Prileganje regresijskih modelov za relativno preživetje
Goodness of fit of relative survival models

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doktorsko delo

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Ljubljana, marec 2007

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The goal of relative survival regression

To estimate the effect of covariates on mortality caused by a disease even though the cause of death is unknown.

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1. Avoid assumptions about

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2. Check

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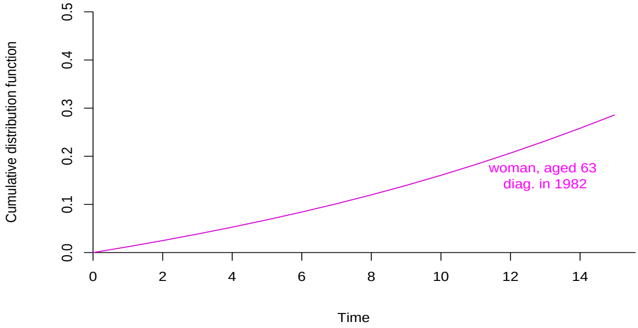
3. Develop software

for all existing and new methods

Transformation approach

published: Stare, Henderson, Pohar, JRSS C, 2005



$$F_P$$

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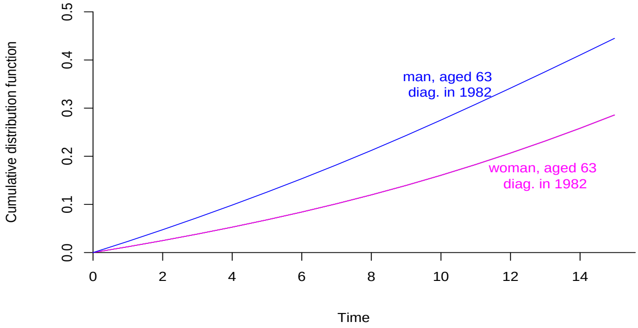

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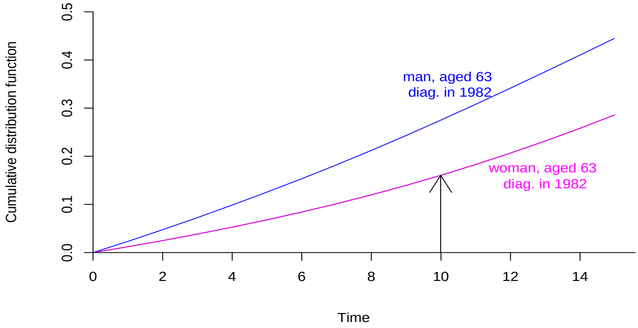

$$F_P(T)$$

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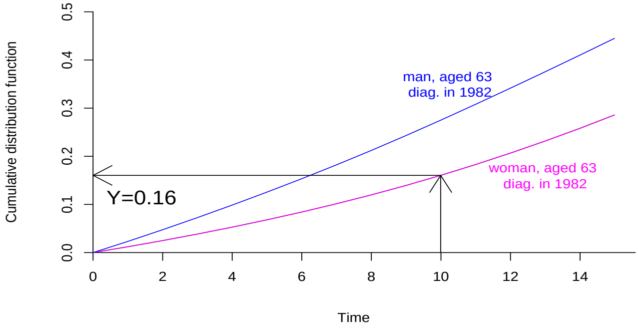

$$Y = F_P(T)$$

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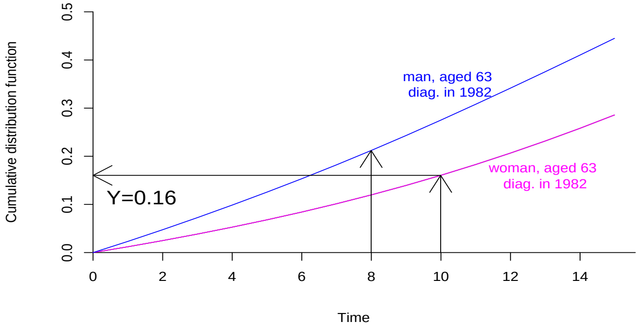

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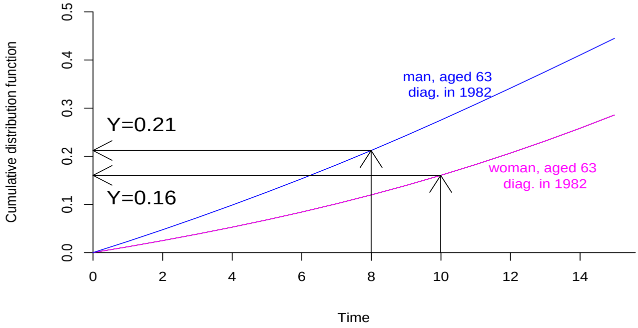

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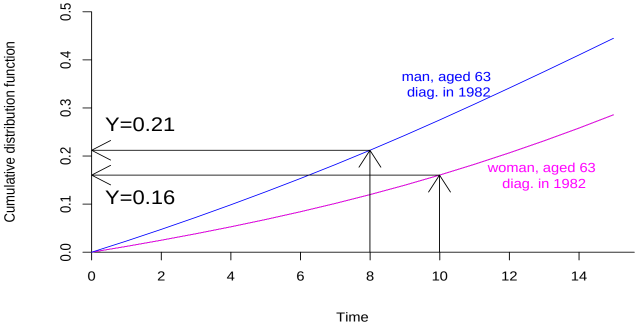


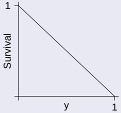
New outcome variable

$$Y = F_P(T)$$

Properties

Properties

- **New outcome variable. Censoring status and covariate values remain unchanged**
- **Any survival analysis method can be used**
- $T \sim F_P \Rightarrow Y \sim U[0, 1]$



- **Patients can live better than the population**

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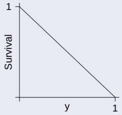


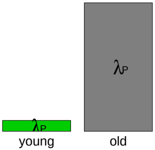
- **Patients can live better than the population**

Cox model $\lambda(y) = \lambda_0(y)e^{bx}$

- **natural choice - new time ordering**
- **the covariates not included in the population tables keep the same coefficient**

Comparison of the models - interpretation

hazard



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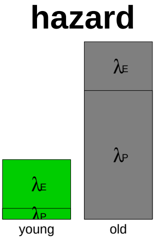

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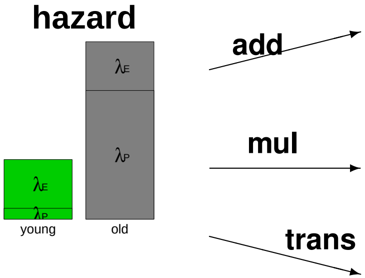

does excess hazard differ?

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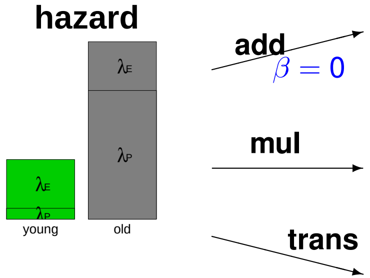

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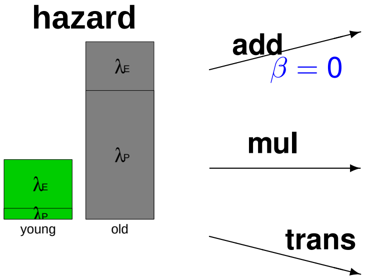

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does the observed hazard ratio differ from the population hazard ratio?

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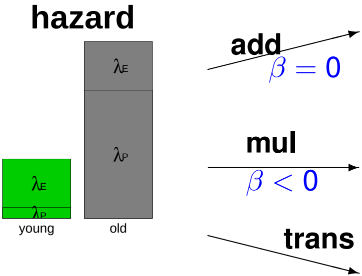

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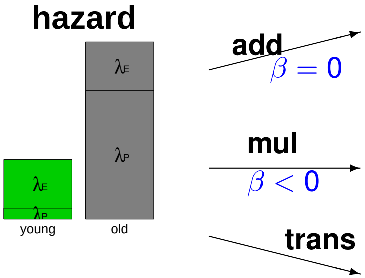

does excess hazard differ?

does the observed hazard ratio differ from the population hazard ratio?

are residual lifetimes equally affected?

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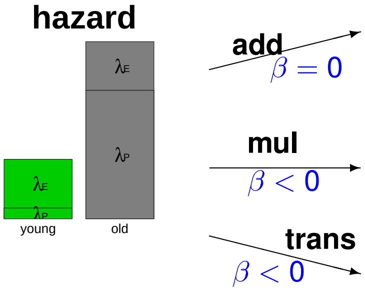

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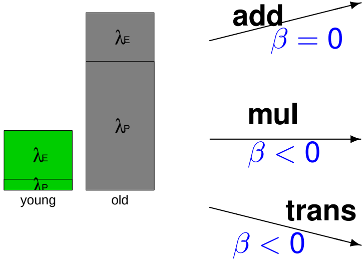
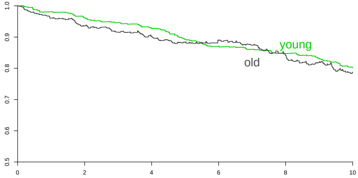


relative survival curve



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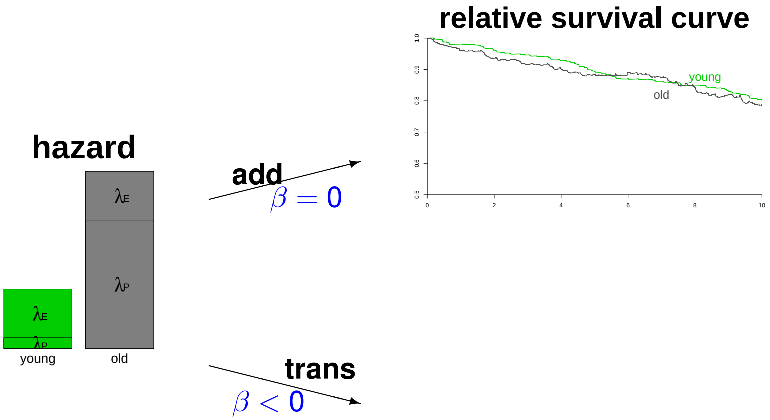

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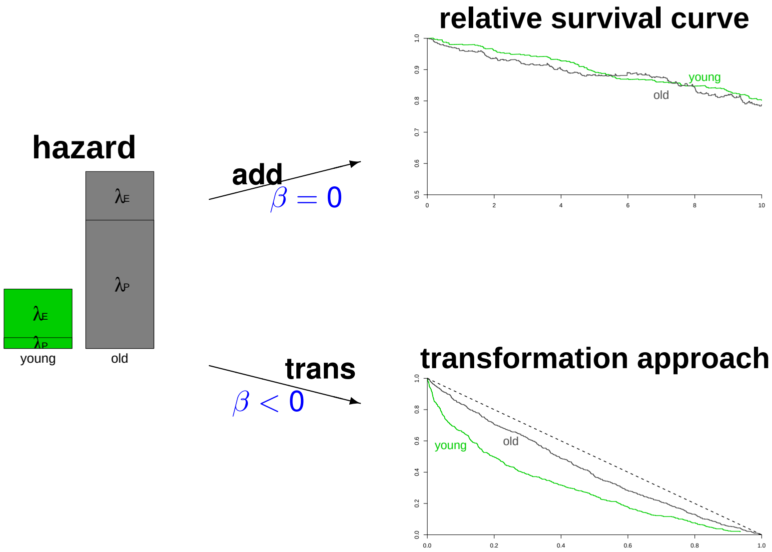

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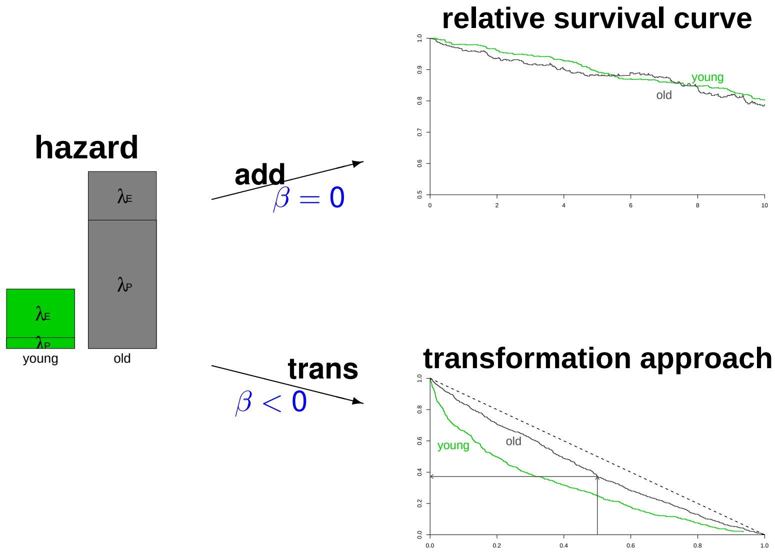

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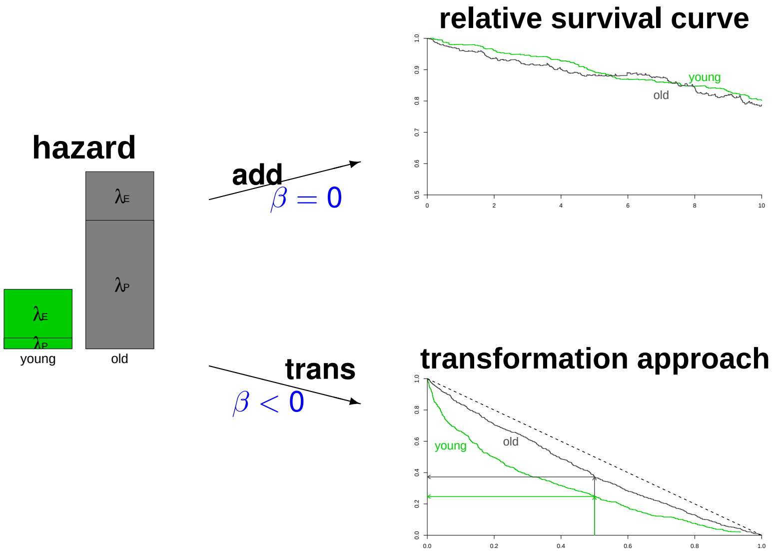

Comparison of the models

The coefficient values (for the covariates used in the population tables) estimated in different models are different and require a different interpretation

- $T \sim F_P \Rightarrow$ **results of all models are equal**
- $\nu_0 = const. \Rightarrow$ **Cox in Y=multiplicative**
- **general case $\Rightarrow$ all models different, but multiplicative and Cox in Y usually closer. The proportional hazards assumption is not met simultaneously.**

Transformation approach

- **Avoids the assumption about the relationship between the observed and population hazard**
- **Provides new information about relative survival**
- **Only the outcome variable changes - all methods from the classical survival analysis can be used**
- **Can be used when certain groups of patients live better than the population (additive model can not!)**

Checking the proportional hazards assumption

published: Stare, Pohar, Henderson; SIM 2005

The Cox model

- **The multiplicative model and the Cox model in transformed time can both be seen as special cases of the Cox model**
- **Schoenfeld residuals can be used for both graphical and formal evaluation of the PH assumption**

The additive model

- **No methods exist**
- **A new kind of residuals is introduced - the partial residuals**

Ideas to be modified for use in relative survival

		Cox	additive
Definition	$U_i = X_i - \hat{E}_i(X\|t_i)$	$X_i - \sum X_j \frac{\lambda_j}{\sum \lambda_k}$	$X_i - \sum X_j \frac{\lambda_{Pj}+\lambda_{Ej}}{\sum(\lambda_{Pk}+\lambda_{Ek})}$

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	$\#$ **covariates** > 1	**X**	**X**

The quality of Brownian bridge approximation

In theory

- **Asymptotic distribution exists**
- **Taylor series expansion:** Brownian bridge + residual
- **Residual size depends on: variance of the covariate in time**

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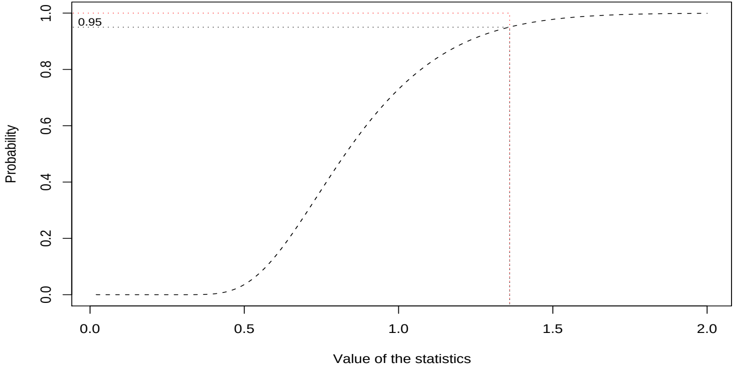
In practice

- **The proportion of tests rejecting under the null hypothesis ($\alpha = 0.05$): 0.03-0.05**
- **The test statistic can only be conservative**
- **Resampling approach (resample fom the distribution defined by the covariates and estimated coefficients)**

Speed of convergence

- Comparable to the ideal case (i.i.d. variables)
- The maximum (weighted) BB statistic: 100 (conservative otherwise)
- The Cramér - Von Mises statistic: 50
- Effective sample size depends on: censoring, baseline excess hazard

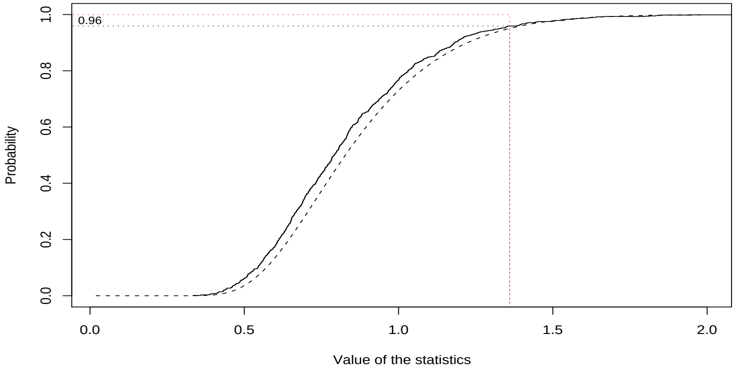
Power


0.95
Probability
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
Value of the statistics

Power

sample size ↑ ↓ $n = 250$ **rejected**$= 4.1\%$

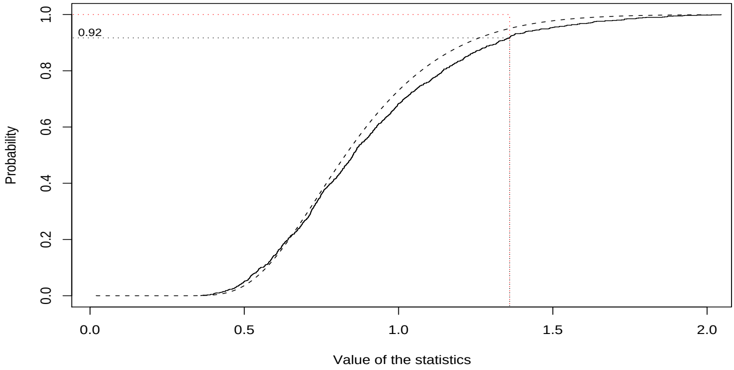
change in β ↑ ↓ $\Delta = 0$



Power

sample size ↑ ↓ $n = 250$ **rejected**$= 8.4\%$

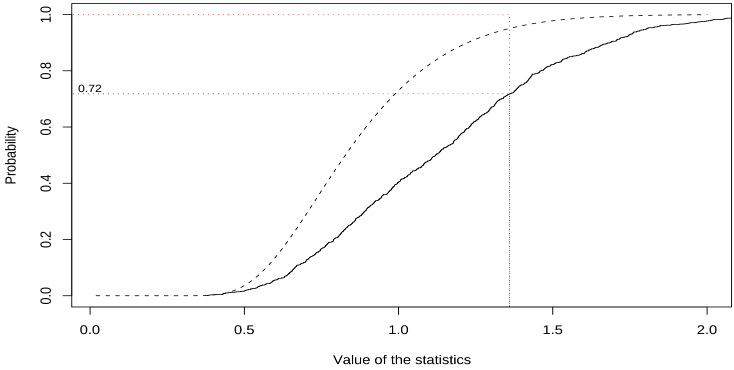
change in β ↑ ↓ $\Delta = 0.25$



Power

sample size ↑ ↓ $n = 250$ **rejected**$= 28.4\%$

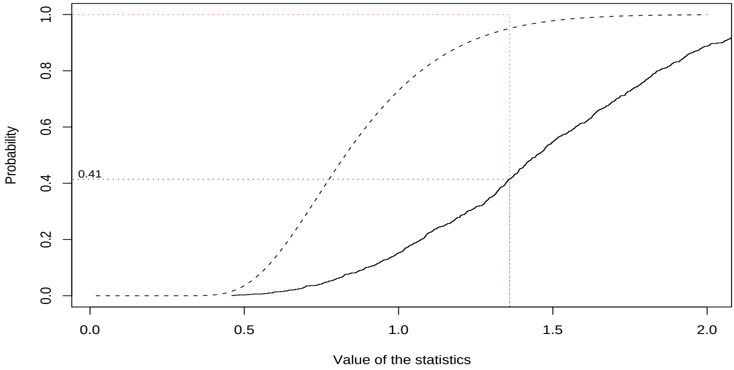
change in β ↑ ↓ $\Delta = 0.5$



Power

sample size ↑ ↓ $n = 250$ **rejected**$= 58.7\%$

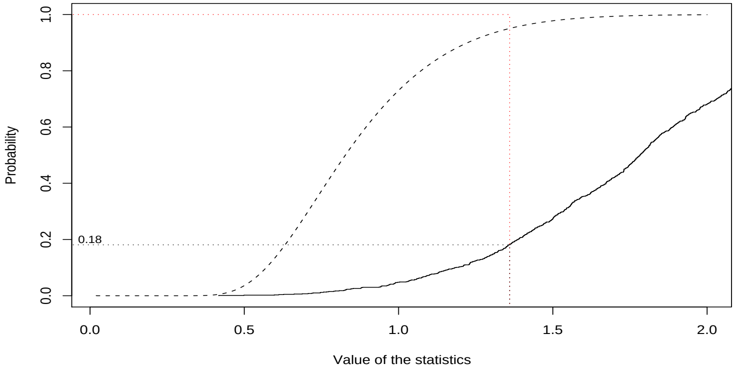
change in β ↑ ↓ $\Delta = 0.75$



Power

sample size ↑ ↓ $n = 250$ **rejected**$= 81.9\%$

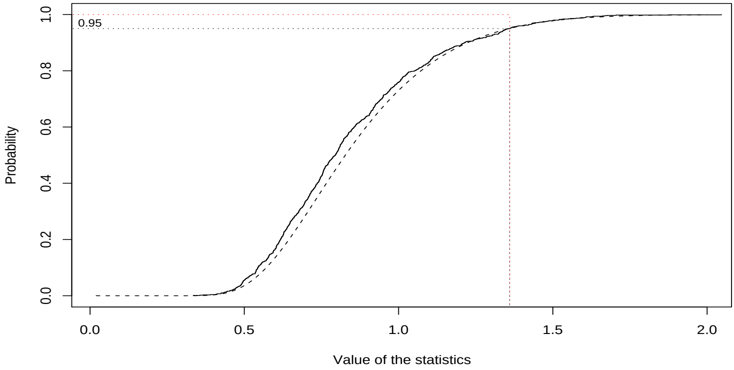
change in β ↑ ↓ $\Delta = 1$



Power

sample size ↑ ↓ $n = 500$ **rejected**$= 5\%$

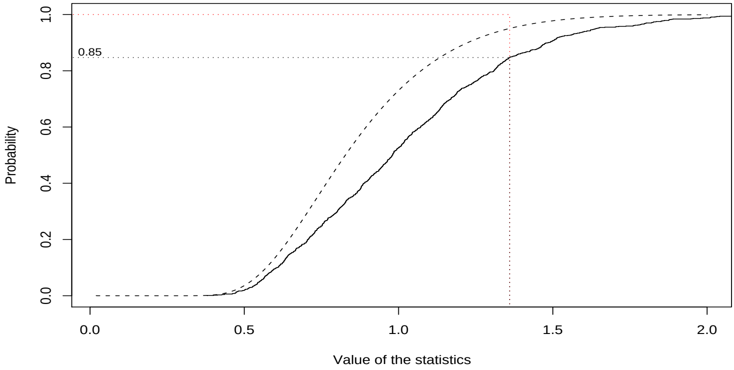
change in β ↑ ↓ $\Delta = 0$



Power

sample size ↑ ↓ $n = 500$ **rejected**$= 15.4\%$

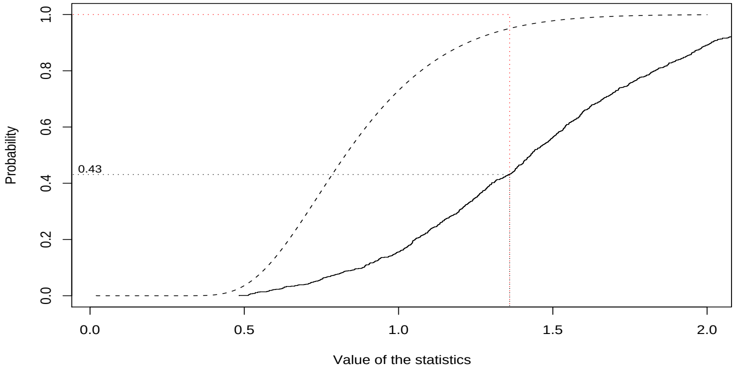
change in β ↑ ↓ $\Delta = 0.25$



Power

sample size ↑ ↓ $n = 500$ **rejected**$= 56.9\%$

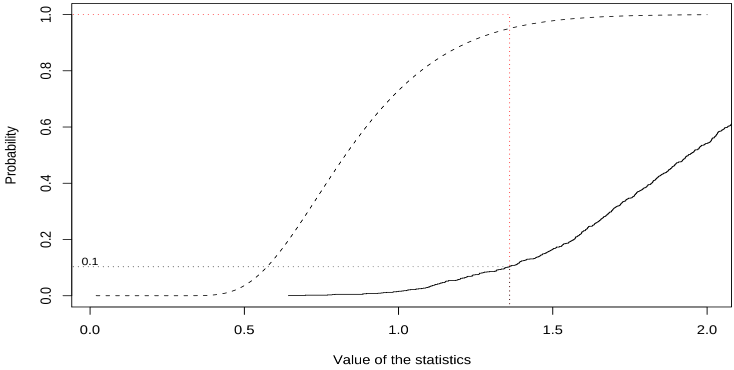
change in β ↑ ↓ $\Delta = 0.5$



Power

sample size ↑ ↓ $n = 500$ **rejected**$= 89.8\%$

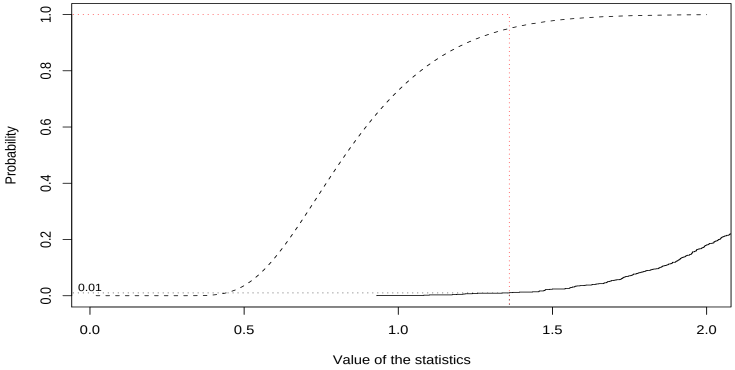
change in β ↑ ↓ $\Delta = 0.75$



Power

sample size ↑ ↓ $n = 500$ **rejected**$= 99\%$

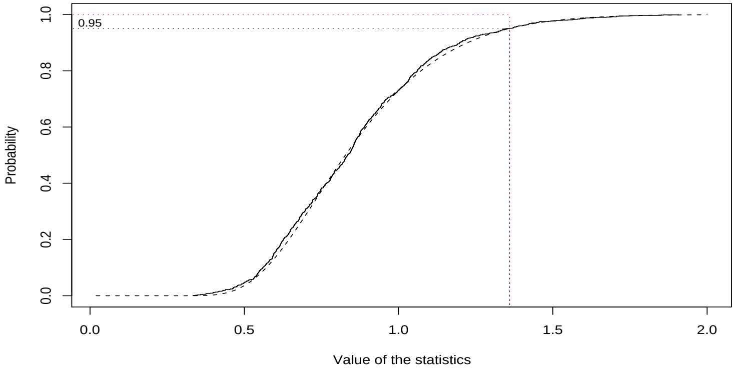
change in β ↑ ↓ $\Delta = 1$



Power

sample size ↑ ↓ $n = 1000$ **rejected**$= 5\%$

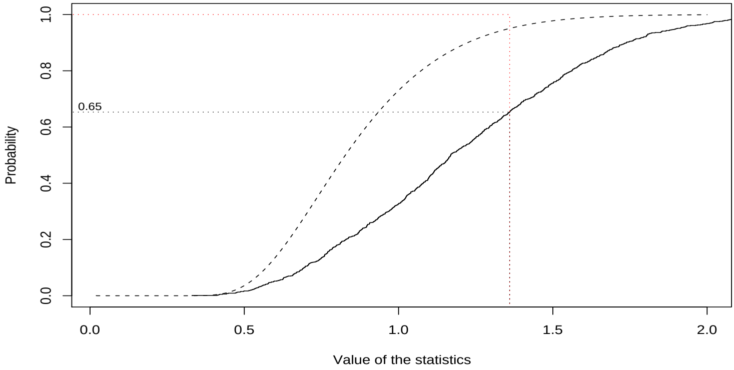
change in β ↑ ↓ $\Delta = 0$



Power

sample size ↑ ↓ $n = 1000$ **rejected**$= 34.9\%$

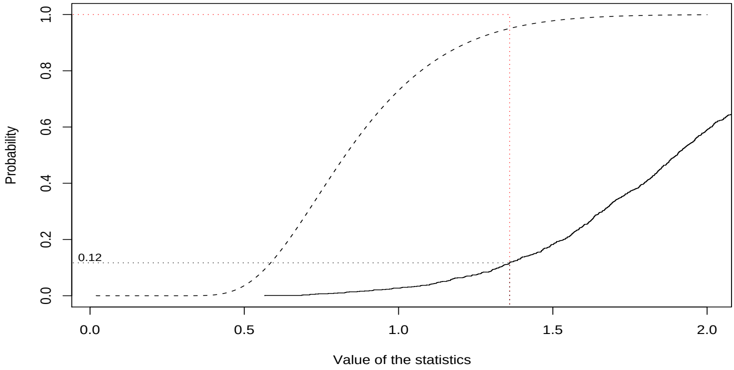
change in β ↑ ↓ $\Delta = 0.25$



Power

sample size ↑ ↓ $n = 1000$ **rejected**$= 88.7\%$

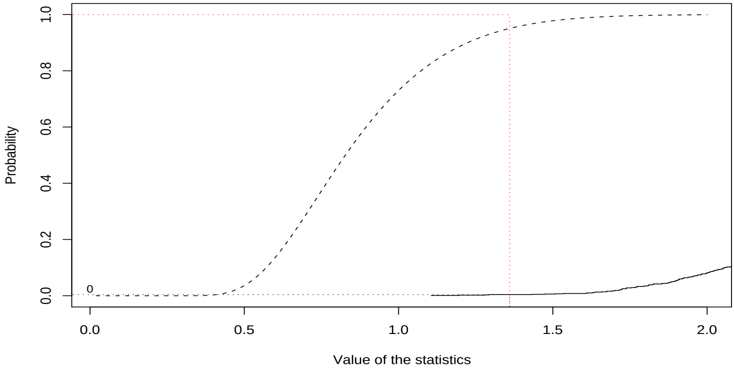
change in β ↑ ↓ $\Delta = 0.5$



Power

sample size ↑ ↓ $n = 1000$ **rejected**$= 99.6\%$

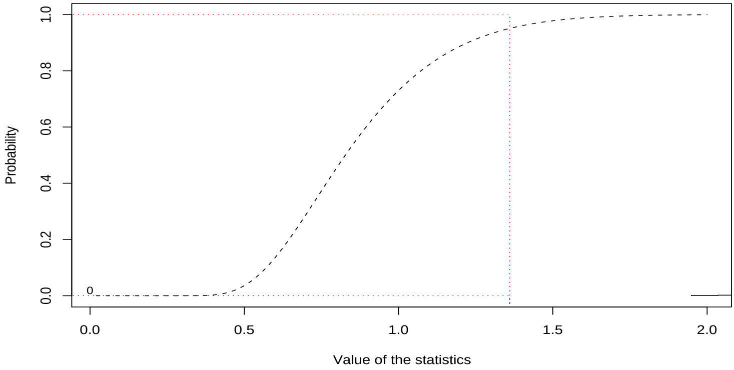
change in β ↑ ↓ $\Delta = 0.75$



Power

sample size ↑ ↓ $n = 1000$ **rejected**$= 100\%$

change in β ↑ ↓ $\Delta = 1$



To sum up

- The partial residuals are useful in checking the PH assumption in the additive model
- Theoretical deficiencies are not important for practical use - the Brownian bridge theory can be used
- The choice of the test statistic should be based on the alternative hypothesis
- The Cramér - Von Mises statistic more appropriate with small sample sizes

relsurv package

published: Pohar, Stare, CMPB 2006; CRAN

The package ensures easy use of relative survival methods

- **provides a uniform syntax for all the models using any format of population tables**

  ```
  > rs.fun(Surv(time,cens) ~ variables,data,ratetable)
  ```

  `rsadd`, `rstrans`, `rsmul`
- **simplifies transformation of population tables into R** **`transrate.hld`, `transrate.hmd`, `transrate`, `joinrate`**
- **functions for checking goodness of fit** **`rs.zph`, `rs.br`**
- **provides methods for plotting results** **`plot.rsurvfit`, `plot.rs.zph`, `plot.rs.br`**

relsurv package

- **available at CRAN**
- **the most complete and flexible package for relative survival**
- **usable with any format of population tables**
- **thoroughly checked and compared to results in other software**
- **enriched by the options required by the users**

Bibliography

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  Relative survival analysis in R
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Definition of residuals

Cox model
Schoenfeld residuals

X_i

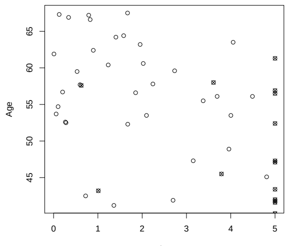
additive model
partial residuals

X_i

Notation

X **covariate**

t_i ***i*th event time**



Definition of residuals

Cox model
Schoenfeld residuals

$$X_i \quad \hat{E}(X, t_i)$$

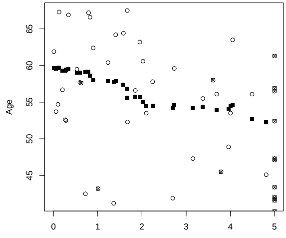
additive model
partial residuals

$$X_i \quad \hat{E}(X, t_i)$$

Notation

X covariate

t_i ith event time



Definition of residuals

Cox model
Schoenfeld residuals

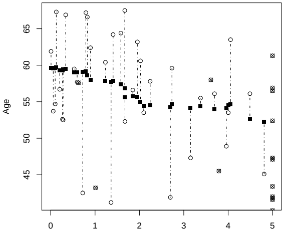
$$X_i - \hat{E}(X, t_i)$$

additive model
partial residuals

$$X_i - \hat{E}(X, t_i)$$

Notation

- X **covariate**
- t_i i**th event time**



Definition of residuals

Cox model
Schoenfeld residuals

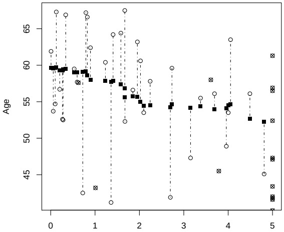
$$U_i \quad = \quad X_i - \hat{E}(X, t_i)$$

additive model
partial residuals

$$U_i : \quad = \quad X_i - \hat{E}(X, t_i)$$

Notation

X	**covariate**
t_i	***i*th event time**
U_i	**residual**



Definition of residuals

Cox model
Schoenfeld residuals

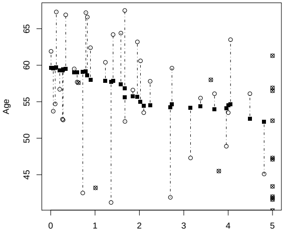
$$U_i = X_i - \hat{E}(X, t_i) = X_i - \sum_{j \in R_i} X_j \frac{\lambda_j}{\sum_{k \in R_i} \lambda_k}$$

additive model
partial residuals

$$U_i := X_i - \hat{E}(X, t_i) = X_i - \sum_{j \in R_i} X_j \frac{\lambda_{Pj} + \lambda_{Ej}}{\sum_{k \in R_i} (\lambda_{Pk} + \lambda_{Ek})}$$

Notation

- X covariate
- t_i ith event time
- U_i residual
- R_i risk set at time i
- λ_j hazard for person j
- λ_P population hazard
- λ_E excess hazard



Properties

Residuals can be expressed as martingales

$$
\begin{aligned}
U(\beta^0, t) &= \sum_{i=1}^{n} \int_0^t \left\{ \mathbf{X_i}(u) - \hat{E}(X|u, \beta^0) \right\} dN_i(u) \\
&= \sum_{i=1}^{n} \int_0^t \underbrace{\left\{ \mathbf{X_i}(u) - \hat{E}(X|u, \beta^0) \right\}}_{\textbf{predictable process}} \underbrace{dM_i(u)}_{\textbf{martingale}}
\end{aligned}
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Therefore,

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\begin{aligned}
E\mathbf{U}(\beta^0, t) &= \mathbf{0} \\
E\mathbf{U_i}(\beta^0, t) &= \mathbf{0} \\
\operatorname{cov}\left(\mathbf{U_i}(\beta^0, \mathrm{t}), \mathbf{U_j}(\beta^0, \mathrm{t})\right) &= \mathbf{0}
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variance of the residual process can be computed

Properties

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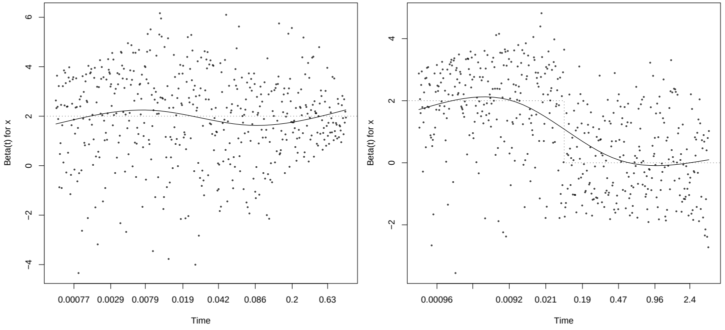
variance of the residual process can be computed

Schoenfeld residuals follow from the score function

$U(\hat{\beta}, \infty) = \sum_{i=1}^{n} U_i(\hat{\beta}) = 0$ **This is not true in the additive model case!**

Graphical inspection



$$\beta^0(t_i) \simeq \hat{\beta} + \left(\frac{\partial}{\partial\beta}\{\hat{E}(X|t_i,\hat{\beta})\}\right)^{-1} E[U(\hat{\beta},t)]$$

Brownian motion constructed as the sum of residuals

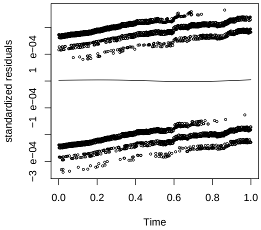
Cox model & additive model

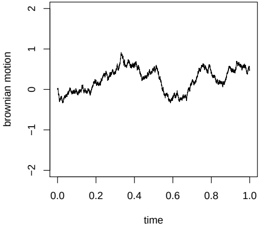
$$B(\beta_0, \frac{k}{n}) = \frac{1}{\sqrt{n}} \sum_{i=1}^{k} \frac{U_i(\beta_0)}{\sqrt{V_i(\beta_0)}} \quad \overset{n\to\infty}{\longrightarrow} \quad \text{Brownian motion}$$

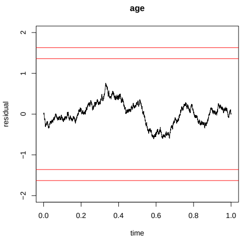
$$BB(\beta_0, \frac{k}{n}) = B(\beta_0, \frac{k}{n}) - \frac{k}{n} B(\beta_0, 1) \overset{n\to\infty}{\longrightarrow} \text{Brownian bridge}$$

Notation

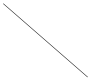
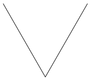
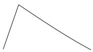
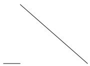
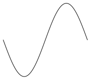
- U_i **Schoenfeld-like residuals**
- V **variance**
- n **number of deaths**
- β_0 **true regression coefficient**







Tests based on Brownian bridge properties

β^0 *in time*	*brownian bridge process*	*test statistic*
		T_1 $max(abs(BB(t))$
		T_2 *max using weighted residuals*
		T_3 Cramer–Von Mises $\int_0^1 BB^2(t)dt - (\int_0^1 BB(t)dt)^2$