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COM–Poisson cure rate survival models and an application to a cutaneous melanoma data

Josemar Rodrigues[a,*], Mário de Castro[b], Vicente G. Cancho[b], N. Balakrishnan[c]

[a]*Universidade Federal de São Carlos, Departamento de Estatística, Caixa Postal 676, 13565-905 São Carlos-SP, Brazil*
[b]*Universidade de São Paulo, Instituto de Ciências Matemáticas e de Computação, Caixa Postal 668, 13560-970 São Carlos-SP, Brazil*
[c]*McMaster University, Department of Mathematics and Statistics, Hamilton, Ontario, Canada L8S4KI*

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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 the Conway–Maxwell Poisson distribution. This model includes as special cases some of the well-known cure rate models discussed in the literature. Next, we discuss the maximum likelihood estimation of the parameters of this cure rate survival model. Finally, we illustrate the usefulness of this model by applying it to a real cutaneous melanoma data.

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. In this paper, we extend the long-term survival models proposed by Berkson and Gage (1952), Yakovlev and Tsodikov (1996) and Chen et al. (1999) through a special case of the weighted Poisson distribution and the long-term survival function formulated recently by Rodrigues et al. (2009). We propose here the Conway–Maxwell Poisson (COM–Poisson) cure rate model as a flexible alternative to the unified cure rate model discussed by Yin and Ibrahim (2005). This model can account for over-dispersion and under-dispersion that is usually encountered in discrete data.

We find applications of cure rate models in areas such as biomedical studies, finance, criminology, demography, manufacturing, and industrial reliability. For instance, in biomedical data, an event of interest can be a patient's death, which can occur due to different competing causes or a tumor recurrence, which can occur due to number of metastasis-component tumor cells for an individual left active after an initial treatment. A metastasis-component tumor cell is a tumor cell which has the potential of metastasizing; see Yakovlev (1994), Yakovlev et al. (1993), Yakovlev and Tsodikov (1996) and Ibrahim et al. (2001). In manufacturing and industrial reliability, an event of interest can be the failure of circuit boards, which can occur due to infant failure or wear-out; see Meeker and Escobar (1998). In financial data, an event under study can be a defaulter or a client churn, which can occur due to different causes; see Hoggart and Griffin (2001).

Let M be a random variable denoting the number of competing causes related to the occurrence of an event of interest, with probability mass function (p.m.f.) $p_m = P[M = m]$ for $m = 0, 1, 2, \ldots$. The variable M is unobservable. Given $M = m$,

* Corresponding author. Tel.: +55 16 33518895; fax: +55 16 33518243.
E-mail address: vjosemar@ufscar.br (J. Rodrigues).

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let W_j $(j=1,2,\ldots,m)$ be independent random variables, independently of M, with a common distribution function $F(y)=1-S(y)$. The random variables W_j denote the time-to-event due to the j-th competing cause, hereafter lifetime, and $S(y)$ denotes the survival function.

In the competing causes scenario (Cox and Oakes, 1984), the number of competing causes M and the lifetime W_j associated with a particular cause are not observable (latent variables), but only the minimum lifetime Y among all causes is usually observed. So, in order to include those individuals who are not susceptible to the event occurrence, the lifetime is defined as

$$Y=\min\{W_0,W_1,W_2,\ldots,W_M\}, \tag{1}$$

where $P[W_0=\infty]=1$, which leads to a proportion p_0 of the population not susceptible to the event occurrence, also called the "cure rate".

This paper is organized as follows. In Section 2, we formulate the Conway–Maxwell Poisson cure rate model as a special case of the weighted Poisson cure model. Maximum likelihood estimation of the parameters of the model is described in Section 3. An application to a real cutaneous melanoma data is illustrated in Section 4. Finally, in Section 5, we make some concluding remarks.

2. The COM–Poisson cure rate model

The long-term survival function of the random variable Y in (1) (Tsodikov et al., 2003; Rodrigues et al., 2009) is given by

$$S_p(y)=P[Y\geqslant y]=A[S(y)]=\sum_{m=0}^{\infty}P[M=m]\{S(y)\}^m, \tag{2}$$

where $A(\cdot)$ is the probability generating function (p.g.f.) of M, which converges when $s=S(y)\in[0,1]$.

Now, let us assume M to be a weighted Poisson random variate with p.m.f.

$$p(m;\eta)=P[M=m;\eta]=\frac{\mathrm{w}(m)p^*(m;\eta)}{E_\eta[\mathrm{w}(M)]},$$

where $\mathrm{w}(\cdot)$ is a non-negative weight function, $p^*(m;\eta)$ is the p.m.f. of a Poisson distribution with parameter $\eta>0$, and $E_\eta[\cdot]$ indicates that the expectation is taken with respect to the Poisson distribution with mean parameter η.

Theorem 1. *Let $\phi\geqslant 0$ and $\theta\in\Theta\subset\mathbb{R}$, and the p.m.f. of the discrete variable M be of the form*

$$p(m;\theta,\phi)=\varphi(m;\phi)\exp\{\theta m-K(\theta,\phi)\},\quad m=0,1,2,\ldots\ . \tag{3}$$

Then, the corresponding p.g.f. is given by

$$A(s)=\exp\{-\eta(1-s)\}\frac{E_{s\eta}[\mathrm{w}(M;\phi)]}{E_\eta[\mathrm{w}(M;\phi)]}, \tag{4}$$

where $\eta=\exp(\theta)$.

Proof. From Kokonendji et al. (2008), we have the following facts:

- The p.m.f. in (3) is a weighted Poisson distribution with respect to the Poisson distribution having mean $\eta=e^\theta$.
- The weight function is given by $\mathrm{w}(m;\phi)=m!\,\varphi(m;\phi)$.
- The cumulant generating function is

$$K(\theta,\phi)=\exp(\theta)+\log E_\eta[\mathrm{w}(M;\phi)]. \tag{5}$$

It is well-known for the exponential family that the logarithm of the moment generating function is

$$\log M(u)=K(\theta+u,\phi)-K(\theta,\phi),\quad u\in\mathbb{R}, \tag{6}$$

and so from (5) and (6), we have

$$\log M(u)=e^\theta(e^u-1)+\log\frac{E_{\eta^*}[\mathrm{w}(M;\phi)]}{E_\eta[\mathrm{w}(M;\phi)]}, \tag{7}$$

with $\eta^* = e^{\theta+u}$. Now, by setting $u = \log(s)$, (7) yields the log of the p.g.f. to be

$$\log A(s) = \log M(\log(s)) = \eta(s-1) + \log \frac{E_{\eta s}[\mathrm{w}(M;\phi)]}{E_{\eta}[\mathrm{w}(M;\phi)]},$$

completing the proof. □

It is worth noting that the result in (4) may be used to generalize the p.g.f. of the first-order Poisson polynomial distribution given by Johnson et al. (2005, p. 487).

From (2) and (4), the weighted Poisson long-term survival function can be expressed as

$$S_p(y) = \exp\{-\eta F(y)\} \frac{E_{\eta S(y)}[\mathrm{w}(M;\phi)]}{E_{\eta}[\mathrm{w}(M;\phi)]}. \tag{8}$$

The function $S_p(y)$ in (8) is not a proper survival function, since $\lim_{y\to\infty} S_p(y) > 0$, as shown in the next theorem.

Theorem 2. *Given a proper survival function $S(y)$ and $\mathrm{w}(0,\phi) > 0$, then*

$$\lim_{y\to\infty} S_p(y) = P[M=0] = p_0 = \exp(-\eta)\frac{\mathrm{w}(0;\phi)}{E_{\eta}[\mathrm{w}(M;\phi)]}, \tag{9}$$

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

Proof. The expression in (9) follows immediately from (8). □

An immune individual means one who is not subject to the event under study. Thus, according to (9), we define p_0 as the weighted Poisson long-term proportion and $S_p(y)$ as the weighted Poisson long-term survival function.

The Conway–Maxwell Poisson distribution, first introduced by Conway and Maxwell (1961), was revived recently by Shmueli et al. (2005). The COM–Poisson distribution generalizes the Poisson distribution in an elegant and flexible way, allowing for under-dispersion as well as over-dispersion. This distribution was also discussed by Kadane et al. (2006) from a Bayesian viewpoint and an elicitation program to find the hyper-parameters from the predictive distribution was discussed as well. The COM–Poisson distribution can be expressed in the exponential form in (3) and can then be viewed as a weighted Poisson distribution with weight function $\mathrm{w}(m;\phi) = (m!)^{1-\phi}$. The p.m.f. of the COM–Poisson distribution for the discrete variable M is given by

$$P[M=m;\eta,\phi] = \frac{1}{Z(\eta,\phi)}\frac{\eta^m}{(m!)^{\phi}}, \quad m = 0,1,2,\ldots, \tag{10}$$

where $Z(\eta,\phi) = \sum_{j=0}^{\infty} \eta^j/(j!)^{\phi}$. Therefore, the cure fraction turns out to be

$$p_0 = P[M=0;\eta,\phi] = \frac{1}{Z(\eta,\phi)} \tag{11}$$

in this case. This result is also consequence of Theorem 2.

When $\phi = 1$, we obtain the Poisson distribution. Values of $\phi > 1$ correspond to under-dispersion while $\phi < 1$ correspond to over-dispersion relative to the Poisson distribution. As $\phi \to \infty$, the COM–Poisson approaches the Bernoulli distribution with parameter $1/(1+\eta)$. When $\phi = 0$ and $\eta < 1$, the COM–Poisson reduces to the geometric distribution with parameter $1-\eta$, and is undefined for $\eta \geqslant 1$.

Theorem 3. *If the discrete variable M follows a COM–Poisson distribution, then the survival function is*

$$S_p(y) = \frac{Z(\eta S(y),\phi)}{Z(\eta,\phi)}, \tag{12}$$

where $\eta = \exp(\theta)$.

Proof. The required result then follows immediately from (8) and (10). □

From (12), we obtain the improper density function

$$f_p(y) = -S_p'(y) = \frac{1}{Z(\eta,\phi)}\frac{f(y)}{S(y)}\sum_{j=1}^{\infty}\frac{j\{\eta S(y)\}^j}{(j!)^{\phi}}, \tag{13}$$

where $f(y)$ denotes the (proper) density function of the lifetime in (1).

The COM–Poisson cure rate model represents a continuous bridge between under-dispersion ($\phi > 1$) and over-dispersion ($\phi < 1$) in the counts of the number of causes. This model encompasses the promotion time cure model when $\phi = 1$ (Yakovlev and Tsodikov, 1996; Chen et al., 1999) and the mixture cure model when $\phi \to \infty$ (Boag, 1949; Berkson and Gage, 1952). In the former model, the cure rate is simply given by $p_0 = 1/Z(\eta, 1) = \exp(-\eta)$.

3. Inference

Let us consider the situation when the time-to-event is not completely observed and is subject to right censoring. Let C_i denote the censoring time. We then observe $T_i = \min\{Y_i, C_i\}$ and $\delta_i = \mathrm{I}(Y_i \leqslant C_i)$, where $\delta_i = 1$ if Y_i is a time-to-event and $\delta_i = 0$ if it is right censored, for $i = 1, \ldots, n$. Let γ denote the parameter vector of the distribution of the time-to-event. 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

$$L(\eta, \phi, \boldsymbol{\gamma}; \boldsymbol{t}, \boldsymbol{\delta}) \propto \prod_{i=1}^{n} f(t_i, \delta_i; \eta, \phi, \boldsymbol{\gamma}), \tag{14}$$

where $\boldsymbol{t} = (t_1, \ldots, t_n)'$ and

$$f(t_i, \delta_i; \eta, \phi, \boldsymbol{\gamma}) = \sum_{m_i=0}^{\infty} \{S(t_i; \boldsymbol{\gamma})\}^{m_i - \delta_i} \{m_i f(t_i; \boldsymbol{\gamma})\}^{\delta_i} p(m_i; \eta, \phi).$$

The likelihood function in (14) can be written as

$$L(\eta, \phi, \boldsymbol{\gamma}; \boldsymbol{t}, \boldsymbol{\delta}) \propto \prod_{i=1}^{n} \{f_p(t_i; \eta, \phi, \boldsymbol{\gamma})\}^{\delta_i} \{S_p(t_i; \eta, \phi, \boldsymbol{\gamma})\}^{1-\delta_i}. \tag{15}$$

Now, we link the parameter η in (12) to covariates $\boldsymbol{x}_i$ by $\eta_i = \exp(\boldsymbol{x}_i'\boldsymbol{\beta})$, $i = 1, \ldots, n$, where $\boldsymbol{\beta} = (\beta_0, \beta_1, \ldots, \beta_k)'$ denotes the vector of regression coefficients. With $\boldsymbol{\vartheta} = (\boldsymbol{\beta}', \phi, \boldsymbol{\gamma}')$, upon substituting (12) and (13) into (15), we obtain the likelihood function as

$$L(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta}) \propto \prod_{i=1}^{n} \frac{1}{Z(\exp(\boldsymbol{x}_i'\boldsymbol{\beta}), \phi)} \left\{ \frac{f(t_i; \boldsymbol{\gamma})}{S(t_i; \boldsymbol{\gamma})} \sum_{j=1}^{\infty} \frac{j\{\exp(\boldsymbol{x}_i'\boldsymbol{\beta}) S(t_i; \boldsymbol{\gamma})\}^j}{(j!)^{\phi}} \right\}^{\delta_i} \{Z(\exp(\boldsymbol{x}_i'\boldsymbol{\beta}) S(t_i; \boldsymbol{\gamma}), \phi)\}^{1-\delta_i}. \tag{16}$$

We shall now assume a Weibull distribution for the time-to-event (W) with

$$F(w; \boldsymbol{\gamma}) = 1 - \exp(-w^{\gamma_1} e^{\gamma_2}) \quad \text{and} \quad f(w; \boldsymbol{\gamma}) = \gamma_1 w^{\gamma_1 - 1} \exp(\gamma_2 - w^{\gamma_1} e^{\gamma_2}) \tag{17}$$

for $w > 0$, $\gamma_1 > 0$, and $\gamma_2 \in \mathbb{R}$.

From the likelihood function in (16), 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 the RS method (Rigby and Stasinopoulos, 2005) available in the gamlss package (Stasinopoulos and Rigby, 2007). The RS method needs only the improper functions (S_p and f_p) and first order derivatives of the logarithm of the improper density function (13), which are presented in the Appendix.

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

$$\widehat{\boldsymbol{\Sigma}}(\widehat{\boldsymbol{\vartheta}}) = \left\{ -\frac{\partial^2 \ell(\boldsymbol{\vartheta}; \boldsymbol{t}, \boldsymbol{\delta})}{\partial \boldsymbol{\vartheta} \partial \boldsymbol{\vartheta}'} \right\}^{-1},$$

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

4. Example

In this section, we illustrate the application of the discussed model to a dataset on cancer recurrence. These data are part of an assay on cutaneous melanoma (a type of malignant cancer) for the evaluation of postoperative treatment performance with a high dose of a certain drug (interferon alfa-2b) in order to prevent recurrence. Patients were included in the study from 1991 to 1995, and follow-up was conducted until 1998. The data, taken from Ibrahim et al. (2001) (see also Kirkwood et al., 2000), present the survival times, representing the time in years until the patient's death or the censoring time. The original sample comprises 427 patients, 10 of whom were removed from our analysis, since their tumor thickness data were missing. The percentage of censored observations was 56%. The observed time has mean $= 3.18$ and standard deviation $= 1.69$. In our application, we selected nodule category (1: $n = 82$; 2: $n = 87$; 3: $n = 137$; 4: $n = 111$) as covariate. As possible models, we picked the commonly used mixture cure model and the promotion time cure model as well as the COM–Poisson cure rate model detailed in the preceding sections.

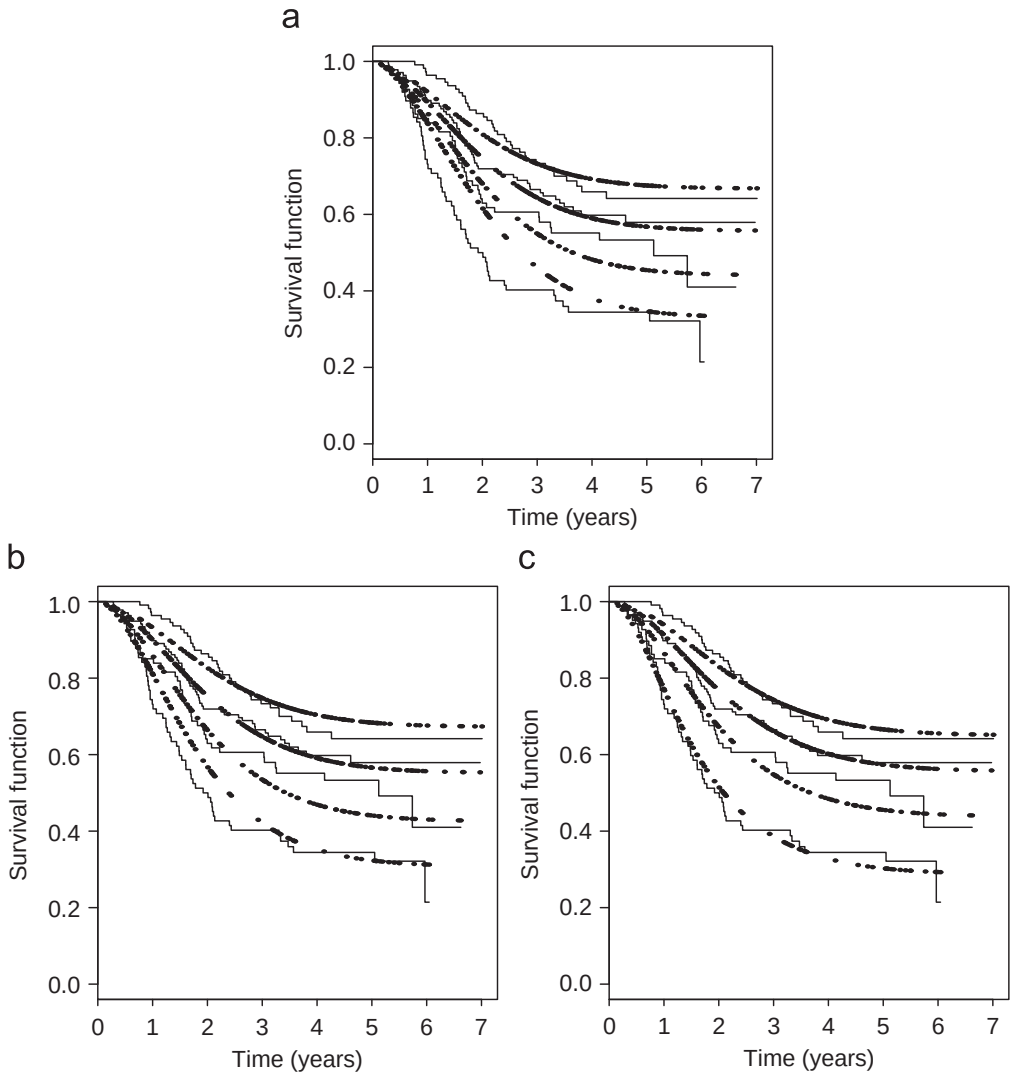

Fig. 1. Kaplan–Meier curves stratified by nodule category (1–4), respectively, and estimates of the survival function according to different models: (a) mixture cure model, (b) promotion time cure model, and (c) COM–Poisson (geometric) cure rate model.

The application was developed in the R system (R Development Core Team, 2008) and computational codes are available from the first author upon request.

The normalizing constant $Z(\eta,\phi)$ in (10)–(13) may be computed by truncating the numerical series. Since the ratio of the terms j and $j-1$ in the series is η/j^{ϕ}, $j\geqslant 1$, by choosing a small ε (0.01, say), we take the smallest k such that $k>(\eta/\varepsilon)^{1/\phi}$ and $Z(\eta,\phi)\approx\sum_{j=0}^{k}\eta^{j}/(j!)^{\phi}$. The density function in (13), the series $Z(\eta,S(y))$ in (12), and the expressions in the Appendix are computed with this number of terms. In a sample we have $\eta_i=\exp(\boldsymbol{x}_i'\boldsymbol{\beta})$. An unique k can be used based on a worst case scenario with $\eta^{*}=\max_{i=1}^{n}\eta_i$. Further, after a preliminary sensitivity study on parameter estimates, in this example we adopted $\varepsilon=0.1$ and k bounded to 50, for computational efficiency.

For these data, we obtained $\widehat{\phi}\approx 0$. So, we test the suitability of the geometric model for the number of causes (M) in (10). Let $\widehat{\boldsymbol{\vartheta}}_0$ be the maximum likelihood estimator of $\boldsymbol{\vartheta}$ under $\mathrm{H}_0:\phi=0$. We use the test statistic $\Lambda=2\{\ell(\widehat{\boldsymbol{\vartheta}};\boldsymbol{t},\boldsymbol{\delta})-\ell(\widehat{\boldsymbol{\vartheta}}_0;\boldsymbol{t},\boldsymbol{\delta})\}$. Taking into account that $\phi=0$ lies on the boundary of the parameter space, the limiting distribution of Λ as "$n\to\infty$" is such that $P[\Lambda\leqslant\lambda]=\frac{1}{2}+\frac{1}{2}P[\chi_1^2\leqslant\lambda]$, where χ_1^2 denotes a variable following a chi-square distribution with 1 degree of freedom (Self and Liang, 1987; Claeskens et al., 2008). In our example, $\Lambda=0.0008$ (p-value$=0.4885$), and we therefore adopt the geometric model as our working model. In this way, the candidate models have the same number of parameters. Furthermore, as $\widehat{\eta}_j=\exp(\widehat{\beta}_0+j\widehat{\beta}_1)<1$, $j=1,\ldots,4$, the distributions corresponding to the nodule categories are legitimate.

For the mixture cure, the promotion time cure, and the COM–Poisson (geometric) cure rate models, the maximized log-likelihood function turned out to be -517.6, -513.3, and -509.7, respectively. Hence, the best fit is achieved with the COM–Poisson cure rate model. This is further ascertained by the plots in Fig. 1. At earlier times, the COM–Poisson model yields a closer concordance with the Kaplan–Meier estimates. Maximum likelihood estimates of the COM–Poisson cure rate model parameters are presented in Table 1. Notice that the estimate of the γ (being away from 1) shows evidence against the exponential distribution in (17).

Table 1
Maximum likelihood estimates of the parameters of the COM–Poisson (geometric) cure rate model.

Parameter	Estimate	Standard error	p-Value
γ_1 (log link)	0.633	0.014	<0.0005
γ_2	−2.041	0.037	<0.0005
β_0	−1.287	0.133	<0.0005
β_1	0.237	0.042	<0.0005

We finally deal with the estimation of the cure rate (p_0). Estimates of the cure rate of patients stratified by nodule category are $\widehat{p_{0j}} = 1/Z(\exp(\widehat{\beta_0} + j\widehat{\beta_1}), \widehat{\phi}), j = 1, \ldots, 4$. With the estimates in Table 1 and (11), we then obtain $\widehat{p_0} = 0.650$, 0.557, 0.438, and 0.289 corresponding to the four nodule categories (1–4).

5. Conclusions

Using the weighted Poisson distribution and the unified theory for cure rate models considered by Rodrigues et al. (2009), it was possible to extend some well-known long-term survival models in a simple and elegant way. In particular, viewing the COM–Poisson distribution as a weighted Poisson distribution (Kokonendji et al., 2008) allows us to propose a cure rate model which includes some of the well-known cure rate models in the literature due to Berkson and Gage (1952), Yakovlev and Tsodikov (1996) and Yin and Ibrahim (2005). The COM–Poisson distribution, introduced by Conway and Maxwell (1961), was revived recently by Shmueli et al. (2005). We have shown that it is very useful to model survival data with a cure rate. It unifies some cure rate models found in the literature and its second parameter (ϕ) allows us to accommodate under-dispersion and over-dispersion with respect to the Poisson distribution.

Appendix

Here, we present expressions for the derivatives of the logarithm of the improper density function in (13). After performing some algebraic manipulations, we arrive at the following expressions:

$$\frac{\partial}{\partial\eta}\log f_p(t;\eta,\phi,\boldsymbol{\gamma}) = S(t;\boldsymbol{\gamma})\,\frac{\sum_{j=1}^{\infty}\dfrac{j^2\{\eta S(t;\boldsymbol{\gamma})\}^{j-1}}{(j!)^{\phi}}}{\sum_{j=1}^{\infty}\dfrac{j\{\eta S(t;\boldsymbol{\gamma})\}^{j}}{(j!)^{\phi}}} - \frac{1}{\eta Z(\eta,\phi)}\sum_{j=1}^{\infty}\frac{j\eta^j}{(j!)^{\phi}},$$

$$\frac{\partial}{\partial\phi}\log f_p(t;\eta,\phi,\boldsymbol{\gamma}) = -\frac{\sum_{j=1}^{\infty}\dfrac{j\log(j!)\{\eta S(t;\boldsymbol{\gamma})\}^{j}}{(j!)^{\phi}}}{\sum_{j=1}^{\infty}\dfrac{j\{\eta S(t;\boldsymbol{\gamma})\}^{j}}{(j!)^{\phi}}} - \frac{1}{Z(\eta,\phi)}\sum_{j=1}^{\infty}\frac{\eta^j\log(j!)}{(j!)^{\phi}},$$

and

$$\frac{\partial}{\partial\gamma_l}\log f_p(t;\eta,\phi,\boldsymbol{\gamma}) = \frac{1}{f(t;\boldsymbol{\gamma})}\frac{\partial}{\partial\gamma_l}f(t;\boldsymbol{\gamma}) + \frac{\partial}{\partial\gamma_l}F(t;\boldsymbol{\gamma})\left\{\frac{1}{S(t;\boldsymbol{\gamma})} - \frac{\sum_{j=1}^{\infty}\dfrac{j^2\eta^j\{S(t;\boldsymbol{\gamma})\}^{j-1}}{(j!)^{\phi}}}{\sum_{j=1}^{\infty}\dfrac{j\{\eta S(t;\boldsymbol{\gamma})\}^{j}}{(j!)^{\phi}}}\right\},$$

$l = 1, 2$. Upon using (17) we obtain

$$\frac{\partial}{\partial\gamma_1}f(t;\boldsymbol{\gamma}) = t^{\gamma_1-1}\exp(\gamma_2 - t^{\gamma_1}e^{\gamma_2})\{1 + \gamma_1(1 - t^{\gamma_1}e^{\gamma_2})\log t\},$$

$$\frac{\partial}{\partial\gamma_2}f(t;\boldsymbol{\gamma}) = \gamma_1 t^{\gamma_1-1}\exp(\gamma_2 - t^{\gamma_1}e^{\gamma_2})(1 - t^{\gamma_1}e^{\gamma_2}),$$

$$\frac{\partial}{\partial\gamma_2}F(t;\boldsymbol{\gamma}) = t^{\gamma_1}\exp(\gamma_2 - t^{\gamma_1}e^{\gamma_2}) \quad \text{and} \quad \frac{\partial}{\partial\gamma_1}F(t;\boldsymbol{\gamma}) = \log t\,\frac{\partial}{\partial\gamma_2}F(t;\boldsymbol{\gamma}).$$

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