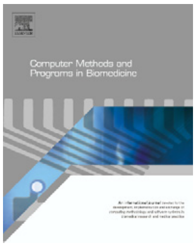

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LSS: An S-Plus/R program for the accelerated failure time model to right censored data based on least-squares principle

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ABSTRACT

Due to lack of proper inference procedure and software, the ordinary linear regression model is seldom used in practice for the analysis of right censored data. This paper presents an S-Plus/R program that implements a recently developed inference procedure [Z. Jin, D.Y. Lin, Z. Ying, On least-squares regression with censored data, Biometrika 93 (2006) 147–161] for the accelerated failure time model based on the least-squares principle. The program is user-friendly and yields outputs similar to S-Plus/R function `lm`.

1. Introduction

For uncensored data, the linear regression model is the most commonly used model in data analysis. It is simple and easy to interpret. The least-squares estimator of the regression parameters is easy to compute and has many well-known theoretical properties. For censored failure time data in survival analysis, however, the linear regression model has been seldom used. The least-squares estimator cannot be calculated in the regular way due to the existence of censoring.

A modified least-squares estimator was proposed by Buckley and James in 1979 [2]. The theoretical properties of the Buckley and James estimator were investigated by many people (Ritov [3] and Lai and Ying [4]). Despite theoretical advances, the method is seldom used in practice due to numerical complexity. The estimating function of Buckley–James estimator is neither monotone nor continuous and its roots may not exist (James and Smith [5]). Although Buckley and James [2] suggested an iterative algorithm which was implemented by an S-Plus function `bj` (Stare et al. [6]), there are several issues in the algorithm. First, the convergence of the algorithm is not guaranteed. Second, even if the algorithm converges, it is unclear if it yields a consistent estimator because the theoretical results were established based on the local linearity assumption. Moreover, the covariance matrix of the Buckley–James estimator is difficult to obtain because it involves the unknown hazard function of the unobserved error term, which may not be well estimated nonparametrically with censored data. The numerical difficulty increases as the dimension of covariates increases. In 2006, Jin et al. [1] developed a new estimation procedure based on the least-squares principle along with rigorous theoretical justification. The new procedure yields a class of estimators which are consistent and asymptotically normal. In addition, the new

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procedure estimates the covariance matrix of the consistent estimators through a resampling approach.

In this paper, we present an S-Plus/R function named `lss` to implement the new procedure developed by Jin et al. [1]. In the next section, we present an outline of statistical theory and computational methods. In Section 3, we describe the `lss` function and its arguments. We use two examples to illustrate the `lss` function in Section 4 and conclude the paper with some remarks in Section 5.

2. Statistical and computational methods

2.1. *Linear model in survival analysis*

Let Y_i and C_i denote the failure time and censoring time (or their transformations) for the ith patient, respectively, and X_i be the associated $(p \times 1)$ covariate. Consider the linear regression model

$$Y_i = X_i^T\beta + \epsilon_i, \quad i = 1, \ldots, n \tag{1}$$

where β is an $(p \times 1)$ unknown regression parameter, and ϵ_is are independent and identically distributed with a common but unknown distribution function F. Because of censoring, Y_is might not be observable. The observed data are $(\tilde{Y}_i, \delta_i, X_i)$ $(i = 1, \ldots, n)$, where $\tilde{Y}_i = \min(Y_i, C_i)$, $\delta_i = 1\{Y_i \le C_i\}$, and $1\{\cdot\}$ is the indicator function. It is assumed that Y_i and C_i are independent conditionally on X_i.

2.2. *Least-squares estimation of β*

When Y_is are completely observed (without any censoring), the classical least-squares estimator of β is the solution of the equation

$$\sum_{i=1}^{n}(X_i - \bar{X})(Y_i - X_i^T\beta) = 0 \tag{2}$$

where $\bar{X} = n^{-1}\sum_{i=1}^{n} X_i$.

In the presence of censoring, we can only observe $\tilde{Y}_i$. Then Eq. (2) cannot be used directly. In 1979, Buckly and James [2] modified Eq. (2) by using:

$$\widehat{Y}_i(\beta) = \delta_i\tilde{Y}_i + (1-\delta_i)\left\{\frac{\int_{e_i(\beta)}^{\infty} u\,d\hat{F}_\beta(u)}{1-\hat{F}_\beta(e_i(\beta))} + X_i^T\beta\right\} \tag{3}$$

to replace Y_i, where $e_i(\beta) = \tilde{Y}_i - X_i^T\beta$ and

$$\hat{F}_\beta(t) = 1 - \prod_{i:e_i(\beta)<t}\left[1 - \frac{\delta_i}{\sum_{j=1}^{n} 1\{e_j(\beta) \ge e_i(\beta)\}}\right],$$

i.e., $\hat{F}_\beta$ is the Kaplan–Meier estimator of F based on $\{e_i(\beta), \delta_i\}$ $(i = 1, \ldots, n)$.

There are two difficult issues in the original Buckley–James estimator: one is that there is no computationally efficient algorithm that guarantees a consistent estimator, the other is that there is no reliable method to estimate the covariance matrix of the resulting estimators.

To overcome these difficulties, Jin et al. [1] developed a new inference procedure to obtain a class of consistent and asymptotically normal estimators, which we describe below.

2.2.1. *Point estimator $\hat{\beta}_{(m)}$*

Define

$$U(\beta, b) = \sum_{i=1}^{n}(X_i - \bar{X})(\hat{Y}_i(b) - X_i^T\beta), \tag{4}$$

or

$$U(\beta, b) = \sum_{i=1}^{n}(X_i - \bar{X})\{\hat{Y}_i(b) - \bar{Y}(b) - (X_i - \bar{X})^T\beta\}, \tag{5}$$

where $\bar{Y}(b) = n^{-1}\sum_{i=1}^{n}\hat{Y}_i(b)$.

When $U(\beta, b) = 0$, we have

$$\beta = L(b) = \left\{\sum_{i=1}^{n}(X_i - \bar{X})^{\otimes 2}\right\}^{-1}\left[\sum_{i=1}^{n}(X_i - \bar{X})\{\hat{Y}_i(b) - \bar{Y}(b)\}\right], \tag{6}$$

where $a^{\otimes 2}$ means aa^T for a vector a.

The expression (6) leads to an iterative algorithm:

$$\hat{\beta}_{(m)} = L(\hat{\beta}_{(m-1)}), \quad m \ge 1. \tag{7}$$

Jin et al. [1] set the Gehan-type rank estimator $\hat{\beta}_G$ as the initial estimator $\hat{\beta}_{(0)}$, which can be obtained by minimizing the following convex function:

$$\sum_{i=1}^{n}\sum_{j=1}^{n}\delta_i\left|e_i(\beta) - e_j(\beta)\right| + \left|M - \beta^T\sum_{k=1}^{n}\sum_{l=1}^{n}\delta_k(X_l - X_k)\right|,$$

where M is a prespecified extremely large number [7]. The minimization can be done with function `l1fit` in S-Plus and `rq` in R package `quantreg` [9]. Then, $\hat{\beta}_{(m)}$ is consistent and asymptotically normal for every m, see Jin et al. [1]. As a result, a class of consistent and asymptotically normal estimators $\{\hat{\beta}_{(m)} : m \ge 1\}$ can be obtained.

2.2.2. *Covariance matrix of $\hat{\beta}_{(m)}$*

Jin et al. [1] also show that the covariance matrix of $\hat{\beta}_{(m)}$ can be approximated by a resampling procedure. First, we generate n (the number of observations) independent and identically distributed positive random variables $Z_i (i = 1, 2, \ldots, n)$ satisfying $E(Z_i) = \mathrm{var}(Z_i) = 1$. In the program, we use the standard exponential distribution to generate Z_is. Then we implement the similar iterative procedure in Section 2.2.1 for the point estimation with data perturbed by Z_is. The details are given below:

Similar to Kaplan–Meier estimator of F, define

$$\hat{F}_b^*(t) = 1 - \prod_{i:e_i(b)<t}\left[1 - \frac{Z_i\delta_i}{\sum_{j=1}^{n} Z_j 1\{e_j(b) \ge e_i(b)\}}\right], \tag{8}$$

and

$$\hat{Y}_i^*(b) = \delta_i\tilde{Y}_i + (1-\delta_i)\left\{\frac{\int_{e_i(b)}^{\infty} u\,d\hat{F}_b^*(u)}{1-\hat{F}_b^*(e_i(b))} + X_i^T b\right\}, \tag{9}$$

$$L^*(b) = \left\{\sum_{i=1}^{n} Z_i(X_i - \bar{X})^{\otimes 2}\right\}^{-1}\left[\sum_{i=1}^{n} Z_i(X_i - \bar{X})\{\hat{Y}_i^*(b) - \bar{Y}^*(b)\}\right]. \tag{10}$$

Then, Eq. (10) leads to an iterative process $\hat{\beta}^*_{(m)} = L^*(\hat{\beta}^*_{(m-1)})$, $m \geq 1$.

Let the initial value $\hat{\beta}^*_{(0)}$ of this iteration process be $\hat{\beta}^*_G$, which is the minimizer of

$$\sum_{i=1}^{n}\sum_{j=1}^{n} Z_i Z_j \delta_i \left|e_i(\beta) - e_j(\beta)\right| + \left|M - \beta^{\mathrm{T}} \sum_{k=1}^{n}\sum_{l=1}^{n} Z_k Z_l \delta_k (X_l - X_k)\right|,$$

where M is the prespecified extremely large number [1]. Again, the minimization can be done with function `l1fit` in S-Plus and `rq` in R.

For a given sample of $(Z_1, \ldots, Z_n)$, the iteration procedure $\hat{\beta}^*_{(k)} = L^*(\hat{\beta}^*_{(k-1)})$ yields a $\hat{\beta}^*_{(k)}$ $(1 \leq k \leq m)$. By generating random samples of $(Z_1, \ldots, Z_n)$ repeatedly N times, we can obtain N realizations of $\hat{\beta}^*_{(m)}$, denoted by $\hat{\beta}^*_{(m),j}$ $(j = 1, \ldots, N)$. For each $m \geq 1$, the covariance matrix of $\hat{\beta}_{(m)}$ can be estimated by

$$s^2 = \frac{1}{N-1}\sum_{j=1}^{N}(\hat{\beta}^*_{(m),j} - \bar{\beta}^*_{(m)})(\hat{\beta}^*_{(m),j} - \bar{\beta}^*_{(m)})^{\mathrm{T}}, \tag{11}$$

where $\bar{\beta}^*_{(m)} = (1/N)\sum_{j=1}^{N}\hat{\beta}^*_{(m),j}$, see Jin et al. [1] for more details.

3. Program description

3.1. General description

The `lss` function is designed similar to the `lm` function in S-Plus [8] and R-package [9] for fitting regular linear regression models. Thus, the `lss` function largely follows the syntax of `lm` function.

The convergence criterion for the procedure in Section 2 is set to be

$$\frac{\left|\hat{\beta}_{(m),l} - \hat{\beta}_{(m-1),l}\right|}{\max\left(\left|\hat{\beta}_{(m),l}\right|, 0.01\right)} < \eta \tag{12}$$

for all $l = 1, 2, \ldots, p$, where $\hat{\beta}_{(m),l}$ stands for the lth component of $\hat{\beta}_{(m)}(p \times 1)$, and η is a prespecified very small number controlling the convergence. The iteration stops and the output is given when the iterative procedure converges or reaches the prespecified maximum iteration number.

In `lss` function, two additional functions are used. One is named `eres`. The function `eres` computes the Kaplan–Meier estimator $\hat{F}_\beta(t)$ and the integral $\left(\int_{e_i(\beta)}^{\infty} u \, d\hat{F}_\beta(u)\right) / \left(1 - \hat{F}_\beta(e_i(\beta))\right)$ in Eq. (3) as well as the generalized Kaplan–Meier estimator $\hat{F}_b^*(t)$ and the integral $\left(\int_{e_i(b)}^{\infty} u \, d\hat{F}_b^*(u)\right) / \left(1 - \hat{F}_b^*(e_i(b))\right)$ in Eq. (9). The other function is named `betag` function, which is used to obtain the initial values $\hat{\beta}_G$ and $\hat{\beta}^*_G$.

3.2. Arguments

The `lss` function can be called with following syntax:

```
lss(formula, data, subset, mcsize
  = 500, maxiter = 50, tolerance = 0.001, trace
  = F, gehenonly = F, cov = F, na.action = na.exclude)
```

The required arguments are:

- `formula`: specifies a model to be fitted. The response and covariates of the model are separated by a ∼ operator. The response, on the left side of ∼, should be a `Surv` object [8,9] with two columns, of which the first column is the survival time or censored time and the second column is the censoring indicator. The covariates or predictors `X`, on the right side of ∼, should be columns with the same length as `Surv` object, e.g., `lss(Surv(time, status)∼X)`.

The optional arguments are:

- `data`: a data frame which contains the `Surv` objects and covariates. If this argument is not specified, a `data$variable` format can be used in the formula specification.
- `subset`: specifies subset of the original data frame data that should be used for the model fit.
- `mcsize`: specifies the resampling number which is the number of random samples of $(Z_1, \ldots, Z_n)$, i.e., the value of N in covariance calculation Eq. (11) in Section 2. The default is 500.
- `maxiter`: specifies the maximum iteration number. The iterations will be stopped after maxiter iterations if the convergence criterion is not met. The default is 50.
- `tolerance`: specifies the value of convergence criterion η in Eq. (12). The default is 0.001.
- `trace`: takes logical values `T` or `F`. If it is set to be `T`, then the summary of every iteration will be kept. The default is `F`.
- `gehanonly`: takes logical values `T` or `F`. If `gehanonly=T`, only Gehan estimator $\hat{\beta}_G$ will be calculated and the least-squares estimator $\hat{\beta}_{(m)}$ will not be calculated. The default is `gehanonly=F`.
- `cov`: takes logical values `T` or `F`. If `cov=T`, the covariance matrices of the Gehan estimator and the least-squares estimator will be printed. The default is `cov=F`.
- `na.action`: takes values `na.exclude` or `na.fail`. The default is `na.exclude`, which deletes the observations with missing values. The other choice is `na.fail`, which returns an error if any missing values are found.

3.3. Output

When `gehanonly=F`, the output consists of:

- The number of observations without any missing values, the number of events, and the number of censored data.
- Iteration number.
- The number of resampling.

Table 1 – Gehan estimator for mayo PBC data

	Estimate	Standard error	Z value	Pr(>|Z|)
Age	−0.024	0.006	−4.107	0.00004
log(alb)	1.537	0.524	2.933	0.0034
log(bili)	−0.558	0.064	−8.756	<0.00001
Edema	−0.931	0.256	−3.642	0.0003
log(protime)	−2.547	0.930	−2.738	0.0062

- The Gehan estimator, the standard error of the Gehan estimator, the Z score and the p-value for testing the hypothesis of $\beta = 0$ based on Gehan estimation.
- The least-squares estimator, the standard error of the least-squares estimator, the Z score and the p-value for testing the hypothesis of $\beta = 0$.
- The covariance matrices of the Gehan estimator and the least-squares estimator, when `cov` is set to be `T`.

When `gehanonly=T`, the output will not have any results related to the least-squares estimation.

If one specifies `trace=T`, which can be used only when `gehanonly=F`, the output will also include:

- The initial estimator $\hat{\beta}_G$.
- Point estimator $\hat{\beta}_{(m)}$ at each iteration.
- Convergence criteria and status.

4. Example

In this section, we use two examples to illustrate the use of `lss` function.

4.1. *Stanford heart transplantation data*

We fit two models as in Miller and Halpern [10]. The first model regresses the base-10 logarithm of the survival time on the patient's age and the mismatch score T5. The model can be fitted as following:

```
lss(Surv(log10(time), status) age + t5, data = stan, mcsize
  = 500, trace = T, gehanonly = F, cov = F, na.action
  = na.exclude)
```

The output:

```
Number of Observations:   157
Number of Events:   102
Number of Censored:  55
Number of Iterations:  7
Resampling Number:  500

Gehan Estimator:
       Estimate Std. Error    Z value   Pr(>|Z|)
age -0.02111191 0.01070803 -1.9715961 0.04865574
 t5 -0.02654734 0.15984560 -0.1660812 0.86809307

Least-Squares Estimator:
        Estimate  Std. Error     Z value  Pr(>|Z|)
age -0.014839424 0.009813829 -1.51209312 0.1305102
 t5 -0.002778499 0.153674503 -0.01808042 0.9855747
```

In addition, `trace=T` gives following information:

```
betag:  -0.02111191 -0.02654734

Iteration:  1
  Beta:  -0.016234611 -0.007534669
Iteration:  2
  Beta:  -0.015144202 -0.003282518
Iteration:  3
  Beta:  -0.014924957 -0.002687894
Iteration:  4
  Beta:  -0.014862588 -0.002685845
Iteration:  5
  Beta:  -0.014847495 -0.002747928
Iteration:  6
  Beta:  -0.014841670 -0.002770323
Iteration:  7
  Beta:  -0.014839424 -0.002778499

Converged. Criteria Satisfied: 0.001
```

Both Gehan estimator and least-squares estimator of the T5 mismatch score are highly nonsignificant, consequently, the T5 is deleted from analysis and the following second model is fitted with the variable age.

The second model regresses the base-10 logarithm of the survival time on age and age^2 as in Miller and Halpern [10]. We also only included the patients who survived for at least 10 days after transplantation as those in their model fitting. This model can be fit by command

```
lss(Surv(log10(time), status) age + I(age^2), data
  = stan, subset=time >= 10, mcsize=500, trace = F, cov = T)
```

This gives the results:

```
Number of Observations:   152
Number of Events:   97
Number of Censored:  55
Number of Iterations:  4
Resampling Number:  500

Gehan Estimator:
             Estimate   Std. Error   Z value   Pr(>|Z|)
     age  0.104556181 0.0521380094  2.005373 0.04492314
I(age^2) -0.001677411 0.0006681163 -2.510657 0.01205068

Gehan Covariance Matrix:
                    age       I(age^2)
     age  0.00271837203 -3.432696e-005
I(age^2) -0.00003432696  4.463794e-007

Least-Squares Estimator:
             Estimate   Std. Error   Z value   Pr(>|Z|)
     age  0.106932613 0.0456285650  2.343545 0.01910144
I(age^2) -0.001669698 0.0005839572 -2.859281 0.00424602

LSE Covariance Matrix:
                    age       I(age^2)
     age  0.00208196595 -2.625689e-005
I(age^2) -0.00002625689  3.410061e-007
```

If we specify `gehanonly=T`, the program will compute the Gehan estimator only and the output will not show the `Least-Squares Estimator` and `LSE Covariance Matrix`.

In the second model, both Gehan and least-squares estimators are similar and significant at the usual significance

Table 2 – Least-squares estimator for mayo PBC data

	Estimate	Standard error	Z value	Pr(>|Z|)
Age	−0.024	0.006	−3.995	0.00006
log(alb)	1.457	0.509	2.865	0.0042
log(bili)	−0.583	0.061	−9.514	<0.00001
Edema	−0.839	0.209	−4.017	0.00006
log(protime)	−2.281	0.856	−2.665	0.0077

level 0.05. The results show that the age effect on the base-10 logarithm survival is quadratic. The results can be used to compare the mean difference of the survival time between subjects with different age levels. Let age_1 and age_2 be the two different age levels, then the difference of two base-10 logarithm survival times is $\beta_1(\text{age}_2 - \text{age}_1) + \beta_2(\text{age}_2^2 - \text{age}_1^2)$. As the age effect is quadratic, the effect of 1-year age difference on survival time depends on the actual age levels. For example, if $\text{age}_1 = 50$ years, and $\text{age}_2 = 51$ years, then the difference of two base-10 logarithm survival times is −0.062 based on both estimators, which indicates that the survival time of 51 years old in average about $\exp\{-0.062\} = 94.0\%$ of the survival time of 50 years old. But if $\text{age}_1 = 40$ years, and $\text{age}_2 = 41$ years, then the difference of two base-10 logarithm survival times is −0.028 based on both estimators, which indicates that the survival time of 41 years old in average about $\exp\{-0.028\} = 97.2\%$ of the survival time of 40 years old.

Both model fits took less than 3 min of computational time.

4.2. Mayo primary biliary cirrhosis data

The Mayo primary biliary cirrhosis data can be found in Fleming and Harrington [11]. Among the 418 subjects in the study, there were 161 deaths. As usual, the response of the model is the natural logarithm of survival time. Five covariates: age, log(albumin), log(bilirubin), edema and log(protime), are included in the model. The least-squares estimator was obtained after six iterations. The command:

```
lss(Surv(log(time), status) age + log(alb)
    +log(bili)+edema + log(protime), data = pbc, mcsize
  = 500, trace = T, tolerance = 0.001, cov = F)
```

Tables 1 and 2 show the Gehan estimator and the least-squares estimator, respectively.

Both the Gehan estimator and the least-squares estimator indicate that the increase in age, bilirubin, edema and protime would shorten the survival time significantly at the usual significance level 0.05, while the increase of albumin level would prolong the survival time significantly at the usual significance level 0.05.

Specifically, the Gehan estimator can be interpreted as follows: (1) for any given age level and fixed bilirubin, edema and protime, on average, the presence of albumin in natural logarithm scale would lead to the survival time $\exp\{1.537\} = 465.1\%$ of that for patients without any change in albumin level; (2) for any given age level and fixed albumin, edema and protime, on average, one unit increase in bilirubin in natural logarithm scale would lead to the survival time $\exp\{-0.558\} = 55.5\%$ of that for patients without any change in bilirubin level; (3) for any given age level and fixed albumin, bilirubin and protime, on average, in the presence of edema would lead to the survival time $\exp\{-0.931\} = 39.1\%$ of that for patients without edema; (4) for any given age level and fixed albumin, bilirubin and edema, on average, one unit increase in protime in natural logarithm scale would lead to the survival time $\exp\{-2.547\} = 7.8\%$ of that for patients without any change in protime level.

The least-squares estimator can be similarly interpreted.

The computational time for this example took about 1 h and 23 min.

5. Remark

The Cox proportional hazards model (Cox, 1972) has been usually used in the analysis of censored failure time data. The interpretation of the results from the Cox model is done with the concept of hazard ratio which is the ratio of two conditional probabilities. Consequently, the Cox model does not provide direct physical interpretation. In this regard, the usual linear regression model or the accelerated failure time model provides an attractive alternative to the Cox model as pointed out by D.R. Cox (Reid, 1994, p. 450) [12], 'accelerated life model are in many ways more appealing [than the proportional hazards model] because of their quite direct physical interpretation'.

In theory, both Gehan and least-squares estimators are valid asymptotically. But the least-squares estimator is the most often used in linear regression analysis of uncensored data. The purpose of the `lss` program is to obtain the least-squares estimator. However, we would like to leave the choice of estimators to users.

The Wald tests on regression coefficients provide a guidance for variable selection. On the other hand, how to assess the goodness of fit for censored linear regression is an open question and requires further investigation.

With the `lss` function, which has solid theoretical justification, we hope that the linear regression model or the accelerated failure time model for censored data is accessible for practitioners.

6. Availability of the program

The program can be freely downloaded from CRAN webpage http://cran.r-project.org/src/contrib/Descriptions/lss.html or http://www.columbia.edu/~zj7.

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