An introduction to survival analysis

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Contents

What is time-to-event (TTE) data?

We can measure **time** in:

- years
- months
- seconds

The **event** could be:

- death from disease
- product failure
- losing a customer

TTE data consists of ($time$, $\overbrace{event}^{\text{yes/no}}$) tuples.

must be a binary variable

Time-to-event (TTE) data

TTE analysis is also known as:

- survival analysis
- failure time analysis
- reliability theory (engineering)
- duration modelling (economics)
- event history analysis (sociology)

Use cases for TTE analysis:

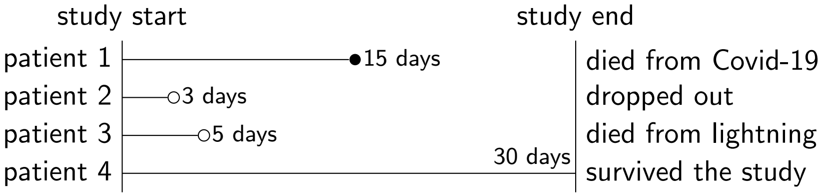
- clinical research
- customer analytics (churn)
- hardware (equipment failure)

Example: Covid-19 treatment trial

A randomised controlled trial ($n = 4$) was conducted to assess the efficacy of drug ABC in treating Covid-19. This is what happened to the patients:

patient	received ABC?	outcome
1	yes	died from Covid-19 on day 15
2	no	dropped out of the study after day 3
3	yes	died by a lightning stroke on day 5
4	no	survived the study (30 days)

Example: Covid-19 treatment trial



The **time** is the number of days since testing positive for Covid-19.
The **event** is whether the patient died due to Covid-19.

Time-to-event data

patient	time	event
1	15	yes
2	$[0, 3]$	no
3	$[0, 5)$	no
4	$[0, 30]$	no

Censoring

Censoring occurs when we have some information about an individual's survival time, but don't know the exact time. Possible reasons include

- not experiencing the event before the study concludes;
- getting lost to follow-up during the study period;
- withdrawing from the study.

We just saw examples of *right-censored* data.

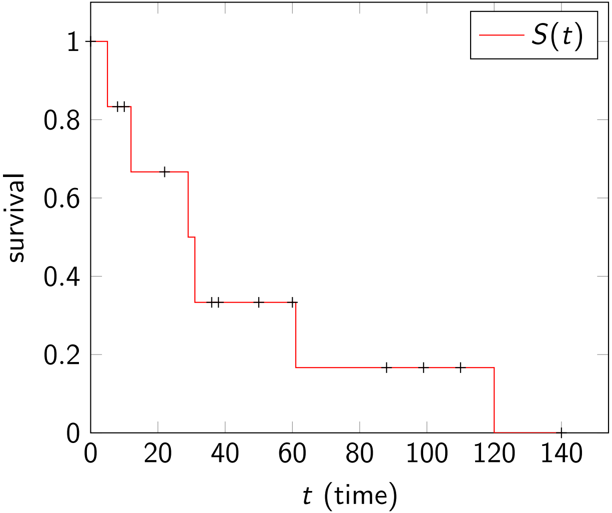
Survival function

Let T be a continuous random variable representing survival time. The **survival function** $S(t)$ is the probability that an individual will survive past time t.

Survival function

$$S(t) = \Pr\left(T > t\right)$$

Survival curve



Modelling the survival function

The **Kaplan-Meier estimator** provides a non-parametric estimate of the survival function $S(t)$ using the survival curve.

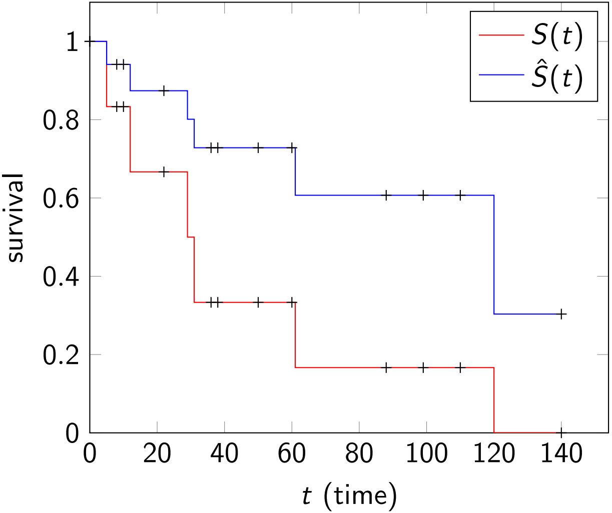
Kaplan-Meier estimator

$$\hat{S}(t) = \prod_{i:t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

where

- t_i is an event time
- d_i is the number of deaths at time t_i
- n_i is the number of individuals *known to have survived* until t_i

Survival curve and Kaplan-Meier estimator



Hazard function

The **hazard function** expresses the *instantaneous rate of occurence* of the event.
Supposing an individual survived until time t, it expresses the probability of dying within a short additional time dt, per unit time.

Hazard function

$$\begin{aligned}\lambda(t) &= \lim_{dt \to 0} \frac{\Pr\left(t \leq T \leq t + dt | T \geq t\right)}{dt} \\ &= \lim_{dt \to 0} \frac{\Pr\left(t \leq T \leq t + dt\right)}{dt \cdot S(t)}\end{aligned}$$

What does survival depend on?

Recall the survival function $S(t) = \Pr(T > t)$ as the probability that an individual will survive past time t. Let's assume that $S(t)$ depends on

1. the **baseline hazard function** (how risk of event occurence changes over time at baseline covariates); and
2. the **effect parameters** (how hazard varies due to the covariates), also known as the *partial hazard*.

Cox's proportional hazards model

Cox's proportional hazards model uses both factors to provide a semi-parametric estimate of the hazard function $\lambda(t)$ conditioned on the covariates $\mathbf{x}$.

Cox's proportional hazards model

$$\lambda(t|\mathbf{x}) = \overbrace{\lambda_0(t)}^{\substack{\text{baseline}\\\text{hazard}}} \overbrace{\exp\left(\sum_{i=1}^{n} \beta_i \mathbf{x}_i\right)}^{\text{partial hazard}}$$

Proportional hazards assumption

The model assumes fixed **proportional hazards**, i.e. the hazard for an individual i in proportion to the hazard of any other individual j is fixed over time. That is,

$$\frac{\lambda_i(t|\mathbf{X}_i)}{\lambda_j(t|\mathbf{X}_j)} = \exp\left(\beta(\mathbf{X}_i - \mathbf{X}_j)\right).$$

Therefore,

- the baseline hazard $\lambda_0(t)$ is independent of the covariates, and
- the partial hazard is time-independent.

Partial likelihood

For each individual i, let

- T_i be a possibly censored survival time random variable, and
- $\mathbf{X}_i$ denote the covariates.

Further, let the **risk set** $\mathcal{R}(t) = \{i : T_i \geq t\}$ be the set of individuals that are "at risk" at time t.
Cox proposed a **partial likelihood** for β without involving $\lambda_0(t)$.
Maximising this function allows us to estimate the parameters $\boldsymbol{\beta}$.

$$L(\boldsymbol{\beta}) = \prod_{j=1}^{N} \Pr\left(\text{individual } j \text{ dies} \mid \text{one death from } \mathcal{R}(T_j)\right)$$

Partial likelihood formula

$$
\begin{aligned}
L(\beta) &= \prod_{j=1}^{N} \Pr\left(\text{individual } j \text{ dies} \mid \text{one death from } \mathcal{R}(T_j)\right) \\
&= \dots \\
&= \prod_{j=1}^{N} \frac{\lambda(T_j|\mathbf{X}_j)}{\sum_{k\in\mathcal{R}(T_j)} \lambda(T_j|\mathbf{X}_k)} \\
&= \prod_{j=1}^{N} \frac{\lambda_0(T_j)\exp\left(\beta\mathbf{X}_j\right)}{\sum_{k\in\mathcal{R}(T_j)} \lambda_0(T_j)\exp\left(\beta\mathbf{X}_k\right)} \\
&= \prod_{j=1}^{N} \frac{\exp\left(\beta\mathbf{X}_j\right)}{\sum_{k\in\mathcal{R}(T_j)} \exp\left(\beta\mathbf{X}_k\right)}
\end{aligned}
$$

Parameter estimation

We can estimate the parameters $\boldsymbol{\beta}$ by minimizing the negative partial log-likelihood, i.e. $-\log L(\boldsymbol{\beta})$, by taking the partial derivatives with respect to the parameters $\boldsymbol{\beta}$ and solving for the minimum using e.g. the Newton-Raphson algorithm.

Hazard ratios

The fraction used to express the proportional hazards assumption is actually the **hazard ratio**, measuring the risk of individual i relative to individual j:

$$HR = \frac{\lambda(t|\mathbf{X}_i)}{\lambda(t|\mathbf{X}_j)} = \exp\left(\boldsymbol{\beta}(\mathbf{X}_i - \mathbf{X}_j)\right).$$

We may be interested in the relative risk associated with a particular covariate c, specifically the risk of said covariate having value c_i compared to c_j. Consider two dummy individuals i and j differing only in the c^{th} covariate, i.e. $\mathbf{X}_{i,k} = \mathbf{X}_{j,k}$ for $k \neq c$. Then the relative risk associated with c_i compared to c_j is

$$HR = \exp\left(\boldsymbol{\beta}_c(c_i - c_j)\right).$$

Interpretation of hazard ratios

- $HR = 1$: no effect
- $HR > 1$: increase in hazard
- $HR < 1$: reduction in hazard