

PH 716 Applied Survival Analysis

Part IV: Accelerated Failure Time Model

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2024/Feb/15 16:29:59

Assumptions

- T_i are independent across i
 - NO longer assumed to share the identical distribution
 - i.e., “personalized” or “individualized”
- log-linear model: $\ln T_i = \beta_0 + \sum_{j=1}^p x_{ij}\beta_j + \sigma\varepsilon_i$
 - Unknown parameters $\sigma > 0$ and $\beta_j \in \mathbb{R}$
 - Error terms ε_i are iid
- Equiv. $T_i = \exp(\beta_0 + \varepsilon_i) \prod_{j=1}^p \exp(x_{ij}\beta_j)$
 - (Why is called “accelerated failure time model”?) The effect of covariates acts multiplicatively on the survival time and accelerates or decelerates the progress along the time axis.

Survival function

- If $\varepsilon_i \stackrel{iid}{\sim} N(0, 1)$,
 - $S_{T_i}(t) = \Pr(\ln T_i > \ln t) = \Pr\{\varepsilon_i > \sigma^{-1}(\ln t - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)\} = 1 - \Phi\{\sigma^{-1}(\ln t - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)\}$
 - * $\Phi(\cdot)$: the cdf of $N(0, 1)$
 - i.e., $T_i \sim \text{log-normal}(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j, \sigma^2)$
- If $\varepsilon_i \stackrel{iid}{\sim}$ the standard Gumbel distribution for minimum (i.e., $F_{\varepsilon_i}(\epsilon) = 1 - \exp(-\exp \epsilon)$),
 - P.S. $\min(X_1, X_2, \dots, X_n) - \ln n \xrightarrow{d}$ standard Gumbel distribution (for minimum) as $n \rightarrow \infty$ if $X_i \stackrel{iid}{\sim} \exp(1)$
 - $S_{T_i}(t) = \Pr\{\varepsilon_i > \sigma^{-1}(\ln t - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)\} = 1 - F_{\varepsilon_i}\{\sigma^{-1}(\ln t - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)\} = \exp[-t^{1/\sigma} \exp\{-(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j)/\sigma\}] = \exp[-\{t/\exp(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j)\}^{1/\sigma}]$
 - i.e., $T_i \sim \text{Weibull}$ with $1/\sigma$ as the “shape” and $\exp(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j)$ as the “scale”
 - * Widely used in practice, with a hazard descending or ascending with respect to t
 - * Specifically, $T \sim \text{exponential}$ if $\sigma = 1$, with a hazard constant with respect to hazard

Likelihood principles (for uncensored data)

- Observed $T_1 = t_1, \dots, T_n = t_n$
- Joint density of $\mathbf{T} = [T_1, \dots, T_n]^\top$ evaluated at $[t_1, \dots, t_n]^\top$: $f_{\mathbf{T}}(t_1, \dots, t_n; \boldsymbol{\theta})$
 - $\boldsymbol{\theta}$: a p -vector of unknown parameters
- Observed-data likelihood $L(\boldsymbol{\theta}) = f_{\mathbf{T}}(t_1, \dots, t_n; \boldsymbol{\theta})$
 - Taken as a function of $\boldsymbol{\theta}$
 - $L(\boldsymbol{\theta}) = \prod_{i=1}^n f_{T_i}(t_i; \boldsymbol{\theta})$ if T_i is independent across i
- Maximum likelihood estimator (MLE): $\hat{\boldsymbol{\theta}}_{\text{ML}} = \max_{\boldsymbol{\theta}} L(\boldsymbol{\theta}) = \max_{\boldsymbol{\theta}} \ell(\boldsymbol{\theta})$

- $\ell(\boldsymbol{\theta}) = \ln L(\boldsymbol{\theta})$
- A closed-form solution for $\hat{\boldsymbol{\theta}}_{\text{ML}}$ usually not available
 - * Resorting to numerical optimization techniques, e.g., Newton's method
- Confidence interval (CI) of $\boldsymbol{\theta}$
 - $\hat{\boldsymbol{\theta}}_{\text{ML}} \approx N(\boldsymbol{\theta}, I(\hat{\boldsymbol{\theta}}_{\text{ML}})^{-1})$ for iid T_i
 - * Because $\sqrt{n}(\hat{\boldsymbol{\theta}}_{\text{ML}} - \boldsymbol{\theta}) \xrightarrow{d} N(0, nI(\boldsymbol{\theta})^{-1})$ for iid T_i
 - * Fisher information (the expectation of Hessian matrix of $\ell(\boldsymbol{\theta})$): $I(\boldsymbol{\theta}) = -E \frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T} \approx -\frac{\partial^2 \ell(\boldsymbol{\theta})}{\partial \boldsymbol{\theta} \partial \boldsymbol{\theta}^T}$
- Likelihood ratio test (LRT)
 - H_0 vs H_1
 - Test statistic: $-2 \ln \frac{L(\hat{\boldsymbol{\theta}}_{\text{ML}, H_0})}{L(\hat{\boldsymbol{\theta}}_{\text{ML}})} = 2\{\ell(\hat{\boldsymbol{\theta}}_{\text{ML}}) - \ell(\hat{\boldsymbol{\theta}}_{\text{ML}, H_0})\}$
 - * $\hat{\boldsymbol{\theta}}_{\text{ML}, H_0}$: the (constrained) MLE under H_0
 - * $\hat{\boldsymbol{\theta}}_{\text{ML}}$: the MLE under $H_0 \cup H_1$
 - Reject H_0 if the value of $-2 \ln \frac{L(\hat{\boldsymbol{\theta}}_{\text{ML}, H_0})}{L(\hat{\boldsymbol{\theta}}_{\text{ML}})}$ is over $\chi^2_{p, 1-\alpha}$
 - * $\chi^2_{p, 1-\alpha}$: the $1 - \alpha$ quantile of $\chi^2(p)$
 - * Because $-2 \ln \frac{L(\hat{\boldsymbol{\theta}}_{\text{ML}, H_0})}{L(\hat{\boldsymbol{\theta}}_{\text{ML}})} \approx \chi^2(p)$
 - p : the difference of free parameters with and without H_0

Ex. 4.1 (uncensored exponential-distributed observations)

- The following $n = 10$ iid failure times are assumed to arise from $\exp(\lambda)$, i.e., $f_T(t) = \lambda \exp(-\lambda t)$.

i	1	2	3	4	5	6	7	8	9	10
t_i	10	12	8	7	2	4	15	6	5	19

- Computing MLE
 1. $f(t_i; \lambda) = \lambda \exp(-\lambda t_i)$, $i = 1, \dots, 10$
 2. $L(\lambda) = \prod_{i=1}^{10} f(t_i; \lambda) = \lambda^{10} \exp(-\lambda \sum_{i=1}^{10} t_i)$
 3. $\ell(\lambda) = \sum_{i=1}^{10} \ln f(t_i; \lambda) = 10 \times (\ln \lambda) - \lambda \sum_{i=1}^{10} t_i$
 - $\ell'(\lambda) = 10/\lambda - \sum_{i=1}^{10} t_i$
 4. $\hat{\lambda}_{\text{ML}} = \arg \max_{\lambda \in (0, \infty)} \ell(\lambda)$
 - $\hat{\lambda}_{\text{ML}} = 10 / \sum_{i=1}^{10} t_i = 10/88$ by solving the score equation $\ell'(\lambda) = 0$
- 95% CI of λ
 1. $\ell''(\lambda) = -10/\lambda^2$
 2. $I(\lambda) = -E\ell''(\lambda) = 10/\lambda^2$
 3. 95% CI of λ : $\hat{\lambda}_{\text{ML}} \pm 1.96 \times I(\hat{\lambda}_{\text{ML}})^{-1/2}$, i.e., $10/88 \pm 1.96 \times \sqrt{10}/88$
 - Because $\lambda \approx N(\hat{\lambda}_{\text{ML}}, I(\hat{\lambda}_{\text{ML}})^{-1}) = N(10/88, 10/88^2)$
 4. Interpretation
- Testing $H_0 : \lambda = .1$ vs $H_1 : \lambda \neq .1$ at the significance level $\alpha = .05$
 1. Test statistic: $2\{\ell(\hat{\lambda}_{\text{ML}}) - \ell(\hat{\lambda}_{\text{ML}, H_0})\} \approx .16$
 - $\hat{\lambda}_{\text{ML}, H_0} = .1$
 2. Compare the value of test statistic with $\chi^2_{p, 1-\alpha}$
 - $\chi^2_{p, 1-\alpha} \approx 3.84$ with $p = 1$
 3. Or, the p -value may be calculated via `pchisq(.16, 1)`
 4. Conclusion

Likelihood principles (for right-censored data)

- Observed $\tilde{T}_i = \tilde{t}_i$ and $\Delta_i = \delta_i$ (event indicator),
 - \tilde{T}_i : the smaller one between T_i (event time) and C_i (right-censoring time)

- Assuming the independence across i
- Assuming the independent and noninformative censoring, i.e.,
 - * $T_i \perp C_i$ (conditional on covariates)
 - * $S_{T_i}(t | \boldsymbol{\theta})$ and $S_{C_i}(t | \boldsymbol{\eta})$ have NO common parameter
- Joint density of \tilde{T}_i and Δ_i : $f_{\tilde{T}_i, \Delta_i}(\tilde{t}_i, \delta_i) =$
 - $f_{T_i}(\tilde{t}_i | \boldsymbol{\theta}) S_{C_i}(\tilde{t}_i | \boldsymbol{\eta})$ if $\delta_i = 1$
 - $S_{T_i}(\tilde{t}_i | \boldsymbol{\theta}) f_{C_i}(\tilde{t}_i | \boldsymbol{\eta})$ if $\delta_i = 0$
 - * Because
 - $\Pr(\tilde{T}_i > t, \Delta_i = 1) = \Pr(C_i \geq T_i, T_i > t) = \int_t^\infty \Pr(C_i \geq u, T_i = u) du = \int_t^\infty S_{C_i}(u | \boldsymbol{\eta}) f_{T_i}(u | \boldsymbol{\theta}) du$
 - $\Pr(\tilde{T}_i > t, \Delta_i = 0) = \Pr(T_i \geq C_i, C_i > t) = \int_t^\infty \Pr(T_i \geq u, C_i = u) du = \int_t^\infty S_{T_i}(u | \boldsymbol{\theta}) f_{C_i}(u | \boldsymbol{\eta}) du$
- Observed-data likelihood: $L(\boldsymbol{\theta}, \boldsymbol{\eta}) = \prod_{i=1}^n f_{\tilde{T}_i, \Delta_i}(\tilde{t}_i, \delta_i) = \prod_{i=1}^n \{f_{T_i}(\tilde{t}_i | \boldsymbol{\theta}) S_{C_i}(\tilde{t}_i | \boldsymbol{\eta})\}^{\delta_i} \{S_{T_i}(\tilde{t}_i | \boldsymbol{\theta}) f_{C_i}(\tilde{t}_i | \boldsymbol{\eta})\}^{1-\delta_i}$
 - Reducing to $\prod_{i=1}^n f_{T_i}(\tilde{t}_i | \boldsymbol{\theta})^{\delta_i} S_{T_i}(\tilde{t}_i | \boldsymbol{\theta})^{1-\delta_i} = \prod_{i=1}^n \lambda_{T_i}(\tilde{t}_i | \boldsymbol{\theta})^{\delta_i} S_{T_i}(\tilde{t}_i | \boldsymbol{\theta})$ if we are only concerned about the MLE of $\boldsymbol{\theta}$

Likelihood principles (for general censored data)

- Assuming the independence across i and independence and noninformative censoring
- Observed-data likelihood:

$$\prod_{i \in \mathfrak{D}} f_{T_i}(\tilde{t}_i) \prod_{i \in \mathfrak{R}} S_{T_i}(\tilde{t}_i) \prod_{i \in \mathfrak{L}} \{1 - S_{T_i}(\tilde{t}_i)\} \prod_{i \in \mathfrak{J}} \{S_{T_i}(\tilde{t}_{iL}) - S_{T_i}(\tilde{t}_{iR})\}$$

- \mathfrak{D} : the set of **uncensored** subjects
- \mathfrak{R} : the set of **right-censored** subjects
- \mathfrak{L} the set of **left-censored** subjects
- \mathfrak{J} : the set of **interval-censored** subjects

Exponential regression for right-censored data

- Observed $\{\tilde{T}_i = \tilde{t}_i, \Delta_i = \delta_i, x_{i1}, \dots, x_{ip}\}$
 - $\tilde{T}_i = \min(T_i, C_i)$
 - $\Delta_i = 1$ if $\tilde{T}_i = T_i$ and zero otherwise
- Assuming independent and non-informative censoring
- Assuming $T_i \sim \exp(\lambda_i)$
 - $\lambda_i = \lambda(x_{i1}, \dots, x_{ip} | \boldsymbol{\beta}) = \exp(\beta_0 + \sum_{j=1}^p x_{ij} \beta_j)$ (Why using the exponential form?)
 - Two distinct forms of parameterization used by different R functions
 - * (`survival::survreg`) density $f_{T_i}(t) = \lambda_i^{-1} \exp(-t/\lambda_i)$, hazard rate $\lambda_{T_i}(t | \boldsymbol{\beta}) = 1/\lambda_i$, and survival function $S_{T_i}(t | \boldsymbol{\beta}) = \exp(-t/\lambda_i)$
 - * (`flexsurv::flexsurvreg`) density $f_{T_i}(t) = \lambda_i \exp(-\lambda_i t)$, hazard rate $\lambda_{T_i}(t | \boldsymbol{\beta}) = \lambda_i$, and survival function $S_{T_i}(t | \boldsymbol{\beta}) = \exp(-\lambda_i t)$
 - Also, there is an inconsistency when the two R functions name some parameters
 - * β_0 : called “(Intercept)” in the output of `survival::survreg`
 - * $\exp(\beta_0)$: called “rate” in the output of `flexsurv::flexsurvreg`
- Likelihood function $L(\boldsymbol{\beta}) = \prod_i \lambda_{T_i}(\tilde{t}_i | \boldsymbol{\beta})^{\delta_i} S_{T_i}(\tilde{t}_i | \boldsymbol{\beta})$
 - $\boldsymbol{\beta} = [\beta_0, \beta_1, \dots, \beta_p]^\top$
- Log-likelihood function $\ell(\boldsymbol{\beta}) = \sum_i \{\delta_i \ln \lambda_{T_i}(\tilde{t}_i | \boldsymbol{\beta}) + \ln S_{T_i}(\tilde{t}_i | \boldsymbol{\beta})\}$

- Score function $U(\beta) = \frac{\partial \ell(\beta)}{\partial \beta} = [\frac{\partial \ell(\beta)}{\partial \beta_0}, \frac{\partial \ell(\beta)}{\partial \beta_1}, \dots, \frac{\partial \ell(\beta)}{\partial \beta_p}]^\top$
 - * In general no closed-form for the solution of score equations $U(\beta) = 0$
- Fisher information $I(\beta) = -E \frac{\partial^2 \ell(\beta)}{\partial \beta \partial \beta^\top}$
 - * $\frac{\partial^2 \ell(\beta)}{\partial \beta \partial \beta^\top} = [\frac{\partial^2 \ell(\beta)}{\partial \beta_i \partial \beta_j}]_{(p+1) \times (p+1)}$
- Newton's method (for maximization)
 1. Start with an initial guess $\hat{\beta}_{(0)}$
 2. Update the current estimate with $\hat{\beta}_{(k+1)} = \hat{\beta}_{(k)} + I(\hat{\beta}_{(k)})^{-1} U(\beta_{(k)})$ until $\hat{\beta}_{(k)}$ and $\hat{\beta}_{(k+1)}$ are close enough
- Interpretation of β_0
 - (`survival::survreg`) $\exp(\beta_0)$ is the baseline of survival times. This baseline refers to the scenario where the effect of covariates is neutral (i.e., all $\beta_j, j > 0$, are zeros).
 - (`flexsurv::flexsurvreg`) $\exp(-\beta_0)$ is the baseline of survival times. This baseline refers to the scenario where the effect of covariates is neutral (i.e., all $\beta_j, j > 0$, are zeros).
- Interpretation of $\beta_j, j \neq 0$ (after fixing all covariates other than the j th one)
 - (`survival::survreg`) one-unit increase in the j th covariate change the survival time by $(\exp(\beta_j) - 1) \times 100\%$ OR the hazard ratio (HR, i.e., the ratio of hazard rates) associated with a one-unit increase in the j th covariate is $\exp(-\beta_j)$
 - (`flexsurv::flexsurvreg`) one-unit increase in the j th covariate change the survival time by $(\exp(-\beta_j) - 1) \times 100\%$ OR the HR associated with a one-unit increase in the j th covariate is $\exp(\beta_j)$.
- Graphically check the correctness of model assumption
 1. Collect residuals $\ln T_i - \hat{\beta}_0 - \sum_j x_{ij} \hat{\beta}_j$ for uncensored subjects
 2. Compare residuals to a gumbel random sample via the Q-Q plot.

-
- Ex 4.2. ([DM] pp.147): The purpose of Steinberg et al. (2009) was to evaluate extended duration of a triple-medication combination versus therapy with the nicotine patch alone in smokers with medical illnesses.

```
head(asauro::pharmacoSmoking)
data.ex42 = asauro::pharmacoSmoking
data.ex42 = data.ex42[data.ex42$ttr != 0,] # ttr=0 not allowed in AFT models
is.factor(data.ex42$grp)
aft.ex42.1 = survival::survreg(
  survival::Surv(ttr, relapse) ~ grp,
  data = data.ex42,
  dist="weibull",
  scale = 1,
  x = T
)
summary(aft.ex42.1)
# Or
aft.ex42.2 = survival::survreg(
  survival::Surv(ttr, relapse) ~ grp,
  data = data.ex42,
  dist="exponential"
)
summary(aft.ex42.2)
# Or using flexsurv::flexsurvreg
aft.ex42.3 = flexsurv::flexsurvreg(
```

```

survival::Surv(ttr, relapse) ~ grp,
data = data.ex42,
dist = "exponential"
)
aft.ex42.3
survminer::ggflexsurvplot(aft.ex42.3, data=data.ex42[data.ex42$grp=='patchOnly',])

# prediction for grp='combination'
exp.beta0 = unname(exp(aft.ex42.1$coefficients[1]))
(ET = exp.beta0) # expectation of T
(medT = log(2)*ET) # median of T
surv.fun = function(t){ # survival function
  return(
    1-pexp(t, rate = 1/exp.beta0)
  )
}
curve(surv.fun, from = 0, to = 1e3) # plot the survival curve for grp='combination'

# Graphically check the correctness of exponential assumption
set.seed(2024)
g.rnd = ordinal::rgumbel(10000,max = F) # gumbel random sample
lnTs.uncen = log(as.vector(data.ex42$ttr[data.ex42$relapse==1]))
res = (
  lnTs.uncen - aft.ex42.1$x[data.ex42$relapse==1,] %*% as.matrix(aft.ex42.1$coefficients)
)
qqplot(
  x = g.rnd,
  y = res,
  xlab = "Theoretical Quantiles",
  ylab = "Sample Quantiles"
)
qqline(res, distribution = function(p){ordinal::qgumbel(p,max=F)})

```

- Interpretation of β_1
 - Compared to the “triple-medication-combination”, the “patch-alone” therapy change the survival time by $(\exp(-0.723) - 1) \times 100\%$, i.e., reduce the survival time by 51.5%. OR, the HR of the “patch-alone” therapy to the “triple-medication-combination” is 2.06, i.e., the hazard of the “patch-alone” therapy is twice as high as the “triple-medication-combination”.

Weibull regression for right-censored data

- Observed $\{\tilde{T}_i = \tilde{t}_i, \Delta_i = \delta_i, x_{i1}, \dots, x_{ip}\}$
- Assuming the independence across i and the independent and non-informative censoring
- Recall that if $\ln T_i = \beta_0 + \sum_{j=1}^p x_{ij}\beta_j + \sigma\varepsilon_i$ and $\varepsilon_i \stackrel{iid}{\sim} F_{\varepsilon_i}(\epsilon) = 1 - \exp(-\exp \epsilon)$, then
 - $S_{T_i}(t) = \exp[-\{t/\exp(\beta_0 + \sum_{j=1}^p x_{ij}\beta_j)\}^{1/\sigma}]$
 - * This parameterization is honored by both `survival::survreg` and `flexsurv::flexsurvreg`
 - * BUT there is an inconsistency when the two R functions name some parameters
 - β_0 : called “(Intercept)” in the output of `survival::survreg`
 - $\exp(\beta_0)$: called “scale” in the output of `flexsurv::flexsurvreg`
 - σ : called “Scale” in the output of `survival::survreg`
 - $1/\sigma$: called “shape” in the output of `flexsurv::flexsurvreg`

- Interpretation of β_0 : $\exp(\beta_0)$ is the baseline of survival times. This baseline refers to the scenario where the effect of covariates is neutral (i.e., all β_j , $j > 0$, are zeros).
- Interpretation of β_j , $j \neq 0$ (after fixing all covariates other than the j th one) one-unit increase in the j th covariate change the survival time by $(\exp(\beta_j) - 1) \times 100\%$
 - Inconvenient to Interpret from the perspective of HR (why?)
- Graphically check the correctness of model assumption
 1. Collect residuals $(\ln T_i - \hat{\beta}_0 - \sum_j x_{ij}\hat{\beta}_j)/\hat{\sigma}$ for uncensored subjects
 2. Compare residuals to a gumbel random sample via the Q-Q plot.
- Ex 4.3. (revisit to Ex. 4.2.)

```
head(asauro::pharmacoSmoking)
data.ex43 = asauro::pharmacoSmoking
data.ex43 = data.ex43[data.ex43$ttr != 0,] # ttr=0 not allowed in AFT models
is.factor(data.ex43$grp)
aft.ex43.1 = survival::survreg(
  survival::Surv(ttr, relapse) ~ grp,
  data = data.ex43,
  dist="weibull",
  x = T
)
summary(aft.ex43.1)
# OR using flexsurv::flexsurvreg
aft.ex43.2 = flexsurv::flexsurvreg(
  survival::Surv(ttr, relapse) ~ grp,
  data = data.ex43,
  dist = "weibull"
)
aft.ex43.2
survminer::ggflexsurvplot(aft.ex43.2)

# prediction for grp='combination'
shape = 1/aft.ex43.1$scale
scale = unname(exp(aft.ex43.1$coefficients[1])) # scale
(ET = scale*gamma(1+1/shape)) # expectation of T
(medT = scale*log(2)^(1/shape)) # median of T
surv.fun = function(t){ # survival function
  return(
    1-pweibull(t, shape = shape, scale = scale)
  )
}
curve(surv.fun, from = 0, to = 1e3) # plot the survival curve for grp='combination'

# Graphically check the correctness of weibull assumption
set.seed(2024)
g.rnd = ordinal::rgumbel(10000,max = F) # gumbel random sample
lnTs.uncen = log(as.vector(data.ex43$ttr[data.ex43$relapse==1]))
res = (
  lnTs.uncen - aft.ex43.1$x[data.ex43$relapse==1,] %*% as.matrix(aft.ex43.1$coefficients)
)/aft.ex43.1$scale
qqplot(
  x = g.rnd,
  y = res,
```

```

xlab = "Theoretical Quantiles",
ylab = "Sample Quantiles"
)
qqline(res, distribution = function(p){ordinal::qgumbel(p,max=F)})

```

- Interpretation of β_1
 - Compared to the “triple-medication-combination”, the “patch-alone” therapy reduce the survival time by $1 - \exp(-1.0325) = 64.4\%$.

Log-normal regression for right-censored data

- Observed $\{\tilde{T}_i = \tilde{t}_i, \Delta_i = \delta_i, x_{i1}, \dots, x_{ip}\}$
- Assuming the independence across i and the independent and non-informative censoring
- Recall that if $\ln T_i = \beta_0 + \sum_{j=1}^p x_{ij}\beta_j + \sigma\varepsilon_i$ and $\varepsilon_i \stackrel{\text{iid}}{\sim} N(0,1)$, then
 - $S_{T_i}(t) = 1 - \Phi\{\sigma^{-1}(\ln t - \beta_0 - \sum_{j=1}^p x_{ij}\beta_j)\}$
 - * This parameterization is honored by both `survival::survreg` and `flexsurv::flexsurvreg`
 - * BUT there is an inconsistency when the two R functions name some parameters
 - β_0 : called “(Intercept)” in the output of `survival::survreg` but “meanlog” in the output of `flexsurv::flexsurvreg`
 - σ : called “Scale” in the output of `survival::survreg` but “sdlog” in the output of `flexsurv::flexsurvreg`
- Interpretation of $\beta_j, j \neq 0$ (after fixing all covariates other than the j th one) one-unit increase in the j th covariate change the survival time by $(\exp(\beta_j) - 1) \times 100\%$
- Graphically check the correctness of model assumption
 1. Collect residuals $(\ln T_i - \hat{\beta}_0 - \sum_j x_{ij}\hat{\beta}_j)/\hat{\sigma}$ for uncensored subjects
 2. Compare residuals to a $N(0,1)$ random sample via the Q-Q plot.

-
- Ex. 4.4. Revisit the data of bladder cancer recurrences which contain three treatment arms for 118 subjects.

```

data.ex44 = survival::bladder1[
  complete.cases(
    survival::bladder1[,c('id', 'treatment', 'start', 'stop', 'status')]
  ),
  c('id', 'treatment', 'start', 'stop', 'status')
]
data.ex44$status = 1*(data.ex44$status %in% c(1,2,3)) # merging status 1, 2,3
data.ex44$tte = data.ex44$stop - data.ex44$start
data.ex44 = data.ex44[data.ex44$tte != 0,] # ttr=0 not allowed in AFT models
is.factor(data.ex44$treatment)
aft.ex44.1 = survival::survreg(
  survival::Surv(tte, status) ~ treatment,
  data = data.ex44,
  dist="lognormal",
  x = T
)
summary(aft.ex44.1)
# OR using flexsurv::flexsurvreg
aft.ex44.2 = flexsurv::flexsurvreg(
  survival::Surv(tte, status) ~ treatment,

```

```

data = data.ex44,
dist = "lognormal"
)
aft.ex44.2
survminer::ggflexsurvplot(aft.ex44.2)

# prediction for treatment='pyridoxine'
sigma = aft.ex44.1$scale
mu = sum(aft.ex44.1$coefficients[1:2])
(ET = exp(mu+sigma^2/2)) # expectation of T
(medT = exp(mu)) # median of T
surv.fun = function(t){ # survival function for treatment='pyridoxine'
  return(
    1-pnorm((log(t)-mu)/sigma)
  )
}
curve(surv.fun, from = 0, to = 1e2) # plot the survival curve

# Graphically check the correctness of log-normal assumption
set.seed(2024)
lnTs.uncen = log(as.vector(data.ex44$tte[data.ex44$status==1]))
res = (
  lnTs.uncen - aft.ex44.1$x[data.ex44$status==1,] %*% as.matrix(aft.ex44.1$coefficients)
)
qqnorm(
  y = res,
  xlab = "Theoretical Quantiles",
  ylab = "Sample Quantiles"
)
qqline(res)
# Shapiro-Wilk test for normality
shapiro.test(res)

```

Pros and cons

- Likelihood principles
 - Clear pathway
 - Exact inference only available for selected (and really simple) cases, i.e., approximations usually employed
 - MLE considered (approximately) the most efficient in regular cases
 - LRT optimal for simple cases but well accepted even in complex cases
- AFT model
 - Easy to interpret coefficients: effects on the failure time directly
 - Distribution assumptions may be too strong
 - Can handle non-standard situations such interval censoring
 - Yields estimates of functions like hazard and survival for all times (even beyond the scope of follow-up)
 - * Also dangerous since the extrapolation beyond the observed data range is not reliable