Statistical Inference of Interval-censored Failure Time Data

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OUTLINE

생존함수 추정
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생존분석이란?
중도절단과 절삭
누적한계추정량
좌절삭된 자료의 생존함수 추정
구간중도절단된 자료의 생존함수 추정
좌중도절단된 자료의 생존함수 추정

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생존함수 추정

What is survival analysis?

- Outcome variable: Time until an event occurs (T)
- Time origin
  - eg, birth date, occurrence of entry into a study or diagnosis of a disease
- Time
  - eg, years, months, weeks or days
- Event
  - eg, death, disease incidence, relapse from remission…

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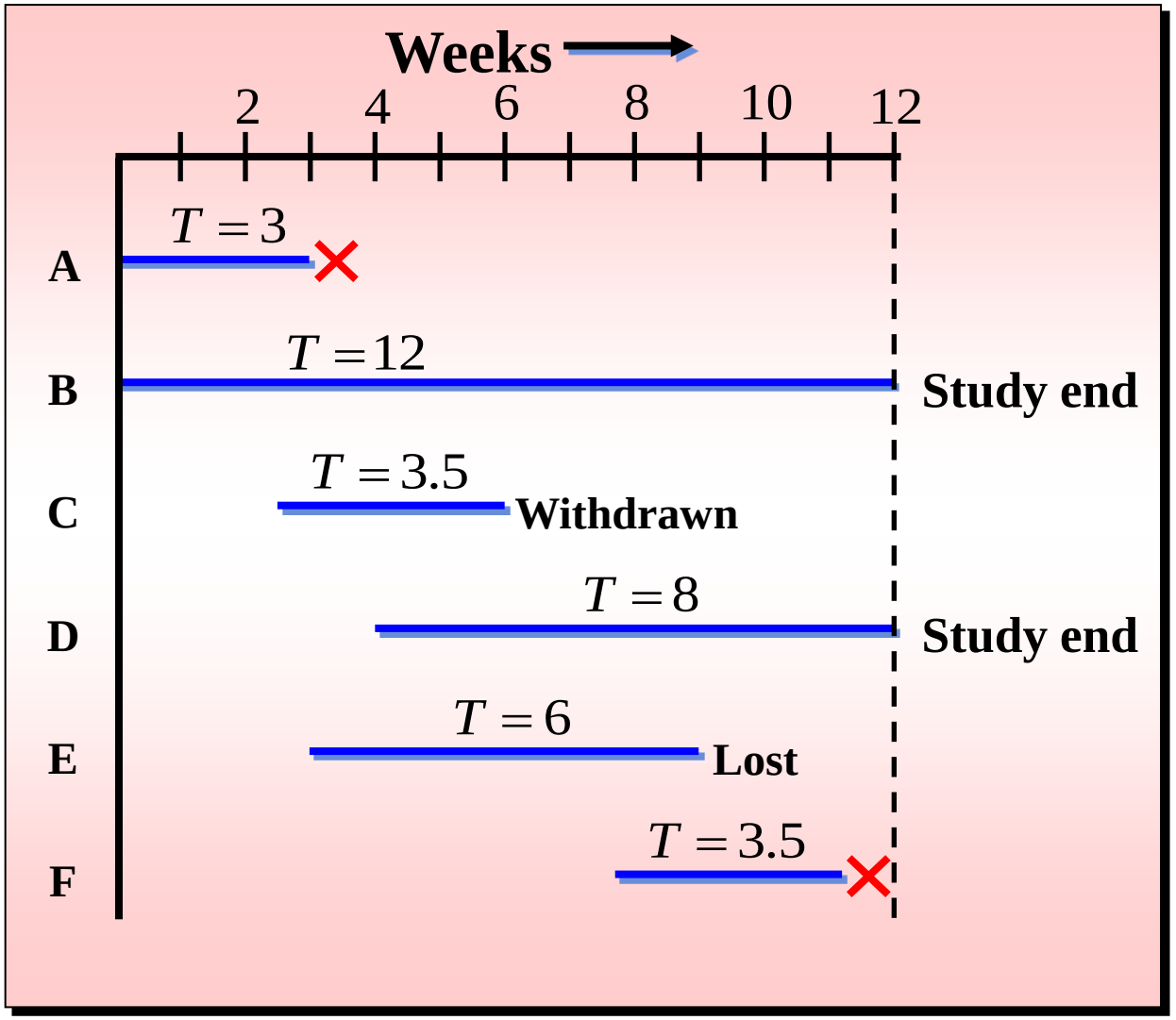
Censoring

- Censoring: Don’t know survival time exactly

- Why censoring may occur?
  - No event before the study ends
  - Lost to follow-up
  - Withdrawn from the study

A hypothetical example



Another types of censoring

- Left censoring: $T \in (0, c)$, observed to fail prior to c
  - eg, Time to first use of marijuana
    - Q: When did you first use marijuana?
    - A: exact age, "I never used it." or "I have used it but can not recall just when the first was."
- Double censoring
- Interval censoring: $T \in (a, b]$
  - eg, Time to cosmetic deterioration of breast cancer patients

Censoring *vs.* Truncation

- When occurs?
  - Only those individuals whose event time lies within a certain observational window (Y_L, Y_R) are observed
- In contrast to censoring where there is at least partial information on each subject
- Left truncation
  - When $Y_R = \infty$
  - eg, Life lengths of elderly residents of a retirement community
- Right truncation
  - When $Y_L = 0$
  - eg, Waiting time from infection at transfusion to clinical onset of AIDS (sampled on June 30, 1986)

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생존함수 추정

Survivor function

- (definition) $S(t) = P(T > t)$
  - Probability that a person survives longer than t
- (properties)
  - Non-increasing
  - $S(0) = 1$
  - $S(\infty) = 0$
    - Eventually nobody would survive

Hazard function

- (definition) $\lambda(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$
  - instantaneous potential per unit time for the event to occur, given that the individual has survived up to t
- (properties)
  - Non-negative
  - No upper bound

Product-limit (or Kaplan-Meier) estimator

- $t_1 < t_2 < \cdots < t_k$: distinct observed failure times
  - Conventionally $t_0 = 0, t_{k+1} = \infty$
- $d_j (j = 0, \ldots, k)$: # of individuals who fail at t_j
- $m_j (j = 0, \ldots, k)$: # of individuals censored at $[t_j, t_{j+1})$
- $n_j = (d_j + m_j) + \cdots + (d_k + m_k)$: # of individuals at risk just prior to t_j
- $\hat{S}(t) = \prod_{j|t_j \le t} \left(1 - \frac{d_j}{n_j}\right)$: PL estimator

Remarks on PL estimator

- Never reduce to zero if $m_k > 0$
  - Not defined for $t >$largest time recorded
- (estimated asymptotic variance)
  - $\mathrm{V}\left(\hat{S}(t)\right) = \hat{S}(t)^2 \sum_{j|t_j \le t} \frac{d_j}{n_j(n_j - d_j)}$: Greenwood's formula
- Pointwise 95% confidence interval for $S(t)$
  - $\hat{S}(t) \pm 1.96 \times se\left(\hat{S}(t)\right)$
  - Linear and symmetric, but possibly lies out of (0,1) and low coverage rate with very small samples
- Nelsen-Aalen estimator for cumulative hazard rate $\Lambda(t)$
  - $\widehat{\Lambda}(t) = \sum_{j|t_j \le t} \frac{d_j}{n_j}$

AML data

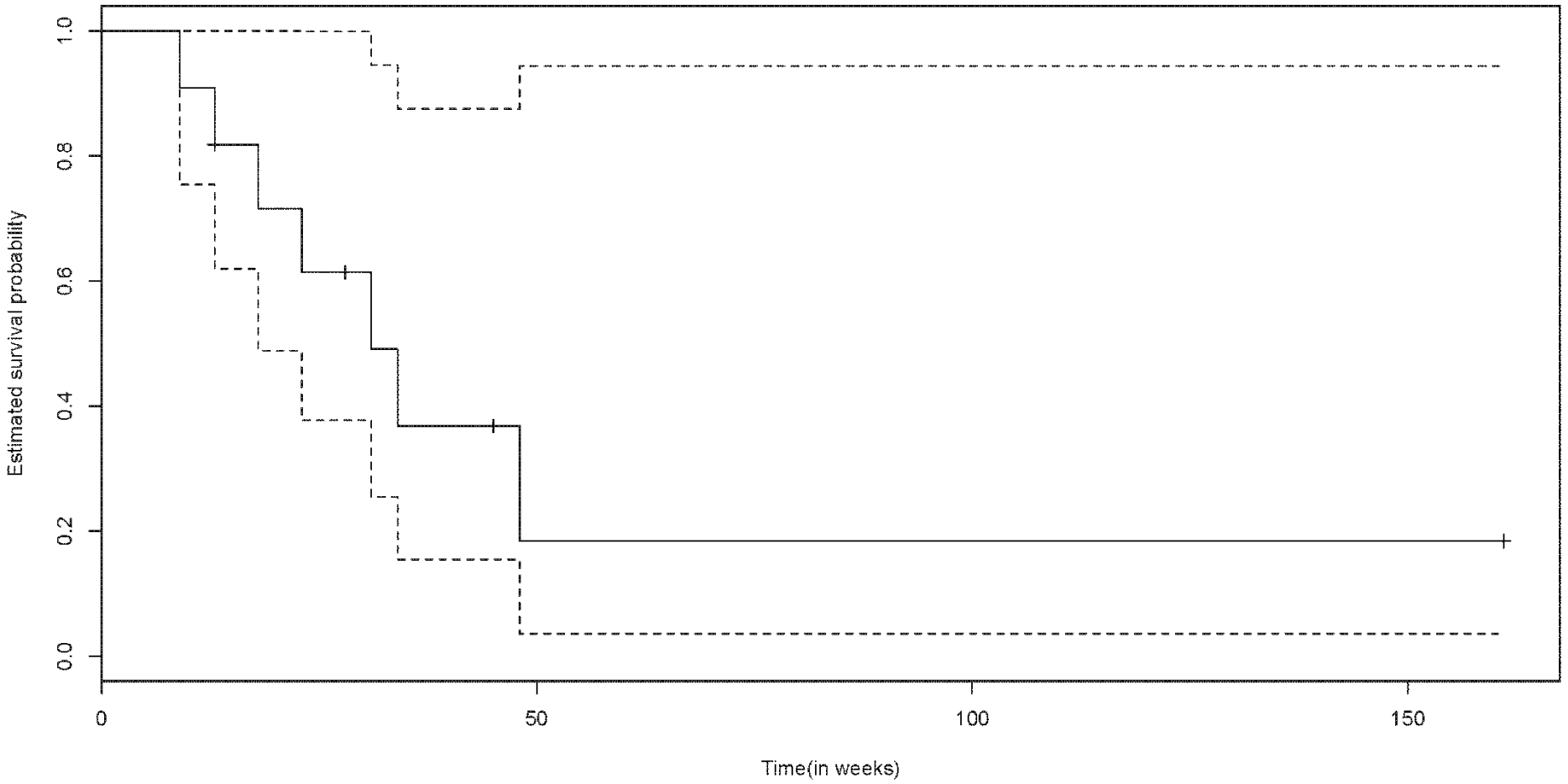
- 화학요법이 백혈병 환자들의 재발시간을 연장하는가? (Embury 등, WesternJMed, 1977)
- R codes
  - Chemo=c(9,13,13,18,23,28,31,34,45,48,161)
  - Non.Chemo=c(5,5,8,8,12,16,23,27,30,33,43,45)
  - Time=c(Chemo,Non.Chemo)
  - C.Status=c(1,1,0,1,1,0,1,1,0,1,0)
  - Non.C.Status=c(1,1,1,1,1,0,1,1,1,1,1,1)
  - Status=c(C.Status,Non.C.Status)
  - Group=rep(c("Chemo","Non.Chemo"),c(length(Chemo),length(Non.Chemo)))
  - aml=data.frame(Time=Time,Status=Status,Group=Group)
  - fit=survfit(Surv(Time,Status)~Group, data=subset(aml,Group=="Chemo"))
  - summary(fit)
  - plot(fit, xlab="Time(in weeks)", ylab="Estimated survival probability")

AML data

```
> summary(fit)
Call: survfit(formula = Surv(Time, Status) ~ Group, data = subset(aml,
    Group == "Chemo"))

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    9     11       1    0.909  0.0867        0.7541        1.000
   13     10       1    0.818  0.1163        0.6192        1.000
   18      8       1    0.716  0.1397        0.4884        1.000
   23      7       1    0.614  0.1526        0.3769        0.999
   31      5       1    0.491  0.1642        0.2549        0.946
   34      4       1    0.368  0.1627        0.1549        0.875
   48      2       1    0.184  0.1535        0.0359        0.944
```

AML data


Estimated survival probability
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
Time(in weeks)

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Bone marrow transplantation data

- 재발과 사망이 주요 관심사건인데 intermediate event (platelet recovery, acute/chronic GvHD)을 경험할 수도 있음
- 골수이식 후 혈소판이 정상수준으로 회복된 환자들의 생존시간에 관심
  - 중간사건을 경험하지 못한 환자는 분석에서 제외됨. 즉, 중간사건을 경험할 때까지 left-truncated 됨
  - 혈소판회복 때까지 시간이 delayed entry time이 됨

Channing house data

- 요양원에 거주하는 462명(남자: 97, 여자: 365)의 노인을 대상으로 사망시간을 관측
- 요양원에 들어온 나이와 사망한 나이 또는 요양원을 떠난 (right-censored) 나이를 포함
- 65세 이상 노인만이 요양원에 들어올 수 있기 때문에 65세 이전에 사망한 노인들은 분석에서 제외됨. 즉, left-truncated 됨

Channing house data

- library(KMsurv)
- library(survival)
- data(channing)
- fit=survfit(Surv(ageentry,age,death)~gender, data=subset(channing,gender==2))
- plot(fit$time, fit$n.risk, xlab="Time(in months)", ylab="Risk set size", type="l")
- fit2=survfit(Surv(ageentry,age,death)~gender, data=subset(channing,age>=816))
- plot(fit2, lty=1:2, xlab="Time(in months)", ylab="Estimated survival probability", xlim=c(804,1215))
- legend("topright",lty=1:2, c("Male","Female"))

Channing house data

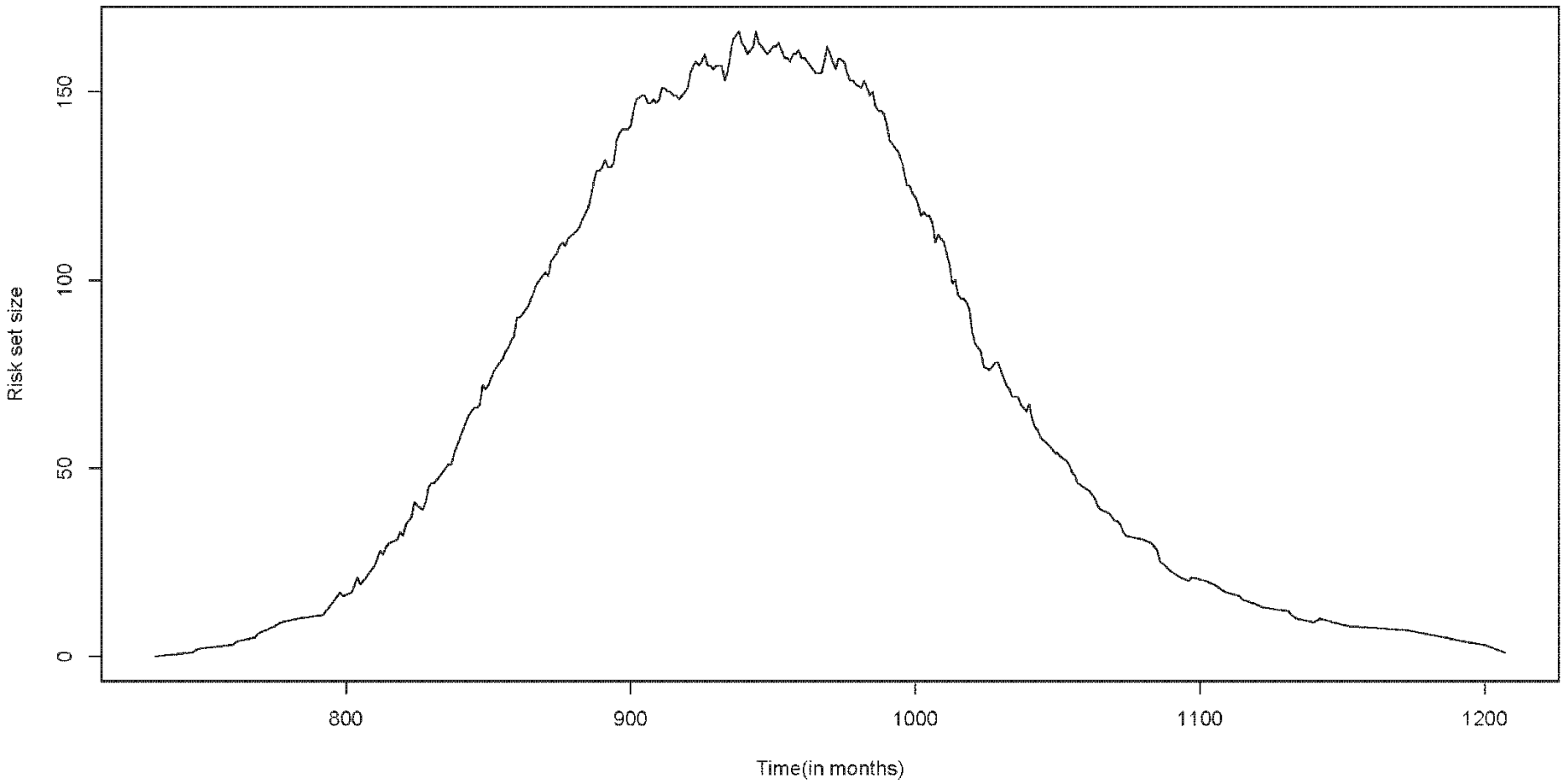
```
> head(channing)
  obs death ageentry  age time gender
1   1     1     1042 1172  130      2
2   2     1      921 1040  119      2
3   3     1      885 1003  118      2
4   4     1      901 1018  117      2
5   5     1      808  932  124      2
6   6     1      915 1004   89      2
```

Channing house data

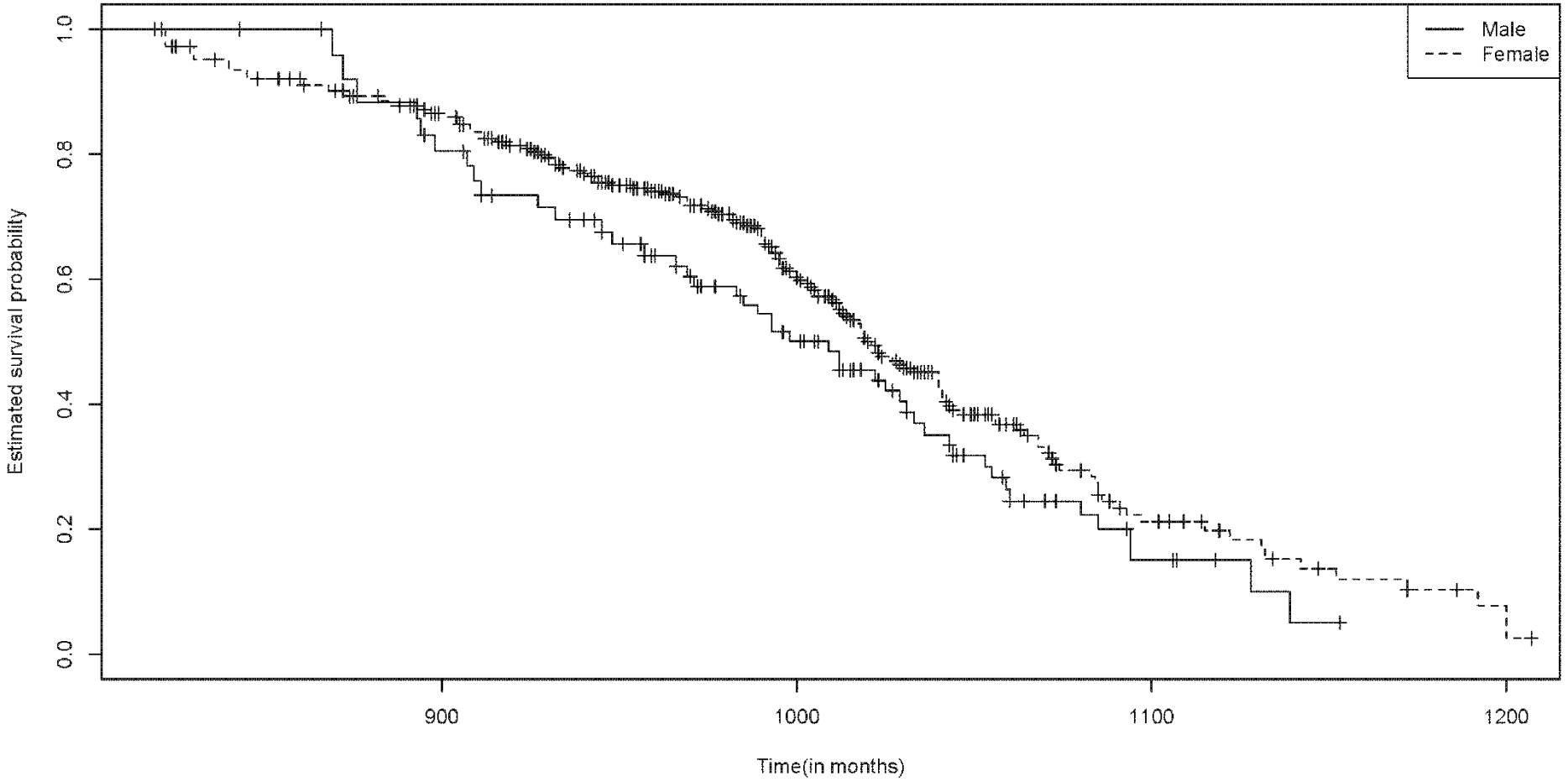
```
> summary(fit)
Call: survfit(formula = Surv(ageentry, age, death) ~ gender, data = subset(channing,
    gender == 2))

3 observations deleted due to missingness
 time n.risk n.event entered censored survival std.err lower 95% CI upper 95% CI
  804     21       1       0        1   0.9524  0.0465      0.86552        1.000
  822     36       1       2        0   0.9259  0.0522      0.82912        1.000
  830     46       1       1        0   0.9058  0.0548      0.80455        1.000
  840     58       1       3        0   0.8902  0.0560      0.78689        1.000
  845     66       1       1        0   0.8767  0.0568      0.77220        0.995
  861     90       1       4        1   0.8670  0.0570      0.76218        0.986
  868    100       1       2        0   0.8583  0.0571      0.75343        0.978
  873    106       1       2        0   0.8502  0.0571      0.74534        0.970
  883    116       1       4        0   0.8429  0.0571      0.73811        0.962
  885    119       1       4        0   0.8358  0.0570      0.73116        0.955
  895    137       1       4        1   0.8297  0.0569      0.72526        0.949
  897    140       1       2        1   0.8237  0.0568      0.71956        0.943
  901    145       1       4        0   0.8181  0.0567      0.71411        0.937
  905    149       2       3        3   0.8071  0.0565      0.70362        0.926
  908    148       2       1        0   0.7962  0.0563      0.69322        0.914
```

Channing house data



Channing house data



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Types of interval-censored data

- Case I interval-censored data or current status data
  - T is only known to be larger or smaller than an observed monitoring time C
  - Either $L = 0$ or $R = \infty$
  - Observed data: $\{(C_i, \delta_i = I(T_i \leq C_i)), i = 1, \ldots, n\}$
  - eg, Cross-sectional studies or tumourigenicity experiments
- Case II interval-censored data
  - Include at least one interval $(L, R]$ with both L and R
  - In experiments with two monitoring times, U and V, with $U \leq V$,
    - $T \leq U, U < T \leq V$, or $T > V$
- Case K interval-censored data
  - In longitudinal studies with periodic follow-up and K monitoring times, $M_1, \ldots, M_K$, the event is only observed between two consecutive inspecting times, M_l and M_{l+1}, and the observed data reduced to $(M_l, M_{l+1}]$

Notation

- Observed data: $\mathcal{F} = \{(l_i, r_i], i = 1, \dots, n\}$
- $0 = t_0 < t_1 < \cdots < t_m < t_{m+1} = \infty$: unique ordered elements of $\mathcal{F}$
- Define $\alpha_{ij} = I\left(\left(t_{j-1}, t_j\right] \subset (l_i, r_i]\right)$ and $p_j = S\left(t_{j-1}\right) - S\left(t_j\right), j = 1, \dots, m+1$

Non-parametric MLE

- Likelihood function for $\boldsymbol{p} = (p_1, \ldots, p_{m+1})'$
  - $L(\boldsymbol{p}) = \prod_{i=1}^{n}[S(L_i) - S(R_i)] = \prod_{i=1}^{n}\sum_{j=1}^{m+1}\alpha_{ij}p_j$
- NPMLE, $\hat{S}$, of S
  - Maximize $L(\boldsymbol{p})$ under $\sum_{j=1}^{m+1} p_j = 1$ and $p_j \geq 0$
  - $\hat{S}$: Right-continuous step function, i.e., $\hat{S}(t) = \hat{S}(t_{j-1}), t_{j-1} \leq t < t_j$
- Remarks
  - Some elements of $\hat{\boldsymbol{p}} = (\hat{p}_1, \ldots, \hat{p}_{m+1})'$ could be 0 and it could help to know these zero components before running a determination process
  - $\hat{p}_j$ could be non-zero only if $t_{j-1} = L_i$ for some i and $t_j = R_k$ for some k, for $i, k = 1, \ldots, n$ (Turnbull (JRSSB, 1976)'s approach)

Illustrative example

i	L_i	R_i
1	0	7
2	0	8
3	6	10
4	7	16
5	7	14
6	17	∞
7	37	∞
8	45	∞
9	46	∞
10	46	∞

Turnbull intervals

Sub. #	t_0	t_1	t_2	t_3	t_4	t_5	t_6	t_7	t_8	t_9	t_{10}	t_{11}	t_{12}
1	0		7										
2	0			8									
3		6			10								
4			7				16						
5			7			14							
6								17					∞
7									37	44			
8											45		∞
9												46	∞
10												46	∞
		(6	7](7	8]					(37	44]		(46	∞)

Breast cosmesis data

- Two treatments for breast cancer, radiation (Rad, n=46), and radiation with chemotherapy (RadChem, n=48)
- Response: Time in months until breast retraction (Finkelstein & Wolfe, BCS, 1985)
- Use R package **interval: icfit** function
  - **icfit** function calculates NPMLE by EM algorithm
  - download package **Icens** from bioconductor
- R codes
  - > library(interval)
  - > data(bcos)
  - > fit=icfit(Surv(left,right,type="interval2")~treatment, data=bcos)
  - > summary(fit)
  - > plot(fit)

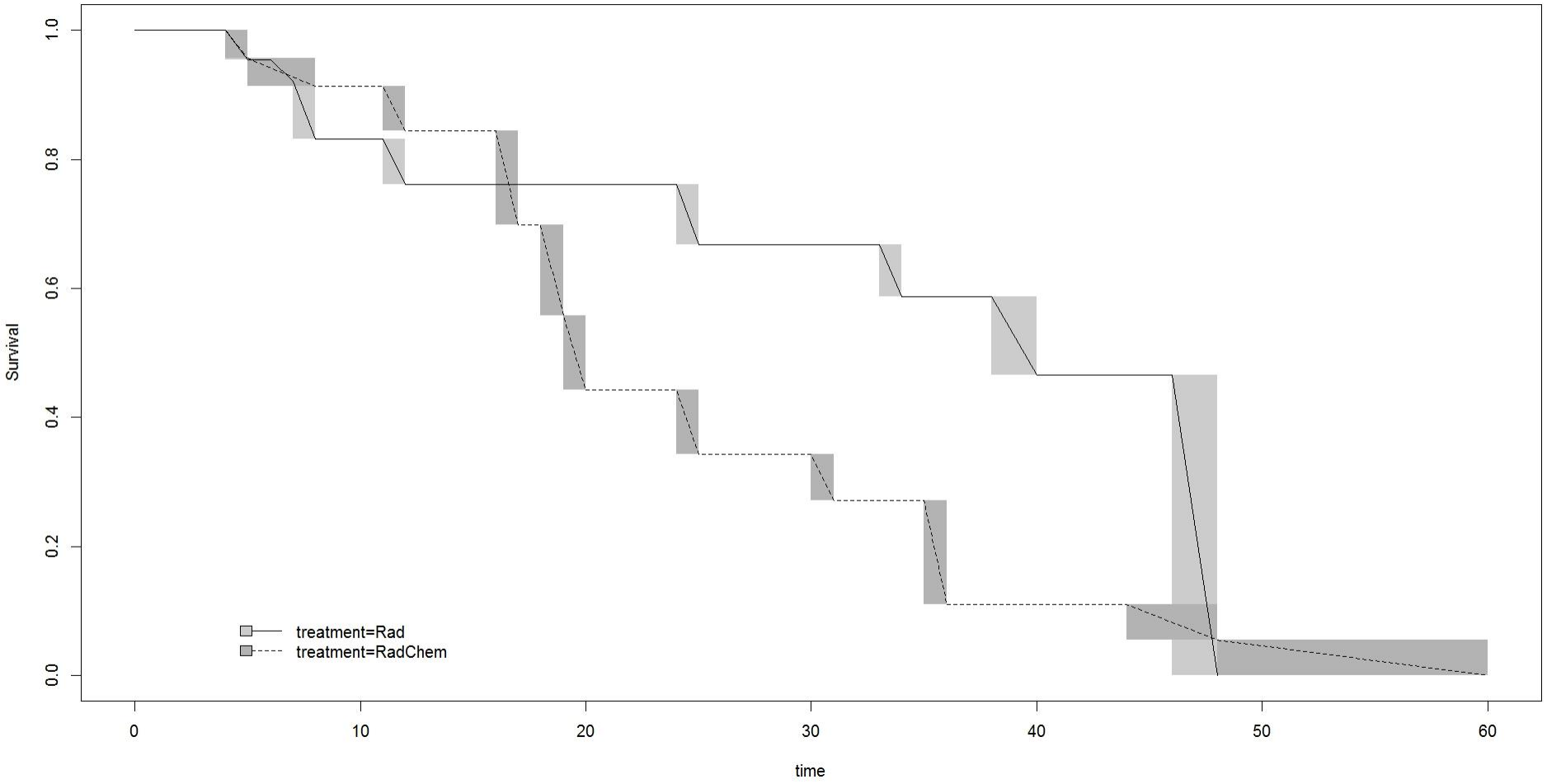
Breast cosmesis data

```
> head(bcos)
  left right treatment
1   45   Inf       Rad
2    6    10       Rad
3    0     7       Rad
4   46   Inf       Rad
5   46   Inf       Rad
6    7    16       Rad
```

Breast cosmesis data

```
> summary(fit)
treatment=Rad:
  Interval Probability
1    (4,5]      0.0463
2    (6,7]      0.0334
3    (7,8]      0.0887
4   (11,12]     0.0708
5   (24,25]     0.0926
6   (33,34]     0.0818
7   (38,40]     0.1209
8   (46,48]     0.4656
treatment=RadChem:
   Interval Probability
1     (4,5]      0.0433
2     (5,8]      0.0433
3    (11,12]     0.0692
4    (16,17]     0.1454
5    (18,19]     0.1411
6    (19,20]     0.1157
7    (24,25]     0.0999
8    (30,31]     0.0709
9    (35,36]     0.1608
10   (44,48]     0.0552
11   (48,60]     0.0552
```

Breast cosmesis data



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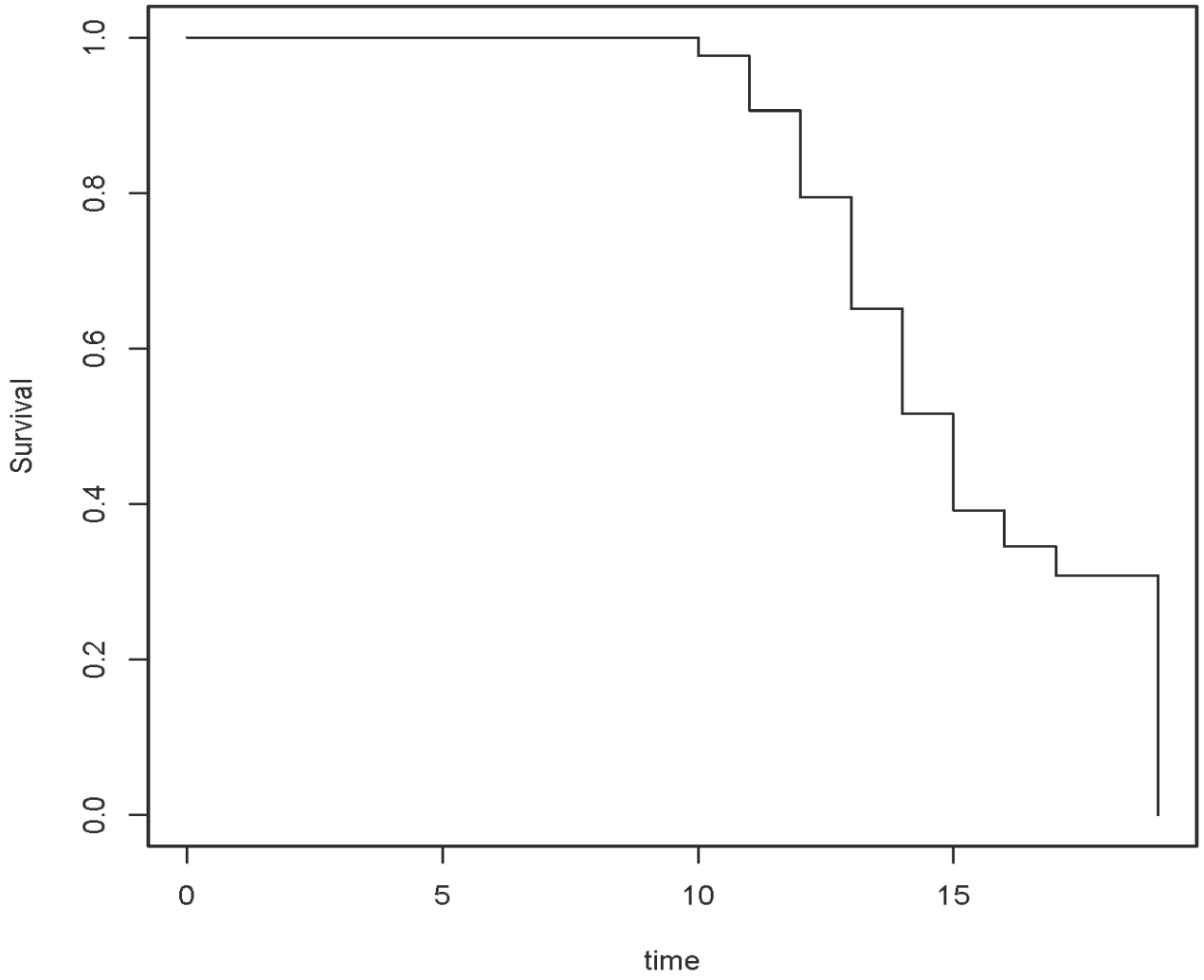
Marijuana data

- library(interval)
- Age=10:19
- Exact=c(4,12,19,24,20,13,3,1,0,4)
- L.Exact=rep(Age,Exact)
- R.Exact=rep(Age,Exact)
- R.Censored=c(0,0,2,15,24,18,14,6,0,0)
- L.R.Censored=rep(Age,R.Censored)
- R.R.Censored=rep(Inf,sum(R.Censored))
- L.Censored=c(0,0,0,1,2,3,2,3,1,0)
- L.L.Censored=rep(0,sum(L.Censored))
- R.L.Censored=rep(Age,L.Censored)
- marijuana=data.frame(left=c(L.Exact,L.R.Censored,L.L.Censored),right=c(R.Exact,R.R.Censored,R.L.Censored))
- fit=icfit(Surv(left,right,type="interval2")~1, data=,marijuana)
- summary(fit)
- plot(fit)

Marijuana data

```
> head(marijuana)
  left right
1   10    10
2   10    10
3   10    10
4   10    10
5   11    11
6   11    11
```

Marijuana data



로그순위검정

구간중도절단자료에서 생존함수 비교

생존함수 비교

로그순위검정

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생존함수 비교

Comparison of survivor functions

- Test whether or not the survivor functions for two or more groups are equivalent
  - $H_o: S_1(\mathrm{t}) = \cdots = S_g(t), \forall t > 0$
- $t_1 < \cdots < t_D$: distinct survival times by pooling all the sample from two groups (set $g = 2$)
- d_{ij}: observed # of failures at t_j in group $i, i = 1,2; j = 1, \ldots, D$
  - $d_j = \sum_{i=1}^{2} d_{ij}$
- n_{ij}: # of individuals at risk just prior to t_j in group i
  - $n_j = \sum_{i=1}^{2} n_{ij}$

Comparison of survivor functions

- Idea: Based on

$$Z_i = \sum_{j=1}^{D} \left(d_{ij} - d_j \frac{n_{ij}}{n_j} \right) = \sum_{j=1}^{D} \left(O_{ij} - \widehat{E}_{ij} \right)$$

- Log-rank statistic
  - $X^2 = \left[\sum_{j=1}^{D} \left(O_{ij} - \widehat{E}_{ij} \right) \right]^2 \Big/ \sum_{j=1}^{D} d_j \frac{n_{ij}}{n_j} \left(1 - \frac{n_{ij}}{n_j} \right) \left(\frac{n_j - d_j}{n_j - 1} \right) \sim \chi^2(1)$ under H_0
  - If $X^2 > \chi^2_\alpha(1)$, reject a test for equality of the survivor functions at level α

Remarks for log-rank test

- Choice of weight function: $W(t_j)$, specially $W(t_j) = 1$ for log-rank test
  - $W(t_j) = \hat{S}(t_j)^p(1 - \hat{S}(t_j)^q$: Fleming-Harrington (CommStat, 1981)
  - $p = q = 0$: log-rank test, $p = 1, q = 0$: Peto-Peto test
- Extension to three or more groups
- Stratification on a set of covariates
- Trend test for ordered alternatives: plugging in any set of scores

Illustration (revisited)

- AML 자료에서 화학요법 지속그룹과 비지속그룹의 재발시간분포가 동일한가?
- Three types of test statistic
  - Log-rank=3.4 (*p*-value=0.0653) with $W(t_j) = 1$
  - Peto-Prentice=2.8 (*p*-value=0.0955) with $W(t_j) = \hat{S}(t_j)$
  - Flaming-Harrington=4.2 (*p*-value=0.041) with $W(t_j) = \hat{S}(t_j)^{-1}$

Illustration (revisited)

- R codes
  - library(survival)
  - fit=survfit(Surv(Time,Status)~Group, data=aml)
  - plot(fit, lty=1:2, xlab="Time(in weeks)", ylab="Estimated survival probability")
  - legend("topright",lty=1:2, c("Chemo","Non-Chemo"))
  - lr.fit=survdiff(Surv(Time,Status)~Group, data=aml)
  - pp.fit=survdiff(Surv(Time,Status)~Group, data=aml, rho=1)
  - fh.fit=survdiff(Surv(Time,Status)~Group, data=aml, rho=-1)

Illustration (revisited)

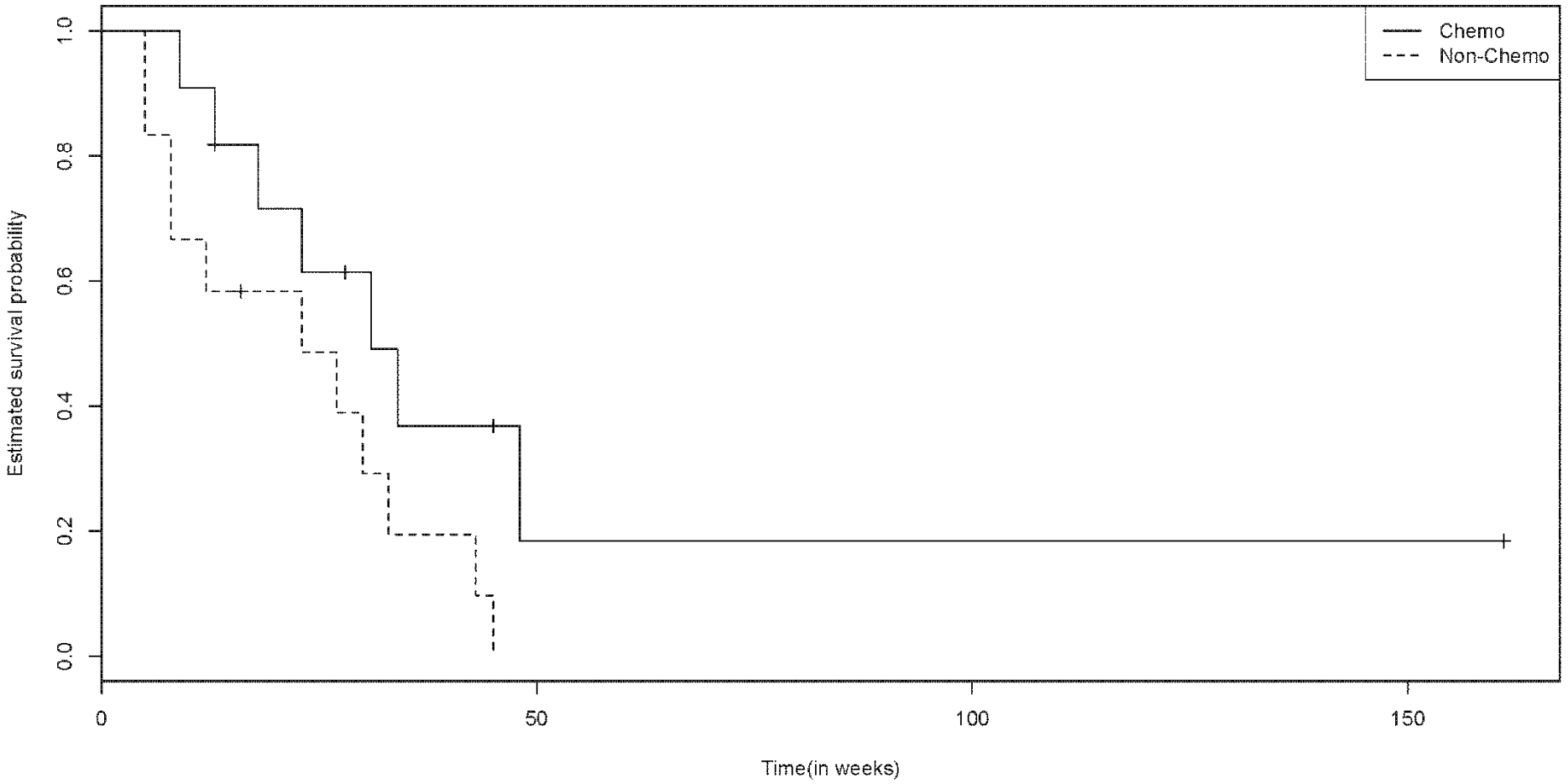


Illustration (revisited)

```
> lr.fit
Call:
survdiff(formula = Surv(Time, Status) ~ Group, data = aml)

                 N Observed Expected (O-E)^2/E (O-E)^2/V
Group=Chemo     11        7    10.69      1.27       3.4
Group=Non.Chemo 12       11     7.31      1.86       3.4

 Chisq= 3.4  on 1 degrees of freedom, p= 0.0653
```

로그순위검정

구간중도절단자료에서 생존함수 비교

생존함수 비교

Notation

- $\hat{S}$: NPMLE of S_i's under $H_0: S_1 = \cdots = S_g$
- $\delta_i = 0$ if right-censored and otherwise, 1
- $\rho_{ij} = I(\delta_i = 0, L_i \geq t_j)$, i.e., $\rho_{ij} = 1$ if T_i is right-censored and subject i is still at risk at t_i-
- Define the estimates of the total observed failures and risk numbers, respectively, as
  - $d_j = \sum_{i=1}^{n} \delta_i \frac{\alpha_{ij}\left[\hat{S}\left(t_j^-\right) - \hat{S}(t_j)\right]}{\sum_{l=1}^{m+1} \alpha_{il}\left[\hat{S}\left(t_l^-\right) - \hat{S}(t_l)\right]}, j = 1, \ldots, m$
  - $n_j = \sum_{i=1}^{n} \delta_i \frac{\sum_{r=j}^{m+1} \alpha_{ir}[\hat{S}(t_r^-) - \hat{S}(t_r)]}{\sum_{l=1}^{m+1} \alpha_{il}\left[\hat{S}\left(t_l^-\right) - \hat{S}(t_l)\right]} + \sum_{i=1}^{n} \rho_{ij}, j = 1, \ldots, m$
- Similarly, define d_{jk} and n_{jk} from subjects in group $k, k = 1,2$

Weighted log-rank tests

- Define $U_1 = \sum_{j=1}^{m} \left(d_{j1} - d_j \frac{n_{j1}}{n_j} \right)$
- Estimation of the variance of U_1 : employ resampling methods such as multiple imputation, bootstrap, and permutation procedures
- Remark
  - With $W(t) = 1$,
    $U_1 = \int_0^{\infty} W(t) \frac{Y_1(t)Y_2(t)}{Y_1(t)+Y_2(t)} \left[d\widehat{\Lambda}_1(t) - d\widehat{\Lambda}_2(t) \right]$
    - $Y_k(t) = \sum_{j|t_j \le t} n_{jk}$ and $\widehat{\Lambda}_k(t) = \sum_{j|t_j \le t} \frac{d_{jk}}{n_{jk}}$

Illustration (revisited)

- 유방암 자료에서 두 가지 치료방법(Rad , RadChem)에 띠라 유방 함몰 시점까지의 분포가 동일한가?
- Three types of test statistic
  - Log-rank=-2.67 (*p*-value=0.008) with $W(t_j) = 1$
  - Finkelstein(BCS, 1986)=-2.69 (*p*-value=0.007) with $W(t_j) \approx 1$
  - Wilcoxon-Mann-Whitney=-2.16 (*p*-value=0.03) with $W(t_j) = \hat{S}(t_j^-)$

Illustration (revisited)

- R codes
  - library(interval)
  - data(bcos)
  - lr.fit=ictest(Surv(left,right,type="interval2")~treatment, data=bcos)
  - f.fit=ictest(Surv(left,right,type="interval2")~treatment, data=bcos, score="logrank2")
  - wmw.fit=ictest(Surv(left,right,type="interval2")~treatment, data=bcos, score="wmw“)

Illustration (revisited)

```
> lr.fit

  Asymptotic Logrank two-sample test (permutation form), Sun's scores

data:  Surv(left, right, type = "interval2") by treatment
Z = -2.6684, p-value = 0.007622
alternative hypothesis: survival distributions not equal

                    n Score Statistic*
treatment=Rad      46        -9.141846
treatment=RadChem 48         9.141846
* like Obs-Exp, positive implies earlier failures than expected
```

콕스비례위험모형

구간중도절된 자료의 콕스비례위험모형

회귀모형

Cox proportional hazards model

- Why regression models need?
  - To predict covariates(or explanatory variables, risk factors) for time to event
- Data: $\{(t_j, \delta_j, z_j); t_j = \min(x_j, c_j), \delta_j = I(t_j = x_j), j = 1, \dots, n\}$
- Cox model: $\lambda(t|z) = \lambda_0(t) \exp\{\beta' z\}$
  - Hazard rate at t for an individual with risk vector z
- A sort of semiparametric model
  - parametrically for the covariate effect + nonparametrically for baseline hazard function
- Why PH is called?
  - RR(or HR)=$\frac{\lambda(t|z)}{\lambda(t|z^*)} = \exp\{\sum_k \beta_k (z_k - z_k^*)\}$ is constant against t

Partial likelihood

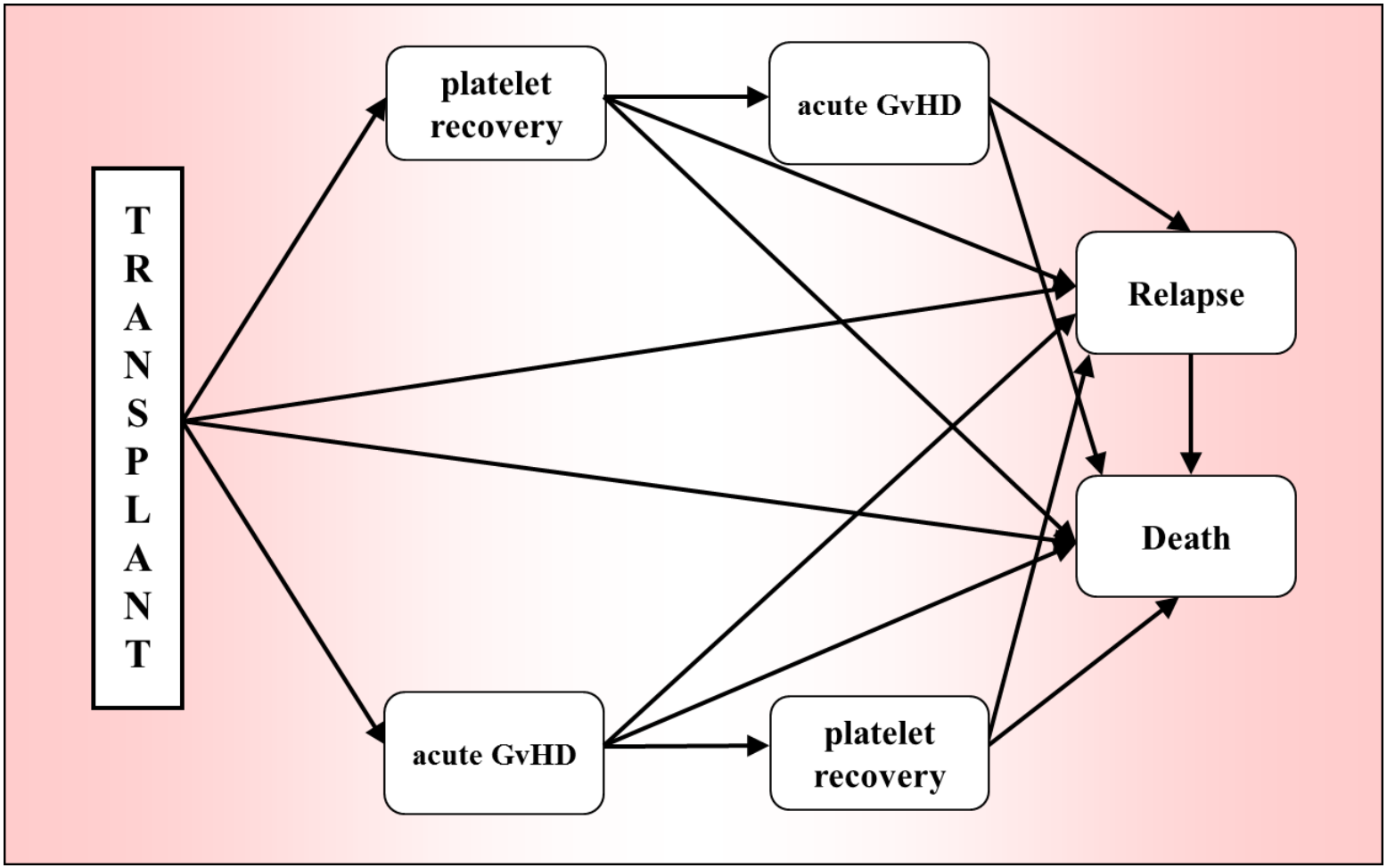
- $t_1 < \cdots < t_D$: ordered event times
- $z_{(i)k}$: kth covariate associated with the individual whose failure time is t_i
- $R(t_i)$: set of individuals who are still under study at a time prior to t_i
- Partial likelihood:

$$L(\beta) = \prod_{i=1}^{D} \frac{\exp\{\sum_k \beta_k z_{(i)k}\}}{\sum_{j \in R(t_i)} \exp\{\sum_k \beta_k z_{jk}\}}$$

BMT data (revisted)

- Data on 137 bone marrow transplant patients
- Risk factors: patient and donor age, sex, and CMV status, waiting time from diagnosis to transplantation, FAB, MTX
- Three groups: AML low risk(54), AML high risk(45), ALL(38)
- Survival times
  - T_1: time(in days) to death or end of study
  - T_2: disease-free survival time(time to relapse, death or end of study)
  - T_A: time to acute GvHD
  - T_C: time to chronic GvHD
  - T_P: time to return of platelets to normal levels

Simplified recovery process from BMT data



Fixed risk factors

- z_1=1 if AML low-risk, z_2=1 if AML high-risk
- z_3=waiting time
- z_4=FAB(binary)
- z_5=MTX(binary)
- z_6=1 if donor: male; z_7=1 if patient: male; $z_8 = z_6 \times z_7$=1 if donor & patient: male
- z_9=1 if donor: CMV positive; z_{10}=1 if patient: CMV positive; $z_{11} = z_9 \times z_{10}$=1 if donor & patient: CMV positive
- z_{12}=donor age-28; z_{13}=patient age-28; $z_{14} = z_{12} \times z_{13}$

BMT data

```
> head(bmt)
  DG   TD  TDF DI RI DFI   TA AI  TC CI TP PI PAGE DAGE PSEX DSEX PCMV DCMV   WT FAB
1  1 2081 2081  0  0   0   67  1 121  1 13  1   26   33    1    0    1    1   98   0
2  1 1602 1602  0  0   0 1602  0 139  1 18  1   21   37    1    1    0    0 1720   0
3  1 1496 1496  0  0   0 1496  0 307  1 12  1   26   35    1    1    1    0  127   0
4  1 1462 1462  0  0   0   70  1  95  1 13  1   17   21    0    1    0    0  168   0
5  1 1433 1433  0  0   0 1433  0 236  1 12  1   32   36    1    1    1    1   93   0
6  1 1377 1377  0  0   0 1377  0 123  1 12  1   22   31    1    1    1    1 2187   0
  H MTX p28 d28
1 1   0  -2   5
2 1   0  -7   9
3 1   0  -2   7
4 1   0 -11  -7
5 1   0   4   8
6 1   0  -6   3
>
```

Local tests

- $H_0: \beta_1 = \beta_{10}, \beta = (\beta_{10}, \beta_{20})$
  - Wald test: $X_W^2 = (b_1 - \beta_{10})'[I^{11}(b)]^{-1}(b_1 - \beta_{10}) \sim \chi^2(q)$
  - Likelihood ratio test: $X_{LR}^2 = 2\{LL(b) - LL[\beta_{10}, b_2(\beta_{10})]\} \sim \chi^2(q)$
  - Score test: $X_{SC}^2 = U_1[\beta_{10}, b_2(\beta_{10})]' I^{11}(\beta_{10}, b_2(\beta_{10})) U_1[\beta_{10}, b_2(\beta_{10})] \sim \chi^2(q)$
- 공변량 z_1, z_2를 포함하여 유의한 공변량을 전진선택법으로 선택하면, $z_4 \rightarrow (z_{12}, z_{13}, z_{14})$ 순으로 선택됨

Tentative model (fixed only)

- R codes
  - library(survival)
  - bmt=read.csv(file="bmt.csv",header=T)
  - fit.fab=coxph(Surv(TDF,DFI)~factor(DG)+FAB, data=bmt)
    # Cox model after adjusting for the risk groups
  - df=1
  - pos=3
  - coef=fit.fab$coefficients[pos]
  - var=fit.fab$var[pos,pos]
  - wald=t(coef)%*%solve(var)%*%coef
  - fab.pvalue=pchisq(wald,df,lower.tail=FALSE)

Tentative model (fixed only)

- bmt$p28=bmt$PAGE-28
- bmt$d28=bmt$DAGE-28
- fit.age=coxph(Surv(TDF,DFI)~factor(DG)+FAB+p28+d28+p28*d28, data=bmt) # Cox model after adjusting for the risk groups and FAB
- df=3
- pos=4:6
- coef=fit.age$coefficients[pos]
- var=fit.age$var[pos,pos]
- wald=t(coef)%*%solve(var)%*%coef
- age.pvalue=pchisq(wald,df,lower.tail=FALSE)

Tentative model (fixed only)

```
> fit.age
Call:
coxph(formula = Surv(TDF, DFI) ~ factor(DG) + FAB + p28 + d28 +
    p28 * d28, data = bmt)


                coef exp(coef) se(coef)      z       p
factor(DG)2 -1.09065     0.336 0.354279 -3.078 0.00210
factor(DG)3 -0.40391     0.668 0.362777 -1.113 0.27000
FAB          0.83742     2.310 0.278464  3.007 0.00260
p28          0.00682     1.007 0.019683  0.347 0.73000
d28          0.00387     1.004 0.018256  0.212 0.83000
p28:d28      0.00316     1.003 0.000951  3.323 0.00089

Likelihood ratio test=32.8  on 6 df, p=1.14e-05  n= 137, number of events= 83
```

Other regression models

- Additive hazards model: $\lambda(t|z) = \lambda_0(t) + \beta' z$
- Accelerated failure time model: $\log T_i = \beta' z + \epsilon$
  - Focus on direct relationship between z and time to event
  - Effect of covariates is multiplicative on t rather than on hazard function
  - Parametric, but providing a good fit if correctly chosen

Refinements of Cox model

- Stratification
  - When the PH assumption is violated for some covariate
  - $\lambda_j(t|z) = \lambda_{0j}(t)\exp\{\beta' z\}, j = 1, \ldots, s$

- Time-dependent covariates
  - eg, BP, cholesterol, size of the tumor, …
  - $\lambda(t|z(t)) = \lambda_0(t)\exp\{\beta' z(t)\}$

BMT data (revisited)

- Platelet recovery를 time-varying 공변량으로 간주한다면,
  - eg, id=1, TDF=2081, DFI=0, TP=13, PI=1:
    - (start,end)=(0,13), p.status=0
    - (start,end)=(13,2081), p.status=1
- 공변량 z_1, z_2를 포함하여 유의한 time-varying 공변량을 전진선택법으로 선택하면, acute GvHD, chronic GvHD, platelet recovery 중에서 platelet recovery 만 선택됨

Making time-varying covariates

```
> head(bmt[1:3,])
  DG   TD  TDF DI RI DFI   TA AI  TC CI TP PI PAGE DAGE PSEX DSEX PCMV DCMV   WT FAB
1  1 2081 2081  0  0   0   67  1 121  1 13  1   26   33    1    0    1    1   98   0
2  1 1602 1602  0  0   0 1602  0 139  1 18  1   21   37    1    1    0    0 1720   0
3  1 1496 1496  0  0   0 1496  0 307  1 12  1   26   35    1    1    1    0  127   0
  H MTX p28 d28
1 1   0  -2   5
2 1   0  -7   9
3 1   0  -2   7
> head(p.bmt)
  id start  end status group p.status
1  1     0   13      0     1        0
2  1    13 2081      0     1        1
3  2     0   18      0     1        0
4  2    18 1602      0     1        1
5  3     0   12      0     1        0
6  3    12 1496      0     1        1
```

Cox PH model (time-varying)

```
> fit.p
Call:
coxph(formula = Surv(start, end, status) ~ factor(group) + p.status,
    data = p.bmt)


                  coef exp(coef) se(coef)     z       p
factor(group)2 -0.497     0.608    0.289 -1.72 0.08600
factor(group)3  0.382     1.465    0.268  1.43 0.15000
p.status       -1.120     0.326    0.329 -3.40 0.00067

Likelihood ratio test=22.9  on 3 df, p=4.29e-05  n= 256, number of events= 83
   (1 observation deleted due to missingness)
> wald
        [,1]
[1,] 11.5813
> p.pvalue
              [,1]
[1,] 0.0006661839
```

Tests of PH assumption

- Use of time-dependent covariate methodology
- To test the proportionality assumption for a fixed-time covariate, z_1, create a time-dependent covariate, $z_2(t) = z_1 \times g(t)$
- In many applications, take $g(t) = \ln t$
- PH model: $\lambda(t|z_1) = \lambda_0(t) \exp\{\beta_1 z_1 + \beta_2 z_2(t)\}$
  - HR=$\frac{\lambda(t|z_1)}{\lambda(t|z_1^*)} = \exp\{\beta_1(z_1 - z_1^*) + \beta_2 g(t)(z_1 - z_1^*)\}$: depend on t if $\beta_2 \neq 0$
  - Test of $H_0: \beta_2 = 0$ is equivalent to test for the proportional hazards assumption
  - Power of detecting non-proportionality: depend on the choice of $g(t)$

BMT data (revisited)

- 공변량들 중에서 MTX만 PH 가정을 만족 못하여 MTX에 대해서는 층화

```
> fit.mtx
Call:
coxph(formula = Surv(TDF, DFI) ~ MTX + tv.mtx, data = bmt)


         coef exp(coef) se(coef)     z       p
MTX     11.65  1.14e+05    1.509  7.72 1.2e-14
tv.mtx -1.95  1.42e-01    0.284 -6.87 6.6e-12

Likelihood ratio test=90.4  on 2 df, p=0  n= 137, number of events= 83
> wald
          [,1]
[1,] 47.12934
> mtx.pvalue
                [,1]
[1,] 6.645335e-12
```

Final model (fixed only)

```
> fit.final
Call:
coxph(formula = Surv(TDF, DFI) ~ factor(DG) + FAB + p28 * d28 +
    strata(MTX), data = bmt)


                coef exp(coef) se(coef)      z      p
factor(DG)2 -1.03391     0.356 0.364650 -2.8354 0.0046
factor(DG)3 -0.33763     0.713 0.367826 -0.9179 0.3600
FAB          0.90843     2.480 0.278913  3.2570 0.0011
p28          0.00547     1.005 0.019968  0.2741 0.7800
d28         -0.00175     0.998 0.018163 -0.0963 0.9200
p28:d28      0.00286     1.003 0.000951  3.0021 0.0027

Likelihood ratio test=31.1  on 6 df, p=2.4e-05  n= 137, number of events= 83
```

콕스비례위험모형

구간중도절된 자료의 콕스비례위험모형

회귀모형

Cox model with IC data

- Data: $\{(l_i, r_i], z_i); i = 1, \ldots, n\}$
- Cox model: $\lambda(t|z) = \lambda_0(t) \exp\{\beta' z\}$
- Unlike right-censored data, estimating β under interval censoring involve estimation of both β and the cumulative baseline hazard function, $\Lambda_0(t) = \int_0^t \lambda_0(s) ds$

ML approach

- Likelihood function: $L = \prod_{i=1}^{n} [S(l_i|z_i) - S(r_i|z_i)]$
  - $S(t|z) = S_0(t)^{\exp\{\beta' z\}}$: Survival function for a subject with covariates z
- Log-likelihood: Assuming that $l_i < r_i, \forall i$,
  - $l(\beta, S_0) = \sum_{i=1}^{n} \log\{[S_0(l_i)^{\exp\{\beta' z\}} - S_0(r_i)^{\exp\{\beta' z\}}]\}$
  - S_0: baseline survival function, $S_0(t) = \exp\{-\Lambda_0(t)\}$
- Focus on estimation of S_0 at the different observation time points, i.e., $0 = t_0 < t_1 < \cdots < t_m < t_{m+1} = \infty$, of the form,
  - $S_0(t) = \prod_{j|t_j \le t} \exp\{e^{\alpha_j}\} = \exp\left\{\sum_{j|t_j \le t} e^{\alpha_j}\right\}$
  - $\alpha = (\alpha_1, \ldots, \alpha_m)$: unknown parameters

ML approach

- $l(\beta, S_0)$ can be rewritten as
  - $l(\beta, \alpha) = \sum_{i=1}^{n} \log\{\sum_{j=1}^{m+1} \alpha_{ij}[\exp\{-a_{j-1}\exp\{\beta' z\}\} - \exp\{-a_j \exp\{\beta' z\}\}]\}$
    - $a_j = \sum_{k=1}^{j} e^{\alpha_k}$
- Use the Newton-Raphson algorithm to determine the MLE of β and α (Finkelstein, BCS, 1986)
- Asymptotic properties (Huang & Wellner, 1997)
  - $\hat{S}_0$: strongly consistent
  - $\hat{\beta}$: asymptotically normal with the usual $\sqrt{n}$-convergence rate and efficient

Breast cosmesis data (revisited)

- intcox package을 사용할 수 있지만 모수 추정만 제공되고 se는 제공 안됨
  - permutation test를 이용
  - 붓스트랩 방법 이용

```
> fit
Call:
intcox(formula = Surv(left, right, type = "interval2") ~ treatment
    data = bcos)


                   coef exp(coef) se(coef)  z  p
treatmentRadChem 0.776      2.17        NA NA NA

Likelihood ratio test=NA  on 1 df, p=NA  n= 94
```

군집생존자료분석
재발사건자료분석
다상태모형
경쟁위험모형

다변량 생존자료분석

다변량 생존자료의 분류

자료유형	순서 존재 여부	
	Yes	No
동일한 유형	재발사건자료 (recurrent event data)	군집생존자료 (clustered survival data)
다른 유형	다상태모형 (multi-state model)	경쟁위험모형 (competing risks model)

군집생존자료분석
재발사건자료분석
다상태모형
경쟁위험모형

다변량 생존자료분석

두 가지 예

- 당뇨병성 환자의 시력 손실 자료
  - 시력 손실을 지연시키기 위한 방법인 laser photocoagulation의 효과를 조사
  - 한쪽 눈에는 레이저 치료를 하고, 다른 한쪽 눈에는 하지 않음
- 발암물질로 인한 쥐의 생존시간 자료
  - 같은 어미에서 태어난 세 마리 새끼를 군집으로 잡고, 그들 중에서 한 마리만 발암물질에 노출시킴

두 가지 예

```
> head(diabetes)
  id      time status trteye treat adult agedx
1  5 46.24967      0      2     1     2    28
2  5 46.27553      0      2     0     2    28
3 14 42.50684      0      1     1     1    12
4 14 31.34145      1      1     0     1    12
5 16 42.30098      0      1     1     1     9
6 16 42.27406      0      1     0     1     9
```

```
> head(rats)
  litter rx time status
1      1  1  101      0
2      1  0   49      1
3      1  0  104      0
4      2  1  104      0
5      2  0  102      0
6      2  0  104      0
```

Conditional vs. Marginal

- Data:
  $\{(t_{ik} = \min(x_{ik}, c_{ik}), \delta_{ik} = I(t_{ik} = x_{ik}), z_{ik}); i = 1, \dots, g, k = 1, \dots, n_i\}$
- Conditional method
  - $\lambda_{ik}(t|z_{ik}, a_i) = \lambda_{0i}(t)\exp(\beta' z_{ik})$
    - λ_{0i}: i번째 군집의 효과
    - z_{ik}가 유일한 binary covariate라면 조건부 방법은 같은 군집 내에 속한 두 그룹을 비교하는 것과 같음. 즉, $\exp(\beta)$는 같은 군집에 속한 두 그룹 간의 사건발생 위험률의 비를 나타냄
  - 군집효과의 추정은, 랜덤효과모형을 이용. 즉, $\lambda_{0i}(t) = \lambda_0(t)\exp(a_i), a_i$ ~Gamma with mean 1 and variance θ,
- Marginal method
  - $\lambda_{ik}(t|z_{ik}) = \lambda_0(t)\exp(\beta' z_{ik})$
    - 군집 내 관측값들이 서로 독립이라고 가정
  - 일치추정량이 되며 (Lin & Wei, JASA, 1989), model misspecificarion은 극복하기 위해 sandwich 분산 추정량을 사용

Diabetic retinopathy data (revisited)

```
> cond.fit
Call:
coxph(formula = Surv(time, status) ~ trt * adult + frailty(id),
    data = drs)

               coef   se(coef) se2   Chisq  DF   p
trt          -0.505 0.225    0.221   5.03  1.0 0.0250
adult         0.397 0.259    0.205   2.35  1.0 0.1300
frailty(id)                          122.55 88.6 0.0098
trt:adult    -0.986 0.362    0.355   7.43  1.0 0.0064

Iterations: 6 outer, 31 Newton-Raphson
     Variance of random effect= 0.926   I-likelihood = -847
Degrees of freedom for terms=  1.0  0.6 88.6  1.0
Likelihood ratio test=218  on 91.1 df, p=1.86e-12  n= 394
```

Diabetic retinopathy data `

```
> marg.fit
Call:
coxph(formula = Surv(time, status) ~ trt * adult + cluster(id),
    data = drs)


             coef exp(coef) se(coef) robust se     z      p
trt        -0.425     0.654    0.218     0.185 -2.30 0.0220
adult       0.341     1.407    0.199     0.196  1.74 0.0810
trt:adult -0.846     0.429    0.351     0.304 -2.79 0.0053

Likelihood ratio test=28.5  on 3 df, p=2.86e-06  n= 394, number of events= 155
```

Rats data (revisited)

```
> rats.cond.fit
Call:
coxph(formula = Surv(time, status) ~ rx + frailty(litter), data = rats)

                 coef  se(coef) se2   Chisq DF   p
rx               0.914 0.323    0.319  8.01  1.0 0.0046
frailty(litter)                       17.69 14.4 0.2400

Iterations: 6 outer, 24 Newton-Raphson
     Variance of random effect= 0.499   I-likelihood = -180.8
Degrees of freedom for terms=  1.0 14.4
Likelihood ratio test=37.6  on 15.4 df, p=0.00124  n= 150
> rats.marg.fit
Call:
coxph(formula = Surv(time, status) ~ rx + cluster(litter), data = rats)


    coef exp(coef) se(coef) robust se    z      p
rx 0.905      2.47    0.318     0.303 2.99 0.0028

Likelihood ratio test=7.98  on 1 df, p=0.00474  n= 150, number of events= 40
```

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다변량 생존자료분석

Bladder data

- 방광암을 앓고 있는 환자에 대해, thiothepa 치료의 종양 재발에 미치는 효과를 조사
- 병원을 방문할 때마다 새로운 종양의 발병여부를 조사하고 제거
- 환자마다 재발시점과 재발횟수가 같지 않음

```
> head(bladder2)
  id rx number size start stop event enum
1  1  1      1    3     0    1     0    1
2  2  1      2    1     0    4     0    1
3  3  1      1    1     0    7     0    1
4  4  1      5    1     0   10     0    1
5  5  1      4    1     0    6     1    1
6  5  1      4    1     6   10     0    2
```

Bladder data

```
> bladder
    id rx number size stop event enum
1    1  1      1    3    1     0    1
2    1  1      1    3    1     0    2
3    1  1      1    3    1     0    3
4    1  1      1    3    1     0    4
5    2  1      2    1    4     0    1
6    2  1      2    1    4     0    2
7    2  1      2    1    4     0    3
8    2  1      2    1    4     0    4
9    3  1      1    1    7     0    1
10   3  1      1    1    7     0    2
11   3  1      1    1    7     0    3
12   3  1      1    1    7     0    4
13   4  1      5    1   10     0    1
14   4  1      5    1   10     0    2
15   4  1      5    1   10     0    3
16   4  1      5    1   10     0    4
17   5  1      4    1    6     1    1
18   5  1      4    1   10     0    2
19   5  1      4    1   10     0    3
20   5  1      4    1   10     0    4
```

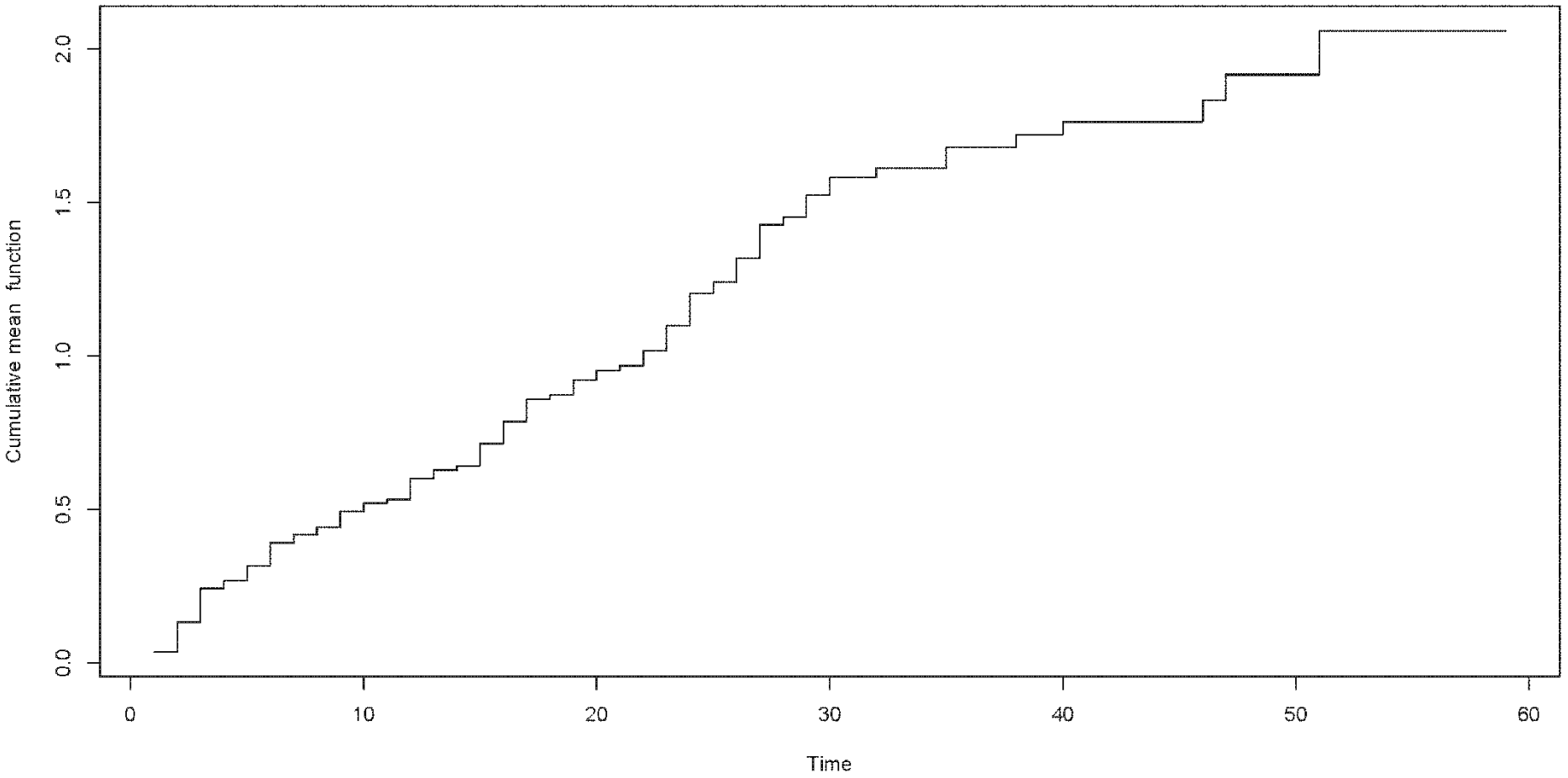
Intensity function vs. Cumulative mean function

- 개체 내 재발사건을 동일한 사건으로 간주
- $t_{i1} < \cdots < t_{im_i} (i = 1, \ldots, n)$: i번째 개체의 재발 사건 시점
- $N_i(t) = \sum_{j=1}^{m_i} I(t_{ij} \leq t)$: i번째 개체의 t 시점까지 발생된 재발사건의 총 횟수
- $H_i(t) = \{N_i(s): 0 \leq s < t\}$: i번째 개체의 t 시점적전까지의 재발사건에 대한 기록
- Intensity function
  - $\lambda(t|H_i(t)) = \lim_{\Delta t \to 0} \frac{P(dN_i(t)=1|H_i(t))}{\Delta t} = \rho(t)$ (w/o covariate)
  - $\lambda(t|H_i(t), z_i) = \rho_i(t) = \rho_0(t) \exp(\beta' z_i)$ (w/ covariate)
- Cumulative mean function
  - $\mu(t) = \int_0^t \rho(s) ds = E\{N_i(t)\}$(w/o covariate)
  - $\mu_i(t|z_i) = \mu_0(t) \exp(\beta' z_i)$ (w/ covariate)
    - $\mu_0(t) = \int \rho_0(s) ds$: baseline cumulative mean function

Non-parametric method

- $t_1 < \cdots < t_H$: distinct event times across all individuals
- NPMLE for $\mu(t)$
  - $\hat{\mu}(t) = \sum_{h:t_h \le t} \frac{\sum_{i=1}^{n} Y_i(t_h) dN_i(t_h)}{\sum_{i=1}^{n} Y_i(t_h)}$
    - $Y_i(t) = I(t \le \tau_i)$, τ_i: termination time, end-of-follow-up time, or censoring time
  - Same as Nelson-Aalen estimator

Bladder data (revisited)



Semi-parametric method

Method	Risk interval	Risk set	Baseline hazard
Andersen & Gill (AG)	Counting process	Unrestricted	Common
Prentice, Williams & Peterson (PWP-CP)	Counting process	Restricted	Event-specific
Prentice, Williams & Peterson (PWP-GP)	Gap time	Restricted	Event-specific
Wei, Lin & Weissfeld (WLW)	Total time	Semi-restricted	Event-specific

Hypothetical example

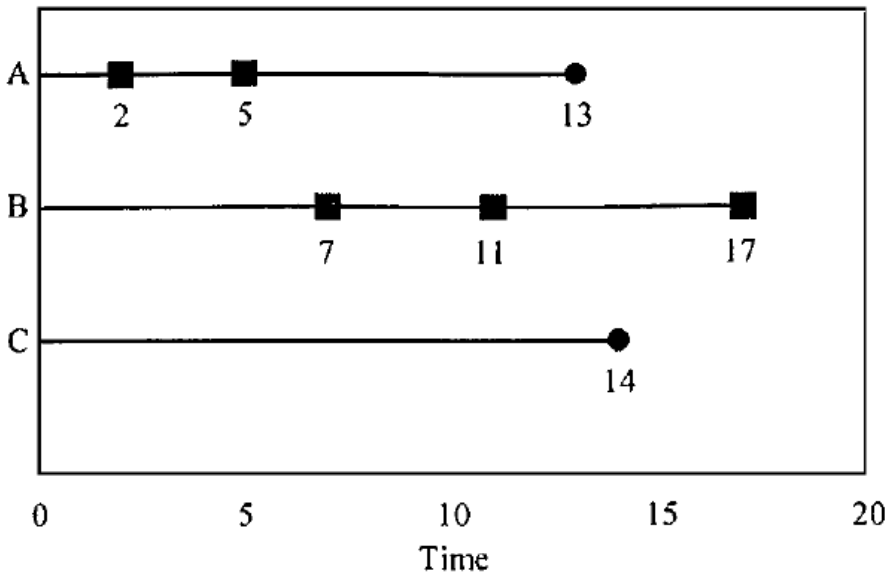


Figure 1. A hypothetical example of three subjects with recurrent events. Observations start at the same time; ■ is the occurrence of an event and ● is censoring. Subject A has two events before being censored; subject B has three events, ending the period of observation with an event; and subject C has no events before being censored

Three types of risk interval

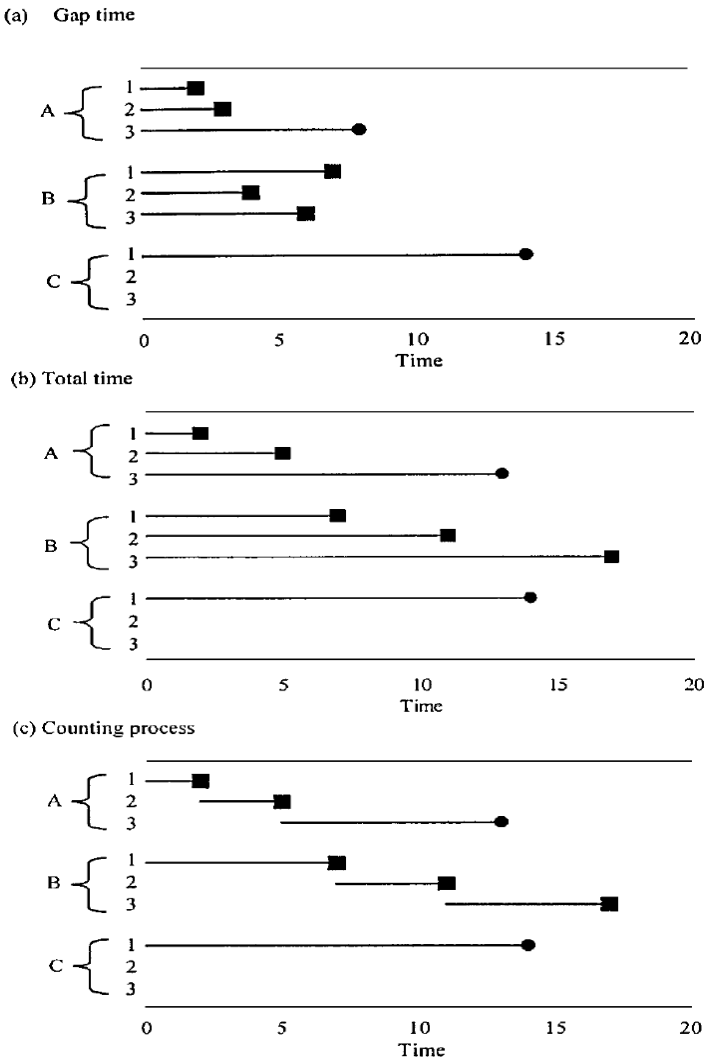


Figure 2. Illustrations of the risk interval formulations: (*a*) gap time; (*b*) total time; (*c*) counting process, using the hypothetical data from Figure 1, where ■ is an event and ● is censoring. Each time to an event or censoring is a separate risk interval, hence subjects A and B have three separate intervals

Partial likelihood

Partial likelihood	Model	Hazard	Example
(a) *Unstratified (unrestricted) models*			
$L(\beta)=\prod_{i=1}^{n}\prod_{k=1}^{K}\left(\frac{e^{\beta' Z_{ik}(X_{ik})}}{\sum_{j=1}^{n}\sum_{l=1}^{K} Y_{jl}(X_{ik})e^{\beta' Z_{jl}(X_{ik})}}\right)^{\delta_{ik}}$	AG	$\lambda_{ik}(t;Z_{ik})=\lambda_0(t)e^{\beta' Z_{ik}(t)}$	$\frac{\lambda_{A1}(2)}{\lambda_{A1}(2)+\lambda_{B1}(2)+\lambda_{C1}(2)}\times\frac{\lambda_{A2}(5)}{\lambda_{A2}(5)+\lambda_{B1}(5)+\lambda_{C1}(5)}$
		$Y_{ik}(t)=I(X_{i,k-1}<t\leqslant X_{ik})$	$\times\frac{\lambda_{B1}(7)}{\lambda_{A3}(7)+\lambda_{B1}(7)+\lambda_{C1}(7)}\times\frac{\lambda_{B2}(11)}{\lambda_{A3}(11)+\lambda_{B2}(11)+\lambda_{C1}(11)}\times\frac{\lambda_{B3}(17)}{\lambda_{B3}(17)}$

Partial likelihood

(b) Stratified models

$$L(\beta) = \prod_{i=1}^{n} \prod_{k=1}^{K} \left(\frac{e^{\beta' Z_{ik}(X_{ik})}}{\sum_{j=1}^{n} Y_{jk}(X_{ik}) e^{\beta' Z_{ik}(X_{ik})}} \right)^{\delta_{ik}}$$

PWP-CP	$\lambda_{ik}(t;Z_{ik}) = \lambda_{0k}(t)e^{\beta' Z_{ik}(t)}$	$\frac{\lambda_{A1}(2)}{\lambda_{A1}(2)+\lambda_{B1}(2)+\lambda_{C1}(2)} \times \frac{\lambda_{A2}(5)}{\lambda_{A2}(5)}$
	$Y_{ik}(t) = I(X_{i,k-1} < t \leqslant X_{ik})$	$\times \frac{\lambda_{B1}(7)}{\lambda_{B1}(7)+\lambda_{C1}(7)} \times \frac{\lambda_{B2}(11)}{\lambda_{B2}(11)} \times \frac{\lambda_{B3}(17)}{\lambda_{B3}(17)}$
PWP-GT	$\lambda_{ik}(t;Z_{ik}) = \lambda_{0k}(t-t_{k-1})e^{\beta' Z_{ik}(t)}$	$\frac{\lambda_{A1}(2)}{\lambda_{A1}(2)+\lambda_{B1}(2)+\lambda_{C1}(2)} \times \frac{\lambda_{A2}(3)}{\lambda_{A2}(3)+\lambda_{B2}(3)}$
	$Z_{jk}(X_{ik})$ replaced by $Z_{ik}(X_{i,k-1}+G_{ik})$	$\times \frac{\lambda_{B1}(7)}{\lambda_{B1}(7)+\lambda_{C1}(7)} \times \frac{\lambda_{B2}(4)}{\lambda_{B2}(4)} \times \frac{\lambda_{B3}(6)}{\lambda_{B3}(6)}$
	$Y_{ik}(t) = I(G_{ik} > t)$	
WLW*	$\lambda_{ik}(t;Z_{ik}) = \lambda_{0k}(t)e^{\beta' Z_{ik}(t)}$	$\frac{\lambda_{A1}(2)}{\lambda_{A1}(2)+\lambda_{B1}(2)+\lambda_{C1}(2)} \times \frac{\lambda_{A2}(5)}{\lambda_{A2}(5)+\lambda_{B2}(5)+\lambda_{C1}(5)}$
	$Y_{ik}(t) = I(X_{ik} \geqslant t)$	$\times \frac{\lambda_{B1}(7)}{\lambda_{B1}(7)+\lambda_{C1}(7)} \times \frac{\lambda_{B2}(11)}{\lambda_{B2}(11)+\lambda_{C1}(11)} \times \frac{\lambda_{B3}(17)}{\lambda_{B3}(17)}$

Bladder data (revisit)

```
> AG.fit
Call:
coxph(formula = Surv(start, stop, event) ~ rx + number + size,
    data = bladder2)


           coef exp(coef) se(coef)      z      p
rx      -0.4647     0.628   0.1997 -2.327 0.0200
number   0.1750     1.191   0.0471  3.717 0.0002
size    -0.0437     0.957   0.0691 -0.632 0.5300

Likelihood ratio test=17.5  on 3 df, p=0.000553  n= 178, number of events= 112

> PWP.CP.fit
Call:
coxph(formula = Surv(start, stop, event) ~ rx + number + size +
    strata(enum), data = bladder2)


            coef exp(coef) se(coef)      z     p
rx      -0.33349     0.716   0.2162 -1.543 0.120
number   0.11962     1.127   0.0533  2.243 0.025
size    -0.00849     0.992   0.0728 -0.117 0.910

Likelihood ratio test=6.51  on 3 df, p=0.0893  n= 178, number of events= 112
```

Bladder data (revisit)

```
> PWP.GP.fit
Call:
coxph(formula = Surv(stop - start, event) ~ rx + number + size +
    strata(enum), data = bladder2)


            coef exp(coef) se(coef)      z      p
rx      -0.27900     0.757   0.2073 -1.346 0.1800
number   0.15805     1.171   0.0519  3.043 0.0023
size     0.00742     1.007   0.0700  0.106 0.9200

Likelihood ratio test=9.33  on 3 df, p=0.0252  n= 178, number of events= 112
> WLW.fit
Call:
coxph(formula = Surv(stop, event) ~ rx + number + size + strata(enum),
    data = bladder)


           coef exp(coef) se(coef)     z       p
rx      -0.5848     0.557   0.2011 -2.91 3.6e-03
number   0.2103     1.234   0.0468  4.50 6.9e-06
size    -0.0516     0.950   0.0697 -0.74 4.6e-01

Likelihood ratio test=25.3  on 3 df, p=1.36e-05  n= 340, number of events= 112
```

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다변량 생존자료분석

Multi-state model

- 두 가지 상태(0:alive, 1:dead)를 가진 생존자료
  - 1: absorbing state (흡수)
- K개의 상태, $\tilde{K} = \{1, \ldots, K\}$, 를 가진 다상태 모형
- Illness-death model: 3 states (0: healthy, 1: diseased, 2:dead)

Transition intensity vs. transition probability

- $P_{hj}(s,t) = P(X(t) = j | X(s) = h, F_s-)$: transition probability
- $\alpha_{hj}(t) = \lim_{\Delta t \to 0} \frac{P_{hj}(t,t+\Delta t)}{\Delta t}$: transition intensity
  - eg, in illness-death model, $\alpha_{01}(t), \alpha_{02}(t), \alpha_{12}(t)$
  - eg, in competing risks model, $\alpha_{01}(t), \ldots, \alpha_{0K}(t)$
- Relation
  - eg, in illness-death model, $P_{00}(s,t) = \exp\{-\int(\alpha_{01}(s) + \alpha_{02}(s))ds\}$
  - eg, in competing risks model, $P_{00}(s,t) = \exp\{-\int -\sum_{k=1}^{K} \alpha_{0k}(s)ds\}$

Estimation of transition probabilities in finite-state Markov processes

- $\alpha_{hji}(t|z_i) = \alpha_{hj0}(t)\exp(\beta'_{hj}z_i)$: transition intensity from state h to state j for the individual i
- Using $\hat{\beta}$ and $\hat{A}_{hj0}(t,\hat{\beta})$, obtain $\hat{A}_{hj}(t|z) = \hat{A}_{hj0}(t,\hat{\beta})\exp(\hat{\beta}'z)$ for $h \neq j$ and $\hat{A}_{hh}(t|z) = -\sum_{j\neq h}\hat{A}_{hj}(t|z)$, and then $P_{hj}(s,t|z)$ can be estimated

BMT data (revisit)

처리그룹	Patients	Platelet recovery 0→1	Relapse or death 0→2	After plate recovry, relapse or death 1→2
ALL	38	35	3	12
AML low risk	54	48	6	9
AML high risk	45	38	7	18
Total	137	121	16	67

BMT (revisited)

```
> p.fit
Call:
coxph(formula = Surv(TP, PI) ~ factor(DG) + p28 * d28 + FAB,
    data = bmt)

                coef exp(coef) se(coef)      z      p
factor(DG)2  0.35769     1.430 0.249368  1.434 0.150
factor(DG)3  0.15916     1.173 0.298347  0.533 0.590
p28          0.01623     1.016 0.016091  1.009 0.310
d28         -0.01447     0.986 0.013804 -1.049 0.290
FAB         -0.11727     0.889 0.236910 -0.495 0.620
p28:d28     -0.00168     0.998 0.000886 -1.901 0.057

Likelihood ratio test=8.83  on 6 df, p=0.184  n= 137, number of events= 120
> d.fit
Call:
coxph(formula = Surv(TDF, status) ~ factor(DG) + p28 * d28 +
    FAB, data = bmt)

                coef exp(coef) se(coef)      z      p
factor(DG)2  0.74966     2.116  0.75997  0.986 0.3200
factor(DG)3  0.74242     2.101  0.91818  0.809 0.4200
p28         -0.14357     0.866  0.05168 -2.778 0.0055
d28          0.13241     1.142  0.04442  2.981 0.0029
FAB         -0.05788     0.944  0.67271 -0.086 0.9300
p28:d28      0.00505     1.005  0.00184  2.743 0.0061

Likelihood ratio test=16.6  on 6 df, p=0.0107  n= 137, number of events= 16
> pd.fit
Call:
coxph(formula = Surv(TP, TDF, pdstatus) ~ factor(DG) + p28 *
    d28 + FAB, data = bmt)

                coef exp(coef) se(coef)     z       p
factor(DG)2 -1.71593     0.180  0.42548 -4.03 5.5e-05
factor(DG)3 -0.75516     0.470  0.40750 -1.85 6.4e-02
p28          0.03860     1.039  0.02178  1.77 7.6e-02
d28         -0.02927     0.971  0.02050 -1.43 1.5e-01
FAB          1.21197     3.360  0.32223  3.76 1.7e-04
p28:d28      0.00268     1.003  0.00123  2.17 3.0e-02

Likelihood ratio test=37.8  on 6 df, p=1.22e-06  n= 120, number of events= 67
   (17 observations deleted due to missingness)
```

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다변량 생존자료분석

Competing risks model

- Multi-state model의 일종, absorbing state가 여러 개 있음
- 한 사건의 발생은 다른 사건의 발생을 중도절단시킴
  - eg, 주관심이 암의 재발일 때 어떤 환자들이 사망한 경우, 사망사건의 발생은 암 재발에 대해서는 중도절단 사건이 됨
  - $K = 2$ 일 때, 한 사건이 다른 사건으로의 전이를 허용하지만 그 역은 성립하지 않는 경쟁위험모형을 준경쟁위험모형(semi-competing risks model)이라고 함

Cause-specific cumulative incidence function

- $\left(T = \min\{T_j : j = 1, \ldots, K\}, \epsilon = argmin_j\{T_j\}\right)$
  - T_j: j번째 원인에 의한 사건발생시간
- $\lambda_j(t) = \lim_{h \to 0} \frac{P(t \le T < t+h, \epsilon = j | T \ge t)}{h}, j = 1, \ldots, K$: 원인별 위험함수
  - $\lambda(t) = \sum_{j=1}^{K} \lambda_j(t)$: t시점에서 어떤 원인에 의해서든 실패할 확률
- $F_j(t) = P(T \le t, \epsilon = j) = \int_0^t S(s-)\lambda_j(s)ds = \int_0^t \lambda_j(s) \exp(-\int_0^s \lambda(u)du)\, ds$: cause-specific cumulative incidence function(CIF), 즉 모든 다른 실패 원인이 존재할 때, t시점까지 원인 j에 의해 실패할 확률
  - $S(t) = P(T > t) = \exp\left\{\int_0^t \lambda(s)ds\right\}$: overall survival function

Estimated CIF

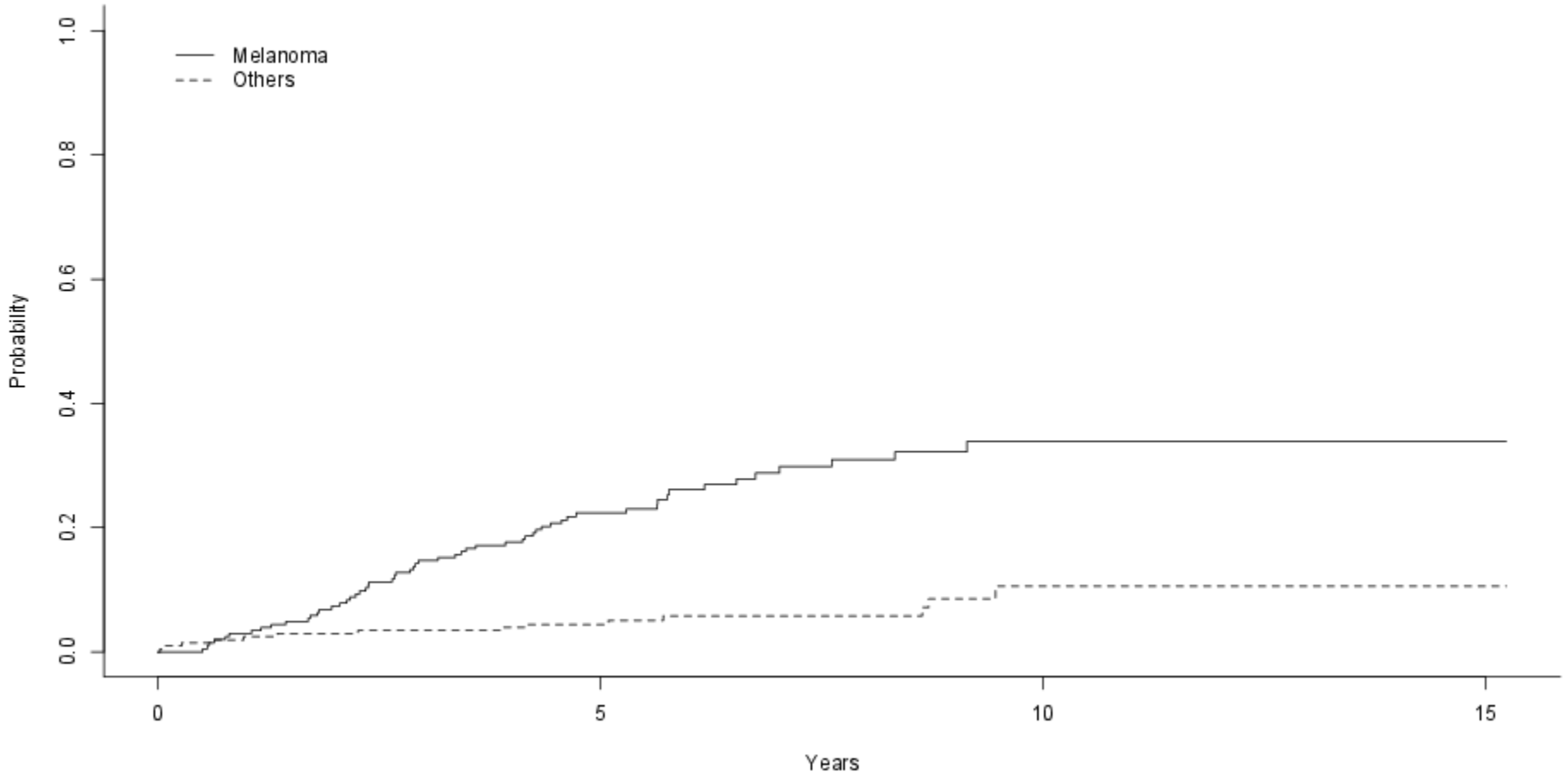
- $t_1 < \cdots < t_r$: unique ordered uncensored time points
- d_{ij}: # of events of type j that occur at time t_j
- n_i: # at risk at t_i
- $\hat{F}_j(t) = \sum_{m:t_m \leq t} \frac{d_{ij}}{n_m} \hat{S}(t_m -)$: estimated CIF
  - $\hat{S}$: PL estimator of the probability of being free of any event by time t
  - $\hat{F}_1(t) \leq 1 - \hat{S}_1(t)$ ('1': event of interest, '2': set of competing risks event), i.e., at risk of being overestimated

Melanoma data

- 피부암 환자 256명을 대상으로 사망원인을 조사
  - 피부암이 원인: 57(status=1), 중도절단: 134(status=2), 다른 원인: 14(status=3),

```
> head(melanoma)
  no status days ulc thick sex
1 789      3   10   1   676   1
2  13      3   30   0    65   1
3  97      2   35   0   134   1
4  16      3   99   0   290   0
5  21      1  185   1  1208   1
6 469      1  204   1   484   1
```

Cause-specific incidence function



Cause-specific hazard function approach

- Cox model for CSH
  - $\lambda_j(t|z_i) = \lambda_{0j}(t)\exp\left(\beta_j' z_i\right), j = 1, \ldots, K$
- Use the partial likelihood principle
  - $t_{1j} < \cdots < t_{n_j,j}$: n_j times of type j failures
  - z_{ij}: covariate for the individual that fails at t_{ij}
  - $L(\beta_1, \ldots, \beta_K) = \prod_{j=1}^{K} \prod_{i=1}^{n_j} \frac{\exp\left\{\beta_j' z_{ij}\right\}}{\sum_{l \in R(t_{ij})} \exp\left\{\beta_j' z_l\right\}}$

Melanoma data (revisited)

```
> m.ftype.fit
Call:
coxph(formula = Surv(days, m.ftype) ~ ulc + thick + sex, data = melanoma)


         coef exp(coef) se(coef)    z       p
ulc   1.16681      3.21 0.311461 3.75 0.00018
thick 0.00113      1.00 0.000379 2.99 0.00280
sex   0.45949      1.58 0.266758 1.72 0.08500

Likelihood ratio test=39.4  on 3 df, p=1.44e-08  n= 205, number of events= 57
> o.ftype.fit
Call:
coxph(formula = Surv(days, o.ftype) ~ ulc + thick + sex, data = melanoma)


          coef exp(coef) se(coef)     z    p
ulc   0.189846      1.21 0.588614 0.323 0.75
thick 0.000904      1.00 0.000844 1.071 0.28
sex   0.521108      1.68 0.543930 0.958 0.34

Likelihood ratio test=2.91  on 3 df, p=0.405  n= 205, number of events= 14
```

Sub-distribution function approach

- j번째 CIF 는 j번째 원인별 위험함수뿐만 아니라 j번째 원인을 제외한 다른 원인별 위험함수의 합에도 의존
- $F_j(t|z) = P(T \le t, \epsilon = j|z)$: sub-distribution function
  - $\lambda_j^s(t|z) = \lim_{\Delta t \to 0} \frac{P(t \le T_j < t+\Delta t | (T \ge t) \cup (T \le t \cap \epsilon \ne j), z)}{\Delta t}$: sub-distribution hazard function
  - 다른 유형으로 이미 사망한 사람도 위험 그룹에 포함됨
  - $F_j(t|z) = 1 - \exp\left\{-\int_0^t \lambda_j^s(s)ds\right\}$
- Parameter estimation: under Cox PH model,
  - Censoring complete data: 중도절단시점을 사전에 앎
  - Inverse probability censoring weight approach: $w_i(t) = I(C_i \ge T_i \wedge t)\frac{\hat{G}_c(t)}{\hat{G}_c(T_i \wedge t)}$, $\hat{G}_c$: PL estimator of G_c

Melanoma data (revisited)

```
> m.crr
convergence:  TRUE
coefficients:
  melanoma.ulc melanoma.thick   melanoma.sex
     1.1360000      0.0009428      0.4187000
standard errors:
[1] 0.3041000 0.0003809 0.2743000
two-sided p-values:
  melanoma.ulc melanoma.thick   melanoma.sex
       0.00019        0.01300        0.13000
> o.crr
convergence:  TRUE
coefficients:
  melanoma.ulc melanoma.thick   melanoma.sex
    -0.0044030      0.0006069      0.4257000
standard errors:
[1] 0.5953000 0.0007646 0.5509000
two-sided p-values:
  melanoma.ulc melanoma.thick   melanoma.sex
          0.99           0.43           0.44
```

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THANK YOU!!!