refer to Louis (1982)). Thus, we can obtain the standard errors of the estimates and then construct corresponding asymptotic confidence intervals for the parameters.
1.8.5 Estimation of the cure rate and its standard error

Suppose \( \hat{\beta} \) is the MLE of the regression coefficient \( \beta \). The estimated cure rate for the corresponding group \( i \) is a function of \( \hat{\beta} \). The standard error of \( \hat{p}_{0i} \) can then be found through delta method as

\[
\text{sd}(\hat{p}_{0i}) = \sqrt{\left( \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, \ldots, \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_p} \right) \text{var} \hat{\beta} \left( \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, \ldots, \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_p} \right)'}.
\]  

(1.54)

1.9 Simulation study and real data analysis

The accuracy, precision, and robustness of the models and the estimation techniques are studied and validated using extensive Monte Carlo simulations. Different scenarios are considered in the simulation studies by varying sample sizes, censoring proportions, cure rates, and the parameters in different distributions. The estimates were calculated through EM method. The empirical Bias, standard errors(SE), root Mean Square Error (RMSE), and 95% coverage probabilities (CPs) are all reported. In addition, the estimated cure rate with corresponding SEs and 95% CPs are also computed. The codes corresponding to the different methods are written in R software with version 3.2.2. The McMaster math department computer Bayes, Anatolius and the shared Hierarchical Academic Research Computing Network (SHARCNET) were used to compile all the R-codes.

For model validation and model discrimination, for the COM-Poisson model, the asymptotic distribution of the test statistic \( \Lambda \), under \( H_0 : \phi = 1 \) follows a \( \chi^2 \) distribution with one degree of freedom. However, the distribution of the test statistic \( \Lambda \) in the boundary cases when \( \phi = 0 \) (Geometric) and \( \phi \rightarrow \infty \) (Bernoulli) has a mixture distribution of \( \chi^2_0 \) and \( \chi^2_1 \) distributions such that \( P(\Lambda \leq \lambda) = \frac{1}{2} + \frac{1}{2} P(\Lambda_1 \leq \lambda_1) \), where \( \Lambda_1 \sim \chi^2_1 \), \( \chi^2_0 \) is chi-square
distribution with 0 degrees of freedom and $\chi^2_1$ is the chi-square distribution with one degree of freedom.

In this thesis, we consider a malignant cancer data, a cutaneous melanoma data, to illustrate the performance of the proposed model and the fitting methodology. These data were first introduced by Kirkwood et al. (2000), and subsequently studied by many authors including Balakrishnan and Pal (2012, 2014, 2015, 2016), Balakrishnan et al. (2017), and Rodrigues et al. (2009). These data were taken from Ibrahim et al. (2005), and were originally used to detect the prospective treatment performance on the high-dose interferon alfa-2b therapy in order to prevent the recurrence of the disease. The study included 427 patients in total from years 1991 to 1995 and followed up until year 1998. Among them, 10 patients were removed in our analysis due to the missingness of the tumor thickness data. The overall percentage of censored observations is 55.6%. The mean and standard deviation of the observed lifetimes are 3.18 and 1.69 in years, respectively. We choose the nodule categories based on the tumor thickness as the only covariate. The subjects were therefore divided into four different nodule categories ($x = 0, 1, 2, 3$), with corresponding sample sizes $n_1 = 111$, $n_2 = 137$, $n_3 = 87$, and $n_4 = 82$. The percentage of censored observations for the group were 67.57%, 61.31%, 52.87%, 32.93%. See Figure 1.1 for a plot of the lifetimes of susceptibles for these four nodule categories.
Another dataset considered in this thesis is the one available in the “timereg” package in R software [see Andersen et al. (2017), and Drzewiecki et al. (1980)], which is a well-known dataset in the literature and studied by many authors including Rodrigues et al. (2011). It includes 205 patients (refer to Figure 1.2) corresponding to the survival of individuals after operation for malignant melanoma and collected at Odense University Hospital by K.T. Drzewiecki during the period 1962 to 1977 and followed until 1977. Among them, there were 57 and 14 patients died from melanoma and other causes, respectively. All rest of them were alive at the end of the study and thus censored.

Figure 1.1: Lifetime of the susceptibles of the four nodule categories in the cutaneous melanoma data
1.10 Scope of the thesis

The following chapters present the detailed choice of link function, specific likelihood function, Q function, step by step EM algorithm, simulation study results and the data analysis results for each described cure rate model. In Chapter 2, a flexible cure rate model is presented by assuming the number of competing causes for the event of interest to follow the COM-Poisson distribution. The lifetimes of susceptible individuals follow a PO model. In Chapter 3, we introduce a flexible destructive cure rate model for lifetime data. We assume the number of competing causes of the event of interest to follow the Weighted Poisson distribution (including LBP, NB, and EWP models) and the lifetimes of the non-cured individuals to follow a proportional odds survival model. The baseline odds distribution is
considered to be either Weibull or Log-logistic distribution. A damage distribution is introduced due to the fact that some of the competing causes may not remain active following a treatment. In Chapter 4, we introduce a gamma frailty cure rate model for lifetime data by assuming the number of competing causes for the event of interest to follow the COM-Poisson distribution and the lifetimes of the non-cured individuals to follow a proportional odds model. The baseline distribution is considered to be either Weibull or Log-logistic distribution. Statistical inference is then developed under right censored data.

For all the models considered, we derive the maximum likelihood estimators (MLEs) with the full usage of expectation maximization (EM) method for all the model parameters, except the dispersion parameter, which is estimated by a profile likelihood approach. Detailed expressions for the Q-functions, the first- and second-derivatives of the Q-functions and the observed information matrix, corresponding to different cure rate models discussed in each chapter, are all presented in Appendices A-C. The model discrimination among some well-known special cases are discussed using both likelihood- and information-based criteria. An extensive Monte Carlo simulation study is carried out by varying censoring rates, sample sizes, distributional parameters, and the cure rates to examine the performance of the proposed model as well as the inferential methods developed in the thesis. Analysis of the cutaneous melanoma data is also carried out for illustrative purposes.
Chapter 2

COM-Poisson Cure Rate Model under Proportional Odds Lifetimes

2.1 Introduction

In this Chapter, we assume a proportional odds model for the distribution of lifetime variable of a susceptible individual $W_j$, with a parametric assumption on the baseline odds function. To be more specific, the odds function of $W_j$ is taken as

$$O(w; x_c) = \theta O_0(w),$$  \hspace{1cm} (2.1)

where $O(w) = S(w)/F(w)$ is the odds of survival up to $w$, the proportionality term $\theta$ is linked to covariates as $e^{x_c' \gamma_2}$ with $x_c = (x_1, \ldots, x_p)'$ being a vector of $p$ covariates, $\gamma_2 = (\gamma_{21}, \ldots, \gamma_{2p})'$ is the vector of proportional odds regression coefficients, and $O_0(w)$
is the baseline odds function. We can then obtain the survival function of $W_j$ as

$$S(w) = [1 + e^{-x'_c \gamma_2} (S_0(w)^{-1} - 1)]^{-1},$$

with the corresponding probability density function (p.d.f.) as

$$f(w) = f_0(w)e^{-x'_c \gamma_2}[(1 - S_0(w))e^{-x'_c \gamma_2} + S_0(w)]^{-2}.$$  \hspace{1cm} (2.3)

The rest of this chapter proceeds as follows. Section 2.2 describes the data and the likelihood, while the estimation of the cure rate and associated inferential issues are discussed in Section 2.3. In Section 2.4, an extensive Monte Carlo simulation study is carried out. In Section 2.5, we discuss model discrimination using information- and likelihood-based methods. A data on cutaneous melanoma is analyzed in Section 2.6 finally for illustrative purpose.

## 2.2 Data and the likelihood

Suppose the time-to-event is not completely observed and is subject to non-informative right censoring, which means that the data above a certain value are not observed. Therefore, the observation time $T_i$ for the $i$th subject, would be the minimum of the censoring time $C_i$ and the actual lifetime $Y_i$, i.e.,

$$T_i = \min \{Y_i, C_i\}, i = 1, \ldots, n.$$  \hspace{1cm} (2.4)

We define an indicator function $\delta_i = I(Y_i \leq C_i)$ for the $i$-th subject such that $\delta_i = 1$ if the lifetime is observed while $\delta_i = 0$ if the lifetime is right censored, $\Delta_0$ and $\Delta_1$ are sets with
all the $i$'s equal to 0 and 1, respectively, and set $\Delta^*$ contains all the $i$'s. It is to be noted
that the cure rate $p_0 = Z(\eta, \phi)^{-1}$ is purely a function of $\eta$ for a fixed value of $\phi$. The range
of $1/p_0$ is from 1 to $\infty$ and it is monotone in $\eta$. Therefore, it is natural to use a logistic
regression model $H_\phi(\eta) = 1 + e^{x'_i\beta}$ to link the covariate $x_1, \ldots, x_p$ to the cured proportion
$p_{0i}$, i.e.,

$$p_{0i} = p_0(\beta, x_i) = Z(\eta, \phi)^{-1} = H_\phi(\eta)^{-1} = (1 + e^{x'_i\beta})^{-1},$$  \hspace{1cm} (2.5)$$

where $p_{0i}$ is the cured proportion for the $i$th category, $x_i = (1, x_{ic}')' = (1, x_{i1}, \ldots, x_{ip})'$ is
a vector of $p + 1$ covariates, and $\beta$ is the vector of regression coefficients. Under this link,
$\eta$ would equal $H^{-1}(1 + e^{x'_i\beta})$, i.e., $\eta$ can be calculated from the inverse function of $H_\phi(.)$
analytically for the Geometric, Poisson and Bernoulli distributions, and by using numerical
method for the general COM-Poisson distribution.

For $n$ pairs of observations $(t, \delta) = \{(t_1, \delta_1), \ldots, (t_n, \delta_n)\}$, the observed data likelihood
function under the non-informative censoring is then given by

$$L(\theta; t, \delta) \propto \prod_{i=1}^{n} \left\{ f_p(t_i; \theta) \right\}^{\delta_i} \left\{ S_p(t_i; \theta) \right\}^{1-\delta_i},$$ \hspace{1cm} (2.6)$$

where $\theta$ is the set of parameters $(\phi, \beta', \gamma')$, which is equivalent to

$$L(\theta; t, \delta) \propto \prod_{i \in \Delta_1} f_p(t_i; \theta) \prod_{i \in \Delta_0} \{ p_0 + (1 - p_0)S_s(t_i; \theta) \}. \hspace{1cm} (2.7)$$

Here, we consider two baseline distributions for the proportional odds survival model cor-
responding to the time-to-event random variable, namely, Weibull and log-logistic distribu-
tions. It should also be noted that log-logistic distribution in fact processes the proportional
odds property, while the Weibull distribution does not. The survival function and p.d.f. of $W$ under a Weibull baseline, for example, are

$$S(w, \gamma) = [1 + e^{-x^t \gamma_2 (e^{(\gamma_1 w)^1/\gamma_0} - 1)}]^{-1}, w > 0,$$

$$f(w, \gamma) = (\gamma_1 w)^{1/\gamma_0} e^{x^t \gamma_2 - (\gamma_1 w)^1/\gamma_0} \left[ e^{-(\gamma_1 w)^1/\gamma_0} (e^{x^t \gamma_2} - 1) + 1 \right]^{-2} / (\gamma_0 w),$$

where $w > 0$, $\gamma_0 > 0$ and $\gamma_1 > 0$ are the shape and scale parameters of the baseline Weibull distribution, respectively. On the other hand, if we assume the baseline distribution to be a log-logistic distribution with $\gamma_0 > 0$ and $\gamma_1 > 0$ as the scale and shape parameters, respectively, then the corresponding odds function of $W_i$ is given by

$$O(w, ; x^t, \gamma) = \frac{\gamma_1}{w \gamma_0} e^{x^t \gamma_2} = O_0(w, ; \gamma_0, \gamma_1) e^{x^t \gamma_2}.$$  

We observe that $W_i$ still follows a two-parameter log-logistic distribution ($\gamma_0, \gamma_1 > 0$) with shape parameter $\gamma_1$ and scale parameter $\gamma_0 e^{-x^t \gamma_2 / \gamma_1}$, and with corresponding survival function

$$S(w, \gamma) = \frac{\gamma_0}{\gamma_1} e^{x^t \gamma_2} / (\gamma_0 e^{x^t \gamma_2} + w \gamma_0), w > 0.$$  

Note that the mean does not exist if $\gamma_1 < 1$ and the variance does not exist if $\gamma_1 < 2$.

### Results for the Special cases of COM-Poisson cure rate model

As mentioned earlier, the COM-Poisson distribution includes the Bernoulli, Poisson and Geometric distributions as special cases. Here, we detail the steps of the EM algorithm for the corresponding three special cure models.
**Bernoulli cure rate model**

Let the competing cause random variable $M$ follow a Bernoulli distribution with probability of success $\eta/(1 + \eta)$. The probability density function for the whole population can then be expressed as

$$f_p(t_i; \theta) = \frac{\eta}{1 + \eta} f(t_i; \gamma). \quad (2.12)$$

The survival function for the susceptible group is just the survival function for the time to event $W$, i.e., $S_s(t_i; \theta) = S(t_i; \gamma)$. The inverse of the cure rate under this setting is $1/p_0 = 1 + \eta$. We, therefore, have $H_\phi(\eta) = 1 + \eta$ under the logistic link with a fixed value of $\phi$, which implies $\eta = e^{x_i' \beta}$. The $Q(\theta^*, \pi^{(k)})$ function is then given by

$$Q(\theta^*, \pi^{(k)}) = Q_1(\beta, \pi^{(k)}) + Q_2(\gamma, \pi^{(k)}), \quad (2.14)$$

$$Q_1(\gamma, \pi^{(k)}) = \sum_{i \in \Delta_1} \log f(t_i; x_i, \gamma) + \sum_{i \in \Delta_0} \pi_i^{(k)} \log S(t_i; x_{ic}, \gamma), \quad (2.15)$$

$$Q_2(\beta, \pi^{(k)}) = \sum_{i \in \Delta_1} x'_i \beta - \sum_{i \in \Delta_0} \log(1 + e^{x_i' \beta}) + \sum_{i \in \Delta_0} \pi_i^{(k)} x'_i \beta, \quad (2.16)$$

It is readily seen that some of the terms in the $Q$ function are only corresponding to $\beta$ while the others are only corresponding to $\gamma$. So, it can be split into two parts as follows:
with the update step

\[
\pi^{(k)}_i = \frac{e^{x_i'\beta^{(k)}} S(t_i; \gamma^{(k)})}{1 + e^{x_i'\beta^{(k)}} S(t_i; \gamma^{(k)})}
\]  

(2.17)

for the \(i\)th censored observation. The required first- and second-order derivatives of \(Q(\theta^*, \pi^{(k)})\) with respect to \(\beta\) and \(\gamma\) are as follows:

\[
\frac{\partial Q}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_j},
\]

\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} x_{il} - \sum_{i \in \Delta^*} x_{il}e^{x_i'\beta} + \sum_{i \in \Delta_0} \pi^{(k)} x_{il},
\]

\[
\frac{\partial^2 Q}{\partial \beta_l \partial \beta_{l'}} = -\sum_{i \in \Delta^*} x_{il}x_{il'}e^{x_i'\beta}, \quad (1 + e^{x_i'\beta})^2,
\]

\[
\frac{\partial^2 Q}{\partial \gamma_j \partial \gamma_{j'}} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log S^2(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}},
\]

for \(l, l' = 0, \ldots, p, j, j' = 1, 2, h = 21, \ldots, 2p\), \(i = 1, \ldots, n\).

**Poisson cure rate model**

Let the competing cause random variable \(M\) follow a Poisson distribution. The probability density function for the whole population in this case can be expressed as

\[
f_p(t_i; \theta) = [\log(1 + e^{x_i'\beta})] f(t_i; \gamma)(1 + e^{x_i'\beta})^{(S(t_i; \gamma) - 1)},
\]

(2.18)

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and the survival function for the susceptible group as

\[ S_s(t_i; \theta) = [(1 + e^{x_i \beta})S(t_i; \gamma) - 1]e^{-x_i \beta}. \]  \hspace{1cm} (2.19)

The cure rate is \( p_0 = e^{-\eta} \). We would then have \( H_0(\eta) = e^\eta \) under the logistic link function with a fixed value of \( \phi \), which implies that \( \eta = \ln(1 + e^{x_i \beta}) \). The \( Q(\theta^*, \pi^{(k)}) \) function is then given by

\[ Q = \sum_{i \in \Delta_1} \log[\log(1 + e^{x_i \beta})] + \sum_{i \in \Delta_1} \log f(t_i; x_i, \gamma) + \sum_{i \in \Delta_1} S(t_i; x_{ic}, \gamma) \log(1 + e^{x_i \beta}) \]

\[ - \sum_{i \in \Delta_*} \log(1 + e^{x_i \beta}) + \sum_{i \in \Delta_0} \pi^{(k)} \log((1 + e^{x_i \beta})S(t_i; x_{ic}, \gamma) - 1) \]  \hspace{1cm} (2.20)

with the update step

\[ \pi^{(k)}_i = 1 - (1 + e^{x_i \beta})^{-S(t_i; \gamma^{(k)})} \]  \hspace{1cm} (2.21)

for the \( i \)th censored observation. The required first- and second-order derivatives of \( Q(\theta^*, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \) are as follows:

\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} \frac{1}{\log(1 + e^{x_i \beta})} \frac{x_{il} e^{x_i \beta}}{1 + e^{x_i \beta}} + \sum_{i \in \Delta_1} \frac{x_{il} e^{x_i \beta} S(t_i; x_{ic}, \gamma)}{1 + e^{x_i \beta}} - \sum_{i \in \Delta_*} \frac{x_{il} e^{x_i \beta}}{1 + e^{x_i \beta}} \\
+ \sum_{i \in \Delta_0} \pi^{(k)} S(t_i; x_{ic}, \gamma) \frac{x_{il} e^{x_i \beta}}{1 + e^{x_i \beta}},
\]

\[
\frac{\partial Q}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\log f(t_i; x_{ic}, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_1} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} \log(1 + e^{x_i \beta}) \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \log((1 + e^{x_i \beta})S(t_i; x_{ic}, \gamma) - 1) \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j}.
\]
Let the competing cause random variable $M$ follow a Geometric distribution. The probability density function for the whole population in this case can be expressed as

$$f_p(t_i; \theta) = \frac{e^{x_i^\beta} f(t_i; \gamma)}{R_G(t_i; \theta)^2}, \quad (2.22)$$

and the survival function for the susceptible group as

$$S_s(t_i; \theta) = \frac{S(t_i; \gamma)}{R_G(t_i; \theta)}, \quad (2.23)$$
where \( R_G(t_i, \theta) = 1 + e^{x_i^\beta} - e^{x_i^\beta}S(t_i; x_{ic}, \gamma) \). The cure rate under this setting is \( p_0 = 1 - \eta \), and under the logistic link function with a fixed value of \( \phi \), we would have \( H_\phi(\eta) = (1 - \eta)^{-1} \), which implies that \( \eta = e^{x_i^\beta}(1 + e^{x_i^\beta})^{-1} \). The \( Q(\theta^*, \pi^{(k)}) \) function is then given by

\[
Q = \sum_{i \in \Delta_1} x_i^\beta + \sum_{i \in \Delta_1} \log f(t_i, x_{ic}, \gamma) - \sum_{i \in \Delta_1} 2\log R_G(t_i, \theta) - \sum_{i \in \Delta_0} \log(1 + e^{x_i^\beta}) + \sum_{i \in \Delta_0} \pi^{(k)} x_i^\beta \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \log S(t_i; \gamma) - \sum_{i \in \Delta_0} \pi^{(k)} \log R_G(t_i, \theta),
\]  

(2.24)

with the update step

\[
\pi^{(k)}_i = \frac{S(t_i; \gamma^{(k)}(k))e^{x_i^{\beta^{(k)}}}}{1 + e^{x_i^{\beta^{(k)}}}}
\]

(2.25)

for the \( i \)th censored observation. The required first- and second-order derivatives of \( Q(\theta^*, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \) are as follows:

\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} x_{il} - 2 \sum_{i \in \Delta_1} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l} - \sum_{i \in \Delta_0} x_{il} e^{x_i^\beta} \frac{1}{1 + e^{x_i^\beta}} + \sum_{i \in \Delta_0} \pi^{(k)} x_{il} - \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l},
\]

\[
\frac{\partial Q}{\partial \gamma_j} = \sum_{i \in \Delta_1} \left( \frac{\partial \log f(t_i; x_{ic}, \gamma)}{\partial \gamma_j} - 2 \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j} \right) + \sum_{i \in \Delta_0} \pi^{(k)} \left( \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} - \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j} \right),
\]

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Hence, the components of the observed information matrix, for a fixed value of $\phi$, are

$\frac{\partial^2 Q}{\partial \beta_l \partial \beta_{l'}} = -2 \sum_{i \in \Delta_1} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l \partial \beta_{l'}} - \sum_{i \in \Delta_0} \frac{x_{il} x_{il'} e^{x_{il}' \beta}}{1 + e^{x_{il}' \beta}} - \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l \partial \beta_{l'}}$,

$\frac{\partial^2 Q}{\partial \beta_l \partial \gamma_j} = -2 \sum_{i \in \Delta_1} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l \partial \gamma_j} - \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l \partial \gamma_j}$,

$\frac{\partial Q^2}{\partial \gamma_j \partial \gamma_{j'}} = \sum_{i \in \Delta_1} \left( \frac{\partial \log f(t_i, x_{ie}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} - 2 \frac{\partial \log R^2_G(t_i, \theta)}{\partial \gamma_j \partial \gamma_{j'}} \right) + \sum_{i \in \Delta_0} \pi^{(k)} \left( \frac{\partial \log S(t_i; x_{ie}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} - \frac{\partial \log R^2_G(t_i, \theta)}{\partial \gamma_j \partial \gamma_{j'}} \right)$.

for $l, l' = 0, \ldots, p$, $j, j' = 1, 2$, $h = 21, \ldots, 2p$, $i = 1, \ldots, n$.

**Observed information matrix**

**COM-Poisson cure rate model:** The score functions, for a fixed value of $\phi$, are

$\frac{\partial l}{\partial \beta_l} = - \sum_{i \in \Delta} x_{il} \frac{e^{x_{il}' \beta}}{1 + e^{x_{il}' \beta}} + \sum_{i \in \Delta_1} e^{x_{il}' \beta} \frac{z_{21,i}}{z_{2,i} z_{01,i}} x_{il} + \sum_{i \in \Delta_0} \frac{z_{21,i} x_{il} e^{x_{il}' \beta}}{z_{01,i} (1 + z_{11,i})}$,

$\frac{\partial l}{\partial \gamma_h} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_1} \left( \frac{z_{21,i}}{z_{2,i}} - 1 \right) \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_0} \frac{z_{2,i}}{1 + z_{1,i}} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h}$.

Hence, the components of the observed information matrix, for a fixed value of $\phi$, are
\[ \frac{\partial^2 l}{\partial \beta_i \partial \beta_{l'}} = -\left\{ -\sum_{i \in \Delta_i} \frac{x_i l' e^{x_i^t \beta}}{(1 + e^{x_i^t \beta})^2} \right\} + \sum_{i \in \Delta_0} \frac{x_i l' e^{x_i^t \beta}}{(z_{2,i}^2 z_{01,i}^2)^2} \left[ z_{2,i} (z_{21,i} z_{01,i} + z_{31,i} e^{x_i^t \beta}) - z_{21,i} [z_{21,i} + \frac{z_{2,i} z_{02,i}^2}{z_{01,i}}] e^{x_i^t \beta} \right] \\
+ \sum_{i \in \Delta_0} \frac{x_i l' e^{x_i^t \beta}}{(z_{2,i} + 1)^2 z_{01,i}} \left[ (z_{21,i} e^{x_i^t \beta} + z_{2,i}) (z_{1,i} + 1) z_{01,i} - z_{2,i} e^{x_i^t \beta} \left[ \frac{z_{02,i}^2}{z_{01,i}} (z_{1,i} + 1) + z_{2,i} \right] \right], \]

\[ \frac{\partial^2 l}{\partial \beta_i \partial \gamma_h} = -\left\{ -\sum_{i \in \Delta_i} \frac{x_i l' e^{x_i^t \beta}}{z_{2,i}^2 z_{01,i}} \right\} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_h} \\
+ \sum_{i \in \Delta_0} \frac{x_i l' e^{x_i^t \beta}}{z_{01,i} (1 + z_{1,i})} \left[ \frac{z_{21,i}^2}{z_{2,i}} - \frac{z_{2,i}^2}{1 + z_{1,i}} \right] \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_h} \}, \]

\[ \frac{\partial^2 l}{\partial \gamma_h \partial \gamma_{l'}} = -\left\{ -\sum_{i \in \Delta_i} \frac{\partial \log f^2(t_i, \gamma)}{\partial \gamma_h \partial \gamma_{l'}} \right\} \]

\[ + \sum_{i \in \Delta_i} \frac{(z_{21,i}^2 - 1)}{z_{2,i}} \frac{\partial \log S^2(t_i; \gamma)}{\partial \gamma_h \partial \gamma_{l'}} \]

\[ + \sum_{i \in \Delta_0} \frac{(z_{21,i}^2 - 1)}{z_{2,i}^2} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_{l'}} + \sum_{i \in \Delta_0} \frac{z_{21,i} z_{1,i} + z_{21,i} - z_{2,i}^2}{1 + z_{1,i}^2} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_{l'}} \}, \]

for \( l, l' = 0, \ldots, p \), \( x_{i0} \equiv 1 \), \( h, h' = 0, 1 \), \( j^*, j^* = 21, 22, \ldots, 2p \), \( i = 1, \ldots, n \).

**Bernoulli cure rate model:** The score functions are

\[ \frac{\partial l}{\partial \beta_i} = \sum_{i \in \Delta_i} x_i l - \sum_{i \in \Delta_0} x_i l e^{x_i^t \beta} + \sum_{i \in \Delta_0} w_i x_i, \]

\[ \frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_0} w_i \frac{\partial \log S(t_i; x_{i0}, \gamma)}{\partial \gamma_j}, \]

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where \( w_i = \frac{e^{x_i'\beta}S(t_i;\gamma)}{1 + e^{x_i'\beta}S(t_i;\gamma)} \).

Hence, the components of the observed information matrix are

\[
- \frac{\partial^2 l}{\partial \beta_l \partial \beta_{l'}} = -\left\{ \sum_{i \in \Delta^*} x_{il}x_{il'}e^{x_i'\beta}(1 + e^{x_i'\beta})^2 + \sum_{i \in \Delta_0} x_{il}x_{il'}w_i(1 - w_i) \right\},
\]

\[
- \frac{\partial^2 l}{\partial \beta_l \partial \gamma_{j'}} = -\left\{ \sum_{i \in \Delta_0} x_{il}w_i(1 - w_i) \frac{\partial \log S(t_i;\gamma)}{\partial \gamma_{j'}} \right\},
\]

\[
- \frac{\partial^2 l}{\partial \gamma_{j} \partial \gamma_{j'}} = -\left\{ \sum_{i \in \Delta_1} \frac{\partial \log f(t_i;\gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_0} w_i \frac{\partial \log S^2(t_i;\gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta_0} w_i(1 - w_i) \frac{\partial \log S(t_i;\gamma)}{\partial \gamma_j} \frac{\partial \log S(t_i;\gamma)}{\partial \gamma_{j'}} \right\},
\]

for \( l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n \).

**Poisson cure rate model**: The score functions are

\[
\frac{\partial l}{\partial \beta_l} = \sum_{i \in \Delta_1} \frac{1}{\log(1 + e^{x_i'\beta})} \frac{x_{il}e^{x_i'\beta}}{1 + e^{x_i'\beta}} + \sum_{i \in \Delta^*} \frac{x_{il}e^{x_i'\beta}(S(t_i;\gamma) - 1)}{1 + e^{x_i'\beta}},
\]

\[
\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i;\gamma)}{\partial \gamma_j} + \sum_{i \in \Delta^*} \frac{\partial S(t_i;\gamma)}{\partial \gamma_j} \log(1 + e^{x_i'\beta}).
\]

Hence, the components of the observed information matrix are

\[
- \frac{\partial^2 l}{\partial \beta_l \partial \beta_{l'}} = -\left\{ \sum_{i \in \Delta_1} x_{il}x_{il'}e^{x_i'\beta}(\log(1 + e^{x_i'\beta}) - e^{x_i'\beta}) \frac{(1 + e^{x_i'\beta})^2}{[\log(1 + e^{x_i'\beta})]^2} + \sum_{i \in \Delta^*} \frac{x_{il}x_{il'}e^{x_i'\beta}}{1 + e^{x_i'\beta}}(S(t_i;\gamma) - 1) \right\},
\]

\[
- \frac{\partial^2 l}{\partial \beta_l \partial \gamma_{j'}} = -\left\{ \sum_{i \in \Delta^*} \frac{\partial S(t_i;\gamma)}{\partial \gamma_j} \frac{x_{il}e^{x_i'\beta}}{1 + e^{x_i'\beta}} \right\},
\]

\[
- \frac{\partial^2 l}{\partial \gamma_{j} \partial \gamma_{j'}} = -\left\{ \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i;\gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta^*} \frac{\partial^2 S(t_i;\gamma)}{\partial \gamma_j \partial \gamma_{j'}} \log(1 + e^{x_i'\beta}) \right\},
\]
Hence, the components of the observed information matrix are

\[
\frac{\partial l}{\partial \beta_i} = \sum_{i \in \Delta_1} x_{il} - 2 \sum_{i \in \Delta_1} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_i} - \sum_{i \in \Delta_0} x_{il} e^{x_i^l \beta} + \sum_{i \in \Delta_0} S(t_i; \gamma) e^{x_i^l \beta} (x_{il} - \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_i}),
\]

\[
\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \left( \frac{\partial \log f(t_i, x_{ie}, \gamma)}{\partial \gamma_j} - \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j} \right) - \sum_{i \in \Delta^*} \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j}.
\]

Hence, the components of the observed information matrix are

\[
-\frac{\partial^2 l}{\partial \beta_i \partial \beta_j} = \left\{\begin{align*}
&=-2 \sum_{i \in \Delta_1} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_i \partial \beta_j} + \sum_{i \in \Delta_0} \frac{x_{il} x_{i'j} e^{x_i^l \beta}}{(1 + e^{x_i^l \beta})^2} (S(t_i; \gamma) - 1) \\
&\quad - \sum_{i \in \Delta_0} \frac{S(t_i; \gamma) e^{x_i^l \beta} \partial \log R_G^2(t_i, \theta)}{\partial \beta_i} - \sum_{i \in \Delta_0} \frac{x_{il} e^{x_i^l \beta} S(t_i; \gamma) \partial \log R_G(t_i, \theta)}{\partial \beta_i}, \\
&\quad - \sum_{i \in \Delta^*} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_i} \partial \gamma_j - \sum_{i \in \Delta^*} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_i} \partial \gamma_j \\
&- \sum_{i \in \Delta_1} \left( \frac{\partial \log f(t_i, x_{ie}, \gamma)}{\partial \gamma_j} - \frac{\partial \log R_G^2(t_i, \theta)}{\partial \gamma_j} \right) - \sum_{i \in \Delta^*} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \gamma_j},
\end{align*}\right.
\]

where \(R_G(t_i, \theta) = 1 - e^{x_i^l \beta} (S(t_i; \gamma) - 1)\), and

\[
\frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j} = -e^{x_i^l \beta} \frac{\partial S(t_i, \theta)}{R_G(t_i, \theta) \partial \gamma_j}, \quad \frac{\partial \log R_G^2(t_i, \theta)}{\partial \gamma_j} = \frac{e^{x_i^l \beta} \partial S^2(t_i, \theta)}{R_G(t_i, \theta)^2} \partial \gamma_j,
\]

\[
\frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_i} = \frac{x_{il} x_{i'j} e^{x_i^l \beta} (1 - S(t_i, \theta))}{R_G(t_i, \theta)^2} - \frac{x_{il} e^{x_i^l \beta} \partial S^2(t_i, \theta)}{R_G(t_i, \theta)^2} \partial \gamma_j,
\]

for \(l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n\).
2.3 Estimation of parameters

We propose an Expectation-Maximization (EM) algorithm for obtaining the MLE of \( \theta \), and a profile likelihood approach for the estimation of the dispersion parameter \( \phi \). It is well-known that EM is an effective technique for finding the MLEs of unknown parameters of a model involving unobserved variables [for further details, refer to McLachlan and Krishnan (2007)]. In our model, the random variable \( I_i \)'s are observed for \( i \) in the set \( \Delta_1 \) and unobserved for \( i \) in the set \( \Delta_0 \), where \( I_i = 1 \) if the individual is susceptible and \( I_i = 0 \) if the individual is cured. Let us denote the set of complete data by \((t, \delta, x, I)\) \(=\{(t_1, \delta_1, x_1, I_1), \ldots, (t_n, \delta_n, x_n, I_n)\}\). The complete data likelihood function is then

\[
L_c(\theta; t, x, \delta, I) \propto \prod_{i \in \Delta_1} f_p(t_i, x_i, \theta) \prod_{i \in \Delta_0} p_0(\beta, x_i)^{1-I_i}[(1 - p_0(\beta, x_i))S_s(t_i, x_i; \theta)]^{I_i},
\]

(2.26)

where \( I = (I_1, \ldots, I_n)' \), \( x_{ic} = (x_{i1}, \ldots, x_{ip})' \) and \( x_i = (1, x_{i'}')' \). The corresponding complete log-likelihood function

\[
l_c(\theta; t, x, \delta, I) = \text{constant} + \sum_{i \in \Delta_1} \log f_p(t_i, x_i, \theta) + \sum_{i \in \Delta_0} (1 - I_i) \log p_0(\beta, x_i)
\]

\[
+ \sum_{i \in \Delta_0} I_i \log[1 - p_0(\beta, x_i)] + \sum_{i \in \Delta_0} I_i \log S_s(t_i, x_i; \theta).
\]

(2.27)

2.3.1 E-step

The expectation step is achieved by calculating the expected value of the complete data log-likelihood function with respect to the conditional distribution of the unobserved \( I_i \)'s.
(i \in \Delta_0), given the observed data \( O = \{(t_i, \delta_i, x_i), i \in \Delta_1\} \) and the current estimates of the parameters \( \theta^{(k)} = (\beta', \gamma')' \) for a fixed value of \( \phi \). Let us denote the function as

\[
Q(\theta, \pi^{(k)}) = E(l_c(\theta, t, x, \delta, I) | O, \theta^{(k)}),
\]  

(2.28)

at the \( k \)-th iteration step. In our model, \( I_i \)'s are Bernoulli random variables and we can easily find the conditional expectation if the \( i \)th individual being susceptible is

\[
\pi_i^{(k)} = E(I_i | O, \theta^{(k)}) = P(I_i = 1 | T > t) = \frac{(1 - p_0(\beta^{(k)}, x_i))S_a(t_i, x_{ic}; \theta^{(k)})}{S_p(t_i, x_{ic}; \theta^{(k)})} |_{\theta = \theta^{(k)}}.
\]

(2.29)

Now, for a fixed value of \( \phi \), the \( Q \) function is given by

\[
Q(\theta, \pi^{(k)}) = \sum_{t \in \Delta_1} \log f_p(t_i, x_i, \theta) + \sum_{i \in \Delta_0} (1 - \pi_i^{(k)}) \log p_0(\beta, x_i)
+ \sum_{i \in \Delta_0} \pi_i^{(k)} \log [1 - p_0(\beta, x_i)] + \sum_{i \in \Delta_0} \pi_i^{(k)} \log S_a(t_i, x_{ic}; \theta)
\]

(2.30)

which can be further simplified as

\[
Q(\theta, \pi^{(k)}) = - \sum_{i \in \Delta_0} \log (1 + e^{x_i}\beta) + \sum_{t \in \Delta_1} \log f(t_i, \gamma) - \sum_{i \in \Delta_1} \log S(t_i, \gamma)
+ \sum_{i \in \Delta_1} \log z_{2,i} + \sum_{i \in \Delta_0} \pi_i^{(k)} \log z_{1,i},
\]

(2.31)
where

\[ z_{1,i} = z_1(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j! \{\eta_i S(t_i; \gamma)\}^j}{(j!)^\phi}, \quad (2.32) \]

\[ z_{2,i} = z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j^j \{\eta_i S(t_i; \gamma)\}^j}{(j!)^\phi}. \quad (2.33) \]

### 2.3.2 M-step

The M-step is achieved by maximizing the \( Q(\theta, \pi^{(k)}) \) function in (2.31) in order to obtain the improved estimate of \( \theta \), i.e.,

\[ \theta^{(k+1)} = \arg \max_{\theta} Q(\theta, \pi^{(k)}). \quad (2.34) \]

The MLEs of \( \beta \) and \( \gamma \) do not have explicit expressions. We therefore adopt the numerical maximization carried out by Newton-Raphson method.

For a fixed value of \( \phi \), the E-step and M-step are alternated until the parameter estimate converges to a desired level of accuracy. The parameter \( \phi \) is determined by using the profile likelihood technique. We consider a range of \( \phi \) with small increment, and then for each value of \( \phi \), the MLEs of other parameters are found, and the estimate with the largest likelihood is chosen as the final estimate. The following subsections present explicit forms of the first- and second-order derivatives of the Q function as well as update function for the general case of COM-Poisson distribution.

### 2.3.3 Results for the COM-Poisson cure rate model

The required first- and second-order derivatives of \( Q(\theta^*, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \), for fixed values of \( \phi \), are as follows:
\[
\begin{align*}
\frac{\partial Q}{\partial \beta_i} &= -\sum_{i \in \Delta_*} x_{il} \frac{e^{x_i^j\beta}}{1 + e^{x_i^j\beta}} + \sum_{i \in \Delta_1} e^{x_i^j\beta} \frac{z_{21,i}}{z_{21,i}} x_{il} + \sum_{i \in \Delta_0} \pi^{(k)} e^{x_i^j\beta} \frac{z_{2,i}}{z_{1,i}} \frac{z_{01,i}}{z_{01,i}} x_{il}, \\
\frac{\partial Q}{\partial \gamma_h} &= \sum_{i \in \Delta_1} \frac{\partial \log f(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_1} \left( \frac{z_{21,i}}{z_{2,i}} - 1 \right) \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{z_{2,i}}{z_{1,i}} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h}, \\
\frac{\partial^2 Q}{\partial \beta_i \partial \beta_{i'}} &= -\sum_{i \in \Delta_*} x_{il} x_{i'l'} e^{x_i^j\beta} (1 + e^{x_i^j\beta})^2 \\
&\quad + \sum_{i \in \Delta_1} \frac{x_{il} x_{i'l'} e^{x_i^j\beta}}{(z_{2,i} z_{01,i})^2} \left[ z_{2,i} \left( z_{21,i} z_{01,i} + z_{31,i} e^{x_i^j\beta} \right) - z_{21,i} \left( z_{21,i} + \frac{z_{2,i} z_{02,i}}{z_{01,i}} \right) e^{x_i^j\beta} \right] \\
&\quad + \sum_{i \in \Delta_0} \pi^{(k)} \frac{x_{il} x_{i'l'} e^{x_i^j\beta}}{(z_{1,i} z_{01,i})^2} \left[ z_{1,i} \left( z_{21,i} e^{x_i^j\beta} + z_{2,i} z_{01,i} \right) - z_{2,i} z_{21,i} + \frac{z_{2,i} z_{02,i}}{z_{01,i}} e^{x_i^j\beta} \right], \\
\frac{\partial^2 Q}{\partial \beta_i \partial \gamma_{h'}} &= \sum_{i \in \Delta_1} \frac{x_{il} e^{x_i^j\beta} z_{31,i} z_{2,i}}{z_{01,i}^2} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}} \\
&\quad + \sum_{i \in \Delta_0} \pi^{(k)} \frac{x_{il} e^{x_i^j\beta} z_{21,i} z_{1,i}}{z_{01,i}^2} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}} + \sum_{i \in \Delta_1} \frac{z_{31,i} z_{2,i} - z_{21,i}^2}{z_{2,i}^2} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}} \\
&\quad + \sum_{i \in \Delta_0} \pi^{(k)} \frac{z_{2,i}}{z_{1,i}} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{z_{21,i} z_{21,i} - z_{2,i}^2}{z_{01,i}^2} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}} \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_{h'}},
\end{align*}
\]

for \( l, l' = 0, \ldots, p \), \( x_{i0} \equiv 1 \), \( h, h' = 0, 1, j^* \), \( j^* = 21, 22, \ldots, 2p \), \( i = 1, \ldots, n \), where

\[
\begin{align*}
z_{21,i} &= z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j^2 \eta_i S(t_i; \gamma)^j}{(j!)^\phi}, \quad z_{31,i} = z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j^3 \eta_i S(t_i; \gamma)^j}{(j!)^\phi}, \\
z_{01,i} &= z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j \eta_i^j}{(j!)^\phi}, \quad z_{02,i} = z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{j^2 \eta_i^j}{(j!)^\phi},
\end{align*}
\]
with \( z_{1,i} \) and \( z_{2,i} \) being as in (2.32) and (2.33), respectively.

### 2.3.4 Standard errors and asymptotic confidence intervals

We may approximate the asymptotic variance-covariance matrix of the MLEs \((\hat{\beta}', \hat{\gamma}')'\) by inverting the observed Fisher information matrix of \(\beta\) and \(\gamma\), for a fixed value of \(\phi\). The components of the observed Fisher information matrix can be calculated from the negative of the second-order derivatives of the complete data likelihood function with respect to \(\beta\) and \(\gamma\) (for detailed information, refer to Louis (1982)). Thus, we can obtain the standard errors of the estimates and then construct corresponding asymptotic confidence intervals for the parameters.

### 2.3.5 Estimation of the cure rate and its standard error

Suppose \(\hat{\beta}\) is the MLE of the regression coefficient \(\beta\). The estimated cure rate for group \(i\) is then \(\hat{p}_{0i} = (1 + e^{x_i'\hat{\beta}})^{-1}\), for \(i = 1, \ldots, \tau\). The standard error of \(\hat{p}_{0i}\) can be found through delta method as

\[
\text{sd}(\hat{p}_{0i}) = \sqrt{\left(\frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, \ldots, \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_p}\right) \var(\hat{\beta}) \left(\frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, \ldots, \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_p}\right)'}.
\]  

(2.35)

### 2.3.6 Equivalent models

**Proposition**: The population survival function under Geometric and Bernoulli cure rate models are equivalent through re-parametrization if baseline odds follow log-logistic distribution.

**Proof**: Cure rates \(p_0\) under Geometric and Bernoulli cure rate models are \(1 - \eta\) and \(\frac{1}{1 + \eta}\),
respectively. If we equate these cure rates, we obtain a relationship between \( \eta_1 \) and \( \eta_3 \) as

\[
\eta_3 = \frac{\eta_1}{1 - \eta_1}.
\]  

(2.36)

Suppose \( S_1 = \frac{\gamma_{11}e^{\gamma_{12}}}{\gamma_{10}e^{\gamma_{12}+\gamma_{10}}} \) and \( S_3 = \frac{\gamma_{31}e^{\gamma_{32}}}{\gamma_{30}e^{\gamma_{32}+\gamma_{12}}} \) are the survival functions of the susceptible group under Geometric and Bernoulli cure rate models, respectively. Then, the population survival function under the Bernoulli case is

\[
S_p = \frac{1 + \eta_3 S_3}{1 + \eta_3}.
\]  

(2.37)

If we fix the relationship between \( \gamma_{30}, \gamma_{10}, \gamma_{32} \) and \( \gamma_{12} \) as

\[
\gamma_{30} e^{\gamma_{32}} = \gamma_{10} e^{\gamma_{12}} p_0 = \gamma_{10} e^{\gamma_{12}} (1 - \eta_1),
\]  

(2.38)

then we obtain from (2.37) that

\[
S_p = 1 - \eta_1 + \eta_1 S_3 = 1 - \eta_1 \frac{t^{\gamma_{11}}}{\gamma_{30} e^{\gamma_{32}} + t^{\gamma_{11}}} = 1 - \frac{t^{\gamma_{11}} \eta_1}{\gamma_{30} e^{\gamma_{32}} (1 - \eta_1) + t^{\gamma_{11}}} = \frac{1 - \eta_1}{1 - \eta_1 S_1},
\]  

(2.39)

which is the population survival function for the Geometric cure rate model under proportional odds assumption. Thus, these two models in this case are re-parametrizations of each other.
2.4 Simulation study

An extensive Monte Carlo simulation study is carried out in this paper to evaluate the performance of the proposed methodology by varying the sample size, cure rate, censoring proportion, the parameters of distributions, and underlying lifetime distribution. We try to mimic the cutaneous melanoma data, and consider 4 possible categories for the individuals, namely, $x = 0, 1, 2, 3$. Three different sample sizes are considered in the study: $n = 200$ ($50, 42, 53, 55$), $n = 400$ ($95, 102, 97, 106$), $n = 800$ ($200, 168, 212, 220$) to reflect small, medium and large sample sizes. Moreover, if we assume that $\beta = (\beta_0, \beta_1)$ has two parameters, fixing the cure rates for the first and fourth categories would be enough to cover all cases as the cure rates for the second and third categories can then be obtained from $\beta$. Here, we take $(p_{00}, p_{03}) = (0.4, 0.2)$ and $(p_{00}, p_{03}) = (0.6, 0.25)$ with respect to categories one and four for low and high cure rates, respectively. Also, the cure rate would be in a decreasing order in this way. The $\beta$’s are then

$$
\beta_0 = \log(1/p_{00} - 1) , \quad \beta_1 = (\log(1/p_{03} - 1) - \beta_0)/3.
\tag{2.40}
$$

We thus obtain the true value of $\beta$ as $(0.405, 0.321)$ and $(-0.405, 0.501)$, respectively. In addition, we consider light and heavy censored data in the simulation. The light and heavy censoring rates are $(0.52, 0.45, 0.37, 0.3)$ and $(0.65, 0.49, 0.4, 0.35)$ for the low cure rates, $(0.7, 0.57, 0.45, 0.34)$ and $(0.8, 0.64, 0.5, 0.38)$ for the high cure rates, respectively. It is natural to assume that the probability of censored population for the susceptible group equal to the difference between the probability of getting censored and cured; i.e.,

$$
P(Y \geq C_x \cap M \geq 1|X = x) = c_x - p_{0x}.
\tag{2.41}
$$
If we assume the censoring time $C_x$ follows an exponential distribution with rate $\lambda_x$ on $x = 0, 1, 2, 3$, Eq. (2.41) can be re-written as

$$
\lambda_x \int_0^\infty S_p(C_x) e^{-\lambda_x c_x} dc_x = c_x.
$$

(2.42)

The choice of $(\gamma_0, \gamma_1)$ in the underlying distribution of the proportional odds survival model are $(0.571, 0.307)$ and $(1.75, 3.25)$ for Weibull and log-logistic distributions, respectively. The odds parameter is specified by $\gamma_2 = -0.75$ to ensure a decreasing lifetime for the four nodule categories. We consider an inverse transform sampling method to simulate the actual survival lifetime $Y_i$ for each individual under different competing risks, i.e.,

$$
w_i = \frac{1}{\gamma_1} \log\left(1 + \left(\frac{u}{1-u} - 1\right) e^{x_i \gamma_2}\right)^{\gamma_0} \text{ and } w_i = \gamma_0 \left(\frac{u}{1-u} e^{x_i \gamma_2}\right)^{1/\gamma_1}, \; i = 1, \ldots, n, \text{ under the proportional odds model with Weibull and log-logistic baseline distribution, respectively,}
$$

where $u$ follows an uniform distribution over 0 to 1.

Under the above setting, the procedure to generate the data from different cure rate models is as follows.

**Geometric cure rate model:** For each individual, we simulate the number of competing risk $M_i$ from Geometric distributions with probability $P(M_i = 0) = p_{0x}$; and we simulate the censoring time $C_x$ from exponential distribution with rate $\lambda_x$, with the parameter $\lambda_x$ found from (2.41). If $M_i$ does not equal zero, we simulate $M_i$ number of actual lifetimes $\{Y_{i1}, \ldots, Y_{iM_i}\}$ from proportional odds survival model, the actual lifetimes $Y_i$ is defined as $\min\{Y_{i1}, \ldots, Y_{iM_i}\}$ and the observed lifetime $T_i$ is taken as the minimum of all the actual lifetimes and the censoring time, i.e., $T_i = \min\{Y_{i1}, \ldots, Y_{iM_i}, C_i\}$. If $Y_i > C_i$, we make the censoring indicator $\delta_i = 0$, otherwise $\delta_i = 1$. On the other hand, $M_i = 0$ means the individual is censored, we assign $C_i$ to the actual lifetime $T_i$, and the censoring indicator is taken to be $\delta_i = 1$. 

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Poisson cure rate model: In this case, the procedure is the same as the Geometric cure rate model except that $M_i$ is simulated from Poisson distribution with parameter $-\log(p_{0x})$.

Bernoulli cure rate model: There are two ways to do the data generation in this case. One is the same as Geometric cure rate model except that $M_i$ is simulated from Bernoulli distribution with probability of success as $1 - p_{0x}$. Another way is a little bit simpler since $M_i$ can only be taken as 0 or 1 in this case. For each individual, we simulate the censoring time $C_x$ from exponential distribution with rate $\lambda_x$. Then, we simulate an uniform random variable $U_i$ and if $U_i \leq p_{0x}$, the observed lifetime $T_i$ is set to $C_x$; otherwise, we generate the observed lifetime $T_i$ from the proportional odds survival model.

In our simulation study, 1000 Monte Carlo runs were considered in each scenario. The estimates were calculated through EM method. We stopped our estimation if the absolute difference between two consecutive estimates was less than $10^{-5}$. We calculated the empirical Bias, standard errors(SE), root Mean Square Error (RMSE), and 95% coverage probabilities (CPs) for the estimates of the parameters. In addition, we computed the cure rate, SE and 95% CPs. Here, the initial values of the parameters $(\beta, \gamma)$ were taken from a grid of parameters with a range from 80% to 120% of the true value, and those values having the maximum likelihood were chosen as the initial value.

Tables 2.1-2.6 present the bias, SE, RMSE, and coverage probabilities for the three special cases. We can see that the estimates are quite accurate under different cure rate models. The Bias, standard error along with RMSE get reduced as the sample size increases. The same follows when the censoring is light or the cure rate is high. The standard errors and RMSE of $\beta_0$ are always larger than those for the other parameters. The coverage probabilities of the confidence intervals based on the asymptotic normality of the MLEs are quite close to the nominal level in most of the cases. To summarize, a larger sample size, and
Table 2.1: Bias, SE, RMSE, and CP for the estimates of the parameters of the Geometric cure rate model under proportional odds with log-logistic baseline.

<table>
<thead>
<tr>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
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<tbody>
<tr>
<td>(n=400, \text{LC})</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>(\beta_0)</td>
<td>0.405</td>
<td>0.003</td>
<td>0.208</td>
<td>0.212</td>
<td>94.7</td>
<td>-0.405</td>
<td>-0.005</td>
<td>0.205</td>
<td>0.208</td>
<td>94.5</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>0.327</td>
<td>0.003</td>
<td>0.116</td>
<td>0.121</td>
<td>94.5</td>
<td>0.501</td>
<td>0.007</td>
<td>0.111</td>
<td>0.111</td>
<td>94</td>
</tr>
<tr>
<td>(\gamma_0)</td>
<td>1.75</td>
<td>0.01</td>
<td>0.147</td>
<td>0.151</td>
<td>93.4</td>
<td>1.75</td>
<td>-0.001</td>
<td>0.154</td>
<td>0.155</td>
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<tr>
<td>(\gamma_1)</td>
<td>3.25</td>
<td>0.021</td>
<td>0.186</td>
<td>0.195</td>
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<td>0.205</td>
<td>0.202</td>
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<tr>
<td>(\gamma_2)</td>
<td>-0.75</td>
<td>-0.003</td>
<td>0.149</td>
<td>0.153</td>
<td>94.7</td>
<td>-0.75</td>
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<td>(n=400, \text{HC})</td>
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<tr>
<td>(\beta_0)</td>
<td>0.405</td>
<td>0.012</td>
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<td>0.133</td>
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<td>0.501</td>
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<td>95.3</td>
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<td>0.199</td>
<td>0.195</td>
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<td>95.8</td>
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</tr>
<tr>
<td>(\beta_0)</td>
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<td>0.004</td>
<td>0.146</td>
<td>0.147</td>
<td>94.3</td>
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<td>0.001</td>
<td>0.077</td>
<td>0.076</td>
<td>95.7</td>
</tr>
<tr>
<td>(\gamma_0)</td>
<td>1.75</td>
<td>0.01</td>
<td>0.104</td>
<td>0.106</td>
<td>95.1</td>
<td>1.75</td>
<td>0</td>
<td>0.11</td>
<td>0.111</td>
<td>95.4</td>
</tr>
<tr>
<td>(\gamma_1)</td>
<td>3.25</td>
<td>0.005</td>
<td>0.13</td>
<td>0.132</td>
<td>95</td>
<td>3.25</td>
<td>0.019</td>
<td>0.144</td>
<td>0.144</td>
<td>94.9</td>
</tr>
<tr>
<td>(\gamma_2)</td>
<td>-0.75</td>
<td>-0.006</td>
<td>0.103</td>
<td>0.102</td>
<td>95.6</td>
<td>-0.75</td>
<td>-0.003</td>
<td>0.109</td>
<td>0.111</td>
<td>93.8</td>
</tr>
<tr>
<td>(n=800, \text{HC})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\beta_0)</td>
<td>0.405</td>
<td>0.007</td>
<td>0.177</td>
<td>0.175</td>
<td>95.6</td>
<td>-0.405</td>
<td>-0.003</td>
<td>0.183</td>
<td>0.184</td>
<td>95.7</td>
</tr>
<tr>
<td>(\beta_1)</td>
<td>0.327</td>
<td>-0.002</td>
<td>0.092</td>
<td>0.091</td>
<td>95.3</td>
<td>0.501</td>
<td>0.003</td>
<td>0.091</td>
<td>0.093</td>
<td>95.5</td>
</tr>
<tr>
<td>(\gamma_0)</td>
<td>1.75</td>
<td>0.012</td>
<td>0.127</td>
<td>0.126</td>
<td>95.5</td>
<td>1.75</td>
<td>0</td>
<td>0.14</td>
<td>0.144</td>
<td>94.4</td>
</tr>
<tr>
<td>(\gamma_1)</td>
<td>3.25</td>
<td>0.011</td>
<td>0.14</td>
<td>0.139</td>
<td>94.7</td>
<td>3.25</td>
<td>0.017</td>
<td>0.157</td>
<td>0.155</td>
<td>95.1</td>
</tr>
<tr>
<td>(\gamma_2)</td>
<td>-0.75</td>
<td>-0.007</td>
<td>0.118</td>
<td>0.115</td>
<td>95.5</td>
<td>-0.75</td>
<td>-0.001</td>
<td>0.126</td>
<td>0.128</td>
<td>95.2</td>
</tr>
</tbody>
</table>

smaller censoring proportion would result in more accurate estimates.

2.5 Model discrimination

The COM-Poisson distribution contains many commonly used discrete distributions for different selection of \(\phi\). It would therefore be of interest to select a suitable \(\phi\) and make full use of the COM-Poisson distribution to get the best fit for the data. So, we focus here on a model discrimination among the three special cases of the COM-Poisson distribution.
Table 2.2: Bias, SE, RMSE, and CP for the estimates of the parameters of the Poisson cure rate model under proportional odds model with log-logistic baseline.

<table>
<thead>
<tr>
<th>Param</th>
<th>low cure rate</th>
<th></th>
<th>high cure rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True</td>
<td>Bias</td>
<td>SE</td>
<td>RMSE</td>
</tr>
<tr>
<td>n=400, LC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0.004</td>
<td>0.207</td>
<td>0.202</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0.003</td>
<td>0.115</td>
<td>0.113</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.001</td>
<td>0.12</td>
<td>0.115</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.031</td>
<td>0.189</td>
<td>0.195</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.004</td>
<td>0.12</td>
<td>0.119</td>
</tr>
<tr>
<td>n=400, HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0.009</td>
<td>0.247</td>
<td>0.248</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0</td>
<td>0.131</td>
<td>0.133</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.004</td>
<td>0.141</td>
<td>0.136</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.048</td>
<td>0.203</td>
<td>0.213</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.013</td>
<td>0.133</td>
<td>0.132</td>
</tr>
<tr>
<td>n=800, LC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0.001</td>
<td>0.146</td>
<td>0.141</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0</td>
<td>0.079</td>
<td>0.077</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0</td>
<td>0.086</td>
<td>0.084</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.014</td>
<td>0.132</td>
<td>0.131</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.001</td>
<td>0.084</td>
<td>0.082</td>
</tr>
<tr>
<td>n=800, HC</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0.008</td>
<td>0.175</td>
<td>0.176</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>-0.002</td>
<td>0.091</td>
<td>0.094</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.006</td>
<td>0.102</td>
<td>0.1</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.018</td>
<td>0.142</td>
<td>0.148</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.008</td>
<td>0.093</td>
<td>0.096</td>
</tr>
</tbody>
</table>
Table 2.3: Bias, SE, RMSE, and CP for the estimates of the parameters of the Bernoulli cure rate model under proportional odds model with log-logistic baseline.

<table>
<thead>
<tr>
<th>Param</th>
<th>Low cure rate</th>
<th></th>
<th>High cure rate</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>True</td>
<td>Bias</td>
<td>SE</td>
<td>RMSE</td>
</tr>
<tr>
<td>n=400, LC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0.002</td>
<td>0.208</td>
<td>0.214</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0.002</td>
<td>0.116</td>
<td>0.117</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.003</td>
<td>0.112</td>
<td>0.114</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.025</td>
<td>0.186</td>
<td>0.193</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.004</td>
<td>0.11</td>
<td>0.111</td>
</tr>
<tr>
<td>n=400, HC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>-0.009</td>
<td>0.25</td>
<td>0.257</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0.009</td>
<td>0.134</td>
<td>0.138</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.011</td>
<td>0.128</td>
<td>0.126</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.028</td>
<td>0.2</td>
<td>0.212</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.012</td>
<td>0.12</td>
<td>0.111</td>
</tr>
<tr>
<td>n=800, LC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>0</td>
<td>0.146</td>
<td>0.146</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0.002</td>
<td>0.08</td>
<td>0.079</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.001</td>
<td>0.079</td>
<td>0.076</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.015</td>
<td>0.131</td>
<td>0.135</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.002</td>
<td>0.077</td>
<td>0.076</td>
</tr>
<tr>
<td>n=800, HC</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405</td>
<td>-0.005</td>
<td>0.177</td>
<td>0.181</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327</td>
<td>0.004</td>
<td>0.092</td>
<td>0.092</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>1.75</td>
<td>0.006</td>
<td>0.091</td>
<td>0.089</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>3.25</td>
<td>0.011</td>
<td>0.14</td>
<td>0.136</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75</td>
<td>-0.005</td>
<td>0.084</td>
<td>0.083</td>
</tr>
</tbody>
</table>
Table 2.4: Bias, SE, RMSE, and CP for the estimates of the parameters of the Geometric cure rate model under proportional odds model with Weibull baseline.

<table>
<thead>
<tr>
<th>Param</th>
<th>n=400, LC</th>
<th>n=800, LC</th>
<th>n=400, HC</th>
<th>n=800, HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>low cure rate</td>
<td>high cure rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>True Bias SE RMSE CP(95%)</td>
<td>True Bias SE RMSE CP(95%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405 -0.002 0.208 0.209 94.589</td>
<td>-0.405 -0.011 0.197 0.199 94.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327 0.004 0.117 0.119 94.6</td>
<td>0.501 0.002 0.107 0.108 95.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>0.571 -0.001 0.033 0.034 94.399</td>
<td>0.571 0.011 0.037 0.044 95.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>0.307 0.005 0.037 0.035 95.884</td>
<td>0.307 0.007 0.037 0.04 94.333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75 -0.003 0.153 0.155 93.265</td>
<td>-0.75 0.004 0.157 0.15 94.425</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=400, HC</td>
<td>n=800, LC</td>
<td>n=800, HC</td>
<td></td>
</tr>
<tr>
<td>$\beta_0$</td>
<td>0.405 0.007 0.274 0.282 94.874</td>
<td>-0.405 -0.028 0.26 0.279 94.668</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.327 0.001 0.143 0.144 95.3</td>
<td>0.501 0.005 0.129 0.133 94.684</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>0.571 0 0.036 0.037 95.19</td>
<td>0.571 0.012 0.046 0.046 93.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>0.307 0.005 0.052 0.054 94.874</td>
<td>0.307 0.015 0.057 0.058 93.443</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>-0.75 -0.002 0.183 0.184 95.33</td>
<td>-0.75 0.005 0.189 0.181 93.552</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.5: Bias, SE, RMSE, and CP for the estimates of the parameters of the Poisson cure rate model under proportional odds model with Weibull baseline.

| Param | n=400, LC | low cure rate | | high cure rate | | n=800, LC | | n=800, HC |
|-------|-----------|---------------|-------------------|-------------------|---------------|-------------------|-------------------|
|       |           | True | Bias | SE | RMSE | CP(95%) | True | Bias | SE | RMSE | CP(95%) | True | Bias | SE | RMSE | CP(95%) |
| β₀    | 0.405     | 0.005 | 0.21 | 0.207 | 96 | -0.405 | 0.005 | 0.207 | 0.212 | 94.3 | | 0.405 | 0.007 | 0.148 | 0.145 | 95.7 |
| β₁    | 0.327     | 0.002 | 0.118 | 0.115 | 95.7 | 0.501 | 0.006 | 0.113 | 0.118 | 94.4 | | 0.327 | 0.001 | 0.081 | 0.08 | 95.4 |
| γ₀    | 0.571     | -0.003 | 0.034 | 0.035 | 94.1 | 0.571 | -0.005 | 0.037 | 0.038 | 94.5 | | 0.571 | -0.001 | 0.024 | 0.025 | 93.3 |
| γ₁    | 0.307     | 0 | 0.028 | 0.028 | 95.4 | 0.307 | 0.002 | 0.031 | 0.032 | 93.8 | | 0.307 | 0.001 | 0.02 | 0.02 | 95.5 |
| γ₂    | -0.75     | -0.009 | 0.12 | 0.119 | 95.1 | -0.75 | -0.009 | 0.132 | 0.132 | 95.3 | | -0.75 | -0.008 | 0.083 | 0.082 | 95.3 |
| β₀    | 0.405     | 0.007 | 0.262 | 0.257 | 95.2 | -0.405 | 0.011 | 0.273 | 0.267 | 95.7 | | 0.405 | 0.003 | 0.185 | 0.187 | 94.8 |
| β₁    | 0.327     | -0.003 | 0.096 | 0.098 | 95.3 | 0.501 | 0.001 | 0.095 | 0.095 | 94.7 | | 0.327 | -0.001 | 0.026 | 0.025 | 95.4 |
| γ₀    | 0.571     | -0.001 | 0.026 | 0.026 | 95 | 0.571 | -0.003 | 0.029 | 0.028 | 94.7 | | 0.571 | -0.001 | 0.003 | 0.003 | 93 |
| γ₁    | 0.307     | 0.003 | 0.095 | 0.097 | 95 | 0.307 | 0.003 | 0.032 | 0.033 | 94 | | 0.307 | -0.006 | 0.107 | 0.11 | 95 |

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Table 2.6: Bias, SE, RMSE, and CP for the estimates of the parameters of the Bernoulli cure rate model under proportional odds model with Weibull baseline.

| Param | n=400, LC | | | | n=400, HC | | | | n=800, LC | | | | n=800, HC |
|-------|-----------|-------|-------|-------|-----------|-------|-------|-------|-----------|-------|-------|-------|-----------|-------|
|       | True      | Bias  | SE    | RMSE | CP(95%)  | True      | Bias  | SE    | RMSE | CP(95%)  | True      | Bias  | SE    | RMSE | CP(95%)  |
| β₀    | 0.405     | 0.011 | 0.209 | 0.207 | 96.2     | -0.405    | -0.008| 0.207 | 0.206 | 96.2     | 0.405     | 0.005 | 0.147 | 0.152 | 94       |
| β₁    | 0.327     | 0.003 | 0.118 | 0.118 | 95.6     | 0.501     | 0.009 | 0.113 | 0.112 | 95.8     | 0.327     | 0.002 | 0.081 | 0.081 | 95.9     |
| γ₀    | 0.571     | -0.001| 0.034 | 0.034 | 95       | 0.571     | 0.004 | 0.038 | 0.038 | 94.1     | 0.571     | 0.001 | 0.074 | 0.073 | 95.7     |
| γ₁    | 0.307     | 0.002 | 0.023 | 0.023 | 94.9     | 0.307     | 0.003 | 0.028 | 0.028 | 95.6     | 0.307     | 0.001 | 0.016 | 0.017 | 93.4     |
| γ₂    | -0.75     | -0.004| 0.107 | 0.103 | 95.5     | -0.75     | 0.006 | 0.12  | 0.125 | 94.2     | -0.75     | -0.011 | 0.135 | 0.14  | 94.4     |
| β₀    | 0.405     | -0.001| 0.255 | 0.266 | 93.6     | -0.405    | 0.004 | 0.266 | 0.266 | 95.9     | 0.405     | 0.005 | 0.147 | 0.152 | 94       |
| β₁    | 0.327     | 0.007 | 0.138 | 0.142 | 93.9     | 0.501     | 0.003 | 0.135 | 0.135 | 94.7     | 0.327     | 0.002 | 0.081 | 0.081 | 95.9     |
| γ₀    | 0.571     | 0.003 | 0.036 | 0.036 | 94.7     | 0.571     | 0.005 | 0.041 | 0.04  | 94.7     | 0.571     | 0.001 | 0.074 | 0.073 | 95.7     |
| γ₁    | 0.307     | 0.004 | 0.028 | 0.029 | 94.5     | 0.307     | 0.003 | 0.036 | 0.038 | 94.2     | 0.307     | 0.001 | 0.016 | 0.017 | 93.4     |
| γ₂    | -0.75     | 0     | 0.116 | 0.121 | 94.5     | -0.75     | 0.011 | 0.135 | 0.14  | 94.4     | -0.75     | -0.004 | 0.084 | 0.086 | 94.2     |
Table 2.7: Bias, SE, RMSE, and CP for the cure rates of the Geometric cure rate model under proportional odds with log-logistic (Weibull) baseline.

<table>
<thead>
<tr>
<th>n</th>
<th>C</th>
<th>p_0</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>light</td>
<td>0.4</td>
<td>-0.001 (0)</td>
<td>0.049 (0.049)</td>
<td>0.051 (0.05)</td>
<td>74 (76.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>-0.001 (0)</td>
<td>0.036 (0.037)</td>
<td>0.036 (0.036)</td>
<td>88 (88.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.257</td>
<td>-0.001 (0)</td>
<td>0.028 (0.029)</td>
<td>0.027 (0.027)</td>
<td>94.6 (95.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.001 (0.001)</td>
<td>0.035 (0.038)</td>
<td>0.035 (0.04)</td>
<td>91.7 (91.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0 (0.001)</td>
<td>0.038 (0.041)</td>
<td>0.039 (0.04)</td>
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Table 2.8: Bias, SE, RMSE, and CP for the cure rates of the Poisson cure rate model under proportional odds with log-logistic (Weibull) baseline.

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<th>RMSE</th>
<th>CP(95%)</th>
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<td>0.035 (0.036)</td>
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<td>0.034 (0.036)</td>
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Table 2.9: Bias, SE, RMSE, and CP for the cure rates of the Bernoulli cure rate model under proportional odds with log-logistic (Weibull) baseline.

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<th>RMSE</th>
<th>CP(95%)</th>
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<td>0 (-0.001 )</td>
<td>0.038 (0.039 )</td>
<td>0.039 (0.039 )</td>
<td>88.3 (87 )</td>
<td></td>
</tr>
<tr>
<td>heavy ( p_0 )</td>
<td>0.6</td>
<td>-0.002 (-0.001 )</td>
<td>0.061 (0.063 )</td>
<td>0.058 (0.063 )</td>
<td>76 (75.3 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.476</td>
<td>0 (0 )</td>
<td>0.04 (0.042 )</td>
<td>0.038 (0.042 )</td>
<td>92.5 (90.8 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.355</td>
<td>0.001 (0 )</td>
<td>0.033 (0.034 )</td>
<td>0.032 (0.034 )</td>
<td>95.7 (95.5 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.003 (0.001 )</td>
<td>0.041 (0.043 )</td>
<td>0.041 (0.042 )</td>
<td>90 (88.6 )</td>
<td></td>
</tr>
<tr>
<td>800 light ( p_0 )</td>
<td>0.6</td>
<td>0.001 (-0.001 )</td>
<td>0.035 (0.035 )</td>
<td>0.035 (0.035 )</td>
<td>77.1 (76.3 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.476</td>
<td>0 (-0.001 )</td>
<td>0.024 (0.024 )</td>
<td>0.024 (0.024 )</td>
<td>92 (90.9 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.355</td>
<td>-0.001 (-0.001 )</td>
<td>0.021 (0.022 )</td>
<td>0.022 (0.023 )</td>
<td>93.7 (93.1 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>-0.001 (0 )</td>
<td>0.026 (0.027 )</td>
<td>0.027 (0.028 )</td>
<td>88.8 (86.3 )</td>
<td></td>
</tr>
<tr>
<td>heavy ( p_0 )</td>
<td>0.6</td>
<td>0 (0.001 )</td>
<td>0.043 (0.045 )</td>
<td>0.041 (0.045 )</td>
<td>75.8 (73.9 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.476</td>
<td>0 (0.001 )</td>
<td>0.029 (0.03 )</td>
<td>0.028 (0.029 )</td>
<td>90.8 (90.7 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.355</td>
<td>0.001 (0 )</td>
<td>0.023 (0.024 )</td>
<td>0.023 (0.024 )</td>
<td>94.7 (95.4 )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.001 (0 )</td>
<td>0.028 (0.029 )</td>
<td>0.028 (0.03 )</td>
<td>90 (89.7 )</td>
<td></td>
</tr>
</tbody>
</table>
We simulated 1000 random samples from the following five choice of \( \phi \) from COM-Poisson distributions: \( \phi = 0 \) (Geometric), \( \phi = 0.5 \), \( \phi = 1 \) (Poisson), \( \phi = 2 \), \( \phi \to \infty \) (Bernoulli). Two different sample sizes were considered: \( n = 400 \) (95, 102, 97, 106) and \( n = 800 \) (200, 168, 212, 220) for small and large sample sizes. The light and heavy censoring rates considered were (0.52, 0.45, 0.37, 0.3) and (0.65,0.49,0.4,0.35) with cure rates (0.4,0.2) if the lifetime follows proportional odds model under Weibull baseline with parameter \( \gamma_0 = 0.571 \), \( \gamma_1 = 0.307 \), \( \gamma_2 = -0.75 \). The light and heavy censoring rates were taken as (0.7, 0.57,0.45,0.34) and (0.8, 0.64, 0.5, 0.38) with cure rate (0.6, 0.25) if the lifetime follows proportional odds model under log-logistic baseline with parameter \( \gamma_0 = 0.75 \), \( \gamma_1 = 3.25 \), \( \gamma_2 = -0.75 \). Here, we carry out the model discrimination by two methods, namely, Likelihood-based method and information-based method.

### 2.5.1 Likelihood-based method

We consider a likelihood ratio test for the null hypothesis \( H_0 \) that the competing risk follows one of the three special cases of COM-Poisson distribution, namely, Geometric \( \phi = 0 \), Poisson \( \phi = 1 \), and Bernoulli \( \phi \to \infty \) versus the alternative hypothesis \( H_a \) that the competing risk follows the general COM-Poisson distribution. The test statistic is \( \Lambda = -2(\hat{l}_0 - \hat{l}) \), where \( \hat{l}_0 \) and \( \hat{l} \) are the values of the maximized log-likelihood function under the null and alternative hypotheses, respectively. The asymptotic distribution of the test statistic \( \Lambda \), under \( H_0 : \phi = 1 \) (Poisson) follows a \( \chi^2 \) distribution with one degree of freedom. However, the boundary distribution of the test statistic \( \Lambda \) when \( \phi = 0 \) (Geometric) and \( \phi \to \infty \) (Bernoulli) has a mixture distribution of \( \chi^2_0 \) and \( \chi^2_1 \) distributions such that \( P(\Lambda \leq \lambda) = \frac{1}{2} + \frac{1}{2} P(\Lambda_1 \leq \lambda_1) \), where \( \Lambda_1 \sim \chi^2_1 \), \( \chi^2_0 \) is chi-square distribution with 0 degrees of freedom and \( \chi^2_1 \) is the chi-square distribution with one degree of freedom.
Figure 2.1: Histogram of $\Lambda$ for the Poisson cure rate model under proportional odds assumption with log-logistic baseline, $n=400$ (left), $n=4000$ (right).

The values of $\phi$ used in the profile likelihood approach for the COM-Poisson distribution are $\{0,0.25,0.5,2/3,1,1.5,2,4,\infty\}$. Figure 2.1 provides the histograms of the test statistics $\Lambda$ on the Poisson cure rate model with proportional odds assumption under log-logistic baseline when sample size equals to 400 and 4000 over 1000 generated datasets. These plots also display the probability density of chi-square distribution with one degree of freedom, and 90% quantiles. The histogram of $\Lambda$ is not close to the asymptotic distribution when sample size is small while they become close as the sample size increases. This suggests a parametric bootstrap method would be better when the sample size is small, and we will describe this method in detail later in the illustrative example section. Incidentally, the same was observed under the proportional odds assumption with Weibull baseline.

### 2.5.2 Information-based method

We use Akaike information criterion (AIC) and Bayesian information criterion (BIC) for model selection among Geometric, Poisson, and Bernoulli distribution cure rate models.
The AIC and BIC are given by

\[ AIC = 2k - 2\hat{l} \quad \text{and} \quad BIC = k \log(n) - 2\hat{l}, \]  

(2.43)

where \( k \) is the number of model parameters to be estimated, \( \hat{l} \) is the maximized likelihood value, and \( n \) is the sample size. We select the model with the smallest value of AIC or BIC. AIC and BIC would give us the same selection rate since \( k = 5, n = 400 \) or 800 are the same in each of the scenarios among Geometric, Poisson, and Bernoulli distributions, i.e., the model with the largest \( \hat{l} \) is the model that fits the data best. We examine the total relative bias (TRB) and total root mean square error (TRMSE) due to misspecification of the cure rate model. TRB is the sum of the absolute bias of the estimated cure rates to that of the true cure rates for each of the four groups. Similarly, TRMSE is the sum of the absolute MSE of the estimated cure rates. TRB and TRMSE due to misspecification is defined as the difference of TRB and TRMSE between the true model and the wrongly specified model (see Tables 2.10 and 2.11).

Table 2.12 shows that the selection rates under AIC or BIC for the correct models increase as the sample size increases, while they decrease as censoring rate increases, and the selection rates for the correct models are always the highest among all the cases. If the true model is under Weibull baseline, the rate to select log-logistic as the true baseline is low, and the rate becomes even lower for large sample size, or under light censoring.

### 2.6 Illustration with melanoma data

Now, let us consider the melanoma data described earlier in Section 1.9. In this case, we have four different cases \((x = 0, 1, 2, 3)\) and the corresponding sample sizes to be \( n_1 = 111, \)
Table 2.10: TRB (in %) in the estimation of cure proportions when fitting different models for a given true model under proportional odds due to misspecification.

<table>
<thead>
<tr>
<th>n</th>
<th>censoring</th>
<th>Fitted Model</th>
<th>Weibull Baseline</th>
<th>Loglogistic Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Geometric Poisson Bernoulli</td>
<td>Geometric Poisson Bernoulli</td>
</tr>
<tr>
<td>400</td>
<td>light</td>
<td>Geometric</td>
<td>- 1.4 -1.5</td>
<td>- 0.3 -0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>- -0.4</td>
<td>0.2 - 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>80.8 1.4</td>
<td>0.4 0.3</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
<td>Geometric</td>
<td>- 0.9 1.5</td>
<td>- 2.6 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>45.9 - 1.1</td>
<td>0.4 - -1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>99.8 0 -</td>
<td>1.1 1.3</td>
</tr>
<tr>
<td>800</td>
<td>light</td>
<td>Geometric</td>
<td>- 1.4 -0.3</td>
<td>- 1.2 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>47.1 - 1.7</td>
<td>1 - 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>82.7 2 -</td>
<td>-0.1 -1.1</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
<td>Geometric</td>
<td>- -0.1 1.5</td>
<td>- 2.5 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>48.3 - 2.5</td>
<td>0.9 - 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>100.6 -0.5 -</td>
<td>0.8 0.3</td>
</tr>
</tbody>
</table>

Table 2.11: TRMSE in the estimation of cure proportions when fitting different models for a given true model under proportional odds due to misspecification.

<table>
<thead>
<tr>
<th>n</th>
<th>censoring</th>
<th>Fitted Model</th>
<th>Weibull Baseline</th>
<th>Loglogistic Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Geometric Poisson Bernoulli</td>
<td>Geometric Poisson Bernoulli</td>
</tr>
<tr>
<td>400</td>
<td>light</td>
<td>Geometric</td>
<td>- 0.999 0.961</td>
<td>- 0.3 -0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>2.081 1.407</td>
<td>0.2 - 0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>3.354 1.434</td>
<td>0.4 0.3</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
<td>Geometric</td>
<td>- 1.013 1.023</td>
<td>- 2.6 1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>1.637 - 1.266</td>
<td>0.4 - -1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>3.73 0.991 -</td>
<td>1.1 1.3</td>
</tr>
<tr>
<td>800</td>
<td>light</td>
<td>Geometric</td>
<td>- 1.026 1</td>
<td>- 1.2 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>3.692 2.071</td>
<td>1 - 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>6.693 1.539 -</td>
<td>-0.1 -1.1</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
<td>Geometric</td>
<td>- 0.967 0.97</td>
<td>- 2.5 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poisson</td>
<td>3.26 - 1.38</td>
<td>0.9 - 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>7.868 0.996 -</td>
<td>0.8 0.3</td>
</tr>
</tbody>
</table>
Table 2.12: Selection rates based on Akaike information criterion under different settings. The data were simulated from proportional odds with Weibull baseline ($\gamma_0 = 0.571$, $\gamma_1 = 0.307$, $\gamma_2 = -0.75$).

<table>
<thead>
<tr>
<th>n</th>
<th>censoring</th>
<th>Fitted Model</th>
<th>True COM-Poisson Model</th>
<th>$\phi = 0$</th>
<th>$\phi = 0.5$</th>
<th>$\phi = 1$</th>
<th>$\phi = 2$</th>
<th>$\phi \rightarrow \infty$</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>light</td>
<td>Weibull</td>
<td>Geometric</td>
<td>0.47</td>
<td>0.0551</td>
<td>0.0828</td>
<td>0.0262</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.235</td>
<td>0.2906</td>
<td>0.4919</td>
<td>0.2553</td>
<td>0.2913</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.19</td>
<td>0.3567</td>
<td>0.3758</td>
<td>0.5146</td>
<td>0.6996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>log-logistic</td>
<td>Geometric</td>
<td>0.039</td>
<td>0.0802</td>
<td>0.0141</td>
<td>0.0585</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.037</td>
<td>0.1283</td>
<td>0.0222</td>
<td>0.0898</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.029</td>
<td>0.0892</td>
<td>0.0131</td>
<td>0.0555</td>
<td>0.002</td>
</tr>
<tr>
<td>800</td>
<td>heavy</td>
<td>Weibull</td>
<td>Geometric</td>
<td>0.344</td>
<td>0.0452</td>
<td>0.1047</td>
<td>0.0241</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.197</td>
<td>0.2199</td>
<td>0.3797</td>
<td>0.204</td>
<td>0.279</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.229</td>
<td>0.3624</td>
<td>0.3867</td>
<td>0.5065</td>
<td>0.677</td>
</tr>
<tr>
<td></td>
<td></td>
<td>log-logistic</td>
<td>Geometric</td>
<td>0.065</td>
<td>0.1014</td>
<td>0.0393</td>
<td>0.0894</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.103</td>
<td>0.1627</td>
<td>0.0584</td>
<td>0.0985</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.062</td>
<td>0.1084</td>
<td>0.0312</td>
<td>0.0774</td>
<td>0.011</td>
</tr>
<tr>
<td>800</td>
<td>light</td>
<td>Weibull</td>
<td>Geometric</td>
<td>0.587</td>
<td>0.0512</td>
<td>0.0849</td>
<td>0.0271</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.266</td>
<td>0.4137</td>
<td>0.5905</td>
<td>0.3601</td>
<td>0.2402</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.105</td>
<td>0.2801</td>
<td>0.3104</td>
<td>0.4935</td>
<td>0.7578</td>
</tr>
<tr>
<td></td>
<td></td>
<td>log-logistic</td>
<td>Geometric</td>
<td>0.015</td>
<td>0.0753</td>
<td>0.0051</td>
<td>0.0411</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.012</td>
<td>0.1265</td>
<td>0.0081</td>
<td>0.0431</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.015</td>
<td>0.0532</td>
<td>0.001</td>
<td>0.0351</td>
<td>0</td>
</tr>
<tr>
<td>800</td>
<td>heavy</td>
<td>Weibull</td>
<td>Geometric</td>
<td>0.433</td>
<td>0.051</td>
<td>0.1085</td>
<td>0.0301</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.245</td>
<td>0.301</td>
<td>0.5136</td>
<td>0.2417</td>
<td>0.283</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.154</td>
<td>0.311</td>
<td>0.3126</td>
<td>0.5035</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td></td>
<td>log-logistic</td>
<td>Geometric</td>
<td>0.055</td>
<td>0.088</td>
<td>0.0111</td>
<td>0.0662</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poisson</td>
<td>0.074</td>
<td>0.159</td>
<td>0.0352</td>
<td>0.0832</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bernoulli</td>
<td>0.039</td>
<td>0.09</td>
<td>0.0191</td>
<td>0.0752</td>
<td>0.002</td>
</tr>
</tbody>
</table>
\( n_2 = 137, n_3 = 87, n_4 = 82 \). The percentage of censored observations for the four groups were 67.57\%, 61.31\%, 52.87\%, 32.93\%. See Figure 1.1 for a plot of the lifetimes of susceptible individuals from the four nodule groups.

The initial values for the EM algorithm were chosen in the following way. We consider the censored rate as the over-estimated cured rate of groups one and four, and then calculated \( \beta_0 \) and \( \beta_1 \). The initial guess for \( \gamma \) were estimated from the linear relationship between Nelson-Aalen estimates of log odds and log \( t \), i.e.,

\[
\log O(t; \gamma) = -\gamma_1 \log(t) + \gamma_1 \log(\gamma_0) + x \gamma_2, \tag{2.44}
\]

\[
\log O(t; \gamma) = x \gamma_2 - \log(e^{\gamma_1 t/\gamma_0} - 1) \approx -\frac{1}{\gamma_0} \log(t) - \frac{1}{\gamma_0} \log(\gamma_1) + x \gamma_2, \tag{2.45}
\]

for log-logistic and Weibull baseline distributions, respectively. We then fitted these data by Geometric (\( \phi = 0 \)), COM-Poisson (\( \phi = 0.5 \)), Poisson (\( \phi = 1 \)), COM-Poisson (\( \phi = 2 \)) and Bernoulli (\( \phi \approx \infty \)) cure rate models. These models, along with cure rate models proposed by Balakrishnan and Pal (2016), and Balakrishnan et al. (2017) are compared on the basis of AIC and BIC. From Table 2.13, we observe that \( \hat{\phi} \approx \infty \) and \( \hat{\phi} = 0 \) provide the maximized log-likelihood values, which means that the Bernoulli and Geometric cure rate models provide a good fit for the data under log-logistic odds and Weibull odds models, respectively. Moreover, the maximized log-likelihood value increases and decreases as \( \phi \) increases under the log-logistic odds and Weibull odds, respectively. The proposed model based on Weibull odds provides smaller values of \( \hat{l}, \ AIC \), and most of BIC values than the model based on Weibull lifetimes and the proportional hazards lifetimes with a Weibull baseline. The proposed model based on log-logistic odds provides the smallest \( \hat{l}, \ AIC \) and most of BIC values among all the models. In conclusion, \( \hat{\phi} = 0 \) under proportional odds model with a log-logistic distribution as the baseline gives the best fit for the data.
Table 2.13: AIC, BIC and $\hat{l}$ under different cure rate models

<table>
<thead>
<tr>
<th>Model</th>
<th>Geometric</th>
<th>Poisson</th>
<th>Bernoulli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\phi = 0$</td>
<td>$\phi = 0.5$</td>
<td>$\phi = 1$</td>
</tr>
<tr>
<td>Proportional AIC</td>
<td>1022.863</td>
<td>1022.845</td>
<td>1022.821</td>
</tr>
<tr>
<td>Odds BIC</td>
<td>1043.029</td>
<td>1043.011</td>
<td>1042.986</td>
</tr>
<tr>
<td>log-logistic  $\hat{l}$</td>
<td>-506.432</td>
<td>-506.423</td>
<td>-506.41</td>
</tr>
<tr>
<td>Proportional AIC</td>
<td>1025.644</td>
<td>1025.644</td>
<td>1025.644</td>
</tr>
<tr>
<td>Odds BIC</td>
<td>1045.809</td>
<td>1046.179</td>
<td>1046.539</td>
</tr>
<tr>
<td>Weibull  $\hat{l}$</td>
<td>-507.822</td>
<td>-508.007</td>
<td>-508.187</td>
</tr>
<tr>
<td>Proportional AIC</td>
<td>1028.676</td>
<td>1028.676</td>
<td>1028.676</td>
</tr>
<tr>
<td>Hazard BIC</td>
<td>1048.842</td>
<td>1052.633</td>
<td>1054.326</td>
</tr>
<tr>
<td>Weibull*  $\hat{l}$</td>
<td>-509.338</td>
<td>-511.238</td>
<td>-512.080</td>
</tr>
<tr>
<td>Weibull** BIC</td>
<td>1026.838</td>
<td>1032.388</td>
<td>1034.788</td>
</tr>
<tr>
<td></td>
<td>-509.419</td>
<td>-512.194</td>
<td>-514.896</td>
</tr>
</tbody>
</table>

* is taken from Balakrishnan and Pal (2016), while ** is taken from Balakrishnan et al. (2017).

Table 2.14: Estimates, standard errors and 95% CI for the cure rates

<table>
<thead>
<tr>
<th>Cure rate model, Baseline</th>
<th>Bernoulli, log-logistic</th>
<th>Geometric, Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>$\hat{p}_0$</td>
<td>SE</td>
</tr>
<tr>
<td>1</td>
<td>0.602</td>
<td>0.053</td>
</tr>
<tr>
<td>2</td>
<td>0.508</td>
<td>0.038</td>
</tr>
<tr>
<td>3</td>
<td>0.415</td>
<td>0.037</td>
</tr>
<tr>
<td>4</td>
<td>0.327</td>
<td>0.049</td>
</tr>
</tbody>
</table>

From Table 2.13, we can see that the maximum difference between $\hat{l}$ is only 0.09, which means that the difference between the maximized likelihood value is $e^{0.09} = 1.09$ among different $\phi$'s. Table 2.14 presents the estimates, standard errors and 95% CI of the cure rates stratified by nodule category. The confidence interval for all the models do not overlap for the first and forth nodule categories. Table 2.15 presents the MLES and their standard errors for different cure rate models under proportional odds assumption. It is to be noted that $\hat{l}$ is very close to each other under proportional odds model with log-logistic baseline even though the estimates are quite different. The same behaviour is also seen in the model discrimination section.
Table 2.15: MLEs and SEs of the model parameters

<table>
<thead>
<tr>
<th>Cure rate model, PO Baseline</th>
<th>Bernoulli, log-logistic MLEs</th>
<th>Geometric, Weibull MLEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Param</td>
<td>MLEs</td>
<td>SE</td>
</tr>
<tr>
<td>β₀</td>
<td>-0.413</td>
<td>0.2226</td>
</tr>
<tr>
<td>β₁</td>
<td>0.379</td>
<td>0.1151</td>
</tr>
<tr>
<td>γ₀</td>
<td>2.461</td>
<td>0.2995</td>
</tr>
<tr>
<td>γ₁</td>
<td>2.266</td>
<td>0.1877</td>
</tr>
<tr>
<td>γ₂</td>
<td>-0.473</td>
<td>0.1254</td>
</tr>
</tbody>
</table>

Figure 2.2: The plot of $\Lambda = -2(\hat{l}_0 - \hat{l}_1)$ vs $\phi$ under log-logistic baseline (left) and Weibull baseline (right) for the cutaneous melanoma data.
In order to further investigate the effect of $\phi$ under the COM-Poisson distribution, we fix $\phi$ from 0 to 5 with an increment of 0.1 and evaluate the maximum log-likelihood value for each $\phi$ through likelihood approach. Then, we test the null hypothesis $H_0 : \phi = \infty$ vs. $H_1 : 0 \leq \phi < \infty$ using the likelihood ratio test for the log-logistic odds baseline, and also $H_0 : \phi = 0$ vs. $H_1 : \phi > 0$ under the Weibull odds baseline. The likelihood ratio test statistic is given by $\Lambda = -2(\hat{l}_0 - \hat{l})$. Figure 2.2 shows that the likelihood ratio test statistic decreases and increases as $\phi$ increases for log-logistic and Weibull odds, respectively, which suggest that the maximized likelihoods increase and decrease as $\phi$ increases.

As we mentioned earlier in the model discrimination part, the asymptotic distribution is not suitable when the sample size is small. So, we use a bootstrap method to obtain the distribution of the likelihood ratio test statistic $\Lambda$. We generated 1000 samples from Geometric, Poisson and Bernoulli cure rate models under proportional odds model with log-logistic and Weibull distributions, respectively. For each of the dataset, we fit the true cure rate model as well as the COM-Poisson cure rate model, and then we calculate the values of $\Lambda$. The histograms of $\Lambda$ are given in Figure 2.3. The p-value is the proportion of times $\Lambda$ is greater than the corresponding value determined from the data. We obtained p-values of 0.142, 0.132 and 0.681 if we test for Geometric, Poisson and Bernoulli cure rate models with log-logistic odds. Also, we obtained p-values of 0.599, 0.001 and 0.000 if we test for Geometric, Poisson and Bernoulli cure rate models under Weibull odds. Moreover, it would be of interest to get an acceptable range of $\phi$ if we are using the Weibull baseline for the proportional odds model. Figure 2.2 presents the values of $\Lambda$ against $\phi$ with $\phi \in [0, 5]$. We may reject the null hypothesis $H_0 : \phi = 0$ with 10% level of significance if $\Lambda$ is greater than 0.3. This implies that $\phi \in [0, 0.4]$, and the Geometric model under Weibull odds adequately fits the data.
We also set up a test on the effect of the proportional odds parameter, namely, $H_0 : \gamma_2 = 0$ as the null hypothesis vs. $H_1 : \gamma_2 \neq 0$ as alternative hypothesis for Geometric, Poisson, Bernoulli cure rate models with $\phi = 0, 1, \infty$ under Weibull (log-logistic) baseline. Note that the covariate or the nodule categories would not affect the analysis if $\gamma_2 = 0$, and the lifetime would just follow a Weibull (log-logistic) distribution. The test statistic values turned out to be 3.194 (14.95), 10.414 (19.564), 17.767 (25.99) with the corresponding p-values as 0.0739 (0.00011), 0.00125 (9.73x10^{-6}), 0.000025 (3.4x10^{-7}). Most of the p-values were less than 0.05, which shows that the proportional odds model does provide a better fit than a constant lifetime model over the four nodule categories.

Deviance residual is examined to check the error, which is defined as

$$D_i = sign(I_i + \log \hat{S}_p(t_i))\sqrt{-2(I_i + \log \hat{S}_p(t_i) + I_i\log[-(\log \hat{S}_p(t_i))])}.$$ (2.46)

Figures 2.6, 2.7 and 2.4, 2.5 present the deviance residuals as well as QQ plots for various fitted cure rate models. It can be seen that the deviance residuals are distributed around 0, and do satisfy the normality assumption.

### 2.6.1 Model diagnosis

In this section, we check if the proportional odds model with log-logistic baseline assumption on the lifetime is suitable for the cutaneous melanoma data that we have discussed in the previous section. From (2.45), we can see that $\log \hat{O}(t(i))$ and $\log t(i)$ should have a
Figure 2.3: The histogram of $\Lambda = -2(\hat{l}_0 - \hat{l})$ from 1000 generated datasets with respect to MLEs on Geometric (top), Poisson (middle), Bernoulli (bottom) cure rate model with the lifetime distribution as a proportional odds model with log-logistic (left) and Weibull (right) baseline.
Figure 2.4: QQ plot for deviance residuals of proportional odds model with log-logistic baseline for the cutaneous melanoma data.

Figure 2.5: QQ plot for deviance residuals of proportional odds model with Weibull baseline for the cutaneous melanoma data.
Figure 2.6: Deviance residuals of proportional odds model with log-logistic baseline for the cutaneous melanoma data.

Figure 2.7: Deviance residuals of proportional odds model with Weibull baseline for the cutaneous melanoma data.
linear relationship between them. For the cutaneous melanoma data, we calculated the cumulative hazard function \( \hat{H}(t) \) as the observed hazard through the non-parametric Nelson-Aalen estimator, and then get the log-odds function accordingly as

\[
\hat{H}(t) = \sum_{t_i \leq t} \frac{d_i}{n_i}; \quad \hat{S}(t) = e^{-\hat{H}(t)}, \quad \log(O) = \log(\hat{S}(t)) - \log(1 - \hat{S}(t)),
\]

(2.47)

where \( d_i \) and \( n_i \) are the number of events and total individuals at risk at time \( t_i \), respectively.

Figure 2.8 presents the scatter plot of \( \log \hat{O}(t_{(i)}) \) vs. \( \log t_{(i)} \) for each category. The plot shows almost a linear relationship among the four groups. It is to be noticed that there is an intersection among \( x = 2 \) and \( x = 3 \) for short survival times which violates our proportional odds assumption. Figure 2.9 shows the difference of log-odds between nodule categories 1, 2, 3 and baseline 0. In this figure, the log odds for each of the nodule categories are calculated by using the linear interpolation within the range of discrete points from 0.4 to 2. From our proportional odds assumption, \( \log O - \log O_0 = x\gamma_2 \), we know that the difference should be a linear horizontal line and does not depend on the time. However, the lines in Figure 2.9 look parallel, but do show give a little curvature. Since our data include the cured individuals and are not independent, linear regression test may not be good for model diagnosis.

We use the parametric bootstrap and Monte Carlo methods to develop a goodness-of-fit test to check whether the Bernoulli cure rate model with proportional odds assumption under log-logistic baseline is sufficient for modeling these data. The critical region for this test will be to the left. We simulated 1000 datasets based on Bernoulli cure rate model with proportional odds survival assumption under log-logistic baseline. The parameters are \( \beta_0 = -0.413, \beta_1 = 0.379, \gamma_0 = 2.461, \gamma_1 = 2.266, \gamma_2 = -0.473 \). The censored proportion for the nodule categories are \((0.676, 0.613, 0.529, 0.329)\), respectively. We calculated the
values of maximum likelihood $\hat{l}_1, \ldots, \hat{l}_{1000}$ for each of these generated datasets, and order them $(\hat{l}_1, \ldots, \hat{l}_{1000})$. Then, we determine the proportion of times $\hat{l}$ is smaller than the maximum likelihood we obtained from the data as -506.342. Figure 2.10 presents the histogram of the log-likelihood over 1000 simulated datasets. We obtained the p-value for this test as 0.895, which indicates that our model is quite suitable for these data.
Figure 2.9: Difference of log-odds between nodule categories against \( \log t \) for the cutaneous melanoma data based on Nelson-Aalen estimator.

Figure 2.10: Histogram of \( \hat{t} \)
2.6.2 Estimation of conditional cure rate

Suppose an individual is in nodule category \( j \), if the information is available for the individual survived up to time \( t \), then he or she would be interested in finding the conditional cure rate based on the individual having survived up to time \( t \), i.e. \( P(I = 0|T > t) \) for \( x = j \). For \( x = j \), the estimate of this probability is then given by,

\[
\hat{q}_0j = \hat{P}(I = 0|T > t) = \frac{\hat{P}(I = 0, T > t)}{\hat{P}(T > t)},
\]

which can be estimated through Bayesian theorem,

\[
\hat{q}_0j = \hat{P}(I = 0|T > t) = \frac{\hat{P}(I = 0, T > t)}{\hat{P}(T > t)} = \frac{\hat{P}(T > t|I = 0)\hat{P}(I = 0)}{\hat{P}(T > t)} = \frac{\hat{P}(I = 0)}{\hat{P}(T > t)} = \frac{\hat{p}_0j}{\hat{p}_0j + (1 - \hat{p}_0j)\hat{S}_{s_2}(t)}.
\]

Based on the melanoma data described earlier in Section 1.9, the corresponding plot on the conditional cure rate for the Bernoulli cure rate model with proportional odds model on log-logistic baseline are presented in Figure 2.11.
2.6.3 Sample size determination

Sample size and power are key elements of study design. It would be of interest to develop a sample size and power analysis study later on for future study based on the estimated parameters and information matrix. Consider the hypothesis testing of the key factor that may affect the cure rate, i.e. for one covariate case,

\[ H_0 : \hat{\beta} = 0 \text{  v.s.  } H_a : \hat{\beta} = \beta^* \]  \hspace{1cm} (2.50)
The probability of at least $1 - \beta$ to reject $H_0$ when $H_a$ is true is given by

$$P\left( \frac{\hat{\beta} - 0}{\sqrt{\text{var}(\hat{\beta})}} > z_\alpha \mid H_0 \right) = \alpha,$$

where $z_\alpha$ is the upper percentage point of the standard normal distribution.

$$P\left( \frac{\hat{\beta} - 0}{\sqrt{\text{var}(\hat{\beta})}} > z_\alpha \mid H_a \right) \geq 1 - \gamma$$

Then the sample size can be determined from the following inequality.

$$P\left( \frac{\hat{\beta} - 0}{\sqrt{\text{var}(\hat{\beta})}} - \frac{\beta^*}{\sqrt{\text{var}(\hat{\beta})}} > z_\alpha - \frac{\beta^*}{\sqrt{\text{var}(\hat{\beta})}} \right) \geq 1 - \gamma$$

$$z_\alpha - \frac{\beta^*}{\sqrt{\text{var}(\hat{\beta})}} \leq z_{1-\gamma}$$

$$\frac{\beta^*}{\sqrt{\text{var}(\hat{\beta})}} \geq z_\alpha - z_{1-\gamma}, \text{ where } \text{var}(\hat{\beta}) = \frac{\sigma^2}{n}$$

$$n \geq \left( \frac{z_\alpha - z_{1-\gamma}}{\frac{\beta^*}{\sigma}} \right)^2.$$

Here, $\sigma$ can be determined from the illustrative data example.
Chapter 3

Destructive Cure Rate Model under Proportional Odds Lifetime

3.1 Introduction

Assume $M$ follows a weighted Poisson distribution undergoing a damaging process as discussed earlier in Section 1.4. The probability mass functions of $M$ and $D$, cure rate, population survival function and population density function for destructive length-biased Poisson (DLBP), destructive negative binomial (DNB) and destructive exponentially weighted Poisson (DEWP) cure rate models are all summarized in Table 3.1.
Table 3.1: The model, cure rate, population survival function and population density function for three special cases of weighted Poisson competing variable.

<table>
<thead>
<tr>
<th>Model</th>
<th>$P[M = m; \eta, \phi]$</th>
<th>$P[D = d; \eta, \phi, p]$</th>
<th>$p_0$</th>
<th>$S_p(y)$</th>
<th>$f_p(y)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNB</td>
<td>$e^{-\eta \phi (m+1)\phi} \Gamma(m+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$e^{-\eta \phi d \phi} \Gamma(d+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$\frac{1}{1+p\phi F(y)}$</td>
<td>$\frac{mpF(y)S_p(y)}{1+p\phi F(y)}$</td>
<td>$S_p(y)f(y)\eta \phi$</td>
</tr>
<tr>
<td>DEWP</td>
<td>$e^{-\eta \phi (m+1)\phi} \Gamma(m+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$e^{-\eta \phi d \phi} \Gamma(d+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$e^{-\eta \phi d \phi} F(y)$</td>
<td>$S_p(y)f(y)\eta \phi$</td>
<td>$S_p(y)f(y)\eta \phi$</td>
</tr>
<tr>
<td>DLBP</td>
<td>$e^{-\eta \phi (m+1)\phi} \Gamma(m+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$e^{-\eta \phi d \phi} \Gamma(d+1)\phi \Gamma(1+\eta \phi)$</td>
<td>$e^{-\eta \phi d \phi} F(y)$</td>
<td>$S_p(y)f(y)\eta \phi$</td>
<td>$S_p(y)f(y)\eta \phi$</td>
</tr>
</tbody>
</table>

with $m = 0, 1, 2, 3 \ldots, d = 0, 1, 2, 3 \ldots, d < m$.

In this Chapter, we assume a proportional odds model for the distribution of $W_j$, with a parametric assumption on the baseline odds function. To be more specific, the odds function of $W_j$ is taken as

$$O(w) = \theta O_0(w), \quad (3.1)$$

where $O(w) = S(w)/F(w)$ is the odds ratio (that is, the ratio of survival to failure by $w$), the term $\theta$ is linked to covariates in the form $e^{x'\gamma_2 + \phi' \gamma_3}$ with $x_c = (x_1, \ldots, x_p)'$ being a vector of $p$ covariates, $z = (z_1, \ldots, z_g)'$ being a vector of $g$ covariates, $\gamma_2 = (\gamma_1, \ldots, \gamma_p)'$, and $\gamma_3 = (\gamma_{p+1}, \ldots, \gamma_{p+g})'$ are the proportional odds regression coefficients. We can further get the survival function and the corresponding probability density function (p.d.f.) for $W_j$ as follows:

$$S(w) = [1 + e^{x'\gamma_2 + \phi' \gamma_3} (S_0(w)^{-1} - 1)]^{-1}, \quad w > 0, \quad (3.2)$$

$$f(w) = f_0(w)e^{x'\gamma_2 + \phi' \gamma_3} [(1 - S_0(w))e^{x'\gamma_2 + \phi' \gamma_3} + S_0(w)]^{-2}, \quad w > 0. \quad (3.3)$$

The rest of this chapter proceeds as follows. Section 3.2 describes the data and the likelihood function. The estimation of the cure rate and other model parameters and their
properties are discussed in Section 3.3. In Section 3.4, an extensive Monte Carlo simulation study is carried out. In Section 3.5, we conduct a model discrimination between DNB and DEWP models using information- and likelihood-based methods. In addition, a malignant melanoma data example is analyzed using the models and inferential methods developed here in Section 3.6 for illustrative purpose.

3.2 Data and the likelihood

Censoring is a common occurrence in lifetime data analysis primarily due to the life expectancy exceeding the duration of trial follow-up. Suppose the time-to-event of event of interest (say, death) is not completely observed and is subject to non-informative right censoring, which means that the lifetime above a certain value is not completely observed. Then, the observation time $T_i$ for the $i$th subject would be the minimum of the censoring time $C_i$ and the actual lifetime $Y_i$, i.e.,

$$T_i = \min\{Y_i, C_i\}, \ i = 1, \ldots, n. \quad (3.4)$$

We define an indicator function $\delta_i = I(Y_i \leq C_i)$ for the $i$-th subject such that $\delta_i = 1$ if the lifetime is observed while $\delta_i = 0$ if the lifetime is right censored, sets $\Delta_0$ and $\Delta_1$ correspond to all the $i$’s being equal to 0 or 1, and set $\Delta^*$ contains all the $i$’s. It is to be noted that the cure rate $p_{0i}$ is purely a function of $\eta_i$ and $p_i$. We, therefore, relate the parameter $p_i$ to covariate $x_i = (1, x_{ic})$ by the logistic link function, and $\eta_i$ to covariate $z_i$ by the log-linear link function for all the destructive cure rate models. More specifically,
we set

\[ p_i = \frac{e^{x_i'\beta_1}}{1 + e^{x_i'\beta_1}}, \quad \eta_i = e^{z_i'\beta_2}, \quad i = 1, \ldots, n, \]  

(3.5)

where \( x_i \) and \( z_i \) are covariates, and \( \beta_1 \) and \( \beta_2 \) are the vectors of the regression coefficients. It is to be noted to be that \( \beta_2 \) should not include an intercept term to retain identifiability.

For \( n \) pairs of observations \( (t, \delta) = \{(t_1, \delta_1), \ldots, (t_n, \delta_n)\} \) corresponding to \( n \) subjects, the observed data likelihood function under non-informative censoring is then given by

\[ L(\theta; t, \delta) \propto \prod_{i=1}^{n} \left\{ f_p(t_i; \theta) \right\}^\delta_i \left\{ S_p(t_i; \theta) \right\}^{1-\delta_i}, \]  

(3.6)

where \( \theta \) is the set of parameters \( (\phi, \beta', \gamma') \), which is equivalent to

\[ L(\theta; t, \delta) \propto \prod_{i \in \Delta_1} f_p(t_i; \theta) \prod_{i \in \Delta_0} \left\{ p_0 + (1-p_0)S(t_i; \theta) \right\}. \]  

(3.7)

In this work, we consider two baseline distributions of the proportional odds survival model for the time-to-event random variable, namely, Weibull and Log-logistic distributions. It should be noted here that Log-logistic distribution actually processes the proportional odds property, while Weibull distribution does not. The survival function and the p.d.f. of \( W \) under a Weibull baseline are as follows:

\[ S(w; \gamma) = [1 + e^{w_2 + w_3 \gamma} (e^{(\gamma_1 w)^{1/\gamma_0}} - 1)]^{-1}, \]  

(3.8)

\[ f(w; \gamma) = \frac{(\gamma_1 w)^{1/\gamma_0} e^{x_2 \gamma_2 + x_3 \gamma_3 - (\gamma_1 w)^{1/\gamma_0}}}{[e^{-(\gamma_1 w)^{1/\gamma_0}} (e^{x_2 \gamma_2 + x_3 \gamma_3} - 1) + 1]^{2 \gamma_0 w}}, \]  

(3.9)

where \( w > 0, \gamma_0 > 0 \) and \( \gamma_1 > 0 \) are the shape and scale parameters of the baseline.
Weibull distribution, respectively. Instead, if we assume that the baseline distribution is a Log-logistic distribution with $\gamma_0 > 0$ and $\gamma_1 > 0$ as the scale and shape parameters, respectively, the corresponding odds function of $W_i$ is seen to be

$$O(w; x, z, \gamma) = \frac{\gamma_0^{\gamma_1}}{w^{\gamma_1}} e^{x^2 \gamma_2 + z^2 \gamma_3} = O_0(w; x, z, \gamma) e^{x^2 \gamma_2 + z^2 \gamma_3}. \quad (3.10)$$

Thus, $W_i$ still follows a two-parameter log-logistic distribution ($\gamma_0, \gamma_1 > 0$) with shape parameter $\gamma_1$ and scale parameter $\gamma_0 e^{-\left(x^2 \gamma_2 + z^2 \gamma_3\right) / \gamma_1}$. The corresponding survival and density functions are

$$S(w, \gamma) = \frac{\gamma_0^{\gamma_1}}{\gamma_0^{\gamma_1} e^{x^2 \gamma_2 + z^2 \gamma_3} + w^{\gamma_1}}, \quad (3.11)$$

$$f(w, \gamma) = \frac{\gamma_0^{\gamma_1} e^{x^2 \gamma_2 + z^2 \gamma_3} \gamma_1^{\gamma_1 - 1}}{\left(\gamma_0^{\gamma_1} e^{x^2 \gamma_2 + z^2 \gamma_3} + w^{\gamma_1}\right)^2}, w > 0. \quad (3.12)$$

Note that the mean does not exist if $\gamma_1 < 1$ and the variance does not exist if $\gamma_1 < 2$.

### 3.3 Estimation of model parameters

We develop here an Expectation-Maximization algorithm to obtain the MLE of $\theta$, and a profile likelihood approach for the estimation of the parameter $\phi$. It is well-known that EM is an effective technique for finding the maximum likelihood estimates of unknown parameters of a model involving unobserved variables [for further discussion, see McLachlan and Krishnan (2007)]. In our model, the random variable $I_i$’s are observed for $i$ in the set $\Delta_1$ while they are unobserved for $i$ in the set $\Delta_0$. Let us denote the set of complete data by

$$\{(t, \delta, x, z, I) = \{(t_1, \delta_1, x_1, z_1, I_1), \ldots, (t_n, \delta_n, x_n, z_n, I_n)\}. $$

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Then, the complete data likelihood function is given by,

\[ L_c(\theta; t, x, z, \delta, I) \propto \prod_{i \in \Delta_1} f_p(t_i, x_i, z_i, \theta) \prod_{i \in \Delta_0} p_0(\beta, x_i, z_i)^{1-I_i} \left[ (1 - p_0(\beta, x_i, z_i))S_s(t_i, x_{ic}; \theta) \right]^{I_i}, \]

(3.13)

where \( I = (I_1, \ldots, I_n)' \), \( x_{ic} = (x_{i1}, \ldots, x_{ip})' \), \( x_i = (1, x_{ic})' \), and \( z_i = (z_{i1}, \ldots, z_{ig})' \). The corresponding complete log-likelihood function (without the constant term) is as follows:

\[
\begin{align*}
    l_c(\theta; t, x, z, \delta, I) &= \sum_{i \in \Delta_1} \log f_p(t_i, x_i, z_i, \theta) + \sum_{i \in \Delta_0} (1-I_i) \log p_0(\beta, x_i, z_i) \\
    &\quad + \sum_{i \in \Delta_0} I_i \{ \log S_s(t_i, x_{ic}; \theta) - p_0(\beta, x_i, z_i) \}.
\end{align*}
\]

(3.14)

The complete log-likelihood (without the constant term) for the special cases of DLBP, DNB, and DEWP are as follows:

\[
\begin{align*}
    l_c = & \sum_{i \in \Delta_1} \log p_i \left[ \eta_i + \frac{1}{1 - p_i F(t_i)} \right] f(t_i) + \sum_{i \in \Delta^*} \left[ \log(1 - p_i F(t_i)) - \eta_i p_i F(t_i) \right], \\
    l_c = & \sum_{i \in \Delta_1} \left( \log \{ \eta_i p_i f(y) \} - (1 + \frac{1}{\phi}) + \log[1 + \eta_i \phi p_i F(y)] \right) \\
    & - \frac{1}{\phi} \sum_{i \in \Delta_0} \log \left[ 1 + \eta_i \phi p_i F(y) \right], \\
    l_c = & \sum_{i \in \Delta_1} \left( \log f(t_i) + \log \eta_i + \log p_i + \phi \right) - \sum_{i \in \Delta^*} \eta_i p_i e^\phi F(t_i),
\end{align*}
\]

(3.15, 3.16, 3.17)

where \( F(t_i) \) follows the proportional odds assumption in (3.1).
3.3.1 E-step

The expectation step is achieved by calculating the expected value of the complete data log-likelihood function with respect to the conditional distribution of the unobserved \( I_i \)’s \((i \in \Delta_0)\), given the observed data \( O = \{(t_i, \delta_i, x_i, z_i), i \in \Delta_1\} \) under the current estimates of the parameters \( \theta^{(k)} = (\beta', \gamma') \) for a fixed value of \( \phi \). Let us define the \( Q \) function as

\[
Q(\theta, \pi^{(k)}) = E(l_c(\theta; t, x, z, I)|O, \theta^{(k)}),
\]

at the \( k \)-th iteration step. In our model, \( I_i \)’s are Bernoulli random variables and we can therefore easily find the conditional expectation of the \( i \)th observation that is censored in the following way:

\[
\pi^{(k)}_i = E(I_i|O, \theta^{(k)})
= P(I_i = 1|T > t) + P(I_i = 0|T > t)
= \frac{P(T > t|I_i = 1)P(I_i = 1)}{P(T > t)} + 0
= \frac{(1 - p_0(\beta^{(k)}, x_i, z_i))S_s(t_i, x_i, z_i, \theta^{(k)})}{S_p(t_i, x_i, z_i; \theta^{(k)})}|_{\theta = \theta^{(k)}}.
\]

For the special cases of DLBP, DNB, and DEWP, \( \pi^{(k)}_i \) are as follows:

\[
\text{DLBP : } \pi^{(k)}_i = 1 - \frac{e^{-\eta_1^{(k)} p_i^{(k)} S(t_i^{(k)})} (1 - p_i^{(k)})}{1 - p_i^{(k)} F(t_i^{(k)})},
\]

\[
\text{DNP : } \pi^{(k)}_i = 1 - \left\{ \frac{1 + \eta_1^{(k)} \phi_1^{(k)} p_i^{(k)} F(t_i^{(k)})}{1 + \eta_1^{(k)} \phi_1^{(k)} p_i^{(k)}} \right\}^{\frac{1}{\phi}},
\]

\[
\text{DEWP : } \pi^{(k)}_i = 1 - \exp\left[ -\eta_i^{(k)} p_i^{(k)} e^{\phi} S(t_i^{(k)}) \right].
\]
Now, for a fixed value of $\phi$, the $Q$ function is given by

$$Q(\theta, \pi^{(k)}) = \sum_{i \in \Delta_1} \log f_p (t_i, x_i, z_i, \theta) + \sum_{i \in \Delta_0} \{(1 - \pi_i^{(k)}) \log p_0(\beta, x_i, z_i)$$

$$+ \pi_i^{(k)} \log [S_p (t_i, x_i, z_i; \theta) - p_0(\beta, x_i, z_i)] \}.$$  \hspace{1cm} (3.23)

For the special cases of DLBP, DNB, and DEWP, the $Q$ function takes on the following forms:

$$Q = \sum_{i \in \Delta_1} \{ \log p_i [\eta_i (1 - p_i F(t_i)) + 1] f(t_i) - \eta_i p_i F(t_i) \} + \sum_{i \in \Delta_0} (1 - \pi_i^{(k)}) \log q_i - \eta_i p_i$$

$$+ \sum_{i \in \Delta_0} \pi_i^{(k)} \log [e^{-\eta_i p_i F(t_i)} (1 - p_i F(t_i)) - q_i e^{-\eta_i p_i}],$$ \hspace{1cm} (3.24)

$$Q = \sum_{i \in \Delta_1} [\log (\eta_i p_i f(t_i)) - (1 + \frac{1}{\phi}) \log (1 + \eta_i \phi p_i F(t_i))] - \sum_{i \in \Delta_0} \frac{1}{\phi} (1 - \pi_i^{(k)}) \log (1 + \eta_i \phi p_i)$$

$$+ \sum_{i \in \Delta_0} \pi_i^{(k)} \log [(1 + \eta_i \phi p_i F(t_i))^{-\frac{1}{\phi}} - (1 + \eta_i \phi p_i)^{-\frac{1}{\phi}}],$$ \hspace{1cm} (3.25)

$$Q = \sum_{i \in \Delta_1} (\log [f(t_i) \eta_i p_i] + \phi - \eta_i p_i e^{\phi} F(t_i)) + \sum_{i \in \Delta_0} \{(1 - \pi_i^{(k)}) \eta_i p_i e^{\phi}$$

$$+ \pi_i^{(k)} \log [e^{-\eta_i p_i e^{\phi} F(t_i)} - e^{-\eta_i p_i e^{\phi}}],$$ \hspace{1cm} (3.26)

where $F(t_i)$ and $S(t_i)$ follow the proportional odds assumption in (3.1).
3.3.2 M-step

The M-step is achieved by maximizing the $Q(\theta, \pi^{(k)})$ function in order to obtain the improved estimate of $\theta$ at the $(k+1)-$th iteration step, i.e.,

$$\theta^{(k+1)} = \arg \max_{\theta} Q(\theta, \pi^{(k)}).$$ \hspace{1cm} (3.27)

As the MLEs of $\beta$ and $\gamma$ do not have explicit expressions, a numerical maximization is carried out by using one-step Newton-Raphson method. The explicit forms for the first- and second-order derivatives of the $Q(\theta^*, \pi^{(k)})$ function that are required for the numerical maximization procedure are presented in the Appendix.

For a fixed value of $\phi$, the E-step and the M-step are alternated until the parameter estimates have converged to a desired level of accuracy. The parameter $\phi$ is determined by using the profile likelihood technique. We consider a range of $\phi$ with small increment for the profile likelihood estimation, and the accuracy of the estimates would be determined by the value of the range and the increment. For each value of $\phi$, the MLEs of all the other parameters are found, and then the value of $\phi$ with the largest likelihood value is chosen as the final estimate of the parameter.

3.3.3 Standard errors and asymptotic confidence intervals

We can approximate the asymptotic variance-covariance matrix of the MLEs $(\hat{\beta}', \hat{\gamma}')'$ by inverting the observed Fisher information matrix of $\beta$ and $\gamma$, under a fixed value of $\phi$. Then, the components of the observed Fisher information matrix can be calculated from the negative second-order derivatives of the complete data likelihood function from the EM algorithm $l(\theta; t, x, \delta)$ with respect to $\beta$ and $\gamma$. Explicit forms of the components of the score
function [for detailed information, refer to Louis (1982)] and the observed information matrix is given in the Appendix. In this way, we can obtain the standard errors as square roots of the variances and then construct the corresponding asymptotic confidence interval for each parameter.

3.3.4 Estimate of the cure rate and its standard error

The cure rate \( p_{0i} \) for group \( i \) is a function of \( \beta \). Suppose \( \hat{\beta} \) is the MLE of the regression coefficient \( \beta \). Then, the MLE of \( p_{0i} \) can be readily found and then the standard error of \( \hat{p}_{0i} \) can be found through delta method as,

\[
\text{sd}(\hat{p}_{0i}) = \sqrt{\left( \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, ..., \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_l} \right) \text{var} \left( \hat{\beta} \right) \left( \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_0}, ..., \frac{\partial \hat{p}_{0i}}{\partial \hat{\beta}_l} \right)'}.
\] (3.28)

3.3.5 Estimate of the destructive probability and its standard error

Suppose \( \hat{\beta} \) is the MLE of the regression coefficient \( \beta \). Then, the estimate of the destructive probability for group \( i \) is calculated as

\[
\hat{p}_i = \frac{e^{x_i'\hat{\beta}_1}}{1 + e^{x_i'\hat{\beta}_1}}, \quad i = 1, ..., n.
\] (3.29)

The standard error of \( \hat{p}_i \) can be found once again through delta method as

\[
\text{sd}(\hat{p}_i) = \sqrt{\left( \frac{\partial \hat{p}_i}{\partial \hat{\beta}_0}, ..., \frac{\partial \hat{p}_i}{\partial \hat{\beta}_l} \right) \text{var} \left( \hat{\beta} \right) \left( \frac{\partial \hat{p}_i}{\partial \hat{\beta}_0}, ..., \frac{\partial \hat{p}_i}{\partial \hat{\beta}_l} \right)'}.
\] (3.30)
3.4 Simulation study

In this section, we perform an extensive Monte Carlo simulation study to demonstrate the EM algorithm developed in the preceding section. For illustrative purpose, we mimic a classical melanoma survival data described in Chapter 1, and consider various scenarios by varying the sample size, destructive probability, and censoring rate. From a medical point of view, the thickness of the tumour cell and whether the ulcer is present or not are thought to be important prognostic variables to determine the chance of survival from malignant melanoma. Therefore, tumour thickness $x$ and ulceration state $z$ are chosen as two covariates. A preliminary analysis of the data shows that 44% of the patients had ulceration status as present. So, we first generated a random number from $\text{Uniform}(0,1)$, and if it was greater than 0.44, we set ulceration status to be 0 which means the ulceration is absent. The real data showed the mean of tumour thickness to be 1.81 mm for this group. Hence, we generated the tumour thickness from an exponential distribution with rate parameter as $1/1.81=0.552$. Otherwise, we set the ulceration status to be 1 which means the ulceration is present and generated the tumour thickness from a Weibull distribution. The real data suggests the mean and standard deviation of tumour thickness are 4.34 mm and 3.22 mm for this group. So, from the mean and the standard deviation, we find the shape and scale parameters $\alpha_1$ and $\alpha_2$ through the following equations:

\[
\left(\frac{3.22}{4.34}\right)^2 + 1 - \frac{\Gamma(1 + \frac{2}{\alpha_1})}{\Gamma(1 + \frac{1}{\alpha_1})^2} = 0, \quad \frac{4.34}{\Gamma(1 + \frac{1}{\alpha_1})} - \alpha_2 = 0.
\]

These values of $\alpha_1$ and $\alpha_2$ were then used to simulate the tumor thickness from the corresponding Weibull distribution.

The censored times were simulated from an exponential distribution with rate 0.05 and
0.1 corresponding to small and large censoring, respectively. We considered the sample sizes to be 300 and 600 corresponding to small and large sample sizes, respectively. In order to generate the damage distribution, we fixed minimum and maximum values of $p$ corresponding to the minimum and maximum values in the covariate $x$. The regression coefficients were then found through the equations

$$
\min(p) = \frac{e^{\beta_0 + \beta_1 \min(x)}}{1 + e^{\beta_0 + \beta_1 \min(x)}}, \quad \max(p) = \frac{e^{\beta_0 + \beta_1 \max(x)}}{1 + e^{\beta_0 + \beta_1 \max(x)}}.
$$

(3.32)

We fixed the minimum and maximum values of $p$ as (0.2,0.6) or (0.3,0.9) for small or large destructive probability. Note that $x$ are random for each simulation, and $\beta_0$ and $\beta_1$ were therefore not fixed throughout the simulation. The value of $\eta$ was chosen to be 3.

For each individual in the Destructive Negative Binomial cure rate model, we generated the censoring time $C_i$ from exponential distribution with rate 0.05 and 0.1 corresponding to small and large censoring. To simulate the number of competing risks, we generated a random variable $M_i$ from a Negative Binomial distribution with parameter $\frac{1}{\phi}$ and probability of success $\frac{1}{1+\phi \eta_i}$. If $M_i = 0$, then we set $D_i = 0$. If $M_i > 0$, we generated $D_i$ from binomial distribution with size $M_i$ and probability of success $p$. If $D_i = 0$, the observed lifetime was taken to be the censoring time. Otherwise, we generated $D_i$ random variables $\{Y_1, \ldots, Y_{D_i}\}$ from a proportional odds model with a parametric baseline. Here, we used $(0.34,0.13,-0.21,1.9)$ for the Weibull baseline, and $(8.15,2.88,-0.24,2.55)$ for the log-logistic baseline for the parameter vector $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)$. The observed lifetimes were then taken to be the minimum of the censoring time and the actual lifetime, i.e., $T_i = \min\{Y_1, \ldots, Y_{D_i}, C_i\}$. The simulation procedure for the Destructive exponentially weighted Poisson cure rate model and Destructive Length-biased Poisson model were the same as that of the destructive negative binomial cure rate model except for the change in
the corresponding competing causes random variable $M_i$.

We considered 1000 simulations for each specific model within each case. The code was written in R-software. We examine the performance of the proposed estimation method through bias, root mean square error, and coverage probability of confidence intervals based on the asymptotic normality of the MLEs. Tables 3.2 - 3.7 present the simulation results for all the models. From these tables, we observe that the estimates are quite accurate under different cure rate models. The Bias, standard error along with RMSE get reduced as the sample size increase. That is also the case when the censoring is light or the destructive probability is high. The coverage probabilities of the confidence intervals based on the asymptotic normality of the MIEs are quite close to the nominal level in most of the cases. In conclusion, good estimates are achieved with large sample, light censoring, and high destructive probability.
Table 3.2: Estimates, bias, standard error, RMSE and CP for DLBP under proportional odds model with Weibull baseline.

<table>
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<tr>
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<th>p</th>
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<th>n = 600</th>
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<td></td>
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<td>0.007</td>
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<tr>
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<td>-0.006</td>
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<tr>
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Table 3.3: Estimates, bias, standard error, RMSE and CP for DLBP under proportional odds model with Log-logistic baseline.

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<th>p</th>
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<th>Bias</th>
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Table 3.4: Estimates, bias, standard error, RMSE and CP for DNB under proportional odds model with Weibull baseline.

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Table 3.5: Estimates, bias, standard error, RMSE and CP for DNB under proportional odds model with Log-logistic baseline.

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Table 3.6: Estimates, bias, standard error, RMSE and CP for DEWP under proportional odds model with Weibull baseline.

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The range of \( (0.005, 0.01, \ldots, 0.19, 0.195, 0.2) \)
Table 3.7: Estimates, bias, standard error, RMSE and CP for DEWP under proportional odds model with Log-logistic baseline.

The range of $\phi$ are (0 . . . 0.005, 0.01, . . ., 0.019, 0.195, 0.2).

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\[ n = 300 \]

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\[ n = 600 \]
3.5 Model discrimination

Among the three models discussed in the preceding sections, DLBP contains one less parameter than the other two models. So, DLBP may get selected often based on AIC or BIC if all three models have a similar log-likelihood value (cf. Occam’s razor principle). For this reason, it will be interesting to do model discrimination between DNB and DEWP cure rate models. We use AIC and BIC as criterion to select the best model, which are

$$AIC = 2p - 2\hat{l}, \quad BIC = p\log(n) - 2\hat{l},$$  \hspace{1cm} (3.33)

where $\hat{l}$ is the maximized log-likelihood value corresponding to the model, $p$ is the number of parameters estimated, and $n$ is the sample size. The model to be chosen as the best model should have the highest likelihood value, or the smallest AIC/BIC value.

Tables 3.8 and 3.9 present the selection rates based on AIC, BIC and maximized log-likelihood value for DNB and DEWP models under proportional odds lifetimes under various cases. Because DNB and DEWP contain the same number of parameters, same selection rate would result based on AIC/BIC/\(\hat{l}\). From the tables, we see that the rate to select DNB as a better model increases from 51.1% to 61.4% for Weibull baseline and from 50.6% to 60.2% for Log-logistic baseline when $\phi$ increases from 0.2 to 3. In addition, the rate to select DEWP as a better model increases from 57.6% to 89.1% for Weibull baseline and from 57.7% to 79.2% for Log-logistic baseline when $\phi$ increases from 0.1 to 1. Figure 3.1 displays the histograms of $\hat{l}$ by fitting the simulated data ($\phi=2$) by DNB and DEWP. The two plots are almost identical which means DEWP and DNB are almost the same in this case. Notice that had we simulated data from DEWP with $\phi = 2$ from Weibull baseline, DEWP would almost always to be selected as a better model compared to DNB cure rate.
model.

Table 3.8: Selection rates based on AIC, BIC and maximized log-likelihood values for DNB, DEWP under proportional odds ($n = 600$, light censoring, low destruction).

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<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>log-logistic</td>
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<td>0.506</td>
<td>0.494</td>
<td>0.506</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNB</td>
</tr>
<tr>
<td></td>
<td>DNB 0.5</td>
<td>0.513</td>
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<td>0.513</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNB</td>
</tr>
<tr>
<td></td>
<td>DNB 2</td>
<td>0.529</td>
<td>0.471</td>
<td>0.529</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>0.398</td>
<td>0.602</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>DEWP 0.1</td>
<td></td>
<td>0.423</td>
<td>0.577</td>
<td>0.423</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>DNB</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.208</td>
<td>0.792</td>
<td>0.208</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNB</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.036</td>
<td>0.964</td>
<td>0.036</td>
</tr>
</tbody>
</table>

95
Figure 3.1: Histograms of \( \hat{l} \) based on 1000 simulated data from DNB cure rate model (with \( \phi = 0.2 \)). The value of \( \phi \) to be selected for the profile likelihood method are (0.1, 0.12, 0.14, \ldots, 0.58, 0.6).
Table 3.9: Selection rates based on AIC, BIC and maximized log-likelihood values for DNB, DEWP under proportional odds lifetimes (n=600).

<table>
<thead>
<tr>
<th>True Models</th>
<th>Fitted Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>DNB (φ = 2)</td>
</tr>
<tr>
<td>Weibull</td>
<td>light</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
</tr>
<tr>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>light</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
</tr>
<tr>
<td></td>
<td>high</td>
</tr>
<tr>
<td>DEWP (φ = 2)</td>
<td>DNB</td>
</tr>
<tr>
<td></td>
<td>light</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
</tr>
<tr>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>light</td>
</tr>
<tr>
<td></td>
<td>heavy</td>
</tr>
<tr>
<td></td>
<td>high</td>
</tr>
</tbody>
</table>

Figures 3.2-3.5 plot the mean, relative bias, and relative RMSE of cure rate corresponding to \( x \) with different \( z \) by fitting DNB and DEWP under proportional odds lifetimes with Weibull and Log-logistic baseline distributions. When we simulated data from DEWP, the mean estimates of the cure rate from both model are very close to the true value. The relative bias is very close to zero, especially for \( z = 0 \) with the range being from -0.015 to 0.005. However, DEWP tends to have a smaller relative bias and relative RMSE compared to DNB. When we simulated data from DNB, the mean estimates of the cure rate from both
model are very close to the true value. The relative bias is very close to zero, especially for  
$z = 0$ with the range being from -0.01 to 0.005. However, DNB tends to have a smaller  
relative bias and relative RMSE compared to DNB. In conclusion, the rate of selecting the  
true model as a better model is larger if we have a larger $\phi$, or larger sample size, or light  
censoring, or low destruction probability.

### 3.6 Illustrative data analysis

Let us now consider the melanoma data described earlier in Section 1.9. In this case, we  
select tumor thickness (in mm) and ulceration status (absent: $n = 115$; present: $n =  
90$) as two covariates. We linked the destructive probability $p$ to tumor thickness and the  
parameter $\eta$ to ulceration status, respectively. The regression coefficients were chosen to  
be $\beta_1 = (\beta_0, \beta_1)$ and $\beta_2 = \beta_2$. The parameter $\beta_2$ does not include an intercept term in  
order to avoid non-identifiability problem as mentioned earlier. A preliminary analysis of  
Kaplan-Meier estimates against time by ulceration status (Figure 3.6) indicates there exists  
cure rates for the group with and without ulceration. We also plot in Figure 3.7 the log-  
odds based on Nelson-Aalen estimates over time stratified by ulceration status to validate  
the proportional odds assumption. The two curves are almost parallel and do not intersect,  
which suggests that the proportional odds assumption on the lifetimes is quite reasonable.

We fitted destructive length-biased Poisson, destructive exponentially weighted Poisson  
and destructive negative binomial cure rate models under proportional odds lifetimes with  
Weibull and log-logistic baseline to these data. In order to employ the profile likelihood  
method on the estimation of $\phi$ for each model, we chose a range of $\phi$ to be (-2,2) and (0,10)  
with an increment of 0.1 in DEWP and DNB models, respectively. These resulted in 41  
and 101 distinct values of $\phi$. We found the estimates for each value of $\phi$, and chose the one
Figure 3.2: Estimates, relative bias and relative RMSE of cure rate by fitting DNB and DEWP under proportional odds lifetimes with Weibull baseline. These figures are based on 1000 simulated data from DNB(ϕ = 0.2) with n = 600, on light censoring and low destruction.
Figure 3.3: Estimates, relative bias and relative RMSE of cure rate by fitting DNB and DEWP under proportional odds lifetimes with Weibull baseline. These figures are based on 1000 simulated dataset from DEWP(φ = 0.1) with n = 600, on light censoring and low destruction.
Figure 3.4: Estimates, relative bias and relative RMSE of cure rate by fitting DNB and DEWP under proportional odds lifetimes with log-logistic baseline. These figures are based on 1000 simulated data from DNB($\phi = 0.2$) with $n = 600$, on light censoring and low destruction.
Figure 3.5: Estimates, relative bias and relative RMSE of cure rate by fitting DNB and DEWP under proportional odds lifetimes with log-logistic baseline. These figures are based on 1000 simulated dataset from DEWP(φ = 0.1) with n = 600, on light censoring and low destruction.
corresponding to the maximized log-likelihood value as the MLE.

Figure 3.6: Kaplan-Meier curves for cutaneous melanoma data by ulceration status.
Figure 3.7: log-odds based on Nelson-Aalen estimates, based on ulceration status.
Figure 3.8 displays the estimated cure rate against tumour thickness with respect to the six different cure rate models. The graph shows that the cure rate is always higher when ulceration status is absent as compared to when it is present, and the cure rate decreases with higher tumour thickness value as expected. It implies that if the tumour thickness is small and there is no ulcer, it is highly likely that the patient gets cured compared.

Note that $\phi = 1$ or $\phi = 0$ in DNB or DEWP leads to a destructive geometric model or destructive Poisson model. To test $\phi = 1$ for the full DNB model, we found the likelihood ratio test statistic to be 2.12 with corresponding p-value as 0.145. To test $\phi = 0$ for the full DEWP model, we found the likelihood ratio test statistic to be 0.16 with corresponding p-value as 0.69. The test statistic is taken as $\Lambda = -2(\hat{l}_0 - \hat{l})$, where $\hat{l}_0$ and $\hat{l}$ are the
values of the maximized log-likelihood function under the null and alternative hypotheses, respectively. The asymptotic distribution of the test statistic $\Lambda$, under $H_0$, follows a $\chi^2$ distribution with one degree of freedom. To validate the heterogeneity among the lifetimes of the susceptibles, we set up the null hypothesis as $\gamma_2 = \gamma_3 = 0$ for the DNB model, and found the likelihood-ratio test statistic to be 4.296 with corresponding p-value 0.12. The test statistic is taken as $\Lambda = -2(\hat{l}_0 - \hat{l})$, where $\hat{l}_0$ and $\hat{l}$ are the values of the maximized log-likelihood function under the null and alternative hypotheses, respectively. The asymptotic distribution of the test statistic $\Lambda$, under $H_0$, follows a $\chi^2$ distribution with two degree of freedom.

We also considered the case when $p = 1$, i.e., the model becomes a standard cure rate model and the destructive mechanism is absent in the malignant cells. In case of DNB, we can get geometric and negative binomial cure rate models upon setting $\phi = 1$, $p = 1$ and $p = 1$, respectively. In the case of DEWP, we can get exponentially weighted Poisson and Poisson cure rate models by setting $\phi = 0$, $p = 1$ and $p = 1$, respectively. When $p = 1$, we can link both $x$ and $z$ to $\eta$ by a log-linear link function of the form $\eta = \exp\{\beta_0 + \beta_1 x + \beta_2 z\}$ to incorporate the two covariates and retain the number of parameters. To test the presence of destruction in DNB, we set the null hypothesis as $H_0 : p_i = 1$ vs. alternative hypothesis $H_a : p_i < 1$ for each individual $i$, and use a Wald type test statistic $\frac{(\hat{p}_i - 1)^2}{\text{var}(\hat{p}_i)}$. It is to be noted that the value of destructive probability $p_i$ is bounded between zero and one, and also we cannot use the standard chi-square distribution as asymptotic distribution for the test statistic. Instead, we use a parametric bootstrap approach to determine the distribution of the test statistic. The critical value at 5% level turned out to be 31.3 from 10,000 bootstrap iterations. Figure 3.9 displays the value of tumour thickness versus the test statistic at 5% level of significance. The test statistic value decreases with increase in tumour thickness,
as expected. This implies that when the tumour is not thick, for example, greater than 1.29 mm, we do not find enough evidence towards the presence of destruction.

In addition, we also linked $\eta$ to tumour thickness and $p$ to ulceration status of the form

$$
p = \frac{e^{\beta_0 + z\beta_1}}{1 + e^{\beta_0 + z\beta_1}}, \quad \eta = e^{x\beta_2}.
$$

Again, the coefficient corresponding to $x$ does not include an intercept term to avoid non-identifiability problem. The resulting maximized log-likelihood value was always lower. Table 3.10 presents the estimates of $\phi$ as well as the maximized log-likelihood value for various models. The destructive negative binomial cure rate model with proportional odds under Weibull lifetimes gives the maximized log-likelihood value as -199.76 and with minimum AIC of 415.51 and BIC of 442.1 with $\phi = 6$. Table 3.11 provides the estimates, standard error and 95% confidence interval corresponding to this model.
Table 3.10: The maximized log-likelihood value for various destructive cure rate models with other link functions.

<table>
<thead>
<tr>
<th>Link function</th>
<th>Model</th>
<th>k</th>
<th>( \hat{\phi} )</th>
<th>( \hat{i} )</th>
<th>AIC</th>
<th>BIC</th>
<th>( \hat{\phi} )</th>
<th>( \hat{i} )</th>
<th>AIC</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p_i = \frac{1}{1 + e^{-\beta_0 - x_i \beta_1}} ) [ \eta_i = e^{x \beta_2} ]</td>
<td>DLBP 7</td>
<td>NA</td>
<td>-200.85</td>
<td>415.69</td>
<td>438.95</td>
<td>NA</td>
<td>-203.66</td>
<td>421.31</td>
<td>449.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DNB 8</td>
<td>6</td>
<td><strong>-199.76</strong></td>
<td><strong>415.51</strong></td>
<td>442.1</td>
<td>5.5</td>
<td>-200.29</td>
<td>416.57</td>
<td>448.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEWP 8</td>
<td>-0.7</td>
<td>-203.57</td>
<td>423.14</td>
<td>449.73</td>
<td>-0.5</td>
<td>-201.23</td>
<td>418.45</td>
<td>450.48</td>
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</tr>
<tr>
<td></td>
<td>DG 7</td>
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<td>-200.82</td>
<td>415.65</td>
<td>438.91</td>
<td>NA</td>
<td>-200.99</td>
<td>415.98</td>
<td>444</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DP 7</td>
<td>NA</td>
<td>-203.45</td>
<td>420.91</td>
<td>444.17</td>
<td>NA</td>
<td>-201.9</td>
<td>417.81</td>
<td>445.84</td>
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</tr>
<tr>
<td>( \eta_i = e^{\beta_0 + \beta_1 x_i + \beta_2 z_i} )</td>
<td>NB 8</td>
<td>10</td>
<td>-200.3</td>
<td>416.59</td>
<td>443.18</td>
<td>8.6</td>
<td>-200.94</td>
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<td></td>
<td>G 7</td>
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<tr>
<td></td>
<td>P 7</td>
<td>NA</td>
<td>-203.65</td>
<td>421.31</td>
<td>444.57</td>
<td>NA</td>
<td>-203.71</td>
<td>421.43</td>
<td>449.45</td>
<td></td>
</tr>
</tbody>
</table>

Note that G: Geometric, P: Poisson, NB: Negative Binomial, D: Destructive.

k is the number of parameter.
Table 3.11: The MLEs and standard errors of the parameters of the destructive negative binomial cure rate model with proportional odds under Weibull lifetimes for the melanoma data.

<table>
<thead>
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<th>Parameter</th>
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</thead>
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<tr>
<td>$\beta_0$</td>
</tr>
<tr>
<td>$\beta_1$</td>
</tr>
<tr>
<td>$\beta_2$</td>
</tr>
<tr>
<td>$\gamma_1$</td>
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<tr>
<td>$\gamma_2$</td>
</tr>
<tr>
<td>$\gamma_3$</td>
</tr>
<tr>
<td>$\gamma_4$</td>
</tr>
</tbody>
</table>
Figure 3.9: $\hat{p}_i = \frac{e^{\hat{\beta}_0 + \hat{\beta}_1 x_i}}{1 + e^{\hat{\beta}_0 + \hat{\beta}_1 x_i}}$. Test statistic $= \frac{(\hat{p}_i - 1)^2}{\text{var}(\hat{p}_i)}$ for testing $H_0: p_i = 1$ vs. $H_a: p_i < 1$ at 5% level of significance.
Chapter 4

Gamma Frailty Cure Rate Model under Proportional Odds Lifetime

4.1 Introduction

In this Chapter, we assume a proportional odds model with frailty term for the distribution of \( W_j \) \((j = 1, \ldots)\), with a parametric assumption on the baseline odds function. To be more specific, the odds function of \( W_j \) is taken as

\[
O(w, x| r) = r\theta O_0(w),
\]

where \( O(w) = S(w)/F(w) \) is the odds of survival up to time \( w \), the proportionality term of \( \theta \) is linked to covariates as \( e^{\alpha' x_c} \) with \( x_c = (x_1, \ldots, x_p)' \) is a vector of \( p \) covariates, \( \alpha = (\alpha_1, \ldots, \alpha_p)' \) is the proportional odds regression coefficients, \( O_0(w) \) is the baseline odds function, and \( r \) is the frailty term following a gamma distribution with shape \( k > 0 \) and scale \( \xi > 0 \). The mean and variance of \( r \) are \( k/\xi \) and \( k/\xi^2 \), as mentioned in Section
1.6.

The rest of this Chapter proceeds as follows. Section 4.2 describes the form of the data and the likelihood, while the estimation of the model parameters and associated inferential issues are discussed in Section 4.3. In Section 4.4, an extensive Monte Carlo simulation study is carried out. In Section 4.5, we discuss model discrimination using information- and likelihood-based methods. A data on cutaneous melanoma as well as a simulated data are then analyzed in Section 4.6 for illustrative purpose.

4.2 Data and the likelihood

Here again, we assume the data are subject to non-informative right censoring. Hence, the observation time $T_i$ would be the minimum of the censoring time $C_i$ and the actual lifetime $Y_i$ for the $i$th subject, i.e.,

$$T_i = \min\{Y_i, C_i\}, \quad i = 1, \ldots, n. \quad (4.2)$$

We define an indicator variable $\delta_i = I(Y_i \leq C_i)$ for the $i$-th subject such that $\delta_i = 1$ if the lifetime is observed while $\delta_i = 0$ if the lifetime is right censored, $\Delta_0$ and $\Delta_1$ are sets with all the $i$’s equal to 0 and 1, respectively, and set $\Delta^*$ contains all the $i$’s. It is to be noted that the cure rate $p_0 = Z(\eta, \phi)^{-1}$ is purely a function of $\eta$ for a fixed value of $\phi$. The range of $1/p_0$ is from 1 to $\infty$ and it is monotone in $\eta$. Therefore, it is natural to use a logistic link function of the form $H_\phi(\eta) = 1 + e^{x_i^T \beta}$ to link the covariates $x$ to the cured proportion $p_{0i}$, i.e.,

$$p_{0i} = p_0(\beta, x_i) = Z(\eta, \phi)^{-1} = H_\phi(\eta)^{-1} = (1 + e^{x_i^T \beta})^{-1}, \quad (4.3)$$
where $p_0$, is the cured proportion for the $i$th category, $x_i = (1, x_i')' = (1, x_{i1}, \ldots, x_{ip})'$ is a vector of $p + 1$ covariates, and $\beta$ is the vector of regression coefficients. Under this link function, $\eta$ can be calculated from $H_{\phi}^{-1}(.)$ analytically for the Geometric, Poisson and Bernoulli distributions, and by using numerical method for the general COM-Poisson distribution.

For $n$ pairs of observations $(t, \delta) = \{(t_1, \delta_1), \ldots, (t_n, \delta_n)\}$ corresponding to $n$ individuals, the observed data likelihood function under non-informative censoring is then given by

$$L(\theta; t, \delta) \propto \prod_{i=1}^{n} \{f_p(t_i; \theta)\}^{\delta_i} \{S_p(t_i; \theta)\}^{1-\delta_i} \prod_{i \in \Delta^*} f_r(r_i), \quad (4.4)$$

where $\theta$ is the set of parameters $(\phi, \beta', z', \gamma')$, which is equivalent to

$$L(\theta; t, \delta) \propto \prod_{i \in \Delta_1} f_p(t_i; \theta) \prod_{i \in \Delta_0} \{p_0 + (1 - p_0)S_s(t_i; \theta)\} \prod_{i \in \Delta^*} f_r(r_i). \quad (4.5)$$

Here, we consider two baseline distributions for the proportional odds survival model corresponding to the time-to-event random variable, namely, Weibull and log-logistic distributions. It should also be noted that log-logistic distribution in fact processes the proportional odds property, while the Weibull distribution does not. The survival function and p.d.f. of $W$ under a Weibull baseline, for example, are

$$S(w, \gamma_0, \gamma_1) = [1 + e^{-x'c/\gamma_1 w}]^{-1}, w > 0, \quad (4.6)$$
$$f(w, \gamma_0, \gamma_1) = \gamma_1 w^{1/\gamma_0} e^{x'c/\gamma_1 w} [e^{-\gamma_1 w^{1/\gamma_0}} (r e^{x'c} - 1) + 1]^{-2}/(\gamma_0 w), w > 0, \quad (4.7)$$

where $\gamma_0 > 0$ and $\gamma_1 > 0$ are the shape and scale parameters of the baseline Weibull
distribution, respectively. Instead, if we assume the baseline distribution to be a log-logistic
distribution with \( \gamma_0 > 0 \) and \( \gamma_1 > 0 \) as the scale and shape parameters, respectively, then
the corresponding odds function of \( W_i \) is given by

\[
O(w; x'_c, \alpha | r) = \frac{\gamma_0^{\gamma_1}}{w^{\gamma_1}} e^{x'_c \alpha} = O_0(w; \gamma_0, \gamma_1) e^{x'_c \alpha}.
\] (4.8)

We observe that \( W_i \) still follows a two-parameter log-logistic distribution \((\gamma_0, \gamma_1 > 0)\)
with shape parameter \( \gamma_1 \) and scale parameter \( \gamma_0 e^{-x'_c \beta / \gamma_1} \), and with corresponding survival
function

\[
S(w; x'_c, \alpha | r) = \frac{r^{-\gamma_1} e^{x'_c \alpha}}{r^{\gamma_1} e^{x'_c \alpha} + w^{\gamma_1}}, w > 0.
\] (4.9)

Note that the mean does not exist if \( \gamma_1 < 1 \) and the variance does not exist if \( \gamma_1 < 2 \).

### 4.3 Estimation of parameters

In this section, we propose an Expectation-Maximization (EM) algorithm for obtaining the
MLEs of \( \theta \), and a profile likelihood approach for the estimation of the dispersion parameter \( \phi \). In our model, the random variable \( I_i \)'s are observed for \( i \) in the set \( \Delta_1 \) and unobserved
for \( i \) in the set \( \Delta_0 \), where \( I_i = 1 \) if the individual is susceptible and \( I_i = 0 \) if the individual
is cured. Let us denote the set of complete data by

\[
(t, \delta, x, I) = \{(t_1, \delta_1, x_1, I_1), \ldots, (t_n, \delta_n, x_n, I_n)\}.
\]
The complete data likelihood is then given by

\[
L_c(t, \delta, x, I, y) = \prod_{i \in \Delta_1} \left\{ (1 - p_{0i}) f(t_i | r_i) \right\} \prod_{i \in \Delta_0} \left\{ p_{0i}^{1 - I_i} [(1 - p_{0i}) S(t_i | r_i)]^{I_i} \right\} \prod_{i \in \Delta^*} f_r(r_i),
\]

(4.10)

where \( I = (I_1, \ldots, I_n)' \), \( x_{ic} = (x_{i1}, \ldots, x_{ip})' \) and \( x_i = (1, x_{ic}')' \). The corresponding complete log-likelihood function

\[
l_c(\theta; t, x, \delta, I) = \text{constant} + \sum_{i \in \Delta_1} \log f_p(t_i, x_i, \theta) + \sum_{i \in \Delta_0} (1 - I_i) \log p_0(\beta, x_i)
\]

\[+ \sum_{i \in \Delta_0} I_i \log [1 - p_0(\beta, x_i)] + \sum_{i \in \Delta_0} I_i \log S_s(t_i, x_{ic}; \theta) + \sum_{i \in \Delta^*} f_r(r_i). \]

(4.11)

4.3.1 E-step

The expectation step is achieved by calculating the expected value of the complete data log-likelihood function with respect to the conditional distribution of the unobserved \( I_i \)'s \((i \in \Delta_0)\), given the observed data \( O = \{(t_i, \delta_i, x_i), i \in \Delta_1\} \) and the current estimates of the parameters \( \theta^{(k)} = (\beta', \gamma')' \), for a fixed value of \( \phi \). Let us denote the function as

\[
Q(\theta, \pi^{(k)}) = E(l_c(\theta; t, x, \delta, I) | O, \theta^{(k)})
\]

(4.12)
at the $k$-th iteration step. In our model, $I_i$'s are Bernoulli random variables and we can easily find the conditional expectation for the $i$th individual who is susceptible to be

\[
E(K_i(t_i|r_i)|\mathcal{O}, \theta^{(k)}) = \frac{E(K_i(t_i|r_i)f_p(t_i|Y)\delta_i S_p(t_i|Y)^{1-\delta_i|\theta^{(k)}}}{E(f_p(t_i|Y)\delta_i S_p(t_i|Y)^{1-\delta_i|\theta^{(k)}}}, \quad (4.13)
\]

\[
E(I_i K_i(t_i|r_i)|\mathcal{O}, \theta^{(k)}) = \frac{(1 - p_{0i}(x_i, \beta^{(k)}))E(S_s(t_i|Y)|\theta^{(k)})}{(1 - p_{0i}(x_i, \beta^{(k)}))E(K_i(t_i|r_i)S_s(t_i|Y)|\theta^{(k)}) + p_{0i}(x_i, \beta^{(k)})}, \quad (4.14)
\]

where $K(\cdot)$ is a function of $t_i$ conditional on $r_i$. Now, for a fixed value of $\phi$, the $Q$ function is given by

\[
Q(\theta, \pi^{(k)}) = Q_1(\beta; \gamma_0, \gamma_1, \alpha) + Q_2(\xi), \quad (4.15)
\]

with

\[
Q_1(\beta; \gamma_0, \gamma_1, \alpha) = \sum_{i \in \Delta_1} E_{3,i} - \sum_{i \in \Delta_0} E_{4,i} + \sum_{i \in \Delta_1} E_{5,i} + \sum_{i \in \Delta_0} E_{6,i} - \sum_{i \in \Delta^*} \log(1 + e^{\beta^t x_i}), \quad (4.16)
\]

\[
Q_2(\xi) = \sum_{i \in \Delta_0} n\xi \log(\xi) - n\log(\Gamma(\xi)) + \sum_{i \in \Delta^*} ((\xi - 1)E_{2i} - \xi E_{1i}), \quad (4.17)
\]

where

\[
E_{1i} = E(r_i|\mathcal{O}, \theta^{(k)}), \quad E_{2i} = E(\log r_i|\mathcal{O}, \theta^{(k)}), \quad E_{3i} = E(\log f_i|\mathcal{O}, \theta^{(k)}),
\]

\[
E_{4i} = E(\log S_i|\mathcal{O}, \theta^{(k)}), \quad E_{5i} = E(\log z_{2,i}|\mathcal{O}, \theta^{(k)}), \quad E_{6i} = E(I_i \log z_{1,i}|\mathcal{O}, \theta^{(k)}),
\]
and

\[ z_{1,i} = z_1(\theta; x_i, t_i) = \sum_{j=1}^{\infty} \frac{\eta_i S(t_i | r_i)^j}{(j!)^{\phi}}, \quad z_{2,i} = z_2(\theta; x_i, t_i) = \sum_{j=1}^{\infty} j \eta_i S(t_i | r_i)^j / (j!)^{\phi}. \]

### 4.3.2 M-step

The M-step is achieved by maximizing the \( Q(\theta, \pi^{(k)}) \) function in (4.15) in order to obtain the improved estimate of \( \theta \), i.e.,

\[ \theta^{(k+1)} = \arg \max_{\theta} Q(\theta, \pi^{(k)}). \]  

(4.18)

The MLEs of \( \beta \) and \( \gamma \) do not have explicit expressions, and so numerical maximization is carried out by using the Newton-Raphson method, for example.

For a fixed value of \( \phi \), the E-step and M-step are alternated until the parameter estimates converge to a desired level of accuracy. The parameter \( \phi \) is determined by using the profile likelihood technique. We consider a range of \( \phi \) with small increment, and then for each value of \( \phi \), the MLEs of other parameters are found, and the value of \( \phi \) with the largest likelihood is chosen as the final estimate. The following subsections present explicit forms of the first- and second-order derivatives of the Q function as well as the update function for the case of COM-Poisson distribution, which are necessary for the numerical computation process.

### 4.3.3 Results for the COM-Poisson cure rate model with gamma frailty

The required first- and second-order derivatives of \( Q(\theta^*, \pi^{(k)}) \) function with respect to \( \beta \) and \( \gamma \), for fixed values of \( \phi \), are as follows:
The first- and second-order derivatives of the $E$ function with respect to different parameters are as follows:

$$E_{3,i} = M_{1,1}((\log f_i)_i), \quad E_{3,i} = M_{1,2}((\log f_i)_i), \quad E_{4,i} = M_{1,1}((\log S_i)_i),$$

$$E_{4,i} = M_{1,2}((\log S_i)_i), \quad E_{5,i} = M_{1,1}((\log z_2)_i), \quad E_{5,i} = M_{1,2}((\log z_2)_i),$$

$$E_{6,i} = M_{2,1}((\log z_2)_i), \quad E_{6,i} = M_{2,2}((\log z_2)_i).$$
The $M_(...)$ functions are given by

$M_{1,1}(K(t_i|r_i)) = \frac{E(\frac{\partial K(t_i|r_i)}{\partial r} f_p(t_i|Y)^{\delta_i} S_p(t_i|Y)^{1-\delta_i} | \theta^{(k)})}{E(f_p(t_i|Y)^{\delta_i} S_p(t_i|Y)^{1-\delta_i} | \theta^{(k)})}$,

(4.19)

$M_{1,2}(K(t_i|r_i)) = \frac{E(\frac{\partial^2 K(t_i|r_i)}{\partial r \partial \theta} f_p(t_i|Y)^{\delta_i} S_p(t_i|Y)^{1-\delta_i} | \theta^{(k)})}{E(f_p(t_i|Y)^{\delta_i} S_p(t_i|Y)^{1-\delta_i} | \theta^{(k)})}$,

(4.20)

$M_{2,1}(K(t_i|r_i)) = \frac{(1 - p_{0i}(x_i, \beta^{(k)})) E(\frac{\partial \log z_{2i}}{\partial \theta} S(t_i|Y) \theta^{(k)})}{(1 - p_{0i}(x_i, \beta^{(k)})) E(S(t_i|Y) \theta^{(k)}) + p_{0i}(x_i, \beta^{(k)})}$,

(4.21)

$M_{2,2}(K(t_i|r_i)) = \frac{(1 - p_{0i}(x_i, \beta^{(k)})) E(\frac{\partial^2 \log z_{2i}}{\partial \theta \partial \theta} S(t_i|Y) \theta^{(k)})}{(1 - p_{0i}(x_i, \beta^{(k)})) E(S(t_i|Y) \theta^{(k)}) + p_{0i}(x_i, \beta^{(k)})}$,

(4.22)

where $\gamma_k$, $\alpha_t$, or $\beta_h$. The first- and second-order derivatives of the log$f_i$ and log$S_i$ with respect to $\gamma_k$, $\alpha_t$, $\beta_h$ under proportional odds model with log-logistic as well as Weibull baseline are presented in the Appendix. The first- and second-order derivatives of the log$z_{1,i}$ with respect to $\gamma_k$, $\alpha_t$, $\beta_h$ are as follows:

$\frac{\partial \log z_{1,i}}{\partial \alpha_t} = \frac{z_{2,i}}{z_{1,i}} \frac{\partial \log S(t_i|r_i)}{\partial \alpha_t}$,

$\frac{\partial \log z_{1,i}}{\partial \beta_h} = \frac{z_{2,i}}{z_{0,1,i}} x_i e^{\beta_h \mathbf{x}}$,

$\frac{\partial^2 \log z_{1,i}}{\partial \alpha_t \partial \beta_h} = \frac{x_i e^{\beta_h \mathbf{x}}}{z_{0,1,i}} \frac{\partial \log S(t_i|r_i)}{\partial \alpha_t} \{ z_{21,i} z_{1,i} - z_{2,i} \}$,

$\frac{\partial^2 \log z_{1,i}}{\partial \alpha_t \partial \alpha_t'} = \frac{z_{2,i} z_{1,i} - z_{2,i}^2}{z_{1,i}^2} \frac{\partial \log S(t_i|r_i)}{\partial \alpha_t} \frac{\partial \log S(t_i|r_i)}{\partial \alpha_t'} + \frac{z_{2,i}}{z_{1,i}} \frac{\partial^2 \log S(t_i|r_i)}{\partial \alpha_t \partial \alpha_t'}$,

$\frac{\partial^2 \log z_{1,i}}{\partial \beta_h \partial \beta_h'} = \frac{x_i x_i e^{\beta_h \mathbf{x}}}{z_{0,1,i} z_{1,i}} \left[ z_{2,i} z_{0,1,i} + \left( z_{21,i} - z_{2,i} \frac{z_{0,2,i}}{z_{0,1,i}} - \frac{z_{2,i}}{z_{1,i}} \right) e^{\beta_h \mathbf{x}} \right]$.

The first- and second-order derivatives of log$z_{2,i}$ with respect to $\gamma_k$, $\alpha_t$, $\beta_h$ are as follows:
sider different scenarios. We mimic the cutaneous melanoma data, and consider 4 possible

\[
\frac{\partial \log z_{2,i}}{\partial \alpha_l} = \frac{z_{21,i}}{z_{2,i}} \frac{\partial \log S(t_i | r_i)}{\partial \alpha_l}, \quad \frac{\partial \log z_{2,i}}{\partial \beta_h} = \frac{z_{21,i} x_{ih} e^{\beta_i x_i}}{z_{01,i} z_{2,i}}, \quad \frac{\partial \log z_{2,i}}{\partial \gamma_k} = \frac{z_{21,i}}{z_{2,i}} \frac{\partial \log S(t_i | r_i)}{\partial \gamma_k},
\]

\[
\frac{\partial^2 \log z_{2,i}}{\partial \beta_h \partial \beta_{h'}} = \frac{z_{21,i}^2}{z_{2,i}^2} \frac{\partial^2 \log S(t_i | r_i)}{\partial \beta_h \partial \beta_{h'}} + \left( z_{31,i} \frac{z_{21,i}}{z_{2,i}^2} + \frac{z_{21,i}}{z_{2,i}} \right) \frac{\partial \log S(t_i | r_i)}{\partial \beta_h} \frac{\partial \log S(t_i | r_i)}{\partial \beta_{h'}},
\]

\[
\frac{\partial^2 \log z_{2,i}}{\partial \alpha_l \partial \alpha_{l'}} = \frac{z_{21,i}}{z_{2,i}} \frac{\partial \log S(t_i | r_i)}{\partial \alpha_l} + \left( z_{31,i} \frac{z_{21,i}}{z_{2,i}^2} + \frac{z_{21,i}}{z_{2,i}} \right) \frac{\partial \log S(t_i | r_i)}{\partial \alpha_l} \frac{\partial \log S(t_i | r_i)}{\partial \alpha_{l'}},
\]

\[
\frac{\partial^2 \log z_{2,i}}{\partial \gamma_k \partial \gamma_{k'}} = \frac{z_{21,i}}{z_{2,i}} \frac{\partial \log S(t_i | r_i)}{\partial \gamma_k} + \left( z_{31,i} \frac{z_{21,i}}{z_{2,i}^2} + \frac{z_{21,i}}{z_{2,i}} \right) \frac{\partial \log S(t_i | r_i)}{\partial \gamma_k} \frac{\partial \log S(t_i | r_i)}{\partial \gamma_{k'}},
\]

where

\[
z_{1,i} = z_1(t_i) = \sum_{j=1}^{\infty} \frac{\eta_j S(t_i | r_i) \phi_j}{(j!)^\phi}, \quad z_{2,i} = z_2(t_i) = \sum_{j=1}^{\infty} \frac{j \eta_j S(t_i | r_i) \phi_j}{(j!)^\phi},
\]

\[
z_{01,i} = z_{01}(t_i) = \sum_{j=1}^{\infty} \frac{j \eta_j^2 \phi_j}{(j!)^\phi}, \quad z_{21,i} = z_{21}(t_i) = \sum_{j=1}^{\infty} \frac{j^2 \eta_j S(t_i | r_i) \phi_j}{(j!)^\phi},
\]

\[
z_{31,i} = z_{31}(t_i) = \sum_{j=1}^{\infty} \frac{j^3 \eta_j S(t_i | r_i) \phi_j}{(j!)^\phi}, \quad z_{02,i} = z_{02}(t_i) = \sum_{j=1}^{\infty} \frac{j^2 \eta_j^2 \phi_j}{(j!)^\phi}.
\]

### 4.4 Simulation study

In this section, an extensive Monte Carlo simulation study is carried out for the special
cases to illustrate the performance of the proposed model and the method of inference.
We vary the sample size, censoring proportion, and underling baseline distribution to con-
sider different scenarios. We mimic the cutaneous melanoma data, and consider 4 possible
categories for the individuals, namely, \( x = 0, 1, 2, 3 \). Two different sample sizes were considered in the study: \( n = 800 \) \((200, 168, 212, 220)\) and \( n = 2000 \) \((500, 420, 530, 550)\) to reflect medium and large sample sizes. Moreover, if we assume that \( \beta = (\beta_0, \beta_1) \) has two parameters, fixing the cure rates for the first and fourth categories would be enough to cover all cases as the cure rates for the second and third categories can then be obtained from \( \beta \).

Here, we took \((p_{00}, p_{03}) = (0.4, 0.2)\) with respect to categories one and four for the cure rate. Also, the cure rate would be in a decreasing order in this way. The \( \beta \)'s turn out to be

\[
\beta_0 = \ln\left(\frac{1}{p_{00}} - 1\right), \quad \beta_1 = \frac{\ln\left(\frac{1}{p_{03}} - 1\right) - \beta_0}{3}.
\] (4.23)

We thus obtain the true value of \( \beta \) as \((0.405, 0.321)\). In addition, we consider light and heavy censoring cases in the simulation. The light and heavy censoring rates are \((0.52, 0.45, 0.37, 0.3)\) and \((0.65, 0.49, 0.4, 0.35)\) for the low cure rates, \((0.7, 0.57, 0.45, 0.34)\) and \((0.8, 0.64, 0.5, 0.38)\) for the high cure rates, respectively. Suppose the probability of getting censored and cured for group \( x \) are \( c_x \) and \( p_{0x} \), respectively. It is natural to consider the proportion of censored individuals for the susceptible group to be equal to the difference between the probability of getting censored and cured; i.e.,

\[
P(Y \geq C_x \cap M \geq 1|X = x) = c_x - p_{0x},
\] (4.24)

where the censoring time \( C_x \) follows an exponential distribution with rate \( \lambda_x \) on \( x = 0, 1, 2, 3 \). The choice of \((\xi, \gamma_0)\) in the underlying distribution of the proportional odds survival model were taken to be \((0.571, 0.307)\) and \((1.75, 3.25)\) for Weibull and log-logistic distributions, respectively. The odds parameter was specified as \( \gamma_1 = -0.75 \) to ensure a
decreasing lifetime for the four nodule categories. We consider an inverse transform sampling method to simulate the actual survival lifetime $w_i$ for each individual under different competing risks, i.e.,

$$w_i = \frac{1}{\gamma_1} \left[ \log \left( 1 + \left( \frac{1}{u} - 1 \right) r_i e^{x_i \alpha} \right) \right]^{\gamma_0}, \quad (4.25)$$

$$w_i = \gamma_0 \left( \frac{u}{1 - u} r_i e^{x_i \alpha} \right)^{1/\gamma_1}, \quad i = 1, \ldots, n, \quad (4.26)$$

under the proportional odds model with Weibull and log-logistic baseline distributions, respectively, where $u$ follows an uniform distribution over 0 to 1.

Under the above setting, the procedure to generate the data from different cure rate models is as follows.

**Geometric cure rate model:** For each individual, we simulate the number of competing risks $M_i$ from Geometric distributions with probability $P(M_i = 0) = p_{0x}$; and we simulate the censoring time $C_x$ from exponential distribution with rate $\lambda_x$. If $M_i$ does not equal zero, we simulate $M_i$ number of actual lifetimes $\{Y_{i1}, \ldots, Y_{iM_i}\}$ from proportional odds survival model, the actual lifetime is defined as $Y_i = \min \{Y_{i1}, \ldots, Y_{iM_i}\}$ and the observed lifetime $T_i$ is taken as the minimum of all the actual lifetimes and the censoring time, i.e., $T_i = \min \{Y_i, C_i\}$. If $Y_i > C_i$, we make the censoring indicator $\delta_i = 0$, otherwise $\delta_i = 1$. On the other hand, $M_i = 0$ means the individual is cured, and so we assign $C_i$ to be the lifetime, and the censoring indicator is taken to be $\delta_i = 0$.

**Poisson cure rate model:** In this case, the procedure is the same as the Geometric cure rate model except that $M_i$ is simulated from Poisson distribution with parameter $-\log(p_{0x})$.

**Bernoulli cure rate model:** There are two ways to do the data generation in this case. One is the same as Geometric cure rate model except that $M_i$ is simulated from Bernoulli
distribution with probability of success as $1 - p_{0x}$. Another way is a little bit simpler since $M_i$ can only take 0 or 1 in this case. For each individual, we simulate the censoring time $C_x$ from exponential distribution with rate $\lambda_x$. Then, we simulate an uniform random variable $U_i$ and if $U_i \leq p_{0x}$, the observed lifetime $T_i$ is set to $C_x$; otherwise, we generate the observed lifetime $T_i$ from the proportional odds survival model.

In our simulation study, 1000 Monte Carlo runs were considered in each scenario. The estimates were calculated through the EM method. We stopped the iteration in estimation when the difference in the log-likelihood values between two consecutive estimates was less than $10^{-7}$. We calculated the empirical Bias, standard error (SE), root Mean Square Error (RMSE), and 95% coverage probabilities (CPs) for all the parameters. Here, the initial values of the parameters $(\beta, \gamma)$ were taken from a grid of parameter values, and those values having the maximum likelihood were then chosen as the initial value.

Tables 4.1 - 4.9 present the bias, SE, RMSE, and CPs for the three special cases. We can see that the estimates are quite accurate under different cure rate models with gamma frailty. The bias, SE, along with RMSE get reduced for low censoring. The coverage probabilities of the confidence intervals based on the asymptotic normality of the MLEs are quite close to the nominal level in most of the cases except for $1/\xi$. This becomes better when the sample size $n$ increases.
Table 4.1: True values of parameters, Bias, SE, RMSE and CP for the Geometric cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.006</td>
<td>0.108</td>
<td>0.104</td>
<td>95.689</td>
<td>-0.75</td>
<td>0.009</td>
<td>0.122</td>
<td>0.12</td>
<td>95.39</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>1.25</td>
<td>-0.003</td>
<td>0.065</td>
<td>0.065</td>
<td>93.653</td>
<td>1.25</td>
<td>-0.005</td>
<td>0.079</td>
<td>0.08</td>
<td>93.388</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>3.75</td>
<td>-0.022</td>
<td>0.189</td>
<td>0.148</td>
<td>96.527</td>
<td>3.75</td>
<td>-0.023</td>
<td>0.202</td>
<td>0.158</td>
<td>97.045</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>0.003</td>
<td>0.146</td>
<td>0.145</td>
<td>95.329</td>
<td>0.405</td>
<td>0.005</td>
<td>0.175</td>
<td>0.17</td>
<td>95.868</td>
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<tr>
<td></td>
<td>β₂</td>
<td>0.327</td>
<td>0.004</td>
<td>0.08</td>
<td>0.081</td>
<td>94.371</td>
<td>0.327</td>
<td>0.002</td>
<td>0.092</td>
<td>0.088</td>
<td>96.222</td>
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<td></td>
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<td>0.152</td>
<td>-0.061</td>
<td>0.085</td>
<td>0.082</td>
<td>54.371</td>
<td>0.152</td>
<td>-0.06</td>
<td>0.086</td>
<td>0.082</td>
<td>55.083</td>
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</tbody>
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Table 4.2: True values of parameters, Bias, SE, RMSE and CP for the Poisson cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.006</td>
<td>0.085</td>
<td>0.086</td>
<td>94.97</td>
<td>-0.75</td>
<td>0.01</td>
<td>0.094</td>
<td>0.099</td>
<td>94.097</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>1.25</td>
<td>-0.005</td>
<td>0.054</td>
<td>0.054</td>
<td>94.611</td>
<td>1.25</td>
<td>-0.006</td>
<td>0.064</td>
<td>0.065</td>
<td>93.388</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
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<td>-0.025</td>
<td>0.151</td>
<td>0.156</td>
<td>92.575</td>
<td>3.75</td>
<td>-0.021</td>
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<td>0.164</td>
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<td>0.405</td>
<td>0.005</td>
<td>0.145</td>
<td>0.143</td>
<td>95.329</td>
<td>0.405</td>
<td>-0.001</td>
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<td>0.167</td>
<td>95.632</td>
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<tr>
<td></td>
<td>β₂</td>
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<td>0.001</td>
<td>0.079</td>
<td>0.079</td>
<td>94.85</td>
<td>0.327</td>
<td>0.004</td>
<td>0.091</td>
<td>0.09</td>
<td>95.396</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
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<td>-0.06</td>
<td>0.053</td>
<td>0.08</td>
<td>53.653</td>
<td>0.152</td>
<td>-0.052</td>
<td>0.056</td>
<td>0.075</td>
<td>61.039</td>
</tr>
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</table>
Table 4.3: True values of parameters, Bias, SE, RMSE and CP for the Bernoulli cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.004</td>
<td>0.079</td>
<td>0.08</td>
<td>94.85</td>
<td>-0.75</td>
<td>0.007</td>
<td>0.085</td>
<td>0.088</td>
<td>94.097</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>1.25</td>
<td>-0.006</td>
<td>0.052</td>
<td>0.052</td>
<td>94.97</td>
<td>1.25</td>
<td>-0.01</td>
<td>0.058</td>
<td>0.06</td>
<td>94.215</td>
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<tr>
<td></td>
<td>γ₁</td>
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<td>-0.028</td>
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<td>95.569</td>
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<td>0.146</td>
<td>94.731</td>
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<td>0.175</td>
<td>0.184</td>
<td>94.097</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
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<td>0.08</td>
<td>0.08</td>
<td>95.808</td>
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<td>93.743</td>
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<tr>
<td></td>
<td>ξ</td>
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<td>16.138</td>
<td>100</td>
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</tr>
<tr>
<td></td>
<td>1/ξ</td>
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<td>0.075</td>
<td>58.922</td>
<td>0.152</td>
<td>-0.051</td>
<td>0.065</td>
<td>0.074</td>
<td>60.803</td>
</tr>
</tbody>
</table>

Table 4.4: True values of parameters, Bias, SE, RMSE and CP for the Geometric cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.004</td>
<td>0.069</td>
<td>0.068</td>
<td>94.897</td>
<td>-0.75</td>
<td>0.003</td>
<td>0.079</td>
<td>0.075</td>
<td>97.054</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>1.25</td>
<td>-0.002</td>
<td>0.041</td>
<td>0.043</td>
<td>93.317</td>
<td>1.25</td>
<td>-0.003</td>
<td>0.05</td>
<td>0.049</td>
<td>94.993</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>3.75</td>
<td>-0.019</td>
<td>0.124</td>
<td>0.1</td>
<td>96.719</td>
<td>3.75</td>
<td>-0.002</td>
<td>0.143</td>
<td>0.103</td>
<td>98.38</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>0.002</td>
<td>0.092</td>
<td>0.092</td>
<td>95.018</td>
<td>0.405</td>
<td>0.005</td>
<td>0.11</td>
<td>0.111</td>
<td>94.845</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
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<td>0.051</td>
<td>95.261</td>
<td>0.327</td>
<td>0.002</td>
<td>0.058</td>
<td>0.057</td>
<td>95.582</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.04</td>
<td>0.058</td>
<td>0.061</td>
<td>66.1</td>
<td>0.152</td>
<td>-0.019</td>
<td>0.069</td>
<td>0.04</td>
<td>83.652</td>
</tr>
</tbody>
</table>
Table 4.5: True values of parameters, Bias, SE, RMSE and CP for the Poisson cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.005</td>
<td>0.054</td>
<td>0.056</td>
<td>93.816</td>
<td>-0.75</td>
<td>0.002</td>
<td>0.06</td>
<td>0.056</td>
<td>96.159</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>1.25</td>
<td>-0.004</td>
<td>0.034</td>
<td>0.036</td>
<td>94.079</td>
<td>1.25</td>
<td>0</td>
<td>0.041</td>
<td>0.039</td>
<td>96.302</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
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<td>-0.02</td>
<td>0.096</td>
<td>0.103</td>
<td>92.763</td>
<td>3.75</td>
<td>-0.015</td>
<td>0.102</td>
<td>0.104</td>
<td>94.168</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>0</td>
<td>0.092</td>
<td>0.095</td>
<td>94.605</td>
<td>0.405</td>
<td>0.005</td>
<td>0.109</td>
<td>0.104</td>
<td>96.302</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>0.327</td>
<td>0.003</td>
<td>0.05</td>
<td>0.049</td>
<td>95.789</td>
<td>0.327</td>
<td>-0.001</td>
<td>0.057</td>
<td>0.055</td>
<td>95.875</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.035</td>
<td>0.039</td>
<td>0.055</td>
<td>69.868</td>
<td>0.152</td>
<td>-0.022</td>
<td>0.042</td>
<td>0.041</td>
<td>82.077</td>
</tr>
</tbody>
</table>

Table 4.6: True values of parameters, Bias, SE, RMSE and CP for the Bernoulli cure rate model with gamma frailty under proportional odds with log-logistic baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.005</td>
<td>0.05</td>
<td>0.05</td>
<td>94.4</td>
<td>-0.75</td>
<td>0.005</td>
<td>0.054</td>
<td>0.055</td>
<td>95.395</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
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<td>-0.006</td>
<td>0.033</td>
<td>0.034</td>
<td>92.7</td>
<td>1.25</td>
<td>-0.006</td>
<td>0.037</td>
<td>0.038</td>
<td>94.194</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>3.75</td>
<td>-0.029</td>
<td>0.097</td>
<td>0.101</td>
<td>93.4</td>
<td>3.75</td>
<td>-0.02</td>
<td>0.105</td>
<td>0.102</td>
<td>94.394</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>0</td>
<td>0.092</td>
<td>0.093</td>
<td>95</td>
<td>0.405</td>
<td>0.004</td>
<td>0.11</td>
<td>0.107</td>
<td>95.596</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>0.327</td>
<td>0.003</td>
<td>0.05</td>
<td>0.05</td>
<td>95.4</td>
<td>0.327</td>
<td>0.001</td>
<td>0.058</td>
<td>0.057</td>
<td>94.795</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.044</td>
<td>0.041</td>
<td>0.063</td>
<td>60.8</td>
<td>0.152</td>
<td>-0.034</td>
<td>0.045</td>
<td>0.056</td>
<td>70.47</td>
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</tbody>
</table>
Table 4.7: True values of parameters, Bias, SE, RMSE and CP for the Geometric cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.006</td>
<td>0.119</td>
<td>0.109</td>
<td>96.134</td>
<td>-0.75</td>
<td>0.008</td>
<td>0.142</td>
<td>0.13</td>
<td>96.482</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.003</td>
<td>0.035</td>
<td>0.025</td>
<td>97.597</td>
<td>0.571</td>
<td>0.003</td>
<td>0.039</td>
<td>0.026</td>
<td>98.593</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
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<td>0.003</td>
<td>0.027</td>
<td>0.027</td>
<td>96.029</td>
<td>0.307</td>
<td>0.005</td>
<td>0.04</td>
<td>0.04</td>
<td>94.684</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>-0.003</td>
<td>0.149</td>
<td>0.143</td>
<td>95.716</td>
<td>0.405</td>
<td>0.002</td>
<td>0.2</td>
<td>0.2</td>
<td>95.888</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
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<td>0.005</td>
<td>0.083</td>
<td>0.081</td>
<td>95.82</td>
<td>0.327</td>
<td>0.004</td>
<td>0.102</td>
<td>0.1</td>
<td>95.884</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.039</td>
<td>0.107</td>
<td>0.062</td>
<td>71.578</td>
<td>0.152</td>
<td>-0.035</td>
<td>0.114</td>
<td>0.058</td>
<td>75.879</td>
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</table>

Table 4.8: True values of parameters, Bias, SE, RMSE and CP for the Poisson cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.004</td>
<td>0.085</td>
<td>0.082</td>
<td>95.929</td>
<td>-0.75</td>
<td>0</td>
<td>0.098</td>
<td>0.097</td>
<td>95.391</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.005</td>
<td>0.024</td>
<td>0.024</td>
<td>94.781</td>
<td>0.571</td>
<td>0.003</td>
<td>0.026</td>
<td>0.027</td>
<td>94.589</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>0.307</td>
<td>0.003</td>
<td>0.021</td>
<td>0.021</td>
<td>94.572</td>
<td>0.307</td>
<td>0.003</td>
<td>0.028</td>
<td>0.029</td>
<td>94.289</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
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<td>-0.001</td>
<td>0.149</td>
<td>0.147</td>
<td>95.929</td>
<td>0.405</td>
<td>0.002</td>
<td>0.19</td>
<td>0.195</td>
<td>94.689</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
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<td>0</td>
<td>0.082</td>
<td>0.083</td>
<td>94.05</td>
<td>0.327</td>
<td>0.003</td>
<td>0.098</td>
<td>0.098</td>
<td>95.09</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
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<td>-0.042</td>
<td>0.058</td>
<td>0.062</td>
<td>63.779</td>
<td>0.152</td>
<td>-0.036</td>
<td>0.062</td>
<td>0.056</td>
<td>71.643</td>
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</table>
Table 4.9: True values of parameters, Bias, SE, RMSE and CP for the Bernoulli cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>LC True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>HC True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>800</td>
<td>α</td>
<td>-0.75</td>
<td>0.005</td>
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<td>0.075</td>
<td>95.687</td>
<td>0.084</td>
<td>0.084</td>
<td>94.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.005</td>
<td>0.026</td>
<td>0.025</td>
<td>95.578</td>
<td>0.003</td>
<td>0.028</td>
<td>95.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>0.307</td>
<td>0.003</td>
<td>0.017</td>
<td>0.017</td>
<td>95.186</td>
<td>0.003</td>
<td>0.021</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>β₁</td>
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<td>0.006</td>
<td>0.148</td>
<td>0.155</td>
<td>94.283</td>
<td>0.005</td>
<td>0.185</td>
<td>95.6</td>
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<td></td>
</tr>
<tr>
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<td>β₂</td>
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<td>0.002</td>
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<td>0.083</td>
<td>93.882</td>
<td>0.001</td>
<td>0.097</td>
<td>94.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.042</td>
<td>0.069</td>
<td>0.064</td>
<td>69.007</td>
<td>0.152</td>
<td>-0.036</td>
<td>0.072</td>
<td>94.4</td>
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</tr>
</tbody>
</table>

Table 4.10: True values of parameters, Bias, SE, RMSE and CP for the Geometric cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>LC True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
<th>HC True</th>
<th>Bias</th>
<th>SE</th>
<th>RMSE</th>
<th>CP(95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.003</td>
<td>0.115</td>
<td>0.092</td>
<td>97.355</td>
<td>-0.75</td>
<td>0.001</td>
<td>0.135</td>
<td>0.1</td>
<td>92.026</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.001</td>
<td>0.027</td>
<td>0.02</td>
<td>98.105</td>
<td>0.571</td>
<td>0.002</td>
<td>0.031</td>
<td>0.02</td>
<td>96.229</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>0.307</td>
<td>0.003</td>
<td>0.028</td>
<td>0.022</td>
<td>98.083</td>
<td>0.307</td>
<td>0.002</td>
<td>0.042</td>
<td>0.03</td>
<td>93.827</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
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<td>-0.004</td>
<td>0.15</td>
<td>0.122</td>
<td>97.679</td>
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<td>0.01</td>
<td>0.198</td>
<td>0.151</td>
<td>91.918</td>
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<tr>
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<td>β₂</td>
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<td>0.004</td>
<td>0.083</td>
<td>0.07</td>
<td>97.376</td>
<td>0.327</td>
<td>-0.002</td>
<td>0.099</td>
<td>0.077</td>
<td>91.866</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
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<td>-0.026</td>
<td>0.049</td>
<td>0.05</td>
<td>78.312</td>
<td>0.152</td>
<td>-0.02</td>
<td>0.055</td>
<td>0.042</td>
<td>83.162</td>
</tr>
</tbody>
</table>
Table 4.11: True values of parameters, Bias, SE, RMSE and CP for the Poisson cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>LC</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True</td>
<td>Bias</td>
</tr>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>0.307</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>-0.001</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>0.327</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.008</td>
</tr>
</tbody>
</table>

Table 4.12: True values of parameters, Bias, SE, RMSE and CP for the Bernoulli cure rate model with gamma frailty under proportional odds with Weibull baseline with light censoring (LC) and heavy censoring (HC).

<table>
<thead>
<tr>
<th>n</th>
<th>Param</th>
<th>LC</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>True</td>
<td>Bias</td>
</tr>
<tr>
<td>2000</td>
<td>α</td>
<td>-0.75</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>γ₀</td>
<td>0.571</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>γ₁</td>
<td>0.307</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>β₁</td>
<td>0.405</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>β₂</td>
<td>0.327</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>1/ξ</td>
<td>0.152</td>
<td>-0.024</td>
</tr>
</tbody>
</table>

4.5 Data illustration

In this section, a clinical data as well as a simulated data are used for illustrating the model and the inferential methods developed in the preceding sections.
4.5.1 Cutaneous melanoma data

Let us now consider the cutaneous melanoma data described earlier in Section 1.9 and also analyzed in Chapter 2. In this case, the subjects were divided into four different categories \((x = 0, 1, 2, 3)\), with corresponding sample sizes \(n_1 = 111\), \(n_2 = 137\), \(n_3 = 87\), \(n_4 = 82\). The percentage of censored observations for the groups are 67.57%, 61.31%, 52.87%, 32.93%. See Figure 1.2 for a plot of the lifetimes of susceptibles. We fitted the data by Geometric \((\phi = 0)\), COM-Poisson \((\phi = 0.5)\), Poisson \((\phi = 1)\), COM-Poisson \((\phi = 2)\) and Bernoulli \((\phi \approx \infty)\) cure rate model under proportional odds models with gamma frailty with Weibull and log-logistic baseline distributions.

Tables 4.13 and 4.14 represent the MLEs and SEs of the parameters under different cure rate models with gamma frailty. Here, we chose the convergence criterion to be the absolute difference between two consecutive likelihood values to be less than \(10^{-7}\). Also 40,000 sample points were simulated for the Monte Carlo integration in the expectation step. In order to check the accuracy of the above used criteria, we generated 100,000 sample points for Monte Carlo integration for Bernoulli cure rate model with gamma frailty under proportional odds model for Weibull baseline, and set convergence criteria to be the absolute difference between two consecutive likelihood values to be less than \(10^{-8}\). The estimates obtained were -0.5221, 0.4663, 0.2847, -0.9557, 0.3975, 0.1166 and their corresponding standard errors were 0.1224, 0.0475, 0.0383, 0.2921, 0.1063, 2.2382, for the parameters \(\alpha, \gamma_0, \gamma_1, \beta_0, \beta_1, 1/\xi\), which are quite close to the values reported in Table 4.13 and Table 4.14.
Table 4.13: MLEs of the model parameters for different PO cure models with gamma frailty

<table>
<thead>
<tr>
<th>Par</th>
<th>PO frailty Weibull baseline</th>
<th>PO frailty Log-logistic baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>φ</td>
<td>0  0.5  1  2  ∞</td>
<td>0  0.5  1  2  ∞</td>
</tr>
<tr>
<td>α</td>
<td>-0.3271 -0.3897 -0.4224 -0.4622 -0.5250</td>
<td>-0.2877 -0.3591 -0.3903 -0.4268 -0.4882</td>
</tr>
<tr>
<td>γ₀</td>
<td>0.4542 0.4616 0.4631 0.4637 0.4636</td>
<td>3.5800 3.4719 3.3720 3.2505 3.1431</td>
</tr>
<tr>
<td>γ₁</td>
<td>0.2591 0.2660 0.2713 0.2778 0.2835</td>
<td>2.3258 2.3033 2.3058 2.3155 2.3284</td>
</tr>
<tr>
<td>β₀</td>
<td>-0.8749 -0.8990 -0.9111 -0.9273 -0.9543</td>
<td>-0.7693 -0.7682 -0.7707 -0.7759 -0.7851</td>
</tr>
<tr>
<td>β₁</td>
<td>0.3717 0.3793 0.3829 0.3879 0.3972</td>
<td>0.3713 0.3699 0.3709 0.3732 0.3767</td>
</tr>
<tr>
<td>1/ξ</td>
<td>0.1483 0.1393 0.1390 0.1400 0.1405</td>
<td>0.1509 0.1487 0.1484 0.1479 0.1479</td>
</tr>
</tbody>
</table>

Table 4.14: SEs of the model parameters for different PO cure models with gamma frailty

<table>
<thead>
<tr>
<th>Par</th>
<th>PO frailty Weibull baseline</th>
<th>PO frailty Log-logistic baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>φ</td>
<td>0  0.5  1  2  ∞</td>
<td>0  0.5  1  2  ∞</td>
</tr>
<tr>
<td>α</td>
<td>0.1433 0.1326 0.1293 0.1267 0.1237</td>
<td>0.1642 0.1482 0.1345 0.1399 0.1642</td>
</tr>
<tr>
<td>γ₀</td>
<td>0.0481 0.0482 0.0484 0.0487 0.0486</td>
<td>0.7984 0.7252 0.5891 0.6371 0.7984</td>
</tr>
<tr>
<td>γ₁</td>
<td>0.0430 0.0412 0.0404 0.0396 0.0386</td>
<td>0.2426 0.2412 0.2404 0.2407 0.2426</td>
</tr>
<tr>
<td>β₀</td>
<td>0.2996 0.2978 0.2964 0.2948 0.2925</td>
<td>0.3212 0.3204 0.3227 0.3217 0.3212</td>
</tr>
<tr>
<td>β₁</td>
<td>0.1056 0.1061 0.1061 0.1062 0.1064</td>
<td>0.1149 0.1141 0.1154 0.1148 0.1149</td>
</tr>
<tr>
<td>1/ξ</td>
<td>0.2960 0.2771 0.2757 0.2769 0.2772</td>
<td>0.3187 0.3115 0.3139 0.3111 0.3064</td>
</tr>
</tbody>
</table>

Table 4.15 lists the AIC, BIC and $\hat{l}$ for proportional odds cure rate model under Weibull and log-logistic baseline distributions with and without frailty term. The proportional odds model under Weibull baseline with frailty term has a higher $\hat{l}$. But, the increase in log-likelihood is not significant enough for AIC or BIC to select this model with frailty over the model without frailty.
Table 4.15: AIC, BIC and $\hat{l}$ for different models for the melanoma data

<table>
<thead>
<tr>
<th>Model</th>
<th>$\phi$</th>
<th>Geometric</th>
<th>Poisson</th>
<th>Bernoulli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Geometric Poisson</td>
<td></td>
<td>1026.8062</td>
<td>1026.8642</td>
<td>1027.0028</td>
</tr>
<tr>
<td>BIC</td>
<td>1051.1469</td>
<td>1051.2049</td>
<td>1051.3435</td>
<td>1051.5283</td>
</tr>
<tr>
<td>Weibull</td>
<td>$\hat{l}$</td>
<td>-507.4031</td>
<td>-507.4321</td>
<td>-507.5014</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>1025.0739</td>
<td>1025.0517</td>
<td>1025.0276</td>
</tr>
<tr>
<td>frailty CRM</td>
<td>BIC</td>
<td>1049.4146</td>
<td>1049.3924</td>
<td>1049.3683</td>
</tr>
<tr>
<td></td>
<td>$\hat{l}$</td>
<td>-506.5369</td>
<td>-506.5259</td>
<td>-506.5138</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>PO</td>
<td>1025.6441</td>
<td>1026.014</td>
<td>1026.374</td>
</tr>
<tr>
<td>CRM</td>
<td>BIC</td>
<td>1045.809</td>
<td>1046.179</td>
<td>1046.539</td>
</tr>
<tr>
<td></td>
<td>$\hat{l}$</td>
<td>-507.822</td>
<td>-508.007</td>
<td>-508.187</td>
</tr>
<tr>
<td></td>
<td>PO</td>
<td>1022.863</td>
<td>1022.845</td>
<td>1022.821</td>
</tr>
<tr>
<td>CRM</td>
<td>BIC</td>
<td>1043.029</td>
<td>1043.011</td>
<td>1042.986</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>$\hat{l}$</td>
<td>-506.432</td>
<td>-506.423</td>
<td>-506.41</td>
</tr>
</tbody>
</table>

The proportional odds model under log-logistic baseline with frailty term has a lower $\hat{l}$. The MLEs and SEs of the cure rate model with gamma frailty under proportional odds model for log-logistic baseline is presented in Table 4.16. The frailty parameter $\xi$ becomes very large, and the proportional odds frailty cure rate model tends to proportional odds assumptions with ordinary cure rate model, and so the likelihood for the model with and without frailty term turn out to be the same; see Table 4.17 for a list of $\hat{l}$, AIC and BICs values.
Table 4.16: MLEs and SEs of the parameters in CRM with gamma frailty under PO with log-logistic baseline (convergence criteria: two consecutive likelihood values to be less than $10^{-10}$)

<table>
<thead>
<tr>
<th></th>
<th>φ</th>
<th>MLEs</th>
<th>SEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>α</td>
<td>-0.271</td>
<td>-0.343</td>
<td>-0.374</td>
</tr>
<tr>
<td>γ₀</td>
<td>3.460</td>
<td>3.355</td>
<td>3.256</td>
</tr>
<tr>
<td>γ₁</td>
<td>2.262</td>
<td>2.240</td>
<td>2.242</td>
</tr>
<tr>
<td>β₀</td>
<td>-0.775</td>
<td>-0.774</td>
<td>-0.776</td>
</tr>
<tr>
<td>β₁</td>
<td>0.373</td>
<td>0.372</td>
<td>0.373</td>
</tr>
<tr>
<td>1/ξ</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Table 4.17: AIC, BIC and $\hat{l}$ for CRM with gamma frailty under PO with log-logistic baseline (convergence criteria: two consecutive likelihood values to be less than $10^{-10}$)

<table>
<thead>
<tr>
<th></th>
<th>φ</th>
<th>Geometric</th>
<th>Poisson</th>
<th>Bernoulli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>PO frailty CRM AIC</td>
<td>1024.8640</td>
<td>1024.8456</td>
<td>1024.8212</td>
<td>1024.7684</td>
</tr>
<tr>
<td>frailty CRM BIC</td>
<td>1049.2047</td>
<td>1049.1863</td>
<td>1049.1619</td>
<td>1049.1091</td>
</tr>
<tr>
<td>log-logistic l</td>
<td>-506.432</td>
<td>-506.423</td>
<td>-506.411</td>
<td>-506.384</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>φ</th>
<th>Geometric</th>
<th>Poisson</th>
<th>Bernoulli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>PO CRM AIC</td>
<td>1022.863</td>
<td>1022.845</td>
<td>1022.821</td>
<td>1022.768</td>
</tr>
<tr>
<td>CRM BIC</td>
<td>1043.029</td>
<td>1043.011</td>
<td>1042.986</td>
<td>1042.933</td>
</tr>
<tr>
<td>log-logistic l</td>
<td>-506.432</td>
<td>-506.423</td>
<td>-506.411</td>
<td>-506.384</td>
</tr>
</tbody>
</table>

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4.5.2 Simulated dataset and analysis

Based on the setting of the cutaneous melanoma data, we simulated from proportional odds cure rate model with gamma frailty having log-logistic and Weibull baseline distributions, respectively. Two simulated datasets were obtained by specifying $\phi$ as $\infty$ (Bernoulli) for Weibull baseline and 1 (Poisson) for log-logistic baseline. Here, we chose the cure rates for the first and fourth groups to be $p_{01} = 0.4$, $p_{04} = 0.2$; the censoring proportions for the four groups to be (0.520, 0.450, 0.370, 0.30), $\xi = 0.5$, $\alpha = -0.75$. $n = 800$ (200, 168, 212, 220), and $(\gamma_0, \gamma_1)$ to be (0.571, 0.307) and (1.25, 3.75) for Weibull and log-logistic baseline, receptively. The simulated datasets for censored and uncensored individuals are plotted in Figures 4.1 and 4.2. The corresponding datasets can be downloaded through the links https://www.dropbox.com/s/wg47izgk9qt15pr/simudata1.csv?dl=0 and https://www.dropbox.com/s/ohefxa4l4jh9vtj/simudata2.csv?dl=0, respectively.
Figure 4.1: Simulated datasets based on FCRM under PO with Weibull baseline
To compare the results between cure rate models with and without frailty term, we then fitted the simulated data by cure rate models under proportional odds model with and without frailty terms.

Table 4.18 presents the MLEs and SEs of the cure rate model parameters. The estimates are quite close to the true parameter values. Table 4.19 compares the AIC, BIC and maximized log-likelihood value $\hat{l}$ for different models. These results show that the cure rate model with frailty term always has larger $\hat{l}$ and smaller AIC and BIC, which suggests that the frailty cure rate model provides a better fit than the cure rate model without frailty when the true model contains frailty term.

Figure 4.2: Simulated datasets based on FCRM under PO with log-logistic baseline
Table 4.18: MLEs and SEs of the frailty cure rate model parameters

<table>
<thead>
<tr>
<th></th>
<th>PO Weibull baseline</th>
<th></th>
<th>PO log-logistic baseline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLEs</td>
<td>SE</td>
<td>MLEs</td>
<td>SE</td>
</tr>
<tr>
<td>$\phi$</td>
<td>$\infty$</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>-0.7033</td>
<td>0.2601</td>
<td>-0.8026</td>
<td>0.1539</td>
</tr>
<tr>
<td>$\gamma_0$</td>
<td>0.578</td>
<td>0.1645</td>
<td>1.4274</td>
<td>0.1041</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>0.3248</td>
<td>0.0623</td>
<td>3.6396</td>
<td>0.3806</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.4347</td>
<td>0.1562</td>
<td>0.463</td>
<td>0.1546</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>0.3016</td>
<td>0.0849</td>
<td>0.3864</td>
<td>0.0866</td>
</tr>
<tr>
<td>$1/\xi$</td>
<td>1.9816</td>
<td>0.9981</td>
<td>1.9444</td>
<td>0.407</td>
</tr>
</tbody>
</table>

Table 4.19: $\hat{l}$, AIC, and BIC for different models

<table>
<thead>
<tr>
<th>$\phi$</th>
<th>With frailty</th>
<th>Without frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\hat{l}$</td>
<td>AIC</td>
</tr>
<tr>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-973.041</td>
<td>1958.081</td>
</tr>
<tr>
<td>PO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>-578.338</td>
<td>1168.677</td>
</tr>
<tr>
<td>0.5</td>
<td>-578.325</td>
<td>1168.654</td>
</tr>
<tr>
<td>log-logistic baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-578.328</td>
<td>1168.655</td>
</tr>
<tr>
<td>2</td>
<td>-578.352</td>
<td>1168.705</td>
</tr>
<tr>
<td>$\infty$</td>
<td>-578.337</td>
<td>1168.674</td>
</tr>
</tbody>
</table>

One important indicator is the probability an individual is cured conditional on that individual having survived up to a specific time $t$, i.e., $P(I = 0|T > t)$. The estimate of
this probability is given by

\[ \hat{P}(I = 0|T > t) = \frac{p_0(1 - \int_0^\infty S(t|r) f(r) dr)}{(1 - p_0) \int_0^\infty S(t|r) f(r) dr + p_0}, \]  

(4.27)

where \( S(t|y) \) is the survival function under proportional odds model which is

\[ S(t|r) = \frac{rS_0(t)e^{\alpha x}}{rS_0(t)e^{\alpha x} + F_0(t)}. \]  

(4.28)

The corresponding plots are presented in Figures 4.3 and 4.4.

Figure 4.3: Cure rate given an individual has survived up to a specific time \( t \) over four covariate groups (From the left to right, the models are proportional odds cure rate model with log-logistic baseline \( \phi = (0, 0.5, 1, 2, \infty) \)).
Figure 4.4: Cure rate given an individual has survived up to a specific time $t$ over four covariate groups (From the left to right, the models are proportional odds cure rate model with Weibull baseline $\phi = (0, 0.5, 1, 2, \infty)$).
Chapter 5

Summary and Conclusions

Due to the significant improvement in medical science and effective treatments for various diseases in the past several decades, it has become possible that some patients, with certain types of cancer, can be cured meaning they do not experience the disease again for a long period of time following a good prognosis and efficient treatment. Hence, the cure rate becomes an important indicator for evaluating the effectiveness of a treatment. Cure and destructive cure rate models have become important tools in survival analysis literature, particularly in the study involving a surviving fraction and time to relapse. For this reason, generalizing these models in different ways (e.g., proportional odds lifetimes) and by accommodating more realistic assumptions are interpretations is highly desirable.

5.1 Summary of research

In this thesis, cure rate and destructive cure rate models under proportional odds lifetime for the susceptibles are studied in detail.

In Chapter 2, we have developed a flexible COM-Poisson cure rate model under a
proportional odds assumption for the lifetime distribution of susceptibles with the baseline function being that of a Weibull distribution or a log-logistic distribution. An EM algorithm has been developed for the maximum likelihood estimation of the model parameters of the proposed cure rate model. We have performed an extensive Monte Carlo simulation study by varying sample sizes, censoring proportion, cure rates, and the parameters in the distributions to evaluate the performance of the proposed model and the fitting methodology. Overall, the developed methodology provides accurate estimates of the model parameters as well as of the cure rates. Moreover, a real data on cutaneous melanoma has been analyzed and model diagnosis has been performed for illustrative purpose.

In Chapter 3, we have developed the EM algorithm for the destructive cure rate model by assuming the competing risks to follow negative binomial, exponentially weighted Poisson and length-biased Poisson models with proportional odds lifetimes with baseline odds to have either Weibull or log-logistic distributions, based on right censored data. We have carried out an extensive Monte Carlo simulation study and have also discussed a model discrimination between the models. We have used a malignant melanoma data to examine the performance of the proposed models and the methods of inference developed in this Chapter.

In Chapter 4, we have developed a flexible proportional odds COM-Poisson cure rate model with gamma frailty with proportional odds lifetime distribution for the susceptibles having baseline function to be either a Weibull distribution or a log-logistic distribution. An EM algorithm has been developed for the maximum likelihood estimation of the parameters of the proposed cure rate model. An extensive Monte Carlo simulation study has been performed by varying sample sizes, censoring proportions, cure rates, and the parameter values in the distributions to evaluate the performance of the proposed model and fitting
methodology. Overall, the proposed method provides accurate estimates of the model parameters as well as of the cure rates. Moreover, a real data on cutaneous melanoma and a simulated dataset have been analyzed and model discrimination has been performed for illustrative purpose.

5.2 Future work

There are many possible extensions to this work. First, the whole thesis is under frequentist framework, a natural extension would be to consider the Bayesian approach by assigning appropriate prior assumptions on the parameters of interest and then develop the corresponding inference. Second, the underlying distribution can be varied for more general scenarios. For example, we consider log-logistic and Weibull as baseline distributions for proportional odds model, but one can investigate the use of other general baseline distributions. One may instead use non-parametric specification of the baseline distribution in the proportional odds assumptions for the lifetime of susceptibles. This may resolve the subjectivity involved in the choice of the baseline distribution. Finally, one may consider the use of a much more generalized model, called transformation survival model, which includes proportional odds, proportional hazards, as well as many other commonly used survival models as special cases for the underlying distribution of the lifetimes of susceptibles.
Appendix A

Appendix corresponding to Chapter 2

As mentioned earlier, the COM-Poisson distribution includes the Bernoulli, Poisson and Geometric distributions as special cases. Here, we detail the steps of the EM algorithm for these three special cure models.

A.1 Bernoulli cure rate model

Let the competing cause random variable $M$ follow a Bernoulli distribution with probability of success $\eta/(1 + \eta)$. The probability density function for the whole population can then be expressed as

$$f_p(t_i; \theta) = \frac{\eta}{1 + \eta} f(t_i; \gamma). \quad (A.1)$$

The survival function for the susceptible group is just the survival function for the time to event $W$, i.e., $S_s(t_i; \theta) = S(t_i; \gamma)$. The inverse of the cure rate under this setting is $1/p_0 = 1 + \eta$. We, therefore, have $H_\phi(\eta) = 1 + \eta$ under the logistic link function with a
fixed value of \( \phi \), which implies \( \eta = e^{x_i' \beta} \). The \( Q(\theta, \pi^{(k)}) \) function is then given by

\[
\sum_{i \in \Delta_1} x_i' \beta + \sum_{i \in \Delta_1} \log f(t_i; x_i, \gamma) - \sum_{i \in \Delta_0} \log(1 + e^{x_i' \beta}) + \sum_{i \in \Delta_0} \pi_i^{(k)} x_i' \beta + \sum_{i \in \Delta_0} \pi_i^{(k)} \log S(t_i; \mathbf{x}_i, \gamma).
\]  

(A.2)

It is readily seen that some of the terms in the \( Q \) function are only corresponding to \( \beta \) while the others are only corresponding to \( \gamma \). So, it can be split into two parts as follows:

\[
Q(\theta, \pi^{(k)}) = Q_1(\beta, \pi^{(k)}) + Q_2(\gamma, \pi^{(k)}),
\]

(A.3)

\[
Q_1(\gamma, \pi^{(k)}) = \sum_{i \in \Delta_1} \log f(t_i; x_i, \gamma) + \sum_{i \in \Delta_0} \pi_i^{(k)} \log S(t_i; \mathbf{x}_i, \gamma),
\]

(A.4)

\[
Q_2(\beta, \pi^{(k)}) = \sum_{i \in \Delta_1} x_i' \beta - \sum_{i \in \Delta_0} \log(1 + e^{x_i' \beta}) + \sum_{i \in \Delta_0} \pi_i^{(k)} x_i' \beta,
\]

(A.5)

with the update step

\[
\pi_i^{(k)} = \frac{e^{x_i' \beta^{(k)}} S(t_i; \gamma^{(k)})}{1 + e^{x_i' \beta^{(k)}} S(t_i; \gamma^{(k)})}
\]

(A.6)

for the \( i \)th censored observation. The required first- and second-order derivatives of \( Q(\theta, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \) are as follows:
\[
\frac{\partial Q}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_j},
\]
\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} x_{il} - \sum_{i \in \Delta^*} \frac{x_{il} e^{x_i \beta}}{1 + e^{x_i \beta}} + \sum_{i \in \Delta_0} \pi^{(k)} x_{il},
\]
\[
\frac{\partial^2 Q}{\partial \beta_l \partial \beta_{l'}} = -\sum_{i \in \Delta^*} \frac{x_{il} x_{il'} e^{x_i \beta}}{(1 + e^{x_i \beta})^2},
\]
\[
\frac{\partial^2 Q}{\partial \gamma_j \partial \gamma_{j'}} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_j} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_{j'}} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log S^2(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}},
\]

for \(l, l' = 0, \ldots, p, j, j' = 1, 2, h = 21, \ldots, 2p, i = 1, \ldots, n\).

### A.2 Poisson cure rate model

Let the competing cause random variable \(M\) follow a Poisson distribution. The probability density function for the whole population in this case can be expressed as

\[
\begin{align*}
&f_p(t_i; \theta) = [\log(1 + e^{x_i \beta})] f(t_i; \gamma)(1 + e^{x_i \beta})(S(t_i; \gamma)^{-1}),
\end{align*}
\]

and the survival function for the susceptible group as

\[
S_s(t_i; \theta) = [(1 + e^{x_i \beta})S(t_i; \gamma) - 1]e^{-x_i \beta}.
\]

The cure rate is \(p_0 = e^{-\eta}\). We would then have \(H_\phi(\eta) = e^\eta\) under the logistic link with a fixed value of \(\phi\), which implies that \(\eta = \ln(1 + e^{x_i \beta})\). The \(Q(\theta, \pi^{(k)})\) function is then given
by

\[
Q = \sum_{i \in \Delta_1} \log \left[ \log (1 + e^{x_i^\beta}) \right] + \sum_{i \in \Delta_1} \log f(t_i; x_i, \gamma) + \sum_{i \in \Delta_1} S(t_i; x_{ic}, \gamma) \log (1 + e^{x_i^\beta}) \\
- \sum_{i \in \Delta_*} \log (1 + e^{x_i^\beta}) + \sum_{i \in \Delta_0} \pi^{(k)} \log ((1 + e^{x_i^\beta})S(t_i; x_{ic}, \gamma) - 1)
\]

(A.9)

with the update step

\[
\pi^{(k)}_i = 1 - (1 + e^{x_i^\beta})^{-S(t_i; \gamma^{(k)})}
\]

(A.10)

for the \(i\)th censored observation. The required first- and second-order derivatives of \(Q(\theta, \pi^{(k)})\) with respect to \(\beta\) and \(\gamma\) are as follows:

\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} \frac{1}{\log (1 + e^{x_i^\beta})} \frac{x_{il} e^{x_i^\beta}}{1 + e^{x_i^\beta}} + \sum_{i \in \Delta_1} \frac{x_{il} e^{x_i^\beta} S(t_i; x_{ic}, \gamma)}{1 + e^{x_i^\beta}} - \sum_{i \in \Delta_*} \frac{x_{il} e^{x_i^\beta}}{1 + e^{x_i^\beta}} \\
+ \sum_{i \in \Delta_0} \frac{\pi^{(k)} S(t_i; x_{ic}, \gamma)}{1 - (1 + e^{x_i^\beta})^{-S(t_i; x_{ic}, \gamma)}} \frac{x_{il} e^{x_i^\beta}}{1 + e^{x_i^\beta}}
\]

\[
\frac{\partial Q}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_{ic}, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_1} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} \log (1 + e^{x_i^\beta}) \\
+ \sum_{i \in \Delta_0} \frac{\pi^{(k)} \log (1 + e^{x_i^\beta})}{1 - (1 + e^{x_i^\beta})^{-S(t_i; x_{ic}, \gamma)}} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j},
\]
\[
\frac{\partial^2 Q}{\partial \beta_l \partial \beta_{l'}} = \sum_{i \in \Delta_1} \frac{x_{il} x_{il'} e^{x_i^l \beta}}{[1 + e^{x_i^l \beta}]^2} \left( \frac{1}{\log(1 + e^{x_i^l \beta})} \left[ 1 - \frac{e^{x_i^l \beta}}{\log(1 + e^{x_i^l \beta})} \right] + S(t_i; x_{ic}, \gamma) \right) - \sum_{i \in \Delta_1} \frac{x_{il} x_{il'} e^{x_i^l \beta}}{[1 + e^{x_i^l \beta}]^2} \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \frac{S(t_i; x_{ic}, \gamma)}{1 - (1 + e^{x_i^l \beta})^{-S(t_i; x_{ic}, \gamma)}} \frac{x_{il} x_{il'} e^{x_i^l \beta}}{[1 + e^{x_i^l \beta}]^2} \left[ 1 - \frac{S(t_i; x_{ic}, \gamma) e^{x_i^l \beta}}{(1 + e^{x_i^l \beta}) S(t_i; x_{ic}, \gamma) - 1} \right],
\]

\[
\frac{\partial^2 Q}{\partial \beta_l \partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} \frac{x_{il} e^{x_i^l \beta}}{1 + e^{x_i^l \beta}} \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \frac{x_{il} e^{x_i^l \beta}}{1 + e^{x_i^l \beta}} \left[ 1 - (1 + e^{x_i^l \beta})^{-S(t_i; x_{ic}, \gamma)} \right] \left( 1 + S(t_i; x_{ic}, \gamma) \log(1 + e^{x_i^l \beta}) \right) \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j},
\]

\[
\frac{\partial^2 Q}{\partial \gamma_j \partial \gamma_{j'}} = \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i; x_{ic}, \gamma)}{\partial \gamma_j} \frac{\partial \log f^2(t_i; x_{ic}, \gamma)}{\partial \gamma_{j'}} + \sum_{i \in \Delta_1} \frac{\partial^2 S(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} \log(1 + e^{x_i^l \beta}) \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \frac{\log(1 + e^{x_i^l \beta})}{1 - (1 + e^{x_i^l \beta})^{-S(t_i; x_{ic}, \gamma)}} \frac{\partial^2 S(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} \\
- \sum_{i \in \Delta_0} \pi^{(k)} \left( 1 + e^{x_i^l \beta} \right)^{-S(t_i; x_{ic}, \gamma)} \left[ \log(1 + e^{x_i^l \beta}) \right]^2 \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_{j'}},
\]

for \( l, l' = 0, \ldots, p, j, j' = 1, 2, h = 21, \ldots, 2p, i = 1, \ldots, n. \)

### A.3 Geometric cure rate model

Let the competing cause random variable \( M \) follow a Geometric distribution. The probability density function for the whole population in this case can be expressed as

\[
f_{p}(t_i; \theta) = \frac{e^{x_i^l \beta} f(t_i; \gamma)}{R_G(t_i; \theta)^2}, \tag{A.11}
\]
and the survival function for the susceptible group as

\[ S_s(t_i; \theta) = \frac{S(t_i; \gamma)}{R_G(t_i; \theta)}, \]  

(A.12)

where \( R_G(t_i; \theta) = 1 + e^{x_i' \beta} - e^{x_i' \beta} S(t_i; x_{ic}, \gamma) \). The cure rate under this setting is \( p_0 = 1 - \eta \), and under the logistic link with a fixed value of \( \phi \), we would have \( H_\phi(\eta) = (1 - \eta)^{-1} \), which implies that \( \eta = e^{x_i' \beta}(1 + e^{x_i' \beta})^{-1} \). The \( Q(\theta, \pi^{(k)}) \) function is then given by

\[
Q = \sum_{i \in \Delta_1} x_i' \beta + \sum_{i \in \Delta_1} \log f(t_i, x_{ic}, \gamma) - \sum_{i \in \Delta_1} 2 \log R_G(t_i, \theta) - \sum_{i \in \Delta_0} \log(1 + e^{x_i' \beta}) + \sum_{i \in \Delta_0} \pi^{(k)} x_i' \beta \\
+ \sum_{i \in \Delta_0} \pi^{(k)} \log S(t_i; \gamma) - \sum_{i \in \Delta_0} \pi^{(k)} \log R_G(t_i, \theta),
\]  

(A.13)

with the update step

\[
\pi^{(k)}_i = \frac{S(t_i; \gamma^{(k)}) e^{x_i' \beta^{(k)}}}{1 + e^{x_i' \beta^{(k)}}}
\]  

(A.14)

for the \( i \)th censored observation. The required first- and second-order derivatives of \( Q(\theta, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \) are as follows:

\[
\frac{\partial Q}{\partial \beta_l} = \sum_{i \in \Delta_1} x_{il} - 2 \sum_{i \in \Delta_1} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l} - \sum_{i \in \Delta_0} x_{il} e^{x_i' \beta} + \sum_{i \in \Delta_0} \pi^{(k)} x_{il} + \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l},
\]

\[
\frac{\partial Q}{\partial \gamma_{ij}} = \sum_{i \in \Delta_1} \left( \frac{\partial f(t_i, x_{ic}, \gamma)}{\partial \gamma_{ij}} - 2 \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_{ij}} \right) + \sum_{i \in \Delta_0} \pi^{(k)} \left( \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_{ij}} - \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_{ij}} \right),
\]
\[
\frac{\partial^2 Q}{\partial \beta_l \partial \beta_{l'}} = -2 \sum_{i \in \Delta_1} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_i \partial \beta_{i'}} - \sum_{i \in \Delta_0} x_{il}x_{il'}e^{x_{il} \beta} - \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_i \partial \beta_{i'}},
\]

\[
\frac{\partial^2 Q}{\partial \beta_l \partial \gamma_j} = -2 \sum_{i \in \Delta_1} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_i \partial \gamma_j} - \sum_{i \in \Delta_0} \pi^{(k)} \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_i \partial \gamma_j},
\]

\[
\frac{\partial^2 Q}{\partial \gamma_j \partial \gamma_{j'}} = \sum_{i \in \Delta_1} \left( \frac{\partial \log f(t_i, x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} - 2 \frac{\partial \log R^2_G(t_i, \theta)}{\partial \gamma_j \partial \gamma_{j'}} \right) + \sum_{i \in \Delta_0} \pi^{(k)} \left( \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} - \frac{\partial \log R^2_G(t_i, \theta)}{\partial \gamma_j \partial \gamma_{j'}} \right),
\]

\[
\frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_j} = \frac{-e^{x_i \beta}}{R_G(t_i, \theta)} \frac{\partial S(t_i, \theta)}{\partial \gamma_j}, \quad \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l} = \frac{x_{il}e^{x_i \beta}(1 - S(t_i, \theta))}{R_G(t_i, \theta)},
\]

\[
\frac{\partial \log R^2_G(t_i, \theta)}{\partial \gamma_j} = \frac{-e^{x_i \beta}}{R_G(t_i, \theta)} \frac{\partial S^2(t_i, \theta)}{\partial \gamma_j} - \frac{e^{x_i \beta}}{R_G(t_i, \theta)^2} \frac{\partial S(t_i, \theta) \partial S(t_i, \theta)}{\partial \gamma_j},
\]

\[
\frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l} = \frac{x_{il}x_{il'}e^{x_i \beta}}{R_G(t_i, \theta)^2(1 - S(t_i, \theta))}, \quad \frac{\partial \log R^2_G(t_i, \theta)}{\partial \beta_l \partial \gamma_j} = -\frac{x_{il}e^{x_i \beta}}{R_G(t_i, \theta)^2} \frac{\partial S(t_i, \theta)}{\partial \gamma_j},
\]

for \( l, l' = 0, \ldots, p, j, j' = 1, 2, h = 21, \ldots, 2p, i = 1, \ldots, n \).

### A.4 Observed information matrix

**COM-Poisson cure rate model:** The score functions, for a fixed value of \( \phi \), are

\[
\frac{\partial l}{\partial \beta_l} = -\sum_{i \in \Delta^*} x_{il} \frac{e^{x_i \beta}}{1 + e^{x_i \beta}} + \sum_{i \in \Delta_1} e^{x_i \beta} \frac{z_{21,i}}{z_{2,i}z_{01,i}} x_{il} + \sum_{i \in \Delta_0} \frac{z_{2,i}x_{il}e^{x_i \beta}}{z_{01,i}(1 + z_{1,i})},
\]

\[
\frac{\partial l}{\partial \gamma_h} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_1} \left( \frac{z_{21,i}}{z_{2,i}} - 1 \right) \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_h} + \sum_{i \in \Delta_0} \frac{z_{2,i} \partial \log S(t_i, \gamma)}{1 + z_{1,i} \partial \gamma_h}.
\]
Hence, the components of the observed information matrix, for a fixed value of $\phi$, are

$$
-\frac{\partial^2 l}{\partial \beta_i \partial \beta_{i'}} = -\left\{ -\sum_{i \in \Delta^*} \frac{x_{i}x'_{i}e^{x_{i}'\beta}}{(1 + e^{x_{i}'\beta})^2} + \sum_{i \in \Delta_1} \frac{x_{i}x'_{i}e^{x_{i}'\beta}}{(z_{21,1} - 1)^2} \left[ z_{21,1} - \frac{z_{21,1}}{1 + z_{1,1}} \right] \right\}.
$$

$$
-\frac{\partial^2 l}{\partial \beta_i \partial \gamma_h} = -\left\{ \sum_{i \in \Delta_1} \frac{x_{i}e^{x_{i}'\beta}}{z_{21,1} - 1} \left[ \frac{z_{21,1}}{1 + z_{1,1}} \right] \right\},
$$

$$
-\frac{\partial^2 l}{\partial \gamma_{h} \partial \gamma_{h'}} = -\left\{ \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i, \gamma)}{\partial \gamma_{h} \partial \gamma_{h'}} + \sum_{i \in \Delta_1} \frac{z_{21,1} - 1}{\partial \gamma_{h} \partial \gamma_{h'}} \left[ \frac{z_{21,1}}{1 + z_{1,1}} \right] \right\}.
$$

$$
\text{for } l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n.
$$
A.4.1 Bernoulli cure rate model

The score functions are

\[
\frac{\partial l}{\partial \beta} = \sum_{i \in \Delta_1} x_{il} - \sum_{i \in \Delta^*} \frac{x_{il} e^{x_i' \beta}}{1 + e^{x_i' \beta}} + \sum_{i \in \Delta_0} w_i x_{il},
\]

\[
\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_i, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta_0} w_i \frac{\partial \log S(t_i; x_{ic}, \gamma)}{\partial \gamma_j},
\]

where \( w_i = \frac{e^{x_i' \theta_s(t_i, \gamma)}}{1 + e^{x_i' \theta_s(t_i, \gamma)}} \).

Hence, the components of the observed information matrix are

\[
-\frac{\partial^2 l}{\partial \beta_l \partial \beta_{l'}} = - \left\{ - \sum_{i \in \Delta^*} \frac{x_{il} x_{il'} e^{x_i' \beta}}{(1 + e^{x_i' \beta})^2} + \sum_{i \in \Delta_0} x_{il} x_{il'} w_i (1 - w_i) \right\},
\]

\[
-\frac{\partial^2 l}{\partial \beta_l \partial \gamma_j} = - \left\{ \sum_{i \in \Delta_0} x_{il} w_i (1 - w_i) \frac{\partial \log S(t_i; \gamma)}{\partial \gamma_j} \right\},
\]

\[
-\frac{\partial^2 l}{\partial \gamma_j \partial \gamma_{j'}} = - \left\{ \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; \gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta_0} w_i \frac{\partial \log S^2(t_i; \gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta_0} w_i (1 - w_i) \frac{\partial \log S(t_i; \gamma) \partial \log S(t_i; \gamma)}{\partial \gamma_j \partial \gamma_{j'}} \right\},
\]

for \( l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n. \)
A.4.2 Poisson cure rate model

The score functions are

\[
\frac{\partial l}{\partial \beta_l} = \sum_{i \in \Delta_1} \frac{1}{\log(1 + e^{x_i^\beta})} \frac{x_{il} e^{x_i^\beta}}{1 + e^{x_i^\beta}} + \sum_{i \in \Delta^*} \frac{x_{il} e^{x_i^\beta} (S(t_i; \gamma) - 1)}{1 + e^{x_i^\beta}},
\]

\[
\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i; x_{ic}, \gamma)}{\partial \gamma_j} + \sum_{i \in \Delta^*} \frac{\partial S(t_i; \gamma)}{\partial \gamma_j} \log(1 + e^{x_i^\beta}).
\]

Hence, the components of the observed information matrix are

\[
-\frac{\partial^2 l}{\partial \beta_l \partial \beta_{l'}} = -\left\{ \sum_{i \in \Delta_1} \frac{x_{il} x_{il'} e^{x_i^\beta} (\log(1 + e^{x_i^\beta}) - e^{x_i^\beta})}{(1 + e^{x_i^\beta})^2 \log(1 + e^{x_i^\beta})^2} + \sum_{i \in \Delta^*} \frac{x_{il} x_{il'} e^{x_i^\beta}}{1 + e^{x_i^\beta}} (S(t_i; \gamma) - 1) \right\},
\]

\[
-\frac{\partial^2 l}{\partial \beta_l \partial \gamma_j} = -\left\{ \sum_{i \in \Delta^*} \frac{\partial S(t_i; x_{ic}, \gamma)}{\partial \gamma_j} x_{il} e^{x_i^\beta} \right\},
\]

\[
-\frac{\partial^2 l}{\partial \gamma_j \partial \gamma_{j'}} = -\left\{ \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} + \sum_{i \in \Delta^*} \frac{\partial^2 S(t_i; x_{ic}, \gamma)}{\partial \gamma_j \partial \gamma_{j'}} \log(1 + e^{x_i^\beta}) \right\},
\]

for \( l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n. \)
A.4.3 Geometric cure rate model

The score functions are

$$\frac{\partial l}{\partial \beta_l} = \sum_{i \in \Delta_l} x_{il} - 2 \sum_{i \in \Delta_l} \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l} - \sum_{i \in \Delta_0} \frac{x_{il} e^{x^l \beta}}{1 + e^{x^l \beta}} + \sum_{i \in \Delta_0} S(t_i; \gamma) e^{x^l \beta} \left( x_{il} - \frac{\partial \log R_G(t_i, \theta)}{\partial \beta_l} \right),$$

$$\frac{\partial l}{\partial \gamma_{jl}} = \sum_{i \in \Delta_l} \left( \frac{\partial \log f(t_i, x_{il}, \gamma)}{\partial \gamma_{jl}} - \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_{jl}} \right) - \sum_{i \in \Delta^*} \frac{\partial \log R_G(t_i, \theta)}{\partial \gamma_{jl}}.$$

Hence, the components of the observed information matrix are

$$- \frac{\partial^2 l}{\partial \beta_l \partial \beta_{l'}} = - \left\{ - 2 \sum_{i \in \Delta_l} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_l \partial \beta_{l'}} + \sum_{i \in \Delta_0} \frac{x_{il} x_{il'} e^{x^l \beta}}{(1 + e^{x^l \beta})^2} (S(t_i; \gamma) - 1) - \sum_{i \in \Delta_0} \frac{S(t_i; \gamma) e^{x^l \beta} \partial \log R_G^2(t_i, \theta)}{1 + e^{x^l \beta}} - \sum_{i \in \Delta_0} \frac{x_{il} e^{x^l \beta} S(t_i; \gamma) \partial \log R_G(t_i, \theta)}{1 + e^{x^l \beta}} \right\},$$

$$- \frac{\partial^2 l}{\partial \beta_l \partial \gamma_{jl}} = - \left\{ - \sum_{i \in \Delta_l} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \beta_l \partial \gamma_{jl}} \right\},$$

$$- \frac{\partial^2 l}{\partial \gamma_{jl} \partial \gamma_{j'l'}} = - \left\{ \sum_{i \in \Delta_l} \left( \frac{\partial \log f(t_i, x_{il}, \gamma)}{\partial \gamma_{jl} \partial \gamma_{j'l'}} - \frac{\partial \log R_G^2(t_i, \theta)}{\partial \gamma_{jl} \partial \gamma_{j'l'}} \right) - \sum_{i \in \Delta^*} \frac{\partial \log R_G^2(t_i, \theta)}{\partial \gamma_{jl} \partial \gamma_{j'l'}} \right\},$$

where $R_G(t_i, \theta) = 1 - e^{x^l \beta} (S(t_i; \gamma) - 1);$
Appendix B

Appendix corresponding to Chapter 3

B.1 Destructive length-biased Poisson cure rate model

The required first- and second-order derivatives of the $Q(\theta, \pi^{(k)})$ function with respect to $\beta$ and $\gamma$, for fixed values of $\phi$, are as follows:

$$\frac{\partial Q}{\partial \beta_{1l}} = \sum_{i \in \Delta_1} x_i q_i \{1 - p_i F(t_i) A_i G_i\} - \sum_{i \in \Delta_0} x_i p_i \{(1 - \pi^{(k)}_i) D_i + \pi^{(k)}_i [q_i F(t_i) S_p(t_i) A_i - p_0 D_i] J_i\},$$

$$\frac{\partial Q}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} z_i k_i \eta_i \left\{ \frac{1}{A_i} - p_i F(t_i) \right\} - \sum_{i \in \Delta_0} z_i k_i \eta_i p_i (1 - \pi^{(k)}_i + \pi^{(k)}_i B_i),$$

$$\frac{\partial Q}{\partial \gamma_r} = \sum_{i \in \Delta_1} \left\{ \frac{\partial \log f(t_i)}{\partial \gamma_r} - p_i \eta_i \frac{\partial F(t_i)}{\partial \gamma_r} K_i \right\} - \sum_{i \in \Delta_0} \pi^{(k)}_i l_{sp} J_i.$$
\[
\frac{\partial^2 Q}{\partial \beta_i \partial \beta_{i'}} = -\sum_{i \in \Delta_1} x_i x_{i'} p_{i} q_i \left( 1 + F(t_i) \left\{ G_i \left( \frac{E_i}{H_i} + r_i A_i \right) - \frac{2\eta_i E_i}{C_i^2} \right\} \right)
\]
\[\]
\[
- \sum_{i \in \Delta_0} x_i x_{i'} (1 - \pi_i(k)) p_{i} q_i (D_i - \eta_i p_i)
\]
\[
- \sum_{i \in \Delta_0} x_i x_{i'} \pi_i(k) J_i[E_i S_p(t_i) \{ E_i + r_i C_i - E_i C_i^2 \}]
\]
\[
- p_i p_{0i} \{ (D_i(q_i - p_i D_i) - p_i \eta_i q_i) \} + (C_i E_i S_p(t_i) - p_{i0} D_i)^2 J_i,
\]
\[
\frac{\partial^2 Q}{\partial \beta_i \partial \beta_{2k}} = -\sum_{i \in \Delta_1} x_i z_{ik} \pi_i(k) F(t_i) \left\{ 1 + \frac{1}{C_i^2} \right\} - \sum_{i \in \Delta_0} x_i z_{ik} \pi_i(k) \left\{ (1 - \pi_i(k)) q_i + \pi_i(k) p_i q_i \right\}
\]
\[
+ \pi_i(k) p_i p_{0i} S(t_i) S_p(t_i) J_i^2 [D_i - q_i F(t_i) A_i] + \pi_i(k) q_i B_i,
\]
\[
\frac{\partial^2 Q}{\partial \beta_{2k} \partial \beta_{2k'}} = \sum_{i \in \Delta_1} z_{ik} z_{ik'} \eta_i \left\{ \frac{1}{A_i} - p_i F(t_i) - \frac{\eta_i}{A_i^2} \right\}
\]
\[
- \sum_{i \in \Delta_0} z_{ik} z_{ik'} \eta_i \left\{ 1 - \pi_i(k) + \pi_i(k) \eta_i p_i (B_i^2 - F_i) + \pi_i(k) B_i \right\},
\]
\[
\frac{\partial^2 Q}{\partial \beta_{1i} \partial \gamma_r} = -\sum_{i \in \Delta_1} x_i q_i \frac{\partial F(t_i)}{\partial \gamma_r} \left\{ A_i G_i + p_i F(t_i) \left\{ \frac{G_i}{H_i^2} - \frac{2A_i \eta_i}{C_i^2} \right\} \right\}
\]
\[
- \sum_{i \in \Delta_0} x_i p_i \frac{\partial F(t_i)}{\partial \gamma_r} \left\{ q_i \left\{ 1 - F(t_i) A_i p_i + \frac{F(t_i) p_i}{C_i H_i} \right\} \right\}
\]
\[
+ J_i p_i (q_i F(t_i) S_p(t_i) A_i - p_{0i} D_0) \right\}
\]
\[
\frac{\partial^2 Q}{\partial \beta_{2k} \partial \gamma_r} = \sum_{i \in \Delta_1} z_{ik} p_i \epsilon_i \left\{ \frac{\eta_i}{A_i} - 1 \right\} \frac{\partial F(t_i)}{\partial \gamma_r}
\]
\[
- \sum_{i \in \Delta_0} z_{ik} \pi_i(k) \eta_i p_i J_i \frac{\partial F(t_i)}{\partial \gamma_r} \left\{ S_p(t_i) - p_{0i} I_i S(t_i) J_i \right\},
\]
\[
\frac{\partial^2 Q}{\partial \gamma_r \gamma_{r'}} = \sum_{i \in \Delta_1} \left\{ \frac{\partial^2 \log f(t_i)}{\partial \gamma_r \gamma_{r'}} - p_i \eta_i \left[ K_i \frac{\partial^2 F(t_i)}{\partial \gamma_r \gamma_{r'}} + \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} \frac{\eta_i p_i}{C_i^2} \right] \right\} \\
- \sum_{i \in \Delta_0} \pi_i^{(k)} p_i J_i \left\{ A_i S_p(t_i) \frac{\partial F^2(t_i)}{\partial \gamma_r \partial \gamma_{r'}} \\
+ \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} \left( \frac{S_p(t_i)p_i}{H_i^2} - A_i I_i + A_i S_p(t_i) I_i J_i \right) \right\},
\]

with

\[
A_i = \eta_i + \frac{1}{H_i}, \\
B_i = (S_p(t_i) F(t_i) - p_{0i}) J_i, \\
C_i = \eta_i H_i + 1, \\
D_i = \eta_i q_i + 1, \\
E_i = \frac{p_i q_i F(t_i)}{H_i}, \\
F_i = (S_p(t_i) F(t_i)^2 - p_{0i}) J_i, \\
G_i = 1 - \frac{1}{C_i^2}, \\
J_i = \frac{1}{S_p(t_i) - p_{0i}}, \\
K_i = 1 + \frac{1}{C_i}, \\
H_i = 1 - p_i F(t_i), \\
I_i = p_i A_i S_p(t_i), \\
l_{sp} = I_i \frac{\partial F(t_i)}{\partial \gamma_r}, \\
r_i = 1 - 2p_i.
\]
B.2 Destructive negative binomial cure rate model

The required first- and second-order derivatives of the $Q(\theta, \pi^{(k)})$ with respect to $\beta$ and $\gamma$, for fixed values of $\phi$, are as follows:

$$\frac{\partial Q}{\partial \beta_{1l}} = \sum_{i \in \Delta_1} x_{il}q_iC_i - \sum_{i \in \Delta_0} (1 - \pi_i^{(k)})x_{il}p_iq_iA_i - \sum_{i \in \Delta_0} \pi_i^{(k)}x_{il}q_ip_iD_iE_i,$$

$$\frac{\partial Q}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} z_{ik}C_i - \sum_{i \in \Delta_0} (1 - \pi_i^{(k)})z_{ik}q_ip_iA_i - \sum_{i \in \Delta_0} \pi_i^{(k)}z_{ik}p_iD_iE_i,$$

$$\frac{\partial Q}{\partial \gamma} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i)}{\partial \gamma} - \sum_{i \in \Delta_1} (1 + \phi)B_i\eta_i\pi_i - \sum_{i \in \Delta_0} \pi_i^{(k)}\eta_iE_iB_iS_p(t_i)\frac{\partial F(t_i)}{\partial \gamma},$$

$$\frac{\partial^2 Q}{\partial \beta_{1l}\partial \beta_{1l'}} = -\sum_{i \in \Delta_1} x_{il}x_{il'}p_iq_iB_i(1 + \eta_i\pi_iF(t_i) + \phi\eta_iq_iF(t_i)C_i)$$

$$-\sum_{i \in \Delta_0} x_{il}x_{il'}(1 - \pi_i^{(k)})\eta_iq_ip_iA_iF_i$$

$$-\sum_{i \in \Delta_0} x_{il}x_{il'}\pi_i^{(k)}\eta_ip_iq_iE_i\{\eta_ip_iq_ip_0S_p(t_i)(F(t_i)B_i - A_i)^2E_i$$

$$-p_0A_iF_i + F(t_i)S_p(t_i)B_iJ_i\},$$

$$\frac{\partial^2 Q}{\partial \beta_{1l}\partial \beta_{2k}} = -(1 + \phi)\sum_{i \in \Delta_1} x_{il}z_{ik}\eta_ip_iq_iF(t_i)B_i^2 - \sum_{i \in \Delta_0} x_{il}z_{ik}(1 - \pi_i^{(k)})\eta_ip_iq_iA_i^2$$

$$-\sum_{i \in \Delta_0} x_{il}z_{ik}q_i\pi_i^{(k)}K_i,$$

$$\frac{\partial^2 Q}{\partial \beta_{2k}\partial \beta_{2k'}} = -(1 + \phi)\sum_{i \in \Delta_1} z_{ik}z_{ik'}\eta_ip_iF(t_i)B_i^2$$

$$-\sum_{i \in \Delta_0} z_{ik}z_{ik'}(1 - \pi_i^{(k)})\eta_ip_iA_i^2 - \sum_{i \in \Delta_0} z_{ik}z_{ik'}\pi_i^{(k)}K_i,$$

$$\frac{\partial^2 Q}{\partial \beta_{1l}\partial \gamma} = -\sum_{i \in \Delta_1} x_{il}q_i\eta_ip_iB_i\frac{\partial F(t_i)}{\partial \gamma}(1 + \phi C_i) - \sum_{i \in \Delta_0} \pi_i^{(k)}x_{il}q_ip_iG_i,$$
\[ \frac{\partial^2 Q}{\partial \beta_k \partial \gamma_r} = - \sum_{i \in \Delta_1} z_{ik} \eta_i p_i B_i \frac{\partial F(t_i)}{\partial \gamma_r} (1 + \phi C_i) - \sum_{i \in \Delta_2} \pi_i^{(k)} z_{ik} \eta_i p_i G_i, \]

\[ \frac{\partial^2 Q}{\partial \gamma_r \partial \gamma_{r'}} = \sum_{i \in \Delta_1} \frac{\partial^2 \log f(t_i)}{\partial \gamma_r \partial \gamma_{r'}} + \sum_{i \in \Delta_1} (1 + \phi) B_i \eta_i p_i \left[ \frac{\eta_i \phi p_i B_i}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial \gamma_r'}{\partial \gamma_{r'}} - \frac{\partial^2 F(t_i)}{\partial \gamma_r \partial \gamma_{r'}} \right] \]

\[ - \sum_{i \in \Delta_0} \pi_i^{(k)} \eta_i p_i B_i \{ \frac{\partial^2 F(t_i)}{\partial \gamma_r \partial \gamma_{r'}} + B_i \eta_i p_i \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} \} \left[ E_i p_0 - \phi \right]. \]

with

\[ A_i = \frac{1}{1 + \eta_i p_i \phi}, \quad B_i = \frac{1}{1 + \eta_i p_i \phi F(t_i)}, \quad q_i = \frac{1}{1 + e^{x_i \beta_i}}, \]

\[ r_i = \frac{1 - e^{x_i \beta_i}}{1 + e^{x_i \beta_i}}, \quad C_i = \frac{1 - \eta_i p_i F(t_i)}{1 + \eta_i p_i \phi F(t_i)}, \]

\[ D_i = S_p(t_i) F(t_i) B_i - p_{0i} A_i, \quad E_i = \frac{1}{S_p(t_i) - p_{0i}}, \]

\[ G_i = B_i S_p(t_i) E_i \{ 1 - F(t_i) B_i \eta_i p_i (1 + \phi) + \eta_i p_i D_i E_i \} \frac{\partial F(t_i)}{\partial \gamma_r}, \]

\[ J_i = 1 - 2 p_i - \phi \eta_i p_i q_i B_i F(t_i)), \]

\[ F_i = 1 - 2 p_i - \phi \eta_i p_i q_i A_i, \]

\[ K_i = \eta_i p_i E_i \{ F(t_i) S_p(t_i) B_i^2 - p_{0i} A_i^2 + \eta_i p_i p_{0i} S_p(t_i) (F(t_i) B_i - A_i)^2 E_i \}. \]

### B.3 Destructive exponentially weighted Poisson cure rate model

The required first- and second-order derivatives of the \( Q(\theta, \pi^{(k)}) \) function with respect to \( \beta \) and \( \gamma \), for fixed values of \( \phi \), are as follows;
\[
\frac{\partial Q}{\partial \beta_{1l}} = \sum_{i \in \Delta_1} x_{il}q_i(1 - l_qiF(t_i)) - \sum_{i \in \Delta_0} (1 - \pi_i^{(k)})x_{il}q_i - \sum_{i \in \Delta_0} \pi_i^{(k)} A_i B_i x_{il}q_i l_qi,
\]

\[
\frac{\partial Q}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} z_{ik}(1 - l_qiF(t_i)) - \sum_{i \in \Delta_0} z_{ik}(1 - \pi_i^{(k)}) l_qi - \sum_{i \in \Delta_0} \pi_i^{(k)} A_i B_i z_{ik} l_qi,
\]

\[
\frac{\partial Q}{\partial \gamma_r} = \sum_{i \in \Delta_1} \left[ \frac{\partial \log f(t_i)}{\partial \gamma_r} - \frac{\partial F(t_i)}{\partial \gamma_r} l_qi \right] - \sum_{i \in \Delta_0} \pi_i^{(k)} l_qi S_p(t_i) B_i \frac{\partial F(t_i)}{\partial \gamma_r},
\]

\[
\frac{\partial^2 Q}{\partial \beta_{1l} \partial \beta_{1l'}} = -\sum_{i \in \Delta_1} x_{il} x_{il'} p_i q_i \{1 + \eta_i r_i e^{\theta} F(t_i)\}
\]

\[
- \sum_{i \in \Delta_0} x_{il} x_{il'} q_i l_qi \{(1 - \pi_i^{(k)}) r_i + \pi_i^{(k)} B_i (r_i A_i + q_i C_i)\},
\]

\[
\frac{\partial^2 Q}{\partial \beta_{1l} \partial \beta_{2k}} = -\sum_{i \in \Delta_1} x_{il} z_{ik} q_i l_qi F(t_i) - \sum_{i \in \Delta_0} x_{il} z_{ik} q_i l_qi (1 - \pi_i^{(k)} + \pi_i^{(k)} B_i (A_i + C_i)),
\]

\[
\frac{\partial^2 Q}{\partial \beta_{2k} \partial \beta_{2k'}} = -\sum_{i \in \Delta_1} z_{ik} z_{ik'} l_qi F(t_i) - \sum_{i \in \Delta_0} z_{il} z_{ik'} l_qi (1 - \pi_i^{(k)} + \pi_i^{(k)} B_i (A_i + C_i)),
\]

\[
\frac{\partial^2 Q}{\partial \beta_{1l} \partial \gamma_r} = -\sum_{i \in \Delta_1} x_{il} q_i l_qi \frac{\partial F(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta_0} \pi_i^{(k)} x_{il} q_i E_i,
\]

\[
\frac{\partial^2 Q}{\partial \beta_{2k} \partial \gamma_r} = -\sum_{i \in \Delta_1} z_{ik} q_i l_qi \frac{\partial F(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta_0} \pi_i^{(k)} z_{ik} E_i,
\]

\[
\frac{\partial^2 Q}{\partial \gamma_r \partial \gamma_{r'}} = \sum_{i \in \Delta_1} \left[ \frac{\partial^2 \log f(t_i)}{\partial \gamma_r \partial \gamma_{r'}} - \frac{\partial^2 F(t_i)}{\partial \gamma_r \partial \gamma_{r'}} l_qi \right]
\]

\[
- \sum_{i \in \Delta_0} \pi_i^{(k)} l_qi S_p(t_i) B_i \left[ \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} l_qi B_i + \frac{\partial^2 F(t_i)}{\partial \gamma_r \partial \gamma_{r'}} \right],
\]

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with

\[ A_i = S_p(t_i)F(t_i) - p_{0i}, \quad B_i = \frac{1}{S_p - p_{0i}}, \quad r_i = 1 - 2p_i, \]

\[ C_i = \eta_i p_{0i} e^\phi S_p(t_i)S(t_i)^2 B_i, \]

\[ l_{qi} = \eta_i p_i e^\phi, \]

\[ E_i = [1 - p_{0i}l_{qi}S(t_i)B_i]l_{qi}S_p(t_i)\frac{\partial F(t_i)}{\partial \gamma_r}B_i. \]

### B.4 Observed information matrix

#### B.4.1 Destructive length-biased Poisson cure rate model

The score functions are

\[
\frac{\partial l}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} x_{id}q_i \left\{ 1 + \frac{p_i F(t_i)}{C_i H_i} \right\} - \sum_{i \in \Delta^*} x_{id}\eta_i p_i q_i F(t_i) - \sum_{i \in \Delta^*} x_{id}E_i,
\]

\[
\frac{\partial l}{\partial \gamma_r} = \sum_{i \in \Delta_1} \frac{p_i \partial F(t_i)}{C_i H_i} + \sum_{i \in \Delta_1} \frac{\partial \log f(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta^*} \frac{p_i \partial F(t_i)}{H_i} \frac{\partial \gamma_r}{\partial \gamma_r}.
\]
Hence, the components of the negative observed information matrix are

\[
\frac{\partial^2 l}{\partial \beta_{1l} \partial \beta_{1l'}} = - \sum_{i \in \Delta_1} x_i x_i' p_i q_i \left[ 1 + F(t_i) \right] \left\{ G_i \left( r_i A_i + \frac{E_i}{H_i} \right) \right\} - \frac{2 \eta_i E_i}{C_i^2},
\]

\[
\frac{\partial^2 l}{\partial \beta_{1l} \partial \beta_{2k}} = - \sum_{i \in \Delta_0} x_i z_i k \eta_i p_i q_i F(t_i),
\]

\[
\frac{\partial^2 l}{\partial \beta_{2k} \partial \beta_{2k'}} = \sum_{i \in \Delta_1} \frac{z_i k z_i' \eta_i}{A_i C_i} - \sum_{i \in \Delta^*} z_i k z_i' \eta_i p_i F(t_i),
\]

\[
\frac{\partial^2 l}{\partial \beta_{1l} \partial \gamma_r} = \sum_{i \in \Delta_1} \frac{x_i p_i}{C_i H_i} \left\{ q_i + \frac{E_i (1 + 2 \eta_i H_i)}{C_i} \right\} \frac{\partial F(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta^*} x_i p_i q_i \frac{\partial F(t_i)}{\partial \gamma_r} \left( \eta_i + \frac{1}{H_i^2} \right),
\]

\[
\frac{\partial^2 l}{\partial \beta_{2k} \partial \gamma_r} = - \sum_{i \in \Delta_1} \frac{z_i k \eta_i q_i}{C_i^2} \frac{\partial F(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta^*} z_i k \eta_i p_i \frac{\partial F(t_i)}{\partial \gamma_r},
\]

\[
\frac{\partial^2 l}{\partial \gamma_r \partial \gamma_{r'}} = \sum_{i \in \Delta_1} \frac{p_i}{C_i H_i} \left\{ \frac{\partial^2 F(t_i)}{\partial \gamma_r \partial \gamma_{r'}} + \frac{p_i (2 \eta_i H_i + 1)}{C_i H_i} \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} \right\} + \sum_{i \in \Delta_1} \frac{\partial^2 \log f(t_i)}{\partial \gamma_r \partial \gamma_{r'}}
\]

- \sum_{i \in \Delta^*} \frac{p_i}{H_i} \left\{ C_i \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} + \frac{p_i}{H_i} \frac{\partial F(t_i)}{\partial \gamma_r} \frac{\partial F(t_i)}{\partial \gamma_{r'}} \right\}.

### B.4.2 Destructive negative binomial cure rate model

The score functions, for a fixed value of \( \phi \), are

\[
\frac{\partial l}{\partial \beta_{1l}} = \sum_{i \in \Delta_1} x_i q_i (1 + \phi) \sum_{i \in \Delta_1} x_i p_i q_i \eta_i B_i(t_i) - \sum_{i \in \Delta_0} x_i p_i q_i \eta_i B_i(t_i),
\]

\[
\frac{\partial l}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} z_i k (1 + \phi) \sum_{i \in \Delta_1} z_i k p_i \eta_i B_i F(t_i) - \sum_{i \in \Delta_0} z_i k p_i \eta_i B_i F(t_i),
\]

\[
\frac{\partial l}{\partial \gamma_r} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i)}{\partial \gamma_r} - (1 + \phi) \sum_{i \in \Delta_1} \eta_i p_i B_i \frac{\partial F(t_i)}{\partial \gamma_r} - \sum_{i \in \Delta_0} \eta_i p_i B_i \frac{\partial F(t_i)}{\partial \gamma_r}.
\]
Hence, the components of the negative observed information matrix, for a fixed value of $\phi$, are

\[
\frac{\partial^2 l}{\partial \beta_1 \partial \beta_1'} = - \sum_{i \in \Delta_1} x_i d_i w_i p_i q_i B_i \{1 + \eta r_i F(t_i) + \phi \eta q_i F(t_i) C_i\} - \sum_{i \in \Delta_0} x_i d_i w_i \eta p_i q_i F(t_i) B_i J_i,
\]

\[
\frac{\partial^2 l}{\partial \beta_1 \partial \beta_2} = -(1 + \phi) \sum_{i \in \Delta_1} x_i d_i z_{ik} \eta p_i q_i F(t_i) B_i B_i' - \sum_{i \in \Delta_0} x_i d_i z_{ik} \eta p_i q_i F(t_i) B_i^2,
\]

\[
\frac{\partial^2 l}{\partial \beta_2 \partial \beta_2'} = -(1 + \phi) \sum_{i \in \Delta_1} z_{ik} z_{ik'} \eta p_i q_i F(t_i) B_i^2
\]

\[
\frac{\partial^2 l}{\partial \beta_1 \partial \gamma_r} = (1 + \phi) \sum_{i \in \Delta_1} x_i d_i p_i q_i \eta B_i \frac{\partial F(t_i)}{\partial \gamma_r} \{p_i \eta \phi B_i F(t_i) - 1\} + \sum_{i \in \Delta_0} x_i d_i p_i q_i \eta B_i \frac{\partial F(t_i)}{\partial \gamma_r} \{p_i \eta \phi B_i F(t_i) - 1\},
\]

\[
\frac{\partial^2 l}{\partial \beta_2 \partial \gamma_r} = (1 + \phi) \sum_{i \in \Delta_1} z_{ik} p_i \eta B_i \frac{\partial F(t_i)}{\partial \gamma_r} \{p_i \eta \phi B_i F(t_i) - 1\} + \sum_{i \in \Delta_0} z_{ik} p_i \eta B_i \frac{\partial F(t_i)}{\partial \gamma_r} \{p_i \eta \phi B_i F(t_i) - 1\},
\]

\[
\frac{\partial^2 l}{\partial \gamma_r \partial \gamma_r'} = \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i)}{\partial \gamma_r \partial \gamma_r'} - (1 + \phi) \sum_{i \in \Delta_1} \eta p_i B_i \left\{ \frac{\partial^2 F(t_i)}{\partial \gamma_r \gamma_r'} - \eta p_i \phi B_i \frac{\partial F(t_i)}{\partial \gamma_r} \frac{F(t_i)}{\gamma_r'} \right\} - \sum_{i \in \Delta_0} \eta p_i B_i \left\{ \frac{\partial^2 F(t_i)}{\partial \gamma_r \gamma_r'} - \eta p_i \phi B_i \frac{\partial F(t_i)}{\partial \gamma_r} \frac{F(t_i)}{\gamma_r'} \right\}.
\]

**B.4.3 Destructive exponentially weighted Poisson cure rate model**

The score functions, for a fixed value of $\phi$, are
\[ \frac{\partial l}{\partial \beta_{1l}} = \sum_{i \in \Delta_1} x_{il}q_i - \sum_{i \in \Delta^*} x_{il} \eta_i p_i q_i \phi F(t_i), \]
\[ \frac{\partial l}{\partial \beta_{2k}} = \sum_{i \in \Delta_1} z_{ik} - \sum_{i \in \Delta^*} z_{ik} \eta_i p_i e^{\phi F(t_i)}, \]
\[ \frac{\partial l}{\partial \gamma_{r}} = \sum_{i \in \Delta_1} \frac{\partial \log f(t_i)}{\partial \gamma_{r}} - \sum_{i \in \Delta^*} \eta_i p_i e^{\phi} \frac{\partial F(t_i)}{\partial \gamma_{r}}. \]

Hence, the components of the negative observed information matrix, for a fixed value of \( \phi \), are

\[ \frac{\partial^2 l}{\partial \beta_{1l} \partial \beta_{1l'}} = -\sum_{i \in \Delta_1} x_{il} x_{il'} p_i q_i - \sum_{i \in \Delta^*} x_{il} x_{il'} \eta_i p_i q_i q_i' \phi F(t_i), \]
\[ \frac{\partial^2 l}{\partial \beta_{1l} \partial \beta_{2k}} = -\sum_{i \in \Delta^*} x_{il} z_{ik} \eta_i p_i q_i \phi F(t_i), \]
\[ \frac{\partial^2 l}{\partial \beta_{2k} \partial \beta_{2k}} = \sum_{i \in \Delta^*} z_{ik} z_{ik} \eta_i p_i \phi F(t_i), \]
\[ \frac{\partial^2 l}{\partial \beta_{1l} \partial \gamma_{r}} = -\sum_{i \in \Delta^*} x_{il} \eta_i p_i q_i \phi \frac{\partial F(t_i)}{\partial \gamma_{r}}, \]
\[ \frac{\partial^2 l}{\partial \beta_{2k} \partial \gamma_{r}} = -\sum_{i \in \Delta^*} z_{ik} \eta_i p_i e^{\phi} \frac{\partial F(t_i)}{\partial \gamma_{r}}, \]
\[ \frac{\partial^2 l}{\partial \gamma_{r} \partial \gamma_{r'}} = 2 \sum_{i \in \Delta_1} \frac{\partial \log f(t_i)}{\partial \gamma_{r}} \frac{\partial \log f(t_i)}{\partial \gamma_{r'}} - \sum_{i \in \Delta^*} \eta_i p_i e^{\phi} \frac{\partial^2 F(t_i)}{\partial \gamma_{r} \partial \gamma_{r'}}. \]

for \( l, l' = 0, \ldots, s, x_{i0} \equiv 1, k, k' = 1, 2, \ldots, s', i = 1, \ldots, n \).
Appendix C

Appendix corresponding to Chapter 4

C.1 Results for the special cases of COM-Poisson cure rate model with gamma frailty

C.1.1 Geometric cure rate model with gamma frailty

Let the competing cause random variable $M$ follow a Geometric distribution. Then, the susceptible survival function and population density function for susceptibles, conditional on $r$, are

\[
S_s(t_i|r_i) = \frac{S(t_i|r_i)}{1 + e^{\beta \mathbf{z}_i} F(t_i| r_i)}, \quad \text{ (C.15)}
\]

\[
f_p(t_i|r_i) = \frac{e^{\beta \mathbf{z}_i} f(t_i| r_i)}{(1 + e^{\beta \mathbf{z}_i} F(t_i| r_i))^2}, \quad \text{ (C.16)}
\]
respectively. The cure rate is \( p_0 = 1 - \eta \), and the parameter \( \eta \) is linked to covariates through the logistic link function \( e^{\beta x_i}(1 + e^{\beta x_i})^{-1} \). The Q-function can then be expressed as

\[
Q = Q_1(\beta, \gamma_0, \gamma_1, \alpha) + Q_2(\xi),
\]

\[
Q_1 = \sum_{i \in \Delta_1} \{ E_{4i} - 2E_{5i} + \beta'x_i \} - \sum_{i \in \Delta_0} \{ \log(1 + e^{\beta'x_i}) + \beta'x_iE_{1i} + E_{6i} - E_{7i} \},
\]

\[
Q_2 = n\xi \log(\xi) - n \log\Gamma(\xi) + (\xi - 1) \sum_{i \in \Delta^*} E_{3i} - \xi \sum_{i \in \Delta^*} E_{2i},
\]

where

\[
E_{1i} = E(I_i|O, \theta^{(k)}), \quad E_{2i} = E(R_i|O, \theta^{(k)}), \quad E_{3i} = E(\log R_i|O, \theta^{(k)}),
\]

\[
E_{4i} = E(\log f_i|O, \theta^{(k)}), \quad E_{5i} = E(\log R_i|O, \theta^{(k)}), \quad E_{6i} = E(I_i\log S_i|O, \theta^{(k)}),
\]

\[
E_{7i} = E(I_i\log R_i|O, \theta^{(k)}), \quad R_i = 1 + e^{\beta'x_i}F(t_i|r_i).
\]

The required first- and second-order derivatives of \( Q(\theta, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \), for a fixed value of \( \phi \), are as follows:

\[
\frac{\partial Q_1}{\partial \alpha_l} = \sum_{i \in \Delta_1} E_{4i}(\alpha) - 2 \sum_{i \in \Delta} E_{5i}(\alpha) + \sum_{i \in \Delta_0} E_{6i}(\alpha) - \sum_{i \in \Delta_0} E_{7i}(\alpha),
\]

\[
\frac{\partial Q_1}{\partial \gamma_k} = \sum_{i \in \Delta_1} E_{4i}(\gamma_k) - 2 \sum_{i \in \Delta} E_{5i}(\gamma_k) + \sum_{i \in \Delta_0} E_{6i}(\gamma_k) - \sum_{i \in \Delta_0} E_{7i}(\gamma_k),
\]

\[
\frac{\partial Q_1}{\partial \beta_h} = -2 \sum_{i \in \Delta_1} E_{5i}(\beta_h) + \sum_{i \in \Delta_1} x_{ik}E_{1i} - \sum_{i \in \Delta_0} \frac{x_{ik}e^{\beta'x_i}}{1 + e^{\beta'x_i}} + \sum_{i \in \Delta_0} x_{ik}E_{1i} - \sum_{i \in \Delta_0} E_{7i}(\beta_h),
\]

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The first- and second-order derivatives of the $E$ function with respect to different parameters are as follows,

\[
\frac{\partial^2 Q_1}{\partial \alpha_i \partial \alpha_{i'}} = \sum_{i \in \Delta_1} E_{4i}(\alpha_i \alpha_{i'}) - 2 \sum_{i \in \Delta} E_{5i}(\alpha_i \alpha_{i'}) + \sum_{i \in \Delta_0} E_{6i}(\alpha_i \alpha_{i'}) - \sum_{i \in \Delta_0} E_{7i}(\alpha_i \alpha_{i'}),
\]
\[
\frac{\partial^2 Q_1}{\partial \alpha_i \partial \gamma_{k'}} = \sum_{i \in \Delta_1} E_{4i}(\alpha_i \gamma_{k'}) - 2 \sum_{i \in \Delta} E_{5i}(\alpha_i \gamma_{k'}) + \sum_{i \in \Delta_0} E_{6i}(\alpha_i \gamma_{k'}) - \sum_{i \in \Delta_0} E_{7i}(\alpha_i \gamma_{k'}),
\]
\[
\frac{\partial^2 Q_1}{\partial \gamma_k \partial \gamma_{k'}} = \sum_{i \in \Delta_1} E_{4i}(\gamma_k \gamma_{k'}) - 2 \sum_{i \in \Delta} E_{5i}(\gamma_k \gamma_{k'}) + \sum_{i \in \Delta_0} E_{6i}(\gamma_k \gamma_{k'}) - \sum_{i \in \Delta_0} E_{7i}(\gamma_k \gamma_{k'}),
\]
\[
\frac{\partial^2 Q_1}{\partial \alpha_i \partial \beta_h} = -2 \sum_{i \in \Delta_1} E_{5i}(\alpha_i \beta_h) - \sum_{i \in \Delta_0} E_{7i}(\alpha_i \beta_h), \quad \frac{\partial^2 Q_1}{\partial \gamma_k \partial \beta_h} = -2 \sum_{i \in \Delta_1} E_{5i}(\gamma_k \beta_h) - \sum_{i \in \Delta_0} E_{7i}(\gamma_k \beta_h),
\]
\[
\frac{\partial^2 Q_1}{\partial \beta_h \partial \beta_{h'}} = -2 \sum_{i \in \Delta_1} E_{5i}(\beta_h \beta_{h'}) - \sum_{i \in \Delta_0} \frac{x_{ii} x_{ii'} e^{B x_i}}{(1 + e^{B x_i})^2} - \sum_{i \in \Delta_0} E_{7i}(\beta_h \beta_{h'}).\]

where $\gamma_k$, $\alpha_i$ or $\beta_h$, functions $M_{1,1}, M_{1,2}, M_{2,1}, M_{2,2}$ are as in (4.19), (4.20), (4.21),
\begin{align*}
\frac{\partial \log R_i}{\partial \alpha_l} &= -\frac{e^{\beta^* x_i} S(t_i | r_i) \alpha_l}{R_i}, \quad \frac{\partial \log R_i}{\partial \gamma_k} = -\frac{e^{\beta^* x_i} S(t_i | r_i) \gamma_k}{R_i}, \\
\frac{\partial \log R_i}{\partial \beta_h} &= -\frac{\gamma_i e^{\beta^* x_i} - \gamma_i e^{\beta^* x_i} S(t_i | r_i)}{R_i}, \\
\frac{\partial^2 \log R_i}{\partial \alpha_l \partial \beta_h} &= \frac{\gamma_i e^{\beta^* x_i} F(t_i | r_i) - R_i S(t_i | r_i) \alpha_l x_i h e^{\beta^* x_i}}{R_i^2}, \\
\frac{\partial^2 \log R_i}{\partial \beta_h \partial \beta_h'} &= \gamma_i x_i h e^{\beta^* x_i} F(t_i | r_i) - \frac{R_i - e^{\beta^* x_i} F(t_i | r_i)}{R_i^2}, \\
\frac{\partial^2 \log R_i}{\partial \alpha_l \partial \gamma_k} &= \frac{\gamma_i e^{\beta^* x_i} S(t_i | r_i) \alpha_l \gamma_k - e^{2\beta^* x_i} S(t_i | r_i) \alpha_l S(t_i | r_i) \gamma_k}{R_i^2}, \\
\frac{\partial^2 \log R_i}{\partial \gamma_k \partial \gamma_k'} &= \frac{e^{\beta^* x_i} S(t_i | r_i) \gamma_k \gamma_k' - e^{2\beta^* x_i} S(t_i | r_i) \gamma_k S(t_i | r_i) \gamma_k'}{R_i^2}.
\end{align*}

### C.1.2 Poisson cure rate model with gamma frailty

Let the competing cause random variable $M$ follow a Poisson distribution. Then the susceptible survival function and population p.d.f., conditional on $r_i$, are

\begin{align*}
S_s(t_i | r_i) &= \left[(1 + e^{\beta^* x_i}) S(t_i | r_i) - 1\right] e^{-\beta^* x_i}, \quad (C.17) \\
f_p(t_i | r_i) &= (1 + e^{\beta^* x_i})^{-F(t_i | r_i)} \log(1 + e^{\beta^* x_i}) F(t_i | r_i), \quad (C.18)
\end{align*}
respectively. The cure rate is \( p_0 = e^{-\eta} \), and \( \eta = \ln(1 + e^{-\beta z_i}) \) under the logistic link function. The Q-function can be expressed as

\[
Q = Q_1(\beta, \gamma_0, \gamma_1, \alpha) + Q_2(\xi),
\]

\[
Q_1 = \sum_{i \in \Delta_1} \{E_{4i} \log(1 + e^{\beta z_i}) + \log \log(1 + e^{\beta z_i}) + E_{3i}\} + \sum_{i \in \Delta_0} E_{5i} - \sum_{i \in \Delta^*} \log(1 + e^{\beta z_i}),
\]

\[
Q_2 = \sum_{i \in \Delta_0} n \xi \log(\xi) - n \log \Gamma(\xi) + (\xi - 1) \sum_{i \in \Delta^*} E_{2i} - \xi \sum_{i \in \Delta^*} E_{1i}.
\]

where

\[
E_{1i} = E(r_i | O, \theta^{(k)}), \quad E_{2i} = E(\log r_i | O, \theta^{(k)}), \quad E_{3i} = E(\log f_i | O, \theta^{(k)}),
\]

\[
E_{4i} = E(S_i | O, \theta^{(k)}), \quad E_{5i} = E(I_i \log B_i | O, \theta^{(k)}), B_i = (1 + e^{\beta z_i}) S(t_i | r_i) - 1.
\]

The required first- and second-order derivatives of \( Q(\theta, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \), for fixed value of \( \phi \), are as follows:
\[
\begin{align*}
\frac{\partial Q_1}{\partial \alpha_i} &= \sum_{i \in \Delta_1} \{ E_{4i(\alpha_i)} \log(1 + e^{\beta^i x_i}) + E_{3i(\alpha_i)} \} + \sum_{i \in \Delta_0} E_{5i(\alpha_i)}, \\
\frac{\partial Q_1}{\partial \gamma_k} &= \sum_{i \in \Delta_1} \{ E_{4i(\gamma_k)} \log(1 + e^{\beta^i x_i}) + E_{3i(\gamma_k)} \} + \sum_{i \in \Delta_0} E_{5i(\gamma_k)}, \\
\frac{\partial Q_1}{\partial \beta_h} &= \sum_{i \in \Delta_1} E_{4i} x_{ih} e^{\beta_h x_i} + \sum_{i \in \Delta_0} \frac{1}{\log(1 + e^{\beta_h x_i})} x_{ih} e^{\beta_h x_i} + \sum_{i \in \Delta_0} E_{5i(\beta_h)} - \sum_{i \in \Delta^*} \frac{x_{ih} e^{\beta^i x_i}}{1 + e^{\beta^i x_i}}, \\
\frac{\partial^2 Q_1}{\partial \beta_h \beta_{h'}} &= \sum_{i \in \Delta_1} \left( E_{4i} + \frac{1}{\log(1 + e^{\beta^i x_i})} - \frac{e^{\beta^i x_i}}{(\log(1 + e^{\beta^i x_i}))^2} \right) \frac{x_{ih} x_{ih'} e^{\beta^i x_i}}{(1 + e^{\beta^i x_i})^2} + \sum_{i \in \Delta_0} E_{5i(\beta_h \beta_{h'})} - \sum_{i \in \Delta^*} \frac{x_{ih} x_{ih'} e^{\beta^i x_i}}{(1 + e^{\beta^i x_i})^2}, \\
\frac{\partial Q_1}{\partial \alpha_i \partial \alpha_{i'}} &= \sum_{i \in \Delta_1} \{ E_{4i(\alpha_i)} \log(1 + e^{\beta^i x_i}) + E_{3i(\alpha_i \alpha_{i'})} \} + \sum_{i \in \Delta_0} E_{5i(\alpha_i \alpha_{i'})}, \\
\frac{\partial Q_1}{\partial \alpha_i \beta_h} &= \sum_{i \in \Delta_1} E_{4i(\alpha_i)} \frac{x_{ih} e^{\beta_h x_i}}{1 + e^{\beta^i x_i}} + \sum_{i \in \Delta_0} E_{5i(\alpha_i \beta_h)}, \\
\frac{\partial^2 Q_1}{\partial \beta_h \gamma_k} &= \sum_{i \in \Delta_1} E_{4i(\gamma_k)} \frac{x_{ih} e^{\beta_h x_i}}{1 + e^{\beta^i x_i}} + \sum_{i \in \Delta_0} E_{5i(\beta_h \gamma_k)}, \\
\frac{\partial Q_1}{\partial \alpha_i \gamma_k} &= \sum_{i \in \Delta_1} \{ E_{4i(\alpha_i \gamma_k)} \log(1 + e^{\beta^i x_i}) + E_{3i(\alpha_i \gamma_k)} \} + \sum_{i \in \Delta_0} E_{5i(\alpha_i \gamma_k)}, \\
\frac{\partial^2 Q_1}{\partial \gamma_k \gamma_{k'}} &= \sum_{i \in \Delta_1} \{ E_{4i(\gamma_k \gamma_{k'})} \log(1 + e^{\beta^i x_i}) + E_{3i(\gamma_k \gamma_{k'})} \} + \sum_{i \in \Delta_0} E_{5i(\gamma_k \gamma_{k'})}.
\end{align*}
\]

The first- and second-order derivatives of the \( E \) function with respect to different parameters are as follows:

\[
E_{3,i(\cdot)} = M_{1,1}((\log f_i)\cdot), \quad E_{3,i(\cdot \cdot)} = M_{1,2}((\log f_i)\cdot \cdot), \quad E_{4,i(\cdot)} = M_{1,1}((S_i)\cdot)\cdot, \\
E_{4,i(\cdot \cdot)} = M_{1,2}((S_i)\cdot \cdot), \quad E_{5,i(\cdot)} = M_{2,1}((\log B_i)\cdot), \quad E_{5,i(\cdot \cdot)} = M_{2,2}((\log B_i)\cdot \cdot),
\]

where \( \cdot \) can be \( \gamma_k, \alpha_i \) or \( \beta_h \), functions \( M_{1,1}, M_{1,2}, M_{2,1}, M_{2,2} \) are as in (4.19), (4.20), (4.21),

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and (4.22), and

\[
\frac{\partial \log B_i}{\partial \alpha_l} = B_{2i} S(t_i | r_i)_{\alpha_l}, \quad \frac{\partial \log B_i}{\partial \gamma_k} = B_{2i} S(t_i | r_i)_{\gamma_k}, \quad \frac{\partial \log B_i}{\partial \beta_h} = S(t_i | r_i) B_{1i} p_0 e^{\beta' x_i}, x_{ih},
\]

\[
\frac{\partial^2 \log B_i}{\partial \alpha_l \partial \alpha_i'} = B_{2i} [S(t_i | r_i)_{\alpha_l} + S(t_i | r_i)_{\alpha_i'} B_{0i} - \frac{\partial \log B_i}{\partial \alpha_i'} S(t_i | r_i)_{\alpha_l}],
\]

\[
\frac{\partial^2 \log B_i}{\partial \alpha_l \gamma_k} = B_{2i} [S(t_i | r_i)_{\alpha_l \gamma_k} + S(t_i | r_i)_{\alpha_l} S(t_i | r_i)_{\gamma_k} B_{0i} - \frac{\partial \log B_i}{\partial \gamma_k} S(t_i | r_i)_{\alpha_l}],
\]

\[
\frac{\partial^2 \log B_i}{\partial \gamma_k \gamma_k'} = B_{2i} [S(t_i | r_i)_{\gamma_k \gamma_k'} + S(t_i | r_i)_{\gamma_k} S(t_i | r_i)_{\gamma_k'} B_{0i} - \frac{\partial \log B_i}{\partial \gamma_k'} S(t_i | r_i)_{\gamma_k}],
\]

\[
\frac{\partial \log B_i}{\partial \alpha_l \beta_h} = S(t_i | r_i)_{\alpha_l x_{ih}} (1 - p_0) \{ B_{1i} + S(t_i | r_i) B_{2i} (1 - B_{1i}) \},
\]

\[
\frac{\partial \log B_i}{\partial \gamma_k \beta_h} = S(t_i | r_i)_{\beta_h x_{ih}} (1 - p_0) \{ B_{1i} + S(t_i | r_i) B_{2i} (1 - B_{1i}) \},
\]

\[
\frac{\partial^2 \log B_i}{\partial \beta_h \beta_{h'}} = \frac{\partial \log B_i}{\partial \beta_h} p_0 x_{ih} (1 - \frac{S(t_i | r_i) e^{\beta' x_i}}{B_i}),
\]

where \(B_{0i} = \log (1 + e^{\beta' x_i})\), \(B_{1i} = \left( \frac{1 + e^{\beta' x_i}}{B_i} \right)^{S(t_i | r_i)}\), and \(B_{2i} = B_{0i} B_{1i}\).

### C.1.3 Bernoulli cure rate model with gamma frailty

Let the competing causes random variable \(M\) follow a Bernoulli distribution with probability of success \(\eta\). The \(Q\)-function can be written as a sum of three parts as follows:

\[
Q = Q_1(\beta) + Q_2(\alpha, \gamma_0, \gamma_1) + Q_3(\xi) \quad \text{(C.20)}
\]
with

\[ Q_1(\beta) = \sum_{i \in \Delta_1} \beta^i x_i - \sum_{i \in \Delta^*} \log(1 + e^{\beta^i x_i}) + \sum_{i \in \Delta_0} E_1(\beta^i x_i), \tag{C.21} \]

\[ Q_2(\alpha, \gamma_0, \gamma_1) = \sum_{i \in \Delta_1} (\alpha^i x_i + \log f_0(t_i) - 2E_{4i}) + \sum_{i \in \Delta_0} (E_{1i}(\alpha^i x_i + E_{1i} \log S_0(t_i) - E_{5i}), \]

\[ Q_3(\xi) = n\xi \log(\xi) - n \log \Gamma(\xi) + (\xi - 1) \sum_{i \in \Delta^*} E_{3i} - \xi \sum_{i \in \Delta^*} E_{2i}, \]

where

\[ E_{1i} = E(I_i|O, \theta^{(k)}), \]
\[ E_{2i} = E(r_i|O, \theta^{(k)}), \]
\[ E_{3i} = E(\log r_i|O, \theta^{(k)}), \]
\[ E_{4i} = E(\log A_i|O, \theta^{(k)}), \]
\[ E_{5i} = E(I_i \log A_i|O, \theta^{(k)}), \]
\[ A_i = r_i S_0(t_i) e^{\alpha^i x_i} + F_0(t_i). \]

The required first- and second-order derivatives of \( Q(\theta, \pi^{(k)}) \) with respect to \( \beta \) and \( \gamma \), for fixed value of \( \phi \), are as follows:
\[
\frac{\partial Q}{\partial \xi} = n \log(\xi) + n - n \psi_0(\xi) + \sum_{i \in \Delta^*}(E_{3i} - E_{2i}),
\]
\[
\frac{\partial Q}{\partial \beta_h} = \sum_{i \in \Delta_1} x_{il} + \sum_{i \in \Delta_0} E_{1i}x_{il} - \sum_{i \in \Delta^*} \frac{e^{\beta \cdot x_t}x_{il}}{1 + e^{\beta \cdot x_t}},
\]
\[
\frac{\partial Q}{\partial \alpha_l} = \sum_{i \in \Delta_1} x_{il} + \sum_{i \in \Delta_0} E_{1i}x_{il} - 2 \sum_{i \in \Delta_1} E_{4i(\alpha_l)} - \sum_{i \in \Delta_0} E_{5i(\alpha_l)},
\]
\[
\frac{\partial Q}{\partial \gamma_k} = \sum_{i \in \Delta_1} \frac{\partial \log f_0(t_i)}{\partial \gamma_k} - 2 \sum_{i \in \Delta_1} E_{4i(\gamma_k)} + \sum_{i \in \Delta_0} E_{1i} \frac{\partial \log S_0(t_i)}{\partial \gamma_k} - \sum_{i \in \Delta_0} E_{5i(\gamma_k)},
\]
\[
\frac{\partial^2 Q}{\partial \beta_h \partial \beta_{h'}} = - \sum_{i \in \Delta^*} \frac{e^{\beta \cdot x_t}x_{il}x_{il'}}{(1 + e^{\beta \cdot x_t})^2},
\]
\[
\frac{\partial^2 Q}{\partial \alpha_l \gamma_k} = - 2 \sum_{i \in \Delta_1} E_{4i(\alpha_l \gamma_k)} - \sum_{i \in \Delta_0} E_{5i(\alpha_l \gamma_k)},
\]
\[
\frac{\partial^2 Q}{\partial \xi^2} = \frac{n}{\xi} - n \psi_1(\xi),
\]
\[
\frac{\partial^2 Q}{\partial \alpha_l \partial \alpha_{l'}} = - 2 \sum_{i \in \Delta_1} E_{4i(\alpha_l \alpha_{l'})} - \sum_{i \in \Delta_0} E_{5i(\alpha_l \alpha_{l'})},
\]
\[
\frac{\partial^2 Q}{\partial \gamma_k \partial \gamma_{k'}} = \sum_{i \in \Delta_1} \left( \frac{\partial^2 \log f_0(t_i)}{\partial \gamma_k \partial \gamma_{k'}} - 2 E_{4i(\gamma_k \gamma_{k'})} \right) + \sum_{i \in \Delta_0} \left( E_{1i} \frac{\partial^2 \log S_0(t_i)}{\partial \gamma_k \partial \gamma_{k'}} - E_{5i(\gamma_k \gamma_{k'})} \right),
\]

where \( \psi_0(.) \) is the digamma function given by \( \psi_0(x) = \frac{\Gamma'(x)}{\Gamma(x)} = -\gamma - \sum_{k=0}^{\infty} \frac{1}{x+k} - \frac{1}{k+1}, \) and \( \gamma = \lim_{n \to \infty} [\sum_{k=1}^{n} \frac{1}{k} - \ln n], \) and \( \psi_1(x) = - \int_0^1 \frac{e^{t-1} - (\ln t)^{m} dt}{1-t}. \)

The first- and second-order derivatives of the \( E \)-function with respect to different parameters are as follows:

\[
E_{4,i(.)} = M_{1,1}((\log A_i).), \quad E_{4,i(.)} = M_{1,2}((\log A_i).),
\]
\[
E_{5,i(.)} = M_{2,1}((\log A_i).), \quad E_{5,i(.)} = M_{2,2}((\log A_i).),
\]

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where $g_k$, $a_l$ or $b_h$, functions $M_{1,1}, M_{1,2}, M_{2,1}, M_{2,2}$ as in (4.19), (4.20), (4.21), and (4.22), and

$$
\frac{\partial \log A_i}{\partial a_l} = \frac{r_i S_0(t_i) e^{\alpha z_i x_{il}}}{A_i}, \quad \frac{\partial \log A_i}{\partial \gamma_k} = \frac{r_i e^{\alpha z_i} - 1}{A_i} S_{0;\gamma_k}
$$

$$
\frac{\partial^2 \log A_i}{\partial a_l \partial a_l'} = A_i^2 \frac{r_i S_0(t_i) F_0(t_i) e^{\alpha z_i x_{il} x_{il}'}}{S_{0;\gamma_k}},
$$

$$
\frac{\partial^2 \log A_i}{\partial a_l \partial \gamma_k} = A_i \frac{r_i e^{\alpha z_i x_{il}} - 1}{S_{0;\gamma_k}} \frac{\partial \log A_i}{\partial a_l} \frac{\partial \log A_i}{\partial \gamma_k'},
$$

$$
\frac{\partial^2 \log A_i}{\partial \gamma_k \partial \gamma_k'} = A_i \frac{r_i e^{\alpha z_i} - 1}{S_{0;\gamma_k \gamma_k'}} - \frac{(r_i e^{\alpha z_i} - 1)^2}{A_i^2} S_{0;\gamma_k} S_{0;\gamma_k'} S_{0;\gamma_k \gamma_k'}.
$$

Please refer to Appendix D for $S_{0;\gamma_k \gamma_k'}$.

### C.2 Observed information matrix

In this section, we present the observed information matrix for the COM-Poisson cure rate model with gamma frailty as well as for its special cases.

#### C.2.1 COM-Poisson cure rate model with gamma frailty

The score functions, for a fixed value of $\phi$, are
Hence, the components of the observed information matrix, for a fixed value of $\phi$, are

\[
\frac{\partial l}{\partial \alpha_i} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{S(t_i|r_i)} \left( \frac{\partial f(t_i|r_i)}{\partial \alpha_i} z_{2,i} + f(t_i|r_i) \left[ \frac{\partial z_{2,i}}{\partial \alpha_i} - \frac{\partial z_{1,i}}{\partial \alpha_i} \right] \right) f_r(r_i) dr_i
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial z_{1,i}}{\partial \alpha_i} f_r(r_i) dr_i,
\]

\[
\frac{\partial l}{\partial \gamma_i} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{S(t_i|r_i)} \left( \frac{\partial f(t_i|r_i)}{\partial \gamma_i} z_{2,i} + f(t_i|r_i) \left[ \frac{\partial z_{2,i}}{\partial \gamma_i} - \frac{\partial z_{1,i}}{\partial \gamma_i} \right] \right) f_r(r_i) dr_i
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial z_{1,i}}{\partial \gamma_i} f_r(r_i) dr_i,
\]

\[
\frac{\partial l}{\partial \beta_h} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{S(t_i|r_i)} \frac{\partial z_{2,i}}{\partial \beta_h} f_r(r_i) dr_i + \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial z_{1,i}}{\partial \beta_h} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{x_{ih} e^{\theta z_i}}{1 + e^{\theta z_i}},
\]

\[
\frac{\partial l}{\partial \xi} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{S(t_i|r_i)} z_{2,i} \frac{\partial f_r(r_i)}{\partial \xi} f_r(r_i) dr_i + \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + z_{1,i}) \frac{\partial f(y(r_i))}{\partial \xi} f_r(r_i) dr_i,
\]

\[
\frac{\partial l}{\partial \xi} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{S(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \xi} dr_i + \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + z_{1,i}) \frac{\partial f(y(r_i))}{\partial \xi} dr_i.
\]

Hence, the components of the observed information matrix, for a fixed value of $\phi$, are

\[
-\frac{\partial^2 l}{\partial \gamma_k \partial \beta_h} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{S(t_i|r_i)} \left( \frac{\partial f(t_i|r_i)}{\partial \gamma_k} \frac{\partial z_{2,i}}{\partial \beta_h} + f(t_i|r_i) \left[ \frac{\partial^2 z_{2,i}}{\partial \gamma_k \partial \beta_h} - \frac{\partial^2 z_{1,i}}{\partial \gamma_k \partial \beta_h} \right] \right) f_r(r_i) dr_i
+ \sum_{i \in \Delta_0} \frac{1}{A_i} \left\{ \int \frac{1}{S(t_i|r_i)} \left( \frac{\partial f(t_i|r_i)}{\partial \gamma_k} z_{2,i} + f(t_i|r_i) \left[ \frac{\partial z_{2,i}}{\partial \gamma_k} - \frac{\partial z_{1,i}}{\partial \gamma_k} \right] \right) f_r(r_i) dr_i \right\}
\times \left\{ \int \frac{f(t_i|r_i)}{S(t_i|r_i)} \frac{\partial z_{2,i}}{\partial \beta_h} f_r(r_i) dr_i \right\}
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial^2 z_{1,i}}{\partial \gamma_k \partial \beta_h} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{1}{B_i^2} \int \frac{\partial z_{1,i}}{\partial \gamma_k} f_r(r_i) dr_i \int \frac{\partial z_{1,i}}{\partial \beta_h} f_r(r_i) dr_i \right\},
\]
\[ -\frac{\partial^2 l}{\partial \alpha_i \partial \beta_h} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial f(t_i | r_i)}{\partial \alpha_l} \frac{\partial z_{2,i}}{\partial \beta_h} + f(t_i | r_i) \left[ \frac{\partial^2 z_{2,i}}{\partial \alpha_l \partial \beta_h} - \frac{\partial z_{1,i}}{\partial \alpha_l \partial \beta_h} \right] \right) f_r(r_i) dr_i \\
+ \frac{1}{A_i} \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial f(t_i | r_i)}{\partial \alpha_l} \frac{\partial z_{2,i}}{\partial \beta_h} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \alpha_l} - \frac{\partial z_{1,i}}{\partial \alpha_l} \right] \right) f_r(r_i) dr_i \right\} \\
\times \left\{ \int f(t_i | r_i) \frac{\partial z_{2,i}}{\partial \beta_h} f_r(r_i) dr_i \right\} \\
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial^2 z_{1,i}}{\partial \alpha_l \partial \beta_h} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{1}{B_i^2} \int \frac{\partial z_{1,i}}{\partial \alpha_l} f_r(r_i) dr_i \int \frac{\partial z_{1,i}}{\partial \beta_h} f_r(r_i) dr_i \right\}, \]

\[ -\frac{\partial^2 l}{\partial \beta_h \partial \beta_h'} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i | r_i)}{S(t_i | r_i)} \frac{\partial^2 z_{2,i}}{\partial \beta_h \partial \beta_h'} f_r(r_i) dr_i \\
- \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left[ \int \frac{f(t_i | r_i)}{S(t_i | r_i)} \frac{\partial z_{2,i}}{\partial \beta_h} f_r(r_i) dr_i \right] \left[ \int \frac{f(t_i | r_i)}{S(t_i | r_i)} \frac{\partial z_{2,i}}{\partial \beta_h'} f_r(r_i) dr_i \right] \\
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial^2 z_{1,i}}{\partial \beta_h \partial \beta_h'} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{1}{B_i^2} \int \frac{\partial z_{1,i}}{\partial \beta_h} \frac{\partial z_{1,i}}{\partial \beta_h'} f_r(r_i) dr_i - \sum_{i \in \Delta^*} \frac{x_{ih} x_{ih'} e^{\beta x_i}}{(1 + e^{\beta x_i})^2} \right\} \]
\[
- \frac{\partial^2 l}{\partial \gamma_k \partial \gamma_{k'}} = - \left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \left\{ \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial^2 f(t_i | r_i)}{\partial \gamma_k \partial \gamma_{k'}} \right) z_{2,i} \right. \right.
\]
\[
+ \frac{\partial f(t_i | r_i)}{\partial \gamma_k} \frac{\partial z_{2,i}}{\partial \gamma_k'} + \frac{\partial f(t_i | r_i)}{\partial \gamma_{k'}} \left[ \frac{\partial z_{2,i}}{\partial \gamma_k} - \frac{\partial z_{1,i}}{\partial \gamma_k} \right] + f(t_i | r_i) \left[ \frac{\partial^2 z_{2,i}}{\partial \gamma_k \gamma_k'} - \frac{\partial^2 z_{1,i}}{\partial \gamma_k \gamma_{k'}} \right]
\]
\[
- \frac{\partial \log S(t_i | r_i)}{\partial \gamma_k} \left\{ \frac{\partial f(t_i | r_i)}{\partial \gamma_k} z_{2,i} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \gamma_k} - \frac{\partial z_{1,i}}{\partial \gamma_k} \right] \right\} f_r(r_i) dr_i
\]
\[
- \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left\{ \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial f(t_i | r_i)}{\partial \gamma_k} z_{2,i} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \gamma_k} - \frac{\partial z_{1,i}}{\partial \gamma_k} \right] \right) f_r(r_i) dr_i \right\} f_r(r_i) dr_i
\]
\[
\int \frac{1}{S(t_i | r_i)} \left( \frac{\partial f(t_i | r_i)}{\partial \gamma_k} z_{2,i} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \gamma_k} - \frac{\partial z_{1,i}}{\partial \gamma_k} \right] \right) f_r(r_i) dr_i
\]
\[
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \frac{\partial z_{1,i}}{\partial \gamma_k \gamma_{k'}} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial z_{1,i}}{\partial \gamma_k} f_r(r_i) dr_i \int \frac{\partial z_{1,i}}{\partial \gamma_{k'}} f_r(r_i) dr_i \right\},
\]
\[-\frac{\partial^2 l}{\partial \alpha_i \partial \alpha'_v} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \left\{ \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial^2 f(t_i | r_i)}{\partial \alpha_i \partial \alpha'_v} z_{2,i} + \frac{\partial f(t_i | r_i)}{\partial \alpha_i} \frac{\partial z_{2,i}}{\partial \alpha'_v} \right) \right. \right. \right. \]

\[ + \frac{\partial f(t_i | r_i)}{\partial \alpha'_v} \left[ \frac{\partial z_{2,i}}{\partial \alpha_i} - \frac{\partial z_{1,i}}{\partial \alpha_i} \right] + f(t_i | r_i) \left[ \frac{\partial^2 z_{2,i}}{\partial \alpha_i \partial \alpha'_v} - \frac{\partial^2 z_{1,i}}{\partial \alpha_i \partial \alpha'_v} \right] \]

\[ - \frac{\partial \log S(t_i | r_i)}{\partial \alpha'_v} \left( \frac{\partial f(t_i | r_i)}{\partial \alpha_i} z_{2,i} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \alpha_i} - \frac{\partial z_{1,i}}{\partial \alpha_i} \right] \right) \right] \Bigg\} f_r(r_i) dr_i \]

\[ - \sum_{i \in \Delta_1} \frac{1}{A_i^2} \int \frac{1}{S(t_i | r_i)} \left( \frac{\partial f(t_i | r_i)}{\partial \alpha_i} z_{2,i} + f(t_i | r_i) \left[ \frac{\partial z_{2,i}}{\partial \alpha_i} - \frac{\partial z_{1,i}}{\partial \alpha_i} \right] \right) \]

\[ f_r(r_i) dr_i \]

\[ + \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{\partial^2 z_{1,i}}{\partial \alpha_i} f_r(r_i) dr_i - \sum_{i \in \Delta_0} \frac{1}{B_i^2} \int \frac{\partial z_{1,i}}{\alpha_i} f_r(r_i) dr_i \int \frac{\partial z_{1,i}}{\alpha'_v} f_r(r_i) dr_i \Bigg\} \],

\[-\frac{\partial^2 l}{\partial \beta_h \partial \gamma_k} = -\left\{ \sum_{i \in \Delta_1} \frac{x_{ih} e^{\beta x_i}}{z_{01,i}^2 1 + z_{1,i}} \left( z_{21,i} \frac{\partial \log S(t_i | r_i)}{\partial \gamma_k} \right) \right. \right. \right. \]

\[ + \sum_{i \in \Delta_1} \frac{x_{ih} e^{\beta x_i}}{z_{01,i} (1 + z_{1,i})} \left( z_{21,i} - \frac{z_{21,i}^2}{1 + z_{1,i}} \right) \right\} \]

\[-\frac{\partial^2 l}{\partial \gamma_k \partial \gamma'_k} = -\left\{ \sum_{i \in \Delta_1} \frac{\partial \log f^2(t_i, \gamma)}{\partial \gamma_k \partial \gamma'_k} \sum_{i \in \Delta_1} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_k} \right. \right. \right. \]

\[ + \sum_{i \in \Delta_1} \left( \frac{z_{21,i} z_{2,i} - z_{21,i}^2}{z_{2,i}} \right) \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_k} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma'_k} \right] \]

\[ + \sum_{i \in \Delta_0} \frac{z_{2,i}}{1 + z_{1,i}} \frac{\partial \log S(t_i, \gamma)}{\partial \gamma_k} \left( 1 + z_{1,i} \right)^2 \frac{\partial \log S(t_i, \gamma)}{\partial \gamma'_k} \right\} \],

\[-\frac{\partial^2 l}{\partial \xi^2} = -\left\{ \frac{n}{\xi} - n \psi_1(\xi) \right\}, \psi_1(x) = -\int_0^1 \frac{t^{x-1}}{1-t} (\ln t)^n dt, \]

where

\[ A_i = \int \frac{f(t_i | r_i)}{S(t_i | r_i)} z_{2,i} f_r(r_i) dr_i, \ B_i = \int (1 + z_{1,i}) f_r(r_i) dr_i \]
for \( l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n \).

### C.2.2 Geometric cure rate model with gamma frailty

Set 
\[
A_i = \int \frac{f(t_i | r_i)}{(1 + e^{\beta' x_i} F(t_i | r_i))^2} f_r(r_i) dr_i, 
B_i = \int \frac{1}{1 + e^{\beta' x_i} F(t_i | r_i)} f_r(r_i) dr_i.
\]

The score functions are

\[
\frac{\partial l}{\partial \beta_h} = \sum_{i \in \Delta_1} x_{ih} - \sum_{i \in \Delta_1} \frac{2x_{ih} e^{\beta' x_i}}{A_i} \int \frac{f(t_i | r_i) F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta' x_i} F(t_i | r_i))^3} dr_i
\]

\[- \sum_{i \in \Delta_0} \frac{x_{ih} e^{\beta' x_i}}{B_i} \int \frac{F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta' x_i} F(t_i | r_i))^2} dr_i,
\]

\[
\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{2e^{\beta' x_i}}{A_i} \int \frac{f(t_i | r_i)}{(1 + e^{\beta' x_i} F(t_i | r_i))^3} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i + \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{(1 + e^{\beta' x_i} F(t_i | r_i))^2} \frac{\partial f(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i
\]

\[- \sum_{i \in \Delta_0} \frac{e^{\beta' x_i}}{B_i} \int \frac{1}{(1 + e^{\beta' x_i} F(t_i | r_i))^2} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i,
\]

\[
\frac{\partial l}{\partial \xi} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i | r_i)}{(1 + e^{\beta' x_i} F(t_i | r_i))^2} \frac{\partial f_r(r_i)}{\partial \xi} dr_i + \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{1}{1 + e^{\beta' x_i} F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \xi} dr_i.
\]
Hence, the components of the observed information matrix are

\[
- \frac{\partial^2 l}{\partial \xi \partial \gamma_j} = - \left\{ - \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \frac{\partial A_i}{\partial \gamma_j} \\
+ 2 \sum_{i \in \Delta_1} \frac{e^{\beta x_i}}{A_i} \int \frac{f(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^3} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \\
- \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{f(t_i | r_i)}{1 + e^{\beta x_i} F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \xi} \frac{\partial B_i}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_0} \frac{e^{\beta x_i}}{B_i} \int \frac{1}{1 + e^{\beta x_i} F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \xi} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \right\},
\]

\[
- \frac{\partial^2 l}{\partial \xi \partial \beta_h} = - \left\{ - \sum_{i \in \Delta_1} \frac{2x_{ih} e^{\beta x_i}}{A_i^2} \int \frac{F(t_i | r_i) f(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^3} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \\
+ 2 \sum_{i \in \Delta_1} \frac{x_{ih} e^{\beta x_i}}{A_i^2} \int \frac{f(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \int \frac{f(t_i | r_i) F(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^3} f_r(r_i) dr_i \\
- \sum_{i \in \Delta_0} \frac{x_{ih} e^{\beta x_i}}{B_i} \int \frac{F(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \\
+ \sum_{i \in \Delta_0} \frac{x_{ih} e^{\beta x_i}}{B_i^2} \int \frac{1}{1 + e^{\beta x_i} F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \xi} dr_i \int \frac{F(t_i | r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} f_r(r_i) dr_i \right\},
\]

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\[
\frac{-\partial^2 l}{\partial \beta \partial \beta'} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \frac{\partial^2 f_r(r_i)}{\partial \xi^2} \, dr_i
\right.
\]

\[
+ \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left[ \frac{f(t_i|r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \frac{\partial f_r(r_i)}{\partial \xi} \right]^2 dr_i
\]

\[
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int \frac{1}{1 + e^{\beta \cdot x_i} F(t_i|r_i)} \frac{\partial^2 f_r(r_i)}{\partial \xi^2} \, dr_i
\]

\[
- \sum_{i \in \Delta_0} \frac{1}{B_i^2} \left[ \int \frac{1}{1 + e^{\beta \cdot x_i} F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \xi} \right]^2 \, dr_i \right\},
\]

\[
\frac{-\partial^2 l}{\partial \beta_h \partial \beta_{h'}} = -\left\{ - \sum_{i \in \Delta_1} \frac{2 x_{ih} x_{ih'} e^{\beta \cdot x_i}}{A_i} \int \frac{f(t_i|r_i) f(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^3} \, dr_i
\right.
\]

\[
+ \sum_{i \in \Delta_1} \frac{6 x_{ih} x_{ih'} e^{\beta' \cdot x_i}}{A_i} \int \frac{f(t_i|r_i) F(t_i|r_i)^2 f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^4} \, dr_i
\]

\[
- \sum_{i \in \Delta_1} \frac{4 x_{ih} x_{ih'} e^{\beta' \cdot x_i}}{A_i^2} \int \frac{f(t_i|r_i) F(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^3} \, dr_i \int \frac{f(t_i|r_i) F(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \, dr_i
\]

\[
- \sum_{i \in \Delta_0} \frac{x_{ih} x_{ih'} e^{\beta' \cdot x_i}}{B_i} \int \frac{F(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \, dr_i
\]

\[
+ \sum_{i \in \Delta_0} \frac{2 x_{ih} x_{ih'} e^{\beta' \cdot x_i}}{B_i} \int \frac{F(t_i|r_i)^2 f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^3} \, dr_i
\]

\[
- \sum_{i \in \Delta_0} \frac{x_{ih} x_{ih'} e^{\beta' \cdot x_i}}{B_i^2} \int \frac{F(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \, dr_i \int \frac{F(t_i|r_i) f_r(r_i)}{(1 + e^{\beta \cdot x_i} F(t_i|r_i))^2} \, dr_i \right\},
\]
\[- \frac{\partial^2 l}{\partial \beta_i \partial \gamma_j} = \left\{ \sum_{i \in \Delta_1} \frac{2x_i e^{\beta x_i}}{A_i} \int \frac{f(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^3} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \right. \\
\left. - \sum_{i \in \Delta_1} \frac{2x_i e^{\beta x_i}}{A_i} \int \frac{F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^3} \frac{\partial f(t_i | r_i)}{\partial \gamma_j} dr_i \\
- \sum_{i \in \Delta_1} \frac{6x_i e^{2\beta x_i}}{A_i} \int \frac{f(t_i | r_i) F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^4} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_1} \frac{2x_i e^{\beta x_i}}{A_i^2} \int \frac{f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial A_i}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_0} \frac{x_i e^{\beta x_i}}{B_i} \int \frac{f(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \\
- \sum_{i \in \Delta_0} \frac{2x_i e^{2\beta x_i}}{B_i} \int \frac{F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_0} \frac{x_i e^{2\beta x_i}}{B_i^2} \int \frac{F(t_i | r_i) f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \int \frac{f_r(r_i)}{(1 + e^{\beta x_i} F(t_i | r_i))^2} \frac{\partial S(t_i | r_i)}{\partial \gamma_j} dr_i \right\}, \]
\[
- \frac{\partial^2 l}{\partial \gamma_j \partial \gamma_{j'}} = - \left\{ \sum_{i \in \Delta_1} \frac{2e^{\beta x_i}}{A_i} \int \frac{f(t_i|t_i)}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial^2 S(t_i|t_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(t_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{2e^{\beta x_i}}{A_i} \int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial S(t_i|t_i)}{\partial \gamma_j} \frac{\partial f(t_i|t_i)}{\partial \gamma_{j'}} f_r(t_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{6e^{\beta x_i}}{A_i} \int \frac{f(t_i|t_i)}{(1 + e^{\beta x_i} F(t_i|t_i))^4} \frac{\partial S(t_i|t_i)}{\partial \gamma_j} \frac{\partial S(t_i|t_i)}{\partial \gamma_{j'}} f_r(t_i) dr_i \\
- \sum_{i \in \Delta_1} \frac{2e^{\beta x_i}}{A_i^2} \int \frac{f(t_i|t_i)}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial^2 S(t_i|t_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(t_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial^2 f(t_i|t_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(t_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{2e^{\beta x_i}}{A_i^2} \int \frac{f(t_i|t_i)}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial f(t_i|t_i)}{\partial \gamma_{j'}} f_r(t_i) \frac{\partial A_i}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_0} \frac{e^{\beta x_i}}{B_i} \int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial^2 S(t_i|t_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(t_i) dr_i \\
+ \sum_{i \in \Delta_0} \frac{2e^{\beta x_i}}{B_i^2} \int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial S(t_i|t_i)}{\partial \gamma_j} \frac{\partial S(t_i|t_i)}{\partial \gamma_{j'}} f_r(t_i) dr_i \\
- \sum_{i \in \Delta_0} \frac{e^{2\beta x_i}}{B_i^2} \int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial S(t_i|t_i)}{\partial \gamma_j} f_r(t_i) dr_i \right\} \\
\int \frac{1}{(1 + e^{\beta x_i} F(t_i|t_i))} \frac{\partial S(t_i|t_i)}{\partial \gamma_{j'}} f_r(t_i) dr_i.
\]
where

\[
\begin{align*}
\frac{\partial A_i}{\partial \beta_h} &= -2x_i h e^{\beta x_i} \int \frac{f(t_i|r_i) F(t_i|r_i)}{(1 + e^{\beta x_i} F(t_i|r_i))^3} f_r(r_i) dr_i, \\
\frac{\partial B_i}{\partial \beta_h} &= -x_i h e^{\beta x_i} \int \frac{F(t_i|r_i)}{(1 + e^{\beta x_i} F(t_i|r_i))^2} f_r(r_i) dr_i, \\
\frac{\partial A_i}{\partial \gamma_j} &= 2e^{\beta x_i} \int \frac{f(t_i|r_i)}{(1 + e^{\beta x_i} F(t_i|r_i))^3} \frac{\partial S(t_i|r_i)}{\partial \gamma_j} f_r(r_i) dr_i \\
&\quad + \int \frac{1}{(1 + e^{\beta x_i} F(t_i|r_i))^2} \frac{\partial f(t_i|r_i)}{\partial \gamma_j} f_r(r_i) dr_i,
\end{align*}
\]

for \(l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n\).
C.2.3 Poisson cure rate model with gamma frailty

Set $A_i = \int (1 + e^{\beta' x_i})^{-F(t_i|r_i)} f(t_i|r_i) f_r(r_i) dr_i$, $B_i = \int (1 + e^{\beta' x_i})^{-F(t_i|r_i)} f_r(r_i) dr_i$. The score functions are

$$\frac{\partial l}{\partial \beta_h} = \sum_{i \in \Delta_1} \frac{1}{\log(1 + e^{\beta' x_i})} \frac{x_{ih} e^{\beta' x_i}}{1 + e^{\beta' x_i}}$$

$$- \sum_{i \in \Delta_1} \frac{x_{ih} e^{\beta' x_i}}{A_i} \int (1 + e^{\beta' x_i}) S(t_i|r_i)^{-2} F(t_i|r_i) f(t_i|r_i) f_r(r_i) dr_i$$

$$- \sum_{i \in \Delta_0} \frac{x_{ih} e^{\beta' x_i}}{B_i} \int (1 + e^{\beta' x_i}) S(t_i|r_i)^{-2} F(t_i|r_i) f_r(r_i) dr_i,$$

$$\frac{\partial l}{\partial \gamma_j} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int (1 + e^{\beta' x_i})^{-F(t_i|r_i)} \frac{\partial S(t_i|r_i)}{\partial \gamma_j} f(t_i|r_i) f_r(r_i) dr_i$$

$$+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + e^{\beta' x_i})^{-F(t_i|r_i)} \frac{\partial f(t_i|r_i)}{\partial \gamma_j} f_r(r_i) dr_i$$

$$+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + e^{\beta' x_i})^{-F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} dr_i.$$

Hence, the components of the observed information matrix are
\[- \frac{\partial^2 l}{\partial \xi \partial \beta_h} = \left\{ - \sum_{i \in \Delta_1} \frac{x_i h e^{\beta x_i}}{A_i} \int \frac{F(t_i | r_i) f(t_i | r_i)}{(1 + e^{\beta x_i})^F(t_i | r_i) + 1} \frac{\partial f_r(r_i)}{\partial \gamma_j} dr_i \right. \\
+ \sum_{i \in \Delta_1} \frac{x_i h e^{\beta x_i}}{A_i^2} \int \frac{f(t_i | r_i)}{(1 + e^{\beta x_i})^F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} dr_i \int \frac{f(t_i | r_i)}{(1 + e^{\beta x_i})^F(t_i | r_i) + 1} f_r(r_i) dr_i \\
- \sum_{i \in \Delta_0} \frac{x_i h e^{\beta x_i}}{B_i} \int \frac{F(t_i | r_i)}{(1 + e^{\beta x_i})^F(t_i | r_i) + 1} \frac{\partial f_r(r_i)}{\partial \gamma_j} dr_i \\
+ \sum_{i \in \Delta_0} \frac{x_i h e^{\beta x_i}}{B_i^2} \int \frac{1}{(1 + e^{\beta x_i})^F(t_i | r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} dr_i \int \frac{F(t_i | r_i)}{(1 + e^{\beta x_i})^F(t_i | r_i) + 1} f_r(r_i) dr_i \right\} \]
- \frac{\partial^2 l}{\partial \xi \partial \gamma_j} = - \left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} \frac{\partial f(t_i|r_i)}{\partial \gamma_j} \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \right. \\
- \sum_{i \in \Delta_1} \frac{1}{A_i} \log(1 + e^{\beta \mathbf{x}_i}) \int \frac{f(t_i|r_i)}{(1 + e^{\beta \mathbf{x}_i})^F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \\
- \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{(1 + e^{\beta \mathbf{x}_i})^F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \\
+ \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{f(t_i|r_i)}{(1 + e^{\beta \mathbf{x}_i})^F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \\
\times \left\{ \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} \frac{\partial S(t_i|r_i)}{\partial \gamma_j} f_r(r_i) \, dr_i ight\},

- \frac{\partial^2 l}{\partial \xi^2} = - \left\{ \sum_{i \in \Delta_1} \frac{1}{A_i} \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} f(t_i|r_i) \frac{\partial^2 f_r(r_i)}{\partial \gamma_j^2} \, dr_i ight. \\
+ \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} \frac{\partial^2 f_r(r_i)}{\partial \gamma_j^2} \, dr_i \\
- \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left[ \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} f(t_i|r_i) \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \right]^2 \\
- \sum_{i \in \Delta_1} \frac{1}{B_i^2} \left[ \int (1 + e^{\beta \mathbf{x}_i})^{-F(t_i|r_i)} \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \right]^2 \right\},

- \frac{\partial^2 l}{\partial \beta_h \partial \beta_{h'}} = - \left\{ \sum_{i \in \Delta_1} \frac{z_{ih} z_{ih'} e^{\beta \mathbf{x}_i} (\log(1 + e^{\beta \mathbf{x}_i}) - e^{\beta \mathbf{x}_i})}{(1 + e^{\beta \mathbf{x}_i})^2 \log(1 + e^{\beta \mathbf{x}_i})^2} - \sum_{i \in \Delta_1} x_{ih} x_{ih'} e^{2 \beta \mathbf{x}_i} \frac{D_i}{A_i^2} \\
- \sum_{i \in \Delta_1} x_{ih} x_{ih'} e^{2 \beta \mathbf{x}_i} \left( \frac{F_i}{A_i} + \frac{D_i^2}{A_i^2} \right) - \sum_{i \in \Delta_0} x_{ih} x_{ih'} e^{\beta \mathbf{x}_i} \frac{C_i}{B_i} - \sum_{i \in \Delta_0} x_{ih} x_{ih'} e^{2 \beta \mathbf{x}_i} \left( \frac{E_i}{B_i} + \frac{C_i^2}{B_i^2} \right) \right\}.
where

\[ C_i = \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) f_r(r_i) dr_i, \]

\[ D_i = \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) f_r(r_i) dr_i, \]

\[ E_i = \int (S(t_i | r_i) - 2) (1 + e^{\beta_i x_i}) S(t_i | r_i) - 3 F(t_i | r_i) f_r(r_i) dr_i, \]

\[ F_i = \int (S(t_i | r_i) - 2) (1 + e^{\beta_i x_i}) S(t_i | r_i) - 3 F(t_i | r_i) f_r(r_i) dr_i, \]

\[-\frac{\partial^2 l}{\partial \beta_i \partial \gamma_j} = \left\{ \sum_{i \in \Delta_1} \frac{x_i h e^{\beta_i x_i}}{A_i} \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f(t_i | r_i) f_r(r_i) dr_i \right. \]

\[-\sum_{i \in \Delta_1} \frac{x_i h e^{\beta_i x_i}}{A_i} \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) \frac{\partial f(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i \]

\[-\sum_{i \in \Delta_1} \frac{x_i h e^{\beta_i x_i}}{A_i} \log(1 + e^{\beta_i x_i}) \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 \frac{\partial S(t_i | r_i)}{\partial \gamma_j} F(t_i | r_i) f(t_i | r_i) f_r(r_i) dr_i \]

\[ + \sum_{i \in \Delta_1} \frac{x_i h e^{\beta_i x_i}}{A_i} \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) f(t_i | r_i) f_r(r_i) dr_i \]

\[(\log(1 + e^{\beta_i x_i})) \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f(t_i | r_i) f_r(r_i) dr_i \]

\[ + \int (1 + e^{\beta_i x_i}) - F(t_i | r_i) \frac{\partial f(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i \]

\[ + \sum_{i \in \Delta_0} \frac{x_i h e^{\beta_i x_i}}{B_i} \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i \]

\[-\sum_{i \in \Delta_0} \frac{x_i h e^{\beta_i x_i}}{B_i} \log(1 + e^{\beta_i x_i}) \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) dr_i \]

\[ + \sum_{i \in \Delta_0} \frac{x_i h e^{\beta_i x_i}}{B_i^2} \log(1 + e^{\beta_i x_i}) \]

\[ \left\{ \int (1 + e^{\beta_i x_i}) S(t_i | r_i) - 2 F(t_i | r_i) f_r(r_i) dr_i \right\}. \]
\[-\frac{\partial^2 l}{\partial \gamma_j \partial \gamma_{j'}} = \left\{ \sum_{i \in \Delta_1} \log(1 + e^{\beta^i x_i}) \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_j} \frac{\partial f(t_i|x_i)}{\partial \gamma_{j'}} f_r(r_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{\log(1 + e^{\beta^i x_i})}{A_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S^2(t_i|x_i)}{\partial \gamma_j \partial \gamma_{j'}} f(t_i|x_i) f_r(r_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{[\log(1 + e^{\beta^i x_i})]^2}{A_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_j} \frac{\partial S(t_i|x_i)}{\partial \gamma_{j'}} f(t_i|x_i) f_r(r_i) dr_i \\
- \sum_{i \in \Delta_1} \frac{\log(1 + e^{\beta^i x_i})}{A_i^2} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial f(t_i|x_i)}{\partial \gamma_{j'}} f_r(r_i) dr_i \\
\int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_{j'}} f(t_i|x_i) f_r(r_i) dr_i \\
+ \frac{1}{A_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial f^2(t_i|x_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(r_i) dr_i \\
+ \sum_{i \in \Delta_1} \frac{\log(1 + e^{\beta^i x_i})}{A_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial f(t_i|x_i)}{\partial \gamma_{j'}} f_r(r_i) dr_i \\
- \frac{1}{A_i^2} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_j} f(t_i|x_i) f_r(r_i) dr_i \\
\int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_{j'}} f(t_i|x_i) f_r(r_i) dr_i + \log(1 + e^{\beta^i x_i}) H_i \right) \\
+ \sum_{i \in \Delta_0} \frac{\log(1 + e^{\beta^i x_i})}{B_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S^2(t_i|x_i)}{\partial \gamma_j \partial \gamma_{j'}} f_r(r_i) dr_i \\
+ \sum_{i \in \Delta_0} \frac{[\log(1 + e^{\beta^i x_i})]^2}{B_i} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_j} \frac{\partial S(t_i|x_i)}{\partial \gamma_{j'}} f_r(r_i) dr_i \\
- \sum_{i \in \Delta_0} \frac{[\log(1 + e^{\beta^i x_i})]^2}{B_i^2} \int \left( 1 + e^{\beta^i x_i} \right)^{-F(t_i|x_i)} \frac{\partial S(t_i|x_i)}{\partial \gamma_j} f_r(r_i) dr_i \right\}
\]
for \( l, l' = 0, \ldots, p, x_{i0} \equiv 1, h, h' = 0, 1, j^*, j^* = 21, 22, \ldots, 2p, i = 1, \ldots, n \).

### C.2.4 Bernoulli cure rate model with gamma frailty

Set \( A_i = \int f(t_i | r_i) f_r(r_i) dr_i \) and \( B_i = \int (1 + e^{\beta x_i} S(t_i | r_i)) f_r(r_i) dr_i \). In this case, the score functions are

\[
\frac{\partial l}{\partial \beta h} = \sum_{i \in \Delta_1} x_{ih} - \sum_{i \in \Delta*} x_{ih} e^{\beta x_i} + \sum_{i \in \Delta_0} \frac{x_{ih} e^{\beta x_i}}{B_i} \int S(t_i | r_i) f_r(r_i) dr_i,
\]

\[
\frac{\partial l}{\partial \gamma j} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int \frac{\partial f(t_i | r_i)}{\partial \gamma j} f_r(r_i) dr_i + \sum_{i \in \Delta_0} \frac{e^{\beta x_i} f_r(r_i)}{B_i} \frac{\partial S(t_i | r_i)}{\partial \gamma j} dr_i,
\]

\[
\frac{\partial l}{\partial \xi} = \sum_{i \in \Delta_1} \frac{1}{A_i} \int f(t_i | r_i) \frac{\partial f_r(r_i)}{\partial \xi} dr_i + \sum_{i \in \Delta_0} \frac{1}{B_i} \int (1 + e^{\beta x_i} S(t_i | r_i)) \frac{\partial f_r(r_i)}{\partial \xi} dr_i.
\]

Hence, the components of the observed information matrix are
\[-\frac{\partial^2 l}{\partial \xi \partial \beta_h} = - \left\{ \sum_{i \in \Delta_0} \frac{1}{B_i} \int x_i h e^{\beta_i x_i} S(t_i | r_i) \frac{\partial f_r(r_i)}{\partial \xi} \, dr_i \right\}, \]

\[-\frac{\partial^2 l}{\partial \xi \partial \gamma_j} = - \left\{ \sum_{i \in \Delta_0} \frac{1}{A_i^2} \left[ \int \frac{\partial f(t_i | r_i)}{\partial \gamma_j} \frac{\partial f_r(r_i)}{\partial \xi} \, dr_i A_i - \int f(t_i | r_i) \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \int \frac{\partial f(t_i | r_i)}{\partial \gamma_j} f_r(r_i) \, dr_i \right] \right. \]
\[\left. + \sum_{i \in \Delta_0} \frac{e^{\beta_i x_i}}{B_i^2} \left[ \int \frac{\partial S(t_i | r_i)}{\partial \gamma_j} \frac{\partial f_r(r_i)}{\partial \xi} \, dr_i B_i \right. \right. \]
\[\left. - \int \left( 1 + e^{\beta_i x_i} S(t_i | r_i) \right) \frac{\partial f_r(r_i)}{\partial \gamma_j} \, dr_i \int \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) \, dr_i \right\} \}

\[-\frac{\partial^2 l}{\partial \beta_h \partial \beta_h'} = - \left\{ - \sum_{i \in \Delta^*} \frac{x_i h x_i h' e^{\beta_i x_i}}{(1 + e^{\beta_i x_i})^2} \right. \]
\[\left. + \sum_{i \in \Delta_0} \frac{x_i h x_i h' e^{\beta_i x_i}}{B_i^2} \left[ \int S(t_i | r_i) f_r(r_i) \, dr_i B_i - e^{\beta_i x_i} \left( \int S(t_i | r_i) f_r(r_i) \, dr_i \right)^2 \right] \right\} \}

\[-\frac{\partial^2 l}{\partial \beta_h \partial \gamma_j} = - \left\{ \sum_{i \in \Delta_0} \frac{x_i e^{\beta_i x_i}}{B_i^2} \left[ \int \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) \, dr_i B_i \right. \right. \]
\[\left. - e^{\beta_i x_i} \int S(t_i | r_i) f_r(r_i) \, dr_i \int \frac{\partial S(t_i | r_i)}{\partial \gamma_j} f_r(r_i) \, dr_i \right\} \}

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\[-\frac{\partial^2 l}{\partial \gamma_j \partial \gamma_j'} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left[ \int \frac{\partial^2 f(t_i|r_i)}{\partial \gamma_j \partial \gamma_j'} f_r(r_i) dr_i A_i \right. \\
\left. - \int \frac{\partial f(t_i|r_i)}{\partial \gamma_j} f_r(r_i) dr_i \int \frac{\partial f(t_i|r_i)}{\partial \gamma_j'} f_r(r_i) dr_i \right] \\
+ \sum_{i \in \Delta_0} \frac{e^{\beta z_i}}{B_i^2} \left[ \int \frac{\partial^2 S(t_i|r_i)}{\partial \gamma_j \partial \gamma_j'} f_r(r_i) dr_i B_i \right. \\
\left. - \frac{e^{\beta z_i} \int \frac{\partial S(t_i|r_i)}{\partial \gamma_j} f_r(r_i) dr_i \int \frac{\partial S(t_i|r_i)}{\partial \gamma_j'} f_r(r_i) dr_i}{\partial \gamma_j} \right] \right\}, \]

\[-\frac{\partial^2 l}{\partial \xi^2} = -\left\{ \sum_{i \in \Delta_1} \frac{1}{A_i^2} \left[ \int f(t_i|r_i) \frac{\partial^2 f_r(r_i)}{\partial \xi^2} dr_i A_i \right. \\
\left. - \int f(t_i|r_i) \frac{\partial f_r(r_i)}{\partial \xi} dr_i \int f(t_i|r_i) \frac{\partial f_r(r_i)}{\partial \xi} dr_i \right] \\
+ \sum_{i \in \Delta_0} \frac{1}{B_i^2} \left[ \int \left( 1 + e^{\beta z_i} S(t_i|r_i) \right) \frac{\partial^2 f_r(r_i)}{\partial \xi^2} dr_i B_i \right. \\
\left. - \left\{ \int \left( 1 + e^{\beta z_i} S(t_i|r_i) \right) \frac{\partial f_r(r_i)}{\partial \xi} dr_i \right\}^2 \right] \right\}, \]

where

\[\int f(t_i|r_i) \frac{\partial^2 f_r(r_i)}{\partial \xi^2} dr_i = E \left( f(t_i|r_i) \left[ \frac{\partial^2 \log f_r(r_i)}{\partial \xi^2} + \frac{\partial \log f_r(r_i)}{\partial \xi} \frac{\partial \log f_r(r_i)}{\partial \xi} \right] \right), \]

\[\int \left[ 1 + e^{\beta z_i} S(t_i|r_i) \right] \frac{\partial f_r(r_i)}{\partial \xi} dr_i = E \left( \left[ 1 + e^{\beta z_i} S(t_i|r_i) \right] \frac{\partial \log f_r(r_i)}{\partial \xi} \right), \]

\[\frac{\partial \log f_r(y)}{\partial \xi} = \log y + 1 + \log \xi - y - \psi_1(\xi), \quad \frac{\partial^2 \log f_r(y)}{\partial \xi^2} = \frac{1}{\xi} - \psi_2(\xi) \]
for \( l, l' = 0, \ldots, p \), \( x_{i0} \equiv 1 \), \( h, h' = 0, 1 \), \( j^*, j^* = 21, 22, \ldots, 2p \), \( i = 1, \ldots, n \).
Appendix D

Derivatives with respect to proportional odds model

D.1 Weibull baseline

\[ S_0(t) = e^{-(\gamma_1 t)^{1/\gamma_0}}, \quad f_0(t) = \frac{(\gamma_1 t)^{1/\gamma_0}}{\gamma_0 t} e^{-(\gamma_1 t)^{1/\gamma_0}}, \]

\[ S_{0;\gamma_0} = \frac{(\gamma_1 t_i)^{1/\gamma_0}}{\gamma_0^2} \log(\gamma_1 t_i) S_0, \quad S_{0;\gamma_0\gamma_1} = -\frac{(\gamma_1 t_i)^{1/\gamma_0}}{\gamma_0 \gamma_1} S_0, \quad S_{0;\gamma_0\gamma_0} = S_{0;\gamma_0} \frac{[(\gamma_1 t_i)^{1/\gamma_0} - 1] \log(\gamma_1 t_i) - 2\gamma_0}{\gamma_0^2}, \]

\[ S_{0;\gamma_1} = S_{0;\gamma_1} \frac{[(\gamma_1 t_i)^{1/\gamma_0} - 1] \log(\gamma_1 t_i) - \gamma_0}{\gamma_0^2}, \quad S_{0;\gamma_1\gamma_1} = S_{0;\gamma_1} \frac{1 - \gamma_0 - (\gamma_1 t_i)^{1/\gamma_0}}{\gamma_0 \gamma_1}; \]

\[ \frac{\partial \log S_0}{\partial \gamma_0} = \frac{(\gamma_1 t_i)^{1/\gamma_0}}{\gamma_0^2} \log(\gamma_1 t_i), \quad \frac{\partial \log S_0}{\partial \gamma_1} = -\frac{(\gamma_1 t_i)^{1/\gamma_0}}{\gamma_0 \gamma_1}, \quad \frac{\partial \log S_0^2}{\partial \gamma_0 \partial \gamma_0} = -\frac{\partial \log S_0}{\partial \gamma_0} \left( \frac{\log(\gamma_1 t_i)}{\gamma_0^2} + \frac{2}{\gamma_0} \right), \]

\[ \frac{\partial \log S_0}{\partial \gamma_0 \partial \gamma_1} = -\frac{\partial \log S_0}{\partial \gamma_1} \left( \frac{\log(\gamma_1 t_i)}{\gamma_0^2} + \frac{1}{\gamma_0} \right), \quad \frac{\partial \log S_0^2}{\partial \gamma_1 \partial \gamma_1} = \frac{\partial \log S_0}{\partial \gamma_1} \left( \frac{1}{\gamma_0 \gamma_1} - \frac{1}{\gamma_1} \right); \]

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\[
\begin{align*}
\frac{\partial \log f_0}{\partial \gamma_0} &= \frac{\partial \log S_0}{\partial \gamma_0} - \frac{1}{\gamma_0} \left( 1 + \frac{\log(\gamma_1 t_i)}{\gamma_0} \right), \\
\frac{\partial \log f_0}{\partial \gamma_1} &= \frac{1}{\gamma_0 \gamma_1} + \frac{\partial \log S_0}{\partial \gamma_1}, \\
\frac{\partial \log f_0^2}{\partial \gamma_0 \partial \gamma_0} &= \frac{\partial \log S_0^2}{\partial \gamma_0 \partial \gamma_0} + \frac{2 \log(\gamma_1 t_i)}{\gamma_0^2}, \\
\frac{\partial \log f_0^2}{\partial \gamma_0 \partial \gamma_1} &= \frac{\partial \log S_0^2}{\partial \gamma_0 \partial \gamma_1} - \frac{1}{\gamma_0 \gamma_1}, \\
\frac{\partial \log f_0^2}{\partial \gamma_1 \partial \gamma_1} &= \frac{\partial \log S_0^2}{\partial \gamma_1 \partial \gamma_1} - \frac{1}{\gamma_0 \gamma_1}. 
\end{align*}
\]

\[
\begin{align*}
\frac{\partial S}{\partial \gamma_0} &= \frac{\partial S_0}{\partial \gamma_0} G_0, \\
\frac{\partial S}{\partial \gamma_1} &= \frac{\partial S_0}{\partial \gamma_1} G_1, \\
\frac{\partial^2 S}{\partial \gamma_0 \partial \gamma_1} &= \frac{\partial^2 S_0}{\partial \gamma_0 \partial \gamma_1} G_0 - 2 \frac{\partial S}{\partial \gamma_0} \frac{\partial S_0}{\partial \gamma_1} G_1, \\
\frac{\partial^2 S}{\partial \gamma_0 \partial \gamma_0} &= \frac{\partial S}{\partial \gamma_0} x_{il} G_2, \\
\frac{\partial^2 S}{\partial \gamma_1 \partial \gamma_1} &= \frac{\partial S}{\partial \gamma_1} x_{il} G_2, \\
\frac{\partial^2 S}{\partial \gamma_0 \partial \alpha_t} &= \frac{\partial S}{\partial \gamma_0} x_{il} G_2. 
\end{align*}
\]

\[
\begin{align*}
\frac{\partial \log S}{\partial \gamma_0} &= \frac{\partial \log S_0}{\partial \gamma_0} 1, \\
\frac{\partial \log S}{\partial \gamma_1} &= \frac{\partial \log S_0}{\partial \gamma_1} 1, \\
\frac{\partial^2 \log S}{\partial \gamma_0 \partial \gamma_0} &= \left( \frac{\partial^2 \log S_0}{\partial \gamma_0 \partial \gamma_0} - \frac{\partial \log S_0}{\partial \gamma_0} \frac{\partial \log S_0}{\partial \gamma_0} G_1 \right) \frac{1}{G}, \\
\frac{\partial^2 \log S}{\partial \gamma_0 \partial \gamma_1} &= \left( \frac{\partial^2 \log S_0}{\partial \gamma_0 \partial \gamma_1} - \frac{\partial \log S_0}{\partial \gamma_0} \frac{\partial \log S_0}{\partial \gamma_1} G_1 \right) \frac{1}{G}, \\
\frac{\partial^2 \log S}{\partial \gamma_1 \partial \gamma_1} &= \left( \frac{\partial^2 \log S_0}{\partial \gamma_1 \partial \gamma_1} - \frac{\partial \log S_0}{\partial \gamma_1} \frac{\partial \log S_0}{\partial \gamma_1} G_1 \right) \frac{1}{G}, \\
\frac{\partial \log S}{\partial \gamma_0 \partial \alpha_{il}} &= - \frac{\partial S}{\partial \gamma_0} x_{il}, \\
\frac{\partial \log S}{\partial \gamma_1 \partial \alpha_{il}} &= - \frac{\partial S}{\partial \gamma_1} x_{il}, \\
\frac{\partial \log S}{\partial \alpha_{il}} &= \frac{\partial S}{\partial \gamma_0} x_{il} F_0, \\
\frac{\partial^2 \log S}{\partial \alpha_{il} \partial \alpha_{il}'} &= - \frac{\partial S}{\partial \alpha_{il}} x_{il}'. 
\end{align*}
\]
\[
\frac{\partial \log f}{\partial \gamma_0} = \frac{\partial \log f_0}{\partial \gamma_0} - 2 \frac{\partial S_0}{\partial \gamma_0} G_1, \\
\frac{\partial \log f}{\partial \gamma_1} = \frac{\partial \log f_0}{\partial \gamma_1} - 2 \frac{\partial S_0}{\partial \gamma_1} G_1, \\
\frac{\partial \log f^2}{\partial \gamma_0 \partial \gamma_0} = \frac{\partial \log f_0^2}{\partial \gamma_0 \partial \gamma_0} - 2 \frac{\partial S_0^2}{\partial \gamma_0 \partial \gamma_0} G_1 + 2 \left( \frac{\partial S_0}{\partial \gamma_0} G_1 \right)^2, \\
\frac{\partial \log f^2}{\partial \gamma_1 \partial \gamma_1} = \frac{\partial \log f_0^2}{\partial \gamma_1 \partial \gamma_1} - 2 \frac{\partial S_0^2}{\partial \gamma_1 \partial \gamma_1} G_1 + 2 \frac{\partial S_0}{\partial \gamma_0} \frac{\partial S_0}{\partial \gamma_1} (G_1)^2, \\
\frac{\partial \log f^2}{\partial \gamma_0 \partial \alpha_l} = -2 \frac{\partial S_0}{\partial \gamma_0} x_i y_i e^{\alpha' x_i}, \\
\frac{\partial \log f^2}{\partial \gamma_1 \partial \alpha_l} = -2 \frac{\partial S_0}{\partial \gamma_1} x_i y_i e^{\alpha' x_i}, \\
\frac{\partial \log f}{\partial \alpha_l} = x_i \left[ 2 - \frac{1}{G} - 1 \right], \\
\frac{\partial \log f^2}{\partial \alpha_l \partial \alpha_{l'}} = -\frac{2 x_i x_i' S_0 F_0 y_i e^{\alpha' x_i}}{G^2},
\]

where

\[
G = 1 + S_0 (y_i e^{x_i' \gamma_1} - 1), \\
G_0 = \frac{f}{f_0}, \\
G_1 = \frac{y_i e^{\beta' x_i} - 1}{G}, \\
G_2 = 2 \frac{F_0}{G} - 1, \\
G_3 = (\gamma_1 t_i)^{1/\gamma_0} S_0 G_1 + 1.
\]
D.2 Log-logistic baseline

\[ S_0 = \frac{\gamma_0^{\gamma_1}}{t_i^{\gamma_1} + \gamma_0^{\gamma_1}}, \quad S = \frac{\gamma_0^{\gamma_1} y_i e^{\alpha x}}{y_i \gamma_0^{\alpha x} + t_i^{\gamma_1}}, \quad f_0 = \frac{\gamma_0^{\gamma_1} \gamma_1 t_i^{\gamma_1-1}}{(t_i^{\gamma_1} + \gamma_0^{\gamma_1})^2}, \quad f = \frac{\gamma_0^{\gamma_1} \gamma_1 t_i^{\gamma_1-1} e^{\alpha x}}{(t_i^{\gamma_1} + \gamma_0^{\gamma_1} e^{\alpha x})^2}. \]

The derivatives of \( S(t_i; \gamma) \) are as follows:

\[
\frac{\partial S_0(t_i; \gamma)}{\partial \gamma_0} = F_0 S_0 \frac{\gamma_1}{\gamma_0}, \quad \frac{\partial S_0(t_i; \gamma)}{\partial \gamma_1} = F_0 S_0 \log \frac{\gamma_0}{t_i},
\]

\[
\frac{\partial S_0^2(t_i; \gamma)}{\partial \gamma_0^2} = - \frac{\partial S_0(t_i; \gamma)}{\partial \gamma_0} 1 + \gamma_1 S_0(t_i; \gamma) + F_0 S_0 \frac{\gamma_1}{\gamma_0} F_0 \frac{\gamma_1}{\gamma_0},
\]

\[
\frac{\partial S_0^2(t_i; \gamma)}{\partial \gamma_0 \partial \gamma_1} = \frac{\partial S_0(t_i; \gamma)}{\partial \gamma_0} \left[ \frac{1}{\gamma_1} + S_0(t_i; \gamma) \log \frac{t_i}{\gamma_0} \right] + F_0 S_0 \frac{\gamma_1}{\gamma_0} S_0 \log \frac{\gamma_0}{t_i},
\]

\[
\frac{\partial S_0^2(t_i; \gamma)}{\partial \gamma_1 \partial \gamma_1} = \frac{\partial S_0(t_i; \gamma)}{\partial \gamma_1} S_0(t_i; \gamma) \log \frac{t_i}{\gamma_0} + F_0 \log \frac{\gamma_0}{t_i} F_0 S_0 \log \frac{\gamma_0}{t_i}.
\]

The derivatives of \( \log S(t_i, \gamma) \) are as follows:

\[
\frac{\partial \log S_0(t_i; \gamma)}{\partial \gamma_0} = t_i^{\gamma_1} \frac{(\gamma_1 / \gamma_0)}{\gamma_0^{\gamma_1} + t_i^{\gamma_1}}, \quad \frac{\partial \log S_0(t_i; \gamma)}{\partial \gamma_1} = \frac{t_i^{\gamma_1} \log(\gamma_0 / t_i)}{\gamma_0^{\gamma_1} + t_i^{\gamma_1}},
\]

\[
\frac{\partial \log S_0^2(t_i; \gamma)}{\partial \gamma_0^2} = - \frac{\partial \log S_0(t_i; \gamma)}{\partial \gamma_0} \left[ 1 + \gamma_1 S_0(t_i; \gamma) \right],
\]

\[
\frac{\partial \log S_0^2(t_i; \gamma)}{\partial \gamma_0 \partial \gamma_1} = \frac{\partial \log S_0(t_i; \gamma)}{\partial \gamma_0} \left[ \frac{1}{\gamma_1} + S_0(t_i; \gamma) \log \frac{t_i}{\gamma_0} \right],
\]

\[
\frac{\partial \log S_0^2(t_i; \gamma)}{\partial \gamma_1 \partial \gamma_1} = \frac{\partial \log S_0(t_i; \gamma)}{\partial \gamma_1} S_0(t_i; \gamma) \log \frac{t_i}{\gamma_0}.\]
The derivatives of $\log f(t_i, \gamma)$ are as follows:

$$\frac{\partial \log f_0(t_i, \gamma)}{\partial \gamma_0} = \frac{\gamma_1 t_i^{\gamma_1} - \gamma_0 t_i^{\gamma_0}}{\gamma_0 \gamma_1^{\gamma_1} + t_i^{\gamma_1}}, \quad \frac{\partial \log f_0(t_i, \gamma)}{\partial \gamma_1} = \frac{\gamma_0 t_i^{\gamma_0} \log \frac{t_i}{\gamma_0} + 1}{\gamma_0 + t_i^{\gamma_1}},$$

$$\frac{\partial \log f_2^0(t_i, \gamma)}{\partial \gamma_0 \partial \gamma_0} = -\frac{\partial \log f_0(t_i, \gamma)}{\partial \gamma_0} \frac{1}{\gamma_0} - \frac{2 \gamma_0 \gamma_1 t_i^{\gamma_1}}{(\gamma_0 + t_i^{\gamma_1})^2 \gamma_0^2},$$

$$\frac{\partial \log f_2^0(t_i, \gamma)}{\partial \gamma_0 \partial \gamma_1} = \frac{\partial \log f_0(t_i, \gamma)}{\partial \gamma_0} \frac{1}{\gamma_0} + \frac{2 \gamma_0 \gamma_1 t_i^{\gamma_1}}{(\gamma_0 + t_i^{\gamma_1})^2 \gamma_0 \log \frac{t_i}{\gamma_0}},$$

$$\frac{\partial \log f_2^0(t_i, \gamma)}{\partial \gamma_1 \partial \gamma_1} = -\frac{2 \gamma_0 \gamma_1 t_i^{\gamma_1}}{(\gamma_0 + t_i^{\gamma_1})^2} \left( \log \frac{t_i}{\gamma_0} - \frac{1}{\gamma_1} \right).$$

The derivatives of $S(t_i | y_i)$ are as follows:

$$\frac{\partial S(t_i)}{\partial \gamma_0} = F(t_i) S(t_i) \frac{\gamma_1}{\gamma_0}, \quad \frac{\partial S(t_i)}{\partial \gamma_1} = -S(t_i) F(t_i) \log \frac{t_i}{\gamma_0}, \quad \frac{\partial S(t_i)}{\partial \alpha_l} = x_i F(t_i) S(t_i),$$

$$\frac{\partial S^2(t_i)}{\partial \gamma_0 \partial \gamma_0} = \frac{\partial S(t_i)}{\partial \gamma_0} \frac{\gamma_1}{\gamma_0} (F(t_i) - S(t_i)) \frac{1}{\gamma_0}, \quad \frac{\partial S^2(t_i)}{\partial \gamma_0 \partial \gamma_1} = \frac{\partial S(t_i)}{\partial \gamma_0} \frac{1}{\gamma_1} \left[ \frac{1}{\gamma_1} - (F(t_i) - S(t_i)) \log \frac{t_i}{\gamma_0} \right],$$

$$\frac{\partial S^2(t_i)}{\partial \gamma_0 \alpha_l} = \frac{\partial S(t_i)}{\partial \gamma_0} (F(t_i) - S(t_i)) x_i, \quad \frac{\partial S^2(t_i)}{\partial \gamma_1 \partial \gamma_1} = \frac{\partial S(t_i)}{\partial \gamma_1} \frac{1}{\gamma_1} (S(t_i) - F(t_i)) \log \frac{t_i}{\gamma_0},$$

$$\frac{\partial S^2(t_i)}{\partial \gamma_1 \alpha_l} = \frac{\partial S(t_i)}{\partial \gamma_1} (F(t_i) - S(t_i)) x_i, \quad \frac{\partial S^2(t_i)}{\partial \alpha_l \alpha_l} = \frac{\partial S(t_i)}{\partial \alpha_l} (F(t_i) - S(t_i)) x_i x_i.$$
The derivatives of \( \log f(t_i|y_i) \) are as follows:

\[
\frac{\partial \log f(t_i)}{\partial \gamma_0} = \frac{\gamma_1}{\gamma_0} V_i, \quad \frac{\partial \log f(t_i)}{\partial \gamma_1} = \frac{1}{\gamma_1} - V_i \log \frac{t_i}{\gamma_0}, \quad \frac{\partial \log f(t_i)}{\partial \alpha_l} = x_i V_i
\]

\[
\frac{\partial \log f^2(t_i)}{\partial \gamma_0 \partial \gamma_0} = -\frac{\partial \log f(t_i)}{\partial \gamma_0} \frac{1}{\gamma_0} - W_i \frac{\gamma_1^2}{\gamma_0^2}, \quad \frac{\partial \log f^2(t_i)}{\partial \gamma_0 \partial \gamma_1} = \frac{\partial \log f(t_i)}{\partial \gamma_0} \frac{1}{\gamma_1} + W_i \frac{\gamma_1}{\gamma_0} \log \frac{t_i}{\gamma_0},
\]

\[
\frac{\partial \log f^2(t_i)}{\partial \gamma_0 \partial \alpha_l} = -W_i \frac{\gamma_1}{\gamma_0} x_i, \quad \frac{\partial \log f^2(t_i)}{\partial \gamma_1 \partial \gamma_1} = -W_i \left( \log \frac{t_i}{\gamma_0} \right)^2 - \frac{1}{\gamma_1^2}, \quad \frac{\partial \log f^2(t_i)}{\partial \gamma_1 \partial \alpha_l} = -W_i x_i x_i W_i,
\]

where \( V_i = F(t_i) - S(t_i) \), \( W_i = \frac{2\gamma_1 y_i e^{\alpha_l x_i} t_i^{\gamma_1}}{(\gamma_0 y_i e^{\alpha_l x_i} + t_i^{\gamma_1})^2} \).
Bibliography


