CHL 5225H
Advanced Statistical Methods for Clinical Trials: Survival Analysis

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Outline

Defining Survival Data

Introduction

Interest centres on patients who are at risk for some event and the time to the occurrence of the event.

Examples: Time to death
Time to stroke
Time to disease recurrence

Definition of Failure Time

Three requirements to precisely determine failure time:

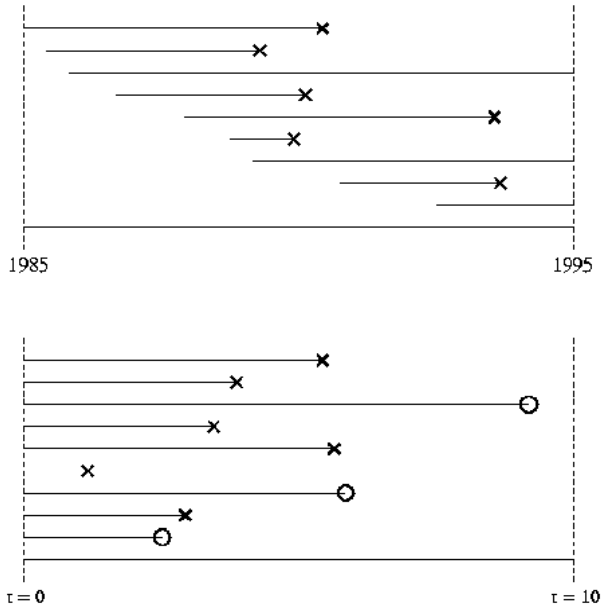
- unambiguous time origin
- scale for measuring the passage of time
- meaning of the failure event must be entirely clear

Censoring

Patients who are not observed to "failure" are called *censored*
Some Causes:

- study concludes before all patients destined to fail have actually failed
- patient withdraws from study before failure observed

Typical Survival Data Arising From a Clinical Trial



Mathematical Definitions

Introduction

- Let the "failure time" be represented by a non-negative random variable T.
- Usually, we consider continuous distributions.
- Discrete and mixed discrete-continuous distributions can also handled.

The Survivor Function

- The *survivor function* $\mathcal{F}(t)$ is defined to be

$$\mathcal{F}(t) = \Pr(T \geq t)$$

- It is sometimes useful to consider the cumulative risk of an event. The *cumulative risk function* is defined by

$$R(t) = 1 - \mathcal{F}(t)$$

- Note that the definition of $\mathcal{F}(t)$ leads to left continuous CDF rather than the usual right continuity.

Probability Density Function

- Continuous T.

$$f(t) = -\mathcal{F}'(t) = \lim_{\Delta \to 0+} \frac{\Pr(t \leq T < t + \Delta)}{\Delta}$$

which gives

$$\mathcal{F}(t) = \int_t^\infty f(u)du$$

- Discrete T.
Usually handled by assigning to the density a component $f_j \delta(t - a_j)$ for an atom f_j at a_j where $\delta(\cdot)$ is the Dirac delta function.

Hazard Function

Continuous Distributions

- The *hazard function* (also called age-specific failure rate or force of mortality is defined by

$$h(t) = \lim_{\Delta \to 0+} \frac{\Pr(t \leq T < t + \Delta | t \leq T)}{\Delta}$$

- By the definition of conditional probability

$$h(t) = f(t)/\mathcal{F}(t)$$

- Sometimes the hazard is denoted by $\lambda(t)$.

Hazard Function

Continuous Distributions (continued)

- By the definitions of $f(t)$ and that $\mathcal{F}(0) = 1$ we have

$$\begin{aligned} h(t) &= -\mathcal{F}'(t)/\mathcal{F}(t) \\ &= -d \log \mathcal{F}(t)/dt \end{aligned}$$

and

$$\begin{aligned} \mathcal{F}(t) &= \exp\left(-\int_0^t h(u)du\right) \\ &= \exp[-H(t)] \end{aligned}$$

where $H(\cdot)$ is called the integrated hazard.

- Finally,

$$f(t) = h(t)exp[-H(t)]$$

Hazard Function

Discrete Distributions

- If there is an atom f_j of probability at time a_j then

$$\begin{aligned} h_j &= f_j/\mathcal{F}(a_j) \\ &= f_j/(f_j + f_{j+1} + \cdots) \end{aligned}$$

- With this definition it can be shown that

$$\mathcal{F}(t) = \prod_{a_j < t} (1 - h_j)$$

- By defining the integrated hazard as

$$H(t) = \sum_{a_j < t} \log(1 - h_j)$$

we still have

$$\mathcal{F}(t) = \exp[-H(t)]$$

The Likelihood Function

We assume each patient has a failure time t_i and a censoring time c_i associated with them. In practice, we observe $x_i = \min(t_i, c_i)$.

$$\begin{aligned} \mathcal{L} &= \prod_u f(t_i;\phi)\prod_c \mathcal{F}(c_i;\phi) \\ \ell &= \sum_u \log f(t_i;\phi) + \sum_c \log \mathcal{F}(c_i;\phi) \\ \ell &= \sum_u \log h(x_i;\phi) + \sum \log \mathcal{F}(x_i;\phi) \end{aligned}$$

Survival Models

- Suppose in addition to survival some covariates z are measured with the intent of modeling their association with survival.
- For some "baseline" hazard function $h_0(t)$ (or survivor function $\mathcal{F}_0(t)$ we have the following commonly used models.
  - The *Accelerated Life* model is defined by

    $$\mathcal{F}(t;z) = \mathcal{F}_0[t\psi(z)] \text{ or } h(t;z) = h_0[t\psi(z)]\psi(z)$$

    The choice of $\mathcal{F}_0$ is dictated by a choice of parametric model.
  - The *Proportional Hazard* model is defined by

    $$\mathcal{F}(t;z) = [\mathcal{F}_0(t)]^{\psi(z)} \text{ or } h(t;z) = \psi(z)h_0(t)$$

    The baseline hazard does not need to be explicitly known for this model.

The Likelihood Function

- We begin by assuming a discrete distribution atoms of probability at g unique failure times $t_1, t_2, \ldots, t_g$.
- It can be shown that the log-likelihood is

  $$\ell = \sum_j [d_j \log h_j + (r_j - d_j)\log(1 - h_j)]$$

  where r_j is the number of patients in view at time t_j and d_j is the number who fail at t_j.
- By convention, r_j includes individuals who are censored at t_j.
- This is identical to the log likelihood for g independent binomials with r_j trials, d_j failures and probability of failure h_j.
- This fact is used in the derivation of the results on the next slide.

Product-Limit or Kaplan-Meier Estimate

- Suppose g unique failure times are observed. Put them in order from smallest to largest.

  $$t_1, t_2, \ldots, t_g$$

- The survivor function is estimated at time t_j by

  $$\hat{\mathcal{F}}(t_j) = \prod_{i=1}^{j}\left(1 - \frac{d_i}{r_i}\right) = \prod_{i=1}^{j}\left(\frac{r_i - d_i}{r_i}\right)$$

- Note the similarity between the first expression above and the expression for a discrete survivor function, $\mathcal{F}(t) = \prod_{a_j<t}(1 - h_j)$ given previously.
- The variance of $\hat{\mathcal{F}}(t)$ at time t_j is (Greenwood's formula)

  $$V(\hat{\mathcal{F}}(t_j)) = [\hat{\mathcal{F}}(t_j)]^2 \sum_{i=1}^{j} \frac{d_i}{r_i(r_i - d_i)}$$

Example

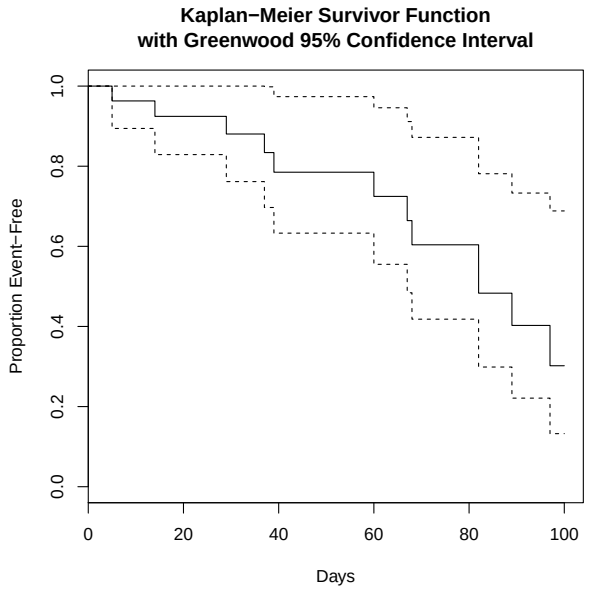
Suppose we had the following data (+ indicates censored observations).

```
 [1]   2+   2+   5    9+  14   16+  16+  17+  29   30+  37
[12]  37+  39   44+  44+  58+  60   67   68   82   82   86+
[23]  86+  89   93+  97   100+ 100+ 100+
```

Example

t_j	r_j	d_j	$P(t_j) = 1 - d_j/r_j$	$\hat{\mathcal{F}}(t_j)$	SE
0	29			1.0	
5	27	1	$1 - 1/27 = 0.9630$	$1.0 \times 0.9630 = 0.963$	0.0363
14	25	1	$1 - 1/25 = 0.9600$	$0.963 \times 0.9600 = 0.924$	0.0514
29	21	1	$1 - 1/21 = 0.9524$	$0.924 \times 0.9524 = 0.880$	0.0651
37	19	1	$1 - 1/19 = 0.9474$	$0.880 \times 0.9474 = 0.834$	0.0764
39	17	1	$1 - 1/17 = 0.9412$	$0.834 \times 0.9412 = 0.785$	0.0863
60	13	1	$1 - 1/13 = 0.9231$	$0.785 \times 0.9231 = 0.725$	0.0985
67	12	1	$1 - 1/12 = 0.9167$	$0.725 \times 0.9167 = 0.664$	0.1072
68	11	1	$1 - 1/11 = 0.9091$	$0.664 \times 0.9091 = 0.604$	0.1132
82	10	2	$1 - 2/10 = 0.8000$	$0.604 \times 0.8000 = 0.483$	0.1185
89	6	1	$1 - 1/6 = 0.8333$	$0.483 \times 0.8333 = 0.403$	0.1231
97	4	1	$1 - 1/4 = 0.7500$	$0.403 \times 0.7500 = 0.302$	0.1270

Example



Example

R Code

```
> library(survival)
> eg1a.km <- survfit(Surv(days, status), data = eg1a)
> summary(eg1a.km)
> plot(eg1a.km, mark.time = FALSE, xlab = "Days",
+      ylab = "Proportion Event-Free",
+      main = "Kaplan-Meier Survivor Function\n
with Greenwood 95% Confidence Interval")
```

Actuarial Estimator

- Suppose instead of exact failure/censoring times we know only the numbers of failures and censored observations between time intervals.
- For each interval $(t_{j-1}, t_j]$ we define r_{j-1} to be the number at risk at t_{j-1}, d_j to be the number who fail during the interval and m_j to be the number censored during the interval.
- Define $r'_j = r_{j-1} - \frac{1}{2}m_j$.
- Then, the actuarial estimator of survival is

$$\tilde{\mathcal{F}}(t_j) = \prod_{k \leq j} \left(1 - \frac{d_k}{r'_k}\right)$$

Comparing Survival

- There are a variety of methods that can be used to compare survival in various ways.
  - Point in time comparison (two groups)
  - Mantel-Haenszel or Log Rank Test (two or more survival curves)
  - Model-based tests (two or more groups)

Point in Time Comparison

- The object is to compare survival between two treatments at a pre-specified time point t_0.
- From the Kaplan-Meier procedure and Greenwood's formula we have,

$$\begin{aligned} \text{Treatment} &: \hat{\mathcal{F}}_T(t_0) \text{ and } V[\hat{\mathcal{F}}_T(t_0)] \\ \text{Control} &: \hat{\mathcal{F}}_C(t_0) \text{ and } V[\hat{\mathcal{F}}_C(t_0)] \end{aligned}$$

- Then, to conduct an approximate test of the null hypothesis $H_0 : \mathcal{F}_T(t_0) = \mathcal{F}_C(t_0)$ we calculate the Z statistic,

$$Z = \frac{\hat{\mathcal{F}}_T(t_0) - \hat{\mathcal{F}}_C(t_0)}{\sqrt{V[\hat{\mathcal{F}}_T(t_0)] + V[\hat{\mathcal{F}}_C(t_0)]}}$$

Under H_0, $Z \sim N(0, 1)$.

Mantel-Haenszel Test

- Consider the two survival curves as a series of 2x2 contingency tables constructed at each time point where one or more events occur. At a time point t_j we have a table of the form:

	Treatment	Control	Total
Dead	d_{T_j}	d_{C_j}	d_j
Alive	$n_{T_j} - d_{T_j}$	$n_{C_j} - d_{C_j}$	$N_j - d_j$
Total	n_{T_j}	n_{C_j}	N_j

Then, from the hypergeometric distribution,

$$\begin{aligned} E(d_{T_j}) &= \frac{n_{T_j} d_j}{N_j} \\ V(d_{T_j}) &= \frac{n_{T_j} n_{C_j} (N_j - d_j) d_j}{N_j^2 (N_j - 1)} \end{aligned}$$

Mantel-Haenszel Test — Continued

- Define the following quantities.

$$O_T = \sum d_{T_j} \qquad E_T = \sum E(d_{T_j})$$
$$O_C = \sum d_j - O_T \qquad E_C = \sum d_j - E_T$$
$$V = \sum V(d_{T_j})$$

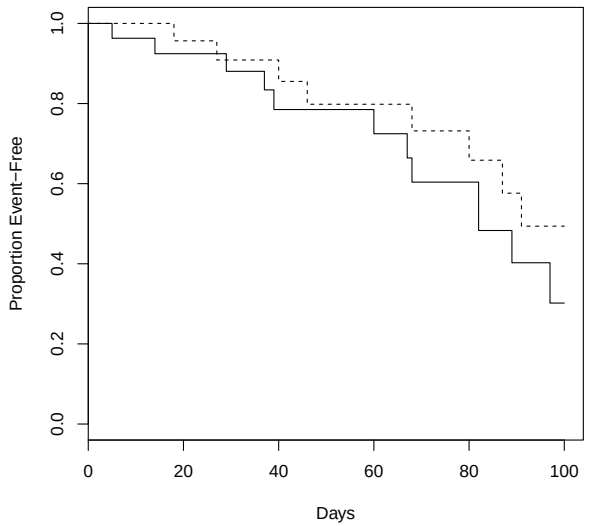
- Now, the null hypothesis $H_0 : \mathcal{F}_T(t) = \mathcal{F}_C(t)$ is usually tested with a $\chi^2_{(1)}$ test, but may also be tested with a Z test.

$$\chi^2 = \frac{(O_T - E_T)^2}{V}$$

and

$$Z = \frac{O_T - E_T}{\sqrt{V}}$$

- This is often called the *Log Rank Test*.



Comparing Survival in R

- In R the `survdiff()` function is used to compare survival curves.
- This performs tests in a family described by Harrington and Fleming (*Biometrika*: 1982) where the weights on each event time are $\mathcal{F}(t)^\rho$.
- The `survdiff()` function accepts an argument `rho`. If `rho = 0` (the default) you get the Mantel-Haenszel test and if `rho = 1` you get the Peto & Peto modification of the Gehan-Wilcoxon test.

Example

```
> survdiff(Surv(days, status) ~ rx, data = eg1b)

Call:
survdiff(formula = Surv(days, status) ~ rx, data = eg1b)

               N Observed Expected (O-E)^2/E (O-E)^2/V
rx=Control    29       12      9.9     0.447     0.898
rx=Treatment  25        8     10.1     0.438     0.898

 Chisq= 0.9  on 1 degrees of freedom, p= 0.343
```

Measuring the Treatment Effect

- Among other things, clinical trials are intended to provide an estimate of the treatment effect.
- For a "survival" outcome, two types of estimates are commonly used.
  - Point in time Risk Ratio or Risk Reduction.
  - All time or whole curve effect measures by means of Hazard Ratios.

Point in Time Treatment Effect

- Suppose a trial is comparing a treatment T to a control C.
- The usual expectation would be that the risk of the event would be lower in the treatment group than the control group.
- There may be situations where there is some clinically meaningful time point t_0 say, that is of interest.
- Consider three point in time estimates of "risk reduction."

$$\begin{aligned} \text{Risk Difference} &= R_C(t_0) - R_T(t_0) \\ \text{Risk Ratio} &= R_T(t_0)/R_C(t_0) \\ \text{Relative Risk Reduction} &= \frac{R_C(t_0) - R_T(t_0)}{R_C(t_0)} \\ &= 1 - \frac{R_T(t_0)}{R_C(t_0)} \end{aligned}$$

Estimating Risk Difference

- Estimate T & C survival curves using Kaplan-Meier procedure and compute.

$$\begin{aligned} \widehat{\text{RD}} &= \hat{R}_C(t_0) - \hat{R}_T(t_0) \\ &= (1 - \hat{\mathcal{F}}_C(t_0)) - (1 - \hat{\mathcal{F}}_T(t_0)) \\ &= \hat{\mathcal{F}}_T(t_0) - \hat{\mathcal{F}}_C(t_0) \end{aligned}$$

- Calculate $V(\hat{\mathcal{F}}_T(t_0))$ and $V(\hat{\mathcal{F}}_C(t_0))$ using Greenwood's formula (ie. SE^2).
- Then, 95% CI on the RD is (approximately):

$$\widehat{\text{RD}} \pm 1.96\sqrt{V(\hat{\mathcal{F}}_T(t)) + V(\hat{\mathcal{F}}_C(t))}$$

Estimating Risk Ratio

- Estimate T & C survival curves using Kaplan-Meier procedure and compute.

$$\begin{aligned} \widehat{\text{RR}} &= \hat{R}_T(t_0)/\hat{R}_C(t_0) \\ &= \frac{1 - \hat{\mathcal{F}}_T(t_0)}{1 - \hat{\mathcal{F}}_C(t_0)} \end{aligned}$$

- Calculate $V(\log \hat{R}_T(t_0))$ and $V(\log \hat{R}_C(t_0))$ using the following formula.

$$V(\log \hat{R}(t_0)) = \frac{V(\hat{\mathcal{F}}(t_0))}{(\hat{R}(t_0))^2}$$

- Then, 95% CI on RR is (approximately):

$$\widehat{\text{RR}} \times e^{\pm 1.96\sqrt{V(\log \hat{R}_T(t_0)) + V(\log \hat{R}_C(t_0))}}$$

Estimating Relative Risk Reduction

- Estimate T & C survival curves using Kaplan-Meier procedure and compute.

$$\begin{aligned}\widehat{\mathrm{RRR}} &= 1 - \frac{\hat{R}_T(t_0)}{\hat{R}_C(t_0)} \\ &= 1 - \widehat{\mathrm{RR}}\end{aligned}$$

- Determine the CI for $\widehat{\mathrm{RR}}$. Say this is $(\mathrm{RR}_L,\ \mathrm{RR}_U)$.
- The the CI for $\widehat{\mathrm{RRR}}$ is $(1 - \mathrm{RR}_U,\ 1 - \mathrm{RR}_L)$.

Estimating Hazard Ratio

- The Mantel-Haenzsel test calculations enable estimation of the hazard ratio.

$$\begin{aligned}\hat{\psi} &= \frac{O_T/E_T}{O_C/E_C} \\ V[\log\hat{\psi}] &= \frac{1}{E_T} + \frac{1}{E_C}\end{aligned}$$

- Various model-based estimates are preferred where appropriate.

Introduction to Parametric Survival Distributions

- We saw earlier that the Kaplan-Meier estimate of survival is not particularly smooth.
- By assuming a particular parametric form for the survival distribution, smooth estimates of survival can be obtained.
- Some commonly used distributions in survival analysis are:
  - Exponential
  - Weibull
  - Log-normal
  - Log-logistic
- We will look at the exponential and Weibull distributions in more detail.

The Exponential Distribution

- For the exponential distribution with parameter ρ and mean $1/\rho$, we have

$$\mathcal{F}(t) = e^{-\rho t}, f(t) = \rho e^{-\rho t}, h(t) = \rho, H(t) = \rho t$$

- A plot of $H(t) = -\log(\hat{\mathcal{F}}(t))$, where $\hat{\mathcal{F}}(t)$ is the Kaplan-Meier estimate versus t will be linear if the exponential distribution is appropriate.
- The MLE for ρ is $\hat{\rho} = d/\sum x_i$ where d is the total number of failures.

The Exponential Likelihood

- For exponential failure times with d failures we get

$$\begin{aligned} \ell(\rho; x) &= \sum_u \log h(x_i; \phi) + \sum \log \mathcal{F}(x_i; \phi) \\ &= \sum_u \log \rho - \rho \sum x_i \\ &= d \log \rho - \rho \sum x_i \\ U(\rho) &= d/\rho - \sum x_i \\ I(\rho) &= d/\rho^2 \end{aligned}$$

- It is easy to show that solving $U(\rho) = 0$ gives $\hat{\rho} = d/\sum x_i$ as the MLE and $\sqrt{1/I(\hat{\rho})}$ is an estimate of its standard error, although not the best to use in practice.
- Confidence intervals based on the likelihood ratio statistic or from a fitted model are preferred.

Likelihood Ratio Based Confidence Interval

- The likelihood ratio statistic for the null hypothesis $\rho = \rho_0$ is

$$W(\rho_0) = W = 2[\ell(\hat{\rho}) - \ell(\rho_0)]$$

- This has a nice simple form in the exponential case and is distributed approximately as a chi-squared variate with 1 degree of freedom.
- A $1 - \alpha$ confidence region is

$$\{\rho : W(\rho) \leq c^*_{1,\alpha}\}$$

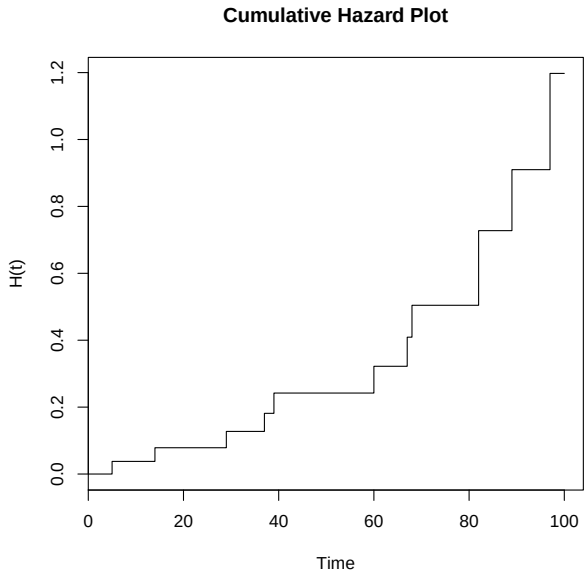
where $c^*_{1,\alpha}$ is the upper α point of the chi-squared distribution with 1 degree of freedom.

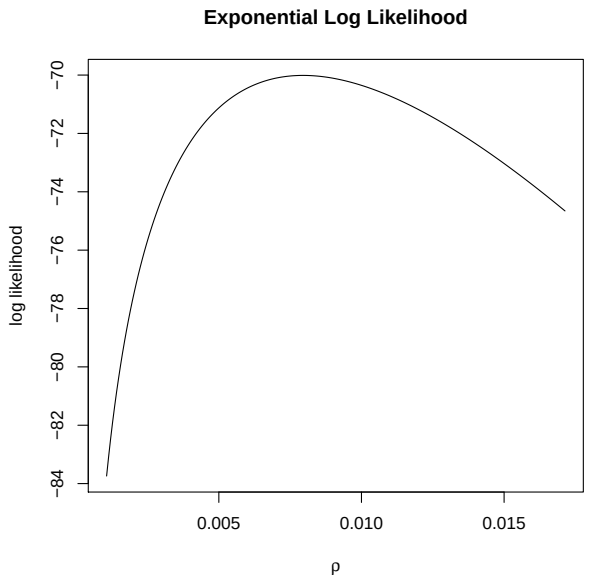
Example

Direct computation of hazard and symmetric 95% CI.

```
> rhohat <- sum(eg1a$status)/sum(eg1a$days)
> se.rhohat <- sqrt(rhohat^2/sum(eg1a$status))
> symci <- rhohat + c(-1, 1) * qnorm(0.975) * se.rhohat
> c(rhohat, symci)
```

```
[1] 0.007952286 0.003452939 0.012451633
```





Example

Model based estimate.

```
> eg1a.sr <- survreg(Surv(days, status) ~ 1, data = eg1a,
+     dist = "exponential")
> summary(eg1a.sr)

Call:
survreg(formula = Surv(days, status) ~ 1, data = eg1a, dist = "exponent
            Value Std. Error    z        p
(Intercept)  4.83      0.289 16.7 6.01e-63

Scale fixed at 1

Exponential distribution
Loglik(model)= -70   Loglik(intercept only)= -70
Number of Newton-Raphson Iterations: 5
n= 29

> exp(-coef(eg1a.sr))

(Intercept)
0.007952286
```

The Two Group Problem

Example

Comparing confidence intervals:

- Symmetric: 0.00345–0.0125
- Likelihood Based: 0.00427–0.0133
- Model Based: 0.00452–0.014

- Suppose you have exponentially distributed failure data for a treatment group T and a control group C.
- Estimate $\hat{\rho}_T = d_T / \sum x_{Ti}$, $\hat{\rho}_C = d_C / \sum x_{Ci}$ and $\hat{\psi} = \hat{\rho}_T / \hat{\rho}_C$.
- It turns out that $V(\log \hat{\psi}) \approx 1/d_T + 1/d_C$ which permits approximate Z-tests and confidence intervals to be calculated.

Example

Direct Calculation

```
> rhohats <- tapply(eg1b$status, eg1b$rx, sum)/tapply(eg1b$days,
+     eg1b$rx, sum)
> hr <- rhohats[2]/rhohats[1]
> lhrse <- sqrt(sum(1/tapply(eg1b$status, eg1b$rx,
+     sum)))
> c(hr, log(hr), lhrse)
```

```
 Treatment  Treatment
 0.6838885 -0.3799604  0.4564355
```

Example

Model based.

```
> eg1b.sr <- survreg(Surv(days, status) ~ rx, data = eg1b,
+     dist = "exponential")
> summary(eg1b.sr)
```

```
Call:
survreg(formula = Surv(days, status) ~ rx, data = eg1b, dist = "exponen
             Value Std. Error      z        p
(Intercept)  4.83      0.289 16.746 6.01e-63
rxTreatment  0.38      0.456  0.832 4.05e-01

Scale fixed at 1

Exponential distribution
Loglik(model)= -119.7   Loglik(intercept only)= -120.1
Chisq= 0.71 on 1 degrees of freedom, p= 0.4
Number of Newton-Raphson Iterations: 5
n= 54
```

Example

Model based (continued).

```
> exp(-coef(eg1b.sr)[2])
```

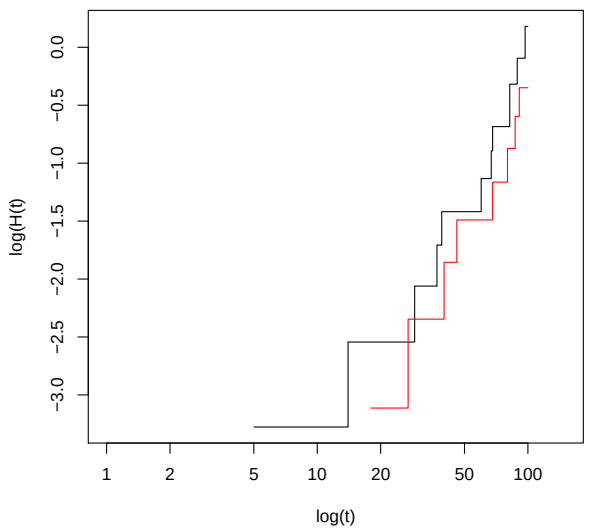
```
rxTreatment
  0.6838885
```

The Weibull Distribution

- The Weibull distribution has the following:

$$\begin{aligned} \mathcal{F}(t) &= \exp[-(\rho t)^{\kappa}] \\ f(t) &= \kappa\rho(\rho t)^{\kappa-1}\exp[-(\rho t)^{\kappa}] \\ h(t) &= \kappa\rho(\rho t)^{\kappa-1} \end{aligned}$$

- Note that if $\kappa = 1$ we are left with an exponential distribution with a hazard of ρ.
- A plot of $\log(-\log(\hat{\mathcal{F}}(t)))$ versus $\log(t)$ will be linear if the Weibull distribution is appropriate.
- The biggest difficulty is that the coefficient estimates don't have nice straight forward interpretations like other models we've used. A scale parameter is estimated and $e^{-\beta_i/\text{scale}}$ gives a hazard ratio.



Example

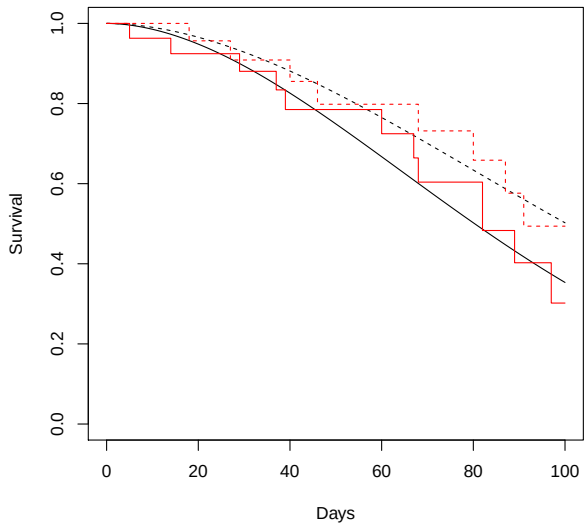
Fitting a Weibull in R

```
> eg2b.sr <- survreg(Surv(days, status) ~ rx, data = eg1b,
+     dist = "weibull")
> summary(eg2b.sr)

Call:
survreg(formula = Surv(days, status) ~ rx, data = eg1b, dist = "weibull
              Value Std. Error      z         p
(Intercept)   4.584      0.162 28.316 2.18e-176
rxTreatment   0.223      0.250  0.894  3.71e-01
Log(scale)   -0.615      0.189 -3.250  1.15e-03

Scale= 0.541

Weibull distribution
Loglik(model)= -115.5   Loglik(intercept only)= -115.9
Chisq= 0.83 on 1 degrees of freedom, p= 0.36
Number of Newton-Raphson Iterations: 8
n= 54
```

Example

The hazard ratio for treatment is given by:

```
> exp(-coef(eg2b.sr)[2]/eg2b.sr$scale)
rxTreatment
  0.6618901
```



Log-logistic and Log-normal Distributions

- These distributions are very similar. Both result in non-proportional hazards models.
- If $\log T$ has a logistic distribution, we say T is *log-logistic*
- If $\log T$ as a normal distribtion, we say T is *log-normal*
- If $\log h(t)$ is non-monotonic in t then these distributions are possible.

Example

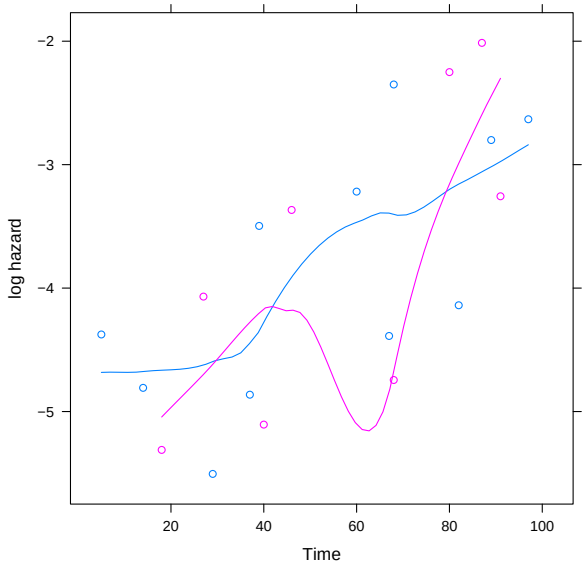
Computing log hazard in R

```
> kmf <- survfit(Surv(days, status) ~ rx, data = eg1b)
> H1 <- -log(kmf[1]$surv)
> H2 <- -log(kmf[2]$surv)
> Ht1 <- eg1b.km[1]$time
> Ht2 <- eg1b.km[2]$time
> dH1 <- diff(H1)/diff(Ht1)
> dH2 <- diff(H2)/diff(Ht2)
> loghaz <- data.frame(ldH = log(c(dH1, dH2)), times = c(Ht1[-1],
+     Ht2[-1]), rx = factor(c(rep(1, length(dH1)),
+     rep(2, length(dH2))), labels = c("Control",
+     "Treatment")))
```

Example

Plotting log hazard in R

```
> library(lattice)
> xyplot(ldH ~ times, data = loghaz, groups = rx,
+     type = c("p", "smooth"), ylab = "log hazard",
+     xlab = "Time")
```



Example

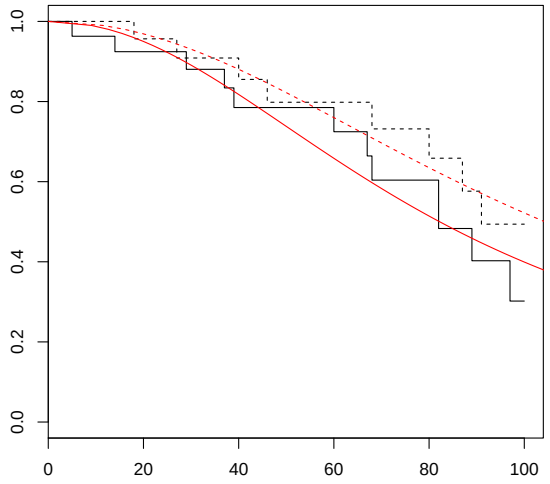
Fitting a log-logistic Model in R

```
> llog.fit <- survreg(Surv(days, status) ~ rx, data = eg1b,
+     dist = "loglogistic")
> summary(llog.fit)

Call:
survreg(formula = Surv(days, status) ~ rx, data = eg1b, dist = "loglogi
             Value Std. Error      z         p
(Intercept)  4.409      0.192 22.969 9.45e-117
rxTreatment  0.238      0.285  0.835  4.04e-01
Log(scale)  -0.734      0.187 -3.931  8.47e-05

Scale= 0.48

Log logistic distribution
Loglik(model)= -116.4   Loglik(intercept only)= -116.8
Chisq= 0.71 on 1 degrees of freedom, p= 0.4
Number of Newton-Raphson Iterations: 5
n= 54
```

Example

Plotting the Result

```
> pct <- 0:99/100
> llog.pred <- predict(llog.fit, newdata = data.frame(rx = factor(1:2,
+     labels = c("Control", "Treatment"))), type = "quantile",
+     p = pct)
> plot(kmf, mark.time = FALSE, lty = 1:2)
> matlines(t(llog.pred), cbind(1 - pct, 1 - pct),
+     col = "red", lty = 1:2)
```

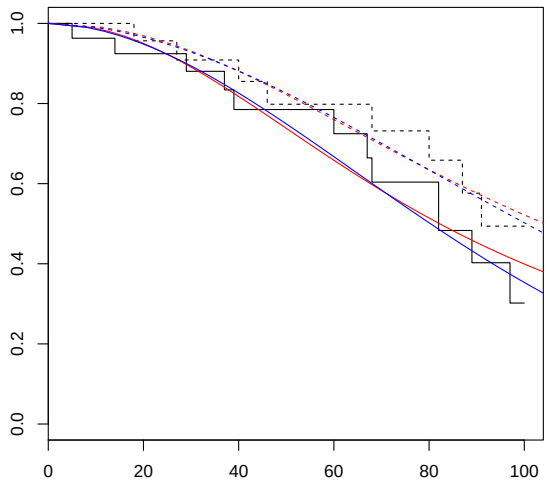


Example

Adding Weibull

```
> weib.pred <- predict(eg2b.sr, , newdata = data.frame(rx = factor(1:2,
+     labels = c("Control", "Treatment"))), type = "quantile",
+     p = pct)
> matlines(t(weib.pred), cbind(1 - pct, 1 - pct),
+     col = "blue", lty = 1:2)
```

References



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- Kalbfleisch J.D. and Prentice R.L. (1980). *The Statistical Analysis of Failure Time Data*. New York: Wiley