How do you carry out survival analysis?

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@IBDNathan

How do you carry out ~~survival~~ time-to-event analysis?

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What will we cover?

- What is survival analysis?
- The core fundamentals of survival analysis
- Kaplan-Meier
- The Cox proportional hazards model
- Accelerated failure time models
- Competing risks survival analysis
- Joint modelling of time-to-event and longitudinal outcomes

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What *is* survival analysis?

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What *is* survival analysis not?

Survival analysis is *not* statistical epidemiology

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What *is* survival analysis?

"The analysis of the expected duration of time until one or more events happen"

-Wikipedia et al.

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What *is* survival analysis?

Usually, we are interested in modelling the time to an event of interest, using observable characteristics.

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What *is* survival analysis?

Applications in

- Drug trials
- Precision/personalised medicine
- NHS resource management
- Engineering
- Criminology

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The core fundamentals of survival analysis

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The core fundamentals of survival analysis

Events of interest. What could an event be?

- Death
- Hospital discharge
- Onset of disease
- Clinical improvement or clinical deterioration
- The failure of a mechanical system
- An ex-prisoner re-offending (recidivism)

The core fundamentals of survival analysis

Assumptions for an event of interest

- The event will happen *eventually* for all individuals in a cohort.
- The event is binary. It can't "half happen".
- The event only happens once for an individual.

The core fundamentals of survival analysis

Defining an initial t_0 value is an important consideration.

- t_0 should represent the onset of risk.
- At t_0, all individuals should be at the same risk.
- No one should have experienced the event at, or before, t_0.
- Possible time points for t_0:
    - Birth
    - Hospital admission
    - Diagnosis
    - Medicine first being prescribed

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The core fundamentals of survival analysis

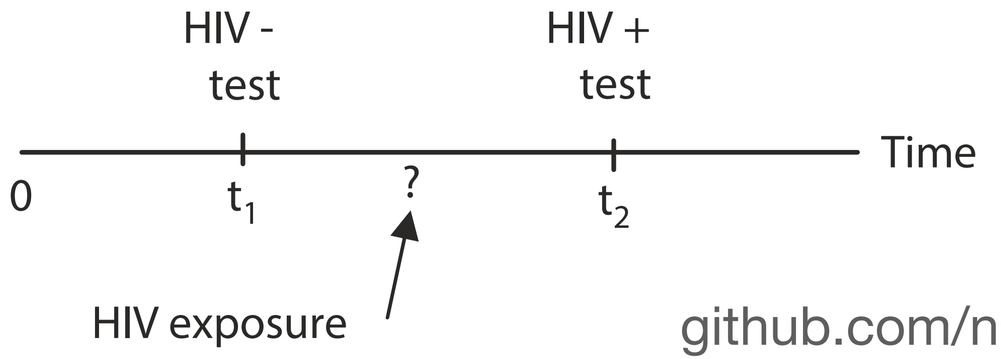
Right-censoring

- In most real-world situations, censoring is encountered in survival analysis.
- This is usually due to:
    - A study ending or reaching maximum follow-up
    - Patient is lost to follow-up
    - Patient withdraws from the study
- These suggestions are all examples of right-censoring.

The core fundamentals of survival analysis

Interval censoring

- We may also encounter interval censoring: where we are only aware of an interval the event occurred in. This is common when a patient has regular tests.



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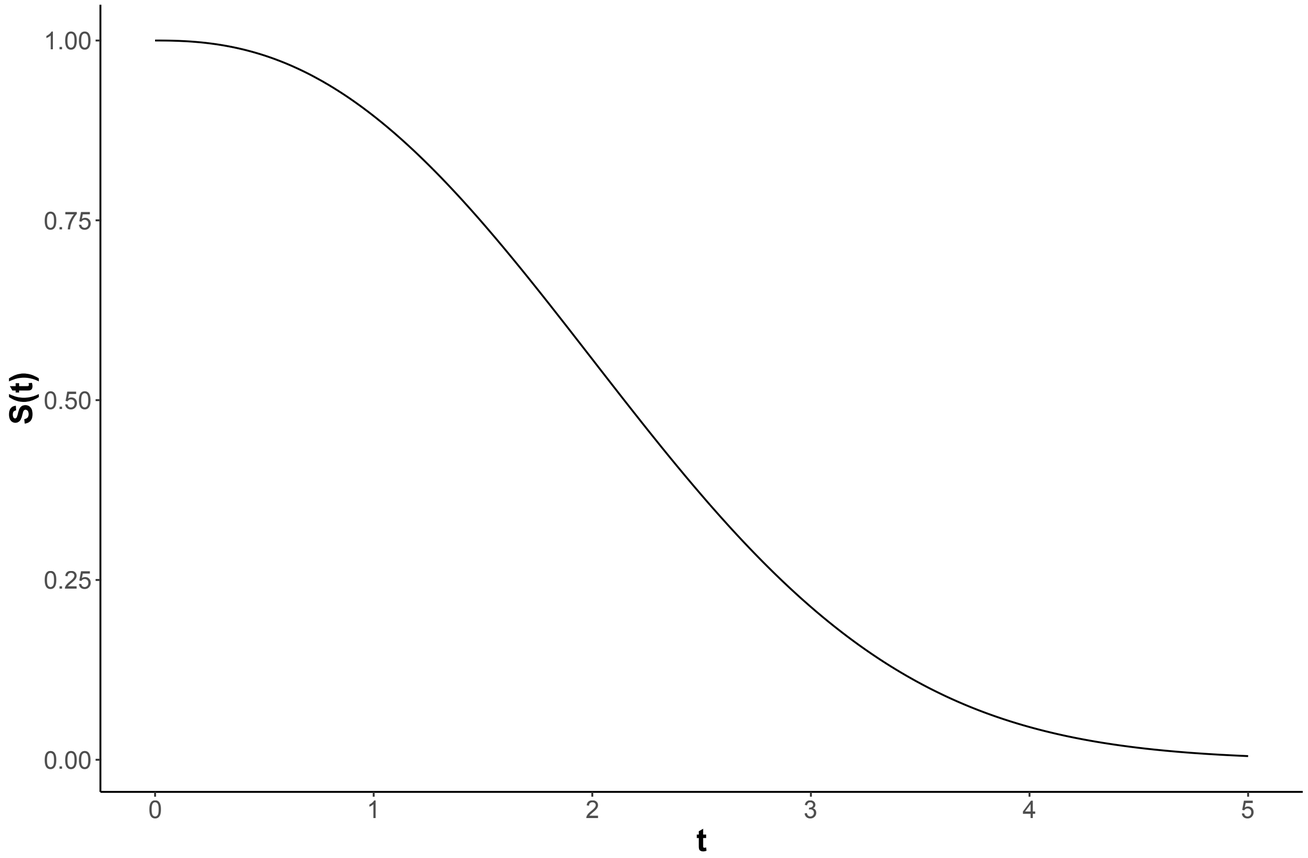
The core fundamentals of survival analysis

Theoretical Survival functions/ curves

- A survival function gives the probability that a person survives longer than some specified value of time, t.
- Theoretically, this function is a smooth curve.



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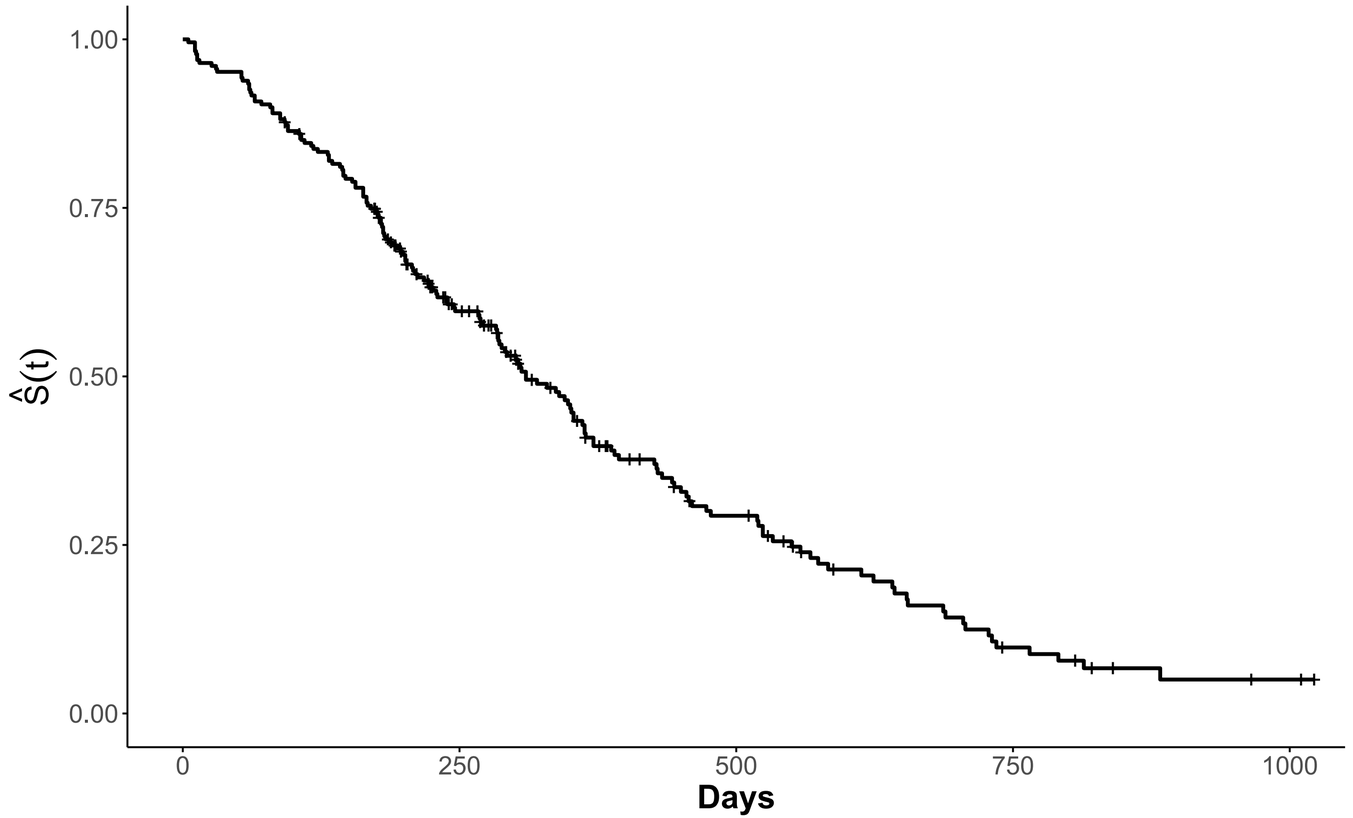
The core fundamentals of survival analysis

Survival functions/ curves in reality…

- Using actual data usually results in a step function.
- We use vertical bars to indicate censoring.



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The core fundamentals of survival analysis

Hazard functions

- A hazard function, $h(t)$, gives the instantaneous potential for the event to occur at time t, given the subject has survived up to this time.
- A conditional failure rate (rather than a probability).
- We typically focus on the hazard function when mathematically modelling survival data, and also present a model via its hazard function.
- If we have a hazard function, we can derive the survival function and vice versa.

Kaplan-Meier

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Kaplan-Meier

Introduction to Kaplan-Meier

- The Kaplan-Meier statistic is a non-parametric statistic which estimates the true survival function.
- Step-wise.
- Can handle right-censored data.
- Can be used to compare the survival times between groups (such as a placebo group and treatment group.
- Extensively used in survival analysis (58,000 < citations).

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Kaplan-Meier

The Kaplan-Meier estimator

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

Where d_i is the number of people who experience the event at time t_i

And n_i is the number of people at risk at time t_i (we call this the risk set)

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Kaplan-Meier

Practical example

$t_{(f)}$	n	Event	Censored	$S(t_{(f)})$
0	20	0	0	$\frac{20}{20} = 1$
1	20	2	0	$1 \times \frac{18}{20} = 0.9$
2	18	4	2	$0.9 \times \frac{14}{18} = 0.7$
3	12	3	1	$0.7 \times \frac{9}{12} = 0.525$

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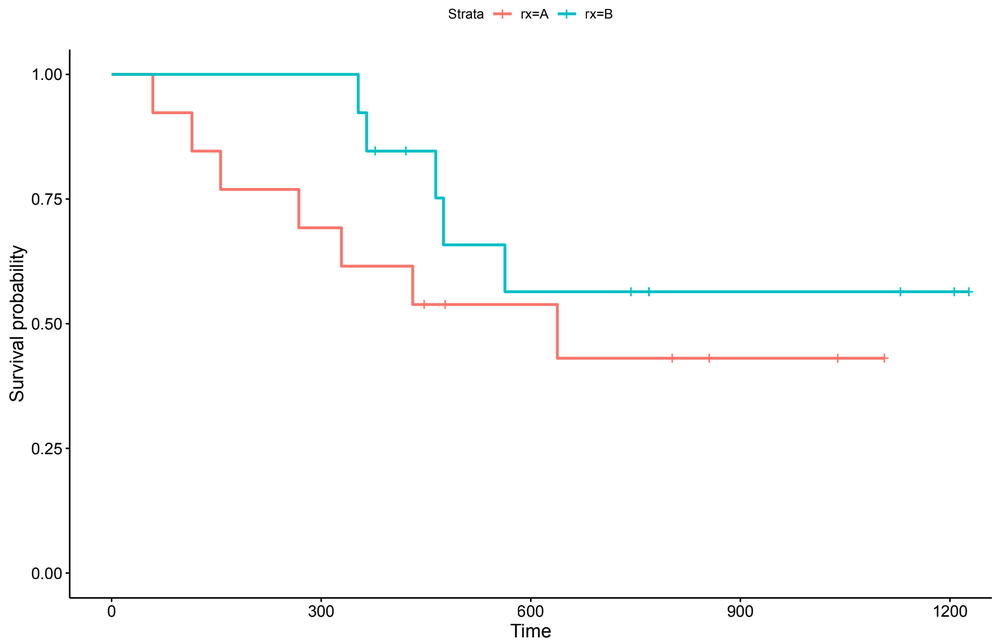
Kaplan-Meier

Stratified Kaplan-Meier

- We may wish to investigate if two groups have equivalent survival curves.
- We can draw separate survival curves for each group (ideally with confidence intervals) to visualise how the survival curves vary over time.
- But, we would like to be able to perform a statistical test to empirically determine if there is a difference between the groups.



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Kaplan-Meier

The log-rank test

- We can generate a test statistic and associated p-value via a log-rank test.
- H_0: The survival curves for all groups are the same.
- H_1: The survival curves for all groups are not the same.
- Easy to perform in statistical software (R examples on the Github repo)

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The Cox proportional hazards model

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The Cox proportional hazards model

Introduction to Cox proportional hazards

- A semi-parametric class of models. This means we do not need to choose a specific statistical distribution (such as the Normal distribution)
- Commonly used in medical statistics
- Uses covariates which do not vary with time
- An extension for time-dependent variables exists (but is often inadvisable to use)

The Cox proportional hazards model

The hazard function 1

- The Cox proportional hazards model is typically presented via the hazard function:

$$h(t, X) = h_0(t) \cdot e^{\beta_0 + \beta_1 x_{1i} + \ldots + \beta_p x_{pi}}$$

Intercept

Covariate effects

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The Cox proportional hazards model

The hazard function 2

- The baseline hazard is dependent only on time, whilst the second term is dependent only on our covariates and their regression coefficients

$$h(t, X) = h_0(t) \cdot e^{\beta_0 + \beta_1 x_{1i} + \ldots + \beta_p x_{pi}}$$

Baseline hazard

Second term

- Interpretation: the baseline hazard is the hazard in the absence of any covariates.

The Cox proportional hazards model

Hazard ratios

- A hazard ratio (HR) is defined as the hazard for one individual/group divided by the hazard for a different individual/group. For example, is a placebo group vs. a treatment group.

$$\text{HR} = \frac{h(t, X = \text{placebo})}{h(t, X = \text{treatment})}$$

- The group with the largest hazard is typically the numerator as hazard ratios ≥ 1 are easier to interpret.

The Cox proportional hazards model

Hazard ratios 2

$$
\begin{aligned}
\text{HR} &= \frac{h_0(t) \cdot e^{(\beta_1 \times 1)}}{h_0(t) \cdot e^{(\beta_1 \times 0)}} \\
&= \frac{e^{\beta_1}}{e^0} \\
&= e^{\beta_1}
\end{aligned}
$$

If x_i is a 0/1 exposure variable, then HR $= e^{\beta_i}$ is the marginal effect size (in terms of HR) of an exposure - provided all other covariates are constant and there are no interaction terms.

The Cox proportional hazards model

Hazard ratio confidence intervals

A 95% confidence interval for the hazard ratio corresponding to the i^{th} covariate can be predicted using

$$\exp\left(\hat{\beta}_i \pm 1.96\sqrt{\hat{Var}\hat{\beta}_i}\right)$$

Where $s_{\hat{\beta}_i} = \sqrt{\hat{Var}\hat{\beta}_i}$

Easy to calculate when there are no interaction effects in the model, much more complicated when there are interaction terms. Fortunately this is also already implemented in most statistical software!

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The Cox proportional hazards model

The proportional hazards assumption.

- HR is assumed to be constant over time. Recall that a hazard ratio does not depend on time.
- If this property is not satisfied then we should consider alternatives such as stratified Kaplan-Meier or accelerated failure time models

The Cox proportional hazards model

Schoenfeld residuals

- We would of course like to be able to statistically test for if the proportional hazards assumption is valid
- A popular method is via Schoenfeld residuals.
- If the proportional hazards assumption is satisfied for a covariate then the Schoenfeld residuals for that covariate will not be related to survival time
- If we rank event times, we can then test the correlation between Schoenfeld residuals and their respective ranks

The Cox proportional hazards model

Parametric proportional hazards

- By specifying a parametric model, for the baseline hazard, we can formulate different kinds of proportional hazards models.
- This is useful for predictive models.
- Popular parametric families used for parametric proportional hazards:
    - Exponential
    - Weibull

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Accelerated failure time models

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Accelerated failure time models

Introduction to AFTs

- Common alternative to Cox proportional hazards
- Fully parametric
- More consistent with theoretical $S(t)$ than Cox (as it is not a step function)
- Hazard & survival function specified
- Results are usually considered more interpretable than Cox. Possible example: patient could be expected to live $15\,\%$ longer if they ceased smoking.

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Accelerated failure time models

The Weibull distribution

Distribution	S(t)	h(t)
Weibull	$e^{-\lambda t^p}$	$\lambda p t^{p-1}$

(λ is reparameterized for regression in terms of predictor variables)

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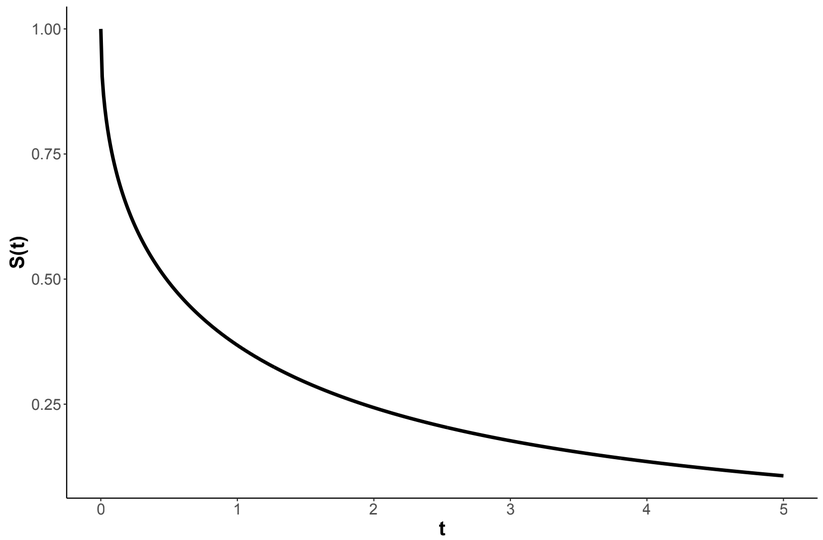
Accelerated failure time models

Weibull survival function plot

P = 0.5



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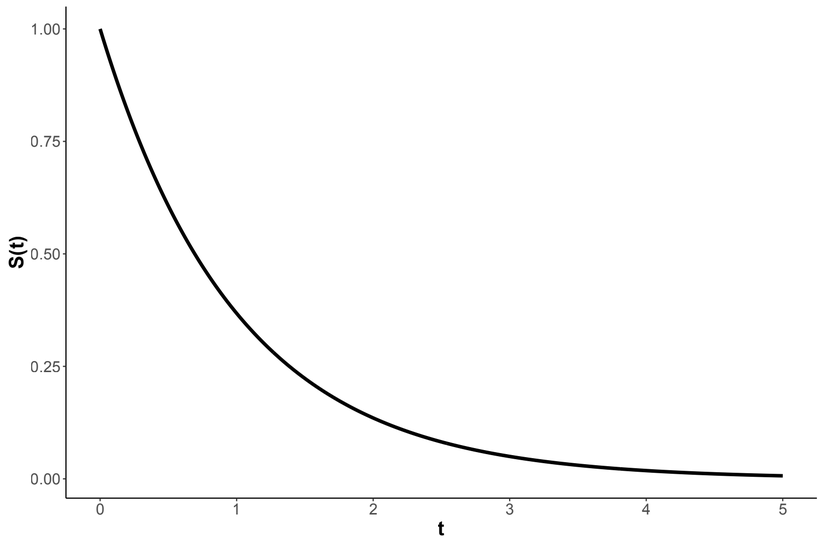

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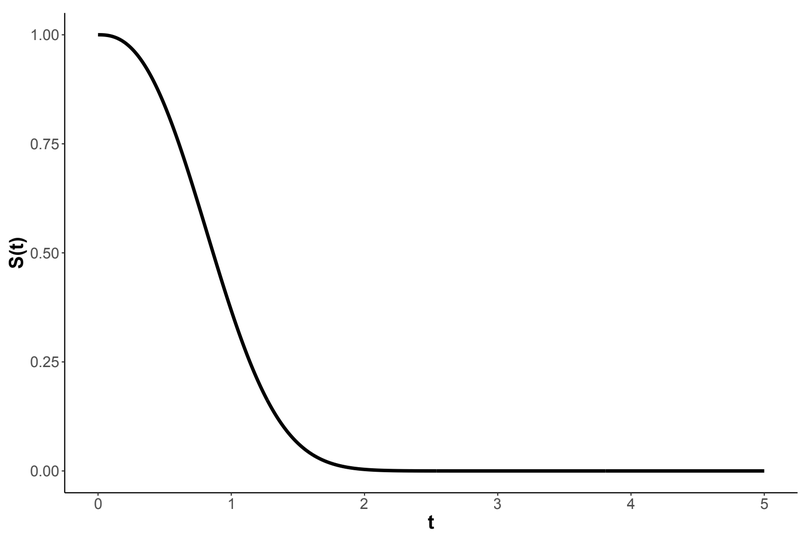

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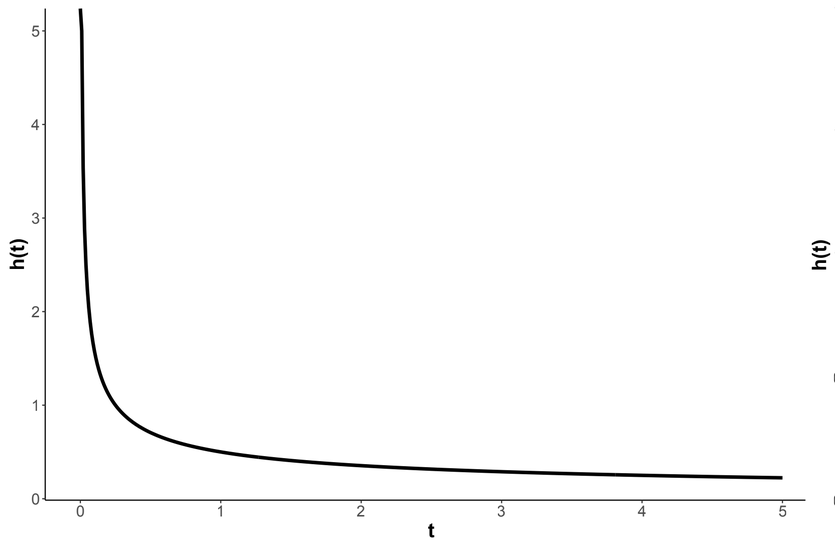
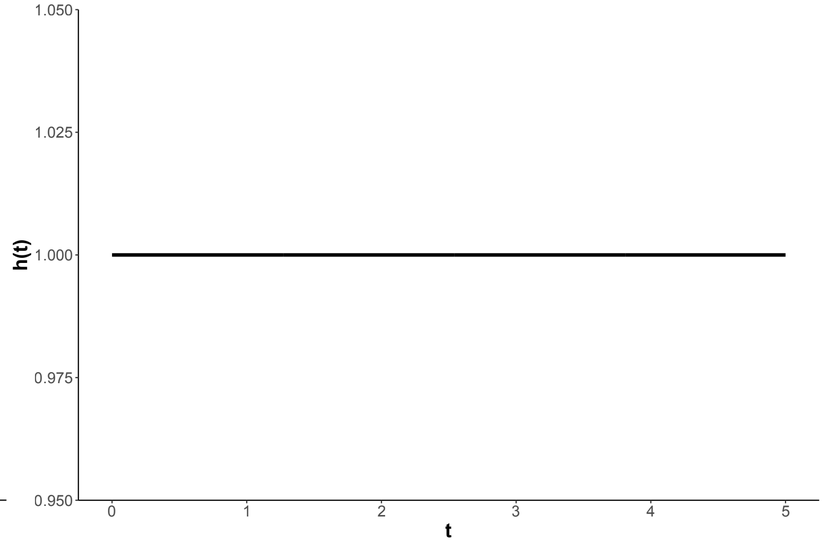
Accelerated failure time models

Weibull hazard function plot

P = 0.5



P = 1



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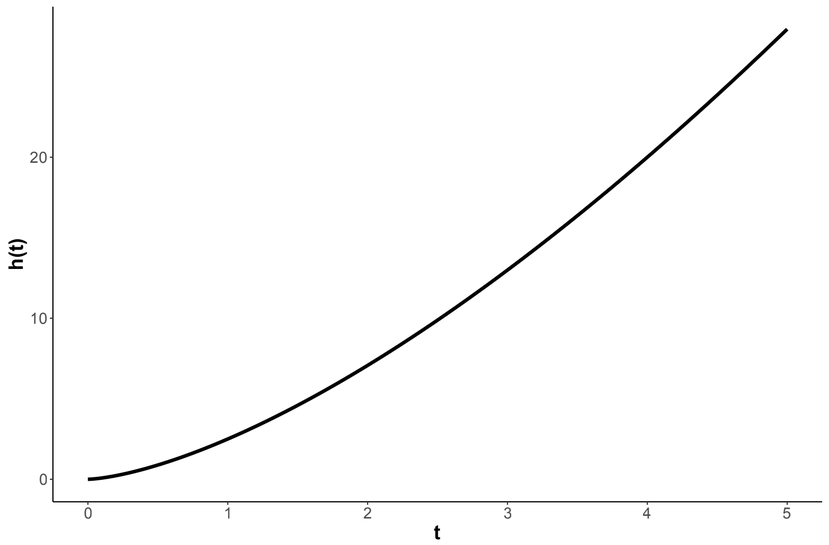

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Accelerated failure time models

The AFT assumption

- The underlying assumption for AFT models is that the effect of covariates is multiplicative with respect to survival time.
- $\log\left(T_i\right) = \beta_0 + \beta_1 x_{i1} + \ldots + \epsilon_i$
- This also means the key measure of association for an AFT is an acceleration factor (instead of a hazard ratio)
- Although the Weibull PH and Weibull AFT models have different underlying assumptions, they are actually the same model (just parameterised differently)

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Competing risks survival analysis

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Competing risks survival analysis

Introduction to Competing Risks

- In the real world, there are many events which prevent another event from occurring such as:
    - Death due to disease of interest & death unrelated to disease
    - Hospital discharge & death
    - Ulcerative colitis flare & pan-proctocolectomy (removal of the colon, rectum and anus)

Competing risks survival analysis

Cause-specific approach

- This approach is the most common in competing risks, and involves performing survival analysis for each event type separately (the other event types are treated as censored)
- Kaplan-Meier-based survival curves have “questionable” interpretations in the context of competing risks
- An alternative to KM-based curves are conditional probability curves which provides a risk probability conditional on an individual not experiencing any of the other competing risks by time t.
- We assume the competing risks are independent (but we cannot verify this with observed data).

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Competing risks survival analysis

How do we handle the independence assumption?

- Decide assumption is valid by clinical/ biological arguments
- Include common risk factors (e.g smoking for cardiovascular disease and cancer)
- Via a sensitivity analysis which considers “worst-case” violations

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Joint modelling of time-to-event and longitudinal outcomes

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Joint modelling of time-to-event and longitudinal outcomes

Introduction to JMs 1

- Up to now, all of our models have used covariates measured at baseline
- What if we wish to incorporate measurements which have been recorded across follow-up? For example:
    - C-reactive protein, CD4 counts, forced expiratory volume (FEV), faecal calprotectin, patient-reported stress
- Time-dependent Cox assumes longitudinal measurements are constant between measurements. Problematic.
- Instead we should model the longitudinal process (usually via a linear mixed effects) and the survival process (usually via Cox proportional hazards)

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Joint modelling of time-to-event and longitudinal outcomes

Introduction to JMs 2

- Modelling these two processes separately leads to biased estimates.
- Instead, we (typically) assume the survival and time-to-event models are interdependent via some shared random effects specific to the individual.
- We call the overall model a joint model (JM), the survival and longitudinal models submodels.
- Multivariate JMs allow for multiple longitudinal variables
- Being able to account for individual variability means we can characterise individual disease progression. This naturally has applicability for precision medicine.

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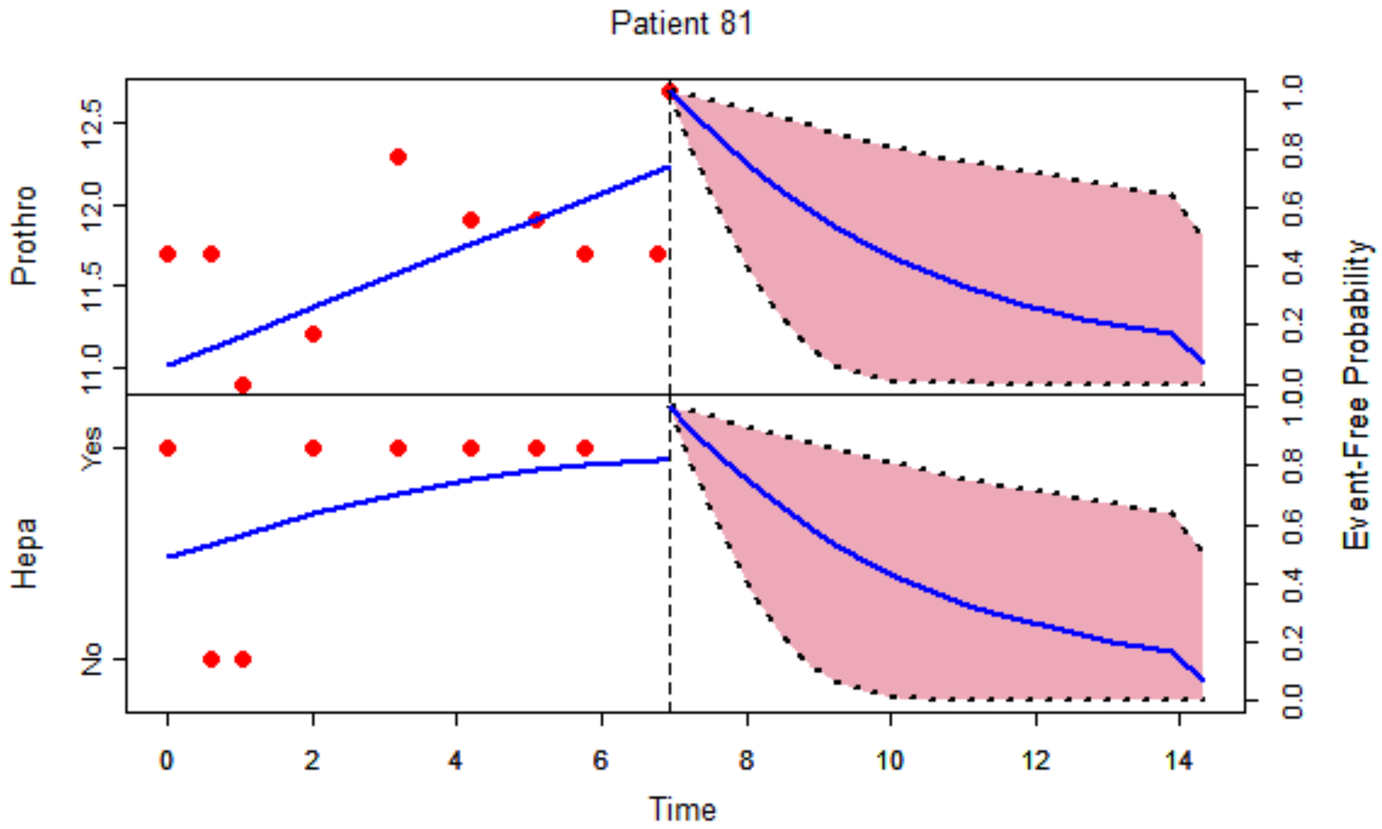
Joint modelling of time-to-event and longitudinal outcomes

JM plot



Rizopoulos, D. “The R Package JMbayes for Fitting Joint Models for Longitudinal and Time-to-Event Data Using MCMC”. Journal of Statistical Software, **2016**, 72, 1-45

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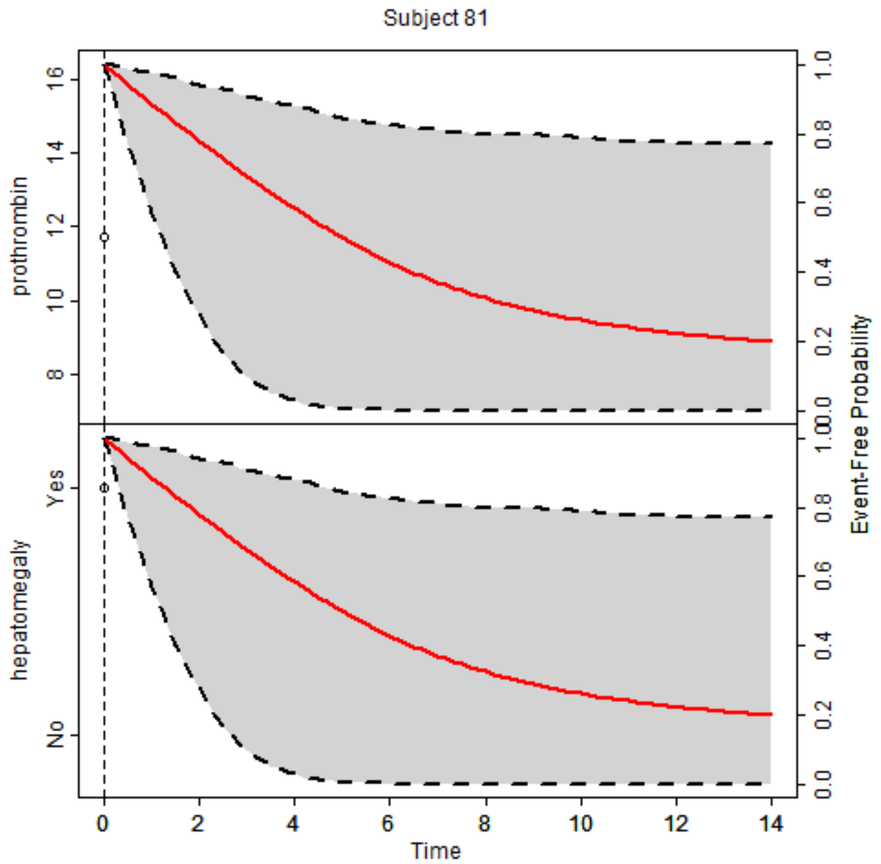
Joint modelling of time-to-event and longitudinal outcomes

Dynamic JM plot



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