Destructive cure models with proportional hazards lifetimes and associated likelihood inference

N. Balakrishnan\textsuperscript{a} and S. Barui\textsuperscript{b}

\textsuperscript{a}Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada; \textsuperscript{b}Quantitative Methods and Operations Management Area, Indian Institute of Management Kozhikode, Kozhikode, India

**ABSTRACT**

In survival analysis, cure models have gained much importance due to rapid advancements in medical sciences. More recently, a subset of cure models, called destructive cure models, have been studied extensively under competing risks scenario wherein initial competing risks undergo a destructive process. In this article, we study destructive cure models by assuming a flexible weighted Poisson distribution (exponentially weighted Poisson, length biased Poisson and negative binomial distributions) for the initial number of competing causes and lifetimes of the susceptible individuals being defined by proportional hazards. The expectation-maximization (EM) algorithm and profile likelihood approach are made use of to estimate the model parameters. An extensive simulation study is carried out under various parameter settings to examine the properties of the models, and accuracy and the robustness of the proposed estimation technique. Effects of model mis-specification on the parameter estimates are also discussed in detail. For further illustration of the proposed methodology, a real-life cutaneous melanoma data set is analyzed.

**ARTICLE HISTORY**

Received February 2022
Accepted January 2023

**KEYWORDS**

EM algorithm; Weibull distribution; maximum likelihood estimation; Akaike's information criterion (AIC); Bayesian information criterion (BIC); cutaneous melanoma data; destructive mechanism; Weighted Poisson distribution

1. Introduction

Classical modeling techniques in survival analysis, such as proportional-odds model or accelerated failure time model, assume every individual under study will inevitably experience the event of interest (e.g., death, relapse, etc.). However, owing to outstanding progress in medical science over the past few decades, there often exists a fraction of subjects who do not encounter the event of interest or recurrences, even when followed-up long enough. These individuals are termed as cured or immune or long-term survivors in the literature, and models in lifetime data analysis consisting of a cure fraction are called cure models. Thus, the population under study consists of a mixture of subjects, *viz.*, cured and susceptible (non-cured). If we assume $I$ to be a binary random variable (r.v.) indicating cured if $I = 0$ and susceptible if $I = 1$, then the population survival
function $S_p(y)$ can be expressed as

$$S_p(y) = P(Y > y) = \sum_{i=0}^{1} P(Y > y | I = i) P(I = i) = \pi_0 + (1 - \pi_0) S_u(y),$$

where $Y$ denotes time to event, $\pi_0 = P(I = 0)$ represents the cured fraction or rate, and $S_u(y) = P(Y > y | I = 1)$ denotes the survival function of susceptible individuals. Note that $S_u(y)$ is a proper survival function whereas $S_p(y)$ is not, since $\lim_{y \to \infty} S_p(y) = \pi_0$. The application of cure models extends beyond survival analysis to many applied fields (Maller and Zhou 1996). One of the primary objectives is to estimate $\pi_0$ along with lifetime parameters of such cure models. However, estimating $\pi_0$ can be complicated, and the estimates are difficult to validate. This is because individuals who are cured are also censored, and the information on all censored individuals are missing. Further, the definition of “cure” is implicit, varies across studies, and not always well defined.

One of the earliest evidences can be found in the works of Boag (1949) in which he introduced the cure model emphasizing on the information loss in conventional five year survival rate from a clinician’s viewpoint. Berkson and Gage (1952) estimated the cure fraction using a least-square method by considering a mixture cure model, followed by Haybittle (1965) who estimated the proportion of treated cancer patients surviving to a specific time with respect to the normal population. Farewell (1982) mapped covariates using a logit-link to the proportion of susceptible and the lifetime distribution as Weibull. Larson and Dinse (1985) considered the failure types to be distributed as multinomial and the conditional distribution of the failure time, given the type, as piecewise exponential under proportional hazards. A semi-parametric generalization of lifetime distribution of the susceptible individuals, as suggested by Farewell (1982), was proposed by Kuk and Chen (1992) by introducing a Cox’s proportional hazard model, where the regression parameters were estimated by maximizing a Monte Carlo approximation of marginal likelihood and baseline survival function by the EM algorithm (Dempster, Laird, and Rubin 1977). Sy and Taylor (2000) further worked with the proportional hazards model, but used a Breslow-type and product-limit estimators for estimating the baseline hazard and baseline survival functions respectively; Peng and Dear (2000) improved on the estimation technique under similar assumptions of the model. A consideration of bounded cumulative hazard function was made by Tsodikov, Ibrahim, and Yakovlev (2003) as an alternative to a two-component mixture model and provided an extension to the proportional hazards regression model. As opposed to the mixture cure models, Chen, Ibrahim, and Sinha (1999) proposed a promotion time cure model considering the underlying biological process generating the failure times based on a Poisson distribution (Yakovlev, Tsodikov,
and Bass 1993; Yakovlev, Tsodikov, and Asselain 1996). By considering a Box-Cox transformation on the population survival function, an intermediate model between a promotion time and mixture cure model was discussed by Yin and Ibrahim (2005). A class of semi-parametric transformation models, with proportional hazards and proportional odds promotion time cure models, as special cases was suggested by Zeng, Yin, and Ibrahim (2006). A theoretical study on the existence, consistency and asymptotic normality of the semi-parametric maximum likelihood (ML) estimator under proportional hazard set-up was done by Fang, Li, and Sun (2005). Rodrigues et al. (2009) introduced a flexible COM-Poisson cure model under competing risks scenario, and this model was studied extensively by Balakrishnan and Pal (2012, 2016, 2014b).

More pragmatic alternative to cure models, called destructive cure models, was introduced by Rodrigues et al. (2011) which assume that the initial competing causes undergo a process of destruction. Specifically, let $M$ be the initial number of latent competing causes related to the event of interest. In cancer studies, often the event of interest is patient’s death which can be caused by one or more malignant metastasis-component (Yakovlev, Tsodikov, and Asselain 1996) tumor cells. After chemotherapy or radiation, only a portion of initial metastasis-component cells remain active and undamaged, thereby, reducing the initial number of competing causes. Given $M = m$, we may consider $X_g$ as a Bernoulli random variable (r.v.), distributed independently of $M$, which takes 1 if the $g$-th competing cause is present (i.e., if the $g$-th malignant tumor cell remains undamaged after the treatment) with probability $p \in (0,1)$ or 0 otherwise. Thus, if we define

$$D = \begin{cases} X_1 + \cdots + X_M, & \text{if } M > 0, \\ 0, & \text{if } M = 0, \end{cases}$$

(2)

then $D$ represents the number of initial competing causes that are not destroyed. Obviously, $D \leq M$ and the conditional distribution of $D$, given $M = m$, is known as the damaged distribution that follows a binomial distribution with parameters $m$ and $p$ if $m > 0$, and $P(D = 0 | M = 0) = 1$. Rodrigues et al. (2011) discussed the destructive cure model by considering the distribution of $M$ as weighted Poisson. The probability mass function (pmf) of $M$ following a weighted Poisson distribution is given by

$$P(M = m; \eta, \phi) = \begin{cases} \frac{\Omega(m; \phi)}{\mathbb{E}_{\eta}[\Omega(M; \phi)]} p^*(m; \eta), & m = 0, 1, 2, \ldots, \\ 0, & \text{otherwise}, \end{cases}$$

(3)

where $\Omega(\cdot; \phi)$ is a nonnegative weight function characterized by $\phi$ with $\phi \in \mathbb{R}$, $p^*(\cdot; \eta)$ is the pmf of a Poisson distribution with parameter $\eta > 0$, and $\mathbb{E}_{\eta}[\cdot]$ is expectation taken with respect to the Poisson pmf. Gallardo, Bolfarine, and Pedroso-de Lima (2016) developed an EM algorithm based technique for the same model to estimate the parameters for the three special cases, viz., destructive length-biased Poisson, destructive exponentially weighted Poisson...
and destructive negative binomial cure models. An extension this model was described by Borges, Rodrigues, and Balakrishnan (2012) by creating a correlation structure between the initiated cells using the generalized power series distribution. A Bayesian method of inference was further proposed in the context of destructive weighted Poisson cure model by Rodrigues et al. (2012). Interested readers can refer to Cancho, Bandyopadhyay, and Louzada Yiqi (2013) and Pal and Balakrishnan (2018, 2016, 2017), for some further discussions in this regard.

Here, we consider the initial number of competing causes $M$ to have a weighted Poisson distribution with weight function $\Omega(m; \phi) = m \cdot e^{\phi m}$ and $\Gamma(m + \phi^{-1})$, following Pal and Balakrishnan (2018, 2016, 2017). The corresponding models are known as destructive length-biased Poisson (DLBP), destructive exponentially weighted Poisson (DEWP) and destructive negative binomial (DNB) cure models, respectively. Given $D = d$, let $W_j$ (latent) be the time-to-event associated with the $j$-th competing cause. Now, $W_j$s are assumed to be independently and identically distributed (i.i.d.) with common cumulative distribution function (cdf) $F(w)$ and common survival function $S(w) = 1 - F(w) = P(W_j > w)$, for all $j = 1, \ldots, d$. In order to accommodate the proportion of individuals who will not encounter the event of interest, we introduce a degenerate r.v. $W_0$ such that $P(W_0 = \infty) = 1$. Thus, we only observe $Y = \min\{W_0, W_1, \ldots, W_D\}$ and the population survival function in this case is given by

$$S_p(y) = P(Y > y) = \sum_{d=0}^{\infty} P(D = d)\{S(y)\}^d = G_D(S(y)),$$

where $G_D(.)$ is the probability generating function of $D$ evaluated at $S(y)$. The population density function is defined as $f_p(y) = -\frac{dS_p(y)}{dy}$. Here, $f_p(.)$ is not a proper density function, but plays a significant role in likelihood-based estimation of model parameters. The novelty of the present work lies in the fact that the model considers a proportional hazards structure with

$$\lambda(w; \gamma, x) = \lambda_0(w) e^{\gamma' x},$$

where $\lambda(w; \gamma, x)$ and $\lambda_0(w)$ are the respective hazard and baseline hazard functions related to $W_j$, for all $j = 1, \ldots, d$, $x$ is a covariate vector with corresponding parameter vector $\gamma$ of same dimension. By assuming proportional hazards structure, lifetime of each subject $i$ is linked to the specific characteristic $x_i$, $i = 1, \ldots, n$, intrinsic to that individual. Thus, this model is a generalization of the one considered by Pal and Balakrishnan (2016), which assumes lifetime distribution to be same across all subjects in the study. Further, the model considered here enables us to verify non-homogeneity in lifetime distribution across individuals by conducting a hypothesis test $H_0 : \gamma = 0$ vs. $H_a : \gamma \neq 0$. Recently, Balakrishnan and Feng (2019) have studied destructive cure model with non-homogeneous lifetimes by assuming a proportional odds structure under the cure rate scenario. Owing to the flexibility and robustness imparted by
the shape and scale parameters, a Weibull distribution is widely used in survival analysis to model lifetimes, and for this reason we consider the baseline hazard function $\lambda_0(w)$ to be a Weibull hazard function.

The rest of the paper proceeds as follows. Model assumptions and formulation are explained in Section 2. The form of the data and the likelihood function are described in Section 3, while the method of estimation of model parameters using EM algorithm and computation of asymptotic standard error (SE) of parameters are provided in Section 4. The proposed model and inferential methods are applied to a real-life data set obtained from a cutaneous melanoma study, and this is discussed in Section 5. An extensive simulation study is carried out with various settings to examine the accuracy of the estimation method, and the details are given in Section 6. A model discrimination is performed and discussed in Section 7. Finally, some concluding remarks are made in Section 8.

2. Model description

2.1. Cure models

As mentioned in the last Section, $M$ is assumed to follow a weighted Poisson distribution with three candidate weight functions $m, e^{\phi m}$ and $\Gamma(m + \phi^{-1})$. The corresponding three models possess the following forms and properties.

2.1.1. Destructive length-biased Poisson cure model

Assuming $\Omega(m; \phi) = m$, the pmf of $M$ is given by

$$P(M = m; \eta, \phi) = \begin{cases} e^{-\eta} \eta^{m-1} \frac{1}{(m-1)!}, & m = 1, 2, \ldots \\ 0, & \text{o.w.} \end{cases}$$

which is a truncated Poisson distribution truncated at $m = 0$. Since $(D|M = m) \sim \text{Bernoulli}(m, p)$, the unconditional pmf of $D$, i.e., the number of active competing causes, is given by

$$P(D = d; \eta, \phi, p) = \sum_{m=d}^{\infty} P(D = d|M = m)P(M = m)$$

$$= \sum_{m=d}^{\infty} \frac{m!}{(m-d)!d!} p^d (1 - p)^{m-d} e^{-\eta} \eta^{m-1} \frac{1}{(m-1)!}$$

$$= \frac{e^{-\eta p}(\eta p)^d}{d!} \left(1 - p + \frac{d}{\eta}\right), \quad d = 0, 1, 2, \ldots$$

The cure rate is then given by

$$\pi_0 = P(D = 0) = e^{-\eta p}(1 - p)$$

while the population survival and the density functions are

$$S_p(y) = e^{-\eta pF(y)} \{1 - pF(y)\}$$
and
\[ f_p(y) = \eta pf(y)e^{-\eta pF(y)} \left\{ 1 - pF(y) - \frac{pf(y)}{\eta} \right\}, \tag{9} \]

where \( f(.) \) is the common probability density function (pdf) of \( W_j \), for all \( j = 1, 2, \ldots, d \).

### 2.1.2. Destructive exponentially weighted Poisson cure model

Under this model, we assume \( \Omega(m; \phi) = e^{\phi m} \) as the weight function, which gives the pmf of \( M \) as
\[
P(M = m; \eta, \phi) = \begin{cases} 
e^{-\eta e^\phi (\eta e^\phi)^m} & , m = 0, 1, 2, \ldots \\
0 & , \text{o.w.} \end{cases} \tag{10} \]

This is readily seen to be a Poisson distribution with rate parameter \( \eta e^\phi \). The unconditional distribution of the undamaged number of initial competing causes \( D \) is given by
\[
P(D = d; \eta, \phi, p) = \sum_{m=d}^{\infty} \frac{m!}{(m-d)!d!} p^d (1 - p)^{m-d} e^{-\eta e^\phi (\eta e^\phi)^m} \frac{m!}{m!}, \quad d = 0, 1, 2, \ldots \tag{11} \]

which is a Poisson probability with rate parameter \( \eta e^\phi \). Consequently,
\[
\pi_0 = e^{-\eta e^\phi}, \tag{12} \]
\[
S_p(y) = e^{-\eta e^\phi F(y)} \tag{13} \]

and
\[
f_p(y) = \eta e^\phi f(y)e^{-\eta e^\phi F(y)}. \tag{14} \]

Note that the model reduces to a destructive Poisson cure model if \( \phi = 0 \). Furthermore, the choice of \( p = 1 \) in (13) yields Poisson or promotion-time cure model.

### 2.1.3. Destructive negative binomial cure model

Let us consider
\[
P(M = m; \eta, \phi) = \begin{cases} \frac{\Gamma(m+\phi^{-1})}{\Gamma\phi^{-1}m!} \left( \frac{\phi \eta}{1+\phi \eta} \right)^m (1 + \phi \eta)^{-\phi^{-1}} & , m = 0, 1, 2, \ldots \\
0 & , \text{o.w.} \end{cases} \tag{15} \]

where \( M \) is a negative binomial r.v. with parameters \( \phi^{-1} \) and \( \frac{\phi \eta}{1+\phi \eta} \). This is also a weighted Poisson distribution with parameter \( \frac{\phi \eta}{1+\phi \eta} \) and the weight function
\( \Omega(m; \phi) = \Gamma(m + \phi^{-1}), \phi > 0 \). Hence, the unconditional pmf of \( D \) is given by

\[
P(D = d; \eta, \phi, p) = \sum_{m=d}^{\infty} P(D = d|M = m)P(M = m)
\]

\[
= \frac{p^d}{d!} \left( \frac{\phi \eta}{1 + \phi \eta} \right)^d (1 + \phi \eta)^{-\phi^{-1}} \sum_{m=d}^{\infty} \frac{\Gamma(m + \phi^{-1})}{(m - d)! \Gamma(\phi^{-1})} \frac{(1 - p) \phi \eta}{1 + \phi \eta}^{m-d}
\]

\[
= \frac{\Gamma(d + \phi^{-1})}{\Gamma \phi^{-1} d!} \left( \frac{p \phi \eta}{1 + p \phi \eta} \right)^d (1 + p \phi \eta)^{-\phi^{-1}}, \quad d = 0, 1, 2, \ldots
\]

Evidently, \( D \) has a negative binomial distribution with parameters \( \phi^{-1} \) and \( \frac{p \phi \eta}{1 + p \phi \eta} \). The corresponding cure rate, population survival function and population density function are given by

\[
\pi_0 = (1 + p \eta \phi)^{-\phi^{-1}},
\]

\[
S_p(y) = (1 + p \eta \phi F(y))^{-\phi^{-1}}
\]

and

\[
f_p(y) = \eta p f(y)(1 + p \eta \phi F(y))^{-(\phi^{-1}+1)}.
\]

Note that this destructive negative binomial cure model includes destructive geometric (\( \phi = 1 \)), negative binomial (\( p = 1 \)) and geometric (\( \phi = 1 \) and \( p = 1 \)) cure models as special cases.

### 2.2. Modeling lifetimes

Given \( D = d \), we assume the hazard function \( \lambda(\cdot; x, z, y_2, y_3) \) of \( W_j \) (\( j = 1, \ldots, d \)) to follow proportional hazards structure, i.e.,

\[
\lambda(w; x, z, y_2, y_3) = \lambda_0(w)e^{y_2'x + y_3'z},
\]

where \( y_2 = (y_{21}, \ldots, y_{2q_1})' \in \mathbb{R}^{q_1}, y_3 = (y_{31}, \ldots, y_{3q_2})' \in \mathbb{R}^{q_2}, \) and \( x \) and \( z \) are respectively \( q_1 \) and \( q_2 \) dimensional covariate vectors, with \( \lambda_0(w) \) being the baseline hazard function which does not depend on the covariates \( x \) and \( z \). The reasons for splitting the covariates into two parts, \( x \) and \( z \), and for considering \( y_2 \) and \( y_3 \) without the intercept terms are discussed in Section 3. In the literature, \( \lambda_0(\cdot) \) has been estimated by assuming either some well-known fully parametric distributions (Farewell 1982; Balakrishnan and Pal 2013, 2016, 2014a; Pal and Balakrishnan 2017), or by non-parametric methods (Kuk and Chen 1992; Sy and Taylor 2000; Balakrishnan et al. 2016; Balakrishnan, Barui, and Milienos 2022). In this article, we assume \( \lambda_0(w) \) to be a Weibull hazard function of the form

\[
\lambda_0(w) = \lambda_0(w; y_0, y_1) = y_0 y_1^{-y_0} w^{y_0-1},\quad w > 0,
\]
where $\gamma_0 > 0$ and $\gamma_1 > 0$ are the respective shape and scale parameters of the Weibull distribution. The Weibull distribution is closed under proportional hazards when the shape parameter remains constant. Moreover, a two-parameter Weibull provides a great degree of flexibility to the lifetimes of susceptible individuals since it includes cases of decreasing ($\gamma_0 < 1$), constant ($\gamma_0 = 1$, i.e., exponential distribution) and increasing ($\gamma_0 > 1$) failure rates. Let us denote $\gamma = (\gamma_0, \gamma_1, \gamma_2', \gamma_3')'$. Thence,

$$\lambda(w; x, z, \gamma) = \gamma_0 \left( \gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}} \right)^{-\gamma_0} w^{\gamma_0 - 1}$$

is also a Weibull hazard function with shape $\gamma_0$ and scale $\gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}}$. Consequently, for $w > 0$,

$$S(w) = S(w; x, z, \gamma) = \exp \left\{ -w^{\gamma_0} \left( \gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}} \right)^{-\gamma_0} \right\},$$

(22)

$$F(w) = F(w; x, z, \gamma) = 1 - \exp \left\{ -w^{\gamma_0} \left( \gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}} \right)^{-\gamma_0} \right\}$$

(23)

and

$$f(w) = f(w; x, z, \gamma)$$

(24)

$$= \gamma_0 \left( \gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}} \right)^{-\gamma_0} w^{\gamma_0 - 1} \exp \left\{ -w^{\gamma_0} \left( \gamma_1 e^{-\frac{\gamma_2' x + \gamma_3' z}{\gamma_0}} \right)^{-\gamma_0} \right\}$$

are the corresponding common cdf, survival function and pdf of each $W_j; j = 1, \ldots, d$.

Pal and Balakrishnan (2016, 2017) proceeded by assuming the lifetime distribution of $W_j$s to be Weibull that is identical for every individual. However, by linking the covariates to the lifetime distribution of $W_j$ using the model in (20), a greater degree of flexibility is added to the model, as the lifetime of the susceptible is different for each individual depending on the values of covariates. Then, testing the hypothesis $H_0 : (\gamma_2', \gamma_3') = 0$ would enable us to infer on the homogeneity of the lifetime distributions across subjects.

3. Observed data and likelihood functions

In clinical studies, right censoring occurs commonly due to patient’s discontinuation, duration of study, or lost to follow-up. For this reason, we assume noninformative right censored data in our analysis. In general, for $i = 1, \ldots, n$, if we consider $Y_i$ to be the actual lifetime and $C_i$ to be the censoring time corresponding to the $i$-th individual, then time to event $T_i$ is defined as

$$T_i = \min\{Y_i, C_i\}.$$
The censoring indicator is given by $\delta_i = I(T_i \leq C_i)$ which takes value 1 when the actual lifetime is observed or 0 when the lifetime is right censored at the time $C_i$ for the $i$-th individual.

For $i = 1, \ldots, n$, two sets of covariates $x_i = (x_{i1}, \ldots, x_{iq_1})'$ and $z_i = (z_{i1}, \ldots, z_{iq_2})'$ are linked to the parameters $\alpha$ and $\beta$ such that $\eta_i = e^{\alpha' z_i}$ is linked using a log-linear function while $p_i = \frac{e^{\beta' x_i}}{1 + e^{\beta' x_i}}$ is linked using a logit function, where $\alpha = (\alpha_1, \ldots, \alpha_{q_1})'$ and $\beta = (\beta_0, \beta_1, \ldots, \beta_{q_1})'$ are new model parameters. To circumvent the issue of non-identifiability of parameters associated with DEWP, DLBP or DNB cure models, $\alpha$ is taken without an intercept term and covariate $x_i$ is assumed to be disjoint of $z_i$ in the sense that they have no common elements (see Li, Taylor, and Sy 2001). The observed data for $n$ individuals is then of the form $(t_i, \delta_i, x_i', z_i')'$, $i = 1, \ldots, n$. Thence, the observed data likelihood function can be expressed as

$$L(\theta; t, \delta, X, Z) \propto \prod_{i=1}^{n} f_p(t_i; x_i, z_i, \theta)^{\delta_i} S_p(t_i; x_i, z_i, \theta)^{1-\delta_i}, \quad (25)$$

where $\theta = (\alpha', \beta', \gamma', \phi)'$, $\alpha = (\alpha_1, \ldots, \alpha_{q_1})'$, $\beta = (\beta_1, \ldots, \beta_{q_1})'$, $\gamma = (\gamma_0, \gamma_1, \gamma_2', \gamma_3')'$, $\gamma_2 = (\gamma_{21}, \ldots, \gamma_{2q_1})'$, $\gamma_3 = (\gamma_{31}, \ldots, \gamma_{3q_2})'$, $t = (t_1, \ldots, t_n)'$, $\delta = (\delta_1, \ldots, \delta_n)'$, $X = (x_1, \ldots, x_n)$ and $Z = (z_1, \ldots, z_n)$. In (25), $f_p(t_i; x_i, z_i, \theta) = f_p(t_i)$ and $S_p(t_i; x_i, z_i, \theta) = S_p(t_i)$ are given by (8), (9), (13), (14), (18), (19), (22), (23), and (24).

4. Estimation of parameters and standard errors

We implement the EM algorithm to estimate $(\alpha', \beta', \gamma')'$ while $\phi$ is estimated using profile likelihood method. The missing data are introduced by defining indicators $I_i$ which take 0 if the $i$-th individual is cured or 1 otherwise. Note that $I_i = 1$ for $i \in \Delta_1$, but $I_i$ is unobserved for $i \in \Delta_0$, with $\Delta_1 = \{i : \delta_i = 1\}$ and $\Delta_0 = \{i : \delta_i = 0\}$. For any $i = 1, \ldots, n$, $\pi_0 = \pi_0(\alpha, \beta; x_i, z_i)$ can be obtained from (7), (12), and (17) for the three cure models described in Section 2. Further, let us denote $I = (I_1, \ldots, I_n)'$.

The complete data are denoted by $\{(t_i, \delta_i, x_i', z_i', I_i)'\}$, $i = 1, \ldots, n$. Then, the complete data likelihood function is given by

$$L_c(\theta; t, x, z, \delta, I) \propto \prod_{i \in \Delta_1} f_p(t_i; x_i, z_i, \theta) \prod_{i \in \Delta_0} \pi_0(\alpha, \beta; x_i, z_i)^{1-I_i} [(1 - \pi_0(\alpha, \beta; x_i, z_i)) S_u(t_i; x_i, z_i, \theta)]^{I_i} \quad (26)$$
and the complete data log-likelihood function as
\[ l_c(\theta; t, x, z, \delta, I) = \text{constant} + \sum_{i \in \Delta_1} \log f_p(t_i; x_i, z_i, \theta) + \sum_{i \in \Delta_0} (1 - I_i) \log \pi_0(\alpha, \beta; x_i, z_i) + \sum_{i \in \Delta_0} I_i \log(1 - \pi_0(\alpha, \beta; x_i, z_i)) + \sum_{i \in \Delta_0} I_i \log S_u(t_i; x_i, z_i, \theta), \] (27)

where \( S_u(t_i; x_i, z_i, \theta) = \frac{S_p(t_i; x_i, z_i, \theta) - \pi_0(\alpha, \beta; x_i, z_i)}{1 - \pi_0(\alpha, \beta; x_i, z_i)} \) using (1). Now, the steps of the EM algorithm proceed as follows.

**E-step:** For a fixed value \( \phi_0 \) of \( \phi \) and at the \((a + 1)\)-th iteration of the EM algorithm, we compute the expected value of \( l_c(\theta; t, x, z, \delta, I) \), given the observed data \( O = \{(t_i, \delta_i, x_i, z_i, I_i) : i = 1, \ldots, n, i^* \in \Delta_1\} \) and the current parameter estimates \( \hat{\theta}^{(a)} \) obtained from the \( a \)-th iteration, where \( \theta^* = (\alpha', \beta', \gamma')' \).

Therefore, from (27), we obtain
\[
\mathbb{E} \left( l_c(\theta; t, x, z, \delta, I) | \hat{\theta}^{(a)}, O \right) = \text{constant} + \sum_{i \in \Delta_1} \log f_p(t_i; x_i, z_i, \theta) + \sum_{i \in \Delta_0} \left(1 - \xi_i^{(a)}(\theta^*)\right) \log \pi_0(\alpha, \beta; x_i, z_i) + \sum_{i \in \Delta_0} \xi_i^{(a)} \log(1 - \pi_0(\alpha, \beta; x_i, z_i)) + \sum_{i \in \Delta_0} \xi_i^{(a)} \log S_u(t_i; x_i, z_i, \theta),
\] (28)

where
\[
\xi_i^{(a)} = \mathbb{E} \left( I_i | \hat{\theta}^{(a)}, O \right) = \frac{(1 - \pi_0(\alpha, \beta; x_i, z_i)) S_u(t_i; x_i, z_i, \theta)}{S_p(t_i; x_i, z_i, \theta)} \bigg|_{\theta^* = \hat{\theta}^{(a)}}.
\]

Define \( Q(\theta^*, \xi^{(a)}) = \mathbb{E} \left( l_c(\theta; t, x, z, \delta, I) | \hat{\theta}^{(a)}, O \right) \), where \( \xi^{(a)} = \left(\xi_i^{(a)} : i \in \Delta_0\right)' \).

**M-step:** In the maximization step, we maximize \( Q(\theta^*, \xi^{(a)}) \) with respect to \( \theta^* \) to find the ML estimate \( \hat{\theta}^{(a+1)} \) of \( \theta^* \) at the \((a + 1)\)-th step of iteration. The numerical maximization is carried out using Nelder-Mead or Quasi-Newton method for fixed \( \phi_0 \). Explicit expressions for \( Q(\theta^*, \xi^{(a)}) \), and the first-order and second-order partial derivatives of \( Q(\theta^*, \xi^{(a)}) \) are presented in Appendices A, B, and C, respectively. The iterative process gets terminated at the \((a + 1)\)-th
step if
\[ \max_{1 \leq k' \leq p^*} \left| \frac{\hat{\theta}^{(a+1)}_{k'} - \hat{\theta}^{(a)}_{k'}}{\hat{\theta}^{(a)}_{k'}} \right| < \epsilon, \ a = 1, 2, \ldots, \]
for some pre-determined tolerance value of \( \epsilon \), where \( \hat{\theta}^{(a)}_{k'} \) is the \( k' \)-th component of \( \hat{\theta}^{(a)} \) and \( p^* \) denotes the dimension of \( \theta^* \).

The estimation of \( \phi \) is carried out using the profile likelihood approach since the likelihood function is relatively flat with respect to \( \phi \). The E-step and M-step are repeated for all \( \phi \in \Phi \), where \( \Phi \) denotes the admissible range of \( \phi \). The value of \( \phi \in \Phi \) that provides the maximum value of the observed likelihood function is accepted as the ML estimate \( \hat{\phi} \) of \( \phi \). For the DEWP cure model, we made use of the ranges \( \Phi = \{-2.0, -1.9, \ldots, 2.0\} \) while for the DNB cure model, \( \Phi = \{0.10, 0.15, \ldots, 7.00\} \).

Under suitable regulatory conditions, it can be established that the ML estimator \( \hat{\theta}^* \) of \( \theta^* \) follows an asymptotic multivariate normal distribution with mean vector \( \theta^* \) and covariance matrix \( \Sigma(\hat{\theta}^*) \), with an estimate of \( \Sigma(\hat{\theta}^*) \) being
\[ \hat{\Sigma}(\hat{\theta}^*) = \left\{- \frac{\partial^2 \log L(\theta; t, \delta, X, Z)}{\partial \theta^* \partial \theta^*'} \right\}^{-1} \bigg|_{\theta^* = \hat{\theta}^*}. \]

For \( \alpha' \in (0, 1) \), \( 100(1 - \alpha') \)\% confidence interval (C.I.) of the parameters can then be readily obtained by using the asymptotic normality of the ML estimators.

5. Analysis of cutaneous melanoma data

For the purpose of illustration of the models and method of inference developed, we consider the data set ‘melanoma’ available in the \texttt{timereg} package in R. The data set contains information from a historically prospective clinical study in the period 1962–1977 on malignant melanoma with 225 patients (Andersen et al. 2012). The following variables are present in the data set: survival time since operation (in years), tumor thickness (in cm), censoring status (1 = died from the disease, 2 = alive at the end of the study, 3 = died from unrelated causes), ulceration status (1 = ulcer present, 0 = ulcer absent), sex (1 = male, 0 = female), age (in years) and year of operation. Out of 225 patients, 20 subjects did not have histological evaluation. Among the remaining 205 patients, 57 patients died before the end of 1977 and the censoring proportion is 72.19%.

The observed time (in years) refers to the time since operation till patient's death or censoring time, with corresponding mean and standard deviation (s.d.) to be 5.89 and 3.07 years, respectively. For our analysis, ulceration status \( z \) (absent: \( n = 115 \); present: \( n = 90 \)) and tumor thickness \( x \) (in mm) are selected as covariates for the study. 44% of the patients had ulceration status present at the beginning of the study. For this group, mean and s.d. of the tumor thicknesses are found to be 4.34 mm and 3.22 mm, respectively. For the group
with ulceration status as absent, the mean and s.d. of the tumor thicknesses are 1.81 mm and 2.19 mm, respectively. The histograms of the tumor thickness for both the groups show positively skewed distributions. Figure 1 represents the Kaplan-Meier (KM) plot categorized by the ulceration status, which possibly indicates the presence of cure proportion in the data.

Note that $\phi = 0$ reduces DEWP cure model to the usual destructive Poisson (DP) cure model studied originally by Rodrigues et al. (2011). Similarly, we obtain exponentially weighted Poisson (EWP) and Poisson cure models by setting $p = 1$ and $(p = 1, \phi = 0)$, respectively. Destructive geometric (DG), negative binomial (NB) and geometric cure models are obtained from DNB cure model by considering $\phi = 1, p = 1$ and $(\phi = 1, p = 1)$, respectively. $p = 1$ represents cases wherein no destructive mechanisms of the malignant cells are involved. When $p = 1$, we link both the covariates to $\eta$ using log-linear link function of the form $\eta = \exp(\beta_0 + \beta_1 x + \alpha z)$.

In Table 1, the number of parameters fitted ($\tilde{k}$), maximized log-likelihood ($\hat{l}$) values, Akaike’s Information Criterion (AIC) and Bayesian Information Criterion (BIC) values for all fitted models, including all sub-models, are presented. For $\hat{\phi} = 5.2$, the DNB cure model provides the best fit to the data with

| Fitted Model | $\tilde{k}$ | $\hat{l}$ | AIC | BIC |
|--------------|-----------|----------|-----|-----|
| DEWP ($\hat{\phi} = -0.7$) | 8 | -202.253 | 420.506 | 447.090 |
| DP | 7 | -203.433 | 420.865 | 444.126 |
| EWP ($\hat{\phi} = -1.5$) | 8 | -205.054 | 426.108 | 452.693 |
| Poisson | 7 | -205.054 | 424.108 | 447.370 |
| DLBP | 7 | -204.979 | 423.959 | 447.220 |
| DNB ($\hat{\phi} = 5.2$) | 8 | -199.108 | **414.216** | 440.800 |
| DG | 7 | -201.536 | 417.073 | **440.334** |
| NB ($\hat{\phi} = 6.9$) | 8 | -199.973 | 415.946 | 442.531 |
| Geometric | 7 | -204.027 | 422.053 | 445.314 |

NOTE: The bold value indicates the model which is the best with respect to a criterion.
Table 2. Estimate, SE, LCL and UCL for DEWP, DLBP, and DNB cure models for the cutaneous melanoma data.

| Fitted model | Measure | α   | β₀  | β₁  | γ₀  | γ₁  | γ₂  | γ₃  | φ    |
|--------------|---------|-----|-----|-----|-----|-----|-----|-----|------|
| DEWP         | EST     | 0.761 | −1.985 | 1.265 | 1.845 | 7.423 | 0.112 | 0.305 | −0.7 |
|              | SE      | 0.218 | 0.909 | 0.646 | 0.219 | 1.904 | 0.043 | 0.492 | −    |
|              | LCL     | 0.333 | −3.768 | −0.002 | 1.414 | 3.689 | 0.027 | −0.660 | −    |
|              | UCL     | 1.188 | −0.202 | 2.532 | 2.276 | 11.156 | 0.196 | 1.270 | −    |
| DLBP         | EST     | 1.527 | −2.119 | 0.081 | 1.822 | 8.011 | 0.115 | 0.433 | −    |
|              | SE      | 0.529 | 0.454 | 0.053 | 0.224 | 2.723 | 0.046 | 0.611 | −    |
|              | LCL     | 0.489 | −3.009 | −0.023 | 1.382 | 2.672 | 0.024 | −0.765 | −    |
|              | UCL     | 2.565 | −1.229 | 0.186 | 2.263 | 13.349 | 0.207 | 1.633 | −    |
| DNB          | EST     | 3.670 | −2.602 | 1.081 | 2.845 | 7.282 | 0.192 | −1.596 | 5.2  |
|              | SE      | 1.205 | 0.925 | 0.537 | 0.328 | 1.342 | 0.071 | 1.236 | −    |
|              | LCL     | 1.306 | −4.416 | 0.027 | 2.201 | 4.650 | 0.052 | −4.019 | −    |
|              | UCL     | 6.033 | −0.788 | 2.136 | 3.489 | 9.913 | 0.332 | 0.826 | −    |

Table 3. Maximized log-likelihood values for destructive cure models with various link functions.

| Link Function | Model | φ | l |
|---------------|-------|---|---|
| L1: \( e^{\alpha z} \), \( e^{\beta_0 + \beta_1 x} \) ** | DEWP | −0.7 | −205.253 |
|              | DLBP | —  | −204.979 |
|              | DNB  | 5.2 | −199.108 |
| L2: \( e^{\alpha z} \), \( e^{\beta_0 + \beta_1 x} \) | DEWP | −0.4 | −205.055 |
|              | DLBP | —  | −208.289 |
|              | DNB  | 6.9 | −199.962 |
| L3: \( e^{\alpha_0 + \alpha_1 z} \), \( e^{\beta_0 + \beta_1 x} \) | DEWP | −1.0 | −203.994 |
|              | DLBP | —  | −206.786 |
|              | DNB  | 7.2 | −201.085 |
| L4: \( e^{\alpha_0 + \alpha_1 z} \), \( e^{\beta_0 + \beta_1 x} \) | DEWP | −0.2 | −205.302 |
|              | DLBP | —  | −206.667 |
|              | DNB  | 6.4 | −200.313 |

** This link is used for subsequent analyses.

The highest maximized log-likelihood (−199.108) and minimum AIC (414.216) values. The estimate, standard error (SE), lower confidence limit (LCL) and upper confidence limit (UCL) of all parameters for the three main models are presented in Table 2. For validating heterogeneity among the lifetimes of susceptible individuals, we carry out a test of hypothesis \( H_0 : \gamma_2 = \gamma_3 = 0 \) vs. \( H_1 \): at least one inequality in \( H_0 \) for the DNB model with \( \phi = 5.2 \). The resultant \( p \)-value of the test is 0.061, indicating non-rejection of \( H_0 \) at 5% level, and the corresponding maximized log-likelihood value for the reduced model is −201.908. On the other hand, on testing \( H_0 : \phi = 0 \) for the full DNB model, we found the \( p \)-value to be 0.027 which does reveal that DNB models provided a better fit than the DG model for this data. It can be observed from Table 1 that incorporating destructive mechanisms to the cure models have resulted in better log-likelihood, AIC and BIC values, which justifies the practicality of applying destructive cure models over regular cure models.

Table 3 demonstrates the effects of using different link functions (L1–L4) on maximized log-likelihood value for the main three destructive cure models. Considering all four possible combinations, we found link L1 (see Section 3)
provided large \( \hat{l} \) consistently. Because the DNB cure model with \( \hat{\phi} = 5.2 \) provided the best fit with link L1, we use this link throughout for our subsequent analyses.

We choose three representative values of the tumor thickness: 0.320, 1.940, and 8.320 mm corresponding to the 5-th, 50-th and 95-th percentiles, and plot corresponding long-term survival functions stratified by the ulceration status (Fig. 2(a)–(c)). The estimated survival function values are found to be higher for the group with ulceration status as absent and smaller tumor thickness values. Figure 3 represents the estimated cure probabilities against tumor thickness values stratified by the ulceration status. A non-parametric test of difference suggests a significant difference (\( p \)-value \(< 2.2 \times 10^{-16} \)) between cure probabilities of the two ulcer groups.

### 6. Simulation study

We now assess the performance of the proposed method of estimation and inference by using an extensive Monte Carlo simulation study. We generate data set in a way that it mimics the real data on cutaneous melanoma discussed in Section 5. For this purpose, we define a random variable \( U \), where \( U \sim \text{Uniform} \ (0, 1) \). If \( U \leq 0.44 \), we assign a r.v. \( Z = 1 \), otherwise \( Z = 0 \), where \( Z \) denotes the ulceration status for each subject. For simulating the tumor
thickness data, we plot histograms of tumor thickness \((X)\) values of individuals from the cutaneous melanoma study. The histograms reveal positively skewed curves for both ulceration statuses; the means and the standard deviations are as given in Section 5. Thus, for \(Z = 1\), we assume \(X\) to follow Weibull distribution with shape and scale parameters as \(\alpha_1\) and \(\alpha_2\), respectively. \(\alpha_1\) and \(\alpha_2\) are estimated by the method of moments by equating \(\alpha_2 \Gamma (1 + 1/\alpha_1)\) to 4.34 and \(\alpha_2^2 \left[ \Gamma \left(1 + \frac{2}{\alpha_1}\right) - \left(\Gamma \left(1 + \frac{1}{\alpha_1}\right)\right)^2 \right]\) to \((3.22)^2\). We generate \(X\) using the estimated values of \(\alpha_1\) and \(\alpha_2\). A similar approach is taken to generate \(X\) for \(Z = 0\), where we assume \(X\) from Weibull \((\alpha_3, \alpha_4)\) with \(\alpha_3\) and \(\alpha_4\) being estimated from \(\alpha_4 \Gamma (1 + 1/\alpha_3) = 1.81\) and \(\alpha_4^2 \left[ \Gamma \left(1 + \frac{2}{\alpha_3}\right) - \left(\Gamma \left(1 + \frac{1}{\alpha_3}\right)\right)^2 \right]\) = \((2.19)^2\).

As mentioned before, we linked \(\eta\) to \(z\) using \(\eta = e^{\alpha z}\) and \(p\) to \(x\) using \(p = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}}\), wherein an intercept term is not taken in the link for \(\eta\) to avoid non-identifiability. Note that \(\eta = 1\) whenever \(z = 0\). Also, a higher value of \(\eta\) signifies greater number of initial competing causes \((M)\). So, we assume \(\eta\) to be more than 1 for \(z = 1\) since patients with the ulceration status as “present” are likely to have greater values of \(M\). Following the work of Pal and Balakrishnan (2017), we assume \(\eta = 3\) for \(z = 1\); thereby, we obtain the true value of \(\alpha = 1.099\). In order to determine true values of \(\beta_0\) and \(\beta_1\), we turn our attention to \(x_{\min} = \min\{x\} = 0.1\) mm and \(x_{\max} = \max\{x\} = 17.42\) mm. As the link \(p = \frac{e^{\beta_0 + \beta_1 x}}{1 + e^{\beta_0 + \beta_1 x}}\) is monotonically increasing in \(x\), we set \(p_{\min} = \min\{p\}\) and \(p_{\max} = \max\{p\}\) and link them to \(x_{\min}\) and \(x_{\max}\), respectively. Two such choices of \((p_{\min}, p_{\max})\) are considered, viz., \((0.2, 0.6)\) and \((0.3, 0.9)\), representing scenarios of lower and higher proportions of active number of competing causes. The true values of \(\beta_0\) and \(\beta_1\) change depending on the generated values of \(x\) for each simulation.

\(M\) is generated from weighted Poisson distribution with parameter \(\eta\). For exponentially weighted Poisson cure model, we set \(\phi = 0.2\) and \(-0.5\), and for

---

**Figure 3.** Cure probability vs. tumor thickness stratified by the ulceration status.
negative binomial cure model, $\phi = 0.5$ and 5.2 are taken. For the length-biased Poisson, $M$ is generated from Poisson $(\eta) + 1$ distribution. Given $M = m > 0$, $D$ is generated from binomial distribution with success probability $p$ and $m$ as the number of trials. If $M = 0$, we put $D = 0$. The true values of the lifetime parameters $(\gamma_0, \gamma_1, \gamma_2, \gamma_3)'$ are set to be $(1.657, 3.764, -0.005, 0.023)'$, which are the parameter estimates obtained from the real data. If $M = d > 0$, we generate $W_1, \ldots, W_d$, where each $W_j (j = 1, \ldots, d)$ is simulated from

$$W_j \sim \text{Weibull}(\gamma_0, \frac{\gamma_1}{\gamma_0} \exp(-\gamma_2 x + \gamma_3 z^{\gamma_0})).$$

We define lifetime $Y = \min\{W_1, \ldots, W_d\}$ and the censoring time $C$ is assumed to be distributed exponentially with rate parameter $\psi$. Hence, the observed time $T$ is defined as $T = \min\{Y, C\}$. Again, if $D = 0$, we assign $T = C$. To assess the effect of censoring on the proposed methodology, we consider three different scenarios: $\psi = 0.05, 0.15, \text{and} 0.25$ representing low, medium and high censoring levels, respectively. On examining $\psi \in \{0.01, 0.02, \ldots, 1.50\}$ and comparing the proportion of censoring (i.e., no. of times $Y > C$) in 1000 replications, we observed that $\psi = 0.05, 0.15, \text{and} 0.25$ correspond to $52\%, 64\%$, and $72\%$ of censoring percentages, respectively. $\psi$ as low as 0.01 gives $45\%$ of censoring whereas $\psi = 1.50$ results in $95\%$ of censored observations. We took the sample size as $n = 400$, though similar results were produced for some other choices of $n$, but are not presented for conciseness.

As mentioned in Section 4, we estimate the parameters using the EM algorithm, except for $\phi$ which is estimated using the profile likelihood approach. The admissible ranges for $\phi$ are taken to be $\Phi = \{-2.00, -1.90, \ldots, 2.00\}$ for the DEWP cure model with true $\phi = 0.2$, whereas $\Phi = \{0.10, 0.15, \ldots, 2.00\}$ for the DNB cure model when true $\phi = 0.5$ and $\Phi = \{3.0, 3.1, \ldots, 7.0\}$ when true $\phi = 5.2$. Apart from $\phi$, an initial parameter value is chosen uniformly from the interval $(0.85 \theta_r, 1.15 \theta_r)$ where $\theta_r$ denotes true value of the parameter. In Tables 4–6, we display the results of our simulation study for some chosen scenarios. The accuracy and robustness of the proposed method of estimation are assessed through average estimated value (EST), standard error (SE), bias (BIAS), root mean squared error (RMSE), 95\% Confidence Interval (CI) and coverage probability (CP). CPs are obtained by assuming the asymptotic normality of the ML estimators and a nominal level of 95\% for the confidence interval thus constructed. The results are based on 500 replications of simulated data for each scenario and all calculations are performed in R-3.1.3.

From Tables 4–6, we observe the estimates to be close to the true parameter values, and the bias are small implying high accuracy of the estimation method. The profile likelihood method seems to perform relatively well in terms of accuracy, when data are generated from the DEWP ($\phi = 0.2$) cure model. However, when the true model is DNB, bias are found to be high for the estimates of $\phi$. It can be attributed to the fact that the likelihood function is very flat with respect to $\phi$. Under-coverage for $\beta_0$ and $\gamma_0$ are observed for
DEWP and DNB cure models, respectively. To explain this under-converage, we consider one such setting in which data are generated from the DEWP model with $\phi = 0.2$ having large sample size ($n = 400$), $(p_{min}, p_{max}) = (0.2, 0.6)$ and low censoring ($\psi = 0.05$). We fit DEWP cure models to the data obtained from
100 replications and compare the effect of estimating \( \phi \) versus fixed \( \phi \) on the coverage probabilities of the other parameters. These results are presented in Table 7 from which we observe that the coverage probability of \( \beta_0 \) reaches the nominal level of 95% when \( \phi \) is not estimated. This immediately points toward the imprecision in estimating \( \phi \) (likely due to the flatness of the likelihood surface) leading to the under-coverage of \( \beta_0 \). The SE and RMSE decrease with an increase in the sample size and decrease in the censoring percentages, as one would naturally expect. For brevity, tables corresponding to other scenarios are not provided here.
\( \alpha \)

To assess the impact of model mis-specification on estimates of the cure rate, a model discrimination is performed here based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The idea is to observe the

### Model discrimination

To assess the impact of model mis-specification on estimates of the cure rate, a model discrimination is performed here based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The idea is to observe the
Table 7. EST, SE, BIAS, RMSE, 95% CI and CP for destructive exponentially weighted Poisson cure model with $\phi = 0.2$ with $(p_{\min}, p_{\max}) = (0.2, 0.6)$ and $\psi = 0.05$ based on $n = 400$.

| $\theta$ | True Value | EST | SE | BIAS | RMSE | 95% CI | CP |
|-----------|-------------|-----|----|------|------|--------|----|
| $\alpha$ | 1.099       | 1.064 | 0.187 | -0.035 | 0.252 | (0.698, 1.430) | 0.929 |
| $\beta_0$ | -1.386      | -1.809 | 0.333 | -0.422 | 1.452 | (-2.462, -1.156) | 0.291 |
| $\beta_1$ | 0.099       | 0.778 | 0.570 | 0.675 | 0.923 | (-0.339, 1.894) | 0.899 |
| $\gamma_0$ | 1.658       | 1.816 | 0.120 | 0.158 | 0.215 | (1.581, 2.050) | 0.758 |
| $\gamma_1$ | 3.765       | 3.953 | 0.391 | 0.188 | 0.555 | (3.187, 4.718) | 0.929 |
| $\gamma_2$ | -0.005      | -0.022 | 0.035 | -0.017 | 0.049 | (-0.091, 0.047) | 0.919 |
| $\gamma_3$ | 0.024       | -0.148 | 0.230 | -0.172 | 0.357 | (-0.598, 0.302) | 0.848 |

| $\theta$ | True Value | EST | SE | BIAS | RMSE | 95% CI | CP |
|-----------|-------------|-----|----|------|------|--------|----|
| $\alpha$ | 1.099       | 1.086 | 0.204 | -0.013 | 0.264 | (0.685, 1.486) | 0.979 |
| $\beta_0$ | -1.386      | -1.348 | 0.208 | 0.038 | 0.276 | (-1.756, -0.941) | 0.97 |
| $\beta_1$ | 0.099       | 0.099 | 0.053 | -0.004 | 0.069 | (-0.005, 0.202) | 0.929 |
| $\gamma_0$ | 1.658       | 1.815 | 0.120 | 0.157 | 0.214 | (1.581, 2.049) | 0.778 |
| $\gamma_1$ | 3.765       | 3.944 | 0.390 | 0.180 | 0.553 | (3.179, 4.709) | 0.959 |
| $\gamma_2$ | -0.005      | -0.022 | 0.036 | -0.016 | 0.050 | (-0.092, 0.049) | 0.939 |
| $\gamma_3$ | 0.024       | -0.154 | 0.230 | -0.178 | 0.362 | (-0.606, 0.297) | 0.870 |

- EST: Parameter Estimate, SE: Standard Error, BIAS: Bias in Estimation, RMSE: Root Mean Squared Error, CI: Confidence Interval, CP: Coverage Probability (Nominal Level of 95%)

frequency with which models other than the true model get selected or rejected by our fitting method of these models. We generate 1,000 samples from five true models each, viz., DEWP ($\phi = -0.5$), DEWP ($\phi = 0.2$), DLBP, DNB ($\phi = 0.5$) and DNB ($\phi = 0.75$) with $(p_{\min}, p_{\max}) = (0.3, 0.9)$, $\eta = 3$ for $Z = 1$ and $\lambda = 0.15$ (i.e., medium censoring). The lifetime parameters are set as $\gamma = (\gamma_0, \gamma_1, \gamma_2, \gamma_3)' = (1.657, 3.764, -0.005, 0.023)'$ (see Section 6). Under these specifications, samples are generated of size $n = 400$.

We fit three candidate models, i.e., DEWP, DLBP and DNB cure models, to these samples with the proposed method of estimation. The model with the least AIC or BIC value gets selected, where

$$AIC = -2\hat{l} + 2\tilde{k}; \quad BIC = -2\hat{l} + \tilde{k}\log(n),$$

with $\hat{l}$ being the maximized log-likelihood value corresponding to the model and $\tilde{k}$ being the number of estimated parameters. The selection rates based on AIC, BIC and $\hat{l}$ are all presented in Table 8.

The selection of true models based on both AIC and BIC values are found to be quite low when the data are generated from DEWP and DNB cure models. It is observed that the values of the log-likelihood function for all the fitted cure models are quite similar. For this reason, the models with one extra parameter (i.e. DEWP and DNB), in terms of AIC and BIC values, do get penalized more when compared to the DLB model. Consequently, when the log-likelihood value ($\hat{l}$) is used as the selection criteria, the results reveal more selections for the true models. Table 9 shows that when $\phi$ is not estimated, true models are more likely to get selected.
Table 8. Selection rates based on AIC, BIC and maximized log-likelihood (\(\hat{l}\)) value for \(n = 400\).

| True models | DEWP | DLB | DNB |
|-------------|------|-----|-----|
| DEWP (\(\phi = -0.5\)) | \(\hat{\phi} = -0.275\) | \(\hat{\phi} = 0.378\) | \(\hat{\phi} = 0.000\) |
| AIC | 0.179 | 0.768 | 0.053 |
| BIC | 0.037 | 0.944 | 0.019 |
| log-lik | 0.630 | 0.152 | 0.218 |
| DEWP (\(\phi = 0.2\)) | \(\hat{\phi} = 0.222\) | \(\hat{\phi} = 0.018\) | \(\hat{\phi} = 0.347\) |
| AIC | 0.125 | 0.843 | 0.032 |
| BIC | 0.063 | 0.919 | 0.018 |
| log-lik | 0.597 | 0.360 | 0.043 |
| DLB | \(\hat{\phi} = -0.077\) | \(\hat{\phi} = 0.347\) | \(\hat{\phi} = 0.000\) |
| AIC | 0.073 | 0.919 | 0.008 |
| BIC | 0.016 | 0.983 | 0.001 |
| log-lik | 0.427 | 0.559 | 0.014 |
| DNB (\(\phi = 0.5\)) | \(\hat{\phi} = 0.311\) | \(\hat{\phi} = 0.336\) | \(\hat{\phi} = 0.000\) |
| AIC | 0.163 | 0.762 | 0.075 |
| BIC | 0.003 | 0.969 | 0.028 |
| log-lik | 0.556 | 0.262 | 0.182 |
| DNB (\(\phi = 0.75\)) | \(\hat{\phi} = 0.545\) | \(\hat{\phi} = 0.346\) | \(\hat{\phi} = 0.000\) |
| AIC | 0.174 | 0.737 | 0.089 |
| BIC | 0.040 | 0.927 | 0.033 |
| log-lik | 0.599 | 0.242 | 0.159 |

AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, log-lik: Maximized log-likelihood value

Table 9. Comparison of model selection rates based on AIC for \(n = 400\).

| Fitted model | True Model | DEWP (\(\phi = -0.5\)) | DNB (\(\phi = 0.5\)) |
|--------------|------------|------------------------|---------------------|
| True Model   | 0.540      | 0.330                  |
| DEWP         | 0.060      | 0.100                  |
| DLBP         | 0.390      | 0.530                  |
| DNB          | 0.010      | 0.040                  |

AIC: Akaike Information Criterion

To emphasize the importance of model discrimination, we examine the bias and MSE involved in the estimation of cure rates of patients under model misspecification. For each model, we compute the total relative bias (TRB) as

\[
TRB = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{\hat{\pi}_{0,i} - \pi_{0,i}}{\pi_{0,i}} \right|
\]

where \(\pi_{0,i}\) and \(\hat{\pi}_{0,i}\) denote true and estimated cure rates for an individual \(i, i = 1, \ldots, n\). Similarly, we define total mean squared error (TMSE) for a model as

\[
TMSE = \frac{1}{n-1} \sum_{i=1}^{n} (\hat{\pi}_{0,i} - \pi_{0,i})^2.
\]

For two candidate models M1 and M2, total relative efficiency (TRE) of M2 with respect to M1 is defined as \(TRE = \frac{TMSE(M2)}{TMSE(M1)}\), where TMSE(M1) and TMSE(M2) denote TMSE values based on M1 and M2, respectively. With these measures
Table 10. TRB (%) (TMSE, \( \hat{\phi} \), TRE) in estimation of cured proportion for all candidate models for \( n = 400 \).

| True model          | DEWP (\( \phi = -0.5 \)) | DEWP (\( \phi = 0.2 \)) | DLBP | DNB (\( \phi = 0.5 \)) | DNB (\( \phi = 0.75 \)) |
|---------------------|---------------------------|---------------------------|------|-------------------------|--------------------------|
|                     | 35.300 (0.003, 1.000)     | 62.365 (0.003, 1.000)     | 86.617 (0.003, 1.000) | 41.663 (0.004, 1.000) | 37.100 (0.003, 1.000)   |
|                     | 37.015 (0.004, 1.000)     | 66.532 (0.004, 1.000)     | 107.147 (0.004, 1.000) | 42.593 (0.004, 1.000) | 39.126 (0.004, 1.000)   |
|                     | 37.730 (0.004, 1.000)     | 61.101 (0.003, 1.000)     | 86.617 (0.003, 1.000) | 42.992 (0.004, 1.000) | 40.846 (0.004, 1.000)   |
|                     | 34.957 (0.003, 1.000)     | 67.786 (0.003, 1.000)     | 193.413 (0.006, 1.000) | 40.039 (0.004, 1.000) | 37.247 (0.003, 1.000)   |

TRB: Total Relative Bias, TMSE: Total Mean Squared Error, TRE: Total Relative Efficiency

Table 11. TRB (%) and TRE when AIC and \( \hat{l} \) are used for model selection for \( n = 400 \).

| True Model          | AIC TRB (%) | TRE | \( \hat{l} \) TRB (%) | TRE |
|---------------------|-------------|-----|-----------------------|-----|
| DEWP (\( \phi = -0.5 \)) | 36.347 | 1.148 | 36.659 | 1.085 |
| DEWP (\( \phi = 0.2 \)) | 62.321 | 1.040 | 65.832 | 1.032 |
| DLBP                | 88.259 | 0.997 | 94.829 | 0.986 |
| DNB (\( \phi = 0.5 \)) | 42.461 | 1.030 | 42.408 | 1.027 |
| DNB (\( \phi = 0.75 \)) | 39.347 | 1.023 | 39.104 | 0.998 |

TRB: Total Relative Bias, TRE: Total Relative Efficiency

defined, we compare the three candidate models. Table 10 presents TRB (in %), TMSE and TRE for the candidate models for \( n = 400 \) when the data are generated from one of the five true models as described earlier in this section.

The model M1 gets chosen always to be the true model. From Table 10, it can be seen that in cases where data are from the DLBP cure model, model mis-specification may lead to large bias and MSE, and consequently, higher TRB and lower TRE are observed on fitting candidate models when the true model is DLBP. For the other true models, TRB values are relatively close to each other which indicate not much precision is lost under model mis-specification. DNB cure models provide lesser TRB and higher TRE in most of the scenarios considered. Table 11 shows TRB and TRE values when using AIC and \( \hat{l} \) as the model selection criteria. The results suggest that allowing AIC or \( \hat{l} \) to select a working model out of a set of candidate models may lead to lesser relative bias. TRE values are greater than one in most cases, which means that estimating the cured proportion by fitting the working model as selected by AIC or \( \hat{l} \) results in higher efficiency.

8. Concluding remarks

In this work, destructive cure models are studied under competing risks scenario wherein the initial competing causes undergo a destructive mechanism. The models are developed and examined assuming that the hazard functions corresponding to the susceptible individuals follow proportional hazards with Weibull baseline hazard function. The model generalizes the previous works of Pal and Balakrishnan (2016, 2017) on destructive cure model by assuming non
i.i.d. lifetimes for the susceptible individuals. This is accomplished by linking covariates to the lifetimes through proportional hazards. The parameter estimates are found to be accurate with low RMSE. A relatively large bias is observed while estimating $\phi$, especially when data are from DNB ($\phi = 0.75$) cure model. The estimates are observed to be more precise under scenarios characterized by low censoring, high proportion of undamaged competing causes and large sample size. In some cases of the simulation study, especially for the DNB and DEWP models, an apparent under-coverage of the intercept parameters $\beta_0$ or $\gamma_0$ is observed. This problem, however, gets resolved when the dispersion parameter $\phi$ is not estimated but a true value of $\phi$ is used, further suggesting that the flatness of likelihood surface with respect to $\phi$ resulting in higher variability of estimated $\phi$ is likely to be responsible for this. A model discrimination is also carried out using information-based criteria. A known real life example on cutaneous melanoma is considered for the purpose of illustrating the models and the method of fit developed here. Destructive negative binomial cure model with $\hat{\phi} = 5.2$ provided the best fit to this data. The assumption of i.i.d. lifetimes among the susceptible subjects could not be rejected at 5% level of significance. It will be of interest to study destructive cure models when covariates are prone to measurement errors. We hope to consider this problem as our future research.

References

Andersen, P. K., O. Borgan, R. D. Gill, and N. Keiding. 2012. Statistical Models Based on Counting Processes. Berlin: Springer.

Balakrishnan, N., S. Barui, and F. Milienos. 2022. “Piecewise Linear Approximations of Baseline under Proportional Hazards based COM-Poisson Cure Models Piecewise Linear Approximations of Baseline under Proportional Hazards based com-Poisson Cure Models.” Communications in Statistics-Simulation and Computation 1–26. DOI:10.1080/03610918.2022.2032157.

Balakrishnan, N., and Feng, T. 2019. “Destructive Cure Rate Models under Proportional Odds and Associated Likelihood Inference.” Communications in Statistics: Case Studies, Data Analysis and Applications 5 (2):121–45.

Balakrishnan, N., M. Koutras, F. Milienos, and S. Pal. 2016. “Piecewise Linear Approximations for Cure Rate Models and Associated Inferential Issues.” Methodology and Computing in Applied Probability 18 (4):937–66.

Balakrishnan, N., and S. Pal. 2012. “EM Algorithm-based Likelihood Estimation for Some Cure Rate Models.” Journal of Statistical Theory and Practice 6:698–724.

Balakrishnan, N., and S. Pal. 2013. “Lognormal Lifetimes and Likelihood-based Inference for Flexible Cure Rate Models based on COM-Poisson family.” Computational Statistics & Data Analysis 67:41–67.

Balakrishnan, N., and S. Pal. 2014a. “COM-Poisson Cure Rate Models and Associated Likelihood-based Inference with Exponential and Weibull Lifetimes.” In Applied Reliability Engineering and Risk Analysis: Probabilistic Models and Statistical Inference, edited by I. B. Frenkel, A. Karagrigoriou, A. Lisienski, 308–48. Chichester, UK: Wiley.

Balakrishnan, N., and S. Pal. 2014b. “An EM Algorithm for the Estimation of Parameters of a Flexible Cure Rate Model with Generalized Gamma Lifetime and Model Discrimination Using Likelihood and Information based Methods.” Computational Statistics 30:151–89.
Balakrishnan, N., and S. Pal. 2016. "Expectation Maximization-based Likelihood Inference for Flexible Cure Rate Models with Weibull Lifetimes." *Statistical Methods in Medical Research* 25 (4):1535–63.

Berkson, J., and R. P. Gage. 1952. "Survival Curve for Cancer Patients Following Treatment." *Journal of the American Statistical Association* 47:501–15.

Boag, J. W. (1949). "Maximum Likelihood Estimates of the Proportion of Patients Cured by Cancer Therapy." *Journal of the Royal Statistical Society. Series B (Methodological)* 11:15–53.

Borges, P., J. Rodrigues, and N. Balakrishnan. 2012. “Correlated Destructive Generalized Power Series Cure Rate Models and Associated Inference with an Application to a Cutaneous Melanoma Data.” *Computational Statistics & Data Analysis* 56 (6):1703–13.

Cancho, V. G., D. Bandyopadhyay, F. Louzada, and B. Yiqi. 2013. "The Destructive Negative Binomial Cure Rate Model with a Latent Activation Scheme." *Statistical Methodology* 13:48–68.

Chen, M. H., J. G. Ibrahim, and D. Sinha. 1999. "A New Bayesian Model for Survival Data with a Surviving Fraction." *Journal of the American Statistical Association.* 94:909–19.

Dempster, A. P., N. M. Laird, and D. B. Rubin. 1977. "Maximum Likelihood from Incomplete Data via the EM Algorithm." *Journal of the Royal Statistical Society. Series B (Methodological)* 39:1–38.

Fang, H. B., G. Li, and J. Sun. 2005. “Maximum Likelihood Estimation in a Semiparametric Logistic/Proportional-Hazards Mixture Model.” *Scandinavian Journal of Statistics* 32:59–75.

Farewell, V. T. (1982). “The Use of Mixture Models for the Analysis of Survival Data with Long-Term Survivors.” *Biometrics* 38:1041–46.

Gallardo, D. I., H. Bolfarine, and A. C. Pedroso-de Lima. 2016. “An EM Algorithm for Estimating the Destructive Weighted Poisson Cure Rate Model.” *Journal of Statistical Computation and Simulation* 86 (8):1497–15.

Haybittle, J. (1965). “A Two-Parameter Model for the Survival Curve of Treated Cancer Patients.” *Journal of the American Statistical Association* 60 (309):16–26.

Kuk, A. Y., and C. H. Chen. 1992. “A Mixture Model Combining Logistic Regression with Proportional Hazards Regression.” *Biometrika* 79:531–41.

Larson, M. G., and G. E. Dinse. 1985. "A Mixture Model for the Regression Analysis of Competing Risks Data." *Applied Statistics* 34:201–211.

Li, C. S., J. M. Taylor, and J. P. Sy. 2001. Identifiability of Cure Models. *Statistics & Probability Letters* 54:389–95.

Maller, R. A., and X. Zhou. 1996. *Survival Analysis with Long-Term Survivors*. New York: Wiley.

Pal, S., and N. Balakrishnan. 2016. "Destructive Negative Binomial Cure Rate Model and EM-based Likelihood Inference under Weibull Lifetime." *Statistics & Probability Letters* 116:9–20.

Pal, S., and N. Balakrishnan. 2017. “Likelihood Inference for the Destructive Exponentially Weighted Poisson Cure Rate Model with Weibull Lifetime and An Application to Melanoma Data.” *Computational Statistics*, 32:429–49.

Pal, S., and N. Balakrishnan. 2018. “Likelihood Inference based on EM Algorithm for the Destructive Length-biased Poisson Cure Rate Model with Weibull Lifetime.” *Communications in Statistics-Simulation and Computation* 47 (3):644–660.

Peng, Y., and K. B. Dear. 2000. "A Nonparametric Mixture Model for Cure Rate Estimation." *Biometrics* 56 (1):237–43.

Rodrigues, J., V. G. Cancho, M. de Castro, and N. Balakrishnan. 2012. “A Bayesian Destructive Weighted Poisson Cure Rate Model and an Application to a Cutaneous Melanoma Data.” *Statistical Methods in Medical Research* 21:585–97.

Rodrigues, J., M. de Castro, N. Balakrishnan, and Cancho, V. G. 2011. “Destructive Weighted Poisson Cure Rate Models.” *Lifetime Data Analysis* 17:333–46.

Rodrigues, J., M. de Castro, V. G. Cancho, and N. Balakrishnan. 2009. “COM-Poisson Cure Rate Survival Models and an Application to a Cutaneous Melanoma Data.” *Journal of Statistical Planning and Inference* 139:3605–11.

Sy, J. P., and J. M. Taylor. 2000. "Estimation in a Cox Proportional Hazards Cure Model." *Biometrics* 56:227–36.
Tsodikov, A., J. Ibrahim, and A. Yakovlev. 2003. “Estimating Cure Rates from Survival Data.” *Journal of the American Statistical Association* 98:1063–78.

Yakovlev, A. Y., A. D. Tsodikov, and B. Asselain. 1996. *Stochastic Models of Tumor Latency and their Biostatistical Applications*, vol. 1. Singapore: World Scientific, OECD Publishing.

Yakovlev, A. Y., A. D. Tsodikov, and L. Bass. 1993. “A Stochastic Model of Hormesis.” *Mathematical Biosciences* 116 (2):197–219.

Yin, G., and J. G. Ibrahim. 2005. “Cure Rate Models: A Unified Approach.” *Canadian Journal of Statistics* 33 (4):559–70.

Zeng, D., G. Yin, and J. G. Ibrahim. 2006, “Semiparametric Transformation Models for Survival Data with a Cure Fraction.” *Journal of the American Statistical Association* 101:670–84.
Appendix

A. The Q-function

For all $i \in \{1, 2, \ldots, n\}$ and following Eqs. (21)–(24) we define:

$$\eta_i = e^{\alpha' z_i}, p_i = \frac{e^{\beta' x_i}}{1 + e^{\beta' x_i}},$$

$$\lambda_i = \lambda(t_i; x_i, z_i, y), S_i = S(t_i; x_i, z_i, y), F_i = F(t_i; x_i, z_i, y), \text{ and } f_i = f(t_i; x_i, z_i, y).$$

A.1. Destructive exponentially weighted Poisson cure model

$$Q(\theta^*, \xi^{(a)}) = \sum_{\Delta_1} \log M_i - \sum_{i=1}^n M_i + \sum_{\Delta_1} M_i S_i + \sum_{\Delta_1} \log f_i + \sum_{\Delta_0} \xi_i^{(a)} \log (e^{M_i S_i} - 1),$$

where

$$\xi_i^{(a)} = 1 - e^{-\eta_i e^{\phi' p_i S_i}} \bigg|_{\theta^* = \hat{\theta}^{(a)}}, \text{ and } M_i = \eta_i e^{\phi' p_i}.$$

A.2. Destructive length-biased Poisson cure model

$$Q(\theta^*, \xi^{(a)}) = \sum_{\Delta_1} \log \eta_i + \sum_{\Delta_1} \log p_i + \sum_{\Delta_1} \log f_i - \sum_{\Delta_1} A_i + \sum_{\Delta_1} B_i$$

$$- \sum_{\Delta_0} \eta_i p_i + \sum_{\Delta_0} \log (1 - p_i) + \sum_{\Delta_0} \xi_i^{(a)} \log (C_i D_i - 1),$$

where

$$\xi_i^{(a)} = 1 - e^{-\eta_i p_i S_i} \left( \frac{1 - p_i}{1 - p_i F_i} \right) \bigg|_{\theta^* = \hat{\theta}^{(a)}},$$

$$A_i = \eta_i p_i F_i, B_i = \log \left( 1 - p_i F_i - \frac{p_i f_i}{\eta_i} \right), C_i = e^{\eta_i p_i (1 - F_i)}, \text{ and } D_i = \frac{1 - p_i F_i}{1 - p_i}.$$

A.3. Destructive negative binomial cure model

$$Q(\theta^*, \xi^{(a)}) = \sum_{\Delta_1} \log \eta_i p_i - \left( \frac{1}{\phi} + 1 \right) \sum_{\Delta_1} \log (1 + E_i F_i) + \sum_{\Delta_1} \log f_i$$

$$- \frac{1}{\phi} \sum_{\Delta_0} \log (1 + E_i) + \sum_{\Delta_0} \xi_i^{(a)} \log \left( G_i^{-1/\phi} - 1 \right),$$

where

$$\xi_i^{(a)} = 1 - G_i \bigg|_{\theta^* = \hat{\theta}^{(a)}}, E_i = \phi \eta_i p_i, \text{ and } G_i = \frac{1 + \phi \eta_i p_i F_i}{1 + \phi \eta_i}.$$
B. The first and second order derivatives of the cumulative distribution \((F)\), survival \((S)\) and probability density \((f)\) functions

B.1. The cumulative distribution function

\[ F_{i,0}' = \frac{\partial F_i}{\partial \gamma_0} = -S_i \log S_i \left( \frac{t_i}{\gamma_1} \right), \]
\[ F_{i,1}' = \frac{\partial F_i}{\gamma_1} = S_i \log S_i \left( \frac{\gamma_0}{\gamma_1} \right), \]
\[ F_{i,2l}' = \frac{\partial F_i}{\partial \gamma_{2l}} = -x_{il} S_i \log S_i, \]
\[ F_{i,3m}' = \frac{\partial F_i}{\gamma_{3m}} = -z_{im} S_i \log S_i, \]
\[ F_{i,00}'' = \frac{\partial^2 F_i}{\partial \gamma_0^2} = -\left[ \log \left( \frac{t_i}{\gamma_0} \right) \right]^2 S_i \log S_i (1 + \log S_i), \]
\[ F_{i,01}'' = \frac{\partial^2 F_i}{\partial \gamma_0 \partial \gamma_1} = \frac{S_i \log S_i}{\gamma_1} \left[ 1 + \gamma_0 \log \left( \frac{t_i}{\gamma_1} \right) (1 + \log S_i) \right], \]
\[ F_{i,11}'' = \frac{\partial^2 F_i}{\partial \gamma_1^2} = -\frac{\gamma_0}{\gamma_1^2} S_i \log S_i \left[ 1 + \gamma_0 \log \left( \frac{t_i}{\gamma_1} \right) \right], \]
\[ F_{i,0(2l)}'' = \frac{\partial^2 F_i}{\partial \gamma_0 \partial \gamma_{2l}} = -x_{il} \log \left( \frac{t_i}{\gamma_1} \right) S_i \log S_i (1 + \log S_i), \]
\[ F_{i,0(3m)}'' = \frac{\partial^2 F_i}{\partial \gamma_0 \partial \gamma_{3m}} = -z_{im} \log \left( \frac{t_i}{\gamma_1} \right) S_i \log S_i (1 + \log S_i), \]
\[ F_{i,1(2l)}'' = \frac{\partial^2 F_i}{\partial \gamma_1 \partial \gamma_{2l}} = x_{il} \left( \frac{\gamma_0}{\gamma_1} \right) S_i \log S_i (1 + \log S_i), \]
\[ F_{i,1(3m)}'' = \frac{\partial^2 F_i}{\partial \gamma_1 \partial \gamma_{3m}} = z_{im} \left( \frac{\gamma_0}{\gamma_1} \right) S_i \log S_i (1 + \log S_i), \]
\[ F_{i,2l(2l)'}'' = \frac{\partial^2 F_i}{\partial \gamma_{2l} \partial \gamma_{2l}'} = -x_{il} x_{il'} S_i \log S_i (1 + \log S_i), \]
\[ F_{i,2l(3m)}'' = \frac{\partial^2 F_i}{\partial \gamma_{2l} \partial \gamma_{3m}} = -x_{il} z_{im} S_i \log S_i (1 + \log S_i), \]

and

\[ F_{i,3m(3m)'}'' = \frac{\partial^2 F_i}{\partial \gamma_{3m} \partial \gamma_{3m}'} = -z_{im} z_{im'} S_i \log S_i (1 + \log S_i), \]

for \(i = 1, \ldots, n; j, j' = 1, \ldots, q_1; k, k' = 0, 1, \ldots, q_2; r, r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; l, l' = 0, 1, \ldots, q_2; m, m' = 1, \ldots, q_1\) and \(x_{i0} = 1\).
\[ S_{i,0}' = -F_{i,0}', \quad S_{i,1}' = -F_{i,1}', \quad S_{i,2l}' = -F_{i,2l}', \quad S_{i,3m}' = -F_{i,3m}', \quad S_{i,00}' = -F_{i,00}' , \]
\[ S_{i,01}' = -F_{i,01}', \quad S_{i,02(2)}' = -F_{i,02(2)}', \quad S_{i,0(3m)}' = -F_{i,0(3m)}', \quad S_{i,11}' = -F_{i,11}' , \]
\[ S_{i,1(2)}' = -F_{i,1(2)}', \quad S_{i,1(3m)}' = -F_{i,1(3m)}', \quad S_{i,2(2l)'} = -F_{i,2(2l)}', \quad S_{i,3m}' = -F_{i,3m}'(3m), \quad \text{and} \quad S_{i,3m}'(3m') = -F_{i,3m}'(3m'). \]

for \( i = 1, \ldots, n; j,j' = 1, \ldots, q; k,k' = 0, 1, \ldots, q; r,r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; l,l' = 0, 1, \ldots, q_2; m,m' = 1, \ldots, q_1 \text{ and } x_{i0} = 1. \)

### B.3 The probability density function

\[ f_{i,0}' = \frac{\partial^2 f_i}{\partial y_0^3} = \left\{ -F_{i,0}' + S_i \left[ \frac{1}{y_0} + \log \left( \frac{t_i}{\gamma_1} \right) \right] \lambda_i , \quad f_{i,1}' = \frac{\partial^2 f_i}{\partial y_1^3} = - \left\{ F_{i,1}' + S_i \left( \frac{y_0}{\gamma_1} \right) \right\} \lambda_i , \]
\[ f_{i,2l}' = \frac{\partial^2 f_i}{\partial y_{2l}^3} = \left\{ -F_{i,2l}' + S_i x_{i l} \right\} \lambda_i , \quad f_{i,3m}' = \frac{\partial^2 f_i}{\partial y_{3m}^3} = \left\{ -F_{i,3m}' + S_i z_{i m} \right\} \lambda_i , \]
\[ f_{i,00}' = \frac{\partial^2 f_i}{\partial y_0 \partial y_1} = \left\{ -F_{i,00}' + S_i \left[ \frac{2}{y_0} + \log \left( \frac{t_i}{\gamma_1} \right) \right] \right\} \lambda_i , \]
\[ f_{i,11}' = \frac{\partial^2 f_i}{\partial y_1^3} = \left\{ -F_{i,11}' + S_i \left( \frac{y_0(y_0 + 1)}{\gamma_1^2} + 2 \frac{y_0}{\gamma_1} \right) \right\} \lambda_i , \]
\[ f_{i,0(2l)}'' = \frac{\partial^2 f_i}{\partial y_0 \partial y_{2l}} = \left\{ -F_{i,0(2l)}'' + (S_i x_{i l} - F_{i,2l}') \left[ \frac{1}{y_0} + \log \left( \frac{t_i}{\gamma_1} \right) \right] \right\} \lambda_i , \]
\[ f_{i,0(3m)}'' = \frac{\partial^2 f_i}{\partial y_0 \partial y_{3m}} = \left\{ -F_{i,0(3m)}'' + (S_i z_{i m} - F_{i,3m}') \left[ \frac{1}{y_0} + \log \left( \frac{t_i}{\gamma_1} \right) \right] \right\} \lambda_i , \]
\[ f_{i,1(2l)''} = \frac{\partial^2 f_i}{\partial y_1 \partial y_{2l}} = \left\{ -F_{i,1(2l)''} - (S_i x_{i l} - F_{i,2l}') \frac{y_0}{\gamma_1} - x_{i l} F_{i,1}' \right\} \lambda_i , \]
\[ f_{i,1(3m)''} = \frac{\partial^2 f_i}{\partial y_1 \partial y_{3m}} = \left\{ -F_{i,1(3m)''} - (S_i z_{i m} - F_{i,3m}') \frac{y_0}{\gamma_1} - z_{i m} F_{i,1}' \right\} \lambda_i , \]
\[ f_{i,2(2l)''} = \frac{\partial^2 f_i}{\partial y_{2l} \partial y_{2l}'} = \left\{ -F_{i,2(2l)''} + S_i x_{i l} x_{i l'} - F_{i,2l}' x_{i l'} - x_{i l} F_{i,2l}' \right\} \lambda_i , \]
\[ f_{i,2(2l)''} = \frac{\partial^2 f_i}{\partial y_{2l} \partial y_{3m}'} = \left\{ -F_{i,2(2l)''} + S_i x_{i l} z_{i m} - F_{i,2l}' z_{i m} - x_{i l} F_{i,2l}' \right\} \lambda_i , \]
\[ f_{i,3m}'(3m') = \frac{\partial^2 f_i}{\partial y_{3m} \partial y_{3m'}} = \left\{ -F_{i,3m}'(3m') + S_i z_{i m} z_{i m'} - F_{i,3m}' z_{i m'} - z_{i m} F_{i,3m}' \right\} \lambda_i , \]

and

\[ \frac{\partial \log f_i}{\partial y_r} = f_i^r, \quad \frac{\partial^2 \log f_i}{\partial y_r \partial y_{r'}} = \frac{f f_{i,i} f_{i,i} - f f_{i,i} f_{i,i}^r}{f^2}, \]

for \( i = 1, \ldots, n; j,j' = 1, \ldots, q; k,k' = 0, 1, \ldots, q; r,r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; l,l' = 0, 1, \ldots, q_2; m,m' = 1, \ldots, q_1 \text{ and } x_{i0} = 1. \)
C. The first and second order derivatives of the Q-function

For \( i \in \{1, 2, \ldots, n\} \) we define \( D_i^\gamma = \frac{e^{\gamma_i} - 1}{e^{\gamma_i} - 1} \).

C.1. Destructive exponentially weighted Poisson cure model

\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \alpha_j} = \sum_{\Delta_1} z_{ij} - \sum_{i=1}^n z_{ij} M_i + \sum_{\Delta_1} z_{ij} M_i S_i + \sum_{\Delta_0} \xi_j^{(a)} z_{ij} D_i^\gamma M_i S_i, \\
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \beta_k} = \sum_{\Delta_1} x_{ik}(1 - p_i) - \sum_{i=1}^n x_{ik} M_i(1 - p_i) + \sum_{\Delta_1} x_{ik} M_i S_i(1 - p_i) \\
+ \sum_{\Delta_0} \xi_j^{(a)} x_{ik} D_i^\gamma M_i S_i(1 - p_i), \\
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_0} = \sum_{\Delta_1} M_i S_{i,0} + \sum_{\Delta_1} \left[ \frac{1}{\gamma_0} + \log \left( \frac{t_i}{\gamma_1} \right) + \frac{S'_{i,0}}{S_i} \right] \right] + \sum_{\Delta_0} \xi_j^{(a)} D_i^\gamma M_i S_{i,0}, \\
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_1} = \sum_{\Delta_1} M_i S'_{i,1} + \sum_{\Delta_1} \left[ \frac{\gamma_0}{\gamma_1} + \frac{S'_{i,1}}{S_i} \right] + \sum_{\Delta_0} \xi_j^{(a)} D_i^\gamma M_i S'_{i,1}, \\
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_2} = \sum_{\Delta_1} M_i S'_{i,2} + \sum_{\Delta_1} \left[ x_{il} + \frac{S'_{i,2}}{S_i} \right] + \sum_{\Delta_0} \xi_j^{(a)} D_i^\gamma M_i S'_{i,2}, \\
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_3} = \sum_{\Delta_1} M_i S'_{i,3} + \sum_{\Delta_1} \left[ z_{im} + \frac{S'_{i,3}}{S_i} \right] + \sum_{\Delta_0} \xi_j^{(a)} D_i^\gamma M_i S'_{i,3}, \\
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \alpha_j} = -\sum_{i=1}^n z_{ij} z_{ij} M_i + \sum_{\Delta_1} z_{ij} z_{ij} M_i S_i + \sum_{\Delta_0} \xi_j^{(a)} z_{ij} z_{ij} D_i^\gamma M_i S_i \left[ 1 - \frac{M_i S_i}{e^{M_i S_i} - 1} \right], \\
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \beta_k} = -\sum_{i=1}^n x_{ik} z_{ik} M_i(1 - p_i) + \sum_{\Delta_1} x_{ik} z_{ik} M_i S_i(1 - p_i) \\
+ \sum_{\Delta_0} \xi_j^{(a)} x_{ik} z_{ij} D_i^\gamma M_i S_i(1 - p_i) \left[ 1 - \frac{M_i S_i}{e^{M_i S_i} - 1} \right], \\
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \beta_k'} = -\sum_{i=1}^n x_{ik} x_{ik'} M_i(1 - p_i)(1 - 2p_i) + \sum_{\Delta_1} x_{ik} x_{ik'} M_i S_i(1 - p_i)(1 - 2p_i) \\
+ \sum_{\Delta_0} \xi_j^{(a)} x_{ik} x_{ik'} D_i^\gamma M_i S_i(1 - p_i)(1 - 2p_i) \left[ 1 - \frac{M_i S_i(1 - p_i)}{(1 - 2p_i)(e^{M_i S_i} - 1)} \right], \\
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \gamma_0} = \sum_{\Delta_1} z_{ij} M_i S'_{i,0} + \sum_{\Delta_0} \xi_j^{(a)} z_{ij} D_i^\gamma M_i S'_{i,0} \left[ 1 - \frac{M_i S_i}{e^{M_i S_i} - 1} \right], \\
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \gamma_1} = \sum_{\Delta_1} z_{ij} M_i S'_{i,1} + \sum_{\Delta_0} \xi_j^{(a)} z_{ij} D_i^\gamma M_i S'_{i,1} \left[ 1 - \frac{M_i S_i}{e^{M_i S_i} - 1} \right],
\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \gamma_{2l}} = \sum_{\Delta_1} z_j M_i S_{i,2l}' + \sum_{\Delta_0} \xi_i^{(a)} z_j D_i' M_i S_{i,2l}' \left[ 1 - \frac{M_i S_i}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \gamma_{3m}} = \sum_{\Delta_1} z_k M_i S_{i,3m}' + \sum_{\Delta_0} \xi_i^{(a)} z_j D_i' M_i S_{i,3m}' \left[ 1 - \frac{M_i S_i}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \gamma_{0}} = \sum_{\Delta_1} x_{l-k} (1-p_l) M_l S_{l,0}' + \sum_{\Delta_0} \xi_i^{(a)} x_{l-k} (1-p_l) D_i' M_i S_{l,0}' \left[ 1 - \frac{M_i S_i}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \gamma_{1}} = \sum_{\Delta_1} x_{l-k} (1-p_l) M_l S_{l,1}' + \sum_{\Delta_0} \xi_i^{(a)} x_{l-k} (1-p_l) D_i' M_i S_{l,1}' \left[ 1 - \frac{M_i S_i}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_0^2} = \sum_{\Delta_1} M_i S_{i,0}' + \sum_{\Delta_1} \left[ -\frac{1}{\gamma_0^2} + \frac{S_i S_{i,0} - (S_i')^2}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i' M_i \left[ S_{i,0}' - \frac{M_i (S_i')^2}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_0 \partial \gamma_1} = \sum_{\Delta_1} M_i S_{i,0}' + \sum_{\Delta_1} \left[ -\frac{1}{\gamma_1} + \frac{S_i S_{i,0}' - S_{i,0} S_{i,1}'}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i' M_i \left[ S_{i,0}' - \frac{M_i S_{i,0} S_{i,1}'}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_0 \partial \gamma_{2l}} = \sum_{\Delta_1} M_i S_{i,0}' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,0}' - S_{i,0} S_{i,2l}'}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i' M_i \left[ S_{i,0}' - \frac{M_i S_{i,0} S_{i,2l}'}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_0 \partial \gamma_{3m}} = \sum_{\Delta_1} M_i S_{i,0}' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,0}' - S_{i,0} S_{i,3m}'}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i' M_i \left[ S_{i,0}' - \frac{M_i S_{i,0} S_{i,3m}'}{e^M S_i - 1} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_1^2} = \sum_{\Delta_1} M_i S_{i,1} + \sum_{\Delta_1} \left[ \frac{\gamma_0^2}{\gamma_1^2} + \frac{S_i S_{i,1}^2 - (S_i')^2}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i' M_i \left[ S_{i,1}' - \frac{M_i (S_i')^2}{e^M S_i - 1} \right].
\]
\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_1 \partial \gamma_2} = \sum_{\Delta_1} M_i S_{i,1(2)}'' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,1(2)}}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i^* M_i \left[ S''_{i,1(2)} - \frac{M_i S_{i,1(2)}}{\alpha M_{\xi_i}} \right],
\]

\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_1 \partial \gamma_3} = \sum_{\Delta_1} M_i S_{i,1(3)m}'' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,1(3)m}}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i^* M_i \left[ S''_{i,1(3)m} - \frac{M_i S_{i,1(3)m}}{\alpha M_{\xi_i}} \right],
\]

\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_2 \partial \gamma_3} = \sum_{\Delta_1} M_i S_{i,2(2)}'' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,2(2)}}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i^* M_i \left[ S''_{i,2(2)} - \frac{M_i S_{i,2(2)}}{\alpha M_{\xi_i}} \right],
\]

\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_2 \partial \gamma_3} = \sum_{\Delta_1} M_i S_{i,2(2)m}'' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,2(2)m}}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i^* M_i \left[ S''_{i,2(2)m} - \frac{M_i S_{i,2(2)m}}{\alpha M_{\xi_i}} \right],
\]

\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_3 \partial \gamma_3} = \sum_{\Delta_1} M_i S_{i,3(3)m}'' + \sum_{\Delta_1} \left[ \frac{S_i S_{i,3(3)m}}{S_i^2} \right] + \sum_{\Delta_0} \xi_i^{(a)} D_i^* M_i \left[ S''_{i,3(3)m} - \frac{M_i S_{i,3(3)m}}{\alpha M_{\xi_i}} \right],
\]

for \(i = 1, \ldots, m; j, j' = 1, \ldots, q; k, k' = 0, 1, \ldots, q_2; r, r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; l, l' = 0, 1, \ldots, q_2; m, m' = 1, \ldots, q_1 \) and \(x_{i0} \equiv 1\).

C.2. Destructive length-biased Poisson cure model

Let us define the following quantities:

\[
A'_{ij} = \frac{\partial A_i}{\partial \alpha_j} = z_{ij} \eta_i p_i F_i, \quad A'_{ik} = \frac{\partial A_i}{\partial \beta_k} = x_{ik} \eta_i (1 - p_i) F_i, \quad A'_{ir} = \frac{\partial A_i}{\partial \gamma_r} = \eta_i p_i F'_{ir},
\]

\[
A''_{ij} = \frac{\partial^2 A_i}{\partial \alpha_i \partial \alpha_j} = z_{ij} z_{ij} \eta_i p_i F_i, \quad A''_{ik} = \frac{\partial^2 A_i}{\partial \alpha_i \partial \beta_j} = x_{ik} x_{ij} \eta_i (1 - p_i) F_i,
\]

\[
A''_{ik} = \frac{\partial^2 A_i}{\partial \beta_k \partial \beta_k} = x_{ik} x_{ik} \eta_i (1 - p_i) (1 - 2p_i) F_i, \quad A''_{ir} = \frac{\partial^2 A_i}{\partial \alpha_i \partial \gamma_r} = z_{ij} \eta_i p_i F''_{ir},
\]

\[
A''_{ik} = \frac{\partial^2 A_i}{\partial \beta_j \partial \gamma_r} = x_{ik} \eta_i (1 - p_i) F'_{ir}, \quad A''_{rr} = \frac{\partial^2 A_i}{\partial \gamma_r \partial \gamma_r} = \eta_i p_i F''_{rr};
\]
\[
B'_{ij} = \frac{\partial B_i}{\partial \alpha_j} = \frac{z_j p_i F_i}{\eta_i e^{B_i}}, \quad B'_{i,k} = \frac{\partial B_i}{\partial \beta_k} = -\frac{x_k p_i (1 - p_i)}{e^{B_i}} \left[ F_i + \frac{f_i}{\eta_i} \right],
\]

\[
B'_{i,r} = \frac{\partial B_i}{\partial \gamma_r} = -e^{-B_i} \left[ p_i F_{i,r} + \frac{p_i f_{i,r}}{\eta_i} \right], \quad B''_{ij} = \frac{\partial^2 B_i}{\partial \alpha_j \partial \alpha_f} = -z_j z_{ij} \frac{p_i F_{i,f} (1 - p_i)}{\eta_i e^{2B_i}},
\]

\[
B''_{i,k} = \frac{\partial^2 B_i}{\partial \beta_k \partial \beta_f} = \frac{-x_k x_{ik} p_i (1 - p_i) (1 - p_i - e^{B_i})}{e^{2B_i}} \left[ F_i + \frac{f_i}{\eta_i} \right],
\]

\[
B''_{i,jr} = \frac{\partial^2 B_i}{\partial \beta_j \partial \gamma_r} = -x_k p_i (1 - p_i) \left( F_{i,r} + \frac{f_{i,r}}{\eta_i} \right) - x_k p_i (1 - p_i) \left[ F_i + \frac{f_i}{\eta_i} \right] p_i F_{i,r} + \frac{f_{i,r}}{\eta_i},
\]

\[
B''_{i,kr} = \frac{\partial^2 B_i}{\partial \gamma_r \partial \gamma_r'} = -p_i \left[ F'_{i,rr'} + \frac{f'_{i,rr'}}{\eta_i} \right] - p_i \left[ F'_{i,r} + \frac{f'_{i,r}}{\eta_i} \right] \left[ F'_{i,r} + \frac{f'_{i,r}}{\eta_i} \right] e^{2B_i},
\]

\[
C_{ij} = \frac{\partial C_i}{\partial \alpha_j} = \frac{z_j p_i (1 - p_i)}{e^{-\eta_i p_i (1 - F_i)}}, \quad C_{i,k} = \frac{\partial C_i}{\partial \beta_k} = \frac{x_k p_i (1 - p_i)}{e^{-\eta_i p_i (1 - F_i)}},
\]

\[
C_{i,r} = \frac{\partial C_i}{\partial \gamma_r} = -\frac{\eta_i p_i F_{i,r}}{e^{-\eta_i p_i (1 - F_i)}},
\]

\[
C'_{ij} = \frac{\partial^2 C_i}{\partial \alpha_j \partial \alpha_f} = \frac{z_j z_{ij} \eta_i p_i (1 - F_i)}{e^{-\eta_i p_i (1 - F_i)} \eta_i p_i (1 - F_i) - 1},
\]

\[
C'_{i,jk} = \frac{\partial^2 C_i}{\partial \alpha_j \partial \beta_f} = \frac{x_k z_{ij} \eta_i p_i (1 - p_i) (1 - F_i)}{e^{-\eta_i p_i (1 - F_i)} \eta_i p_i (1 - F_i) - 1},
\]

\[
C'_{i,kk} = \frac{\partial^2 C_i}{\partial \beta_k \partial \beta_f} = \frac{x_k \eta_i p_i (1 - p_i) (1 - F_i) e^{\eta_i p_i (1 - F_i)}}{[1 - 2 p_i + \eta_i p_i (1 - p_i) (1 - F_i)]^{-1}},
\]

\[
C'_{i,jr} = \frac{\partial^2 C_i}{\partial \alpha_j \partial \gamma_r} = \frac{-z_j \eta_i p_i F_{i,r}}{e^{-\eta_i p_i (1 - F_i)} \eta_i p_i (1 - F_i) - 1},
\]

\[
C'_{i,kr} = \frac{\partial^2 C_i}{\partial \beta_j \partial \gamma_r} = \frac{-x_k \eta_i p_i (1 - p_i) F_{i,r}}{e^{-\eta_i p_i (1 - F_i)} \eta_i p_i (1 - F_i) - 1},
\]

\[
C'_{i,rr} = \frac{\partial^2 C_i}{\partial \gamma_r \partial \gamma_r'} = -\frac{\eta_i p_i \left( F'_{i,rr'} - \eta_i p_i F_{i,r}' F_{i,rr'} \right)}{e^{-\eta_i p_i (1 - F_i)}},
\]

\[
D'_{ij} = \frac{\partial D_i}{\partial \alpha_j} = 0, \quad D'_{i,k} = \frac{\partial D_i}{\partial \beta_k} = \frac{x_k p_i (1 - F_i)}{1 - p_i}, \quad D'_{i,r} = \frac{\partial D_i}{\partial \gamma_r} = -\frac{p_i F_{i,r}}{1 - p_i},
\]

\[
D''_{ij} = \frac{\partial^2 D_i}{\partial \alpha_j \partial \alpha_f} = 0, \quad D''_{i,jk} = \frac{\partial^2 D_i}{\partial \alpha_j \partial \beta_f} = 0, \quad D''_{i,kk} = \frac{\partial^2 D_i}{\partial \beta_k \partial \beta_f} = 0,
\]
\[D_{i,j}'' = \frac{\partial^2 D_i}{\partial \xi \partial \gamma_r} = x_{ik} x_{ik'} p_{i1} (1 - F_i) \quad 1 - p_i, \quad D_{i,k}'' = \frac{\partial^2 D_i}{\partial \beta_j \partial \gamma_r} = -x_{ik} p_{i'1} F_{i,r'}, \quad D_{i,r}'' = \frac{\partial^2 D_i}{\partial \gamma_r \partial \gamma_{r'}} = -p_{i'1} F_{i,r'} \]

for \(i = 1, \ldots, m; j, j' = 1, \ldots, q_2; k, k' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; 1, 1', \ldots, q_3; m, m' = 1, \ldots, q_2; m, m' = 1, \ldots, q_2 \text{ and } x_{i0} \equiv 1.

Therefore,

\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \alpha_j} = \sum_{\Delta_1} z_{ij} - \sum_{\Delta_1} A'_{ij} + \sum_{\Delta_1} B'_{ij} - \sum_{\Delta_0} z_{ij} \eta_i p_i + \sum_{\Delta_0} \xi_i^{(a)} \frac{C'_{ij} D_i}{C_i D_i - 1},
\]

\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_r} = \sum_{\Delta_1} \frac{\partial \log f_i}{\partial \gamma_r} - \sum_{\Delta_1} A'_{i,j} + \sum_{\Delta_1} B'_{i,j} + \sum_{\Delta_0} \xi_i^{(a)} \frac{C'_{i,j} D_i + D'_{i,j} C_i}{C_i D_i - 1},
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \alpha_j} = -\sum_{\Delta_1} A''_{i,j} + \sum_{\Delta_1} B''_{i,j} - \sum_{\Delta_0} z_{ij} z_{ij} \eta_i p_i 
+ \sum_{\Delta_0} \xi_i^{(a)} D_i \left[ \frac{D_i (C_i C''_{i,j} - C''_{j,i}) - C''_{i,j}}{(C_i D_i - 1)^2} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \beta_k} = -\sum_{\Delta_1} A''_{i,j,k} + \sum_{\Delta_1} B''_{i,j,k} + \sum_{\Delta_0} \xi_i^{(a)} D_i \left[ \frac{D_i (C_i C''_{i,j,k} - C''_{j,i,k}) - C''_{i,j,k}}{(C_i D_i - 1)^2} \right],
\]

\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \beta_k} = -\sum_{\Delta_1} x_{ik} x_{ik'} p_{i1} (1 - p_i) - \sum_{\Delta_1} A''_{i,k,k'} + \sum_{\Delta_1} B''_{i,k,k'} + \sum_{\Delta_0} x_{ik} x_{ik'} p_{i1} (1 - p_i) 
- \sum_{\Delta_1} x_{ik} x_{ik'} \eta_i p_i (1 - 2p_i) 
- \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{[C_i D''_{i,k,k'} + D_i C''_{i,k,k'} + C''_{i,k} D'_{i,k} + C'_{i,k} D'_{i,k}]}{(C_i D_i - 1)^2} \right] 
+ \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{D_i^2 [C_i C''_{i,k,k'} - C''_{i,k} C'_{i,k}] + C_i^2 [D_i D''_{i,k,k'} - D'_{i,k} D'_{i,k}]}{(C_i D_i - 1)^2} \right].
\]
\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \beta_k \partial \gamma_k} = -\sum_{\Delta_1} (A''_{i,k} - B''_{i,k}) - \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{[C_iD''_{i,k} + D_iC''_{i,k} + C'_{i,k}D''_{i,r} + C'_{i,r}D''_{i,k}]}{(C_iD_i - 1)^2} \right] \\
+ \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{D''_i(C_iC''_{i,k} - C'_{i,k}C'_{i,r}) + C''_i(D_iD''_{i,k} - D'_{i,r}D''_{i,k})}{(C_iD_i - 1)^2} \right],
\]

and
\[
\frac{\partial^2 Q(\theta^*, \xi^{(a)})}{\partial \gamma_r \partial \gamma_r'} = \sum_{\Delta_1} \partial^2 \log f_i \\
- \sum_{\Delta_1} A''_{i,r}r' + \sum_{\Delta_1} B''_{i,r}r' - \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{[C_iD''_{i,r} + D_iC''_{i,r} + C'_{i,r}D''_{i,r} + C'_{i,r}D''_{i,r}]}{(C_iD_i - 1)^2} \right] \\
+ \sum_{\Delta_0} \xi_i^{(a)} \left[ \frac{D''_i(C_iC''_{i,r} - C'_{i,r}C'_{i,r}) + C''_i(D_iD''_{i,r} - D'_{i,r}D''_{i,r})}{(C_iD_i - 1)^2} \right].
\]

for \( i = 1, \ldots, m; j, j' = 1, \ldots, q; k, k' = 0, 1, \ldots, q; r, r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; \\
l, l' = 0, 1, \ldots, q_2; m, m' = 1, \ldots, q_1 \) and \( x_{i0} \equiv 1. \)

### C.3. Destructive negative binomial cure model

Let us define the following quantities:
\[
G'_{i,j} = \frac{\partial G_i}{\partial \gamma_j} = \frac{z_{ij}E_i(F_i - 1)}{(1 + E_i)^2}, \quad G'_{i,k} = \frac{\partial G_i}{\partial \beta_k} = \frac{x_{ik}E_i(1 - p_i)(F_i - 1)}{(1 + E_i)^2}, \quad G'_{i,r} = \frac{\partial G_i}{\partial \gamma_r} = \frac{E_iF'_i}{(1 + E_i)}, \quad G''_{i,k} = \frac{\partial^2 G_i}{\partial \beta_k \partial \beta_k} = \frac{x_{ik}x_{ik}E_i(1 - p_i)^2(1 - E_i)(F_i - 1)}{(1 + E_i)^3}, \quad G''_{i,r} = \frac{\partial^2 G_i}{\partial \gamma_r \partial \gamma_r} = \frac{x_{ir}F'_i}{(1 + E_i)^2}, \quad G''_{i,rr} = \frac{\partial^2 G_i}{\partial \gamma_r \partial \gamma_r} = \frac{x_{ir}F''_i}{(1 + E_i)^2},
\]

\[
G''_{i,rr} = \frac{\partial^2 G_i}{\partial \gamma_r \partial \gamma_r} = \frac{x_{ir}F''_i}{(1 + E_i)^2}, \quad \text{and} \quad G''_{i,rr} = \frac{\partial^2 G_i}{\partial \gamma_r \partial \gamma_r} = \frac{x_{ir}F''_i}{(1 + E_i)^2}.
\]

where \( i = 1, \ldots, n; j, j' = 1, \ldots, q; k, k' = 0, 1, \ldots, q; r, r' = 0, 1, 20, 21, \ldots, 2q_2, 31, 32, \ldots, 3q_1; l, l' = 0, 1, \ldots, q_2; m, m' = 1, \ldots, q_1 \) and \( x_{i0} = 1. \)

Therefore,
\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \alpha_j} = \sum_{\Delta_1} z_{ij} - \frac{1}{\phi} + 1 \sum_{\Delta_1} z_{ij} - \frac{1}{\phi} \sum_{\Delta_0} z_{ij} \frac{E_iF_i}{1 + E_iF_i} - \frac{1}{\phi} \sum_{\Delta_0} \xi_i^{(a)} \frac{G'_{ij}}{\phi G_i(G'^{1/\phi} - 1)},
\]

\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \beta_k} = \sum_{\Delta_1} x_{ik}(1 - p_i) - \frac{1}{\phi} \sum_{\Delta_1} x_{ik} \frac{E_iF_i(1 - p_i)}{1 + E_iF_i} - \frac{1}{\phi} \sum_{\Delta_0} x_{ik} \frac{E_i(1 - p_i)}{1 + E_i} + \sum_{\Delta_0} \xi_i^{(a)} \frac{G'_{ik}}{\phi G_i(G'^{1/\phi} - 1)},
\]

\[
\frac{\partial Q(\theta^*, \xi^{(a)})}{\partial \gamma_r} = -\left( \frac{1}{\phi} + 1 \right) \sum_{\Delta_1} \frac{E_iF'_i}{1 + E_iF_i} + \sum_{\Delta_1} \frac{\partial \log f_i}{\partial \gamma_r} + \sum_{\Delta_0} \xi_i^{(a)} \frac{G'_{i,r}}{\phi G_i(G'^{1/\phi} - 1)},
\]
\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \alpha'_j} = -\left(1 + \frac{1}{\phi} + 1\right) \sum_{\Delta_1} z_{ij} E_i F_{i,r} \frac{z_{ij} E_i (1 + F_i)}{(1 + E_i)^2} - \frac{1}{\phi} \sum_{\Delta_0} z_{ij} E_i (1 + E_i)^2
\]
\[
+ \sum_{\Delta_0} \xi^{(a)}_i \left[ \frac{G''_{ij} G_i (G_i^{1/\phi} - 1) - G'_{ij} G'_{i,r} \{ (1/\phi + 1) G_i^{1/\phi} - 1 \}}{\phi \left( G_i^{1/\phi+1} - 1 \right)^2} \right],
\]
\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \beta_k} = -\left(1 + \frac{1}{\phi} + 1\right) \sum_{\Delta_1} z_{ij} E_i F_{i,r} (1 - p_i)(1 - 2p_i - E_i F_i p_i) \frac{z_{ij} E_i (1 + F_i)}{(1 + E_i)^2} - \frac{1}{\phi} \sum_{\Delta_0} z_{ij} E_i (1 + E_i)^2
\]
\[
+ \sum_{\Delta_0} \xi^{(a)}_i \left[ \frac{G''_{ij} G_i (G_i^{1/\phi} - 1) - G'_{ij} G'_{i,k} \{ (1/\phi + 1) G_i^{1/\phi} - 1 \}}{\phi \left( G_i^{1/\phi+1} - 1 \right)^2} \right],
\]
\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \alpha_j \partial \gamma_r} = -\left(1 + \frac{1}{\phi} + 1\right) \sum_{\Delta_1} z_{ij} E_i F_{i,r} \frac{z_{ij} E_i (1 + F_i)}{(1 + E_i)^2}
\]
\[
+ \sum_{\Delta_0} \xi^{(a)}_i \left[ \frac{G''_{ij} G_i (G_i^{1/\phi} - 1) - G'_{ij} G'_{i,r} \{ (1/\phi + 1) G_i^{1/\phi} - 1 \}}{\phi \left( G_i^{1/\phi+1} - 1 \right)^2} \right],
\]
and
\[
\frac{\partial^2 Q (\theta^*, \xi^{(a)})}{\partial \gamma_r \partial \gamma_{r'}} = -\left(1 + \frac{1}{\phi} + 1\right) \sum_{\Delta_1} E_i F_{i,r} E_i F_{i,r'} \frac{E_i F_{i,r} E_i F_{i,r'}}{(1 + E_i)^2} + \sum_{\Delta_1} \frac{\partial^2 \log f_i}{\partial \gamma_r \partial \gamma_{r'}}
\]
\[
+ \sum_{\Delta_0} \xi^{(a)}_i \left[ \frac{G''_{i,r} G_i (G_i^{1/\phi} - 1) - G'_{i,r} G'_{i,r'} \{ (1/\phi + 1) G_i^{1/\phi} - 1 \}}{\phi \left( G_i^{1/\phi+1} - 1 \right)^2} \right].
\]