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:

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

  - $Z_i = 0/1$ 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,

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

- Perspective 3: weighted difference on covariates, because

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

- Story continues:

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

- the second sum is zero, because

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

- 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:

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

- Asymptotics under H$_0$: $\lambda(t \mid Z_i) = \lambda(t)$
  - $$U_n(t) = n^{-1/2} \sum_{i=1}^{n} \int_0^t W(u)\left\{Z_i - \bar{Z}(u)\right\} dM_i(u)$$
  - weighted Log-rank statistic: $W = n^{1/2} U_n(\tau)$
  - $\mathscr{F}_t = \sigma\{N_i(u), Y_i(u), Z_i; i = 1, 2, \ldots n, 0 \le u \le t\}$
  - $M_i(\cdot)$ are $\mathscr{F}_t$-martingales
  - $H_i(u) = n^{-1/2} W(u)\left\{Z_i - \bar{Z}(u)\right\}$ are $\mathscr{F}_t$-predictable
  - $U_n(t) = \sum_{i=1}^{n} \int_0^t H_i(u) dM_i(u)$

- Martingale CLT
  - $U_n(t) = \sum_{i=1}^n \int_0^t n^{-1/2} W(u)\{Z_i - \bar{Z}(u)\} dM_i(u)$
  - $< U_n, U_n > (t)$ should be

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

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

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

- $< U_{n,\epsilon}, U_{n,\epsilon} > (t) \rightarrow_P$ 0, because

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

- therefore, $U_n \Rightarrow U$

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

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

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

- Standardized weighted Log-rank test statistic:

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

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

- We know
  - $\alpha(t)$ equals

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

  - $\widehat{\lambda}(t)dt = d\widehat{\Lambda}(t) = dN(t)/Y(t)$
  - $\widehat{E}I(X \geq u) = Y(u)/n$
  - $\widehat{\text{var}}(Z \mid X \geq u) = \widehat{p}\widehat{q}$, where

$$\widehat{p} = \widehat{E}(Z \mid X \geq u) = \bar{Z}(u)$$

  - $\widehat{\alpha}(\tau)$ 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

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

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

- Reject H_0 when

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

for type-I error of 5%

- What is weighted Log-rank test statistic anyway?
  - $$\frac{n^{-1/2}W}{\sqrt{\widehat{\alpha}(\tau)}} = \frac{\sum_{i=1}^{n}\int_0^\tau W(u)\{Z_i - \bar{Z}(u)\}dN_i(u)}{\{\sum_{i=1}^{n}\int_0^\tau W(u)^2\bar{Z}(u)[1-\bar{Z}(u)]dN_i(u)\}^{1/2}}$$
  - 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 ith 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 $\mathrm{H}_0 : \lambda_0(t) = \lambda_1(t) = \lambda(t)$,

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

- Alternative hypothesis
  - $\mathsf{H}_1 : \lambda_1(t) = \lambda_0(t)e^{\beta_n \times \theta(t)}$
  - $\log[\lambda_1(t \mid Z_i)/\lambda_0(t)] = \beta_n Z_i \times \theta(t)$
  - $\theta(t)$: take into account [redacted] nonproportionality
  - β_n: distance between the null and an alternative
    1. $n^{1/2}\beta_n \to \xi \in (0, \infty)$
    2. local alternatives: $\beta_n \to 0$

- Given a sample size n,

$$\text{Power} = \Pr\left\{\left|n^{-1/2}W/\sqrt{\widehat{\alpha}(\tau)}\right| > z_{1-\alpha/2} \mid \mathsf{H}_1\right\}$$

- Aysmptotic 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,

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

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

  - apply MCLT

- Aysmptotic 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$_1$,

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

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

- Term I: predictable variation

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

  - $\beta_n \longrightarrow 0 \Rightarrow e^{\beta_n Z_i \times \theta(u)} \longrightarrow 1$ and $\mathrm{H}_{1n} \rightarrow \mathrm{H}_0$
  - Term I $\longrightarrow \int_0^\tau w(u)^2 E[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$
  - Term I asymptotically

$$\mathcal{N}(0, \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du)$$

- 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

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

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

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

$$\to\int_0^\tau w(u)E_{\mathrm{H}_0}[(Z_i-\mu_Z(u))^2I(X\geq u)]\times\xi\times\theta(u)\lambda_0(u)du$$

$$=\xi\int_0^\tau w(u)\theta(u)E_{\mathrm{H}_0}[(Z_i-\mu_Z(u))^2I(X\geq u)]\lambda_0(u)du$$

- Term IIc
  - $|O(\beta_n^2)/\beta_n^2| < M \Rightarrow nO(\beta_n^2) = O(n\beta_n^2)$
  - $n^{1/2}O(\beta_n^2) = n^{-1/2}O(n\beta_n^2) = o(n^{-1/2})$

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

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

$$\xi \int_0^\tau w(u)\theta(u)E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Recall on Term I

$$\mathcal{N}(0, \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du)$$

- Under H_{1n}:
  - $A(w^2) = \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du)$
  - $$n^{-1/2}W \sim \mathcal{N}(\xi A(\theta w), A(w))$$

- Recap on power calculation of weighted Log-rank
  - $n^{-1/2}W = n^{-1/2}\sum_{i=1}^{n}\int_0^{\tau} W(u)\{Z_i - \bar{Z}(u)\}dN_i(u)$
  - Under H_0, $n^{-1/2}W \sim \mathcal{N}(0, \alpha(\tau))$
  - Alternative hypothesis: $\mathrm{H}_{1n} : \lambda_1(t) = \lambda_0(t)e^{\beta_n \times \theta(t)}$
  - A breakdown

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

- Term I:
  - mean zero
  - contribute random variation
  - Term I asymptotically

$$\mathscr{N}(0, \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du)$$

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

- Term IIa is zero:

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

- Term IIb converges to

$$\xi \int_0^{\tau} w(u)\theta(u)E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Term IIc converges to zero

- Term I converges in distribution to

$$\mathcal{N}(0, \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Term II converges in probability to

$$\xi \int_0^\tau w(u)\theta(u) E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Let's define:

$$A(w^2) = \int_0^\tau w(u)^2 E_{\mathrm{H}_0}[(Z_i - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$$

- Under H_{1n}:

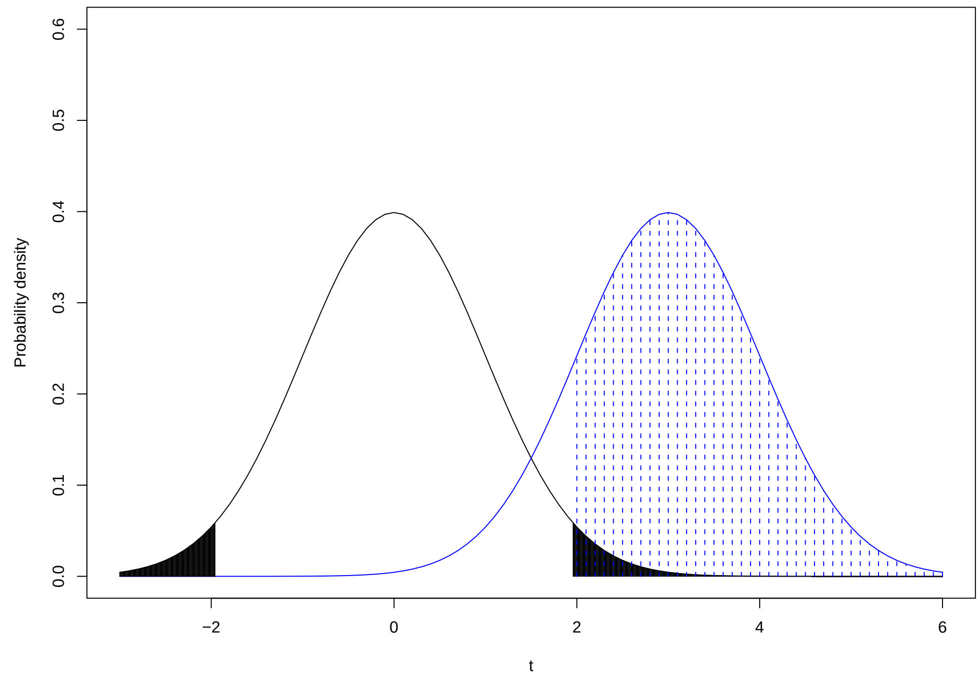
$$n^{-1/2} W \sim \mathcal{N}(\xi A(\theta w), A(w^2))$$

- Summary on $n^{-1/2}W$
  - Under H$_0$: $n^{-1/2}W \sim \mathcal{N}(0, A(w^2))$
  - Under H$_{1n}$: $n^{-1/2}W \sim \mathcal{N}(\xi A(\theta w), A(w^2))$

- Binary versus Time-to-event

	Binary	Time-to-event
T.S.	$\widehat{p}_1 - \widehat{p}_0$	weighted Log-rank
H$_0$	$p_1 = p_0$	$\lambda_1(t) = \lambda_0(t)$
Dist'n	$\mathcal{N}(0, \sigma_0^2)$	$\mathcal{N}(0, A(w^2))$
H$_1$	$p_1 = p_0 + d$	$\lambda_1(t) = \lambda_0(t)e^{\beta_n \theta(u)}$
Dist'n	$\mathcal{N}(d, \sigma_1^2)$	$\mathcal{N}(\xi A(\theta w), A(w^2))$

- Power



$$P = \Phi\left(\frac{\xi A(\theta w)}{A(w^2)^{1/2}} - z_{1-\alpha/2}\right)$$

- What would affect power?
  - $\frac{\xi A(\theta w)}{A(w^2)^{1/2}}$ increases, power increases
  - ξ: usually predetermined
  - $w(u)$: weight functions
- How do we choose w to maximize $\frac{A(\theta w)}{A(w^2)^{1/2}}$

- Consider $A(\cdot)$: for any constant b
  - $A[(w-b\theta)^2] \geq 0$

$$\begin{aligned} A[(w-b\theta)^2] =& A(w^2 - 2bw\theta + b^2\theta^2) \\ =& A(\theta^2)b^2 - 2bA(w\theta) + A(w^2) \geq 0 \end{aligned}$$

  - $A(w\theta)^2 - A(\theta^2)A(w^2) \leq 0$

$$\frac{A(\theta w)}{A(w^2)^{1/2}} \leq A(\theta^2)^{1/2}$$

  - equality satisfied only when

$$w(u) = \theta(u).$$

  - Cauchy-Schwarz Inequality

- Some examples of optimal $w(u)$ in nonproportional alternatives
  - Additive hazards model (Lin & Ying, 1994, BMKA):

$$\lambda(t \mid Z) = \lambda_0(t) + \beta Z \approx \lambda_0(t) e^{\frac{\beta Z}{\lambda_0(t)}} \Rightarrow w(u) = \frac{1}{\lambda_0(u)}$$

  - Accelerated hazards model (Chen & Wang, 1999, JASA):

$$\lambda(t \mid Z) = \lambda_0(te^{\beta Z}) \approx \lambda_0(t) + \lambda_0'(t) t \beta Z \Rightarrow w(u) = \frac{\lambda_0'(u) u}{\lambda_0(u)}$$

- Why $n^{1/2}\beta_n \to \xi$
  - suppose $n^k\beta_n \to \xi$ for some $k \geq 0$
  - $n^{1/2}\beta_n = n^{1/2-k}n^k\beta_n \approx n^{1/2-k}\xi$, we can verify in Term IIb
    * if $k > 1/2$, $n^{1/2}\beta_n \to 0$;
      Term II goes to 0 $\Rightarrow$ no power whatsoever
    * if $k < 1/2$, $n^{1/2}\beta_n \to \infty$;
      Term II goes to ∞ $\Rightarrow$ always 100% power for any $w(u)$

3. Sample size calculation

- In practice, we have a fixed β_0 to be detected
  - $\mathsf{H}_0 : \lambda_1(t) = \lambda_0(t)$
  - $\mathsf{H}_1 : \lambda_1(t) = \lambda_0(t)e^{\beta_0 \times \theta(u)}$

- Standardized weighted Log-rank TS:
  - under H_0: $TS \sim \mathcal{N}(0, 1)$
  - under H_1:

$$TS \doteq \mathcal{N}\left(\frac{n^{1/2}\beta_0 A(\theta w)}{A(w^2)^{1/2}}, 1\right)$$

- Power $P = \Pr\{|TS| \geq z_{1-\alpha/2}\} = 1 - \beta$
  -
  $$\frac{n^{1/2}\beta_0 A(\theta w)}{A(w^2)^{1/2}} = z_{1-\alpha/2} + z_{1-\beta} \Rightarrow n = \frac{(z_{\alpha/2} + z_\beta)^2 A(w^2)}{\beta_0 A(\theta w)^2}$$
  - $w = \theta = 1$
    * Log-rank for proportional hazards model
    * sample size
    $$n = \frac{(z_{\alpha/2} + z_\beta)^2}{\beta_0^2 A(1)}$$

- what is $A(1)$?
  - recall on $A(1) = \int_0^\infty E[(Z - \mu_Z(u))^2 I(X \geq u)]\lambda_0(u)du$
  - $A(1) = \pi_Z(1 - \pi_Z)\,\mathrm{Pr}(\Delta = 1)$
- Sample size is then

$$n\,\mathrm{Pr}(\Delta = 1) = \frac{(z_{\alpha/2} + z_\beta)^2}{\beta_0^2 \pi_Z(1 - \pi_Z)}$$

- Expected # failures/events: $E_D = n\,\mathrm{Pr}(\Delta = 1)$
  - $HR = e^\beta$ is hazards ratio
  - 1-to-1 treatment-control assignment
  -

$$E_D = \frac{4(z_{\alpha/2} + z_\beta)^2}{(\log HR)^2}$$

- Example:
  - type-I error: 5%
  - power: 90%
  - $HR = 2$
  - $E_D = 42/(\log HR)^2$: 88

- Summary on comparing survival functions
  - Weighted Log-rank statistic
    - perspectives
    - asymptotics
    - power calculation
  - Alternatives
  - Yet to cover
    - stratified Log-rank
    - K-samples
    - staggered entry in sample size calculation