Syllabus

1. Introduction
   - Survival data
   - Censoring mechanism
   - Application in medical field
2. Concepts and definitions
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   - Hazard function
3. Non-parametric approach
   - Life table
   - Kaplan-Meier survival estimate
   - Hazard function
   - Median and percentile survival time
4. Hypothesis testing
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   - Log-rank
   - Wilcoxon
   - Gehan test
5. Study design and sample size estimation
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   - Survival sample size estimation
   - Accrual time and Study duration
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   - Inference
   - Time varying covariates
   - Stratification
7. Model checking in the PH model
   - Model checking
   - Residuals
8. Parametric model
   - Parametric proportional hazard model
   - Accelerate failure model
9. Other topics
   - Competing risk
   - Recurrent events
   - Non-proportional hazard ratio
   - **Interval censoring**

Interval Censor Data

- Interval censor data are represented as $(T_L, T_R]$
- Events may occur
  - $(-\infty, T_R]$ before T_R --- left censoring
  - $(T_L, T_R]$ during the interval --- interval censoring
  - (T_L, ∞) after T_L --- right censoring

- Methods for interval censoring
  - Estimating survival function
  - Comparing survival function
  - Modeling with covariates

Interval Censor Data

- Occur in “soft” endpoints
  - Disease progression
  - Recovery from illness

- Disease assessments cannot be done continuously
  - Disease assessment may require invasive procedures
  - High burden to patients

- In oncology trials, often treatments are administered by cycles
  - Ex.: receive infusion every 4 weeks
  - Assessments are aligned with treatment schedule

Questions Before Analysis

- How frequent are the assessments?
  - Frequent assessments may be OK to ignore the interval censoring
  - Power can be an issue if assessments are less frequent
  - Long intervals may be problematic in one-sample problem
    - May raise FDA's concern
    - Artificially pro-long median survival
- Are the intervals equal overtime?
  - Assessments are more frequent at the beginning and less frequent later
- What would be the problem of unequal intervals between different arms?
  - Potential bias

Interval Censoring Data

- Let T_i, $\mathrm{i} = 1, \dots, \mathrm{n}$ be the survival time for n subjects,
  - Observed within the interval $(L_i, R_i]$
  - Note, T_i is not observed, $T_i \in (L_i, R_i]$
- Define Turnbull intervals $(q_s, p_s), s = 1, \dots, m$
  - Order L_i, R_i with L and R identity
  - Identify adjacent intervals with L and R identity
  - Example: $(L_i, R_i]$: $(1,3), (2,4), (5,6)$
    - Order the intervals $1_L, 2_L, 3_R, 4_R, 5_L, 6_R$
    - Turnbull intervals: (2,3), (5,6)

Example – Temp Data (Turnbull Interval)

```
data temp;
  input C1 C2;
  datalines;
 .    3
 4    4
 6    6
 8    8
 .    10
 12   12
;
proc iclifetest data=temp method=turnbull plots=survival
            impute(seed=1234);
  time (c1,c2);
run;
```

The ICLIFETEST Procedure

Nonparametric Survival Estimates					
		Probability Estimate		Imputation	
Time Interval		Failure	Survival	Standard Error	Lagrange Multiplier
3	4	0.2083	0.7917	0.1811	0.0000
4	6	0.4167	0.5833	0.2179	0.0000
6	8	0.6250	0.3750	0.2099	0.0000
8	12	0.8333	0.1667	0.1521	0.0000
12	Inf	1.0000	0.0000	0.0000	0.0000

Estimating Survival Function

- Nonparametric survival function estimation
  - Step function jump over at Turnbull intervals
  - Unknown between Turnbull intervals

- Let $\theta_s = P\big(t \in (q_s, p_s)\big), s = 1, \dots, m$

- The likelihood function for $\theta = \{\theta_s, s = 1, \dots, m\}$ is

$$L(\theta) = \prod_{i=1}^{n} \sum_{s=1}^{m} \alpha_{is}\theta_s$$

where $\alpha_{is} = I\big((q_s, p_s) \in (L_i, R_i)\big)$

Estimating Survival Function

- Turnbull proposed an expectation-maximization (EM) algorithm

$$\hat{\theta}_s^{(k)} = \frac{1}{n}\sum\nolimits_{i=1}^{n} \frac{\alpha_{is}\hat{\theta}_s^{(k-1)}}{\sum_{l=1}^{m}\alpha_{il}\hat{\theta}_l^{(k-1)}}$$

$\hat{\theta}$ are iteratively updated until $\sum_{s=1}^{m}\left|\hat{\theta}_s^{(k)} - \hat{\theta}_s^{(k-1)}\right| < \varepsilon$ for a specified $\varepsilon > 0$

- Other algorithms are available to improve the Turnbull algorithm
  - The iterative convex minorant (ICM) algorithm
  - The hybrid EMICM algorithm – converge to MLE
- The nonparametric survival function can be estimated as

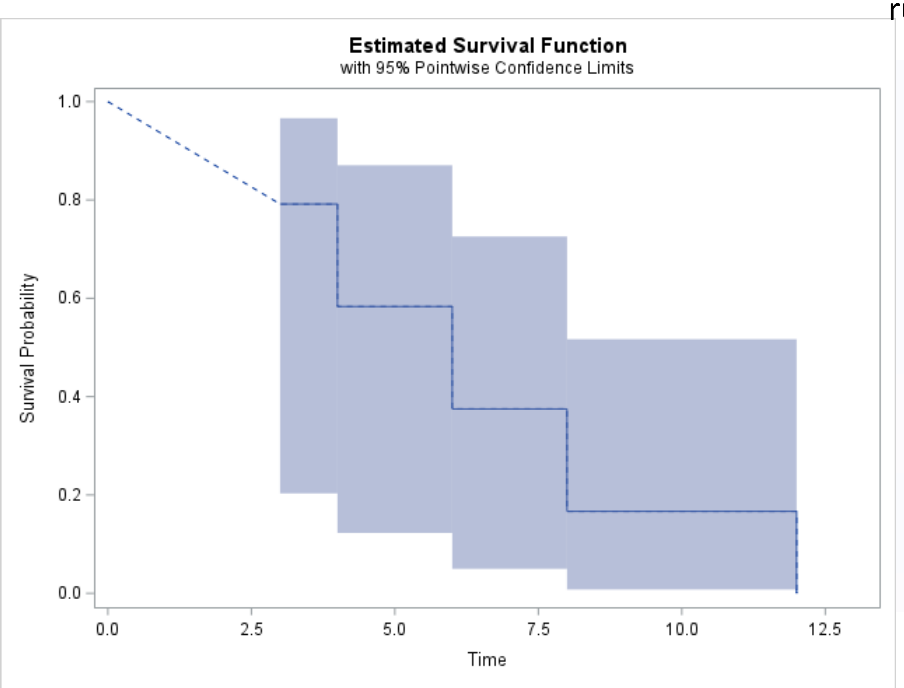
$$\hat{S}(\mathrm{t}) = \sum\nolimits_{l:p_l>t}\hat{\theta}_l$$

Estimating Survival Function

- Variance estimation
  - Likelihood function may not be appropriate due to a large volume of parameters
  - Resampling approaches were proposed
    - Multiple imputation
    - Bootstrap methods

Example – Temp Data

```
proc iclifetest data=temp method=turnbull plots=survival(cl)
          impute(seed=1234);
  time (c1,c2);
run;
```



The ICLIFETEST Procedure

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		Probability Estimate		Imputation Standard Error	Lagrange Multiplier
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Comparing Survival Functions

- Suppose we have K groups of survival data
- To test hypotheses

$$H_0\colon S_1(t) = \cdots = S_K(t)$$
$$H_A\colon \text{ the survival functions are not all equal}$$

- Define
  - n_k be the number of subjects in Group k
  - $n = \sum_{k=1}^{K} n_k$
  - $z_i = (z_{i1}, \dots, z_{iK})'$ - group indicators for subject i

Comparing Survival Functions

- Further define
  - d_{kj} - expected number of events in (q_j, p_j) for Group k

$$d_{kj} = \sum_{i=1}^{n} z_{ik} \frac{\alpha_{ij}\hat{\theta}_j}{\sum_{l=1}^{m} \alpha_{il}\hat{\theta}_l}$$

  - d_j - expected number of events in (q_j, p_j)

$$d_j = \sum_{k=1}^{K} d_{kj}$$

  - n_{kj} - expected number of subjects at risk before (q_j, p_j) for Group k

$$n_{kj} = \sum_{l=j}^{m} d_{kl}$$

  - n_j - expected number of subjects at risk before (q_j, p_j)

$$n_j = \sum_{k=1}^{K} n_{kj}$$

Comparing Survival Functions

- The test statistics for the k^{th} group

$$U_k = \sum_{j=1}^{M} U_{kj} = \sum_{j=1}^{M} \omega_{kj}\left(d_{kj} - \frac{d_j}{n_j} n_{kj}\right)$$

where ω_{kj} is weight

The choices of weight function that PROC ICLIFETEST supports are given in Table 1.

Table 1 Weight Functions for Various Tests

Test	**Weights**
Sun (1996)	1.0
Fay (1996)	$\hat{S}(p_{j-1})$
Finkelstein (1986)	$\frac{\hat{S}(p_{j-1})[\log \hat{S}(p_{j-1}) - \log \hat{S}(p_j)]}{\hat{S}(p_{j-1}) - \hat{S}(p_j)}$
Harrington-Fleming (p,q)	$[\hat{S}(p_{j-1})]^p[1 - \hat{S}(p_{j-1})]^q$, $p \geq 0, q \geq 0$

Comparing Survival Functions

- Multiple imputations developed by Huang, et al (2008) to estimate variance
- Impute data sets for the n subjects H times, $h = 1, \dots, H$
- For the i^{th} subject in the h^{th} sample, the survival time T_i^h is randomly generated based on the discrete survival function

$$\hat{S}_i\left(T_i^h = p_j\right) = \frac{\hat{S}\left(q_j\right) - \hat{S}(R_i +)}{\hat{S}(L_i) - \hat{S}(R_i +)},$$
$$q_j \in (L_i, R_i],$$
$$j = 1, \dots, m$$

Comparing Survival Functions

- Obtain the log-rank test statistics and variance for the imputed data sets
  - Test statistics: $U^{*h} = \left(U_1^{*h}, \dots, U_K^{*h}\right)'$
  - Covariance matrix $V^{*h} = V_1^{*h} + \cdots + V_m^{*h}$
- The covariance matrix of U is estimated as
  $V = \frac{1}{H}\sum_{h=1}^{H} V^{*h} - \frac{1}{H-1}\sum_{h=1}^{H}[U^{*h} - \bar{U}]\,[U^{*h} - \bar{U}]'$
  where $\bar{U} = \frac{1}{H}\sum_{h=1}^{H} U^{*h}$

- The test statistics for comparing the K survival groups is

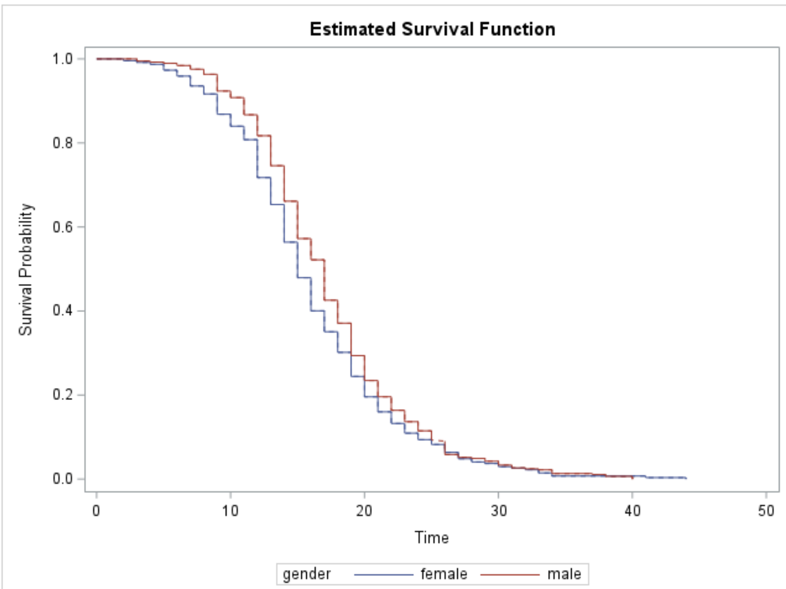
$$U'V^{-1}U \sim \chi^2_{K-1}$$

Example – Diabetic Retinopathy Data

left	right	gender
24	27	male
22	22	female
37	39	male
20	20	male
1	16	male
8	20	female
14	14	male
21	21	male
18	18	male
1	13	female
1	16	male
8	26	male
15	15	male
22	22	male
1	13	male
4	32	female
4	35	male
10	10	female
29	29	male
28	28	female
14	14	male

Example – Diabetic Retinopathy Data

```
proc iclifetest data=blind
impute(seed=1234);
time (Left, Right);
test gender;
run;
```



Covariance Matrix for the Generalized Log-Rank Statistics		
gender	female	male
female	138.182	-138.182
male	-138.182	138.182

Test of Equality over Group			
Weight	Chi-Square	DF	Pr > Chi-Square
SUN	3.5121	1	0.0609

Number of Censored and Uncensored Values						
			Type of Censoring			
Group ID	gender	Total	Left	Interval	Right	Uncensored
1	female	277	1 (0.4%)	39 (14.1%)	0 (0.0%)	237 (85.6%)
2	male	454	0 (0.0%)	96 (21.1%)	0 (0.0%)	358 (78.9%)
Total		731	1 (0.1%)	135 (18.5%)	0 (0.0%)	595 (81.4%)

Obtain Survival Probability and CI

```
proc iclifetest data=blind outsurv=out
impute(seed=1234);
time (Left, Right);
test gender;
run;
Proc print data=out;
Run;
```

Obs	gender	LeftBoundary	RightBoundary	SurvProb	FailProb	IMStderr	LagrangeMult	SurvProb_LCL	SurvProb_UCL	ConfType
1	female	2	2	0.99581	0.00419	0.004110	0.000	0.97160	0.99939	LOGLOG
2	female	3	3	0.99155	0.00845	0.005868	0.000	0.96725	0.99784	LOGLOG
3	female	4	4	0.98707	0.01293	0.007295	0.000	0.96117	0.99574	LOGLOG
4	female	5	5	0.97313	0.02687	0.010597	0.000	0.94211	0.98763	LOGLOG
5	female	6	6	0.95902	0.04098	0.012957	0.000	0.92423	0.97802	LOGLOG
6	female	7	7	0.93550	0.06450	0.016060	0.000	0.89544	0.96055	LOGLOG
7	female	8	8	0.91659	0.08341	0.017932	0.000	0.87348	0.94547	LOGLOG
8	female	9	9	0.86827	0.13173	0.021512	0.000	0.81939	0.90470	LOGLOG
9	female	9	10	0.86827	0.13173	0.021512	202.759	0.81939	0.90470	LOGLOG
10	female	10	10	0.83975	0.16025	0.023322	0.000	0.78779	0.87996	LOGLOG
11	female	10	11	0.83975	0.16025	0.023322	206.325	0.78779	0.87996	LOGLOG
12	female	11	11	0.80781	0.19219	0.025047	0.000	0.75297	0.85168	LOGLOG
13	female	11	12	0.80781	0.19219	0.025047	216.061	0.75297	0.85168	LOGLOG
14	female	12	12	0.71752	0.28248	0.028340	0.000	0.65761	0.76881	LOGLOG
15	female	12	13	0.71752	0.28248	0.028340	220.095	0.65761	0.76881	LOGLOG
16	female	13	13	0.65349	0.34651	0.029937	0.000	0.59132	0.70858	LOGLOG
17	female	14	14	0.56384	0.43616	0.031135	0.000	0.50052	0.62228	LOGLOG
18	female	14	15	0.56384	0.43616	0.031135	231.937	0.50052	0.62228	LOGLOG
19	female	15	15	0.47928	0.52072	0.031248	0.000	0.41685	0.53893	LOGLOG
20	female	15	16	0.47928	0.52072	0.031248	234.404	0.41685	0.53893	LOGLOG
21	female	16	16	0.40047	0.59953	0.030618	0.000	0.34030	0.45983	LOGLOG
22	female	17	17	0.35069	0.64931	0.029724	0.000	0.29292	0.40893	LOGLOG
23	female	18	18	0.30160	0.69840	0.028455	0.000	0.24694	0.35797	LOGLOG
24	female	19	19	0.24432	0.75568	0.026463	0.000	0.19430	0.29754	LOGLOG
25	female	19	20	0.24432	0.75568	0.026463	240.204	0.19430	0.29754	LOGLOG
26	female	20	20	0.19583	0.80417	0.024385	0.000	0.15050	0.24565	LOGLOG

PH Model

- Let $((L_i, R_i], Z_i)$ be interval censored data with covariate Z_i
  - $L_i = R_i$, complete data $T_i = L_i = R_i$
  - $L_i = 0$, left-censored
  - $R_i = \infty$, right-censored
  - $0 < L_i < R_i < \infty$, interval censored

- Let $S(t, Z_i)$, $f(t, Z_i)$, $h(t,\ Z_i)$ denote the survival, density, and hazard functions for subjects with covariate Z_i

- The full log likelihood function can be written as

$$
\begin{aligned}
\log L = & \sum \log f(L_i,\ Z_i) \\
& + \sum \log S(L_i,\ Z_i) \\
& + \sum \log[1 - S(R_i,\ Z_i)] \\
& + \sum \log[S(L_i,\ Z_i) - S(R_i,\ Z_i)]
\end{aligned}
$$

PH Model

- Assume PH model

$$h(t,\ Z_i) = h_0(t)e^{\beta' z_i}$$
$$S(t,\ Z_i) = S_0(t)^{e^{\beta' z_i}}$$
$$f(t,\ Z_i) = h(t,\ Z_i)S(t,\ Z_i) = h_0(t)e^{\beta' z_i}S_0(t)^{e^{\beta' z_i}}$$

- Re-write log-likelihood

$$\begin{aligned}\log L = &\sum \log h_0(L_i)e^{\beta' z_i}S_0(L_i)^{e^{\beta' z_i}} \\ &+ \sum \log S_0(L_i)^{e^{\beta' z_i}} \\ &+ \sum \log[1 - S_0(R_i)^{e^{\beta' z_i}}] \\ &+ \sum \log[S_0(L_i)^{e^{\beta' z_i}} - S_0(R_i)^{e^{\beta' z_i}}]\end{aligned}$$

PH Model

- Estimate baseline hazard function
  - Assume parametric distribution
  - Assume piecewise constant hazard rate for a set of disjoint intervals
    $h_0(t) = h_j$ if $t_{j-1} \leq t < t_j, \quad j = 1,2, \ldots, J$
  - Semiparametric Model
    - Identify a set of discrete times by ranking R_i
    - $s_0 = 0 < s_1 < \cdots < s_{m+1} = \infty$
    - Assume piecewise
  - Cubic spline model by Royston and Parmar (2002)

Example – Diabetic Retinopathy Data

```
proc icphreg data=blind;
   class gender;
   model (Left, Right) = gender / base=piecewise;
   hazardratio gender;
run;
```

Convergence criterion (ABSGCONV=0.00001) satisfied.

Fit Statistics	
-2 Log Likelihood	4055.607
AIC (Smaller is Better)	4067.607
AICC (Smaller is Better)	4067.723
BIC (Smaller is Better)	4095.173

Analysis of Maximum Likelihood Parameter Estimates

Effect	gender	DF	Estimate	Standard Error	95% Confidence Limits		Chi-Square	Pr > ChiSq
Haz1		1	0.0056	0.0010	0.0036	0.0076		
Haz2		1	0.0618	0.0048	0.0523	0.0712		
Haz3		1	0.1604	0.0103	0.1402	0.1807		
Haz4		1	0.1788	0.0186	0.1423	0.2152		
Haz5		1	0.2335	0.0437	0.1478	0.3192		
gender	female	1	0.1407	0.0778	-0.0117	0.2931	3.27	0.0704
gender	male	0	0.0000					

Hazard Ratios for gender

Description	Point Estimate	95% Wald Confidence Limits	
gender female vs male	1.151	0.988	1.341

References

- Finkelstein, D. M. (1986). “A Proportional Hazards Model for Interval-Censored Failure Time Data.” *Biometrics* 42:845–854.
- Turnbull, B. W. (1976), “The Empirical Distribution Function with Arbitrarily Grouped, Censored, and Truncated Data,” Journal of the Royal Statistical Society, Series B, 38, 290–295.
- Sun, J. (2001), “Variance Estimation of a Survival Function for Interval-Censored Survival Data,” Statistics in Medicine, 20, 1249–1257.
- Zhao, Q. and Sun, J. (2004), “Generalized Log-Rank Test for Mixed Interval-Censored Failure Time Data,” Statistics in Medicine, 23, 1621–1629.
- Sun, J., Zhao, Q., and Zhao, X. (2005), “Generalized Log-Rank Test for Interval-Censored Failure Time Data,” Scandinavian Journal of Statistics, 32, 49–57.
- Royston, P., and Parmar, M. K. B. (2002). “Flexible Parametric Proportional-Hazards and Proportional-Odds Models for Censored Survival Data, with Application to Prognostic Modelling and Estimation of Treatment Effects.” *Statistics in Medicine* 21:2175–2197.

Homework