

Biostatistics

Applications in Medicine

Nuno Sepúlveda, 14.11.2024

Syllabus

1. General review

- a. What is Biostatistics?
- b. Population/Sample/Sample size
- c. Type of Data – quantitative and qualitative variables
- d. Common probability distributions
- e. Work example – Malaria in Tanzania

2. Applications in Medicine

- a. Construction and analysis of diagnostic tools – Binomial distribution, sensitivity, specificity, ROC curve, Rogal-Gladen estimator
- b. Estimation of treatment effects - generalized linear models
- c. Survival analysis - Weibull regression, Kaplan-Meier curve, log-rank test, Cox's proportional hazards model

3. Applications in Genetics, Genomics, and other 'omics data

- a. Genetic association studies – Hardy-Weinberg test, homozygosity, minor allele frequencies, additive model, multiple testing correction
- b. Methylation association studies – M versus beta values, estimation of biological age
- c. Gene expression studies based on RNA-seq experiments – Tests based on Poisson and Negative-Binomial

4. Other Topics

- a. Estimation of Species diversity – Diversity indexes, Poisson mixture models
- b. Serological analysis – Gaussian (skew-normal) mixture models
- c. Advanced sample size and power calculations

Exercise:

Covariates: Age, Gender, Infection trigger, Disease Duration

Use logit, probit, cloglog, loglog, cauchit.

Compare models/Use a feature selection strategy

**Packages ordinal,
glm, and MASS**

What will be your final model to understand the effect of treatment better?



RESEARCH ARTICLE

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

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Exercise:

data about recovery from a SARS-CoV-2 infection

16 patients from a Beijing hospital between
January 28 and February 9, 2020



time to end of symptoms

time to negative PCR test

Package MASS

Fit exponential, gamma, lognormal, and weibull distributions to each endpoint

Select the best model to each endpoint and plot the corresponding survival and hazard functions

Draw your conclusions

Weibull distribution

$$f_{\gamma,\lambda}(t) = \frac{\gamma}{\lambda} \left(\frac{t}{\lambda} \right)^{\gamma-1} e^{-(t/\lambda)^\gamma}, \quad t > 0$$

Shape parameter

$$\gamma \in (0, +\infty)$$

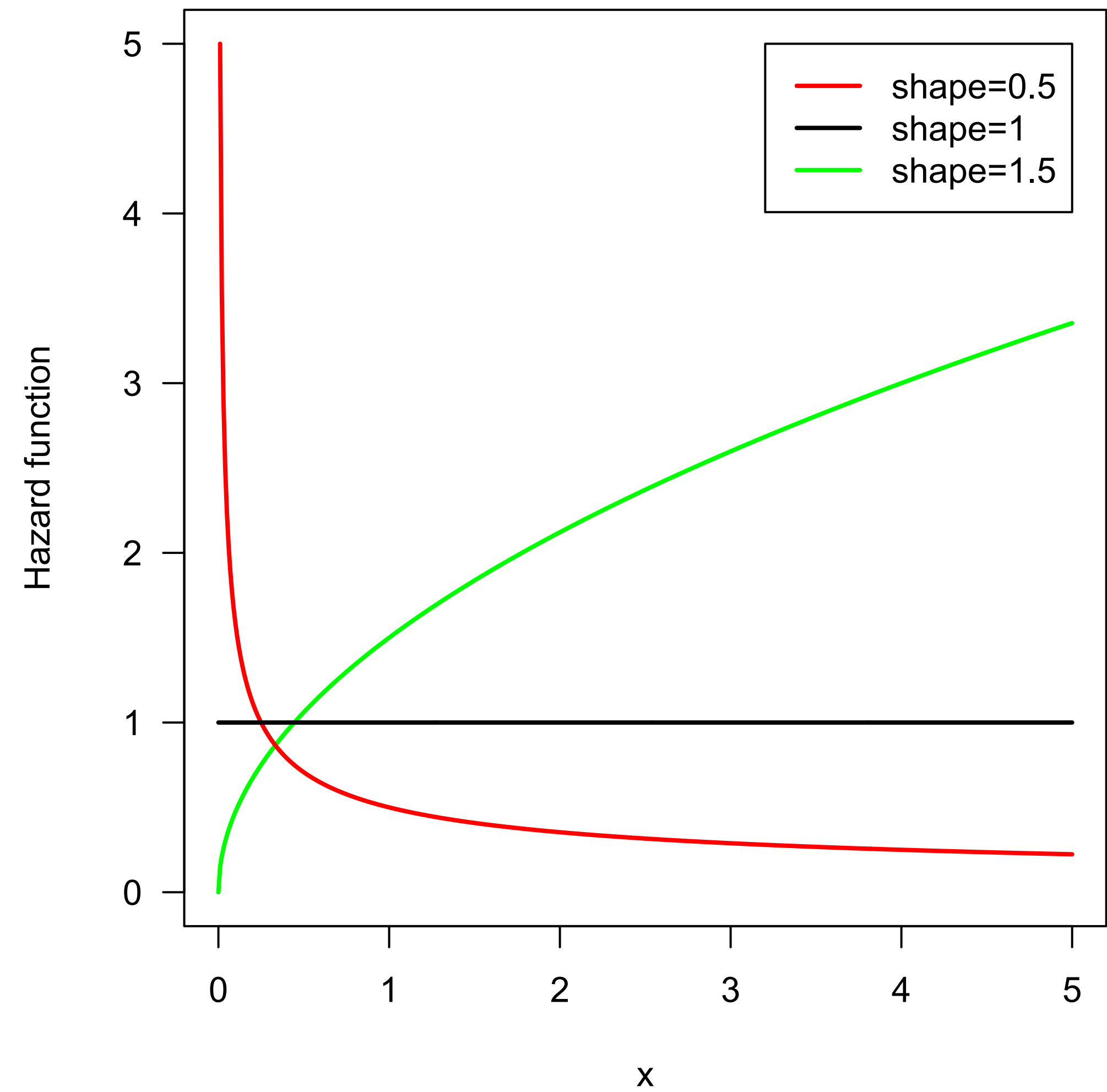
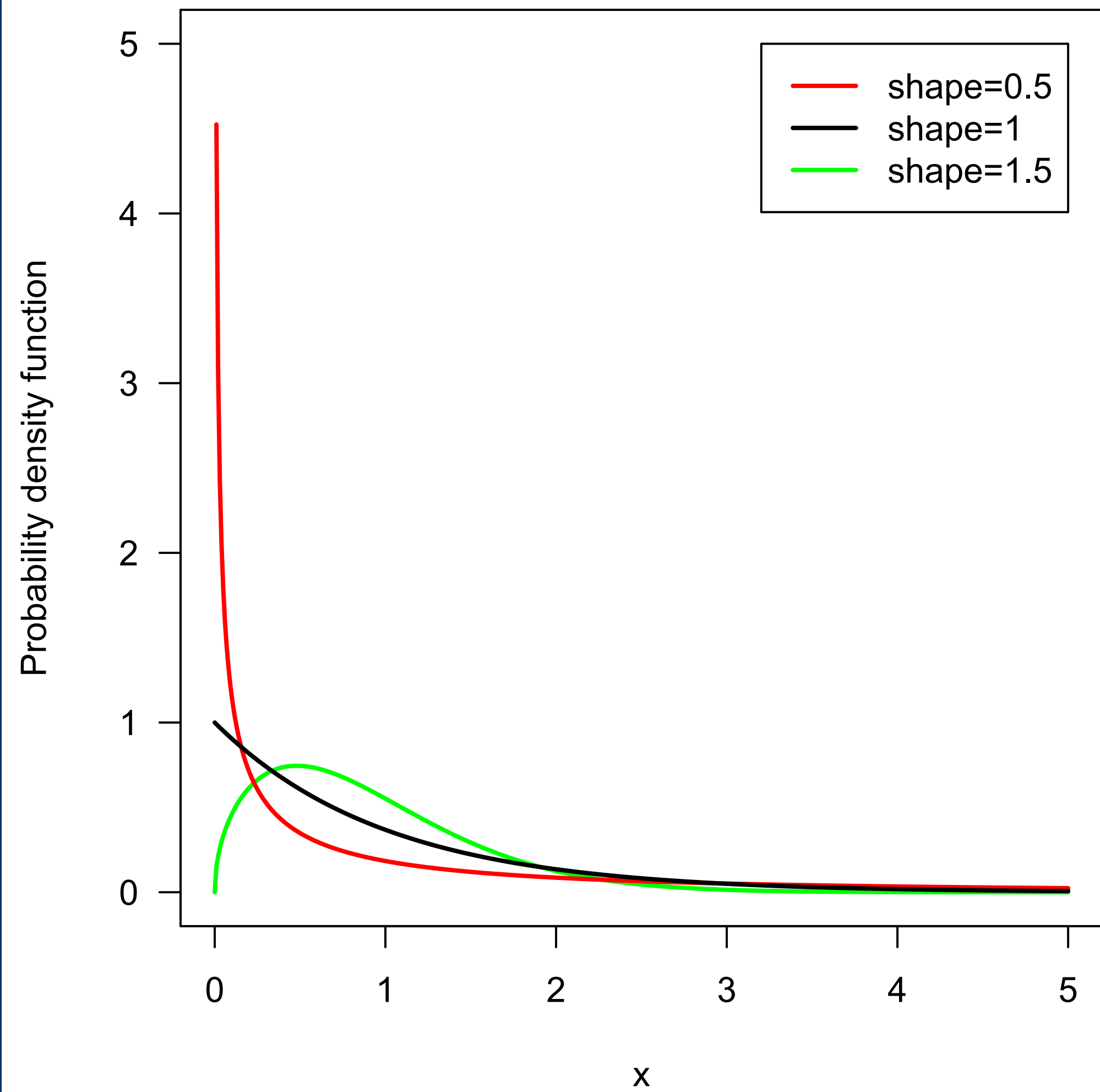
$$F_{\gamma,\lambda}(t) = 1 - e^{-(t/\lambda)^\gamma}, \quad t > 0$$

Scale parameter

$$\lambda \in (0, +\infty)$$

$$h_{\gamma,\lambda}(t) = \frac{\gamma}{\lambda} \left(\frac{t}{\lambda} \right)^{\gamma-1}, \quad t > 0$$

Weibull distribution in Survival Analysis



Weibull distribution and its relationship with the Exponential distribution

$$T | \lambda \rightsquigarrow \text{Exponential}(\lambda) \Rightarrow X^\gamma \rightsquigarrow \text{Weibull}(\gamma, \lambda)$$

$$T \rightsquigarrow \text{Exponential}(1) \Rightarrow \left(\frac{X}{\lambda} \right)^\gamma \rightsquigarrow \text{Weibull}(\gamma, \lambda)$$

$$\gamma = 1 \Rightarrow T | \lambda \rightsquigarrow \text{Exponential}(\lambda)$$

Why is this relationship important?

Weibull distribution and its relationship with the Gumbel distribution

$$T | \gamma, \lambda \rightsquigarrow \text{Weibull}(\gamma, \lambda) \Rightarrow \log T | \gamma, \lambda \rightsquigarrow \text{Gumbel}(\mu = \frac{\log \lambda}{\gamma}, \sigma = \frac{1}{\gamma})$$

$$T | \mu, \sigma \rightsquigarrow \text{Gumbel}(\mu, \sigma) \Rightarrow e^T | \mu, \sigma \rightsquigarrow \text{Weibull}(\lambda = e^{\frac{\mu}{\sigma}}, \gamma = \frac{1}{\sigma})$$

Why is this relationship important?

How to assess the adequacy of the Weibull distribution in a given data set?

Visualisation method

Do you know any method?

How to assess the adequacy of the Weibull distribution in a given data set?

Visualisation method

$$F_{\gamma,\lambda}(t) = 1 - e^{-(t/\lambda)^\gamma}$$

$$t_1, \dots, t_n \quad \hat{\gamma} \text{ and } \hat{\lambda}$$

$$1 - F_{\gamma,\lambda}(t) = e^{-(t/\lambda)^\gamma}$$

$$\hat{F}(t_i) = \text{empirical cumulative distributions}$$

$$\log(1 - F_{\gamma,\lambda}(t)) = -(t/\lambda)^\gamma$$

Make the plot

$$\log(-\log(1 - F_{\gamma,\lambda}(t))) = -\gamma \log \lambda + \gamma \log t$$

$$\log t_i \text{ versus } \log(-\log(1 - \hat{F}(t_i)))$$

Interpretation:

If the Weibull distribution fits well the data,
the plot should look like a straight line

How to assess the adequacy of the Weibull distribution in a given data set?

Formal Hypothesis testing

Kolmogorov-Smirnov test

What are the null and alternative hypotheses?

What is the decision rule of the test?

Eventual problems?

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time to end of symptoms

time to negative PCR test
(Homework)

Assess the adequacy of the Weibull distributions to model “time to end of symptoms” using the visualisation method and a formal hypothesis testing

Weibull regression model

Log-linear formulation (similar to linear regression)

$$\log T_i = \beta_0 + \sum_j \beta_j x_{ij} + \sigma_0 \epsilon_i \quad \epsilon_i | \rightsquigarrow \text{Gumbel}(\mu = 0, \sigma = 1)$$

$$\log T_i \rightsquigarrow \text{Gumbel} \left(\mu = \beta_0 + \sum_j \beta_j x_j, \sigma = \sigma_0 \right)$$

(see slide 17)

$$T_i \rightsquigarrow \text{Weibull} \left(\lambda = \exp \left\{ \frac{\beta_0 + \sum_j \beta_j x_j}{\sigma} \right\}, \gamma = \frac{1}{\sigma} \right)$$

Weibull regression model as a proportional hazard model

$$T_i \rightsquigarrow \text{Weibull} \left(\lambda = \exp \left\{ \frac{\beta_0 + \sum_j \beta_j x_j}{\sigma} \right\}, \gamma = \frac{1}{\sigma} \right)$$

$$h_{\gamma, \lambda}(t) = \frac{\gamma}{\lambda} \left(\frac{t}{\lambda} \right)^{\gamma-1}, \quad t > 0$$

$$h_{\gamma, \{\beta_j\}}(t) = \frac{1}{\sigma e^{\frac{\beta_0 + \sum_j \beta_j x_j}{\sigma}}} \left(\frac{t}{e^{\frac{\beta_0 + \sum_j \beta_j x_j}{\sigma}}} \right)^{\frac{1}{\sigma}-1}$$

Weibull regression model as a proportional hazard model

$$\begin{aligned}h_{\gamma, \{\beta_j\}}(t) &= \frac{1}{\sigma e^{\frac{\beta_0 + \sum_j \beta_j x_j}{\sigma}}} \left(\frac{t}{e^{\frac{\beta_0 + \sum_j \beta_j x_j}{\sigma}}} \right)^{\frac{1}{\sigma} - 1} \\&= \frac{1}{\sigma e^{\frac{\beta_0}{\sigma}}} \left(\frac{t}{e^{\frac{\beta_0}{\sigma}}} \right)^{\frac{1}{\sigma} - 1} \left(\frac{1}{e^{\frac{\sum_j \beta_j x_j}{\sigma}}} \right)^{\frac{1}{\sigma}} \\&= \frac{1}{\sigma e^{\frac{\beta_0}{\sigma}}} \left(\frac{t}{e^{\frac{\beta_0}{\sigma}}} \right)^{\frac{1}{\sigma} - 1} e^{-\frac{\sum_j \beta_j x_j}{\sigma^2}}\end{aligned}$$

Estimation and statistical validation

Maximum likelihood estimation using numerical methods (e.g., Newton-Raphson)

$$\left\{ \hat{\beta}_j, j = 0, \dots, p \right\}, \hat{\sigma}$$

Validation of the model

Standardized residuals: $\hat{e}_i = \frac{\log t_i - \log \hat{t}_i}{\hat{\sigma}}$

they should follow a Gumbel distribution with $\mu=0$ and $\sigma=1$

Cox-Snel residuals: $\tilde{e}_i = \left(t_i e^{-\log \hat{t}_i} \right)^{1/\hat{\sigma}}$

they should follow a Exponential distribution with parameter 1
(See slide 7)

Weibull regression model is not a generalized linear model

Weibull distribution does not belong to the exponential family of distributions.

Homework!

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time to end of symptoms

time to negative PCR test
(Homework)

Package survival

Fit a Weibull regression model with time to end of symptoms as the outcome and age
and gender as the covariate

Assess the validity of the model by testing a Gumbel distribution in the residuals