

# PH 716 Applied Survival Analysis

## Part I: Basic quantities of survival models

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“All models are wrong, but some are useful.”

— G. E. P. Box. (1976). *Journal of the American Statistical Association*, 71:791–799.

### What is a statistical model?

- The (joint) distribution of RV(s) of interest
  - Reformulate linear regression and logit regression models
  - Parametric vs non-parametric vs semi-parametric

### Statistical modelling

Random variable (RV) of interest → data collection and cleaning → model specification → model fitting and inference → interpretation

### Motivating examples for survival models

- ([DM] Example 1.2) This is a Phase II clinical trial of Xeloda and oxaliplatin (XELOX) chemotherapy given before surgery to 48 advanced gastric cancer patients with paraaortic lymph node metastasis (Wang et al., 2014). An important survival outcome of interest is progression-free survival, which is the time from entry into the clinical trial until progression or death, whichever comes first.

```
head(asauro::gastricXelox)
```

```
##   timeWeeks delta
## 1         4      1
## 2         8      1
## 3         8      1
## 4         8      1
## 5         9      1
## 6        11      1
```

- ([DM] Example 1.5) The purpose of Steinberg et al. (2009) was to evaluate extended duration of a triple-medication combination versus therapy with the nicotine patch alone in smokers with medical illnesses.

```
head(asauro::pharmacoSmoking[, 2:8])
```

```
##   ttr relapse      grp age gender    race employment
## 1 182       0  patchOnly 36  Male  white          ft
## 2  14       1  patchOnly 41  Male  white        other
## 3   5       1 combination 25 Female white        other
```

##	4	16	1 combination	54	Male	white	ft
##	5	0	1 combination	45	Male	white	other
##	6	182	0 combination	43	Male	hispanic	ft

- The event of interest may be, e.g.,
  - death, cancer incidence, disease remission
  - HIV infection, AIDS onset
  - organ rejection, transplant failure
  - bankruptcy, economic recovery

## Basic quantities of survival models

### Recall random variables

- An RV is a real-valued function.
- The cumulative distribution function (cdf) of  $X$ , say  $F_X$ , is defined as

$$F_X(x) = \Pr(X \leq x), \quad x \in \mathbb{R}.$$

- $F_X$  satisfies following three properties:
  - \* (right continuous)  $\lim_{x \rightarrow x_0^+} F_X(x) = F_X(x_0)$ ;
  - \* (non-decreasing)  $F_X(x_1) \leq F_X(x_2)$  for  $x_1 \leq x_2$ ;
  - \* (ranging from 0 to 1)  $F_X(-\infty) = 0$  and  $F_X(\infty) = 1$ .
- Reversely, any function satisfying the three properties must be a cdf for certain RV.
- Discrete RV
  - RV  $X$  merely outputs countable different values
  - Probability mass function (pmf):  $p_X(x) = \Pr(X = x)$
- Continuous RV
  - RV  $X$  is continuous iff its cdf  $F_X$  is (absolutely) continuous, i.e., there exists  $f_X$  such that

$$F_X(x) = \int_{-\infty}^x f_X(u) du, \quad \forall x \in \mathbb{R}.$$

- Probability density function (pdf):  $f_X(x) = dF_X(x)/dx = \lim_{\delta \rightarrow 0^+} \frac{\Pr(x < X \leq x + \delta)}{\delta}$ .

### Survival function

- $T (\geq 0)$ : survival time or, more specifically, the time elapsed from time 0 to the event of interest (abbr. time to event); the RV of interest in survival analysis
  - The time origin, 0, often represents
    - \* the time point when a disease was first detected,
    - \* the initiation time of therapy/procedure, or
    - \* certain meaningful time point
  - E.g.,
    - \* In a clinical trial: time 0 might be the time of randomization;
    - \* Among heart transplant patients: time 0 is the end of transplantation
- $S_T(t) = \Pr(T > t) = 1 - F_T(t)$ :
  - The probability that the event of interest has not yet occurred by time  $t$
  - (right continuous)  $\lim_{t \rightarrow t_0^+} S_T(t) = S_T(t_0)$ ;
  - (non-increasing)  $S_T(t_1) \geq S_T(t_2)$  for  $t_1 \leq t_2$ ;
  - (ranging from 0 to 1)  $S_T(0) = 1$  and  $S_T(\infty) = 0$ .

## Hazard function (aka. hazard rate)

- $\lambda_T(t)$ : the instantaneous risk of experiencing the event of interest at time  $t$ , assuming the subject has survived up to  $t$ 
  - Non-negative for all  $t$
- If  $T$  is continuous with pdf  $f_T$  (i.e., the event may occur at any time point in  $[0, \infty)$ )
  - $\lambda_T(t) = \lim_{\delta \rightarrow 0+} \frac{\Pr(t \leq T < t + \delta | T \geq t)}{\delta} \stackrel{\text{Why?}}{=} f_T(t)/S_T(t)$
  - Conditional density (not a probability), given that the event has not yet occurred prior to time  $t$
- If  $T$  is discrete with pmf  $p_T$  (i.e., the event may only occur at  $0 = t_0 < t_1 < t_2 < \dots$ ),
  - $\lambda_T(t_j) = \Pr(T = t_j | T \geq t_j) = p_T(t_j)/S_T(t_{j-1})$  and zero elsewhere,  $j = 1, 2, \dots$ 
    - \* Conditional failure probability, given that the event has not yet occurred prior to time  $t$

- Ex. 1.1 ([JM] Ex. 2.3): Suppose that  $T$  has pmf  $p_T(t_j) = 1/3$ ,  $j = 1, 2, 3$ . Find the survival and hazard functions.
- Ans. to Ex. 1.1: The survival function is

$$S_T(t) = \Pr(T > t) = \sum_{j: t_j > t} p_T(t_j) = \begin{cases} 1 & \text{if } 0 \leq t < t_1 \\ 2/3 & \text{if } t_1 \leq t < t_2 \\ 1/3 & \text{if } t_2 \leq t < t_3 \\ 0 & \text{if } t \geq t_3. \end{cases}$$

It is a right-continuous descending step function. The hazard function is then

$$\lambda(t_j) = \frac{p_T(t_j)}{S_T(t_{j-1})} = \begin{cases} 1/3 & j = 1 \\ 1/2 & j = 2 \\ 1 & j = 3 \\ 0 & \text{elsewhere.} \end{cases}$$

## Cumulative hazard function

- $\Lambda_T(t)$ : the integrated risk of the event occurring from time 0 to  $t$ 
    - $\Lambda_T(t) = \int_0^t \lambda_T(s) ds$  if  $T$  is continuous
    - $\Lambda_T(t) = \sum_{t_j \leq t} \lambda_T(t_j)$  if  $T$  is discrete
- 
- Ex. 1.2 (exponential distribution): Suppose that  $T$  has pdf  $f_T(t) = \lambda \exp(-\lambda t)$ ,  $\lambda > 0$ . Find the survival, hazard and cumulative hazard functions.
    - Memorylessness: constant hazard rate  $\Rightarrow \Pr(T > t + t_0 | T > t_0) = \Pr(T > t)$  i.e., the survival probability would not be influenced by the history
    - This is the only continuous distribution with constant hazard rate
    - Not often used to model human subjects unless followed for relatively short duration; more often used in engineering or for illustrative purposes.
  - Ans. to Ex. 1.2:  $F_T(t) = 1 - \exp(-\lambda t)$ ,  $t > 0 \Rightarrow S_T(t) = \exp(-\lambda t)$  if  $t > 0$  and 1 otherwise. So,  $\lambda_T(t) = \lambda$  and  $\Lambda_T(t) = \lambda t$ .

- Ex. 1.3 (Weibull distribution): Find survival, hazard and cumulative hazard functions for the following three equivalent parameterizations of Weibull pdf: for  $t \geq 0$ ,
  - $f_T(t) = (k/\lambda)(t/\lambda)^{k-1} e^{-(t/\lambda)^k}$  (used in  $R$  with  $k$  as “shape” and  $\lambda$  as “scale”),
  - $f_T(t) = b k t^{k-1} e^{-b t^k}$  (i.e.,  $b = \lambda^{-k}$ ),
  - $f_T(t) = \beta k (\beta t)^{k-1} e^{-(\beta t)^k}$  (i.e.,  $\beta = \lambda^{-1}$ ).
- For the Weibull distribution with any of the three parameterizations

- $k > 1$ : monotone increasing hazard rate
- $k < 1$ : monotone decreasing hazard rate
- $k = 1$ : reducing to the exponential distribution
- Ans. to Ex. 1.3:
  - $F_T(t) = 1 - \exp\{-(t/\lambda)^k\}$  for  $t \geq 0$  and zero elsewhere
  - $F_T(t) = 1 - \exp(-bt^k)$  for  $t \geq 0$  and zero elsewhere
  - $F_T(t) = 1 - \exp\{-(\beta t)^k\}$  for  $t \geq 0$  and zero elsewhere

## More identities

- When  $T$  is continuous
  - $\lambda_T(t) = -d\{\ln S_T(t)\}/dt$  (Why?)
    - \* Proof:  $\lambda_T(t) = f_T(t)/S_T(t) = F'_T(t)/S_T(t) = \frac{d\{1-S_T(t)\}}{dt} \frac{1}{S_T(t)} = -d\{\ln S_T(t)\}/dt$
    - The last equality holds due to the chain rule
  - $\Lambda_T(t) = -\ln S_T(t)$
  - $S_T(t) = \exp\{-\Lambda_T(t)\}$
  - $f_T(t) = S_T(t)\lambda_T(t)$
- When  $T$  is discrete with potential values  $0 \leq t_0 < t_1 < \dots$ 
  - $\lambda_T(t_j) = 1 - S(t_j)/S_T(t_{j-1})$  (Why?)
  - If  $t_J \leq t < t_{J+1}$ , then  $S_T(t) = \prod_{j:t_j \leq t} \{1 - \lambda_T(t_j)\} = \prod_{j=1}^J \{1 - \lambda_T(t_j)\}$  (Why?)
    - \* Noting that  $1 - \lambda_T(t_j) = S(t_j)/S_T(t_{j-1})$
- So, knowing one of  $f_T$ ,  $S_T$ ,  $\lambda_T$  and  $\Lambda_T$  is sufficient to confirm the distribution of  $T$

## Other quantities

- Mean residual lifetime (for continuous  $T$ ):  $r(t) = E(T - t \mid T \geq t) = \int_t^\infty (s - t)f_T(s)ds/S_T(t) = \int_t^\infty S_T(s)ds/S_T(t)$  (Why?)
  - The average remaining lifetime for an individual alive at time  $t$
  - Proof:  $\int_t^\infty (s - t)f_T(s)ds/S_T(t) = \int_t^\infty (\int_t^s du)dF_T(s)/S_T(t) \stackrel{\text{Tonelli's theorem}}{=} \int_t^\infty (\int_u^\infty dF_T(s))du/S_T(t) = \int_t^\infty \Pr(T > u)du/S_T(t) = \int_t^\infty S_T(u)du/S_T(t)$
- Mean lifetime (or life expectancy, i.e.,  $E(T)$  and also  $r(0)$ )
  - When  $T$  is continuous,  $E(T) = \int_0^\infty t f_T(t)dt = \int_0^\infty S_T(t)dt$ 
    - \* The area under the survival curve  $S_T(t)$
  - When  $T$  is discrete,  $E(T) = \sum_j t_j p_T(t_j)$
- Median lifetime: the smallest  $t$  such that  $S_T(t) \leq .5$ 
  - The earliest time at which half the cohort will have died

## Censoring

- $T$  is potentially unobserved in full for all the subjects
  - Subjects whose survival times are unobserved during follow-up are said to be censored.
- Cause of censoring
  - Administrative censoring
    - \* Study ends before the event of interest has occurred
    - \* Usually independent of survival time
  - Withdrawal from study
    - \* E.g.,
      - a patient drops out of clinical trial because he/she is too sick to participate
      - a subject discontinues participation in trial because her symptoms have subsided
    - \* Depending on the censoring
- Types of censoring
  - Right-censoring (by default here):
    - \* For a censored subject,  $T$  is not known exactly, but  $\geq$  the censoring time;
    - \* i.e., there is a lower bound for the event time.

- Left-censoring
  - \* For a censored subject there is a upper bound for the event time
  - \* E.g.,
    - ([DM] Example 3.4) “In early childhood learning centers, interest often focuses upon testing children to determine when a child learns to accomplish certain specified tasks. The age at which a child learns the task would be considered the time-to-event. Often, some children can already perform the task when they start in the study. Such event times are considered left censored.”
- Interval-censoring
  - \* For a censored subject there are both lower and upper bounds for the event time
  - \* E.g.,
    - ([DM] Example 3.5) “In the Framingham Heart Study, the ages of first occurrence of the subcategory angina pectoris may be known only to be between two clinical examinations, approximately two years apart (Odell et al., 1992). Such observations would be interval-censored.”
- Independent censoring (by default here)
  - The censoring time is independent of survival time