

Summary on One-sample Nonparametric Estimation

- Two estimators
 1. Kaplan-Meier estimator
 2. Nelson-Aalen estimator
- Connection with life-tables
- Asymptotics
 1. counting processes & martingales
 2. martingale central limit theorem
 3. functional Delta method
- Yet to be covered:
 1. small-sample properties: (Fleming & Harrington)
 2. optimality: Wellner (1982, *Ann. Stat.*)

Chapter 4. Comparing Survival Curves

1. Log-rank statistic
2. weighted Log-rank statistics
3. Sample size calculation

1. Log-rank statistic

- Goal: test equality of survival functions
- Review on Mantel-Haenszel method
 - study association between $Y = 0/1$ and $X = 1/2$ stratified by $Z = 0/1$
 - multiple 2×2 tables

Z	X	$Y = 1$	$Y = 0$
$Z = 0$	$X = 1$	$O_1(E_1)$	
	$X = 2$		
$Z = 1$	$X = 1$	$O_2(E_2)$	
	$X = 2$		

- prototype M-H test statistic

$$\frac{\{\sum(O - E)\}^2}{\sum \text{var}(O)} \sim \chi_1^2$$

- Two sample log-rank test statistic

t	X	$Y = 1$	$Y = 0$	N
$t = t_{(1)}$	$X = 1$	D_{11}	$Y_{11} - D_{11}$	Y_{11}
	$X = 2$	D_{21}	$Y_{21} - D_{21}$	Y_{21}
		D_1	$Y_1 - D_1$	Y_1
$t = t_{(k)}$	$X = 1$	D_{1k}	$Y_{1k} - D_{1k}$	Y_{1k}
	$X = 2$	D_{2k}	$Y_{2k} - D_{2k}$	Y_{2k}
		D_k	$Y_k - D_k$	Y_k

– test statistic

$$\frac{\{\sum_k (D_{1k} - E_{1k})\}^2}{\sum_k \text{var}(D_{1k})} \sim \chi_1^2$$

– assumptions

1. $D_{1k} \sim B(Y_{1k}, \lambda_1)$ and $D_{2k} \sim B(Y_{2k}, \lambda_2)$

2. Given D_k , D_{1k} is hypergeometric

$$\binom{D_k}{D_{1k}} \binom{Y_k - D_k}{Y_{1k} - D_{1k}} / \binom{Y_k}{Y_{1k}}$$

3. $ED_{1k} = D_k Y_{1k} / Y_k$, $\text{var}(D_{1k}) = Y_{1k} Y_{2k} D_k (Y_k - D_k) / [Y_k^2 (Y_k - 1)]$

- example: Breast cancer prognosis (D. Collett)
- issues
 1. when would the log-rank test be most powerful?
 2. when would the log-rank test be least powerful?
 3. does it take into account the actual time?

- Extension to multiple samples

t	X	Events	No Events	N
$t = t_{(k)}$	$X = 0$	D_{0k}	$Y_{0k} - D_{0k}$	Y_{0k}
	$X = 1$	D_{1k}	$Y_{1k} - D_{1k}$	Y_{1k}

	$X = j$	D_{jk}	$Y_{jk} - D_{jk}$	Y_{jk}

	$X = m$	D_{mk}	$Y_{mk} - D_{mk}$	Y_{mk}
		D_k	$Y_k - D_k$	Y_k

- assumptions:

1. $D_{jk} \sim B(Y_{jk}, \lambda_k), j = 0, 1, \dots, m$

2. Given $D_k, (D_{0k}, \dots, D_{mk})$ is multivariate hypergeometric

$$\binom{Y_{0k}}{D_{0k}} \cdots \binom{Y_{mk}}{D_{mk}} / \binom{Y_k}{D_k}$$

t	X	Events	No Events	N
$t = t_{(k)}$	$X = 0$	D_{0k}	$Y_{0k} - D_{0k}$	Y_{0k}
	$X = 1$	D_{1k}	$Y_{1k} - D_{1k}$	Y_{1k}

	$X = j$	D_{jk}	$Y_{jk} - D_{jk}$	Y_{jk}

	$X = l$	D_{lk}	$Y_{lk} - D_{lk}$	Y_{lk}

$X = m$	D_{mk}	$Y_{mk} - D_{mk}$	Y_{mk}	
		D_k	$Y_k - D_k$	Y_k

- $O_k - E_k = (D_{1k} - E_{1k}, \dots, D_{mk} - E_{mk})$ with

$$E_{jk} = D_k Y_{jk} / Y_k$$

- $\text{var}(O_k) = (\sigma_{jl,k}^2)_{m \times m}$

- $\text{var}(O_{jk}) = \sigma_{jj,k}^2 = Y_{jk}(Y_k - Y_{jk})D_k(Y_k - D_k) / [Y_k^2(Y_k - 1)]$

- $\text{cov}(O_{jk}, O_{lk}) = \sigma_{jl,k}^2 = -Y_{jk}Y_{lk}D_k(Y_k - D_k) / [Y_k^2(Y_k - 1)]$

- test statistics: define $O - E = \sum_k (O_k - E_k)$, $\text{var}(O) = \sum_k \text{var}(O_k)$

$$(O - E)\text{var}^{-1}(O)(O - E)^T \sim \chi_m^2$$

- Counting processes representation of $O - E$
 - sample 1: $j = 1, 2, \dots, n_1$
 1. data: $X_{1j} = \min(T_{1j}, C_{1j}), \Delta_{1j} = I(T_{1j} \leq C_{1j})$
 2. counting processes: $N_{1j}(t) = I(X_{1j} \leq t, \Delta_{1j} = 1), N_1(t) = \sum_j N_{1j}(t)$
 3. at-risk processes: $Y_{1j}(t) = I(X_{1j} \geq t), Y_1(t) = \sum_j Y_{1j}(t)$
 - sample 2: $j = 1, 2, \dots, n_2$
 1. data: $X_{2j} = \min(T_{2j}, C_{2j}), \Delta_{2j} = I(T_{2j} \leq C_{2j})$
 2. counting processes: $N_{2j}(t) = I(X_{2j} \leq t, \Delta_{2j} = 1), N_2(t) = \sum_j N_{2j}(t)$
 3. at-risk processes: $Y_{2j}(t) = I(X_{2j} \geq t), Y_2(t) = \sum_j Y_{2j}(t)$
 - total sample: $N(t) = N_1(t) + N_2(t), Y(t) = Y_1(t) + Y_2(t)$

$$- O_k = D_{1k} = \sum_{j=1}^{n_1} dN_{1j}(t_{(k)})$$

$$\Rightarrow O = \sum_{t(k)} O_k = \sum_{j=1}^{n_1} \int_0^\infty dN_{1j}(u)$$

$$- E_k = D_k Y_{1k} / Y_k = \sum_{i=1}^2 \sum_{j=1}^{n_i} dN_{ij}(t_{(k)}) Y_1(t_{(k)}) / Y(t_{(k)})$$

$$\Rightarrow E = \sum_{t(k)} E_k = \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_{ij}(u)$$

- Then

$$\begin{aligned} O - E &= \sum_{j=1}^{n_1} \int_0^\infty dN_{1j}(u) - \sum_{i=1}^2 \sum_{j=1}^{n_i} \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_{ij}(u) \\ &= \sum_{j=1}^{n_1} \int_0^\infty dN_{1j}(u) - \sum_{j=1}^{n_1} \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_{1j}(u) - \sum_{j=1}^{n_2} \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_{2j}(u) \\ &= \sum_{j=1}^{n_1} \int_0^\infty \frac{Y_2(u)}{Y(u)} dN_{1j}(u) - \sum_{j=1}^{n_2} \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_{2j}(u) \\ &= \int_0^\infty \frac{Y_2(u)}{Y(u)} dN_1(u) - \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_2(u) \end{aligned}$$

– (continued)

$$\begin{aligned} O - E &= \int_0^\infty \frac{Y_2(u)}{Y(u)} dN_1(u) - \int_0^\infty \frac{Y_1(u)}{Y(u)} dN_2(u) \\ &= \int_0^\infty \frac{Y_1(u)Y_2(u)}{Y(u)} \left\{ \frac{dN_1(u)}{Y_1(u)} - \frac{dN_2(u)}{Y_2(u)} \right\} \\ &= \int_0^\infty \frac{Y_1(u)Y_2(u)}{Y(u)} \left\{ d\hat{\Lambda}_1(u) - d\hat{\Lambda}_2(u) \right\} \end{aligned}$$

– or alternatively,

$$O - E = \int_0^{\infty} \frac{Y_2(u)dN_1(u) - Y_1(u)dN_2(u)}{Y(u)}$$

where the numerator is indeed

$$dN_1(u)[Y_2(u) - dN_2(u)] - dN_2(u)[Y_1(u) - dN_1(u)]$$

– c.f. single 2×2 table at a specific u

$u \geq 0$	X	Events	No Events	At-Risk
u	$X = 1$	$a = dN_1(u)$	$b = Y_1(u) - dN_1(u)$	$Y_1(u)$
	$X = 2$	$c = dN_2(u)$	$d = Y_2(u) - dN_2(u)$	$Y_2(u)$

- view 1: log-rank test statistic is simply sum of $(ad - bc)$ over 2×2 tables

- Log-rank statistic

$$\int_0^{\infty} \frac{Y_1(u)Y_2(u)}{Y_1(u) + Y_2(u)} \left\{ d\hat{\Lambda}_1(u) - d\hat{\Lambda}_2(u) \right\}$$

- why $\{Y_1(u)Y_2(u)\}/\{Y_1(u) + Y_2(u)\}$?
- harmonic mean

$$\propto \frac{Y_1(u)Y_2(u)}{Y_1(u) + Y_2(u)} = \frac{1}{\frac{1}{Y_1(u)} + \frac{1}{Y_2(u)}}$$

- variance of difference in two proportions under null

$$\text{var}(\hat{p}_1 - \hat{p}_2) = pq \left(\frac{1}{n_1} + \frac{1}{n_2} \right) \propto \frac{1}{n_1} + \frac{1}{n_2}$$

- view 2: log-rank statistic is a cumulative difference between two rates weighted by the inverse of its variance

2. Weighted Log-rank statistics

- A general form

$$W = \int_0^{\infty} W(u) \frac{Y_1(u)Y_2(u)}{Y_1(u) + Y_2(u)} \left\{ d\hat{\Lambda}_1(u) - d\hat{\Lambda}_2(u) \right\}$$

- statistics of the class K (Gill, 1980)
- $W(\cdot)$: weight function
- weighted differences in cumulative hazard functions

- Choices of weight function $W(\cdot)$
 - $W(t) = 1$: Log-rank
 - $W(t) = c \cdot Y(t)$: Wilcoxon rank-sum, Gehan-Wilcoxon
 - $W(t) = \hat{S}(t-)$: Prentice-wilcoxon
 - $W(t) = \hat{S}(t-)^{\rho}, \rho > 0$: G^{ρ} -family
 - $W(t) = \hat{S}(t-)^{\rho}[1 - \hat{S}(t-)]^{\gamma}$: $G^{\rho, \gamma}$ -family
 - $W(t) = K(t)[n_1 n_2 / (n_1 + n_2)]^{1/2} [Y_1(t) + Y_2(t)] / Y(t)$: the class K

2. Weighted Log-rank statistics

- Weighted Log-rank statistic

$$W = \int_0^{\infty} W(u) \frac{Y_1(u)Y_2(u)}{Y_1(u) + Y_2(u)} \left\{ \frac{dN_1(u)}{Y_1(u)} - \frac{dN_2(u)}{Y_2(u)} \right\}$$

- How do we view it?
 1. Perspective 1: weighted difference in cumulative hazard functions
 2. Perspective 2: weighted sum of $(ad - bc)$ of the 2×2 tables over time

- An equivalent form:

$$\begin{aligned}
 W &= \int_0^\infty W(u) \frac{Y_0(u)Y_1(u)}{Y_0(u) + Y_1(u)} \left\{ \frac{dN_1(u)}{Y_1(u)} - \frac{dN_0(u)}{Y_0(u)} \right\} \\
 &= \int_0^\infty W(u) \left\{ \frac{Y_0(u)}{Y(u)} dN_1(u) - \frac{Y_1(u)}{Y(u)} dN_0(u) \right\}
 \end{aligned}$$

– $Z_i = 0/1$ in group 0/1, respectively

– $Y_1(u) = \sum_{i=1}^n Z_i Y_i(u)$

–

$$\frac{Y_1(u)}{Y(u)} = \frac{\sum_{i=1}^n Z_i Y_i(u)}{\sum_{i=1}^n Y_i(u)} = \bar{Z}(u)$$

–

$$\frac{Y_0(u)}{Y(u)} = 1 - \bar{Z}(u)$$

- After substitution,

$$\begin{aligned}
W &= \int_0^\infty W(u) \left\{ \frac{Y_0(u)}{Y(u)} dN_1(u) - \frac{Y_1(u)}{Y(u)} dN_0(u) \right\} \\
&= \int_0^\infty W(u) \{ [1 - \bar{Z}(u)] dN_1(u) + [0 - \bar{Z}(u)] dN_0(u) \} \\
&= \int_0^\infty W(u) \sum_{i=1}^n \{ Z_i - \bar{Z}(u) \} dN_i(u) \\
&= \sum_{i=1}^n \int_0^\infty W(u) \{ Z_i - \bar{Z}(u) \} dN_i(u)
\end{aligned}$$

- Perspective 3: weighted difference on covariates, because

$$\bar{Z}(u) = \frac{\sum_{i=1}^n Z_i Y_i(u)}{\sum_{i=1}^n Y_i(u)} \rightarrow \frac{E[ZI(X \geq u)]}{\Pr(X \geq u)} = E(Z | X \geq u) = \mu_Z(u)$$

- Story continues:

$$\begin{aligned}
 W &= \sum_{i=1}^n \int_0^{\infty} W(u) \{Z_i - \bar{Z}(u)\} dN_i(u) \\
 &= \sum_{i=1}^n \int_0^{\infty} W(u) \{Z_i - \bar{Z}(u)\} [dN_i(u) - Y_i(u)\lambda(u)du] \\
 &\quad + \sum_{i=1}^n \int_0^{\infty} W(u) \{Z_i - \bar{Z}(u)\} Y_i(u)\lambda(u)du
 \end{aligned}$$

- the second sum is zero, because

$$\sum_{i=1}^n \{Z_i - \bar{Z}(u)\} Y_i(u) = \sum_{i=1}^n \left\{ Z_i - \frac{\sum_{i=1}^n Z_i Y_i(u)}{\sum_{i=1}^n Y_i(u)} \right\} Y_i(u) = 0$$

- Eureka!

$$W = \sum_{i=1}^n \int_0^{\infty} W(u) \{Z_i - \bar{Z}(u)\} dM_i(u)$$

- cf. linear regression model $y_i = \beta_0 + \beta_1 x_i + e_i$
- LS estimation of the second equation w.r.t. β_1 :

$$\sum_{i=1}^n x_i (y_i - \hat{y}_i) = \sum_{i=1}^n x_i \hat{e}_i = \sum_{i=1}^n (x_i - \bar{x}) \hat{e}_i$$

- Asymptotics under $H_0 : \lambda(t | Z_i) = \lambda(t)$

–

$$U_n(t) = n^{-1/2} \sum_{i=1}^n \int_0^t W(u) \{Z_i - \bar{Z}(u)\} dM_i(u)$$

- weighted Log-rank statistic: $W = n^{1/2}U_n(\tau)$

- $\mathcal{F}_t = \sigma\{N_i(u), Y_i(u), Z_i; i = 1, 2, \dots, n, 0 \leq u \leq t\}$

- $M_i(\cdot)$ are \mathcal{F}_t -martingales

- $H_i(u) = n^{-1/2}W(u) \{Z_i - \bar{Z}(u)\}$ are \mathcal{F}_t -predictable

- $U_n(t) = \sum_{i=1}^n \int_0^t H_i(u) dM_i(u)$

- Martingale CLT

- $U_n(t) = \sum_{i=1}^n \int_0^t n^{-1/2} W(u) \{Z_i - \bar{Z}(u)\} dM_i(u)$

- $\langle U_n, U_n \rangle (t)$ should be

$$\begin{aligned} & \sum_{i=1}^n \int_0^t \left[n^{-1/2} W(u) \{Z_i - \bar{Z}(u)\} \right]^2 Y_i(u) \lambda(u) du \\ &= \int_0^t \frac{1}{n} \sum_{i=1}^n W(u)^2 \{Z_i - \bar{Z}(u)\}^2 Y_i(u) \lambda(u) du \end{aligned}$$

- Assume that $W(u) \rightarrow w(u)$

$$\langle U_n, U_n \rangle (t)$$

$$\begin{aligned} & \rightarrow_P \int_0^t w(u)^2 E \left[\{Z - \mu_Z(u)\}^2 I(X \geq u) \right] \lambda(u) du \\ & = \alpha(t) \end{aligned}$$

– $\langle U_{n,\epsilon}, U_{n,\epsilon} \rangle (t) \rightarrow_P 0$, because

$$\sum_{i=1}^n \int_0^t \left[n^{-1/2} W(u) \{Z_i - \bar{Z}(u)\} \right]^2 \\ \times I \left\{ \left| n^{-1/2} W(u) \{Z_i - \bar{Z}(u)\} \right| \geq \epsilon \right\} Y_i(u) \lambda(u) du$$

– therefore, $U_n \Rightarrow U$

$$\text{var}[U(t)] = \alpha(t)$$

$$= \int_0^t w(u)^2 E \left[\{Z - \mu_Z(u)\}^2 I(X \geq u) \right] \lambda(u) du$$

$$= \int_0^t w(u)^2 \frac{E \left[\{Z - \mu_Z(u)\}^2 I(X \geq u) \right]}{EI(X \geq u)} EI(X \geq u) \lambda(u) du$$

$$= \int_0^t w(u)^2 \text{var}(Z \mid X \geq u) EI(X \geq u) \lambda(u) du$$

- Weighted Log-rank statistic: $W = n^{1/2}U_n(\tau)$

$$n^{-1/2}W \rightarrow_D \mathcal{N}(0, \alpha(\tau))$$

- Standardized weighted Log-rank test statistic:

$$\frac{n^{-1/2}W}{\sqrt{\alpha(\tau)}} \rightarrow_D \mathcal{N}(0, 1)$$

- How to estimate $\alpha(\tau)$?

- We know

- $\alpha(t)$ equals

$$\int_0^t w(u)^2 \text{var}(Z | X \geq u) EI(X \geq u) \lambda(u) du$$

- $\hat{\lambda}(t)dt = d\hat{\Lambda}(t) = dN(t)/Y(t)$

- $\hat{EI}(X \geq u) = Y(u)/n$

- $\widehat{\text{var}}(Z | X \geq u) = \hat{p}\hat{q}$, where

$$\hat{p} = \hat{E}(Z | X \geq u) = \bar{Z}(u)$$

- $\hat{\alpha}(\tau)$ is estimated by

$$n^{-1} \int_0^t W(u)^2 \bar{Z}(u) [1 - \bar{Z}(u)] dN(u)$$

- Standardized weighted Log-rank statistics

$$\frac{n^{-1/2}W}{\sqrt{\hat{\alpha}(\tau)}} = \frac{\sum_{i=1}^n \int_0^{\tau} W(u) \{Z_i - \bar{Z}(u)\} dN_i(u)}{\left\{ \sum_{i=1}^n \int_0^{\tau} W(u)^2 \bar{Z}(u) [1 - \bar{Z}(u)] dN_i(u) \right\}^{1/2}}$$

goes to $\mathcal{N}(0, 1)$

- Reject H_0 when

$$\left| \frac{n^{-1/2}W}{\sqrt{\hat{\alpha}(\tau)}} \right| > 1.96$$

for type-I error of 5%

- What is weighted Log-rank test statistic anyway?

–

$$\frac{n^{-1/2}W}{\sqrt{\hat{\alpha}(\tau)}} = \frac{\sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dN_i(u)}{\{\sum_{i=1}^n \int_0^\tau W(u)^2 \bar{Z}(u) [1 - \bar{Z}(u)] dN_i(u)\}^{1/2}}$$

– if $\Delta_i = 0$, then $dN_i(u) = 0$

– if $\Delta_i = 1$,

* $dN_i(t) = 1$ at $t = X_i$ and 0 elsewhere

* $\int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dN_i(u) = W(X_i) \{Z_i - Y_1(X_i)/Y(X_i)\} = w_i \{Z_i - Y_{i1}/Y_i\}$

– Numerator is $\sum_{i=1}^n w_i \Delta_i (Z_i - Y_{i1}/Y_i)$

– Denominator is $\{\sum_{i=1}^n w_i^2 \Delta_i Y_{i1} Y_{i0} / Y_i^2\}^{1/2}$

- Numerator is $\sum_{i=1}^n w_i \Delta_i (Z_i - Y_{i1}/Y_i)$
- Denominator is $\{\sum_{i=1}^n w_i^2 \Delta_i Y_{i1} Y_{i0} / Y_i^2\}^{1/2}$
- 2×2 table for i th failure, $\Delta_i = 1$

t	Z	$dN(t) = 1$	$Y(t) - dN(t)$	$Y(t)$
X_i	$Z_i = 1$	1	$Y_{i1} - 1$	Y_{i1}
	$Z_i = 0$	0	Y_{i0}	Y_{i0}
		1	$Y_i - 1$	Y_i
X_i	$Z_i = 1$	0	Y_{i1}	Y_{i1}
	$Z_i = 0$	1	$Y_{i0} - 1$	Y_{i0}
		1	$Y_i - 1$	Y_i

- $O_i = Z_i = 0/1, E_i = 1 * Y_{i1}/Y_i$
- $\text{var}(O_i) = 1 * (Y_i - 1) * Y_{i1} * Y_{i0} / [Y_i^2 (Y_i - 1)]$

- Power analysis of weighted Log-rank test statistics

1. type-I error: $\alpha = 5\%$

2. power level

3. alternative hypothesis

4. error bound

- Under $H_0 : \lambda_0(t) = \lambda_1(t) = \lambda(t)$,

$$n^{-1/2}W \sim \mathcal{N}(0, \alpha(\tau))$$

- Alternative hypothesis

- $H_1 : \lambda_1(t) = \lambda_0(t)e^{\beta_n \times \theta(t)}$

- $\log[\lambda_1(t | Z_i)/\lambda_0(t)] = \beta_n Z_i \times \theta(t)$

- $\theta(t)$: take into account of nonproportionality

- β_n : distance between the null and an alternative

- 1. $n^{1/2}\beta_n \rightarrow \xi \in (0, \infty)$

- 2. local alternatives: $\beta_n \rightarrow 0$

- Given a sample size n ,

$$\text{Power} = \Pr \left\{ \left| n^{-1/2}W / \sqrt{\hat{\alpha}(\tau)} \right| > z_{1-\alpha/2} \mid H_1 \right\}$$

- Asymptotic distribution of $n^{-1/2}W$ under H_1

- $n^{-1/2}W = n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dN_i(u)$

- under H_1 ,

$$E[dN_i(u) \mid \mathcal{F}_{u-}] = Y_i(u) \lambda_i(u) du = Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du$$

–

$$n^{-1/2}W = n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dM_i(u) \\ + n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du$$

- apply MCLT

- Asymptotic distribution of $n^{-1/2}W$ under H_1

- $n^{-1/2}W = n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dN_i(u)$

- under H_1 ,

$$E[dN_i(u) \mid \mathcal{F}_{u-}] = Y_i(u) \lambda_i(u) du = Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du$$

–

$$\begin{aligned} n^{-1/2}W &= n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} dM_i(u) \\ &+ n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du \\ &= \text{Term I} + \text{Term II} \end{aligned}$$

- **Term I**: predictable variation

$$\int_0^\tau n^{-1} \sum_{i=1}^n W(u)^2 \{Z_i - \bar{Z}(u)\}^2 Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du$$

- $\beta_n \rightarrow 0 \Rightarrow e^{\beta_n Z_i \times \theta(u)} \rightarrow 1$ and $H_{1n} \rightarrow H_0$

- **Term I** $\rightarrow \int_0^\tau w(u)^2 E[(Z_i - \mu_Z(u))^2 I(X \geq u)] \lambda_0(u) du$

- **Term I** asymptotically

$$\mathcal{N}\left(0, \int_0^\tau w(u)^2 E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)] \lambda_0(u) du\right)$$

- Term II:

$$n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} Y_i(u) \lambda_0(u) e^{\beta_n Z_i \times \theta(u)} du$$

- Taylor expansion: $e^{\beta_n Z_i \times \theta(u)} = 1 + \beta_n Z_i \times \theta(u) + O(\beta_n^2)$
- $O(\beta_n^2)/\beta_n^2$ is bounded
- Term II = Term IIa + Term IIb + Term IIc

- Term IIa

$$n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} Y_i(u) \lambda_0(u) du = 0$$

- Term IIb

$$\begin{aligned}
& n^{-1/2} \sum_{i=1}^n \int_0^\tau W(u) \{Z_i - \bar{Z}(u)\} Z_i Y_i(u) \beta_n \theta(u) \lambda_0(u) du \\
&= \int_0^\tau W(u) n^{-1} \sum_{i=1}^n \{Z_i - \bar{Z}(u)\} Z_i Y_i(u) \times n^{1/2} \beta_n \times \theta(u) \lambda_0(u) du \\
&= \int_0^\tau W(u) n^{-1} \sum_{i=1}^n \{Z_i - \bar{Z}(u)\}^2 Y_i(u) \times n^{1/2} \beta_n \times \theta(u) \lambda_0(u) du \\
&\rightarrow \int_0^\tau w(u) E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)] \times \xi \times \theta(u) \lambda_0(u) du \\
&= \xi \int_0^\tau w(u) \theta(u) E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)] \lambda_0(u) du
\end{aligned}$$

- Term IIc

- $|O(\beta_n^2)/\beta_n^2| < M \Rightarrow nO(\beta_n^2) = O(n\beta_n^2)$

- $n^{1/2}O(\beta_n^2) = n^{-1/2}O(n\beta_n^2) = o(n^{-1/2})$

$$\begin{aligned} & n^{-1/2} \sum_{i=1}^n \int_0^\tau \{Z_i - \bar{Z}(u)\} Y_i(u) O(\beta_n^2) \lambda_0(u) du \\ &= \int_0^\tau W(u) n^{-1} \sum_{i=1}^n \{Z_i - \bar{Z}(u)\} Y_i(u) o(n^{-1/2}) \lambda_0(u) du \\ &\rightarrow 0 \end{aligned}$$

- **Term II** = Term IIa + Term IIb + Term IIc converges to

$$\xi \int_0^{\tau} w(u)\theta(u)E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Recall on **Term I**

$$\mathcal{N}(0, \int_0^{\tau} w(u)^2 E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du)$$

- Under H_{1n} :

- $A(w^2) = \int_0^{\tau} w(u)^2 E_{H_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$

-

$$n^{-1/2}W \sim \mathcal{N}(\xi A(\theta w), A(w))$$