3-Lecture Minicourse on Statistics of Survival Data

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I. (11/6) **Death Hazards & Competing Risks**

Concepts:
(i) Statistical Estimation as mathematical problem,
(ii) Identifiability, nonparametric vs. nonparametric.

II. (11/13) **Population Cohorts & Martingales**

Concepts:
(iii) Counting process models,
(iv) "Innovations" and Statistics

III. (11/20) **Models and Likelihoods with ∞-Dimensional Parameters**

Concepts:
(v) Nuisance parameters,
(vi) Statistical Efficiency.

Lecture Slides (incl. annotated references) at :
www.math.umd.edu/~evs/SurvSlid.pdf

Data Format for a Survival Study

Subjects enter at random times E_i , 'followed up' until
$E_i + T_i = \min(E_i + X_i,\ E_i + C_i)$ (not both observed)
'death-time' ($X_i =$ *lifetime*), or 'censoring time'
(e.g., $C_i = E_{\max} - E_i + \tau$ *administrative*)

DATA: $\{(E_i,\ T_i,\ \Delta_i,\ Z_i)\ ,\ i = 1, \ldots, n\}$ or

$$\mathbf{D} \ = \ \{(T_i,\ \Delta_i)\ ,\ i = 1, \ldots, n\}$$ *where*

$T_i =$ *time-on-test* or *event time*

$\Delta_i \ = \ I_{[X_i \le C_i]}$ *death indicator*

Z_i *auxiliary covariates*, e.g. treatment gp

Assumptions: random vectors $(E_i,\, X_i,\, C_i,\, Z_i)$ independent and identically distributed (*iid*), $i = 1,\ \ldots,\ n$;

also (X_i, C_i) have continuous *joint density*, i.e.

$$\lim_{\delta \searrow 0} \frac{1}{\delta^2}\, P(X_1 \in (x, x+\delta),\, C_1 \in (c, c+\delta)) \ = \ f_{X,C}(x, c)$$

OBJECTIVE: to *estimate* the *marginal survival function* $S_X(t) = P(X_1 > t) = 1 - F_X(t)$ consistently from the data $\mathbf{D}$, which means ...

Definition. Say that a sequence of (measurable) mappings

$$\hat{F}^{(n)} \;:\; (\mathbf{R}^+ \times \{0,1\})^n \;\longrightarrow \{F :\; \text{dist.fcns on } \;\mathbf{R}^+\;\}$$

are **consistent estimators** of $F_X = 1 - S_X$ based on the *iid* pairs (T_i, Δ_i) if

$$\|\hat{F}^{(n)}(\{(T_i,\Delta_i)\}_{i=1}^n) \,-\, F_X\|_\infty \longrightarrow 0$$

in expectation or (more restrictively) with probability 1.

Say that a function(al) $\vartheta = \vartheta(f_{X,C})$ of the joint probability density of (each subject's underlying) data (X_i, C_i) is **identifiable** if it depends only on

$$f_{T,\Delta}(t,j) \;=\; \lim_{\delta \searrow 0} \frac{1}{\delta} P(\min(X_1,C_1) \in (t,t+\delta),\, \Delta_1 = j)$$

$$=\; \int_t f_{X,C}(t,c)\,dc\, I_{[\mathrm{j}=1]} \;+\; \int_t f_{X,C}(s,t)\,ds\, I_{[\mathrm{j}=0]}$$

Joint prob. density function $f_{T,\Delta}$ (mixed-type continuous & discrete) **is**, due to the *Law of Large Numbers* (pointwise for each t) and *Glivenko-Cantelli Theorem* (uniformly in $t \in [0,\infty)$) consistently estimated by the (derivative with respect to t of the) *empirical subdistribution functions*

$$\hat{F}_{T,\Delta=j}(t) \;=\; \frac{1}{n} \sum_{i=1}^{n} I_{[T_i \le t,\, \Delta_i = j]}$$

Summary So Far: from def'ns, consistent estimation generally *requires* identifiability. Identifiability plus suitable continuity in the parameter-functional implies a consistent estimator-sequence can be found.

In the *LATENT FAILURE MODEL*, want to identify in $S_X(t)$ what the survival probabilities *would* be with no removals due to C_i .

This makes clearer sense if C_i is administrative censoring and E_i is unrelated to health than if C_i is due to death from another cause. (In that case, called *Competing Risks*, death-variable X_i following C_i is **counterfactual**.) *We have no data on deaths following removals !*

Assume X_i, C_i independent (densities f_X, f_C). Following D. Bernoulli (1760), Kaplan & Meier (1958), S. Berman (1960) we show S_X **identifiable**, **consistently estimated**.

Idea: Actuarial concept of *Death Hazards.* Actuaries call this topic "multiple decrement tables" to find e.g. probabilities of wife's survival probabilities following husband's death, for joint-insurance premiums.

Death Hazards

In general, define **hazard intensity**

$$h_X(t) \;\equiv\; \lim_{\delta \to 0} \frac{1}{\delta} P(X \in (t, t+\delta) \,|\, X > t) \;=\; \frac{f_X(t)}{S_X(t)}$$

Then

$$h_X(t) = -\frac{d}{dt} \ln S_X(t) \quad \Longrightarrow \quad S_X(t) = \exp\left(- \int_0^t h_X(s)\, ds \right)$$

In terms of observed data (T_i, Δ_i),

$$S_T(t) \;=\; P(T_1 > t) \;=\; P([X_1 > t] \cap [C_1 > t])$$

$$= \; P(X_1 > t)\, P(C_1 > t) \;=\; S_X(t)\, S_C(t)$$

and also

$$P(t < T_1 < t{+}\delta,\ \Delta_1 = 1) \;\approx\; P(t < X_1 < t{+}\delta,\ C_1 > t)$$

$$\approx\; \delta\, f_X(t)\, S_C(t)$$

So determine

$$\delta\, h_X(t) \;\approx\; \frac{P(t < T_1 < t < \delta,\ \Delta_1 = 1)}{P(T_1 > t)}$$

$$S_X(x) \;=\; \exp\left(\int_0^x \frac{1}{S_T(t)} \frac{d}{dt} P(T_1 > t,\ \Delta_1 = 1)\, dt \right)$$

Kaplan-Meier Curve

The 'empirical' estimators are:

$$\text{for} \quad S_T(t) \ : \quad \frac{1}{n} \sum_{i=1}^{n} I_{[T_i > t]}$$

$$\text{for} \quad (P(T_1 > t,\, \Delta_1 = 1) \ : \quad \frac{1}{n} \sum_{i=1}^{n} I_{[t < T_i < C_i)]}$$

$$\text{for} \quad S_X(x) \ : \quad \prod_{0 \le t \le x} \left(1 - \sum_{i=1}^{n} I_{[T_i = t,\, \Delta_i = 1]} \Big/ \sum_{i=1}^{n} I_{[T_i \ge t]}\right)$$

This is the **Kaplan-Meier** (1958) estimator, known to actuaries in discretized form 80 years earlier.

WHAT IF X_i, C_i ARE DEPENDENT ?

Depends on the unknowable counterfactual hazards:

$$\lim_{\delta \to 0} \frac{1}{\delta} P(T \in (t, t+\delta) \,|\, C = s) \qquad \text{for} \quad s < t$$

ANYWAY:

$$\hat{S}_X^{KM}(x) \ \longrightarrow \ \exp\left(\int_0^x \frac{1}{S_T(t)} \frac{d}{dt} P(T_1 > t,\ \Delta_1 = 1)\, dt \right)$$

Parametric vs Nonparametric Models

So what do biostatisticians do to identify S_X ?

Main approaches:

(1) (*cf.* David & Moeschberger 1978 book) *Parametrize* joint density $f_{X,C} = f_{X,C}(\cdot, \cdot\,|\vartheta)$ and therefore $f_{T,\Delta}(t,j) = f_{T,\Delta}(t,j|\vartheta)$ (untestable assumption !).

Idea: $(P(T > t, \Delta = 1), P(T > t)) \mapsto \vartheta \mapsto S_X$

Example: $(\log X, \log C) \sim \mathcal{N}$ bivariate-normal !

Assumptions about $f_{T,\Delta}$ can be tested from large datasets using $n^{-1} \sum_{i=1^n} I_{[T_i > t,\, \Delta = j]}$, but assumptions about $f_{X,C}$ cannot !

(2) Find qualitative assumption just enough to render S_X identifiable.

(3) Models for additional observed variables V and qualitative assumptions they satisfy wrt (X, C).

Since S_X is **not identifiable nonparametrically**, what additional piece of information would be just enough for identifiability ?

Slud & Rubinstein (1983) show based on $f_{T,\Delta}$ that S_X is monotone $\searrow$ functional (expressed as ODE sol'n) of

$$\rho(t) = \lim_{\delta \to 0} \frac{P(X < t + \delta \,|\, T < t, \, X > t)}{P(X < t + \delta \,|\, T > t)}$$

One-to-one correspondence: $S_X \longleftrightarrow \rho$

Cases.

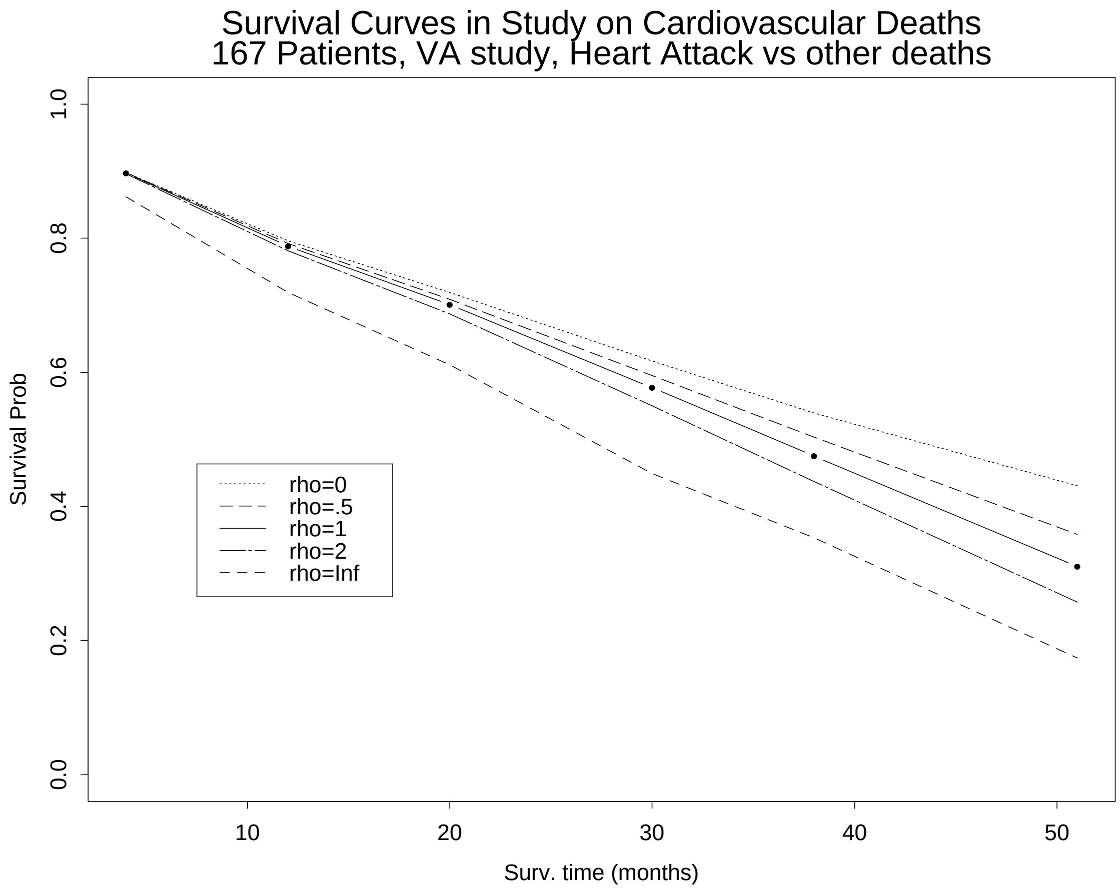
$\rho \equiv 1$: includes independence of X, C
Kaplan-Meier estimator consistent.

$\rho \approx 0$: minimal, $S_X(t) \approx P(\Delta = 0 \cup T > t)$
censored never die .

$\rho \nearrow \infty$: maximal $S_X(t) \approx S_T(t)$
death just after censoring.

Outcome: bounds $r_1 < \rho(\cdot) < r_2$ give (consistently estimated) bounds on S_X .

General Problem: Assumptions on ρ needed for identifiability, but not testable from data !


Survival Curves in Study on Cardiovascular Deaths
167 Patients, VA study, Heart Attack vs other deaths
Survival Prob
0.0
0.2
0.4
0.6
0.8
1.0
10
20
30
40
50
Surv. time (months)
rho=0
rho=.5
rho=1
rho=2
rho=Inf

Formulations Using 'Covariates'

(A) (X, C) conditionally independent given V

Nonparametric regression Cheng 1989 & others

$$f_{X,C,V}(x,c,v) \;=\; f_V(v)\, f_{X|V}(x|v)\, f_{C|V}(c|v)$$

S_X can be estimated from (T_i, Δ_i, V_i) using density estimates or regression models. (Think: Kaplan-Meier on subpopulations with $V_i = v$ if V is discrete.)

$$S_X(t) = \int \exp\left(- \int_0^t \frac{dP(X \le \min(s,C)|V=v)}{P(\min(X,C) \ge s|V=v)} \right) dF_V(v)$$

Under this assumption, can use **testable** *regression models for* (X, V) *and/or* (C, V) *dependence ! This is the starting point for Lectures 2,3.*

(B) C, V conditionally indep. given X. Under regularity conditions

(a) $\int f^2_{C|X}(c|x)\, f_X(x)\, dx < \infty \qquad \forall\, c$

(b) the functions $\{f_{V|X}(v|\cdot) : v \in \mathbf{R}\}$ are linearly dense in $L^2(f_X(x)dx)$

Slud (1992) proves S_X is uniquely determined by F_1, S_T . (Estimation involves *nonparametric mixture density*, very inaccurate.)

Nonparametric assumptions specifying dependence between X_i, C_i

EXAMPLE: Zheng & Klein (1995, *Biometrika*) assume known form of 'Copula' with $f_X,\ f_C$ unknown

$$K(u,v) \equiv\ P(F_X(X) \le u,\ F_C(C) \le v)$$

and prove: if K is bivariate distribution function on $[0,1]^2$ with Uniform$[0,1]$ marginals assigning positive probability to all open sets of $[0,1]^2$, then $f_X,\ f_C,\ f_{X,C}$ are uniquely determined by $F_1,\ S_T$.

EXAMPLE: Emoto & Matthews (1990) assume for (unknown) measure π on $[0,1]$ that

$$P(X > x,\ C > y)\ =\ \exp\Big(-\int \max(px^\alpha, (1-p)y^\beta)\ \pi(dp)\Big)$$

with $\alpha \ne \beta > 0$, and show that $\pi,\ f_{X,C}$ are uniquely determined by F_1, S_T.

Statistically, these models beg the question how dependence model could be known !?

Annotated References, Lecture 1

Probability Theory:

books by M. Loeve; P. Billingsley, ...
Law of Large Numbers, Glivenko-Cantelli Thm.

Statistics:

Bickel & Doksum, **Mathematical Statistics** (1975; 2002) *back in print*

R. Miller, **Survival Analysis** (1980) *good general book, also back in print*

Competing Risks:

D. Bernoulli (1760): removing Smallpox mortality

Gail, M. (1975), *Biometrics* review article
(also 1980 Encycl. Statist. Sci. article)

Tsiatis, A. (1975) *PNAS* **nonidentifiability**

Prentice, R. et al. (1976) *Biometrics*, **counterfactuals**

David, H. and Moeschberger, M. (1978) **Theory of Competing Risks**

Slud, E. and Rubinstein, L. (1983) *Biometrika* *summarizes Dependent Competing Risks problem, defines* $\rho(t)$ *function, obtains estimation results.*

Slud, E. and Byar, D. (1989) *Biometrics*
shows that estimating survival under assumption of independence between survival and censoring within two risk-groups could exactly reverse the actual ordering between the groupwise survival functions.

Slud, E. (1992) proceedings paper: *showed that* S_X *is identifiable underregularity conditions from* S_T, F_1 *if* C, V *are conditionally independent given* X.

Slud, E. and Kopylev (1996): proceedings paper, *competing risks with time-dependent covariates.*

Cox, D.R. (1972) **Jour Roy Stat Soc B**
seminal paper on survival-analysis regression models based on V *, when* C, X *are conditionally independent given* V.

Cheng, P. (1989) *Jour Stat Planning & Inference, nonparametric estimation of* S_X *when* C, X *are conditionally independent given* V.

Emoto & Matthews (1990) *Ann. Stat.,*
identifiability of $f_{X,C}$ *under an unnatural nonparametric assumption on dependence of* X_i, C_i.

Zheng & Klein (1995) *Biometrika,*
identifiability of $f_{X,C}$ *under a nonparametric assumption on dependence of* X_i, C_i.