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Destructive weighted Poisson cure rate models

Josemar Rodrigues · Mário de Castro · N. Balakrishnan · Vicente G. Cancho

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Abstract In this paper, we develop a flexible cure rate survival model by assuming the number of competing causes of the event of interest to follow a compound weighted Poisson distribution. This model is more flexible in terms of dispersion than the promotion time cure model. Moreover, it gives an interesting and realistic interpretation of the biological mechanism of the occurrence of event of interest as it includes a destructive process of the initial risk factors in a competitive scenario. In other words, what is recorded is only from the undamaged portion of the original number of risk factors.

Keywords Competing risks · Cure rate models · Long-term survival models · Weighted Poisson distribution · Conway-Maxwell Poisson (COM-Poisson) distribution

1 Introduction

Models for survival data with a surviving fraction (also known as cure rate models or long-term survival models) play an important role in reliability and survival analysis.

J. Rodrigues (✉)
Departamento de Estatística, Universidade Federal de São Carlos, Via Washington Luís, km 235, Caixa Postal 676, São Carlos, SP, 13565-905, Brazil
e-mail: vjosemar@ufscar.br

M. de Castro · V. G. Cancho
Instituto de Ciências Matemáticas e de Computação, Universidade de São Paulo, Caixa Postal 668, São Carlos, SP, 13560-970, Brazil

N. Balakrishnan
Department of Mathematics and Statistics, McMaster University, Hamilton, ON L8S 4KI, Canada

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In this paper, we extend the proposal of Yakovlev and Tsodikov (1996) (see also Chen et al. 1999) through a special case of the compound weighted Poisson distribution. The proposed compound weighted cure rate survival model is a more realistic alternative to the unified cure rate model discussed by Rodrigues et al. (2008) and it presumes that the original number of risk factors produced by nature undergoes a destructive process and what is recorded is only the undamaged portion of the original observations which is represented by a compound variable. Furthermore, this model can account for over-dispersion and under-dispersion that is commonly encountered in discrete data.

We find applications of cure rate models in a wide array of areas such as biomedical studies, finance, criminology, demography, manufacturing, and industrial reliability. For instance, in biomedical studies, an event of interest can be the patient's death, which can occur due to different competing causes or a tumor recurrence, which can occur due to metastasis-component tumor cells in the individual left active after an initial treatment. A metastasis-component tumor cell is a tumor cell which has the potential of metastasizing (Yakovlev and Tsodikov 1996).

Let M^{w} be an unobservable weighted Poisson random variable denoting the initial number of competing causes related to the occurrence of an event of interest, with probability mass function (pmf)

$$p^{\mathrm{w}}(m;\eta,\phi) = P[M^{\mathrm{w}} = m;\eta,\phi] = \frac{\mathrm{w}(m;\phi)\,p^{*}(m;\eta)}{E_{\eta}[\mathrm{w}(M;\phi)]},\ m = 0,1,2,\ldots, \quad (1)$$

where $\mathrm{w}(\cdot;\phi)$ is a non-negative weight function with parameter $\phi \geq 0$, $p^{*}(\cdot;\eta)$ is the pmf of a Poisson distribution with parameter $\eta > 0$, and $E_{\eta}[\cdot]$ indicates that the expectation is taken with respect to the variable M following a Poisson distribution with mean parameter η. We refer to (1) as the weighted Poisson distribution with parameter η and weight function $\mathrm{w}(\cdot;\phi)$ or, alternatively, the weighted version of M.

Given $M^{\mathrm{w}} = m$, let X_j, $j = 1,2,\ldots,m$, be independent random variables, independently of M^{w}, following a Bernoulli distribution with success probability p indicating the presence of the j-th competing cause. The total damaged D^{w}, representing the total number of competing causes among the M^{w} initial competing causes which are not destroyed, is defined as

$$D^{\mathrm{w}} = \begin{cases} X_1 + X_2 + \cdots + X_{M^{\mathrm{w}}}, & \text{if } M^{\mathrm{w}} > 0, \\ 0, & \text{if } M^{\mathrm{w}} = 0. \end{cases} \quad (2)$$

By damage or destruction, we mean that $D^{\mathrm{w}} \leq M^{\mathrm{w}}$. The conditional distribution of D^{w}, given $M^{\mathrm{w}} = m$, will therefore be referred to as damaged distribution.

Another way of looking at (2) was described by Yang and Chen (1991) in a bioassay study. They assumed that the initial risk factors are primary initiated malignant cells where X_j in (2) denotes the number of living malignant cells that are descendants of the j-th initiated malignant cell during some time interval. In this case, D^{w} denotes the total number of living malignant cells at some specific time.

With respect to the weighted distributions, they were introduced first by Fisher (1934), but it was Rao (1965) who studied the weighted distributions in a unified way. Rao (1965) pointed out that in many situations the recorded observations cannot be

considered as a random sample from the original distribution due to many reasons such as non-observability of some events, damage caused to original observations and adoption of unequal probability sampling. For instance, the weighted distribution with identity weight function is called the length-biased distribution. The length-biased distribution has found applications in biomedical problems such as early detection of a disease (Zelen and Feinleib 1969). Rao (1965) used the length-biased distribution in the study of human families and wildlife population. It has also been used by Cnaan (1985) in a cardiology study involving two phases.

The rest of this paper is organized as follows. In Sect. 2, we formulate the compound weighted cure survival function. Some illustrative examples are then given in Sect. 3. Maximum likelihood estimation of the parameters of the model is described in Sect. 4. An application to a real data set is detailed in Sect. 5. Finally, some concluding comments are made in Sect. 6.

2 Model formulation

In the competing causes scenario, the number of competing causes D^{w} in (2) and the lifetimes V associated with its causes are not observable (latent variables). So, in order to include those individuals who are not susceptible to the event occurrence, the lifetime is defined as

$$Y = \min\{V_1, V_2, \ldots, V_{D^{\mathrm{w}}}\} \tag{3}$$

for $D^{\mathrm{w}} \geq 1$, and $Y = \infty$ if $D^{\mathrm{w}} = 0$, which leads to a proportion p_0 of the population not susceptible to the event occurrence, also called the "cured fraction".

According to Tsodikov et al. (2003) and Rodrigues et al. (2008), among others, the compound or destructive weighted cure survival function of the random variable Y in (3) is given by

$$S_{\mathrm{pop}}(y) = P[Y \geq y] = A_{D^{\mathrm{w}}}(S(y)) = \sum_{m=0}^{\infty} P[D^{\mathrm{w}} = m]\{S(y)\}^m, \tag{4}$$

where $S(\cdot)$ denotes the common survival function of the unobserved lifetimes in (3) and $A_{D^{\mathrm{w}}}(\cdot)$ is the probability generating function (pgf) of the compound variable D^{w}, which converges when $s = S(y) \in [0, 1]$. In the next theorem, we present the survival function of the observed lifetime in (3).

Theorem 2.1 *Let $\phi \geq 0, \theta \in \Theta \subset \mathbb{R}$, and the pmf of the number of competing causes M^w be of the form*

$$p^w(m; \theta, \phi) = \varphi(m; \phi)\exp\{\theta m - K(\theta, \phi)\}, \ m = 0, 1, 2, \ldots. \tag{5}$$

Then, the destructive weighted Poisson cure rate survival function is given by

$$S_{pop}(y; \eta, \phi, p) = \exp\{-\eta p F(y)\}\frac{E_{\eta\{1-pF(y)\}}[w(M; \phi)]}{E_{\eta}[w(M; \phi)]}, \tag{6}$$

where $\eta = \exp(\theta)$, $F(\cdot) = 1 - S(\cdot)$ and $w(m; \phi) = m!\varphi(m; \phi)$.

Proof The pgf of the Bernoulli variables in (2) is $h(s;\, p) = 1 - p + ps$. Since the pmf in (1) can be written as in (5), the result follows from a straightforward application of Theorem 1 in Rodrigues et al. (2009) and the theorem in Feller (1968, p. 287). □

If we take $p = 1$, we get the weighted Poisson long-term survival function obtained by Rodrigues et al. (2009, Theorem 1). The function in (6) is not a proper survival function, as shown in the next theorem.

Theorem 2.2 *Given a proper survival function $S(y)$ and $w(0;\, \phi) > 0$, we have*

$$\lim_{y\to\infty} S_{pop}(y;\, \eta, \phi, p) = p_0 = \exp(-\eta p)\frac{E_{\eta(1-p)}[w(M;\, \phi)]}{E_{\eta}[w(M;\, \phi)]}, \tag{7}$$

where p_0 denotes the proportion of "cured" or "immune" individuals present in the population from which the data were taken.

Proof The expression in (7) follows immediately from (6). □

An immune individual means one who is not subject to the event under study. Thus, according to (7), we define p_0 as the compound weighted Poisson long-term proportion and $S_{\text{pop}}(\cdot;\, \eta, \phi, p)$ in (6) as the compound weighted Poisson long-term survival function.

In the next theorem, we present the pmf of the total damaged D^{w} in (2).

Theorem 2.3 *Let the pmf of the discrete variable M^w be as in Theorem 2.1. Then, the compound variable D^w is a weighted Poisson distribution with parameter ηp and with weight function*

$$w_p(j;\, \eta, \phi, p) = E_{\eta(1-p)}[w(j + U;\, \phi)], \tag{8}$$

where $U = M - j$ is a Poisson variable with parameter $\eta(1 - p)$.

Proof It follows from the fundamental formula for conditional probabilities that

$$P[D^{\text{w}} = j;\, \theta, \phi, p] = \sum_{m=0}^{\infty} \underbrace{p^{\text{w}}(m;\, \theta, \phi)}_{\text{weighted Poisson}} \overbrace{P[D^{\text{w}} = j | M^{\text{w}} = m;\, p]}^{\text{damaged distribution}}. \tag{9}$$

From (1) and using the pmf of a binomial variable, after some direct algebra, we obtain

$$P[D^{\text{w}} = j;\, \eta, \phi, p] = \frac{e^{-\eta p}(\eta p)^j}{j! E_{\eta}[\text{w}(M;\, \phi)]} E_{\eta(1-p)}[\text{w}(j + U;\, \phi)]. \tag{10}$$

Since $E_{\eta}[\text{w}(M;\, \phi)] = E_{\eta p}[\text{w}_p(D;\, \eta, \phi, p)]$, the result follows from (10), where D is a Poisson random variable with parameter ηp and D^{w} is the weighted version of D. □

Theorem 2.4 *Let the destructive random variable $U = M - D$ be as in Theorem 2.3. Then, U^w is a weighted Poisson random variable with parameter $\eta(1-p)$ and with weight function*

$$w_p^*(j;\eta,\phi,p) = E_{\eta p}[w(j+D;\phi)], \tag{11}$$

or, $M^w = D^w + U^w$.

Proof We have

$$P[U^{\mathrm{w}} = j] = \frac{(1-p)^j e^{-\eta}}{E_\eta[\mathrm{w}(M;\phi)]j!}\sum_{m=j}^{\infty}\frac{\mathrm{w}(m;\phi)\eta^m p^{m-j}}{(m-j)!}. \tag{12}$$

Since $E_\eta[\mathrm{w}(M;\phi)] = E_{\eta(1-p)}[\mathrm{w}_p^*(U;\eta,\phi,p)]$, the result readily follows. □

It is very important to emphasize here that the weighted Poisson random variables D^{w} and U^{w} are independent if, and only if, the weight function $\mathrm{w}(m,\phi)$ is constant, that is, M^{w} is the standard Poisson variable with parameter η. This result was mentioned by Rao and Rubin (1964) in a very particular case.

The next result gives an exact expression for the mean and variance of D^{w} which will be very important to study dispersion problems (Kokonendji et al. 2008).

Theorem 2.5 *Assuming that M^w is a weighted Poisson distribution with parameter η and with weight function $w(\cdot;\phi)$, and a binomial damaged distribution, we have*

$$Var[D^w] = E[D^w] + \eta^2\frac{d^2}{d\eta^2}\log\{E_{\eta p}[w_p(D;\eta,\phi,p)]\}$$

with

$$E[D^w] = \eta p + \eta\frac{d}{d\eta}\log\{E_{\eta p}[w_p(D;\eta,\phi,p)]\},$$

where D is a Poisson random variable with parameter ηp.

Proof The result follows from (8) and a straightforward application of the lemma in Kokonendji et al. (2008). □

In order to be more clear about the damaged distribution, what we mean is that there is a positive probability of the value m of M^{w} to be reduced to some value j of D^{w} or, after some destructive process, $m-j$ of the m initial risk factors remain active in a competitive scenario.

3 Some illustrative examples

In this section, we present a few specific models that arise from our general formulation. In Table 1, we present the surviving function and the cured fraction corresponding to these models, as well as the improper density function $f_{\mathrm{pop}}(y) = -dS_{\mathrm{pop}}(y)/dy$. As expected, the greater the values of p and η, the smaller the cured fraction.

Table 1 Survival function (S_{pop}), density function (f_{pop}), and cured fraction (p_0) for different models

Destructive model	$S_{\text{pop}}(y)$	$f_{\text{pop}}(y)$	p_0
Length-biased			
Poisson	$e^{-\eta pF(y)}\{1-pF(y)\}$	$p\left\{\eta+\dfrac{1}{1-pF(y)}\right\}S_{\text{pop}}(y)f(y)$	$(1-p)e^{-\eta p}$
Exponentially weighted Poisson	$\exp\{-\eta pe^{2\phi}F(y)\}$	$\eta pe^{2\phi}S_{\text{pop}}(y)f(y)$	$\exp\{-\eta pe^{2\phi}\}$
Negative binomial	$\{1+\phi\eta pF(y)\}^{-1/\phi}$	$\dfrac{\eta p}{1+\phi\eta pF(y)}S_{\text{pop}}(y)f(y)$	$(1+\phi\eta p)^{-1/\phi}$
COM-Poisson	$\dfrac{Z(\eta\{1-pF(y)\},\phi)}{Z(\eta,\phi)}$	$\dfrac{pf(y)}{Z(\eta,\phi)\{1-pF(y)\}}\displaystyle\sum_{j=1}^{\infty}\dfrac{j[\eta\{1-pF(y)\}]^j}{(j!)^\phi}$	$\dfrac{Z(\eta(1-p),\phi)}{Z(\eta,\phi)}$

3.1 Destructive length-biased Poisson model

When the weight function of M^{w} is $\text{w}(m;\phi)=m$, then the weight function of D^{w} has an explicit form given by $\text{w}_p(j;\eta,p)=j+\eta(1-p)$. Recall that, in this case, M^{w} has a Poisson distribution with parameter η shifted up by one, and is underdispersed, since $\text{Var}[M^{\text{w}}]<E[M^{\text{w}}]$. Also, note that the compound Poisson distribution of D^{w} is not shifted-Poisson, since its pmf is of the form

$$P[D^{\text{w}}=j;\eta,p]=\frac{\exp(-\eta p)(\eta p)^j}{j!}\left(1-p+\frac{j}{\eta}\right),\ j=0,1,2,\ldots. \tag{13}$$

From (6), we obtain the destructive length-biased Poisson cure rate survival function in Table 1. It is interesting to note that for $p=1$ it is a proper survival function, since the initial number of risk factors is truncated at 0.

3.2 Destructive exponentially weighted Poisson model

When the weight function of the initial number of risk factors is exponential, $\text{w}(m;\phi)=e^{\phi m}$, $\phi\in\mathbb{R}$, then the weight function of the damaged random variable D^{w} has an explicit form $\text{w}_p(j;\eta,\phi,p)=E_{\eta(1-p)}[\exp\{\phi(j+U)\}]=\exp\{\phi j-\eta(1-p)(1-e^{\phi})\}$. It is easy to see that M^{w} has a Poisson distribution with parameter ηe^{ϕ} and that the total damaged variable, D^{w}, has a weighted Poisson distribution with the above weight function and parameter ηpe^{ϕ}.

3.3 Destructive negative binomial model

Let us consider the initial number of risk factors, M^{w}, as a variable with a negative binomial distribution with parameters $\phi>0$ and $\eta>0$, that is,

$$P[M^{\mathrm{w}} = m; \eta, \phi] = \frac{\Gamma(\phi^{-1} + m)}{\Gamma(\phi^{-1})m!} \left(\frac{\phi\eta}{1+\phi\eta}\right)^m (1+\phi\eta)^{-1/\phi},\ m = 0, 1, 2, \ldots. \tag{14}$$

Note that $\phi = 1$ leads to the geometric distribution with parameter $1/(1+\phi\eta)$. Comparing with (1), we realize that (14) is a weighted Poisson distribution with parameter $\phi\eta/(1+\phi\eta)$ and weight function $\mathrm{w}(m;\phi) = \Gamma(\phi^{-1}+m)$. So, we arrive at a closed-form expression for the weight function $\mathrm{w}_p(j;\eta,\phi,p)$, as

$$\begin{aligned}\mathrm{w}_p(j;\eta,\phi,p) &= E_{\phi\eta(1-p)/(1+\phi\eta)}[\Gamma(\phi^{-1}+j+U)] \\ &= \exp\{-\phi\eta(1-p)/(1+\phi\eta)\}\left\{\frac{1}{1-\phi\eta(1-p)/(1+\phi\eta)}\right\}^j \\ &\quad \times \frac{\Gamma(\phi^{-1}+j)}{\{1-\phi\eta(1-p)/(1+\phi\eta)\}^{1/\phi}}.\end{aligned}$$

However, in this case, after some algebraic manipulations, we find

$$E_{\eta p}[\mathrm{w}_p(D;\eta,\phi,p)] = \exp\{-\phi\eta/(1+\phi\eta)\}\Gamma(\phi^{-1})(1+\phi\eta p)^{1/\phi}$$

and

$$P[D^{\mathrm{w}} = j; \eta, \phi, p] = \frac{\Gamma(\phi^{-1}+j)}{\Gamma(\phi^{-1})j!}\left(\frac{\phi\eta p}{1+\phi\eta p}\right)^j (1+\phi\eta p)^{-1/\phi},\ j = 0, 1, 2, \ldots.$$

3.4 Destructive COM-Poisson model

Let us suppose that the initial number of risk factors or competing causes follows a COM-Poisson distribution with parameters $\eta > 0$ and $\phi > 0$ (Shmueli et al. 2005), with probability mass function

$$P[M^{\mathrm{w}} = m; \eta, \phi] = \frac{1}{Z(\eta,\phi)}\frac{\eta^m}{(m!)^\phi},\ m = 0, 1, 2, \ldots, \tag{15}$$

where $Z(\eta,\phi) = \sum_{j=0}^{\infty} \eta^j/(j!)^\phi$. In particular, when $\phi = 0$ and $\eta < 1$, the COM-Poisson distribution reduces to the geometric distribution with parameter $1-\eta$. The distribution in (15) may also be viewed as a weighted Poisson distribution with weight function $\mathrm{w}(m;\phi) = (m!)^{1-\phi}$. Therefore, by using (6), we get the corresponding entries in Table 1. In Sect. 5, the truncation of the $Z(\eta,\phi)$ series is done as described by Rodrigues et al. (2009).

From (8), for integer ϕ, the weight function of the total damaged variable D^{w} is given by

$$\begin{aligned}
\mathrm{w}_p(j;\eta,\phi,p) &= E_{\eta(1-p)}[\{(j+U)!\}^{1-\phi}] \\
&= \exp\{-\eta(1-p)\}(j!)^{1-\phi}\sum_{m=0}^{\infty}[(j+1)(j+2)\times\cdots\times(j+m)]^{1-\phi}\frac{\{\eta(1-p)\}^m}{m!} \\
&= \exp\{-\eta(1-p)\}(j!)^{1-\phi}\,{}_1\mathcal{F}_\phi(j+1;j+1,\ldots,j+1;\eta(1-p)), \qquad (16)
\end{aligned}$$

where the generalized hypergeometric function is defined by

$${}_{\mathrm{u}}\mathcal{F}_{\mathrm{v}}(a_1,\ldots,a_u;b_1,\ldots,b_v;x)=\sum_{m=0}^{\infty}\frac{(a_1)_m(a_2)_m\times\cdots\times(a_{\mathrm{u}})_m}{(b_1)_m(b_2)_m\times\cdots\times(b_{\mathrm{v}})_m}\frac{x^m}{m!},$$

with $(a)_m = a(a+1)\times\cdots\times(a+m-1)$ (Gradshteyn and Ryzhik 2000). Taking $j=0$ and $p=0$ in (16), we obtain from (6) a closed-form expression for the destructive COM-Poisson cure rate model as

$$S_{\mathrm{pop}}(y;\eta,\phi,p)=\exp\{-\eta pF(y)\}\frac{{}_1\mathcal{F}_\phi(1;1,\ldots,1;\eta\{1-pF(y)\})}{{}_1\mathcal{F}_\phi(1;1,\ldots,1;\eta)}.$$

In this case, the distribution of the total damaged variable is

$$P[D^{\mathrm{w}}=j;\eta,\phi,p]=e^{-\eta p}\,\frac{{}_1\mathcal{F}_\phi(1;j+1,\ldots,j+1;\eta(1-p))}{{}_1\mathcal{F}_\phi(1;1,\ldots,1;\eta)},\quad j=0,1,2,\ldots.$$

4 Inference

Let us consider the situation when the lifetime in (3) is not completely observed and is subject to right censoring. Let C_i denote the censoring time. In a sample of size n, we then observe $T_i=\min\{Y_i,C_i\}$ and $\delta_i=\mathrm{I}(Y_i\le C_i)$, where $\delta_i=1$ if T_i is a lifetime and $\delta_i=0$ if it is right censored, for $i=1,\ldots,n$. Let $\boldsymbol{\gamma}$ denote the parameter vector of the distribution of the unobserved time in (3). We propose to relate the parameters p and η of the models in Sect. 3 to covariates $\boldsymbol{x}_{1i}$ and $\boldsymbol{x}_{2i}$, respectively. We adopt the link functions

$$\log\left(\frac{p_i}{1-p_i}\right)=\boldsymbol{x}_{1i}^{\top}\boldsymbol{\beta}_1\quad\text{and}\quad\log(\eta_i)=\boldsymbol{x}_{2i}^{\top}\boldsymbol{\beta}_2, \qquad (17)$$

$i=1,\ldots,n$, where $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ denote vectors of coefficients. Note that the exponentially weighted Poisson and the negative binomial models in Sects. 3.2 and 3.3 are unidentifiable in the sense of Li et al. (2001). To circumvent this problem, when fitting these models, the covariates $\boldsymbol{x}_{1i}$ and $\boldsymbol{x}_{2i}$ do not share common elements and $\boldsymbol{\beta}_2$ does not include an intercept term.

From n pairs of times and censoring indicators $(t_1, \delta_1), \ldots, (t_n, \delta_n)$, the likelihood function under non-informative censoring is given by

$$L(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta}) \propto \prod_{i=1}^{n} \left\{ f_{\text{pop}}(t_i; \boldsymbol{\vartheta}) \right\}^{\delta_i} \left\{ S_{\text{pop}}(t_i; \boldsymbol{\vartheta}) \right\}^{1-\delta_i}, \tag{18}$$

where $\boldsymbol{\vartheta} = (\phi, \boldsymbol{\beta}_1^\top, \boldsymbol{\beta}_2^\top, \boldsymbol{\gamma}^\top)^\top$, $\boldsymbol{t} = (t_1, \ldots, t_n)^\top$, and $\boldsymbol{\delta} = (\delta_1, \ldots, \delta_n)^\top$, whereas $f_{\text{pop}}(\cdot; \boldsymbol{\vartheta})$ and $S_{\text{pop}}(\cdot; \boldsymbol{\vartheta})$ for the models in Sect. 3 can be found in Table 1. We shall now assume a Weibull distribution for the unobserved lifetime in (3) with $F(v; \boldsymbol{\gamma}) = 1 - \exp(-v^{\gamma_1} e^{\gamma_2})$ and $f(v; \boldsymbol{\gamma}) = \gamma_1 v^{\gamma_1 - 1} \exp(\gamma_2 - v^{\gamma_1} e^{\gamma_2})$, for $v > 0$, $\gamma_1 > 0$, and $\gamma_2 \in \mathbb{R}$.

From the likelihood function in (18), the maximum likelihood estimation of the parameter $\boldsymbol{\vartheta}$ is carried out. Numerical maximization of the log-likelihood function $\ell(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta}) = \log\{L(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta})\}$ is accomplished by using existing software (R Development Core Team 2010). The computational program is available from the authors upon request. Under suitable regularity conditions, it can be shown that the asymptotic distribution of the maximum likelihood estimator $\widehat{\boldsymbol{\vartheta}}$ is multivariate normal with mean vector $\boldsymbol{\vartheta}$ and covariance matrix $\boldsymbol{\Sigma}(\widehat{\boldsymbol{\vartheta}})$, which can be estimated by

$$\widehat{\boldsymbol{\Sigma}}(\widehat{\boldsymbol{\vartheta}}) = \left\{ - \frac{\partial^2 \ell(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta})}{\partial \boldsymbol{\vartheta} \partial \boldsymbol{\vartheta}^\top} \right\}^{-1}, \tag{19}$$

evaluated at $\boldsymbol{\vartheta} = \widehat{\boldsymbol{\vartheta}}$. The required second derivatives are computed numerically.

Different models can be compared penalizing over-fitting by using the Akaike information criterion given by $AIC = -2\ell(\widehat{\boldsymbol{\vartheta}}) + 2\#(\boldsymbol{\vartheta})$ and the Schwartz-Bayesian criterion defined by $SBC = -2\ell(\widehat{\boldsymbol{\vartheta}}) + \#(\boldsymbol{\vartheta}) \log(n)$, where $\#(\boldsymbol{\vartheta})$ is the number of model parameters. The model with the smallest value of any of these criteria (among all models considered) is commonly taken as the preferred model for describing the given dataset.

5 Application

In this section, we demonstrate an application of the models detailed in Sect. 3. The dataset 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 to 5565 days (from 0.0274 to 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, as well as patients still alive at the end of the study are censored observations (72%). We take ulceration status (absent, $n = 115$; present, $n = 90$) and tumor thickness (in mm, mean = 2.92 and standard deviation = 2.96) as covariates. Remembering the identifiability issue in Sect. 4, in the destructive exponentially weighted Poisson and the negative binomial models the probability p is linked only to tumor thickness, whereas the parameter η is linked only to ulceration

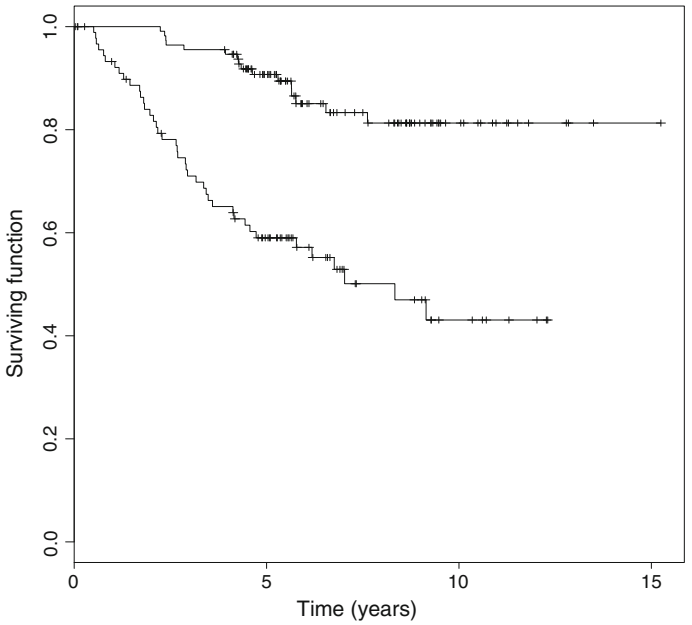

Fig. 1 Kaplan–Meier curves stratified by ulceration status (*upper*: present, *lower*: absent)

Table 2 Statistics from the adjusted models

	Statistic	
Model	AIC	SBC
Destructive length-biased Poisson	437.1	463.7
Destructive exponentially weighted Poisson	424.6	447.8
Destructive negative binomial	411.9	435.2
Destructive COM-Poisson	422.2	452.1
Destructive geometric	418.5	438.5
Negative binomial	415.0	435.0
Geometric	420.8	437.5

status. Kaplan–Meier curves stratified by ulceration status (ulc) in Fig. 1 level off between above 0.4. This behavior indicates that models that ignore the possibility of cure will not be suitable for these data.

Model comparison can be performed with the results shown in Table 2. Two particular cases of the destructive negative binomial were also fitted to the data; namely, the negative binomial ($p = 1$) and the geometric ($p = 1, \phi = 1$). In this way, the destruction mechanism is absent. For these models, the parameter η is linked to the two covariates.

According to the AIC and SBC criteria, the destructive negative binomial and the negative binomial models stand out as the best ones. We emphasize that the destructive length-biased Poisson and the destructive COM-Poisson models, even with the

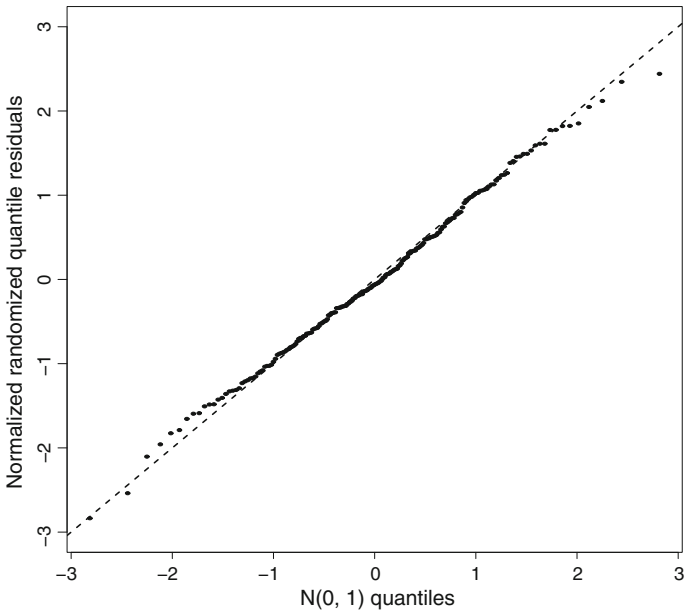

Fig. 2 QQ plot of the normalized randomized quantile residuals with identity line for the destructive negative binomial model (each point corresponds to the median of five sets of ordered residuals)

Table 3 Maximum likelihood estimation for the destructive negative binomial model

Parameter	Estimate (est)	Standard error (se)	|est|/se
γ_1	3.52	1.01	–
γ_2	−7.49	2.34	3.21
$\beta_{1,\text{intercept}}$	−6.44	2.47	2.60
$\beta_{1,\text{thickness}}$	1.28	0.499	2.57
$\beta_{2,\text{ulc:absent}}$	4.26	2.67	1.59
$\beta_{2,\text{ulc:present}}$	6.43	3.19	2.02
ϕ	8.34	4.28	–

parameters p and η linked to both the covariates, do not yield a fit as good as these ones. The QQ plot of the normalized randomized quantile residuals (Dunn and Smyth 1996; Rigby and Stasinopoulos 2005) in Fig. 2 suggests that the destructive negative binomial model is acceptable. Each point in Fig. 2 corresponds to the median of five sets of ordered residuals. Taking into account the criteria in Table 2 and the QQ plot in Fig. 2, we select the destructive negative binomial model as our working model. Maximum likelihood estimates of the coefficients are in Table 3. The estimate of the shape parameter (γ_1) furnishes an evidence against the exponential distribution ($\gamma_1 = 1$) for the unobserved lifetimes.

Figure 3 displays the surviving function for patients with tumor thickness equal to 0.320, 1.94, and 8.32 mm, which correspond to the 5, 50, and 95% quantiles.

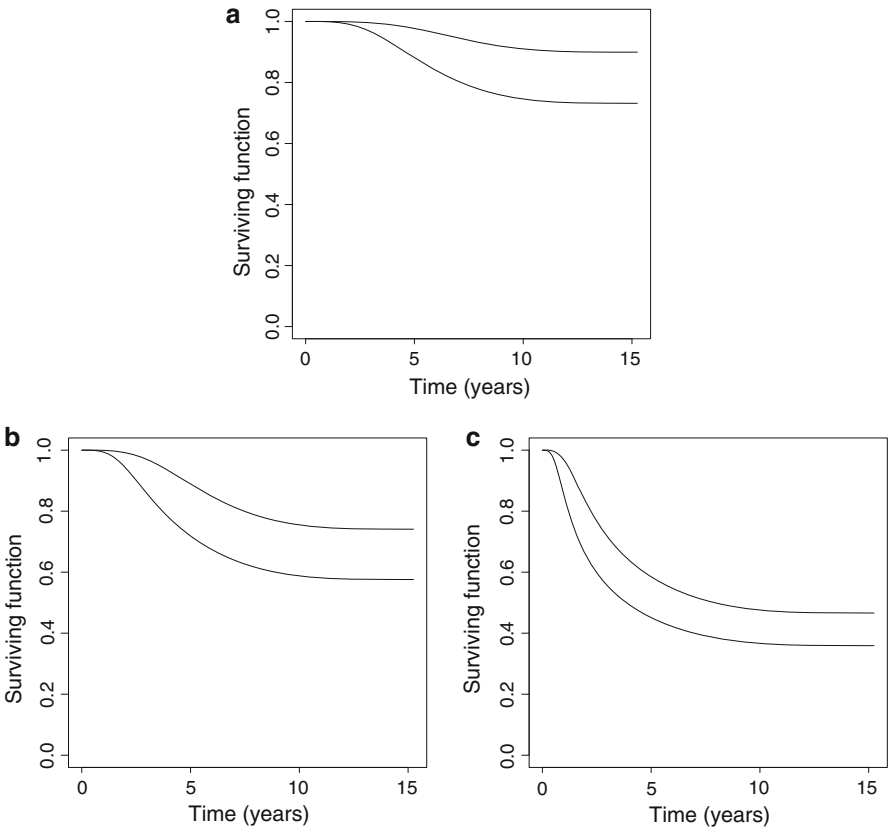

Fig. 3 Surviving function under the destructive negative binomial model stratified by ulceration status (*upper*: absent, *lower*: present) for patients with tumor thickness equal to (**a**) 0.320, (**b**) 1.94, and (**c**) 8.32 mm

The surviving probability decreases more rapidly for patients with thicker tumors. In Fig. 3a, the surviving function does not fall below 0.7.

The destructive exponentially weighted Poisson and the negative binomial models were fitted with the parameters p and η linked to tumor thickness and ulceration status, respectively. If we swap these covariates, there is no improvement in the fit with respect to the criteria in Table 2, since the values of (AIC, SBC) for these models change to (427.7, 447.6) and (417.0, 436.9), respectively.

Finally, we turn out our attention to the role of the covariates on the cured fraction p_0 (see Table 1). The estimates of the $\beta_{2,\text{ulc}}$ coefficients in Table 3 indicate that the mean number of competing causes is greater when ulceration is present, so that the cured fraction decreases. Since $\widehat{\beta}_{1,\text{thickness}} > 0$ in Table 3, higher values of tumor thickness imply smaller cured fraction estimates. Figure 4 displays the combined effect of these covariates on the cured fraction. The lines run almost parallel and the cured fractions, after a steep decrease, reach two plateaux for tumor thickness greater than 5 mm at 46.5 and 35.9% with ulceration status absent and present, respectively.

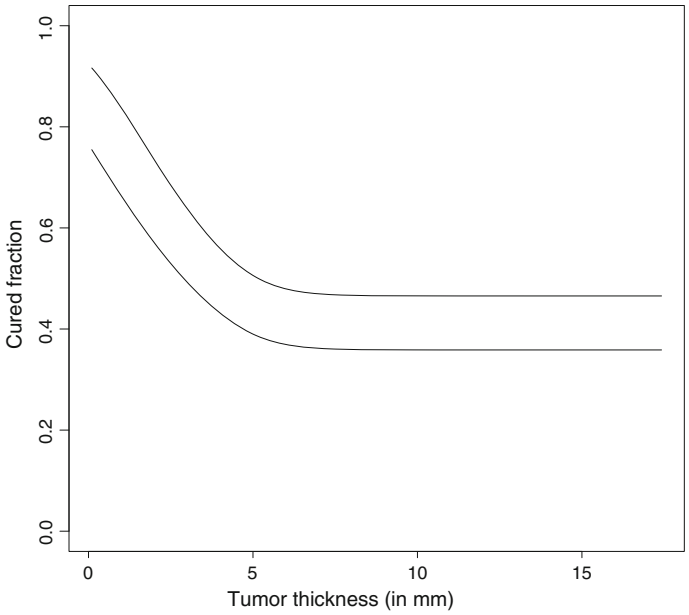

Fig. 4 Cured fraction for the destructive negative binomial model *versus* tumor thickness stratified by ulceration status (*upper*: absent, *lower*: present)

6 Conclusion

It is important to note that the total damaged variable D^{w} in (2) can be recognized as the weighted Poisson processes on the interval [0, 1] formulated by Balakrishnan and Kozubowski (2008). Therefore, most of the results in this paper can be obtained from this viewpoint. In this paper, we look at the problem in a different way, that is, the initial number of risk factors in a competitive scenario is subject to damage according to the binomial probability law. We feel strongly that the length-biased Poisson cure rate survival function truncated at 0 is more realistic than the Poisson distribution to represent, for instance, the number of metastasis-component tumor cells for an individual before the treatment and the untruncated compound discrete distribution to consider the chance of cure after a given treatment. For the practical purpose, the destructive weighted Poisson cure rate model formulated in this paper may be helpful to assess whether the probability of the presence of the j-th competing cause or the cured proportion are significant to justify the fitness, follow-up time and risk prediction.

Finally, we believe that the destructive Poisson cure rate models are very helpful for the global understanding of the variety of infection processes and the carcinogenic effect of prolonged irradiation during some specified period of time (Klebanov et al. 1993; Tournoud and Ecochard 2007). Indeed, these will be a subject of a future research from the classical and Bayesian points of view.

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