A Projected Non-Linear Conjugate Gradient Algorithm for Destructive Negative Binomial Cure Rate Model

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Abstract

In this paper, we propose a new estimation methodology based on a projected non-linear conjugate gradient (PNCG) algorithm for the destructive negative binomial cure rate model. We show that the PNCG algorithm can simultaneously maximize all model parameters even though the likelihood surface is flat with respect to some model parameters, where, in such a scenario, a profile likelihood approach has been proposed in the literature. We compare the performance of the PNCG algorithm with the well studied expectation maximization (EM) algorithm and show, in particular, that the PNCG algorithm results in more precise and accurate estimates of cure rates. We further show that the PNCG algorithm is computationally less expensive when compared to the EM algorithm with profile likelihood. Finally, we apply the proposed PNCG algorithm on a well-known melanoma data.

Keywords: EM algorithm; constrained optimization; line-search; first-order necessary conditions; long-term survivors

1 Introduction

Due to the advancements in the treatment of certain types of disease, including cancer and heart disease, we see a significant number of patients to respond favorably to the treatment and not show recurrence until the end of a long follow-up time. In literature, these patients are called recurrence-free survivors. It may be possible that some of these recurrence-free survivors will not show recurrence for a sufficiently long period after the follow-up time since they may reach a stage where the disease is undetectable as well as harmless. These patients, among the recurrence-free survivors, are called long-term survivors or “cured”. It is to be noted that the estimation of this long-term survivor rate or cure rate cannot be readily obtained from a given survival data since we are not in a position to identify which of the recurrence-free survivors can be considered as long-term survivors. This issue arises because a patient who is susceptible to disease recurrence soon after the follow-up time may also show no recurrence and survive until the end of the follow-up time. However, the estimation of a treatment-specific cure rate is crucial to observe the trend in the survival of patients suffering from a particular disease. Furthermore, it is an important measure to judge the efficacy of a treatment and its adoption in practice, as opposed to the standard treatment.

The literature on cure rate models is vast and the topic itself is one of the most emerging areas of modern research. The early work on cure rate model dates back to the work of Boag (1949) followed by Berkson and Gage (1952), which is known in the literature as the mixture cure rate model. According

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to the mixture cure rate model, the overall survival function (also called the population survival function) of the time-to-event variable $Y$ can be split into two parts, one corresponding to the cured group and the other corresponding to the susceptible group. Such a survival function is given by

$$S_{\text{pop}}(y) = p_0 + (1 - p_0)S_s(y),$$

(1)

where $p_0$ is the proportion of cured subjects (cure rate) and $S_s(y)$ is a proper survival function for the susceptible subjects; see Sy and Taylor (2000) and Kannan et al. (2010). Note that $S_{\text{pop}}(y)$ is not a proper survival function as $\lim_{y \to \infty} S_{\text{pop}}(y) = p_0 (\neq 0)$. One major drawback of the mixture cure rate model in (1) is that it does not incorporate a scenario where several risk factors may compete to produce the event of interest; known as the competing risks scenario. To circumvent this problem, Chen et al. (1999) proposed the promotion time cure rate model by considering a competing risks scenario and assuming the latent number of risk factors to follow a Poisson distribution. The corresponding population survival function is given by

$$S_{\text{pop}}(y) = e^{-\eta(1-S(y))},$$

(2)

where $\eta$ is the mean number of risk factors and $S(y)$ is the common survival function of the progression times, defined as the time taken by each risk factor to produce the event. Note that in this case the cure rate is given by $e^{-\eta}$. Rodrigues et al. (2009) unified the mixture and promotion time cure rate models by proposing the Conway-Maxwell Poisson (COM-Poisson) cure rate model, which assumes the number of risk factors to follow a COM-Poisson distribution that can handle both over-dispersion and under-dispersion. For this unified cure rate model, the population survival function is given by

$$S_{\text{pop}}(y) = \frac{Z(\eta S(y), \phi)}{Z(\eta, \phi)},$$

(3)

where $Z(a, \phi) = \sum_{j=0}^{\infty} \frac{a^j}{j! \phi^j}$ and $\phi$ is the dispersion parameter of the COM-Poisson distribution. In (3), $\eta$ is related to the mean number of risk factors and $S(y)$ is as defined before for the promotion time model. In this case, the cure rate is given by $\frac{1}{Z(\eta, \phi)}$. Note that if $\phi \to \infty$ in (2), the COM-Poisson model reduces to the mixture model in (1) with $p_0 = \frac{1}{1+\eta}$, whereas, if $\phi = 1$ in (3), the COM-Poisson model reduces to the promotion time model in (2); see Cancho et al. (2011), Balakrishnan and Pal (2015), Balakrishnan and Pal (2016), and Balakrishnan and Feng (2018) for some recent works on cure rate model using COM-Poisson distribution. To develop the associated inferential procedures, several approaches have been proposed in the literature. In this regard, one may refer to parametric approaches (Farewell, 1986; deFreitas and Rodrigues, 2013; Balakrishnan and Pal, 2013); semi-parametric approaches (Kuk and Chen, 1992; Li and Taylor, 2002; Balakrishnan et al., 2017); and non-parametric approaches (Maller and Zhou, 1996; Balakrishnan et al., 2016). Rodrigues et al. (2011) first brought in a practical and interesting interpretation of the biological mechanism of the occurrence of an event of interest; see Cooner et al. (2007). They proposed a flexible cure rate model, known as the destructive cure rate model, by considering the possible elimination (or destruction) of risk factors after an initial treatment. Since then, several papers have been published in the context of destructive model and interested readers may refer to Cancho et al. (2013), Pal and Balakrishnan (2016), Balakrishnan (2016), Pal et al. (2018), and Gallardo et al. (2016), among others.

In this paper, we consider a competing risks scenario and assume the initial number of risk factors to follow a negative binomial distribution. Moreover, we accommodate elimination of risk factors and the corresponding model is termed as the destructive negative binomial (DNB) cure rate model. Recently, Pal and Balakrishnan (2016) considered the DNB cure rate model and showed that the distribution of the number of active risk factors (after the destruction) is also negative binomial. For
the maximum likelihood estimation (MLE) of the DNB model parameters, the authors developed the expectation maximization (EM) algorithm (McLachlan and Krishnan, 2008); see also Gallardo et al. (2016). However, they noted that the likelihood surface is flat with respect to the parameters $\gamma_1$ and $\phi$ (using the same notation as in Pal and Balakrishnan, 2016) and as such simultaneous maximization of all model parameters was not possible. To circumvent this problem, the authors proposed a two-way profile likelihood technique within the EM algorithm. Although the proposed approach performed satisfactorily, few drawbacks were noted. For instance, the root mean square error (RMSE) of the regression parameters and $\phi$ turned out to be high. Furthermore, the bias in the estimate of $\phi$ was also high when compared to the other model parameters. Since in the DNB model, the cure rate is a pure function of the regression parameters and $\phi$, inaccuracies in the estimates of these parameters would ultimately result in inaccurate estimation of cure rates. Hence, the inference on overall population survival will be less precise. Note also that the two-way profile likelihood approach suggested by Pal and Balakrishnan (2016) requires the EM algorithm to be run for several fixed pairs $(\gamma_1, \phi)$ and then selecting the pair as the MLE for which the log-likelihood function value is the maximum. This procedure is computationally expensive and an admissible choice of pairs is also an issue. To evade these issues with the developed EM algorithm, we propose a new estimation procedure based on a projected non-linear conjugate gradient (PNCG) algorithm that (i) allows simultaneous maximization of all model parameters; (ii) results in more precise estimates, specifically for the parameters associated with the cure rate; and (iii) is computationally less expensive. To the best of our knowledge, we are the first one to propose the PNCG algorithm in the context of cure rate models.

The rest of the paper is organized as follows. In Section 2, we define the destructive negative binomial cure rate model. In Section 3, we present the form of the data and the likelihood function. In Section 4, we describe the PNCG algorithm in detail. In Section 5, we present the results of a detailed simulation study where we compare the performance of the proposed PNCG algorithm with the already developed EM algorithm. In Section 6, we apply our proposed estimation algorithm to a well-known melanoma data. Finally, in Section 7, we make some concluding remarks and discuss some future research in this direction.

## 2 Destructive negative binomial cure rate model

We can define the DNB cure rate model as follows. First, we assume that there are $M$ latent risk factors competing to produce an event of interest (for instance, death due to cancer or recurrence of a disease). These risk factors being unobserved, we assume them to follow a negative binomial distribution with the following mass function

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

(4)

With the passage of time or after an initial treatment, we consider the possibility of elimination of risk factors, which we assume to occur according to a Binomial law. More specifically, we define the number of active risk factors after elimination, i.e., those risk factors that are still capable of producing the event, as

$$D = \begin{cases} X_1 + X_2 + \ldots + X_M, & M > 0, \\ 0, & M = 0, \end{cases}$$

(5)

where $X_j$'s are independent Bernoulli random variables with $P[X_j = 1] = p$, for $j = 1, 2, \ldots, M$, with $p$ denoting the activation probability of each risk factor. Note that these assumptions are in line with
the assumptions of Rodrigues et al. (2011) who first proposed the destructive cure rate model; see also Yang and Chen (1991). Given \( D = d \), we now let \( W_j (j = 1, 2, \ldots, d) \) to denote the time taken by the \( j \)-th active risk factor to produce the event, also called the progression time. Once again, using the same assumptions as in Rodrigues et al. (2011), we let the progression times \( W_j's \) to be independently distributed and distributed independently of \( D \) with distribution function \( F(\cdot) = 1 - S(\cdot) \), where \( S(\cdot) \) is the corresponding survival function. Note that the individual progression times are not observed, however, we only observe the time taken by the first active risk factor to produce the event, which we term as the lifetime. Notationally, such a lifetime in a competing risks scenario is defined as

\[
Y = \begin{cases} 
\min\{W_1, \ldots, W_D\}, & D > 0 \\
\infty, & D = 0.
\end{cases}
\]

The infinite lifetime corresponding to \( D = 0 \) leads to a proportion, say \( p_0 \), of the population who are not susceptible to the occurrence of the event. We term this proportion as the “cure rate” and its estimation is of great interest to us. Using (4) and noting that the conditional distribution of \( D \) given \( M = m \) is Binomial \((m,p)\), Pal and Balakrishnan (2016) showed that the mass function of \( D \) can be expressed as

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

which is once again a negative binomial distribution. Rodrigues et al. (2011) showed that the overall survival function or the population survival function of the lifetime variable \( Y \) in (6) can be expressed as

\[
S_{\text{pop}}(y) = P[Y > y] = \left\{1 + \phi \eta p F(y)\right\}^{-\frac{1}{\phi}}
\]

and the corresponding density function, called the population density function, can be expressed as

\[
f_{\text{pop}}(y) = \frac{\eta p}{1 + \phi \eta p F(y)} S_{\text{pop}}(y)f(y),
\]

where \( f(\cdot) \) is the density function corresponding to \( F(\cdot) \). Noting that cure rate is the long-term survival probability, we can easily obtain the cure rate as

\[
p_0 = \left\{\frac{1}{1 + \phi \eta p}\right\}^{\frac{1}{\phi}}.
\]

In this regard, Pal and Balakrishnan (2016) showed that the overall cure rate can be decomposed into pre-destructive and post-destructive components. From (10), we note that the cure rate is a decreasing function of both \( \eta \) and \( p \). As pointed out by Rodrigues et al. (2011), the DNB cure rate model is not identifiable as per Li et al. (2001). One way to circumvent this issue, as suggested by Rodrigues et al. (2011), is to bring in the effect of prognostic factors (or covariates). For instance, we can relate the parameter \( p \) to a set of covariates \( x \) using the logistic link function \( p = \frac{\exp(x' \beta_1)}{1 + \exp(x' \beta_1)} \) and the parameter \( \eta \) to another set of covariates \( z \) using the log-linear link function \( \eta = \exp(z' \beta_2) \), where \( \beta_1 \) and \( \beta_2 \) represents the vectors of regression coefficients. Furthermore, we have to make sure that either \( \beta_1 \) or \( \beta_2 \) does not include the intercept term to retain identifiability. Note that \( x \) and \( z \) cannot share common elements.
3 Data and likelihood function

We consider a scenario where the lifetime data may not be completely observed and is thus subject to right censoring. We let $T_i$ and $C_i$ denote the actual failure time and censoring time, respectively, $i = 1, 2, \ldots, n$, where $n$ denotes the sample size. The lifetime that we observed is then given by $Y_i = \min\{T_i, C_i\}$. We let $\delta_i$ denote the right censoring indicator, i.e., $\delta_i$ takes the value 1 if the lifetime is observed and 0 if it is right censored. The observed data can then be represented by $O = \{(y_i, \delta_i, x_i, z_i), i = 1, 2, \ldots, n\}$. On assuming non-informative right censoring, we can define the observed data likelihood function as

$$L(\theta) = \prod_{i=1}^{n} \{f_{\text{pop}}(y_i | x_i, z_i)\}^{\delta_i} \{S_{\text{pop}}(y_i | x_i, z_i)\}^{1-\delta_i},$$

(11)

where $\theta = (\phi, \beta_1', \beta_2', \gamma')'$ is the vector of unknown parameters with $\gamma$ denoting the parameter vector associated with $F(\cdot)$. As done in Pal and Balakrishnan (2016), we will assume $F(\cdot)$ and $f(\cdot)$ to be the distribution function and density function, respectively, of a two-parameter Weibull distribution defined as

$$F(y) = 1 - \exp\{- (\gamma_2 y)^{\frac{\gamma_1}{\gamma_2}}\}$$

and

$$f(y) = \frac{1}{\gamma_1 y^{\frac{\gamma_1}{\gamma_2}}} \{1 - F(y)\}$$

(12)

for $y > 0$, $\gamma_1 > 0$, and $\gamma_2 > 0$. Thus, we now have $\gamma = (\gamma_1, \gamma_2)'$.

4 Estimation method: projected non-linear conjugate gradient algorithm

We, now, desire to estimate the optimal parameter set $\theta$ that maximizes the likelihood function given in (11). Applying the natural logarithm on both sides of (11), we obtain the log-likelihood function as follows

$$l(\theta) = \sum_{i=1}^{n} [\delta_i \log\{f_{\text{pop}}(y_i | x_i, z_i)\} + (1 - \delta_i) \log\{S_{\text{pop}}(y_i | x_i, z_i)\}].$$

(13)

Then the corresponding maximization problem to obtain the optimal $\theta^*$ is given by

$$\theta^* = \arg \max_{\theta \in U} l(\theta),$$

(14)

where the feasible set of constraints $U$ is defined as

$U = \{\theta : \gamma_1 > 0, \gamma_2 > 0, \ 0 < \alpha \leq 1\}$.

The function $l$ is non-linear with respect to $\theta$ and, thus, gives rise to a non-linear maximization problem. To solve such a non-linear maximization problem (14), we use the non-linear conjugate gradient method (NCG). This method has been primarily used in the context of solving partial differential equation (PDE)-constrained optimal control problems arising in mathematical models of crowd motion, game theory, and medical imaging (Roy et al., 2016; Roy et al., 2017; Roy et al., 2018; Adesokan et al., 2018). The NCG scheme has significant advantages over traditional Newton-based schemes (for instance, the EM algorithm in Pal and Balakrishnan, 2016, where the maximization step was carried out using a one-step Newton Raphson method). For example, even though Newton’s method
potentially converges faster, it is highly expensive and time consuming to compute the Hessian in
a Newton-based method, specially for optimization problems with large number of parameters and
bigger sample size \( n \). On contrary, in the NCG method, only the gradient is required to be evaluated,
leading to a much faster convergence than the Newton-based schemes. This is also observed in the
simulation studies presented in Section 5.

To start the NCG scheme, we use an initial guess \( \theta_0 \) for the parameter set. It has been observed
that the performance of the NCG method remains the same for a large choice of initial guesses, which
suggests the robustness of the method; see Roy et al., 2017 and Adesokan et al., 2018. Due to the fact
that the maximum rate of increase of a function is along the positive gradient direction, the initial
guess is updated by moving in the search direction given by the gradient \( d_0 = g_0 = \nabla \theta l(\theta_0) \) of the
function \( l \). In subsequent iterations, the search directions are recursively given by the formula

\[
d_{k+1} = g_{k+1} + \xi_k d_k, \quad k = 0, 1, 2, \ldots,
\]

where \( g_k = \nabla \theta l(\theta_k) \) and \( \xi_k \) is given by the formula of Hager-Zhang (Hager and Zhang, 2005) as follows

\[
\xi_k = \frac{1}{d_k' w_k} \left( w_k - 2d_k w_k' d_k' w_k \right) g_{k+1}
\]

with \( w_k = g_{k+1} - g_k \). We update our parameter set \( \theta \) using a steepest ascent scheme given below

\[
\theta_{k+1} = \theta_k + s_k d_k,
\]

where \( s_k > 0 \) is a steplength obtained through a line search algorithm. An accurate estimate of
the steplength \( s_k \) is crucial because a very large \( s_k \) would result in deviating from the path of the
maximizer, whereas a very small \( s_k \) would lead to slow convergence of the NCG scheme. Thus, we
deploy a line-search algorithm to obtain \( s_k \) that uses the following Armijo condition (Annunziato and
Borzi, 2013) of sufficient increase of \( l \)

\[
l(\theta_k + s_k d_k) \geq l(\theta_k) + \lambda d_k' g_k
\]

with \( 0 < \lambda < 1/2 \). Such a method leads to an optimal steplength \( s_k \) resulting in a fast and accurate
optimal solution through the NCG.

Traditional gradient-based schemes look for an optimum in a global space of parameters. But
for the maximization problem given in (14), one needs to determine the maximizer that lies in the
constraint set \( U \). Thus, we need to ensure that the solution obtained at the end of each iterative step
in the NCG scheme lies in the constraint set \( U \). For this purpose, we use a projection step onto the
constraint set \( U \) that is applied to the parameter update step (16) through the following way

\[
\theta_{k+1} = P[\theta_k + s_k d_k],
\]

where

\[
P[\theta] = \{\max(10^{-10}, \min(1, \phi)), \beta_1, \beta_2, \max(10^{-10}, \gamma_1), \max(10^{-10}, \gamma_2)\}.
\]

The projection step ensures that the parameter values obtained in each iteration lies inside the con-
straint set \( U \). We call our new scheme as the projected NCG (PNCG) scheme. The scheme is
terminated once the relative difference between two successive iterates is less than a specified toler-
ance level or the number of iterations exceed the maximum number of iterations. The algorithm of
the PNCG scheme is summarized below.
Algorithm 4.1 (PNCG Scheme)

1. Input: initial guess $\theta_0$. Evaluate $d_0 = \nabla_{\theta} l(\theta_0)$, index $k = 0$, maximum $k = k_{\text{max}}$, tolerance = $tol$

2. While ($k < k_{\text{max}}$), do

3. Set $\theta_{k+1} = P[\theta_k + s_k d_k]$, where $s_k$ is obtained using the line-search algorithm

4. Compute $g_{k+1} = \nabla_{\theta} l(\theta_{k+1})$

5. Compute $\xi_k$ using $[15]$

6. Set $d_{k+1} = g_{k+1} + \xi_k d_k$

7. If $\|\theta_{k+1} - \theta_k\| < tol$, terminate

8. Set $k = k + 1$

9. End while.

The convergence of the PNCG scheme, as described in Algorithm 4.1, follows from Neittaanmaki and Tiba (1994, Lemma 1.6, p. 235).

5 Simulation study

To demonstrate the performance of our proposed PNCG algorithm, we carried out a detailed Monte Carlo simulation study. For this purpose, we chose $k_{\text{max}} = 500$, $\lambda = 0.1$, and $tol = 0.001$. Note that we also tried the algorithm for other values of $\lambda$ within its range, and our findings were similar. We present the calculated bias and root mean square (RMSE) of the estimates obtained using PNCG algorithm and compare these with the bias and RMSE obtained using the EM algorithm developed by Pal and Balakrishnan (2016). Note that in the EM algorithm, the maximization step was carried out using a one-step Newton Raphson method. To facilitate this comparison, we stick to the same simulation setup as in Pal and Balakrishnan (2016) and describe it below.

For the purpose of this simulation study, we mimic the real melanoma dataset that we analyze in the next section. For this dataset, two covariates of interest are tumor thickness (measured in mm) and ulceration status (presence of ulcer denoted by 1 and absence denoted by 0). A preliminary analysis of this data indicates that 44% of patients had the presence of ulcer. For this group of patients, the mean and standard deviation of tumor thickness turned out to be 4.34 mm and 3.22 mm, respectively. On the other hand, for the group of patients without the presence of ulcer, the mean and standard deviation of tumor thickness turned out to be 1.81 mm and 2.19 mm, respectively. Moreover, as noted by Pal and Balakrishnan (2016), histograms of tumor thickness for two groups suggest that a Weibull distribution may be suitable for the group with presence of ulcer, whereas an exponential distribution may be suitable for the group without the presence of ulcer. Thus, to generate the ulceration status data, we first generated a Uniform (0,1) random variable, say, $U$. If $U \leq 0.44$, we took ulceration status ($x$) to be 1 and then generated the tumor thickness ($z$) from a Weibull distribution. For the choice of the Weibull parameters here, we equated the theoretical mean and variance of the Weibull distribution to 4.34 and 10.37, respectively. On the other hand, if $U > 0.44$, we took ulceration status ($x$) to be 0 and generated tumor thickness ($z$) from an exponential distribution. For a choice of this exponential parameter, we simply equated the exponential mean to 1.81. To make the model identifiable, we linked the parameter $\eta$ to ulceration status without the intercept term and the parameter $p$ to tumor
thickness (including the intercept term). Thus, we have the following link functions: \( \eta = \exp(\beta_2 z) \) and \( p = \frac{\exp(\beta_0 + \beta_1 x)}{1 + \exp(\beta_0 + \beta_1 x)} \). To decide on the true value of the regression parameter \( \beta_2 \), we note that the absence of ulcer would simply imply \( \eta \) taking on the value 1. Intuitively, with the presence of ulcer, \( \eta \) is expected to be higher since it is related to the mean number of active competing risks. Thus, we chose \( \eta \) to be 3 in the presence of ulcer, which gave us the true value of \( \beta_2 \) as \( \log(3) = 1.099 \).

To decide on the true values of the regression parameters \( \beta_0 \) and \( \beta_1 \) corresponding to \( p \), we chose a low and a high value of \( p \) as 0.3 and 0.9, respectively. Also, from the generated tumor thickness data, we identified the minimum \( (x_{\text{min}}) \) and the maximum \( (x_{\text{max}}) \) tumor thickness values. Then, we came up with the following two equations to solve for \( \beta_0 \) and \( \beta_1 \).

\[
\frac{\exp(\beta_0 + \beta_1 x_{\text{min}})}{1 + \exp(\beta_0 + \beta_1 x_{\text{min}})} = 0.3
\]
\[
\frac{\exp(\beta_0 + \beta_1 x_{\text{max}})}{1 + \exp(\beta_0 + \beta_1 x_{\text{max}})} = 0.9.
\]

Note that the true values of \( \beta_0 \) and \( \beta_1 \) depends on the generated tumor thickness data and as such cannot be kept fixed across the generated data sets; see Pal and Balakrishnan (2016). To incorporate random censoring, the censoring time \( (C) \) distribution was chosen to be exponential with censoring rate 0.15. Next, to generate the lifetime data from the DNB model, we followed the following steps:

(i) Generate the initial number of risk factors \( M \) from a negative binomial distribution with mass function as in (4) for a chosen value of \( \phi \).

(ii) If \( M = 0 \) in (i), set the number of active risk factors \( D = 0 \).

(iii) If \( M > 0 \) in (i), generate \( D \) from a Binomial distribution with the observed value of \( M \) as the number of trials and success probability \( p \).

(iv) From (ii) and (iii), if \( D = 0 \), set the observed lifetime \( Y \) as the censoring time, i.e., \( Y = C \).

(v) From (ii) and (iii), if \( D > 0 \), generate \( D \) Weibull random variables \( \{W_1, W_2, \ldots, W_D\} \) with density function as in (12) for chosen values of \( \gamma_1 \) and \( \gamma_2 \). Then, take the observed lifetime as \( Y = \min\{\min\{W_1, W_2, \ldots, W_D\}, C\} \).

(vi) From (iv) and (v), if \( Y = C \), set \( \delta = 0 \), otherwise, set \( \delta = 1 \).

As done in Pal and Balakrishnan (2016), we considered the following true choices: \((\gamma_1, \gamma_2) = (0.215, 0.183)\) and \((0.316, 0.179)\); \( n = 300 \) and \( 400 \); and \( \phi = 0.5 \) and \( 0.75 \). We ran our simulations in R statistical software and all results were based on 500 Monte Carlo runs. To come up with a choice of initial values to start the PNCG algorithm, we first created an interval for each model parameter by taking 20% deviation off its true value and then selected a value at random from the created interval, which was used as the parameter’s initial value.

### 5.1 Discussion

In Tables 1 and 2, we present the simulation study results, in terms of bias and root mean square error (RMSE), for the DNB model when the true value of \( \phi \) is 0.50 and 0.75, respectively. When we employed the PNCG algorithm, we did not face any issue with simultaneous maximization of all model parameters (including the parameters \( \gamma_1 \) and \( \phi \)). This is a nice behavior of the PNCG algorithm and is unlike the EM algorithm developed by Pal and Balakrishnan (2016), where simultaneous maximization was not possible and the authors had to keep the parameters \( \gamma_1 \) and \( \phi \) fixed for the EM procedure to work. This is a big advantage of the PNCG algorithm over the EM algorithm. It is clear that
the PNCG algorithm provides estimates that are very close to the true parameter values. Both bias and RMSE are found to decrease with an increase in sample size, which is also a very satisfactory property. When compared to the estimates produced by EM algorithm, we first note that the bias in the estimates of the PNCG algorithm is lower than that of the EM algorithm. Note, in particular, the reduction in the bias of $\phi$ that the PNCG algorithm results when the true value of $\phi$ is 0.75. When compared to the EM algorithm, the PNCG algorithm also results in a significant reduction in the RMSE for the regression parameters ($\beta_0, \beta_1, \beta_2$) as well as for the parameter $\phi$. This is another big advantage of the PNCG algorithm over the EM algorithm, noting that the cure rate is a pure function of the regression parameters and $\phi$ only. For the lifetime parameters $\gamma_1$ and $\gamma_2$, both algorithms result in similar bias and RMSE. From the above findings, it is very clear that the PNCG algorithm results in more accurate and precise estimates of the DNB cure rate model parameters and is thus preferred over the EM algorithm.

Table 1: Comparison of PNCG algorithm with EM algorithm in terms of bias and RMSE with true value of $\phi$ as 0.50

| $n$   | $(\gamma_1, \gamma_2)$ | Parameter | Bias   | RMSE   |
|-------|-------------------------|-----------|--------|--------|
|       |                         |           | PNCG   | EM     | PNCG   | EM     |
| 300   | (0.215,0.183)           | $\beta_2$ | 0.021  | 0.035  | 0.229  | 0.339  |
|       |                         | $\beta_0$ | -0.028 | -0.120 | 0.271  | 0.462  |
|       |                         | $\beta_1$ | 0.015  | 0.115  | 0.139  | 0.396  |
|       |                         | $\gamma_1$| -0.002 | -0.003 | 0.019  | 0.019  |
|       |                         | $\gamma_2$| 0.001  | 0.000  | 0.006  | 0.007  |
|       |                         | $\phi$     | -0.012 | 0.012  | 0.138  | 0.370  |
| 400   | (0.215,0.183)           | $\beta_2$ | 0.019  | 0.024  | 0.181  | 0.309  |
|       |                         | $\beta_0$ | -0.018 | -0.070 | 0.201  | 0.379  |
|       |                         | $\beta_1$ | 0.013  | 0.053  | 0.106  | 0.253  |
|       |                         | $\gamma_1$| -0.001 | -0.002 | 0.017  | 0.017  |
|       |                         | $\gamma_2$| 0.000  | 0.000  | 0.005  | 0.007  |
|       |                         | $\phi$     | -0.005 | 0.011  | 0.106  | 0.368  |
| 300   | (0.316,0.179)           | $\beta_2$ | 0.033  | 0.041  | 0.294  | 0.336  |
|       |                         | $\beta_0$ | -0.076 | -0.117 | 0.364  | 0.468  |
|       |                         | $\beta_1$ | 0.053  | 0.114  | 0.219  | 0.421  |
|       |                         | $\gamma_1$| -0.006 | -0.006 | 0.028  | 0.027  |
|       |                         | $\gamma_2$| 0.000  | 0.000  | 0.010  | 0.011  |
|       |                         | $\phi$     | 0.036  | 0.062  | 0.275  | 0.410  |
| 400   | (0.316,0.179)           | $\beta_2$ | 0.033  | 0.027  | 0.245  | 0.289  |
|       |                         | $\beta_0$ | -0.039 | -0.071 | 0.288  | 0.377  |
|       |                         | $\beta_1$ | 0.028  | 0.066  | 0.144  | 0.268  |
|       |                         | $\gamma_1$| -0.006 | -0.004 | 0.024  | 0.025  |
|       |                         | $\gamma_2$| 0.001  | 0.000  | 0.009  | 0.011  |
|       |                         | $\phi$     | 0.025  | 0.025  | 0.218  | 0.410  |

We next turn out attention to comparison of CPU times between the PNCG and EM algorithms. For this purpose, we present the CPU times (in seconds) in Table 3, where each reported time represents the total time taken by an algorithm to produce the estimates for one simulated data set. It is important to mention here that the technique of finding the initial values for the PNCG algorithm did
Table 2: Comparison of PNCG algorithm with EM algorithm in terms of bias and RMSE with true value of $\phi$ as 0.75

| $n$   | $(\gamma_1, \gamma_2)$ | Parameter | Bias  | RMSE  |
|-------|-------------------------|-----------|-------|-------|
|       |                         |           | PNCG  | EM    | PNCG  | EM    |
| 300   | (0.215,0.183)           | $\beta_2$ | 0.018 | 0.013 | 0.247 | 0.368 |
|       |                         | $\beta_0$ | -0.050 | -0.138 | 0.263 | 0.486 |
|       |                         | $\beta_1$ | 0.027 | 0.077 | 0.153 | 0.354 |
|       |                         | $\gamma_1$ | -0.004 | -0.001 | 0.020 | 0.018 |
|       |                         | $\gamma_2$ | 0.001 | 0.002 | 0.007 | 0.008 |
|       |                         | $\phi$   | 0.000 | -0.140 | 0.159 | 0.422 |
| 400   | (0.215,0.183)           | $\beta_2$ | 0.002 | -0.018 | 0.195 | 0.318 |
|       |                         | $\beta_0$ | -0.029 | -0.094 | 0.209 | 0.417 |
|       |                         | $\beta_1$ | 0.025 | 0.043 | 0.115 | 0.231 |
|       |                         | $\gamma_1$ | -0.002 | 0.000 | 0.017 | 0.017 |
|       |                         | $\gamma_2$ | 0.001 | 0.002 | 0.006 | 0.007 |
|       |                         | $\phi$   | 0.003 | -0.138 | 0.119 | 0.408 |
| 300   | (0.316,0.179)           | $\beta_2$ | 0.029 | -0.002 | 0.300 | 0.352 |
|       |                         | $\beta_0$ | -0.063 | -0.143 | 0.370 | 0.458 |
|       |                         | $\beta_1$ | 0.039 | 0.056 | 0.193 | 0.290 |
|       |                         | $\gamma_1$ | -0.006 | -0.003 | 0.029 | 0.027 |
|       |                         | $\gamma_2$ | 0.001 | 0.003 | 0.010 | 0.012 |
|       |                         | $\phi$   | 0.006 | -0.168 | 0.274 | 0.445 |
| 400   | (0.316,0.179)           | $\beta_2$ | 0.034 | 0.003 | 0.269 | 0.312 |
|       |                         | $\beta_0$ | -0.045 | 0.077 | 0.315 | 0.385 |
|       |                         | $\beta_1$ | 0.028 | 0.055 | 0.166 | 0.265 |
|       |                         | $\gamma_1$ | -0.004 | -0.004 | 0.025 | 0.025 |
|       |                         | $\gamma_2$ | 0.001 | 0.001 | 0.010 | 0.010 |
|       |                         | $\phi$   | 0.022 | -0.101 | 0.256 | 0.418 |

not work for the EM algorithm. As mentioned in Pal and Balakrishnan (2016), for the EM algorithm, one needs to apply a grid search on model parameters to find the initial values, which itself is time consuming. Furthermore, the two-way profile likelihood approach to estimate $\gamma_1$ and $\phi$ within the EM framework adds to the computation time. This is clearly seen in Table 3, where the CPU time taken by the EM algorithm is more than the PNCG algorithm by a factor of at least 184. Thus, the PNCG algorithm not only results in more accurate and precise estimates but also results in huge gain in computational efficiency.

6 Real data analysis

To illustrate the proposed PNCG algorithm, we analyzed a well-known melanoma data that is available in the “timereg” package of R software. The dataset contains 205 patients who were observed after operation for removal of malignant melanoma in the period 1962-1977 and then followed until 1977. The observed time is recorded in years and refers to the time until the patient’s death or the censoring time. It has a mean of 5.9 years and a standard deviation of 3.1 years. Patients who survived the end of the study and patients who died due to some other causes were considered as censored observations.
Table 3: CPU times (in seconds) for PNCG and EM algorithms

| n (φ, γ₁, γ₂)       | CPU Time (in seconds) |
|---------------------|-----------------------|
|                     | PNCG      | EM        |
| 300 (0.50, 0.215, 0.183) | 2.55      | 550.61    |
| 400 (0.50, 0.215, 0.183) | 2.58      | 692.67    |
| 300 (0.50, 0.316, 0.179) | 1.58      | 730.43    |
| 400 (0.50, 0.316, 0.179) | 1.78      | 1000.41   |
| 300 (0.75, 0.215, 0.183) | 3.00      | 552.39    |
| 400 (0.75, 0.215, 0.183) | 3.48      | 696.66    |

The percentage of censored observations is 72%. For our analysis, we selected the ulceration status (presence of ulcer for 90 patients and absence of ulcer for 115 patients) and tumor thickness (measured in mm with a mean of 2.92 and a standard deviation of 2.96) as prognostic factors. As done in Pal and Balakrishnan (2016), we linked the parameter \( p \) to tumor thickness and the parameter \( η \) to ulceration status to retain identifiability of model parameters; see also Rodrigues et al. (2011).

We employed the proposed PNCG algorithm and it simultaneously maximized all model parameters. The results are presented in Table 4. For comparison purpose, we also present the EM estimates and the corresponding standard errors, which are taken from Table 3 of Pal and Balakrishnan (2016). Note that in the EM algorithm, the M-step was carried out using a one-step Newton Raphson method and the estimates of \( γ₁ \) and \( φ \) were obtained by employing a two-way profile likelihood approach within the EM algorithm. Furthermore, the standard errors corresponding to the EM estimates were obtained by inverting the observed information matrix under the assumption that \( γ₁ \) and \( φ \) were fixed. Corresponding to the PNCG estimates, we tried to compute the standard errors by inverting the observed information matrix (with respect to all model parameters), however, we noticed that the second-order derivatives of the observed log-likelihood function were highly unstable, specifically with respect to the parameter \( φ \). As such, we recommend a bootstrap technique here. The standard errors in Table 4 corresponding to the PNCG algorithm were calculated using the non-parametric bootstrap method. Note that the PNCG bootstrap standard errors are much lower than the EM standard errors although there is no significant difference in the estimates of the model parameters. The maximized log-likelihood values with the PNCG and EM estimates (both having the same number of parameters) turned out to be -199.067 and -199.185, respectively. Therefore, the PNCG algorithm results in a better fit.

To check for the adequacy of the DNB model with the PNCG estimation method, we computed the normalized randomized quantile residuals as suggested by Dunn and Smyth (1996). The QQ plot, where each point corresponds to the median of five sets of ordered residuals, is presented in Figure 1. It is clear that the plot shows a linear pattern. We also tested for the normality of residuals using the Kolmogorov-Smirnov test and the p-value turned out to be 0.999. This clearly provides very strong evidence of normality of residuals.

### 7 Concluding remarks

In this paper, we proposed a new algorithm, based on a projected non-linear conjugate gradient method, for the maximum likelihood estimation of the DNB cure rate model parameters. We showed
Table 4: MLEs and standard errors of the parameters of the destructive negative binomial cure rate model.

| Parameter          | Estimate PNCG | EM | Standard Error PNCG | EM |
|--------------------|---------------|----|---------------------|----|
| $\beta_1, \text{intercept}$ | -5.841        | -5.882 | 0.573               | 1.183 |
| $\beta_1, \text{thickness}$    | 1.183         | 1.197 | 0.383               | 0.354 |
| $\beta_2, \text{ulc:present}$   | 5.434         | 5.490 | 0.523               | 1.001 |
| $\beta_2, \text{ulc:absent}$    | 3.533         | 3.484 | 0.479               | 1.154 |
| $\gamma_1$         | 0.314         | 0.300 | 0.029               | -    |
| $\gamma_2$         | 0.122         | 0.127 | 0.020               | 0.021 |
| $\phi$             | 6.654         | 6.600 | 0.604               | -    |

Figure 1: QQ plot of normalized randomized quantile residuals

that our proposed method results in estimates that have smaller bias and smaller RMSE when compared to the estimates obtained from the EM algorithm. The reduction in the RMSE is more pronounced for the parameters that are associated with the cure rate. Furthermore, we showed that our proposed method is significantly computationally less expensive than the EM algorithm. We do believe that we are the first one to propose the PNCG algorithm in the context of cure rate model and hope that other researchers will also consider it, given the advantages we have pointed out. In this regard, our proposed algorithm can also be used for other complex cure rate models, for instance, the COM-Poisson cure rate model (Balakrishnan and Pal, 2016) and the destructive COM-Poisson cure rate model (Pal et al., 2018). We are currently working on these and hope to report the findings in a future paper.
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