Section 8

Time-to-events and survival analysis

The Moderna vaccine

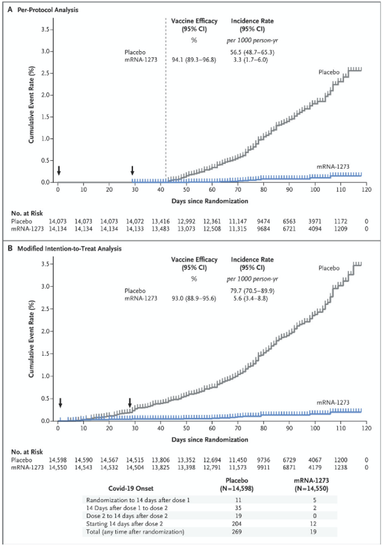


Figure 3: Survival analysis is e.g. used to present results from vaccine trials.

Time to events are all over the place

- Time from birth to death.
- Time from birth to cancer diagnosis.
- Time from disease onset to death.
- Time from entry to a study to cancer relapse.
- Time from marriage to divorce.
- Time from production until a machine is broken.
- Time from origin of the coronavirus until a stock (marked) crashes.

Take metrics with a grain of salt, but...

NEWS FEATURE

THE TOP 100 PAPERS

Nature explores the most-cited research of all time.

STATISTICS

Although the top-100 list has a rich seam of papers on statistics, says Stephen Stigler, a statistician at the University of Chicago in Illinois and an expert on the history of the field, "these papers are not at all those that have been most important to us statisticians". Rather, they are the ones that have proved to be most useful to the vastly larger population of practising scientists.

Much of this crossover success stems from the ever-expanding stream of data coming out of biomedical labs. For example, the most frequently cited statistics paper (number 11) is a 1958 publication[15] by US statisticians Edward Kaplan and Paul Meier that helps researchers to find survival patterns for a population, such as participants in clinical trials. That introduced what is now known as the Kaplan–Meier estimate. The second (number 24) was British statistician David Cox's 1972 paper[16] that expanded these survival analyses to include factors such as gender and age.

Figure 4: The two most cited statistics papers concern survival analysis

Some common questions

- What is survival under treatment A vs B?
- What is the duration of a certain component in the machine?
- How long does it take before a stock marked crashes?

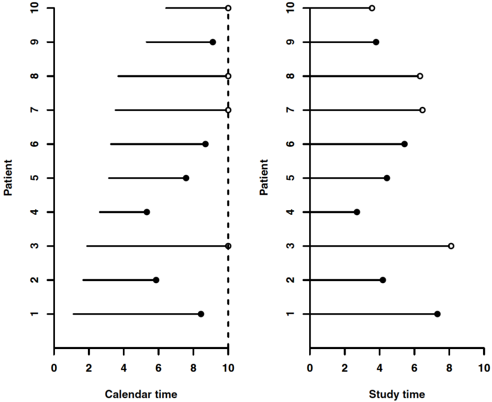
`PS: These questions are very often about causal effects....`

An overview of the time-to-event data structure

- We follow units of over time;
  humans, animals, engines, etc.
- The events of interest may be **the time to** deaths, cancer diagnoses, divorces, child births, engine failures, etc.
- We often stop the study before everyone has experienced the event of interest.

Censored survival times (illustration)

Consider 10 patients with newly diagnosed cancer. Let $T \in (0, \tau]$ be a survival time.



7.32, 4.19, 8.11, 2.70, 4.42, 5.43, 6.46, 6.32, 3.80, 3.50.
How do you estimate $\mathbb{E}(T)$, that is, the mean survival?

One way to define censoring

Definition (Censoring)

A censoring event is any event occurring in the study by time t that ensures the values of all future (possibly counterfactual) outcomes of interest under a regime g are unknown, even for an individual receiving the intervention g.

- This definition covers observational (non-causal) settings as a special case, by considering a regime g which implements exactly the decision rule that was used in the observed data.
- Many other definitions exist in the literature. I will argue why this definition is useful.

Why not use "standard methods"?

- We have incomplete observations.
- Instead of observing the survival time $T_i \in (0, \infty)$ we observe $(\tilde{T}_i, D_i)$,

$$\tilde{T}_i = T_i \text{ if } D_i = 1,$$
$$\tilde{T}_i < T_i \text{ if } D_i = 0.$$

  where D_i is a censoring indicator.

  We want to use our information on $\tilde{T}_i$ to make inference on T_i.
- There is a strong link to causal inference and "what if" questions: What would happen if we observed T_i instead of $\tilde{T}_i$.
- We must make assumptions about the censoring, similarly to assumptions in causal inference.

Let's start with a single outcome process

Assume $T > 0$ is an absolutely continuous random variable.

Definition (Survival function)

The survival function is $S(t) = P(T > t)$, that is, the probability that the survival time T exceeds t.

Definition (Hazard rate)

The hazard rate $\alpha(t) = \lim_{dt \to 0} \frac{1}{dt} P(t + dt > T \geq t \mid T \geq t)$ is the rate of events per unit of time.

Informally, $\alpha(t)dt = P(t + dt > T > t \mid T \geq t)$ is the probability that the event will happen between time t and time $t + dt$ given that it has not happened earlier.[13]

[13] PS: We are going to extend this to multiple events later.

Cumulative hazard and some relations

Define the cumulative hazard,

$$H(t) = \int_0^t \alpha(s)ds.$$

Then,

$$H'(t) = \alpha(t) = \lim_{dt \to 0} \frac{1}{dt} \frac{S(t) - S(t+dt)}{S(t)} = -\frac{S'(t)}{S(t)} = \frac{f(t)}{S(t)}.$$

By integration

$$\int_0^t \alpha(s)ds = -\log\{S(t)\},$$

and thus

$$S(t) = \exp\{-\int_0^t \alpha(s)ds\}.$$

$\alpha(t)$ completely determines the distribution of survival times T.

Illustration of hazards and survival functions

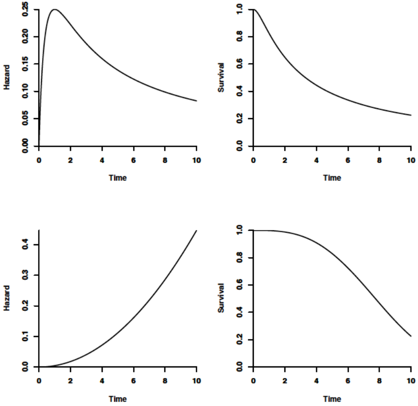


Fig. 1.2 *Illustrating hazard rates and survival curves. The hazard rates on the left correspond to the survival curves on the right.*

Section 9

Processes

Many of you are familiar with stochastic processes

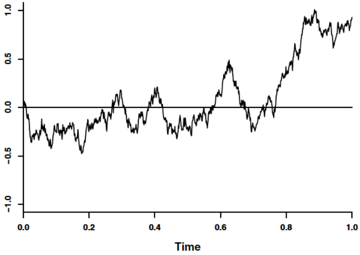
Here I will review *basic* concepts and results on stochastic processes.
I will give definitions and proceed at a "working technical" level.
We will focus on counting processes and martingales.
There are rigorous courses on stochastic processes at EPFL, such as:

- MATH-330 Martingales et mouvement brownien (Prof. Aru).
- MATH-332 Stochastic processes (Prof. Mountford).

Stochastic process

- A stochastic process is a time-indexed collection of random variables, say, $\{X(t) : t \in [0, \tau]\}$.
- Consider a probability space $(\Omega, \mathcal{F}, P)$, that is, sample space, event space and a probability function.
- A filtration $\{\mathcal{F}_t\}_{t>0}$ is an increasing right-continuous family of sub-σ-algebras of $\mathcal{F}$ such that $\mathcal{F}_s \subset \mathcal{F}_t$ whenever $s \leq t$.
  Think about the filtration as representing the **past**, that is, the history.
- We denote $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t>0}, P)$ a filtered probability space.

Example



Wiener process (Brownian motion)

Definition (Wiener process)

The $W = \{W(t) : t \in [0, \tau]\}$ is a process satisfying

- $W(0) = 0$,
- independent increments, that is, $W(t+u) - W(t)$ $u \geq 0$ are independent of $W(s)$, for all $s \leq t$,
- Gaussian increments, that is, $W(t+u) - W(t) \sim \mathcal{N}(0, u)$,
- continuous sample paths, that is, $W(t)$ is continuous in t.

Adapted process

Definition (Adapted process)

A stochastic process $X = \{X(t); t \in [0, \tau]\}$ is adapted to $\{\mathcal{F}_t\}$ if $X(t)$ is $\mathcal{F}_t$ measurable for each t.

`Intuitively, the value of` $X(t)$ `is known at` t`.`

PS: We will also consider the stronger notion of a *predictable* processes. We omit a formal definition of *predictable* but state the sufficient conditions that a process $X = \{X(t); t \in [0, \tau]\}$ is predictable if

- X is adapted to $\{\mathcal{F}_t\}$, and
- the sample paths of X are left-continuous.[14]

`Intuitively, the value of` $X(t)$ `is known just before` t`.`

[14] A sample path is a realization of X, which is a function of t.

Martingale

Definition (Martingale)

A stochastic process $M = \{M(t); t \in [0, \tau]\}$ is a martingale relative to $\{\mathcal{F}_t\}$ if M is adapted to $\{\mathcal{F}_t\}$ and $\mathbb{E}(M(t) \mid \mathcal{F}_s) = M(s)$ for all $t > s$.

Informally, the expected change is zero, $\mathbb{E}(dM(t) \mid \mathcal{F}_{t-}) = 0$, where $\mathcal{F}_{t-}$ is the filtration just before t.

$\mathcal{F}_{t-}$ is the smallest σ algebra containing all $\mathcal{F}_s$, $s < t$.

We will consider integrable Martingales, that is, $\mathbb{E}(|M(t)|) < \infty$, for all t.

Martingale intuition

Definition (Discrete martingale)

Let $M = \{M_0, M_1, M_2, \dots\}$ be a *discrete* stochastic process adapted to $\{\mathcal{F}_n\}$.
The discrete process M is a martingale if

$$\mathbb{E}(M_n \mid \mathcal{F}_{n-1}) = M_{n-1}.$$

- Heuristic: Think about the Martingale as cumulative noise, similar to random errors in "standard" statistical models.

Some features of (discrete) Martingales

- The definition is equivalent to saying that $\mathbb{E}(M_n \mid \mathcal{F}_m) = M_m$ for $m < n$. Hint: use iterative expectations.
- Suppose $M_0 = 0$. Then $\mathbb{E}(M_n) = 0$ because $\mathbb{E}(M_n) = \mathbb{E}(\mathbb{E}(M_n \mid \mathcal{F}_0)) = \mathbb{E}(M_0) = 0$.
- It also follows that (you can show this using iterative expectations)

$$\text{Cov}(M_m, M_n - M_m) = 0, \forall n > m.$$

Some features of (discrete) Martingales

- The *predictable variation process* $\langle M \rangle_n$ for $n > 0$ is the sum of conditional variances of martingale differences,

$$\langle M \rangle_n = \sum_{i=1}^{n} \mathbb{E}\{(M_i - M_{i-1})^2 \mid \mathcal{F}_{i-1}\} = \sum_{i=1}^{n} \text{Var}(\Delta M_i \mid \mathcal{F}_{i-1}),$$

where $\Delta M_i := M_i - M_{i-1}$. and $\langle M \rangle_0 = 0$.

- The *optional variation process* $[M]_n$ for $n > 0$ is

$$[M]_n = \sum_{i=1}^{n} (M_i - M_{i-1})^2 = \sum_{i=1}^{n} (\Delta M_i)^2,$$

where $[M]_0 = 0$.

Take the limits

In continuous time, define:

- the *predictable variation process* $\langle M \rangle_n$ as the limit in probability of the discrete process (If this limit exists), that is,

$$\langle M \rangle(t) = \lim_{n \to \infty} \sum_{k=1}^{n} \mathrm{Var}(\Delta M_k \mid \mathcal{F}_{(k-1)t/n})$$

  where $[0, t]$ is partitioned into n subintervals of length t/n and $\Delta M_k = M(kt/n) - M((k-1)t/n)$.
  Informally, $\mathcal{F}_{(k-1)t/n} = \mathcal{F}_{t-}$.

- the *optional variation process* $[M]_n$ as

$$[M](t) = \lim_{n \to \infty} \sum_{k=1}^{n} (\Delta M_k)^2.$$

ΔM_k are often called "innovations" because, heuristically, they represent what is new and unexpected given the past.

Some characteristics

- $M^2 - \langle M \rangle$ is a mean zero martingale.
- $M^2 - [M]$ is a mean zero martingale.
- Thus, $\text{Var}(M(t)) = \mathbb{E}\{M(t)^2\}) = \mathbb{E}\langle M \rangle(t) = \mathbb{E}\{[M](t)\}$.

Submartingale

Definition (Submartingale)

A $\{\mathcal{F}_t\}$-adapted stochastic process $X = \{X(t); t \in [0, \tau]\}$ is a submartingale relative to $\{\mathcal{F}_t\}$ if $\mathbb{E}(X(t) \mid \mathcal{F}_s) \geq X(s)$ for all $t > s$.

That is, $X(t)$ is a process that is expected to increase as time goes on.

Doob-Meyer decomposition

Suppose that X is a submartingale wrt. $\{\mathcal{F}_t\}$.
The Doob-Meyer decomposition theorem states that X can be uniquely decomposed into

$$X = X^* + M,$$

where

- X^* is a non-decreasing predictable process called the "compensator" wrt. $\{\mathcal{F}_t\}$.
- M is a mean zero martingale wrt. $\{\mathcal{F}_t\}$.

We will not show this important result.
However, we will give an argument for discrete processes.

Discrete Doob decomposition

Let $M = \{M_0, M_1, M_2, \dots\}$ be a *discrete* stochastic process adapted to $\{\mathcal{F}_n\}$.
Reminder: the discrete process M is a martingale if

$$\mathbb{E}(M_n \mid \mathcal{F}_{n-1}) = M_{n-1}$$

Now, let $X = \{X_0, X_1, X_2, \dots\}$ be some process with $X_0 = 0$ wrt $\{\mathcal{F}_n\}$, and define $M' = \{M'_0, M'_1, M'_2, \dots\}$ by

$$M'_0 = X_0$$
$$M'_n - M'_{n-1} = X_n - \mathbb{E}(X_n \mid \mathcal{F}_{n-1}).$$

M' is a martingale wrt $\{\mathcal{F}_n\}$ because
$\mathbb{E}(M'_n - M'_{n-1} \mid \mathcal{F}_{n-1}) = \mathbb{E}(X_n - \mathbb{E}(X_n \mid \mathcal{F}_{n-1}) \mid \mathcal{F}_{n-1}) = 0.$
Furthermore,

$$X_n = \mathbb{E}(X_n \mid \mathcal{F}_{n-1}) + \Delta M'_n, \text{ where } \Delta M'_n = M'_n - M'_{n-1}.$$