

# Applied survival analysis

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# Survival Analysis: Introduction

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# Introduction

Survival Analysis typically focuses on **time to event** data. In the most general sense, it consists of techniques for positive-valued random variables, such as

- time to death
- time to onset (or relapse) of a disease
- length of stay in a hospital
- duration of a strike
- money paid by health insurance
- viral load measurements
- time to finishing a doctoral dissertation!

## Kinds of survival studies

Survival studies include:

- clinical trials
- prospective cohort studies
- retrospective cohort studies

Typically, survival data are not fully observed, but rather are *censored*.

## Goals of this course

In this course, we will:

- describe survival data
- compare survival of several groups
- explain survival with covariates
- design studies with survival endpoints

## Some useful references

- Collett: *Modelling Survival Data in Medical Research*
- Cox and Oakes: *Analysis of Survival Data*
- Kleinbaum: *Survival Analysis: A self-learning text*
- Klein & Moeschberger: *Survival Analysis: Techniques for censored and truncated data*
- Cantor: *Extending SAS Survival Analysis Techniques for Medical Research*
- Allison: *Survival Analysis Using the SAS System*

## Definitions and notation

Failure time random variables are always **non-negative**.

That is, if we denote the failure time by  $T$ , then  $T \geq 0$ .

$T$  can either be **discrete** (taking a finite set of values, e.g.  $a_1, a_2, \dots, a_n$ ) or **continuous** (defined on  $(0, \infty)$ ).

A random variable  $X$  is called a **censored failure time random variable** if  $X = \min(T, U)$ , where  $U$  is a non-negative censoring variable.

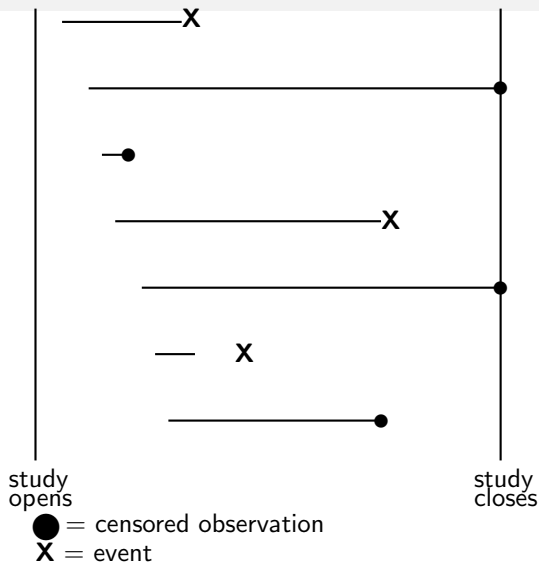
## Defining a time random variable

In order to define a failure time random variable, we need:

- (1) an unambiguous **time origin**  
(e.g. randomization to clinical trial, purchase of car)
- (2) a **time scale**  
(e.g. real time (days, years), mileage of a car)
- (3) definition of the **event**  
(e.g. death, need a new car transmission)



## Illustration of survival data



The illustration of survival data on the previous page shows several features which are typically encountered in analysis of survival data:

- individuals do not all enter the study at the same time
- when the study ends, some individuals still haven't had the event yet
- other individuals drop out or get lost in the middle of the study, and all we know about them is the last time they were still “free” of the event

The first feature is referred to as “**staggered entry**”

The last two features relate to “**censoring**” of the failure time events.

## Types of censoring

### Right-censoring

We have right censoring when only the r.v.  $X_i = \min(T_i, U_i)$  is observed due to

- loss to follow-up
- drop-out
- study termination

We call this right-censoring because the true unobserved event is to the right of our censoring time; i.e., all we know is that the event has not happened at the end of follow-up.

## Failure events

In addition to observing  $X_i$ , we also get to see the **failure indicator**:

$$\delta_i = \begin{cases} 1 & \text{if } T_i \leq U_i \\ 0 & \text{if } T_i > U_i \end{cases}$$

Some software packages instead assume we have a **censoring indicator**:

$$c_i = \begin{cases} 0 & \text{if } T_i \leq U_i \\ 1 & \text{if } T_i > U_i \end{cases}$$

Right-censoring is the most common type of censoring assumption we will deal with in survival analysis.

## Left-censored data

### Left censoring

We have left censoring when we can only observe  $Y_i = \max(T_i, U_i)$  and the failure indicators:

$$\epsilon_i = \begin{cases} 1 & \text{if } U_i \leq T_i \\ 0 & \text{if } U_i > T_i \end{cases}$$

e.g. In studies of time to HIV seroconversion, some of the enrolled subjects have already seroconverted at entry into the study - they are left-censored.

## Interval-censored data

### Interval censoring

We have interval censoring when we observe  $(L_i, R_i)$  where  $T_i \in (L_i, R_i)$

ex #1: Time to prostate cancer, observe longitudinal PSA measurements

ex #2: Time to undetectable viral load in AIDS studies, based on measurements of viral load taken at each clinic visit

## Independent versus informative censoring

We say censoring is **independent** (non-informative) if  $U_i$  is independent of  $T_i$ .

- **ex.1** If  $U_i$  is the planned end of the study (say, 2 years after the study opens), then it is usually independent of the event times
- **ex.2** If  $U_i$  is the time that a patient drops out of the study because they've gotten much sicker and/or had to discontinue taking the study treatment, then  $U_i$  and  $T_i$  are probably not independent

## What does “independent censoring” mean?

In plain language, independent censoring simply means

**An individual censored at  $U$  should be representative of all subjects who survive to  $U$ .**

This means that censoring at  $U$  *could* depend on prognostic characteristics measured at baseline, but that among all those with the same baseline characteristics, the probability of censoring prior to or at time  $U$  should be the same.



## Informative censoring

Censoring is considered **informative** if the distribution of  $U_i$  contains any information about the parameters characterizing the distribution of  $T_i$ .

## Types of censoring times

Suppose we have a sample of observations on  $n$  people:

$$(T_1, U_1), (T_2, U_2), \dots, (T_n, U_n)$$

There are three main types of censoring times:

- **Type I:** All the  $U_i$ 's are the same  
e.g. animal studies, all animals sacrificed after 2 years
- **Type II:**  $U_i = T_{(r)}$ , the time of the  $r$ th failure.  
e.g. animal studies, stop when 4/6 have tumors
- **Random:** the  $U_i$ 's are random variables,  $\delta_i$ 's are failure indicators:

$$\delta_i = \begin{cases} 1 & \text{if } T_i \leq U_i \\ 0 & \text{if } T_i > U_i \end{cases}$$

## Example A. Duration of nursing home stay

Morris et al., *Case Studies in Biometry*, Ch 12

The National Center for Health Services Research studied 36 for-profit nursing homes to assess the effects of different financial incentives on length of stay.

“Treated” nursing homes received higher per diems for Medicaid patients, and bonuses for improving a patient’s health and sending them home.

The study included 1601 patients admitted between May 1, 1981 and April 30, 1982.

## Example A (cont'd)

Variables include:

**LOS** - Length of stay of a resident (in days)

**AGE** - Age of a resident

**RX** - Nursing home assignment (1:bonuses, 0:no bonuses)

**GENDER** - Gender (1:male, 0:female)

**MARRIED** - (1: married, 0:not married)

**HEALTH** - health status (2:second best, 5:worst)

**FAIL** - Failure/Censoring indicator (1:discharged,0:censored)

First few lines of data:

```
37 86 1 0 0 2 0
```

```
61 77 1 0 0 4 0
```

## Example B. Fecundability

Women who had recently given birth were asked to recall how long it took them to become pregnant, and whether or not they smoked during that time. The outcome of interest is time to pregnancy (in menstrual cycles).

Cycle	Smokers	Non-smokers
1	29	198
2	16	107
3	17	55
4	4	38
5	3	18
6	9	22
7	4	7
8	5	9
9	1	5
10	1	3
11	1	6
12	3	6
12+	7	12

## Example C: MAC Prevention Clinical Trial

ACTG 196 was a randomized clinical trial to study the effects of combination regimens on prevention of MAC (*mycobacterium avium complex*), one of the most common OIs in AIDS patients.

The **treatment regimens** were:

- clarithromycin (new)
- rifabutin (standard)
- clarithromycin plus rifabutin

Other characteristics of trial:

- Patients enrolled between April 1993 and February 1994
- Follow-up ended August 1995
- In February 1994, rifabutin dosage was reduced from 3 pills/day (450mg) to 2 pills/day (300mg) due to concern over **uveitis**<sup>1</sup>

The main intent-to-treat analysis compared the 3 treatment arms without adjusting for this change in dosage.

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<sup>1</sup>Uveitis is an adverse experience resulting in inflammation of the uveal tract in the eyes (about 3-4% of patients reported uveitis).

## Example D: Time to first tuberculosis (TB) episode

These data come from a longitudinal surveillance study of Kenyan children. The data have multiple lines per patient that correspond to multiple visits to the clinic. Data gathered at each visit are:

**PATID** - Patient identification

**timetotb** - Time from entry in the study until TB

**first\_tb** - Whether this is the first TB episode

**cd4** - Absolute CD4-positive lymphocyte count

**cd4per** - CD4 percent

**orphan** - Orphaned status

**onARV** - Is the patient currently receiving antiretroviral (ARV) therapy? **age** -

Age (in years) at each visit

The difference of these data is that the explanatory variables (e.g., ARV therapy, CD4 count, percent and so on) change over time.

## More Definitions and Notation

There are several equivalent ways to characterize the probability distribution of a survival random variable. Some of these are familiar; others are special to survival analysis. We will focus on the following terms:

- The density function  $f(t)$
- The survivor function  $S(t)$
- The hazard function  $\lambda(t)$
- The cumulative hazard function  $\Lambda(t)$



## The survival density function

Suppose that  $T$  takes values in  $a_1, a_2, \dots, a_n$ . Then, the survival density function (or Probability Mass Function) for discrete r.v.'s is defined as:

$$\begin{aligned} f(t) &= \Pr(T = t) \\ &= \begin{cases} f_j & \text{if } t = a_j, j = 1, 2, \dots, n \\ 0 & \text{if } t \neq a_j, j = 1, 2, \dots, n \end{cases} \end{aligned}$$

## The survival density function for continuous r.v.'s

The survival density function for continuous r.v.'s is defined as follows:

$$f(t) = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} Pr(t \leq T \leq t + \Delta t)$$

## The Survivorship Function

The survivorship function is as follows:  $S(t) = P(T \geq t)$ .

In other settings, the cumulative distribution function,  $F(t) = P(T \leq t)$ , is of interest.

In survival analysis, our interest tends to focus on the survival function,  $S(t)$ .

## Survivorship function for continuous and discrete r.v.'s

For a continuous random variable:

$$S(t) = \int_t^{\infty} f(u) du$$

For a discrete random variable:

$$\begin{aligned} S(t) &= \sum_{u \geq t} f(u) \\ &= \sum_{a_j \geq t} f(a_j) = \sum_{a_j \geq t} f_j \end{aligned}$$

## Notes

- From the definition of  $S(t)$  for a continuous variable,  
 $S(t) = 1 - F(t)$  as long as  $f(t)$  is absolutely continuous
- For a discrete variable, we have to decide what to do if an event occurs exactly at time  $t$ ; i.e., does that become part of  $F(t)$  or  $S(t)$ ?
- To get around this problem, several books define  
 $S(t) = \Pr(T > t)$ , or else define  $F(t) = \Pr(T < t)$   
(eg. Collett)

## The Hazard function

The Hazard Function  $\lambda(t)$ .

Sometimes called an *instantaneous failure rate*, the *force of mortality*, or the *age-specific failure rate*.

## The hazard function for continuous r.v.'s

The hazard function is defined as follows for continuous random variables:

$$\begin{aligned}\lambda(t) &= \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \Pr(t \leq T < t + \Delta t | T \geq t) \\&= \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \frac{\Pr([t \leq T < t + \Delta t] \cap [T \geq t])}{\Pr(T \geq t)} \\&= \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} \frac{\Pr(t \leq T < t + \Delta t)}{\Pr(T \geq t)} \\&= \frac{f(t)}{S(t)}\end{aligned}$$

## The hazard function for discrete random variables

The hazard function is defined as follows for discrete random variables:

$$\begin{aligned}\lambda(a_j) \equiv \lambda_j &= Pr(T = a_j | T \geq a_j) \\ &= \frac{P(T = a_j)}{P(T \geq a_j)} \\ &= \frac{f(a_j)}{S(a_j)} \\ &= \frac{f(t)}{\sum_{k: a_k \geq a_j} f(a_k)}\end{aligned}$$



## The Cumulative Hazard function

The Cumulative Hazard function  $\Lambda(t)$  is defined as follows:

- **Continuous random variables:**

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

- **Discrete random variables:**

$$\Lambda(t) = \sum_{k: a_k < t} \lambda_k$$

## Comment

The cumulative hazard does not have a very intuitive interpretation.

However, it turns out to be very useful for certain graphical assessments:

- consistency with certain parametric models
- evaluation of proportional hazards assumption for Cox models

## Relationship between $S(t)$ and $\lambda(t)$

We've already shown that, for a continuous r.v.

$$\lambda(t) = \frac{f(t)}{S(t)}$$

For a left-continuous survivor function  $S(t)$ , we can show:

$$f(t) = -S'(t) \quad \text{or} \quad S'(t) = -f(t)$$

We can use this relationship to show that:

$$\begin{aligned} -\frac{d}{dt}[\log S(t)] &= -\left(\frac{1}{S(t)}\right) S'(t) \\ &= -\frac{-f(t)}{S(t)} = \frac{f(t)}{S(t)} \end{aligned}$$

So another way to write  $\lambda(t)$  is as follows:

$$\lambda(t) = -\frac{d}{dt}[\log S(t)]$$

## Relationship between $S(t)$ and $\Lambda(t)$ : Continuous case

In the case of continuous time we have

$$\begin{aligned}\Lambda(t) &= \int_0^t \lambda(u) du \\ &= \int_0^t \frac{f(u)}{S(u)} du \\ &= \int_0^t -\frac{d}{du} \log S(u) du \\ &= -\log S(t) + \log S(0) \\ &\Rightarrow S(t) = e^{-\Lambda(t)}\end{aligned}$$

## Relationship between $S(t)$ and $\Lambda(t)$ : Discrete case

Suppose that  $a_j < t \leq a_{j+1}$ . Then

$$\begin{aligned} S(t) &= P(T \geq a_1, T \geq a_2, \dots, T \geq a_{j+1}) \\ &= P(T \geq a_1)P(T \geq a_2 | T \geq a_1) \cdots P(T \geq a_{j+1} | T \geq a_j) \\ &= (1 - \lambda_1) \times \cdots \times (1 - \lambda_j) \\ &= \prod_{k: a_k < t} (1 - \lambda_k) \end{aligned}$$

Cox defines  $\Lambda(t) = \sum_{k: a_k < t} \log(1 - \lambda_k)$  so that  $S(t) = e^{-\Lambda(t)}$  in the discrete case, as well.

## Some hazard shapes seen in applications

Hazard shapes seen in application are as follows:

- **increasing**

e.g. aging after 65

- **decreasing**

e.g. survival after surgery

- **bathtub**

e.g. age-specific mortality

- **constant**

e.g. survival of patients with advanced chronic disease

## Estimating the survival or hazard function

We can estimate the survival (or hazard) function in two ways:

- by specifying a parametric model for  $\lambda(t)$  based on a particular density function  $f(t)$
- by developing an empirical estimate of the survival function (i.e., non-parametric estimation)

## Under no censoring

If no censoring:

The empirical estimate of the survival function,  $\tilde{S}(t)$ , is the proportion of individuals with event times greater than  $t$ .



## Estimation under censoring

With censoring:

If there are censored observations, then  $\tilde{S}(t)$  is not a good estimate of the true  $S(t)$ , so other non-parametric methods must be used to account for censoring (life-table methods, Kaplan-Meier estimator)

## Measuring Central Tendency in Survival

- **Mean survival** - call this  $\mu$

$$\begin{aligned}\mu &= \int_0^{\infty} uf(u)du \quad \text{for continuous } T \\ &= \sum_{j=1}^n a_j f_j \quad \text{for discrete } T\end{aligned}$$

- **Median survival** - call this  $\tau$ , is defined by

$$S(\tau) = 0.5$$

Similarly, any other percentile could be defined.

In practice, we don't usually hit the median survival at exactly one of the failure times. In this case, the estimated median survival is the *smallest* time  $\tau$  such that

$$\hat{S}(\tau) \leq 0.5$$

## Some Parametric Survival Distributions

The **Exponential** distribution (1 parameter)

$$f(t) = \lambda e^{-\lambda t} \text{ for } t \geq 0$$

$$S(t) = \int_t^{\infty} f(u) du = e^{-\lambda t}$$

$$\begin{aligned} \lambda(t) &= \frac{f(t)}{S(t)} \\ &= \lambda \quad \text{constant hazard!} \end{aligned}$$

$$\begin{aligned} \Lambda(t) &= \int_0^t \lambda(u) du \\ &= \int_0^t \lambda du = \lambda t \end{aligned}$$

**Check:** Does  $S(t) = e^{-\Lambda(t)}$  ?

## Characteristics of the exponential distribution

median:

solve  $0.5 = S(\tau) = e^{-\lambda\tau}$ :

$$\Rightarrow \tau = \frac{-\log(0.5)}{\lambda}$$

mean:

$$\int_0^{\infty} u\lambda e^{-\lambda u} du = \frac{1}{\lambda}$$

## Weibull distribution (2 parameters)

Generalizes exponential:

$$S(t) = e^{-\lambda t^{\kappa}}$$

$$f(t) = \frac{-d}{dt} S(t) = \kappa \lambda t^{\kappa-1} e^{-\lambda t^{\kappa}}$$

$$\lambda(t) = \kappa \lambda t^{\kappa-1}$$

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

$\lambda$  - the *scale* parameter

$\kappa$  - the *shape* parameter

## Weibull distribution (cont'd)

The Weibull distribution is convenient because of simple forms. It includes several hazard shapes:

$\kappa = 1 \rightarrow$  constant hazard

$0 < \kappa < 1 \rightarrow$  decreasing hazard

$\kappa > 1 \rightarrow$  increasing hazard

## The Rayleigh distribution

The Rayleigh distribution is another 2-parameter generalization of exponential:

$$\lambda(t) = \lambda_0 + \lambda_1 t$$

## The Compound Exponential distribution

This is given by the following definition:  $T \sim \exp(\lambda)$ ,  $\lambda \sim g$

$$f(t) = \int_0^{\infty} \lambda e^{-\lambda t} g(\lambda) d\lambda$$



## The log-normal and log-logistic distributions

Possible distributions for  $T$  obtained by specifying for  $\log T$  any convenient family of distributions, e.g.

$\log T \sim \text{normal}$  (non-monotone hazard)

$\log T \sim \text{logistic}$

## The inverse Gaussian distribution

First passage time of Brownian motion to linear boundary.

## When to use each one

Why use one versus another?

- technical convenience for estimation and inference
- explicit simple forms for  $f(t)$ ,  $S(t)$ , and  $\lambda(t)$ .
- qualitative shape of hazard function

One can usually distinguish between a one-parameter model (like the exponential) and two-parameter (like Weibull or log-Normal) in terms of the adequacy of fit to a dataset.

Without a lot of data, it may be hard to distinguish between the fits of various 2-parameter models (i.e., Weibull vs log-normal)

## Preview of Coming Attractions

Next class we will discuss the most famous non-parametric approach for estimating the survival distribution, called the *Kaplan-Meier estimator*.

To motivate the derivation of this estimator, we will first consider a set of survival times where there is no censoring.

The following are **times to relapse** (weeks) for 21 leukemia patients receiving control treatment (Table 1.1 of Cox & Oakes):

1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

How would we estimate  $S(10)$ , the probability that an individual survives to time 10 or later?

What about  $\tilde{S}(8)$ ? Is it  $\frac{12}{21}$  or  $\frac{8}{21}$ ?