Notes on survival analysis*

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Abstract

This is a slighly revised version of a cheatsheet on survival analysis dated 2007-05-14.

1 Conventions

The most general framework that we will consider is that of staggered entry, static covariate and right censoring. Let's begin with the following definitions

*Revisions: `https://github.com/erwannr/statistics/commits/main/survanal`

Conventions		
t^{cal}		calendar time
t^{in}		entry time
t^{out}		exit time
$t^{\dagger}$		failure time
$t^{+}(t)$	$(t-t^{\text{in}})^{+}$	time on study
$t^{\text{c}}(t)$	$t^{\text{out}} \wedge t^{+}(t)$	censoring time
$t^{*}(t)$	$t^{\dagger} \wedge t^{\text{c}}(t)$	first event time
$\delta(t)$	$1\{t^{\dagger} < t^{\text{c}}(t)\}$	failure observed
$R(t,s)$	$1\{s \leq t^{*}(t)\}$	at risk
$N(t,s)$	$\delta(t)1\{t^{\dagger} \leq s\}$	observed failure prior to
$x^{\text{nuis}}(t)$		nuisance covariate
$z(t)$		treatment indicator
$x(t)$	$(z(t), x^{\text{nuis}}(t))$	covariate
$y(t)$	$(t^{*}(t), \delta(t))$	response
n		index for order of entry
$n_{*}(t)$		count of entries
$n_{\dagger}(t)$	$\sum_{\{n \leq n_{*}(t)\}} \delta_n(t)$	count of observed failures
$\mathbf{x}(t)$	$(x_1, ..., x_{n_{*}(t)})$	covariate data
$\mathbf{y}(t)$	$(y_1, ..., y_{n_{*}(t)})$	response data
$D(t)$	$D(t) = (\mathbf{x}(t), \mathbf{y}(t))$	data
β_{nuis}		effect of nuisance covariate
θ		treatment effect
β	$(\theta, \beta_{\text{nuis}})$	covariate effect
ϕ		baseline hazard parameter
ξ		all parameters

Note that t^{in} is measured on the same scale as t^{cal} whereas t^{out} and $t^{\dagger}$ are clocks that are started at t^{in}. In principle, we need to define a joint distribution for $(t^{\text{in}}, t^{\dagger}, t^{\text{out}})$, but in the definition of D we are implicitly treating $(t^{\text{in}}, t^{\text{out}})$ as ancillary variables. The staggered entry and static covariate assumptions imply $x(t) = x(t^{\text{in}}), t \geq t^{\text{in}}$, which justifies our definition of D. When the context specifies that we fix $t^{\text{cal}} = t$, we ommit t in all expressions that depend on it, e.g. we write D instead of $D(t)$.

1.1 Likelihood and derived quantities

We restrict the class of model, either parametric or semi–parametric, to the proportional hazard. It is standard convention that $f(.)$, $F(.)$, $S(.)$, $h(.)$ and $H(.)$ denote the PDF and CDF of time–to-event, survival, hazard and cumulative hazard functions, respectively. The relations between them are given by

$$S(t) = 1 - F(t) = \exp\left(-\int_0^t h(u)\right) du = \exp(-H(t)) \tag{1}$$

and $F(t) = \int_0^t f(u)du$. The proportional hazard assumption made at the beginning is given by $h(t|x) = h_0(t)\exp(x'\beta)$, which together with (1), implies

$S(t) = S_0(t)^{\exp(x'\beta)}$. The name derives from the property that $h(t|x_0)/h(t|x_1)$, $x_0 \neq x_1$, is independent of t. For the particular case $x = z$, $\forall t$,

$$\theta = \log(h(t|z=1)/h(t|z=0)) \tag{2}$$
$$= \log\left(\log(S(t|z=1))/\log(S(t|z=0))\right) \tag{3}$$

From the first equality θ is often referred to as the log hazard ratio. The second is useful in the Bayesian process of prior elicitation from expert knowledge.

Suppose we postulate a parametric family for $F(.)$ indexed by $\xi \in \Xi$. For example, in the case $t \sim \mathcal{W}(t|\alpha, \gamma)$, $F(t) = 1 - \exp(-\gamma t^{\alpha})$, and $h(t) = \alpha\gamma t^{\alpha-1}$, so that $\xi = (\alpha, \gamma)$. Furthermore, if $\gamma = \exp(x'\beta)$, then $h(.|\xi, x)$ is a proportional hazard with baseline $h_0(t|\phi) = \alpha t^{\alpha-1}$, $\phi \equiv \alpha$. Suppose we fix $t^{\text{cal}} = t$. The likelihood, in terms of ξ is

$$L(D|\xi) = \prod_{\{n:\delta_n=1\}} f(t_n^{\dagger}|\xi) \prod_{\{n:\delta_n=0\}} S(t_n^{\text{c}}|\xi) \tag{4}$$

The proportional hazard also permits an important semi–parameric formulaulation under which $h_0(.)$ is unspecified and the following partial likelihood[1] may be justified:

$$l_{\text{Cox}}(t|\beta) = \sum_n \int_{[0,t]} \log\left(\frac{\exp(x_n'\beta)}{\sum_l R_l(t,s)\exp(x_l\beta)}\right) N_n(t, ds) \tag{5}$$
$$= \sum_n \delta_n(t)\left(x_n'\beta - \log\left(\sum_l R_l(t, t_n^{\dagger})\exp(x_n'\beta)\right)\right) \tag{6}$$

The term inside the parenthesis of (6) can be interpreted as the probability that failure is on individual n, conditional on failure time equating $t_n^{\dagger}$ and the risk set $\{l : R_l(t, t_n^{\dagger}) = 1\}$. The score and information matrix (adapted from [4], Chapter 7) are

$$U_{\text{Cox}}(t|\beta) = \nabla_{\beta} l_{\text{Cox}}(t|\beta) \tag{7}$$
$$= \sum_n \delta_n(t)(x_n - \bar{x}(t, t_n^{\dagger}|\beta)) \tag{8}$$
$$I_{\text{Cox}}(t|\beta) = -\partial^2_{\beta,\beta'} l_{\text{Cox}}(t|\beta) \tag{9}$$
$$= \sum_n \delta_n(t) \frac{\sum_l R_l(t, t_n^{\dagger})\exp(x_l'\beta)(x_l - \bar{x}(t, t_n^{\dagger}|\beta))(x_l - \bar{x}(t, t_n^{\dagger}|\beta))'}{\sum_l R_l(t, t_n^{\dagger})\exp(x_l'\beta)} \tag{10}$$

where

$$\bar{x}(t, t_n^{\dagger}|\beta) = \frac{\sum_l R_l(t, t_n^{\dagger}) x_l \exp(x_l'\beta)}{\sum_l R_l(t, t_n^{\dagger})\exp(x_l'\beta)} \tag{11}$$

For practical purposes, we may treat the partial likelihood as a standard likelihood so that for fixed t but sufficiently large n_*, the following approximations hold:

$$n^{-1/2}U_{\text{Cox}}(t|\beta) \sim N(0, n^{-1}I_{\text{Cox}}(t|\beta)) \tag{12}$$

$$\hat{\beta}_{\text{Cox}}(t|\beta) \sim N(\beta, I^{-1}_{\text{Cox}}(t|\hat{\beta}_{\text{Cox}})) \tag{13}$$

where $\hat{\beta}_{\text{Cox}}$ solves the estimating equation $U_{\text{Cox}}(t|\hat{\beta}_{\text{Cox}}) = 0$. The second line follows from $U_{\text{Cox}}(t|\hat{\beta}_{\text{Cox}}) \approx U_{\text{Cox}}(t|\beta) + (\hat{\beta} - \beta)I_{\text{Cox}}(t|\beta)$.

For the particular case $x \equiv z$, $U_{\text{Cox}}(t|\theta = 0)$ is an estimate for the observed$-$expected number of events in a treatment group, and it is called the log–rank test statistic. Let $\tilde{U}_{\text{Cox}}(t|\theta) = I^{-1/2}_{\text{Cox}}(t|\theta)U_{\text{Cox}}(t|\theta)$. It underpins the popular test of equality between two lifetime distributions: reject if $|\tilde{U}_{\text{Cox}}(t|\theta = 0)| > c_\alpha$. Let $\tilde{U}_{\theta_*,\text{Cox}}(t|\theta) = I^{-1/2}_{\text{Cox}}(t|\theta_*)U_{\text{Cox}}(t|\theta)$. This quantity is useful for sequential analysis. Specifically, if $i = 1, ..., i_*$ indexes interim analyses, according to Chapter 9 of [5], for θ close to 0, $\tilde{U}_{\theta_*,\text{Cox}}(t_1, ..., t_{i_*}|\theta) = \{\tilde{U}_{\theta_*,\text{Cox}}(t_1|\theta), ..., \tilde{U}_{\theta_*,\text{Cox}}(t_{i_*}|\theta)\}$ is a normal vector such that

$$\tilde{U}_{\theta_*,\text{Cox}}(t_i|\theta) \sim N(I^{1/2}_{\text{Cox}}(t_i|\theta_*)\theta, 1)) \tag{14}$$

$$\text{Cov}(\tilde{U}_{\theta_*,\text{Cox}}(t_i|\theta), \tilde{U}_{\theta_*,\text{Cox}}(t_{i+k}|\theta))|\theta_* = I^{1/2}_{\text{Cox}}(t_i|\theta_*)I^{-1/2}_{\text{Cox}}(t_{i+k}|\theta_*) \tag{15}$$

todo: make contiguity argument precise (Chapters 7&9[3] and [2]) **todo**Although [5] use $\theta_* = 0$ would it not be better to take $\theta_* = \hat{\theta}$, the mle?

Formulations that are intermediary between the fully parameterized version of $L(.|\xi)$ and the partial likelihood $L_{\text{Cox}}(.|\beta)$ include the piecewise constant hazard model, such that $\xi = (\lambda, \beta)$ where λ is a vector of constants.

Bibliography

[1] T. Sellke and D. Siegmund. "Sequential analysis of the proportional hazards model". In: *Biometrika* 70.2 (Aug. 1983), pp. 315–326. ISSN: 0006-3444. DOI: `10.1093/biomet/70.2.315`. eprint: `https://academic.oup.com/biomet/article-pdf/70/2/315/632076/70-2-315.pdf`.

[2] Yannis Bilias, Mingao Gu, and Zhiliang Ying. "Towards A General Asymptotic Theory For Cox Model With Staggered Entry". In: *Annals of Statistics* 25.2 (1997), pp. 662–682.

[3] Adrianus Willem van der Vaart. *Asymptotic Statistics*. Cambridge Series in Statistical and Probabilistic Mathematics, 3. Cambridge University Press, 1998. ISBN: 9780521496032.

[4] Jerald F. Lawless. *Statistical Models and Methods for Lifetime Data, Second Edition*. Wiley Series in Probability and Statistics. Wiley, Nov. 2002. ISBN: 9781118033005. DOI: `10.1002/9781118033005`.

[5] Joseph G. Ibrahim, Ming-Hui Chen, and Debajyoti Sinha. *Bayesian Survival Analysis*. Springer, Dec. 2004. ISBN: 9780387952772.