Statistical Practice in Epidemiology 2018

Survival analysis with competing risks

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Points to be covered

1. Survival or time to event data & censoring.
2. Competing risks: event-specific cumulative incidences & hazards.
3. Kaplan–Meier and Aalen–Johansen estimators.
4. Regression modelling of hazards: Cox model.
5. Packages `survival`, `mstate`, `cmprisk`.
6. Functions `Surv()`, `survfit()`, `plot.survfit()`, `coxph()`, `Cuminc()`.

Survival time – time to event

Time spent (`lex.dur`) in a given **state** (`lex.Cst`) from its beginning till a certain *endpoint* or *outcome* **event** (`lex.Xst`) or *transition* occurs, changing the state to another.

Examples of such times and outcome events:

- lifetime: birth → death,
- duration of marriage: wedding → divorce,
- healthy exposure time:
  start of exposure → onset of disease,
- clinical survival time:
  diagnosis of a disease → death.

Ex. Survival of 338 oral cancer patients

Important variables:

- `time` = duration of patientship from diagnosis (**entry**) till death (`death`) or censoring (`Alive`), (`lex.Cst` is (`Alive`))
- `event` = indicator for the outcome and its observation at the end of follow-up (**exit**):
  0 = censoring,
  1 = death from oral cancer

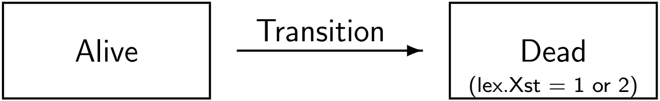
Special features:

- Two possible endpoints
- Censoring – incomplete observation of the survival time.

Set-up of classical survival analysis

- **Two-state model**: only one type of event changes the initial state.

- Major applications: analysis of lifetimes since birth and of survival times since diagnosis of a disease until death from any cause.



- **Censoring**: Death and final lifetime not observed for some subjects due to emigration or closing the follow-up while they are still alive

Distribution concepts: hazard function

The **hazard rate** or **intensity** function $\lambda(t)$

$$\lambda(t) = P(t < T \leq t + \Delta | T > t)/\Delta, \ \mathit{forsmall} \Delta$$

- $\approx$ the conditional probability that the event occurs in a short interval $(t, t + \Delta]$, given that it does not occur before t, divided by interval length.

In other words, during a short interval

$$\text{risk of event} \approx \text{hazard} \times \text{interval length}$$

Distribution concepts: survival and cumulative hazard functions

Survival function

$$S(t) = P(T > t),$$

$=$ probability of avoiding the event at least up to t
(the event occurs only after t).
The **cumulative hazard** (or integrated intensity):

$$\Lambda(t) = \int_0^t \lambda(u) du$$

Connections between the functions:

$$S(t) \ = \ \exp\{-\Lambda(t)\}$$

Observed data on survival times

For individuals $i = 1, \ldots, n$ let

$T_i =$ time to outcome event,

$U_i =$ time to censoring.

Censoring is assumed **noninformative**, *i.e.* independent from occurrence of events.

We observe

$y_i = \min\{T_i, U_i\}$, *i.e.* the exit time, and

$\delta_i = 1_{\{T_i < U_i\}}$, indicator $(1/0)$ for the outcome event occurring first, before censoring.

Censoring must properly be taken into account in the statistical analysis.

Approaches for analysing survival time

- **Parametric model** (like Weibull, gamma, etc.) on hazard rate $\lambda(t)$ → Likelihood:

$$L = \prod_{i=1}^{n} \lambda(y_i)^{\delta_i} S(y_i)$$

- **Piecewise constant rate** model on $\lambda(t)$
  – see Bendix's lecture on time-splitting (Poisson likelihood).

- **Non-parametric** methods, like
  Kaplan–Meier (KM) estimator of survival curve $S(t)$ and Cox proportional hazards model on $\lambda(t)$.

R package `survival`

Tools for analysis with one outcome event.

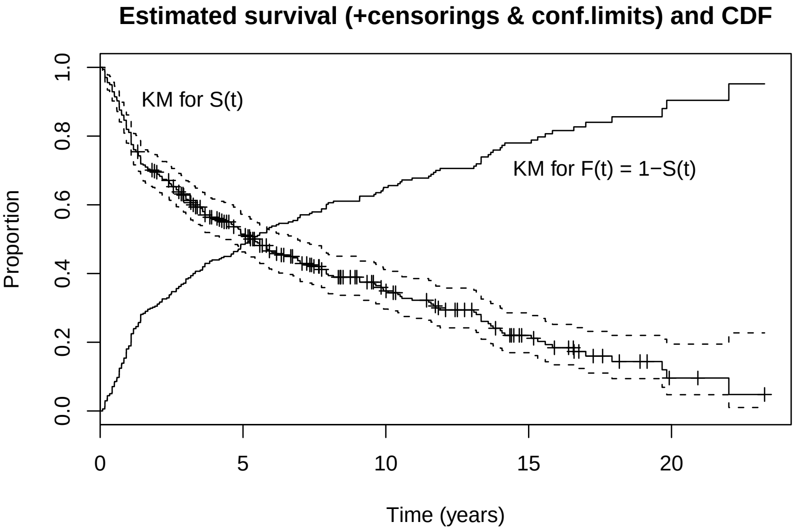
- `Surv(time, event) -> sobj`
  creates a **survival object** `sobj` assuming that all start at 0, containing pairs (y_i, δ_i),
- `Surv(entry, exit, event) -> sobj2`
  creates a survival object from `entry` and `exit` times,
- `survfit(sobj ~ x) -> sfo`
  creates a **survfit** object `sfo` containing KM or other non-parametric estimates (also from a fitted Cox model),
- `plot(sfo)`
  plot method for survival curves and related graphs,
- `coxph(sobj ~ x1 + x2)`
  fits a Cox model with covariates `x1` and `x2`.
- `survreg()` – parametric survival models.

Ex. Oral cancer data (cont'd)

```
> orca$suob <- Surv(orca$time, 1*(orca$event > 0) )

> orca$suob[1:7]    #  + indicates censored observation
[1] 5.081+ 0.419  7.915  2.480  2.500  0.167  5.925+

> km1 <- survfit( suob ~ 1, data = orca)
> km1                  #  brief  summary
records   n.max n.start  events  median 0.95LCL 0.95UCL
 338.00  338.00  338.00  229.00    5.42    4.33    6.92

> summary(km1)       #  detailed KM-estimate
```

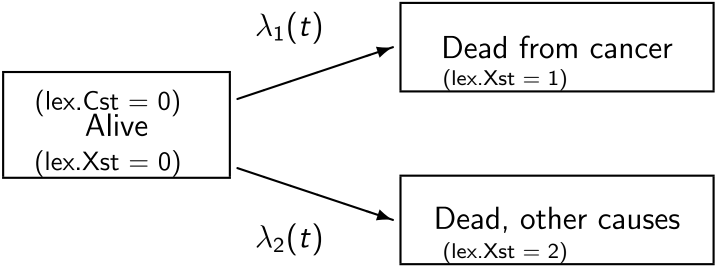
```
  time n.risk n.event survival std.err lower 95\% CI upper 95\% CI
 0.085    338       2   0.9941 0.00417       0.9859        1.000
 0.162    336       2   0.9882 0.00588       0.9767        1.000
 0.167    334       4   0.9763 0.00827       0.9603        0.993
 0.170    330       2   0.9704 0.00922       0.9525        0.989
 0.246    328       1   0.9675 0.00965       0.9487        0.987
  ...
```

Oral cancer: Kaplan-Meier estimates



Competing risks model: causes of death

- Often the interest is focused on the risk or hazard of dying from one specific cause.
- That cause may eventually not be realized, because a **competing cause** of death hits first.



- Generalizes to several competing causes.

Competing events & competing risks

In many epidemiological and clinical contexts there are competing events that may occur before the target event and remove the person from the population at risk for the event, *e.g.*

- *target event*: occurrence of endometrial cancer,
  competing events: hysterectomy or death.
- *target event*: relapse of a disease
  (ending the state of remission),
  competing event: death while still in remission.
- *target event*: divorce,
  competing event: death of either spouse.

Event-specific quantities

Cumulative incidence function (CIF) or

$$F_c(t) = P(T \leq t \text{ and } C = c), \quad c = 1, 2,$$

From these one can recover

- $F(t) = \sum_c F_c(t)$, CDF of event-free survival time T, *i.e.* cumulative risk of any event by t.
- $S(t) = 1 - F(t)$, **event-free survival function**, *i.e.* probability of avoiding all events by t, but $S(t) \neq F_1(t) + F_2(t)$

Event-specific quantities (cont'd)

Event- or **cause-specific hazard function**

$$\lambda_c(t) = \lim_{\Delta \to 0} \frac{P(t < T \leq t + \Delta \text{ and } C = c \mid T > t)}{\Delta}$$
$$= \frac{f_c(t)}{1 - F(t)}$$

CIF = risk of event c over risk period $[0, t]$ in the presence of competing risks, also obtained

$$F_c(t) = \int_0^t \lambda_c(v) S(v) dv, \quad c = 1, 2,$$

Warning of "net risk" and "cause-specific survival"

- The "**net risk**" of outcome c by time t, assuming hypothetical elimination of competing risks, is often defined as

$$F_1^*(t) = 1 - S_1^*(t) = 1 - \exp\{-\Lambda_1(t)\} \neq S(t)$$

- In clinical survival studies, function $S_1^*(t)$ is often called "**cause-specific survival**", or "**net survival**"

- Yet, these *-functions, $F_1^*(t)$ and $S_1^*(t)$, lack proper probability interpretation when competing risks exist.

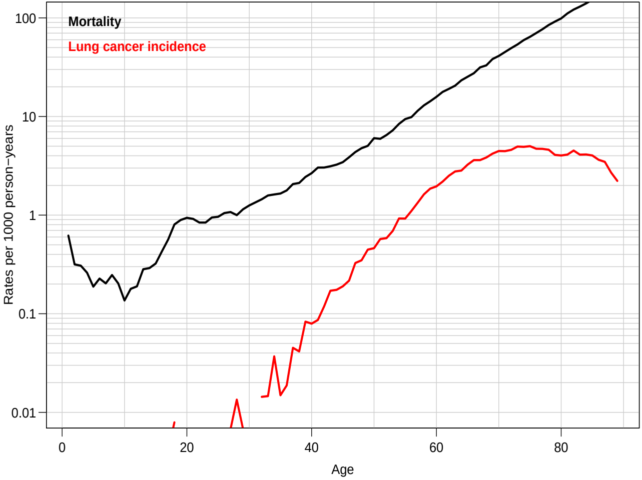
- Hence, their use should be viewed critically (Andersen & Keiding, *Stat Med*, 2012)

Example: Risk of lung cancer by age *a*?

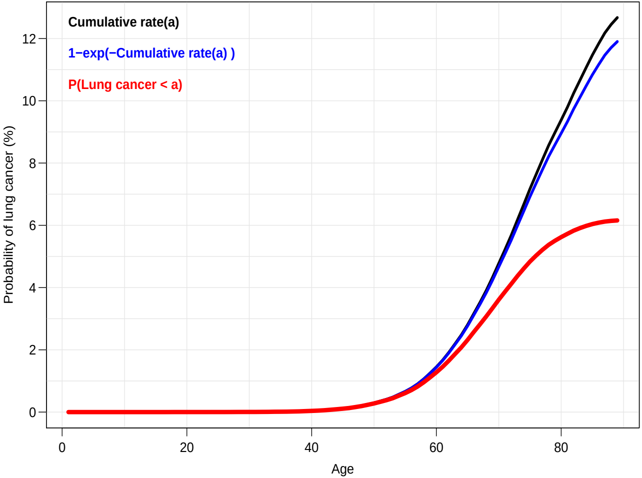
- Nordcan & Globocan give "**cumulative risk**" by 75 y of age, computed from $1 - \exp\{-\mathrm{CR}(75)\}$, as an estimate of the probability of getting cancer before age 75 y, assuming that death were avoided by that age. This is based on deriving "net risk" from cumulative hazard:
$$F_1^*(a) = 1 - \exp\{-\Lambda_c(a)\}.$$
- Yet, cancer occurs in a mortal population.
- As such CR(75) is a sound age-standardized summary measure for comparing cancer incidence across populations based on a neutral standard population.

Example. Male lung cancer in Denmark

Event-specific hazards: $\lambda_1(a)$ (lung cancer) death $\lambda_2(a)$ by age estimated by age-spec. rates.



Cumulative incidence of lung cancer by age



Both CR and $1 - \exp(-\mathrm{CR})$ tend to overestimate the real cumulative incidence CI after 60 y.

Analysis with competing events

Let U_i = censoring time, T_i = time to first event, and C_i = variable for event 1 or 2. We observe

- $y_i = \min\{T_i, U_i\}$, *i.e.* the exit time, and
- $\delta_{ic} = 1_{\{T_i < U_i \ \& \ C_i = c\}}$, indicator (1/0) for event c being first observed, $c = 1, 2$.

Non-parametric estimation of CIF

- Let $t_1 < t_2 < \cdots < t_K$ be the K distinct time points at which any outcome event was observed,
  Let also $\widetilde{S}(t)$ be KM estimator for overall $S(t)$.
- **Aalen-Johansen estimator** (AJ) for the cumulative incidence function $F(t)$ should be used

R tools for competing risks analysis

Package `mstate`

- `Cuminc(time, status, ...)`: AJ-estimates (and SEs) for each event type (`status`, value 0 indicating censoring)

Package `cmprsk`

- `cuminc(ftime, fstatus, ...)` computes CIF-estimates, `plot.cuminc()` plots them.
- `crr()` fits Fine–Gray models for the hazard $\gamma_c(t)$ of the subdistribution

Package `Epi` – `Lexis` tools for multistate analyses

- will be advertised by Bendix!

Ex. Survival from oral cancer

- Creating a Lexis object with two outcome events and obtaining a summary of transitions

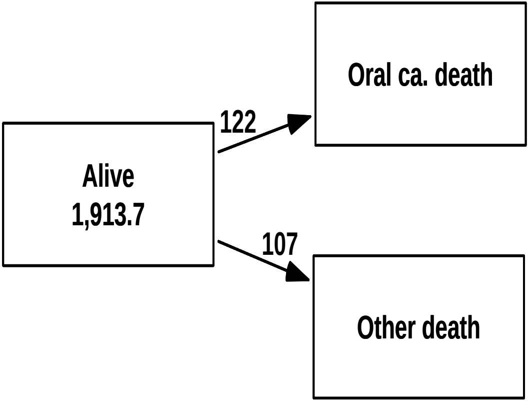
```
> orca.lex <- Lexis(exit = list(stime = time),
           exit.status = factor(event,
    labels = c("Alive", "Oral ca. death", "Other death") ),
                  data = orca)
```

```
> summary(orca.lex)
Transitions:
     To
From    Alive Oral ca. Other  Records:  Events: Risk time:
  Alive   109      122   107        338      229    1913.67
```

Box diagram for transitions

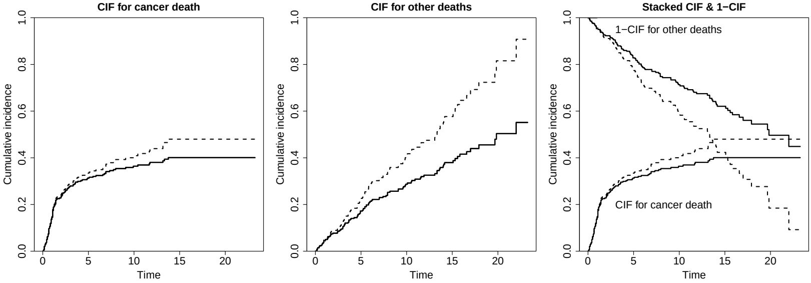
Interactive use of function `boxes()`.

```
> boxes(orca.lex)
```



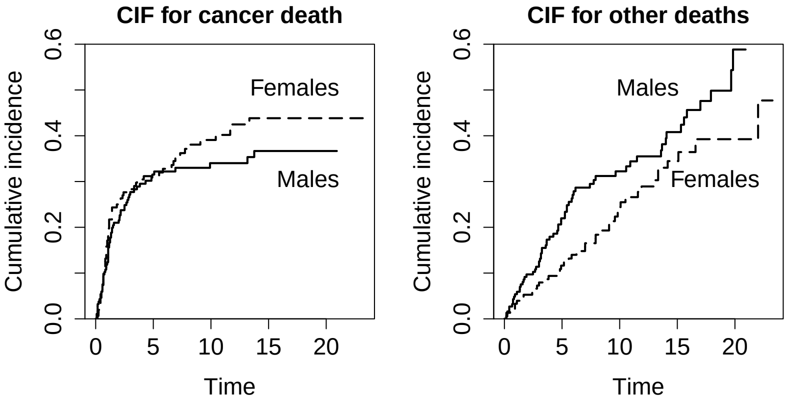
Ex. Survival from oral cancer

- AJ-estimates of CIFs (solid) for both causes.
- Naive KM-estimates of CIF (dashed) $>$ AJ-estimates
- CIF curves may also be stacked (right).



NB. The sum of the naive KM-estimates of CIF exceeds 100% at 13 years!

Ex. CIFs by cause in men and women



CIF for cancer higher in women (chance?) but for other causes higher in men (no surprise).

Regression models for time-to-event data

Regression models for hazards can be defined *e.g.* for

(a) hazards, multiplicatively:

$$\lambda_i(t) = \lambda_0(t;\alpha) r(\eta_i), \quad \text{where}$$

$\lambda_0(t;\alpha)$ = baseline hazard and
$r(\eta_i)$ = relative rate function, typically $\exp(\eta_i)$

(b) hazards, additively:

$$\lambda_i(t) = \lambda_0(t;\alpha) + \eta_i.$$

Relative hazards model or Cox model

In model (b), the baseline hazard $\lambda_0(t, \alpha)$ may be given a parametric form (*e.g.* Weibull) or a piecewise constant rate (exponential) structure.

Often a parameter-free form $\lambda_0(t)$ is assumed. Then

$$\lambda_i(t) = \lambda_0(t) \exp(\eta_1),$$

specifies the **Cox model** or the **semiparametric proportional hazards model**.

$\eta_i = \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$ not depending on time.

Generalizations: **time-dependent**
covariates $x_{ij}(t)$

PH model: interpretation of parameters

Present the model explicitly in terms of x's and β's.

$$\lambda_i(t) = \lambda_0(t) \exp(\beta_1 x_{i1} + \cdots + \beta_p x_{ip})$$

Consider two individuals, i and i', having the same values of all other covariates except the j^{th} one.

The ratio of hazards is constant:

$$\frac{\lambda_i(t)}{\lambda_{i'}(t)} = \frac{\exp(\eta_i)}{\exp(\eta_{i'})} = \exp\{\beta_j(x_{ij} - x_{i'j})\}.$$

Thus $e^{\beta_j} = \text{HR}_j =$ **hazard ratio** or relative rate associated with a unit change in covariate X_j.

Ex. Total mortality of oral ca. patients

Fitting Cox models with sex and sex + age.

```
> cm0 <- coxph( suob ~ sex, data = orca)
> summary( cm0)
        coef exp(coef) se(coef)    z Pr(>|z|)
sexMale 0.126     1.134    0.134 0.94     0.35
        exp(coef) exp(-coef) lower .95 upper .95
sexMale      1.13      0.882     0.872      1.47

> cm1 <- coxph( suob ~ sex + age, data = orca)
> summary(cm1)
        exp(coef) exp(-coef) lower .95 upper .95
sexMale      1.49      0.669      1.14      1.96
age          1.04      0.960      1.03      1.05
```

The M/F contrast visible only after age-adjustment.

Predictions from the Cox model

- Individual survival *times* cannot be predicted but ind'l survival *curves* can. PH model implies:

$$S_i(t) = [S_0(t)]^{\exp(\beta_1 x_{i1} + \ldots + \beta_p x_{ip})}$$

- Having estimated β by partial likelihood, the baseline $S_0(t)$ is estimated by Breslow method
- From these, a survival curve for an individual with given covariate values is predicted.
- In R: `pred <- survfit(mod, newdata=...)` and `plot(pred)`, where `mod` is the fitted `coxph` object, and `newdata` specifies the covariate values.

Modelling with competing risks

Main options, providing answers to different questions.

(a) Cox model for event-specific hazards $\lambda_c(t) = f_c(t)/[1 - F(t)]$, when *e.g.* the interest is in the biological effect of the prognostic factors on the fatality of the very disease that often leads to the relevant outcome.

(b) **Fine–Gray model** for the hazard of the subdistribution $\gamma_c(t) = f_c(t)/[1 - F_c(t)]$ when we want to assess the impact of the factors on the overall cumulative incidence of event c.
– Function `crr()` in package `cmprsk`.