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The Pareto IV power series cure rate model with applications

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Abstract

Cutaneous melanoma is thought to be triggered by intense, occasional exposure to ultraviolet radiation, either from the sun or tanning beds, especially in people who are genetically predisposed to the disease. When skin cells are damaged by ultraviolet light in this way, often showing up as a sunburn, they are more prone to genetic defects that cause them to rapidly multiply and form potentially fatal (malignant) tumors. Melanoma originates in a type of skin cell called a melanocyte, such cells help produce the pigments of our skin, hair, and eyes. We propose a new cure rate survival regression model for predicting cutaneous melanoma. We assume that the unknown number of competing causes that can influence the survival time is governed by a power series distribution and that the time until the tumor cells are activated follows the Pareto IV distribution. The parameter estimation is based on the EM algorithm which for this model can be implemented in a simple way in computational terms. Simulation studies are presented, showing the good performance of the proposed estimation procedure. Finally, two real applications related to a cutaneous melanoma and melanoma data sets are presented.

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Keywords: Competing risks, cure rate models, EM algorithm, Pareto IV distribution, power series distribution.

1. Introduction

Cancer is a process of uncontrolled growth and dissemination of cells. It can occur in practically any location in the body. The tumor can invade the neighbouring region of the body and can also provoke metastasis in parts of the body remote from the original site. Many types of cancer can be prevented by avoiding exposure to common risk factors

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such as, for example, tobacco smoke. Moreover, a major proportion of cancers can be cured by surgery, chemotherapy or radiation, especially if they are detected at an early stage. Melanoma that occurs on the skin, called cutaneous melanoma, is the most common type of melanoma. This type of melanoma occurs in all parts of the skin, including the soles of feet, on the palms of the hand, in between toes and fingers, and underneath the finger and toe nails.

Skin melanoma occurs most frequently in people with a light complexion, since they are least protected against UV radiation. Also, people with more than 50 moles, a family history of melanoma, a weakened immune system, or those who sunbathe or use tanning beds, are at increased risk. Melanoma is the fastest growing cancer in men and the second fastest growing cancer in women (after lung cancer).

Regression 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. These models typically assume that all units under study are susceptible to an event of interest and will eventually experience it if follow-up is sufficiently long. However, there are situations in which a fraction of individuals are not expected to experience the event of interest, that is, those individuals are cured or not susceptible. For example, researchers may be interested in analysing the recurrence of a disease. Many individuals may never experience a recurrence; therefore, a cured fraction of the population exists. Cure rate models have been applied to investigate the possible existence of a cured fraction. An approach for those models is the following.

Let M be a random variable denoting the initial number of carcinogenic cells of an individual. Several different assumptions about the probability mass function of M have appeared in the literature: Bernoulli (Berkson and Gage, 1952), Poisson (Yakolev and Tsodikov, 1996), Negative Binomial (Rodrigues et al., 2009a), among others. A generalization that includes all these models is the power series distribution (Noack, 1950) used by Cancho, Louzada and Ortega (2013a) in the cure rate context. Evidently this model doesn't include all distributions that can be used in this context (see for instance, Rodrigues et al., 2009b and Rodrigues et al., 2015).

On the other hand, let W_a be a random variable expressing the time at which the a-th cell produces a detectable cancer. In their proposal, Cancho et al. (2013a) used the Weibull distribution. Other approaches include the generalized gamma (Ortega et al., 2014), the Beta-Weibull (Ortega et al., 2015) and the Birnbaum-Saunders distribution (Cordeiro et al., 2016). Our proposal is one in which we assume for each W_a a Pareto IV distribution (Arnold 1983, 2015). This is a very flexible model which includes some interesting distributions as particular cases and which has the characteristic that both, the survival and density functions, have analytic tractable forms.

The sections of this paper are organized in the following manner. In Section 2, we explain the model formulation and give some of its main properties. In Section 3, we develop parameter estimation for the model based on the EM algorithm. In Section 4, two real data applications are discussed. In Section 5, a simulation study is presented. Finally, some conclusions are given in Section 6.

2. The Pareto IV power series cure rate model

The model proposed in Cancho et al. (2013a) can be defined as follows. Let M be a random variable denoting the initial number of carcinogenic cells of an individual with probability mass function given as in Noack (1950) by

$$P(M=m;\theta)=\frac{a_m\theta^m}{A(\theta)},\quad m=0,1,2,\ldots, \tag{1}$$

where $a_m>0$ and $A(\theta)=\sum_{m=0}^{\infty}a_m\theta^m$. θ is the so-called power parameter of the distribution and $A(\theta)$ is the series function. We denote the distribution in (1) by $\mathrm{PS}(\theta,A(\theta))$. Table 1 shows some particular cases of this distribution. Θ denotes the parameter space for θ in each model.

Table 1: *Some particular cases of* $PS(\theta,A(\theta))$.

Distribution	a_m	$A(\theta)$	$E_\theta[M^d]$, $d=1,2$	Θ
Poisson	$(m!)^{-1}$	e^θ	$\theta+(d-1)\theta^2$	$(0,\infty)$
Logarithmic	$(m+1)^{-1}$	$-\frac{\log(1-\theta)}{\theta}$	$1-\frac{\theta}{(1-\theta)\log(1-\theta)}\left(\frac{3+2\theta}{1-\theta}\right)^{d-1}$	$(0,1)$
Negative Binomial	$\binom{m+q-1}{m}$	$(1-\theta)^{-q}$	$\left(\frac{\theta}{1-\theta}\right)\left(\frac{1+q\theta}{1-\theta}\right)^{d-1}$	$(0,1)$
Binomial	$\binom{q}{m}$	$(1+\theta)^q$	$q\left(\frac{\theta}{1+\theta}\right)\left(\frac{q\theta^2+(q+1)\theta+1}{q(1+\theta)}\right)^{d-1}$	$(0,\infty)$

Note: We denote those distributions as $\mathrm{Po}(\theta)$, $\mathrm{Lo}(\theta)$, $\mathrm{NB}(q,\theta)$ and $\mathrm{Bin}(q,\theta)$ respectively. In both, $\mathrm{NB}(q,\theta)$ and $\mathrm{Bin}(q,\theta)$, q is considered known.

Denote by W_a the random variable representing the time at which the a-th cell produces a detectable cancer. For non-cured patients, $M>0$ and $W_a,\ a=1,2,\ldots,M$, are conditionally independent given M and identically distributed with common cumulative distribution and survival functions $F(t;\lambda)$ and $S(t;\lambda)=1-F(t;\lambda)$, where λ is a vector of unknown parameters. For cured patients, $M=0$ and it is assumed that $P(W_0=\infty)=1$. The distribution F is assumed to be a proper distribution function. The time until the event of interest depends upon the count variable (M) and the survival time variables $(W_1,\ldots,W_M)$ and can be expressed by $T=\min\{W_a,\ 0\le a\le M\}$. As mentioned by Cancho et al. (2013a), it can be verified that the survival function for T (also known as population survival function) is given by

$$S_{pop}(t;\theta,\lambda)=\frac{A(\theta S(t;\lambda))}{A(\theta)}. \tag{2}$$

From (2), it is possible to verify that the cure fraction of the model is $p_0 = A(0)/A(\theta) = a_0/A(\theta)$ and the corresponding density function for (2) is given by

$$f_{pop}(t;\theta,\lambda) = \frac{A'(\theta S(t;\lambda))}{A(\theta)}\theta f(t;\lambda),$$

where $A'(\eta) = \frac{\partial A(\eta)}{\partial \eta}$ and $f(t;\lambda)$ is the density function corresponding to time till the event of interest for each of the carcinogenic cells W_a.

The Weibull distribution is extensively used in survival analysis because it explains biological processes relatively well and because it is a distribution that is easy to work with. For these reasons, Cancho et al. (2013a) considered this distribution.

However, the Pareto IV distribution is more flexible than the Weibull distribution and is not markedly more difficult to work with in the cure rate models context. For this reason, we propose to use the Pareto IV distribution for modeling the time until the activation of the carcinogenic cells.

The Pareto IV distribution (Arnold 1983, 2015) is very flexible and has the convenient feature that its survival function is available in a simple analytic form. Let W be a random variable with a Pareto IV distribution and corresponding vector of parameters $(\mu,\sigma,\gamma,\alpha)$. (We denote this by $W \sim \text{P4}(\mu,\sigma,\gamma,\alpha)$). The survival function of W is

$$S(w;\mu,\sigma,\gamma,\alpha) = \left[1+\left(\frac{w-\mu}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}, \quad w>\mu, \mu\in R, \sigma,\gamma,\alpha>0,$$

with the corresponding density function

$$f(w;\mu,\sigma,\gamma,\alpha) = \frac{\alpha}{\gamma\sigma}\left[1+\left(\frac{w-\mu}{\sigma}\right)^{1/\gamma}\right]^{-\alpha-1}\left(\frac{w-\mu}{\sigma}\right)^{1/\gamma-1}, w>\mu, \mu\in R, \sigma,\gamma,\alpha>0.$$

The s-th moment of this distribution is given by

$$E(W^s) = \frac{\sigma^s\Gamma(\alpha-\gamma s)\Gamma(1+\gamma s)}{\Gamma(\alpha)}, \quad \text{if } -1<\gamma s<\alpha, \tag{3}$$

and the pth quantile, say w_p, is given by

$$w_p = \sigma(p^{-1/\alpha}-1)^{\gamma}, \quad 0<p<1. \tag{4}$$

Since we are working in a context of positive variables which are not bounded away from 0, we fix $\mu = 0$. Thus, the parameter vector related to the initial concurrent causes are defined by $\boldsymbol{\lambda} = (\sigma,\gamma,\alpha)$.

Some particular cases of this distribution are the following

- $\gamma = 1$: The Pareto II distribution (P2) also known as Lomax distribution.
- $\alpha = 1$: The Pareto III distribution (P3).

Since these models are particular cases of the P4 distribution, it is possible to use, for instance, likelihood ratio tests to decide between the hypothesis $H_0 : \gamma = 1$ ($\alpha = 1$) and $H_1 : \gamma \neq 1$ ($\alpha \neq 1$).

The model in (2) in which we assume that $S(\cdot;\boldsymbol{\lambda})$ is the survival function of a P4 distribution will be called the Pareto IV Power series cure rate model (henceforth, P4PS). Below we describe some particular cases of this model.

- **The Binomial Pareto IV (BP4) model.** If $A(\theta) = (1+\theta)^q$, then $M \sim \text{Bin}(q,\theta)$. Note that q is a positive integer that can be interpreted as the maximum number of carcinogenic cells for each individual. The cure rate is $p_0 = (1+\theta)^{-1}$. The case $q = 1$ ($M \sim \text{Bernoulli}(\theta)$) corresponds to the first survival model with cure rate in the literature (*the mixture model*) proposed in Berkson and Gage (1952). The population survival function of the BP4 model is

$$S_{pop}(t;\theta,\lambda) = \left(\frac{1+\theta\left[1+\left(\frac{t}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}}{1+\theta} \right)^q .$$

- **The Poisson Pareto IV (PP4) model.** If $A(\theta) = e^{\theta}$, then $M \sim \text{Po}(\theta)$. This is the same assumption used in Yakolev and Tsodikov (1996), the so-called *promotion time cure rate model* and it is the only cure rate model with proportional hazard structure (see Theorem 5 in Rodrigues et al., 2009a). The cure rate of the model is $p_0 = e^{-\theta}$. The population survival function is

$$S_{pop}(t;\theta,\lambda) = \exp\left\{ -\theta\left(1 - \left[1+\left(\frac{t}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}\right)\right\}.$$

- **The Negative Binomial Pareto IV model.** If $A(\theta) = (1-\theta)^{-q}$, then $M \sim \text{NB}(q,\theta)$. Here, typically, q is a positive integer although the definition remains valid if q is any positive real number. The Negative Binomial distribution includes the Poisson distribution as a limiting case. Moreover an extended definition of the Negative Binomial distribution (introduced by Piegorsch, 1990) allowing q to be negative permits one to view the binomial and Bernoulli distributions as particular cases. This observation was used in Rodrigues et al. (2009a) in unifying the *mixture model* and the *promotion time cure rate model* (the most popular cure rate model

until then). The cure rate is given by $p_0 = (1-\theta)^q$. The particular case $q = 1$, i.e., when M has a Geometric distribution, it is usually used in literature. (For instance, Cancho, Louzada and Barriga, 2013b and Gómez and Bolfarine, 2016). The population survival function is

$$S_{pop}(t;\theta,\boldsymbol{\lambda}) = \left(\frac{1-\theta}{1-\theta\left[1+\left(\frac{t}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}} \right)^q.$$

- **The Logarithmic Pareto IV model.** If $A(\theta) = -\theta^{-1}\log(1-\theta)$, then $M \sim \text{Lo}(\theta)$ in contrast to the other models, the mode of M in this case is zero implying that the probabilities for M are decreasing. The cure rate is given by $p_0 = -\theta/\log(1-\theta)$. This is not a very common model in literature. The population survival function is

$$S_{pop}(t;\theta,\boldsymbol{\lambda}) = \frac{\log\left(1-\theta\left[1+\left(\frac{t}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}\right)}{\left[1+\left(\frac{t}{\sigma}\right)^{1/\gamma}\right]^{-\alpha}\log(1-\theta)}.$$

3. Estimation

In this section, we discuss the estimation for the P4PS cure rate model using a classical approach. Assume that the data are obtained with right censoring. Thus, the observed data for the i-th individual can be represented by $T_i = \min(T_i^*, C_i)$ and $\delta_i = I(T_i^* \leq C_i)$, $1,\ldots,n$, where T_i^* and C_i denote failure and censoring times respectively. Denote the observed data by $D_{obs} = (\boldsymbol{t},\boldsymbol{\delta},\boldsymbol{z})$, with $\boldsymbol{t} = (t_1,\ldots,t_n)^\intercal$, $\boldsymbol{\delta} = (\delta_1,\ldots,\delta_n)^\intercal$ and $\boldsymbol{z} = (z_i,\ldots,z_n)^\intercal$, where $\boldsymbol{z}_i$ is a vector of covariates (of dimension $r \times 1$) related to the cure of the i-th individual. For each individual, those covariates can be introduced into the model by allowing the parameter θ to depend on the covariates in the following manner,

$$\theta_i = \begin{cases} \exp(\boldsymbol{z}_i^\intercal\boldsymbol{\beta}) & \text{for the Poisson and Binomial models} \\ \dfrac{\exp(\boldsymbol{z}_i^\intercal\boldsymbol{\beta})}{1+\exp\{\boldsymbol{z}_i^\intercal\boldsymbol{\beta}\}} & \text{for the Logarithmic and Negative Binomial models} \end{cases} \tag{5}$$

where $\boldsymbol{\beta} = (\beta_1,\beta_2,\ldots,\beta_r)^\intercal$ is a vector of parameters of dimension r. Note that this specification guarantees the identifiability of the model in the sense of Li et al. (2001) and Hanin and Li-Shang (2014).

On the other hand, note that the vector $\boldsymbol{M} = (M_1,\ldots,M_n)$ is non-observable and thus the complete data are $D_{comp} = (\boldsymbol{t},\boldsymbol{\delta},\boldsymbol{z},\boldsymbol{M})$. In Cancho et al. (2013a), the estimation procedure for $\boldsymbol{\psi} = (\boldsymbol{\beta},\boldsymbol{\lambda})$ was performed maximizing the observed likelihood, i.e., maximizing the following expression

$$\ell(\boldsymbol{\psi} \mid D_{obs}) = \sum_{i=1}^{n} \left[\delta_i \log f_{pop}(t_i;\boldsymbol{\psi}) + (1-\delta_i)\log S_{pop}(t_i;\boldsymbol{\psi})\right] = \sum_{i=1}^{n} \Big[\log A(\theta_i S(t_i;\boldsymbol{\lambda})) + \delta_i \left(\log\theta_i + \log f(t_i;\boldsymbol{\lambda}) + \log A'(\theta_i S(t_i;\boldsymbol{\lambda})) - \log A(\theta_i S(t_i;\boldsymbol{\lambda}))\right) - \log A(\theta_i)\Big]. \tag{6}$$

However, the maximization of $\ell(\cdot)$ can be difficult because there are many parameters, especially when the number of covariates that are used is high. For this reason, in a cure rate model context there are many proposals based on the EM algorithm (see for instance, Gallardo, Bolfarine and Pedroso-de-Lima, 2016a; Gallardo and Bolfarine, 2016b; Gallardo, Romeo and Meyer, 2016c and Pal and Balakrishnan, 2016). Particu-

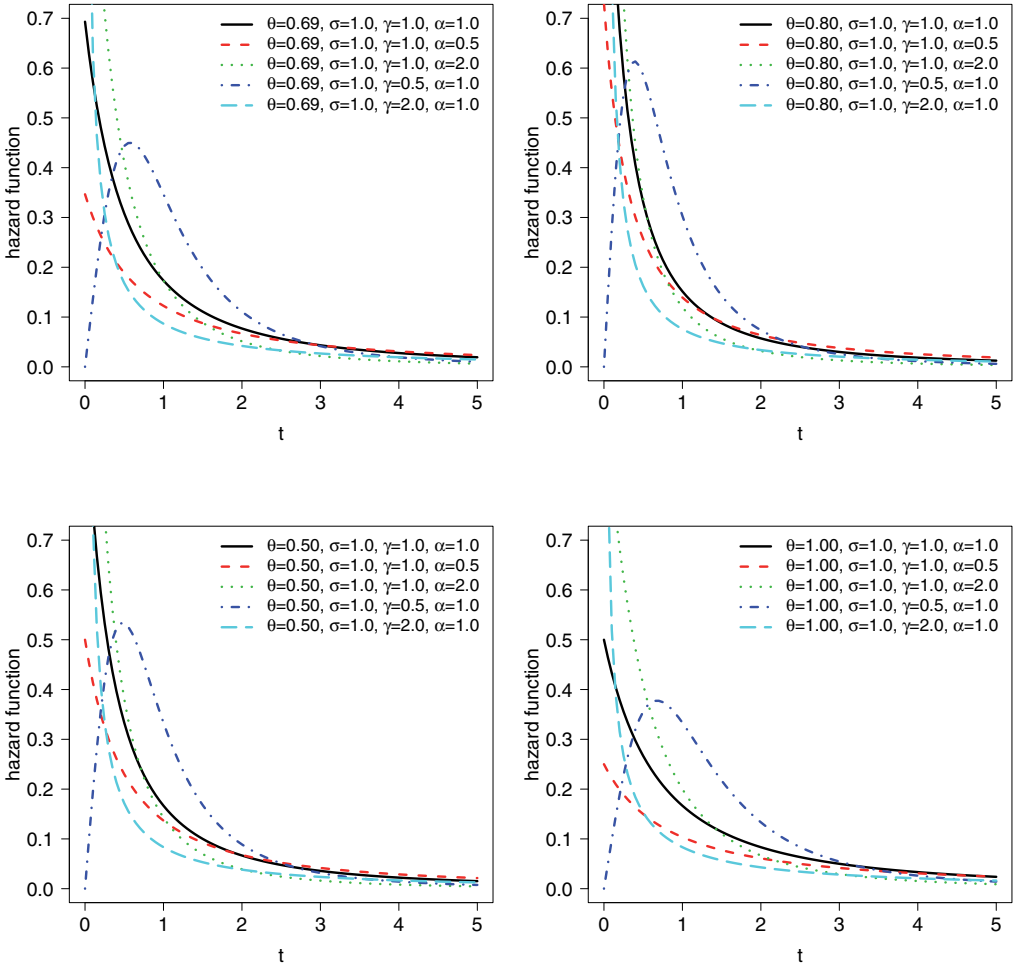

Figure 1: *Population hazard function for P4PS model with different parameters and cure rate fixed at 50%. Left upper: Poisson. Right upper: Logarithmic. Left lower: Negative Binomial ($q = 1$). Right lower: Binomial ($q = 1$).*

larly, we follows a similar scheme that Gallardo et al. (2016c) and we omit technical details about the method.

The k-th iteration of the algorithm (assuming q is known in the Binomial and Negative Binomial cases) takes the form:

- **E-step**: Define $\mu_i^{(k)} = \theta_i^{(k)} S(t_i;\boldsymbol{\lambda}^{(k)})$ and $\kappa_i^{(k)} = \left(1 - \frac{\mu_i^{(k)}}{\left(1-\mu_i^{(k)}\right)\log\left(1-\mu_i^{(k)}\right)}\right)$ and compute for $i = 1,\ldots,n$,

$$\widetilde{M}_i^{(k)} = \begin{cases} \delta_i + \mu_i^{(k-1)} & \text{for Poisson model} \\ (1-\delta_i)\kappa_i^{(k-1)} + \delta_i \frac{\left(1-\mu_i^{(k-1)}\right)^2 \log\left(1-\mu_i^{(k-1)}\right) - \mu_i^{(k-1)}\left(3+2\mu_i^{(k-1)}\right)}{\left(1-\mu_i^{(k-1)}\right)\log\mu_i^{(k-1)} - \mu_i^{(k-1)}} & \text{for Logarithmic model} \\ \frac{\delta_i + \mu_i^{(k-1)} + (q-1)\delta_i\mu_i^{(k-1)}}{1-\mu_i^{(k-1)}} & \text{for NB model} \\ (1-\delta_i)q\left(\frac{\mu_i^{(k-1)}}{1+\mu_i^{(k-1)}}\right) + \delta_i\left(\frac{q\left[\mu_i^{(k-1)}\right]^2 + (q+1)\mu_i^{(k-1)} + 1}{q\left(1+\mu_i^{(k-1)}\right)}\right) & \text{for Binomial model} \end{cases}$$

- **CM-step I**: Using $\boldsymbol{M}^{(k)} = (M_1^{(k)},\ldots,M_n^{(k)})$ obtained previously in the E-step, update $\widehat{\beta}^{(k)}$ maximizing

$$Q_1(\beta \mid \boldsymbol{\psi}^{(k)}) = \sum_{i=1}^{n}\left[\widetilde{M}_i^{(k)}\log\theta_i - \log A(\theta_i)\right]$$

  with respect to β.

- **CM-step II**: Update $\widehat{\alpha}^{(k)}$ as follows

$$\widehat{\alpha}^{(k)} = \frac{\sum_{i=1}^{n}\delta_i}{\sum_{i=1}^{n} M_i^{(k)}\log\left(1+\left(\frac{t_i}{\widehat{\sigma}^{(k-1)}}\right)^{\frac{1}{\widehat{\gamma}^{(k-1)}}}\right)}$$

- **CM-step III**: With $\boldsymbol{M}^{(k)}, \alpha^{(k)}$ and $\gamma^{(k-1)}$, update $\widehat{\sigma}^{(k)}$ solving the following nonlinear equation for σ

$$\sum_{i=1}^{n}\left[\frac{\left(\alpha^{(k)}M_i^{(k)} + 2\delta_i\right)\left(\frac{t_i}{\sigma}\right)^{1/\gamma^{(k-1)}} + \delta_i}{\left(1+\left(\frac{t_i}{\sigma}\right)^{1/\gamma^{(k-1)}}\right)}\right] = 0$$

- **CM-step IV**: With $\boldsymbol{M}^{(k)}, \alpha^{(k)}$ and $\sigma^{(k)}$, update $\widehat{\gamma}^{(k)}$ solving the following non-linear equation for γ

$$\sum_{i=1}^{n} \frac{\left(\frac{t_i}{\sigma^{(k)}}\right)^{1/\gamma}\left(2\delta_i \log\left(\sigma^{(k)}\right) - \alpha^{(k)} M_i^{(k)} \log\left(\frac{t_i}{\sigma^{(k)}}\right) + \gamma\delta_i\right) + \delta_i\left(\log\left(\sigma^{(k)} t_i\right) + \gamma^{(k)}\right)}{\left(1+\left(\frac{t_i}{\sigma^{(k)}}\right)^{1/\gamma^{(k)}}\right)} = 0.$$

The E and CM-I/CM-IV steps are alternated repeatedly until a suitable convergence rule is satisfied, e.g., the difference in successive values of the estimates is less than a tolerance value. The variance of $(\boldsymbol{\beta}, \alpha, \sigma, \gamma)$ can be estimated based on the inverse of minus the hessian matrix of the model. Details about this matrix can be seen in the additional material.

Finally, for the binomial and the negative binomial distributions for which q will typically be unknown, we can consider a grid of values for q, say $\mathfrak{Q} = q_1, q_2, \ldots, q_B$ and we apply the EM algorithm for each value in $\mathfrak{Q}$, obtaining for each q_j, $j = 1, \ldots, B$, a set of estimates parameters, say $\widehat{\boldsymbol{\psi}}_1, \widehat{\boldsymbol{\psi}}_2, \ldots, \widehat{\boldsymbol{\psi}}_B$. Then, we choose $q = q_b$ as the value in $\mathfrak{Q}$ such that

$$\max_{j=1,\ldots,B} \ell(\widehat{\boldsymbol{\psi}}_j \mid D_{obs}) = \ell(\widehat{\boldsymbol{\psi}}_b \mid D_{obs}),$$

where $\ell(\cdot)$ is the observed likelihood function defined in (6).

3.1. Interpreting the parameters

We highlight that, up till now, we have been unable to find in the literature any work where the regression coefficients are interpreted in a cure rate model context, except in the case in which $M_i \sim \text{Bin}(1, \theta)$ corresponding to the *mixture model*. In that setting the coefficients can be interpreted in terms of the log-odds ratio, similar to the case of logistic regression for dichotomic responses.

In general, efforts to interpret the coefficients are limited to illustrating the behaviour in the cure rate when varying a continuous covariate and fixing the others (as we shall illustrate this issue in the application Section). To this end, we propose the following methodology. Note that, based on a Taylor expansion of the first order around the intercept (or another convenient point) of the logarithm of the cure rate, we can write $q_{0i} \approx \exp\{a_0 + b_0 \boldsymbol{z}_i^{\top}\boldsymbol{\beta}\}$, where a_0 and b_0 depends on the respective model and the value for the intercept. If $\boldsymbol{z}_{i(j)}$ represents the $\boldsymbol{z}_i$ vector with the j-th element increased in 1 unit, then the ratio between $q_{0i(j)}$ and q_{0i} is

$$\frac{q_{0i(j)}}{q_{0i}} \approx \frac{\exp\{a_0 + b_0 \boldsymbol{z}_{i(j)}^{\top}\boldsymbol{\beta}\}}{\exp\{a_0 + b_0 \boldsymbol{z}_i^{\top}\boldsymbol{\beta}\}} = \exp\{b_0 \beta_j\},$$

providing an approximate way to interpret the β_j's in terms of the percentage increment (or decrease) in the cure rate, maintaining the rest of the covariates fixed.

Finally, in relation to the vector $\boldsymbol{\lambda}$, rather than interpreting each component it may be of more interest to evaluate descriptive measure related to the distribution of W_a's. For instance, mean, variance and quantiles can be obtained using (3) or (4). Confidence intervals can also be constructed for those quantities using the delta method Sen, Singer and Pedroso-de-Lima (2010).

4. Applications

In this section we consider two applications of the PSP4 model to real data sets.

4.1. Cutaneous melanoma data set

This data set refers to patients involved in a Phase III cutaneous melanoma clinical trial presented in Ibrahim, Chen and Sinha (2001) and is available at `http://merlot.stat.uconn.edu/~mhchen/survbook/`, labeled as E1690 data. The data set comes from a clinical trial for the evaluation of postoperative treatment performance with a high dose of the drug interferon alpha-2b in order to prevent recurrence. Patients were included in the study from 1991 to 1995, and follow-up was conducted until 1998. The response is considered to be the relapse-free survival time (in years). The data set includes information on 408 patients, for each of which the following covariates were measured: treatment (0: placebo, 198 patients; 1: interferon alpha-2b, 210 patients); tumor thickness (in mm, mean = 3.98 and standard deviation = 3.22) and nodal category (1: 110 patients; 2: 131 patients; 3: 86 patients; 4: 81 patients). Figure 2 shows the Kaplan-Meier (KM)

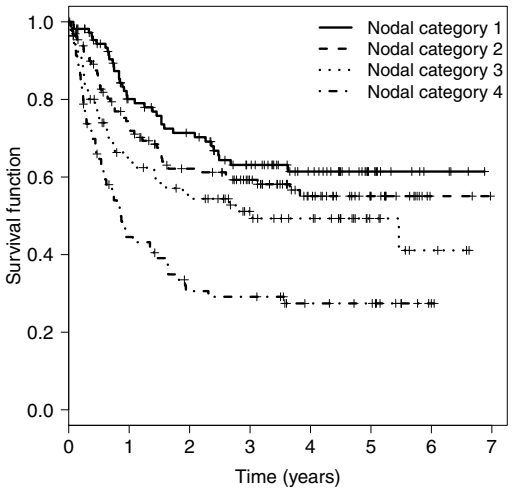

Figure 2: *KM estimator by nodal category for Phase III cutaneous melanoma clinical trial.*

estimator of the survival function by nodal category. As expected, the survival function decrease faster in more advanced categories. However, in all cases the survival function is stabilized at a certain value, suggesting that there is a proportion of patients for whom the malignant melanoma will never recur (in all nodal categories).

We fit the P2PS, P3PS and P4PS model for four particular cases. Model selection was performed based on the AIC and SBC criteria (Akaike, 1974 and Schwarz, 1978, respectively). Those criteria are presented in Table 2. We also fit the gamma and Birnbaum-Saunders (BS) PS model for the concurrent causes. The Birnbaum-Saunders model has been the subject of intense research in cure rate models in recent years. For instance, Cancho et al. (2013b) and Cordeiro et al. (2016).

Table 2: *AIC and SBC criterion for power series cure rate model with Pareto IV and BS distribution for concurrent causes.*

	P2	P3	P4	Gamma	BS
Poisson	841.42/873.51	835.66/867.75	837.23/873.33	837.96/874.06	888.27/924.37
Logarithmic	849.52/881.61	**826.26/858.35**	827.78/863.89	828.10/864.20	927.71/963.81
Geometric	841.70/873.79	830.14/862.23	831.64/867.74	831.76/867.87	907.44/943.54
Binomial	844.87/876.96	840.33/872.42	842.38/878.48	845.14/881.24	875.33/911.43

Both criterion suggest that the Logarithmic cure rate model with a Pareto III distribution for the concurrent causes is the best model. For this model, we also tested the hypotheses $H_0 : \alpha = 1$ versus $H_1 : \alpha \neq 1$ using the log-likelihood ratio (LR) test and the Wald test. In both cases, we failed to reject the null hypothesis at the 5% of significance and consequently we prefer the P3 instead of the P4 distribution for the time-to-event in the concurrent causes.

Estimates of the parameters of the selected model, i.e., the Logarithmic P3 cure rate model, are presented in Table 3. Based on the Taylor expansion of first order (around zero in this case) discussed in Section 3.1 for the logarithmic model, we obtain $b_0 \approx -0.1596685$. For this reason, we present the following approximated interpretations for the regression coefficients:

- $\exp\left(b_0 \times (\widehat{\beta}_{nodule1} - \widehat{\beta}_{nodule2})\right) = 1.193$, i.e., the cure rate for patients with nodule in stage one is 19.3% greater than the cure rate for patients in stage two.
- $\exp\left(b_0 \times (\widehat{\beta}_{nodule1} - \widehat{\beta}_{nodule3})\right) = 1.342$, i.e., the cure rate for patients with nodule in stage one is 34.2% greater than the cure rate for patients in stage three.
- $\exp\left(b_0 \times (\widehat{\beta}_{nodule1} - \widehat{\beta}_{nodule3})\right) = 1.624$, i.e., the cure rate for patients with nodule in stage one is 62.4% greater than the cure rate for patients in stage four.
- $\exp\left(-b_0 \times \widehat{\beta}_{thickness}\right) = 1.019$, i.e., for each mm that is increased the tumor thickness the cure rate is decreased in 1.9%.

- $\exp\left(b_0 \times \widehat{\beta}_{treatment}\right) = 1.079$, i.e., the cure rate for patients receiving treatment is 7.9% greater than the cure rate for patients witouth treatment.

On the other hand, the mean and median of the time-to-event of carcinogenic cells are 3.97 and 1.82 years respectively with their respective 95% confidence intervals (1.74,6.21) and (1.18,2.46).

Table 3: *Estimates, standard errors (s.e.) and 95% confidence interval for logarithmic P3 cure rate model for Phase III cutaneous melanoma clinical trial.*

Parameter	estimate	s.e.	95% Conf. Interval	
$\beta_{nodule1}$	0.2471	0.2584	−0.2594	0.7536
$\beta_{nodule2}$	1.3547	0.1658	1.0296	1.6797
$\beta_{nodule3}$	2.0878	0.2186	1.6593	2.5163
$\beta_{nodule4}$	3.2853	0.2736	2.7491	3.8216
$\beta_{thickness}$	0.1178	0.0034	0.1111	0.1245
$\beta_{treatment}$	−0.4738	0.0973	−0.6645	−0.2832
σ	1.8368	0.1126	1.6161	2.0575
γ	0.6415	0.0023	0.6370	0.6460

We also show in Figure 3 some plots showing the cure rate in terms of tumor thickness for combinations of nodule and treatment.

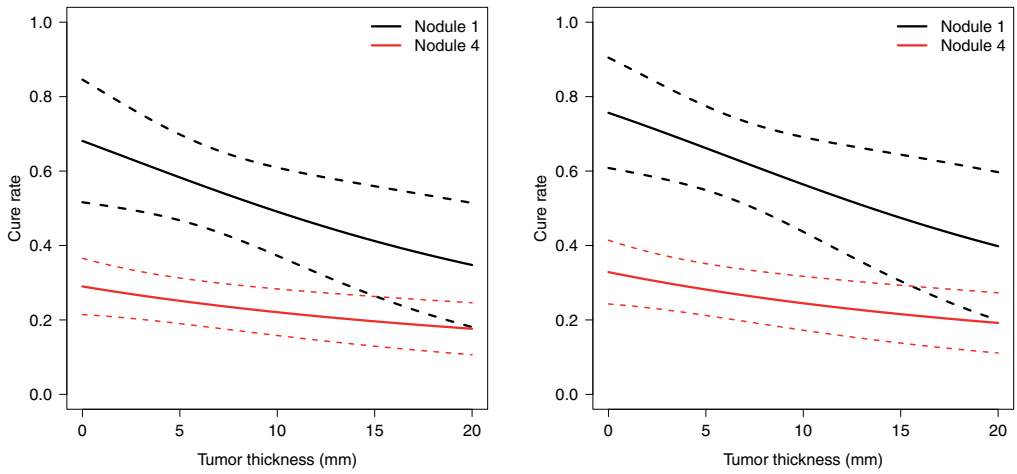

Figure 3: *Estimated cure rate for patients that received and not received treatment (left and right panel respectively) and nodule in stage 1 and 4. The continuous line represent the point estimation and the dashed line represent the respective 95% confidence interval.*

Additionally, in order to analyse possible influential observations, we compute the jackknife residuals defined by

$$J_i = \left(\widehat{\boldsymbol{\psi}} - \widehat{\boldsymbol{\psi}}_{(i)}\right)^{\mathsf{T}} \widehat{\boldsymbol{H}}^{-1} \left(\widehat{\boldsymbol{\psi}} - \widehat{\boldsymbol{\psi}}_{(i)}\right), \quad i = 1, \ldots, n.$$

where $\boldsymbol{\psi}_{(i)}$ represents the estimator of $\boldsymbol{\psi}$ without the i-th observation. Figure 4 show these residuals. Note that observation 11 is a potentially influential observation. This observation corresponded to an individual with a nodule in stage 1 who received treatment. Table 4 show a descriptive comparison of this observation with the others in same nodule stage and with treatment. Observation 11 was a patient who died in a short time when compared with others patients in similar conditions. Also his tumor thickness was very big in relation to other patients in similar conditions.

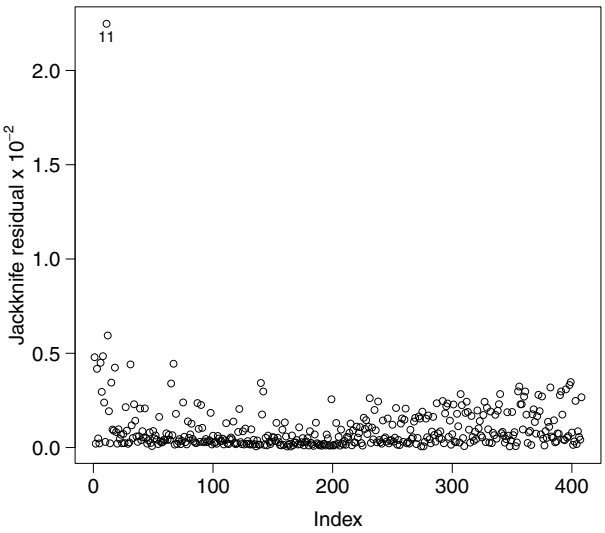

Figure 4: *Jackknife residuals for cutaneous melanoma data set.*

Table 4: *Descriptive analysis for observation 11.*

Observation	t_i	δ_i	thickness
11	0.0767	1	14.000
Mean*	5.900	0.34	5.900
Median*	2.437	0.00	6.611

*Considering the 56 observations in stage 1 that received treatment.

Finally, Table 5 shows the estimates for all parameters with observation 11 deleted from the data set. Note that the magnitudes of the estimates are different from thecorresponding values in Table 3. However, the significance and the sense of all parameter estimates is maintained.

Table 5: *Estimates, standard errors (s.e.) and 95% confidence interval for logarithmic P3 cure rate model for Phase III cutaneous melanoma clinical trial without observation 11.*

Parameter	estimate	s.e.	95% Conf. Interval	
$\beta_{nodule1}$	0.3335	0.2516	−0.1597	0.8267
$\beta_{nodule2}$	1.4401	0.1674	1.1120	1.7681
$\beta_{nodule3}$	2.1708	0.2216	1.7365	2.6050
$\beta_{nodule4}$	3.3909	0.2787	2.8446	3.9372
$\beta_{thickness}$	0.0989	0.0032	0.0926	0.1053
$\beta_{treatment}$	−0.5190	0.0980	−0.7110	−0.3269
σ	1.8228	0.1071	1.613	2.0327
γ	0.6336	0.0022	0.6292	0.638

4.2. Melanoma data set

This data set is available at `timereg` package in R Scheike (2015). The data set refers to 205 patients with malignant melanoma, followed up after removing the lesions. The following covariates were measured: ulceration (absent: 115 patients; present: 90 patients); tumor thickness (in mm, mean = 2.92 and standard deviation = 2.96). Figure 5 shows the KM estimator by ulceration status. Note that the survival function is lower for patients with ulceration. On the other hand, the survival function is stabilized at a certain value, suggesting in this study also the existence of a proportion of patients for whom the malignant melanoma will never recur.

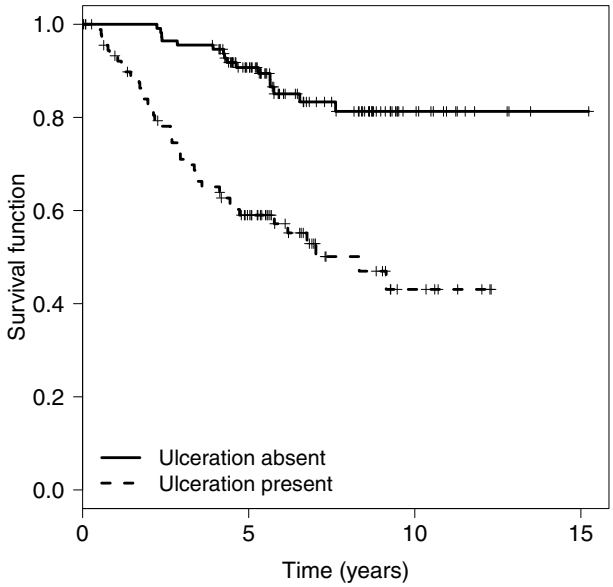

Figure 5: *KM estimator by nodal category ulceration status for melanoma data set.*

Table 6: *AIC/SBC criteria for power series cure rate model with Pareto IV and BS distribution for concurrent causes in the melanoma data set.*

	P2	P3	P4	Gamma	BS
Poisson	438.55/458.49	427.77/447.70	427.59/447.53	427.42/447.35	430.16/450.10
Logarithmic	447.47/467.41	**418.31/438.25**	418.39/438.33	**418.31/438.25**	425.88/445.82
Geometric	438.13/458.07	423.04/442.98	422.76/442.70	422.83/442.77	428.63/448.56
Binomial	441.42/461.36	432.79/452.72	432.79/452.73	432.84/452.78	432.84/452.78

In this case, we also fit the P2PS, P3PS and P4PS model for four particular cases, together with the gamma and BS models. The AIC and SBC criteria are presented in Table 6.

Both criterion suggest that the Logarithmic cure rate model with a Pareto III and gamma distributions for the concurrent causes are the best models, both yielding similar results. We also tested the hypotheses $H_0 : \alpha = 1$ versus $H_1 : \alpha \neq 1$ using the log-likelihood ratio (LR) test and the Wald test. In both cases, we failed to reject the null hypothesis at the 5% significance level and consequently, we prefer the P3 instead of the P4 distribution for the time-to-event in the concurrent causes. Parameter estimates of both selected model are presented in Table 7.

Table 7: *Estimates and standard errors (s.e.) for logarithmic P3 and gamma cure rate models for melanoma data set.*

	Estimate	s.e.		Estimate	s.e.
$\beta_{intercept}$	−0.8874	0.5714	$\beta_{intercept}$	−0.9761	0.5967
$\beta_{ulceration}$	1.9991	0.5864	$\beta_{ulceration}$	1.9619	0.5846
$\beta_{thickness}$	0.3753	0.1304	$\beta_{thickness}$	0.3774	0.1339
σ	7.3228	2.3068	α	2.6801	0.5092
γ	0.4325	0.0594	ν	0.3399	0.1726

Note that all parameters related to the regression are significantly different from zero in both models. Once more, based on a Taylor expansion of first order (around the intercept in this case) for the logarithmic model, we obtain $b_0 \approx -0.1162651$. In this manner, we present the following approximate interpretations of the regression coefficients:

- $\exp\left(-b_0 \times \widehat{\beta}_{thickness}\right) = 1.045$, i.e., for each mm that is increased the tumor thickness the cure rate is decreased in 4.5%.
- $\exp\left(-b_0 \times \widehat{\beta}_{ulceration}\right) = 1.262$, i.e., patients without ulceration have a cure rate 26.2% greater than patients with ulceration.

On the other hand, the mean and median of the time-to-event of carcinogenic cells are 10.18 and 7.32 years respectively with their respective 95% confidence intervals

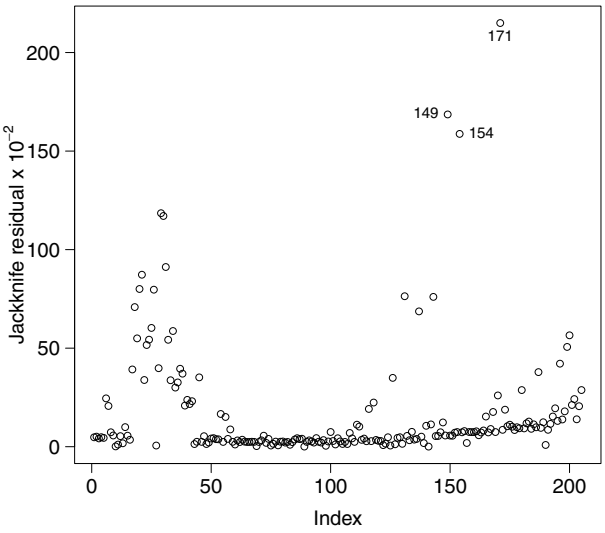

Figure 6: *Jackknife residuals for melanoma data set.*

Table 8: *Estimates, standard errors (s.e.) and 95% confidence interval for logarithmic P3 cure rate model for Phase III cutaneous melanoma clinical trial without possible influence observations.*

	deleted observations							
	149		154		171		149, 154 and 171	
	estimate	s.e.	estimate	s.e.	estimate	s.e.	estimate	s.e.
$\beta_{intercept}$	−1.0667	0.5242	−1.0099	0.5208	−1.0247	0.5151	−1.2670	0.4673
$\beta_{ulceration}$	2.0037	0.5691	1.9633	0.5728	1.9602	0.5722	1.9473	0.5536
$\beta_{thickness}$	0.3656	0.1269	0.3708	0.1296	0.3712	0.1297	0.3614	0.1271
σ	6.6195	1.8311	6.6301	1.8278	6.5522	1.7669	5.5503	1.2191
γ	0.4262	0.0587	0.4229	0.0583	0.4205	0.0579	0.4026	0.0558

(2.54,17.82) and (2.80,11.84). It can be verified that both models provide similar results in terms of estimated cure rates and survival functions. For this reason, henceforth we will continue the analysis based only on the logarithmic P3 model. Figure 6 shows the Jackknife residuals for this data set, suggesting that observations 149, 154 and 171 are possible influential observations. Based on a simple descriptive analysis, we note that those observations present large observed times even though the respective tumor thickness also are large.

Table 8 shows the estimates for the logarithmic P3 model deleting the possible influence observations separately and jointly. Note that in all cases the significance of parameters is unchanged and the estimates are very close to the estimations using the complete data set. Finally, Figure 7 presents the estimated cure rate and the respective

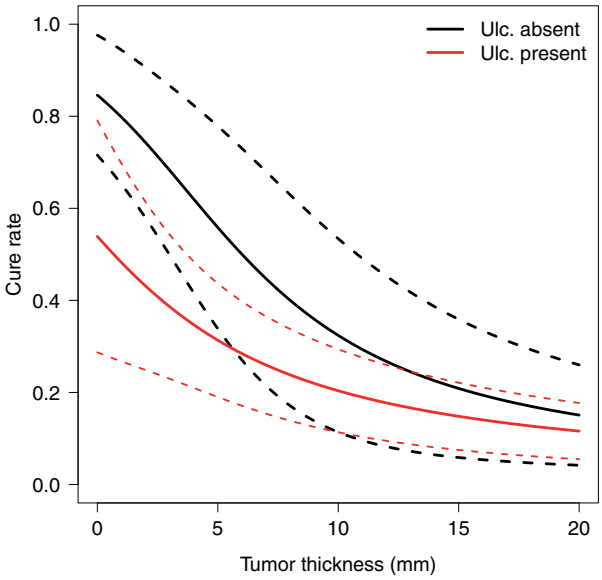

Figure 7: *Estimated cure rate for patients with ulceration status absent and present. The continuous line represent the point estimation and the dashed line represent the respective 95% confidence interval.*

95% confidence intervals, suggesting that ulceration is a risk factor. On the other hand, tumor thickness influences in the cure rate of patients subject to this intervention mainly for small tumors.

5. Simulation study

In this section we report a simulation study to assess the recovery of known parameters by the proposed estimation procedure. The data were drawn in conformity with the P4PS model. We assume the Pareto IV distribution with parameters $\alpha = 0.4$, $\sigma = 1$ and $\gamma = 0.6$ for the concurrent causes, i.e., a similar scheme to that fitted in the applications. We assume that observations belong to two groups, say $z_1 = 0$ or $z_1 = 1$. In addition, we assume a second continuous covariate, say z_2. For $i = 1, \ldots, n$, we drew z_{1i} and z_{2i} from a Bernoulli distribution with success probability equal to 0.5 and a Uniform distribution in the interval $(0, 20)$ respectively. For each model, the parameters related to the cure were computing by fixing cure rates (say q_0 and q_1) at determined values for each group, without considering the effect of covariate z_{2i}. We consider three kinds of cure rates: high ($q_0 = 0.8$ and $q_1 = 0.65$), medium ($q_0 = 0.6$ and $q_1 = 0.45$) and low ($q_0 = 0.4$ and $q_1 = 0.25$). To achieve this, the values for β_0 and β_1 for each distribution assumed for M are given in Table 9.

On the other hand, the value for β_2 was fixed as 0.1 in all cases. Using this setup, for each $i = 1, \ldots, n$ the value of θ_i was computed according to (5) and M_i was simulated

Table 9: *Values for β_0 and β_1 assumed in the simulation study.*

Distribution	High cure rate		Medium cure rate		Lower cure rate	
assumed for M	β_0	β_1	β_0	β_1	β_0	β_1
Poisson	−1.4999	0.6578	−0.6717	0.4467	−0.0874	0.4141
Logarithmic	−0.5264	0.9607	0.7343	0.9857	2.1180	1.7826
NB ($q=1$)	−1.3863	0.7673	−0.4055	0.6061	0.4055	0.6931
Binomial ($q=1$)	−1.3863	0.7673	−0.4055	0.6061	0.4055	0.6931

depending on each of the four power series distributions. We define $W_{0i}=\infty$ and for $M_i>0$, we drew $W_{1i},\ldots,W_{M_i i}$ from a Pareto IV distribution (if $U\sim U(0,1)$, so $\sigma(U^{-\frac{1}{\alpha}}-1)^{\gamma}\sim P4(\alpha,\sigma,\gamma)$). Then, we define $T_i^*=\min(W_{0i},W_{1i},\ldots,W_{M_i i})$. The failure time was defined as $T_i=\min(T_i^*,10)$ and $\delta_i=I(T_i^*\leq 10)$. We consider three sample sizes: $n=50$, $n=100$ and $n=200$. Each case was replicated 10,000 times and we report the average bias (AB) and the average of mean square error (AMSE) of the estimates. Results are presented in Table 10.

Table 10: *Simulation study for PSP4 model with cure rate.*

Distribution		$n=50$		$n=100$		$n=200$	
for M		bias	MSE	bias	MSE	bias	MSE
				High cure rate			
Poisson	β_0	−0.050	0.423	−0.024	0.186	−0.015	0.085
	β_1	0.043	0.203	0.016	0.092	0.011	0.042
	β_2	0.007	0.002	0.003	0.001	0.002	0.000
	α	0.040	0.254	0.033	0.163	0.021	0.094
	σ	0.098	0.501	0.054	0.201	0.031	0.103
	γ	−0.010	0.341	−0.005	0.119	−0.001	0.052
Logarithmic	β_0	0.030	2.320	−0.012	0.607	−0.020	0.245
	β_1	0.143	1.105	0.048	0.392	0.030	0.185
	β_2	0.016	0.009	0.006	0.003	0.003	0.001
	α	0.045	0.287	0.037	0.195	0.019	0.087
	σ	0.116	0.592	0.076	0.257	0.024	0.121
	γ	−0.037	0.320	−0.017	0.067	−0.007	0.045
Geometric	β_0	−0.053	0.668	−0.027	0.286	−0.017	0.132
	β_1	0.059	0.379	0.025	0.171	0.012	0.082
	β_2	0.007	0.003	0.003	0.001	0.002	0.001
	α	0.045	0.237	0.037	0.195	0.019	0.057
	σ	0.136	0.574	0.065	0.266	0.091	0.078
	γ	−0.019	0.219	−0.008	0.110	−0.004	0.055

Table 10: *Simulation study for PSP4 model with cure rate (continuation).*

Distribution for M		$n = 50$		$n = 100$		$n = 200$	
		bias	MSE	bias	MSE	bias	MSE
				High cure rate			
Bernoulli	β_0	−0.088	0.798	−0.079	0.355	−0.038	0.156
	β_1	0.065	0.541	0.050	0.307	0.019	0.112
	β_2	0.015	0.006	0.008	0.003	0.003	0.001
	α	0.058	0.277	0.037	0.178	0.019	0.051
	σ	0.100	0.612	0.063	0.186	0.022	0.067
	γ	−0.023	0.321	−0.004	0.009	−0.002	0.005
				Medium cure rate			
Poisson	β_0	−0.010	0.255	−0.013	0.116	−0.003	0.054
	β_1	0.030	0.134	0.013	0.061	0.006	0.029
	β_2	0.007	0.001	0.004	0.001	0.002	0.000
	α	0.034	0.233	0.029	0.136	0.015	0.087
	σ	0.087	0.452	0.051	0.186	0.027	0.092
	γ	−0.009	0.321	−0.004	0.100	−0.001	0.043
Logarithmic	β_0	0.168	2.616	0.025	0.656	0.011	0.269
	β_1	0.147	1.234	0.072	0.492	0.023	0.223
	β_2	0.014	0.010	0.007	0.004	0.002	0.002
	α	0.039	0.254	0.031	0.143	0.015	0.076
	σ	0.102	0.475	0.062	0.212	0.021	0.112
	γ	−0.034	0.287	−0.014	0.062	−0.006	0.038
Geometric	β_0	−0.009	0.518	0.005	0.225	0.001	0.103
	β_1	0.040	0.314	0.017	0.141	0.008	0.069
	β_2	0.008	0.003	0.003	0.001	0.001	0.001
	α	0.040	0.212	0.032	0.171	0.015	0.043
	σ	0.117	0.534	0.061	0.247	0.072	0.054
	γ	−0.015	0.192	−0.007	0.087	−0.003	0.049
Bernoulli	β_0	−0.074	0.542	−0.057	0.314	−0.032	0.139
	β_1	0.055	0.451	0.043	0.236	0.015	0.100
	β_2	0.011	0.005	0.006	0.002	0.002	0.001
	α	0.041	0.243	0.037	0.141	0.011	0.034
	σ	0.081	0.517	0.052	0.159	0.015	0.053
	γ	−0.019	0.259	−0.003	0.008	−0.002	0.004

Table 10: *Simulation study for PSP4 model with cure rate (continuation).*

Distribution for M		$n = 50$		$n = 100$		$n = 200$	
		bias	MSE	bias	MSE	bias	MSE
Poisson	β_0	0.045	0.231	0.017	0.098	0.009	0.045
	β_1	0.025	0.115	0.009	0.050	0.004	0.024
	β_2	0.007	0.001	0.004	0.000	0.002	0.000
	α	0.029	0.198	0.025	0.119	0.011	0.053
	σ	0.075	0.276	0.043	0.150	0.021	0.076
	γ	−0.008	0.276	−0.003	0.086	−0.000	0.033
Logarithmic	β_0	0.350	0.253	0.013	1.014	0.044	0.427
	β_1	0.253	3.837	0.082	0.789	0.044	0.341
	β_2	0.013	1.993	0.007	0.005	0.003	0.002
	α	0.032	0.214	0.028	0.113	0.012	0.059
	σ	0.089	0.429	0.053	0.189	0.018	0.097
	γ	−0.021	0.253	−0.010	0.042	−0.004	0.025
Geometric	β_0	0.063	0.012	0.030	0.232	0.013	0.106
	β_1	0.050	0.287	0.021	0.134	0.007	0.065
	β_2	0.005	0.002	0.003	0.001	0.001	0.001
	α	0.030	0.193	0.023	0.154	0.011	0.031
	σ	0.109	0.497	0.053	0.212	0.053	0.049
	γ	−0.011	0.153	−0.005	0.067	−0.002	0.032
Bernoulli	β_0	−0.049	0.417	−0.049	0.284	−0.023	0.097
	β_1	0.043	0.445	0.035	0.200	0.009	0.071
	β_2	0.007	0.004	0.004	0.002	0.001	0.001
	α	0.029	0.210	0.027	0.119	0.007	0.029
	σ	0.065	0.471	0.047	0.132	0.010	0.043
	γ	−0.017	0.212	−0.002	0.006	−0.001	0.002

Table 10 reveals an acceptable bias and MSE for all parameters and cases, except for the parameter σ for which a high bias and MSE was encountered for the small sample size. The bias and MSE decrease when the sample size is increased, suggesting that the parameter estimators are consistent. Finally, the bias and MSE decreases when the cure rate is decreased, which also is expected because for a lower cure rate, we expect more failure times observed in the sample, i.e., more precise information.

6. Final discussion

The Pareto IV power series cure rate model has been shown to outperform an analogous competing Birnbaum Saunders model for modeling a cutaneous melanoma data set. A

simulation study confirms that, with reasonable sample sizes, accurate parameter estimation is feasible within this model. An EM algorithm approach to obtaining maximum likelihood estimates can be recommended for these models. It is interesting to note that the rarely used logarithmic distribution turns out to be the distribution of choice among the four power series models considered.

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