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A Bounded Cumulative Hazard Model with A change-Point According to a Threshold in a covariate for Right-Censored Data

Fauzia Taweab[1,3,*], *Noor Akma Ibrahim*[1,2] *and Jayanthi Arasan*[2]

[1] Institute for Mathematical Research, Universiti Putra Malaysia, 43400, Serdang, Selangor Darul Ehsan, Malaysia
[2] Department of Mathematics, Faculty of Science, Universiti Putra Malaysia, 43400, Serdang, Selangor Darul Ehsan, Malaysia
[3] Department of Statistics, University of Tripoli, Libya

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Abstract: In most recent clinical studies, the focus is on estimation of the proportion of patients who are cured and who will therefore never experience the event of interest again. This article investigates a survival model with cure fraction and change-point effect based on the bounded cumulative hazard model (BCH). The maximum likelihood approach to estimate the unknown parameters is used. A major difficulty here is that the likelihood function is not differentiable with respect to a change point parameter. To address this problem a smoothed likelihood approach is proposed. Simulation studies have been conducted in this study to assess the efficiency of the estimators under various practical situations. Numerical results show the satisfying performance of the proposed estimates and that the proposed model represents a useful addition to the literature of the BCH model.

Keywords: BCH model, change-point model, smoothing, right-censoring, maximum likelihood estimation

1 Introduction

The survival cure rate models are usually used for analyzing life time data, particularly in cancer studies in which a proportion of patients are cured and will not experience the adverse event. In the literature there are two major approaches to modelling survival cure data. The first one is the mixture model which was proposed by [1] to study cases where a proportion of the patients are cured. This model has been studied extensively by many authors including [2,3,4,5,6] among others. The second approach to modeling the cure rate appeared in the works of [7,8]. In this approach, the survival times are modeled based on the assumption that the treatment leaves the subject with a number of cancer cells that may grow slowly over time and produce a detectable cancer. This model is known as the non-mixture cure model or the bounded cumulative hazard model (BCH). Many researchers have already adopted this approach to cure fraction modeling (e.g., [9,10,11,12,13,14]).
The existent BCH models assume that the covariates act smoothly on the cure probability or the survival rate. However, in many applications a smooth link function can not describe the possible relationships between the covariates and the failure rate or cure probability. For example, cancer incidence rates remain relatively stable in young people but change drastically after a certain age threshold [15]. So far, a number of studies discussing the survival model under change-point scenario have been released to the literature (e.g., [16,17,18]). However, these models are not appropriate for modeling data with a cure fraction. Recently, [19] incorporated change-point effect in mixture cure models. In this paper, we develop a BCH model that accommodates a change-point effect in covariates. The estimation method is based on a parametric maximum likelihood approach in which lognormal distribution is used to model failure time for the uncured subjects.

* Corresponding author e-mail: taweabf@yahoo.com.my

2 The bounded cumulative hazard model (BCH)

In 1999, Chen [8] defined the BCH model as follows. Let N denote the number of carcinogenic cells that remain active and capable of developing a cancer for the i^{th} subject. Assume that N has a Poisson distribution with a mean of λ. Let $Z_j, j = 1,2,...,N$ express the random time for the j^{th} cancer cell which can produce a detectable cancer mass where Z_j is assumed to be independently and identically distributed with $F(t)$. Then, the time to relapse of cancer can be defined by the random variable $T = \min\{Z_j, j = 1,2,...,N\}$. The survival function for the population is given by

$$\begin{aligned} S(t) &= P[\text{No cancer by time t}] \\ &= P[N=0] + P[Z_1 > t, Z_2 > t, \cdots, Z_N > t, N \geq 1] \\ &= \exp(-\lambda) + \sum_{N=1}^{\infty} \Big(S(t)\Big)^N \Big[\frac{\exp(-\lambda)\lambda^N}{N!}\Big] \\ &= \exp(-\lambda F(t)) \\ &= \eta^{F(t)}, \end{aligned} \tag{1}$$

where η is the probability of cure, which can be defined as

$$\eta = \lim_{t\to\infty} S(t) \equiv P(N=0) = \exp(-\lambda). \tag{2}$$

Let y_i refer to the survival time for individual i, which may be right censored, then $y_i = \min(T_i, C_i)$ in which $T_i = \min\{Z_{i1}, Z_{i2}, \cdots, Z_{iN_i}\}$, and C_i is a right−censored variable. Let δ_i represent the censoring indicator, which equals 1 if y_i is failure time and 0 if it is right censored. Considering that censoring times are independent and non-informative, [8,20,21] showed that the likelihood function for the model takes the form

$$L_i = \Pi_{i=1}^{n}\Big[-\log(\eta) f(y_i)\Big]^{\delta_i} S(y_i). \tag{3}$$

We can further incorporate covariates X into the cure probability and the distribution function of the uncured subjects. Moreover, a parametric model can be specified for the survival time. In this paper, we consider a lognormal distribution to fit the failure time of uncured subjects. The density and cumulative distribution function (cdf) for this distribution are:

$$f(y) = \frac{1}{y\sigma\sqrt{2\pi}} \exp\Big[-\frac{(\ln y - \mu)^2}{2\sigma^2}\Big]$$

and

$$F(y) = \Phi\left(\frac{\ln y - \mu}{\sigma}\right),$$

respectively.

3 The bounded cumulative hazard model with a change point effect

In the model with change-point covariates we are dealing with covariates that may be dichotomized according to some unknown threshold. For now, assume X as scalar and suppose that the change-point of the model depends on X, and that at this point τ the survival rate or cure probability takes a sudden jump or fall. If $X \leq \tau$, then $\eta(X) = p_1$ and $S(X) = S_1$ while if $X > \tau$, then $\eta(X) = p_2$ and $S(X) = S_2$. In other words,

$$\begin{aligned} \eta(X) &= p_1 I(X \leq \tau) + p_2 I(X > \tau) \quad \textit{and} \\ S(X) &= S_1 I(X \leq \tau) + S_2 I(X > \tau), \end{aligned}$$

The complete observed data are (y_i, δ_i, X_i) and the unknown parameters are defined by $\theta = (p_1, p_2, \mu_1, \mu_2, \sigma_1, \sigma_2, \tau)$. Hence, the likelihood function under change−point τ is defined as:

$$\begin{aligned} L_n^*(\theta) = \prod_{i=1}^{n} \Big([-\log(p_1) f_1(\theta, y_i)]^{\delta_i} p_1^{F_1(\theta, y_i)}\Big)^{I(X_i \leq \tau)} \times \\ \times \Big([-\log(p_2) f_2(\theta, y_i)]^{\delta_i} p_2^{F_2(\theta, y_i)}\Big)^{I(X_i > \tau)} \end{aligned} \tag{4}$$

With the classical likelihood approach, the likelihood function (4) is not differentiable with respect to the unknown change point parameter τ. Consequently, standard Taylor series methods cannot be used.

4 Smoothed likelihood approach

To handle the critical problem of non−smoothing of the likelihood function, we approximate the indicator functions $I(X \leq \tau)$ and $I(X > \tau)$ by using a continuous and differentiable function $K(.)$ which satisfies: $\lim_{u\to-\infty} K(u) = 0$ and $\lim_{u\to\infty} K(u) = 1$. By definition, $K_n(u) = K(u/h_n)$ and h_n is a small positive constant that depends on the sample size [19]. A special case of this class of function is the logistic function, where $K_n(u) = \frac{\exp[u/h_n]}{1+\exp[u/h_n]}$. Thus, the smoothed likelihood function for the observed data (y_i, δ_i, X_i) is

$$\begin{aligned} L_n(\theta) = \prod_{i=1}^{n} \Big([-\log(p_1) f_1(\theta, y_i)]^{\delta_i} p_1^{F_1(\theta, y_i)}\Big)^{K_n(\tau - X_i)} \times \\ \times \Big([-\log(p_2) f_2(\theta, y_i)]^{\delta_i} p_2^{F_2(\theta, y_i)}\Big)^{1-K_n(\tau - X_i)}, \end{aligned} \tag{5}$$

and the log−the likelihood function can be written as

$$l_n(\theta) = \sum_{i=1}^{n} [K_n(\tau - X_i) l_1(\theta, w_i) + \{1 - K_n(\tau - X_i)\} l_2(\theta, w_i)], \tag{6}$$

where $w_i = (y_i, \delta_i)$ for $i = 1, 2, \cdots, n$ and

$$l_j(\theta, w_i) = \delta_i[\log(-\log p_j) + \log f_j(\theta, y_i)] + F_j(\theta, y_i)(\log p_j),$$

$for\ j = 1,2$.
The maximum likelihood estimation of the parameters can be obtained by using the Newton−Raphson iterative procedure. The smoothing parameter h_n is a key component of the log-likelihood function and it can therefore be defined as a function of n that approaches 0.

5 Simulation studies

Simulation studies have been conducted to examine the performance of the proposed method. Two simulation scenarios for two censoring rates were considered. The first scenario used a uniform (0, 1) random variable with a change-point at 0.5 while the second scenario employed a truncated normal (1, 1, 0, 2) random variable with a change-point at 1. The random survival times were generated by inverting the survival function $S(t) = \eta^{F(t)}$. Thus, a uniform (0, 1) random variable u was generated and the subject is cured if $u \leq \eta$. Otherwise, the failure time, y, was set to the solution of $u = \eta^{F(t)}$. Censoring times followed a lognormal distribution (μ, σ), where the values of μ and σ would be adjusted to get the desired approximate censoring rate in the data.
Summary statistics based on 1000 replications of sample sizes of 300 and 500 subjects are presented in Tables 1.1 and 1.2. The standard errors (SE) and the mean squared error (MSE) are reported along with the average and the median of the estimates for each parameter.
The simulation studies suggest that the proposed method has very small biases as the average and median of the estimates are very close to the respective true values. The estimation of the change-point τ is quite accurate and stable throughout all settings. The SE values, as well as the MSE values decrease with the increase in sample sizes. With respect to the censoring rate, the estimator of θ performs well for low levels of censoring.
The simulation studies have also been conducted with different choice of the smoothing function $K(u)$, where it was chosen as the cumulative distribution function of the standard normal distribution; $K(u) = \frac{1}{(2\pi)^{\frac{1}{2}}} \int_{-\infty}^{u} e^{-\frac{t^2}{2}} dt$.
The results are presented in Table 2.1 and 2.2. Note that the estimated values are very similar for the two different K(u), and thus the precision of the estimates are not sensitive to the choice of the smoothing function.

6 Conclusion

In this paper, a change point cure model for censored data is proposed. It extends the existing BCH models by allowing a covariate to have non- smoothly effect on the survival rate and cure probability. To estimate the

Table 1.1 Parameters estimates based on logistic function for two censoring rates

		$X \sim \text{Uniform}(0,1)$				
Scenario 1		True	Mean	Median	SE	MSE×1000
Moderate censoring $(35\% - 40\%)$						
n=300	p_1	0.4	0.381	0.381	0.037	1.730
	μ_1	0.3	0.322	0.324	0.009	0.565
	σ_1	0.1	0.106	0.106	0.006	0.072
	p_2	0.3	0.322	0.324	0.032	1.508
	μ_2	0.4	0.384	0.384	0.010	0.356
	σ_2	0.1	0.106	0.105	0.006	0.072
	τ	0.5	0.501	0.500	0.055	3.026
n=500	p_1	0.4	0.383	0.383	0.028	1.073
	μ_1	0.3	0.320	0.321	0.008	0.464
	σ_1	0.1	0.106	0.106	0.005	0.061
	p_2	0.3	0.317	0.318	0.027	1.018
	μ_2	0.4	0.387	0.386	0.008	0.233
	σ_2	0.1	0.105	0.105	0.005	0.050
	τ	0.5	0.497	0.499	0.048	2.313
Heavy censoring $(60\% - 65\%)$						
n=300	p_1	0.4	0.377	0.377	0.046	2.645
	μ_1	0.3	0.324	0.324	0.014	0.772
	σ_1	0.1	0.106	0.106	0.009	0.117
	p_2	0.3	0.318	0.319	0.048	2.628
	μ_2	0.4	0.386	0.386	0.015	0.421
	σ_2	0.1	0.106	0.106	0.009	0.117
	τ	0.5	0.508	0.505	0.071	5.105
n=500	p_1	0.4	0.381	0.380	0.036	1.657
	μ_1	0.3	0.321	0.321	0.010	0.541
	σ_1	0.1	0.106	0.105	0.007	0.085
	p_2	0.3	0.317	0.317	0.038	1.733
	μ_2	0.4	0.387	0.387	0.012	0.313
	σ_2	0.1	0.105	0.105	0.007	0.074
	τ	0.5	0.508	0.506	0.055	3.089

Table 1.2. Parameters estimates based on logistic function for two censoring rates

		$X \sim tN(1,1,0,2)$				
Scenario 2		True	Mean	Median	SE	MSE×1000
Moderate censoring $(35\% - 40\%)$						
n=300	p_1	0.4	0.388	0.385	0.037	1.513
	μ_1	0.3	0.313	0.313	0.010	0.269
	σ_1	0.1	0.104	0.104	0.007	0.065
	p_2	0.3	0.311	0.312	0.032	1.145
	μ_2	0.4	0.390	0.390	0.011	0.221
	σ_2	0.1	0.104	0.104	0.007	0.065
	τ	1	0.985	0.976	0.084	7.281
n=500	p_1	0.4	0.389	0.389	0.030	1.021
	μ_1	0.3	0.311	0.311	0.008	0.185
	σ_1	0.1	0.104	0.104	0.005	0.041
	p_2	0.3	0.309	0.310	0.029	0.922
	μ_2	0.4	0.391	0.392	0.008	0.145
	σ_2	0.1	0.103	0.104	0.005	0.034
	τ	1	0.989	0.994	0.061	3.842
Heavy censoring $(60\% - 65\%)$						
n=300	p_1	0.4	0.390	0.390	0.048	2.404
	μ_1	0.3	0.313	0.312	0.015	0.394
	σ_1	0.1	0.103	0.103	0.010	0.109
	p_2	0.3	0.319	0.317	0.050	2.861
	μ_2	0.4	0.390	0.390	0.016	0.356
	σ_2	0.1	0.104	0.104	0.009	0.097
	τ	1	0.986	0.996	0.094	9.032
n=500	p_1	0.4	0.390	0.393	0.042	1.864
	μ_1	0.3	0.310	0.310	0.012	0.244
	σ_1	0.1	0.103	0.103	0.008	0.073
	p_2	0.3	0.309	0.310	0.040	1.681
	μ_2	0.4	0.392	0.392	0.012	0.208
	σ_2	0.1	0.104	0.104	0.007	0.065
	τ	1	0.992	0.995	0.074	5.540

Table 2.1. Parameters estimates based on logistic function for two censoring rates

Scenario 1		$X \sim$ Uniform(0,1) True	Mean	Median	SE	MSE×1000
Moderate censoring (35% – 40%)						
n=300	p_1	0.4	0.388	0.388	0.036	1.44
	μ_1	0.3	0.313	0.313	0.011	0.29
	σ_1	0.1	0.104	0.103	0.007	0.065
	p_2	0.3	0.313	0.313	0.036	1.465
	μ_2	0.4	0.391	0.391	0.011	0.202
	σ_2	0.1	0.104	0.104	0.007	0.065
	τ	0.5	0.496	0.497	0.056	3.152
n=500	p_1	0.4	0.388	0.388	0.029	0.985
	μ_1	0.3	0.312	0.312	0.008	0.208
	σ_1	0.1	0.104	0.104	0.006	0.052
	p_2	0.3	0.312	0.312	0.029	0.985
	μ_2	0.4	0.392	0.392	0.008	0.128
	σ_2	0.1	0.103	0.102	0.006	0.045
	τ	0.5	0.497	0.494	0.043	1.858
Heavy censoring (60% – 65%)						
n=300	p_1	0.4	0.388	0.387	0.052	2.848
	μ_1	0.3	0.314	0.314	0.015	0.421
	σ_1	0.1	0.103	0.103	0.009	0.090
	p_2	0.3	0.313	0.311	0.054	3.085
	μ_2	0.4	0.391	0.390	0.016	0.337
	σ_2	0.1	0.103	0.103	0.011	0.130
	τ	0.5	0.506	0.508	0.072	5.220
n=500	p_1	0.4	0.388	0.387	0.040	1.744
	μ_1	0.3	0.312	0.312	0.012	0.288
	σ_1	0.1	0.103	0.104	0.007	0.058
	p_2	0.3	0.308	0.307	0.041	1.745
	μ_2	0.4	0.393	0.393	0.013	0.218
	σ_2	0.1	0.103	0.102	0.008	0.073
	τ	0.5	0.505	0.502	0.052	2.729

Table 2.2. Parameters estimates based on logistic function for two censoring rates

Scenario 2		$X \sim tN(1,1,0,2)$ True	Mean	Median	SE	MSE×1000
Moderate censoring (35% – 40%)						
n=300	p_1	0.4	0.393	0.394	0.038	1.493
	μ_1	0.3	0.306	0.307	0.011	0.157
	σ_1	0.1	0.102	0.102	0.008	0.068
	p_2	0.3	0.309	0.309	0.037	1.45
	μ_2	0.4	0.394	0.393	0.011	0.157
	σ_2	0.1	0.102	0.102	0.007	0.053
	τ	1	0.991	0.993	0.076	5.857
n=500	p_1	0.4	0.398	0.397	0.030	0.904
	μ_1	0.3	0.305	0.306	0.008	0.089
	σ_1	0.1	0.102	0.102	0.006	0.040
	p_2	0.3	0.307	0.308	0.028	0.833
	μ_2	0.4	0.395	0.395	0.008	0.089
	σ_2	0.1	0.102	0.102	0.005	0.029
	τ	1	0.991	0.995	0.057	3.330
Heavy censoring (60% – 65%)						
n=300	p_1	0.4	0.393	0.391	0.055	3.074
	μ_1	0.3	0.306	0.305	0.015	0.261
	σ_1	0.1	0.101	0.101	0.010	0.101
	p_2	0.3	0.310	0.307	0.053	2.909
	μ_2	0.4	0.394	0.394	0.017	0.325
	σ_2	0.1	0.103	0.103	0.010	0.109
	τ	1	0.989	0.997	0.101	10.322
n=500	p_1	0.4	0.399	0.393	0.039	1.522
	μ_1	0.3	0.306	0.306	0.012	0.180
	σ_1	0.1	0.101	0.102	0.008	0.065
	p_2	0.3	0.307	0.305	0.040	1.649
	μ_2	0.4	0.394	0.395	0.012	0.180
	σ_2	0.1	0.102	0.102	0.008	0.068
	τ	1	0.975	0.977	0.075	6.250

parameters in the model, we used a modified objective function so as to eliminate the non-smoothness problem of the likelihood function and then the maximum likelihood method was employed. The efficiency of the estimation procedure was examined via simulation studies. It was shown that the proposed parametric estimation method has a good performance in the situations considered. In addition, it was found that the estimation method is more efficient when the censoring rate is low than when it is high.

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Appendix

General considerations For $j = 1,2$, define the density and distribution functions as follow:

$$f_j(\theta,y) = \frac{1}{\sigma_j y\sqrt{2\pi}} \exp\left(-\frac{1}{2}\left(\frac{\ln y-\mu_j}{\sigma_j}\right)^2\right)$$

$$F_j(\theta,t) = \Phi\left(\frac{\ln y-\mu_j}{\sigma_j}\right).$$

Let $w_i = (y_i,\delta_i)$ for $i = 1,2,...,n$. Write the censored data log likelihood corresponding to $f_j(\theta,y)$ and $F_j(\theta,y)$ as

$$l_j(\theta) = \delta_i[\log(-\log p_j)+\log f_j(\theta,y_i)]+F_j(\theta,y_i)(\log p_j),$$

for $j = 1,2$. The averaged log-likelihood is

$$l_n(\theta) = n^{-1}\sum_{i=1}^n[K_n(\tau-X_i)l_1(\theta,w_i)+\{1-K_n(\tau-X_i)\}l_2(\theta,w_i)].$$

Next we use the definition of the two functions $\varphi\left(\frac{\ln y-\mu}{\sigma}\right)$ and $G(\tau,X)$ as:

$$\varphi\left(\frac{\ln y-\mu}{\sigma}\right) = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{1}{2}\left(\frac{\ln y-\mu}{\sigma}\right)^2\right)$$

$$G(\tau,X_i) = (2-j)K_n(\tau-X_i)+(j-1)\{1-K_n(\tau-X_i)\}, \quad j = 1,2.$$

Write the score equations for $l_n(\theta)$ with respect to θ as

$$\begin{aligned} R_n(\theta) &= \left(R_{np_1}(\theta),R_{n\mu_1}(\theta),R_{n\sigma_1}(\theta),R_{np_2}(\theta),R_{n\mu_2}(\theta),R_{n\sigma_2}(\theta),R_{n\tau}(\theta)\right) \\ &= \left(R_{n\phi}(\theta),R_{n\tau}(\theta)\right), \qquad \text{for } j = 1,2. \end{aligned}$$

$$R_{np_j}(\theta) = n^{-1}\sum_{i=1}^n\left[G(\tau,X_i)\times\left(\frac{\delta_i}{p_j(\log p_j)}+\frac{\Phi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{p_j}\right)\right]$$

$$R_{n\mu_j}(\theta) = n^{-1}\sum_{i=1}^{n}\left[G(\tau,X_i)\times\left(\delta_i\left(\frac{\ln y_i-\mu_j}{\sigma_j^2}\right)-(\log p_j)\times\frac{\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j}\right)\right]$$

where $\varphi(.)$ is the probability density function (PDF) of the standard normal distribution.

$$R_{n\sigma_j}(\theta) = n^{-1}\sum_{i=1}^{n}\Bigg[G(\tau,X_i)\times\Bigg(\delta_i\left(\frac{-1}{\sigma_j}+\frac{(\ln y_i-\mu_j)^2}{\sigma_j^3}\right)- - (\log p_j)(\ln y_i-\mu_j)\times\frac{\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^2}\Bigg)\Bigg]$$

$$R_{n\tau}(\theta) = n^{-1}\sum_{i=1}^{n}\dot{K}_n(\tau-X_i)\left[l_1(\theta,y_i)-l_2(\theta,y_i)\right]$$

General considerations

We write the second derivation of the likelihood function:
Let $Q_n(\theta) = \partial(R_n(\theta)/\partial(\theta)$

$$Q_{np_jp_j}(\theta) = \frac{\partial R_{np_j}(\theta)}{\partial p_j} = n^{-1}\sum_{i=1}^{n}\left[G(\tau,X_i)\times\left(\delta_i\left(-\frac{(1+\log p_j)}{(p_j\log p_j)^2}\right)-\frac{\Phi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{p_j^2}\right)\right]$$

$$Q_{n\mu_j\mu_j}(\theta) = \frac{\partial R_{n\mu_j}(\theta)}{\partial\mu_j} = n^{-1}\sum_{i=1}^{n}\left[G(\tau,X_i)\times\left(\frac{-\delta_i}{\sigma_j^2}-(\log p_j)\left(\frac{(\ln y_i-\mu_j)\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^3}\right)\right)\right]$$

$$Q_{n\sigma_j\sigma_j}(\theta) = \frac{\partial R_{n\sigma_j}(\theta)}{\partial\sigma_j} = n^{-1}\sum_{i=1}^{n}\Bigg[G(\tau,X_i)\times\Bigg(\delta_i\left(\frac{1}{\sigma_j^2}-\frac{3(\ln y_i-\mu_j)^2}{\sigma_j^4}\right)-(\log p_j)\times \times\left[\frac{(\ln y_i-\mu_j)^3\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^5}-\frac{2(\ln y_i-\mu_j)\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^3}\right]\Bigg)\Bigg]$$

$$Q_{n\mu_jp_j}(\theta) = \frac{\partial R_{n\mu_j}(\theta)}{\partial p_j} = n^{-1}\sum_{i=1}^{n}\left[G(\tau,X_i)\times\left(\frac{-\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_jp_j}\right)\right]$$

$$Q_{n\sigma_jp_j}(\theta) = \frac{\partial R_{n\sigma_j}(\theta)}{\partial p_j} = n^{-1}\sum_{i=1}^{n}\left[G(\tau,X-i)\times\left(\frac{-(\ln y_i-\mu_j)}{p_j\sigma_j^2}\times\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)\right)\right]$$

$$Q_{n\sigma_j\mu_j}(\theta) = \frac{\partial R_{n\sigma_j}(\theta)}{\partial\mu_j} = n^{-1}\sum_{i=1}^{n}\Bigg[G(\tau,X_i)\Bigg(\delta_i\left[\frac{-2(\ln y_i-\mu_j)}{\sigma_j^3}\right]-(\log p_j)\times \times\left[\frac{(\ln y_i-\mu_j)^2\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^4}-\frac{\varphi\left(\frac{\ln y_i-\mu_j}{\sigma_j}\right)}{\sigma_j^2}\right]\Bigg)\Bigg]$$

$$Q_{n\tau\tau}(\theta) = \frac{\partial R_{n\tau}(\theta)}{\partial\tau} = n^{-1}\sum_{i=1}^{n}\ddot{K}_n(\tau-X_i)[l_1(\theta,y_i)-l_2(\theta,y_i)]$$

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Fauzia Taweab is PhD student at the Institute for mathematical research, Universiti Putra Malaysia. She is also a Lecture of statistics at the Department of Statistics, Faculty of Science, Tripoli University, Libya. Her research interests are in the areas of applied statistics, survival analysis / cure models, censored data, simulation techniques, and generalized linear model. She has published several research articles in peer reviewed national and international journals and proceedings.

Noor Akma Ibrahim is Professor of Statistics at the Department of Mathematics, Universiti Putra Malaysia. Her major research areas include survival analysis and diagnostics influence in regression. Her active participation in research has earned her awards at university, national and international levels. She has published more than 150 research papers in journals and proceedings. She is a life-member of ISOSS and PERSAMA, and an active member of ISM and ASA. She is in the Editorial Board of local and international journals and has been appointed as referee for many scientific papers for local and international journals in the framework of Bayesian estimation, censored data and survival analysis.

Jayanthi Arasan is Associate Professor at department of Mathematics, faculty of science, Universitu Putra Malaysia. She received her PhD degree in Statistics at Oxford University. She is referee of several international journals in the frame of survival analysis and bootstrapping technique. Her main research interests are survival/ reliability analysis, Grouped and Truncated Data with Time Varying Covariates and computational statistics, which mostly focus on the modeling of parallel and repairable system failures.