

Estimating survival from Gray's flexible model

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- V. Estimating survival from Gray's model (with examples)
- VI. Impact of misspecifying the survival model – simulation study results
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I. Introduction

- Let Y be a random variable capturing time to occurrence of a certain event of interest. The **hazard function** $h(y)$ is at time y formally defined as follows:

$$h(y) = \lim_{\Delta y \rightarrow 0} \frac{P(y \leq Y < y + \Delta y | Y \geq y)}{\Delta y}, \quad (1)$$

where $P(\cdot)$ denotes conditional probability, that an event of interest would occur immediately after time y , given it did not prior to this time.

- It follows from (1) that the hazard function may only take non-negative values.

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I. Introduction

- Let $F(Y)$ denote a cumulative distribution function of the random variable Y , i.e. $F(Y) = P(Y \leq y)$. We assume that Y is absolutely continuous with density $f(y)$. The expression (1) may be then written as:

$$\begin{aligned} h(y) &= \lim_{\Delta y \rightarrow 0} \frac{P(y \leq Y < y + \Delta y | Y \geq y)}{\Delta y} \\ &= \lim_{\Delta y \rightarrow 0} \frac{P(y \leq Y < y + \Delta y)}{P(Y \geq y)\Delta y} \\ &= \frac{1}{P(Y \geq y)} \frac{d}{dy} F(y) = \frac{f(y)}{P(Y \geq y)} \\ &= \frac{f(y)}{S(y)}, \end{aligned} \quad (2)$$

where $S(y)$ denotes the value of the **survival function** at time y .

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I. Introduction

- We define a **cumulative hazard function** $H(t)$ at time t as:

$$H(t) = \int_0^t h(y)dy \quad (3)$$

It follows from (2) that $S(\cdot)$ and $H(\cdot)$ capture equivalent information:

$$H(t) = -\ln(S(t)) \quad (4)$$

- Furthermore, it follows from (4) that we can determine the value of the **survival function** $S(t)$ at time t whenever we are able to evaluate the cumulative hazard function $H(t)$:

$$S(t) = \exp\{-H(t)\} \quad (5)$$

II. Semi-parametric survival models

- **Multiplicative models:**

- **Cox PH model:**

$$h(y|Z) = h_0(y) \cdot \exp(\beta'Z) \quad (6)$$

- **Gray's flexible model:**

$$h(y|Z) = h_0(y) \cdot \exp\{\beta(y)'Z\} \quad (7)$$

- **Additive models:**

- **Aalen's linear model:**

$$h(y|Z) = h_0(y) + \beta(y)'Z \quad (8)$$

II. Semi-parametric survival models

Note: Aalen's linear model (8) may be embedded in the class of **multiplicative models**:

- **Aalen's model:**

$$h(y|Z) = h_0(y) + \beta(y)'Z$$

$$\exp(h(y|Z)) = \exp\{h_0(y) + \beta(y)'Z\} \quad (9)$$

$$h^1(y|Z) = h_0^1(y) \cdot \exp\{\beta(y)'Z\}$$

The class of multiplicative models represented by the Cox PH and Gray's flexible model **includes the whole class of models proposed by Aalen**.

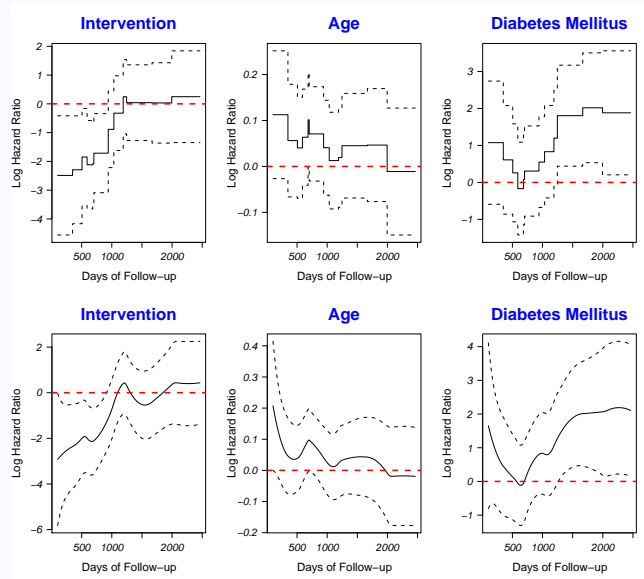
III. Gray's model introduction

- Let us recall the definition of **Gray's flexible model**: (7):

$$h(y|Z) = h_0(y) \cdot \exp\{\beta(y)'Z\}$$

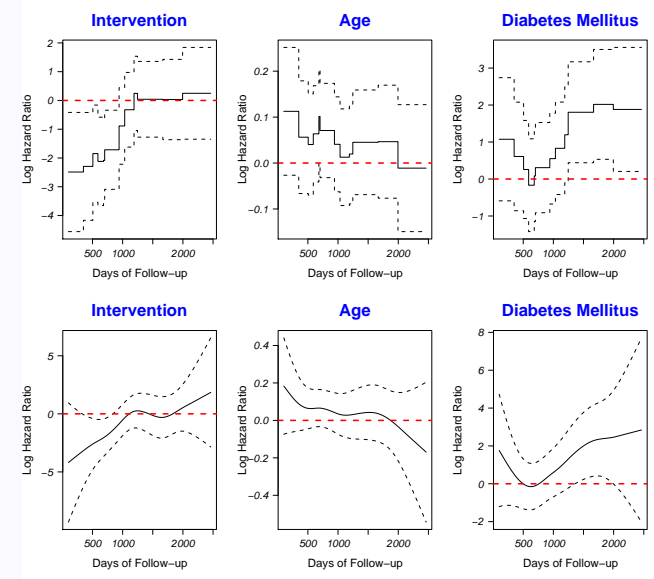
- Gray's model uses **penalized B-splines** for modelling time-varying effects $\beta(y)$. B-splines allow for flexible modelling of the covariate effects $\beta(y)$ and the hazard function over time.
- In the context of **Gray's model using piecewise-constant time-varying regression coefficients** the $\beta(y)$ remain constant for $y \in [\tau_{j-1}, \tau_j)$. We can thus write $\beta(y) = \beta_j = (\beta_{j1}, \beta_{j2}, \dots, \beta_{jp})$, where p denotes the number of model covariates and $j = 1, \dots, M+1$ indexes the intervals on time axis. Here τ_j denote the knots that allow for a change of the regression coefficients β_j .

Piecewise-constant vs. quadratic penalized splines



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Piecewise-constant vs. cubic penalized splines



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IV. Survival estimates based on semi-parametric models

- Cox PH model:

$$\begin{aligned} S(t|Z) &= \exp \left\{ - \int_0^t h_0(y) \cdot \exp(\beta'Z) dy \right\} \\ &= \exp \left\{ -H_0(t) \cdot \exp(\beta'Z) \right\} \\ &= [S_0(t)]^{\exp(\beta'Z)}, \end{aligned} \quad (10)$$

where $S_0(t)$ represents **baseline survival function estimate** at time t .

IV. Survival estimates based on semi-parametric models

- Aalen's linear model:

$$h(y|Z) = h_0(y) + \beta(y)'Z \quad (11)$$

$$h(y|Z) = \tilde{\beta}(y)' \tilde{Z},$$

while $\tilde{\beta}(y) = (h_0(y), \beta(y))$ a $\tilde{Z} = (1, Z)$.

- Survival function estimates based on Aalen's model use cumulative regression coefficients $\tilde{B}(t)$, where $\tilde{B}_i(t) = \int_0^t \tilde{\beta}_i(y) dy$. Estimating survival based on Aalen's model may then proceed as follows:

$$S(t|Z) = \exp \left\{ -\tilde{B}(t)' \tilde{Z} \right\} \quad (12)$$

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V. Estimating survival from Gray's model

- **Survival function estimate based on Gray's model^a** using piecewise-constant penalized splines may be obtained as follows:

$$S(t|Z) = \exp \left\{ - \sum_{j=1}^{M+1} H_{0j}(t) \cdot \exp(\beta'_j Z) \right\}, \quad (13)$$

where Z denotes p -dimensional vector of patient's characteristics, and

$$H_{0j}(t) = \int_{[\tau_{j-1}, \tau_j)} I(u \leq t) dH_0(u) \quad (14)$$

represents a **contribution to the cumulative baseline hazard function $H_0(t)$ on the interval $[\tau_{j-1}, \tau_j)$, $j = 1, \dots, M + 1$.**

^aValenta Z et al, Statistics in Medicine 2002.

V. Estimating survival from Gray's model

- Derivation of **confidence limits** for the survival function estimate based on Gray's model uses the **Delta method**.
- Recall **the Taylor formulae** for a function $f(X)$ of a random variable X with expectation μ :

$$f(X) = \sum_{k=0}^n \frac{f^{(k)}(\mu)}{k!} (X - \mu)^k + R_n \quad (15)$$

- **Delta method:**

$$\begin{aligned} \text{Var}(f(X)) &\approx \text{Var}[f(\mu) + f'(\mu)(X - \mu)] \\ &= [f'(\mu)]^2 \cdot \text{Var}(X) \end{aligned} \quad (16)$$

V. Estimating survival from Gray's model

- If X is a **random vector** the Delta method $G(X)$ takes the form:

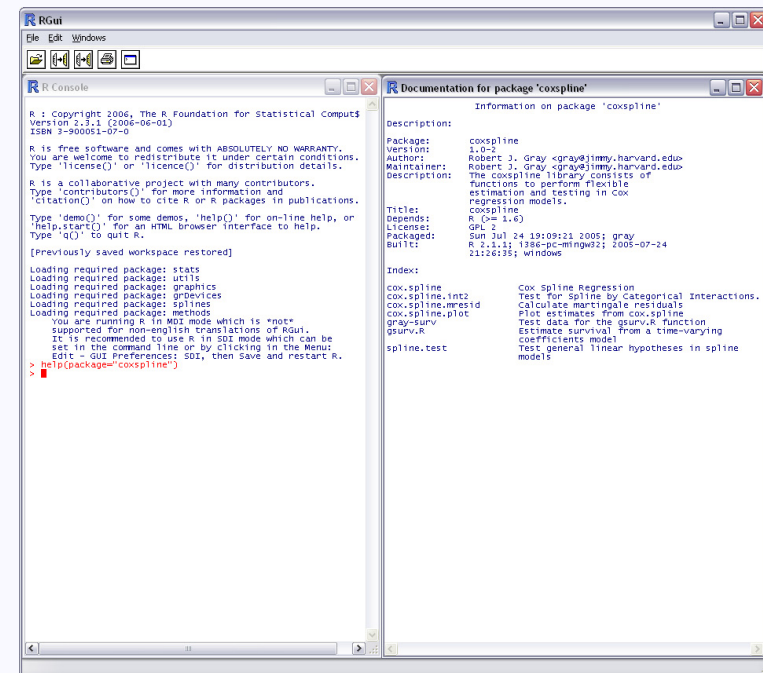
$$\text{Var}(G(X)) \approx \nabla G'(\mu) \cdot \text{Var}(X) \cdot \nabla G(\mu), \quad (17)$$

where $\nabla G(\mu)$ is a column vector of first partial derivatives of G .

- **Confidence limits estimates^a** were derived for a log- and log(- log)-transformed survival function $S(t)$ and are reported simultaneously in R.

^aValenta Z et al, Statistics in Medicine 2002.

"coxpline" package in R



"cox.spline" R-routine

```
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> help(package='cox.spline')
> cox.spline

R Help on 'cox.spline'
package:cox.spline
R Documentation
Cox Spline Regression
Description:
  Model survival data using splines and penalized partial likelihood
Usage:
  cox.spline(model.type, time, status, spline.cov, linear.cov, strata,
            df, nknot, spline.knot, smooth.opt, smooth.param,
            output.opt="tests", nest, maxIter=90, eps=0.0001, pascal=TRUE,
            ord=0, generalized, sctimes)
Arguments:
  model.type: "a" for a nested additive model, "i" for a time varying coefficient model, "ii" for a single 2 way interaction model with tensor product B-splines
  time: vector of failure times. Missing values ('NA's) are allowed.
  status: 1 if failure, 0 if censored. Missing values ('NA's) are allowed. Must have the same length as 'time'.
  spline.cov: matrix of covariates to be modeled with splines. Missing values ('NA's) are allowed. Must have the same number of rows as 'time'. If model.type="i", must have exactly 2 columns.
  linear.cov: matrix of covariates entering in model as ordinary linear term. (default is none). Missing values ('NA's) are allowed. Must have the same number of rows as 'time'.
  strata: stratification variable (numeric, character, or category). (default is all observations in one strata. Missing values ('NA's) are allowed. Must have the same length as 'time'.
  df: degrees of freedom for the spline fits. Ignored if smooth.param is specified. Default is 3 for nonlinearity (about 4 total) for each variable when model.type="a", 3 for each variable when model.type="i", and 2 for the tensor product term when model.type="ii". If length of df is not of the appropriate length (1 for "i", the number of columns in spline.cov for "a" or "ii"), a warning message is printed, and df replicated to the appropriate length.
  nknot: number of knots for spline variables (length 1 for "a" or "ii", since the same value is used for all the covariates, and length 2 for "ii").
  spline.knot: locations of knots for splines. Each set of knots must be an augmented knot sequence of length nknots, with something <= min for the first three entries, then the interior knots, then something >= the max for the last three entries. If "a", then a set of knots is needed for each column of spline.cov. If "ii", 2 sets of knots are needed, and if "ii" only one is needed. Default is for the program to choose knot locations based on equal numbers of observations between knots.
  smooth.opt: smoothing parameter option. If smooth.param is not
```

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"cox.spline" R-routine (cont.)

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Loading required package: splines
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> help(package='cox.spline')
> cox.spline

R Help on 'cox.spline'
METHODS:
  "a": uses penalized likelihood estimation to fit fixed knot cubic splines for covariates in a proportional hazards model. This fits the additive model described in Gray (1992), with penalty proportional to the integrated squared second derivative.
  "i": uses tensor product cubic B-splines to model the joint effect of spline.cov on the hazard, and estimates the parameters using penalized partial likelihood with a two variable Laplacian penalty function. Test statistics (not reliable) are calculated as described by Gray (1992).
  "ii": The coefficient of each covariate in spline.cov is modeled with spline functions of time, to allow the effect of the variable on the hazard to vary over time in a flexible fashion. The parameters are then estimated using penalized likelihood methods. The penalty function when ord=0 is proportional to the sum of squared jumps at the knot points, if ord=1 it is the integrated squared first derivative, and if ord=2 it is the integrated squared second derivative.
  Knot locations are chosen with roughly equal amounts of data (or failures, for "i") between them, if knots are not specified, which is a linear combination of chi-squares. The eigenvalues defining the linear combination are returned in the eig component. Cases with missing values in any of time, status, linear.cov, spline.cov, or strata are excluded.
Note:
  DFCT function written by Bob Gray. Send problems, comments, questions to gray@att10my.harvard.edu. Last update 11-10-11.
References:
  Gray RJ (1992) Flexible methods for analyzing survival data using splines, with applications to breast cancer prognosis. JASA, 87:942-951.
  Gray RJ (1994) Spline based tests in survival analysis. Biometrics, 50:640-652.
See Also:
  cox.spline.plot cox.spline.int2 cox.spline.mresid
Examples:
  set.seed(10)
  brca.data <- data.frame(protocol=ifelse(runif(400)<.33,"E6177","E5177"),age=sample(20:70,400,replace=TRUE),enrstatus=ifelse(runif(400)<.4,"neg","pos"),p50=ifelse(runif(400)<.15,20,400),race=TRUE,proc=c(0,1,10,1,rep(1,14)/60),time=runif(400,1,6*10),recstat=ifelse(runif(400)<.5,1,0),rectime=exp(400*(age-1))
  # fit additive model for age and time2, using enrstatus as strata:
  # splines with 45 knots penalized to 3 df for nonlinearity in each variable
  ul <- cox.spline("a",brca.data$rectime,brca.data$recstat,brca.data[,c(2,5)],strata=brca.data$enrstatus,df=c(3,3),nknot=15)
  ul$test
```

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R-function "gsurv.R"

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> help(package='cox.spline')
> cox.spline
> gsurv.R

R Help on 'gsurv.R'
package:cox.spline
R Documentation
Estimate survival from a time-varying coefficients model
Description:
  Estimate survival function and pointwise confidence limits from Gray's time-varying coefficients model using piecewise-constant penalized splines (fit using cox.spline())
Usage:
  gsurv.R(graymodel, time, cens, x, ptcovar, go, conf.level = 0.95)
Arguments:
  graymodel: object resulting from fitting the Gray's "cox.spline" routine with options model.type="a" and ord=0 (uses something piecewise-constant, penalized splines in fitting time-varying coefficients model)
  time: vector of failure times. Missing values ('NA's) are allowed.
  cens: Coded 1 for failure and 0 for censored observations. Missing values ('NA's) are allowed. Must have the same length as time.
  x: Matrix of covariates modeled with splines. Missing values ('NA's) are allowed. Must have the same length as time.
  ptcovar: vector(s) of covariate values (multiple subjects allowed)
  go: Concatenated names of model variables
  conf.level: Desired confidence level for calculating pointwise confidence bands
Details:
  ptcov: specifies new covariate values where the predicted survival curve will be estimated.
Value:
  Returns a list with components
  $g.log: matrix of survival function estimates and pointwise C.L. (on the log-scale)
  $g.llog: giving matrix of survival function estimates and pointwise C.L. (on the log(-log)-scale)
  ptcov.dat: vector(s) of patient covariate combinations used for estimating survival
  conf.level: confidence level used for calculating the pointwise bands
Note:
  Send problems, comments, questions to valenta@uromsice.cz. Last revision May 2, 2005.
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R-function "gsurv.R" (cont.)

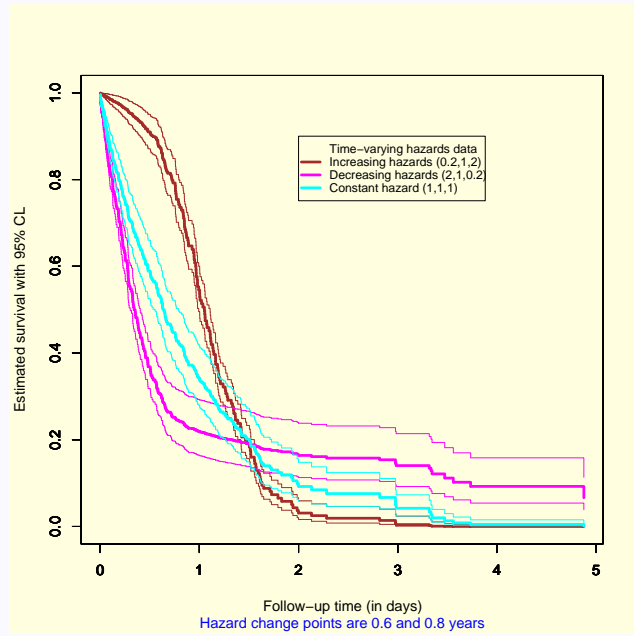
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> help(package='cox.spline')
> cox.spline
> gsurv.R

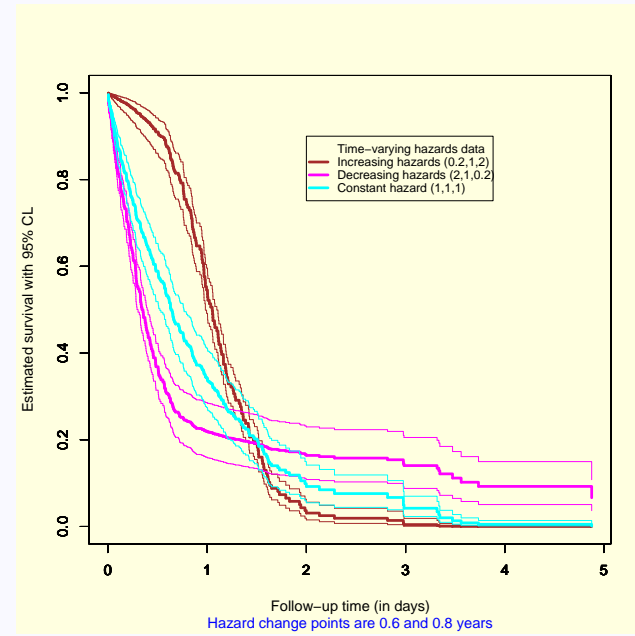
R Help on 'gsurv.R'
Author(s):
  Zdenek Valenta
References:
  Valenta Z, Weissfeld L (2002). Estimation of the survival function for Gray's piecewise-constant time-varying coefficients model. Statistics in Medicine.
See Also:
  'cox.spline'
Examples:
  ## This example uses simulated right-censored survival data from piecewise-est
  ## Not run:
  data("gray-surv") # data set installed in data subdirectory
  gm <- cox.spline("a",y,fall,spline.cov.data,df=c(4,2),nknot=10)
  gm$test
  ##$1
  # overall nonprop
  #stat 43.77577 43.31577
  #p 0.00000 0.00000
  #df 3.499048 3.007931
  ##$2
  # overall nonprop
  #stat 36.18232 35.36749
  #p 0.00000 0.00000
  #df 3.299514 3.007968
  # Estimate survival function with 95
  gsurv.res <- gsurv.R(graymodel=gm, time=c=fall, x=data, ptcovar=c(1,5)
  # overlaid plot of corresponding survival estimates with 95% CL:
  attach(gsurv.res$g.log)
  par(bg="lightyellow",col.main=4,col.sub=4,rlm=c(10,5),mfrow=c(1,1))
  plot(time,surv1,type="n",xlab="Follow-up time (in years)",ylab="Estimated $
  par(new=TRUE)
  plot(time,surv1,type="s",xlab="","ylab="","lty=1,col="brown",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,UCL1,type="s",xlab="","ylab="","lty=1,col="brown",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,UCL1,type="s",xlab="","ylab="","lty=1,col="brown",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,surv2,type="n",xlab="","ylab="","lty=1,col="magenta",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,UCL2,type="s",xlab="","ylab="","lty=1,col="magenta",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,UCL2,type="s",xlab="","ylab="","lty=1,col="magenta",ylim=c(0,1),lwd=5
  par(new=TRUE)
  plot(time,surv3,type="n",xlab="","ylab="","lty=1,col="cyan",ylim=c(0,1),lwd=5
  par(new=TRUE)
```

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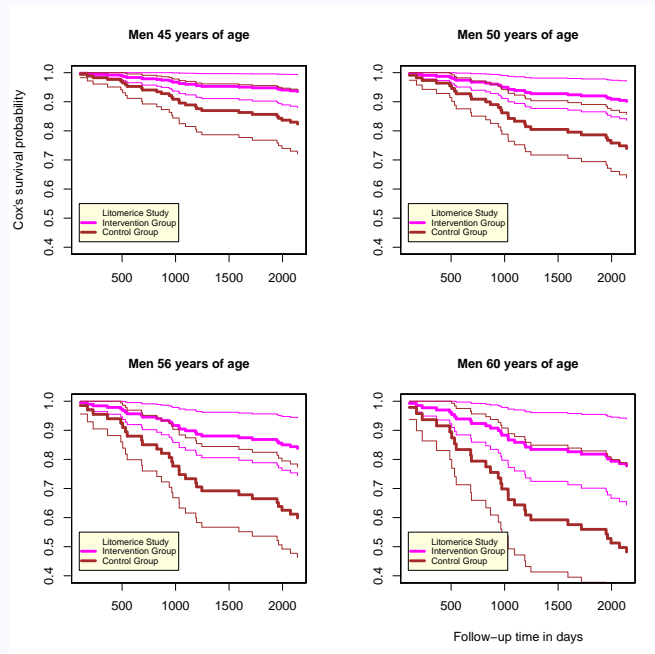
Example 1: survival estimates from Gray's model with 95% C.L. (log-transf.)



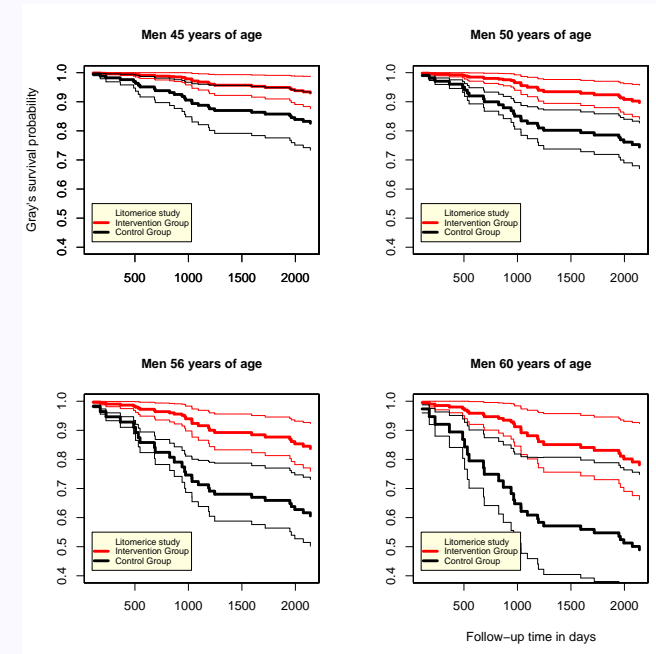
Example 1: survival estimates from Gray's model with 95% C.L. (log-log-transf.)



Example 2: Secondary prevention trial of CHD in Litomerice men after MI (Cox PH model results)



Example 2: Secondary prevention trial of CHD in Litomerice men after MI (Gray's model results)



V. Estimating survival from Gray's model

- Implementation of the “**coxpline**” package for R statistical system is available from the Dr. Gray's website (*Harvard University and Dana-Farber Cancer Institute, Boston, USA*).
- **Web address:**
<http://biowww.dfci.harvard.edu/~gray/>
- Package “**coxpline**”, version 1.0-2, implements Gray's model in R, including the survival function estimation using R-function “**gsurv.R**”.
- Current version of the “**coxpline**” package is compatible with the latest release of **R 2.3.1**. (2006-06-01):

<http://www.r-project.org/>



VI. Impact of misspecifying the survival model^a

- In three simulation studies we generated right-censored survival data that would satisfy exactly one of the semi-parametric survival models under consideration (i.e. **Aalen, Cox, Gray**).
- The data obtained were subsequently analyzed using each of the three models considered.
- The performance of each model was assessed using the **Bias** and **Mean Square Error (MSE)** of the estimated (conditional) survival distribution.

^aValenta Z et al, Model misspecification effect in univariable regression models for right-censored survival data, Proceedings of the 2002 Joint Statistical Meeting of the American Statistical Society.

VI. Impact of misspecifying the survival model

- **Bias** of the survival estimator $\hat{S}(t|Z)$:

$$\text{Bias}(\hat{S}(t|Z)) = \frac{1}{n_s} \sum_{i=1}^{n_s} \hat{S}^{(i)}(t|Z) - S(t|Z) \quad (18)$$

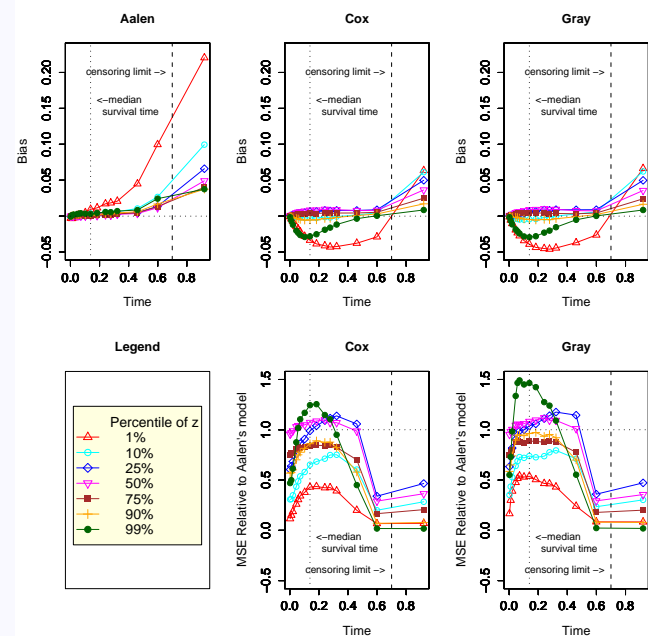
- **Mean Square Error** of the estimated survival $\hat{S}(t|Z)$:

$$\text{MSE}(\hat{S}(t|Z)) = \frac{1}{n_s} \sum_{i=1}^{n_s} (\hat{S}^{(i)}(t|Z) - S(t|Z))^2 \quad (19)$$

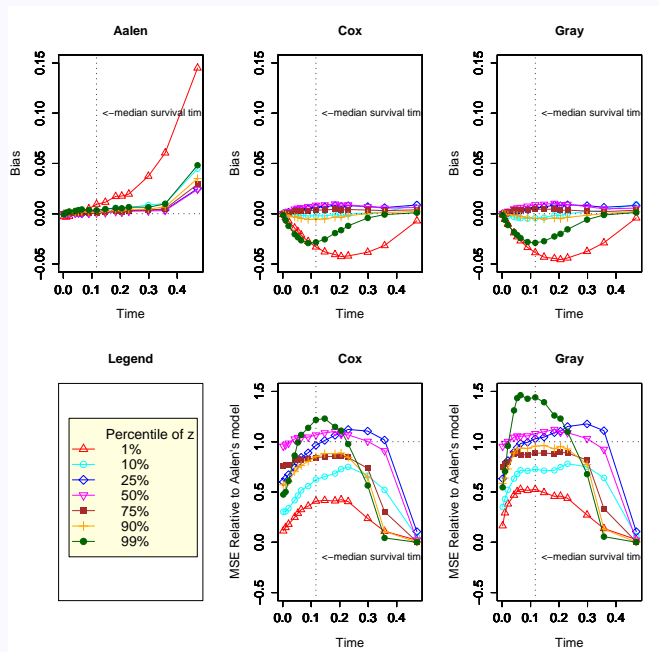
- **Bias-variance trade-off:**

$$\text{MSE}(\hat{S}(t|Z)) = \text{var}(\hat{S}) + \text{Bias}(\hat{S})^2 \quad (20)$$

Aalen's model with constant β

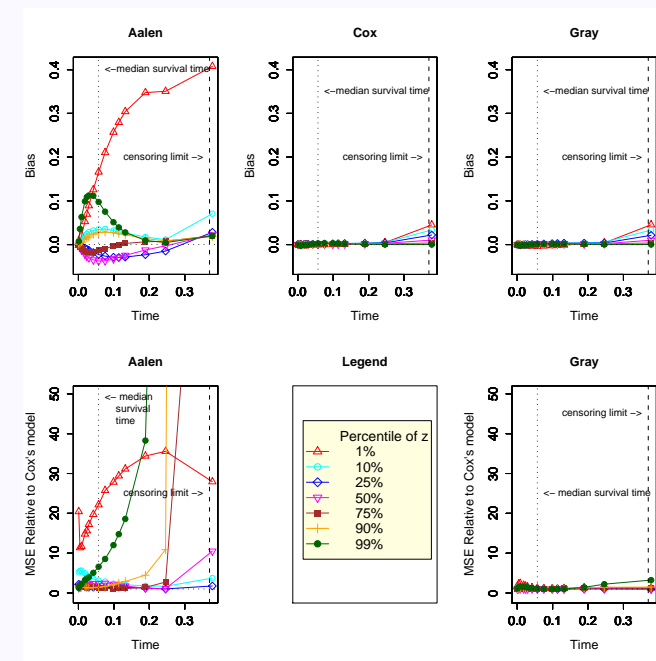


Aalen's model with time-varying $\beta(t)$



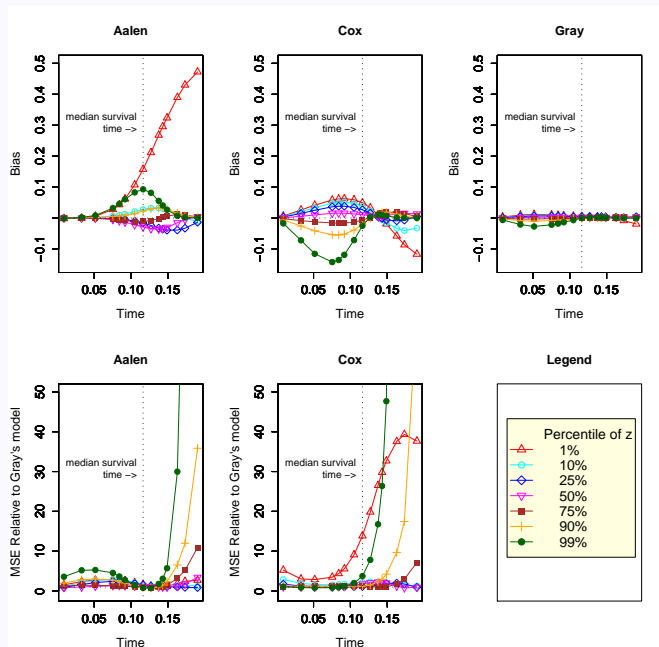
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Cox PH model



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Gray's model with time-varying $\beta(t)$



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VII. Discussion

- When the data satisfied **Aalen's linear model**, both Cox's and Gray's model rendered biased survival estimates. They have, however, often shown a lower MSE than the native model for the data at hand.
- When analyzing **Cox PH model** data using the Gray's routine, we observed no dramatic increase in bias and MSE relative to native model, while using the same criteria the survival estimates based on Aalen's model appeared to be highly distorted.
- When the data followed **Gray's model** with time-varying covariate effects, both Cox's and Aalen's model rendered in terms of bias and MSE highly unreliable estimates of the conditional survival distribution. In other words, there was no alternative to using the native model in this instance.

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References

- [1] Cox DR: **Regression Models and Life Tables (with discussion)**, *Journal of the Royal Statistical Society*, 1972, Vol. 34, pp. 187–220.
- [2] Aalen OO: **A linear regression model for the analysis of life times**, *Statistics in Medicine*, 1989, Vol. 8, pp. 907–925.
- [3] Gray RJ: **Flexible methods for analyzing survival data using splines, with application to breast cancer prognosis**, *Journal of the American Statistical Association*, 1992, Vol. 87, pp. 942–951.
- [4] Gray RJ: **Spline-based tests in survival analysis**, *Biometrics*, 1994, Vol. 50., pp. 640–652.
- [5] Valenta Z and Weissfeld LA: **Estimation of the Survival Function for Gray's Piecewise-Constant Time-Varying Coefficients Model**, *Statistics in Medicine*, 2002, Vol. 21(5), pp. 717-727.

Thank you for your attention!