Lecture nineteen: Fitting and comparing the AFT Models

1. Log-linear form of the AFT model (cont.)

   The log transformation of survival times is used by default in the SAS PROC LIFEREG, namely

   $$log\, T_i = \mu + \alpha_1 x_{1i} + \ldots + \alpha_p x_{pi} + \sigma\epsilon_i.$$

   Thus, the output is in terms of parameterization of μ, α and σ.

   (a) For Weibull distribution, the relation between two sets of parameters (PH and AFT) is (page 179 and 199)

   $$\lambda = exp(-\mu/\sigma), \qquad \gamma = \sigma^{-1}, \qquad \beta_j = -\alpha_j/\sigma,$$

   (b) For log-logistic distribution (θ, κ and μ, σ)

   Assume ϵ has $logistic(\theta = 0, \kappa = 1)$ distribution with density $f(\epsilon) = \frac{e^\epsilon}{(1+e^\epsilon)^2}$, and $S(\epsilon) = \frac{1}{1+e^\epsilon}$, then the survival function under log-linear model is

   $$\begin{aligned} S_i(t) = P(T_i \geq t) & \\ &= P(log\, T_i \geq logt) \\ &= P(\epsilon_i \geq \frac{log\, t - \mu - \alpha_1 x_{1i} - \ldots - \alpha_p x_{pi}}{\sigma}) \\ &= [1 + exp\{\frac{log\, t - \mu - \alpha_1 x_{1i} - \ldots - \alpha_p x_{pi}}{\sigma}\}]^{-1} \end{aligned}$$

   Under another parameterization and AFT model,

   $$S_i(t) = \frac{1}{1 + e^{\theta - \kappa\eta_i} t^\kappa}$$

   where $\eta_i = \alpha_1 x_{1i} + \ldots + \alpha_p x_{pi}$. Thus,

   $$\theta = -\mu/\sigma, \qquad \kappa = \sigma^{-1}.$$

   (c) We can get the relations in similar derivation for other distributions (see also Table 6.2, and Table 6.3 in the 3rd edition).

(d) In order to interpret the parameter estimates, it is important to know how the model is parameterized.

2. Fitting the AFT models

   (a) The likelihood approach (see section 5.13 for details)

$$L(\alpha, \mu, \sigma) = \prod_{i=1}^{n} f_i^{\delta_i}(t_i) S_i^{1-\delta_i}(t_i)$$

   (b) Checking the AFT assumption

      i. AFT is a very strong assumption: $S_1(t) = S_0(t/\phi)$.

      ii. If a covariate is categorical

         A. plotting survival cures (KM estimates) for each stratum: 1) no crossing, 2) departing farther with time before converging.

         B. without censoring (or small portion of censoring): QQ-plot of one sample versus another - straight line.

         C. With censoring: PP-plot based on the percentiles of KM estimate of survival (see the example in lecture notes 18).

      iii. If covariate is continuous:

         A. plot residuals vs fitted value

         B. plot residuals vs each covariates

      iv. Residuals (Cox-Snell, martingale) can be defined from the fitted survival function, but they are not in the **PROC lifereg** output (SAS).

      Deviance residuals are available in output of Splus function **survreg() and censorReg()**.

3. Example 5.14: Prognosis for women with breast cancer

   (a) Under Weibull (PH and AFT):

```
Model Information

Dependent Variable              Log(SURVT)
Name of Distribution               WEIBULL
Log Likelihood                -60.88396152
```

Analysis of Parameter Estimates

Variable	DF	Estimate	Standard Error	Chi-Square	Pr > ChiSq	Label
Intercept	1	5.85436	0.49888	137.7124	<.0001	Intercept
GROUP	1	-0.99666	0.54409	3.3555	0.0670	
Scale	1	1.06678	0.17855			Extreme value scale

Notice that $\lambda = exp(-\mu/\sigma)$, $\gamma = \sigma^{-1}$, $\beta_j = -\alpha_j/\sigma$ (page 238 under PH assumption). We have

$\hat{\lambda} = exp(-5.85/1.06678) = 0.00415$
$\hat{\gamma} = 1.06678^{-1} = 0.937$
$\hat{\beta} = 0.99666/1.06678 = 0.934$
The estimated hazard ratio under PH model is: $e^{\hat{\beta}} = e^{0.934} = 2.55$
The estimated median survival time (Use expression (5.69)): 236 days (HPA-) and 87 days (HPA+)
The estimated acceleration factor: $e^{-\hat{\alpha}} = 2.71$

(b) Under log-logistic:

Model information

Dependent Variable	Log(SURVT)
Name of Distribution	LLOGISTC
Log Likelihood	-59.24726035

****

Analysis of Parameter Estimates

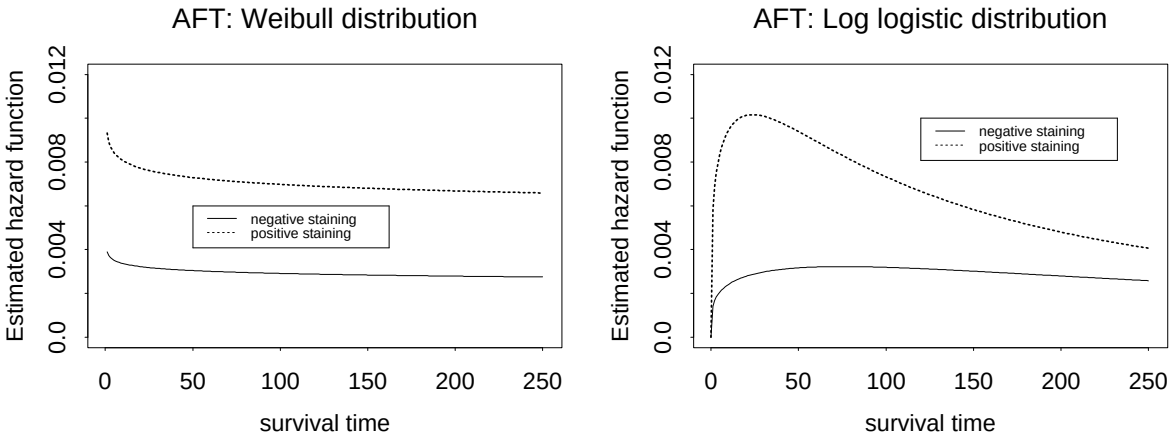
Variable	DF	Estimate	Standard Error	Chi-Square	Pr > ChiSq	Label
Intercept	1	5.46110	0.46037	140.7193	<.0001	Intercept
GROUP	1	-1.14906	0.52022	4.8787	0.0272	
Scale	1	0.80470	0.13298			Logistic scale

Notice that $\theta = -\mu/\sigma$, $\kappa = \sigma^{-1}$. We have

$\hat{\theta} = -5.46/0.805 = -6.783$
$\hat{\kappa} = 0.805^{-1} = 1.242$
$\hat{\alpha} = -1.149$
The estimated acceleration factor is $e^{-\hat{\alpha}} = 3.16$
The estimated median survival time (see expression (5.72)): 235 days (HPA-) and 75 days (HPA+).

(c) Figures:

Figure 1:



(d) Which one to choose? (Check residuals)

(e) SAS program:

```
options pagesize=60 linesize=79 nodate nonumber;
libname fu '../../sdata';
data work;
        set fu.hpa;
proc lifereg;
        model survt*censor(0) = group/distribution = weibull;
proc lifereg;
        model survt*censor(0) = group/distribution = llogistic;
run;
```

4. Example 5.15: Prostatic cancer study

   (a) SAS program: available at the course website.

   (b) The parsimonious model

Table 1: Values of $-2log\,\hat{L}$ for models excluding treatment

Terms in model	$-2log\,\hat{L}$
null model	35.806
AGE	35.752
SHB	35.700
SIZE	27.754
INDEX	27.965
AGE+SHB	35.657
AGE+SIZE	27.652
AGE+INDEX	27.859
SHB+SIZE	27.722
SHB+INDEX	26.873
SIZE+INDEX	23.112
AGE+SHB+SIZE	27.631
AGE+SHB+INDEX	26.870
AGE+SIZE+INDEX	23.002
SHB+SIZE+INDEX	22.895
AGE+SHB+SIZE+INDEX	22.727

Analysis of Parameter Estimates

Variable	DF	Estimate	Standard Error	Chi-Square	Pr > ChiSq	Label
Intercept	1	7.08815	1.63311	18.8380	<.0001	Intercept
SIZE	1	-0.02893	0.01864	2.4086	0.1207	
INDEX	1	-0.29272	0.15110	3.7528	0.0527	
TREAT	1	0.57266	0.47254	1.4686	0.2256	
Scale	1	0.33831	0.11750			Logistic scale

The fitted hazard function from the final model is

$$\hat{h}_i(t) = e^{-\hat{\eta}_i}\hat{h}_0(e^{-\hat{\eta}_i}t),$$

where

$$\hat{\eta}_i = -0.029SIZE_i - 0.293INDEX_i + 0.573TREAT_i$$

(c) Interpretation of treatment effect Controling other factors, the estimated 'relative' acceleration factor is $e^{-0.573} = 0.56$, the effect of the treatment with DES is to slow down the progression of the cancer by a factor of about 2.

5. The proportional odds model

(a) The model

$$\frac{S_i(t)}{1 - S_i(t)} = e^{\eta_i}\frac{S_0(t)}{1 - S_0(t)},$$

where

$$\eta_i = \beta_1 x_{1i} + \ldots + \beta_p x_{pi}$$

(b) The covariates act multiplicatively on the odds of survival beyond t.

(c) The log-odd ratio is simply β if consider treatment only.

(d) The hazard ratio $h_i(t)/h_0(t)$ converges unity when t tends to infinity.

(e) It makes sense in practical applications: The difference of treatment effect wears off over time.

(f) 1) Software is not generally available; 2) give similar results to Cox model that include a time-dependent covariate.

(g) The log-logistic proportional odds model

i. The proportional odds property: If assume survival time has a log-logistical distribution, then

$$S_0(t) = [1 + e^{\theta} t^{\kappa}]^{-1}$$

and

$$\frac{S_0(t)}{1 - S_0(t)} = e^{-\theta} t^{-\kappa}.$$

Thus, for the ith individual under proportional odds model

$$\frac{S_i(t)}{1 - S_i(t)} = e^{\eta_i - \theta} t^{-\kappa}.$$

Thus, the survival time of the ith individual has a log-logistic distribution with parameters $\theta - \eta_i$ and κ.

ii. The log-logistic distribution is the only parametric distribution with both a proportional odds and an AFT representation (Klein and Moeschberger).

iii. The relationship between two sets of parameters:

Let the survival functions under AFT and proportional odds equal, i.e.

$$[1 + e^{\theta - \kappa\alpha' x_i} t^{\kappa}]^{-1} = [1 + e^{\tilde{\theta} - \beta' x_i} t^{\tilde{\kappa}}]^{-1},$$

then we have $\tilde{\kappa} = \kappa$, $\tilde{\theta} = \theta$, and $\beta = \kappa\alpha$. Recall $\kappa = \sigma^{-1}$.

iv. For other proportional odds models, see section 6.9; SAS/JMP?

v. EDA (exploratory Data Analysis): The log-odds is

$$log\{\frac{S_i(t)}{1 - S_i(t)}\} = \eta_i - \theta - \kappa log\, t,$$

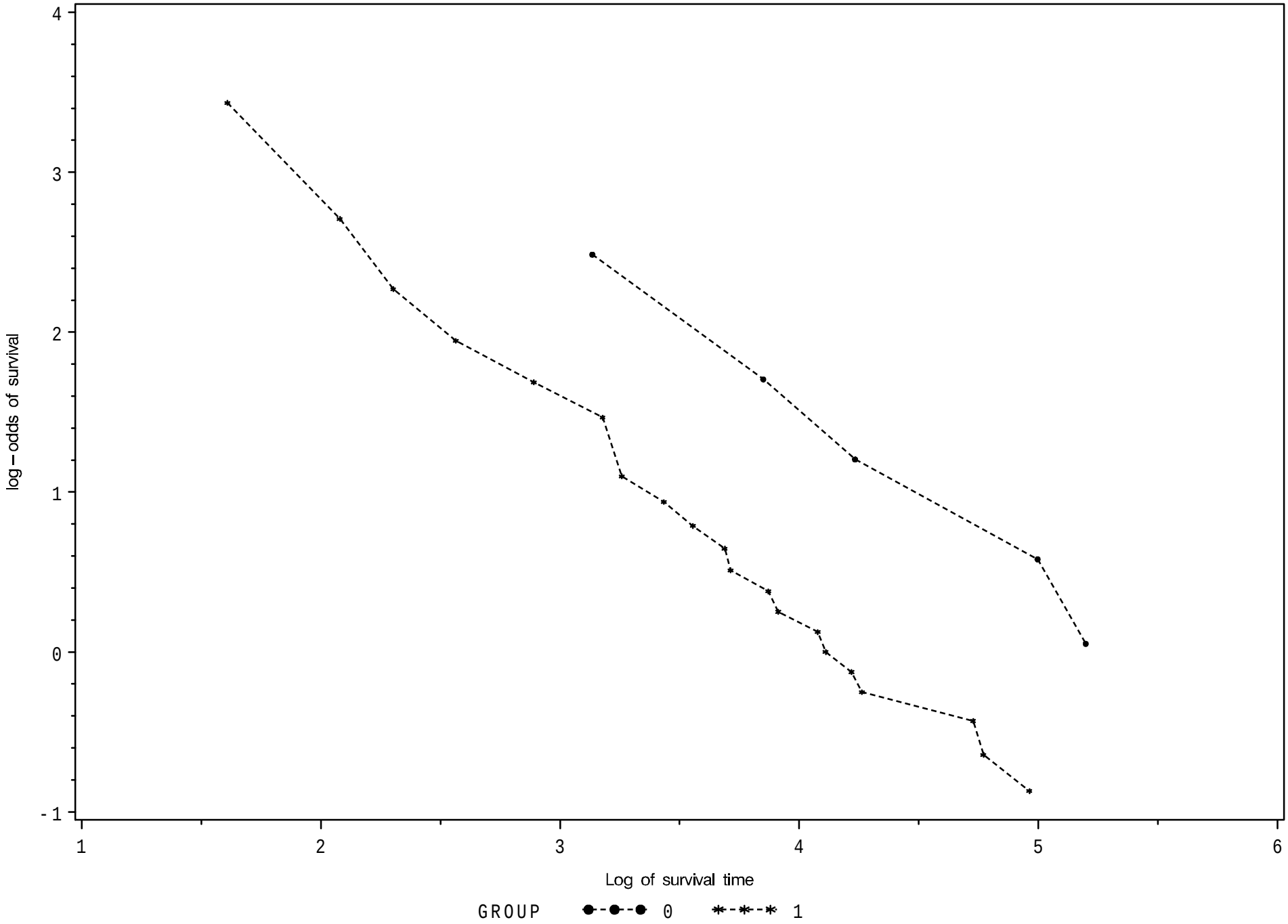
vi. Example 5.17 (Breast cancer study): Plot - log-odds of survival vs log of survival time.

vii. The estimated value of β in the linear component of the proportional odds model is $\hat{\beta} = \hat{\kappa}\hat{\alpha} = -1.149 * 1.243 = -1.428$. The corresponding odds ratio is $exp(-1.428) = 0.24$, so that the odds of a woman with negatively stained tumor surviving beyond t are four times of that of women with positively stained tumor.

viii. Example 5.17: SAS program

```
options pagesize=60 linesize=78 nodate nonumber;
libname fu '../../sdata';
data work;
        set fu.hpa;
filename x 'loddshpa.pdf';
goptions gsfname=x ROTATE=LANDSCAPE gsfmode=append device=pdf;
proc lifetest plots=(lls) method =km outsurv=tmp;
        time survt*censor(0);
        strata group;
data work1;
        set tmp;
        if survt = 0 or survival = 0 or survival = 1 then delete;
        if _CENSOR_ = 1 then delete;
        logodds = log(survival/(1-survival));
        logt = log(survt);
proc reg;
        model logodds = logt;
axis1 label=(h=1 f=swiss 'Log of survival time') minor=(n=1);
axis2 label=(h=1 f=swiss a=90 'log-odds of survival') minor=(n=4);
symbol1 c=black i=join l=2 v=dot height=0.5;
symbol2 c=black i=join l=2 v=star height=0.5;
proc gplot;
        plot logodds*logt = group/vaxis=axis2 haxis = axis1;
run;
```

Assignment ten: Using Weibull accelerated failure time model to fit the data of bone marrow transplantation (Table B.4, page 503, also available on the course website). Provide your program and output of it. Interpret your results and calculate the acceleration factors for the significant prognostic variables (i.e. those with $p \leq 0.05$).


4
3
2
1
0
-1
log-odds of survival
1
2
3
4
5
6
Log of survival time
GROUP
0
1