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A Piece-Wise Modelling Function of Survival Analysis Data

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Abstract

One of the fundamental assumptions in survival analysis is that it enable a straight forward interpretation of hazard rates of subject's covariate(s) on some reference categories or in situations where variables are continuous in nature, the hazard rates must be constant through time. This is also known as the proportional hazard assumption for cox regression. This assumption is always violated in medical practice where subject's vital statistics or measures are mostly varying, as their medical situations changes with time. This paper therefore develops a Piece-wise survival model, where three levels of Weibull distribution were assumed for baseline hazards. The sensitivity of the baselines were accessed under several censoring percentages (0%, 25%, 50%, and 75%) and sample sizes (n=100, n=500 and n=1000) when models were Single Parametric (SPM) and Partitioned – Piece wise Parametric Model (PPM). A Piece-wise Bayesian hazard model with structured additive predictors in which the functional form of time varying covariate incorporated in a non-proportional hazards framework was also developed, capable of incorporating complex situations in a more flexible framework. Analysis was done utilizing MCMC simulation technique. Results revealed on comparison that the PPM outperformed the SPM with smaller DIC values and larger predictive powers with the LPML criterion and consistently so throughout all simulations.

Keywords: Parametric model, Proportional hazard, Survival model, Time varying covariates, Violation.

1. Introduction

Survival analysis is a statistical technique for data analysis where by the outcome variable of interest is time until an event will occurs. By time, such as years, months, weeks, or days from the beginning of take-note or follow-up of an individual until an event occur. Event here refer to death, disease incidence, re-lapse from remission, recovery (e.g., return to work) or any chosen experience of interest that may happen to an individual [1]. Analysis of survival times data has received a substantial attention, most especially in the field of medicine, where the conventional connotation 'Survival analysis' arises from [2]. In a number of other bio-statistical applications on censored follow-up time data, the interest lies generally on the prognostic role of clinical/biological covariates. On this note, non-parametric and semi-parametric methods have always been preferred over parametric ones. The most usually adopted tool is the Cox model,

which avoids any assumption of functional form of the hazard function on time. However, such feature is not always useful if the interest lies on investigation of the shape of the hazard or in predictive modeling when the cox-model is extended to the time-varying covariates and time-dependent effects, which when combined, gives the most general version of the hazard [3]. Also, further progress would require indicating the form of this function of time. In such situation where time is observed to be truly continuous, a flexible or semi-parametric strategy is essential, where some mild assumptions are made about the baseline hazard $\lambda_0(t)$. Specifically, we may further subdivide time into reasonably small intervals and then assume that the baseline hazard is constant in each interval, resulting to a piece-wise survival model. According to [4], the Piecewise Model (PM) arises as a rather attractive alternative to parametric models for analyzing of time to event data. Although parametric in a strict sense; the PM can be thought of as a nonparametric model as much as it does not have a closed form for the hazard function. This nice characteristic of the PM permit us to use this model to approximate satisfactorily hazard functions of several shapes. Hence, the PM has been widely used to model time to event data in diverse context, such as; Clinical articles including kidney infection [5], heart transplant data [6]. Hospital mortality data [7], and cancer studies including leukemia [8], gastric cancer [9], breast cancer [10], application to interval-censored data [11], Melanoma [12] and nasopharynx cancer [13] among others. The PM has also been used in reliability [9, 14], and economics problems [9] and [15]. Time-Varying Effect of Tumor Size and Soft Tissue Sarcoma Data by [16]. The paper modify a Piecewise Weibull hazard baseline function of survival model which can cope better with changes in baseline rate over time, leading to a better fit. This paper will also investigates, by employing three levels of Weibull distributions as baseline; the effects of ignoring time varying effects and regularized estimation of non-linear functions applied often in prognostic factors. The aim of this simulation study is to investigate: How the baseline hazards behave under functional forms of time varying effect and continuous covariates in the presence of spatial correlations and investigate the performance of Single hazard models or Single Parametric models (SPM) and the modified Piece-wise model extension or Piece-wise Parametric models (PPM) under various censoring percentages and sample sizes employing there levels of Weibull distributions as baseline.

2. Materials and Method

The risk data used for this paper was simulated from a Weibull baseline hazard distribution which was used to generate survival times for sample sizes of 100, 500 and 1000 respectively. Various censoring levels or percentages of: no censoring “0%”, low “about 25%”, moderate “about 50%” and high “about 75%” were used.

A. Model Specification

The cox hazard model

$$\lambda_i(t, X) = \lambda_0(t) \exp\left(\sum_{j=1}^{p} \beta_j X_j\right). \quad (1)$$

The baseline hazard rate is unspecified, and assumes that covariates $x = (x_1, \ldots, x_p)$ act multiplicatively on the hazard rate through the exponential link function [17].

An additive representation of model 1

$$\eta(t; w, z, x, s) = f_0(t) + \sum_{j=1}^{p} f_j(t) z_j + x'\gamma \quad (2)$$

This is a re-parameterization of the cox model

where $f_0(t) = log\lambda_0(t)$ which implies, $\exp\big(f_0(t)\big)$,is the baseline function, other aspects of the models include the functions $f_1(t)z_1$, $f_1(t)z_2 \ldots\ldots f_p(t)z_p$ are possibly functional form of time varying covariate $z_1, z \ldots, z_p$ andγ is the usual linear part of the predictor for some categorical covariates [18, 2].

2.2 Modification

The proposed model in bits of intervals is given as

$$\lambda_{PE}(t; \nu, x, s) = \{I(t \epsilon T_{\mathrm{h}}(f_{\mathrm{h}}(t)\} + \sum_{j=1}^{p} f_j(t) z_j + f_{spat}(s_{ih}) \quad (3)$$

With its various terms defined as

The function $f_h = log\lambda_h$ is the baseline effect for the kth interval of PEM

The functions $f_j(z_{1h}),\ldots,f_p(z_{ph})$ are functional forms of time varying covariates $z_{1h}, \ldots, z_{ph}$ in the h^{th} interval and

$f_{spat}(s_{ih})$is a structured spatial effect, where s, s =1, . . . ,s is either a spatial index, with $s = s_i$ if subject i in the h^{th} bit (interval) is from area s or it is an exact spatial coordinate $s = (x_i, y_s)$,e.g. for centriods of regions or if exact locations of individuals are known.

2.1 Model Likelihood function

$$L_{PE}\left(\underline{\lambda}, \underline{\beta}; D, \Delta, X, s\right) = \prod_{i=1}^{n} \prod_{h=1}^{H_i} (\lambda_h \exp(X_i^T \underline{\beta} + s_{ih})^{d_{ih}} . \exp(\lambda_h \exp\left(X_i^T \underline{\beta} + s_{ih}\right) \Delta_{ih}). \quad (4)$$

where for each subject i there is a product of h_i terms, H_i being the number of intervals in which the subject is followed. In the expression above, d_{ih} is the status of the i^{th} subject within the interval T_h (0 = alive or censored, 1 = failed); Δ_{ih} is the time spent in T_h by the subject. From (3) it may be seen that L_{PE} is proportional to the product of Poisson likelihoods for D_{ih} with mean parameters: $\mu_{ih} = \lambda_h \exp\left(X_i^T \underline{\beta} + s_{ih}\right) \Delta_{ih}$. As a consequence, the expression of the Poisson regression model is:

$$D_{ij} \sim POISSON(\mu_{ih}); \log(\mu_{ih}) = \underline{\alpha_h} + X_0^T \underline{\beta} + s_{ih} + \log(\Delta_{ih}) . \quad (5)$$

Where $h(i)$ indicate the interval where t_i falls, i.e. the interval where individual i died or was censored.

where $\underline{\alpha_h}$ = $\log(\lambda_h)$ are log-hazard parameters, and the term $\log(\Delta_{ih})$ is an offset.

The expression of the Piecewise model with regularized effects is the following:

$$\begin{cases} V_{ij} \sim POISSON(\mu_{ih}) \\ \log(\mu_{ih}) = \underline{B_0^T \alpha} + \sum_{j=1}^{p} Z_{1j,i} \underline{B_0^T} \underline{\gamma_{1j}} + v_{ij} + \log(\Delta_{ih}) \\ \cdot \\ \left(\underline{\alpha} \middle| \tau^2\right) \sim RW(\tau^2, P_d);\ \tau^2 \sim \pi_{\tau^2} \\ \left(\underline{\gamma_{ij}} \middle| \tau_j^2\right) \sim RW\left(\tau_j^2, P_d^{(j)}\right);\ \tau_j^2 \sim \pi_{\tau^2 j}; j = 1, \dots, p \\ \cdot \\ V_i / \{v_j\}_{j \neq i} \sim N\left(-\sum_{\{j: j \neq i\}} P_{ij} V_{ij} / P_{ii}, \tau^2 / P_{ii}\right) \end{cases} \quad (6)$$

The time-dependent effects for each covariate are: $Z_{1j,i}\underline{B_0^T \gamma_{1j}}$; j = 1, …,p. Thus, for each Z_{1j}, its values multiplied for a piecewise constant function: $\underline{B_0^T \gamma_{1j}}$; in the parameters. $\gamma_{1j} = (\gamma_{1,j,1}, \dots, \gamma_{1,j,H})^T$. This enables the effect of each Z_{1j} to vary in each interval T_h of the original partition of the follow-up:
$\underline{B_0^T \alpha} + Z_{1j,i}\underline{B_0^T} = \alpha_h + z_{1j,i}\gamma_{1j,h}$for t∈$T_h$.

2.2 Gaussian Random Field (GRF) Priors

For geo-referenced data, it is commonly assumed that $v_i = v(s_i)$ arises from a Gaussian random field (GRF) $\{v(s), s \epsilon S\}$ such that $v = (v_1, \dots, v_m)$ follows a multivariate Gaussian distribution as $v \sim N_m(0, \tau^2 R)$, where τ^2 measures the amount of spatial variation across locations and the (i,j) element of R is modeled as $R[i,j] = \rho(s_i, s_j)$. Here $\rho(.,.)$ is a correlation function controlling the spatial dependence of v(s). In "survregbayes" package in R, the powered exponential correlation function $\rho(s_i, s_j)$. = $\rho(s_i, s_j, \varphi)$.= $\exp\{-(\varphi \|s - s'\|)^v\}$ is used, where φ> 0 is a range parameter controlling the spatial decay over distance, $v \epsilon$ (0,2] is a prespecied shape parameter, and $\|s - s'\|$ refers to the distance (e.g., Euclidean, great-circle) between s and s' Therefore, the prior GRF$(\tau^2, \emptyset)$ is defined as

$$V_i / \{v_j\}_{j \neq i} \sim N\left(-\sum_{\{j: j \neq i\}} P_{ij} V_{ij} / P_{ii}, \tau^2 / P_{ii}\right) \quad (7)$$

$i = 1, \dots, m$ where P_{ij} is the (I,j) element of R^{-1} (Zhou *et al*., 2017).

2.3 Test for Non-Proportionality

To test the hypothesis that the proportional hazard assumption is valid, the following statement of hypothesis is made.

H_0: $\delta_1 = \delta_2 = \cdots = \delta_p$(Assumption is valid)

H_1: $at\ least\ one\ of\ the\ \delta_i's\ is\ not\ equal\ to\ zero$ (Assumption violated)

Decision rule: Reject H_0 if $p - value \leq \alpha$ αlevel of significance)

Residual measures are used to investigate the departure from the proportional hazard assumption. Schoenfeld residual is used to test the assumption of proportionality. Schoenfeld residuals are usually calculated at every failure of time under the proportional hazard assumption, and usually not defined for censored observations. The overall significance test is called the global test [19].

3. Data Analysis

The simulations apply the functional form of time varying covariate by [20], given as

$f(t) = 0.5\sqrt{t} * y.\quad y \sim binom(N, 1, 0.5)$ (8)

For spatial frailty we propose, S= p norm(v) and $v \sim$mvrnorm$(1, \Sigma)$; if S=p norm(v) then $S \sim mvrnorm$, enhanced in simulations via the Mass package in R. Where Σ is the covariance matrix for spatial correlation in form frailty model

Co-ordinates for spatial correlations follow the uniform distribution. $s_1 = run\ if(N, 0,\ 40)$ and $s_2 = run\ if(N, 0, 100)$.

[21] obtained the shape and scale parameters of the Weibull distribution from the formulas below

$$\eta = \frac{1}{\Gamma(1+\frac{1}{\alpha})} \quad (9)$$

and

$$\left(\frac{\Gamma\left(1+\frac{2}{\alpha}\right)}{(\Gamma(1+\frac{1}{\alpha}))^2} - 1\right) = 0.5 \quad (10)$$

for a convenience choice of mean 1 and variance 0.5. Using the uniroot function in R. parameters were given to be approximately $\alpha = 1.435523$ and $\eta = 1.101321$. We considered studying the impact of increasing and decreasing the variance of the Weibull distribution while keeping the mean at 1. The result is displayed TABLE 1 below

Table 1: Shape and scale parameters of the Weibull distributions

E(T)	Var(T)	α	η
1	0.25	2.101377	1.129063
1	0.5	1.435523	1.101321
1	0.75	1.157975	1.052847

3.1. Model Specification to advance Simulation

Model1: $\lambda_{PI}(t; z) = f_0(t) + f(t)z_j + f_{spat}(s_{ih})$.

Model2: $\lambda_{PD}(t; z) = \{I(t \epsilon T_{\mathrm{h}}(f_{\mathrm{h}}(t))\} + f_{\mathrm{h}}(t)z_j + f_{spat}(s_{ih})$.

where λ_{PI} is the hazard function when Partitioning is Ignored (PI) or Single Parametric model (SPM). Where λ_{PD} is the hazard function when Partitioning is done (PD) or Piece wise Parametric model (PPM). Simulations and analysis were carried out in R using the coda package for spBayesSurv, version 3.6.2. Comparisons were done using Deviance Information Criterion (DIC) (smaller is better) which places emphasis on the relative quality of model fitting and log pseudo marginal likelihood (LPML) (larger is better) focuses on the predictive performance. Both criteria are readily computed from the MCMC output.

$DIC = \overline{D}(\theta) + pD.$ (11)

3.2 Results and Interpretation of Simulation Study

Table 2: DIC and LPML of $\beta(t)$ by three (3) levels of Weibull baseline hazard and level of censoring for all sample sizes and β=0.5$\sqrt{t}$ executed for models I and II.

n=100

Weibull baseline with low variance of 0.25									
Partitioning is ignored (PI)				PPM (PD)		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.083	900.3891	-450.8276	878.2437	-444.161	2.1120	-1.6191	-2.8592	-29.978
25%	0.9342	671.157	-336.9246	664.8024	-334.399	0.8049	-0.0379	0.8172	-9.0184
50%	1.062	503.4064	-252.7583	500.7776	-251.824	0.7330	0.6288	1.1786	-88.591
75%	1.147	284.3667	-143.1534	287.7841	-148.394	0.4906	1.0942	2.4062	-14.162
Weibull baseline with intermediate variance of 0.5									
PI				PD		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.388	1008.247	-504.8157	986.830	-494.999	2.4477	-1.3555	-2.7600	-3.4787
25%	1.305	732.8461	-367.927	725.413	-364.1833	1.2463	-0.2178	0.5533	-91.743
50%	1.296	540.0572	-271.5071	538.297	-270.9676	0.9155	0.5045	1.6572	-107.66
75%	1.665	296.9573	-149.734	287.729	-145.1475	0.4918	0.4660	10.515	5.8117
Weibull baseline with high variance of 0.75									
PI				PD		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.598	1078.553	-540.2496	1065.927	-536.175	2.3533	-1.1581	-2.5135	-8.2776
25%	1.542	772.0216	-387.4007	755.6687	-381.620	1.6048	-0.4414	1.4104	1.2518
50%	1.432	570.3035	-286.657	570.6291	-289.261	1.0935	-0.1834	2.9965	2.1824
75%	1.586	311.8024	-157.3363	210.647	-105.213	1.1233	1.13243	2.8323	2.3014

n=500

Weibull baseline with low variance of 0.25									
Partitioning is ignored				Partitioning is done		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	0.7422	4033.102	-2017.044	4020.982	-2011.72	0.8626	-0.5374	-0.1370	-2.0944
25%	0.99	3278.719	-1639.99	3269.356	-1636.23	1.0717	-0.0804	-0.6797	0.9899
50%	1.113	2364.521	-1182.72	2369.647	-1186.77	1.2679	-0.1969	0.30105	-0.6474
75%	1.201	1243.873	-622.8476	1248.3	-625.933	0.9743	0.2131	0.1425	1.2370
Weibull baseline with intermediate variance of 0.5									
PI				PD		Parameter Estimates for PEM			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.061	4686.231	-2343.574	4664.45	-2333.295	1.2189	-0.7703	0.7253	-2.9976
25%	1.35	2519.796	-1260.203	2518.78	-1261.124	1.6592	-0.5801	-1.2489	0.06127
50%	1.297	2638.277	-1319.477	2624.79	-1313.904	1.5359	-0.6076	-0.8941	3.3212
75%	1.397	1364.274	-682.8361	1349.48	-676.838	1.4953	-0.3659	-0.9157	15.9160
Weibull baseline with high variance of 0.75									
PI				PD		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.314	5117.817	-2559.707	5109.984	-2556.26	1.7013	-0.7955	-1.1526	-0.5874

25%	1.398	3898.273	-1949.766	3869.554	-1935.94	1.5475	-0.3632	-0.8892	4.3118
50%	1.544	2651.088	-1326.259	2645.09	-1323.97	1.9363	-1.0053	-1.0276	0.3476
75%	1.739	1390.576	-696.2893	1385.082	-694.934	1.8493	-1.1994	1.0844	1.8478

n=1000

Weibull baseline with low variance of 0.25									
Partitioning is ignored				Partitioning is done		Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	0.825	9506.566	-4754.146	9466.548	-4734.02	1.1574	-0.6495	-0.7254	-1.396
25%	0.7595	6310.06	-3155.877	6306.177	-3154.69	0.8024	-0.2136	-0.1869	2.0150
50%	0.8459	4573.932	-2287.615	4570.375	-2286.98	1.0371	-0.4995	-0.6433	2.5102
75%	0.9339	2461.439	-1231.467	2472.358	-1238.24	1.2121	-0.6227	-0.2574	-0.8896
Weibull baseline with intermediate variance of 0.5									
PI				PD		PM Parameter Estimates			
No censoring	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.123	10820.7	-5411.503	10776.3	-5389.516	1.4273	-0.8297	0.9314	-0.6932
25%	0.9805	7083.88	-3542.516	7086.044	-3544.98	1.0542	-0.3835	-0.2667	1.65377
50%	1.101	4991.19	-2495.927	4998.826	-2501.537	1.1879	-0.2026	-0.8005	0.24082
75%	1.26	2616.16	-1308.904	2619.639	-1312.382	1.5240	-0.6691	-0.3263	-0.7864
Weibull baseline with high variance of 0.75									
				PM		Parameter Estimates			
0%	$\hat{\beta}$	DIC	LPML	DIC	LPML	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$	$\hat{\beta}_4$
	1.359	11679.5	-5841.049	11615.29	-5808.81	1.487	6.407e-01	7.365e-01	2.760e+04
25%	1.212	7489.133	-3744.906	7432.219	-3789.62	1.2854	-0.3711	0.11473	0.8471
50%	1.317	5213.994	-2607.245	5204.697	-2603.91	1.4699	-0.3473	-0.6845	-0.6357
75%	1.593	2647.961	-1324.38	2632.603	-1327.79	1.8139	-0.5563	-0.6096	0.3036

4. Discussion of Results

Table 2 present the mean posterior estimates, DIC and LPML across all sample sizes and censoring percentages for single models and for the modified Piece wise models in the presence of the functional form of Time changing covariate, we observed that the values of estimates when models were fitted with data partitioning having observed the graph of beta against time for appropriate cut points are different (not constant), which indicate a change of effect parameters over time. We observed that the PPMs perform better than the single models throughout the simulations, for all censoring percentages and sample sizes. When variance parameters for the Weibull baseline hazard were examined for low at 0.25, moderate or intermediate at 0.5 & high at 0.75, estimates became worse with increase in variance and sample sizes, reflective in high DIC values and weak predictive power. In all of these, the Piece wise models out-performed the single ones; we again, noticed that the mean posterior estimates were better with increase in censoring percentages.

5. Conclusion

In all simulations considered, increase in sample sizes in non-proportional hazard may not necessarily improve precision as is the case in most statistical applications, where DIC values were seen to be higher with increase in sample sizes. Increase with regards to peusdo-subjects (PPM) within the block of each of the sample sizes, and across the censoring percentages for the models improves precision and predictive power. Again we see that with large samples, estimate are best when PPM were fitted and censoring percentages high, notably at 75%, which further suggest that a reduced event times within bits of interval enhances our model. This is practically reasonable as subjects in clinical trials should improve precision in bit of intervals where hazards are seen to be constant through time. It is observed that the mean posterior estimates when the PPM - Model II was fitted, indicates change in effect parameters over time in all four intervals, with DIC and LPML values suggesting that PPM performs better than the Single model, for all censoring percentages & sample sizes. When the Weibull baseline hazard were examined for the three (3) levels considered, the mean posterior estimates became worse as the baseline distribution gain spread, reflective in high DIC values and weak predictive power. In all of these, the PPM out-performed the SPM; it was also noticed that the mean posterior estimates were better with increase in censoring percentages.

6. Recommendations

The Weibull baseline hazard applications is found adequate hence should adopted in modelling function of survival analysis data. The researcher recommends that: other life distributions should be assumed as baseline to study the behavior of the models and combinations of baseline distributions should be used to study competing risk problems.

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