Introduction to survival analysis

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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 = $\begin{cases} 1 & \text{if event is observed } (T_i \leq C_i) \\ 0 & \text{if event is not observed } (T_i > C_i) \end{cases}$
- $Y_i = \min(T_i, C_i)$ = 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:

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

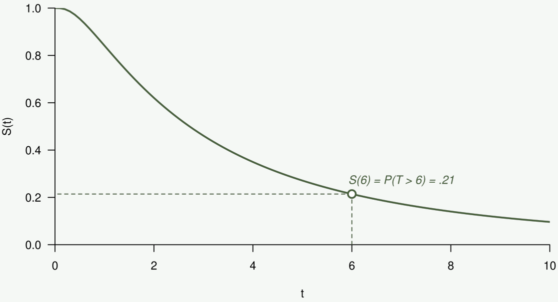
Survival function

$$\boxed{S(t) = P(T > t) = 1 - F(t)}$$

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.



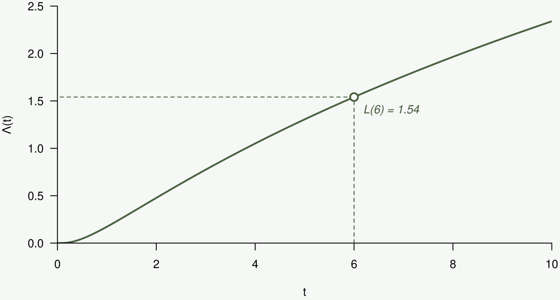
Cumulative hazard function

$$\boxed{\Lambda(t) = -\log(S(t))}$$

Idea:
Accumulated risk up until time t.

Properties:

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



Hazard function

$$\boxed{\lambda(t) = \Lambda'(t)}$$

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:

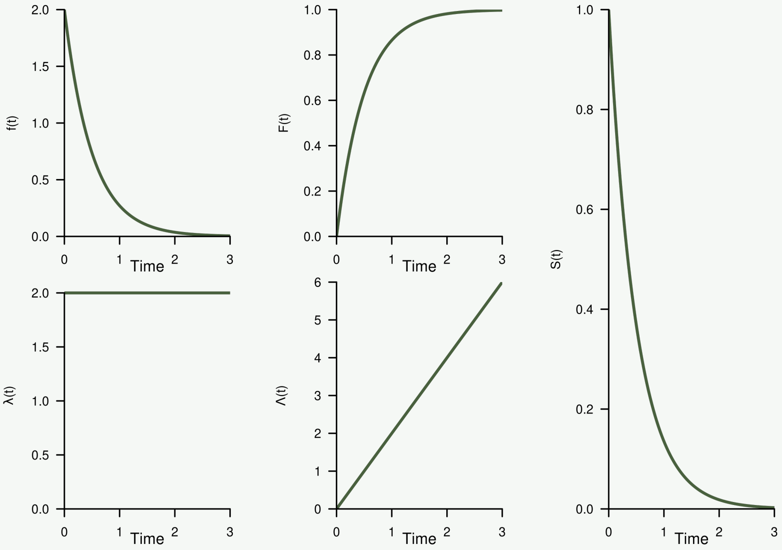
- the exponential distribution;
- the Weibull distribution.

These models (still) include no covariates, thus:

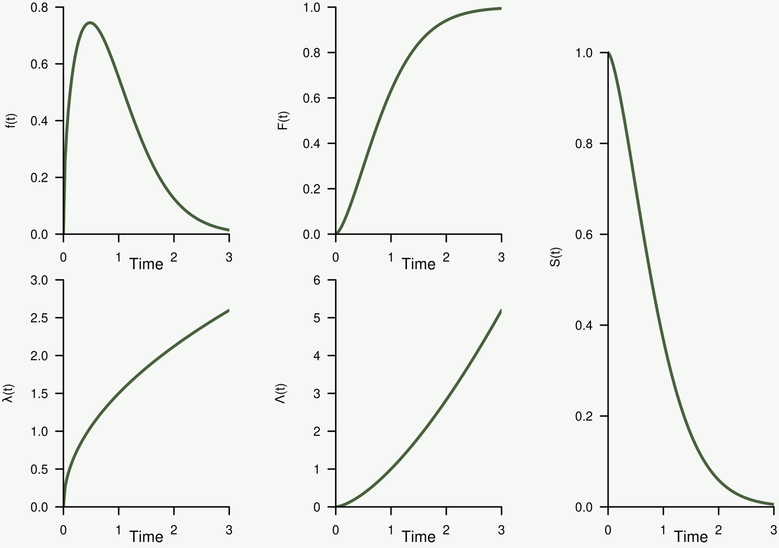
- Each subject in the sample is assumed to have the same distribution of T.

No formulas.
Instead: Let's plot.

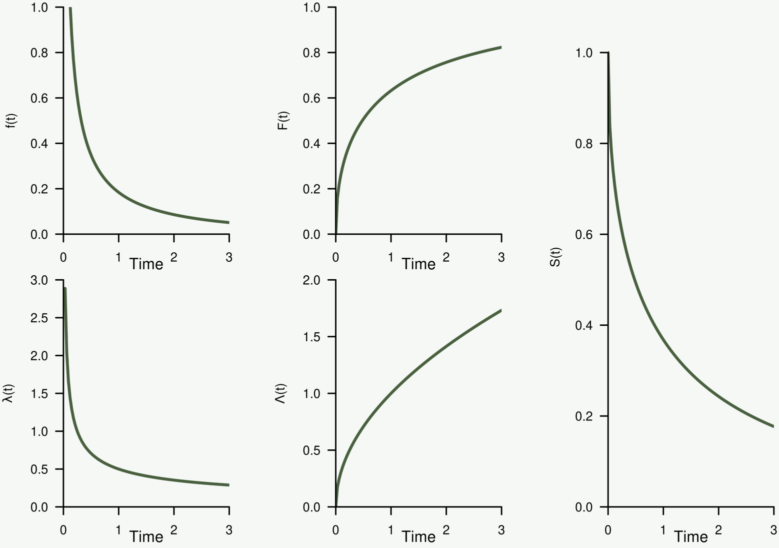
Exponential survival distribution



Weibull survival distribution (I)



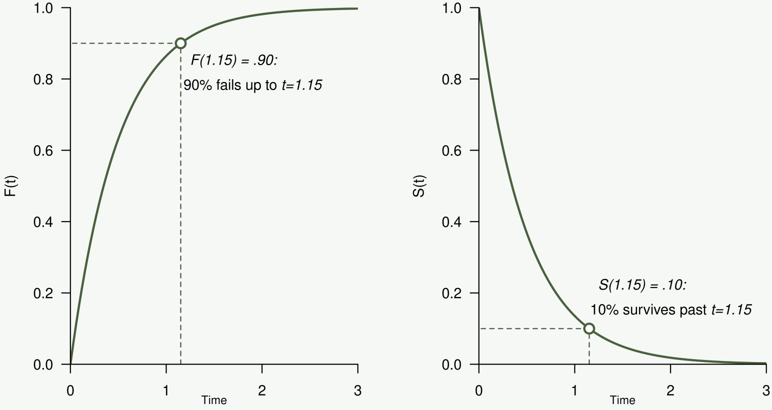
Weibull survival distribution (II)



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., $S(t_q) = 1 - q$.



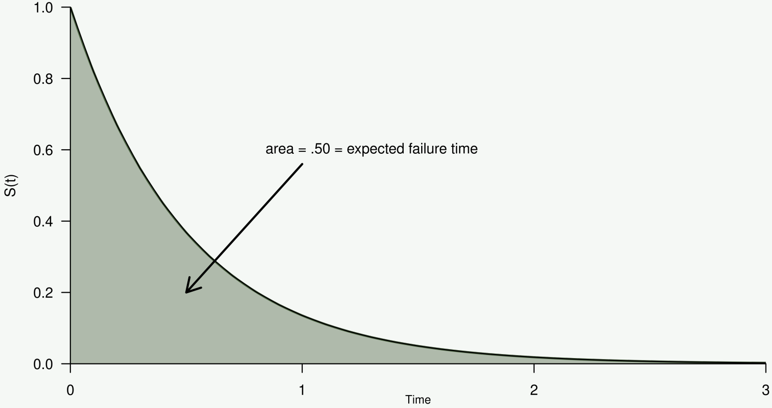
In particular, median survival time = $t_{.50}$.

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

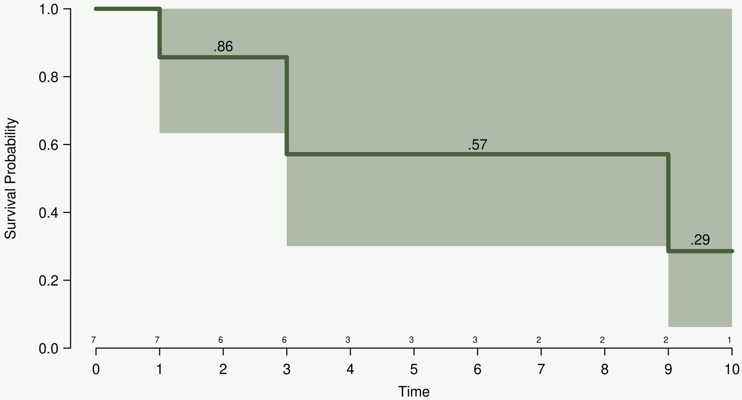
Day	No. subjects at risk	Deaths	Censored	$S(t) = S(t-1) \times$ $\times(1 - P(T \leq t \| T > t-1))$
1	7	1	0	$1 \times (1 - 1/7) = 6/7$
3	$7 - (1 + 0) = 6$	2	1	$6/7 \times (1 - 2/6) = 4/7$
6	$6 - (2 + 1) = 3$	0	1	$4/7 \times (1 - 0/3) = 4/7$
9	$3 - (0 + 1) = 2$	1	0	$4/7 \times (1 - 1/2) = 2/7$
10	$2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

Hence:

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

*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

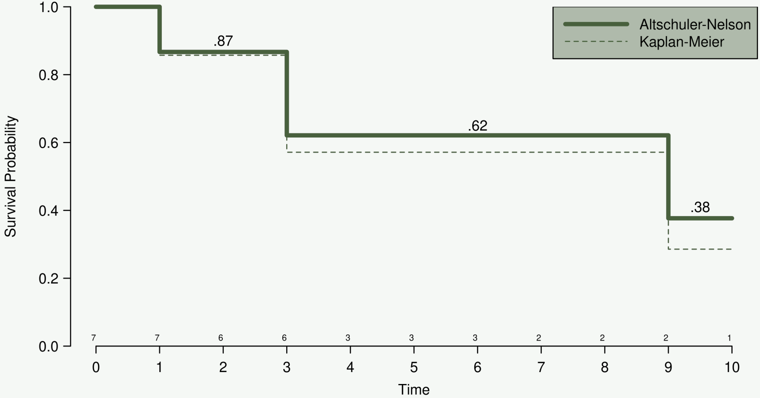
Data: Seven subjects; failure times $T = 1, 3, 3, 3+, 6+, 9, 10+$.

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.

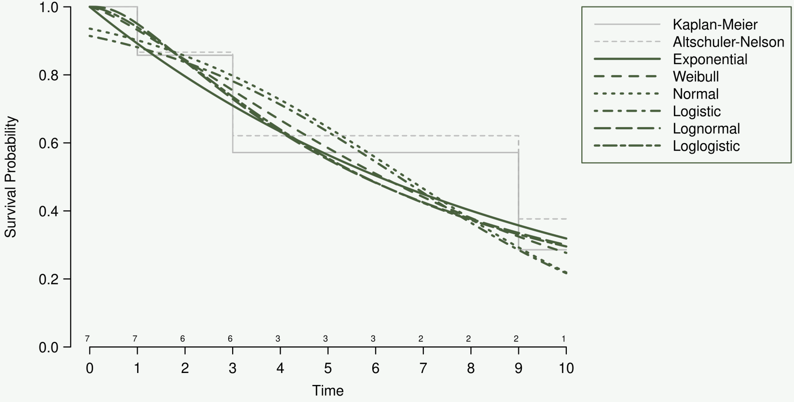
Most common examples:

- 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!).

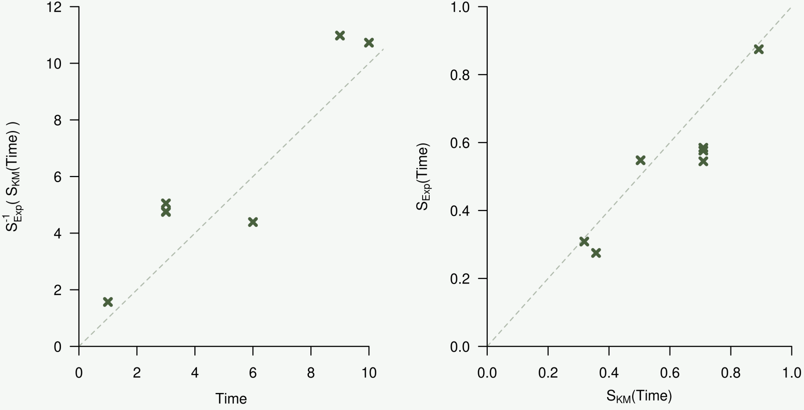
We show an example:
Assess the fit of the exponential model.

Two plotting options, akin to QQ-plots:

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

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 $\lambda(t)$:

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

- $\lambda(t|X)$ = 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

$$\boxed{\lambda(t|X) = \lambda(t)\exp(X\beta)}$$

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 ($j = 1, \dots, k$)?

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

- 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:

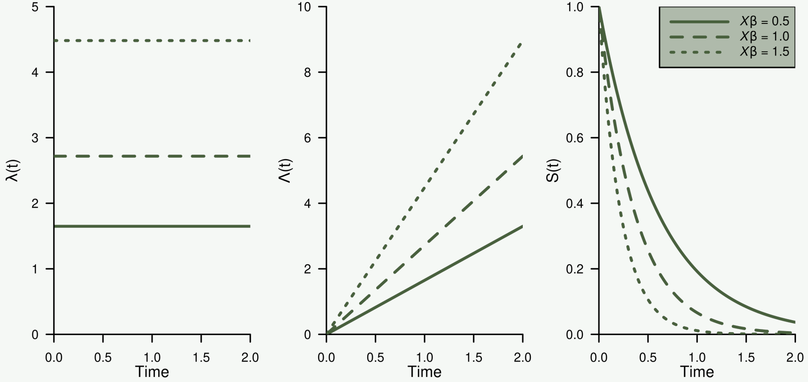
$$\frac{\lambda(t|\dots, X_j + 1, \dots)}{\lambda(t|\dots, X_j, \dots)} = \exp(\beta_j).$$

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

Example: Exponential PH survival model

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

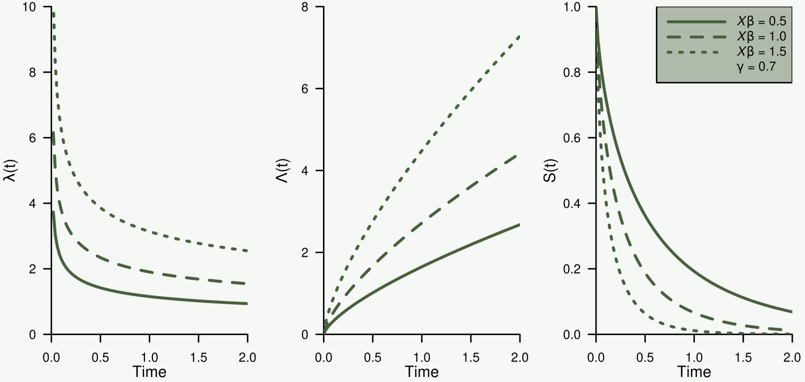
$$\lambda(t|X) = \exp(X\beta)$$
$$\Lambda(t|X) = t\exp(X\beta)$$
$$S(t|X) = \exp(-t)^{\exp(X\beta)}$$



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:

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

- 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:

$$\boxed{\lambda(t|X) = \lambda(t)\exp(X\beta)}$$

- 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

Y_i =***time***	e_i=***status***
306	2
455	2
1010	1
210	2
883	2
1022	1
⋮	⋮

Predictors

age	***sex***	***ph.ecog***	***ph.karno***	***wt.loss***
74	1	1	90	NA
68	1	0	90	15
56	1	0	90	15
57	1	1	90	11
60	1	0	100	0
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

Lung data

- $\{Y_i, e_i\}$ completey define the DV T (time until event).
- T can be computed through the `Surv()` function.

Time and censoring

Y_i =***time***	e_i=***status***
306	2
455	2
1010	1
210	2
883	2
1022	1
$\vdots$	$\vdots$

```r
Surv(lung$time, lung$status) %>% head
```

```
## [1]  306   455  1010+  210   883  1022+
```

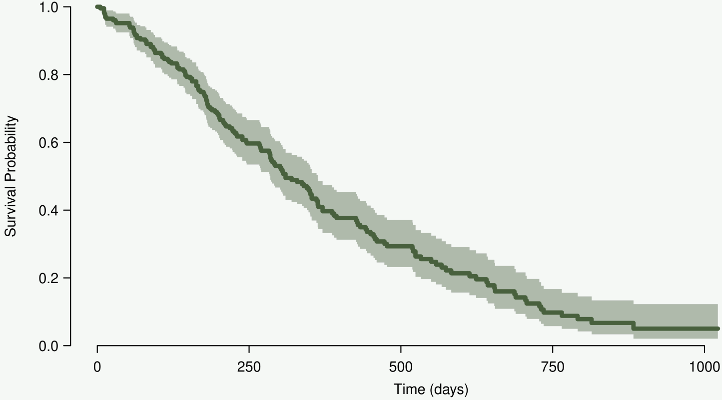
In R

There are loads of packages and options to go about:

- *rms*
- *survival*
- *survminer*

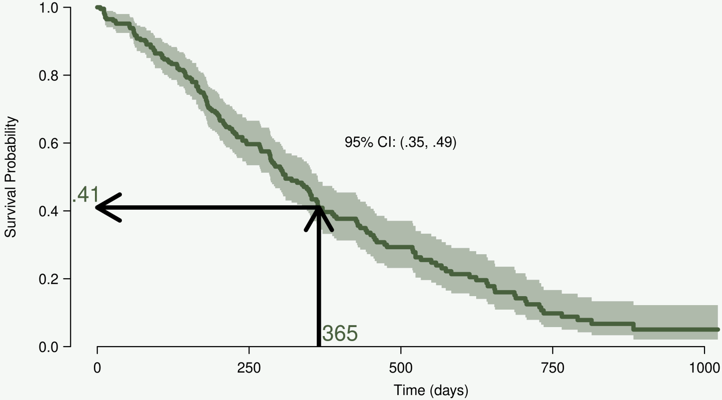
I'll use functions from various packages depending on functionality and eye-candyness.

Lung data: Kaplan-Meier



Lung data: Kaplan-Meier

What is $P(t > 365 \; days)$*?*



Lung data: Kaplan-Meier

What is the average (median) survival time?