Lecture sixteen: Parametric PH Models: The Weibull and Gompertz PH models

1. The Weibull PH model (cont.)

   (a) Survival, hazard, and density functions

   Unlike in the Cox models, survival, hazard and density functions are determined if the parameters are estimated, say, $\hat{\beta}_1, \hat{\beta}_2, \ldots, \hat{\beta}_p, \hat{\lambda}$ and $\hat{\gamma}$. The hazard and survival functions are

   $$\hat{h}_i(t) = exp(\hat{\beta}_1 x_{i1} + \hat{\beta}_2 x_{i2} + \ldots + \hat{\beta}_p x_{ip})\hat{\lambda}\hat{\gamma}t^{\hat{\gamma}-1},$$

   and

   $$\hat{S}_i(t) = exp\{-\hat{\lambda}exp(\hat{\beta}' x_i)t^{\hat{\gamma}}\}.$$

   and the pth percentile

   $$\hat{t}_i(p) = [\frac{1}{\hat{\lambda}_i} log\,(\frac{100}{100-p})]^{1/\hat{\gamma}}.$$

   where $\hat{\lambda}_i = \hat{\lambda}exp(\hat{\beta}' x_i)$. The variance of $\hat{t}_i(p)$ can be obtained by the general delta-method ((5.50) on page 178). See equation (5.52) on page 179.

   Given the particular values of the covariates, these functions can be plotted against survival time t.

   (b) Exploratory analyses

   log-cumulative hazard plot can be used to assess PH assumption in Weibull model.

   i. Factors
   ii. Continuous variables
   iii. Ignore some of the factors (or continuous variables)?

   If there are too many groups, then some of them will end up with insufficient number of individuals for valid estimate of survival.

   iv. Example 5.9: numerical illustration based on an artificial dataset

```
/* log-cumulative hazard plot stratified by A */
options ls=80;
libname fu '../../sdata';
data fu.t51;
infile '../../data/t51.dat';
input st A B censor;
filename x1 'ex59a.pdf';
goptions reset=all gunit=pct border ftext=swissb htitle=6
htext=2.5 gsfname=x1 ROTATE=LANDSCAPE gsfmode=replace device=pdf;
title1 'Log-cumulative hazard plot: A';
symbol1 c=black i=join v=triangle height=3;
symbol2 c=blue i=join v=star height=3;
proc lifetest  notable plot = (lls) method=pl;
        time st*censor(0);
        strata A;
run;
/* log-cumulative hazard plot stratified by B:
                              Similar to A. Omit it here */
/* log-cumulative hazard plot by levels of A & B */
options ls=80;
libname fu '../../sdata';
data w;
        set fu.t51;
filename x2 'ex59ab.pdf';
goptions reset=all gunit=pct border ftext=swissb htitle=6
htext=2.5 gsfname=x2 ROTATE=LANDSCAPE gsfmode=replace device=pdf;
title1 'Log-cumulative hazard plot: A & B';
symbol1 c=black i=join v=triangle height=3;
symbol2 c=blue i=join v=star height=3;
symbol3 c=green i=join v=circle height=3;
symbol4 c=red i=join v=dot height=3;
proc lifetest  notable plot = (lls) method=pl;
        time st*censor(0);
        strata A B;
run;
```

Why the log-cumulative hazard plot for B ignoring A is misleading?

```
# Check interaction between A and B: Splus program
ex58.s <- function(){
        tmpdf <- importData("../../sdata/t51.sas7bdat")
        trellis.device(motif)
        attach(tmpdf)
        interaction.plot(a, b, st, xlab="Factor A",
            ylab="Mean of survival times", lty=1:2, col=c(3,4),
            trace.label="Factor B")
        detach()
}
```

v. Checking the validity of the adequacy of the fitted models (Cox model: chapter 4, parametric (Weibull) models: chapter 7).

2. Comparing alternative Weibull models

   Use the methods similar to the ones for the Cox PH model. The differences are that, in the Weibull model, the baseline hazard is known, and also the **likelihood** rather than the **partial likelihood** is used.

   (a) Example 5.10: Kidney cancer study (Table 3.6)

      i. sas program

```
options ls = 80 nodate;
libname fu '../../sdata';
data work;
        set fu.kidney;
        if age = 2 then A2 = 1; else A2 = 0;
        if age = 3 then A3 = 1; else A3 = 0;
        A2N=A2*neph;
        A3N=A3*neph;
proc lifereg;
        model survt*censor(0)= / covb dist=weibull;
proc lifereg;
        model survt*censor(0)= A2 A3 / covb dist=weibull;
proc lifereg;
        model survt*censor(0)= neph / covb dist=weibull;
proc lifereg;
        model survt*censor(0)= neph A2 A3 / covb dist=weibull;
```

```
proc lifereg;
        model survt*censor(0)= A2 A3 neph A2N A3N
                                / covb dist=weibull;
run;
```

ii. The log-likelihood

In the sas output from PROC LIFEREG, $log\,\hat{L}$ rather than $-2log\,\hat{L}$ is reported.

Table 1: Example 5.10: values of $-2log\,\hat{L}$ on five models

Terms in model	variables in model	$-2log\,\hat{L}$
null model (1)	none	104.886
α_j (2)	A2, A3	96.4
ν_k (3)	N	96.384
$\alpha_j + \nu_k$ (4)	A2, A3, N	87.758
$\alpha_j + \nu_k + (\alpha\nu)_{jk}$ (5)	A2, A3, N, A2N, A3N	83.064

iii. Interaction?

Comparing model (4) and (5), using Weibull model: p = 0.096 (some degree of interaction); using Cox model: p = 0.22 (no interaction).

iv. The estimates for model (5)

Analysis of Parameter Estimates

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr>ChiSq
Intercept	1	2.5590	0.3727	1.8285	3.2894	47.15	<.0001
A2	1	0.0548	0.5259	-0.9759	1.0855	0.01	0.9170
A3	1	-0.0741	0.7437	-1.5317	1.3836	0.01	0.9207
NEPH	1	1.5676	0.4095	0.7649	2.3702	14.65	0.0001
A2N	1	-0.0781	0.6056	-1.2649	1.1088	0.02	0.8974
A3N	1	-1.6334	0.8283	-3.2568	-0.0100	3.89	0.0486
Scale	1	0.6436	0.0938	0.4837	0.8563		
Weibull Shape	1	1.5538	0.2264	1.1678	2.0674		

Don't forget to convert the estimates in terms of β, λ and γ

when calculate the hazard ratio.

v. hazard ratios

Table 2: Example 5.10, hazard ratios, Table 5.4 at page 186

Age-group	No nephrectomy	Nephrectomy
< 60	1	0.09
$60 - 70$	0.92	0.09
> 70	1.12	1.24

vi. Median survival times

Table 3: Example 5.10, median survival times, Table 5.5 at page 186

Age-group	No nephrectomy	Nephrectomy
< 60	10.21	48.94
$60 - 70$	10.78	47.81
> 70	9.48	8.87

(b) Example 5.11: The ovarian cancer study

```
SURVT: survival time in days,        CENS: censoring indicator
TREAT: treatment, Surgery + chemotherapy (1: single, 2: combined)
AGE: age of patient in years
RDISEASE: extent of residual disease (1: imcomplete, 2: complete)
PERF: performance status (1: good, 2: poor)
```

i. sas program

```
options ls = 80 nodate;
libname fu '../../sdata';
data fu.ovarian;
infile '../../data/ovarian.dat';
input id survt cens treat age rdisease perf;
data w;
        set fu.ovarian;
treat = treat - 1;
trtage = treat * age;
proc lifereg;
```

```
        model survt*cens(0) = age treat /covb dist=weibull;
proc lifereg;
        model survt * cens (0) = /covb dist = weibull;
proc lifereg;
        model survt * cens (0) = age /covb dist = weibull;
proc lifereg;
        model survt * cens (0) = rdisease /covb dist = weibull;
proc lifereg;
        model survt * cens (0) = perf /covb dist = weibull;
proc lifereg;
        model survt*cens(0)=age rdisease /covb dist = weibull;
proc lifereg;
        model survt * cens (0) = age perf /covb dist = weibull;
proc lifereg;
        model survt * cens (0) = age treat trtage
                                          /covb dist = weibull;
run;
```

ii. The Log-likelihood for various models

Table 4: Example 5.11: Table 5.7

Variables in model	$-2log\,\hat{L}$
null model (1)	59.534
TREAT (2)	58.354
AGE (3)	43.566
RDISEASE (4)	55.382
PERF (5)	58.849
AGE, RDISEASE (6)	41.663
AGE, PERF (7)	43.518
AGE, TREAT (8)	41.126
AGE, TREAT, TREAT * AGE (9)	39.708

In the univariate analysis, both AGE and RDISEASE are significant (likelihood ratio test), but RDISEASE is not significant from Wald test ($p = 0.074$). By comparing model (3) and (6), we conclude that only AGE is important variable. Interaction: Is treatment difference consistent over age?

iii. sas output for model (8)

Analysis of Parameter Estimates

Parameter	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr>ChiSq
Intercept	1	10.9868	1.2763	8.4853	13.4884	74.10	<.0001
AGE	1	-0.0790	0.0198	-0.1177	-0.0402	15.97	<.0001
TREAT	1	0.5615	0.3399	-0.1048	1.2277	2.73	0.0986
Scale	1	0.5489	0.1291	0.3461	0.8705		
Weibull Shape	1	1.8218	0.4286	1.1487	2.8891		

What's the hazard ratio for the two treatments?

3. The Gompertz PH model

$$f(t) = \lambda e^{\theta t} exp[\frac{\lambda}{\theta}(1 - e^{\theta t})],$$

where $\lambda, \theta > 0, t \geq 0$.

$$S(t) = exp[\frac{\lambda}{\theta}(1 - e^{\theta t})],$$

what if $\theta < 0$?(Cure rate, Ref.: *Survival Analysis with Long-Term Survivors, Maller; Zhou, 1996*)

$$h(t) = \lambda e^{\theta t},$$

The hazard of death is to increase or decrease with time.

(a) the median survival time

$$t(50) = \frac{1}{\theta} log\{1 + \frac{\theta}{\lambda} log\, 2\}.$$

(b) Plot: hazard function (see Splus function gompertz.s on the website)

(c) The proportional hazards property
If $h_0(t) = \lambda e^{\theta t}$, then $\psi h_0(t)$ is Gompertz hazard function with parameter $\psi\lambda$ and θ.

(d) The general Gompertz PH model

$$h_i(t) = exp(\beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip})\lambda e^{\theta t},$$

(e) MLE and Software: Not available in SAS LIFEREG.

(f) Example 5.12: Ovarian cancer - Gompertz PH model

SAS program:

```
options ls = 78 nodate;
libname fu '../../sdata';
data w;
        set fu.ovarian;
/* Age alone */
proc nlmixed data = w;
parms lambda = 0.00002 theta = 0.0016 beta1 = 0;
        xb = beta1 * age;
        phi = exp(xb);
        St = exp((lambda * phi / theta)*(1 - exp(theta * survt)));
        ft = lambda * phi * exp(theta * survt) * St;
        ll = (cens = 1) * log(ft) + (cens = 0) * log(St);
        model ll ~ general(ll);
/* age and treatment (treat) */
proc nlmixed data = w;
parms lambda = 0.00002 theta = 0.0016 beta1 = 0 beta2 = 0.3;
        xb = beta1 * age + beta2 * treat;
        phi = exp(xb);
        St = exp((lambda * phi / theta)*(1 - exp(theta * survt)));
        ft = lambda * phi * exp(theta * survt) * St;
        ll = (cens = 1) * log(ft) + (cens = 0) * log(St);
        model ll ~ general(ll);
run;
```

Part of SAS output:

Parameter Estimates

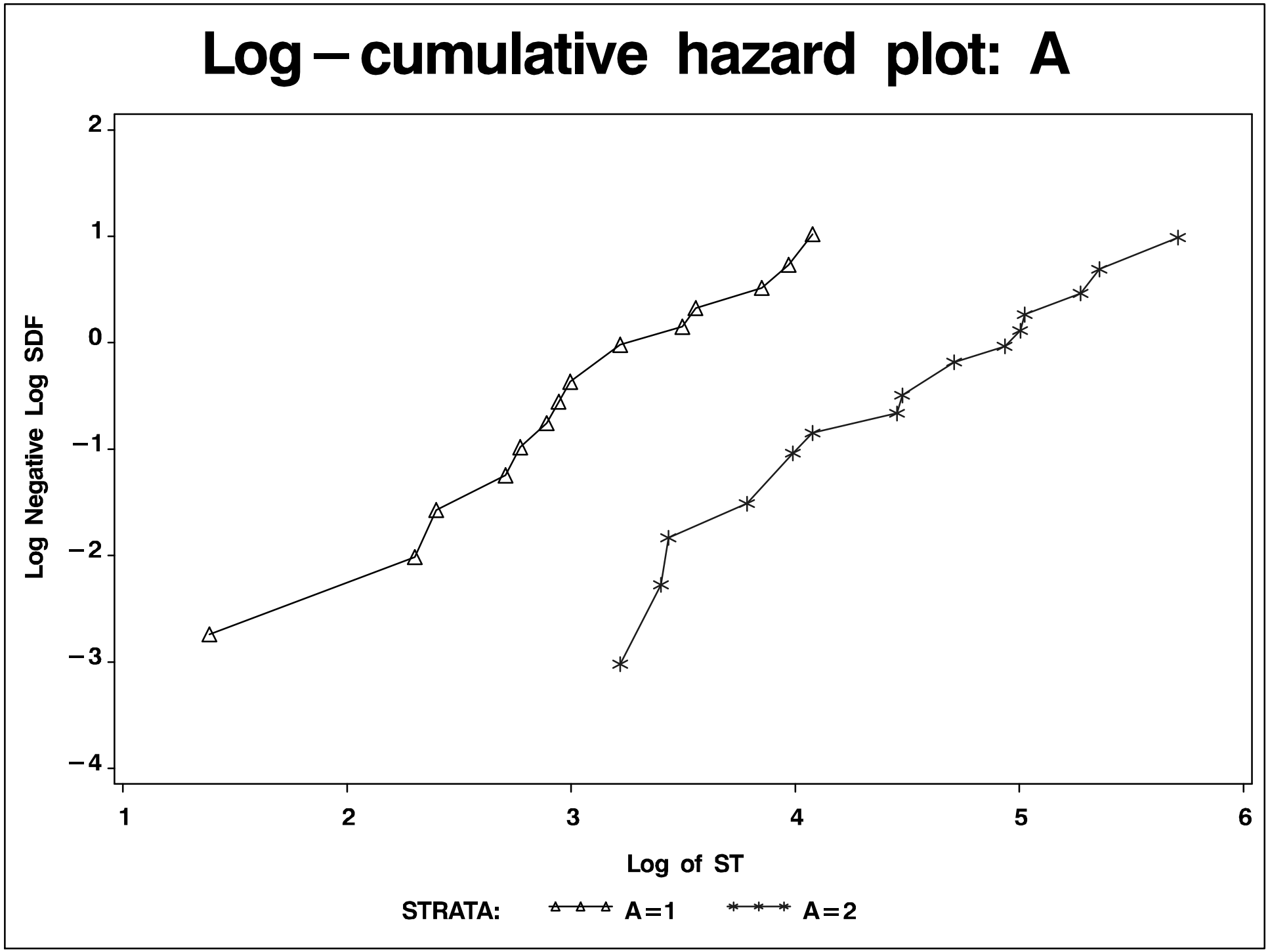
Parameter	Estimate	Standard Error	DF	t Value	Pr > |t|
lambda	1.706E-6	.	26	.	.

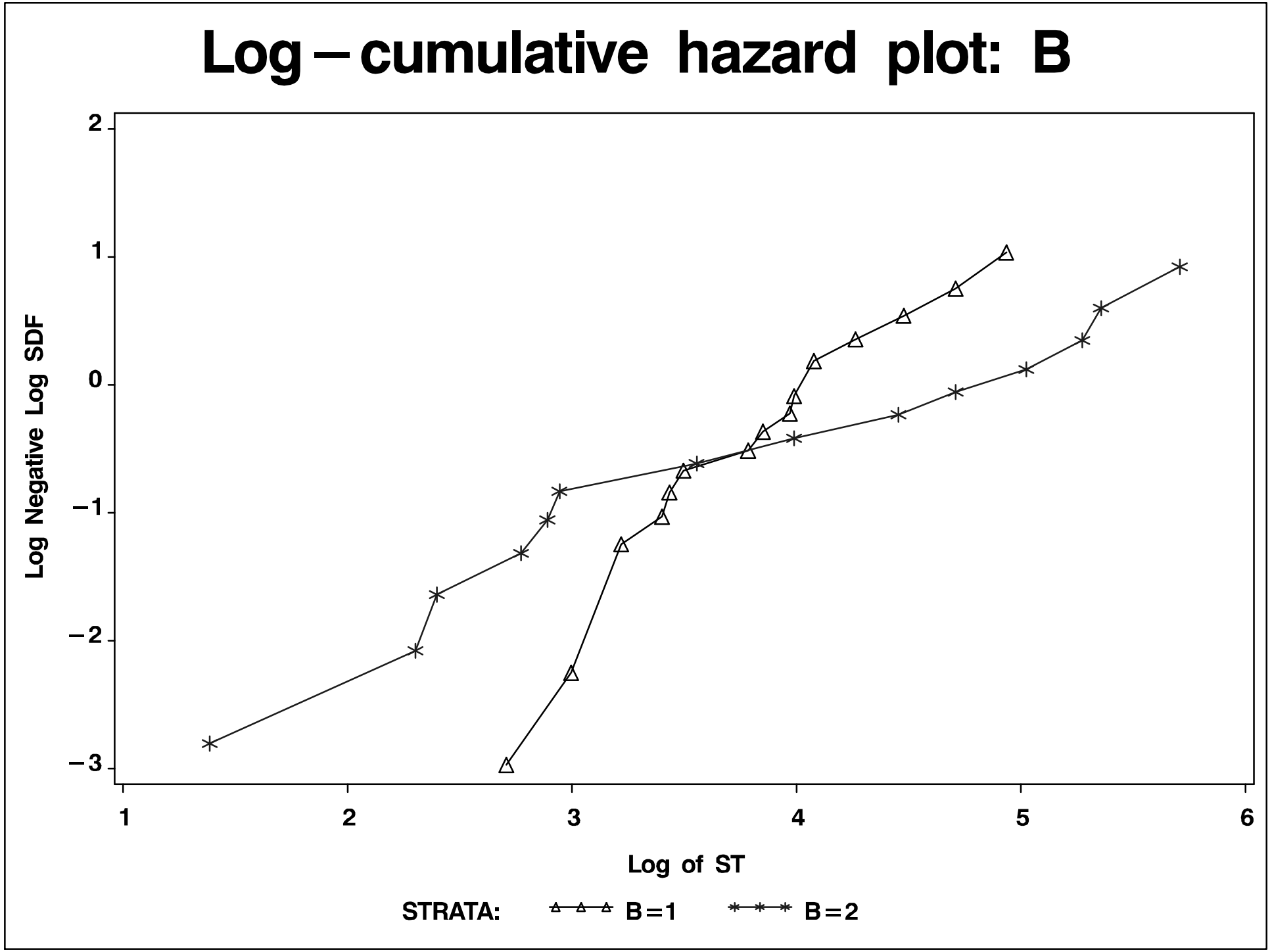
theta	0.001377	0.001053	26	1.31	0.2023
beta1	0.1222	0.008692	26	14.05	<.0001
beta2	-0.8482	0.5942	26	-1.43	0.1653

Corrections:
page 189, line 3 from bottom, 1.686 (P = 0.184) should be 1.7 (P = 0.192)
page 155, line 3 from bottom, $f(t)$ should be

$$f(t) = (\frac{\lambda}{2\pi t^3})^{1/2} exp\{\frac{\lambda(t-\mu)^2}{2\mu^2 t}\},$$

Assignment nine: Using Weibull proportional hazards model to fit the data of recurrence of bladder cancer (Table B.2, page 501). Provide your program and output of your program. Calculate the hazard ratio between two treatment groups (i.e. placebo versus thiotepa) and its 95% confidence interval and interpret your results.


Log – cumulative hazard plot: A
Log Negative Log SDF
2
1
0
−1
−2
−3
−4
1
2
3
4
5
6
Log of ST
STRATA:
A=1
A=2


Log – cumulative hazard plot: B
Log Negative Log SDF
2
1
0
−1
−2
−3
1
2
3
4
5
6
Log of ST
STRATA:
B=1
B=2

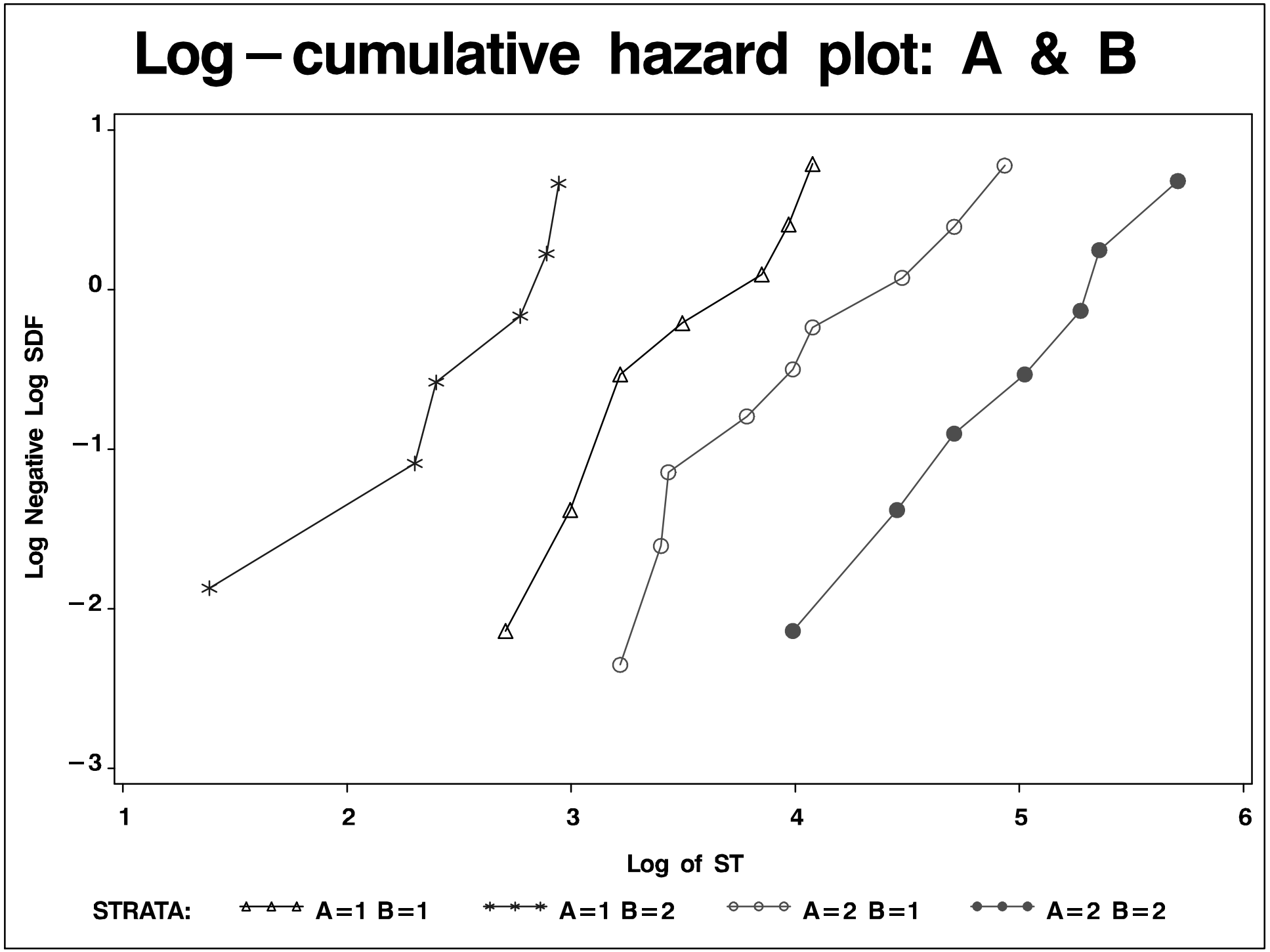

Log – cumulative hazard plot: A & B
Log Negative Log SDF
1
0
−1
−2
−3
1
2
3
4
5
6
Log of ST
STRATA:
A=1 B=1
A=1 B=2
A=2 B=1
A=2 B=2

Figure 4:

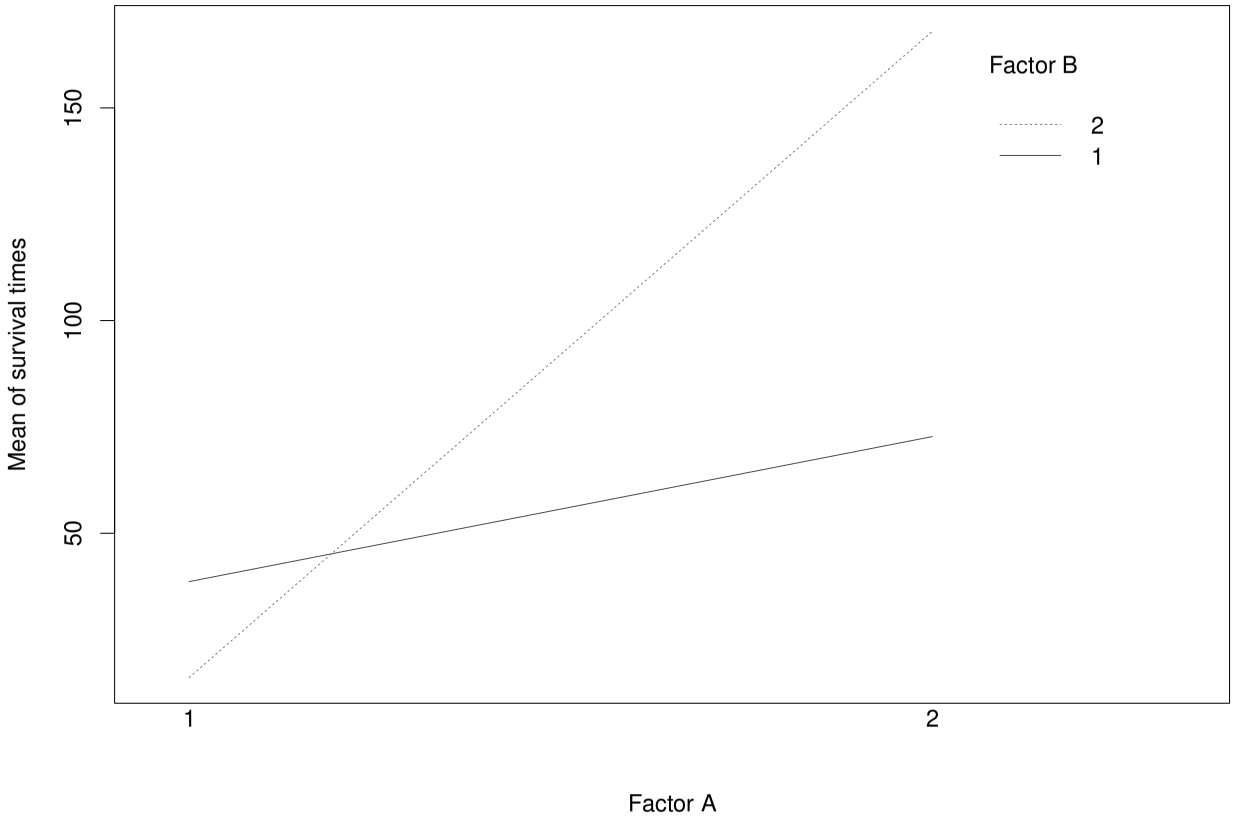
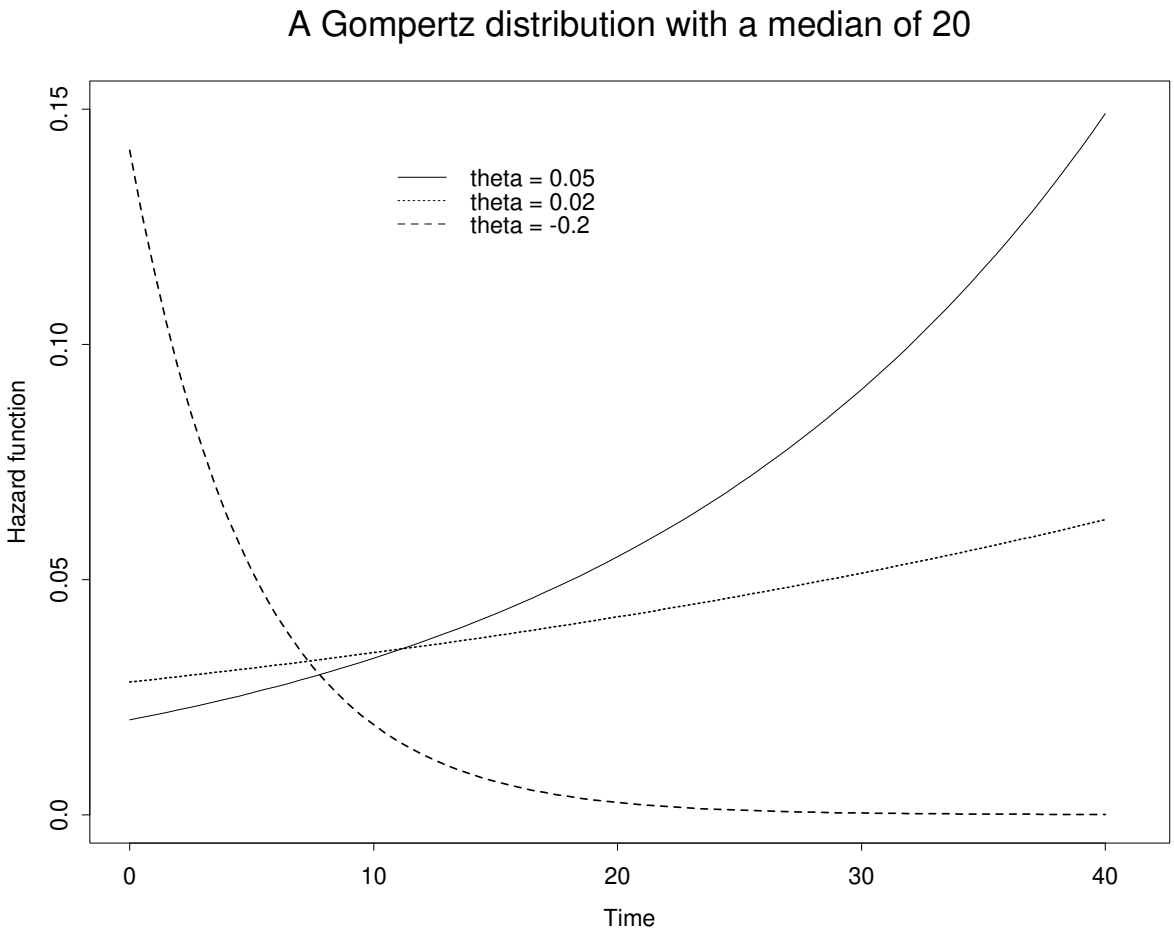


Figure 5:


A Gompertz distribution with a median of 20
Hazard function
0.0
0.05
0.10
0.15
theta = 0.05
theta = 0.02
theta = -0.2
0
10
20
30
40
Time