Introduction to survival analysis

Jorge N. Tendeiro

Department of Psychometrics and Statistics
Faculty of Behavioral and Social Sciences
University of Groningen

✉ j.n.tendeiro@rug.nl
🌐 www.jorgetendeiro.com
 jorgetendeiro/Seminar-2020-Survival-Analysis

Plan for today

Gentle introduction to survival analysis.

Source:
Harrell, F. E., Jr. (2015). *Regression Modeling strategies*, 2nd edition.
Springer

Chapters:
17, 18, and 20.

Survival analysis (SA)

Data:
For which the *time until the event* is of interest.

▶ This goes beyond *logistic regression*, which focuses on the *occurrence* of the event.

Outcome variable:

▶ T = Time until the event.
▶ Often referred to as *failure time*, *survival time*, or *event time*.

Examples

Survival time: Time until. . .

- ▶ death, desease, relapse.
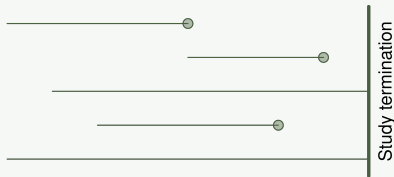
Failure time: Time until. . .

- ▶ product malfunction.

Event time: Time until. . .

- ▶ graduation, marriage, divorce.

Advantages of SA over typical regression models

▶ SA allows modeling units that did not fail up to data collection (*censored on the right* data).

▶ Regression could be considered to model the expected survival time. *But*:

   ✓ Survival time is often not normally distributed.

   ✓ $P(\text{survival} > t)$ is often more interesting than $\mathbb{E}(\text{survival time})$.

Censoring

Some subjects:

- ▶ Did not experiment the event up to the end of data collection;
- ▶ Withdrew from study;
- ▶ Were lost to follow-up.

These data are right-censored.

Define random variables for the ith subject:

- ▶ T_i = time to event
- ▶ C_i = censoring time
- ▶ e_i = event indicator = $\left\{ \begin{array}{ll} 1 & \text{if event is observed } (T_i \leq C_i) \\ 0 & \text{if event is not observed } (T_i > C_i) \end{array} \right.$
- ▶ $Y_i = \min(T_i, C_i)$ = what occurred first (failure or censoring)

Variables $\{Y_i, e_i\}$ include all the necessary information.

Typical data set
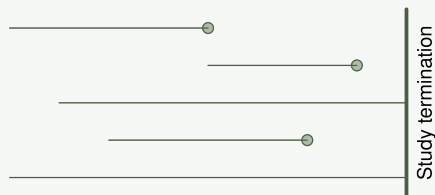
T_i	C_i	Y_i	e_i
5	10	5	1
4	12	4	1
13+	13	13	0
5	10	5	1
15+	15	15	0

Observe the flexibility of SA data:

▶ Subjects may join the study at different moments.
▶ Censoring times may differ among subjects.

$\{Y_i, e_i\}$ does include all the necessary information.

But, *assumption*: Censoring is **non-informative**, i.e., it is independent of the risk of the event.

Three main functions

Recall that the outcome variable is T = time until event.

▶ Survival function:

$$S(t) = P(T > t) = 1 - F(t),$$

where $F = P(T \leq t)$ is distribution function of T.

▶ Cumulative hazard function:

$$\Lambda(t) = -\log(S(t))$$

▶ Hazard function:
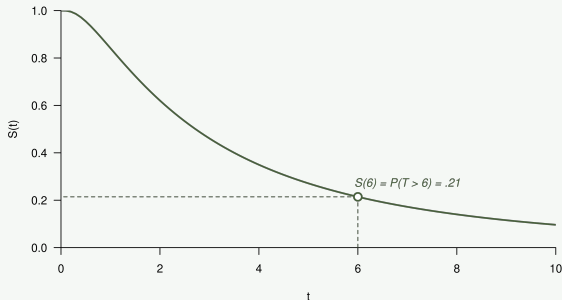
$$\lambda(t) = \Lambda'(t)$$

Survival function

$$S(t) = P(T > t) = 1 - F(t)$$

Example:
If event = death, then $S(t)$ = prob. that death occurs after time t.

Properties:

- ▶ $S(0) = 1$, $S(\infty) = 0$.
- ▶ Non-increasing function of t.

$S(6) = P(T > 6) = .21$
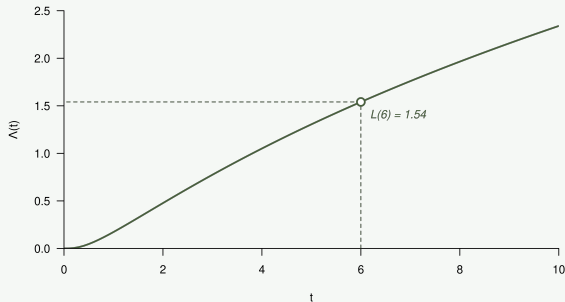
Cumulative hazard function

$$\Lambda(t) = -\log(S(t))$$

Idea:
Accumulated risk up until time t.

Properties:

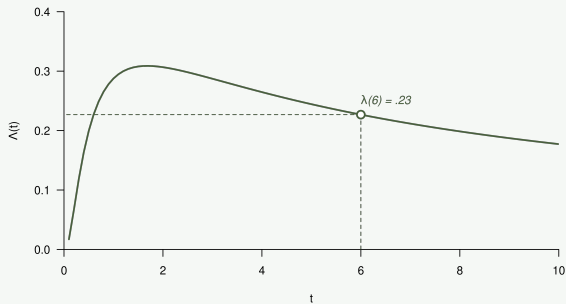- $\Lambda(0) = 0$.
- Non-decreasing function of t.

Hazard function

$$\lambda(t) = \Lambda'(t)$$

Idea:
Instantaneous event rate at time t.

Relation between the three functions

All functions are related:
Any two functions can be derived from the third function.

► The three functions are **equivalent ways** of describing the same random variable (T = time until event).

More generally, all the following functions give mathematically equivalent specifications of the distribution of T:

► $F(t)$: Distribution function
► $f(t)$: Density function
► $S(t)$: Survival function
► $\lambda(t)$: Hazard function
► $\Lambda(t)$: Cumulative hazard function.

Examples

Next are two primary examples of parametric survival distributions:

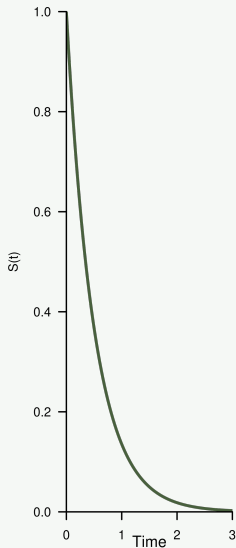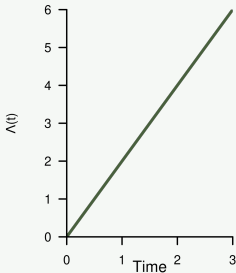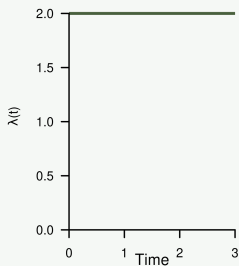- ▶ the exponential distribution;
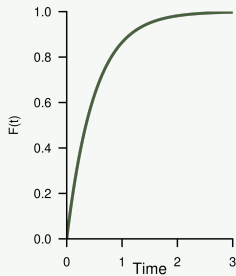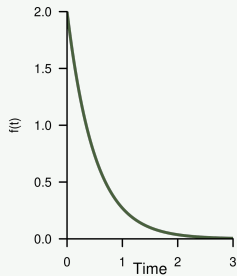- ▶ the Weibull distribution.

These models (still) include no covariates, thus:

- ▶ Each subject in the sample is assumed to have the same distribution of T.

No formulas.
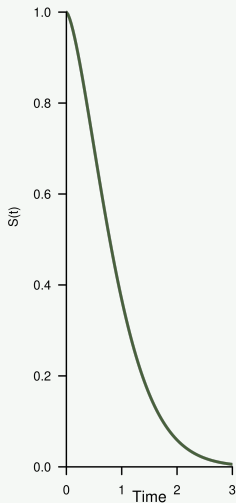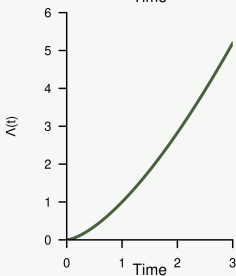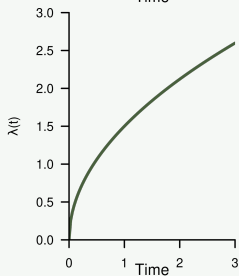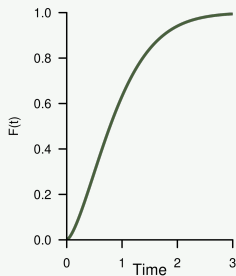Instead: Let's plot.

Exponential survival distribution

Weibull survival distribution (I)
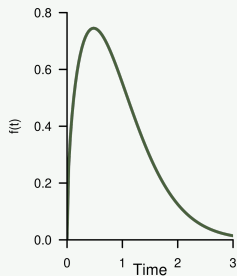
Weibull survival distribution (II)
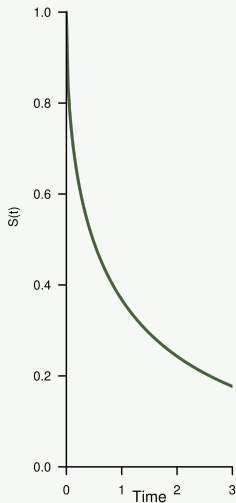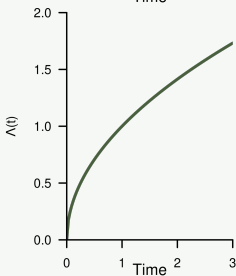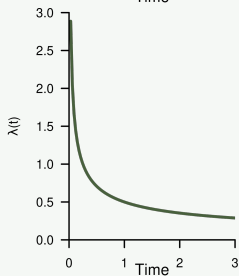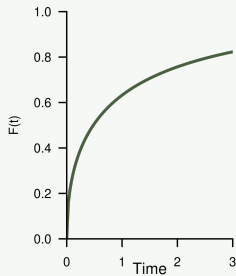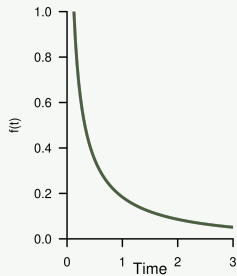
Quantiles

Q: What is the time by which $(100q)\%$ of the population will fail?

A: Value t_q such that $F(t_q) = q$, or, equiv., $S(t_q) = 1 - q$.
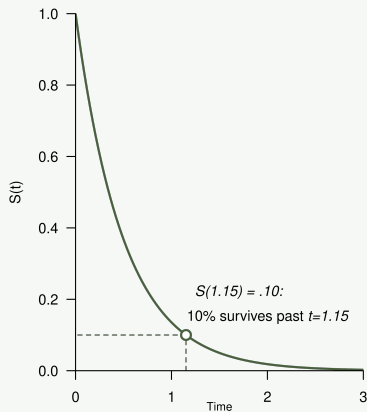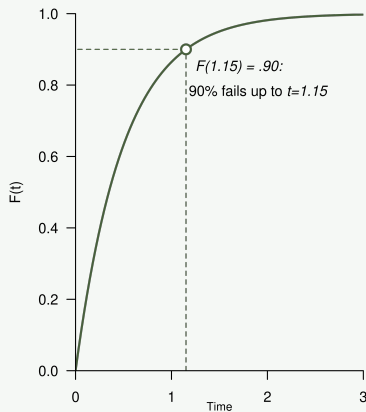
In particular, **median** survival time = $t_{.50}$.

Expected failure time

(Note: T is skewed, so the mean is not the best summary. Better use median.)

Q: What is the expected failure time?

A: It is the area under the survival function.
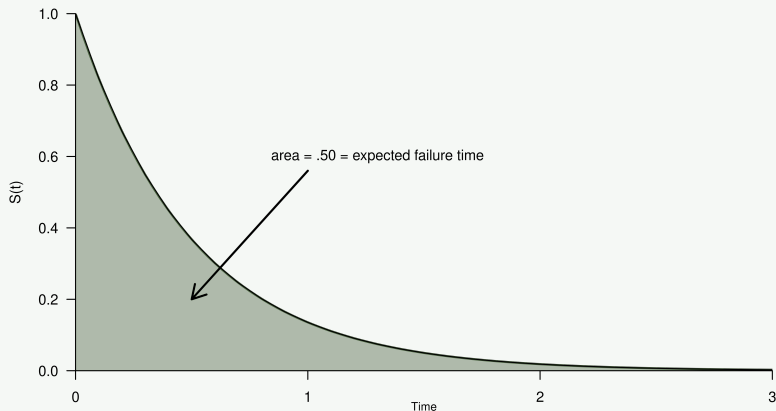
Various estimation approaches

There are several options available to estimate the survival function (and friends).

Here we will briefly go through only a few:

- ▶ Not parametric and homogeneous (i.e., without predictors):
  - ✓ Kaplan-Meier estimator
  - ✓ Altschuler-Nelson estimator
- ▶ Parametric:
  - ✓ Homogeneous (i.e., no predictors): Exponential, Weibull, normal, logistic, log-normal, log-logistic,…
  - ✓ Proportional hazards models
- ▶ Semi-parametric:
  - ✓ Cox proportional hazards regression model

After a brief intro to each, I will use them all on an empirical dataset.

Kaplan-Meier estimator

- ▶ Also known as the *product-limit* estimator.
- ▶ Non parametric, and super simple to do even manually.
- ▶ Key ingredient: *Conditional probabilites*.

Assume $t = 0, 1, 2, \dots$
We have that $S(0) = P(T > 0) = 1$. For $t \geq 1$ we then have that

$$P(T > t | T > t-1) = \frac{P(T > t, T > t-1)}{P(T > t-1)} = \frac{P(T > t)}{P(T > t-1)}$$

and so

$$P(T > t) = P(T > t-1) \times P(T > t | T > t-1),$$

or in terms of the survival function,

$$S(t) = S(t-1) \times P(T > t | T > t-1)$$

$$\boxed{S(t) = S(t-1) \times (1 - P(T \leq t | T > t-1))}$$

Kaplan-Meier estimator – Example

Data: Seven subjects; failure times $T = 1, 3, 3, 3+, 6+, 9, 10+$.

Day	No. subjects at risk	Deaths	Censored	$S(t) = S(t-1) \times \\ \times (1 - P(T \le t \| T > t-1))$
1	7	1	0	$1 \times (1 - 1/7) = 6/7$
3	$7 - (1+0) = 6$	2	1	$6/7 \times (1 - 2/6) = 4/7$
6	$6 - (2+1) = 3$	0	1	$4/7 \times (1 - 0/3) = 4/7$
9	$3 - (0+1) = 2$	1	0	$4/7 \times (1 - 1/2) = 2/7$
10	$2 - (1+0) = 1$	0	1	$2/7 \times (1 - 0/1) = 2/7$

Hence:

$$S(t) = \begin{cases} 1, & 0 \le t < 1 \\ 6/7 = .86, & 1 \le t < 3 \\ 4/7 = .57, & 3 \le t < 9 \\ 2/7 = .29, & 9 \le t < 10 \\ \text{undefined}^*, & t \ge 10 \end{cases}.$$

*Not everyone failed by $t = 10$, so we cannot tell what happened after that.

Kaplan-Meier estimator – Example
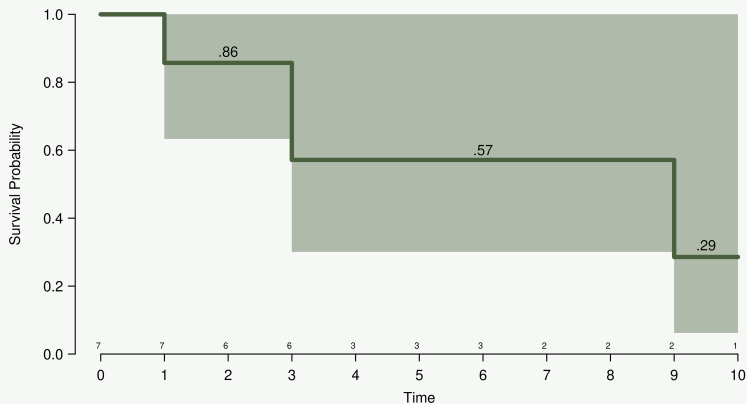
Altschuler-Nelson estimator

- ▶ Non parametric, also simple.
- ▶ Similar to Kaplan-Meier, but based on $\Lambda(t)$.

Recall that $\Lambda(t) =$ accumulated risk up until time t.

Hence it makes sense to estimate $\Lambda(t)$ by

$$\widehat{\Lambda}(t) = \sum_{i:t_i \leq t} \frac{\text{\# failures at } t_i}{\text{\# subjects at risk at } t_i}.$$

Then,

$$\widehat{S}(t) = \exp(-\widehat{\Lambda}(t)).$$

Interesting property: $\sum_i \widehat{\Lambda}(Y_i) =$ total number of events.

Altschuler-Nelson estimator – Example

Data: Seven subjects; failure times $T = 1, 3, 3, 3+, 6+, 9, 10+$.

Day	No. subjects at risk	Deaths	Censored	$\Lambda(t)$
1	7	1	0	$1/7$
3	$7 - (1+0) = 6$	2	1	$1/7 + 2/6 = 10/21$
6	$6 - (2+1) = 3$	0	1	$10/21 + 0/3 = 10/21$
9	$3 - (0+1) = 2$	1	0	$10/21 + 1/2 = 41/42$
10	$2 - (1+0) = 1$	0	1	$41/42 + 0/1 = 41/42$
		$\sum_i = 4$		$\sum_i = 4$

Hence:

$$S(t) = \exp(-\Lambda(t)) = \begin{cases} \exp(0) = 1, & 0 \leq t < 1 \\ \exp(-1/7) = .87, & 1 \leq t < 3 \\ \exp(-10/21) = .62, & 3 \leq t < 9 \\ \exp(-41/42) = .38, & 9 \leq t < 10 \\ \text{undefined}, & t \geq 10 \end{cases}.$$

Altschuler-Nelson estimator – Example
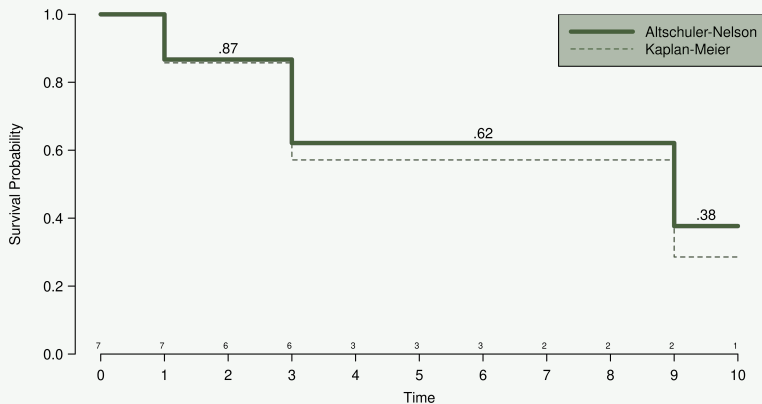
Homogeneous parametric models

Q: How about *continuous*, parametric, counterparts to KM and AN?
   Still incorporating no predictors?

A: There are really *a lot* of possibilities.

Most common examples:

- ▶ Exponential
- ▶ Weibull
- ▶ Normal
- ▶ Logistic
- ▶ Log-normal
- ▶ Log-logistic
- ▶ …

My advice:
Just fit several of these and compare.
There is no 'best' model, it depends on the data.

Homogeneous parametric models

Data: $T = 1, 3, 3, 3+, 6+, 9, 10+$.
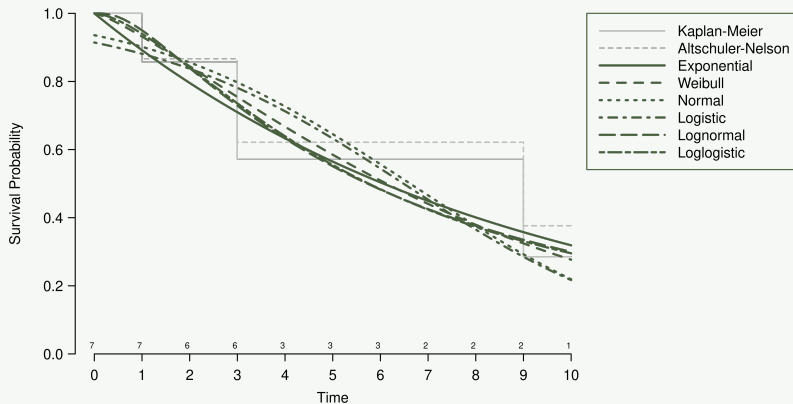
Assessing model fit

I like Harrell's take on this:

▶ To assess model fit, use **graphical methods**
   (and no tests; yeah, that's right!).

We show an example:
Assess the fit of the exponential model.

Two plotting options, akin to *QQ*-plots:

▶ Plot $S_{\mathrm{Exp}}^{-1}(S_{\mathrm{KM}}(T))$ versus T;
▶ Plot $S_{\mathrm{Exp}}(T)$ versus $S_{\mathrm{KM}}(T)$.

Assessing model fit

Data: $T = 1, 3, 3, 3+, 6+, 9, 10+$.

Parametric proportional hazards model

First model until now that allows incorporating predictor variables
$X = \{X_1, X_2, \ldots, X_k\}$.

▶ X_i can be continuous, dichotomous, polytomous, etc.

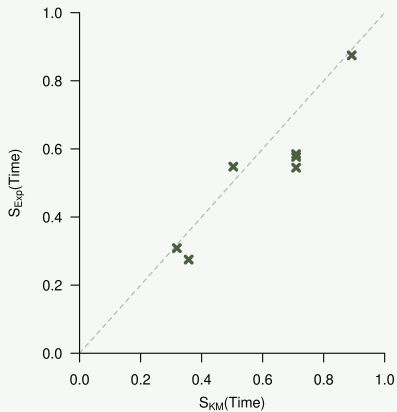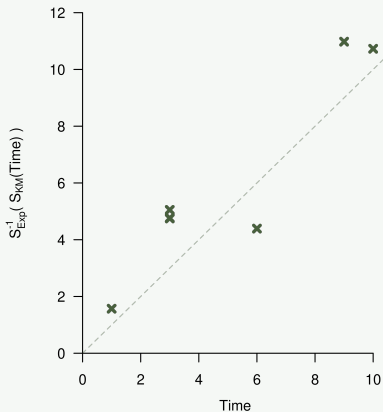The proportional hazards (PH) model generalizes the hazard function
$\lambda(t)$:

$$\lambda(t|X) = \lambda(t)\overbrace{\exp(\underbrace{\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k}_{X\beta})}^{\text{relative hazard function}} = \lambda(t)\exp(X\beta)$$

▶ $\lambda(t|X)$ = hazard function for T given the predictors X.
▶ $\lambda(t)$ = 'underlying' hazard function (for a subject with $X\beta = 0$).
▶ $\exp(X\beta)$ describes the *relative* effects of the predictors.

Note: The intercept β_0 may be omitted (kind of 'absorbed' into $\lambda(t)$).

Parametric proportional hazards model

$$\lambda(t|X) = \lambda(t) \exp(X\beta)$$

Here are the 'friends':

$$\Lambda(t|X) = \Lambda(t) \exp(X\beta)$$
$$S(t|X) = S(t)^{\exp(X\beta)}$$

▶ $\Lambda(t) = $ 'underlying' cumulative hazard function (for a subject with $X\beta = 0$).
▶ $S(t) = $ 'underlying' survival function (for a subject with $X\beta = 0$).

Parametric proportional hazards model

It is easiest to consider the log-model versions:

$$\log \lambda(t|X) = \log \lambda(t) + X\beta$$
$$\log \Lambda(t|X) = \log \Lambda(t) + X\beta$$
$$\log S(t|X) = \underbrace{\log S(t)}_{\text{time}} \times \underbrace{\exp(X\beta)}_{\text{predictors}}$$

▶ Observe that we separated the time and the predictors components.

Important consequence due to the separability of t and X:

▶ The effect of X is assumed to be the same at all values of t.
▶ I.e.: We assume no $t \times X$ interaction effect.

Parametric proportional hazards model

How to interpret regression coefficient β_j $(j = 1, \ldots, k)$?

$$\log \lambda(t|X) = \log \lambda(t) + (\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k)$$

$$\log \Lambda(t|X) = \underbrace{\log \Lambda(t)}_{\text{time}} + \underbrace{(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k)}_{\text{predictors}}$$

▶ Additive interpretation:
  ✓ $\log \lambda(t|X)$ increases by β_j units when X_j increases by 1 unit at any time point t, holding all the other predictors constant:

  $$\log \lambda(t|\ldots, X_j + 1, \ldots) = \log \lambda(t|\ldots, X_j, \ldots) + \beta_j.$$

  ✓ Same for $\log \lambda(t|X)$.

Parametric proportional hazards model

How to interpret regression coefficient β_j $(j = 1, \ldots, k)$?

$$\lambda(t|X) = \lambda(t) \quad \times \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k)$$
$$\Lambda(t|X) = \Lambda(t) \quad \times \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k)$$
$$\log S(t|X) = \underbrace{\log S(t)}_{\text{time}} \times \underbrace{\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k)}_{\text{predictors}}$$

▶ Multiplicative interpretation:
  ✓ $\lambda(t|X)$ is multiplied by $\exp(\beta_j)$ units when X_j increases by 1 unit at any time point t, holding all the other predictors constant:

$$\frac{\lambda(t|\ldots, X_j + 1, \ldots)}{\lambda(t|\ldots, X_j, \ldots)} = \exp(\beta_j).$$

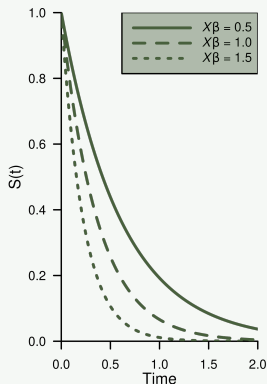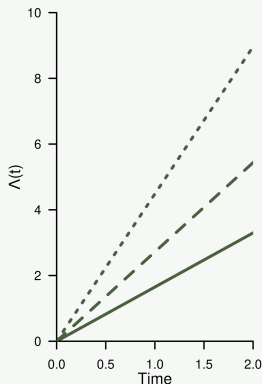 ✓ Same for $\lambda(t|X)$.
  ✓ Same for $\log S(t|X)$.

Example: Exponential PH survival model

$X\beta = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k.$

$$\lambda(t|X) = \exp(X\beta)$$
$$\Lambda(t|X) = t\exp(X\beta)$$
$$S(t|X) = \exp(-t)^{\exp(X\beta)}$$

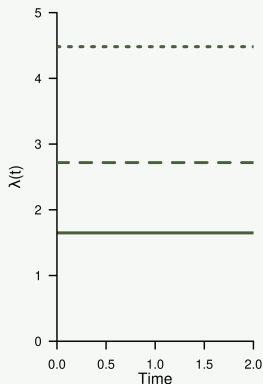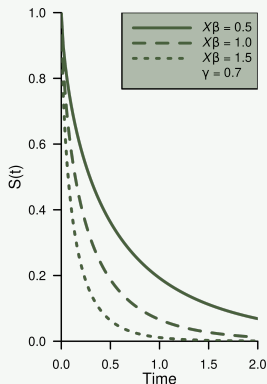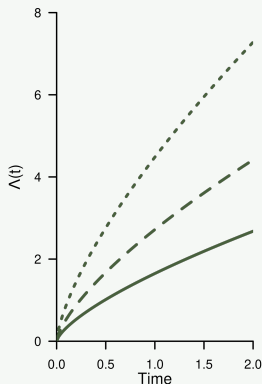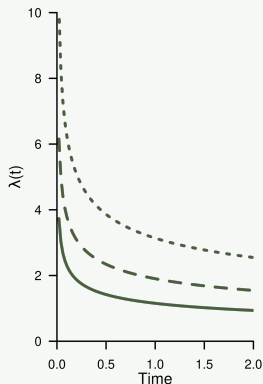## Example: Weibull PH survival model

$$X\beta = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_x X_k.$$

$$\lambda(t|X) = \gamma t^{\gamma-1} \exp(X\beta)$$
$$\Lambda(t|X) = t^\gamma \exp(X\beta)$$
$$S(t|X) = \exp(-t^\gamma)^{\exp(X\beta)}$$

Accelerated failure time models

The predictors in the PH models shown so far have an effect through multiplication on the hazard function:

$$\lambda(t|X) = \lambda(t) \exp(X\beta).$$

We can instead make the predictors have a multiplicative effect on the failure time. Or, equiv., have an additive effect on the log failure time.

▶ These are accelerated failure time models.
▶ The failure time accelerates as X increases.

General form:

$$S(t|X) = \psi\left(\frac{\log(t) - X\beta}{\sigma}\right)$$

▶ ψ: e.g., normal, logistic, extreme value distribution.
▶ σ: scale parameter.

I won't pursue this type of models today, so just FYI.

Cox proportional hazards model

Seemingly the most popular survival model used.

The Cox PH model:

$$\lambda(t|X) = \lambda(t) \exp(X\beta)$$

- ► Looks the same as the general PH model!
- ► But, it is semiparametric:
  - ✓ It makes a parametric assumption in $X\beta = \beta_1 X_1 + \cdots + \beta_x X_k$.
    (NB: No intercept is typical for the Cox PH model.)
  - ✓ But, it assumes no parametric model for the hazard function $\lambda(t)$.
    Actually, it won't even be estimated!

Rationale:

- ► The true hazard function $\lambda(t)$ may be too complex.
- ► The effect of the predictors is more relevant than the shape of $\lambda(t)$.

The Cox PH model allows bypassing $\lambda(t)$.

Cox proportional hazards model

But how does this *magic* work?

▶ Use the rank ordering of *T*.

Advantages:

▶ Better protection against outliers.
▶ The Cox PH model is more efficient than parametric PH models when parametric assumptions are strongly violated.
▶ Surprisingly, the Cox PH model is as efficient as parametric PH models even when parametric assumptions hold.

Final worked out example

I will use the *lung* dataset from the *survival* package in R.

▶ The data concern survival in patients with advanced lung cancer.
▶ These data have been analyzed *ad nauseam*, e.g.:
  ✓ Tutorial 1
  ✓ Tutorial 2
  ✓ Tutorial 3
  ✓ Using Bayesian statistics and Stan!

I will just run some basics.

Want something else to play afterwards?

▶ Check other datasets in the *survival* R package, it has plenty (e.g., *ovarian*, *veteran*).
▶ Bayesian analysis on mastectomy data (*HSAUR* R package)
▶ Recidivism data (*carData* R package)

Lung data

	Time and censoring				Predictors		
$Y_i =$ **time**	$e_i=$ **status**		*age*	*sex*	*ph.ecog*	*ph.karno*	*wt.loss*
306	2		74	1	1	90	NA
455	2		68	1	0	90	15
1010	1		56	1	0	90	15
210	2		57	1	1	90	11
883	2		60	1	0	100	0
1022	1		74	1	1	50	0
⋮	⋮		⋮	⋮	⋮	⋮	⋮

- ► *time*: Survival time in days

- ► *status*: Censoring (1=censored, 2=dead)

- ► *age*: Age in years

- ► *sex*: Male=1, Female=2

- ► *ph.ecog*: ECOG performance score (0=good, ..., 5=dead)

- ► *ph.karno*: 0-100 performance score (physician)

- ► *wt.loss*: Weight loss in last 6 months