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ABSTRACT
We propose a cure rate survival model by assuming that the number of competing causes of the event of interest follows the negative binomial distribution and the time to the event of interest has the Birnbaum-Saunders distribution. Further, the new model includes as special cases some well-known cure rate models published recently. We consider a frequentist analysis for parameter estimation of the negative binomial Birnbaum-Saunders model with cure rate. Then, we derive the appropriate matrices for assessing local influence on the parameter estimates under different perturbation schemes. We illustrate the usefulness of the proposed model in the analysis of a real data set from the medical area.

1. Introduction

The Birnbaum-Saunders's (1969) (BS) distribution is a positively skewed model with nonnegative support that has received considerable attention in the last two decades. This is primarily due to its derivation that is based on physical consideration, its attractive properties, its close relationship with the normal distribution and its applicability in a wide variety of fields. For details about various applications of the BS distribution, including in the medical area, see Johnson et al. (1995), Balakrishnan et al. (2007), Leiva et al. (2008a), and Cancho et al. (2010). The BS survival function (for $t > 0$) is given by

$$S_{BS}(t) = \Phi \left[-\frac{1}{\alpha} \left(\sqrt{\frac{t}{\lambda}} - \sqrt{\frac{\lambda}{t}} \right) \right], \tag{1}$$

where $\Phi(\cdot)$ is the standard normal cumulative function and $\alpha > 0$ and $\lambda > 0$ are shape and scale parameters, respectively. The cumulative distribution function (cdf) and probability density function (pdf) of the BS distribution are easily obtained from (1) as

$$F_{BS}(t) = 1 - S_{BS}(t) = \Phi \left[\frac{1}{\alpha} \left(\sqrt{\frac{t}{\lambda}} - \sqrt{\frac{\lambda}{t}} \right) \right] \tag{2}$$

and

$$f_{BS}(t) = \frac{t^{-3/2}\,(t+\lambda)}{2\alpha\,\sqrt{2\pi\lambda}}\,\exp\left[-\frac{1}{2\alpha^2}\left(\frac{t}{\lambda}+\frac{\lambda}{t}-2\right)\right], \tag{3}$$

respectively. The parameter λ is the median of the distribution: $F_{BS}(\lambda) = \Phi(0) = 1/2$. The mean and the variance of the BS distribution are

$$\mathrm{E}(T) = \lambda\left(1+\frac{\alpha^2}{2}\right) \quad \text{and} \quad \mathrm{Var}(T) = \alpha^2\,\lambda^2\left(\frac{5}{4}\alpha^2+1\right).$$

Some proposals have been made recently in the literature by replacing the relationship between the BS and normal distributions by more general classes of distributions. For example, Dáaz-Garcáa and Leiva-Sánchez (2005) pioneered the generalized Birnbaum-Saunders (GBS) distribution by considering the elliptical family of distributions. The main motivation for using the GBS distribution is to make the kurtosis flexible compared to the BS model. Sanhueza et al. (2008) presented a complete compilation of the results related to the GBS distribution, Gómez et al. (2009) introduced an extension of the GBS model based on the slash-elliptical distributions and Cancho et al. (2010) proposed a Bayesian approach for log-Birnbaum-Saunders Student-t regression model under right-censored survival data. Further, Cordeiro and Lemonte (2011) defined the β-Birnbaum-Saunders distribution for fatigue life modeling, Cancho et al. (2011) introduced the geometric cure rate model for analyzing survival data with cure fraction and Ortega et al. (2012) proposed a new log-β-Birnbaum-Saunders regression model that can be applied to censored data and be used more effectively in survival analysis.

Cure rate models for survival data (also called "lifetime models with a surviving fraction" or "long-term survival models") are often used to model cure proportions of subjects who may not remain susceptible to the event of interest. These models have become very popular due to significant progress and advancements in treatment therapies leading to enhanced cure rates. The proportion of these "cured" units is termed the cure fraction. In clinical studies, the event of interest can be the death of a patient (which can happen due to different competing causes) or a tumor recurrence (which can be attributed to metastasis-component tumor cells left active after an initial treatment).

Models to accommodate a cure fraction have been widely developed. Perhaps the most popular type of cure rate model is the mixture distribution introduced by Boag (1949) and Berkson and Gage (1952). Further, mixture models are based on the assumption that only a cause is responsible for the occurrence of the event of interest. However, in clinical studies, the patient's death, which is the event of interest, may happen due to different latent competing causes, in the sense that there is no information about which cause was responsible for the individual death. A tumor recurrence can be attributed to metastasis-component tumor cells left active after initial treatment. A metastasis-component tumor cell is a tumor cell with potential to metastasize (Yakovlev and Tsodikov, 1996). The literature on distributions which accommodates different latent competing causes is rich and growing rapidly. The book by Ibrahim et al. (2001) and the works by Cooner et al. (2007), Ortega et al. (2008, 2009), and Cancho et al. (2009) can be mentioned as key references. Recently, Louzada-Neto et al. (2013) proposed the FGM long-term bivariate survival copula model, Cancho et al. (2013a) studied the power series cure rate model with an application to a cutaneous melanoma data, Cancho et al. (2013b) presented the destructive negative binomial cure rate model with a latent activation scheme and Fachini et al. (2014) introduced a location-scale model for bivariate

survival times based on the copula to model the dependence of bivariate survival data with cure fraction.

In this context, we propose a new model called the *negative binomial Birnbaum-Saunders* (NBBS) *cure rate model*, conceived inside a latent competing causes scenario with cure fraction, where there is no information about which cause was responsible for the individual death or tumor recurrence, but only the minimum lifetime value among all risks is observed and a part of the population is not susceptible to the event of interest. As point out by Cancho et al. (2012), in many medical problems, such as chronic cardiac diseases and various different types of cancer, accumulative individual damage may be caused by various unknown causes or risk factors. This degradation leads to a fatigue process, whose propagation lifetimes can be suitably modeled by the BS distribution. For the assessment of model adequacy, we develop diagnostic studies to detect possible influential or extreme observations that can cause distortions on the results of the analysis through the local influence approach, where we investigate how the results of the estimation are changed under small perturbations in the model or data.

Cook (1986) proposed a general framework to detect the influence of the observations to indicate how sensitive the analysis is when small perturbations in the data or model occur. Several authors have applied the local influence methodology in regression analysis with censoring. Silva et al. (2008) investigated local influence in log-Burr XII regression models with censored data and Fachini et al. (2008) adapted local influence methods to polyhazard models under the presence of covariates. Cancho et al. (2009) derived curvature calculations under various perturbation schemes in log-exponentiated Weibull regression models with cure rate and Hashimoto et al. (2010) determined the appropriate matrices for assessing local influences on the parameter estimates under different perturbation schemes in the log-exponentiated Weibull regression model for interval-censored data. Here, we propose a similar methodology to detect influential subjects on the NBBS cure rate model.

The plan of this article is as follows. In Sec. 2, we address the model formulation. The inference on the parameters is discussed in Sec. 3. In Sec. 4, we obtain the normal curvatures of local influence under some usual perturbations. In Sec. 5, we evaluate the performance of the parameter estimation procedure for the proposed model using Monte Carlo simulation. An applications to a real data set is performed in Sec. 6. Section 7 provides some conclusions.

2. Model formulation

Let M be the unobservable number of causes of the event of interest for an individual in the population. We assume that M follows a negative binomial (NB) distribution with parameters θ and η (Piegorsch, 1990; de Castro et al., 2010) and probability mass function

$$P[M = m; \theta, \eta] = \frac{\Gamma(\eta^{-1} + m)}{\Gamma(\eta^{-1})m!} \left(\frac{\eta\theta}{1 + \eta\theta}\right)^m (1 + \eta\theta)^{-1/\eta}, \ m = 0, 1, 2, \ldots, \quad (4)$$

where $\theta > 0$, $\eta \geq -1$ and $\eta\theta + 1 > 0$. Negative values of $-1 \leq \eta < 0$ lead to a range for m from 0 to the largest integer less than η^{-1} (Ross and Preece, 1985). Since

$$\mathrm{E}(M) = \theta \quad \text{and} \quad \mathrm{var}(M) = \theta + \eta\theta^2, \quad (5)$$

the values of $\eta > 0 \, (< 0)$ correspond to over (under)-dispersion relative to the Poisson distribution. The time for the jth cause to produce the event of interest is denoted by Z_j, $j = 1, \ldots, M$.

Accordingly, conditional on M, we assume that the Z_j's are i.i.d. random variables having the BS distribution (2) which can represent the times for the occurrence of the event of interest due to some causes or risk factors. Further, these events happen due to the cumulative individual damage caused by various unknown causes or risk factors leading to the main motivation for adopting the BS model. Further, we consider that $Z_1, Z_2, \ldots$ are independent of M. The observable time to the event of interest is defined by the random variable $T = \min\{Z_1, \ldots, Z_M\}$, and $T = \infty$ if $M = 0$ with $P(T = \infty|M = 0) = 1$. Under this setup, the survival function (which is not a proper survival function) for the entire population is

$$
\begin{aligned}
S_{\text{pop}}(t) &= P(M = 0) + P(Z_1 > t, \ldots, Z_M > t|M \geq 1) \\
&= \sum_{m=1}^{\infty} [S_{BS}(t)]^m \, P[M = m; \theta, \eta] \\
&= [1 + \eta \, \theta \, F_{BS}(t)]^{-1/\eta}.
\end{aligned}
\tag{6}
$$

The last step comes from the definition of the probability generating function (Tsodikov et al., 2003). The cured fraction is $p_0 = (1 + \eta\theta)^{-1/\eta}$ and the corresponding density function becomes

$$
f_{\text{pop}}(t) = \theta \, f_{BS}(t) \, [1 + \eta \, \theta \, F_{BS}(t)]^{-1/\eta-1},
\tag{7}
$$

whereas the hazard function for the population reduces to

$$
h_{\text{pop}}(t) = \theta \, f_{BS}(t) \, [1 + \eta \, \theta \, F_{BS}(t)]^{-1}.
\tag{8}
$$

We note that $f_{\text{pop}}(t)$ and $h_{\text{pop}}(t)$ are improper functions, since $S_{\text{pop}}(t)$ is not a proper survival function. When $\eta \to 0$, the NBBS cure rate (NBBScr) model approaches the Poisson Birnbaum-Saunders (PBS) cure rate model, whereas for $\eta = -1$, it is a mixture BS cure rate model. For $\eta = 1$, the NBBScr reduces to the GBS cure rate model (Cancho et al., 2011).

The (proper) surviving function for the non-cured population (or NBBS survival function), say S_{NBBS}, is given by

$$
S_{\text{NBBS}}(t) = \frac{[1 + \theta\eta F_{BS}(t)]^{-1/\eta} - (1 + \theta\eta)^{-1/\eta}}{1 - (1 + \theta\eta)^{-1/\eta}}, \quad t > 0.
\tag{9}
$$

We note that $S_{\text{NBBS}}(0) = 1$ and $S_{\text{NBBS}}(\infty) = 0$, so that it is a proper survival function. The pdf for the non-cured population (or the NBBS density function) is given by

$$
f_{\text{NBBS}}(t) = \frac{\theta \, f_{BS}(t) \, [1 + \theta\eta F_{BS}(t)]^{-(1/\eta+1)}}{1 - (1 + \theta\eta)^{-1/\eta}}, \quad t > 0
\tag{10}
$$

From Eq. (10), we note that the parameter λ controls the scale of the distribution, whereas the parameters α, η, and θ control its shape. As $\eta = -1$, the NBBS distribution reduces to the BS distribution. Figure 1 displays the plots of the NBBS density functions for selected values of η and θ. These plots indicate that the NBBS distribution is very flexible and that the values of these parameters have a substantial effect on its skewness and kurtosis.

From Eqs. (9) and (10), the hazard rate function (hrf) for the non-cured population becomes

$$
h_{\text{NBBS}}(t) = \frac{\theta \, f_{BS}(t) \, [1 + \theta\eta F_{BS}(t)]^{-(1/\eta+1)}}{[1 + \theta\eta F_{BS}(t)]^{-1/\eta} - (1 + \theta\eta)^{-1/\eta}}, \quad t > 0.
\tag{11}
$$

For $\eta \to 0$, the NBBS hrf approaches the PBS hrf and, for $\eta = 1$, it reduces to the GBS hrf. Figure 2 displays plots of the NBBS hrf for selected parameter values.
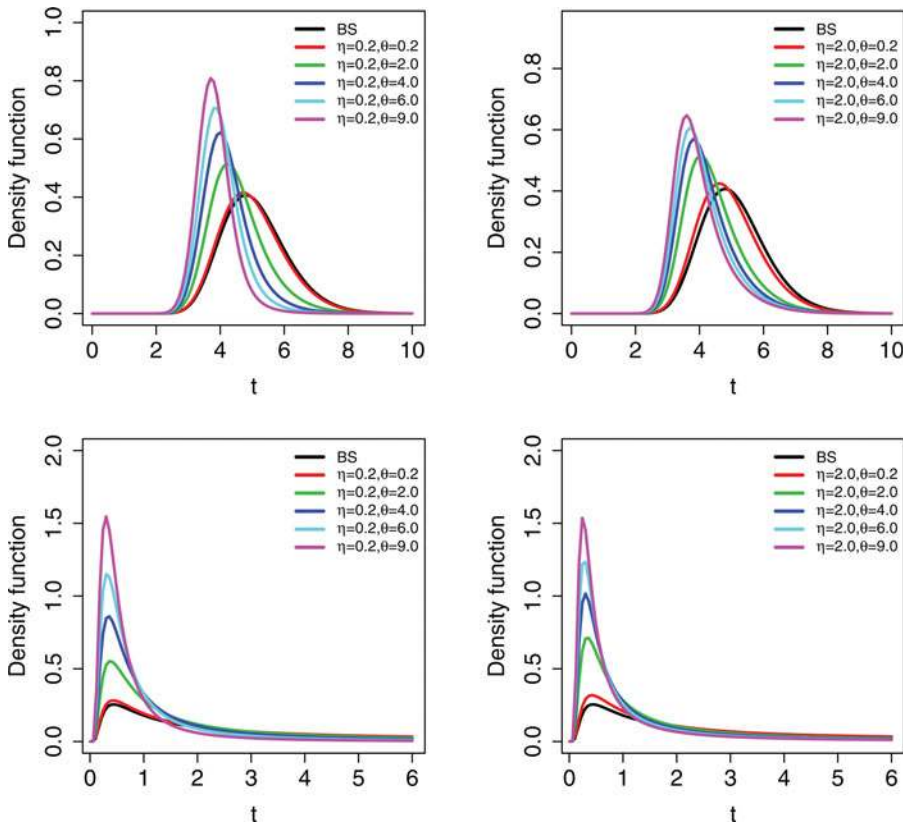
Figure 1. The NBBS density function for some parameters.

There is a mathematical relationship between the model (6) and the mixture cure rate model (Boag, 1949; Berkson and Gage, 1952). We can write

$$S_{\text{pop}}(t) = (1 + \eta\theta)^{-1/\eta} + [1 - (1 + \eta\theta)^{-1/\eta}] S_{\text{NBBS}}(t),$$

where $S_{\text{NBBS}}(t)$ is given by (9). Thus, $S_{\text{pop}}(t)$ is a mixture cure rate model with cure fraction equal to $p_0 = (1 + \eta\theta)^{-1/\eta}$ and survival function $S_{\text{NBBS}}(t)$ for the non-cured population. These facts imply that every mixture cure rate model corresponds to some model of the form (6) for any η, θ, and $F_{\text{BS}}(\cdot)$ (this result holds for any distribution function).

3. Inference

Hereafter, we suppose that the time to the event of interest is not completely observed and may be subject to right censoring. Let C_i denote the censoring time. We observe $Y_i = \min\{T_i, C_i\}$ and $\delta_i = \text{I}(T_i \le C_i)$ is such that $\delta_i = 1$ if T_i is the recurrence time to the event of interest and $\delta_i = 0$ if it is right censored, $i = 1, \ldots, n$. Let γ denote the parameter vector of the BS distribution of the time to event Z in (6). From n pairs of times and censoring indicators $(y_1, \delta_1), \ldots, (y_n, \delta_n)$, the corresponding likelihood function (Cancho et al., 2011) under uninformative censoring can be expressed as

$$L(\gamma, \eta, \theta) \propto \prod_{i=1}^{n} [f_{\text{pop}}(y_i; \gamma, \eta, \theta)]^{\delta_i} [S_{\text{pop}}(y_i; \gamma, \eta, \theta)]^{1-\delta_i}, \tag{12}$$
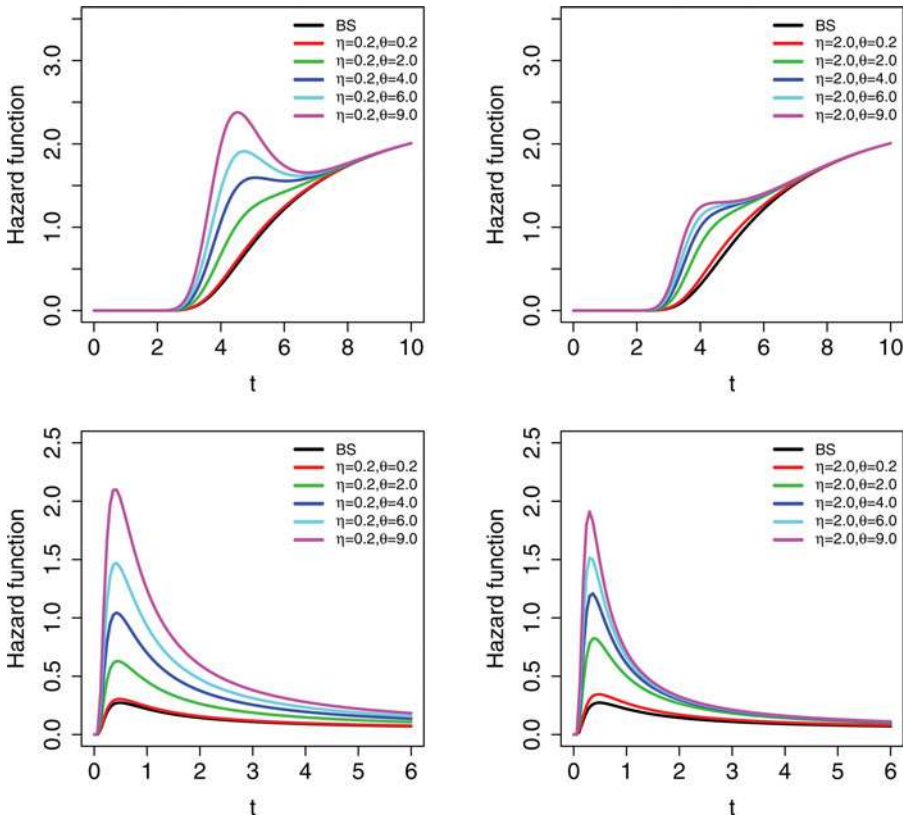
Figure 2. The NBBS hrf. The parameters are fixed at $\theta = 0, 0.1, 0.2, 0.4, 0.6, 0.8$ and $\lambda = 5, \alpha = 0.2$ (left panel), $\alpha = 2$ (right panel).

where $S_{\text{pop}}(y_i; \gamma, \eta, \theta)$ and $f_{\text{pop}}(y_i; \gamma, \eta, \theta)$ are given in Eqs. (6) and (7), respectively, and $\gamma = (\alpha, \lambda)^\top$ is the vector of BS parameters.

Following de Castro et al. (2009) we considered the Fisher's parametrization of the NB distribution (Ross and Preece, 1985), and for $\eta \geq -1$, we define $\theta = (p_0^{-\eta} - 1)/\eta$, if $\eta \neq 0$, and $\theta = -\log(p_0)$, if $\eta = 0$. We incorporate covariates for the parametric cure rate model (6) through the cure parameter p_0. When covariates are included, we have a different cure rate parameter p_{0i} for each subject, $i = 1, \ldots, n$. The cure fraction to covariates x_i is modeled by the logistic link, i.e.,

$$\log\left(\frac{p_{0i}}{1 - p_{0i}}\right) = x_i^\top \boldsymbol{\beta} \quad \text{or} \quad p_{0i} = \frac{\exp(x_i^\top \boldsymbol{\beta})}{1 + \exp(x_i^\top \boldsymbol{\beta})}, \tag{13}$$

$i = 1, \ldots, n$, where $\boldsymbol{\beta}$ stands for the vector of regression coefficients.

From Eq. (5), $\text{var}(M_i) = \text{E}(M_i) \, p_{0i}^{-\eta}$. Thus, extra variability in the number of competing causes due to omitted covariates is governed by the dispersion parameter η. Under this relation, the improper functions in (6) and (7) can be expressed as

$$S_{\text{pop}}(y_i; \gamma, \boldsymbol{\beta}, \eta) = \begin{cases} [1 + (p_{0i}^{-\eta} - 1) \, F_{BS}(y_i; \gamma)]^{-1/\eta}, & \text{if } \eta \neq 0; \\ p_{0i}^{F_{BS}(y_i; \gamma)}, & \text{if } \eta = 0, \end{cases} \tag{14}$$

and

$$f_{\text{pop}}(y_i; \gamma, \boldsymbol{\beta}, \eta) = \begin{cases} [1 + (p_{0i}^{-\eta} - 1)F_{BS}(y_i; \gamma)]^{-1/\eta-1} \left(\frac{p_{0i}^{-\eta}-1}{\eta} \right) f_{BS}(y_i; \gamma), & \text{if } \eta \neq 0; \\ -\log(p_{0i}) \, p_{0i}^{F_{BS}(y_i;\gamma)} \, f_{BS}(y_i; \gamma), & \text{if } \eta = 0. \end{cases}$$

(15)

Based on the NB distribution with $\eta \geq -1$, and using (13), (14) and (15), the likelihood function (12) becomes

$$L(\boldsymbol{\vartheta}; \mathcal{D}) \propto \begin{cases} \prod_{i=1}^{n} \left[\left(\frac{p_{0i}^{-\eta}-1}{\eta} \right) f_{BS}(y_i; \gamma) \right]^{\delta_i} \left[1 + (p_{0i}^{-\eta} - 1)F_{BS}(y_i; \gamma) \right]^{-\delta_i - 1/\eta}, & \text{if } \eta \neq 0; \\ \prod_{i=1}^{n} \left[-\log(p_{0i}) f_{BS}(y_i; \gamma) \right]^{\delta_i} p_{0i}^{F_{BS}(y_i;\gamma)}, & \text{if } \eta = 0, \end{cases}$$

(16)

where $\boldsymbol{\vartheta} = (\boldsymbol{\gamma}^\top, \boldsymbol{\beta}^\top, \eta)^\top$, $\mathcal{D} = (n, \boldsymbol{y}, \boldsymbol{\delta}, \boldsymbol{X})$ and $\boldsymbol{X} = (\boldsymbol{x}_1^\top, \dots, \boldsymbol{x}_n^\top)$.

The parameter $\boldsymbol{\vartheta}$ is estimated by numerical maximization of the log-likelihood function $\ell(\boldsymbol{\vartheta}; \mathcal{D}) = \log[L(\boldsymbol{\vartheta}; \mathcal{D})]$ obtained from (16) using the R software (de Castro et al., 2010). The computational program is available from the authors upon request. Under suitable regularity conditions, the maximum likelihood estimator (MLE) $\widehat{\boldsymbol{\vartheta}}$ can be approximated by the multivariate normal distribution with mean vector $\boldsymbol{\vartheta}$ and covariance matrix $\boldsymbol{\Sigma}(\widehat{\boldsymbol{\vartheta}})$ estimated at $\boldsymbol{\vartheta} = \widehat{\boldsymbol{\vartheta}}$, namely

$$\boldsymbol{\Sigma}(\boldsymbol{\vartheta}) = \left[-\frac{\partial^2 \ell(\boldsymbol{\vartheta}; \mathcal{D})}{\partial \boldsymbol{\vartheta} \partial \boldsymbol{\vartheta}^\top} \right]^{-1}.$$

The required second derivatives can be computed numerically.

Besides estimation, hypothesis tests are another important topic to be addressed. Let $\boldsymbol{\vartheta}_1$ and $\boldsymbol{\vartheta}_2$ be proper disjoint subsets of $\boldsymbol{\vartheta}$. We aim to test $H_0 : \boldsymbol{\vartheta}_1 = \boldsymbol{\vartheta}_{01}$ against $H_1 : \boldsymbol{\vartheta}_1 \neq \boldsymbol{\vartheta}_{01}$, $\boldsymbol{\vartheta}_2$ unspecified. Let $\hat{\boldsymbol{\vartheta}}_0$ maximize $L(\boldsymbol{\vartheta}; \mathcal{D})$ constrained to H_0 and define the likelihood ratio (LR) statistic

$$w = 2 \log \left[\frac{L(\hat{\boldsymbol{\vartheta}}; \mathcal{D})}{L(\hat{\boldsymbol{\vartheta}}_0; \mathcal{D})} \right].$$

Under H_0 and some regularity conditions, w converges in distribution to the chi-square distribution with $\dim(\boldsymbol{\vartheta}_1)$ degrees of freedom.

4. Diagnostic analysis

In order to assess the sensitivity of the MLEs, the local influence under three perturbation schemes are carried out. Another approach is suggested by Cook (1986), where instead of removing observations, weights are given to them. Local influence calculation can be carried out for model (9) and (10). If likelihood displacement $LD(\boldsymbol{\omega}) = 2\{l(\hat{\boldsymbol{\vartheta}}) - l(\hat{\boldsymbol{\vartheta}}_{\boldsymbol{\omega}})\}$ is used, where $\hat{\boldsymbol{\vartheta}}_{\boldsymbol{\omega}}$ denotes the MLE under the perturbed model, the normal curvature for $\boldsymbol{\vartheta}$ at the direction $\mathbf{d}$, $\| \mathbf{d} \| = 1$, is given by $C_{\mathbf{d}}(\boldsymbol{\vartheta}) = 2|\mathbf{d}^\top \boldsymbol{\Delta}^\top [\ddot{\mathbf{L}}(\boldsymbol{\vartheta})]^{-1} \boldsymbol{\Delta} \mathbf{d}|$, where $\boldsymbol{\Delta}$ is a $(p + 3) \times n$ matrix that depends on the perturbation scheme, whose elements are given by $\Delta_{vi} = \partial^2 l(\boldsymbol{\vartheta}|\boldsymbol{\omega})/\partial \phi_v \partial \omega_i$, $i = 1, \dots, n$ and $v = 1, \dots, p + 3$, evaluated at $\hat{\boldsymbol{\vartheta}}$ and $\boldsymbol{\omega}_0$, where $\boldsymbol{\omega}_0$ is the no perturbation vector. The elements of the matrix $\boldsymbol{\Delta}$ are derived in the Appendix for some common perturbation schemes. For the NBBS regression model with long term survivors, the elements of $\ddot{\mathbf{L}}(\boldsymbol{\vartheta})$ are calculated numerically. We can also determine the normal curvatures $C_{\mathbf{d}}(\boldsymbol{\gamma})$, $C_{\mathbf{d}}(\boldsymbol{\beta})$, and $C_{\mathbf{d}}(\eta)$ to perform various index plots, for instance, the

Table 1. Averages of the MLEs, SEs, SRMSEs and CP of the cure fractions $p_0^{(0)}$ and $p_0^{(1)}$ for simulated data from the BS cure rate model.

| n	Average of the MLEs		SE of the MLEs		SRMSE		CP
50	0.678	0.438	0.089	0.093	0.101	0.115	0.923
100	0.645	0.402	0.075	0.088	0.098	0.095	0.939
200	0.634	0.400	0.058	0.042	0.053	0.072	0.943
400	0.628	0.389	0.028	0.025	0.035	0.066	0.949
800	0.625	0.399	0.018	0.021	0.029	0.050	0.952

index plot of $\mathbf{d}_{max}$, the eigenvector corresponding to $C_{\mathbf{d}_{max}}$, the largest eigenvalue of the matrix $\mathbf{B} = -\mathbf{\Delta}^\top \left[\ddot{\mathbf{L}}(\boldsymbol{\vartheta}) \right]^{-1} \mathbf{\Delta}$, and the index plots of $C_{\mathbf{d}_i}(\boldsymbol{\gamma})$, $C_{\mathbf{d}_i}(\boldsymbol{\beta})$ and $C_{\mathbf{d}_i}(\eta)$, called the total local influence, where $\mathbf{d}_i$ denotes an $n \times 1$ vector of zeros with one at the ith position. Thus, the curvature at direction $\mathbf{d}_i$ takes the form $C_i = 2|\mathbf{\Delta}_i^\top \left[\ddot{\mathbf{L}}(\boldsymbol{\vartheta}) \right]^{-1} \mathbf{\Delta}_i|$, where $\mathbf{\Delta}_i^\top$ denotes the ith row of $\mathbf{\Delta}$. It is usual to point out those cases such that $C_i \geq 2\bar{C}$, where $\bar{C} = \frac{1}{n} \sum_{i=1}^n C_i$. Another influence measure for the ith observation is $U_i = \sum_{k=1}^{n_1} \kappa_k e_{ki}^2$, where $\{(\kappa_k, \mathbf{e}_k) | k = 1, \ldots, n\}$ are the eigenvalue-eigenvector pairs of $\mathbf{B}$ with $\kappa_1 \geq \cdots \geq \kappa_{n_1} \geq \kappa_{n_1+1} = \cdots = \kappa_n = 0$ and $\{\mathbf{e}_k = (e_{k1}, \ldots, e_{kn})^\top\}$ is the associated orthonormal basis. Zhu and Zhang (2004) studied the influence measure u_i systematically under a case weighted perturbation. Hence, this influence measure expresses local sensitivity to the log-likelihood of the perturbations.

5. Simulation study

To evaluate the performance of the parameter estimation procedure for the proposed models, we conduct a simulation study. Here, we consider the proposed model, where the event times (Z) have the BS distribution with parameters $\alpha = 2$ and $\lambda = 2$. The number of causes for the event of interest for the ith individual (N_i, $i = 1, \ldots, n$) is generated from the NB distribution with parameters $\eta = 2$ and $\theta_i = (p_{0i}^{-\eta} - 1)/\eta$, where $p_{0i} = \exp(\beta_0 + \beta_1 x_i)/[1 + \exp(\beta_0 + \beta_1 x_i)]$. For the simulations, we consider a binary covariate x with values drawn from a Bernoulli distribution with parameter 0.5. We take $\beta_0 = 0.5$ and $\beta_1 = -1$ such that the cure fraction for the two levels of x are $p_0^{(0)} = 0.62$ and $p_0^{(1)} = 0.38$, respectively. For each simulation, we obtain the MLEs of the model parameters.

The censoring times are sampled from the uniform distribution on the interval $(0, \tau)$, where τ was set in order to control the proportion of censored observations. In this study, the proportion of censored observations was on average, approximately, equal to 50%.

The sample sizes are $n = 50, 100, 200, 400$ and $n = 800$. For each set up, we conduct 1,000 simulations and then calculate the averages of the MLEs of the cure fractions ($p_0^{(0)}$ and $p_0^{(1)}$), standard errors (SEs) of the MLEs, the square root of the mean square errors (SRMSEs) of these estimates and coverage probability (CP) of the 95% confidence intervals. The simulation results are displayed in Table 1 from the fits of the NBBScr model. We can observe that the average of the MLEs are closer to the true parameter values of the model, and that the SDs and SRMSEs decrease as the sample size increases. Also, the CP becomes closer to the nominal value as the sample size increases. Further, we examine the distribution of the MLEs of $p_0^{(0)}$ and $p_0^{(1)}$ and plot the empirical distributions of the MLEs of $p_0^{(0)}$ and $p_0^{(1)}$ for sample size 100 (top panel) and 200 (bottom panel). They are displayed in Fig. 3. These plots indicate that the normal distribution provides reasonable approximation to the distribution of the MLEs of $p_0^{(0)}$ and $p_0^{(1)}$.
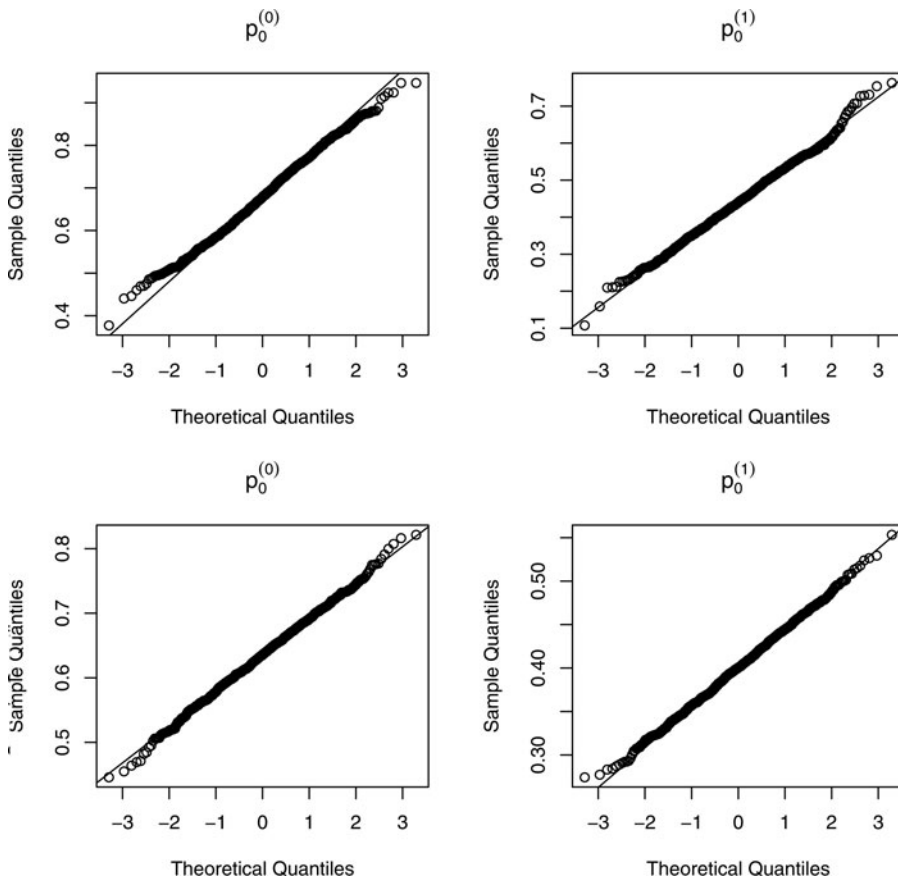
Figure 3. Q-Q plot of the empirical distribution of the MLEs of $p_0^{(0)}$ and $p_0^{(1)}$ against the normal distribution.

6. Application

In this section, we work out an example employing the models presented in Sec. 2. The data set includes 205 patients observed after operation for removal of malignant melanoma in the period 1962–1977. The patients were followed until 1977. These data are available in the timereg package in R (Scheike, 2009). The observed time (T) ranges from 10–5565 days (from 0.0274–15.25 years, with mean = 5.9 and standard deviation = 3.1 years) and refers to the time until the patient's death or the censoring time. Patients dead from other causes and the patients that are still alive at the end of the study are censored observations (72%). The covariates are as follows: ulceration: x_{i1} (absent, $n = 115$; present, $n = 90$), x_{i2}: sex (female, $n = 126$; male, $n = 79$) and tumor thickness (x_{i3}) (in mm, mean = 2.92 and standard deviation=2.96) as covariates. We are interested in the effect of these explanatory variables on the cure fraction. The Kaplan–Meier curves stratified by ulceration status in Fig. 4 (left panel) can not decay below 0.4. This behavior indicates that models that ignore the possibility of cure will not be suitable for these data.

First, we fit the model described in Sec. 2. For comparison of nested models, which is the case when comparing the NBBScr model with the mixture BS cure rate model, we can compute the maximum values of the unrestricted and restricted log-likelihoods to obtain the LR statistics given in (3). For testing $H_0 : \eta = -1$ vs. $H_1 : \eta \neq -1$, we use the LR statistic w taking into account that the test is performed in the boundary of the parameter space (Self and
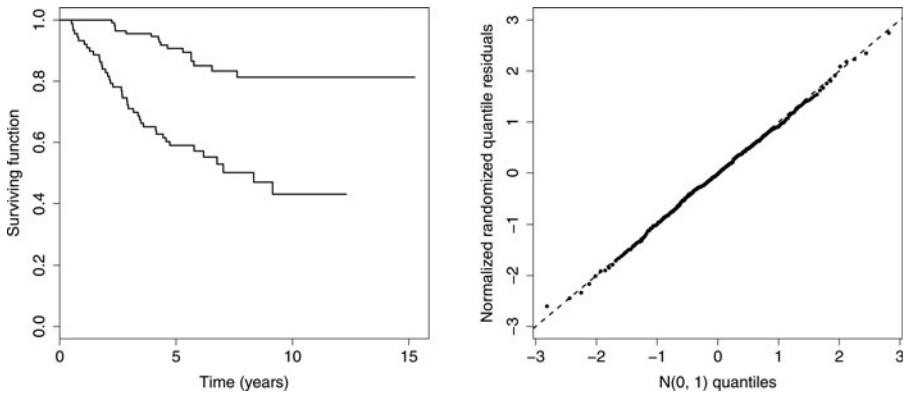
Figure 4. Left panel: The Kaplan-Meier estimate of the survival function stratified by ulceration (upper: present, lower: absent). Right panel: QQ plot of the normalized randomized quantile residuals with identity line for the NBBScr model (each point corresponds to the median of five sets of ordered residuals).

Liang, 1987). The statistic w is assumed to be asymptotically distributed as a symmetric mixture of a chi-squared distribution with one degree of freedom and a point-mass at zero. Then, $\lim_{n\to\infty} P(w \leq c) = 1/2 + 1/2\,P(\chi_1^2 \leq c)$, where $P(\chi_1^2 \leq c)$ denotes a random variable having a chi-square distribution with one degree of freedom. Large positive values of w gives favorable evidence to the full model. Thus, w is equal to 4.008 leading to a p-value < 0.02, which provides evidence in favor of the NBBScr model.

Further, we compare the NBBScr and PBS cure rate models based on the Akaike information criterion (AIC) and Schwartz Bayesian criterion (SBC) given by $AIC = -2\ell(\widehat{\boldsymbol{\vartheta}}; \mathcal{D}) + 2\#(\boldsymbol{\vartheta})$ and $SBC = -2\ell(\widehat{\boldsymbol{\vartheta}}; \mathcal{D}) + \#(\boldsymbol{\vartheta})\log(n)$, respectively, where $\#(\boldsymbol{\vartheta})$ denotes the number of model parameters. The model with the smallest value of any of these criteria (among all competing models) is commonly taken as the preferred model for describing these data. Table 2 gives these statistics in increasing order of AIC. The NBBScr model stands out as the best model and then it is chosen to be our working model.

6.1. *Local influence analysis*

Here, we analyze the local influence for the cutaneous melanoma dataset.

Case-weight perturbation

By applying the local influence methodology described in Sec. 4, where case-weight perturbation is used, the value $C_{\mathbf{d}_{max}}(\boldsymbol{\vartheta}) = 2.51$ was found as a maximum curvature. In Fig. 5, we display the index plots of $\mathbf{d}_{max}(\boldsymbol{\vartheta})$ and C_i for all points. Clearly, the cases ♯5, ♯8, and ♯43 are the most influential observations on $\widehat{\boldsymbol{\vartheta}}$ (see Figs. 5a and 5b).

Table 2. Some statistics from the fitted models.

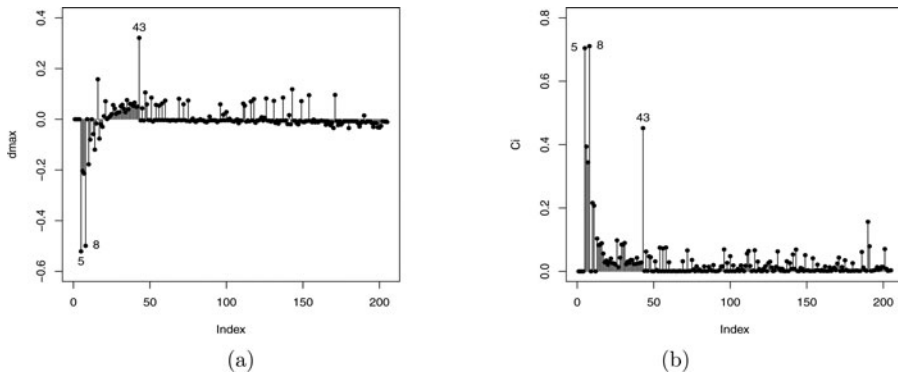| Model	Statistic		
	$-2\max \ell(\boldsymbol{\vartheta})$	AIC	SBC
colrule Negative binomial BS	413.02	425.02	444.95
Poisson BS	415.07	427.07	447.01
Mixture BS	417.02	429.02	448.96

Figure 5. Index plot of the case-weight perturbation for ϑ on the myeloma data. (a). $\mathbf{d}_{max}$. (b) C_i.

Influence using response variable perturbation

Next, we examine the influence of perturbations on the observed survival times. The value for the maximum curvature is $C_{\mathbf{d}_{max}}(\vartheta) = 196.14$. Figure 6 displays plots for $\mathbf{d}_{max}(\vartheta)$ and C_i for all points. The plots in Figs. 6a and 6b suggest that the case $\sharp 5$ is the most influential observation on $\hat{\vartheta}$.

Influence using explanatory variable perturbation

The perturbation of the explanatory variable age (x_3) is investigated here. After the perturbation of this explanatory variable, the value $C_{\mathbf{d}_{max}}(\vartheta) = 1.04$ was obtained as the maximum curvature. The corresponding index plots of $\mathbf{d}_{max}(\vartheta)$ and C_i are displayed in Fig. 7. The results in Figs. 7a and 7b suggest that the observations $\sharp 5$ and $\sharp 43$ are the most influential on $\hat{\vartheta}$.

The observation $\sharp 5$ refers to the shorter survival time and the observations $\sharp 8$ and $\sharp 43$ have the highest value of the covariate tumor thickness.

6.2. *Impact of the detected influential observations*

The diagnostic analysis detected, as potentially influential, the following three cases: $\sharp 5$, $\sharp 8$, and $\sharp 43$. The observation $\sharp 5$ refers to shorter survival time and the observations $\sharp 8$ and $\sharp 43$ have the highest value of the covariate tumor thickness. In order to reveal the impact of these

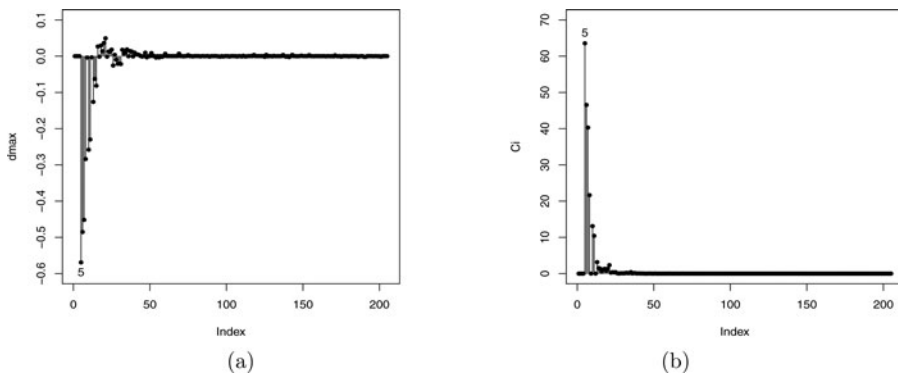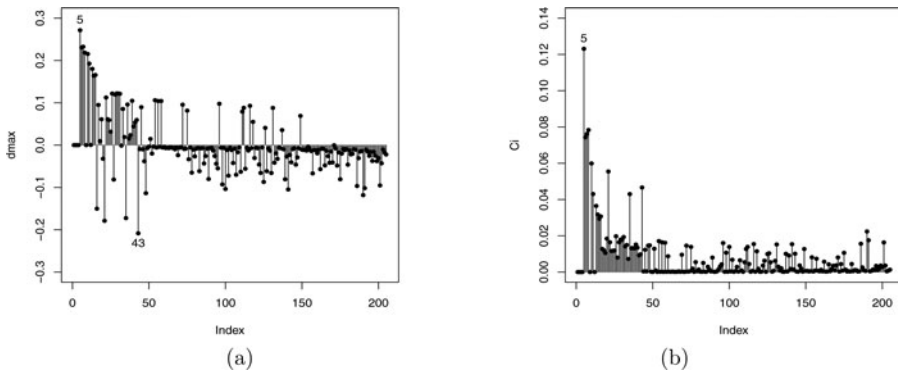**Figure 6.** Index plot of the response perturbation scheme for ϑ on the myeloma data. (a). $\mathbf{d}_{max}$. (b) C_i.

Figure 7. Index plot of the perturbation of the explanatory variable *tumor thickness* for ϑ on the myeloma data. (a) $\mathbf{d}_{max}$. (b) C_i.

three observations on the parameter estimates, we refitted the model under some situations. First, we individually eliminate each one of these three cases. Next, we remove the totality of potentially influential observations from set "A″ (original data set).

In Table 4, we have the relative changes (in percentage) of the parameter estimates, defined by $\mathbf{RC}_{\vartheta_j} = [(\hat{\vartheta}_j - \hat{\vartheta}_{j(I)})/\hat{\vartheta}_j] \times 100$, parameter estimates and the corresponding p-values, where $\hat{\vartheta}_{j(I)}$ denotes the MLE of ϑ_j after the set "I″ of observations has been removed. Note that $I_1 = \{\sharp 5\}$, $I_2 = \{\sharp 8\}$, $I_3 = \{\sharp 43\}$, $I_4 = \{\sharp 5, \sharp 8\}$, $I_5 = \{\sharp 5, \sharp 43\}$, $I_6 = \{\sharp 8, \sharp 43\}$, and $I_7 = \{\sharp 5, \sharp 8, \sharp 43\}$.

From Table 4, we note that the MLEs are not highly sensitive under deletion of the outstanding observations. In general, the significance of the parameter estimates does not change (at the level of 5%) after removing the set I. Therefore, we do not have inferential changes after removing the observations handed out in the diagnostic plots.

The QQ plot of the normalized randomized quantile residuals (Dunn and Smyth, 1996; Rigby and Stasinopoulos, 2005) in Fig. 4 (right panel) suggests that the NBBScr model is acceptable. Each point in Fig. 4 (right panel) corresponds to the median of five sets of ordered residuals. Taking into account the criteria in Table 2, the LR statistic and the QQ plot in Fig. 4 (right panel), reveal that the NBBScr model is the best model. The MLEs of the parameters in Table 3 are significant at a 10% level.

Table 5 displays the survival function stratified by ulceration status and sex (A: absent and female, B: present and female, C: absent and male, D: present and male) for patients with tumor thickness equal to 0.64, 1.94, and 6.63 mm, which correspond to the 10, 50, and 90 percentiles. These plots highlight the combined impact of the covariates on the cure fraction. Finally, approximate 95% confidence intervals are obtained after application of the delta method.

Table 3. The MLEs of the parameters for the NBBScr model.

| Parameter	Estimate (est)	Standard error (se)	|est| / se
α	1.336	0.517	—
λ	10.735	8.489	—
η	1.448	1.140	—
$\beta_{\text{intercept}}$	1.465	0.562	2.610
$\beta_{\text{ulceration}}$	− 1.316	0.380	3.466
β_{sex}	− 0.592	0.315	1.877
$\beta_{\text{thickness}}$	− 0.149	0.052	2.867

Table 4. Relative changes [**RC**-in %], estimates and the corresponding p-values in parentheses for the regression coefficients to explain the survival times.

Drooping	α	λ	η	$\beta_{intercept}$	$\beta_{ulceration}$	β_{sex}	$\beta_{thickness}$
A	—	—	—	—	—	—	—
	1.336	10.735	1.448	1.465	−1.316	−0.592	−0.149
	(-)	(-)	(-)	(0.009)	(0.001)	(0.060)	(0.004)
A-l_1	[1]	[3]	[19]	[7]	[−5]	[−2]	[−7]
	1.323	11.071	1.188	1.354	−1.374	−0.579	−0.138
	(-)	(-)	(-)	(0.038)	(0.001)	(0.080)	(0.020)
A-l_2	[0]	[3]	[36]	[5]	[−8]	[−1]	[3]
	1.334	10.438	0.928	1.384	−1.422	−0.596	−0.144
	(-)	(-)	(-)	(0.031)	(0.001)	(0.087)	(0.032)
A-l_3	[2]	[−4]	[−37]	[−3]	[6]	[15]	[−9]
	1.311	11.180	2.009	1.512	−1.232	−0.501	−0.163
	(-)	(-)	(-)	(0.005)	(0.000)	(0.093)	(0.001)
A-l_4	[2]	[−1]	[43]	[12]	[−11]	[3]	[12]
	1.305	10.882	0.839	1.282	−1.464	−0.576	−0.131
	(-)	(-)	(-)	(0.098)	(0.001)	(0.115)	(0.083)
A-l_5	[1]	[−8]	[−12]	[6]	[2]	[15]	[2]
	1.316	11.621	1.641	1.377	−1.288	−0.500	−0.146
	(-)	(-)	(-)	(0.025)	(0.000)	(0.105)	(0.007)
A-l_6	[1]	[−3]	[3]	[4]	[0]	[13]	[0]
	1.328	11.047	1.419	1.399	−1.319	−0.516	−0.148
	(-)	(-)	(-)	(0.020)	(0.000)	(0.107)	(0.009)
A-l_7	[2]	[−8]	[12]	[13]	[−3]	[15]	[13]
	1.310	11.602	1.282	1.271	−1.358	−0.503	−0.130
	(-)	(-)	(-)	(0.076)	(0.001)	(0.131)	(0.037)

We end up our application dealing with the estimation of the proportion of non-cured patients, who survived beyond a certain fixed time. For sake of illustration, we choose a period of five years. This proportion is estimated from (9) as $\hat{S}_{NBBS}(5)$. The estimates $\hat{S}_{GBS}(5)$ stratified by ulceration status and sex (A: absent and female, B: present and female, C: absent and male, D: present and male) for non-cured patients with tumor thickness equal to 0.32, 1.94 and 6.32 mm are given by $(A : 0.662, B : 0.532, C : 0.619, D : 0.431)$, $(A : 0.650, B : 0.502, C : 0.600, D : 0.394)$ and $(A : 0.588, B : 0.373, C : 0.506, D : 0.259)$, respectively. In Fig. 8 (right panel), we display the surviving function stratified by ulceration status for the non-cured patients with selected tumor thickness.

Table 5. The MLEs of the cured fraction stratified by ulceration status, sex, and selected tumor thickness under the NBBScr model.

Tumor thickness	Ulceration	Sex	Estimate	Standard error	95% confidence interval
0.64	Absent	Female	0.797	0.090	(0.622, 0.973)
		Male	0.685	0.121	(0.449, 0.922)
	Present	Female	0.4513	0.137	(0.244, 0.783)
		Male	0.343	0.137	(0.073, 0.612)
1.94	Absent	Female	0.764	0.098	(0.572, 0.957)
		Male	0.642	0.127	(0.393, 0.891)
	Present	Female	0.465	0.135	(0.200, 0.730)
		Male	0.325	0.126	(0.077, 0.572)
6.63	Absent	Female	0.617	0.137	(0.348, 0.887)
		Male	0.472	0.148	(0.181, 0.762)
	Present	Female	0.302	0.124	(0.060, 0.544)
		Male	0.193	0.097	(0.003, 0.383)
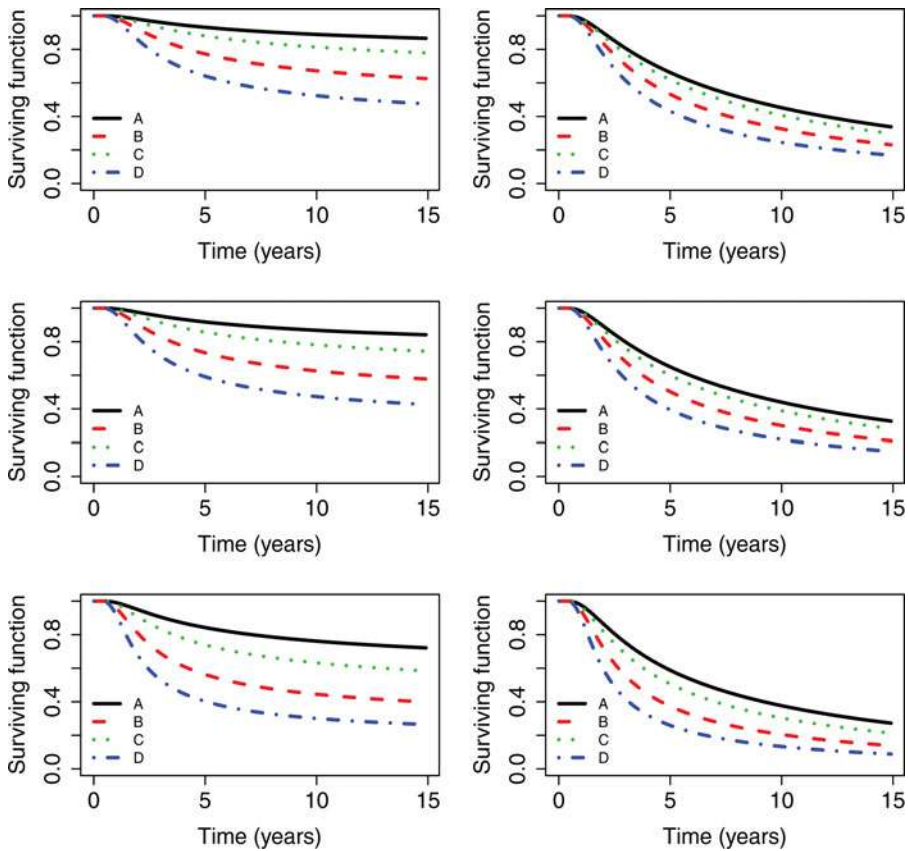
Figure 8. Left panel: The survival function for the NBBRcr model stratified by ulceration status and sex (A: absent and female, B: present and female, C: absent and male, D: present and male) for patients with tumor thickness equals to 0.64 (top), 1.94 (middle), and 6.63 mm (bottom). Right panel: Estimated survival function for the non-cured NBBS population.

7. Concluding remarks

The Birnbaum-Saunders (BS) distribution has been extensively used for modeling fatigue lifetimes in several fields such as medical sciences, biological studies, engineering, economics and insurance. For modeling fatigue lifetimes in several medical problems, there is a clear need for using the BS distribution, such as chronic cardiac diseases and various different types of cancer. The cumulative individual damage may be caused by various unknown causes or risk factors leading to a fatigue process, whose propagation lifetimes can be suitably modeled by the BS distribution (Cancho et al. 2012; Leiva et al., 2008). The fatigue or cumulative damage justifies the use of the BS distribution. In this article, we propose a model for lifetime data conceived inside a latent competing causes scenario with cure fraction called the negative binomial Birnbaum-Saunders Regression (NBBScr for short) distribution. There is a mathematical relationship among the BS cure rate model, the mixture cure rate model (Boag, 1949; Berkson and Gage, 1952) and the NBBS distribution. Hence, the proposed cure rate model has the structure of the mixture cure rate model and the NBBS distribution represents the distribution associated with the individuals at risk.

Some structural properties of the NBBS distribution for the non-cured population are investigated. Maximum likelihood inference is implemented straightforwardly and asymptotic theory may be considered for generating confidence intervals for the parameters and

hypothesis tests. The practical importance of the new model was demonstrated in an application to a real data set, where it provides a better fit in comparison with the mixture Birnbaum-Saunders cure rate model. The interpretation of the role of the covariates is easy due to the considered parametrization in the cure fraction. We observe that the surviving probability decreases more rapidly for patients with thicker tumors and that the cure fraction is lower for patients with ulceration.

Acknowledgments

Funding

Appendix: Matrix Δ calculations

Next, we calculate for three perturbation schemes, the matrix

$$\Delta = (\Delta_{vi})_{\left[(p+3) \times n\right]} = \left(\frac{\partial^2 l(\vartheta; \mathcal{D}|\omega)}{\partial \vartheta_v \partial \omega_i}\right)_{\left[(p+3) \times n\right]},$$

where $v = 1, \ldots, p+3$ and $i = 1, \ldots, n$. We shall consider the model defined in (9), (10), and its likelihood function given by (16).

A.1. Case-weight perturbation

First, we consider a case weight perturbation which modifies the weight given to each subject in the log-likelihood. Consider the vector of weights $\omega = (\omega_1, \ldots, \omega_n)^\top$.

In this case, the log-likelihood function takes the form

$$l(\vartheta; \mathcal{D}|\omega) = \begin{cases} \sum_{i=1}^{n} \omega_i \delta_i \log\left[\frac{p_{0i}^{-\eta}-1}{\eta} f_{BS}(y_i; \gamma)\right] - \\ \sum_{i=1}^{n} \omega_i(\delta_i + 1/\eta) \log\left[1 + (p_{0i}^{-\eta} - 1)F_{BS}(y_i; \gamma)\right], & \text{if } \eta \neq 0; \\ \sum_{i=1}^{n} \omega_i \delta_i \log\left[-\log(p_{0i}) f_{BS}(y_i; \gamma)\right] + \sum_{i=1}^{n} \omega_i F_{BS}(y_i; \gamma) \log(p_{0i}), & \text{if } \eta = 0, \end{cases}$$

where $0 \leq \omega_i \leq 1$ and $\omega_0 = (1, \ldots, 1)^\top$. The matrix $\Delta = (\Delta_\gamma^\top, \Delta_\beta^\top, \Delta_\eta^\top)^\top$ has elements that can be calculated numerically.

A.2. Response perturbation

Since y_i values have different variances, they require a scaling of the perturbation vector ω by an estimator of the standard deviation of y_i. We will consider here that each y_i is perturbed as $y_{i\omega} = y_i + \omega_i S_y$, where S_y is a scale factor that may be estimated by the standard deviation of y and $\omega_i \in \mathbf{R}$.

Here, the perturbed log-likelihood function can be expressed as

$$
l(\boldsymbol{\vartheta}; \mathcal{D}|\boldsymbol{\omega}) =
\begin{cases}
\sum_{i=1}^{n} \delta_i \log\left[\frac{p_{0i}^{-\eta}-1}{\eta} f_{BS}(y_i^*; \gamma) \right] - \\
\sum_{i=1}^{n} (\delta_i + 1/\eta) \log\left[1 + (p_{0i}^{-\eta}-1) F_{BS}(y_i^*; \gamma) \right], & \text{if } \eta \neq 0; \\
\sum_{i=1}^{n} \delta_i \log\left[-\log(p_{0i}) f_{BS}(y_i^*; \gamma) \right] + \sum_{i=1}^{n} F_{BS}(y_i^*; \gamma) \log(p_{0i}), & \text{if } \eta = 0,
\end{cases}
$$

where $y_i^* = (y_i + \omega_i S_t)$ and $\boldsymbol{\omega}_0 = (0, \ldots, 0)^\top$. The elements of the matrix $\boldsymbol{\Delta} = (\boldsymbol{\Delta}_\gamma^\top, \boldsymbol{\Delta}_\beta^\top, \boldsymbol{\Delta}_\eta^\top)^\top$ can be calculated numerically.

A.3. Explanatory variable perturbation

Cook (1986) described a general scheme for perturbing the whole design matrix X in linear regression models. Some authors have studied the perturbation of explanatory variables. This perturbation has a more complicated impact on the estimates. The errors-in-variable model considers the errors of the explanatory variables so that the local influence under the perturbation of the explanatory variables may be in connection with the model. We take an additive perturbation on a particular continuous explanatory variable, namely x_t, by setting $x_{it\omega} = x_{it} + \omega_i S_x$, where S_x is a scaled factor, $\omega_i \in \mathbf{R}$. This perturbation scheme leads to the perturbed log-likelihood function

$$
l(\boldsymbol{\vartheta}; \mathcal{D}|\boldsymbol{\omega}) =
\begin{cases}
\sum_{i=1}^{n} \delta_i \log\left[\frac{p_{0i}^{**-\eta}-1}{\eta} f_{BS}(y_i; \gamma) \right] - \\
\sum_{i=1}^{n} (\delta_i + 1/\eta) \log\left[1 + (p_{0i}^{**-\eta}-1) F_{BS}(y_i; \gamma) \right], & \text{if } \eta \neq 0; \\
\sum_{i=1}^{n} \delta_i \log\left[-\log(p_{0i}^{**}) f_{BS}(y_i; \gamma) \right] + \sum_{i=1}^{n} F_{BS}(y_i; \gamma) \log(p_{0i}^{**}), & \text{if } \eta = 0,
\end{cases}
$$

where $p_{0i}^{**} = \frac{\exp(x_i^{**\top}\boldsymbol{\beta})}{1+\exp(x_i^{**\top}\boldsymbol{\beta})}$, $(x_i^{**\top}\boldsymbol{\beta}) = \beta_1 x_{i1} + \cdots + \beta_t(x_{it} + \omega_i S_x) + \cdots + \beta_p x_{ip}$ and $\boldsymbol{\omega}_0 = (0, \ldots, 0)^T$. The elements of the matrix $\boldsymbol{\Delta} = (\boldsymbol{\Delta}_\gamma^\top, \boldsymbol{\Delta}_\beta^\top, \boldsymbol{\Delta}_\eta^\top)^\top$ are calculated numerically.

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