Survival analysis:
Parametric and non-parametric survival

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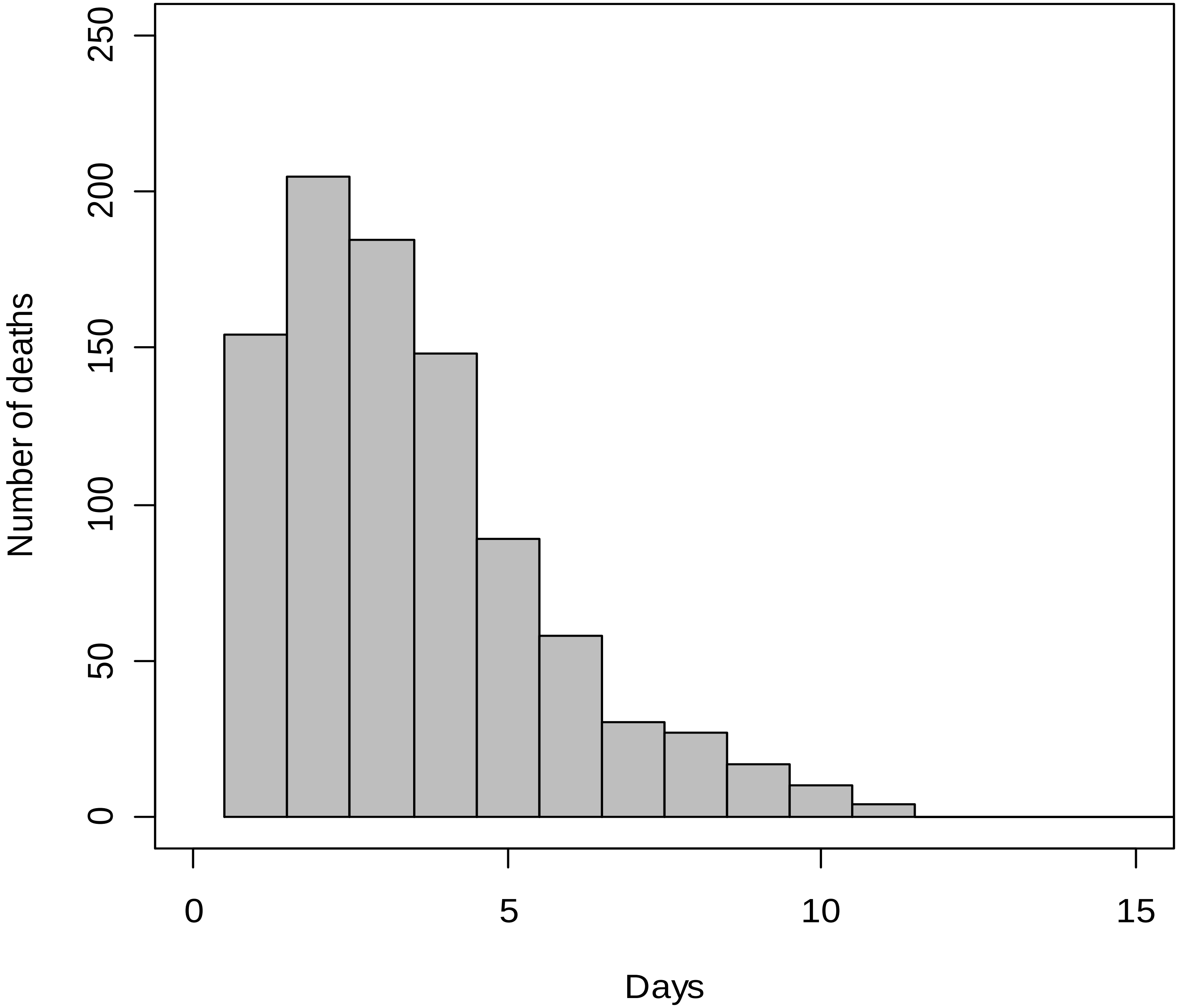
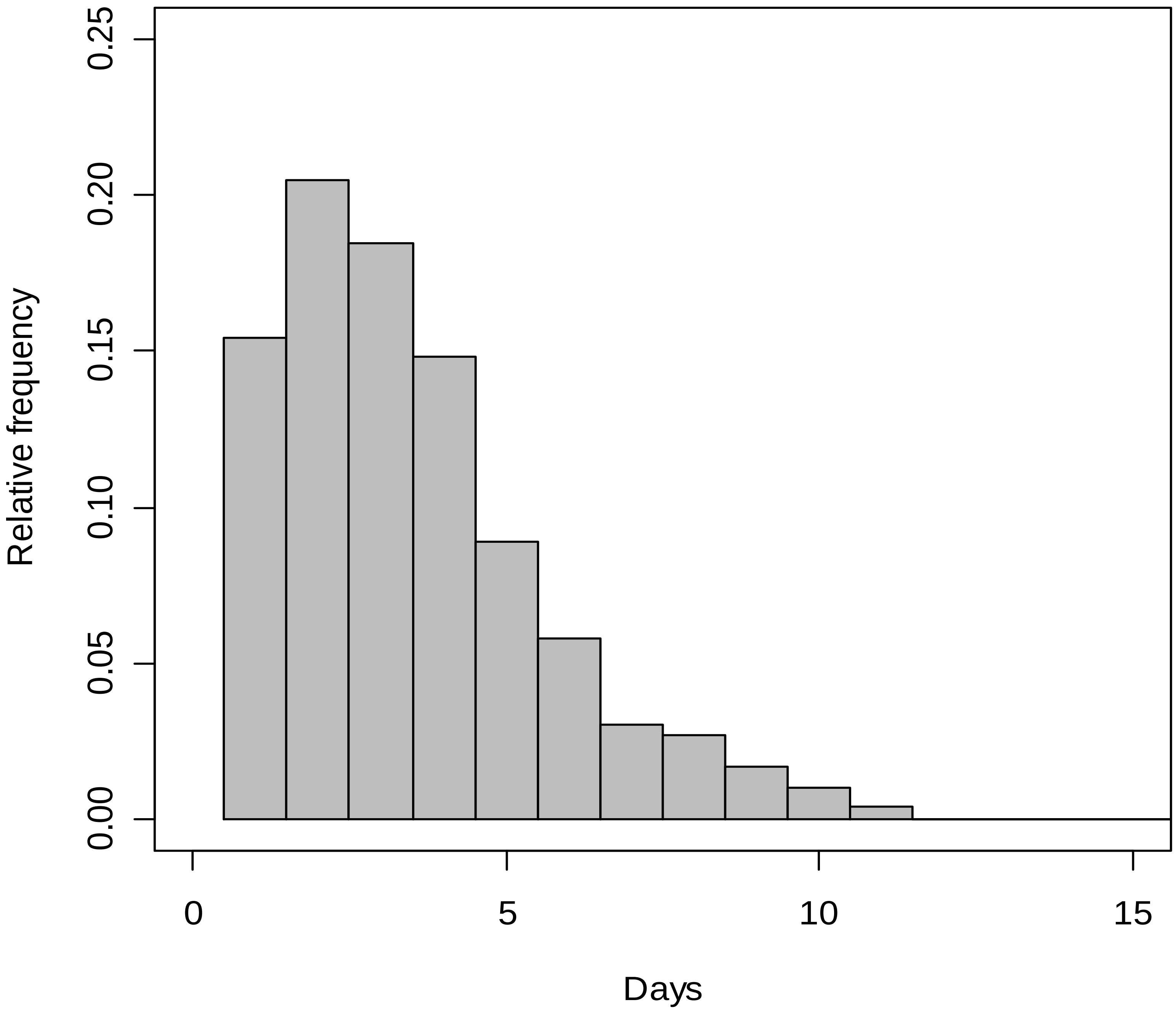
Roadmap

- Survival and hazard
- Parametric survival functions
  - Exponential
  - Weibull
- Non-parametric survival functions
- Presentation

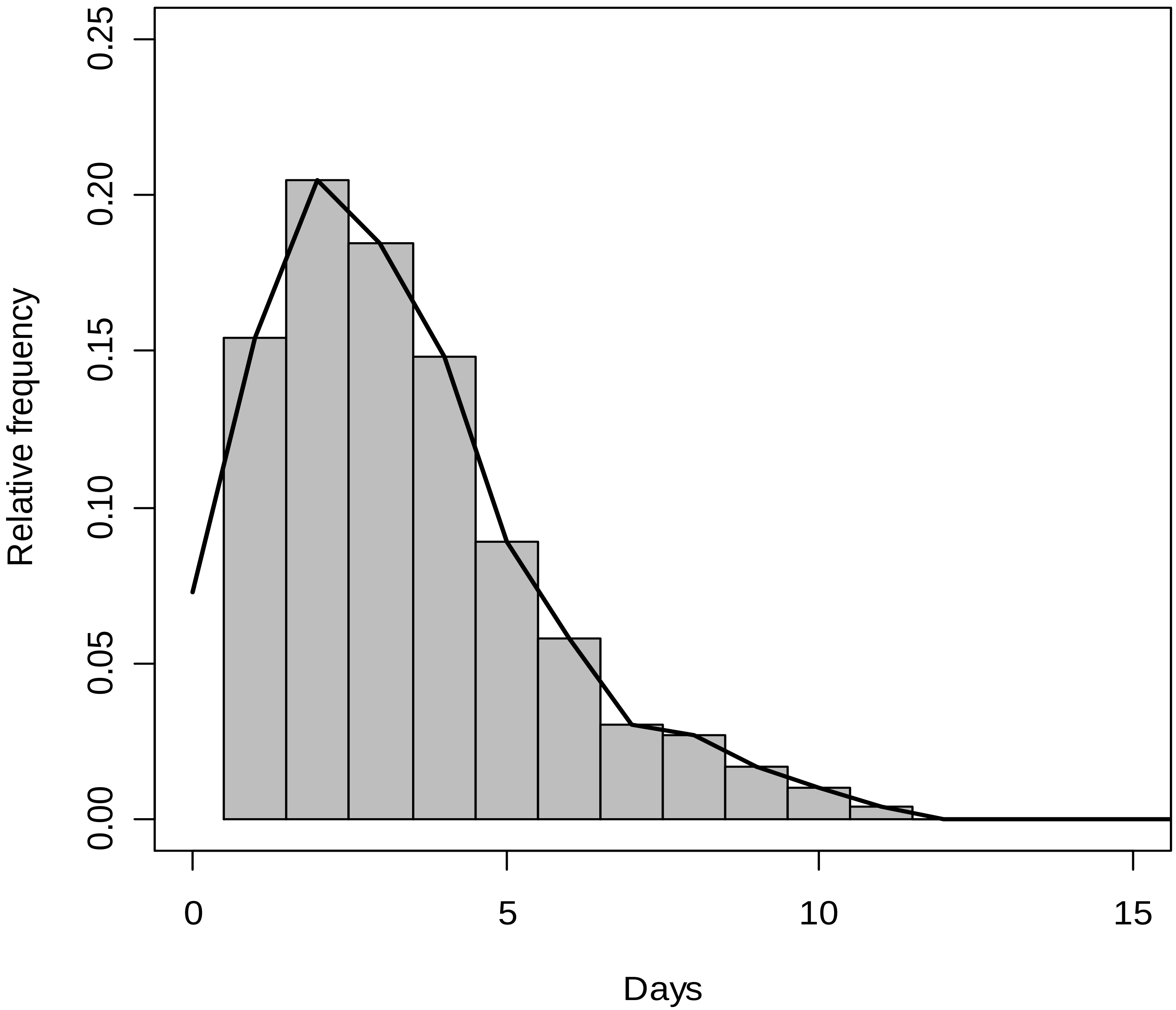
Frequency histogram showing the number of deaths as a function of time.



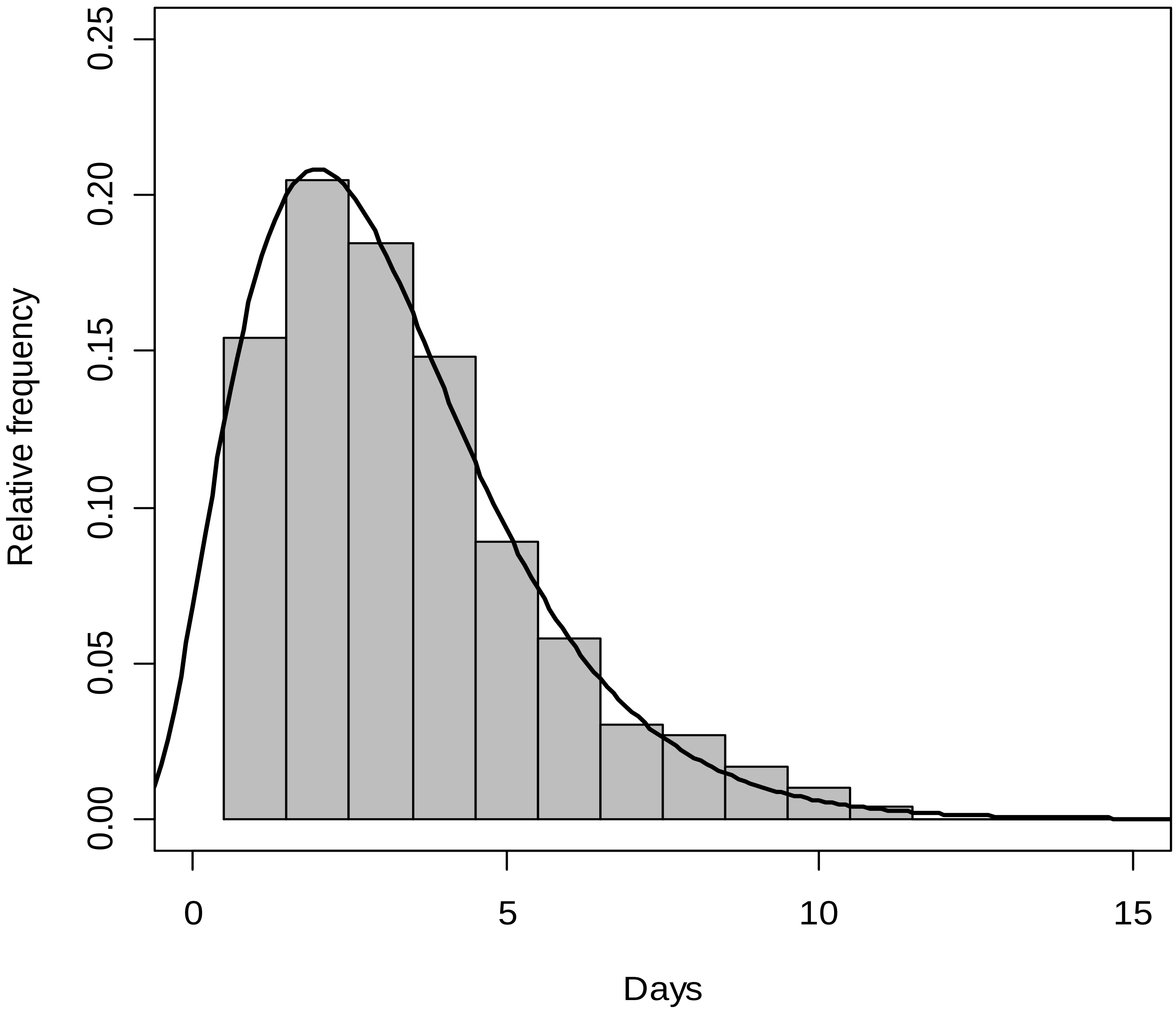
Frequency histogram showing the relative frequency of deaths as a function of time.



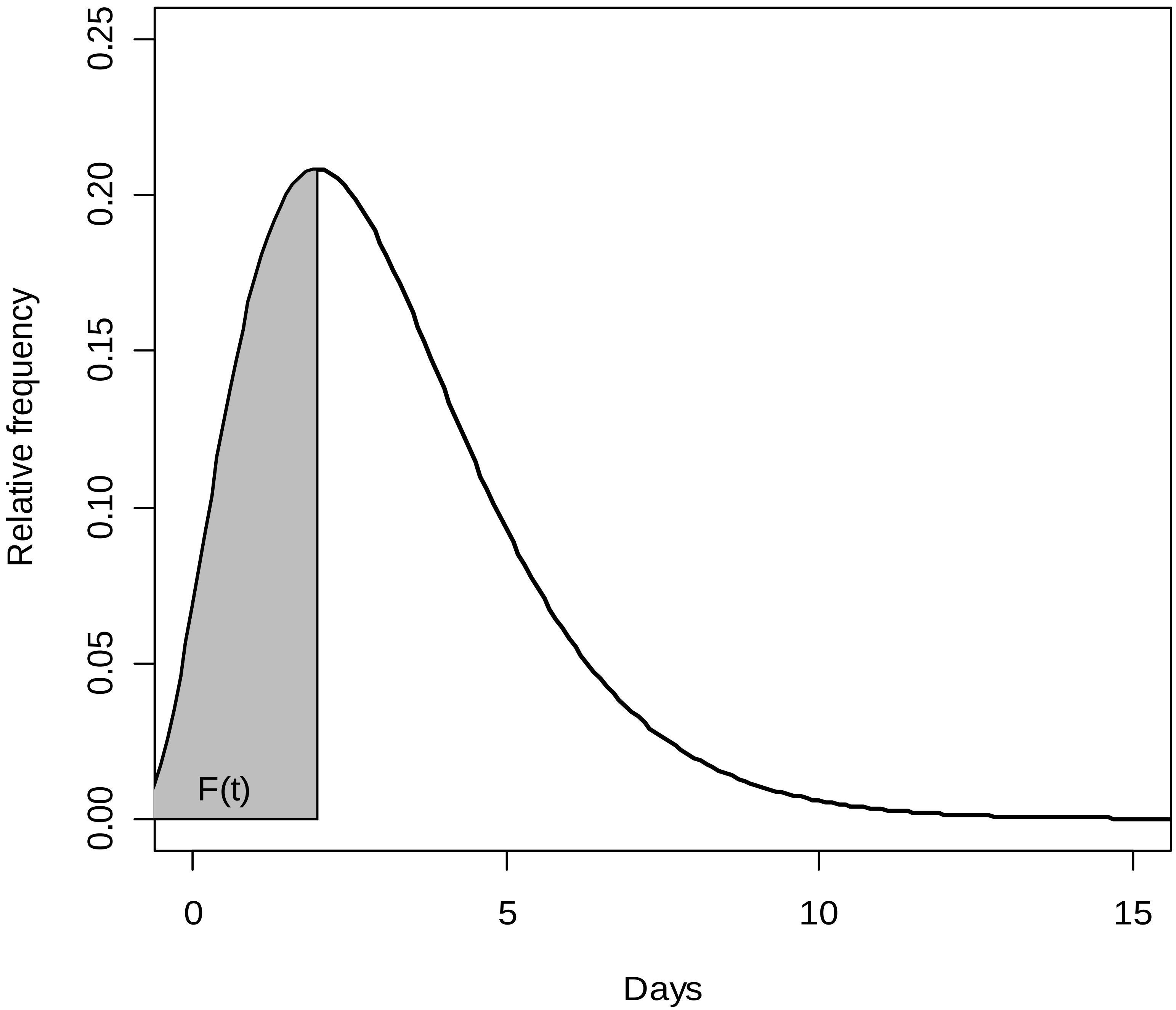
$f(t)$ = death density function.



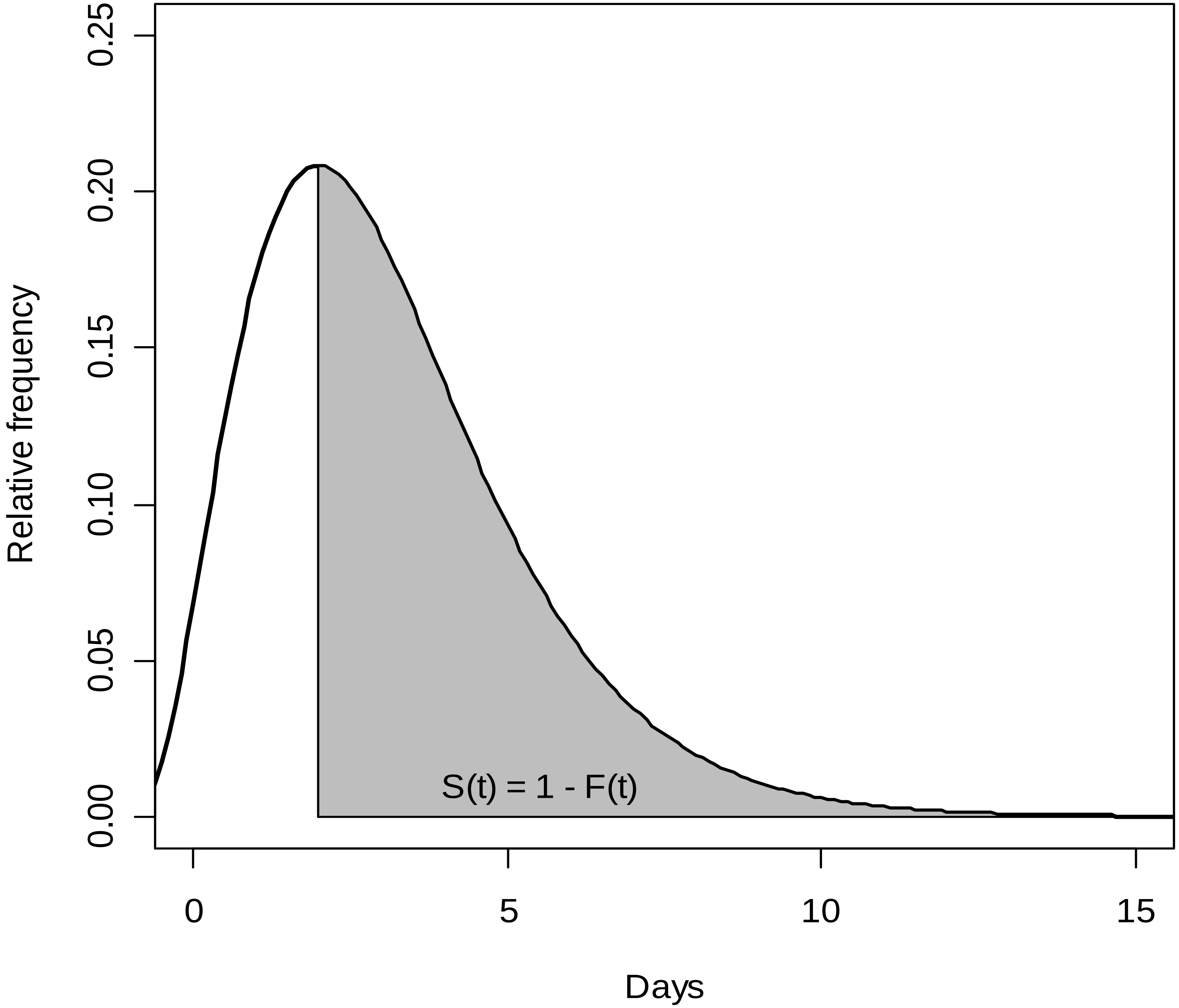
f(t) = death density function.



F(t) = the failure function = the proportion not surviving past time t.



S(t) = survival function = the proportion of the group that survive up to time t = 1 - F(t).



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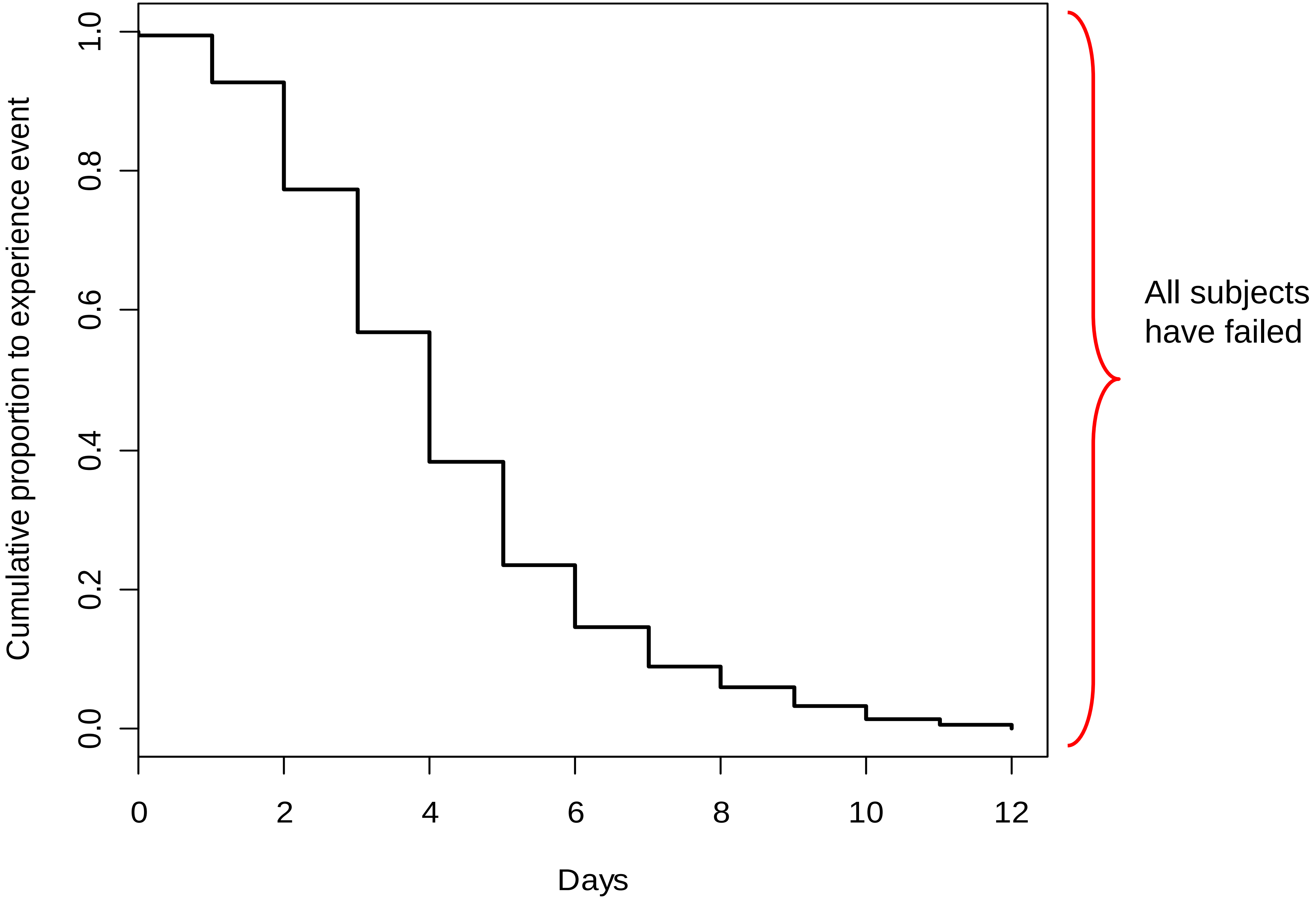


Failurefunction: $F(t) = 1 - S(t)$ Probability of not surviving past time *t*

Instantaneous failure rate: $f(t) = \dfrac{dF(t)}{dt}$ The slope of function of F(t)

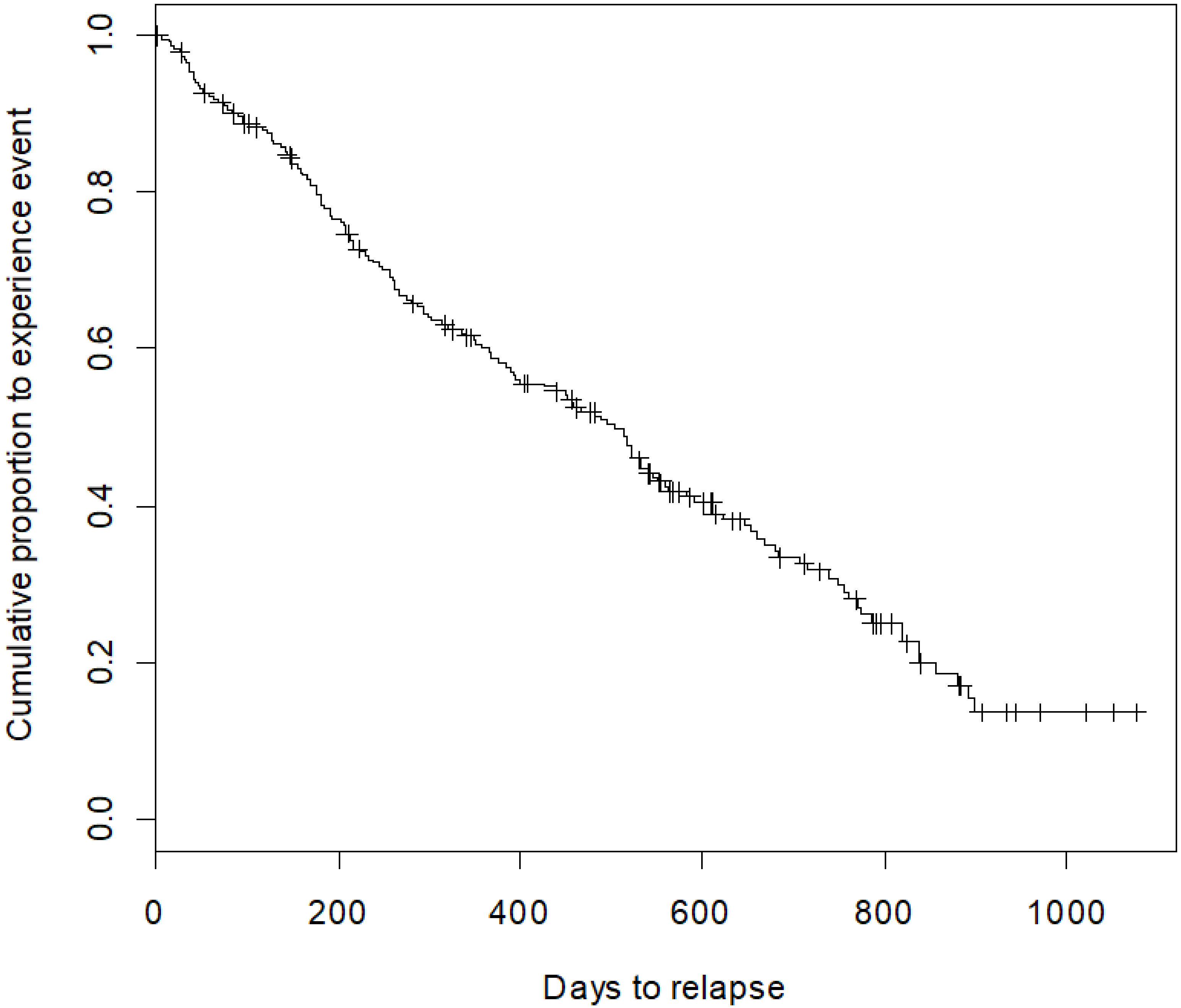
Instantaneous hazard function: $h(t) = \dfrac{f(t)}{S(t)}$ Probability of failure at time *t*

Cumulative hazard function: $H(t) = -\ln S\,(t)$ The accumulated hazard over time

Survival and hazard

- Instantaneous hazard h(t)
  - ≡ 'hazard' (Dohoo and Martin)
  - the probability of an event occurring at time t, given that it hasn't occurred already

Kaplan-Meier survival curve showing the cumulative proportion of drug addict population that had not relapsed following discharge from treatment event as a function of calendar date.



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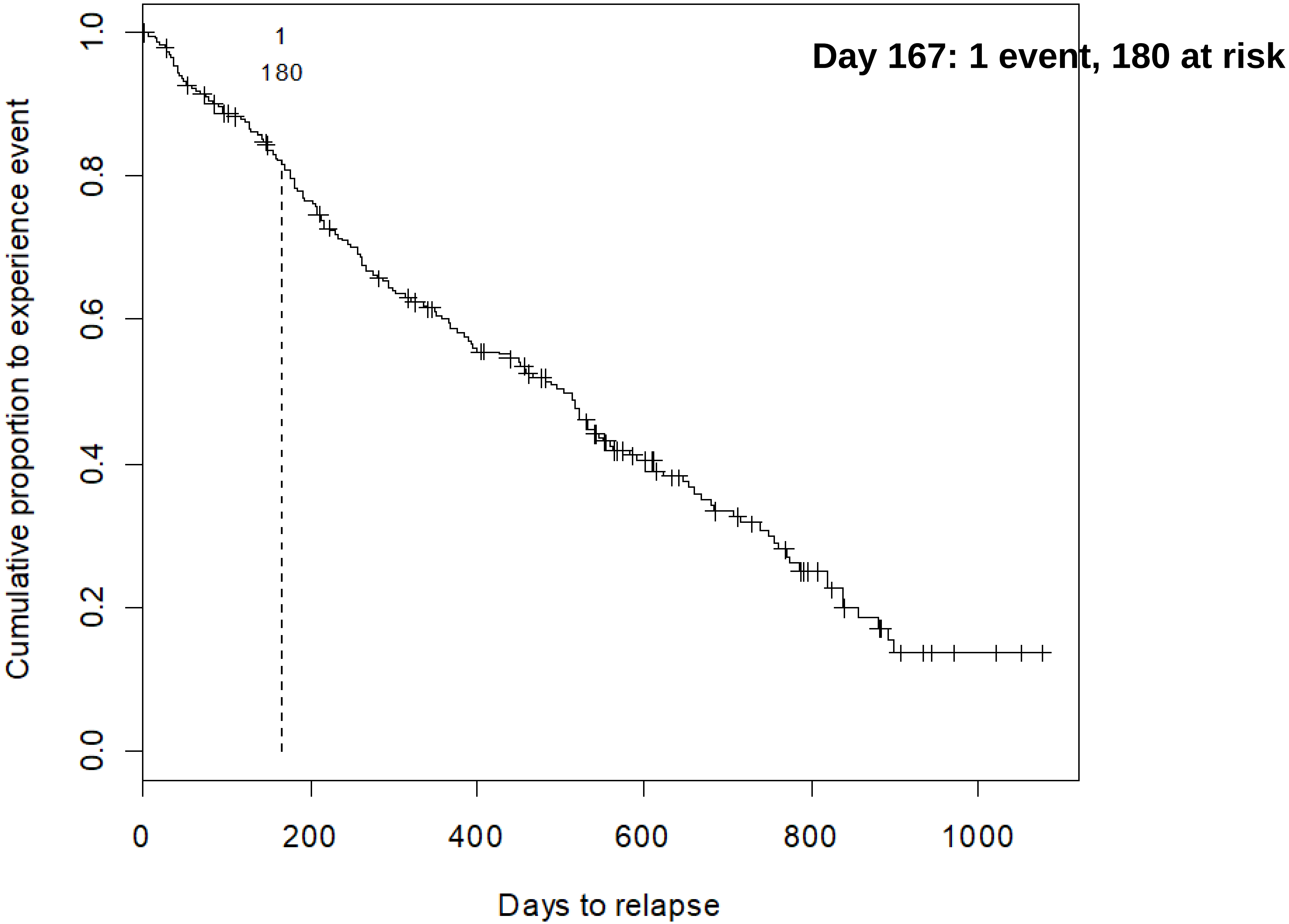

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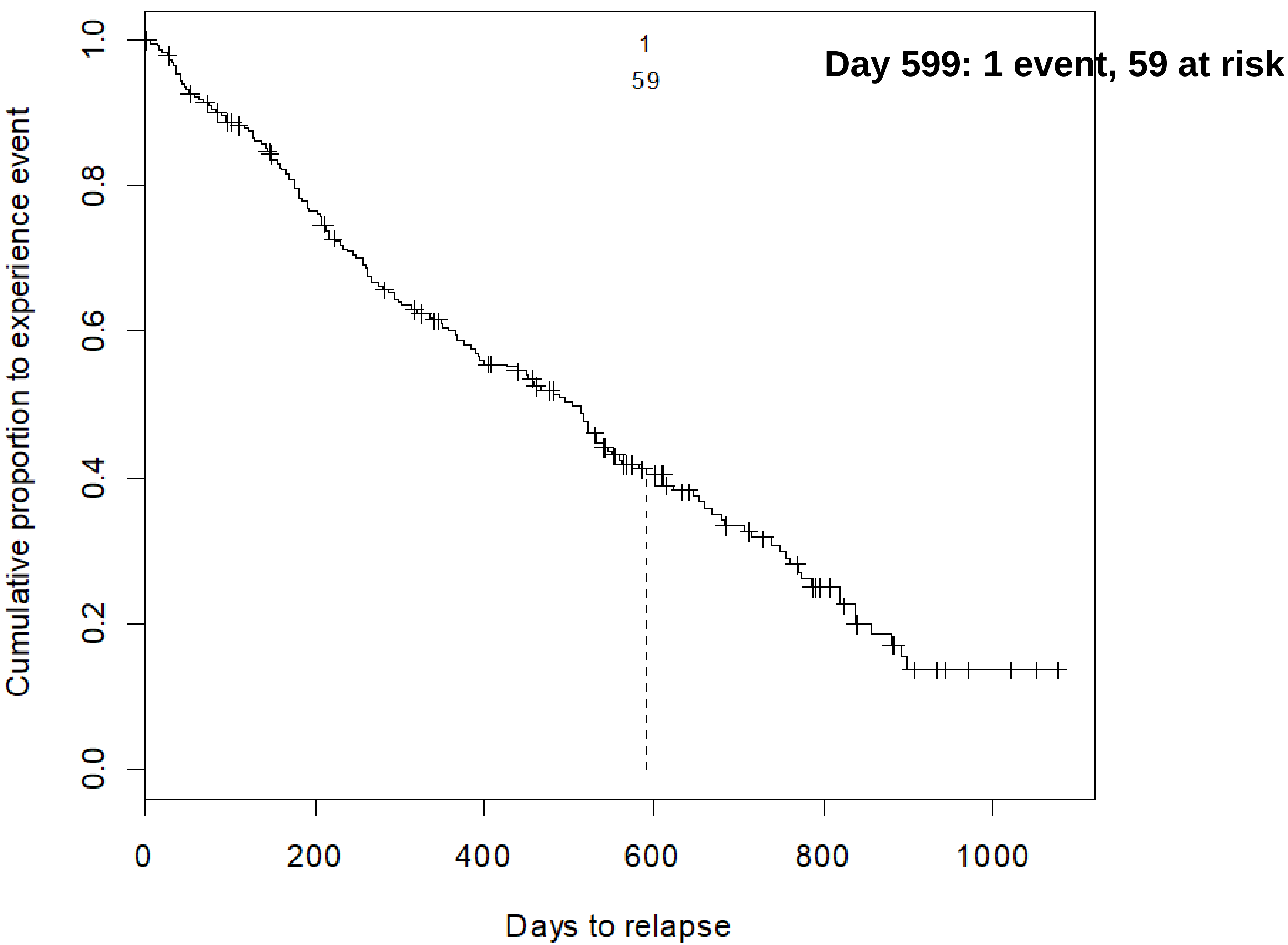
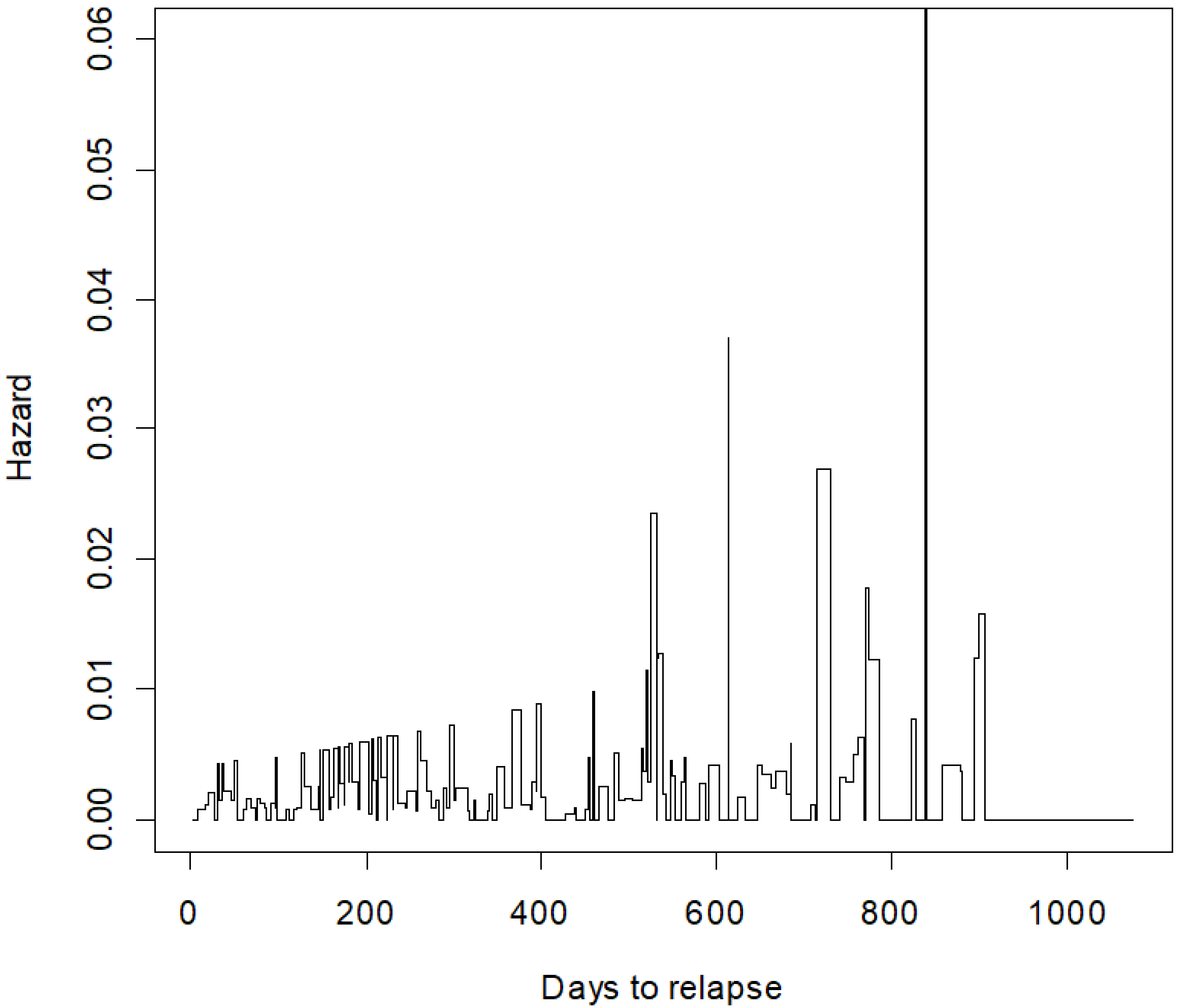


Instantaneous hazard of relapse in drug addicts following discharge from rehabilitation.



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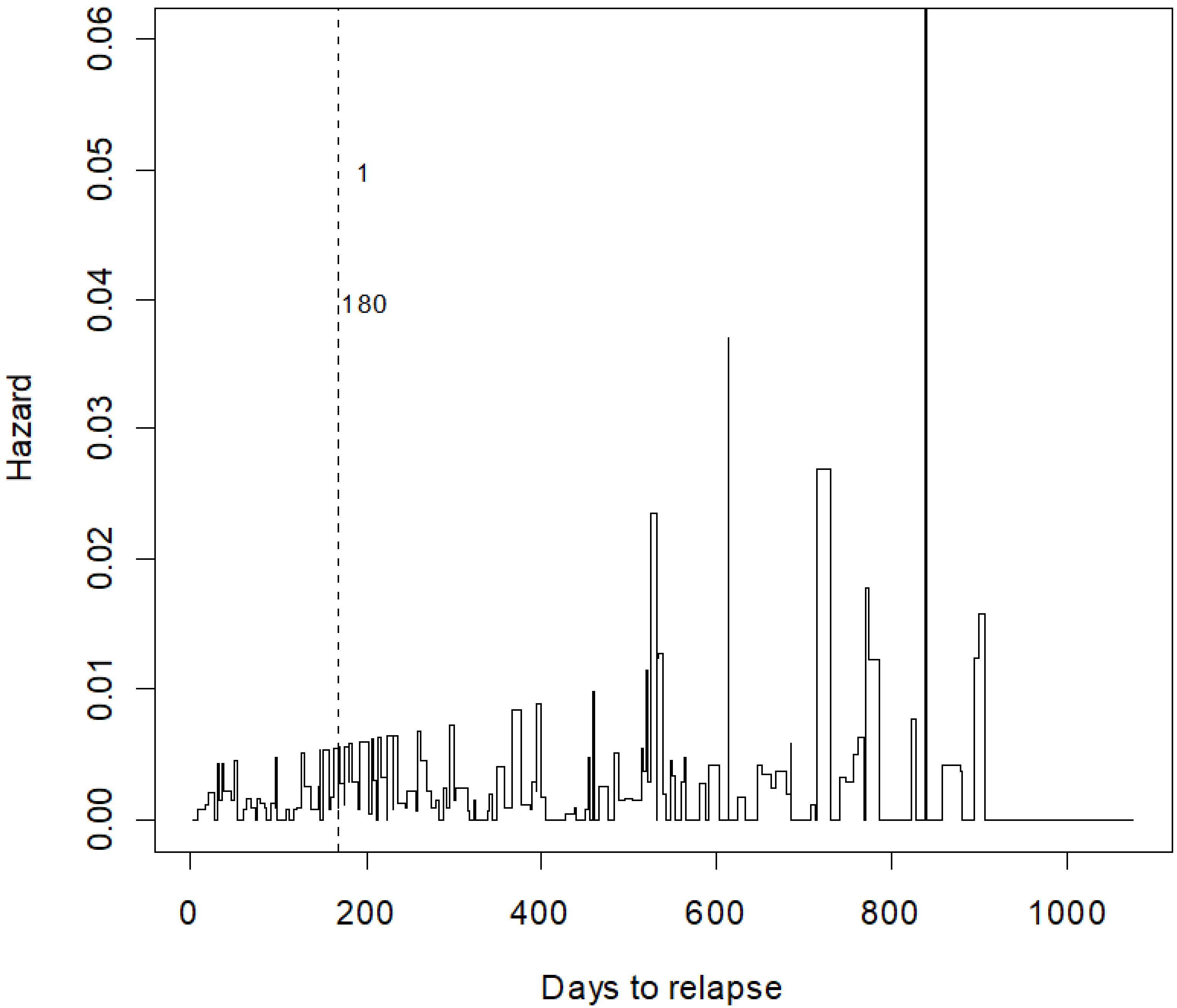

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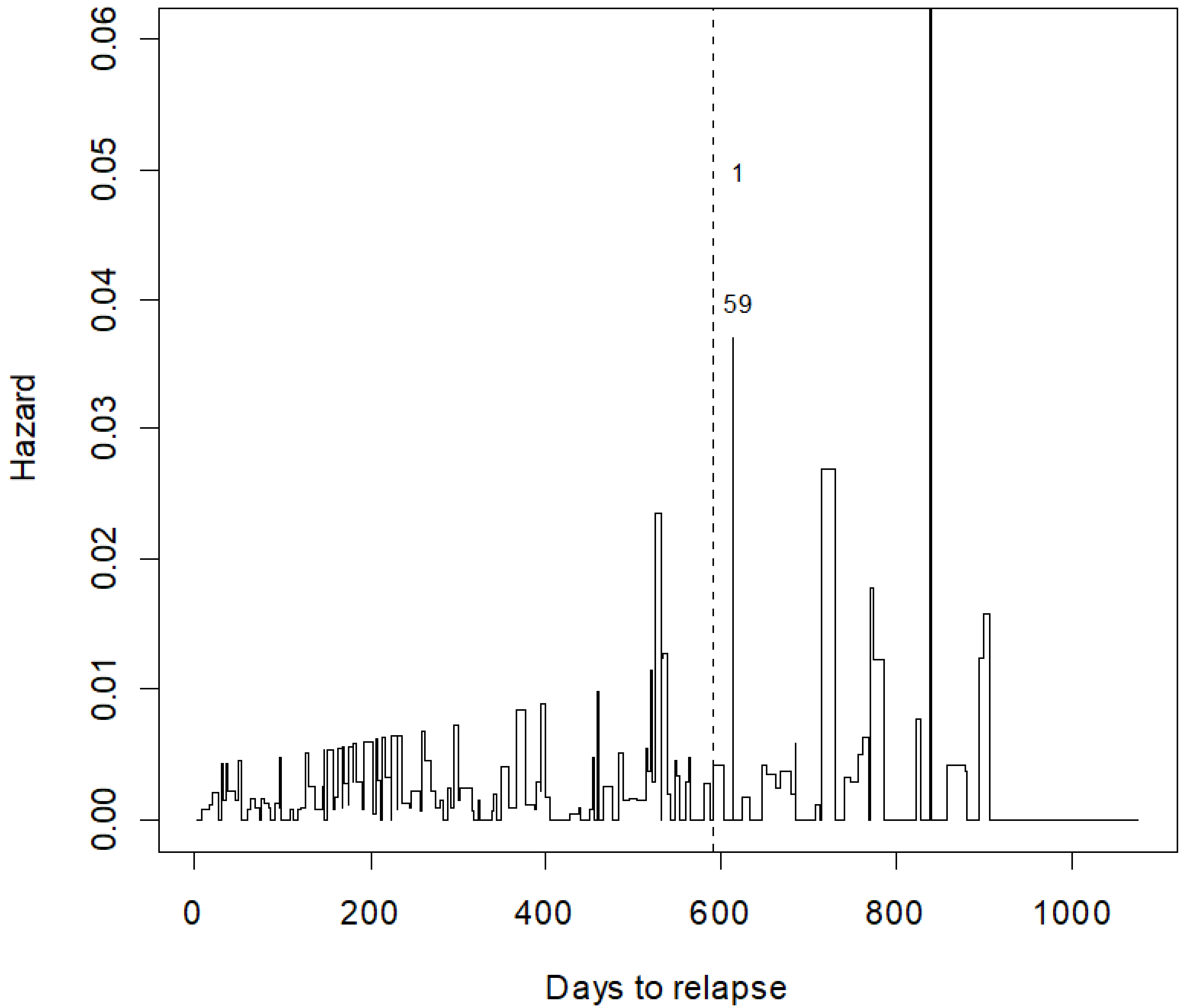

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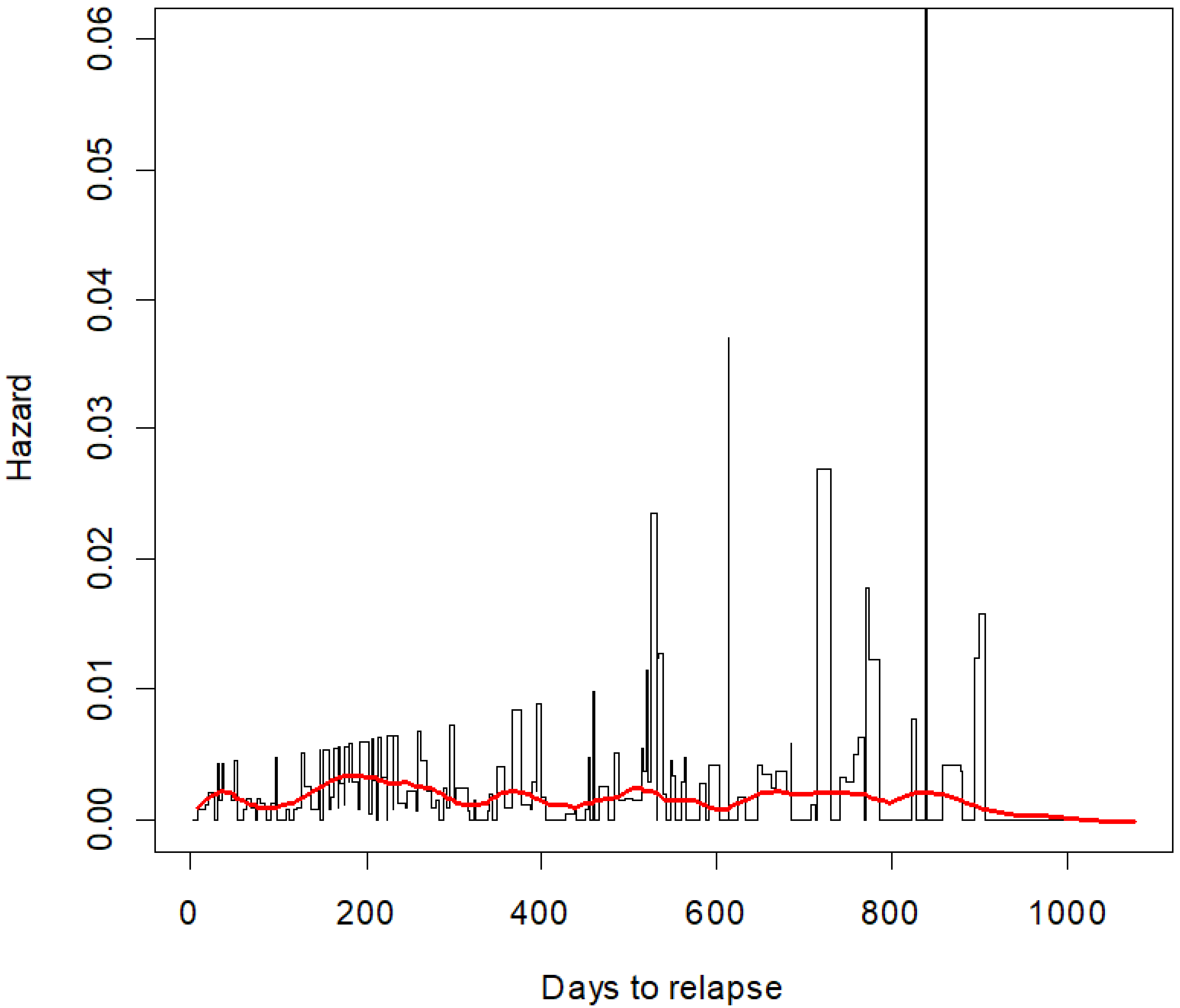
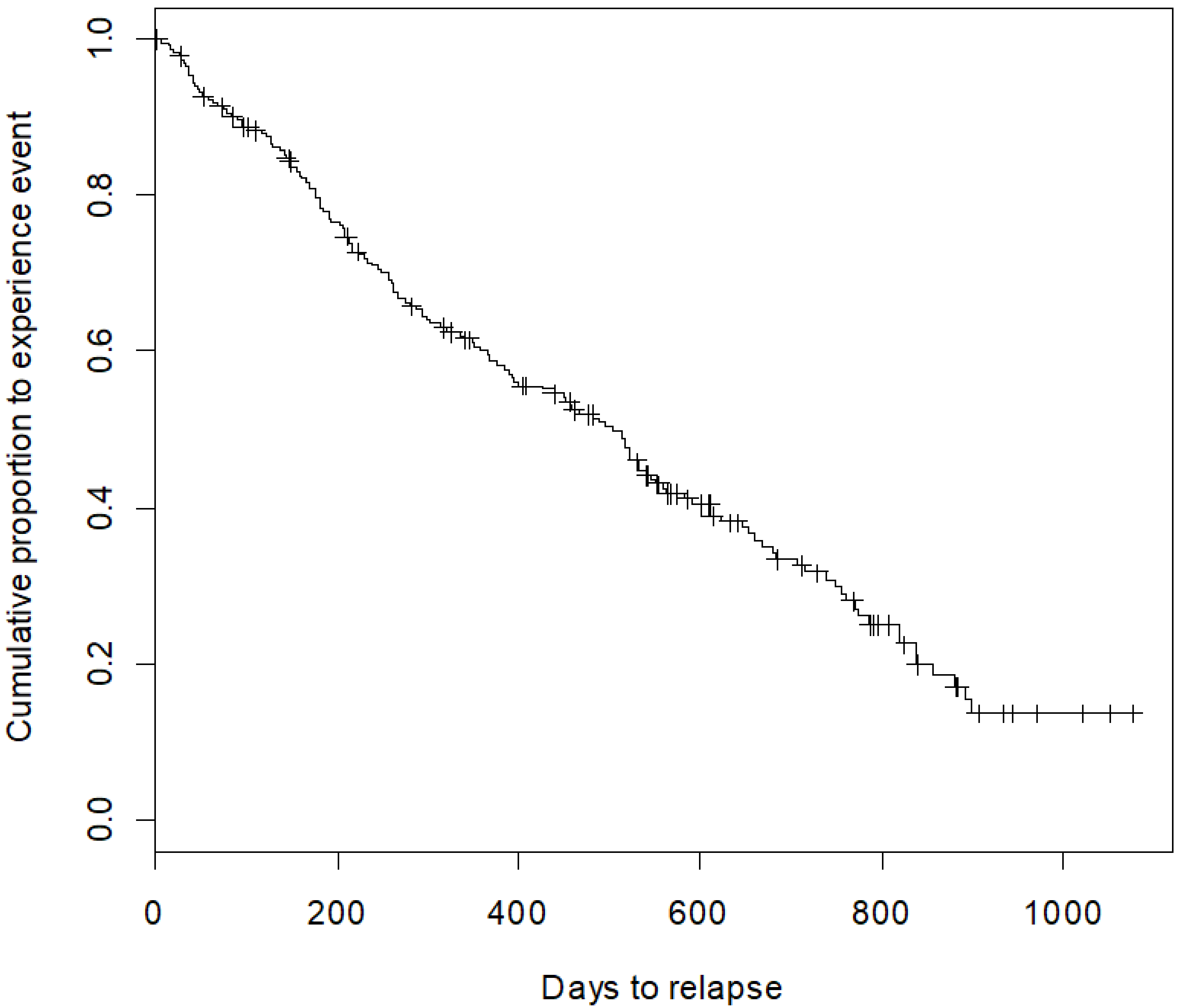


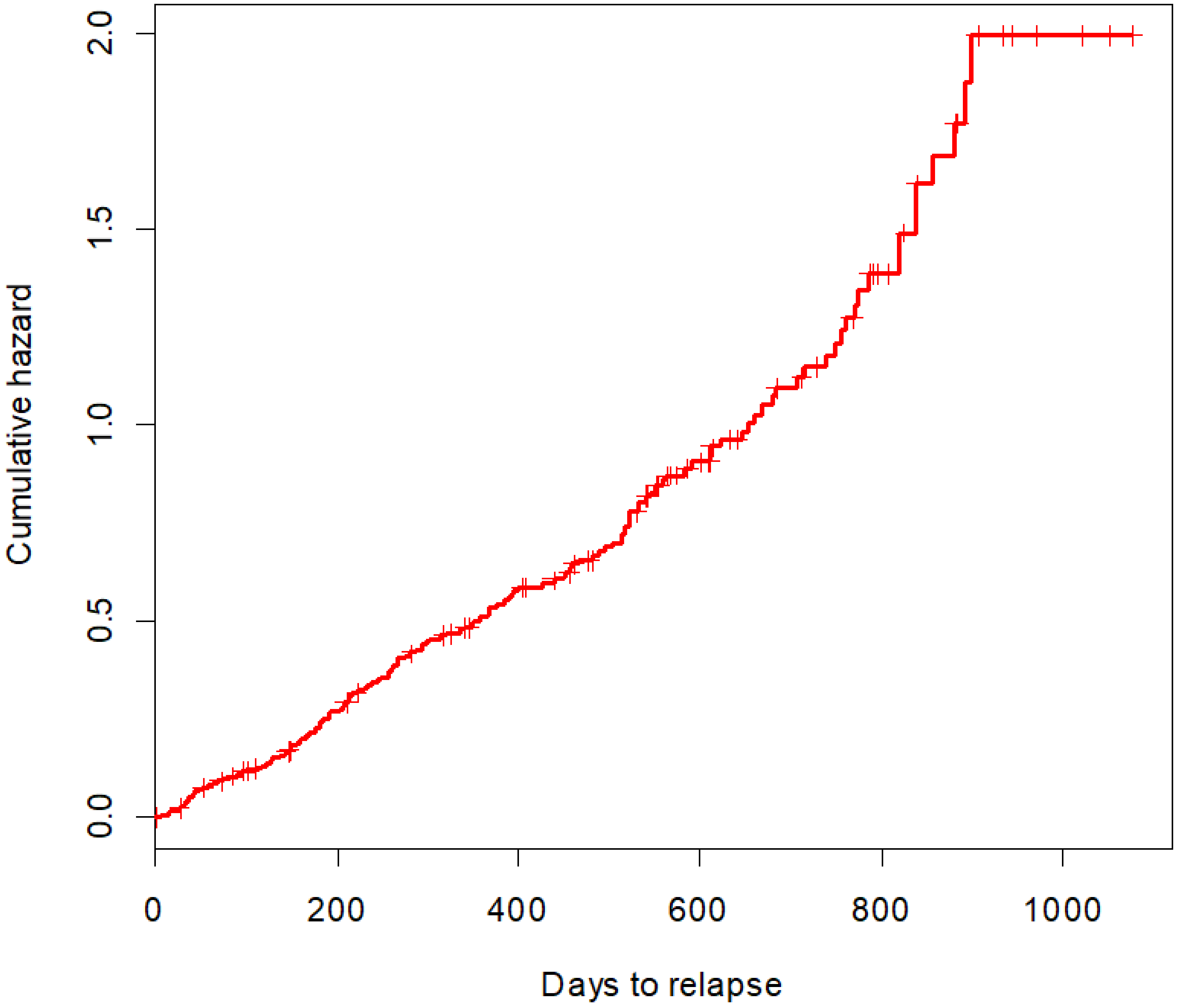
Survival and hazard

- Cumulative hazard H(t)
  - also referred to as ‘integrated hazard’
  - equals the total amount of accumulated risk that an individual has encountered from the beginning of the observation period
  - represents the expected number of events that would have occurred by time *t*

Kaplan-Meier survival curve showing the cumulative proportion of drug addict population that had not relapsed following discharge from treatment event as a function of calendar date.



Cumulative hazard of relapse in drug addicts following discharge from rehabilitation.



Roadmap

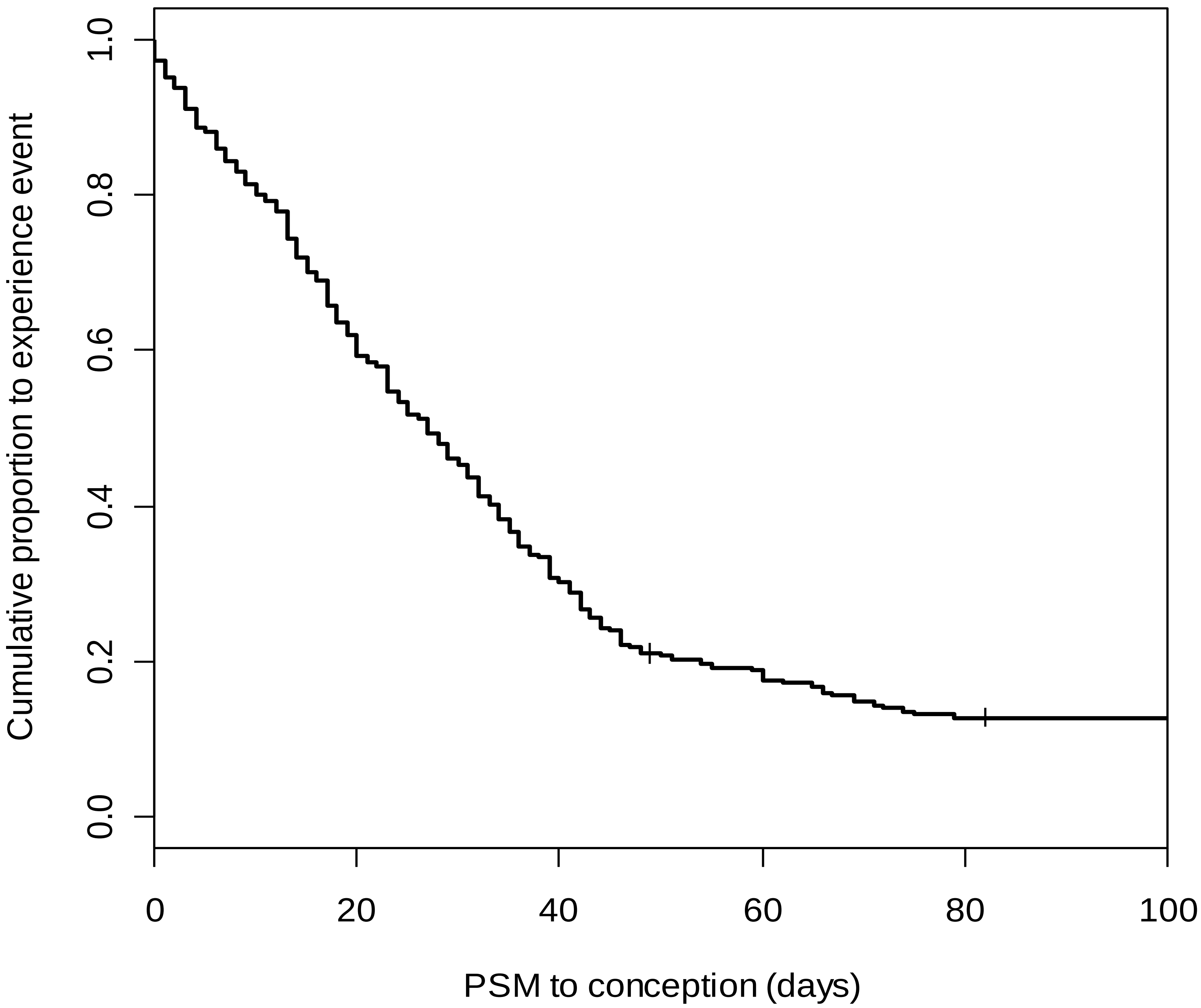
- Survival and hazard
- <u>Parametric survival functions</u>
  - Exponential
  - Weibull
- Non-parametric survival functions
- Presentation

Parametric survival distributions

- In the last lecture we talked about ways to describe survivorship
  - x axis: time
  - y axis: proportion of group that had not experienced event

- Some survival functions ‘predictable’ …

Days to conception as a function of days after Planned Start of Mating date in dairy cows.

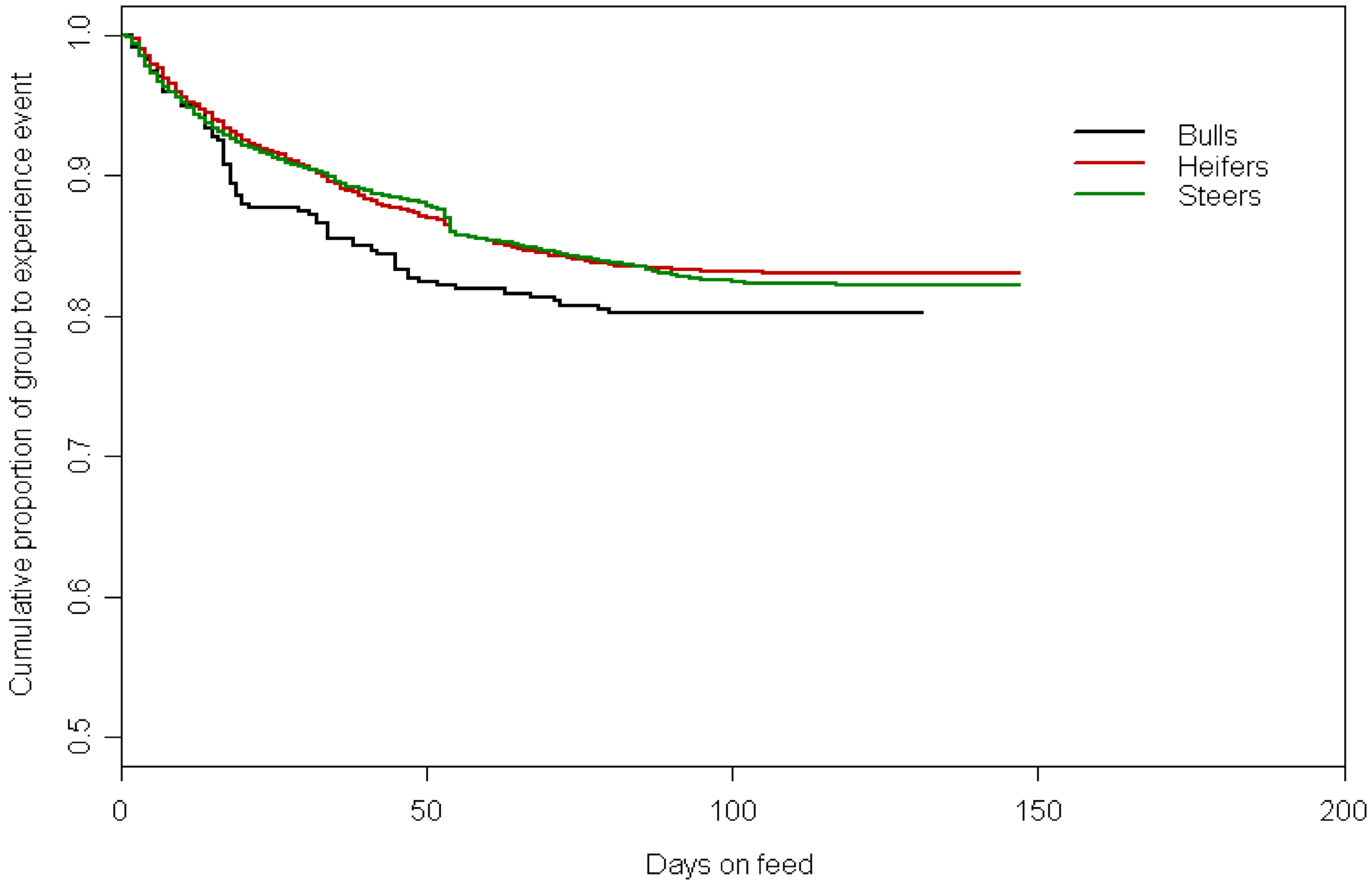


Parametric survival distributions

- Some survival functions ‘unpredictable’ …

Indonesian feedlot.

Kaplan-Meier survival curve showing cumulative proportion of animals pulled for all reasons as a function of calendar date, by stock class.



Parametric survival distributions

- Those distributions follow a nice, well-defined pattern can be described by <u>parametric</u> distributions

- Those distributions that are irregular in shape can only be described by <u>non-parametric</u> distributions

Parametric survival distributions

- The advantage of the parametric approach is that survival can be predicted (because we know how the curve will behave beyond the last observation)

- Non-parametric models are not suitable for prediction because there is uncertainty about the nature of the distribution beyond the last observation

Parametric survival functions

- Several parametric distributions are available, each characterised by different hazard functions:

Distribution	**h(t)**	**f(t)**	**S(t)**
Exponential	λ	$\lambda \exp[-\lambda t]$	$\exp[-\lambda t]$
Weibull	$\lambda p t^{p-1}$	$\lambda p t^{p-1} \exp[-\lambda t^p]$	$\exp[-\lambda t^p]$
Log-logistic	$[ab(at)^{b-1}] / [1 + (at)^b]$	$[ab(at)^{b-1}] / [1 + (at)^b]^2$	$[1 + (at)^b]^{-1}$

$$f(t) = h(t) \times S(t)$$

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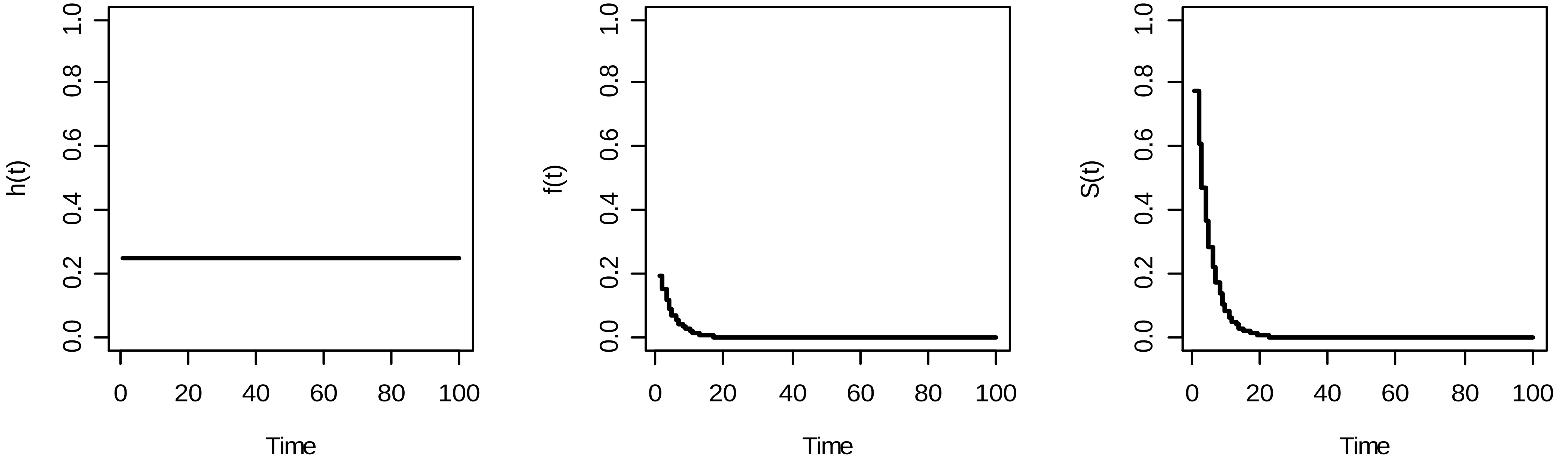
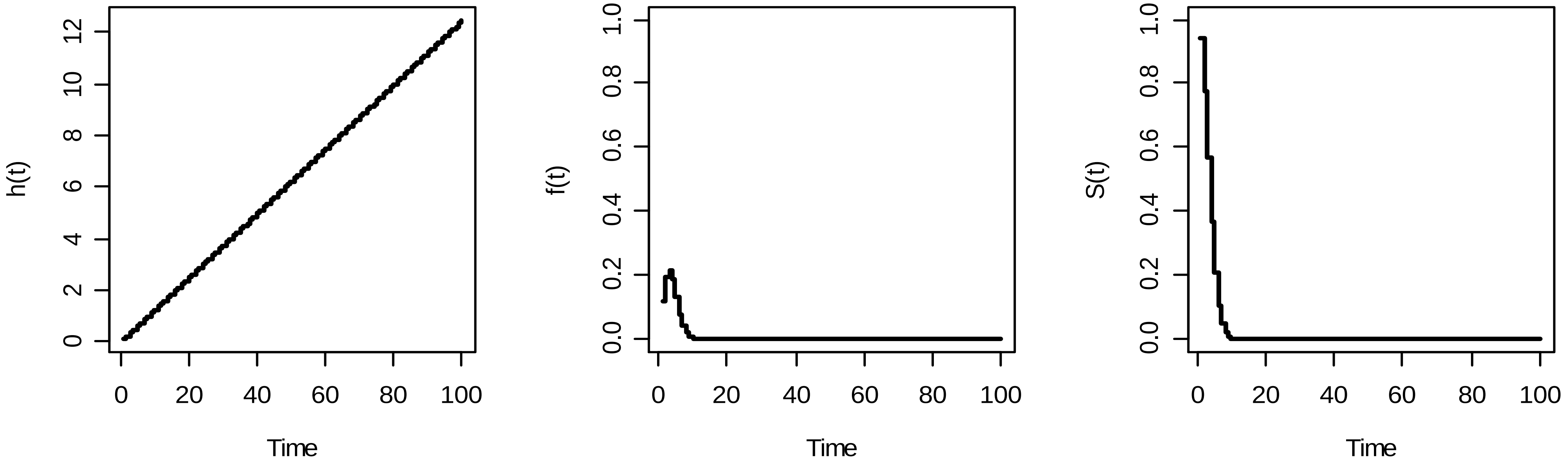
Exponential distribution = hazard constant over time.




```
t <- seq(from = 1, to = 100, by = 1)
lambda = 0.25
ht <- lambda
ft <- lambda * exp(-lambda * t)
St <- exp(-lambda * t)
```

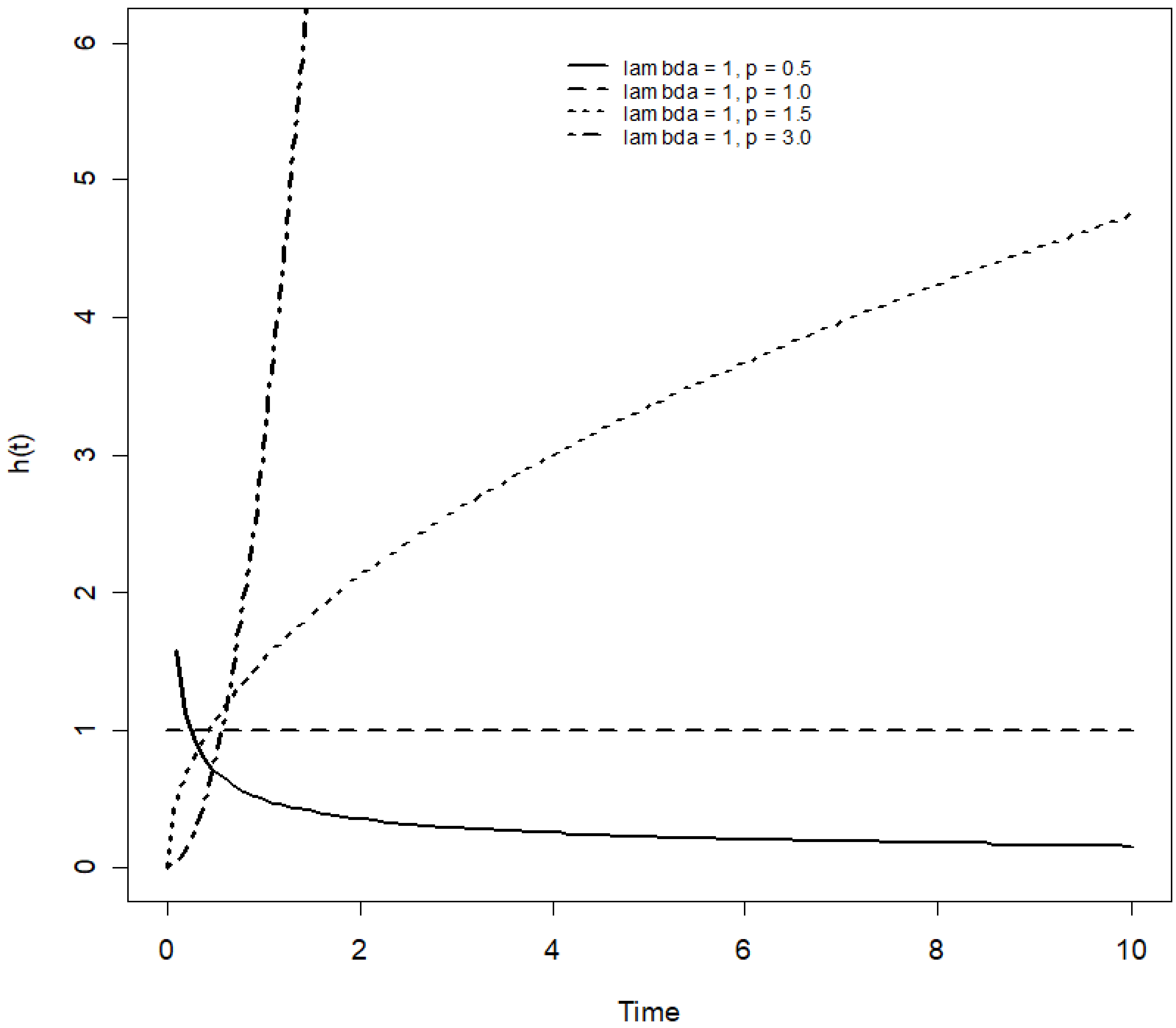
Weibull distribution = hazard varies according to lambda and p.




```
t <- seq(from = 1, to = 100, by = 1)
lambda = 0.25; p = 2
ht <- (lambda * p) * (lambda * t)^(p - 1)
ft <- (lambda * p) * (lambda * t)^(p - 1) * exp(-(lambda * t)^p)
St <- exp(-(lambda * t)^p)
```

Parametric survival functions

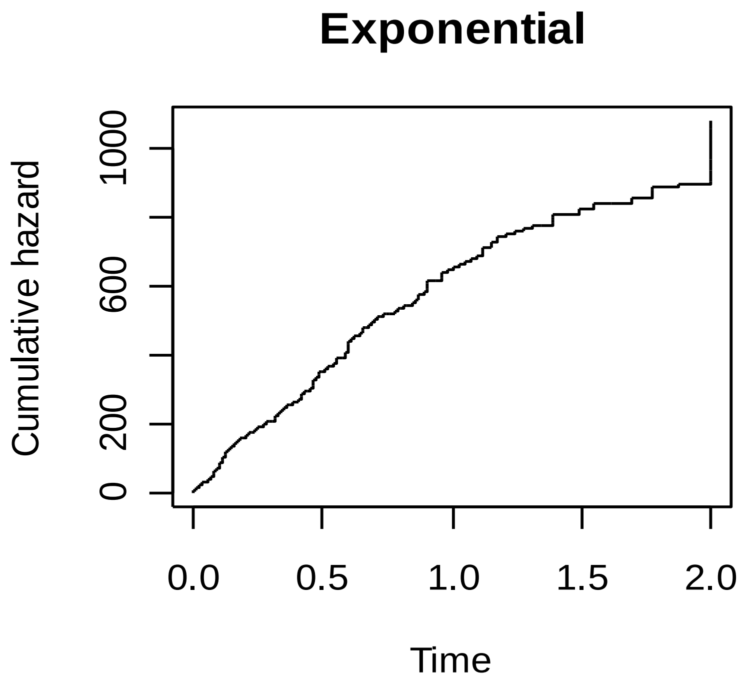
- Exercise
  - for the Weibull distribution, evaluate the effect of changing λ (the scale parameter) and p (the shape parameter)
  - what happens to hazard when
    - $p < 1$?
    - $p = 1$?
    - $p > 1$?

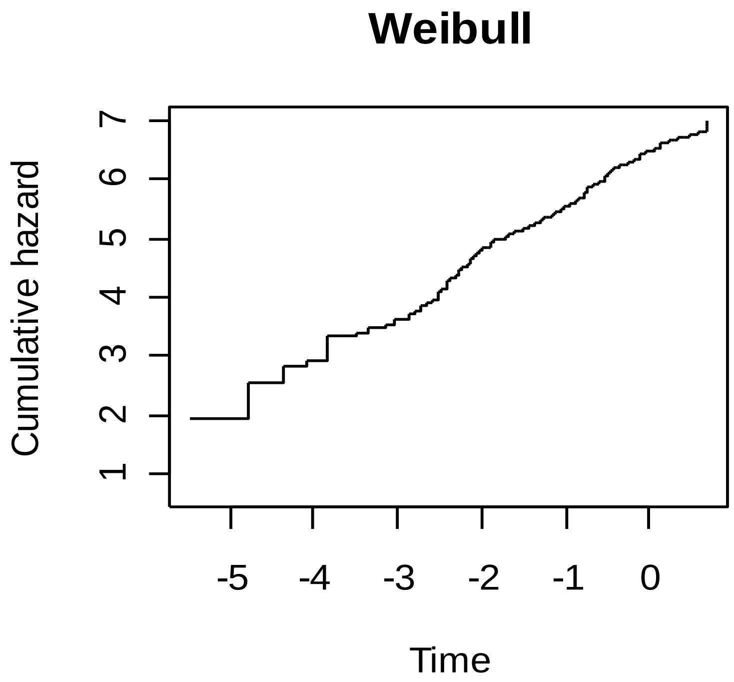


lam bda = 1, p = 0.5
lam bda = 1, p = 1.0
lam bda = 1, p = 1.5
lam bda = 1, p = 3.0
h(t)
0
1
2
3
4
5
6
0
2
4
6
8
10
Time

Parametric survival functions

- Is a parametric distribution appropriate for our data?
  - exponential distribution
    - plot the <u>cumulative hazard</u> as a function of t
    - if distribution appropriate, should be a straight line
  - Weibull distribution
    - plot the <u>log cumulative hazard</u> as a function of log t
    - if distribution appropriate, should be a straight line






```
library(survival); setwd("D:\\TEMP")
dat <- read.table("addict.csv", header = TRUE, sep = ",")
addict.km <- survfit(Surv(stop, status) ~ 1, conf.type = "none",
type = "kaplan-meier", data = dat)
Ht <- -log(addict.km$surv)
t <- addict.km$time

par(mfrow = c(2,2))
plot(Ht, t, type = "s", xlab = "Time", ylab = "Cumulative hazard",
main = "Exponential")
plot(log(Ht), log(t), type = "s", xlab = "Time", ylab = "Cumulative
hazard", main = "Weibull")
```

Parametric survival functions

- Other distributions
  - gamma
  - log-normal
  - log-logistic

  - see Dohoo and Martin page 427

Roadmap

- Survival and hazard
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  - Exponential
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- <u>Non-parametric survival functions</u>
- Presentation

Non-parametric survival functions

- Non-parametric methods are used when no theoretical distribution adequately fits the data
  - less efficient than parametric methods
  - frequently (always?) used in epidemiology
  - two non-parametric methods for estimating the way survival changes over time:
    - the Kaplan-Meier method
    - life table methods

Non-parametric survival functions

- Kaplan-Meier method
  - also known as the Product Limit method
  - based on individual survival times and assumes that censoring is independent of survival time (that is, the reason an observation is censored is unrelated to the cause of failure)

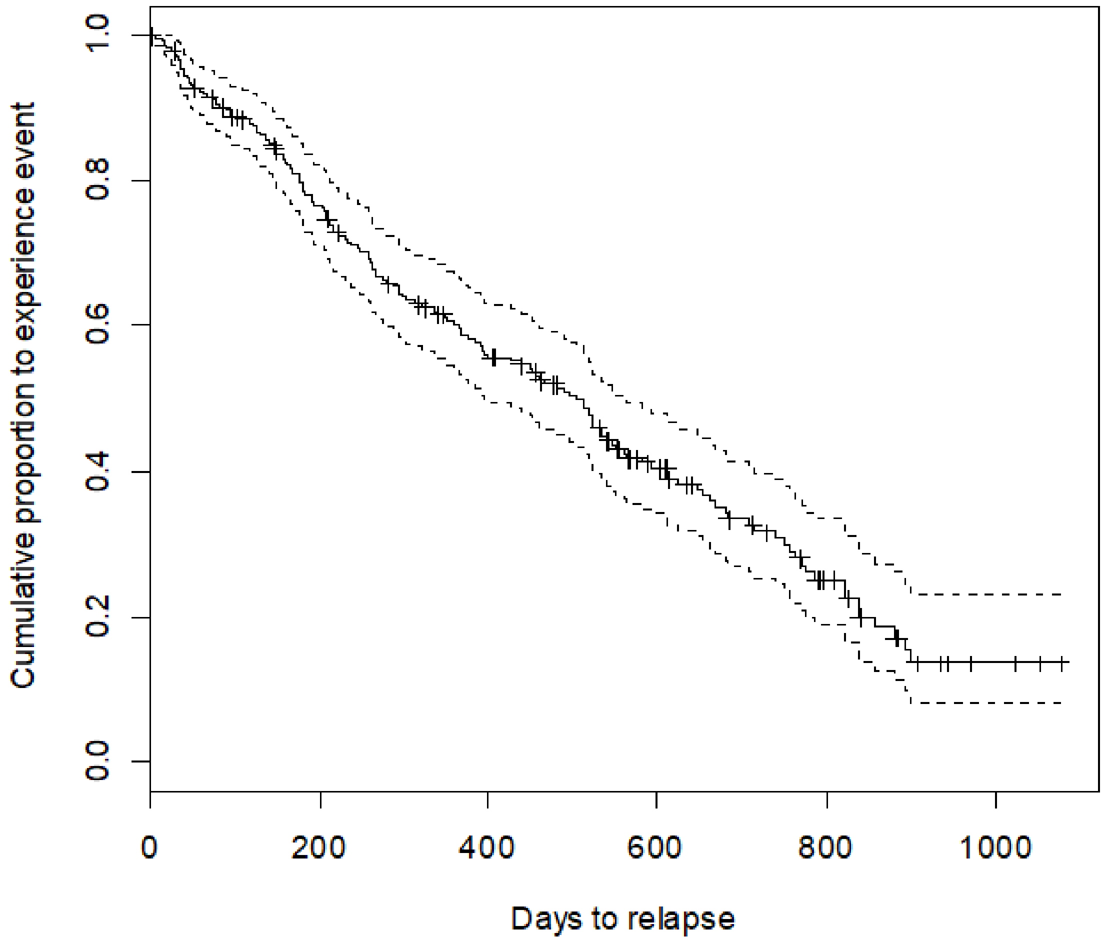
Non-parametric survival functions

- Kaplan-Meier method:

Time	Start n_i	Fail d_i	Censor w_i	At risk $r_i = (n_i - w_i)$	Surv prob $p_i = 1 - [d_i \div (n_i - w_i)]$	Cum surv
0	31	2	3	31-3 = 28	0.93	0.93 × 1.00 = 0.93
1	26	1	2	26-2 = 24	0.96	0.96 × 0.93 = 0.89
2	23	1	2	23-2 = 21	0.95	0.95 × 0.89 = 0.85
3	20	1	2	20-2 = 18	0.94	0.94 × 0.85 = 0.80
etc						

Non-parametric survival functions

- Confidence intervals
  - standard errors of survival estimate can be calculated at each point in time
  - standard errors can be used to calculate confidence intervals
  - standard errors can be used to test for differences in survival among strata




```
library(survival); setwd(("D:\\temp")
dat <- read.table("addict.csv", header = TRUE, sep = ",");

addict.km <- survfit(Surv(stop, status) ~ 1, type = "kaplan-meier",
data = dat);
plot(addict.km, xlab = "Days to relapse", ylab = "Cumulative
proportion to experience event", conf.int = TRUE);
```

Non-parametric survival functions

- Life-table (Cutler-Ederer) method

Time	Start ni	Fail di	Censor wi
0 to 1	31	3	4
2 to 3	24	2	4
etc			

Non-parametric survival functions

- Life-table (Cutler-Ederer) method

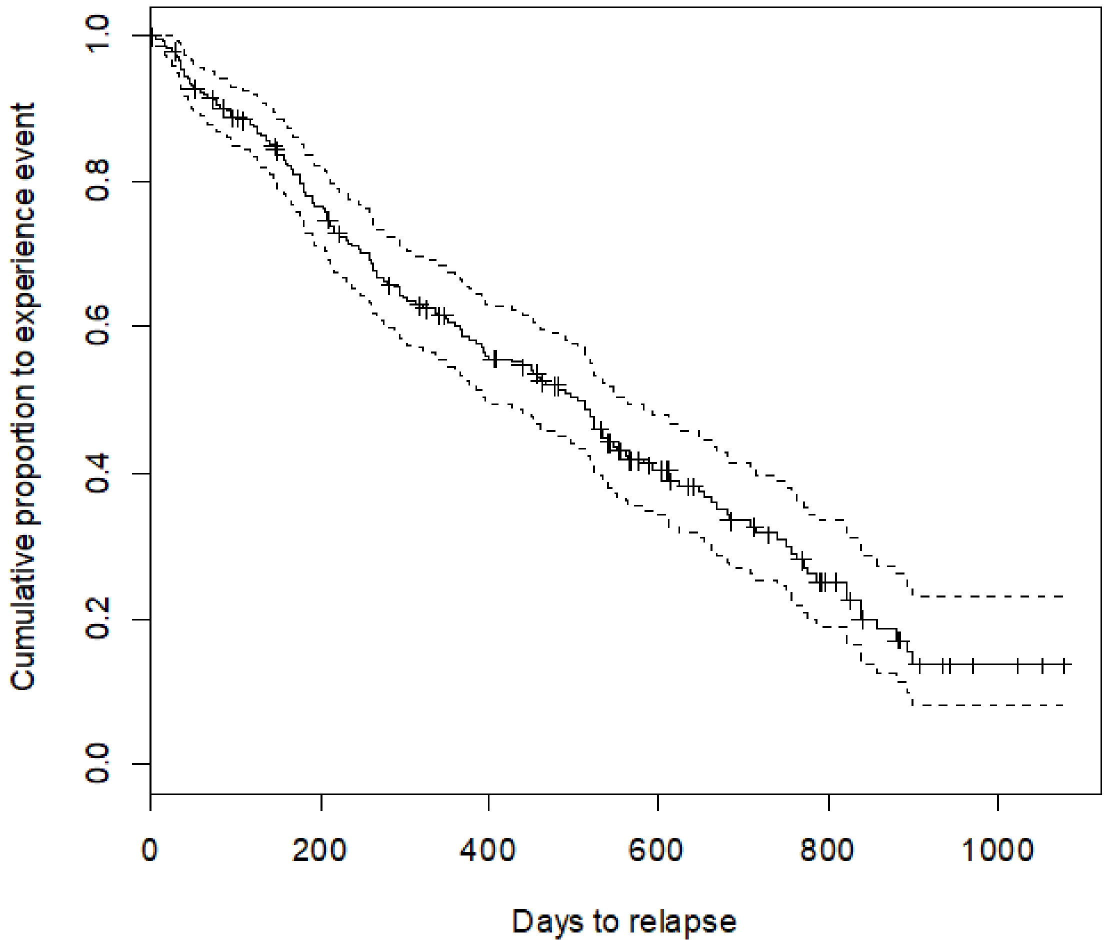
Time	Fail prob $q_i = d_i / [n_i - (w_i/2)]$	Surv prob $p_i = 1 - q_i$	Cum surv
0 to 1	0.10	0.90	0.90
2 to 3	0.09	0.91	$0.91 \times 0.90 = 0.92$
etc			

Non-parametric survival functions

- Life-table (Cutler-Ederer) method
  - assumes that subjects are withdrawn randomly throughout each interval – therefore, on average, they are withdrawn half way through the interval
  - this is not an important issue when the time intervals are short, but bias may introduced when time intervals are long
  - often used to produce life tables from large scale population surveys (e.g. death registers)
  - not often used these days

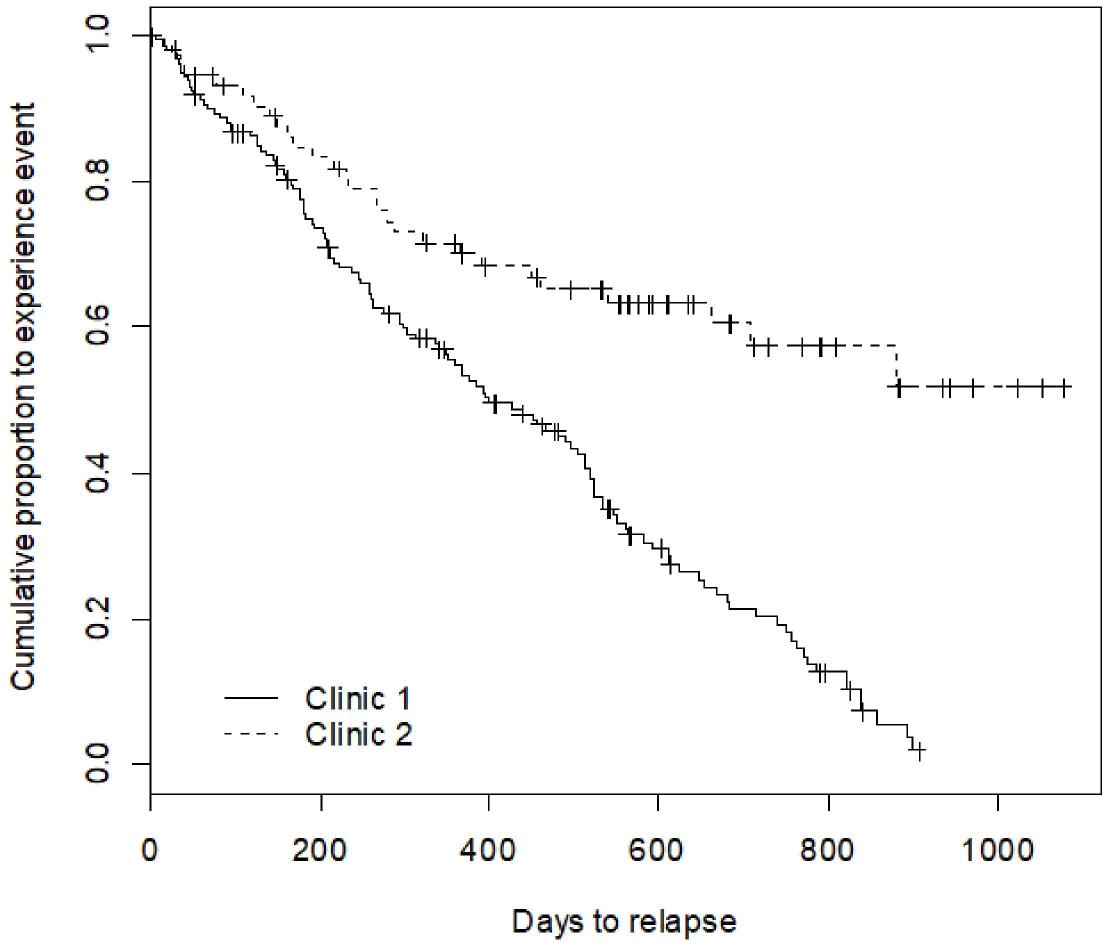
Non-parametric survival functions

- Caplehorn and others (1991)
  - compared retention in two methadone treatment clinics for heroin addicts
  - a patient's ‘survival’ time was determined as the time in days until the patient dropped out of the clinic or was censored at the end of the study
  - the two clinics differed according to their overall treatment policies
  - reference: Caplehorn J et. al. (1991). Methadone dosage and retention of patients in maintenance treatment. Medical Journal of Australia, 154:195 - 199.




```
library(survival); setwd(("D:\\temp")
dat <- read.table("addict.csv", header = TRUE, sep = ",");

addict.km <- survfit(Surv(stop, status) ~ 1, conf.type = "none",
type = "kaplan-meier", data = dat);
plot(addict.km, xlab = "Days to relapse", ylab = "Cumulative
proportion to experience event");
```




```
library(survival); setwd(("D:\\temp")
dat <- read.table("addict.csv", header = TRUE, sep = ",")

addict.km <- survfit(Surv(stop, status) ~ clinic, type = "kaplan-
meier", data = dat)
plot(addict.km, xlab = "Days to relapse", ylab = "Cumulative
proportion to experience event", lty = c(1,2), legend.text =
c("Clinic 1","Clinic 2"), legend.pos = 0, legend.bty = "n")
```

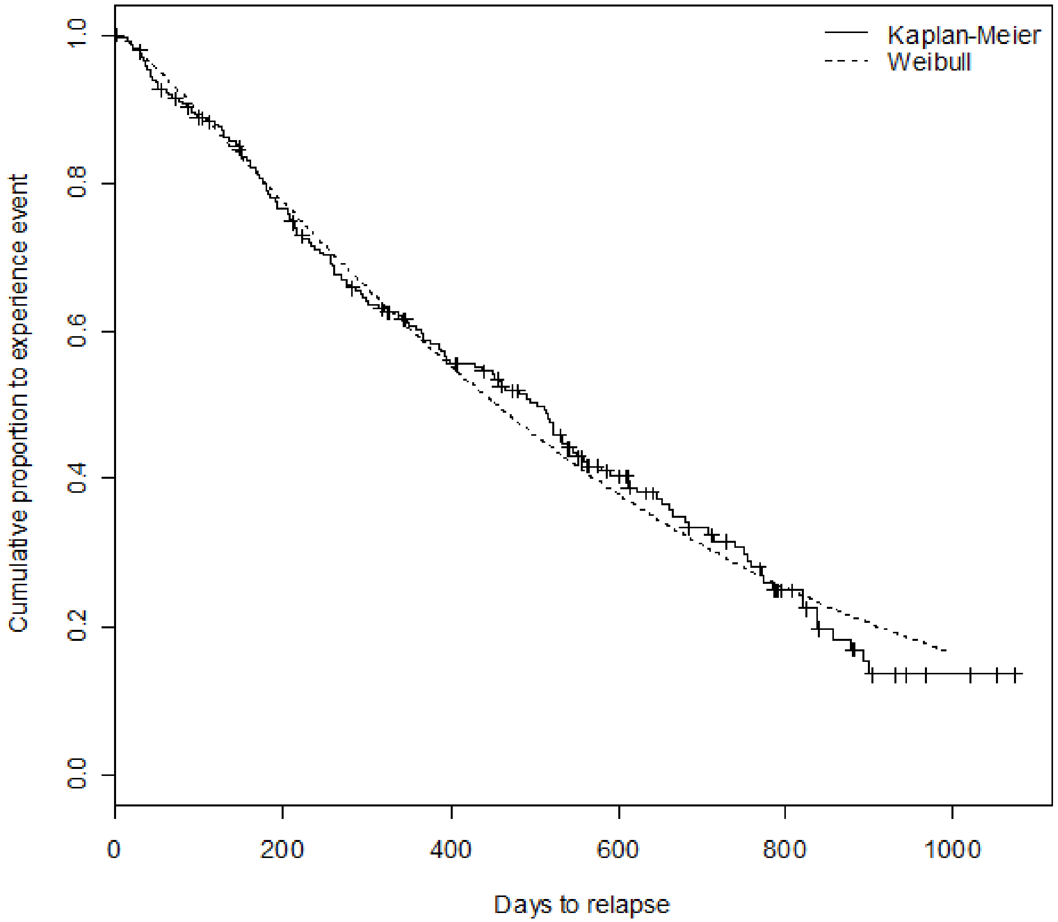
Comparison of Kaplan-Meier and Weibull estimates of survival:

```
library(survival); setwd(("D:\\temp")
dat <- read.table("addict.csv", header = TRUE, sep = ",")

addict.we <- survreg(Surv(stop, status) ~ 1, dist = "weib", data =
dat)
addict.km <- survfit(Surv(stop, status) ~ 1, conf.type = "none",
type = "kaplan-meier", data = dat)
```

Using the Weibull distribution μ (the intercept) = -log(λ) and σ (scale) = 1 / p. Thus the scale parameter λ = exp(-μ) and p = 1 / σ. See Tableman and Kim p 78.

```
p <- 1 / addict.we$scale
lambda <- exp(-addict.we$coeff[1])
t <- 1:1000
St <- exp(-(lambda * t)^p)
addict.we <- as.data.frame(cbind(t = t, St = St))
```




```
plot(addict.km, xlab = "Days to relapse", ylab = "Cumulative
proportion to experience event")
lines(addict.we$t, addict.we$St, lty = 2)
legend(x = "topright", legend = c("Kaplan-Meier", "Weibull"), lty =
c(1,2), bty = "n")
```

Non-parametric survival functions

- We conclude that the Weibull distribution provides an adequate fit to the observed data up to day 500, then it tends to underestimate survivorship

Roadmap

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Presentation

- Presentation of survival curves:
  - should be vertical step
  - good idea to mark censoring points
  - curves often become unstable at end of study period
  - good idea in figure title to quote number of events and number of censored observations
  - y-axis: "*Cumulative proportion to experience ...*"
  - x-axis: *"PSM to conception (days)"*

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