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A Confidence Interval for Median Survival Time in the Additive Risk Model

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ABSTRACT

Let $\xi_p(z_0)$ be the pth quantile of the distribution of the survival time of an individual with time-invariant covariate vector z_0 in the additive risk model. We propose an estimator of $\xi_p(z_0)$ and derive its asymptotic distribution, and then construct an approximate confidence interval of $\xi_p(z_0)$. Simulation studies are carried out to investigate performance of the proposed estimator for practical sample sizes in terms of empirical coverage probabilities. Also, the estimator is illustrated on small cell lung cancer data taken from Ying, Jung, and Wei (1995).

Keywords: Additive Risk Model; Censoring; Confidence Interval; Median Survival Time

1. INTRODUCTION

The additive risk model specifies that the hazard function for the survival time T of an individual with time-invariant covariates $z = (z_1, \ldots, z_r)^T$ has the form

$$\lambda(t|z) = \lambda_0(t) + \beta_0^T z, \tag{1.1}$$

where $\beta_0 = (\beta_{01}, \ldots, \beta_{0r})^T$ is a vector of unknown coefficients, and $\lambda_0(t)$ is the unspecified baseline hazard function (Lin and Ying (1994)).

Let $Z_1, \ldots, Z_n$ be independent and identically distributed r-dimensional vectors of covariates, and $T_1, \ldots, T_n$ be independent survival times. Suppose that given $Z_i = z_i$, $T_1, \ldots, T_n$ follow model (1.1). Let $C_1, \ldots, C_n$ be independent censoring times, and for $i = 1, \ldots, n$, let $Y_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \le C_i)$, where $I(\cdot)$ is the indicator function of the specified event. Assume that the Z_i's are bounded, and that conditional on Z_i, T_i and C_i are independent. For each

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$i = 1, \ldots, n$, define $N_i(t) = I(T_i \le t, \delta_i = 1)$ and $J_i(t) = I(Y_i \ge t)$. Under model (1.1), the counting process N_i can be uniquely decomposed so that

$$M_i(t) = N_i(t) - \int_0^t J_i(u)\{d\Lambda_0(u) + \beta_0^T Z_i du\} \qquad (i = 1, \ldots, n),$$

where $M_i(\cdot)$ is a square integrable martingale, and $\Lambda_0(\cdot)$ is the cumulative hazard function associated with λ_0.

As in Lin and Ying (1994), statistical inference on β_0 is based on the following equation

$$U(\beta, t) = \sum_{i=1}^{n} \int_0^t \{Z_i - \bar{Z}(u)\}\{dN_i(u) - J_i(u)\beta^T Z_i du\},$$

where $\bar{Z}(t) = \sum J_i(t) Z_i / \sum J_i(t)$. Note that $U(\beta, t)$ mimics the partial likelihood score function for the Cox proportional hazards model. The estimator $\hat{\beta}$, defined as the solution to $U(\beta, \infty) = 0$, takes the explicit form

$$\hat{\beta} = \left[\sum_{i=1}^{n} \int_0^\infty J_i(u)\{Z_i - \bar{Z}(u)\}^{\otimes 2} du\right]^{-1} \int_0^\infty \{Z_i - \bar{Z}(u)\} dN_i(u), \qquad (1.2)$$

where $a^{\otimes 2} = aa^T$ for a column vector a. Lin and Ying (1994) have shown that the estimator $\hat{\beta}$ is consistent and asymptotically normally distributed. Also, they proposed to estimate $\Lambda_0(t)$ by

$$\hat{\Lambda}_0(\hat{\beta}, t) = \int_0^t \{\sum_{i=1}^{n} J_i(u)\}^{-1} \sum_{i=1}^{n} \{dN_i(u) - J_i(u)\hat{\beta}^T Z_i du\}, \qquad (1.3)$$

and have shown that this estimator converges weakly to a zero-mean Gaussian process.

The influence of the covariates on survival time is measured by β_0 since $\beta_{0j} (j = 1, \ldots, r)$ represents the increase in hazard as Z_j is increased one unit. In some applications, it is often also useful to consider how the median survival time is affected by the covariates, and in this case we need methods for estimating median survival time given a value of the covariate vector. Recently, Dabrowska and Doksum (1987) have developed a procedure to estimate confidence interval of the median survival time in the Cox proportional hazards model, and Burr and Doss (1993) have extended the work of Dabrowska and Doksum (1987) to obtain confidence bands for the median survival time as a function of covariates. In this article we introduce a confidence interval estimate of median survival time in model (1.1) based on the arguments of Burr and Doss (1993) and on the results of Lin and Ying (1994, 1995) for estimations of the regression parameter β_0 and the cumulative hazard function Λ_0.

For $0 < p < 1$, let $\xi_p(z_0)$ be the pth quantile of the distribution of survival time T of an individual with time-invariant covariate vector, say z_0, in model (1.1). First, note that for an arbitrary cumulative hazard function H, the survival function corresponding to H is the product integral

$$S(t) = \Pi_{u \leq t}\{1 - H(du)\}$$

(see Kalbfleish and Prentice (1980), pp. 8-10), and that the pth quantile of $1 - S$ is $(1 - S)^{-1}(p)$. For the case of the hazard function $\Lambda(t|z_0) = \Lambda_0(t) + \int_0^t \beta_0^T z_0 du$ given by (1.1), this gives

$$\xi_p(z_0) = \sup\{t | 1 - \Pi_{u \leq t}\{1 - \Lambda_0(du) - \beta_0^T z_0 du\} \leq p\}.$$

Substituting $\hat{\Lambda}_0$ in (1.3) for Λ_0 and $\hat{\beta}$ in (1.2) for β_0, we obtain a natural estimator of $\xi_p(z_0)$, given by

$$\hat{\xi}_p(z_0) = \sup\{t | 1 - \Pi_{u \leq t}\{1 - \hat{\Lambda}_0(\hat{\beta}, du) - \hat{\beta}^T z_0 du\} \leq p\}.$$

In the next section, we derive the asymptotic distribution of the estimator $\hat{\xi}_p(z_0)$, and then construct an approximate confidence interval for $\xi_p(z_0)$. Section 3 reports the results of Monte Carlo simulation studies to investigate performance of the proposed estimator in terms of empirical coverage probability. Finally, Section 4 illustrates the estimator on the small cell lung cancer data taken from Ying, Jung, and Wei (1995).

2. ASYMPTOTIC DISTRIBUTION OF $\hat{\xi}_p(z_0)$

Define $\bar{J}(t) = n^{-1} \sum J_i(t)$, $S^{(0)}(\beta_0, t) = \sum J_i(t) \beta_0^T Z_i / \sum J_i(t)$, $S^{(1)}(\beta_0, t) = \sum J_i(t) \beta_0^T Z_i Z_i / \sum J_i(t)$. Also, let $\bar{j}(t) = E\{\bar{J}(t)\}$, $\bar{z}(t) = E\{\bar{Z}(t)\}$, and for $r = 1, 2$, $s^{(r)}(\beta_0, t) = E\{S^{(r)}(\beta_0, t)\}$. As in Lin and Ying (1995), assume the following conditions:

Condition 1: There exists a function b such that as $n \to \infty$,

$$\sup_{t \in (0,\infty)} \left| n^{-1} \sum_{i=1}^{n} J_i(t)\{\lambda_0(t) + \beta_0^T Z_i\}\{Z_i - \bar{Z}(t)\}^{\otimes 2} - b(t) \right| = o_p(1).$$

Condition 2: There exists a nonsingular matrix A such that as $n \to \infty$,

$$\left| n^{-1} \sum_{i=1}^{n} \int_0^\infty J_i(t)\{Z_i - \bar{Z}(t)\}^{\otimes 2} dt - A \right| = o_p(1).$$

Condition 3: For every $t \in (0, \infty)$, the $\bar{Z}(t)$, $\bar{J}(t)$, $S^{(0)}(\beta_0, t)$, and $S^{(1)}(\beta_0, t)$ converge in probability to $\bar{z}(t)$, $\bar{j}(t)$, $s^{(0)}(\beta_0, t)$, and $s^{(1)}(\beta_0, t)$, respectively.

Define

$$Q(t, p|z_0) = \Lambda_0(t) + \int_0^t \beta_0^T z_0 du + \ln(1-p),$$

and

$$\hat{Q}(t, p|z_0) = \hat{\Lambda}_0(\hat{\beta}, t) + \int_0^t \hat{\beta}^T z_0 du + \ln(1-p).$$

Theorem 2.1. *For $0 < p_1 \leq p_2 < 1$, let $q_i = \xi_{p_i}(z_0)$, $i = 1, 2$. Let $B = \int_0^\infty b(u) du$ and $a_z(t) = -\int_0^t \bar{z}(u) du$. Under the conditions stated earlier, as $n \to \infty$, $n^{\frac{1}{2}}\{\hat{\xi}_p(z_0) - \xi_p(z_0)\}$ converges weakly to a zero-mean Gaussian process $V(p, z_0)$ with covariance function*

$$\zeta^2(p_1, p_2|z_0) = \left[\{\beta_0^T z_0 + \lambda_0(q_1)\}\{\beta_0^T z_0 + \lambda_0(q_2)\}\right]^{-1} \gamma(p_1, p_2|z_0), \tag{2.1}$$

where

$$\begin{aligned}\gamma(p_1, p_2|z_0) = & \int_0^{q_1} \bar{j}(u)^{-1}\{\lambda_0(u) + s^{(0)}(\beta_0, u)\} du \\ & + \{q_1 z_0 + a_z(q_1)\}^T A^{-1} B A^{-1} \{q_2 z_0 + a_z(q_2)\} \\ & + \{q_1 z_0 + a_z(q_1)\}^T A^{-1} \int_0^{q_2} \{s^{(1)}(\beta_0, u) - s^{(0)}(\beta_0, u)\bar{z}(u)\} du \\ & + \{q_2 z_0 + a_z(q_2)\}^T A^{-1} \int_0^{q_1} \{s^{(1)}(\beta_0, u) - s^{(0)}(\beta_0, u)\bar{z}(u)\} du.\end{aligned}$$

Proof: For simplicity, let $q_0 = \xi_p(z_0)$ and $\hat{q}_0 = \hat{\xi}_p(z_0)$. Note that substituting q_0 for t in $Q(t, p|z_0)$ and $\hat{q}_0$ in $\hat{Q}(t, p|z_0)$, we directly obtain

$$0 = n^{\frac{1}{2}}\{\hat{\Lambda}_0(\hat{\beta}, \hat{q}_0) - \Lambda_0(q_0)\} + n^{\frac{1}{2}}(\hat{q}_0 - q_0)\hat{\beta}^T z_0 + q_0 n^{\frac{1}{2}}(\hat{\beta} - \beta_0)^T z_0. \tag{2.2}$$

According to Lin and Ying (1995), for any $t \in (0, \infty)$,

$$n^{\frac{1}{2}}\{\hat{\Lambda}_0(\hat{\beta}, t) - \hat{\Lambda}_0(\beta_0, t)\} = n^{\frac{1}{2}}(\hat{\beta} - \beta_0)^T a_z(t) + o_p(1),$$

and this implies

$$n^{\frac{1}{2}}[\{\hat{\Lambda}_0(\hat{\beta},\hat{q}_0) - \hat{\Lambda}_0(\beta_0,\hat{q}_0)\} - \{\hat{\Lambda}_0(\hat{\beta},q_0) - \hat{\Lambda}_0(\beta_0,q_0)\}]$$
$$= n^{\frac{1}{2}}(\hat{\beta} - \beta_0)^T\{a_z(\hat{q}_0) - a_z(q_0)\} + o_p(1). \tag{2.3}$$

Also, since a_z is continuous and $\hat{\beta}$ is $n^{\frac{1}{2}}$-consistent, $|\hat{q}_0 - q_0|$ being enough small, the left hand side of (2.3) is $o_p(1)$. Clearly,

$$n^{\frac{1}{2}}\{\hat{\Lambda}_0(\beta_0,\hat{q}_0) - \hat{\Lambda}_0(\beta_0,q_0)\} = n^{\frac{1}{2}}\int_{q_0}^{\hat{q}_0}\{\sum_{j=1}^n J_j(u)\}^{-1}\sum_{i=1}^n dM_i(u) + n^{\frac{1}{2}}\int_{q_0}^{\hat{q}_0} d\Lambda_0(u) \tag{2.4}$$

The first term in (2.4) is $o_p(1)$ by Lenglart's inequality, and by Taylor expansion of Λ_0 about q_0, the second term is $n^{\frac{1}{2}}(\hat{q}_0 - q_0)\lambda_0(q_0) + o_p(1)$. From these results, the first term in (2.2) is asymptotically equivalent to $n^{\frac{1}{2}}\{\hat{\Lambda}_0(\hat{\beta},\hat{q}_0) - \Lambda_0(q_0)\} + n^{\frac{1}{2}}(\hat{q}_0 - q_0)\lambda_0(q_0)$. Thus, we have

$$n^{\frac{1}{2}}(\hat{q}_0 - q_0) = -\{\hat{\beta}^T z_0 + \lambda(q_0)\}^{-1}$$
$$\times \left[n^{\frac{1}{2}}\{\hat{\Lambda}_0(\hat{\beta},q_0) - \Lambda_0(q_0)\} + q_0 n^{\frac{1}{2}}(\hat{\beta} - \beta_0)^T z_0\right] + o_p(1).$$

Furthermore, it follows from the asymptotic expressions of $n^{\frac{1}{2}}(\hat{\beta} - \beta_0)$ and $n^{\frac{1}{2}}$ $\{\hat{\Lambda}_0(\hat{\beta},q_0) - \Lambda_0(q_0)\}$ in Lin and Ying (1994, 1995) that

$$n^{\frac{1}{2}}(\hat{q}_0 - q_0) = -\{\beta_0^T z_0 + \lambda(q_0)\}^{-1}$$
$$\times \left[n^{\frac{1}{2}}\sum_{i=1}^n\int_0^\infty\{\sum_{j=1}^n J_j(u)\}^{-1}I(u < q_0)dM_i(u)\right.$$
$$\left. +\{q_0 z_0 + a_z(q_0)\}^T A^{-1} n^{-\frac{1}{2}}\sum_{i=1}^n\int_0^\infty\{Z_i - \bar{Z}(u)\}dM_i(u)\right] + o_p(1),$$

which implies the desired weak convergence from the standard counting process arguments. □

In the present context estimating λ_0 is based on kernel smoothers, which are computationally convenient and also their asymptotic properties have already been studied by Ramlau-Hansen (1983). To describe them, let K be a function of bounded variation with support on $[-1,1]$ and whose integral is 1, and let bandwidth, depending on n, $h \to 0$ and $nh^2 \to \infty$, as $n \to \infty$. Define the kernel estimator of λ_0 by

$$\hat{\lambda}_0(t) = h^{-1} \int_0^\infty K\left(\frac{t-u}{h}\right) d\hat{\Lambda}_0(\hat{\beta}, u).$$

Here, the specific choices of K and h have been extensively discussed in many literatures including Silverman (1986, pp. 40-72).

Corollary 2.1. *Let $\hat{q}_i = \hat{\xi}_{p_i}(z_0)$, $i = 1, 2$. Let $\hat{A} = n^{-1} \sum \int_0^\infty J_i(u)\{Z_i - \bar{Z}(u)\}^{\otimes 2} du$, $\hat{B} = n^{-1} \sum \int_0^\infty \{Z_i - \bar{Z}(u)\}^{\otimes 2} dN_i(u)$, and $\hat{a}_z(t) = -\int_0^t \bar{Z}(u)du$. Under the same conditions as in Theorem 1, the covariance function $\zeta^2(p_1, p_2|z_0)$ is consistently estimated by*

$$\hat{\zeta}^2(p_1, p_2|z_0) = [\{\hat{\beta}^T z_0 + \hat{\lambda}_0(\hat{q}_1)\}\{\hat{\beta}^T z_0 + \hat{\lambda}_0(\hat{q}_2)\}]^{-1} \hat{\gamma}(p_1, p_2|z_0),$$

where

$$\begin{aligned}
\hat{\gamma}(p_1, p_2|z_0) = & \int_0^{\hat{q}_1} \bar{J}(u)^{-1}\{d\hat{\Lambda}_0(u) + S^{(0)}(\hat{\beta}, u)\}du \\
& + \{\hat{q}_1 z_0 + \hat{a}_z(\hat{q}_1)\}^T \hat{A}^{-1} \hat{B} \hat{A}^{-1} \{\hat{q}_2 z_0 + \hat{a}_z(\hat{q}_2)\} \\
& + \{\hat{q}_1 z_0 + \hat{a}_z(\hat{q}_1)\}^T \hat{A}^{-1} \int_0^{\hat{q}_2} \{S^{(1)}(\hat{\beta}, u) - S^{(0)}(\hat{\beta}, u)\bar{Z}(u)\}du \\
& + \{\hat{q}_2 z_0 + \hat{a}_z(\hat{q}_2)\}^T \hat{A}^{-1} \int_0^{\hat{q}_1} \{S^{(1)}(\hat{\beta}, u) - S^{(0)}(\hat{\beta}, u)\bar{Z}(u)\}du,
\end{aligned}$$

and then an approximate 100(1-α)% confidence interval for $\xi_p(z_0)$ is

$$\hat{\xi}_p(z_0) \pm z_{\frac{1}{2}\alpha} n^{-\frac{1}{2}} \hat{\zeta}(p, p|z_0), \tag{2.5}$$

where $z_{\frac{1}{2}\alpha}$ is the $(1 - \frac{1}{2}\alpha)$th quantile of the standard normal distribution.

Proof: It can be shown that $\sup_{t \in (0,\infty)} |\hat{\lambda}_0(t) - \lambda_0(t)| = o_p(1)$ by the results of Ramlau-Hansen (1983), and also from Theorem 1, $\sup_{p \in (0,1)} |\hat{\xi}_p(z_0) - \xi_p(z_0)| = o_p(1)$. If in (2.1) the unknowns β_0, $\xi_p(z_0)$, λ_0, Λ_0, a_z, $s^{(0)}$, $s^{(1)}$, A, and B are replaced by their consistent estimates $\hat{\beta}$, $\hat{\xi}_p(z_0)$, $\hat{\lambda}_0$, $\hat{\Lambda}_0$, $\hat{a}_z$, $S^{(0)}$, $S^{(1)}$, $\hat{A}$, and $\hat{B}$, respectively, we have a consistent estimator $\hat{\zeta}^2(p_1, p_2|z_0)$ of $\zeta^2(p_1, p_2|z_0)$. Also, (2.5) directly holds. □

Table 3.1 : Empirical Coverage Probabilities of 95% Confidence Intervals of $\xi_p(z_0)$ for p=0.25, 0.5 and 0.75 under model $\lambda(t; z_0) = 1 + 0.05z_0$ with a 0-1 binary covariate z_0

		*p*th Quantile								
		0.25			0.5			0.75		
		% Censoring			% Censoring			% Censoring		
n	z_0	10	25	50	10	25	50	10	25	50
50	1	.939	.936	.931	.934	.926	.922	.927	.923	.924
	0	.950	.951	.948	.946	.949	.966	.950	.953	.972
100	1	.945	.946	.937	.945	.941	.939	.944	.940	.936
	0	.950	.952	.953	.952	.949	.951	.952	.948	.974

3. NUMERICAL RESULTS

3.1. Simulation Studies

Simulation studies were carried out to investigate performance of the estimator $\hat{\xi}_p(z_0)$ for practical sample sizes. Survival times were generated from an additive risk model with a 0-1 binary covariate z, $\lambda(t; z_0) = 1 + 0.05z_0$, and censoring times from exponential distribution with mean set to give the desired degree of censoring. The three different values of the censoring mean are 8.74, 2.95, and 0.97 corresponding to 10%, 25%, and 50% censoring. To estimate λ_0, Epanechnikov kernel function, defined by $K(t) = 0.75(1 - |t|^2)I(|t| \leq 1)$, is used, and bandwidth is chosen using the maximum likelihood cross-validation method at each simulation (see Härdle (1991), pp. 93-95). Based on 10,000 simulations, Table 3.1 presents the empirical coverage probabilities of confidence intervals of $\xi_p(z_0)$ for p=0.25, 0.5, and 0.75 at nominal confidence coefficient 0.95. Table 3.1 implies that the empirical coverage probabilities substantially achieves the nominal level in any configuration. In case $z_0 = 1$, the proposed estimator being slightly conservative, the coverage rates tend to increase as sample sizes increase. When the fraction of censoring is heavy, the estimator becomes unstable. This trend is remarkable at upper tail.

3.2. A Real Example

We illustrate the proposed estimator $\hat{\xi}_p(z_0)$ for $p = 0.5$ with a dataset taken from Ying, Jung, and Wei (1995). This dataset consists of the survival times of 121 patients with small cell lung cancer. Fifty-nine of 121 patients are given etopocide followed by cisplatin, say group 1, and the remaining 62 patients are given cisplatin followed by etopocide, say group 2. Recently, Kim and Song (1995) and Kim and Lee (1996) have shown that this dataset satisfies the additive risk assumption using different goodness-of-fit tests for checking whether or not the difference in hazard rates between two groups is constant. Figure 3.1 displays maximum likelihood cross-validation score function, defined by

$$CV(h) = n^{-1} \sum_{i=1}^{n} \ln \left[\sum_{i \neq j} K\left(\frac{Y_j - Y_i}{h}\right) \{\hat{\Lambda}_0(\hat{\beta}, Y_j) - \hat{\Lambda}_0(\hat{\beta}, Y_j^-)\} \right] - \ln(h),$$

for Epanechnikov kernel function, where $x(t-) = \lim_{u \uparrow t} x(u)$, and Figure 3.2 displays kernel estimate of hazard rate λ_0 corresponding to optimizing bandwidth, 0.37. The estimated median survival times of patients in group 1 and group 2 are 2.638 and 2.795, respectively, and their approximate 95% confidence interval estimates are $(2.332, 2.945)$ for patients in group 1 and $(2.518, 3.073)$ for patients in group 2.

4. DISCUSSION

We may note that the choice of $\beta_0 = 0.05$ in simulation studies represents a situation in which the hazard functions in the two groups are nearly equal. Results not reported here show that the empirical coverage rates of the proposed estimator do not depart from the nominal confidence level 0.95 for the additive risk model with $\beta_0 = 1.0$. For the practical sample size, say, $n = 30$, the proposed estimator is slightly more conservative than the results in Table 1, which was tabulated for $n = 50, 100$.

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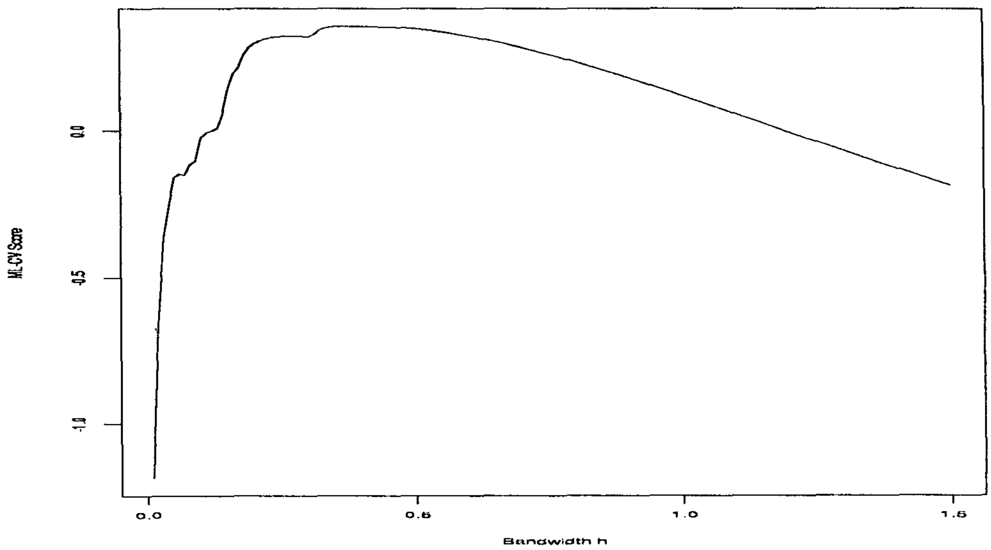

Figure 3.1 : Maximum Likelihood Cross-Validation Score Function for Epanechnikov Kernel Function

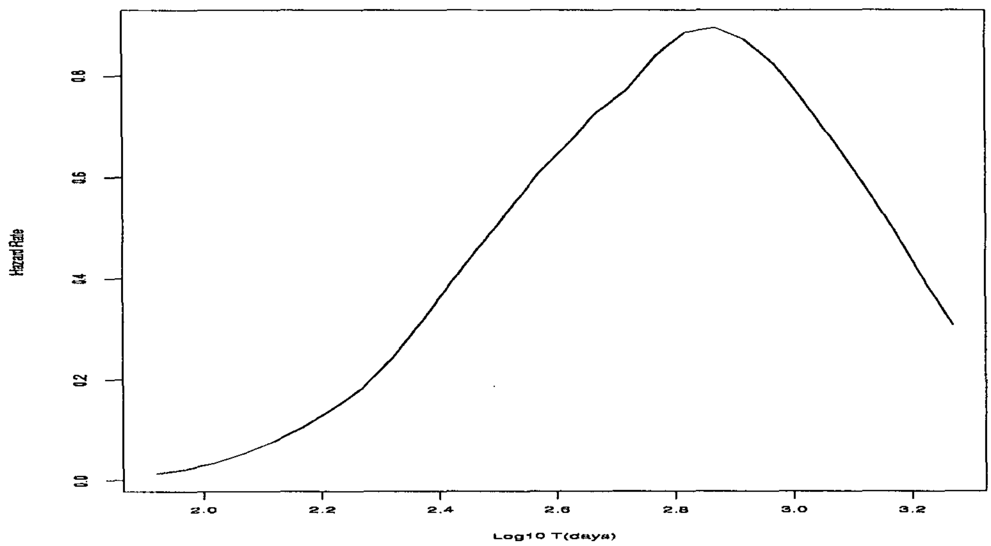

Figure 3.2 : Kernel Estimate of the Hazard Rate Corresponding to Optimizing Bandwidth, 0.37

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