

# 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

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

Thus, the output is in terms of parameterization of  $\mu$ ,  $\alpha$  and  $\sigma$ .

- (a) For Weibull distribution, the relation between two sets of parameters (PH and AFT) is (page 203 and 238)

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

- (b) For log-logistic distribution ( $\theta$ ,  $\kappa$  and  $\mu$ ,  $\sigma$ )

Assume  $\epsilon$  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

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

Under another parameterization and AFT model,

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

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

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

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

- (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 6.6 for details)
- (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 curves (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 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 **tensorReg()**.

3. Example 6.3: 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 |            |            | Label               |
|-----------|----|----------|----------|------------|------------|---------------------|
|           |    |          | Error    | Chi-Square | Pr > ChiSq |                     |
| 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 (6.16) or (6.19)): 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 | LLOGISTIC    |
| Log Likelihood       | -59.24726035 |

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Analysis of Parameter Estimates

| Variable  | DF | Estimate | Standard |            |            | Label          |
|-----------|----|----------|----------|------------|------------|----------------|
|           |    |          | Error    | Chi-Square | Pr > ChiSq |                |
| 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

$$\hat{\theta} = -5.46/0.805 = -6.783$$

$$\hat{\kappa} = 0.805^{-1} = 1.242$$

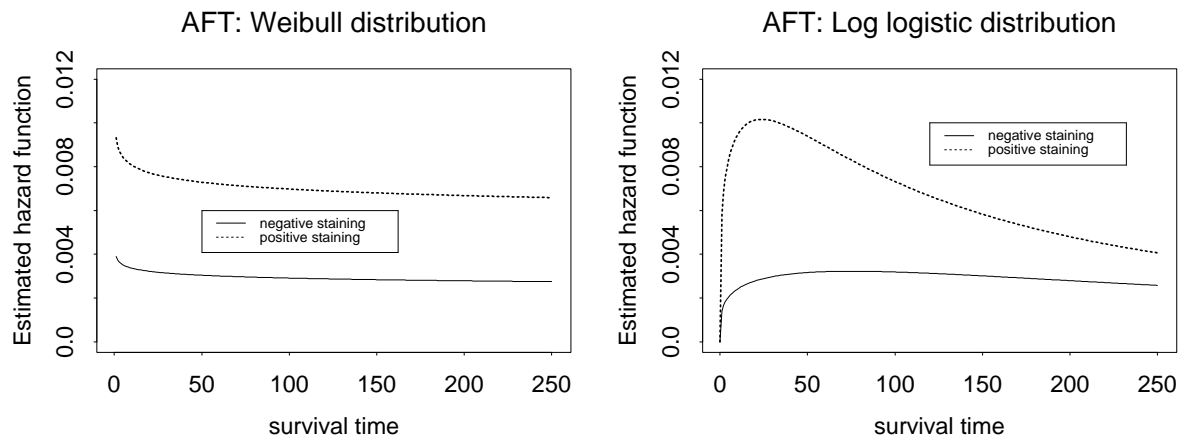
$$\hat{\alpha} = -1.149$$

The estimated acceleration factor is  $e^{-\hat{\alpha}} = 3.16$

The estimated median survival time (see expression (6.22)): 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 6.4: Prostatic cancer study

- (a) SAS program: available at the course website.
- (b) The parsimonious model

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

| Terms in model     | $-2\log \hat{L}$ |
|--------------------|------------------|
| 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<br>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 Controlling 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

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

- (b) The covariates act multiplicatively on the odds of survival beyond t.
- (c) The log-odd ratio is simply  $\beta$  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  $i$ th 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  $i$ th individual has a log-logistic distribution with parameters  $\theta - \eta_i$  and  $\kappa$ .

- 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

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

- vi. Example 6.5 (Breast cancer study): Plot - log-odds of survival vs log of survival time.
- vii. The estimated value of  $\beta$  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 6.5: 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 496, 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  $p \leq 0.05$ ).

