QMWS - Survival Analysis
Regression models for survival analysis

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We've seen how to get multiple survival curves and how to test for differences (log-rank test).

However, we may want to do more sophisticated modelling, with multiple continuous and/or categorical variables affecting survival probabilities.

We have many techniques for **regression analysis** in the context of survival data.

- To begin, we will do a **very short** review of linear regression.
- It is assumed you have seen multiple linear regression before.

Review of simple linear regression

In **simple linear regression**, we wish to study the relationship between a **predictor** variable x_i and an **outcome** variable y_i, where $i = 1, \ldots, n$.

The predictor x_i is assumed to be **fixed** and the outcome y_i is assumed to be **random**. **Examples:**

- y_i is blood pressure, x_i is age.
- y_i is a measure of user satisfaction after using a web portal, $x_i \in \{0, 1\}$ is one of two portal designs.

A basic probabilistic model for linear regression

The linear regression model takes the form:

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i$$

where ϵ_i is a random error term, e.g. a random variable with zero mean and finite variance ($E[\epsilon_i] = 0, \text{var}[\epsilon_i] = \sigma^2$); it represents the error present in the measurement of y_i.

Terminology:

- β_0 - **Intercept** parameter
- β_1 - **Slope** parameter

A basic probabilistic model for linear regression

- $\beta_1 > 0$: increasing y_i with increasing x_i
- $\beta_1 < 0$: decreasing y_i with increasing x_i
- $\beta_1 = 0$: no *linear* relationship between x_i and y_i

We sometimes write Y_i when we think of the outcome as a **random variable**. We have that:

$$E[Y_i|x] = \beta_0 + \beta_1 x_i$$

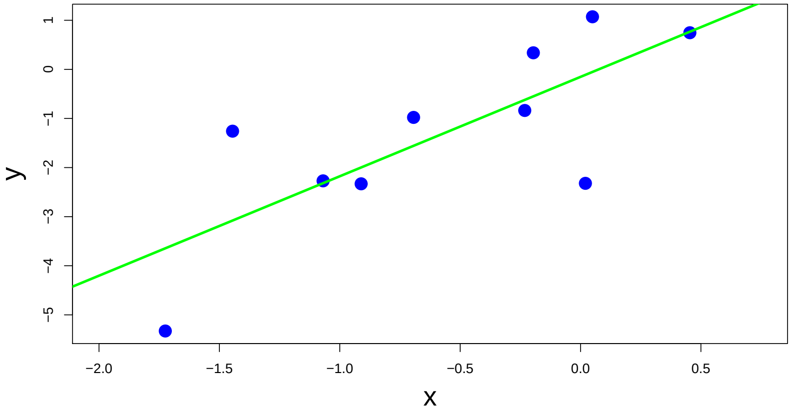
where $E[Y_i|x_i]$ is the expected (mean) value of Y_i for fixed value of x_i.

Interpreting linear regression coefficients

$$E[Y_i|x_i] = \beta_0 + \beta_1 x_i$$

- β_1 is the expected difference in response Y_i between two groups of individuals, where one group has covariate value x_i one unit greater than the other group.
- β_0 is the expected value of Y_i in a group of individuals with covariate value $x_i = 0$.

Linear regression



Distributional assumption

We also assume a **normal distribution** for the error term ϵ_i:

$$\epsilon_i \sim \text{Normal}(0, \sigma^2)$$

This is equivalent to saying that:

$$Y_i | x_i \sim \text{Normal}\left(\beta_0 + \beta_1 x_i,\, \sigma^2\right)$$

Multiple linear regression

In **multiple linear regression** we have p predictor variables $x_{i1}, \ldots, x_{ip}$ and outcome y_i for each $i = 1, \ldots, n$ and assume that:

$$y_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + \epsilon_i,$$

where $\epsilon_i \sim \text{Normal}(0, \sigma^2)$ and the observations are independent.

Alternatively we have:

$$y_i | x_i \sim \text{Normal}\left(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}, \sigma^2\right)$$

Interpreting multiple regression coefficients

We have that:

$$E[Y_i|x_{i1}, \ldots, x_{ip}] = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$$

- β_j is the expected difference in response Y_i between two individuals, where one individual has predictor value x_j one unit greater than the other individual, **assuming all other predictors are held constant**.
- β_0 is the expected value of Y_i in an individual with **all** covariate values set to $x_{ij} = 0$.

How do we perform regression analysis in survival data?

In linear regression, we modelled the **mean** of the outcome given the predictors:

$$E[Y_i | x_{i1}, \dots, x_{ip}] = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$$

For regression in survival analysis, we typically model the **hazard function** as a function of covariates.

- Interpretability: the hazard function describes the chance of having an event given you've survived up to time t:

$$\lambda(t, x_{i1}, \dots, x_{ip}) = h(t, x_i^\top \beta)$$

for some non-negative function $h(\cdot, \cdot)$.

Exponential regression

In **exponential regression**, we assume that the underlying time-to-event data is $z_i \sim \text{Exp}(\theta_i)$, for $i = 1, \ldots, n$.

For now, we'll assume **right-censored** data. Our **observed** time variable t_i is defined like usual:

- If individual i is censored, t_i is the censoring time.
- If we observe the event, then t_i is the event time z_i.

Like before $\delta_i = 0$ if right censored, $\delta_i = 1$ if the event is observed.

Now, assume we have p predictors measured for each individual $x_{i1}, \ldots, x_{ip}$.

- We want to study the effect of each predictor on the time to an event.

Exponential regression: hazard

Recall that the exponential distribution has **constant hazard**. The hazard function for the exponential distribution is:

$$\lambda(t) = \theta_i$$

To study the effects of $x_{i1}, \ldots, x_{ip}$ on θ_i (the hazard), we need to choose some function h so that:

$$\theta_i = h(\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip})$$

Exponential regression: hazard

What if we choose h as the **identity function**? That is:

$$h(x) = x$$

Therefore, our model would be:

$$\theta_i = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}$$

Problem: We need $\theta_i > 0$. This means we would need to somehow constrain β_0, β_1, $\ldots \beta_p$ to make sure θ_i is in the proper range.

- This is quite difficult.

Exponential regression: hazard

Alternative choice:

$$h(x) = \exp\{x\}$$

In this case, our model would be:

$$\theta_i = \exp\{\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}\}$$

By doing this, we **guarantee** that $\theta_i > 0$, regardless of the values of the β parameters or the predictors.

- **Advantage**: We do not have to constrain the β parameters, each θ_j could be any real number.

Exponential regression: interpretation

Interpretation of exponential regression parameters:

$$\lambda(x_i) = \theta_i = \exp\{\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}\}$$

What happens if we have two individuals, such that $x_{1j} = a$ and $x_{2j} = a + 1$, and all other predictors the same between the two? Consider the **ratio** of their hazard functions:

$$\frac{\theta_2}{\theta_1} =$$

Thus, when x_{ij} increases by one unit, the hazard function is multiplied by a factor of $\exp\{\beta_j\}$.

Exponential regression: interpretation

Interpretation of exponential regression parameters:

$$\lambda(x_i) = \theta_i = \exp\{\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}\}$$

Similarly, $\exp\{\beta_0\}$ is the hazard when all $x_j = 0$ for $j = 1, \ldots, p$.

If $x_j = 0$ is possible for all $j = 1, \ldots, p$ in the data, then we call:

$$\exp\{\beta_0\}$$

the **baseline hazard**.

Regression techniques in survival analysis

In **exponential regression**, we modelled the **hazard function** of the exponential distribution with rate parameter θ_i as:

$$\lambda(x_i) = \exp\{\beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}\}$$

Remember, the exponential distribution assumes **constant hazard**; this means the chance of an event **does not change over time**.

In many cases, this assumption does not hold.

- Ex: All cause mortality, with $t = 0$ being birth. The chance of death is higher in infancy and in old age.
- Exponential regression is **not appropriate** in cases like this.

Weibull regression

One alternative is **Weibull regression**.

One parameterization of the Weibull distribution is:

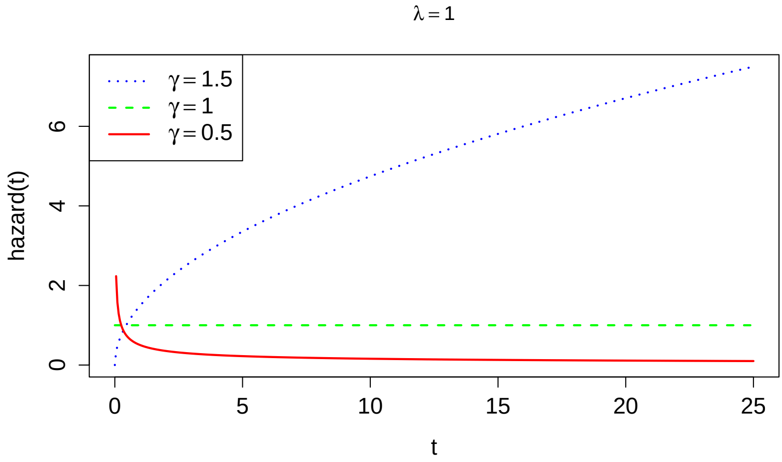
$$f(t) = \lambda\gamma\,(\lambda t)^{\gamma-1}\,e^{-(\lambda t)^{\gamma}} \qquad\qquad (t > 0)$$

where $\lambda > 0$ and $\gamma > 0$.

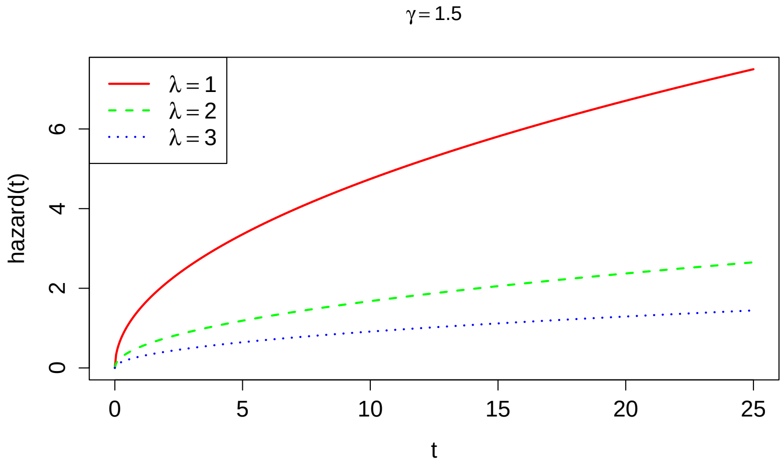
The **hazard function** for the Weibull distribution is given by:

$$\lambda(t) = \lambda\gamma(\lambda t)^{\gamma-1}$$

Weibull hazard



Weibull hazard



Weibull regression

In **Weibull regression**, we posit the following model for the hazard function, as a function of a vector of covariates $x_i = (x_{i1}, \ldots, x_{ip})$,

$$\lambda(t, x_i) = \gamma(\lambda t)^{\gamma - 1} \exp\left\{\beta_1 x_{i1} + \cdots + \beta_p x_{ip}\right\},$$

where $\beta = (\beta_1, \ldots, \beta_p)^\top$.

Note: **there is no intercept.** Why not?

Weibull regression

Interpretation of parameters: Once again, assume that we have two individuals whose covariate j differs by exactly one unit: $x_{1j} = a$ and $x_{2j} = a + 1$.

Assume that $x_{1k} = x_{2k}$ for all other covariates $k \neq j$.

$$\lambda(t, x_i) = \gamma(\lambda t)^{\gamma - 1} \exp\left\{x_i^\top \beta\right\},$$

The **ratio** of the hazards between indiviual 2 and 1 at time t is:

Weibull hazard: veterans example

Example: Veteran lung cancer dataset. Outcome is death. Two covariates we'll use in the model are:

- `age`: Ranges from 34-81 years.
- `karno`: Karnofsky score. Higher value corresponds to higher ability for a patient to care for themselves. Very low score refers to hospitalization.

We'll fit a Weibull regression model with `age` and `karno` as predictors.

Weibull hazard: veterans example

Result: The maximum likelihood estimates of γ and λ are:

$$\widehat{\gamma} = 14.26 \qquad \widehat{\lambda} = 1.02$$

The coefficients for `age` and `karno` (respectively) are:

$$\beta_{\texttt{age}} = 0.00018 \qquad \beta_{\texttt{karno}} = -0.03419$$

Interpretation of $\beta_{\texttt{karno}}$:

Weibull hazard: veterans example