Lecture 1: Time-to-event analysis

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Spatial and Temporal Statistical Modelling for Population Health Sciences

Outline of the day

- Morning: 1-hour lecture + 2-hour computer-lab session on general principles and estimation
- Afternoon: 1-hour lecture + 2-hour computer-lab session on regression

What are time-to-event data?

- Data from any study in which the response from each subject is the time at which an event of interest occurs
- Relevant for analysing data of the sort:
  - Survival time following surgery
  - The length of time from birth to development of calf pneumonia
  - The time taken for a cow to conceive following fertility treatment

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Analytical approaches

Analytical methods fall into two categories:

Survival analysis

Each subject provides at most one event-time

Recurrent event analysis

Each subject provides a (possibly empty) sequence of event-times, which can be considered ordered or unordered, for different or similar events

This course will focus mainly on survival analysis

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Analytical approaches

- The endpoint for survival analysis does not have to be death or 'failure', nor does it have to be a negative event — it can be a positive event (e.g. time to winning the lottery)[1]

- Always be clear about what the time origin is, e.g.
  - Time of treatment
  - Date of birth

[1] We use terms 'survival' and 'failure' interchangeably regardless of outcome

Example dataset

Observational dataset on survival of 10 renal failure patients receiving peritoneal dialysis (PD). Each row denotes a unique patient. The follow-up time column is the number of days since starting treatment to either death (Status = 1) or censoring (Status = 0). Also shown is the treatment type (CAPD = Continuous Ambulatory PD, APD = Automated PD) and age at the start of dialysis.

Patient ID	Follow-up time (days)	Status	Treatment	Age (years)
1	3444	0	APD	41
2	3499	0	APD	35
3	6230	0	APD	41
4	1324	1	APD	67
5	6230	0	APD	29
6	147	1	CAPD	55
7	709	1	APD	54
8	6230	0	APD	42
9	422	1	CAPD	45
10	5096	0	CAPD	46

Probability

Random variable

Let T denote the time to event, with cumulative distribution function $F(t) = P(T \leq t)$

Survival function

The probability the event occurs **after** time t is $S(t) = 1 - F(t) = P(T > t)$

Lifetime distribution

The probability density function is $f(t) = dF(t)/dt$

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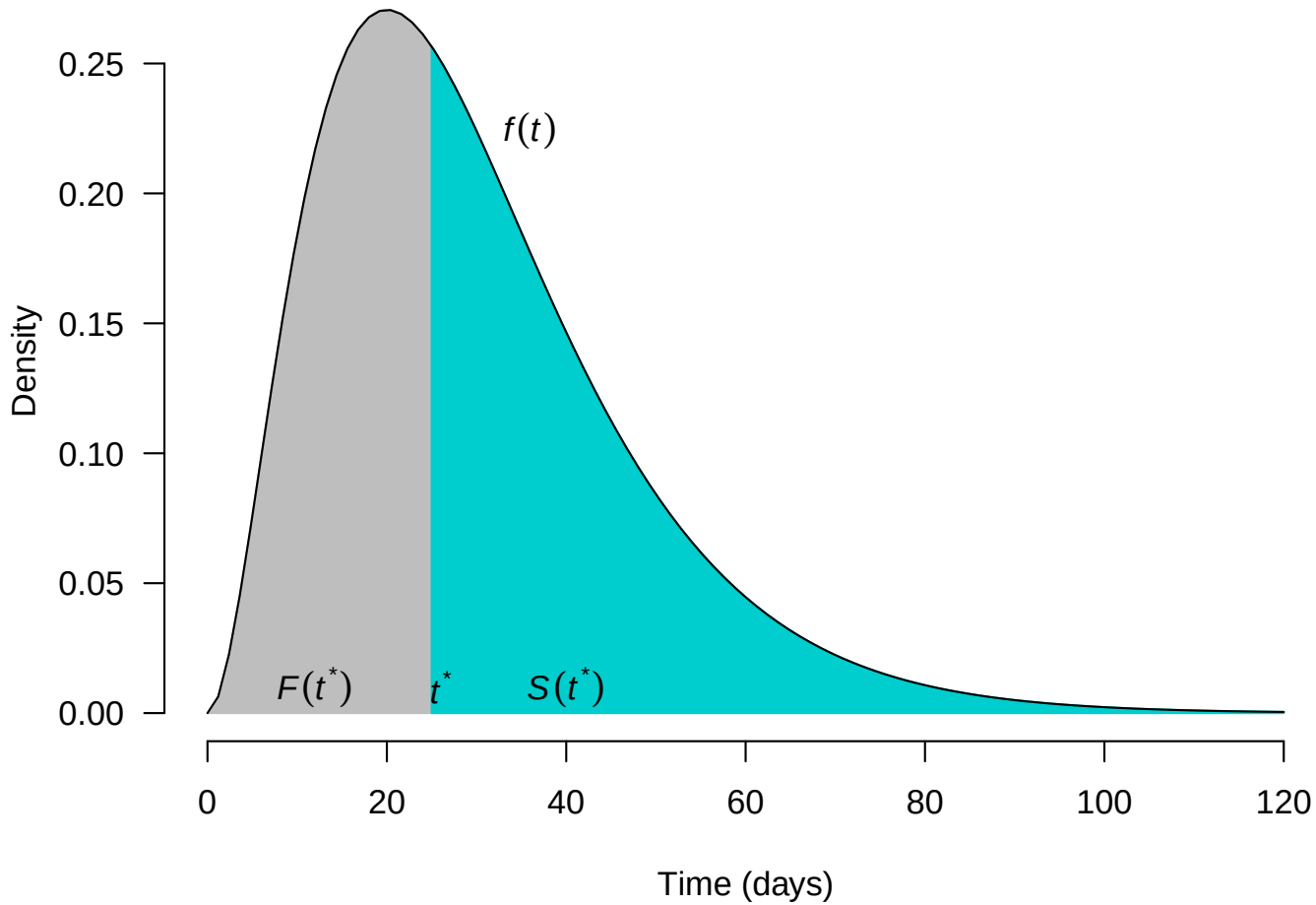
A hypothetical lifetime distribution [density] function, $f(t)$. The grey shaded area to the left of t^* denotes $F(t^*)$ — the proportion of subjects who experience an event before time t^*. The cyan shaded area to the right of t^* denotes $S(t^*)$ — the proportion of subjects who have survived to time t^*.



Hazard

Conditional on the subject having survived up until time t, we consider $P(t < T \leq t + \Delta t | T > t)/\Delta t$

Hazard function

If we let $\Delta t \rightarrow 0$, then we get the instantaneous hazard rate

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

Cumulative hazard

The area under the hazard function up until time t gives a measure for the risk of failure

$$H(t) = \int_0^t h(u)du$$

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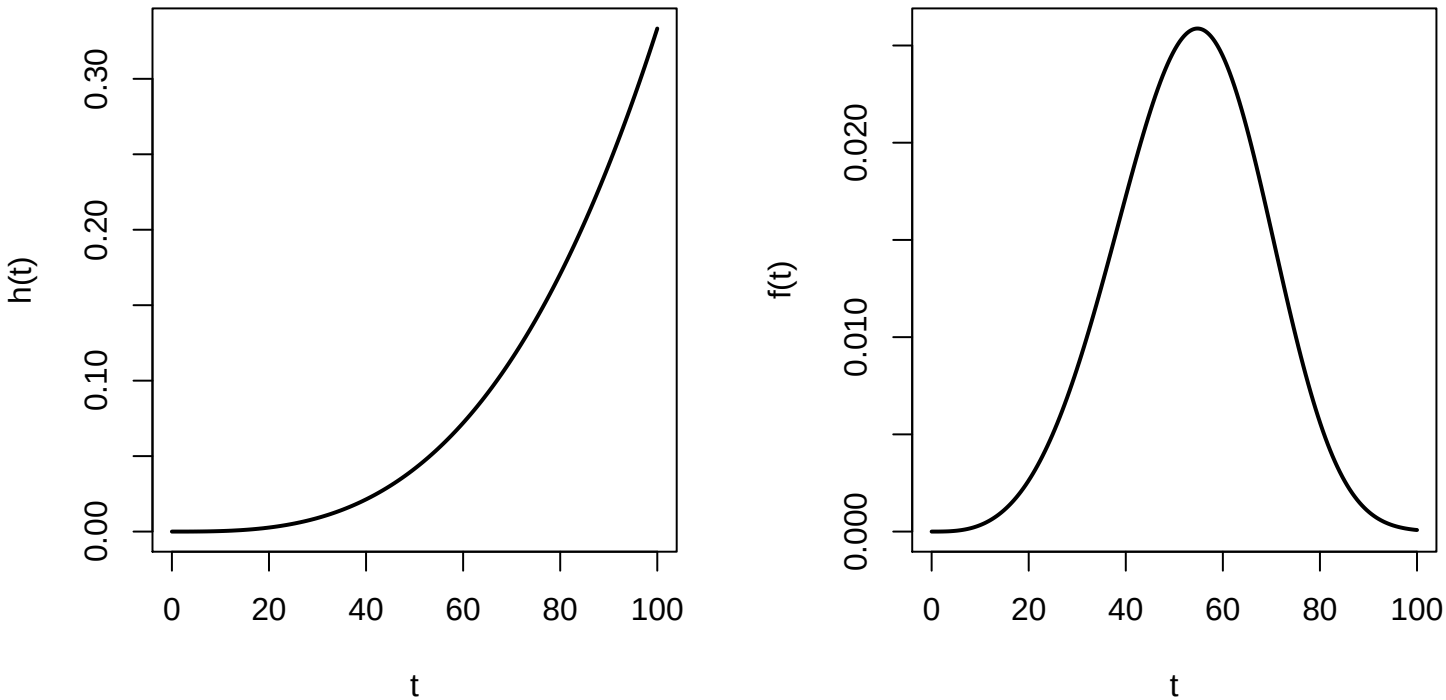
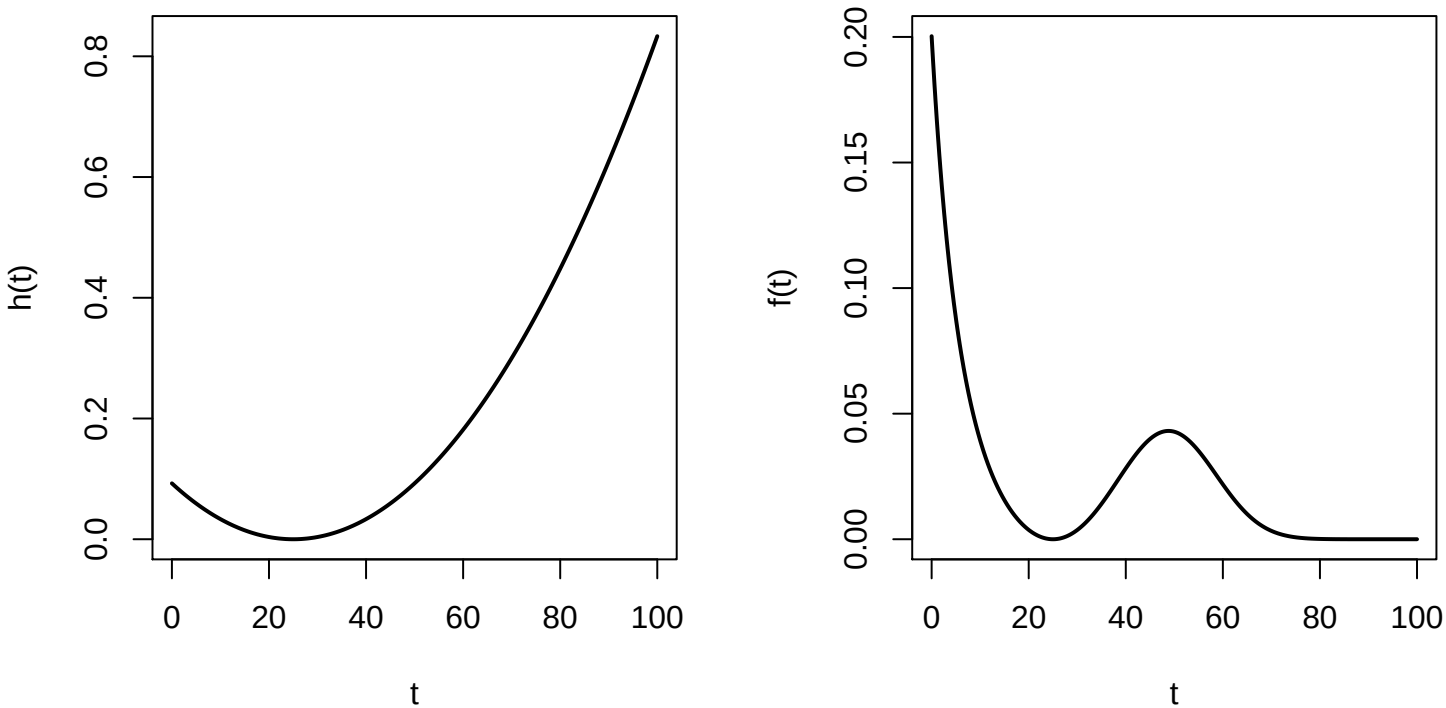
An increasing hazard function $h(t)$ (left panel) and its corresponding lifetime distribution $f(t)$ (right panel)



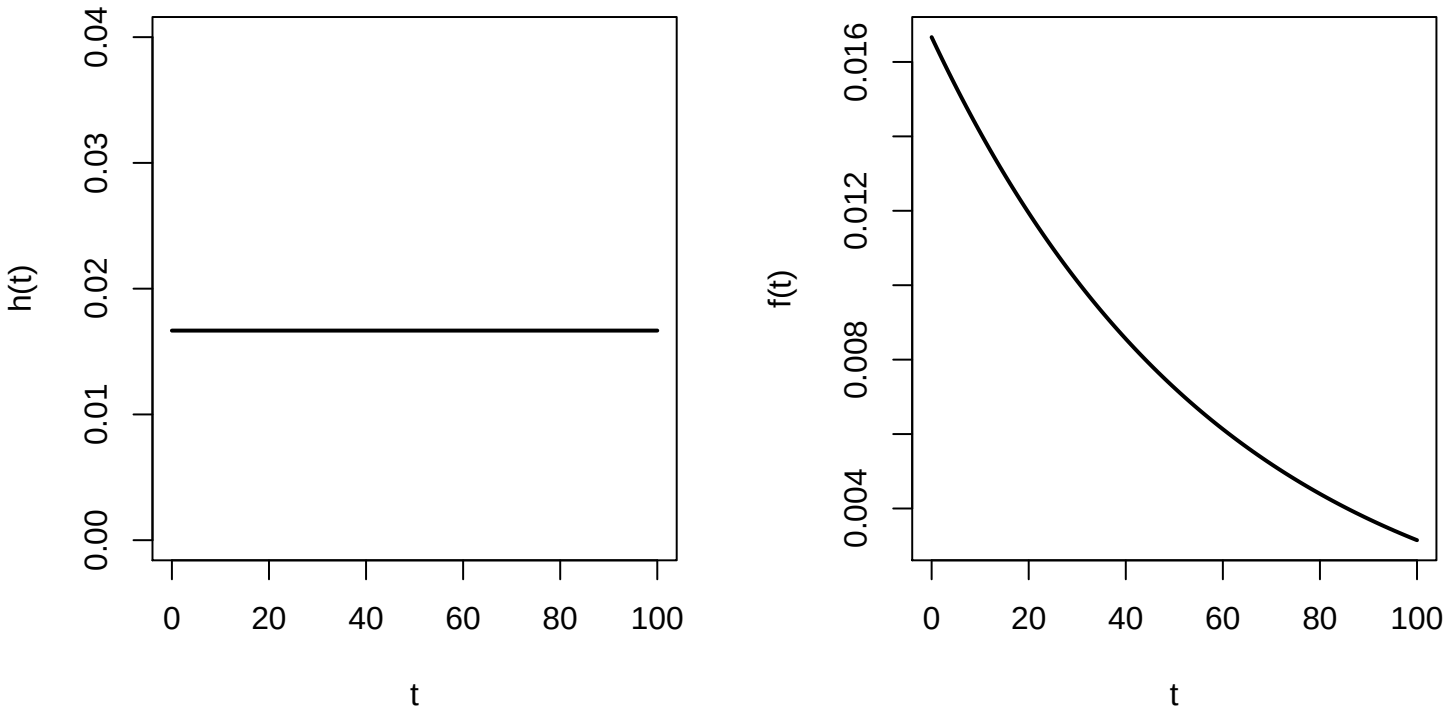
Appropriate for: death rates among adult animals

A decreasing then increasing hazard function $h(t)$ (left panel) and its corresponding lifetime distribution $f(t)$ (right panel)



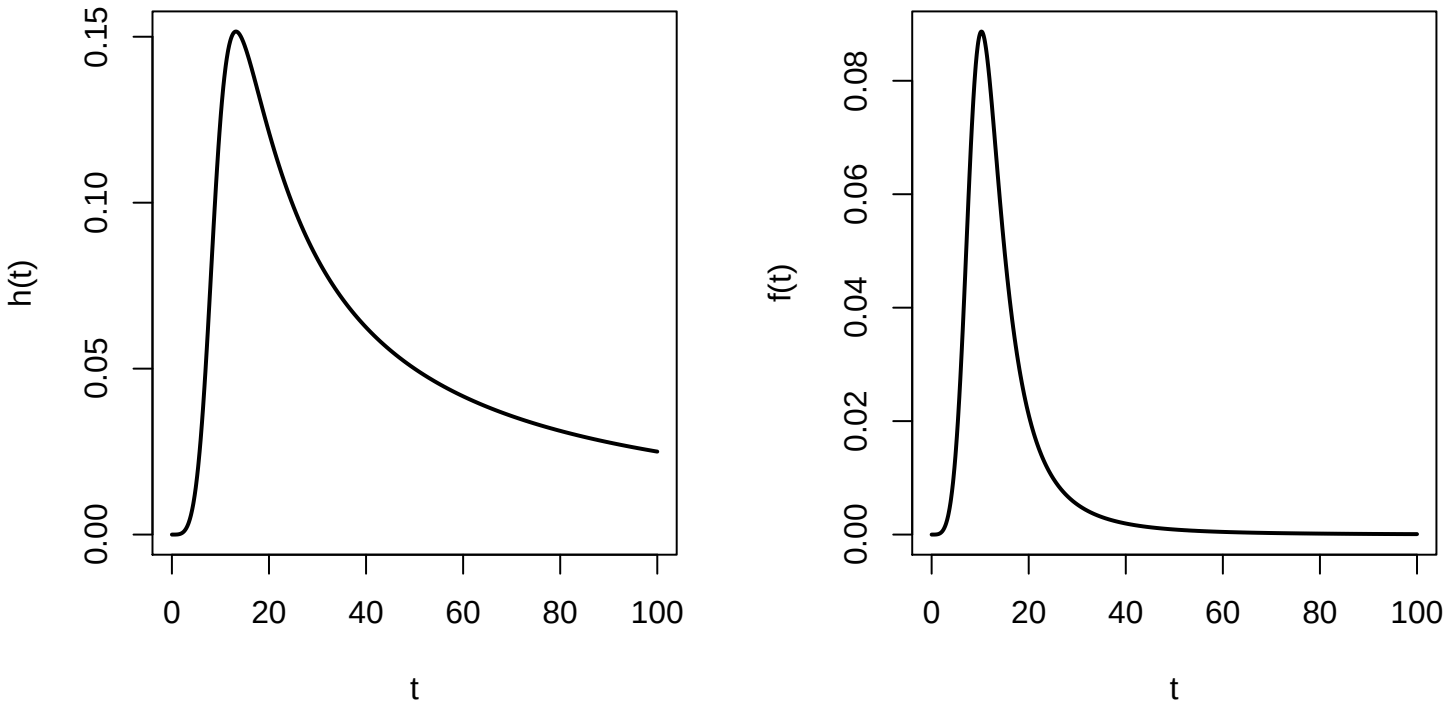
Appropriate for: lifespan of animals ("force of mortality")

A constant hazard function $h(t)$ (left panel) and its corresponding lifetime distribution $f(t)$ (right panel)



Appropriate for: time until next case of influenza in a non-seasonal country

An increasing then decreasing hazard function $h(t)$ (left panel) and its corresponding lifetime distribution $f(t)$ (right panel)



Appropriate for: survival following tuberculosis infection

What if the event does not occur?

Censoring

The time to event is only partially known

Example: time to death following surgery is > 15.4 years

Truncation

A variant of censoring whereby if the time is censored, we do not observe it at all

Example: patients with AIDS are enrolled onto a study to model the time from infection with HIV to development of AIDS, but not everyone infected with HIV has yet developed symptoms of AIDS

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Censoring types

Observed

$T = t_0$: We get to observe the time to the event

Right-censored

$T > t_0$: E.g. when a study specifies a maximum follow-up time

Left-censored

$T < t_0$: E.g. unsure when HIV was contracted

Interval-censored

$t_0 < T < t_1$: E.g. a patient seroconverted between hospital visits

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Relevance to epidemiological studies

- Most survival analysis studies specify a maximum follow-up time: subjects still alive at the end of follow-up are right-censored
- Most statistical methods assume that censoring is independent of survival time

Estimation

Methods are classified into two categories:

1. Non-parametric methods
   - Kaplan-Meier estimator
   - Actuarial (life tables) method[2]
   - Nelson-Aalen estimator
2. Parametric modelling

[2] Not discussed in this lecture

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Kaplan-Meier method

Kaplan-Meier estimator

An estimator for the survival function is given by

$$\hat{S}(t) = \prod_{i:t_i \leq t} \frac{(n_i - d_i)}{n_i}, \text{ for } 0 < t \leq t_N$$

Where

- $t_1 < t_2 < \cdots < t_N$ are the ordered unique **failure** times (i.e. times for subjects who experienced the event)
- d_i is the number of failures at failure time t_i
- n_i is the number of subjects at risk (i.e. have not yet experienced a failure) just before time t_i

Example

Consider the following fake time-to-event dataset, which we have ordered by time

Subject	Follow-up time	Status
4	9	1
1	13	0
3	15	1
5	35	0
2	49	1

Example

- There are 5 times to consider: 9, 13^+, 15, 35^+, 49
- Only 3 (red) are failure times — we calculate the Kaplan-Meier at these points
- 2 are right-censored — note the use of $+$ superscripts

Time of event (t_i)	Number at risk just before event (n_i)	Number of failures (d_i)	Survival probability $P_i = (n_i - d_i)/n_i$	Cumulative survival $S_i = P_i \times P_{i-1}$
9	5	1	$4/5 = 0.80$	$0.80 \times 1.00 = 0.80$

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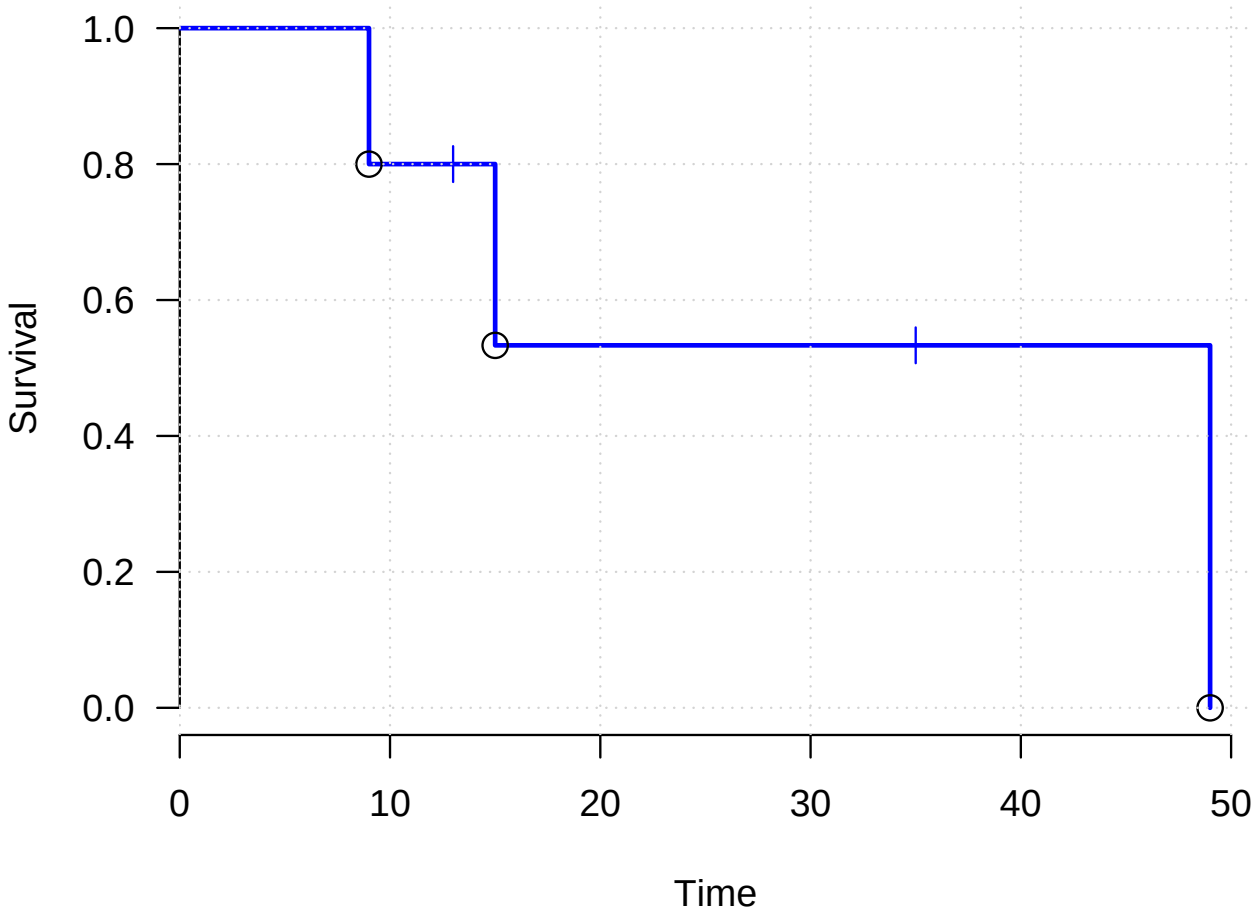
15	3	1	$2/3 = 0.67$	$0.67 \times 0.80 = 0.53$
49	1	1	$0/1 = 0.00$	$0.00 \times 0.53 = 0.00$

A Kaplan-Meier curve for our fake data: points denote failure times; ticks denote censoring times



Nelson-Aalen estimator

An estimator of the cumulative hazard is given by the Nelson-Aalen estimator

Nelson-Aalen estimator

$$\hat{H}(t) = \sum_{i:t_i \leq t} \frac{(d_i)}{n_i}, \text{ for } 0 < t \leq t_N$$

We can combine this with the relationship that

$$S(t) = e^{-H(t)}$$

to yield the so-called Flemington-Harrington survival curve estimator

Parametric methods

- As an alternative to non-parametric methods, we might model the survival distribution according to some known parametric model
- Pros ☺
  - Survivorship pattern might be dictated by laws of nature
  - Can be used for prediction
  - Can flexibly incorporate complex structures
- Cons ☹
  - Might mis-specify the model
  - Requires us to think

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Exponential distribution

Properties

- Lifetime distribution: $f(t) = \lambda \exp(-\lambda t), \ \ \lambda > 0$
- Hazard function: $h(t) = \lambda$
- Survival function: $S(t) = \exp(-\lambda t)$
- Cumulative hazard: $H(t) = \lambda t$

Key features

- Hazard rate is constant
- Memoryless

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Weibull distribution

Properties

- Lifetime distribution: $f(t) = \lambda p t^{p-1} \exp(-\lambda t^p), \ \lambda > 0, \ p > 0$
- Hazard function: $h(t) = \lambda p t^{p-1}$
- Survival function: $S(t) = \exp(-\lambda t^p)$
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Key features

- Parameterised by rate, λ, and shape, p
- Flexible: $p = 1 \rightarrow$ exponential; $p < 1 \rightarrow$ monotonically decreasing hazard with time; $p > 1 \rightarrow$ monotonically increasing hazard with time

Weibull distribution

Properties

- Lifetime distribution: $f(t) = \lambda p t^{p-1} \exp(-\lambda t^p)$, $\lambda > 0$, $p > 0$
- Hazard function: $h(t) = \lambda p t^{p-1}$
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Key features

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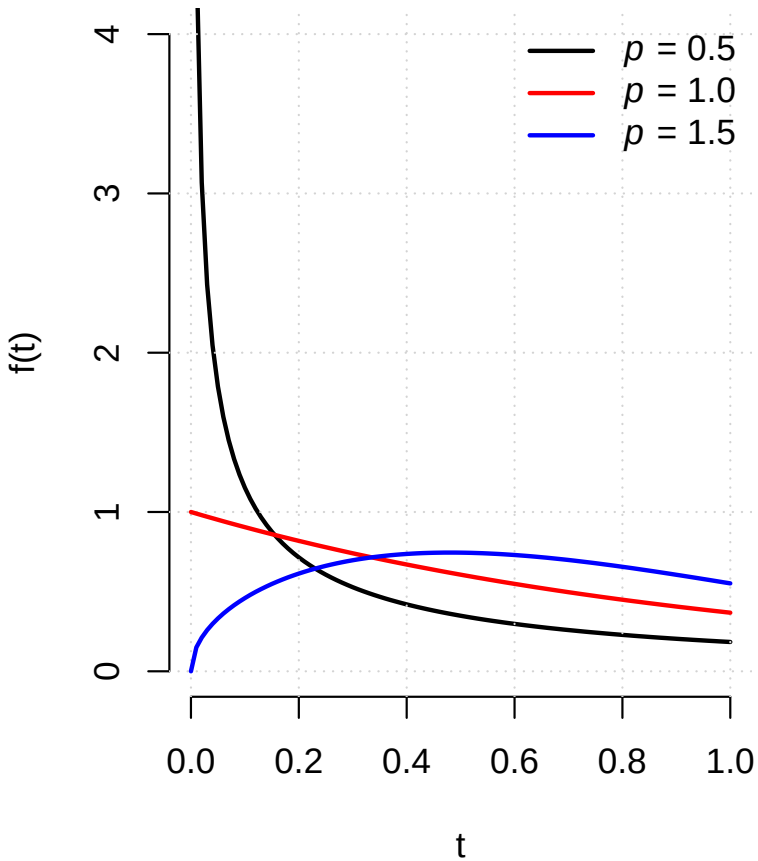
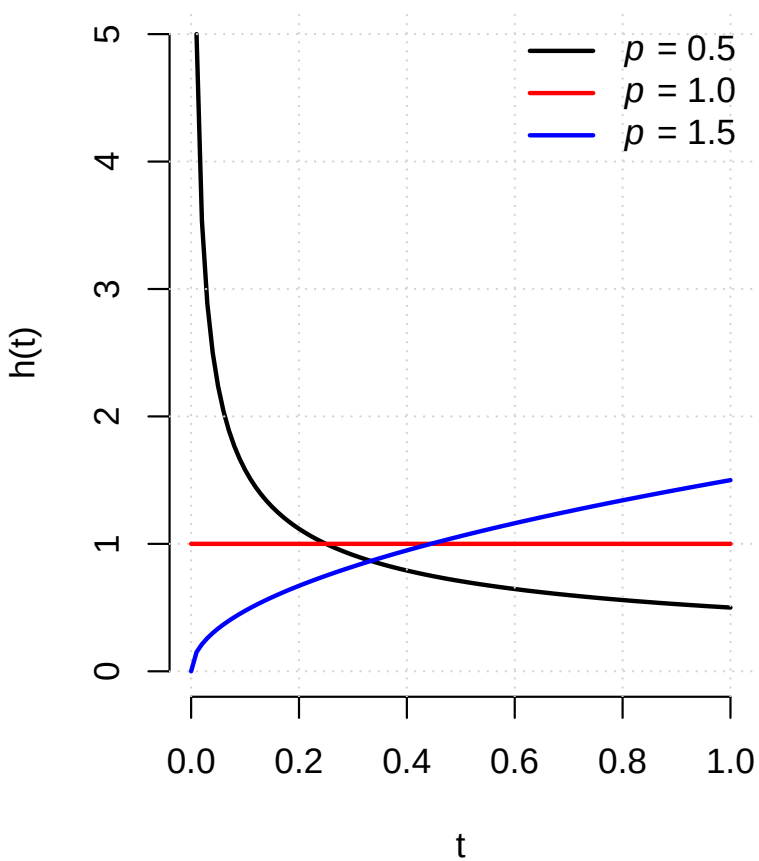
- Flexible: $p = 1 \rightarrow$ exponential; $p < 1 \rightarrow$ monotonically decreasing hazard with time; $p > 1 \rightarrow$ monotonically increasing hazard with time

There are many other distributions, e.g. log-logistic, Gompertz, etc., but exponential and Weibull common choices as they are sufficiently flexible for many applications





Which one to use?

Simple test

1. Plot $\log\left[-\log\left(\hat{S}(t)\right)\right]$ against $\log(t)$
2. If a straight-line, then test slope: If $= 1 \Rightarrow$ exponential; otherwise $\Rightarrow$ Weibull
3. If not straight-line, need a different model

How to estimate parameters

To estimate the model parameters θ, e.g. $\theta = (p, \lambda)$ for Weibull model:

- For non-censored subjects, the contribution to the likelihood function is $f(t_i \mid \theta)$
- For right-censored subjects, the contribution to the likelihood function is $S(t_i \mid \theta)$
- Assuming censoring independent of t_i, the likelihood function is:

$$\left(\prod_{\substack{i:\ \text{failure time} \\ \text{observed}}} f(t_i \mid \theta) \right) \times \left(\prod_{\substack{i:\ \text{failure time} \\ \text{right-censored}}} S(t_i \mid \theta) \right)$$

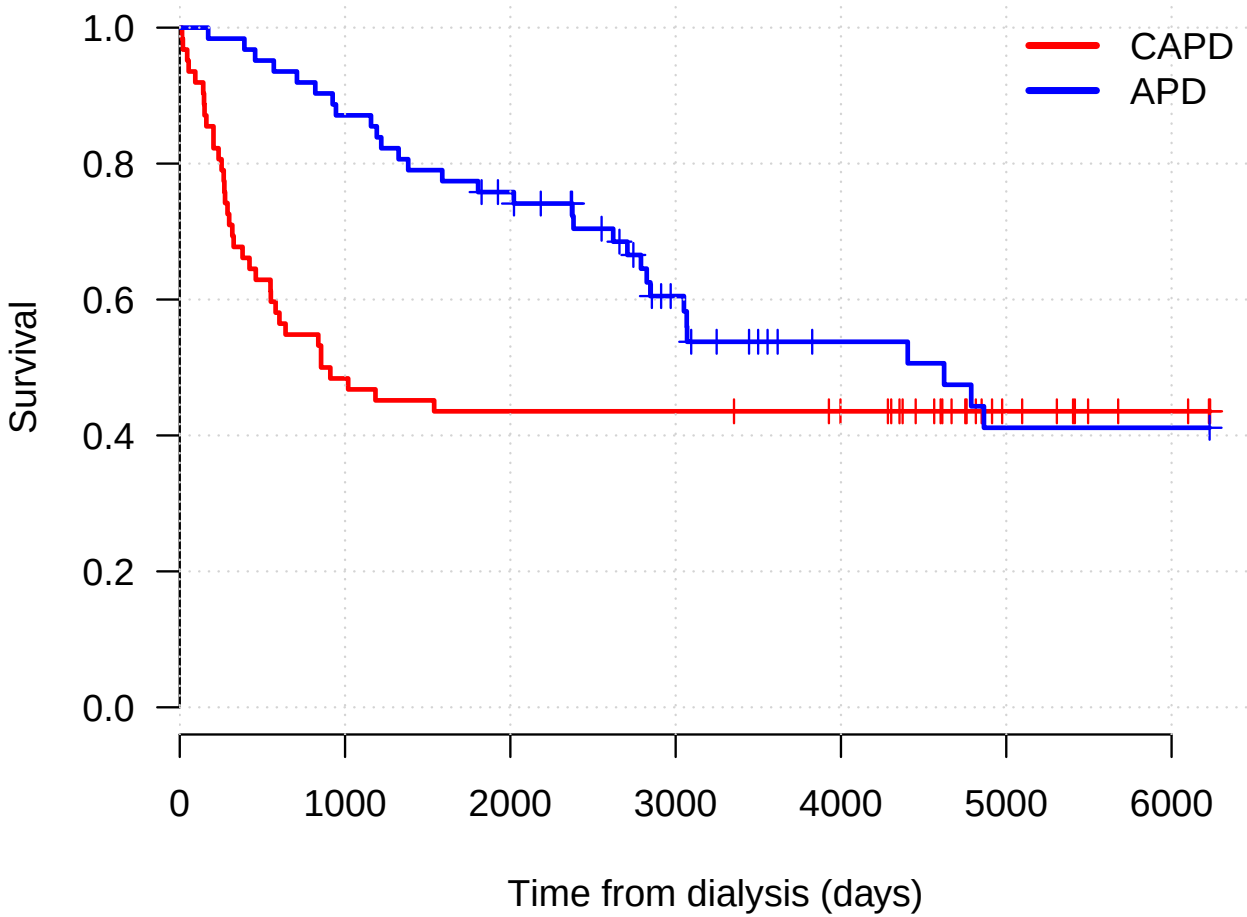
How can we compare survival between groups?

Examples

- Do patients survive longer after treatment that those without?
- Do males take longer to quit smoking compared to females?

If no censoring present, then can use Mann-Whitney U-test (or Kruskal-Wallis one-way ANOVA test)

Recall the peritoneal dialysis data had two treatment arms: APD ($n = 62$) and CAPD ($n = 62$) — do they have different survival distributions?



The log-rank test

Null hypothesis

Survival times are from the same distribution, i.e. there is no difference in group survivorship

Test

1. At each failure time t_i, there are $n_i = n_{i1} + n_{i2}$ subjects at risk just before, and there are $d_i = d_{i1} + d_{i2}$ failures
2. The probability of any subject experiencing the event under the null hypothesis is $p_i = d_i/n_i$
3. The expected number of failures in group 1 and 2 at t_i is $n_{i1}p_i$ and $n_{i2}p_i$ respectively
4. Repeat for every failure time and aggregate to calculate a Cochran-Mantel-Haenszel statistic, which has an (approximate) χ^2 distribution on 1 *df*

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The log-rank test

1. Consider the 10 dialysis patient (3 CAPD and 7 APD) failure times[3] shown earlier, the first failure time was 147 days
2. The probability of a death is $\frac{1}{10}$ just before this time, so under the null hypothesis we would have expected $3 \times \frac{1}{10} = 0.3$ deaths in the CAPD group and $7 \times 110 = 0.7$ deaths in the APD group
3. We observed 1 failure in the CAPD group, and 0 in the APD group
4. This gives us the data for the first contribution to the χ^2 test statistic
5. And so on...

[3] In the interests of brevity, we pretend there are only 10 patients, although the actual dataset has 124 patients

Situations that require more complex methods

- **Interval censoring**
  Example: survival times subject to gross round-off error
- **Competing risks**
  Example: multiple causes of death
- **Informative censoring**
  Example: subjects censored because their condition is deteriorating

Suggested reading

- Diggle PJ, Chetwynd AG (2011). Statistics and Scientific Method: An Introduction for Students and Researchers. Oxford: *Oxford University Press*.
  - ✎ Chapter 8 covers much of the material presented in this course
- Collett D. Modelling Survival Data in Medical Research (1994). Boca Raton: *Chapman & Hall/CRC*.
  - ✎ Comprehensive text on survival data
- Bland JM, Altman DG (2004). The logrank test. *BMJ*, 328:1073.
  - ✎ 1-page round-up of the log-rank test
- Guo Z, et al. (2009). Modeling repeated time-to-event health conditions with discontinuous risk intervals: an example of a longitudinal study of functional disability among older persons. *Methods of Information in Medicine*, 47(2), 107-116.
  - ✎ Extensions to repeated/multiple events
- Putter H, et al. (2007). Tutorial in biostatistics: Competing risks and multi-state models. *Statistics in Medicine*, 26, 2389-2430.
  - ✎ Introduction to competing risk models