Lecture 7

Proportional Hazards Model - Handling Ties and Survival Estimation

Statistics 255 - Survival Analysis

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Tied Data
- Construction of the likelihood - Discrete Time
- Construction of the likelihood - Continuous Time
- Approximations to the exact partial likelihood
- Example : Implementation in R

Estimating $\Lambda_0(t)$ and $S_0(t)$
- Interpretation of $S_0(t)$
- Ex: Catheter infection
- Ex: Duration of breastfeeding
- Review of univariate case
- Incorporation of covariates via the PH model

Cox Regression Model - Tied Data

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Recall

- If there is one failure at $t_{(j)}$ and any number of censorings, by *convention* we assume that censorings *immediately follow* the failure
- Suppose at $t_{(j)}$, there are *multiple failures*:
  - $R_{(j)}$ is the set of subjects *at risk* for failure at $t_{(j)}$
  - $D_{(j)}$ is the set of subjects *failing* at $t_{(j)}$
  - $d_{(j)}$ is the number of subjects in $D_{(j)}$
- The subjects in $D_{(j)}$ are said to be *tied*

Cox Regression Model - Tied Data

Construction of the likelihood

- How to construct the likelihood?

- Recall for *untied data*

$$L_{(j)} = \Pr\{x_{(j)} \text{ fails at } t_{(j)} \mid \text{ one subject in } R_{(j)} \text{ failed at } t_{(j)}\}$$

where $x_{(j)}$ is the (column) vector of covariates for the subject that failed at time $t_{(j)}$

- There are multiple approaches that have been proposed to account for ties in the partial likelihood that include:
  - Cox's (1972) "exact discrete" method
  - Breslow's approximation
  - Efron's approximation
  - Kalbfleisch and Prentice's exact method

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Cox Regression Model - Tied Data

Cox's (1972) "exact discrete" method

- Cox suggested an approach that presumed true ties could actually occur, which would be in the case of a discrete time model
- In this case we could formulate the contribution to the partial likelihood at failure time $t_{(j)}$ as follows:

$$
\begin{aligned}
L_{(j)} &= \Pr\{\text{all } x_i \in D_{(j)} \text{ fail at } t_{(j)} \mid d_{(j)} \text{ subjects in } R_{(j)} \text{ fail at } t_{(j)}\} \\
&= \frac{\Pr\{\text{all } x_i \in D_{(j)} \text{ fail at } t_{(j)}\}}{\Pr\{d_{(j)} \text{ subjects in } R_{(j)} \text{ fail at } t_{(j)}\}}
\end{aligned}
$$

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Cox Regression Model - Tied Data

Cox's (1972) "Exact Discrete" Method : Simple Example

- Suppose data are:

$$(7, x_1), (9^+, x_2), (18, x_3), (18, x_4), (19^+, x_5)$$

- What is $L_{(j)}$ at $t_{(j)} = 18$ ($j = 2$)?

$$D_{(2)} = \{x_3, x_4\} \text{ and } d_{(2)} = 2$$

$$R_{(2)} = \{x_3, x_4, x_5\}$$

$$L_{(2)} = \frac{\Pr\{x_3 \text{ and } x_4 \text{ fail at } 18\}}{\Pr\{\text{any 2 subjects in } R_{(2)} \text{ fail at } 18\}}$$

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Cox Regression Model - Tied Data

Cox's (1972) "Exact Discrete" Method : Simple Example

- **Numerator:**

$$\begin{aligned}\Pr\{x_3 \text{ and } x_4 \text{ fail at } 18\} &= \Pr\{x_3 \text{ fails at } 18\} \times \Pr\{x_4 \text{ fails at } 18\} \\ &= \lambda_3(18)(\Delta t)\lambda_4(18)(\Delta t)\end{aligned}$$

...the product of the risks of the failed subjects

- **Denominator:**

$$\begin{aligned}&\Pr\{\text{any 2 subjects in } R_{(2)} \text{ fail at } 18\} \\ &\quad= \Pr\{x_3 \text{ fails at } t_{(2)}\} \times \Pr\{x_4 \text{ fails at } t_{(2)}\} \\ &\quad\quad+\Pr\{x_3 \text{ fails at } t_{(2)}\} \times \Pr\{x_5 \text{ fails at } t_{(2)}\} \\ &\quad\quad+\Pr\{x_4 \text{ fails at } t_{(2)}\} \times \Pr\{x_5 \text{ fails at } t_{(2)}\} \\ &\quad= \lambda_3(18)(\Delta t)\lambda_4(18)(\Delta t) \\ &\quad\quad+\lambda_3(18)(\Delta t)\lambda_5(18)(\Delta t) \\ &\quad\quad+\lambda_4(18)(\Delta t)\lambda_5(18)(\Delta t)\end{aligned}$$

...sum of product of risks for all possible *pairs* of failed subjects

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Cox's (1972) "Exact Discrete" Method : Simple Example

- The $(\Delta t)'$s and baseline hazards cancel and give:

$$L_{(2)} = \frac{e^{\beta^T x_3} e^{\beta^T x_4}}{e^{\beta^T x_3} e^{\beta^T x_4} + e^{\beta^T x_3} e^{\beta^T x_5} + e^{\beta^T x_4} e^{\beta^T x_5}}$$

- In general, let $(R_{(j)}; d_{(j)})$ be the *set* of subsets of $R_{(j)}$ of size $d_{(j)}$.
  - In example above:

$$\begin{aligned} R_{(2)} &= \{3, 4, 5\} \\ (R_{(2)}; d_{(2)}) &= \{(3,4), (3,5), (4,5)\} \end{aligned}$$

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Cox Regression Model - Tied Data

Exact Discrete Partial Likelihood for Ties

- The partial likelihood for the jth failure time is

$$L_{(j)}^{ED} = \frac{\prod_{i \in D_{(j)}} \text{ risk for subject } i \text{ at } t_{(j)}}{\sum_{l \in (R_{(j)}; d_{(j)})} \left\{ \prod_{i \in l} \text{ risk for subject } i \text{ at } t_{(j)} \right\}}$$

- This is the *"exact discrete"* partial likelihood for tied failure times and is implemented in `R` using the `coxph()` function wth the option `ties="exact"`
- In SAS, this method for handling ties is obtained using the option "discrete"

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Cox Regression Model - Tied Data

Kalbfleisch and Prentice's "exact" method

- Kalbfleisch and Prentice proposed an approach that presumes time is truly continuous
- Under this setting, if there are tied failure times then the tie is due to the imprecise nature of our measurement of time, and that there must be some true ordering of the times
- In this case we can consider the average partial likelihood contribution at time $t_{(j)}$ that arises from breaking the ties in all possible ways

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Cox Regression Model - Tied Data

Kalbfleisch and Prentice's "exact" method : Simple Example

- Returning to the previous example, suppose that at failure time $t_{(2)}$

$$D_{(2)} = \{x_3, x_4\} \text{ and } \quad d_{(2)} = 2$$

$$R_{(2)} = \{x_3, x_4, x_5\}$$

Then the average partial likelihood contribution at time $t_{(j)}$ is

$$L_{(2)} = \frac{1}{2}\left[\frac{e^{\beta^T x_3}}{e^{\beta^T x_3} + e^{\beta^T x_4} + e^{\beta^T x_5}} \times \frac{e^{\beta^T x_4}}{e^{\beta^T x_4} + e^{\beta^T x_5}} + \frac{e^{\beta^T x_4}}{e^{\beta^T x_3} + e^{\beta^T x_4} + e^{\beta^T x_5}} \times \frac{e^{\beta^T x_3}}{e^{\beta^T x_3} + e^{\beta^T x_5}}\right]$$

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Kalbfleisch and Prentice's "exact continuous" method : Simple Example

- In general, if we let
  - $Q_{(j)}$ denote the set of $d_{(j)}!$ permutations of the subjects failing at time t_j
  - $P = (p_1, \ldots, p_{d_{(j)}})$ be an element in $Q_{(j)}$
  - $R(j, P, r) = R_{(j)} - \{p_1, \ldots, p_{r-1}\}$

then the average partial likelihood contribution at $t_{(j)}$ is given by

$$L_{(j)}^{EC} = \frac{1}{d_{(j)}!} \exp\{\beta^T s_{(j)}\} \sum_{P \in Q_{(j)}} \prod_{r=1}^{d_{(j)}} \left\{ \sum_{\ell \in R(j,P,r)} \exp\{\beta^T x_\ell\} \right\}^{-1}$$

where $s_{(j)} = \sum_{i=1}^{d_{(j)}} x_i$

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Cox Regression Model - Tied Data

Kalbfleisch and Prentice's "exact continuous" method : Simple Example

- This albfleisch and Prentice's "exact continuous" method for ties is currently not available in `R`
- This method is available in SAS via the option “exact" for handling ties
- Because `R` and SAS provide different likelihood when a user specifies the “exact" option, this often leads to confusion and explains differential results between the two packages!

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Cox Regression Model - Tied Data

Breslow Method for Ties

- The denominator in $L^{ED}_{(j)}$ and $L^{EC}_{(j)}$ can be painful to compute if there are many ties
- For large risk sets, we can approximate

$$\sum_{l \in (R_{(j)}; d_{(j)})} \left\{ \prod_{i \in l} \text{risk for subject } i \text{ at } t_{(j)} \right\}$$

$$\approx \{ \sum_{i \in R_{(j)}} \text{risk for subject } i \text{ at } t_{(j)} \}^{d_{(j)}}$$

- This gives the *Breslow approximation* to the partial likelihood for the *j*th failure time:

$$L^{B}_{(j)} = \frac{\prod_{i \in D_{(j)}} \text{risk for subject } i \text{ at } t_{(j)}}{\{\sum_{i \in R_{(j)}} \text{risk for subject } i \text{ at } t_{(j)}\}^{d_{(j)}}}$$

$$= \frac{\prod_{i \in D_{(j)}} \exp\{\beta^T x_i\}}{\left\{\sum_{i \in R_{(j)}} \exp\{\beta^T x_i\}\right\}^{d_{(j)}}}$$

Cox Regression Model - Tied Data

Efron Method for Ties

- Nearly all software packages default to the Breslow method for handling ties....except R!
- One issue with the Breslow method is that it considers each of the events at a given time as distinct and allows all failed subjects to contribute fully to the risk set
- The *Efron* approximation allows for partial contributions to the risk set for each of the members that fail at time $t_{(j)}$:

$$L_{(j)}^{Efron} = \frac{\prod_{i \in D_{(j)}} \exp\{\beta^T x_i\}}{\prod_{h=1}^{d_{(j)}} \left\{ \sum_{i \in R_{(j)}} \exp\{\beta^T x_i\} - \frac{h-1}{d_i} \sum_{k \in D_{(j)}} \exp\{\beta^T x_k\} \right\}}$$

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Example : Implementation in R

- Consider the data on time to death among larynx cancer patients where focus was on the diagnostic utility of disease staging (K & M Section 1.8)

```
> larynx <- read.table( "http://www.ics.uci.edu/~dgillen/
                  STAT255/Data/larynx.txt" )
> larynx[1:10,]
   stage t2death age year death
1      1     0.6  77   76     1
2      1     1.3  53   71     1
3      1     2.4  45   71     1
4      1     2.5  57   78     0
5      1     3.2  58   74     1
6      1     3.2  51   77     0
7      1     3.3  76   74     1
8      1     3.3  63   77     0
9      1     3.5  43   71     1
10     1     3.5  60   73     1
>
> ##
> #####        Check for ties
> ##
> sum( duplicated(larynx$t2death[ larynx$death==1 ] ) )
[1] 16
```


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Example : Implementation in R

- Efron Approximation

```
> ##
> #####        Efron approximation
> ##
> fit.efron <- coxph( Surv( t2death, death ) ~ age + factor(stage),
                     data=larynx )
> summary( fit.efron )

  n= 90, number of events= 50

                   coef exp(coef) se(coef)     z Pr(>|z|)
age              0.0190    1.0192   0.0143 1.33    0.182
factor(stage)2 0.1400    1.1503   0.4625 0.30    0.762
factor(stage)3 0.6424    1.9010   0.3561 1.80    0.071 .
factor(stage)4 1.7060    5.5068   0.4219 4.04  5.3e-05 ***
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1

               exp(coef) exp(-coef) lower .95 upper .95
age                 1.02      0.981     0.991      1.05
factor(stage)2      1.15      0.869     0.465      2.85
factor(stage)3      1.90      0.526     0.946      3.82
factor(stage)4      5.51      0.182     2.409     12.59

Likelihood ratio test= 18.3  on 4 df,   p=0.00107
Wald test            = 21.1  on 4 df,   p=0.000296
Score (logrank) test = 24.8  on 4 df,   p=5.57e-05
```


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Example : Implementation in R

- Breslow Approximation

```
> ##
> #####        Breslow approximation
> ##
> fit.breslow <- coxph( Surv( t2death, death ) ~ age + factor(stage),
                      data=larynx, method="breslow" )
> summary( fit.breslow )

  n= 90, number of events= 50

                   coef exp(coef) se(coef)     z Pr(>|z|)
age              0.0189    1.0191   0.0143 1.33    0.185
factor(stage)2 0.1386    1.1486   0.4623 0.30    0.764
factor(stage)3 0.6383    1.8934   0.3561 1.79    0.073 .
factor(stage)4 1.6931    5.4361   0.4222 4.01  6.1e-05 ***
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1

               exp(coef) exp(-coef) lower .95 upper .95
age                 1.02      0.981     0.991      1.05
factor(stage)2      1.15      0.871     0.464      2.84
factor(stage)3      1.89      0.528     0.942      3.80
factor(stage)4      5.44      0.184     2.376     12.44

Likelihood ratio test= 18.1  on 4 df,   p=0.0012
Wald test            = 20.8  on 4 df,   p=0.000344
Score (logrank) test = 24.3  on 4 df,   p=6.87e-05
```


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Example : Implementation in R

- Cox Exact Discrete Method

```
> ##
> #####        Exact discrete (Cox) method
> ##
> fit.exact <- coxph( Surv( t2death, death ) ~ age + factor(stage),
                    data=larynx, method="exact" )
> summary( fit.exact )

  n= 90, number of events= 50

                  coef exp(coef) se(coef)    z Pr(>|z|)
age             0.0193    1.0195   0.0144 1.34    0.181
factor(stage)2 0.1410    1.1515   0.4648 0.30    0.762
factor(stage)3 0.6475    1.9108   0.3587 1.81    0.071 .
factor(stage)4 1.7346    5.6669   0.4294 4.04  5.4e-05 ***
---
Signif. codes:  0 Ô***Õ 0.001 Ô**Õ 0.01 Ô*Õ 0.05 Ô.Õ 0.1 Ô Õ 1

                exp(coef) exp(-coef) lower .95 upper .95
age                  1.02      0.981     0.991      1.05
factor(stage)2       1.15      0.868     0.463      2.86
factor(stage)3       1.91      0.523     0.946      3.86
factor(stage)4       5.67      0.176     2.442     13.15

Likelihood ratio test= 18.4  on 4 df,   p=0.00102
Wald test            = 21  on 4 df,   p=0.000317
Score (logrank) test = 24.7  on 4 df,   p=5.9e-05
```

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Cox Regression Model - Tied Data

Summary

- Why are data tied?
  - Is time truly discrete or do we have a crude measure of a continuous outcome?
  - Are the data interval censored? If so, might consider another method (later in course)
- Questions:
  - Are there any times with many failures (e.g. more than 10% of risk set fails at a given time)?
  - Are there many times with a few ties each?
  - If so, do sensitivity analysis: – use Efron (or Breslow) method for model building – check some model fits (including final model) with exact algorithm relative to the true nature of the outcome (discrete or continuous)
- Efron method best for everyday use.

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Estimating the $\Lambda_0(t)$ and $S_0(t)$

Recall

- In the PH Model

$$\lambda_i(t \mid x_i) = \lambda_0(t) \exp(\beta^T x_i)$$

  and

$$\Lambda_i(t \mid x_i) = \Lambda_0(t) \exp(\beta^T x_i)$$

- Thus

$$\begin{aligned} S_i(t \mid x_i) &= e^{-\Lambda_i(t|x_i)} \\ &= e^{-\Lambda_0(t) \exp(\beta^T x_i)} \\ &= \{e^{-\Lambda_0(t)}\}^{\exp(\beta^T x_i)} \\ &= \{S_0(t)\}^{\exp(\beta^T x_i)} \end{aligned}$$

- $\lambda_0(t)$, $\Lambda_0(t)$, and $S_0(t)$ are the functions corresponding to $x_i = 0$ ... they are called the *baseline* hazard, cumulative hazard and survival functions

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Estimating the $\Lambda_0(t)$ and $S_0(t)$

Example

- In patients with renal insufficiency, catheters are placed surgically (1) or percutaneously (2)
- A study to compare the two methods was mounted with the interest of reducing the rate of catheter exit site infections (K & M Section 1.4)
  - Time origin: placement of catheter
  - Failure event: occurrence of exit site infection
  - Primary reason for censoring: catheter failure (is censoring independent?)
- Reference: Nahman el at. *J. Am Soc. Nephrology* 3 (1992): 103-107.

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Estimating the $\Lambda_0(t)$ and $S_0(t)$

Example

- Fit PH model to renal insufficiency data, with covariate `cathpla` and estimate survival for the placement groups

```
> ##
> #####
> #####        Kidney catheter example from K & M (1.4)
> #####
> ##
> catheter <- read.table( "http://www.ics.uci.edu/~dgillen/
                  STAT255/Data/kidneycatheter.txt" )
> names( catheter ) <- c( "time", "infect", "cathpla" )
> catheter[1:5,]
   time infect cathpla
1   1.5      1       1
2   3.5      1       1
3   4.5      1       1
4   4.5      1       1
5   5.5      1       1

>
> ##
> #### Fit Cox model for type of placement
> fit <- coxph( Surv( time, infect ) ~ cathpla, data=catheter )
> estSurv <- survfit( fit, newdata=data.frame( cathpla=c(1,2) ) )
```


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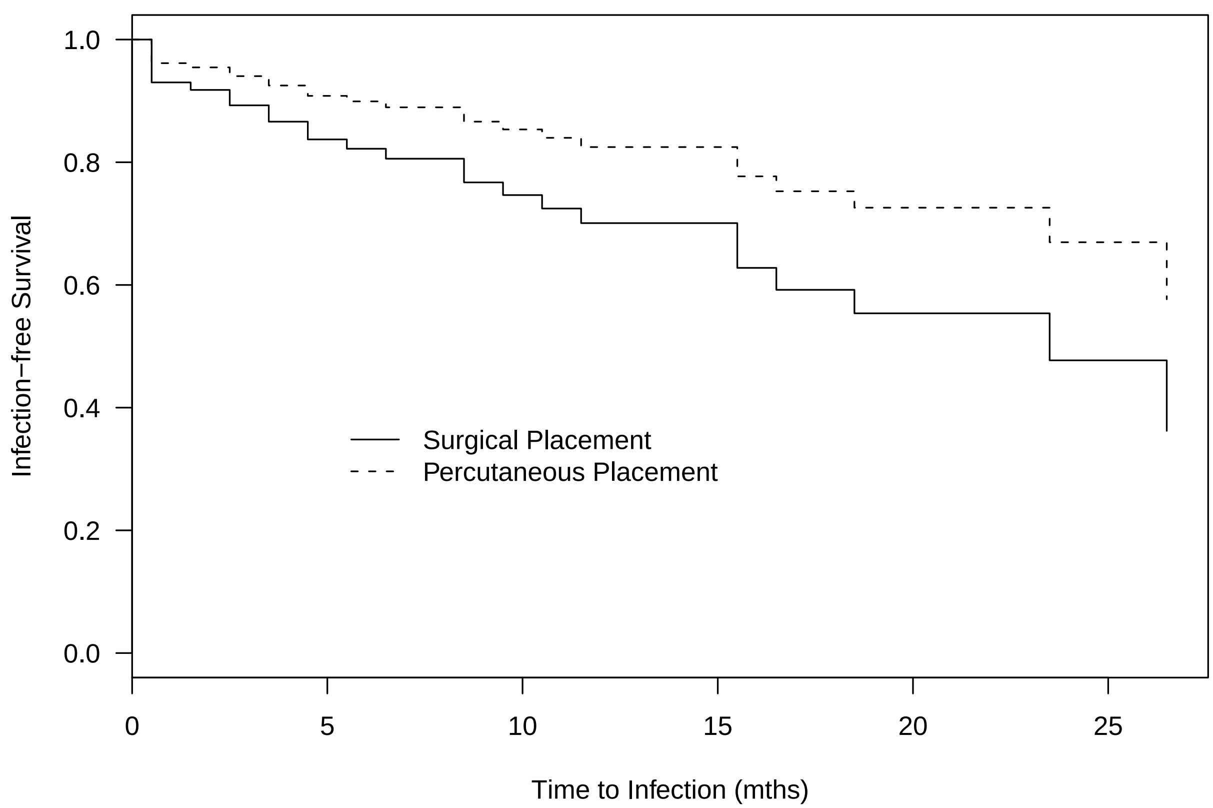
Estimating $\Lambda_0(t)$ and $S_0(t)$

Example

- Now, plot fitted survival functions for `cathpla` $= 1$ (surgically placed) and `cathpla` $= 2$ (percutaneously placed)

```
> plot( estSurv, lty=1:2, las=1, ylab="Infection-free Survival",
        xlab="Time to Infection (mths)" )
> legend( 5, .4, lty=1:2, legend=c("Surgical Placement",
        "Percutaneous Placement"), bty="n" )
```



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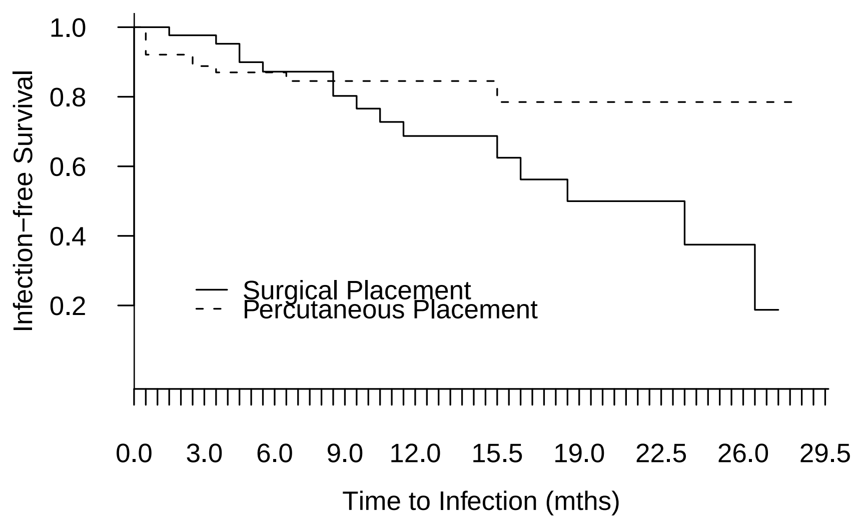
Example

- **Note:** The previous curves are *fitted* curves (subject to PH assumption). The “raw” KM survival fits are below

```
> kmFit <- survfit( Surv( time, infect ) ~ cathpla, data=catheter )
> kmPlot( kmFit, xscale=1, ylab="Infection-free Survival",
+         xlab="Time to Infection (mths)",
+         groupLabels=c("Surgical Placement",
+         "Percutaneous Placement") )
> legend( 2, .3, lty=1:2, legend=c("Surgical Placement",
        "Percutaneous Placement"), bty="n" )
```



Surgical Placement	43 (0)	22 (8)	9 (13)	0 (15)
Percutaneous Placement	76 (0)	27 (10)	11 (11)	1 (11)
Total	119 (0)	49 (18)	20 (24)	1 (26)

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Interpretation of $S_0(t)$

- $\hat{S}_0(t)$ is the *fitted* survival function:
  1. For $x_i = 0$ and
  2. Under the PH assumption
- *If* PH assumption is correct, $\hat{S}_0(t)$ can be though of as an *adjusted* survival function, where the adjustment is to the case where *all subjects* have $x_i = 0$
- What if *no subjects* have $x_i = 0$?
  - Then $\hat{S}_0(t)$ is a **meaningless extrapolation** (e.g. if $x_i = \texttt{age}_i$ and all subjects over 65 years)
- Therefore: make sure you construct your covariates so that $x_i = 0$ is representative of a subject who could appear in your sample...another good reason to *center* your covariates

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Example

- Breast feeding duration among new mothers (K & M Section 1.14)
- Data are available on time (weeks) from birth to weaning for 927 first born children
- Here, we will consider the “survival" experience, adjusting for birth year (`yob`)...

```
##
#####
#####         Breastfeeding example from K & M (1.14)
#####
##
> bfeed <- read.table( "http://www.ics.uci.edu/~dgillen/
        STAT255/Data/bfeed.txt" )
> names( bfeed ) <- c(  "duration", "icompbf", "racemom", "poverty",
+   "momsmoke", "momdrink", "momage", "yob", "momeduc", "precare" )
```


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Example

- Estimate and plot the baseline survival curve after "centering" birth year at 1980

```
> ##
> ##### (Roughly) center year of birth to 1980
> bfeed$yob.80 <- bfeed$yob - 80
>
> ##
> ##### Fit Cox model with year of birth as single
> ##### covariate and plot baseline survival
> fit.80 <- coxph( Surv( duration, icompbf ) ~ yob.80, data=bfeed )
> estSurv <- survfit( fit.80, newdata=data.frame( yob.80=c(0) ) )
> plot( estSurv, ylab="Proportion Breastfeeding",
>         xlab="Time from Birth (wks)" )
> legend( 50, .8, lty=1:2,
+         legend=c("Baseline Survival Estimate (1980 birth year)",
+         "95% Pointwise CI"), bty="n" )
```

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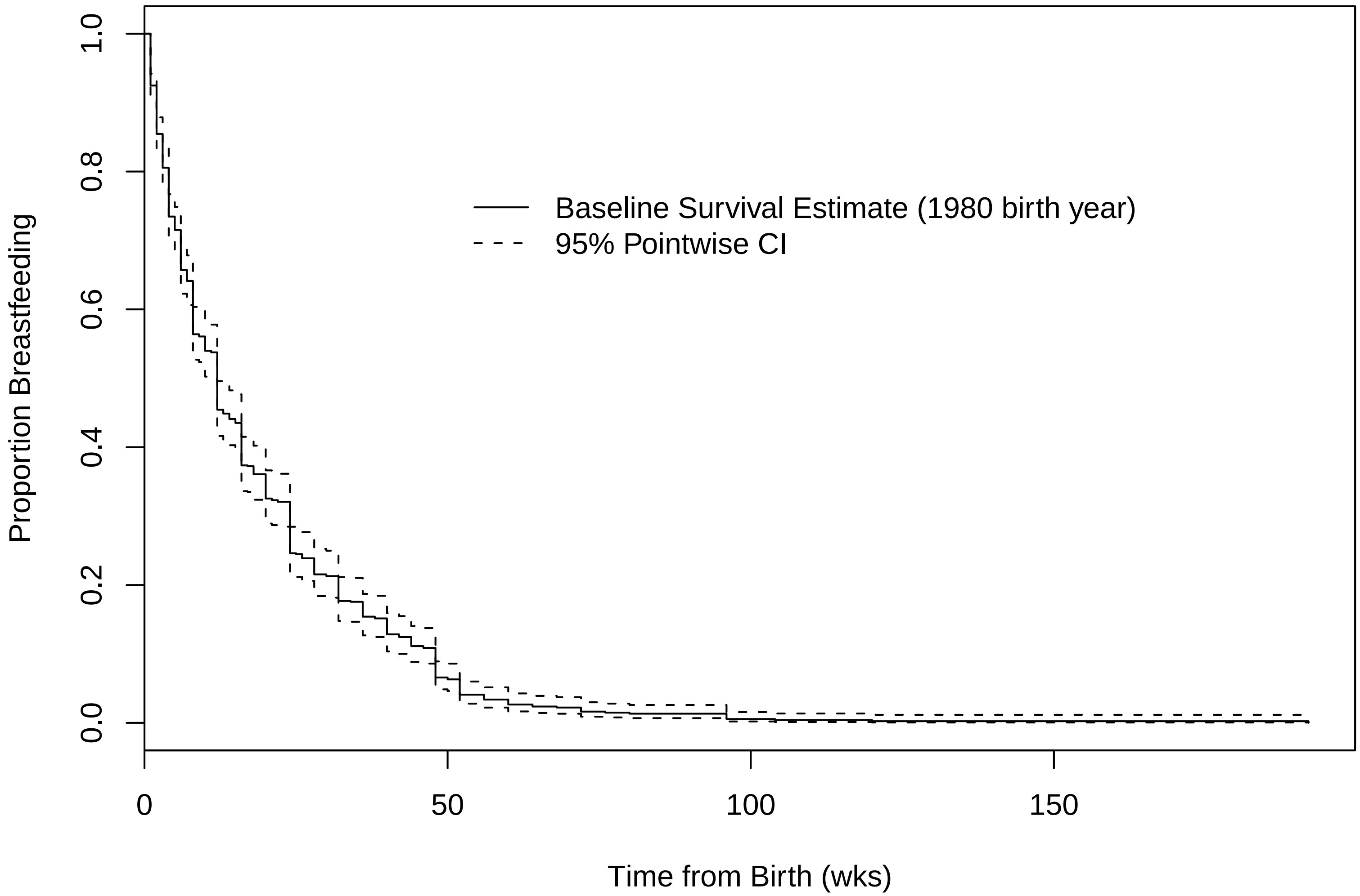
Example

- Resulting baseline survival curve after “centering" birth year at 1980



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Example

- Compare with baseline survival curve without “centering" birth year at 1980

```
> ##
> #####        Compare with baseline estimate for "non-centered" fit
> fit.00 <- coxph( Surv( duration, icompbf ) ~ yob, data=bfeed )
> estSurv <- survfit( fit.00, newdata=data.frame( yob=c(0) ) )
> plot( estSurv, ylab="Proportion Breastfeeding",
        xlab="Time from Birth (wks)" )
> legend( 10, .4, lty=1:2,
+         legend=c("Baseline Survival Estimate (1900 birth year)",
+         "95% Pointwise CI"), bty="n" )
```


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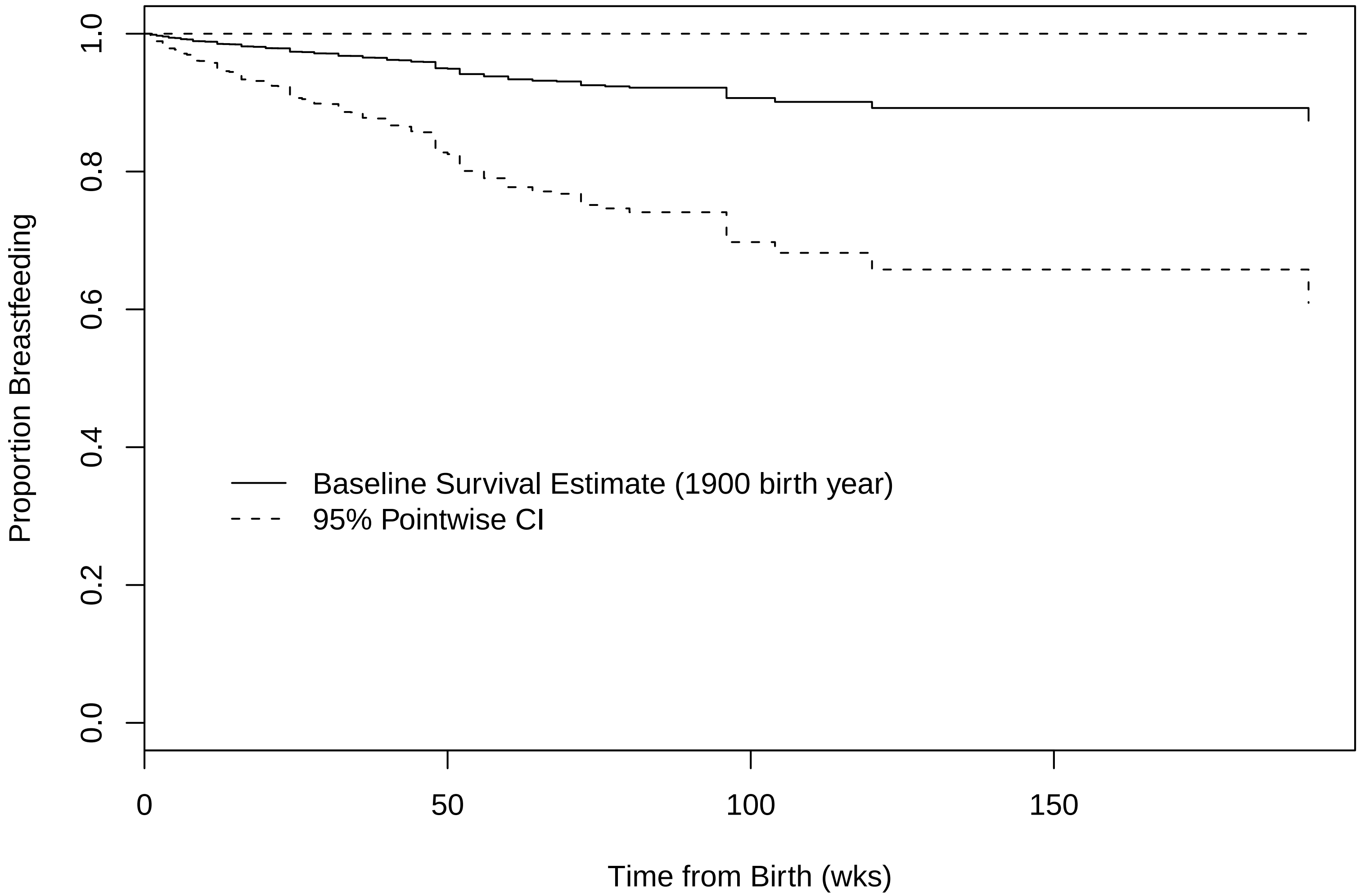
Example

- Resulting baseline survival curve without “centering" birth year at 1980



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Estimation of $\Lambda_0(t)$ and $S_0(t)$

- Recall in the **univariate** case:

$$\hat{S}_{\mathrm{KM}}(t) = \prod_{j:t_j \le t} \left(1 - \frac{d_j}{n_j}\right)$$

$$\Lambda_{NA}(t) = \sum_{j:t_j \le t} \frac{d_j}{n_j}$$

- For 1 subject alive at $t_j - \Delta t$:

$$\Pr\{\text{failure in } (t_j - \Delta t, t_j] \mid \text{alive at } t_j - \Delta t\} \approx \lambda(t_j)(\Delta t)$$

- For n_j subjects alive at $t_j - \Delta t$ (i.e. in R_j):

$$d_j = \sum_{i \in R_j} I\{\text{subject } i \text{ failed at } t_j\}$$

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- Then:

$$E\{\text{\# failures in } (t_j - \Delta t, t_j] \mid n_j \text{ alive at } t_j - \Delta t\} = E\{d_j \mid R_j\}$$

- But:

$$\begin{aligned} E\{d_j \mid R_j\} & \\ &= \sum_{i \in R_j} \Pr\{\text{subj } i \text{ fails in } (t_j - \Delta t, t_j] \mid \text{subj} i \text{ alive at } t_j - \Delta t\} \\ &\approx \sum_{i \in R_j} \lambda(t_j)(\Delta t) \\ &= n_j \lambda(t_j)(\Delta t) \end{aligned}$$

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Estimation of $\Lambda_0(t)$ and $S_0(t)$

- Now, **estimate** $\lambda(t)$ by replacing $\mathrm{E}\{d_j \mid R_j\}$ with d_j (this is like setting **expected** equal to **observed**):

$$d_j = n_j \hat{\lambda}(t_j)(\Delta t)$$

or

$$\hat{\lambda}(t) = \begin{cases} \frac{d_j}{n_j(\Delta t)} & , \quad t \in (t_j - \Delta t, t_j] \\ 0 & , \quad \text{o.w.} \end{cases}$$

Estimating $\Lambda_0(t)$ and $S_0(t)$

Estimation of $\Lambda_0(t)$ and $S_0(t)$

- This gives rise to the Nelson-Aalen estimator:

$$\begin{aligned}
\hat{\Lambda}(t) &= \int_0^t \hat{\lambda}(u)\,du \\
&= \sum_{j:t_j \le t} \hat{\lambda}(t_j)(\Delta t) \\
&= \sum_{j:t_j \le t} \frac{d_j}{n_j}
\end{aligned}$$

and we can think of the Kaplan-Meier estimator as:

$$\begin{aligned}
\hat{S}(t) &= \prod_{j:t_j \le t} \left(1 - \frac{d_j}{n_j}\right) \\
&= \prod_{j:t_j \le t} \left(1 - \hat{\lambda}(t_j)(\Delta t)\right)
\end{aligned}$$

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Estimation of $\Lambda_0(t)$ and $S_0(t)$

- Now, suppose we introduce covariates (via the PH model):

$$\lambda_i(t) = \lambda_0(t) \exp(\beta^T x_i)$$

Then:

$$\begin{aligned}
& \mathrm{E}\{d_j \mid R_j\} \\
& \quad = \sum_{i \in R_j} \Pr\{\text{ind } i \text{ fails in } (t_j - \Delta t, t_j] \mid \text{ind } i \text{ alive at } t_j - \Delta t\} \\
& \quad \approx \sum_{i \in R_j} \lambda_i(t_j)(\Delta t) \\
& \quad = \sum_{i \in R_j} \lambda_0(t_j) \exp(\beta^T x_i)(\Delta t) \\
& \quad = \lambda_0(t_j)(\Delta t) \sum_{i \in R_j} \exp(\beta^T x_i)
\end{aligned}$$

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Estimation of $\Lambda_0(t)$ and $S_0(t)$

- Again, **estimate** $\lambda_0(t)$ by replacing $E\{d_j \mid R_j\}$ with d_j

$$d_j = \hat{\lambda}_0(t_j)(\Delta t) \sum_{i \in R_j} \exp(\beta^T x_i)$$

or

$$\hat{\lambda}_0(t) = \begin{cases} \frac{d_j}{(\Delta t) \sum_{i \in R_j} \exp(\beta^T x_i)} & , \quad t \in (t_j - \Delta t, t_j] \\ 0 & , \quad \text{otherwise} \end{cases}$$

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- So the baseline cumulative hazard can be estimated as

$$\hat{\Lambda}_0(t) = \sum_{j:t_j \le t} \frac{d_j}{\sum_{i \in R_j} \exp(\beta^T x_i)}$$

and the baseline survival function as

$$\hat{S}_0(t) = \prod_{j:t_j \le t} \left(1 - \frac{d_j}{\sum_{i \in R_j} \exp(\beta^T x_i)}\right)$$

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