Regression Models for Censored Data: When it's NOT a good idea to use PH, AFT and other such models?

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Outline

This is a joint work with **Dr. Muhtarjan Osman** at Amgen

- Why/When are PHs, POs & AFT models not adequate?
- Conditional Models for Censored Data
- Theoretical Properties
- Numerical Illustrations
- Concluding Remarks

Why/When PHs, POs & AFTs are not adequate?

- Consider a gastric cancer study [Stablein et al. (1981)]
- A total of $n = 90$ patients with locally advanced gastric carcinoma were randomized to two treatment groups:
  - one group ($z = 0$) received only chemotherapy (45 patients); and
  - another group ($z = 1$) received radiotherapy together with the same chemotherapy
- The study was followed over eight years
- Is there a difference between the two treatments?
- Can we analyze these using one of the popular models: proportional hazards (PHs), proportional odds (POs) or accelerated failure time (AFT) models?

- Let $z = 0$ denote chemotherapy group and $z = 1$ denote the radiotherapy together with chemotherapy group
- Let $T =$ time to cancer remission since study entry
- Let $S_0(t) = \Pr[T > t|z = 0]$ and $S_1(t) = \Pr[T > t|z = 1]$ denote survival functions from chemo and chemp+radio therapy groups, respectively
- The goal is to find if $S_0(t)$ is 'different' from $S_1(t)$ using a suitable metric (e.g. $D(a, b) = \int_a^b |S_0(t) - S_1(t)|dt$ for some $[a, b] \subseteq (0, \infty)$)
- Suppose the study is censored at a time C and we observe only censored time $Y = \min(T, C)$ and its censoring indicator $\Delta = \mathbb{I}(T \leq C)$
- Thus, for each subject $i = 1, 2, \ldots, n$, we observe the triplet (Y_i, Δ_i, z_i) where $Y_i = \min(T_i, C_i)$ and $\Delta_i = \mathbb{I}(T_i \leq C_i)$
- Assume $(T_i, C_i, Z_i) \overset{iid}{\sim} (T, C, Z)$ for $i = 1, \ldots, n$ where $T \perp C|Z$

- How do we model the conditional survival function $S(t|z)$?

- Three popular models are based on conditional hazard function $h(t|z) = \frac{\partial}{\partial t}(-\log S(t|z))$. Let $h_j(t) = h(t|z = j)$ for $j = 0, 1$

  (i) Proportional hazards (PH): $h_1(t) = \eta h_0(t)$ for some $\eta > 0$
  Equivalently, $S_1(t) = S_0(t)^\eta$

  (ii) Accelerated Failure Time (AFT): $h_1(t) = \eta h_0(\eta t)$ for some $\eta > 0$
  Equivalently, $S_1(t) = S_0(t\eta)$

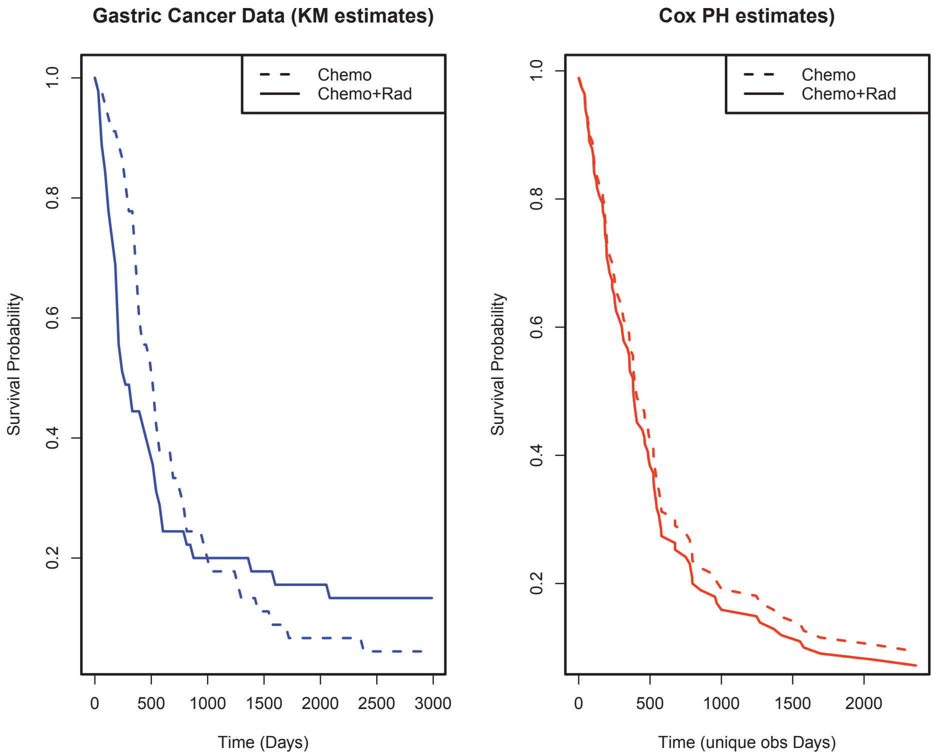
  (iii) Proprtional Odds (PO): $\frac{1-S_1(t)}{S_1(t)} = \eta \frac{1-S_0(t)}{S_0(t)}$ for some $\eta > 0$

- There are only two possibilities for any of these three models:

  (a) If $\eta > 1$, then $S_1(t) < S_0(t)$ for all $t > 0$

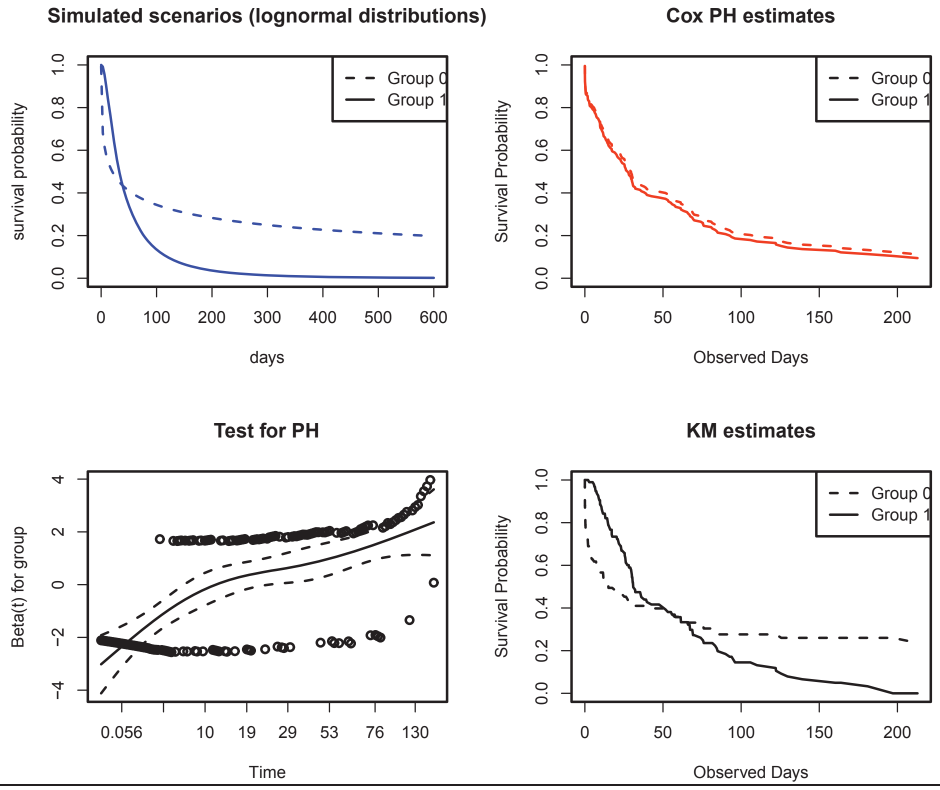
  (b) If $\eta < 1$, then $S_1(t) > S_0(t)$ for all $t > 0$

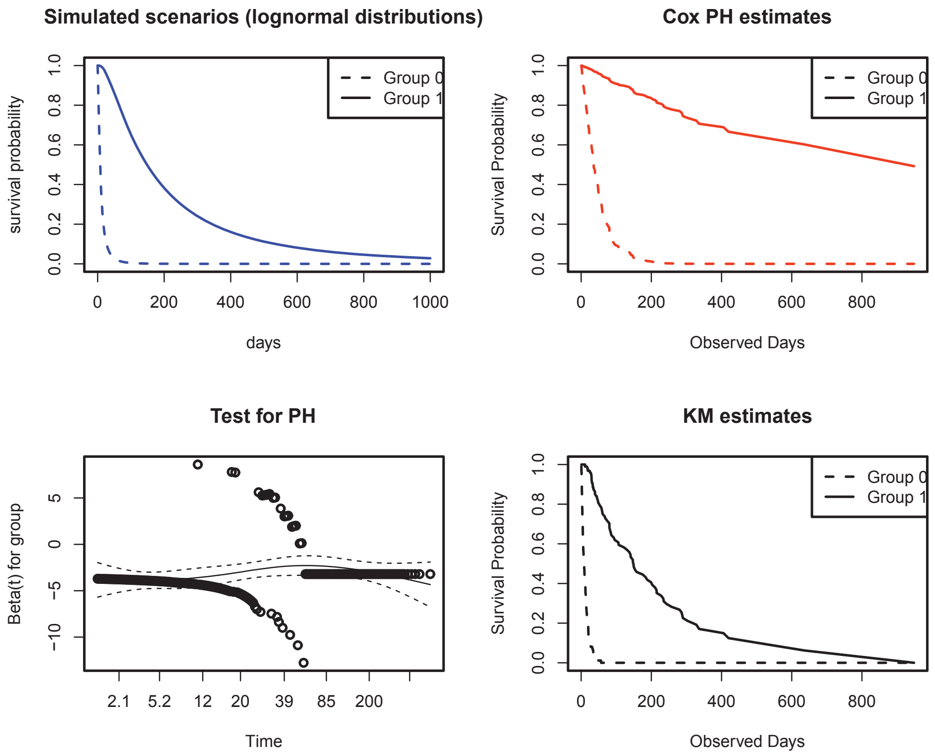
- Thus, **any of these three models will NOT allow the possibility of crossing survival functions**, i.e., $\nexists\, t_0 > 0$ such that $S_1(t_0) = S_0(t_0)$



Consider the following simulated scenarios:

- Suppose $T|Z = z \sim LogNorm(\mu_z, \sigma_z)$ where $z \in \{0, 1\}$
- Suppose $C \sim Exp(\lambda)$ with mean $1/\lambda$
- We observe $Y = \min(T, C)$ for $z \in \{0, 1\}$ and $\Delta = \mathbb{I}(T \leq C)$
- Observed data: $\{(Y_i, \Delta_i, Z_i)\}$ for $i = 1, \ldots, n$
- Obtain estimates of the survival functions: $S(t|z)$ for $z = 0, 1$
  (i) Using Kaplan-Meier estimates separately for each group
  (ii) Assuming proportional hazard: $S(t|z = 1) = S(t|z = 0)^\eta$ for some $\eta > 0$
- Consider two scenarios with $\lambda = 1/400$ and $n = 100$:
  - Case 1: $\mu_0 = 3, \sigma_0 = 4, \mu_1 = 3.5, \sigma_1 = 1$
  - Case 2: $\mu_0 = 2, \sigma_0 = 1, \mu_1 = 5, \sigma_1 = 1$ (AFT with $\eta = e^{-3}$)





Simulated scenarios (lognormal distributions)

Cox PH estimates

Test for PH

KM estimates

```
#Case 1:
mu0=3; sigma0=4; mu1=3.5; sigma1=1
#Case 2:
#mu0=2; sigma0=1; mu1=5; sigma1=1
S0=function(t){
pnorm(log(t),mean=mu0,sd=sigma0,lower.tail=F)
              }
S1=function(t){
pnorm(log(t),mean=mu1,sd=sigma1,lower.tail=F)
              }
#Plot true survival functions:
par(mfrow=c(2,2),lwd=2)
title1="Simulated scenarios (lognormal distributions)"
days=seq(0.001,1000,l=200)
plot(days, S1(days), type="l", col="blue", ylab="survival probability",
ylim=c(0, 1), main=title1)
lines(days, S0(days), lty=2, col="blue")
legend("topright", legend = c("Group 0", "Group 1"), lty = c(2,1))
```

```
#Generate samples and fit KM & PH curves:
n=100 #number of observation in each group
T0=exp(rnorm(n,mean=mu0,sd=sigma0))
T1=exp(rnorm(n,mean=mu1,sd=sigma1))
T=c(T0,T1); Cen=rexp(2*n,rate=1/400)
Y=pmin(T,Cen); Delta=as.numeric(T<=Cen)
group=c(rep(0,n),rep(1,n))

library(survival)
fit.ph=coxph(Surv(Y,Delta)~group)
summary(fit.ph); eta.hat=exp(as.numeric(fit.ph$coef))
details.ph=coxph.detail(fit.ph)
obs.days=details.ph$time
S0.PH<-exp(-cumsum(details.ph$hazard)); S1.PH<-S0.PH^eta.hat

title2="Cox PH estimates"
plot(obs.days,S0.PH,type="l",lty=2,main=title2,ylab="Survival Probability",
lines(obs.days,S1.PH,lty=1,col=’red’)
legend("topright", legend = c("Group 0", "Group 1"), lty = c(2, 1))
```

```
#Perform test for PH assumption
test.ph<-cox.zph(fit.ph)
print(test.ph)
title3="Test for PH"
plot(test.ph, main=title3)

#Obtain KM estmates
library(splines)
fit.km=summary(survfit(Surv(Y,Delta)~group),times=obs.days,extend=TRUE)
m=length(obs.days)
S0.KM=fit.km$surv[1:m]
S1.KM=fit.km$surv[(m+1):(2*m)]

title4="KM estimates"
plot(obs.days,S0.KM,type="l",lty=2,main=title4,
ylab="Survival Probability",xlab="Observed Days", ylim=c(0,1))
lines(obs.days,S1.KM,lty=1)
legend("topright", legend = c("Group 0", "Group 1"), lty = c(2, 1))
```

Consider a more general set-up with vector valued covariate Z

- T: survival time for a patient with baseline covariate (vector) Z
- C: censoring time (typically independent of T) given Z
- $Y = \min(T, C)$: Observed survival time
- $\Delta = I(T \leq C)$: Observed censoring indicator
- Observe data: $\{(Y_i, \Delta_i, Z_i),\ i = 1, \ldots, n\}$
- Our goal is to estimate the conditional survival function: $S(t|z) = \Pr[T > t|Z = z]$ based on the observed data
- A reasonable assumption is that $(T_i, C_i, Z_i) \overset{iid}{\sim} (T, C, Z)$ where we further assume that $T \perp C \mid Z$
- Often further simplifying assumptions are made to estimate $S(t|z)$ or equivalently conditional hazard function $h(t|z) = \frac{\partial}{\partial t}(-\log S(t|z))$

- Three of the most popular models:
  (i) Proportional Hazard (PH) model: $h(t|z) = h_0(t)\eta(z^\intercal\beta)$ or equivalently $S(t|z) = S_0(t)^{\eta(z^\intercal\beta)}$ for some baseline survival function $S_0(t)$
  (ii) Accelerated Failure Time (AFT) model: $S(t|z) = S_0(t\eta(z^\intercal\beta))$
  (iii) Proportional Odds (PO) model: $\frac{1-S(t|z)}{S(t|z)} = \eta(z^\intercal\beta)\frac{1-S_0(t)}{S_0(t)}$
  where $\eta(\cdot)$ is non-negative increasing function with $\eta(0) = 1$ (e.g., $\eta(u) = e^u$)
- Notice that in the simplest case with $z \in \{0, 1\}$:
  (i) PH: $S_1(t) = S_0(t)^\eta$ (ii) AFT: $S_1(t) = S_0(t\eta)$ (iii) PO: $\frac{1-S_1(t)}{S_1(t)} = \eta\frac{1-S_0(t)}{S_0(t)}$
  where $S_1(t) = S(t|z = 1)$ and $S_0(t) = S(t|z = 0)$
  (a) None of these models allows for crossing survival functions
  (b) Even when survival functions don’t cross but if we fit a PH model to an AFT model we get biased estimates of survival functions
- Hence, there is a need to develop more flexible models for $S(t|z)$

- Many extensions are available but often such models are computationally not as efficient as the PH model
- The most popular extension is to include a time-varying effect $\beta(t)$ by replacing β within the PH model
- Most of the methodologies involving the time-varying effect may turn out to be computationally intensive
- Clearly, *the appealing feature of easy interpretation and estimation of the PH model comes from the separation of time and covariate effects*
- Once such separation (and hence interpretation and simpler estimation) is lost, why should we insist on (time-varying) PH structure at all?
- Another important extension in this line of research is referred to as HARE (Hazard Regression), where log of conditional hazard function is modeled as linear splines

Conditional Models for Censored Data

- We consider nonparametric hazard regression based on a sequence of basis functions for right-censored data: $\{(Y_i, \Delta_i, Z_i); i = 1, \ldots, n\}$
- First, we consider the one-sample right-censored data with no covariates
- Following standard practice, assume that $\tau = \inf\{t : S(t) = 0\} < \infty$
- Notice that likelihood contribution of i-th observation (Y_i, Δ_i) is $\Delta_i \log h(Y_i) - H(Y_i)$ where $H(t) = \int_0^t h(s)$ is the cumulative hazard function
- Thus, it is sufficient to model the hazard function $h(t)$
- For $m = 2, 3, \ldots$, we approximate $h(\cdot)$ by a sieve of basis functions:

$$h_m(t, \boldsymbol{\gamma}) = \sum_{k=1}^{m} \gamma_k g_{m,k}(t) = \boldsymbol{\gamma}^{\mathsf{T}} \boldsymbol{g}_m(t), \; 0 \le t < \infty, \tag{1}$$

- The pre-specified known basis functions $\boldsymbol{g}_m(t) = (g_{m,1}(t), ..., g_{m,m}(t))^\mathsf{T}$ satisfy $g_{m,k}(\cdot) \geq 0$ for $k = 1, \ldots, m$
- The coefficients $\boldsymbol{\gamma}_m = (\gamma_1, \gamma_2, ..., \gamma_m)^\mathsf{T}$ satisfy $\gamma_k \geq 0, \ \forall k, m$
- The corresponding cumulative hazard function is given by

$$H_m(t, \boldsymbol{\gamma}) = \sum_{k=1}^{m} \gamma_k G_{m,k}(t) = \boldsymbol{\gamma}^\mathsf{T} \boldsymbol{G}_m(t), \ 0 \leq t < \infty, \tag{2}$$

where $\boldsymbol{G}_m(t) = (G_{m,1}(t), ..., G_{m,m}(t))^\mathsf{T}$ with $G_{m,k}(t) = \int_0^t g_{m,k}(u)du$

- Clearly, the monotonicity of $H_m(\cdot)$ is enforced by the restriction that $\gamma_k \geq 0$ and $g_{m,k}(\cdot) \geq 0$ for $k = 1, 2, ..., m$
- Notice that both hazard and cumulative hazard functions are linear in unknown coefficient $\boldsymbol{\gamma}$, which leads to huge computational gain
- Next, we choose a sequence of basis functions that provides uniform convergence

- We use the sequence of Bernstein basis functions: $g_{m,k}(t) = \frac{m}{\tau}\binom{m-1}{k-1}(\frac{t}{\tau})^{k-1}(1-\frac{t}{\tau})^{m-k}\mathbb{I}(0 \leq t \leq \tau)$ for $m = 2, 3, \ldots$ which can be expressed as a density of $Beta(k, m-k+1)$ at t/τ
- More specifically, for any continuous hazard function $h(t)$, we can show that

$$\max_{t \in [0,\tau]} |h_m(t, \boldsymbol{\gamma}) - h(t)| \to 0 \ \text{ as } m \to \infty$$

if we choose $\gamma_k = h(\frac{k-1}{m-1}\tau)$ for $k = 1, \ldots, m$

- Notice that a legitimate hazard function besides being non-negative should also satisfy $\int_0^\infty h(t)dt = \infty$ (because $S(\infty) = 0$)
- Thus, to complete the model specification, we define

$$h_m(t, \gamma) = \sum_{k=1}^{m} \gamma_k g_{m,k}(t)\mathbb{I}(0 \leq t \leq \tau) \ + \ \frac{m}{\tau}\mathbb{I}(t \geq \tau)$$

- Thus, it follows that the log-likelihood function of $\boldsymbol{\gamma}$ can be written as

$$\begin{aligned} l(\boldsymbol{\gamma}) &= \sum_{i=1}^{n} \{\Delta_i \log(h_m(Y_i, \boldsymbol{\gamma})) - H_m(Y_i, \boldsymbol{\gamma})\} \\ &= \sum_{i=1}^{n} \{\Delta_i \log(U_i^T \boldsymbol{\gamma}) - V_i^T \boldsymbol{\gamma}\}, \qquad (3) \end{aligned}$$

where $\boldsymbol{\gamma} \in \mathcal{C}_m = [0, \infty)^m$, $U_i = \boldsymbol{g}_m(Y_i)$, and $V_i = \boldsymbol{G}_m(Y_i)$

- Notice that the existence and uniqueness of the (sieve) maximum likelihood estimator follows from strict concavity of the log-likelihood function

- Moreover, as the gradient and Hessian of the log-likelihood is available in closed forms, a modified quasi-Newton method can be easily implemented (`optim` in R)

- Next, we show that *the form of log-likelihood of no-covariate case remains essentially the same of that with covariates*

- For simplicity, consider again the two-groups case with $Z \in \{0, 1\}$

- The hazard and cumulative hazard are given by

$$\begin{aligned} h_m(t, \boldsymbol{\gamma}|Z) &= \{(1-Z)\boldsymbol{\gamma_0}^T + Z\boldsymbol{\gamma_1}^T\}\boldsymbol{g}_m(t) \text{ and} \\ H_m(t, \boldsymbol{\gamma}|Z) &= \{(1-Z)\boldsymbol{\gamma_0}^T + Z\boldsymbol{\gamma_1}^T\}\boldsymbol{G}_m(t), \qquad (4) \end{aligned}$$

where $\boldsymbol{\gamma} = (\boldsymbol{\gamma_0}^T, \boldsymbol{\gamma_1}^T)^T = (\gamma_{01}, \gamma_{02}, ..., \gamma_{0m}, \gamma_{11}, \gamma_{12}, ..., \gamma_{1m})^T$

- Accordingly, the log-likelihood function becomes

$$\begin{aligned} l(\boldsymbol{\gamma}) &= \sum_{i=1}^{n} \{\Delta_i \log(h_m(Y_i, \boldsymbol{\gamma}|Z_i)) - H_m(Y_i, \boldsymbol{\gamma}|Z_i)\} \\ &= \sum_{i=1}^{n} \{\Delta_i \log(U_i^T \boldsymbol{\gamma}) - V_i^T \boldsymbol{\gamma}\}, \qquad (5) \end{aligned}$$

where

$$U_i = \begin{bmatrix} (1 - Z_i)\boldsymbol{g}_m(X_i) \\ Z_i\boldsymbol{g}_m(X_i) \end{bmatrix} \text{ and } V_i = \begin{bmatrix} (1 - Z_i)\boldsymbol{G}_m(X_i) \\ Z_i\boldsymbol{G}_m(X_i) \end{bmatrix}.$$

- Thus, the log-likelihood function in (5) is of the same form as in the case of one-sample data with no covariates (see eq. (3))
- The model described in (4) can be regarded as modeling the discretized hazard function using 1-way ANOVA
- As a result, it can be further extended to the cases when there are multiple categorical covariates and each may have more than 2 levels
- Hence the existence and uniqueness of maximum likelihood estimate $\hat{\gamma}$ follow by the strict concavity of the log-likelihood function
- Similarly, it can be shown that the same form of the likelihood form is retained even when the covariates are continuous (see Osman & Ghosh, 2012)

Theoretical Properties

- The consistency and the rate of the convergence are obtained using the Hellinger distance as the metric of choice

$$d(\theta_1, \theta_2) = \left\{ \int (\sqrt{p_{\theta_1}} - \sqrt{p_{\theta_2}})^2 d\mu \right\}^{1/2}, \qquad (6)$$

where $\theta_j = \theta_j(\cdot)$ denote hazard functions and p_{θ_j}, the induced density ($j = 1, 2$)

- Asymptotic properties of $\hat{h}_m(\cdot)$ are established using the following boundness and smoothness of the true hazard function h_0:

(I) $\tau = \inf\{t > 0 : \int_0^t h_0(u)du = \infty\} < \infty.$

(II) $h_0(\cdot)$ *is continuous on* $[0, \tau]$ *and* $h_0(t) \geq \varepsilon$ *for all* $t \in [0, \tau]$ *for some* $\varepsilon > 0$

(III) The first derivative denoted by $h_0^{(1)}(\cdot)$, *is Holder continuous with the exponent* α_0

- Hence the parameter space is given by

$$\Theta = \{\theta(\cdot) \in C[0, \tau] : \theta(\cdot) \text{ satisfies (I)-(III)}\}. \tag{7}$$

- The parameter space Θ is approximated by smaller finite dimensional space so called the sieve given by

$$\Theta_m = \left\{ \theta_m(t) = \sum_{k=1}^{m} \gamma_k g_{m,k}(t) : \boldsymbol{\gamma} = (\gamma_1, \gamma_2, ..., \gamma_m)^T \in [0, L_\gamma]^m \right\}, \tag{8}$$

Theorem 1. *(Consistency) Suppose the conditions (I)-(II) hold and the sieve Θ_m is defined as in (8), then $\hat{h}_{m,n}(\cdot) \rightarrow_{a.s.} h_0(\cdot)$ as $m, n \rightarrow \infty$.*

Theorem 2. *(Rate of Convergence) Suppose the conditions (I)-(III) hold and the sieve Θ_m is defined as in (8), if $m = o(n^{\kappa})$ with $\kappa = \frac{2}{3+2\alpha_0}$, then $d(\hat{h}_{m,n}, h_0) = O_p(n^{-\frac{1+\alpha_0}{3+2\alpha_0}})$.*

The proofs of these two theorems are given in Osman and Ghosh (2012)

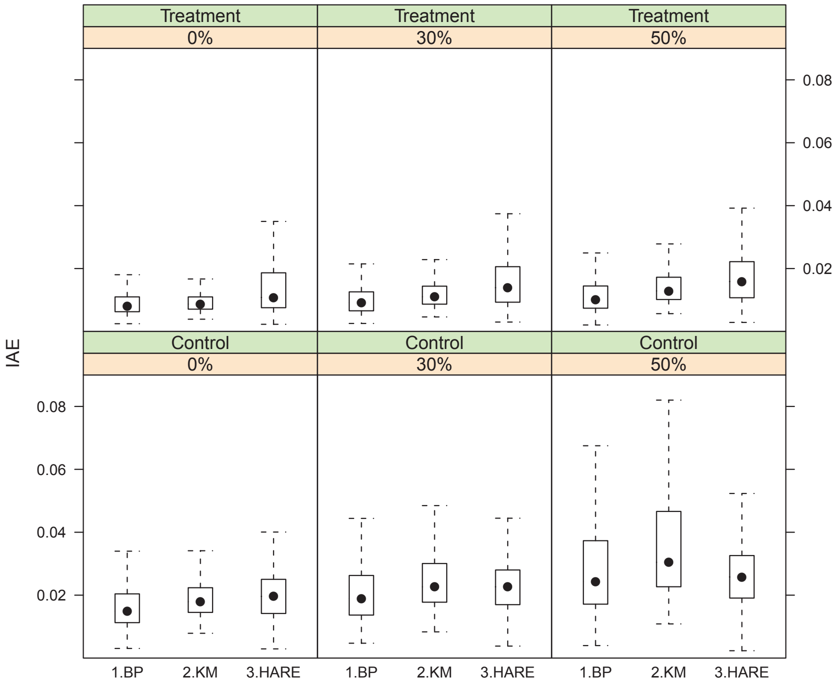
Numerical Illustrations

- We conducted several simulation studies to investigate the empirical performance of the proposed Bernstein polynomial based conditional hazard estimates
- Compared it with some popular nonparametric and semiparametric models
- We focused on the estimation of the survival function, which should give clinical practitioners more information under nonproportional hazards
- We used the integrated absolute error (IAE) defined by

$$IAE = \int_0^{\tau} |\hat{S}(t) - S_{true}(t)| dt$$

  where τ is chosen so that $S_{true}(\tau) \leq 0.001$
- Several practical scenarios were explored with varying rates of censoring
- Both categorical and continuous covariate cases were investigated

Two Group model: $T_0 \sim LN(-0.1, 0.5^2), T_1 \sim LN(0, 0.25^2), C \sim Exp(\lambda);\ \ n_0 = n_1 = 50; 1000$ MC runs



	Control			Treatment		
	0%	30%	50%	0%	30%	50%
	Median IAE $(\times 100)$					
BP	1.49	1.89	2.43	0.80	0.91	1.02
KM	1.79	2.26	3.05	0.87	1.10	1.29
HARE	1.96	2.27	2.58	1.08	1.39	1.59
	Smallest IAE Achieved					
BP	64%	61%	54%	49%	64%	72%
KM	3%	2%	2%	25%	12%	6%
HARE	33%	37%	46%	26%	24%	22%

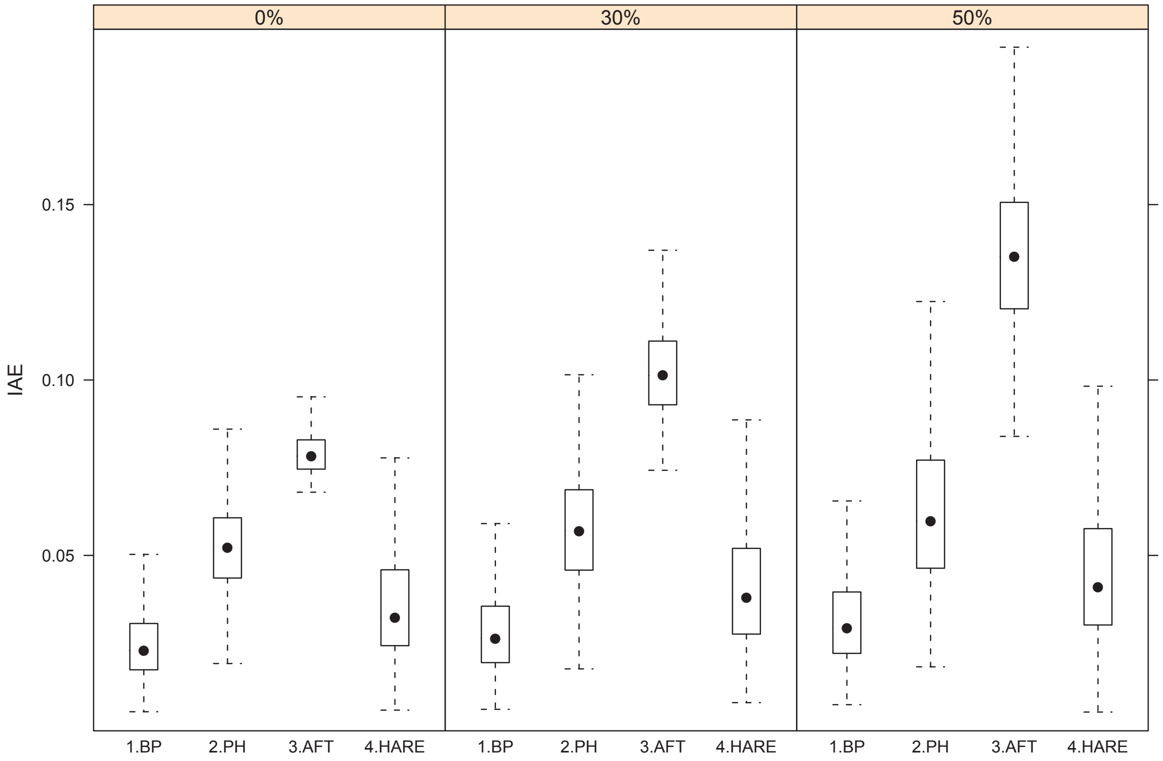
Continuous covariate case: The (T, Z) were generated by the following model:

$$\log T = \mu(Z) + \varepsilon,$$

where $\mu(Z) = \cos(\pi Z)$ and $\varepsilon|Z \sim N(0, \sigma(Z))$ with $\sigma(Z) = |Z|$ and $Z \sim U(0, 1)$

	Median IAE at $z = 0.5$ ($\times 100$)			Smallest IAE Achieved		
	0%	30%	50%	0%	30%	50%
BP	2.29	2.63	2.93	75%	76%	71%
PH	5.22	5.70	5.97	3%	6%	7%
AFT	7.83	10.13	13.51	0%	0%	0%
HARE	3.23	3.80	4.09	22%	19%	22%

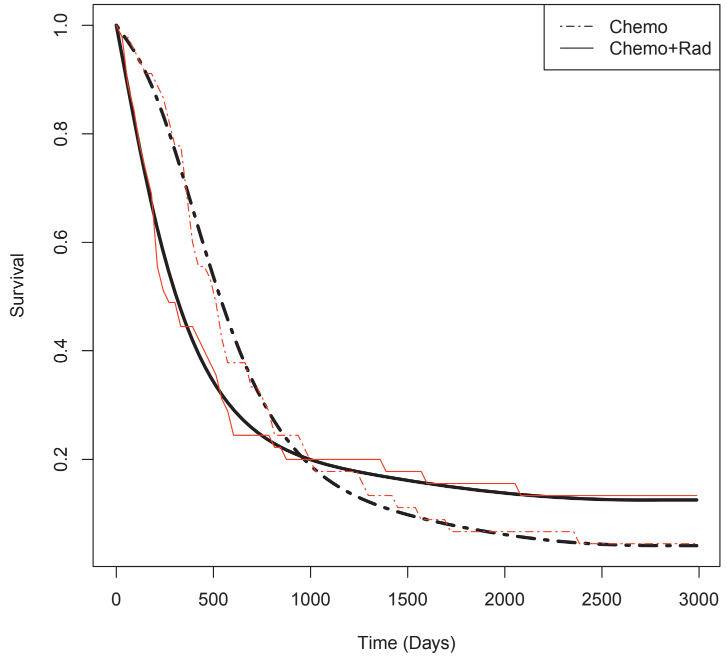
Remark: The PH and AFT models were fitted both with the mean function $\mu(Z)$ misspecified as a linear function of Z. Also, the baseline distribution of the parametric AFT model is misspecified to be exponential distribution.



Analysis of Gastric Cancer Data

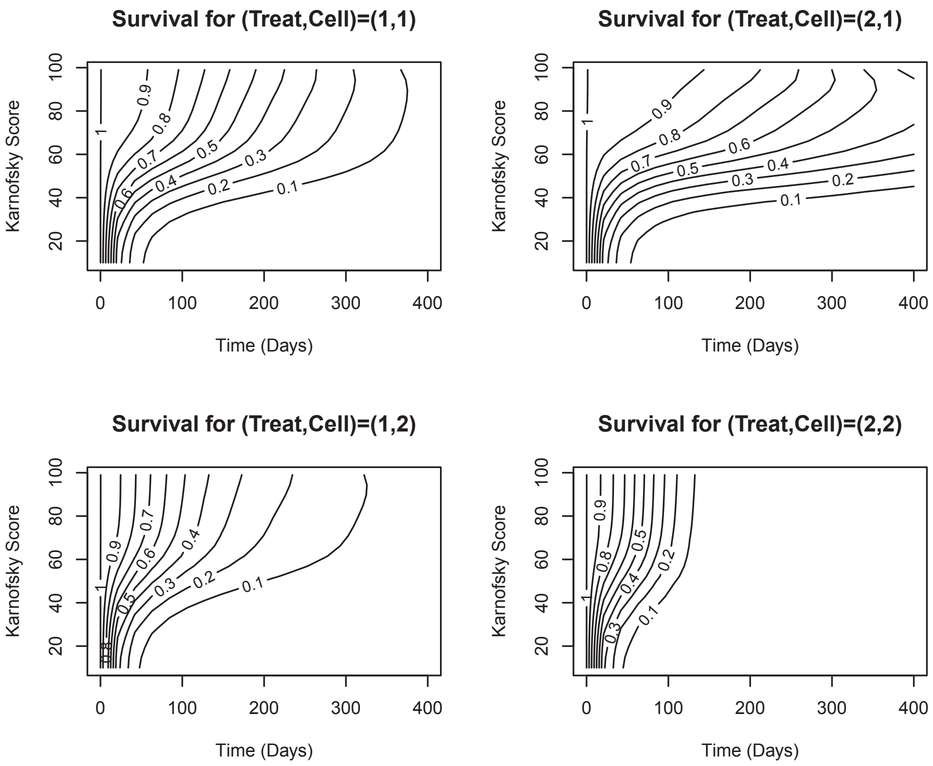
- Recall that $n = 90$ patients with locally advanced gastric carcinoma were randomized to two treatment groups (45 patients per group)
- One group only received chemotherapy while the other group received radiotherapy together with the same chemotherapy.
- As shown by the Kaplan-Meier curves, before the crossing point at approximately 1000 days the patients in the group receiving only chemotherapy had better survival rates while the benefit of combination treatment of chemotherapy and radiotherapy started to emerge at a later stage of the study
- We estimated the survival functions using the BP model with the order $m = [n^{0.5}] = 10$
- The results indicate that the estimated smooth curves cross at $t = 952$ days

Estimated smooth survival curves along with KMEs:**Gastric Cancer Data**



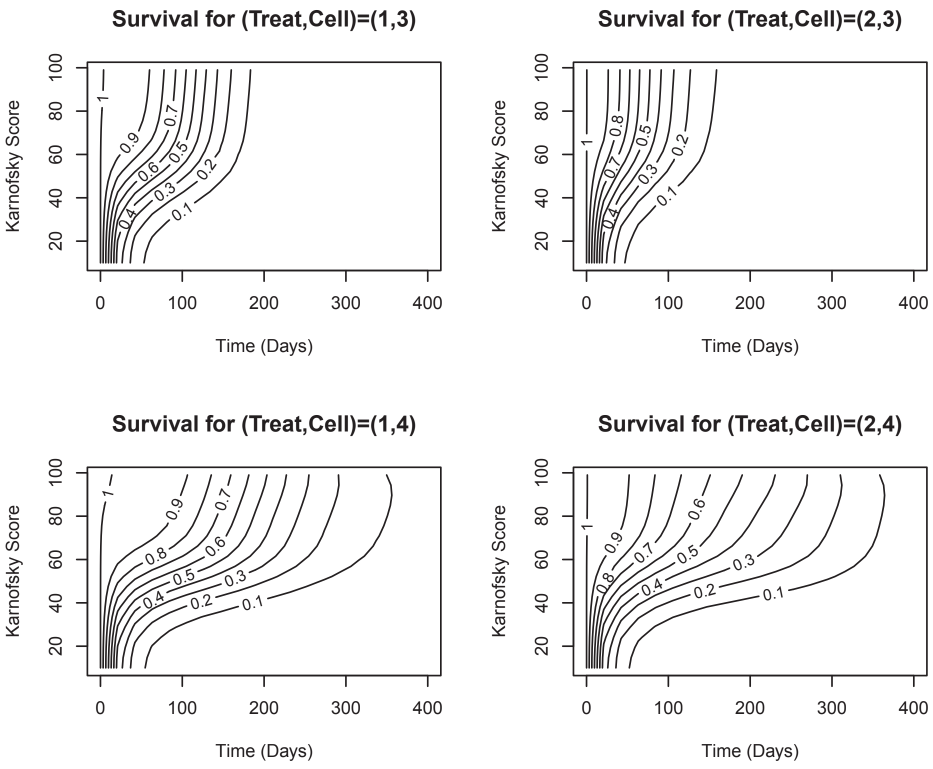
Analysis of Veterans Administration Data

- In the Veterans Administration lung cancer study $n = 137$ male patients were assigned to two treatment groups: standard chemotherapy and test chemotherapy
- In addition, 5 other baseline covariates were recorded
- Following previous works we only used Karnofsky performance score and cell type as important covariates
- Karnofsky score is a continuous variable that takes value from 0 to 100
- Cell type has fours levels: squamous cell, small cell, adenocarcinoma and large cell
- We analyzed the data using the partially linear coefficient model described at the end of section with the order $m = [n^{0.5}] = 12$



Survival for (Treat,Cell)=(1,3)
Survival for (Treat,Cell)=(2,3)

(contd.)



- Generally, patients with higher Karnofsky scores have higher survival rates
- But such association differs across treatment groups and cell types
- Overall, the patients with small cell type in the test treatment group underwent the sharpest decline in survival rates
- While the patients with squamous cell type receiving the test chemotherapy had the best survival profiles among all groups
- Among the patients with small cell type, the patients receiving the standard chemotherapy appear to have better survival rates than those receiving the test chemotherapy
- On the contrary, the patients with squamous cell type, those receiving the test treatment had better survival rates than the ones receiving the standard treatment
- For the patients with adenocarcinoma or large cell type, survival contours are similar across the treatment groups.

Concluding Remarks

- The most remarkable feature of the proposed method is that the log-likelihood, its gradient, and the Hessian matrix all take a relatively simple form
- Additionally, we show that the general simple form of the log-likelihood function holds even in the presence of categorical and continuous covariates
- Under some mild conditions, the proposed sieve maximum likelihood estimator is shown to be consistent and the corresponding rate of convergence is obtained
- The proposed method provides similar or slightly better estimates than the HARE model but the proposed method has computational stability compared to HARE
- Data driven choice of m could deserve more future studies
- Extension of the proposed model to high-dimensional covariates requires careful analysis

Questions?

Osman, M. and Ghosh, S. K. (2012). Nonparametric Regression Models for Right-censored Data using Bernstein Polynomials, Computational Statistics and Data Analysis, 56, 559-573.
Weblink: `https://doi.org/10.1016/j.csda.2011.08.019`

For R code email: sujit.ghosh@ncsu.edu