Log-symmetric models with cure fraction with application to leprosy reactions data

Joyce B. Rocha¹, Francisco M. C. Medeiros¹ and Dione M. Valença¹
Department of Statistics, Federal University of Rio Grande do Norte, Natal, Brazil.

Abstract

In this paper, we propose a log-symmetric survival model with cure fraction, considering that the distributions of lifetimes for susceptible individuals belong to the log-symmetric class of distributions. This class has continuous, strictly positive, and asymmetric distributions, including the log-normal, log-$t$-Student, Birnbaum-Saunders, log-logistic I, log-logistic II, log-normal-contaminated, log-exponential-power, and log-slash distributions. The log-symmetric class is quite flexible and allows for including bimodal distributions and outliers. This includes explanatory variables through the parameter associated with the cure fraction. We evaluate the performance of the proposed model through extensive simulation studies and consider a real data application to evaluate the effect of factors on the immunity to leprosy reactions in patients with Hansen’s disease.

Keywords: Cure rate. Log-symmetric models. Maximum likelihood. Survival analysis.

1 Introduction

In the parametric approach of survival analysis, some probabilistic models such as exponential, Weibull, log-normal, and log-logistic are often used to fit lifetime data in practical situations (see Lawless (2011), Kalbfleisch and Prentice (2002), and Cox and Oakes (1984) for applications and inferential properties). Several proposals for generalized and extended distributions have been presented to provide more flexibility in modeling lifetime data. We can cite the generalized gamma (Stacy, 1962), $F$-generalized (Peng et al., 1998), generalized inverse Gaussian (Jorgensen, 1982), and generalized modified Weibull (Carrasco et al., 2008) distributions, among others. Lai (2013) describes some common methods for constructing lifetime distributions.

However, there are several distributions in the literature defined on the positive real line that can fit survival data. Here, the interest lies in the log-symmetric class of distributions, which is obtained from an exponential transformation of a random variable with symmetric distribution and characterized by continuous, strictly positive, and asymmetric distributions (see Vanegas and Paula (2016)). According to Medeiros and Ferrari (2017), this class includes distributions with lighter and heavier tails than log-normal distributions, such as the log-normal, log-logistic, log-$t$-Student, Harmonic law, Birnbaum-Saunders, Birnbaum-Saunders-$t$, Birnbaum-Saunders generalized, log-normal-contaminated, log-exponential-power, and log-slash. Vanegas and Paula (2016) studied the statistical properties of this class and verified that the two parameters are interpreted directly as location and scale. The scale parameter is the dispersion of the data and the location is the median, which is a robust measure in the presence of outliers and informative in survival analysis. In fact, according to
Lawless (2011) for lifetime distributions, the median is more used than the mean since it is easier to estimate when the data are censored and always exists for proper distributions, while the mean may not exist.

Vanegas and Paula (2017) studied log-symmetric models to fit survival data. They proposed a semi-parametric regression model to analyze strictly asymmetric data in the presence of non-informative censoring. The authors used a nonlinear structure for the median and a non-parametric structure to model the asymmetry (dispersion) parameter considering models of the log-symmetric class. These models relax the assumption of log-normal errors, including other distributions of this class.

A basic assumption of classic survival analysis is that all individuals will present the event of interest if they are followed for a sufficient time. However, in some situations, this is not true since some individuals could not be susceptible to the event, even for a long follow-up. These individuals are called immune or cured (Maller and Zhou, 1996). Survival models that deal with these situations are known as long-term models or cure rate models. The best-known long-term models are the standard mixture model, introduced by Boag (1949) and Berkson and Gage (1952), and the promotion time model (also known as bounded cumulative hazards), proposed by Yakovlev et al. (1993) and extended by Chen et al. (1999).

Rodrigues et al. (2009) proposed a unified long-term model, in which not only the distribution of the times until the occurrence of the event of interest (also called latency distribution) may take different forms, but also the distribution of the number of competing causes for the occurrence of the event of interest (also known as incidence distribution). In this approach, the standard mixture and promotion time models represent particular cases in which the incidence distribution assumes, respectively, Bernoulli and Poisson distributions. Ortega et al. (2009) presented the promotion time model with the generalized log-gamma distribution for the latency. Cancho et al. (2012) presented a cure rate model assuming the geometric distribution for the incidence and the Birnbaum-Saunders distribution for the latency. Fonseca et al. (2013) presented a simulation study considering missing covariates in the promotion time model, with Weibull as the distribution of latency. Hashimoto et al. (2014) proposed a survival promotion time model in which the latency follows a Birnbaum-Saunders distribution. In the present paper, we propose the log-symmetric model with cure fraction. We consider that the latency follows a member of the log-symmetric class of distributions, and for the incidence we study the Bernoulli, Poisson and geometric distributions. Thus, results in Hashimoto et al. (2014) and Cancho et al. (2012) follow as special cases of the more general results given here.

This paper is organized as follows. Section 2 defines the log-symmetric model with cure rate. In Section 3 we obtain the likelihood and score functions for the general model and some particular cases. In Section 4 we evaluate the performance of the proposed model through an extensive Monte Carlo simulation study. In Section 5, we present and discuss an empirical application on patients with leprosy to evaluate the effect of factors on immunity to leprosy reactions and show the applicability of the proposed model. Section 6 closes the paper with final remarks.

2 The model

For an individual \(i\) in the population, let \(M_i\) be a latent variable denoting the number of causes or risks competing for the occurrence of the event of interest with probability function \(p_0(m_i) = P_0(M_i = m_i)\) (incidence distribution). The time-to-event (for the \(i\)-th individual) due to \(j\)-th cause is denoted by \(Z_{ij}, i = 1, \ldots, n\) and \(j = 1, \ldots, M_i\). Given \(M_i = m_i\), we assume that \(Z_{i1}, Z_{i2}, \ldots, Z_{im_i}\)
are independent and identically distributed with common probability density function (latency distribution) given by

\[ f(z; \eta, \phi) = \frac{g(\tilde{z})}{z\sqrt{\phi}} \quad z > 0, \]

where \( \tilde{z} = \log \left[ \frac{(z/\eta)^{1/2}}{\phi} \right] \), \( \eta > 0 \) is the median of \( Z_{ij} \), and \( \phi > 0 \) is a shape (skewness or relative dispersion) parameter, for some function \( g: \mathbb{R} \to [0, \infty) \) (called density generating function) such that \( \int_0^\infty u^{-1/2}g(u)du = 1 \). We write \( Z_{ij} \sim \text{LS}(\eta, \phi^2; g(\cdot)) \) and denote its common survival function by \( S(z; \eta, \phi) \).

This class of distributions is called log-symmetric because \( W = \log(Z_{ij}) \) belongs to the symmetric class of distributions with parameters \( \mu = \log(\eta) \) and \( \phi \), density generating function \( g(\cdot) \), and probability density function given by \( f_W(w; \mu, \phi) = g((w - \mu)^2/\phi)/\sqrt{\phi}, w \in \mathbb{R} \). In particular, a symmetric distribution with \( \mu = 0 \) and \( \phi = 1 \) is called standard symmetric distribution with probability density and distribution functions represented here, respectively, by \( f_0(w) = g(w^2) \) and \( F_0(w) = \int_{-\infty}^w g(u^2)du \). Different choices for the density generating function \( g(\cdot) \) lead to different distributions in (1). See Table 1 for some examples.

Let \( T_i \) be a random variable representing the time-to-event defined as \( T_i = \min\{Z_{i0}, Z_{i1}, \ldots, Z_{iM_i}\} \), where the sequence \( Z_{i0}, Z_{i1}, \ldots \) does not depend on \( M_i \) and \( P(Z_{i0} = \infty) = 1 \). This assumption permits the occurrence of immune individuals (infinite lifetimes) since \( M_i = 0 \) means that there are no causes or risks for the occurrence of the event. Under this setup, the long-term survival function, the sub-density function, and the sub-hazard rate function for \( T_i \) are given, respectively, by

\[
S_p(t) = P(T_i > t) = p_0(0) + \sum_{m=1}^{\infty} p_0(m)S_0(\tilde{t})^m,
\]

\[
f_p(t) = -\frac{\partial S_p(t)}{\partial t} = \frac{g(\tilde{t}^2)}{t\sqrt{\phi}} \sum_{m=0}^{\infty} mp_0(m)S_0(\tilde{t})^{m-1},
\]

\[
h_p(t) = \frac{f_p(t)}{S_p(t)} = \frac{g(\tilde{t}^2)}{t\sqrt{\phi}} \sum_{m=0}^{\infty} mp_0(m)S_0(\tilde{t})^{m-1},
\]

where \( S_0(\cdot) = 1 - F_0(\cdot) \) is the survival function of the standard symmetric distribution and \( \tilde{t} = \log \left[ \frac{(t/\eta)^{1/2}}{\phi} \right] \). Hence, \( S_p(t) \) is an improper survival function since \( \lim_{t \to \infty} S_p(t) = p_0(0) > 0 \), where \( p_0(0) \) represents the cure fraction (proportion of cured or immune individuals) in the population. Below, we present a few specific models that arise from our general formulation. Particularly, we consider situations where \( M_i \) has Bernoulli, Poisson, and geometric distributions.

1. Log-symmetric standard mixture model: If \( M_i \) follows a Bernoulli distribution with \( p_0(1) = (1 - \theta) \) \((0 < \theta < 1)\), we obtain the classical mixture model (Boag 1949; Berkson and Gage 1952), where the proportion of cured individuals in the population is given by \( \theta = p_0(0) \). The long-term survival function, the sub-density, and sub-hazard rate functions for \( T_i \) are, respectively,

\[
S_p(t) = \theta + (1 - \theta)S_0(\tilde{t}),
\]

\[
f_p(t) = \frac{1}{t\sqrt{\phi}}(1 - \theta)g(\tilde{t}^2),
\]

\[
h_p(t) = \frac{(1 - \theta)g(\tilde{t}^2)}{t\sqrt{\phi}[\theta + (1 - \theta)S_0(\tilde{t})]}.
\]
Table 1: Density generating function for some log-symmetric distributions.\(^{a}\)

| Distribution          | \(g(u), \ u > 0\)                                                                 |
|-----------------------|-----------------------------------------------------------------------------------|
| log-normal            | \(\frac{\exp(-u/2)}{\sqrt{2\pi}}\)                                              |
| log-\(t\)-Student     | \(\frac{\nu^{-1/2}}{B(1/2, \nu/2)}\left(1 + \frac{u}{\nu}\right)^{-\frac{(\nu + 1)}{2}}, \ \nu \in \mathbb{R}\) |
| Birnbaum-Saunders     | \(\frac{1}{\sqrt{2\pi}} \exp\left(-\frac{2}{\sqrt{\alpha^2 \sinh^2(\sqrt{u})}}\right) \frac{2}{\alpha} \cosh(\sqrt{u}), \ \alpha > 0\) |
| type I log-logistic   | \(c \frac{e^{-u}}{(1 + e^{-u})^2}, \ c \approx 1.4843\)                          |
| type II log-logistic  | \(\frac{e^{-\sqrt{u}}}{(1 + e^{-\sqrt{u}})^2}\)                               |
| log-power-exponential | \(\frac{1}{\Gamma(1 + \frac{1+k}{2})(1+k)} \exp\left(-\frac{1}{2} u^{1/(1+k)}\right), \ -1 < k \leq 1\) |

\(^{a}\) \(B(\cdot, \cdot)\) and \(\Gamma(\cdot)\) are the beta and gamma functions, respectively.

2. **Log-symmetric promotion time model:** If \(M_i\) follows a Poisson distribution with mean \(\theta > 0\), we obtain the model proposed by [Chen et al. (1999)](#) with cure fraction given by \(\exp(-\theta) = p_{\theta}(0)\). The long-term survival function, the sub-density, and sub-hazard rate functions for \(T_i\) are, respectively, given by

\[
S_p(t) = \exp[-\theta F_0(\tilde{t})], \\
\frac{\theta g(\tilde{t}^2) \exp[-\theta F_0(\tilde{t})]}{t \sqrt{\phi}}, \\
\frac{\theta g(\tilde{t}^2) \exp[-\theta F_0(\tilde{t})]}{t \sqrt{\phi} \exp[-\theta F_0(t)]}.
\]

3. **Log-symmetric geometric model:** If \(M_i\) follows a geometric distribution with probability function \(p_{\theta}(m) = \theta(1 - \theta)^m\), where \(0 < \theta < 1\), the long-term survival function, the sub-density function, and the sub-hazard rate function are defined, respectively, by

\[
S_p(t) = \frac{\theta}{1 - (1 - \theta) S_0(t)}, \\
\frac{\theta (1 - \theta) g(\tilde{t}^2)}{t \sqrt{\phi} [1 - (1 - \theta) S_0(\tilde{t})]^2}, \\
\frac{(1 - \theta) g(\tilde{t}^2)}{t \sqrt{\phi} [1 - (1 - \theta) S_0(\tilde{t})]}.
\]

The cure fraction is given by \(\theta = p_{\theta}(0)\).
3 Inference

Consider that the time-to-event may not always be observed, being subject to a right censoring time (random and non-informative). For each individual \(i, i = 1, \ldots, n\), denote by \(C_i\) the censoring time variable and let \(Y_i = \min\{T_i, C_i\}\) be the observable lifetime, where \(C_i\) is independent of \(T_i\). Let \(\delta_i\) be the failure/censoring indicator, with \(\delta_i = 1\) if \(T_i \leq C_i\) and \(\delta_i = 0\) if \(T_i > C_i\).

We incorporate covariates in the parametric cure rate model through the relation \(\theta_i = q(x_i^\top; \beta)\), where \(x_i = (x_{i0}, x_{i1}, \ldots, x_{ip})^\top\) is the vector of covariates associated to the \(i\)-th observation \((x_{i0} = 1, \forall i)\), \(\beta = (\beta_0, \beta_1, \ldots, \beta_p)^\top\) is the vector of unknown parameters, and \(q(\cdot)\) is a continuous, invertible, and twice differentiable function, called the link function, which links the covariates \(x_i\) to the parameter of interest \(\theta_i\). Note that when covariates are included in the model, we have different cure rate parameters, \(\theta_i, i = 1, \ldots, n\), for each individual. We assume that \(X = (x_1, \ldots, x_n)^\top\) is a full-rank \(n \times p\) matrix, i.e. \(\text{rank}(X) = p\), and that usual regularity conditions for likelihood inference are valid (Cox and Hinkley, 1974, Chap.9). To simplify the notation, consider the \(n\)-dimensional vectors of observations \(y = (y_1, y_2, \ldots, y_n)^\top, \delta = (\delta_1, \delta_2, \ldots, \delta_n)^\top\), and \(m = (m_1, m_2, \ldots, m_n)^\top\). Hence, the complete dataset is denoted by \(D_c = (n, y, \delta, m, X)\), and the dataset without the latent variables is denoted by \(D = (n, y, \delta, X)\). In the standard mixture and geometric models, the most used relation to associate the parameter \(\theta_i\) with the covariates is the logistic link function (Maller and Zhou, 1996) given by

\[
\theta_i = \frac{\exp(x_i^\top \beta)}{1 + \exp(x_i^\top \beta)}.
\]

In the promotion time model, the relation often used to associate the parameter \(\theta_i\) with the covariates is given by the logarithmic link function (Chen et al., 1999), expressed by

\[
\theta_i = \exp(x_i^\top \beta).
\]

Thus, the vector of unknown parameters in the model is denoted by \(\lambda = (\beta^\top, \eta, \phi)^\top\), and after some algebra, it can be shown that the log-likelihood function for the complete data \(D_c\) is given by

\[
\ell(\lambda; D_c) = \sum_{i=1}^{n} \delta_i \log m_i + \sum_{i=1}^{n} m_i \log S(y_i; \eta, \phi) + \sum_{i=1}^{n} \delta_i \log \frac{f(y_i; \eta, \phi)}{S(y_i; \eta, \phi)} + \sum_{i=1}^{n} \log p_{0i}(m_i). \tag{6}
\]

Note that the likelihood (6) is not observable since it depends on the latent variables. The marginal likelihood for the observed data is obtained by summing over all possible values for the variables \(M_i, i = 1, \ldots, n\).

Therefore, the logarithm of the marginal likelihood function is given by

\[
\ell(\lambda; D) = \sum_{i=1}^{n} \delta_i \log f_p(y_i; \lambda) + \sum_{i=1}^{n} (1 - \delta_i) \log S_p(y_i; \lambda), \tag{7}
\]

where in a regression context associated with the incidence model, \(f_p(y_i; \lambda)\) and \(S_p(y_i; \lambda)\) are obtained in (2) by replacing \(\theta\) by \(\theta_i = q(x_i^\top; \beta)\). The use of marginal likelihood in cure rate models is common (see for example Tsodikov, 1998; Cancho et al., 2011; Mizoi et al., 2007; Rodrigues et al., 2009; Ortega et al., 2009; Fonseca et al., 2013; Loose et al., 2018). In addition to the marginal likelihood being considered an ordinary likelihood (Cox, 1975), an additional attraction for using this approach...
is that (7) appears to be a generalization of the usual (log) likelihood considered in survival models with the presence of censoring. The demonstration of (7) can be found in Carneiro and Valença (2016).

The score vector for $\lambda = (\beta^T, \eta, \phi)^T$ is given by $U(\lambda) = (U_\beta(\lambda)^T, U_\eta(\lambda), U_\phi(\lambda))^T$, where $U_\beta(\lambda) = \partial \ell(\lambda; D)/\partial \beta = (U_{\beta_1}(\lambda), \ldots, U_{\beta_p}(\lambda))_p^{\times 1}$, $U_\eta(\lambda) = \partial \ell(\lambda; D)/\partial \eta$, and $U_\phi(\lambda) = \partial \ell(\lambda; D)/\partial \phi$.

The maximum likelihood estimate $\hat{\lambda} = (\hat{\beta}^T, \hat{\eta}, \hat{\phi})^T$ is obtained by simultaneously solving the nonlinear equations $U_\beta(\lambda) = 0$, $U_\eta(\lambda) = 0$, and $U_\phi(\lambda) = 0$. This system of equations cannot be analytically solved and statistical software can be used to solve it numerically. In general, in the presence of censored observations, the expected Fisher information matrix cannot be obtained. Thus, inferences are based on the observed information matrix. Asymptotically,

$$(\hat{\beta}^T, \hat{\eta}, \hat{\phi})^T \sim N_{p+2}((\beta^T, \eta, \phi)^T, \check{L}(\lambda)^{-1}),$$

where $\check{L}(\lambda) = -\partial^2 \ell(\lambda; D)/\partial \lambda \partial \lambda^T$ is the $(p + 2) \times (p + 2)$ observed information matrix.

Next, we present the log-likelihood function and score vector for $\lambda = (\beta^T, \eta, \phi)^T$ considering models (3), (4), and (5).

1. Log-symmetric standard mixture model

i) Marginal log-likelihood function:

$$\ell(\lambda; D) = \sum_{i=1}^n \delta_i \left[ \log(1 - \theta_i) + \log g(\tilde{y}_i^2) - \log(y_i \sqrt{\phi}) \right] + \sum_{i=1}^n (1 - \delta_i) \log \left( \theta_i + (1 - \theta_i)(1 - F_0(\tilde{y}_i)) \right).$$

ii) Components of the score vector:

$$U_{\beta_l}(\lambda) = \sum_{i=1}^n \delta_i \theta_l x_{il} + \sum_{i=1}^n \frac{(1 - \delta_i) F_0(\tilde{y}_i) \theta_l (1 - \theta_i)}{\theta_i + (1 - \theta_i)(1 - F_0(\tilde{y}_i))} x_{il}, \text{ for } l = 0, 1, \ldots, p,$$

$$U_{\eta}(\lambda) = \sum_{i=1}^n \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \eta} + \frac{1}{\eta \sqrt{\phi}} \sum_{i=1}^n \frac{(1 - \delta_i)(1 - \theta_i)f_0(\tilde{y}_i)}{\theta_i + (1 - \theta_i)(1 - F_0(\tilde{y}_i))},$$

$$U_{\phi}(\lambda) = \sum_{i=1}^n \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \phi} + \frac{1}{2\phi} \sum_{i=1}^n \frac{(1 - \delta_i)(1 - \theta_i)f_0(\tilde{y}_i)\tilde{y}_i}{\theta_i + (1 - \theta_i)(1 - F_0(\tilde{y}_i))}.$$

2. Log-symmetric promotion time model

i) Marginal log-likelihood function:

$$\ell(\lambda; D) = \sum_{i=1}^n \delta_i \left[ \log(\theta_i) + \log g(\tilde{y}_i^2) - \theta_i F_0(\tilde{y}_i) - \log(y_i \sqrt{\phi}) \right] - \sum_{i=1}^n (1 - \delta_i) \theta_i F_0(\tilde{y}_i).$$
ii) Components of the score vector:

\[ U_{\lambda}(\lambda) = \sum_{i=1}^{n} \delta_i x_{il} - \sum_{i=1}^{n} F_0(\tilde{y}_i)\theta_i x_{il}, \quad \text{for } l = 0, 1, \ldots, p, \]

\[ U_{\eta}(\lambda) = \sum_{i=1}^{n} \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \eta} - \frac{1}{\eta \sqrt{\phi}} \sum_{i=1}^{n} \theta_i f_0(\tilde{y}_i), \]

\[ U_{\phi}(\lambda) = \sum_{i=1}^{n} \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \phi} - \frac{1}{2\phi} \sum_{i=1}^{n} \delta_i + \frac{1}{2\phi} \sum_{i=1}^{n} \theta_i f_0(\tilde{y}_i)\tilde{y}_i. \]

3. Log-symmetric geometric model

i) Marginal log-likelihood function:

\[ \ell(\lambda; D) = \sum_{i=1}^{n} \delta_i \left[ \log(\theta_i) + \log(1 - \theta_i) + \log g(\tilde{y}_i^2) - \log(\tilde{y}_i \sqrt{\phi}) \right] \]

\[ + \sum_{i=1}^{n} \delta_i [-2 \log(\theta_i + (1 - \theta_i)F_0(\tilde{y}_i))] \]

\[ + \sum_{i=1}^{n} (1 - \delta_i) [\log(\theta_i) - \log(\theta_i + (1 - \theta_i)F_0(\tilde{y}_i))]. \]

ii) Components of the score vector (for \( l = 0, 1, \ldots, p \)):

\[ U_{\lambda}(\lambda) = \sum_{i=1}^{n} \delta_i (1 - 2\theta_i) x_{il} + \sum_{i=1}^{n} (1 - \delta_i)(1 - \theta_i) x_{il} - \sum_{i=1}^{n} \frac{(1 + \delta_i)(1 - F_0(\tilde{y}_i))\theta_i(1 - \theta_i)}{\theta_i + (1 - \theta_i)F_0(\tilde{y}_i)} x_{il}, \]

\[ U_{\eta}(\lambda) = \sum_{i=1}^{n} \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \eta} + \frac{1}{\eta \sqrt{\phi}} \sum_{i=1}^{n} \frac{(1 + \delta_i)(1 - \theta_i)f_0(\tilde{y}_i)}{\theta_i + (1 - \theta_i)F_0(\tilde{y}_i)}, \]

\[ U_{\phi}(\lambda) = \sum_{i=1}^{n} \frac{\delta_i}{g(\tilde{y}_i^2)} \frac{\partial g(\tilde{y}_i^2)}{\partial \phi} - \frac{1}{2\phi} \sum_{i=1}^{n} \delta_i + \frac{1}{2\phi} \sum_{i=1}^{n} \frac{(1 + \delta_i)(1 - \theta_i)f_0(\tilde{y}_i)\tilde{y}_i}{\theta_i + (1 - \theta_i)F_0(\tilde{y}_i)}. \]

4 Simulation results

In this section, we shall present a Monte Carlo simulation study to investigate and compare the performance of the maximum likelihood estimators in log-symmetric promotion time cure models. We considered the following latency distributions: log-normal, log-t-Student with \( \nu = 3 \) degrees of freedom, and Birnbaum-Saunders extended with \( \alpha = 1.5 \). The values for \( x_{i1} \) and \( x_{i3} \) were obtained as random draws from a uniform distribution in the interval \((0, 1)\), and the values for \( x_{i2} \) were randomly obtained from the Bernoulli distribution with a success probability of 0.5. The censoring times \( C_i \) were generated as independent random variables uniformly distributed in the interval \([0, u]\), where \( u \) was suitably chosen to produce the following censoring percentages: 15% and 30%.

To define the proportion of censoring used in the simulation, we considered the approach given in Fonseca et al. (2013) and the following relation:

\[ c_{p\text{total}} = c_p(1 - cf) + cf, \]
where \( cp \) is the censoring proportion among those susceptible to the event, \( c_{p_{\text{total}}} \) is the censoring proportion in relation to all units under study (susceptible or cured) and \( cf \) is the cure fraction. Although in real data applications \( c_{p_{\text{total}}} \) is the only calculable measure, we also considered the censoring among uncured \((cp)\) since this allows us to distinguish between censored and cured individuals in the simulation study.

Three different sample sizes were considered: \( n = 250, n = 500, \) and \( n = 1000 \). For the \( i \)-th cured individual, \( M_i \) was generated as a Poisson distribution with mean \( \theta_i = \exp(x_i^T\beta) \), representing the incidence distribution, \( \beta = (\beta_0, \beta_1, \beta_2, \beta_3)^T \). Different cure fractions in the sample were obtained by changing the value of \( \beta \). Thus, \( \beta = (0.42, 0.25, 0.24, 0.34)^T \) leads to \( cf = 10\% \) and \( \beta = (0.10, 0.05, 0.07, 0.03) \) leads to \( cf = 30\% \). The median and shape parameter are \( \eta = 5 \) and \( \phi = 1 \), respectively.

The number of Monte Carlo replicates was 5000 and all simulations were performed in the R software [R Core Team, 2020]. All the parameters, except the assumed known parameters \( \nu \) (log-\( t \)-Student) and \( \alpha \) (Birnbaum-Saunders extended), were estimated by the maximum likelihood method. The optimizations were performed using the quasi-Newton method BFGS (Broyden-Fletcher-Goldfarb-Shanno) through the function \textit{optim}. The evaluation of the point estimation was carried out based on the following quantities for each sample size: mean, relative bias, the root of the relative mean square error, and standard error, which are given, respectively, by

\[
\text{mean}(\hat{\gamma}) = \frac{1}{5000} \sum_{r=1}^{5000} \hat{\gamma}_r, \quad \text{RB} = \frac{\text{mean}(\hat{\gamma}) - \gamma}{\gamma},
\]

\[
\text{RMSE} = \sqrt{\frac{1}{5000} \sum_{r=1}^{5000} \left( \frac{\hat{\gamma}_r - \gamma}{\gamma} \right)^2}, \quad \text{se} = \sqrt{\frac{\sum_{r=1}^{5000} (\hat{\gamma}_r - \text{mean}(\hat{\gamma}))^2}{5000 - 1}},
\]

where \( \hat{\gamma} \) is the parameter estimate of the \( r \)-th replicate. The results are presented in Tables 2 and 3 (log-normal); Tables 4 and 5 (log-\( t \)-Student); and Tables 6 and 7 (Birnbaum-Saunders extended).

The results suggest that the estimates of parameters \( \beta_1, \beta_2, \) and \( \beta_3 \) are close to their true values, even with high censure proportion. For instance, for \( n = 500, \text{cp} = 30\% \), and \( cf = 30\% \), the estimates of the parameters for the log-normal promotion time model (Table 2) are 0.051, 0.072, and 0.031, for the log-\( t \)-Student promotion time model (Table 4) we obtain 0.054, 0.076, and 0.031, respectively, and for the Birnbaum-Saunders promotion time model (Table 6) we have 0.053, 0.073, and 0.030.

We note that the relative bias of \( \beta_0, \eta, \) and \( \phi \) increases as the censoring proportion and cure fractions increase. For example, consider the log-\( t \)-Student promotion time model with \( n = 250 \) in Tables 4 and 5 the relative bias of \( \hat{\beta}_0 \) increases from -0.145 (\( cp = 15\% \) and \( cf = 10\% \)) to 0.600 (\( cp = 30\% \) and \( cf = 30\% \)), and the relative bias of \( \hat{\eta} (\hat{\phi}) \) increases from -0.010 (0.028) (with \( cp = 15\% \) and \( cf = 10\% \)) to 0.338 (0.195) (with \( cp = 30\% \) and \( cf = 30\% \)). Comparing the results presented in these tables, we observe that as the sample size increases, in general, the bias of the estimators reduces, as expected.

## 5 Empirical application

To illustrate the applicability of the proposed log-symmetric model with cure fraction, we considered data on leprosy patients. Leprosy is a chronic and contagious disease with slow evolution
Table 2: Log-normal promotion time model: Estimates of the regression coefficients for different values of $n$, censoring percentage ($cp$), and cure fraction ($cf$), with true values of $\beta$ for each $cf$ ($\beta_{cf}$) given by $\beta_{10} = (0.42, 0.25, 0.24, 0.34)^\top$ and $\beta_{30} = (0.10, 0.05, 0.07, 0.03)^\top$.

| $n$ | $cp$ | $cf$ | $\hat{\beta}_0$ mean | $\hat{\beta}_0$ RSME | $\hat{\beta}_0$ se | $\hat{\beta}_1$ mean | $\hat{\beta}_1$ RSME | $\hat{\beta}_1$ se | $\hat{\beta}_2$ mean | $\hat{\beta}_2$ RSME | $\hat{\beta}_2$ se | $\hat{\beta}_3$ mean | $\hat{\beta}_3$ RSME | $\hat{\beta}_3$ se |
|-----|------|------|------------------------|----------------------|------------------|------------------------|----------------------|------------------|------------------------|----------------------|------------------|------------------------|----------------------|------------------|
| 15  | 10   | 0.362 | -0.138                 | 0.235                | 0.228            | 0.265                   | 0.060                | 0.257            | 0.256                   | 0.046                | 0.150            | 0.149                   | 0.366                | 0.076            |
|     | 30   | -0.890 | 0.255                | 0.239                | 0.053            | 0.100                   | 0.291                | 0.291            | 0.070                   | 0.000                | 0.167            | 0.167                   | 0.027                | -0.100           |
|     | 10   | 0.565 | 0.345                | 0.408                | 0.382            | 0.268                   | 0.072                | 0.283            | 0.254                   | 0.058                | 0.166            | 0.165                   | 0.372                | 0.094            |
|     | 30   | 1.230 | 0.408                | 0.389                | 0.055            | 0.100                   | 0.322                | 0.322            | 0.072                   | 0.029                | 0.185            | 0.185                   | 0.031                | 0.033            |
| 250 | 15   | 0.356 | -0.152               | 0.178                | 0.166            | 0.264                   | 0.056                | 0.178            | 0.250                   | 0.042                | 0.105            | 0.104                   | 0.354                | 0.041            |
|     | 30   | -0.910 | 0.198                | 0.176                | 0.051            | 0.020                   | 0.203                | 0.203            | 0.070                   | 0.000                | 0.117            | 0.117                   | 0.031                | 0.033            |
|     | 10   | 0.537 | 0.379                | 0.288                | 0.263            | 0.268                   | 0.072                | 0.196            | 0.253                   | 0.054                | 0.117            | 0.116                   | 0.361                | 0.062            |
|     | 30   | 0.970 | 0.281                | 0.264                | 0.051            | 0.020                   | 0.224                | 0.224            | 0.072                   | 0.029                | 0.130            | 0.130                   | 0.031                | 0.033            |
| 500 | 15   | 0.354 | -0.157               | 0.133                | 0.116            | 0.261                   | 0.044                | 0.126            | 0.249                   | 0.038                | 0.074            | 0.073                   | 0.354                | 0.053            |
|     | 30   | -0.920 | 0.153                | 0.121                | 0.051            | 0.020                   | 0.142                | 0.142            | 0.071                   | 0.014                | 0.082            | 0.082                   | 0.029                | -0.033           |
|     | 10   | 0.521 | 0.240                | 0.206                | 0.180            | 0.265                   | 0.060                | 0.140            | 0.253                   | 0.054                | 0.081            | 0.081                   | 0.360                | 0.059            |
|     | 30   | 0.880 | 0.203                | 0.183                | 0.053            | 0.060                   | 0.158                | 0.158            | 0.073                   | 0.043                | 0.090            | 0.090                   | 0.030                | 0.000            |

Table 3: Log-normal promotion time model: Estimates of $\eta$ and $\phi$ (with true values $\eta = 5$ and $\phi = 1$).

| $n$ | $cp$ | $cf$ | $\hat{\eta}$ mean | $\hat{\eta}$ RSME | $\hat{\eta}$ se | $\hat{\phi}$ mean | $\hat{\phi}$ RSME | $\hat{\phi}$ se |
|-----|------|------|-------------------|-------------------|-----------------|-------------------|-------------------|-----------------|
| 250 | 15   | 5.067 | 0.013             | 0.932             | 0.930           | 1.020             | 0.020             | 0.174           |
|     | 30   | 4.842 | -0.032            | 0.714             | 0.696           | 1.010             | 0.010             | 0.176           |
|     | 10   | 7.190 | 0.438             | 5.676             | 5.237           | 1.201             | 0.201             | 0.384           |
|     | 30   | 7.861 | 0.572             | 14.798            | 14.521          | 1.312             | 0.312             | 0.521           |
| 500 | 15   | 4.972 | -0.006            | 0.598             | 0.597           | 1.015             | 0.015             | 0.122           |
|     | 30   | 4.785 | -0.043            | 0.508             | 0.460           | 1.007             | 0.007             | 0.122           |
|     | 10   | 6.482 | 0.296             | 2.586             | 2.119           | 1.179             | 0.179             | 0.282           |
|     | 30   | 6.752 | 0.350             | 2.938             | 2.359           | 1.281             | 0.281             | 0.388           |
| 1000| 15   | 4.928 | -0.014            | 0.412             | 0.406           | 1.014             | 0.014             | 0.084           |
|     | 30   | 4.749 | -0.050            | 0.405             | 0.318           | 1.002             | 0.002             | 0.087           |
|     | 10   | 6.192 | 0.238             | 1.682             | 1.187           | 1.166             | 0.166             | 0.222           |
|     | 30   | 6.489 | 0.298             | 2.007             | 1.347           | 1.269             | 0.269             | 0.326           |
Table 4: Log-t-Student promotion time model: Estimates of the regression coefficients for different values of \( n \), censoring percentage \((cp)\), and cure fraction \((cf)\), with true values of \( \beta \) for each \( cf \) \((\beta_{cf})\) given by \( \beta_{10} = (0.42, 0.25, 0.24, 0.34)^\top \) and \( \beta_{30} = (0.10, 0.05, 0.07, 0.03)^\top \).

| \( n \) | \( cp \) | \( cf \) | \( \hat{\beta}_0 \) | \( \text{se} \) | \( \hat{\beta}_1 \) | \( \text{se} \) | \( \hat{\beta}_2 \) | \( \text{se} \) | \( \hat{\beta}_3 \) | \( \text{se} \) |
|-------|--------|--------|----------------|---------|----------------|---------|----------------|---------|----------------|---------|
| 250   | 15     | 10     | 0.359         | -0.146  | 0.227          | 0.219   | 0.260          | 0.256   | 0.252          | 0.152   |
|       |        | 30     | 0.014         | -0.860  | 0.247          | 0.231   | 0.057          | 0.278   | 0.071          | 0.168   |
|       |        | 10     | 0.541         | 0.288   | 0.379          | 0.359   | 0.263          | 0.284   | 0.253          | 0.168   |
|       |        | 30     | 0.160         | 0.600   | 0.344          | 0.339   | 0.057          | 0.310   | 0.072          | 0.184   |
| 500   | 15     | 10     | 0.351         | -0.164  | 0.175          | 0.161   | 0.260          | 0.179   | 0.249          | 0.101   |
|       |        | 30     | 0.014         | -0.860  | 0.191          | 0.171   | 0.051          | 0.200   | 0.074          | 0.117   |
|       |        | 10     | 0.514         | 0.224   | 0.255          | 0.238   | 0.265          | 0.199   | 0.250          | 0.112   |
|       |        | 30     | 0.133         | 0.330   | 0.237          | 0.235   | 0.054          | 0.223   | 0.067          | 0.130   |
| 1000  | 15     | 10     | 0.353         | -0.160  | 0.133          | 0.115   | 0.258          | 0.129   | 0.247          | 0.075   |
|       |        | 30     | 0.012         | -0.880  | 0.152          | 0.124   | 0.055          | 0.143   | 0.072          | 0.082   |
|       |        | 10     | 0.508         | 0.210   | 0.186          | 0.165   | 0.259          | 0.142   | 0.249          | 0.082   |
|       |        | 30     | 0.127         | 0.270   | 0.168          | 0.166   | 0.055          | 0.157   | 0.074          | 0.091   |

Table 5: Log-t-Student promotion time model: Estimates of \( \eta \) and \( \phi \) (with true values \( \eta = 5 \) and \( \phi = 1 \)).

| \( n \) | \( cp \) | \( cf \) | \( \hat{\eta} \) | \( \text{se} \) | \( \hat{\phi} \) | \( \text{se} \) |
|-------|--------|--------|----------------|---------|----------------|---------|
| 250   | 15     | 10     | 4.948         | -0.010  | 0.820          | 0.818   |
|       |        | 30     | 4.726         | -0.055  | 0.686          | 0.628   |
|       |        | 10     | 6.512         | 0.302   | 3.145          | 2.757   |
|       |        | 30     | 6.691         | 0.338   | 3.770          | 3.370   |
| 500   | 15     | 10     | 4.883         | -0.023  | 0.567          | 0.555   |
|       |        | 30     | 4.677         | -0.065  | 0.533          | 0.424   |
|       |        | 10     | 6.196         | 0.239   | 1.915          | 1.495   |
|       |        | 30     | 6.164         | 0.233   | 2.018          | 1.649   |
| 1000  | 15     | 10     | 4.848         | -0.030  | 0.409          | 0.380   |
|       |        | 30     | 4.654         | -0.069  | 0.457          | 0.298   |
|       |        | 10     | 6.041         | 0.208   | 1.433          | 0.984   |
|       |        | 30     | 5.996         | 0.199   | 1.462          | 1.070   |
Table 6: Birnbaum-Saunders promotion time model: Estimates of the regression coefficients for different values of $n$, censoring percentage ($cp$), and cure fraction ($cf$), with true values of $\beta$ for each $cf$ ($\beta_{cf}$) given by $\beta_{10} = (0.42, 0.25, 0.24, 0.34)^\top$ and $\beta_{30} = (0.10, 0.05, 0.07, 0.03)^\top$.

| $n$ | $cp$ | $cf$ | $\hat{\beta}_0$ | $\hat{\beta}_1$ | $\hat{\beta}_2$ | $\hat{\beta}_3$ |
|-----|------|------|-----------------|-----------------|-----------------|-----------------|
|     | 15   | 30   | mean | RB | $\sqrt{\text{RSME}}$ | se | mean | RB | $\sqrt{\text{RSME}}$ | se | mean | RB | $\sqrt{\text{RSME}}$ | se | mean | RB | $\sqrt{\text{RSME}}$ | se |
| 250 | 10   | 0.353 | −0.169 | 0.237 | 0.227 | 0.274 | 0.096 | 0.260 | 0.259 | 0.258 | 0.075 | 0.151 | 0.159 | 0.366 | 0.076 | 0.272 | 0.271 |
|     | 30   | −0.016 | −1.160 | 0.263 | 0.236 | 0.053 | 0.060 | 0.293 | 0.293 | 0.072 | 0.029 | 0.168 | 0.168 | 0.030 | 0.000 | 0.302 | 0.302 |
|     | 10   | 0.554 | 0.319 | 0.334 | 0.306 | 0.272 | 0.088 | 0.279 | 0.279 | 0.261 | 0.088 | 0.167 | 0.166 | 0.363 | 0.068 | 0.297 | 0.296 |
|     | 30   | 0.243 | 1.430 | 0.345 | 0.314 | 0.051 | 0.020 | 0.317 | 0.317 | 0.076 | 0.086 | 0.188 | 0.188 | 0.029 | −0.033 | 0.330 | 0.330 |
| 500 | 15   | 0.345 | −0.179 | 0.180 | 0.164 | 0.265 | 0.060 | 0.178 | 0.178 | 0.260 | 0.083 | 0.107 | 0.105 | 0.363 | 0.068 | 0.191 | 0.190 |
|     | 30   | −0.021 | −1.210 | 0.214 | 0.177 | 0.051 | 0.020 | 0.203 | 0.203 | 0.074 | 0.057 | 0.118 | 0.118 | 0.035 | 0.167 | 0.219 | 0.219 |
|     | 10   | 0.520 | 0.238 | 0.237 | 0.214 | 0.270 | 0.080 | 0.196 | 0.195 | 0.259 | 0.079 | 0.115 | 0.114 | 0.366 | 0.076 | 0.206 | 0.204 |
|     | 30   | 0.233 | 1.330 | 0.260 | 0.224 | 0.053 | 0.060 | 0.222 | 0.222 | 0.073 | 0.043 | 0.131 | 0.131 | 0.030 | 0.000 | 0.233 | 0.233 |
| 1000| 15   | 0.342 | −0.186 | 0.139 | 0.115 | 0.267 | 0.068 | 0.129 | 0.128 | 0.256 | 0.067 | 0.076 | 0.074 | 0.365 | 0.074 | 0.132 | 0.130 |
|     | 30   | −0.021 | −1.210 | 0.172 | 0.123 | 0.056 | 0.120 | 0.143 | 0.143 | 0.073 | 0.043 | 0.083 | 0.083 | 0.029 | −0.033 | 0.146 | 0.146 |
|     | 10   | 0.514 | 0.224 | 0.175 | 0.147 | 0.266 | 0.064 | 0.140 | 0.139 | 0.258 | 0.075 | 0.084 | 0.082 | 0.365 | 0.074 | 0.144 | 0.142 |
|     | 30   | 0.227 | 1.270 | 0.201 | 0.155 | 0.052 | 0.049 | 0.155 | 0.155 | 0.076 | 0.086 | 0.092 | 0.092 | 0.033 | 0.100 | 0.159 | 0.159 |

Table 7: Birnbaum-Saunders promotion time model: Estimates of $\eta$ and $\phi$ (with true values $\eta = 5$ and $\phi = 1$).

| $n$ | $cp$ | $cf$ | $\hat{\eta}$ | $\hat{\phi}$ |
|-----|------|------|--------------|--------------|
|     | mean | RB | $\sqrt{\text{RSME}}$ | se | mean | RB | $\sqrt{\text{RSME}}$ | se |
| 250 | 15   | 10  | 5.122 | 0.024 | 0.657 | 0.646 | 1.048 | 0.048 | 0.196 | 0.191 |
|     | 30   | 10  | 4.848 | −0.030 | 0.424 | 0.396 | 0.986 | −0.014 | 0.141 | 0.140 |
|     | 30   | 10  | 6.320 | 0.264 | 2.363 | 1.959 | 1.324 | 0.324 | 0.513 | 0.397 |
|     | 30   | 30  | 6.783 | 0.357 | 2.906 | 2.294 | 1.482 | 0.482 | 0.659 | 0.450 |
| 500 | 15   | 10  | 5.049 | 0.010 | 0.415 | 0.413 | 1.036 | 0.036 | 0.131 | 0.126 |
|     | 30   | 10  | 4.823 | −0.035 | 0.321 | 0.267 | 0.983 | −0.017 | 0.098 | 0.097 |
|     | 30   | 10  | 5.992 | 0.198 | 1.390 | 0.974 | 1.266 | 0.266 | 0.356 | 0.237 |
|     | 30   | 30  | 6.518 | 0.304 | 1.856 | 1.069 | 1.444 | 0.444 | 0.516 | 0.264 |
| 1000| 15   | 10  | 5.027 | 0.005 | 0.283 | 0.282 | 1.032 | 0.032 | 0.093 | 0.087 |
|     | 30   | 10  | 4.809 | −0.038 | 0.264 | 0.182 | 0.982 | −0.018 | 0.068 | 0.065 |
|     | 30   | 10  | 5.886 | 0.177 | 1.080 | 0.617 | 1.245 | 0.245 | 0.293 | 0.159 |
|     | 30   | 30  | 6.431 | 0.286 | 1.575 | 0.656 | 1.431 | 0.431 | 0.465 | 0.173 |
and a high degree of disability. Some leprosy patients have reactive states or leprosy reactions. These reactions are the main causes of patients’ physical disabilities and deformities, but they may not occur for some patients.

The dataset refers to a retrospective study conducted between 2010 and 2014 at the Institute of Tropical Medicine (IMT) of the Universidade Federal do Rio Grande do Norte, Brazil. The medical records of 263 patients diagnosed with leprosy were evaluated. For each patient, the lifetime corresponds to the time (in months) between the disease diagnosis and the first leprosy reaction. For 44% of the patients, the leprosy reaction was not observed, which corresponds to the censoring proportion.

In Figure 1, we present the Kaplan-Meier curve of the observed data. There are indications of the use of the survival cure rate model since the survival curve does not tend to zero in a sufficiently long follow-up time but stabilizes around 40%.

Initially, we did not consider covariates in the regression structure and fitted the following cure rate models: standard mixture, promotion time, and geometric models, considering the Weibull, log-normal, log-$t$-Student, and Birnbaum-Saunders distributions for the latency. Although the Weibull distribution does not belong to the log-symmetric class of distributions, it was used for comparison. In terms of model selection criteria, we can use the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) (Burnham and Anderson, 2004). According to Table 8, the log-$t$-Student standard mixture model with $\nu = 8$ presented the smallest values of AIC and BIC, thus being the best distribution fitted to these data.

5.1 Including covariates

To evaluate the effect of factors on the proportion of individuals immune to leprosy reactions, we considered the variables gender, age, and Leprosy Classification. The Leprosy Classification (LC) in patients was according to the clinical form of the disease (Tuberculoid, Dimorfa, or Virchowiana) and the operational classification (Paucibacillary - cases with up to 5 lesions and Multibacillary - cases with over 5 lesions). Thus, in this factor, patients could only be classified as Paucibacillary and Tuberculoid, Multibacillary and Dimorfa, and Multibacillary and Virchowian. In Figures 2a and

![Figure 1: Empirical survivor function (Kaplan-Meier) for the data.](image-url)
Table 8: Values of AIC and BIC for the fitted distributions.

| Incidence distribution | Latency distribution | Add parameter | AIC  | BIC  |
|------------------------|----------------------|---------------|------|------|
| Bernoulli              |                      | Measured      | 1196.727 | 1267.526 |
| log normal             |                      | -             | 1194.764 | 1265.563 |
| log-t-student          |                      | 2, 4, 6, 8    |      |      |
|                        |                      | 2             | 1201.386 | 1272.185 |
|                        |                      | 4             | 1194.542 | 1265.341 |
|                        |                      | 6             | 1193.161 | 1263.960 |
|                        |                      | 8             | **1192.809** | **1263.608** |
| Birnbaum-Saunders      |                      | 1.2, 2, 2.8, 3.6 |      |      |
|                        |                      | 1.2           | 1207.747 | 1278.546 |
|                        |                      | 2             | 1215.362 | 1286.161 |
|                        |                      | 2.8           | 1224.626 | 1295.425 |
|                        |                      | 3.6           | 1233.847 | 1304.646 |
| Poisson                |                      | Measured      | 1195.096 | 1265.896 |
| log normal             |                      | -             | 1195.034 | 1265.833 |
| log-t-student          |                      | 2, 4, 6, 8    |      |      |
|                        |                      | 2             | 1203.658 | 1274.457 |
|                        |                      | 4             | 1195.095 | 1265.894 |
|                        |                      | 6             | 1193.396 | 1264.195 |
|                        |                      | 8             | 1192.960 | 1263.760 |
| Birnbaum-Saunders      |                      | 1.2, 2, 2.8, 3.6 |      |      |
|                        |                      | 1.2           | 1203.082 | 1273.881 |
|                        |                      | 2             | 1203.003 | 1273.802 |
|                        |                      | 2.8           | 1202.687 | 1273.486 |
|                        |                      | 3.6           | 1202.526 | 1273.325 |
| Geometric              |                      | Measured      | 1193.831 | 1264.630 |
| log normal             |                      | -             | 1195.399 | 1266.198 |
| log-t-student          |                      | 2, 4, 6, 8    |      |      |
|                        |                      | 2             | 1205.927 | 1276.726 |
|                        |                      | 4             | 1195.498 | 1266.297 |
|                        |                      | 6             | 1193.555 | 1264.355 |
|                        |                      | 8             | 1193.098 | 1263.897 |
| Birnbaum-Saunders      |                      | 1.2, 2, 2.8, 3.6 |      |      |
|                        |                      | 1.2           | 1199.522 | 1270.321 |
|                        |                      | 2             | 1199.443 | 1270.243 |
|                        |                      | 2.8           | 1199.378 | 1270.178 |
|                        |                      | 3.6           | 1199.347 | 1270.146 |
we present the Kaplan-Meier curves according to the categorical variables gender and Leprosy Classification, respectively.

The log-t-Student standard mixture model with $\nu = 8$ was fitted to the data. Considering likelihood ratio tests, the final model contains only the factor LC. The results of the final model are presented in Table 9.

We used the fitted model to estimate the immune fraction for each level of the factor LC according to

$$p_{\hat{\eta}}(0) = \frac{\exp(-1.551 - 3.264 x_{i1} + 3.063 x_{i2})}{1 + \exp(-1.551 - 3.264 x_{i1} + 3.063 x_{i2})}.$$  

The results are summarized in Table 10. We can see that the immune fraction of patients with Multibacillary and Dimorphic leprosy classification was 17.5\%, whereas patients with Multibacillary and Virchowian classification (the most severe) had a cure fraction of 0.8\%, that is, there are practically no immune patients in this classification. Patients with leprosy classification as Paucibacillary and Tuberculoid (the early stage of the disease) had little chance of having these reactions since the estimated immune fraction was 82\%. The estimated median time until the leprosy reaction of susceptible individuals was $\hat{\eta} = 8.79$ months, which is close to the empirical median time (7.37). Figure 3 indicates a good fit of the final model.
Figure 3: Empirical survivor function (Kaplan-Meier) for the data according to Leprosy Classification and curves fitted by final model.
Table 10: Estimated immune fraction to leprosy reaction for levels of the LC factor with log-\(t\)-Student standard mixture model fitted to the data.

| Leprosy Classification                  | Indicator variables | cure fraction |
|-----------------------------------------|---------------------|--------------|
| Multibacilar and Dimorfa                | 0 0                 | 17.5%        |
| Multibacilar and Virchowiana            | 1 0                 | 0.8%         |
| Paucibacilar and Tuberculoide           | 0 1                 | 82.0%        |

6 Final remarks

In this paper, we proposed the long-term log-symmetric model. We considered a cure rate model in which the latency distribution belongs to the class of log-symmetric distributions. For the incidence, we considered the Bernoulli, Poisson, and geometric distributions. Covariates were included only in the parameter of the incidence distribution.

We evaluated the performance of the maximum likelihood estimators of the model for some special cases of the log-symmetric promotion time model through extensive Monte Carlo simulation studies. In general, the bias and variability of the maximum likelihood estimators increase as the censoring proportion and cure fraction increase, but they decrease as the sample size increases. We noted that the estimates for the intercept, \(\eta\), and \(\phi\) are more affected in the presence of censoring and cure fraction than the estimates of the regression coefficients.

In the empirical application, we verified that the log-\(t\)-Student standard mixture model presented the best fit to the data on time to leprosy reaction. The model could identify that the proportion of individuals immune to reactions differs with respect to the classification of leprosy, providing estimates to the proportion of immunity according to the classification. Moreover, the proposed model also provided a general estimate of the median time until the reaction for susceptible individuals.

Considering the importance of a correct choice of the latency distribution and obtaining adequate estimates for the cure fraction, Yu et al. (2004), we believe that this new class is helpful since it allows for adjusting several latency distributions. This was illustrated in the application, where we fitted different models to the data, including four distributions for latency and three for incidence, and according to AIC and BIC criteria, we could choose the best one.

In future work, we envisage to extend this proposed class to accommodate covariates in the latency part (suitably incorporated in the \(\eta\) (median) parameter) to allow for separate interpretation of the effects of the covariates on the cure fraction and failure time distribution of the uncured. In the simulation studies, we noted an influence of the choice of the value representing the length of the follow-up on the estimation of the intercept in the incidence distribution. Yu et al. (2004) have studied this in a mixture model context, so extending this study to the log-symmetric promotion time and geometric models is another interesting topic for future work.

References

Berkson, J. and Gage, R. P. (1952). Survival curve for cancer patients following treatment. Journal of the Amer
Boag, J. W. (1949). Maximum likelihood estimates of the proportion of patients cured by cancer therapy. *Journal of the Royal Statistical Society. Series B (Methodological),* 11(1), 15–53.

Burnham, K.P., Anderson, D.R. (2004). Multimodel inference: understanding AIC and BIC in model selection. *Sociological methods & research* 33, 261–304.

Cancho, V. G., Louzada, F. and Barriga, G. D. (2012). The Geometric Birnbaum-Saunders regression model with cure rate. *Journal of Statistical Planning and Inference,* 142(4), 993-1000.

Cancho, V. G., Rodrigues, J.r and de Castro, M. (2011). A flexible model for survival data with a cure rate: a Bayesian approach. *Journal of Applied Statistics,* 38(1), 57-70.

Carneiro, H. and Valença, D. M. (2016). Gradient and likelihood ratio tests in cure rate models. *International Journal of Statistics and Probability,* 5(4), 9-21.

Carrasco, J. M., Ortega, E. M. and Cordeiro, G. M. (2008). A generalized modified Weibull distribution for lifetime modeling. *Computational Statistics and Data Analysis,* 53(2), 450–462.

Chen, M. H., Ibrahim, J. G. and Sinha, D. (1999). A new Bayesian model for survival data with a surviving fraction. *Journal of the American Statistical Association,* 94(447), 909-919.

Cox, D. R. (1975). Partial likelihood. *Biometrika,* 62(2), 269-276.

Cox, D. R. and Hinkley, D. V. (1974). *Theoretical Statistics.* Chapman & Hall, London.

Cox, D. R. and Oakes, D. (1984). *Analysis of Survival Data.* Chapman & Hall.

Fonseca, R. S., Valença, D. M. and Bolfarine, H. (2013). Cure rate survival models with missing covariates: a simulation study. *Journal of Statistical Computation and Simulation,* 83(1), 97-113.

Hashimoto, E. M., Ortega, E. M., Cordeiro, G. M. and Cancho, V. G. (2014). The Poisson Birnbaum-Saunders model with long-term survivors. *Statistics,* 48(6), 1394-1413.

Jorgensen, B. (2012). *Statistical Properties of the Generalized Inverse Gaussian Distribution.* Springer Science & Business Media. New York.

Kalbfleisch, J. D. and Prentice, R. L. (2002). *The statistical analysis of failure time data.* John Wiley & Sons.

Lai, C. D. (2013). Constructions and applications of lifetime distributions. *Applied Stochastic Models in Business and Industry,* 29(2), 127–140.

Lawless, J. F. (2011). *Statistical models and methods for lifetime data.* John Wiley & Sons. New Jersey.

Loose, L. H., Valença, D. M. and Bayer, F. M. (2018). On bootstrap testing inference in cure rate models. *Journal of Statistical Computation and Simulation,* 17, 3437–3454.

Maller, R. A. and Zhou, X. (1996). *Survival analysis with long-term survivors.* New York: Wiley.

Medeiros, F. M. C. and Ferrari, S. L. P. (2017). Small-sample testing inference in symmetric and log-symmetric linear regression models. *Statistica Neerlandica,* 71(3), 200–224.

Mizoi, M. F., Bolfarine, H. and Pedroso-De-Lima, A. C. (2007). Cure rate model with measurement errors. *Communications in Statistics - Simulation and Computation,* 36(1), 185–196.
Ortega, E. M., Cancho, V. G. and Paula, G. A. (2009). Generalized log-gamma regression models with cure fraction. *Lifetime Data Analysis*, **15**(1), 79.

Peng, Y., Dear, K. B. and Denham, J. W. (1998). A generalized F mixture model for cure rate estimation. *Statistics in medicine*, **17**(8), 813–830.

R Core Team (2020). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. [http://www.R-project.org/](http://www.R-project.org/).

Rodrigues, J., Cancho, V. G., de Castro, M. and Louzada-Neto, F. (2009). On the unification of long-term survival models. *Statistics and Probability Letters*, **79**(6), 753-759.

Stacy, E. W. (1962). A generalization of the gamma distribution. *The Annals of mathematical statistics*, **33**, 1187–1192.

Tsodikov, A. (1998). A proportional hazards model taking account of long-term survivors. *Biometrics*, **54**(4), 1508-1516.

Vanegas, L. H. and Paula, G. A. (2016). Log-symmetric distributions: statistical properties and parameter estimation. *Brazilian Journal of Probability and Statistics*, **30**(2), 196–220.

Vanegas, L. H. and Paula, G. A. (2017). Log-symmetric regression models under the presence of non-informative left-or right-censored observations. *TEST*, **26**(2), 405-428.

Yakovlev, A. Y., Asselain, B., Bardou, V. J., Fourquet, A., Hoang, T., Rochefediere, A. and Tsodikov, A. D. (1993). A simple stochastic model of tumor recurrence and its application to data on premenopausal breast cancer. *Biometrie et analyse de donnees spatio-temporelles*, **12**, 66-82.

Yu, B., Tiwari, R. C., Cronin, K. A. and Feuer, E. J. (2004). Cure fraction estimation from the mixture cure models for grouped survival data. *Statistics in Medicine*, **23**, 1733-1747.