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

must be a binary variable

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

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:

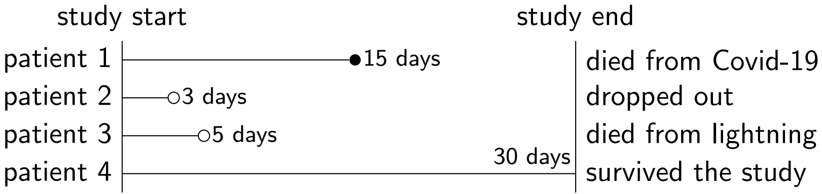
- TODO

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

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

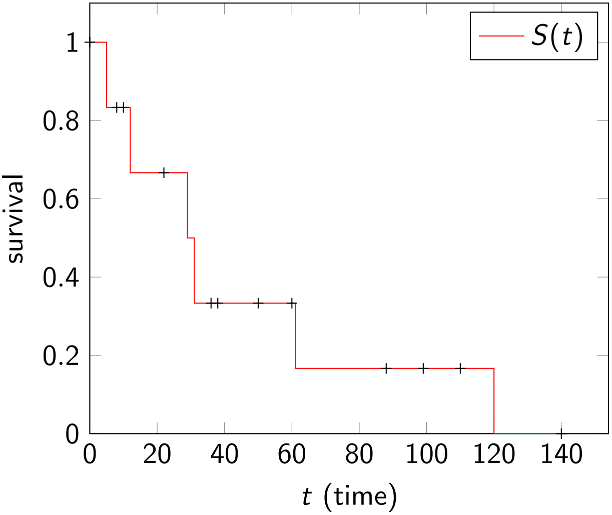
Survival function

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

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

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.

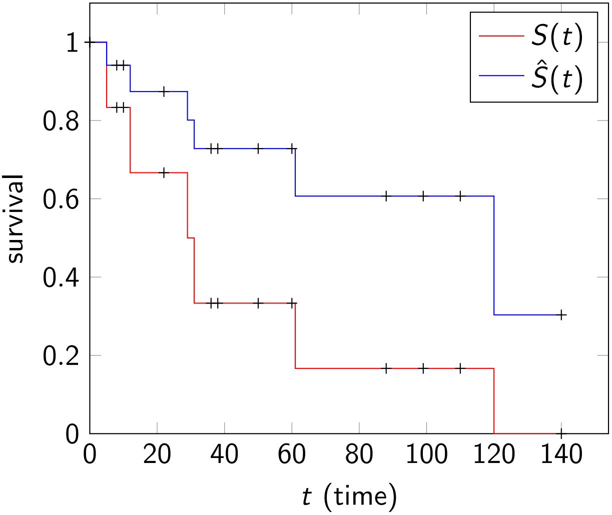
Kaplan-Meier estimator

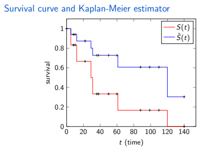
$$\hat{S}(t) = \prod_{i:t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

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





- When there is no censoring, $S(t) = \hat{S}(t)$.
- Commonly used to compare two study populations.
- Does not control for covariates.

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

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

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

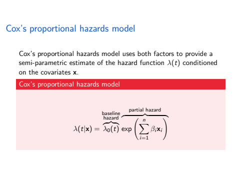
1. the **baseline hazard function** (how risk of event occurence changes over time at baseline covariates); and
2. the **effect parameters** (how hazard varies due to the covariates), also known as the *partial hazard*.

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

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



- $\lambda_0(t)$ is a population-level baseline hazard that changes over time (for a reference individual with zeroed covariates).
- The partial hazard is a linear function of the covariates that is exponentiated. Each coefficient β_i is the relative risk associated with covariate $\mathbf{x}_i$.

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.

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The so-called **extended Cox model** allows the partial hazard to vary with time, and therefore no longer satisfies the proportional hazards assumption.

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 $\boldsymbol{\beta}$ without involving $\lambda_0(t)$.
Maximising this function allows us to estimate the parameters $\boldsymbol{\beta}$.

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

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- $L_j(\beta)$ is a *partial* likelihood because it considers only patients who died, not those that are censored.

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** of individuals i and j.

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