Epidemiologic Data Analysis using R
Part 4: Time-slitting in cohort studies

Janne Pitkäniemi
(Esa Läärä)

Finnish Cancer Registry, Finland, <janne.pitkaniemi@cancer.fi>
(University of Oulu, Finland, <esa.laara@oulu.fi>)

University of Tampere
Faculty of Social Sciences
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Main R functions to be covered, all in `Epi` package

- ▶ `Lexis()`
- ▶ `splitLexis()`
- ▶ `timeBand()`

Time to event analysis

Analysis of incidences = analysis of *times to event* or *failure times* or *survival times* (censored).

Mathematical concepts:

$$
\begin{aligned}
T &= \text{time to outcome event – random variable,} \\
S(t) &= P(T > t) = \textbf{survival} \text{ function of } T, \\
&= \text{probability of avoiding the event up to given time } t, \\
\lambda(t) &= -S'(t)/S(t) = \textbf{intensity} \text{ or } \textbf{hazard} \text{ function,} \\
\Lambda(t) &= \int_0^t \lambda(u)du = -\log S(t) = \textbf{cumulative hazard}, \\
F(t) &= 1 - S(t) = 1 - \exp\{-\Lambda(t)\} = \textbf{risk} \text{ function} \\
&= \text{probability of the outcome to occur by } t \\
&= \text{cumulative distribution function of } T.
\end{aligned}
$$

Hazard rate or intensity function

Can be viewed as *theoretical incidence rate*. Formally

$$
\lambda(t) = \lim_{\Delta \to 0} \frac{P(t < T \leq t + \Delta \mid T > t)}{\Delta}
$$

≈ Probability of failure occurring in a short interval $]t, t + \Delta]$, given "survival" or avoidance of event up to its start t, divided by the interval length.

This is equivalent to saying that over this short interval

$$
\text{risk} \approx \text{rate} \times \text{length of interval}
$$

or $\quad P(t < T \leq t + \Delta \mid T > t) \approx \lambda(t) \times \Delta.$

Exponential or constant hazard model

Simplest probability model for time to event:
Exponential distribution, $\mathrm{Exp}(\lambda)$, in which

$$\lambda(t) = \lambda \text{ (constant)} \quad \Rightarrow \quad \Lambda(t) = -\log S(t) = \lambda t$$

Analysis of failure data of n individuals. For subject i let

$$
\begin{aligned}
y_i &= \text{ time to event or time to censoring,} \quad Y = \sum y_i \\
d_i &= \text{ indicator for observing the event,} \quad D = \sum d_i
\end{aligned}
$$

$\mathrm{Exp}(\lambda)$ model $\Rightarrow$ **Likelihood function** of λ is

$$L(\lambda) = \prod_{i=1}^{n} \lambda(y_i)^{d_i} S(y_i) = \prod_{i=1}^{n} \lambda^{d_i} e^{-\lambda y_i} = \exp(D \log \lambda - \lambda Y)$$

Constant rate – Poisson model

This is actually equivalent to the *Poisson-likelihood*, i.e. likelihood of λ assuming that the number of cases D is distributed according to the **Poisson distribution** with expected value λY.

With randomly censored exponential times D is only approximately Poisson. This is sufficient, though, for likelihood-based (& asymptotic frequentist) inference.

Solving the *score equation*: $d \log L(\lambda)/d\lambda = 0$
$\rightarrow$ **maximum likelihood estimator** (MLE) of λ is

$$\widehat{\lambda} = \frac{D}{Y} = \frac{\text{number of cases}}{\text{total person-time}} = \text{ empirical incidence rate!}$$

Time to event – when to start the clock?

Incidence can be studied on various time scales, *e.g.*

- age (starting point = birth),
- exposure time (first exposure),
- follow-up time (entry to study),
- duration of disease (diagnosis).

Age is usully the strongest time-dependent determinant of health outcomes.

Age is also often correlated with duration of "chronic" exposure (*e.g.* years of smoking).

Therefore, adjustment for *current age* is needed rather than for *age at entry* to follow-up (like in clinical survival studies).

Age to event split into agebands

Let T = age at which outcome event occurs.
Parametric form of $\lambda(t)$, hazard by age – usually unknown.

Piecewise exponential model or **piecewise constant hazards' model** – an approximation for $\lambda(t)$:

$$\lambda(t) = \lambda_k, \qquad t \in \ ]a_{k-1}, a_k], \quad \Delta_k = a_k - a_{k-1},$$

where cutpoints $0 = a_0 < a_1 < \cdots < a_K$ divide the age range into disjoint **agebands**, each with constant rate.

In chronic disease epidemiology agebands with $\Delta_k = 5$ years (0-4, 5-9, ..., 80-84) or 10 years are commonly used.

Age-specific incidence rates

For empirical estimation of rates we calculate in each ageband

$$D_k = \quad \text{number of cases occurring in ageband } k,$$

$$Y_k = \sum_{i=1}^{n} y_{ik} = \text{total person-time in ageband } k,$$

where y_{ik} is the time slot that subject i spends in ageband k out of his/her whole **follow-up time** (from **entry** to **exit**).

ML estimators of $\lambda_1, \ldots, \lambda_K$: **age-specific incidence rates**

$$\widehat{\lambda}_k = I_k = D_k/Y_k, \quad k = 1, \ldots, K$$

based on log-likelihood $\quad \log L = \sum_k (D_k \log \lambda_k - \lambda_k Y_k).$

Cumulative rates & risks

In this model, the cumulative hazard and risk functions are

$$\Lambda(t) = \sum_{a_j < t} \lambda_j \Delta_j + \lambda_k(t - a_{k-1}), \qquad t \in]a_{k-1}, a_k]$$

$$F(t) = 1 - S(t) = 1 - \exp\{-\Lambda(t)\},$$

the latter assuming that no **competing risks** are present.

Estimation: Plug in empirical rates $\widehat{\lambda}_j = D_j/Y_j$ to get the cumulative rate C and incidence proportion R by t:
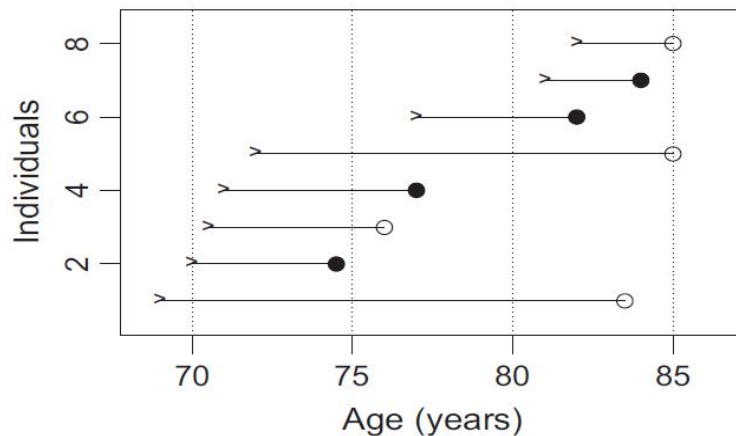
$$C = \widehat{\Lambda}(t) = \sum_{a_j < t} \widehat{\lambda}_j \Delta_j + \widehat{\lambda}_k(t - a_{k-1}), \qquad t \in]a_{k-1}, a_k]$$

$$R = \widehat{F}(t) = 1 - \widehat{S}(t) = 1 - \exp\{-\widehat{\Lambda}(t)\}$$

Example: Follow-up of a small geriatric cohort

No's of cases/p-years & rates (/100 y) in 5-y agebands:

$$1/21 = 4.8, \quad 1/16 \text{life} = 6.2, \quad 2/16.5 = 12.1$$

Splitting follow-up by Lexis() in package Epi

Individual ages at entry and at exit, as well as outcomes are assigned into vectors and stored in a data frame coh:

```
> ag.entry <- c(69, 70, 70.5, 71, 72, 76.9, 81, 81.9)
> ag.exit <- c(83.5, 74.5, 76, 77, 85, 82, 84, 85)
> event <- c(0,1,0,1,0,1,1,0) ; ind <- 1:8
> coh <- data.frame( ind, ag.entry, ag.exit, event)
```

Function Lexis() specifies the time scale(s) to be considered. It creates an enriched data frame belonging to class Lexis.

```
> coh.L <- Lexis(entry = list(age = ag.entry),
+                 exit = list(age = ag.exit),
+          exit.status = event, data = coh, id = ind)
```

Data frame of class Lexis

```
> coh.L
   age lex.dur lex.Cst lex.Xst lex.id ind ag.entry ag.exit event
1 69.0    14.5       0       0      1   1     69.0    83.5     0
2 70.0     4.5       0       1      2   2     70.0    74.5     1
3 70.5     5.5       0       0      3   3     70.5    76.0     0
4 71.0     6.0       0       1      4   4     71.0    77.0     1
5 72.0    13.0       0       0      5   5     72.0    85.0     0
6 76.9     5.1       0       1      6   6     76.9    82.0     1
7 81.0     3.0       0       1      7   7     81.0    84.0     1
8 81.9     3.1       0       0      8   8     81.9    85.0     0
```

Interpretation of new columns

$$\text{age} = \text{age at entry to follow-up,}$$
$$\text{lex.dur} = \text{duration of follow-up,}$$
$$\text{lex.Cst} = \text{current status at entry,}$$
$$\text{lex.Xst} = \text{status at exit from follow-up.}$$

Splitting follow-up times by agebands

Function `splitLexis()` splits individual follow-up times into given agebands and expands the data frame.

```
> coh.A <- splitLexis(coh.L,
+         br = c(70,75,80,85), time.scale="age")

> coh.A
   lex.id  age lex.dur lex.Cst lex.Xst ind ag.entry ag.exit event
1       1 69.0     1.0       0       0   1     69.0    83.5     0
2       1 70.0     5.0       0       0   1     69.0    83.5     0
3       1 75.0     5.0       0       0   1     69.0    83.5     0
4       1 80.0     3.5       0       0   1     69.0    83.5     0
5       2 70.0     4.5       0       1   2     70.0    74.5     1
6       3 70.5     4.5       0       0   3     70.5    76.0     0
7       3 75.0     1.0       0       0   3     70.5    76.0     0
...
13      6 76.9     3.1       0       0   6     76.9    82.0     1
14      6 80.0     2.0       0       1   6     76.9    82.0     1
15      7 81.0     3.0       0       1   7     81.0    84.0     1
16      8 81.9     3.1       0       0   8     81.9    85.0     0
```

Splitted Lexis object

▶ Function `splitLexis()` expanded the original data frame such that for all cohort members one or more rows were created, one for each ageband into which a subject contributes person time.

▶ Ex: Subject 1 has been under follow-up in all agebands considered, but subjects 7 and 8 only in $80- < 85$ y.

▶ Function `timeBand()` converts variable age into factor ageband. Also, shorthand names for person-time slots and occurrence of outcome event are given.

```
> coh.A$ageband <- timeBand(coh.A, "age", "factor")
> coh.A$y_ik <- coh.A$lex.dur # person-time slot
> coh.A$d_ik <- coh.A$lex.Xst # occurrence of outcome
```

Splitted Lexis object (cont'd)

```
> coh.A[, c(1,10:12)]
   lex.id    ageband y_ik d_ik
1       1  (-Inf,70]  1.0    0
2       1   (70,75]  5.0    0
3       1   (75,80]  5.0    0
4       1   (80,85]  3.5    0
5       2   (70,75]  4.5    1
6       3   (70,75]  4.5    0
7       3   (75,80]  1.0    0
8       4   (70,75]  4.0    0
9       4   (75,80]  2.0    1
10      5   (70,75]  3.0    0
11      5   (75,80]  5.0    0
12      5   (80,85]  5.0    0
13      6   (75,80]  3.1    0
14      6   (80,85]  2.0    1
15      7   (80,85]  3.0    1
16      8   (80,85]  3.1    0
```

$\text{lex.id} = $ subject index in original data frame,

$\text{ageband} = $ ageband and its limits,

$\text{y_ik} = $ person-time slot spent in ageband

$\text{d_ik} = $ indicator for event occurring in ageband.

Subject 1's follow-up time ($14.5 \text{ y} = 1 + 5 + 5 + 3.5$ y) is split into 4 agebands, ..., subject 8 contributes only to 1 ageband.

Tabulation of cases, rates etc. by ageband

Event indicators & person-time slots are summed over the rows of the split-expanded data frame in categories of ageband:

```
>  D <- with(coh.A, tapply(d_ik, ageband, sum))
>  Y <- with(coh.A, tapply(y_ik, ageband, sum))
```

Incidence rates (I), cumulative rates (C) and incidence proportions (R), the latter two by the end of each ageband:

```
>  I <- 100*D/Y; C <- cumsum((D/Y)*5); R <- 1-exp(-C)
>  round(cbind(D,Y,I,C,R),3)[2:4, ]
         D    Y      I     C     R
(70,75]  1 21.0  4.762 0.238 0.212
(75,80]  1 16.1  6.211 0.549 0.422
(80,85]  2 16.6 12.048 1.151 0.684
```

Example: The Diet Study (see C&H)

A cohort of 337 men in three occupational groups in England, aged 30 to 67 y at entry, recruited in '50s and '60s, followed-up until mid '70s for incidence of CHD events.

Risk factors of interest, measured by dietary survey at entry.

$$
\begin{aligned}
\texttt{energy} \;&=\; \text{total energy intake (kcal/d)}, \\
\texttt{energy.grp} \;&=\; \text{energy dichotomized:} \\
&\quad\; 1: \text{``}{\leq}2750 \text{ KCals''}, \; 2: \text{``}{>}2750 \text{ KCals''}, \\
\texttt{fat} \;&=\; \text{fat intake (g/d)}, \\
\texttt{fibre} \;&=\; \text{dietary fibre intake (g/d)}, \\
&\quad\; \texttt{height, weight, bmi,} \; etc.
\end{aligned}
$$

Important dates and outcome event

The data set `diet` in `Epi` contains three dates:

$$
\begin{aligned}
\texttt{dob} \;&=\; \text{date of } \textbf{birth}, \\
\texttt{doe} \;&=\; \text{date of } \textbf{entry} \text{ into follow-up}, \\
\texttt{dox} \;&=\; \text{date of } \textbf{exit}, \text{ end of follow-up.}
\end{aligned}
$$

These are given in format `yyyy-mm-dd` but implicitly stored as *number of days since 1.1.1970.*

In addition, the outcome event is represented by

$$
\begin{aligned}
\texttt{chd} \;&=\; \text{indicator for } \textbf{status} \text{ at exit:} \\
&\quad\; 1 = \text{CHD event occurred}, \; 0 = \text{censored.}
\end{aligned}
$$

Data diet: creating a Lexis object

First convert all dates into fractional calendar years using function `cal.yr()` in `Epi`

```
diet <- transform(diet, doe = cal.yr(doe),
    dox = cal.yr(dox), dob = cal.yr(dob) )
```

Convert the data frame into a Lexis object.

```
> dietL <- Lexis( entry = list(age = doe-dob),
+                  exit = list(age = dox-dob),
+            exit.status = chd, data = diet )
```

In the nexty step the Lexis object is splitted according to 3 agebands (y): $30- < 50$, $50- < 60$, $60- < 70$

Splitting the Lexis object into agebands

```
dietA <- splitLexis(dietL, br = c(30,50,60,70),
                    time.scale = "age")
dietA$ageband <- timeBand(dietA, "age", "factor")
dietA$y_ik <- dietA$lex.dur ; dietA$d_ik <- dietA$lex.Xst
```

```
   id    dob    doe    dox    y chd  energy.grp ageband  age y_ik d_ik
1 102 1939.2 1976.0 1986.9 10.9   0 <=2750 KCals (30,50] 36.9 10.9    0
2  59 1912.5 1973.5 1982.5  9.0   0 <=2750 KCals (60,70] 61.0  9.0    0
3 126 1920.0 1970.2 1984.2 14.0   1 <=2750 KCals (50,60] 50.2  9.8    0
4 126 1920.0 1970.2 1984.2 14.0   1 <=2750 KCals (60,70] 60.0  4.2    1
5  16 1906.7 1969.4 1970.0  0.6   1 <=2750 KCals (60,70] 62.7  0.6    1
6 247 1918.5 1968.2 1979.5 11.3   1 <=2750 KCals (30,50] 49.7  0.3    0
7 247 1918.5 1968.2 1979.5 11.3   1 <=2750 KCals (50,60] 50.0 10.0    0
8 247 1918.5 1968.2 1979.5 11.3   1 <=2750 KCals (60,70] 60.0  1.0    1
```

Properties of the original data frame and the expanded object:

```
> str(diet)
'data.frame':    337 obs. of  17 variables:
> str(dietA)
Classes Lexis and data.frame   729 obs. of 25 variables
```

Relevelling of energy.grp and some tabulations

The energy.grp variable is relevelled such that "high energy" is taken as the reference or "unexposed" category and "low energy" as the "exposed" one.

```
dietA$eg2 <- Relevel( dietA$energy.grp,
         ref = ">2750 KCals" )
```

Tabulation of cases, person-years and rates:

```
tab.ae <- stat.table( list( ageband, eg2),
      list( D = sum(d_ik), Y = sum(y_ik),
            I = ratio(d_ik, y_ik, 1000) ),
      margin = T, data = dietA )
print(tab.ae, digits= c(sum=0, ratio=1))
```

Rates by ageband and energy intake

```
-------------------------------------
          -----------eg2-----------
ageband      >2750   <=2750    Total
             KCals    KCals
-------------------------------------
(-Inf,30]       NA       NA       NA
...
(30,50]          4        2        6
               622      381     1003
               6.4      5.2      6.0
(50,60]          6       12       18
              1128      979     2107
               5.3     12.3      8.5
(60,70]          8       14       22
               794      699     1493
              10.1     20.0     14.7
(70,Inf]        NA       NA       NA
...
Total           18       28       46
              2544     2059     4604
               7.1     13.6     10.0
-------------------------------------
```

Crude rate ratio
```
> tab.ae[3, 6, 2] /
+ tab.ae[ 3, 6, 1]
[1] 1.921747
```

Rate ratios by ageband:
```
> IRs <- tab.ae[3, 2:4, 2]/
+        tab.ae[3, 2:4, 1]
> round(IRs,2)
30-<50 50-<60 60-<70
  0.82   2.30   1.99
```

▶ Low intake risky?

▶ No effect in young?

Poisson model on age and exposure

Let D_{kj}, Y_{kj}, and I_{kj} be cases, p-years & rate in ageband k & exposure category j (1="unexposed", 2="exposed").
Piecewise Exp-model in both exposure categories assumed:

$$\lambda_{kj} = \text{ theoretical rate in cell } kj.$$

Theoretical rate ratio $\rho_k = \lambda_{k2}/\lambda_{k1}$,
comparing exposed *vs.* unexposed.

(a) What are the "true" values of ρ_k?

(b) Can we assume $\rho_k = \rho$, same rate ratio in all agebands?

(c) What is the value of the common rate ratio ρ?

Poisson model (cont'd)

Assuming common rate ratio the true rates are modelled

$$\log \lambda_{kj} = \alpha_k + \beta_j = \sum_{k=1}^{K} \alpha_k A_k + \sum_{j=1}^{2} \beta_j X_j,$$

where A_k and X_j are indicator (1/0) variables for level k of ageband and level j of exposure. In exponential form

$$\lambda_{kj} = \exp(\alpha_k + \beta_j) = e^{\alpha_k} e^{\beta_j}.$$

Set $\beta_1 = 0$ ("unexposed" as reference) $\Rightarrow$ Interpretation:

$$
\begin{aligned}
\alpha_k &= \log(\lambda_{k1}) = \text{log-rate of unexposed in ageband } k \\
\beta_2 &= \log(\lambda_{k2}/\lambda_{k1}) = \log(\rho) = \text{log-common rate ratio}
\end{aligned}
$$

Fitting the Poisson model

Use function `glm()` on the expanded data frame:

```
> m.ea <- glm( d_ik/y_ik ~ ageband + eg2,
+          fam = poisson, w = y_ik, data = dietA )

> round(ci.lin(m.ea, Exp=T)[ , -(3:4)], 4 )
                 Estimate StdErr exp(Est.)   2.5%  97.5%
(Intercept)       -5.4033 0.4390    0.0045 0.0019 0.0106
ageband(50,60]     0.3027 0.4721    1.3535 0.5366 3.4145
ageband(60,70]     0.8456 0.4613    2.3294 0.9431 5.7535
eg2<=2750 KCals    0.6233 0.3027    1.8651 1.0306 3.3753
```

The estimated rate ratio for "low" vs. "high" energy consumption, adjusted for age, is thus 1.87 [1.03 to 3.38], only slightly lower than the unadjusted one 1.92 [1.06 to 3.47].

Concluding remarks

▶ Modelling could continue from this to include other confounders, continuous covariates, interactions, *etc.*

▶ Agebands may well be much narrower than in our example. With infinitely narrow bands Poisson regression equals the famous Cox model.

▶ Splitting by many time scales (*e.g.* age, calendar time, time since first exposure, *etc.*) simultaneously and the corresponding data frame expansion is straightforward using these tools. More about this in the next lecture.